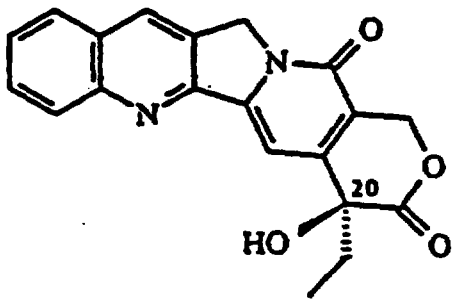
New analogues of camptothecin, preparation processes, their use as medicaments and the pharmaceutical compositions containing them

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 fused with an α-hydroxylactone with six links. 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 has 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.

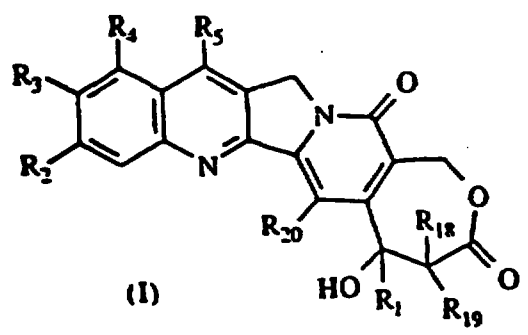
It has been indicated that α-hydroxylactone was an absolute requirement both for the *in vivo* and *in vitro* activity of campotothecin (Camptothecins: New Anticancer Agents, Putmesil, M et al, ed., p. 27 (CRC Press, 1995); Wall M. et al, Cancer Res. 55:753 (1995); Hertzberg et al, J. Med. Chem. 32:715 (1982) and Crow et al, J. Med. Chem. 35:4160 (1992)). The present invention relates to a new class of compounds of

camptothecin, in which a replaces the natural α-hydroxylactone of camptothecin. The compounds according to the present invention present a powerful biological activity which is unexpected with regard to the state of the prior art.

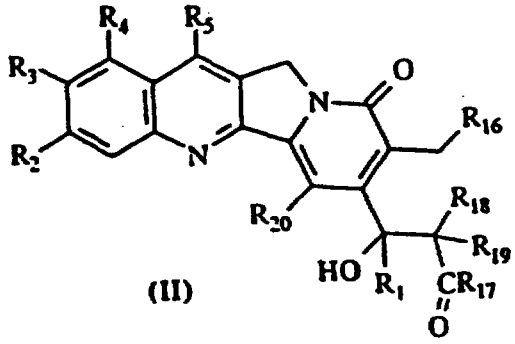
Therefore a subject of the invention is new compounds of camptothecin which differ from all known compounds of camptothecin in the sense that they contain β-hydroxylactone (or its open hydroxycarboxylic form) instead of an α-hydroxylactone (or its open hydroxycarboxylic form); or a pharmaceutically acceptable salt of the latter. By compound of camptothecin is meant a compound having the same structural skeleton as that of camptothecin (i.e. an indolizino[1,2-b]quinoline fragment fused with an α-hydroxylactone with six links), with or without other chemical substitutions on the skeletal structure (for example the compounds of camptothecin). Different compounds of camptothecin are well known by specialists, as described above. By β-hydroxylactone is meant a lactone which contains an additional carbon atom between the carbon of the carboxyl and the α-carbon carrying the hydroxyl group in the α-hydroxylactone. The β-hydroxylactone can be a "closed" or "open" ring with seven members, in which the bond between the carbonyl group and the adjacent oxygen atom is hydrolyzed, which leads to the formation of a carboxylic acid group and a hydroxyl group, which groups can be substituted or non substituted.

A compound of camptothecin according to the invention can therefore contain substitutions on the indolizino[1,2-b]quinoline fragment (for example in order to improve the solubility of the compound) or on the open or closed β-hydroxylactone (for example in order to improve the stability of the compound). Examples of substitutions on the closed β-hydroxylactone include an alkyl substitution (for example ethyl) on the β-carbon.. Examples of substitutions on the open β-hydroxylactone include alkyl substitutions on the β-carbon, substitutions (for example an amidation) on the resultant carboxylic acid and substitutions (for example an esterification) or suppressions of the resultant hydroxyl group.

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 alkyl lower alkoxy or lower alkyl lower alkylthio;

R_2, R_3 and R_4 represent, independently, H, halo, lower alkyl halo, lower alkyl, lower alkenyl, cyano, lower alkyl cyano, nitro, lower alkyl nitro, amido, lower alkyl amido, hydrazino, lower alkyl hydrazino, azido, lower alkyl azido, $(CH_2)_mNR_6R_7$, $(CH_2)_mOR_6$, $(CH_2)_mSR_6$, $(CH_2)_mCO_2R_6$, $(CH_2)_mNR_6C(O)R_8$, $(CH_2)_mC(O)R_8$, $(CH_2)_mOC(O)R_8$, $O(CH_2)_mNR_6R_7$, $OC(O)NR_6R_7$, $OC(O)(CH_2)_mCO_2R_6$ 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}), aryl or lower alkyl substituted(i.e. substituted between once and four times on the aryl group or the heterocycle) or non substituted, in which the substituent is a lower alkyl, halo, nitro, amino, lower alkylamino, lower haloalkyl, lower alkyl hydroxy, lower alkoxy or lower alkyl lower alkoxy or R_2 and R_3 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 alkyl halo, lower alkyl, lower alkoxy, lower alkyl lower alkoxy, lower alkyl lower alkylthio, cycloalkyl, lower alkyl cycloalkyl, cyano, alkyl cyano, lower alkyl sulphonyl lower alkyl, lower

alkyl hydroxy, 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 $(CH_2)_n[N\approx X]$, $OC(O)[N\approx X]$, $(CH_2)_mOC(O)[N\approx X]$, aryl or lower alkyl aryl substituted (i.e. substituted between once and four times on the aryl or heteroaryl group) or non substituted, in which the substituent is a lower alkyl, halo, nitro, amino, amino lower alkyl, lower alkyl halo, lower alkyl hydroxy, lower alkoxy or lower alkyl lower alkoxy;

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

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

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

R_{10} represents H, a lower alkyl, lower alkyl halo, 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 alkyl halo, lower alkyl hydroxy or lower alkyl lower alkoxy;

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 $C(O)CH_2)_mCH_3$;

m is an integer comprised between 0 and 6;

n is 1 or 2; and

q represents an integer from 0 to 2; and $[N\approx X]$ 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}: or a pharmaceutically acceptable salt of the latter.

A particular subject of the invention is the compounds of formulae I and II as defined above in which R_1 represents a lower alkyl, lower alkenyl, lower alkyl halo, lower alkyl lower alkoxy or lower alkyl lower alkylthio; R_5 represents H, a halo, lower alkyl halo, lower alkyl, lower alkoxy, lower alkyl lower alkoxy, lower alkyl lower alkylthio, cycloalkyl, lower alkyl cycloalkyl, cyano, alkyl cyano, lower alkyl hydroxy, nitro, $(CH_2)_mC(O)R_8$, $(CH_2)_mNR_6C(O)R_8$, $(CH_2)_mNR_6R_7$, $(CH_2)_mN(CH_3)(CH_2)_nNR_6R_7$, $(CH_2)_mOC(O)R$, $(CH_2)_mOC(O)NR_6R_7$, or $(CH_2)_n[N\approx X]$, $OC(O)[N\approx X]$, $(CH_2)_mOC[N\approx X]$, aryl or lower alkyl aryl substituted or non substituted; R_{12} and R_{13} represent, independently, a lower alkyl; R_{16} represents OR_{21}; and R_{18} , R_{19} and R_{20} represent H.

A particular subject of the invention is the compounds of formulae I and II as defined above in which R_1 represents a lower alkyl, lower alkenyl, lower alkyl halo or lower alkyl lower alkoxy; R_2 , R_3 and R_4 represent, independently, H, halo, lower alkyl halo, lower alkyl, nitro, amido, lower alkyl amido, hydrazino, lower alkyl hydrazino, azido, lower alkyl azido, $(CH_2)_mNR_6R_7$, $(CH_2)_mOR_6$, $(CH_2)_mSR_6$, $(CH_2)_mC(O)R_8$, $OC(O)NR_6R_7$, $(CH_2)_n[N\approx X]$ or $(CH_2)_mOC(O)[N\approx X]$ substituted or non substituted, or $OC(O)[N\approx X]$, or R_2 and R_3 together form a chain with 3 or 4 members, in which the said elements of the chain are chosen from the group constituted by CH, CH_2, O, S, N or NR_9; R_5 represents H, halo, lower alkyl halo, lower alkyl, lower alkoxy, lower alkyl lower alkoxy, lower alkyl lower alkylthio, lower alkyl hydroxy, nitro, $(CH_2)_mC(O)R_8$, $(CH_2)_mNR_6C(O)R_8$, $(CH_2)_mNR_6R_7$, $(CH_2)_mN(CH_3)(CH_2)_nNR_6R_7$, $(CH_2)_mOC(O)R_8$, $(CH_2)_mOC(O)NR_6R_7$, $(CH_2)_n[N\approx X]$ or $OC(O)[N\approx X]$, substituted or non substituted, or $(CH_2)_mOC(O)[N\approx X]$; R_6 and R_7 represent, independently, H, a lower alkyl, lower alkyl hydroxy, lower alkyl amino lower alkyl, lower alkyl amino, cycloalkyl, lower alkyl cycloalkyl, lower alkyl lower alkoxy, aryl, lower alkyl aryl or lower alkyl halo; R_8 represents H, a lower alkyl, lower alkyl hydroxy, amino lower alkyl, lower alkyl amino lower alkyl, lower alkyl amino, cycloalkyl, lower alkyl cycloalkyl, lower alkenyl, lower alkoxy, lower alkyl lower alkoxy, lower alkyl halo, lower aryl or lower alkyl aryl; R_9 represents H, a lower alkyl or a lower alkyl halo; R_{10} represents H, a lower alkyl, lower alkyl halo or lower alkoxy; R_{11} represents a lower alkyl; and R_{14} and R_{15} represent, independently, H or a lower alkyl.

A more particular subject of the invention is the compounds of formula I as defined above in which R_1 represents the ethyl group; R_2 and R_3 represent, independently, H, a lower alkyl, halo, lower alkyl halo or $(CH_2)_mOR_6$, or R_2 and R_3 together form a methylenedioxy or an ethylenedioxy; and R_4 and R_5 represent, independently, H, a lower alkyl, $(CH_2)_mNR_6R_7$ or $(CH_2)_n[N\approx X]$ non substituted or substituted by a lower alkyl. Preferably R_4 represents H or $(CH_2)_mNR_6R_7$ in which R_6 and R_7 represent, independently, H or a lower alkyl, and R_5 represents H, a lower alkyl or $(CH_2)_n[N\approx X]$ substituted or non substituted by a lower alkyl; as an example of substituted or non substituted $[N\approx X]$, there can be mentioned the piperidyl, morpholinyl, piperazinyl, imidazolyl and 4-methylpiperazinyl radical.

In a more preferred manner, R_2 represents H or halo and preferably H, chloro or fluoro; and R_3 represents H, a lower alkyl, halo or OR_6 in which R_6 represents H, a lower alkyl or a lower alkyl aryl and preferably H, fluoro, chloro, methyl or methoxy. Also in a more preferred manner, R_2 and R_3 together form a methylenedioxy or an ethylenedioxy.

A more particular subject of the invention is the products described hereafter in the examples and in particular the products corresponding to the following formulae:

- 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
- 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
- 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
- 10-benzyloxy-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
- 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
- 11-(dimethylamino)methyl-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
- 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
- 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
- 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
- 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
- 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

- 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
- 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
- 5-ethyl-9-flouro-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
- 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
- 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
- 10-chloro-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
- 5,12-diethyl-4,5-dihydro-5,10-dihydroxy-11-morpholino methyl-1*H*-oxepino [3',4':6,7]indolizino[1,2-*b*]quinoline-3,15 (4*H*,13*H*)-dione
- 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
- 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
- 9-chloro-5-ethyl-4,5-dihydro-5-hydroxy-10-methoxy-12-(4-methyl piperazinomethyl) -1*H*-oxepino[3',4':6,7]indolizino [1,2-*b*] quinoline-3,15(4*H*,13*H*)-dione
- 9-chloro-5-ethyl-4,5-dihydro-5-hydroxy-10-methoxy-12-morpholinomethyl-1*H*-oxepino[3',4':6,7]indolizino[1,2-*b*]quinoline-3,15(4*H*,13*H*)-dione
- 5-ethyl-4,5-dihydro-5-hydroxy-12-(4-methyl piperazinomethyl)-1*H*-oxepino [3',4':6,7] indolizino [1,2-*b*] quinoline-3,15(4*H*,13*H*)-dione
- 5-ethyl-4,5-dihydro-5-hydroxy-12-piperidinomethyl-1*H*-oxepino [3',4':6,7]indolizino [1,2-*b*]quinoline-3,15(4*H*,13*H*)-dione
- 5-ethyl-4,5-dihydro-5-hydroxy-12-morpholinomethyl-1*H*-oxepinol[3',4':6,7] indolizino [1,2-*b*]quinoline-3,15(4*H*,13*H*)-dione
- 5-ethyl-10-fluoro-4,5-dihydro-5-hydroxy-12-(4-methylpiperazinomethyl)-1*H*-oxepino[3',4':6,7]indolizino [1,2-*b*] quinoline-3,15(4*H*,13*H*)-dione
- 5-ethyl-10-fluoro-4,5-dihydro-5-hydroxy-12-morpholinomethyl-1*H*-oxepino [3',4':6,7]indolizino[1,2-*b*]quinoline-3,15(4*H*,13*H*)-dione

- 5-ethyl-9-fluoro-4,5-dihydro-5-hydroxy-10-methyl-12-(4-methylpiperazinomethyl)-1*H*-oxepino[3',4':6,7]indolizino[1,2-*b*] quinoline-3,15(4*H*,13*H*)-dione
- 5-ethyl-9-fluoro-4,5-dihydro-5-hydroxy-10-methyl-12-morpholinomethyl-1*H*-oxepino[3',4':6,7]indolizino[1,2-*b*]quinoline-3,15(4*H*,13*H*)-dione
- 5-ethyl-9-fluoro-4,5-dihydro-5-hydroxy-10-methyl-12-piperidinomethyl-1*H*-oxepino[3',4':6,7] indolizino [1,2-*b*] quinoline-3,15(4*H*,13*H*)-dione
- 8-ethyl-2,3,8,9-tetrahydro-8-hydroxy-16-(4-methyl piperazinomethyl)-10*H*,12*H*-[1,4] dioxino [2,3-*g*] oxepino [3',4':6,7] indolizino [1,2-*b*] quinoline-10,13[15*H*]-dione
- 9-chloro-5-ethyl-10-fluoro-4,5-dihydro-5-hydroxy-12-morpholinomethyl-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.

A more particular subject of the invention is also the compounds of formula II as defined above, in which R_1 represents the ethyl group; R_2 and R_3 represent, independently, H, a lower alkyl, halo, lower alkyl halo or $(CH_2)_mOR_6$, or R_2 and R_3 form together a methylenedioxy or an ethylenedioxy; R_4 and R_5 represent, independently, H, a lower alkyl, $(CH_2)_mNR_6R_7$, or $(CH_2)_n[N{\approx}X]$ non substituted or substituted by a lower alkyl; R_{20} represents H and R_{17} represents OR_6, in which R_6 represents H or a lower alkyl, or NR_6R_7 in which R_6 and R_7, independently, represent H, a lower alkyl, aryl or lower alkyl aryl. Preferably, R_4 represents H or $(CH_2)_mNR_6R_7$, in which R_6 and R_7 represent, independently, H or a lower alkyl; R_5 represents H, a lower alkyl or $(CH_2)_n[N{\approx}X]$ non substituted or substituted by a lower alkyl; and R_{17} represents OR_6 in which R_6 represents H or a lower alkyl; or a pharmaceutically acceptable salt of the latter. As an example of substituted or non substituted [N≈X], there can be mentioned the piperidyl, morpholinyl, piperazinyl, imidazolyl and 4-methylpiperazinyl radical.

In a preferred manner, R_2 represents H or halo and preferably H, chloro or fluoro; R_3 represents H, a lower alkyl, halo or OR_6 in which R_6 represents H, a lower alkyl or a lower alkyl aryl and preferably H, fluoro, chloro, methyl or methoxy. Also in a more preferred manner R_2 and R_3 form together dioxymethylene or dioxyethylene.

A more particular subject of the invention is the products described hereafter in the examples, in particular the products corresponding to the following formulae:

- *tert*-butyl β-ethyl-β-hydroxy-γ-(8-hydroxymethyl-9-oxo (11*H*)-indolizino-[1,2-*b*] quinoline-7-yl)-propionate
- ethyl β-ethyl-β-hydroxy-γ-(8-hydroxymethyl-9-oxo (11*H*)-indolizino-[1,2-*b*] quinoline-7-yl)-propionate
- β-ethyl-β-hydroxy-γ-(8-hydroxymethyl-9-oxo (11*H*)-indolizino-[1,2-*b*] quinoline-7-yl)-propionic acid
- methyl β-ethyl-β-hydroxy-γ-(8-hydroxymethyl-9-oxo (11*H*)-indolizino-[1,2-*b*] quinoline-7-yl)-propionate
- ethyl β-ethyl-α,α-difluoro-β-hydroxy-γ-(8-hydroxymethyl-9-oxo (11*H*)-indolizino-[1,2-*b*] quinoline-7-yl)-propionate
- ethyl β-ethyl-β-hydroxy-γ-(8-hydroxymethyl-9-oxo (11*H*)-indolizino-[1,2-*b*] quinoline-7-yl)-priopionate
- *tert*-butyl β-ethyl-β-hydroxy-γ-(8-hydroxymethyl-9-oxo (11*H*)-indolizino-[1,2-*b*] quinoline-7-yl)-propionate
- β-ethyl-γ-(12-ethyl-8-hydroxymethyl-9-oxo (11*H*)-indolizino-[1,2-*b*] quinoline-7-yl)-β-hydroxy-propionic acid
- γ-(12-benzyloxy-8-hydroxymethyl-9-oxo (11*H*)-indolizino [1,2-*b*] quinoline-7-yl)-β-ethyl-β-hydroxy-propionic acid (E)

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

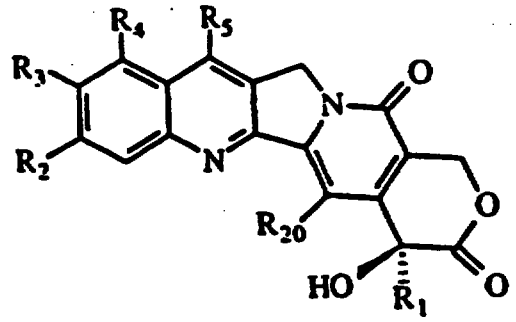
designates a ring with 3 to 7 carbons, such as for example, the cyclopropyl, cyclobutyl, cyclopentyl or cyclohexyl groups. The term aryl designates a mono- di- or tricyclic hydrocarbon compound with at least one aromatic ring, each ring containing a maximum of 7 members, such as for example, phenyl, naphthyl, anthracyl, biphenyl or indenyl. The term halo signifies chloro, bromo, iodo or fluoro. The radicals corresponding to the expressions lower alkyl halo, lower alkyl cyano, lower alkyl nitro, lower alkyl amido, lower alkyl hydrazino, lower alkyl azido, lower alkyl aryl, lower alkyl hydroxy, lower alkyl lower alkoxy, lower alkyl lower alkylthio, 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 amino lower alkyl radical can contain one or two lower alkyl groups and represent, for example, $NHCH_3$, $NHCH_2CH_3$, $N(CH_3)_2$ or $N(CH_3)(CH_2CH_3)$. Examples of [N≈X] include the piperidinyl, morpholinyl, piperizinyl and imidazolyl groups.

As has been observed for camptothecin, the carbon atom carrying the hydroxy function in the β-hydroxylactone or the β-hydroxycarboxylate group of the compounds according to the present invention, is asymmetrical. Consequently, 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.

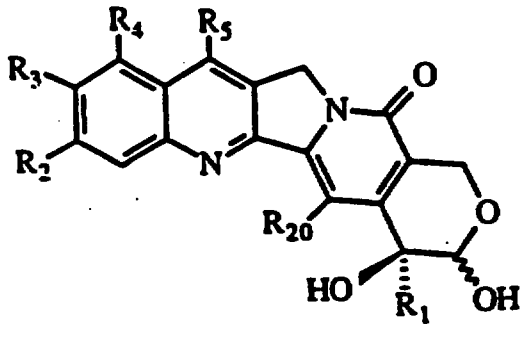
A subject of the invention is also preparation processes for the compounds of general formulae I and II, either starting with camptothecin or substituted camptothecins, or by total chemical synthesis.

Therefore the invention relates to a preparation process for the compounds of formulae I and II according to the invention starting with camptothecin or substituted camptothecins characterized in that:

- camptothecin α-hydroxylactone of general formula



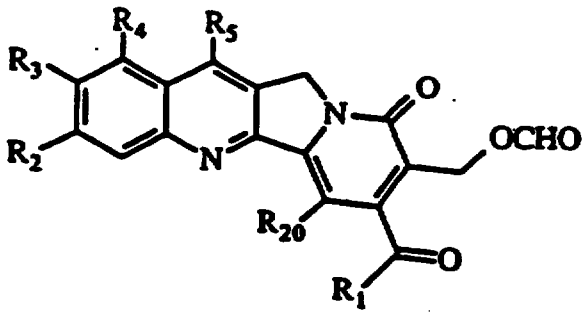
in which R_1, R_2, R_3, R_4, R_5 and R_{20} have the meaning indicated above, is reduced in order to obtain the α-hydroxylactol of general formula A



A

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

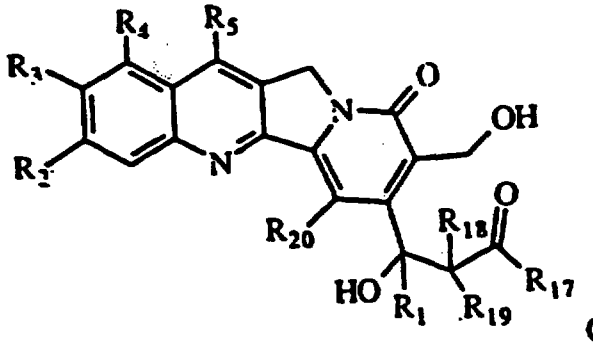
- in compound A thus formed, the carbon-carbon bond linking the adjacent carbinols, is cut by treatment with an appropriate oxidizing agent so as to produce a compound of formula B



B

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

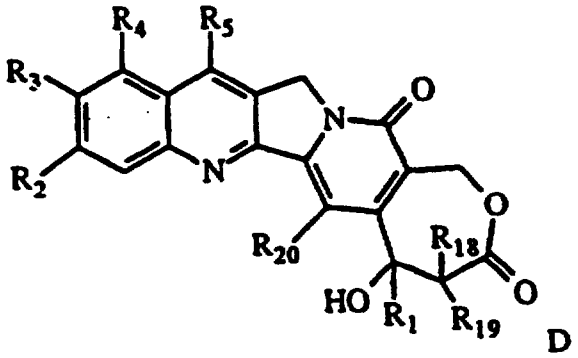
- then treatment is carried out with a functionalized alkylating agent and the formyl function of the compound of formula B is cut in order to produce a β-hydroxyester of general formula C



C

in which R_1, R_2, R_3, R_4, R_5, R_{18}, R_{19} and R_{20} have the meaning indicated above, and R_{17} represents OR_6 and R_6 represents a lower alkyl, cycloalkyl, lower alkyl cycloalkyl, lower alkenyl, lower alkyl lower alkoxy or aryl or lower alkyl aryl;

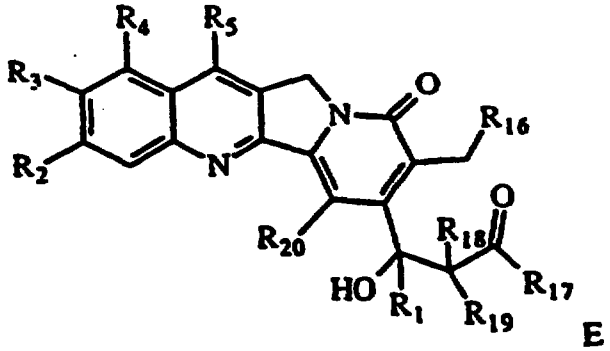
- said compound of general formula C is cyclized in order to produce the β-hydroxylactonic compound of general formula D



D

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

- the lactone of general formula D is opened in order to produce the compound of formula E



E

in which R_1, R_2, R_3, R_4, R_5, 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 alkyl cycloalkyl, lower alkenyl, lower alkyl lower alkoxy or aryl or lower alkyl aryl.

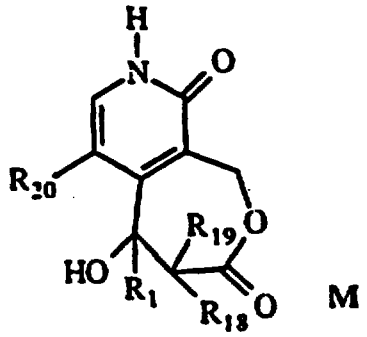
Certain compounds of general formula E can also be obtained by hydrolysis of the ester function of the corresponding compounds of formula C. The compounds of general formula E in which R_{16} and/or R_{17} represent, independently, the hydroxy radical, can be esterified or amidified under standard conditions known to a person skilled in the art in order to obtain the corresponding esters or amides of formula E.

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)). During this process, the reduction is carried out using a reducing agent in an appropriate solvent, such as, for example, sodium borohydride in methanol. The stage corresponding to the formation of compound B starting from compound A is implemented under oxidizing conditions, such as, for example, with lead tetraacetate, periodic acid or sodium metaperiodate in an appropriate solvent, such as, for example, acetic acid. The treatment with a functionalized alkylating agent can be implemented using a metallic derivative for example, of lithium or zinc, of a carboxylic ester in an anhydrous aprotic solvent such as, for example, tetrahydrofuran. The lactonization stage which allows compound D to be obtained starting from compound C is generally carried out under acid conditions, such as, for example, by treatment with trifluoroacetic acid or hydrochloric gas dissolved in an anhydrous solvent such as dichloromethane or dioxan. The opening of the lactonic ring of compound D in order to obtain compound E, can be carried out, for example, by hydrolysis under alkaline conditions followed by neutralization.

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.

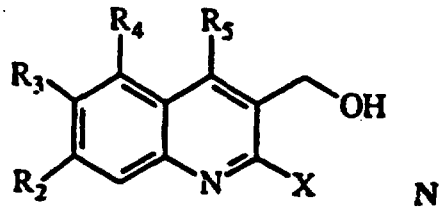
Therefore, the invention also relates to a preparation process for the compounds of formulae I and II, characterized in that

- a compound of general formula M



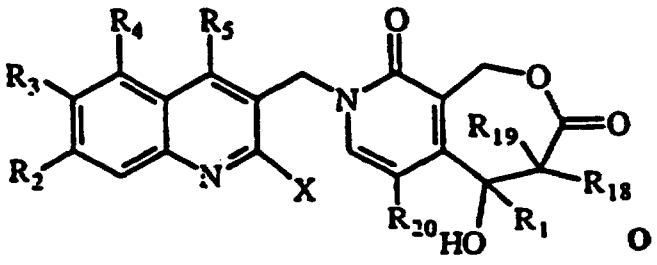
M

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



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;

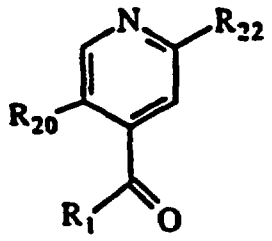
- then the compound of general formula O is cyclized in order to obtain the compound of general formula D as defined above.

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

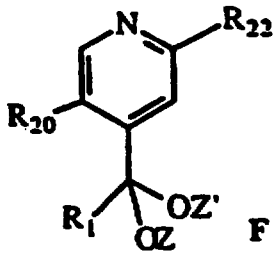
Mitsunobu, O. et al. *Synthesis*, p.1 (1981)). The hydroxyl function of compound N is displaced by a nucleophile such as compound M or a deprotonated derivative of the latter, by a treatment with a phosphine, for example triphenylphosphine, and an azodicarboxylate derivative, for example diethyl azodicarboxylate, 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 are new. They can be prepared according to a process characterized in that

- the carbonyl of a pyridine of general formula

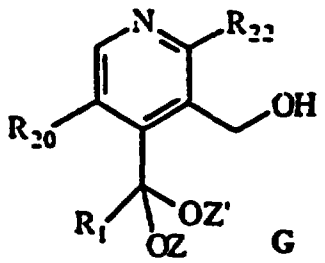


in which R_1 and R_{20} have the meaning indicated above and R_{22} represents a halogen atom or a lower alkoxy, is protected with an acetal function, in order to produce the compound of general formula F



in which R_1, R_{20} and R_{22} 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:

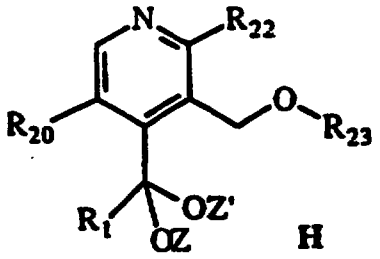
- a hydroxymethyl function is introduced into the compound of general formula F in order to obtain a compound of general formula G



G

in which R_1, R_{20}, R_{22}, Z and Z' have the meaning indicated above,

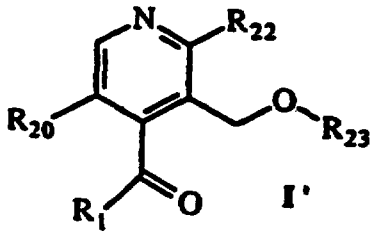
- then the alcohol function of the compound of general formula G is protected in order to produce a compound of general formula H



H

in which R_1, R_{20}, R_{22}, Z and Z' have the meaning indicated above and R_{23} represents a protective group of the alcohol function.

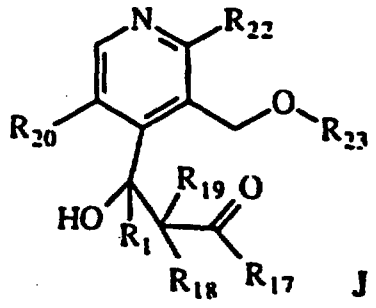
- the acetal of the compound of general formula H is deprotected in order to produce the compound of general formula I'



I'

in which R_1, R_{20}, R_{22} and R_{23} have the meaning indicated above,

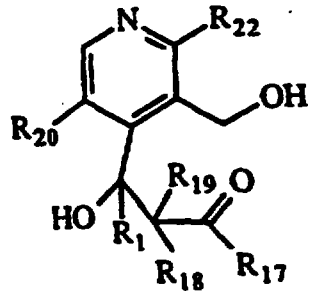
- the compound of formula I' is treated with a functionalized alkylating agent in order to produce a β-hydroxyester of general formula J



J

in which R_1, R_{20}, R_{22} and R_{23} have the meaning indicated above, R_{18} and R_{19} are as defined in general formula II and R_{17} represents OR_6 and R_6 represents a lower alkyl, cycloalkyl, lower alkyl cycloalkyl, lower alkenyl, lower alkyl lower alkoxy or aryl or lower alkyl aryl,

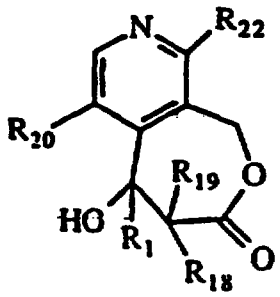
- the protective group R_{23} of the compound of general formula J is cleaved in order to produce a compound of general formula K,



K

in which R_1, R_{18}, R_{19}, R_{20} and R_{22} have the meaning indicated above, and R_{17} represents OR_6 and R_6 represents a lower alkyl, cycloalkyl, lower alkyl cycloalkyl, lower alkenyl, lower alkyl lower alkoxy or aryl or lower alkyl aryl,

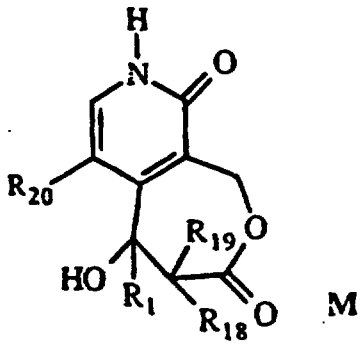
- the compound of general formula K is cyclized into the compound of general formula L



L

in which R_1, R_{18}, R_{19}, R_{20} and R_{22} have the meaning indicated above, and finally

- the R_{22} radical of compound L is converted into carbonyl in order to obtain the compound of general formula M



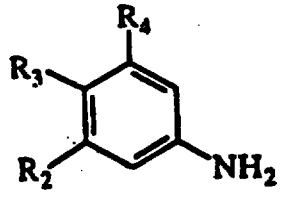
M

in which R_1, R_{18}, R_{19}, R_{20}, and R_{22} have the meaning indicated above.

The carbonyl function of a 4-acyl-2-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)). When R_{22} is a chloro or fluoro, 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_{23} 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_{23} 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_{23} 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 *NN*-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.

A subject of the invention is also, as new industrial products and in particular as new industrial products intended for the preparation of the products of formula I or II; the products of formulae I' and M as described above.

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 posses useful pharmacological properties. Thus the compounds of the present invention have an inhibitory effect of 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.

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 of formula (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 of formula (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 and II suitable for pharmaceutical use. A subject of the present Application is also, as medicaments, the products of formula I and II as defined above as well as the addition salts with pharmaceutically acceptable mineral or organic acids of said products of formula I and 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 slow 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 and 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".

An illustration of the pharmacological properties of the compounds according to the invention will be found hereafter in the experimental part.

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

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

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-γ-(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 tetrahydrofuran (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 (31%) of sought product to be obtained in the form of a pale yellow solid, m.p. 146-149°C.

NMR - ^1H ($CDCl_3$) : 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 -C^{13} ($CDCl_3$) : 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 ; 151 ; 1726.

Example 2 : ethyl β-ethyl-β-hydroxy-γ-(8-hydroxymethyl-9-oxo (11*H*)-indolizino-[1,2-*b*] quinoline-7-yl)-propionate

A suspension of zinc (500 mg, 7.64 mmol) and 8-formyloxymethyl-7-propionylindolizino [1,2-*b*] quinoline-9 (11*H*)-one (400 mg, 1,15 mmol) in anhydrous tetrahydrofuran (20 ml) containing 10 mg of hydroquinone is heated to reflux under argon. The heating bath is removed and the exothermic reaction is initiated by the addition of a drop of ethyl bromoacetate and a small crystal of iodine. Reflux is maintained by the dropwise addition of ethyl bromoacetate (500 µl, 4.48 mmol) then the reaction mixture is again heated to reflux for one hour. After cooling down to ambient temperature, the reaction is stopped by the addition of saturated ammonium chloride (10 ml) and methanol (30 ml). The resultant mixture is agitated for 5 minutes then filtered and evaporated. The residue is dissolved in dichloromethane (30 ml), washed with water and dried over sodium sulphate. Then the solvent is eliminated and purification using column chromatography is carried out (SiO_2, CH_2Cl_2/MeOH 98/2), which produces 230 mg (49 %) of sought compound in the form of a yellow solid, m.p. 157-161° C.

NMR-^1H ($CDCl_3$) : 0.93 (t, 3H) ; 1.20 (t, 3H) ; 2.02 (m, 2H) ; 3.07 (dd, 2H) ; 4.11 (q, 2H) ; 4.9 (se, 1H) ; 5.08 (s, 2H) ; 5.23 (s, 2H) ; 7.45 (s,1H) ; 7.62 (t, 1H) ; 7.80 (t,1H) ; 7.90 (d, 1H) ; 8.22 (d, 1H) ; 8.36 (s,1H).

NMR-C^{13} ($CDCl_3$) : 8.09 ; 14.01 ; 34.67 ; 44.85 ; 49.94 ; 58.31 ; 61.09 ; 77.21 ; 100.78 ; 127.78 ; 127.96 ; 128.11 ; 128.72 ; 129.16 ; 129.65 ; 130.60 ; 131.32 ; 142.76 ; 148.28 ; 152.55 ; 155.09 ; 162.22 ; 172.59.

IR (KBr) : 766 ; 1009 ; 1184 ; 1582 ; 1647 ; 1750.

Example 3 : 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-γ-(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-C^{13} (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.

Example 4 : β-ethyl-β-hydroxy-γ-(8-hydroxymethyl-9-oxo (11*H*)-indolizino-[1,2-*b*] quinoline-7-yl)-propionic acid

An aqueous solution of potassium hydroxide (0.1*N*, 30 ml) is added to 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 (500 mg, 1,38 mmol) and the resultant suspension is agitated at ambient temperature for 16 hours, which produces a virtually limpid solution which is filtered. The filtrate is acidified to pH 3.5 with 1*N* hydrochloric acid, and the yellow precipitate is recovered by filtration, washed with water and with acetone then dried under reduced pressure. 415 mg (79 %) of sought compound is obtained in the form of a monohydrate, m.p. 165-167° C.

NMR-^{1}H (DMSO) : 0.82 (t, 3H) ; 2.10 (m, 2H) ; 2.83 (d, 2H) ; 3.12 (d, 2H) ; 3.25 (se, 1H) ; 4.81 (s, 2H) ; 5.26 (s, 2H) ; 5.76 (se, 1H) ; 7.38 (s, 1H) ; 7.71 (t, 1H) ; 7.84 (t, 1H) ; 8.10 (d, 1H) ; 8.18 (d, 1H) ; 8.34 (s, 1H) ; 12.15 (se, 1H).

NMR-C^{13} (DMSO) : 8.16 ; 34.80 ; 46.71 ; 50.36 ; 55.73 ; 76.53 ; 100.17 ; 127.50 ; 128.00 ; 128.26 ; 128.69 ; 129.06 ; 130.01 ; 130.45 ; 131.63 ; 142.57 ; 148.09 ; 153.19 ; 156.07 ; 161.22 ; 172.27.

IR (KBr) : 1020 ; 1188 ; 1413 ; 1586 ; 1651 ; 1694.

Example 5 : methyl β-ethyl-β-hydroxy-γ-(8-hydroxymethyl-9-oxo (11*H*)-indolizino-[1,2-*b*] quinoline-7-yl)-propionate

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 (180 mg, 0.5 mmol), in suspension in methanol (50 ml) is treated with 6*N* dry hydrogen chloride in methanol (0.5 ml) and maintained under reflux until complete dissolution (4 hours). The volatile compounds are evaporated off and the residue is dissolved in dichloromethane (50 ml), washed with dilute sodium hydroxide (0.05 *N*, 15 ml) and brine (15 ml). The organic fraction is dried over sodium sulphate and evaporated. The solid residue is purified by chromatography in a silica gel column (MeOH at 3 % / CH_2Cl_2) and the purified product is taken up in diethyl ether, filtered and dried, which produces 120 mg (58 %) of sought compound in the form of a pale yellow solid, m.p. 163-166° C.

NMR-^{1}H ($CDCl_3$) : 0.93 (t, 3H) ; 2.2 (m, 2H) ; 3.05 (dd, 2H) ; 3.49 (s, 3H) ; 3.62 (s, 3H) ; 4.93 (s, 2H) ; 5.22 (d, 2H) ; 5.52 (s, 1H) ; 7.21 (s, 1H) ; 7.62 (t, 1H) ; 7.81 (t, 1H) ; 7.91 (d, 1H) ; 8.22 (d, 1H) ; 8.36 (s, 1H).

NMR-C^{13} ($CDCl_3$) : 7.74 ; 35,54 ; 46.82 ; 50.15 ; 51.67 ; 58.10 ; 65.33 ; 78.03 ; 100.17 ; 125.57 ; 127.70 ; 128.04 ; 128.10 ; 128.35 ; 129.53 ; 130.39 ; 130.94 ; 143.87 ; 148.75 ; 152.94 ; 157.83 ; 161.74 ; 171.35.

IR (KBr) : 1207 ; 1595 ; 2655 ; 1709.

Example 6 : ethyl β-ethyl-α,α-difluoro-β-hydroxy-γ-(8-hydroxymethyl-9-oxo (11*H*)-indolizino-[1,2-*b*] quinoline-7-yl)-propionate

Approximately half of a total quantity of ethyl bromodifluoroacetate (1.8 ml, 14 mmol), 8-formyloxymethyl-7-propionylindolizino [1,2-*b*] quinoline-9 (11*H*)-one (2,0 g,

5,75 mmol, as obtained in Example 1.b.) in suspension in anhydrous THF (10 ml), are added dropwise under argon to a suspension of zinc (1.25 g, 17.2 mmol) in anhydrous THF under reflux (40 ml) then the remaining part of the ethyl bromodifluoroacetate is added. The reaction mixture is maintained under reflux for another half an hour. After cooling down to ambient temperature, the reaction is stopped by the addition of saturated ammonium chloride (20 ml) and the reaction mixture is extracted with dichloromethane (3 x 20 ml). The combined organic extracts are dried and concentrated. The residue is taken up in diethyl ether (10 ml), filtered and purified by column chromatography (SiO_2, CH_2Cl_2 / MeOH:98/2), which produces 664 mg (26 %) of product in the form of a yellow solid, m.p. 208-209° C.

NMR-^{1}H ($CDCl_3$) : 0.91 (t, 3H) ; 1.38 (t, 3H) ; 2.32 (m, 2H) ; 4.8 (se, 1H) ; 4.38 (q, 2H) ; 5.09 (d, 2H) ; 5.13 (dd, 2H) ; 7.42 (s,1H) ; 7.55 (t, 1H) ; 7.72 (t, 1H) ; 7.79 (d, 1H) ; 8.08 (d, 1H) ; 8.22 (s, 1H)

NMR-C^{13} ($CDCl_3$) : 6.97 ; 13.93 ; 28.63 ; 50.18 ; 56.27 ; 63.15 ; 77.20 ; 81.96 (t) ; 101.27 ; 116.40 (t) ; 127.67 ; 127.77 ; 127.97 ; 128.31 ; 129.26 ; 130.33 ; 130.94 ; 131.23 ; 143.16 ; 148.34 ; 150.20 ; 151.91 ; 161.21 ; 163.21 (t).

IR (KBr) : 1124 ; 1308 ; 1591 ; 1647 ; 1748.

Example 7 : ethyl β-ethyl-β-hydroxy-γ-(8-hydroxymethyl-9-oxo (11*H*)-indolizino-[1,2-*b*] quinoline-7-yl)-propionate

A suspension of zinc (1.25 g, 19.1 mmol), 8-methyl-7-propionylindolizino [1,2-*b*]quinoline-9-(11*H*)-one (500 mg, 1.43 mmol, as obtained by Kingsburry, W. D., Tetrahedron Lett. 29:6847 (1988)) and silver acetate (250 mg, 1.50 mmol) in anhydrous tetrahydrofuran (10 ml) is agitated at ambient temperature under an argon atmosphere. After 10 minutes, the reaction mixture is activated by the dropwise addition of a molar solution of chlorodiethylaluminium (10 ml, 10 mmol), then ethyl bromoacetate (1.25 ml, 11.3 mmol) is added dropwise and the resultant mixture is left to react for another 5 hours. The reaction is stopped by the successive addition of ethyl alcohol (10 ml) and a saturated solution of potassium and sodium tartrate (10 ml). The resultant mixture is agitated for another hour, filtered and concentrated

under reduced pressure. The residue is taken up in dichloromethane (30 ml), washed with water, dried, concentrated and purified by column chromatography (SiO_2, CH_2Cl_2 / MeOH:98/2), which produces 93 mg (15 %) of desired product in the form of a pale yellow solid, m.p. 185-188° C.

NMR-^{1}H ($CDCl_3$) : 0.91 (t, 3H) ; 1.17 (t, 3H) ; 1.99 (m, 2H) ; 2.49 (s, 3H) ; 3.10 (dd, 2H) ; 4.11 (q, 2H) ; 4.6 (se, 1H) ; 5.25 (s, 2H) ; 7.65 (t, 1H) ; 7.67 (s,1H) ; 7.80 (t, 1H) ; 7.90 (d, 1H) ; 8.22 (d, 1H) ; 8.34 (s, 1H).

NMR-C^{13} ($CDCl_3$) : 8.02 ; 13.99 ; 14.72 ; 33.14 ; 43.97 ; 50.02 ; 61.0 ; 76.54 ; 101.90 ; 127.65 ; 127.84 ; 128.08 ; 128.81 ; 128.88 ; 130.74 ; 131.59 ; 131.65 ; 140.33 ; 147.64 ; 152.96 ; 153.61 ; 162.11 ; 172.91.

IR (KBr) : 762 ; 1192 ; 1576 ; 1653 ; 1740.

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

Acetic anhydride (70 µl, 0.7 mmol) is added dropwise to a solution of *tert*-butyl *β*-ethyl-*β*-hydroxy-*γ*-(8-hydroxymethyl-9-oxo (11*H*)-indolizino-[1,2-*b*] quinoline-7-yl)-propionate (200 mg, 0.46 mmol) and triethylamine (140 µl, 1 mmol) in dichloromethane (5 ml) and the resultant mixture is agitated at ambient temperature for 21 hours. The volatile components are evaporated off and the residue is purified by chromatography on a silica gel column (1-2 % MeOH / CH_2Cl_2), which produces 152 mg of sought compound in the form of a yellow solid, m.p. 195-196° C.

NMR-^{1}H ($CDCl_3$) : 0.88 (t, 3H) ; 1.32 (s, 9H) ; 1.93 (m, 2H) ; 2.07 (s, 3H) ; 2.97 (dd, 2H) ; 4.8 (se, 1H) ; 5.28 (s, 2H) ; 5.59 (dd, 2H) ; 7.39 (s, 1H) ; 7.63 (t, 1H) ; 7.80 (t, 1H) ; 7.90 (d, 1H) ; 8.23 (d, 1H) ; 8.34 (s, 1H).

NMR-C^{13} ($CDCl_3$) : 8.02 ; 21.06 ; 27.91 ; 35.05 ; 45.58 ; 50.16 ; 59.23 ; 77.52 ; 82.26 ; 100.59 ; 124.21 ; 127.91 ; 128.10 ; 128.14 ; 128.97 ; 129.18 ; 130.68 ; 131.46 ; 142.85 ; 148.29 ; 152.43 ; 158.49 ; 161.83 ; 171.13 ; 171.90.

Example 9 : 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 and collaborators, 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-C^{13} (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 ; 159.26 ; 172.08.

Example 10 : **β-ethyl-γ-(12-ethyl-8-hydroxymethyl-9-oxo (11*H*)-indolizino-[1,2-*b*] quinoline-7-yl)- *β*-hydroxy-propionic acid**

This compound is prepared in a similar manner to Example 4, except that the 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 is used instead of the 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. It is presented in the form of a slightly dirty white solid, m.p. 238-239° C.

NMR-^{1}H (DMSO) : 0.82 (t, 3H) ; 1.35 (t, 3H) ; 2.01 (m, 2H) ; 2.85 (d, 2H) ; 3.18 (d, 2H) ; 3.22 (q, 2H) ; 4.81 (s, 2H) ; 5.00 (se, 1H) ; 5.24 (s, 2H) ; 5.78 (se, 1H) ; 7.38 (s, 1H) ; 7.77 (t, 1H) ; 7.86 (t, 1H) ; 8.18 (d, 1H) ; 8.28 (d, 1H) ; 12.10 (se, 1H).

NMR-C^{13} (DMSO) : 8.12 ; 14.15 ; 22.41 ; 34.78 ; 46.74 ; 49.65 ; 55.71 ; 76.51 ; 100.04 ; 124.22 ; 126.63 ; 127.48 ; 128.12 ; 128.21 ; 129.94 ; 130.02 ; 143.10 ; 145.59 ; 148.69 ; 152.62 ; 156.03 ; 161.22 ; 172.22.

Example 11 : **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**

11.a. 2-ethyl-2-(2-methoxy-4-pyridyl)-1,3-dioxolan (F)

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 liquid.

11.b. 2-ethyl-2-(3-hydroxymethyl-2-methoxy-4-pyridyl)-1,3-dioxolan (G)

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-dioxolan (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.

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

A solution of 2-ethyl-2-(3-hydroxymethyl-2-methoxy-4-pyridyl)-1,3-dioxolan (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.

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

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

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

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 liquid.

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

tert-butyl β-ethyl-β-hydroxy-γ-(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.

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

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.

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

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.

11.i. 6,7-ethylenedioxy-2-iodo-3-quinoline-methanol (N)

The procedures 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); and Nakasimhan et al J. Am. Chem. Soc. 112, p. 4431 (1990),are used. 3,4-ethylenedioxyacetanilide (22 g, 113 mmol) is added to the Vilsmeyer reagent obtained by the dropwise addition of phosphoryl oxychloride (71 ml, 0.77 mol) to anhydrous dimethylformamide (23 ml, 0.28 mol), cooled down with a water/ice bath and agitated again for 0.5 hours under an argon atmosphere. The resultant mixture is heated at 75°C for 16 hours. After cooling down to ambient temperature, the reaction mixture is added to a mixture of ice and water (300 ml) and extracted with dichloromethane (5 x 200 ml). The combined organic extracts are dried over sodium sulphate, filtered and concentrated. The solid residue is suspended in dichloromethane (20 ml), filtered and dried under reduced pressure, which produces 10 g (35%) of 2-chloro-6,7-ethylenedioxyquinoline-3-carbaldehyde in the form of a yellow solid, m.p. 222-224°C. This intermediate is treated with sodium iodide (30 g, 0.2 mol) and concentrated hydrochloric acid (1.5 ml) in acetonitrile under reflux (150 ml) for 24 hours. After cooling down to ambient temperature, the solvent is eliminated under reduced pressure and the residue is taken up in aqueous tetrahydrofuran at 50% (200 ml), filtered, washed with tetrahydrofuran and dried under reduced pressure, which produces 12 g of 6,7-ethylenedioxy-2-iodoquinoline-3-carbaldehyde in the form of a yellow solid, m.p. 155-157°C. The above intermediate is treated with sodium borohydride (2 g, 52 mmol) in methanol (200 ml) at ambient temperature for 0.5 hours. The solvent is eliminated under reduced pressure and the residue is taken up in water and filtered. The resultant solid is dried under reduced pressure in the presence of phosphorus pentoxide, which produces 11 g of (6,7-ethylenedioxy-2-iodoquinoline-3-yl)-methanol in the form of a yellow solid, m.p. 178-180°C.

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

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 11.i. (770 mg, 2.23 mmol) and triphenylphosphine (934 mg, 3.58 mmol) in a mixture of anhydrous THF/DMSO (8/1 v/v, 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 chloroform (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.

11.k. 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

5-ethyl-8-(6,7-ethylenedioxy-2-iodoquinoline-3-yl) methyl-4,5-dihydro-5-hydroxy-(1H,3H) oxepino [3,4-c] pyridine-3-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 clear yellow 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-C^{13} (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.

<u>Example 12</u> : 10-benzyloxy-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

12.a. (6-benzyloxy-2-iodo-3-quinoline)-methanol

This compound is prepared in a similar manner to that indicated in stage 11.i. of Example 11, but by using 4-benzyloxyacetanilide instead of 3,4-ethylenedioxyacetanilide. Purification by chromatography on a silica gel column and the use of dichloromethane as eluant are necessary in order to isolate the intermediate 6-benzyloxy-2-chloroquinoline-3-carbaldehyde, m.p. 180-182° C (yield 8 %) with sufficient purity. Then, the halogen exchange produces 6-benzyloxy-2-iodoquinoline-3-carbaldehyde, m.p. 155-157° C and a subsequent reduction with sodium borohydride produces (6-benzyloxy-2-iodoquinoline-3-yl)-methanol, m.p. 147-149° C.

12.b. 8-(6-benzyloxy-2-iodo-3-quinolinemethyl)-1,5-dihydroxy-5-ethyl-5-hydroxy-oxepino [3,4-c] pyridine-3,9(4*H*, 8*H*)-dione

This compound is prepared in a similar manner to that indicated in stage 11.j. of Example 11, but by using (6-benzyloxy-2-iodoquinoline-3-yl)-methanol instead of (6,7-ethylenedioxy-2-iodoquinoline-3-yl)-methanol. This compound is presented in the form of a white solid m.p. 197-199° C.

12.c. 10-benzyloxy-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 prepared in a similar manner to that indicated in stage 11.k. of Example 11, but by using 8-(6-benzyloxy-2-iodo-3-quinolinemethyl)-1,5-dihydroxy-5-ethyl-5-hydroxy-oxepino [3,4-c] pyridine-3,9(4*H*, 8*H*)-dione instead of 5-ethyl-8-(6,7-ethylenedioxy-2-iodoquinoline-3-yl)methyl-4,5-dihydro-5-hydroxy-(1*H*, 3*H*)oxepino [3,4-c] pyridine-3-dione. The sought compound is presented in the form of a clear yellow solid m.p. > 250° C.

NMR-^{1}H (DMSO) : 0.90 (t, 3H) ; 1.85 (m, 2H) ; 3.08 (d, 1H) ; 3.50 (d, 1H) ; 5.25 (s, 2H) ; 5.30 (s, 2H) ; 5.50 (dd, 2H) ; 6.05 (s, 1H) ; 7.30-7.70 (m, 8H) ; 8.10 (d, 1H) ; 8.55 (s, 1H).

NMR-C^{13} (DMSO) : 8.43 ; 36.48 ; 38.28 ; 50.65 ; 61.42 ; 70.00 ; 73.32 ; 99.05 ; 107.71 ; 122.05 ; 123.42 ; 128.18 ; 128.26 ; 128.70 ; 129.40 ; 130.19 ; 130.48 ; 130.63 ; 136.65 ; 144.18 ; 144.90 ; 150.53 ; 155.91 ; 157.31 ; 159.24 ; 172.06.

Example 13 : γ-(12-benzyloxy-8-hydroxymethyl-9-oxo (11*H*)-indolizino [1,2-*b*] quinoline-7-yl)-β-ethyl-β-hydroxy-propionic acid (E)

This compound is prepared in a similar manner to that indicated in Example 4, but by using 10-benzyloxy-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 instead of 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. It is presented in the form of a yellow solid, m.p. 171-173° C.

NMR-^{1}H (DMSO) : 0.80 (t, 3H) ; 2.00 (m, 2H) ; 2.85 (d, 1H) ; 3.15 (d, 1H) ; 4.80 (s, 2H) ; 5.25 (s, 2H) ; 5.30 (s, 2H) ; 5.75 (se, 1H) ; 7.30 (s, 1H) ; 7.35-7.70 (m, 7H) ; 8.10 (d, 1H) ; 8.55 (s, 1H).

NMR-C^{13} (DMSO) : 8.11 ; 34.75 ; 46.68 ; 50.35 ; 55.70 ; 69.97 ; 76.51 ; 99.45 ; 107.78 ; 123.28 ; 127.64 ; 128.18 (2C) ; 128.26 ; 128.70 (2C) ; 129.33 ; 130.17 ; 130.47 ; 130.57 ; 136.69 ; 142.79 ; 144.17 ; 150.93 ; 156.03 ; 157.19 ; 161.20.

Example 14 : 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-1*H*-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 under 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 sought crude compound 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-C^{13} (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.

Example 15 : **11-(dimethylamino)methyl-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**

15.a. 11-(dimethylamino)methyl-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

A suspension of 10-benzyloxy-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 (260 mg, 0,69 mmol) in acetic acid (15 ml) is treated with aqueous formaldehyde at 37 % (500 µl) and aqueous dimethylamine at 40 % (500 µl) and the resultant mixture is agitated at ambient temperature for 16 hours. The reaction mixture is concentrated to dryness and the residue is purified by column chromatography (SiO_2, CH_2Cl_2/MeOH: 100/0 to 90/10) followed by crystallization from acetonitrile, which produces 102 mg of sought compound.

15.b. 11-(dimethylamino)methyl-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 hydrochloride

Dilute hydrochloric acid (1*N*) is added dropwise to a suspension of 11-(dimethylamino) methyl-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 (102 mg) in water until complete dissolution. The water is evaporated off under reduced pressure and the residue is suspended in acetonitrile (5 ml) and filtered, which produces 103 mg of the sought salt m.p. 248° C (d).

NMR-^{1}H (DMSO) : 0,88 (t, 3H) ; 1,85 (m, 2H) ; 2,84 (s, 6H) ; 3,08 (d, 1H) ; 3,5 (d, 1H) ; 4,73 (s, 2H) ; 5,25 (s, 2H) ; 5,47 (dd, 2H) ; 7,33 (s, 1H) ; 7,38 (s,1H) ; 7,72 (d, 1H) ; 8,19 (d, 1H) ; 8,99 (s, 1H) ; 9,92 (se, 1H) ; 11,45 (s, 1H).

NMR-C^{13} (DMSO) : 8,46 ; 34,36 ; 42,44 (3C) ; 50,61 (2C) ; 61,42 ; 73,35 ; 99,19 ; 108,63 ; 122,21 ; 122,36 ; 126,86 ; 129,13 ; 130,61 ; 133,09 ; 143,53 ; 144,70 ; 149,76 ; 155,98 ; 157,17 ; 159,27 ; 172,06.

Example 16 : **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 in stages 11i, 11j and 11k of Example 11. 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-C^{13} (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.

Example 17 : **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 in stages 11i, 11j and 11k of Example 11. 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-C^{13} (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.

Example 18 : **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**

This compound is obtained from 3,4-difluoroaniline according to the method illustrated in stages 11i, 11j and 11k of Example 11. 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-C^{13} (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.

Example 19 : **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 in stages 11i, 11j and 11k of Example 11. 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-C^{13} (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.

Example 20 : **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 in stages 11i, 11j and 11k of Example 11. 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-C^{13} (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.

Example 21 : **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 in stages 11.i., 11.j. and 11.k. of Example 11. 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-C^{13} (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.

Example 22 : 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 in stages 11.i., 11.j. and 11.k. of Example 11. 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-C^{13} (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.

Example 23 : **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 in stages 11.i., 11.j. and 11.k. of Example 11. 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-C^{13} (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.

Example 24 : **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 in stages 11.i., 11.j. and 11.k. of Example 11. 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-C^{13} (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.

Example 25 : **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 in stages 11.i., 11.j. and 11.k. of Example 11. 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-C^{13} (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.

Example 26 : **10-chloro-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**

This compound is obtained from 4-chloro-3-fluoroaniline according to the method illustrated in stages 11.i., 11.j. and 11.k. of Example 11. 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-C^{13} (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.

Example 27 : **5,12-diethyl-4,5-dihydro-5,10-dihydroxy-11-morpholino 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 morpholine according to the method illustrated in Example 15.a. White solid, m.p. > 250° C.

NMR-^{1}H (DMSO) : 0.85 (t, 3H) ; 1.87 (q, 2H) ; 2.53 (s, 4H) ; 3.03 (d, 1H) ; 3.45 (d, 1H) ; 3.57 (s, 4H) ; 4.02 (s, 2H) ; 5.01 (s, 2H) ; 5.38 (d, 1H) ; 5.52 (d, 1H) ; 6.0 (se, 1H) ; 7.30 (s, 1H) ; 7.42 (d, 1H) ; 7.95 (d, 1H) ; 8.82 (s, 1H).

NMR-C^{13} (DMSO) : 8.45 ; 3.49 ; 42.58 ; 53.04 ; 61.44 ; 66.33 ; 73.33 ; 98.81 ; 113.78 ; 121.81 ; 122.74 ; 126.80 ; 129.05 ; 129.91 ; 143.72 ; 145.07 ; 149.24 ; 155.06; 156.92 ; 159.28 ; 172.08.

IR (KBr) : 1515 ; 1595 ; 1654 ; 1736.

Example 28 : 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

28.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.

28.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.

28.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.

28.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.

28.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 11.j. of Example 11. The resultant coupled product is cyclized according to the procedure described in stage 11.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-C^{13} (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.

Example 29 : **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 28.b., 28.c. and 28.d. is applied to 2-acetylaniline in order to produce 2-chloro-4-methyl-3-quinolinemethanol. The latter coupled to compound (M) as described in stage 11.j. of Example 11. The resultant coupled product is cyclized according to the procedure of stage 11.k. A yellow solid is obtained, m.p. > 260° C.

NMR ^{1}H (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-C^{13} (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.

Example 30 : **9-chloro-5-ethyl-4,5-dihydro-5-hydroxy-10-methoxy-12-(4-methyl piperazinomethyl)-1*H*-oxepino[3',4':6,7]indolizino [1,2-*b*] quinoline-3,15(4*H*,13*H*)-dione**

30.a. 5-chloro-2-chloroacetyl-4-methoxyaniline

This product is obtained according to Sugasawa T; Toyoda T; Adachi M; Sasakura K, *J. Am. Chem. Soc.*, 100 (1978), p.4842-4852. A molar solution of boron trichloride in hexane (164 ml, 164 mmol), chloroacetonitrile (11,4 ml, 180 mmol), and a molar solution of diethylaluminium chloride in hexane (164 ml, 164 mmol). are added dropwise and successively under an inert atmosphere at 0° C to a solution of 3-chloro-4-methoxy-aniline (23,6 g, 150 mmol). The reaction medium is heated under reflux for 1 hour, cooled down to 0° C, hydrolyzed by cautiously adding 2N hydrochloric acid (90 ml), then heating to reflux for 1 hour. The reaction medium is cooled down and a

concentrated soda solution is added until pH 14. Extraction is carried out with ethyl acetate, the organic phase is washed with water, then with salt water. Followed by drying over magnesium sulphate, filtering and evaporating under reduced pressure. The residue is taken up in isopentane, followed by decanting, then the insoluble part is taken up in the minimum amount of isopropyl ether, isopentane is added in order to precipitate the product, followed by filtering and drying under vacuum. 17.26 g of a brown solid is obtained.

NMR-^{1}H ($CDCl_3$) : 3.82 (s, 3H) ; 4.60 (s, 2H) ; 6.11 (s, 2H) ; 6.78 (s, 1H) ; 7.11 (s, 1H).

30.b. ethyl 7-chloro-4-chloromethyl-2-hydroxy-6-methoxy-3-quinoline-carboxylate

A solution of ethylmalonyl chloride (17 ml, 131 mmol) is added dropwise under argon and at 0°C to a solution of 5-chloro-2-chloroacetyl-4-methoxyaniline (17 g, 73 mmol) and triethylamine (18,5 ml, 131 mmol) in anhydrous acetonitrile (310 ml). Agitation is carried out for 2 hours at ambient temperature, then a solution sodium ethanolate in ethanol (obtained by 1.88 g, 80 mmol, of sodium in 90 ml of ethanol) is added dropwise at 0°C. Agitation is carried out for 12 hours at ambient temperature. 300 ml of water is added, and agitation is again carried out for 20 minutes. The precipitate is filtered out ; washed with water, with ethanol, and with ethyl ether. After drying under vacuum 16.7 g of a yellowish solid is obtained.

NMR-^{1}H (DMSO) : 1.31 (t, 3H) ; 3.95 (s, 3H) ; 4.36 (q, 2H) ; 4.95 (s, 2H) ; 7.46 (s, 1H) ; 7.49 (s,1H).

30.c. ethyl 2,7-dichloro-4-chloromethyl-6-methoxy-3-quinoline-carboxylate

A suspension of ethyl 7-chloro-4-chloromethyl-2-hydroxy-6-methoxy-3-quinolinecarboxylate (116.7 g, 50 mmol) in phosphoryl chloride (100 ml) is heated to reflux for 6 hours. The phosphoryl chloride is distilled off. The residue is taken up in water and agitation is carried out for 30 min. The precipitate is filtered out and washed with water until neutrality. The precipitate is taken up in dichloromethane and with a saturated solution of sodium chloride. After filtering through a bed of celite the filtrate is decanted. The organic phase is washed again with a saturated solution of sodium chloride, followed by drying over magnesium sulphate, filtering and evaporating under reduced pressure. 15.88 g of a brown oil is obtained.

NMR-^{1}H ($CDCl_3$) : 1.47 (t, 3H) ; 4.08 (t, 3H) ; 4.55 (q, 2H) ; 4.87 (s, 2H) ; 7.35 (s, 1H) ; 8.09 (s, 1H).

30.d. **ethyl 2,7-dichloro-6-methoxy-4-(4-methylpiperazinomethyl)-3-quinoline-carboxylate**

A mixture of ethyl 2,7-dichloro-4-chloromethyl-6-methoxy-3-quinoline-carboxylate (6.9 g, 20 mmol) and *N*-methylpiperazine (9 ml, 80 mmol) is heated to 60° C for 30 min. The reaction mass is diluted with water and extraction is carried out with ethyl acetate. After decanting, the organic phase is washed with water, followed by drying over magnesium sulphate, filtering and evaporating under reduced pressure. The residue is taken up in water, agitated for 15 minutes, filtered, washed with water and dried under vacuum. The residue is purified by column chromatography (SiO_2, MeOH/CH_2Cl_2: 5/95 to 8/92). 6,7 g of product, a beige solid, is obtained.

NMR-^{1}H ($CDCl_3$) : 1.45 (t, 3H) ; 2.28 (s, 3H) ; 2.35-2.70 (m, 8H) ; 3.86 (s, 2H) ; 4.04 (s, 3H) ; 4.48 (q, 2H) ; 7.77 (s, 1H) ; 8.05 (s, 1H).

30.e. **2,7-dichloro-6-methoxy-4-(4-methylpiperazinomethyl)-3-quinoline-methanol**

Ethyl 2,7-dichloro-6-methoxy-4-(4-methylpiperazinomethyl)-3-quinoline carboxylate (6 g, 14,5 mmol) is dissolved in methylene chloride (120 ml). A molar solution of diisobutylaluminium hydride in methylene chloride (60 ml, 60 mmol) is added slowly. Agitation is carried out for one hour at ambient temperature. The reaction mass is slowly poured into 300 ml of a 20% solution of Rochelle salt. Agitation is carried out for one hour, followed by filtering on celite and decanting; the organic phase is washed with a saturated solution of sodium chloride, dried over magnesium sulphate, filtered and evaporated under reduced pressure. The solid is taken up in isopropyl ether, filtered and dried under vacuum. 4.3 g of sought product (80 %) is obtained, in the form of a yellow solid.

NMR-^{1}H ($CDCl_3$) : 2.27 (s, 3H) ; 2.30-2.80 (m, 8H) ; 4.03 (s, 3H) ; 4.08 (s, 2H) ; 4.96 (s, 2H) ; 5.95 (s, 1H) ; 7.37 (s, 1H) ; 8.05 (s, 1H).

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

2,7-dichloro-6-methoxy-4-(4-methylpiperazinomethyl)-3-quinoline-methanol is coupled to compound (M) as described in stage 11.j. of Example 11. The resultant coupled product is cyclized according to the procedure of stage 11.k. A yellow solid is obtained, m.p. > 250° C.

NMR-^{1}H (DMSO) : 0.87 (t, 3H) ; 1.84 (q, 2H) ; 2.53 (s, 4H) ; 3.08 (d, 1H) ; 3.47 (d, 1H) ; 3.58 (s, 4H) ; 4.06 (s, 5H) ; 5.30 (s, 2H) ; 5.42 (q, 2H) ; 6.03 (s, 1H) ; 7.31 (s, 1H) ; 7.91 (s, 1H) ; 8.16 (s, 1H).

NMR-C^{13} (DMSO) : 8.42 ; 36.53 ; 50.65 ; 53.30 ; 56.67 ; 62.00 ; 66.50 ; 73.32 ; 99.31 ; 104.86 ; 122.32 ; 126.94 ; 127.70 ; 129.83 ; 130.44 ; 138.89 ; 144.22 ; 144.85 ; 151.05 ; 153.17 ; 155.92 ; 159.19 ; 172.06.

IR (KBr) : 862 ; 1063 ; 1116 ; 1248 ; 1595 ; 1655 ; 1744 ; 3449.

Example 31 : **9-chloro-5-ethyl-4,5-dihydro-5-hydroxy-10-methoxy-12-morpholinomethyl-1*H*-oxepino[3',4':6,7]indolizino[1,2-*b*]quinoline-3,15(4*H*,13*H*)-dione**

The procedure described in Examples 30.a., 30.b. and 30.c. is applied to 3-chloro-4-methoxyaniline in order to produce ethyl 2,7-dichloro-4-chloromethyl-6-methoxy-3-quinoline-carboxylate which is treated according to the procedure of Example 30.d., by using morpholine instead of N-methylpiperazine, then reduced according to the method of Example 30.e. into the corresponding quinolinemethanol. The latter is coupled to compound (M) as described in stage 11.j. of Example 11. The resultant coupled product is cyclized according to the procedure of stage 11.k. A beige solid is obtained, m.p. > 250° C.

NMR-^{1}H (DMSO) : 0.87 (t, 3H) ; 1.84 (q, 2H) ; 2.15 (s, 3H) ; 2.32 (s, 4H) ; 2.50 (s, 4H) ; 3.08 (d, 1H) ; 3.47 (d, 1H) ; 4.06 (s, 5H) ; 5.29 (s, 2H) ; 5.46 (q, 2H) ; 6.06 (s, 1H) ; 7.31 (s, 1H) ; 7.92 (s, 1H) ; 8.17 (s, 1H).

NMR-C^{13} (DMSO) : 8.42 ; 36.51 ; 42.57 ; 45.93 ; 50.66 ; 52.83 ; 55.05 ; 56.09 ; 56.72 ; 61.44 ; 73.29 ; 99.30 ; 104.89 ; 122.32 ; 126.89 ; 127.63 ; 129.85 ; 130.16 ; 138.78 ; 144.18 ; 144.81 ; 151.03 ; 153.10 ; 155.10 ; 159.17 ; 172.07.

IR (KBr) : 1055 ; 1252 ; 1596 ; 1655 ; 1747 ; 3449.

Example 32 : **5-ethyl-4,5-dihydro-5-hydroxy-12-(4-methyl piperazinomethyl)-1H-oxepino[3',4':6,7] indolizino [1,2-b] quinoline -3,15(4H,13H)-dione**

The procedure described in Examples 30.a., 30.b. and 30.c. is applied to aniline in order to produce ethyl 2-chloro-4-chloromethyl-3-quinolinecarboxylate which is treated according to the procedure of Example 30.d., with N-methylpiperazine, then reduced according to the method of Example 30.e. into the corresponding quinolinemethanol. The latter is coupled to compound (M) as described in stage 11.j. of Example 11. The resultant coupled product is cyclized according to the procedure of stage 11.k. A yellow solid is obtained, m.p. > 260° C.

NMR-^{1}H (DMSO) : 0.86 (t, 3H) ; 1.87 (q, 2H) ; 2.14 (s, 3H) ; 2.32-2.60 (m, 8H) ; 3.05 (d, 1H) ; 3.48 (d, 1H) ; 4.09 (q, 2H) ; 5.42 (d, 1H) ; 5.52 (d, 1H) ; 6.03 (se, 1H) ; 7.40 (s, 1H) ; 7.72 (t, 1H) ; 7.85 (t, 1H) ; 8.16 (d, 1H) ; 8.45 (d, 1H).

IR (KBr) : 1652 ; 1735 ; 3424.

Example 33 : **5-ethyl-4,5-dihydro-5-hydroxy-12-piperidinomethyl-1*H*-oxepino [3',4':6,7]indolizino[1,2-*b*]quinoline-3,15(4*H*,13*H*)-dione**

The procedure described in Examples 30.a., 30.b. and 30.c. is applied to aniline in order to produce ethyl 2-chloro-4-chloromethyl-3-quinoline carboxylate which is treated according to the procedure of Example 30.d., by using piperidine instead of N-methylpiperazine, then reduced according to the method of Example 30.e. into the corresponding quinolinemethanol. The latter is coupled to compound (M) as described in stage 11.j. of Example 11. The resultant coupled product is cyclized according to the procedure of stage 11.k. A yellow solid is obtained, m.p. > 260° C.

NMR-^{1}H (DMSO) : 0.86 (t, 3H) ; 1.40 (se, 2H) ; 1.48 (se, 4H) ; 1.87 (q, 2H) ; 2.50 (s, 4H) ; 3.05 (d, 1H) ; 3.48 (d, 1H) ; 4.04 (q, 2H) ; 5.33 (s, 2H) ; 5.42 (d, 1H) ; 5.51 (d, 1H) ; 6.07 (se, 1H) ; 7.75 (t, 1H) ; 7.85 (t, 1H) ; 8.15 (d, 1H) ; 8.45 (d, 1H).

NMR-C^{13} (DMSO) : 8.47 ; 23.50 ; 25.82 ; 36.50 ; 42.50 ; 50.68 ; 54.47 ; 58.00 ; 61.42 ; 73.35 ; 99.55 ; 122.61 ; 125.31 ; 127.58 ; 129.54 ; 129.55 ; 129.56 ; 129.57 ; 140.49 ; 144.95 ; 148.63 ; 152.41 ; 155.90 ; 159.23 ; 172.07.

IR (KBr) : 1659 ; 1727 ; 3408.

Example 34 : **5-ethyl-4,5-dihydro-5-hydroxy-12-morpholinomethyl-1*H*-oxepino[3';4':6,7]indolizino[1,2-*b*]quinoline-3,15(4*H*,13*H*)-dione**

The procedure described in Examples 30.a., 30.b. and 30.c. is applied to aniline in order to produce ethyl 2-chloro-4-chloromethyl-3-quinolinecarboxylate which is treated according to the procedure of Example 30.d., by using morpholine instead of N-methylpiperazine, then reduced according to the method of Example 30.e. into the corresponding quinolinemethanol. The latter is coupled to compound (M) as described in stage 11.j. of Example 11. The resultant coupled product is cyclized according to the procedure of stage 11.k. A yellow solid is obtained, m.p. > 260° C.

NMR-^{1}H (DMSO) : 0.86 (t, 3H) ; 1.87 (q, 2H) ; 3.05 (d, 1H) ; 3.30 (s, 4H) ; 3.49 (d, 1H) ; 3.55 (se, 4H) ; 4.10 (q, 2H) ; 5.35 (s, 2H) ; 5.40 (d, 1H) ; 5.54 (d, 1H) ; 6.04 (s, 1H) ; 7.72 (t, 1H) ; 7.85 (t, 1H) ; 8.16 (d, 1H) ; 8.47 (d, 1H).

NMR-C^{13} (DMSO) : 8.42 ; 36.51 ; 42.57 ; 50.68 ; 53.51 ; 56.06 ; 61.42 ; 66.41 ; 73.34 ; 99.56 ; 122.64 ; 125.25 ; 127.56 ; 129.81 ; 139.55 ; 144.92 ; 148.62 ; 152.39 ; 155.89 ; 159.21 ; 172.05.

IR (KBr) : 1657 ; 1729 ; 3347.

Example 35 : **5-ethyl-10-fluoro-4,5-dihydro-5-hydroxy-12-(4-methylpiperazinomethyl)-1*H*-oxepino[3',4':6,7]indolizino [1,2-*b*] quinoline-3,15(4*H*,13*H*)-dione**

The procedure described in Examples 30.a., 30.b. and 30.c. is applied to 4-fluoroaniline in order to produce ethyl 2-chloro-4-chloromethyl-6-fluoro-3-quinolinecarboxylate which is treated according to the procedure of Example 30.d. with N-methylpiperazine, then reduced according to the method of Example 30.e. into the corresponding quinolinemethanol. The latter is coupled to compound (M) as described in stage 11.j. of Example 11. The resultant coupled product is cyclized according to the procedure of stage 11.k. A yellow solid is obtained, m.p. > 275° C.

NMR-^{1}H (DMSO) : 0.87 (t, 3H) ; 1.85 (q, 2H) ; 2.15 (s, 3H) ; 2.31 (m, 4H) ; 2.50 (m, 4H) ; 3.07 (d, 1H) ; 3.48 (d, 1H) ; 4.04 (m, 2H) ; 5.31 (s, 2H) ; 5.40 (d, 1H) ; 5.53 (d, 1H) ; 6.05 (s, 1H) ; 7.38 (s, 1H) ; 7.77 (m, 1H) ; 8.19 (m, 2H).

NMR-C^{13} (DMSO) : 8.43 ; 36.51 ; 42.54 ; 45.89 ; 50.67 ; 52.92 ; 54.93 ; 55.92 ; 73.32 ; 99.56 ; 122.69 ; 130.43 ; 132.40 ; 139.69 ; 144.70 ; 145.84 ; 152.19 ; 155.90 ; 159.17 ; 172.05.

IR (KBr) : 836 ; 1051 ; 1217 ; 1291 ; 1612 ; 1662 ; 1726.

Example 36 : 5-ethyl-10-fluoro-4,5-dihydro-5-hydroxy-12-morpholinomethyl-1*H*-oxepino[3',4':6,7]indolizino[1,2-*b*]quinoline-3,15(4*H*,13*H*)-dione

The procedure described in Examples 30.a., 30.b. and 30.c. is applied to 4-fluoroaniline in order to produce ethyl 2-chloro-4-chloromethyl-6-fluoro-3-quinolinecarboxylate which is treated according to the procedure of Example 30.d., by using morpholine instead of N-methylpiperazine, then reduced according to the method of Example 30.e. into the corresponding quinolinemethanol. The latter is coupled to compound (M) as described in stage 11.j. of Example 11. The resultant coupled product is cyclized according to the procedure of stage 11.k. A beige solid is obtained, m.p. > 250° C.

NMR-^{1}H (DMSO) : 0.87 (m, 3H) ; 1.85 (m, 2H) ; 2.51 (m,4H) ; 3.06 (d, 1H) ; 3.48 (d, 1H) ; 3.56 (m, 4H) ; 4.05 (m, 2H) ; 5.34 (s, 2H) ; 5.40 (d, 1H) ; 5.53 (d, 1H) ; 6.04 (s, 1H) ; 7.38 (s, 1H) ; 7.77 (m, 1H) ; 8.21 (m, 2H).

NMR-C^{13} (DMSO) : 8.40 ; 36.47 ; 42.52 ; 50.59 ; 53.40 ; 56.14 ; 61.44 ; 66.41 ; 73.29 ; 99.58 ; 109.05 ; 109.28 ; 120.11 ; 120.37 ; 122.68 ; 128.53 ; 130.53 ; 132.43 ; 139.13 ; 144.62 ; 145.79 ; 152.07 ; 155.94 ; 159.14 ; 161.59 ; 172.04.

IR (KBr) : 834 ; 860 ; 1061 ; 1118 ; 1215 ; 1286 ; 1516 ; 1609 ; 1658 ; 1734.

Example 37 : 5-ethyl-9-fluoro-4,5-dihydro-5-hydroxy-10-methyl-12-(4-methylpiperazinomethyl)-1*H*-oxepino[3',4':6,7]indolizino[1,2-*b*] quinoline-3,15(4*H*,13*H*)-dione

The procedure described in Examples 30.a., 30.b. and 30.c. is applied to 3-fluoro-4-methylaniline in order to produce ethyl 2-chloro-4-chloromethyl-7-fluoro-6-methyl-3-quinolinecarboxylate which is treated according to the procedure of Example 30.d. with N-methylpiperazine, then reduced according to the method of Example 30.e. into the corresponding quinolinemethanol. The latter is coupled to compound (M) as

described in stage 11.j. of Example 11. The resultant coupled product is cyclized according to the procedure of stage 11.k. A yellow solid is obtained, m.p. > 260° C.

NMR-^{1}H ($CDCl_3$) : 1.00 (t, 3H) ; 2.00 (q, 2H) ; 2.35 (s, 3H) ; 2.50 (s, 3H) ; 2.61 (m, 8H) ; 3.33 (d, 1H) ; 3.39 (d, 1H) ; 3.97 (d, 1H) ; 4.07 (d, 1H) ; 5.17 (d, 1H) ; 5.38 (d, 1H) ; 5.52 (d, 1H) ; 5.63 (d, 1H) ; 7.13 (d, 1H) ; 7.28 (s, 1H) ; 7.99 (d, 1H).

IR (KBr) : 1652 ; 1747 ; 3430.

Example 38 : **5-ethyl-9-fluoro-4,5-dihydro-5-hydroxy-10-methyl-12-morpholinomethyl-1*H*-oxepino[3',4':6,7]indolizino[1,2-*b*]quinoline-3,15(4*H*,13*H*)-dione**

The procedure described in Examples 30.a., 30.b. and 30.c. is applied to 3-fluoro-4-methylaniline in order to produce ethyl 2-chloro-4-chloromethyl-7-fluoro-6-methyl-3-quinolinecarboxylate which is treated according to the procedure of Example 30.d., by using morpholiine instead of N-methylpiperazine, then reduced according to the method of Example 30.e. into the corresponding quinolinemethanol. The latter is coupled to compound (M) as described in stage 11.j. of Example 11. The resultant coupled product is cyclized according to the procedure of stage 11.k. A yellow solid is obtained, m.p. > 260° C.

NMR-^{1}H (DMSO + CDCl3) : 1.00 (t, 3H) ; 2.02 (q, 2H) ; 2.57 (s, 3H) ; 2.60 (s, 4H) ; 3.23 (d, 1H) ; 3.45 (d, 1H) ; 3.75 (s, 4H) ; 4.11 (s, 2H) ; 5.44 (s, 2H) ; 5.47 (d, 1H) ; 5.65 (d, 1H) ; 7.62 (s, 1H) ; 7.73 (d, 1H) ; 8.24 (d, 1H).

NMR-C^{13} (CF_3CO_2D) : 8.35 ; 13.93 ; 16.01 ; 22.24 ; 25.29 ; 38.18 ; 43.42 ; 54.19 ; 56.04 ; 56.74 ; 64.16 ; 65.09 ; 77.48 ; 108.29 ; 108.57 ; 128.07 ; 128.70 ; 129.90 ; 135.64 ; 138.03 ; 139.86 ; 141.10 ; 141.56 ; 147.78 ; 158.30 ; 161.87 ; 178.72.

IR (KBr) : 117 ; 1609 ; 1654 ; 1750 ; 3437.

Example 39 : **5-ethyl-9-fluoro-4,5-dihydro-5-hydroxy-10-methyl-12-piperidinomethyl-1*H*-oxepino [3',4':6,7] indolizino [1,2-*b*] quinoline-3,15(4*H*,13*H*)-dione**

The procedure described in Examples 30.a., 30.b. and 30.c. is applied to 3-fluoro-4-methylaniline in order to produce ethyl 2-chloro-4-chloromethyl-7-fluoro-6-methyl-3-quinolinecarboxylate which is treated according to the procedure of Example 30.d., by

using piperidine instead of N-methylpiperazine, then reduced according to the method of Example 30.e. into the corresponding quinolinemethanol. The latter is coupled to compound (M) as described in stage 11.j. of Example 11. The resultant coupled product is cyclized according to the procedure of stage 11.k. A yellow solid is obtained, m.p. > 260° C.

NMR-^{1}H (CF_3CO_2D) : 1.09 (s, 3H) ; 1.70 (t, 1H) ; 2.03 (m, 5H) ; 2.25 (s, 2H) ; 2.70 (s, 3H) ; 3.54 (d, 3H) ; 3.88 (d, 1H) ; 4.01 (se, 2H) ; 5.30 (q, 2H) ; 5.65 (d, 1H) ; 5.96 (d, 1H) ; 6.10 (s, 2H) ; 8.16 (d, 1H) ; 8.35 (s, 1H) ; 8.61 (s, 1H).

NMR-C^{13} (CF_3CO_2D) : 8.47 ; 16.07 ; 20.93 ; 22.18 ; 24.76 ; 38.28 ; 43.53 ; 54.30 ; 56.12 ; 58.33 ; 64.24 ; 77.56 ; 108.37 ; 111.30 ; 128.20 ; 129.02 ; 129.98 ; 135.60 ; 138.29 ; 139.90 ; 141.60 ; 142.26 ; 147.57 ; 158.28 ; 161.90 ; 167.63 ; 170.31 ; 178.82.

IR (KBr) : 1605 ; 1657 ; 1728 ; 3399.

Example 40 : **8-ethyl-2,3,8,9-tetrahydro-8-hydroxy-16-(4-methyl piperazinomethyl)-10*H*,12*H*-[1,4] dioxino [2,3-*g*] oxepino [3',4':6,7] indolizino [1,2-*b*] quinoline-10,13[15*H*]-dione**

The procedure described in Examples 30.a., 30.b. and 30.c. is applied to 3,4-ethylenedioxyaniline in order to produce ethyl 2-chloro-4-chloromethyl-6,7-ethylènedioxy-3-quinolinecarboxylate which is treated according to the procedure of Example 30.d. with N-methylpiperazine, then reduced according to the method of Example 30.e. into the corresponding quinolinemethanol. The latter is coupled to compound (M) as described in stage 11.j. of Example 11. The resultant coupled product is cyclized according to the procedure of stage 11.k. A yellow solid is obtained, m.p. > 260° C.

NMR-^{1}H (DMSO) : 0.92 (t, 3H) ; 1.89 (q, 2H) ; 2.16 (s, 3H) ; 2.50 (m, 8H) ; 3.12 (d, 1H) ; 3.50 (d, 1H) ; 3.95 (s, 2H) ; 4.47 (s, 4H) ; 5.19 (q, 2H) ; 5.43 (d, 1H) ; 5.56 (d, 1H) ; 7.35 (s, 1H) ; 7.54 (s, 1H) ; 7.76 (s, 1H).

NMR-C^{13} (DMSO) : 8.45 ; 24.80 ; 36.51 ; 42.48 ; 45.90 ; 50.45 ; 52.98 ; 54.91 ; 56.10 ; 61.44 ; 64.43 ; 73.30 ; 99.03 ; 109.46 ; 113.51 ; 121.95 ; 123.51 ; 127.76 ;

137.99 ; 145.00 ; 145.14 ; 145.27 ; 147.24 ; 150.53 ; 155.99 ; 159.18 ; 172.27 ; 177.00.

IR (KBr) : 1656 ; 1743 ; 3422.

Example 41 : **9-chloro-5-ethyl-10-fluoro-4,5-dihydro-5-hydroxy-12-morpholinomethyl-1*H*-oxepino[3',4':6,7]indolizino[1,2-*b*]quinoline-3,15(4*H*,13*H*)-dione**

The procedure described in Examples 30.a., 30.b. and 30.c. is applied to 3-chloro-4-fluoroaniline in order to produce ethyl 2,7-dichloro-4-chloromethyl-6-fluoro-3-quinolinecarboxylate which is treated according to the procedure of Example 30.d., by using morpholine instead of N-methylpiperazine, then reduced according to the method of Example 30.e. into the corresponding quinolinemethanol. The latter is coupled to compound (M) as described in stage 11.j. of Example 11. The resultant coupled product is cyclized according to the procedure of stage 11.k. A beige solid is obtained, m.p. > 250° C.

NMR-^{1}H (CF_3COOD) : 1.09 (t, 3H) ; 2.30 (m, 2H) ; 3.50 (d, 1H) ; 3.90 (d, 1H) ; 3.98 (d, 4H) ; 4.36 (s, 4H) ; 5.38 (q, 2H) ; 5.64 (d, 1H) ; 5.96 (d, 1H) ; 6.23 (q, 2H) ; 8.57 (d, 1H) ; 8.60 (s, 1H) ; 8.85 (d, 1H).

NMR-C^{13} (CF_3COOD) : 8.10 ; 37.80 ; 43.11 ; 54.31 ; 55.78 ; 63.75 ; 65.11 ; 77.06 ; 128.28 ; 129.55 ; 130.33 ; 136.26 ; 137.11 ; 138.40 ; 139.67 ; 139.85 ; 148.58 ; 157.54 ; 159.74 ; 161.31 ; 178.00.

IR (KBr) : 848 ; 1042 ; 1230 ; 1609 ; 1658 ; 1750 ; 3310 ; 3387.

Example 42 : **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 HPLC. 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.

By using the procedures indicated above, the following products, which also form part of the invention and which constitute preferred products, can also be prepared:

10-benzyloxy-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 ;

5,12-diethyl-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 ;

5,12-diethyl-4,5-dihydro-5,10-dihydroxy-11-dimethylaminomethyl-1*H*-oxepino [3',4':6,7] indolizino [1,2-*b*] quinoline-3,15 (4*H*, 13*H*)-dione ;

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

10-bromo-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 ;

11-bromo-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 ;

5-ethyl-12-diethylaminomethyl-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-4,5-dihydro-5-hydroxy-1*H*,3*H*-cyclopenta [*g*] oxepino [3',4':6,7] indolizino [1,2-*b*] quinoline-3,16 [14*H*]-dione ;

7-ethyl-7,8-dihydro-7-hydroxy-16-(4-methylpiperazino methyl)-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 ;

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

8-ethyl-8,9-dihydro-8-hydroxy-10*H*, 12*H*-oxepino [3',4':6,7] indolizino [1,2-*b*] pyrido [2,3-*g*] quinoline-10,13 [15*H*]-dione ;

5-ethyl-4,5,9,10,11,12-hexahydro-5-hydroxy-1*H*, 3*H*-benzo [*g*] oxepino [3',4':6,7] indolizino [1,2-*b*] quinoline-3,17 [15*H*]-dione ;

8-ethyl-8,9-dihydro-8-hydroxy-14*H*, 10*H*, 12*H*-[1,3] dioxino [4,5-*g*] oxepino [3',4':6,7] indolizino [1,2-*b*] quinoline-10,13 [15*H*]-dione ;

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

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

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

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

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

Pharmacological study of the products according to the invention

1. 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) at 50 mM, 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 (Gibco-BRL, Paisley, United Kingdom) and is carried out for 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 camera and the fluorescent intensity is measured with a bioProfil camera (Vilber Lourmat, Lyon, France) with a view to determining the percentage of relaxed DNA. Each experiment is carried out at least three times in duplicate.

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 control, the supercoiled plasmid DNA is incubated in the presence of 500 µM of compound to be tested with enzyme or without enzyme plus the compound to be tested, at concentrations of 10 µM, 100 µM, 200 µM et 500 µM. As indicated in Table, Examples 2, 3, 4, 9, 10 and 11 inhibit the relaxation activity encouraged by topoisomerase 1 in a dose-dependent manner.

TABLE I

PERCENTAGE OF RELAXED DNA				
EXAMPLE	CONCENTRATION (µM)			
	10	100	200	500
Example 2	97.9	78.3	73.2	51.1
Example 3	79.9	59.9	55.0	45.7
Example 4	99.1	82.2	67.6	32.9
Example 9	77.1	33.9	29.7	20.4
Example 10	96.9	45.4	26.2	8.7
Example 11	65.0	50.3	39.8	31,0

2. Test on cell proliferation

Eight tumoral cell lines are used in this study: L1210 (mouse lymphocytic leukemia), HCT15 and LOVO (cell lines of human colon adenocarcinoma), A549 (human lung carcinoma), A172, U373 et U87 (human glioblastoma). All these lines are obtained from the American Type Culture Collection (ATCC), Rockville, Md. The L1210 cell cultures in suspension are cultured in Dulbecco's modified Eagle's medium (DMEM) (BioWhitaker, Verviers, Belgium) together with 10 % of foetal calf serum inactivated by heating, 2 mM of glutamine, 50 U/ml of penicillin and 50 µg/ml of streptomycin. The HT29 cells are cultured in mono-layer cultures in a McCoy 5a medium (Gibco, Paisley, United Kingdom) together with 10 % of foetal calf serum inactivated by heat plus 2 mM of glutamine and 50 µg/ml of gentamycin. The other cells are cultured in an Earle's modified essential medium (EMEM ; Gibco, Paisley, United Kingdom) together with 5 % foetal calf serum inactivated by heat, 2 mM of glutamine, 50 U/ml

of penicillin and 50 µg/ml of streptomycin. All the cell lines are cultured at 37° C in a humidified atmosphere containing 95 % air and 5 % CO_2.

Inhibition of the tumor cell line proliferation is determined using an MTT test. 1500 L1210 cells in a culture medium (according to the needs of the cell medium) are seeded in a well of a micro-well plate (tissue culture level: 96 wells, flat bottom) 24 hours before treatment with the compounds to be tested. For these dose-response studies, the cells are incubated with each of the compounds to be tested or their corresponding solvent (controls) for 48 hours over a final concentration range of 1.10^{-10} to 1.10^{-4} M. All the compounds are dissolved just before use in dimethylsulphoxide (DMSO) at a concentration of 50 mM. Other dilutions of the medicaments are carried out in the culture medium. The final concentration of DMSO never exceeds 0.2 % (v/v). As controls, the solutions of medicaments are replaced with the solvent which is diluted successively in the same way as the compounds to be tested.

After the incubation period, the labeling reagent MTT (3-[4,5-dimethylthiazol-2-yl]-2,5-diphenyltetrazolium bromide; Thiazol blue, Sigma M 565, Sigma, St Louis, MO) is added at a final concentration of 0.3 mg/ml to each well. The cells are incubated for 4 hours at 37° C in a humidified atmosphere. This stage allows the mitochondrial dehydrogenase of the living cells to convert the yellow tetrazolium salt MTT into crimson formazan crystals. The supernatant part is eliminated and the formazan crystals formed are solubilized with DMSO. The resultant coloured solution is quantified by absorbance at 570 nm by using a multi-cuvette scanning spectrophotometer. The data concerning the proliferation is expressed as a percentage of living cells in the treated wells, divided by the living cells in the controls. Each point represents the average of three independent experiments, each experiment represents six determinations.

For the other cell lines (HCT15, LOVO, A549, A172, U373, U87), 1000 to 2000 cells are seeded in the well of a micro-well plate 24 hours before medicinal treatment. They are incubated with each of the compounds to be tested or their corresponding solvent (controls) for 72 hours over a final concentration range of 1.10^{-10} to 1.10^{-6} M.

The results are expressed as percentages of the calculated proliferation by the optical density (OD) of the cells treated with a medicament divided by the OD of the control

cells (cells treated with DMSO). As represented in Table II, the compounds to be tested have inhibited the proliferation of cells in a dose-dependent manner.

TABLE II

PERCENTAGE OF CELL PROLIFERATION								
EXAMPLE	Cell line	CONCENTRATION (nM)						
		0.1	1	10	100	1 000	10 000	100 000
Example 3	L1210	87.22	68.92	42.64	26.85	10.83	2.11	2.20
	HCT15	86.00	84.00	58.00	44.00	18.00	9.00	13.00
	LOVO	108.00	86.00	54.00	31.00	23.00	10.00	12.00
	A549	132.00	111.00	75.00	39.00	35.00	10.00	11.00
	A172	89.00	101.00	68.00	37.00	27.00	10.00	7.00
	U373	99.00	98.00	40.00	24.00	17.00	13.00	9.00
	U87	108.00	85.00	42.00	23.00	15.00	5.00	6.00
Example 4	L1210	92.14	97.14	91.08	86.28	46.79	27.80	8.09
	HCT15	91.00	92.00	86.00	78.00	54.00	20.00	7.00
	LOVO	80.00	75.00	79.00	69.00	38.00	21.00	5.00
	A549	71.00	76.00	71.00	56.00	36.00	22.00	12.00
	A172	93.00	92.00	98.00	97.00	44.00	31.00	10.00
	U373	86.00	85.00	89.00	63.00	30.00	16.00	2.00
	U87	98.00	101.00	98.00	74.00	11.00	6.00	2.00
Example 9	L1210	74.04	62.05	44.72	34.01	20.20	4.34	1.58
	HCT15	94.00	89.00	59.00	35.00	15.00	8.00	3.00
	LOVO	74.00	85.00	44.00	31.00	21.00	4.00	2.00
	A549	91.00	88.00	50.00	31.00	23.00	5.00	3.00
	A172	97.00	89.00	44.00	36.00	19.00	3.00	1.00
	U373	89.00	69.00	24.00	18.00	8.00	3.00	1.00
	U87	105.00	72.00	14.00	7.00	4.00	2.00	6.00
Example 10	L1210	91.51	97.94	89.28	67.32	31.51	19.78	3.65
	HCT15	111.00	87.00	103.00	63.00	42.00	17.00	9.00
	LOVO	71.00	76.00	77.00	52.00	29.00	18.00	4.00
	A549	71.00	76.00	71.00	56.00	36.00	22.00	7.00
	A172	93.00	92.00	91.00	60.00	39.00	15.00	3.00
	U373	96.00	104.00	87.00	35.00	20.00	10.00	2.00
	U87	96.00	79.00	89.00	17.00	6.00	5.00	2.00
Example 11	L1210	91.99	81.37	23.16	16.83	5.59	1.45	1.04
	HCT15	71.00	63.00	45.00	23.00	12.00	9.00	9.00
	LOVO	66.00	42.00	29.00	21.00	8.00	3.00	3.00
	A549	82.00	44.00	29.00	26.00	4.00	3.00	2.00
	A172	95.00	53.00	47.00	39.00	12.00	3.00	2.00
	U373	50.00	30.00	25.00	8.00	2.00	1.00	2.00
	U87	40.00	21.00	12.00	6.00	1.00	1.00	1.00

3. Development test *in vivo*

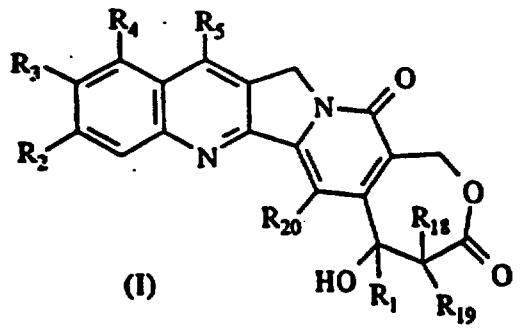
The compounds according to the invention are tested *in vivo* by using the mouse L1210 lymphoblastic leukemia cell line. The tumor cells are maintained by serial passage by i.p. route in DBA/2 mice (Lafacedu, Lyon, France). For experimental purposes, 10^6 cells / 0.2 ml are injected by i.p. route into female B6D2F1 mice. The treatment starts on day 1 after inoculation of the leukemia and continues until day 4 or day 8. The compounds to be tested are injected by i.p or i.v. route at different concentrations and the volume injected is adjusted to 0.1 ml / 10 g of body weight. The non-treated mice die between day 9 and day 14, after the injection of L1210 lymphoblastic leukemia cells and the survival of the treated mice is monitored for a period extending up to 60 days.

The experiment is carried out with 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. This compound increases the life span of the mice by 50% at concentrations between 0.32 and 2.5 mg/kg administered by i.p. route for 4 days and at concentrations between 0.32 and 5.0 mg/kg administered by i.v. route for 8 days.

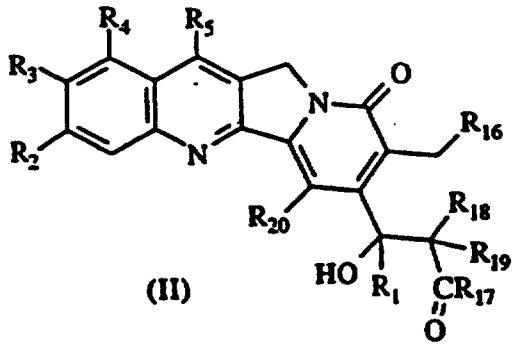
CLAIMS

1. An analogue of camptothecin, characterized in that the hydroxy lactone of camptothecin is a β-hydroxy lactone or the corresponding β-hydroxy acid; resulting from the opening of this lactone, or a derivative of this β-hydroxy acid; or a pharmaceutically acceptable salt of the latter.

2. A compound according to claim 1, 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 alkyl lower alkoxy or lower alkyl lower alkylthio;

R_2, R_3 and R_4 represent, independently, H, halo, lower alkyl halo, lower alkyl, lower alkenyl, cyano, lower alkyl cyano, nitro, lower alkyl nitro, amido, lower alkyl amido, hydrazino, lower alkyl hydrazino, azido, lower alkyl azido, $(CH_2)_mNR_6R_7$, $(CH_2)_mOR_6$, $(CH_2)_mSR_6$, $(CH_2)_mCO_2R_6$, $(CH_2)_mNR_6C(O)R_8$, $(CH_2)_mC(O)R_8$, $(CH_2)_mOC(O)R_8$, $O(CH_2)_mNR_6R_7$, $OC(O)NR_6R_7$, $OC(O)(CH_2)_mCO_2R_6$ or $(CH_2)_n[N\approx X]$, $OC(O)[N\approx X]$, $(CH2)_mOC(O)[N\approx X]$, aryl or lower alkyl substitutedor non substituted, in which the substituent is a lower alkyl, halo, nitro, amino, lower alkylamino, lower haloalkyl, lower alkyl hydroxy, lower alkoxy or lower alkyl lower alkoxy or R_2 and R_3 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 alkyl halo, lower alkyl, lower alkoxy, lower alkyl lower alkoxy, lower alkyl lower alkylthio, cycloalkyl, lower alkyl cycloalkyl, cyano, alkyl cyano, lower alkyl sulphonyl lower alkyl, lower alkyl hydroxy, 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 a $(CH_2)_n[N\approx X]$, $OC(O)[N\approx X]$, $(CH_2)_mOC(O)[N\approx X]$, aryl or lower alkyl aryl radical substituted or non substituted, in which the substituent is a lower alkyl, halo, nitro, amino, amino lower alkyl, lower alkyl halo, lower alkyl hydroxy, lower alkoxy or lower alkyl lower alkoxy;

R_6 and R_7 represent, independently, H, a lower alkyl, lower alkyl hydroxy, lower alkyl amino lower alkyl, lower alkyl amino, cycloalkyl, lower alkyl cycloalkyl, lower alkenyl, lower alkyl lower alkoxy, lower alkyl halo, or aryl or lower alkyl aryl or non substituted, in which the substituent is a lower alkyl, halo, nitro, amino, amino lower alkyl, lower alkyl halo, lower alkyl hydroxy, lower alkoxy or lower alkyl lower alkoxy;

R_8 represents H, a lower alkyl, lower alkyl hydroxy, amino, amino lower alkyl, lower alkyl amino lower alkyl, lower alkyl amino, cycloalkyl, lower alkyl cycloalkyl, lower alkenyl, lower alkoxy, lower alkyl lower alkoxy, lower alkyl halo, or the aryl or lower alkyl aryl radical substituted or non substituted, in which the substituent is a lower alkyl, halo, nitro, amino, amino lower alkyl, lower alkyl halo, lower alkyl hydroxy, lower alkoxy or lower alkyl lower alkoxy;

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

R_{10} represents H, a lower alkyl, lower alkyl halo, lower alkoxy, aryl or aryl substituted by one or more groups chosen from the following radicals: lower alkyl, lower alkyl halo, lower alkyl hydroxy or lower alkyl lower alkoxy;

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 $C(O)(CH_2)_mCH_3$;

m is an integer comprised between 0 and 6;

n is 1 or 2; and

q represents an integer from 0 to 2; and $[N\approx X]$ 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}: or a pharmaceutically acceptable salt of the latter.

3. A compound according to claim 2, characterized in that

R_1 represents a lower alkyl, a lower alkenyl, a lower alkyl halo, a lower alkyl lower alkoxy or lower alkyl lower alkylthio;

R_5 represents H, halo, lower alkyl halo, lower alkyl, lower alkoxy, lower alkyl lower alkoxy, lower alkyl lower alkylthio, cycloalkyl, lower alkyl cycloalkyl, cyano, alkyl cyano, lower alkyl hydroxy, nitro, $(CH_2)_mC(O)R_8$, $(CH_2)_mNR_6C(O)R_8$, $(CH_2)_mNR_6R_7$, $(CH_2)_mN(CH_3)(CH_2)_nNR_6R_7$, $(CH_2)_mOC(O)R_8$, $(CH_2)_mOC(O)NR_6R_7$ or $(CH_2)_n[N\approx X]$, $OC(O)[N\approx X]$, $(CH_2)_mOC[N\approx X]$, aryl or lower alkyl aryl substituted or non substituted;

R_{12} and R_{13} represent, independently, a lower alkyl; and

R_{16} represents OR_{21};

R_{18},R_{19} and R_{20} represent H;

or a pharmaceutically acceptable salt of the latter.

4. A compound according to claim 3, characterized in that

R_1 represents a lower alkyl, a lower alkenyl, a lower alkyl halo or a lower alkyl lower alkoxy;

R_2, R_3 and R_4 represent, independently, H, a halo, lower alkyl halo, lower alkyl, nitro, amido, lower alkyl amido, hydrazino, lower alkyl hydrazino, azido, lower alkyl azido, $(CH_2)_mNR_6R_7$, $(CH_2)_mOR_6$, $(CH_2)_mSR_6$, $(CH_2)_mC(O)R_8$, $OC(O)NR_6R_7$, $(CH_2)_n[N\approx X]$ or $(CH_2)_mOC(O)[N\approx X]$ substituted or non substituted or $OC(O)[N\approx X]$, or R_2 and R_3 form together a chain with 3 or 4 members in which the said 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 alkyl halo, lower alkyl, lower alkoxy, lower alkyl lower alkoxy, lower alkyl lower alkylthio, lower alkyl hydroxy, nitro, $(CH_2)_mC(O)R_8$, $(CH_2)_mNR_6C(O)R_8$, $(CH_2)_mNR_6R_7$, $(CH_2)_mN(CH_3)(CH_2)_nNR_6R_7$, $(CH_2)_mOC(O)R_8$, $(CH_2)_mOC(O)NR_6R_7$, $(CH_2)_n[N\approx X]$ or $OC(O)[N\approx X]$, substituted or non substituted or $(CH_2)_mOC(O)[N\approx X]$;

R_6 and R_7 represent, independently, H, a lower alkyl, lower alkyl hydroxy, lower alkyl amino lower alkyl, lower alkyl amino, cycloalkyl, lower alkyl cycloalkyl, lower alkyl lower alkoxy, aryl, lower alkyl aryl or lower alkyl halo;

R_8 represents H, a lower alkyl, lower alkyl hydroxy , lower alkyl amino, lower alkyl amino lower alkyl, lower alkyl amino, cycloalkyl, lower alkyl cycloalkyl, lower alkenyl, lower alkoxy, lower alkyl lower alkoxy, lower alkyl halo, aryl or lower alkyl aryl;

R_9 represents H, a lower alkyl or lower alkyl halo;

R_{10} represents H, a lower alkyl, lower alkyl halo or lower alkoxy;

R_{11} represents a lower alkyl; and

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

or a pharmaceutically acceptable salt of the latter.

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

6. A compound according to claim 5 characterized in that said compound is of formula (I); or a pharmaceutically acceptable salt of the latter.

7. A compound according to claim 5 characterized in that said compound is of formula (II); or a pharmaceutically acceptable salt of the latter.

8. A compound according to claim 6, characterized in that R_2 and R_3 represent, independently, H, a lower alkyl, halo, lower alkyl halo or $(CH_2)_mOR_6$, or R_2 and R_3, together, form a methylenedioxy or an ethylenedioxy; and R_4 and R_5 represent, independently, H, a lower alkyl $(CH_2)_mNR_6R_7$ or $(CH_2)_n[N\approx X]$ non substituted or substituted by a lower alkyl; or a pharmaceutically acceptable salt of the latter.

9. A compound according to claim 8, characterized in that R_4 represents H or $(CH_2)_mNR_6R_7$ in which R_6 and R_7 represent, independently, H or a lower alkyl, and R_5 represents H, a lower alkyl or $(CH_2)_n[N\approx X]$ substituted or non substituted and $[N\approx X]$ represents the piperazinyl or morpholinyl group and said substituent is a lower alkyl; or a pharmaceutically acceptable salt of the latter.

10. A compound according to claim 9, characterized in that R_2 represents H or a halo; and R_3 represents H, a lower alkyl, halo, or OR_6 in which R_6 represents H, a lower alkyl or lower alkyl aryl; or a pharmaceutically acceptable salt of the latter.

11. A compound according to claim 10, characterized in that R_2 represents H, chloro or fluoro; and R_3 represents H, fluoro, chloro, methyl or methoxy; or a pharmaceutically acceptable salt of the latter.

12. A compound according to claim 9, characterized in that R_2 and R_3 together form a methylenedioxy or an ethylenedioxy; or a pharmaceutically acceptable salt of the latter.

13. A compound according to claim 6, characterized in that said compound is selected from the products corresponding to the following formulae:

- 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
- 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
- 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
- 10-benzyloxy-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
- 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
- 11-(dimethylamino)methyl-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
- 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
- 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
- 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
- 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
- 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
- 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
- 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
- 5-ethyl-9-flouro-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
- 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

- 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
- 10-chloro-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
- 5,12-diethyl-4,5-dihydro-5,10-dihydroxy-11-morpholino methyl-1*H*-oxepino [3',4':6,7]indolizino[1,2-*b*]quinoline-3,15 (4*H*,13*H*)-dione
- 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
- 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
- 9-chloro-5-ethyl-4,5-dihydro-5-hydroxy-10-methoxy-12-(4-methyl piperazinomethyl) -1*H*-oxepino[3',4':6,7]indolizino [1,2-*b*] quinoline-3,15(4*H*,13*H*)-dione
- 9-chloro-5-ethyl-4,5-dihydro-5-hydroxy-10-methoxy-12-morpholinomethyl-1*H*-oxepino[3',4':6,7]indolizino[1,2-*b*]quinoline-3,15(4*H*,13*H*)-dione
- 5-ethyl-4,5-dihydro-5-hydroxy-12-(4-methyl piperazinomethyl)-1*H*-oxepino [3',4':6,7] indolizino [1,2-*b*] quinoline-3,15(4*H*,13*H*)-dione
- 5-ethyl-4,5-dihydro-5-hydroxy-12-piperidinomethyl-1*H*-oxepino [3',4':6,7]indolizino [1,2-*b*]quinoline-3,15(4*H*,13*H*)-dione
- 5-ethyl-4,5-dihydro-5-hydroxy-12-morpholinomethyl-1*H*-oxepinol[3',4':6,7] indolizino [1,2-*b*]quinoline-3,15(4*H*,13*H*)-dione
- 5-ethyl-10-fluoro-4,5-dihydro-5-hydroxy-12-(4-methylpiperazinomethyl)-1*H*-oxepino[3',4':6,7]indolizino [1,2-*b*] quinoline-3,15(4*H*,13*H*)-dione
- 5-ethyl-10-fluoro-4,5-dihydro-5-hydroxy-12-morpholinomethyl-1*H*-oxepino [3',4':6,7]indolizino[1,2-*b*]quinoline-3,15(4*H*,13*H*)-dione
- 5-ethyl-9-fluoro-4,5-dihydro-5-hydroxy-10-methyl-12-(4-methylpiperazinomethyl)-1*H*-oxepino[3',4':6,7]indolizino[1,2-*b*] quinoline-3,15(4*H*,13*H*)-dione
- 5-ethyl-9-fluoro-4,5-dihydro-5-hydroxy-10-methyl-12-morpholinomethyl-1*H*-oxepino[3',4':6,7]indolizino[1,2-*b*]quinoline-3,15(4*H*,13*H*)-dione
- 5-ethyl-9-fluoro-4,5-dihydro-5-hydroxy-10-methyl-12-piperidinomethyl-1*H*-oxepino[3',4':6,7] indolizino [1,2-*b*] quinoline-3,15(4*H*,13*H*)-dione
- 8-ethyl-2,3,8,9-tetrahydro-8-hydroxy-16-(4-methyl piperazinomethyl)-10*H*,12*H*-[1,4] dioxino [2,3-*g*] oxepino [3',4':6,7] indolizino [1,2-*b*] quinoline-10,13[15*H*]-dione

- 9-chloro-5-ethyl-10-fluoro-4,5-dihydro-5-hydroxy-12-morpholinomethyl-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.

14. A compound according to claim 7, characterized in that R_2 and R_3 represent, independently, H, a lower alkyl, halo, lower alkyl halo or $(CH_2)_mOR_6$, or R_2 and R_3 together form a methylenedioxy or ethylenedioxy; R_4 and R_5 represent, independently, H, a lower alkyl, $(CH_2)_mNR_6R_7$ or $(CH_2)_n[N{\approx}X]$ non substituted or substituted by a lower alkyl; R_{20} represents H; R_{17} represents OR_6, in which R_6 represents H or a lower alkyl, or NR_6R_7 in which R_6 and R_7, independently, represent H, a lower alkyl, aryl or lower alkyl aryl; or a pharmaceutically acceptable salt of the latter.

15. A compound according to claim 13, characterized in that R_4 represents H or $(CH_2)_mNR_6R_7$ in which R_6 and R_7, independently, represent H or a lower alkyl, R5 represents H, a lower alkyl or $(CH_2)_n[N{\approx}X]$ non substituted or substituted by a lower alkyl and $[N{\approx}X]$ is the piperizinyl or morpholinyl group; and R_{17} represents OR_6, in which R_6 represents H or a lower alkyl; or a pharmaceutically acceptable salt of the latter.

16. A compound according to claim 14, characterized in that R_2 represents H or halo; R_3 represents H, a lower alkyl, halo or represents OR_6, in which R_6 represents H, a lower alkyl or a lower alkyl aryl; or a pharmaceutically acceptable salt of the latter.

17. A compound according to claim 16, characterized in that R_2 represents H, chloro or fluoro; and R_3 represents H, fluoro, chloro, methyl or methoxy; or a pharmaceutically acceptable salt of the latter.

18. A compound according to claim 15, characterized in that R_2 and R_3 together form dioxymethylene or dioxyethylene; or a pharmaceutically acceptable salt of the latter.

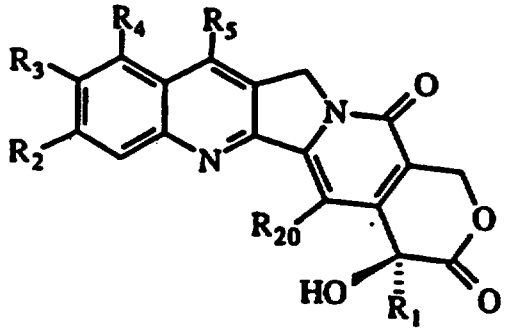
19. A compound according to claim 7, characterized in that said compound is selected from the products corresponding to the following formulae:

- *tert*-butyl β-ethyl-β-hydroxy-γ-(8-hydroxymethyl-9-oxo (11*H*)-indolizino-[1,2-*b*] quinoline-7-yl)-propionate
- ethyl β-ethyl-β-hydroxy-γ-(8-hydroxymethyl-9-oxo (11*H*)-indolizino-[1,2-*b*] quinoline-7-yl)-propionate
- β-ethyl-β-hydroxy-γ-(8-hydroxymethyl-9-oxo (11*H*)-indolizino-[1,2-*b*] quinoline-7-yl)-propionic acid
- methyl β-ethyl-β-hydroxy-γ-(8-hydroxymethyl-9-oxo (11*H*)-indolizino-[1,2-*b*] quinoline-7-yl)-propionate
- ethyl β-ethyl-α,α-difluoro-β-hydroxy-γ-(8-hydroxymethyl-9-oxo (11*H*)-indolizino-[1,2-*b*] quinoline-7-yl)-propionate
- ethyl β-ethyl-β-hydroxy-γ-(8-hydroxymethyl-9-oxo (11*H*)-indolizino-[1,2-*b*] quinoline-7-yl)-priopionate
- *tert*-butyl β-ethyl-β-hydroxy-γ-(8-hydroxymethyl-9-oxo (11*H*)-indolizino-[1,2-*b*] quinoline-7-yl)-propionate
- β-ethyl-γ-(12-ethyl-8-hydroxymethyl-9-oxo (11*H*)-indolizino-[1,2-*b*] quinoline-7-yl)-β-hydroxy-propionic acid
- γ-(12-benzyloxy-8-hydroxymethyl-9-ozo (11*H*)-indolizino [1,2-*b*] quinoline-7-yl)-β-ethyl-β-hydroxy-propionic acid (E)

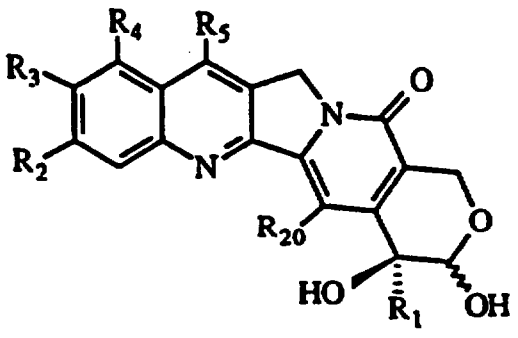
or a pharmaceutically acceptable salt of the latter.

20. Preparation process for the compounds of formulae I and II according to any one of claims 2 to 19, characterized in that:

- camptothecin α-hydroxylactone of general formula



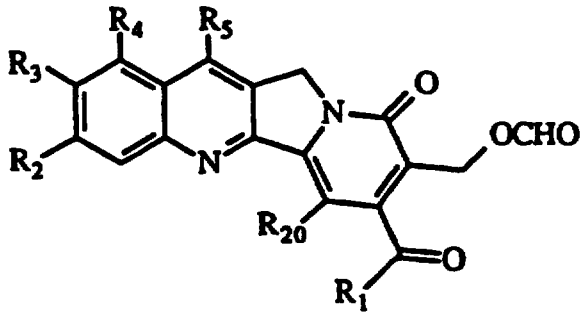
in which R_1, R_2, R_3, R_4, R_5 and R_{20} have the meaning indicated above, is reduced in order to obtain the α-hydroxylactol of general formula A



A

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

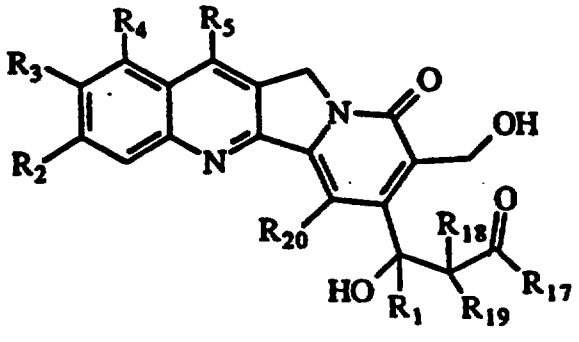
- in compound A thus formed, the carbon-carbon bond linking the adjacent carbinols, is cut by treatment with an appropriate oxidizing agent so as to produce the corresponding carbonyls in order to obtain a compound of formula B



B

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

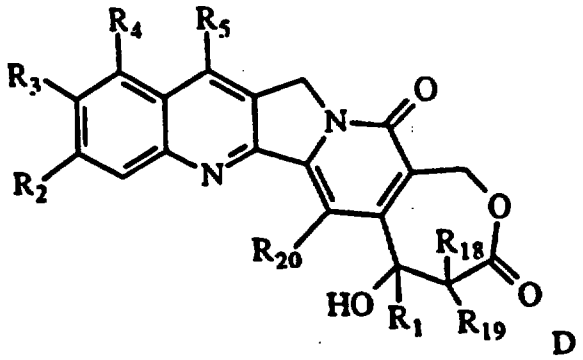
- then treatment is carried out with a functionalized alkylating agent and the formyl function of the compound of formula B thus formed is cut in order to produce a β-hydroxyester of general formula C



C

in which R_1, R_2, R_3, R_4, R_5, R_{18}, R_{19} and R_{20} have the meaning indicated above, and R_{17} represents OR_6 and R_6 represents a lower alkyl, cycloalkyl, lower alkyl cycloalkyl, lower alkenyl, lower alkyl lower alkoxy or aryl or lower alkyl aryl;

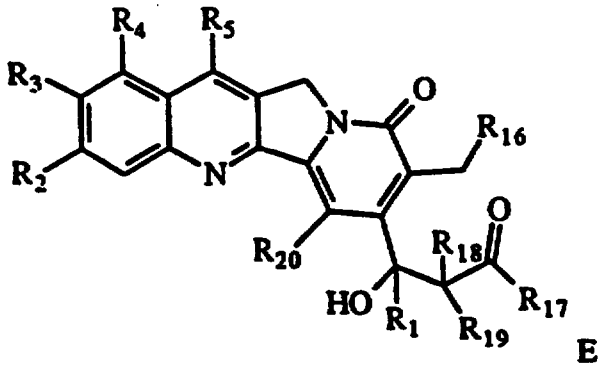
- said compound of general formula C is cyclized in order to produce the β-hydroxylactonic compound of general formula D



D

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

- the lactone of general formula D is opened in order to produce the compound of formula E

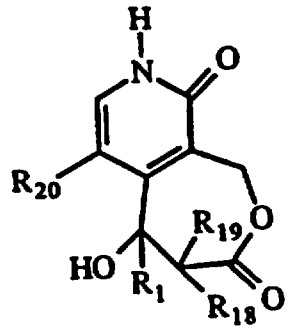


E

in which R_1, R_2, R_3, R_4, R_5, 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 alkyl cycloalkyl, lower alkenyl, lower alkyl lower alkoxy or aryl or lower alkyl aryl.

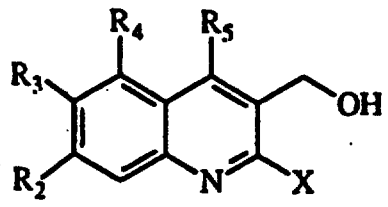
21. Preparation process for the compounds of formulae I and II according to any one of claims 2 to 19, characterized in that:

- a compound of general formula M



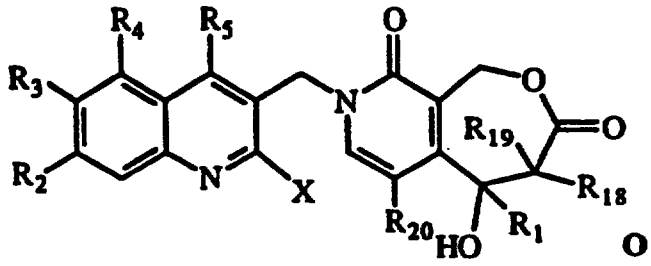
M

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_1, 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

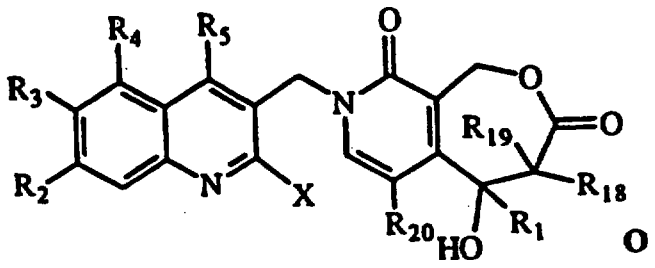


O

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.

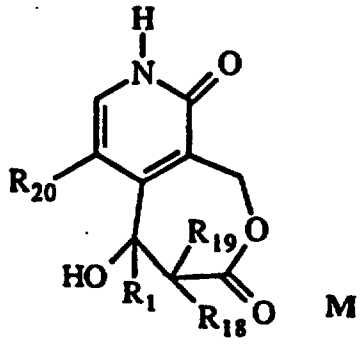
22. As new industrial products, the compounds of formula I'



in which

R_1 is a lower alkyl, a lower alkenyl, lower alkynyl, lower alkyl halo, lower alkyl lower alkoxy or lower alkyl lower alkylthio; R_{20} is H or halo; R_{22} is F, Cl or lower alkoxy; and R_{23} is a protective group of the primary hydroxyl.

23. As new industrial products, the compounds of formula M



M

in which

R_1 is a lower alkyl, lower alkenyl, lower alkynyl, lower alkyl halo, lower alkyl lower alkoxy or lower alkyl lower alkylthio; R_{18} and R_{19} represent, independently, H, halo, lower alkyl, lower alkoxy or hydroxy; and R_{20} represents H or halo.

24 Compounds according to claim 23, characterized in that R_1 represents ethyl and R_{18}, R_{19} and R_{20} represent H.

25. As medicaments, the products as defined in claim 1, as well as their addition salts with pharmaceutically acceptable mineral or organic acids.

26. As medicaments , the products of formula (I) or (II) as defined in claims 2 to 19, as well as their addition salts with pharmaceutically acceptable mineral or organic acids of said products of formula (I) or (II).

27. Pharmaceutical compositions containing at least one of the medicaments defined in one of claims 25 to 26 as active ingredient.

28. Use of the products of formula (I) and (II) as defined in any one of claims 1 to 19 for the preparation of medicaments intended to inhibit topoisomerase.

29. Use of the products of formula (I) and (II) as defined in any one of claims 1 to 19 for the preparation of anti-tumoral medicaments.

30. Use of the products of formula (I) and (II) as defined in any one of claims 1 to 19 for the preparation of anti-viral medicaments.

31. Use of the products of formula (I) and (II) as defined in any one of claims 1 to 19 for the preparation of anti-parasitic medicaments.