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(54) Title: OPTICALLY PURE CAMPTOTHECIN ANALOGUES, OPTICALLY PURE SYNTHESIS INTERMEDIATE AND METHOD FOR PREPARING SAME

(54) Titre: ANALOGUES OPTIQUEMENT PURS DE LA CAMPTOTHECINE, INTERMEDIAIRE DE SYNTHESE OPTIQUEMENT PUR ET SON PROCEDE DE PREPARATION

(57) Abstract

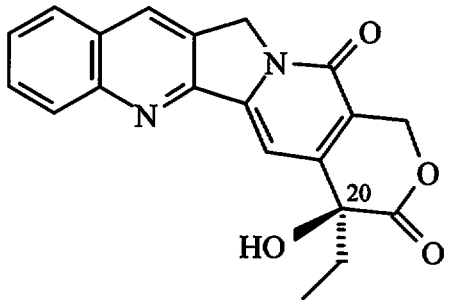
The invention concerns novel camptothecin analogues and in particular products corresponding to the following formulae: (+)–5–ethyl–9, 10–difluoro–5–hydroxy–4, 5,13,15–tetrahydro–1H, 3H–oxepino[3',4':6, 7]indolizino[1,2–b] quinoline–3,15–dione; (+)–1–[9–chloro–5– ethyl–5–hydroxy–10–methyl–3, 15–dioxo–4,5,13, 15–tetrahydro–1H,3H–oxepinol[3' ,4':6,7]indolizino [1,2–b]quinoline–12–ylmethyl] –4–methyl–hexahydropyridinium chloride; their application as medicine, pharmaceutical compositions containing them and their use for producing antitumoral, antiviral or antiparasitic medicines. The invention also concerns a novel synthesis intermediate of said products and a method for preparing said intermediate.

(57) Abrégé

L'invention concerne de nouveaux analogues de la camptothécine et en particulier les produits répondant aux formules suivantes: (+)–5–éthyl–9, 10–difluoro–5–hydroxy–4, 5,13,15–tétrahydro–1H, 3H–oxépino[3',4':6, 7]indolizino[1,2–b] quinoline–3,15–dione; (+)–chlorure de 1–[9–chloro–5– éthyl–5–hydroxy–10–méthyl–3, 15–dioxo–4,5,13, 15–tétrahydro–1H,3H–oxépino[3' ,4':6,7]indolizino [1,2–b]quinolin–12–ylméthyl] –4–méthyl–hexahydropyridinium; leur application comme médicaments, les compositions pharmaceutiques les renfermant et leur utilisation pour la réalisation de médicaments antitumoraux, antiviraux ou antiparasitaires. Elle concerne également un nouvel intermédiaire dans la synthèse des produits susmentionnés ainsi qu'un procédé de préparation dudit intermédiaire.

OPTICALLY PURE ANALOGUES OF CAMPTOTHECIN, OPTICALLY PURE SYNTHETIC INTERMEDIATE AND THEIR PREPARATION PROCESS

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:

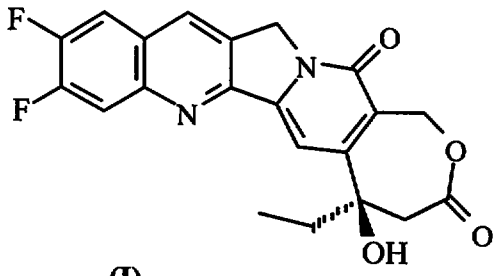


Camptothecin has an anti-proliferative activity in several cancerous cell lines, including the cell lines of human tumors of the colon, lung and breast (Suffness, M et al: The Alkaloids Chemistry and Pharmacology, Bross A., ed., Vol. 25, p. 73 (Acedemic Press, 1985)). It is suggested that the anti-proliferative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

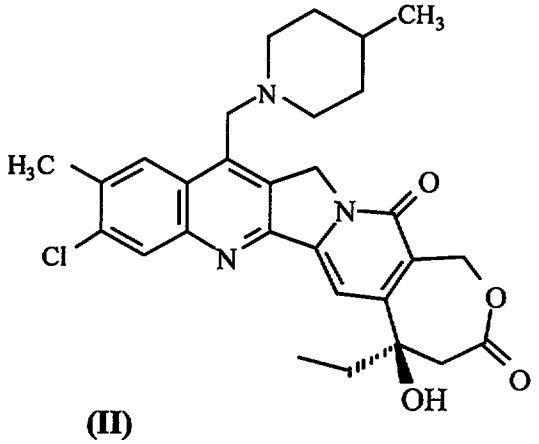
It has been indicated that α-hydroxylactone was an absolute requirement both for the *in vivo* and *in vitro* activity of camptothecin (Camptothecins: New Anticancer Agents, Putmesil, M et al, ed., p. 27 (CRC Press, 1995); Wall M. et al, Cancer Res. 55:753 (1995); Hertzberg et al, J. Med. Chem. 32:715 (1982) and Crow et al, J. Med. Chem. 35:4160 (1992)). More recently, the Applicant has perfected a new class of analogues of camptothecin, in which a *β*-hydroxylactone replaces the natural *α*-hydroxylactone of camptothecin (cf. Patent Application WO 97/00876).

A subject of the invention is a new preparation process for an enantiomerically pure synthetic intermediate, as well as new enantiomerically pure analogues of camptothecin.

Firstly, a subject of the invention is therefore new analogues of camptothecin which are different from any known compound, characterized in that it has the respective formulae **(I)** and **(II)** represented below

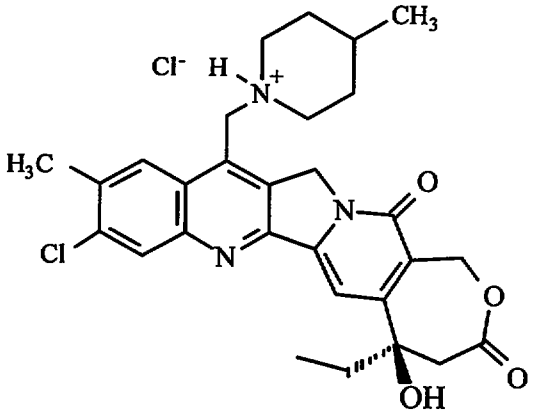


(I)



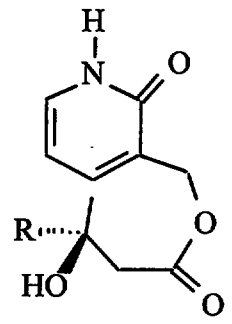
(II)

or in that it is the salts of the compound of formula **(II)** such as for example that of formula **(III)** represented below



(III)

A key intermediate in the synthesis of this type of optically pure compounds is a product of general formula **M** represented below

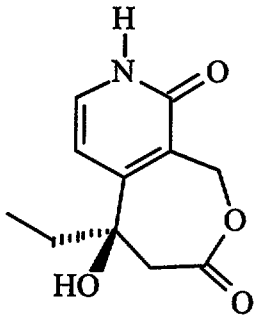


M

in which R represents a linear or branched alkyl radical containing from 1 to 10 carbon atoms. Preferably, R represents an ethyl radical.

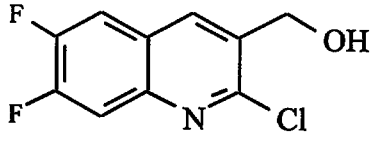
The compounds of formulae **(I)** and **(II)** can be prepared in the following fashion :

- the compound of formula

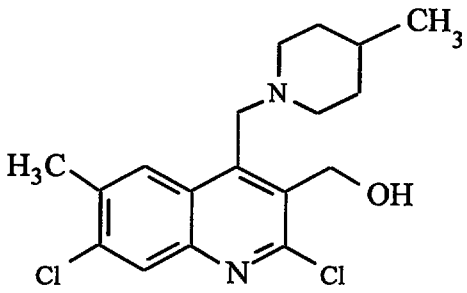


(+)-EHHOPD

is coupled respectively with one or other of the compounds of formulae N_1 or N_2 represented below :

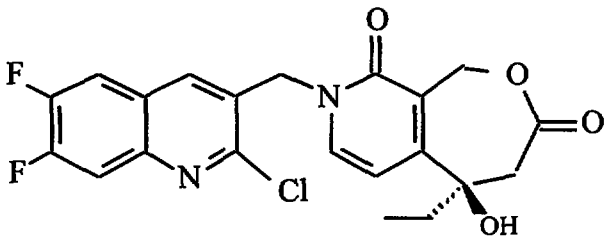


N_1

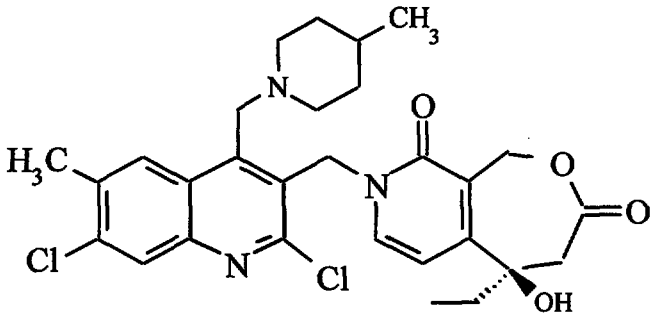


N_2

in order to produce the compound of formula O_1 or the compound of formula O_2 respectively:



O_1



O_2

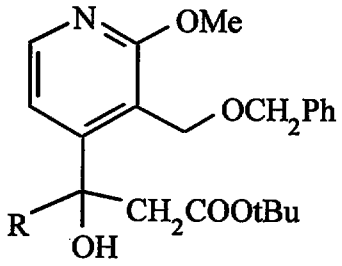
- compound O_1 is then cyclized, and the compound of formula **(I)** is then obtained; the cyclization of compound O_2 produces the compound of formula **(II)**, which can, after salification, produce the compound of formula **(III)**.

The formation of compound O_1 or O_2 starting from the compound of general formula **M** for which R represents an ethyl radical and N_1 or N_2 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 or diisopropyl azodicarboxylate, in an aprotic solvent such as, for example, tetrahydrofuran or *N,N*-dimethylformamide. The cyclization of compounds O_1 and O_2 in order to produce the compounds of formulae **(I)** and **(II)** 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 invention also offers, as a new industrial product, a compound of general formula **M** as defined previously. This product can be used for the manufacture of medicaments.

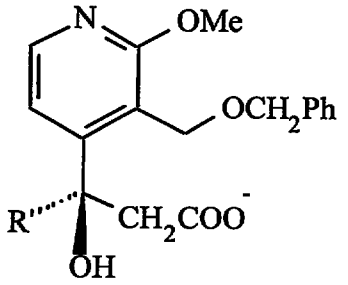
The compound of formula **M** is synthesized according to a new process which is part of the invention and includes the following successive stages:

- the racemic *t*-butyl ester represented below

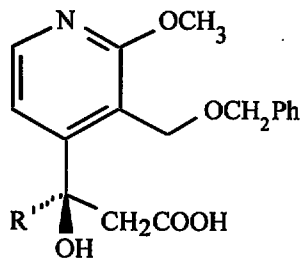


(for its preparation, refer in particular to the Patent Application WO 97/00876) is treated with trifluoroacetic acid for 18 hours at ambient temperate in order to produce the corresponding carboxylic acid ;

- then the quinidine salt of the acid obtained previously is heated in isopropyl alcohol at a temperature greater than 30° C, and preferably at about 50° C, before leaving the reaction medium to cool down to ambient temperatue, so that the salt of one of the enantiomers of the above-mentioned acid crystallizes while the salt of the other enantiomer, the anion of which is represented below, remains in solution

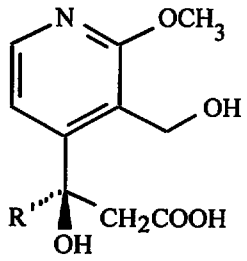


- the solution in isopropyl alcohol of the salt of the enantiomer which has not crystallized is concentrated and treated with hydrochloric acid and agitated, producing the compound of general formula **A** represented below



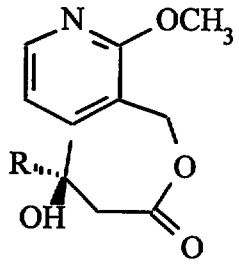
A

- the compound of general formula **A** is then put in contact with palladium on damp carbon, then ammonium formate or formic acid is added to the mixture in order to produce the debenzylated product of general formula **B** represented below



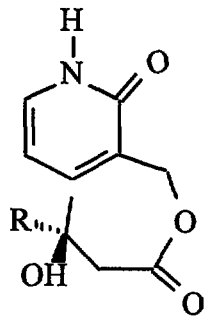
B

- then the compound of general formula **B** is cyclized by the action of dicyclohexylcarbodiimide in order to obtain the lactonic compound of general formula **C** represented below



C

- finally, the -OCH_3 group of the lactonic compound of general formula **C** is converted into carbonyl, by the action of sodium iodide and trimethylsilyl chloride, in order to obtain a compound of general formula **M** represented below.

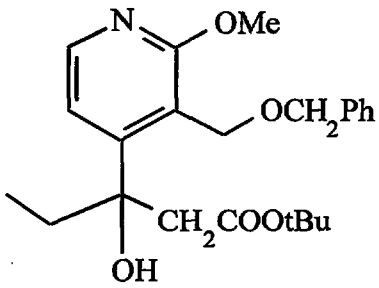


M

For the process described above, the reaction leading from the compound of general formula **A** to the compound of general formula **B** will preferably take place in methanol, and preferably by heating the reaction medium to about 40° C after the addition of the ammonium formate. The cyclization of the compound of general formula **B** in order to produce the compound **C** can be carried out in THF, preferably at a temperature of about 50° C, while the reaction will preferably be carried out at ambient temperatue with acetonitrile as solvent in the reaction leading from the compound of general formula **C** to the compound of general formula **M**.

In the particular case where R represents an ethyl group, the compound of formula **M** is synthesized according to the process constituted by the following successive stages:

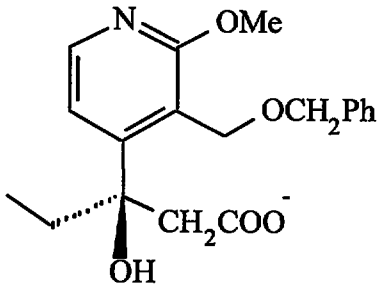
- the racemic *t*-butyl ester represented below



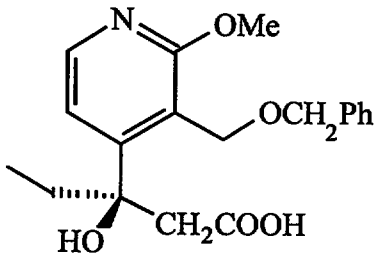
(for its preparation, refer in particular to the Patent Application WO 97/00876) is treated with trifluoroacetic acid for 18 hours at ambient temperatue in order to produce the corresponding carboxylic acid ;

- the quinidine salt of 3-(3-benzyloxymethyl-2-methoxy-4-pyridyl)-3-hydroxy-pentanoic acid is heated in isopropyl alcohol at a temperature higher than 30° C, and preferably at about 50° C, before leaving the reaction medium to cool down to ambient temperature, so that the salt of the (+) enantiomer of 3-(3-benzyloxymethyl-2-methoxy-4-pyridyl)-3-

hydroxy-pentanoic acid crystallizes whilst the salt of the (-) isomer, the anion of which is represented below, remains in solution

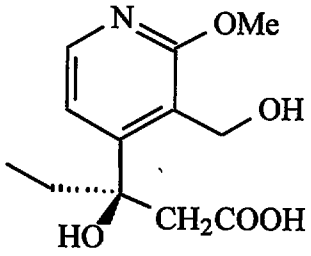


- the solution in isopropyl alcohol of the salt of the (-) enantiomer of 3-(3-benzyloxymethyl-2-methoxy-4-pyridyl)-3-hydroxy-pentanoic acid is concentrated and treated with hydrochloric acid and agitated, producing the compound of formula **A'** represented below



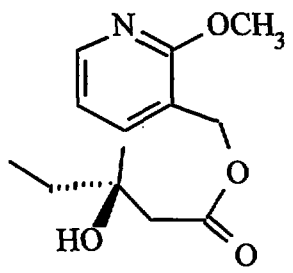
A'

- the compound **A'** is then put in contact with palladium on damp carbon, then ammonium formate or formic acid is added to the mixture in order to produce the debenzylated product **B'** represented below



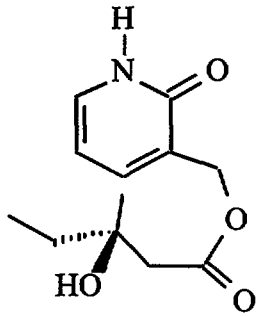
B'

- then the compound of formula **B'** is cyclized by the action of dicyclohexylcarbodiimide in order to obtain the lactonic compound of formula **C'** represented below



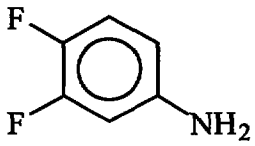
C'

- finally, the $-OCH_3$ group of the lactonic compound of formula **C'** is converted into carbonyl, by the action of sodium iodide and trimethylsilyl chloride, in order to obtain (+)-5-ethyl-5-hydroxy-1,3,4,5,8,9-hexahydrooxepino[3,4-c]pyridin-3,9-dione (or **(+)-EHHOPD**) represented below.



(+)-EHHOPD

The compound of formula $\mathbf{N_1}$ can be obtained starting with the aniline of formula $\mathbf{P_1}$ represented below

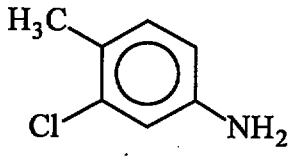


$\mathbf{P_1}$

according to the following process: the aniline of formula $\mathbf{P_1}$ is *N*-acetylated by treatment with an acetylating agent such as, for example, acetic anhydride. The acetanilide thus obtained is treated at a temperature comprised between 50°C and 100°C, preferably 75°C, with a reagent known to a person skilled in the art under the name Vilsmeyer's reagent (obtained by the action of phosphoryl oxychloride on *N,N*-dimethylformamide at a temperature comprised between 0°C and 10°C) in order to produce the corresponding 2-chloro-3-quinolinecarbaldehyde (for example, refer to Meth-Cohn et al. *J. Chem. Soc., Perkin Trans. I* p.1520 (1981); Meth-Cohn et al. *J. Chem. Soc., Perkin Trans. I* p.2509 (1981); and Nakasimhan et al. *J. Am. Chem. Soc.,*

112 p.4431 (1990)). The 2-chloro-6,7-difluoro-3-quinolinecarbaldehyde is easily reduced to the corresponding 2-chloro-6,7-difluoro-3-quinolinemethanol of formula N_1, 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 compound of formula N_2 can be obtained according to the following process: the aniline of formula P_2 represented below



P_2

is ortho-acylated by reaction with chloroacetonitrile 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 alcoholate, for example, sodium methylate in methanol, in order to produce ethyl 7-chloro-4-chloromethyl-6-methyl-2-oxo-1,2-dihydro-3-quinoline carboxylate. The latter is converted into ethyl 2,7-dichloro-4-chloromethyl-6-methyl-3-quinolinecarboxylate by treatment with phosphoryl oxychloride. Then a nucleophilic substitution is carried out by treatment with 4-methylpiperidine. The ethyl carboxylate function is then reduced with diisobutylaluminium hydride in an aprotic solvent such as dichloromethane in order to produce the compound of formula N_2. The order in which the last two stages is carried out may optionally be reversed.

Analogues of the intermediate compounds of N_1 or N_2 type have been described in the literature and in particular in the Application PCT 95/05427.

The compound of formula **(II)** can be converted into 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. For

other examples of pharmaceutically acceptable salts one can refer to "Pharmaceutical Salts", J. Pharm. Sci. 66:1 (1977).

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

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

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)**, or of a pharmaceutically acceptable salt of a compound of formula **(II)**, or also of any mixture of the last-named compounds.

The compounds according to the invention 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 said patient of a therapeutically effective quantity of a compound of formula **(I)** or of formula **(II)**, or of a pharmaceutically acceptable salt of a compound of formula **(II)**, or also of any mixture of the last-named compounds. 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 formulae **(I)** and **(II)** suitable for pharmaceutical use. A subject of the present Application is also, as medicaments, the products of formulae **(I)** and **(II)** as defined above as well as the addition salts with

pharmaceutically acceptable mineral or organic acids of the product of formula **(II)**, such as for example the salt of formula **(III)** described previously, or also of any mixture of the last-named compounds. Similarly the invention relates to 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, transdermic or subcutaneous). 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, such as for example, powders, pills, granules, tablets, liposomes, gelatin capsules or suppositories. The pill, tablet or gelatin capsule can be covered in a substance which is capable of protecting the composition from the action of gastric acid or enzymes in the stomach of the subject for a sufficient period of time to allow this composition to pass in a non-digested form into the small intestine of the latter. The compound can also be administered locally, for example, at the same location as the tumor. The compound can also be administered according to a sustained release process (for example a sustained release composition or an infusion pump). The appropriate solid supports can be, for example, calcium phosphate, magnesium stearate, magnesium carbonate, talc, sugars, lactose, dextrin, starch, gelatin, cellulose, methyl cellulose, sodium carboxymethyl cellulose, polyvinylpyrrolidine and wax. The pharmaceutical compositions containing a compound according to the invention can also be presented in liquid form such as, for example, solutions, emulsions, suspensions or a sustained release formulation. The appropriate liquid supports can be, for example, water, organic solvents such as glycerol or glycols such as polyethylene glycol, similarly their mixtures, in varied proportions, in water.

A subject of the invention is also the use of the products of formulae **(I)** and **(II)** as defined above, or addition salts with pharmaceutically acceptable mineral or organic acids of a product of formula **(II)**, such as for example the salt of formula **(III)** described previously, or also a mixture of the last-named compounds, for the preparation of medicaments intended to inhibit topoisomerase and more particularly topoisomerases 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 infections or 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 to be treated 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 here called "effective therapeutic quantity".

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

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

EXPERIMENTAL PART :

Example 1 : ***(+)-5-Ethyl-5-hydroxy-1,3,4,5,8,9-hexahydrooxepino[3,4-c]pyridin-3,9-dione [(+)-EHHOPD]***

1.a. Quinidine salt of 3-(3-benzyloxymethyl-2-methoxy-4-pyridyl)-3-hydroxy-pentanoic acid:

Tertiobutyl 3-(3-benzyloxymethyl-2-methoxy-4-pyridyl)-3-hydroxy-pentanoate (40 g; 100 mmol) is treated with trifluoroacetic acid (150 ml) and the reaction medium is agitated for 18 hours at 20°C. After evaporation of the trifluoroacetic acid, methylene chloride (200 ml) is poured in and a saturated solution of sodium bicarbonate is introduced until the pH = 7.5-8. After decantation, the aqueous phase is washed with 100 ml of methylene chloride. The pH of the aqueous phase is then adjusted to 1 by the addition of a solution of 6N hydrochloric acid. The product is then extracted from the aqueous phase with methylene chloride (2 times 200 ml). The solution is dried over magnesium sulphate and concentrated. The 3-(3-benzyloxymethyl-2-methoxy-4-pyridyl)-3-hydroxy-pentanoic acid (31.1 g; 90 mmol) thus obtained, taken up in isopropyl alcohol (30 ml), is treated with a solution of quinidine (29.2 g; 90 mmol) in isopropyl alcohol (30 ml) at 50°C under agitation until complete dissolution. Then the reaction medium is left so that temperature reduces to 40°C, the agitation is stopped and the temperature allowed to drop to 20°C. The medium is taken to 0°C without agitation then maintained at this temperature for 16 hours. Then the temperature is allowed to rise to 20°C and agitation is carried out until crystallization. The medium is diluted with isopropyl alcohol then filtered. The precipitate is rinsed with isopropyl alcohol. The salt of the (+) enantiomer precipitates (m=26.6 g) while the salt of the (-) enantiomer

remains in solution in the isopropyl alcohol. Thus the filtrate is recovered which is concentrated in order to produce an oil (34 g) which is used without other purification in the following stage.

The products are analyzed by HPLC on a 5µ CHIRAL AGP column (10 cm x 4mm) eluted with a 30/920/50 isopropyl alcohol/water/phosphate buffer mixture, pH = 6.5, at a flow rate of 1.2 ml/min, UV detection at 280 nm. The retention times obtained are 6.4 minutes for the (-) enantiomer and 2.8 minutes for the (+) enantiomer. The (-) enantiomer / (+) enantiomer ratio is 83/17.

1.b. (-)-3-(3-benzyloxymethyl-2-methoxy-4-pyridyl)-3-hydroxy-pentanoic acid

The solution in isopropyl alcohol of the quinidine salt of the (-) enantiomer of 3-(3-benzyloxymethyl-2-methoxy-4-pyridyl)-3-hydroxy-pentanoic acid (Stage 1.a) is concentrated. The concentrate is taken up in 270 ml of methylene chloride and 270 ml of a 1N solution of hydrochloric acid. The reaction medium is agitated for 16 hours at 20°C. After decantation, the organic phase is concentrated, the concentrate is taken up in methanol in order to be used in the following stage.

13.5 g of product (yield of 87%) and a (-)enantiomer / (+) enantiomer proportion of 85/15 are obtained.

The HPLC retention times (same protocol as in 1.a.) are:
- (-) enantiomer: 6.4 minutes
- (+) enantiomer: 2.8 minutes

1.c. (+)-5-Ethyl-5-hydroxy-1,3,4,5,8,9-hexahydrooxepino[3,4-c] pyridin-3,9-dione:

(-)-3-(3-benzyloxymethyl-2-methoxy-4-pyridyl)-3-hydroxy-pentanoic acid (13.5 g; 39 mmol; Stage 1.b) is put in solution in 87 ml of methanol. This solution is poured under nitrogen onto 10% Palladium on damp carbon at 50% (27.7 g; 13 mmol). The reaction medium is agitated for 5 minutes, then it is poured into a solution of ammonium formate (11,5 g; 183 mmol) in 135 ml of methanol. The reaction medium is agitated for 30 minutes while allowing the temperature to rise, then it is heated at 40°C for 30 minutes. The medium is then filtered on a bed of Clarcel followed by concentrating. 40 ml of toluene is poured in which is evaporated off; this operation is repeated in order to eliminate the methanol. The residue thus obtained is taken up in 45 ml of THF. Then a solution of dicyclohexylcarbodiimide (7.180 g; 34.5 mmol) in 20 ml of THF is then poured in. The reaction medium is heated to 50°C for 1 hour. The mixture is taken to 20°C then the dicyclohexylurea is filtered. The filtrate is concentrated to dryness. The

residue is put in solution in 46 ml of acetonitrile, 6.0 g (40.5 mmol.) of sodium iodide then 5.13 ml (40.5 mmol) of trimethylsilyl chloride are added. The reaction medium is maintained under agitation at ambient temperatue for 5 hours. Then 28 ml of acetonitrile and 5.6 ml of water are added. The precipitate obtained is filtered then taken up in 1 ml of water, and the pH is adjusted to 7.5 by the addition of a solution of ammonium hydroxide. The solid obtained is filtered and dried. m = 4.2 g of final product is obtained with a yield of 34 % and a (+) enantiomer / (-) enantiomer proportion of 88.4/11.6.

HPLC analysis is carried out on a Chiralcel OD column 25 cm x 4.6 mm, the eluants used are heptane 600 and ethanol 400, the flow rate is 1 ml/min 210 nm. The retention times obtained are:
- (-) enantiomer: 7.1 minutes
- (+) enantiomer: 9 minutes.

The product is taken up in acetone (40 ml), then water (150 ml) is added. The reaction is left to precipitate and 3 g of product is obtained with a (+) enantiomer / (-) enantiomer proportion of 99.4 / 0.6.

NMR ^{1}H (250 MHz, DMSO D6): 0.8 (*t*, 3H, CH_3-CH_2); 1.65 (*m*, 2H, CH_2-CH_3); 3.00-3.35 (*q*, 1H+1H, -CH_2-C=O); 5.3 (*q*, 2H, CH_2-O); 5.7 (*s*, -OH); 6.35 (*d*, aromatic 1H); 7.3 (*d*, aromatic 1H); 11.7 (*s*, N-H).

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

2.a. N-(3,4-difluorophenyl)acetamide:

A mixture of 3,4-difluoroaniline (50 ml; 0.5 mole) and triethylamine (70 ml; 0.5 mol) in dichloromethane (1.5 l) is cooled down using an ice bath. Acetic anhydride (71.5 ml; 0.75 mol) is added dropwise and the reaction mixture is then agitated for 1 hour at ambient temperatue. The mixture obtained is then washed successively with water, a 10% solution of sodium bicarbonate and saturated salt water. The organic fraction is dried over sodium sulphate and concentrated under reduced pressure. The residue is suspended in pentane, filtered and dried under reduced pressure in order to produce the product in the title (78 g; 91 % yield) in the form of a whitish solid (M.p. 126-127.5°C).

NMR ^{1}H (DMSO): 2.15 (s, 3H); 7.10-7.65 (m, 2H); 7.65-8.10 (m, 1H); 10.30 (wide peak, 1H).

2.b. 2-chloro-6,7-difluoro-3-quinoline-3-carbaldehyde:

The general procedure described by Meth-Cohn *et al.*, *J. Chem. Soc. Perkin Trans. I*, **1981**, 1520 and 2509 is used.

The product of Stage 2.a (32 g; 220 mmol) is added to a Vilsmeyer reagent, obtained by the dropwise addition under an argon atmosphere of phosphorus oxychloride (103 ml; 1.1 mol) in anhydrous DMF (34 ml; 440 mmol) cooled down in an ice bath and agitated for 30 minutes before leaving the temperature to rise to ambient temperature. The mixture thus obtained is agitated at 70°C for 16 hours. After returning the reaction medium to ambient temperature, it is added dropwise to a water-ice mixture (400 ml) and agitated for 2 hours. The precipitate obtained is filtered and washed with water, then dried in order to produce the product in the title (9 g; 18 % yield) in the form of a yellow solid (M.p. 226.5-229°C).

NMR ^{1}H (DMSO): 8.17 (dd, 1H); 8.39 (dd, 1H); 8.97 (d, 1H); 10.34 (d, 1H).

IR (KBr): 888, 1061, 1262, 1507, 1691 cm^{-1}.

2.c. 2-chloro-6,7-difluoro-3-quinolylmethanol:

A suspension of the product of Stage 2.b (9 g; 39 mmol) in methanol (400 ml) is treated with sodium borohydride (2 g; 53 mmol) at ambient temperature for half an hour. The excess borohydride is destroyed with acetic acid (2 ml). The volatile substances are eliminated under reduced pressure. The residue is dissolved in ethyl acetate (500 ml), the mixture obtained then being washed successively with a dilute solution of sodium bicarbonate, water and saturated salt water, followed by drying over magnesium sulphate and concentration under reduced pressure. The residue is recrystallized from 1,2-dichloroethane in order to produce the product in the title (8 g; 80 % yield) in the form of a beige solid (M.p. 166.5-167°C).

NMR ^{1}H (DMSO): 4.67 (d, 2H); 5.80 (t, 1H); 8.01 (dd, 1H); 8.22 (dd, 1H); 8.48 (s, 1H).

IR (KBr): 871, 1038, 1253, 1513 cm^{-1}.

2.d. (+)-8-(2-chloro-6,7-difluoro-3-quinolinemethanol)-5-ethyl-5-hydroxy-1,3,4,5,8,9-hexahydrooxepino[3,4-c]pyridine-3,9-dione:

Diethylazodicarboxylate (1.24 ml; 7.87 mmol) is added dropwise at ambient temperature and under an argon atmosphere to a solution in anhydrous DMF (30 ml) of **(+)-EHHOPD** (1.58 g; 7.08 mmol; Stage 1.c.), the product of Stage 2.c (1.62 g; 7.06 mmol) and tributylphosphine (1.91 ml; 7.87 mmol). The mixture thus obtained is then agitated for 16 hours. The reaction medium is then evaporated to dryness under reduced pressure. The residue is purified by chromatography on a silica column (eluant: ethyl acetate). The solid obtained is taken up in diethylether, filtered and dried in order

to produce the product in the title (1.56 g; 51 % yield) in the form of a whitish solid (M.p. 196°C).

NMR ^1H (DMSO): 0.84 (t, 3H); 1.74 (m, 2H); 3.02 (d, 1H); 3.34 (d, 1H); 5.29 (s, 2H); 5.31 (dd, 2H); 5.75 (s, 1H); 6.51 (d, 1H); 7.80 (d, 1H); 8.03 (dd, 1H); 8.07 (s, 1H); 8.17 (dd, 1H).

IR (KBr): 875, 1057, 1360, 1507, 1574, 1647, 1749 cm^{-1}.

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

A mixture of the product of Stage 2.d (1.53 g; 3.52 mmol; Stage 2.d.), tetrabutylammonium bromide (1.25 g; 3.87 mmol), potassium acetate (520 mg; 5.28 mmol), triphenylphosphine (180 mg; 0.70 mmol) and palladium (II) acetate (79 mg; 0,35 mmol) is agitated under an argon atmosphere in anhydrous acetonitrile heated at reflux for 22 hours. After the reaction medium has returned to ambient temperature, concentration under reduced pressure is carried out before chromatography on a silica column (eluant: CH_2Cl_2/MeOH mixture 98/2). The product in the title is then obtained (960 mg; yield 68 %; purity determined by HPLC: 97.1 %). This product is taken up in anhydrous CH_2Cl_2 (100 ml) and agitation is carried out for 24 hours, followed by filtering and drying under reduced pressure in order to produce the purified product of the title (850 mg; yield 61 %; purity determined by HPLC: 99.6 %) in the form of a white solid.

NMR ^1H (DMSO): 0.87 (t, 3H); 1.85 (m, 2H); 3.08 (d, 1H); 3.44 (d, 1H); 5.26 (s, 2H); 5.39 (d, 2H); 5.52 (d, 2H); 5.99 (wide peak, 1H); 7.39 (s, 1H); 8.15 (dd, 1H); 8.23 (dd, 1H); 8.68 (s, 1H).

IR (KBr): 871, 1261, 1512, 1579, 1654, 1746 cm^{-1}.

Example 3: ***(+)1-[9-chloro-5-ethyl-5-hydroxy-10-methyl-3,15-dioxo-4,5,13,15-tetrahydro-1H,3H-oxepino[3',4':6,7]indolizino[1,2-b]quinolin-12-ylmethyl]-4-methyl-hexahydropyridinium chloride***

3.a. 1-(2-amino-4-chloro-5-methylphenyl)-2-chloro-ethanone:

3-chloro-4-methylaniline (44.4 ml; 0.366 mol) in 1,2-dichloroethane (440 ml), under an argon atmosphere, is cooled down in an ice bath. The following are added dropwise and in the order of this mixture: boron trichloride (1M in heptane; 400 ml; 0.4 mol), chloroacetonitrile (28 ml; 0.44 mol) and diethylaluminium chloride (1M in heptane; 400 ml; 0.4 mol). For the addition, the temperature is maintained below 20° C. The resultant mixture is then heated at reflux for 3 hours, then cooled down to 10° C. The hydrolysis of the reaction medium is then carried out cautiously using 2N hydrochloric acid (240

ml) and it is heated at reflux for 1 hour. Water (1 l) and ethyl acetate (1 l) are added, the mixture obtained is agitated for 15 minutes before separating the phases. The aqueous phase is again extracted with ethyl acetate (200 ml), and the combined organic phases are washed with water (500 ml). After drying over magnesium sulphate the organic phase is concentrated. The residue is taken up in petroleum ether (fraction having a boiling point of 45 to 60°C; 150 ml) and the mixture thus obtained is left for 16 hours at 4°C. The resultant precipitate is collected by filtration, washed with petroleum ether and dried under reduced pressure in order to produce the product in the title (25 g; 31 % yield). M.p. 129-130°C.

NMR ^{1}H (DMSO): 2.20 (s, 3H); 4.98 (s, 2H); 6.90 (s, 1H); 7.15 (wide peak, 2H); 7.70 (s, 1H).

IR (KBr): 871, 1018, 1183, 1225, 1270, 1533, 1577, 1619, 1662 cm^{-1}.

3.b. Ethyl 7-chloro-4-chloromethyl-6-methyl-2-oxo-1,2-dihydro-3-quinolinecarboxylate:

The product of Stage 3.a (25 g; 0.11 mol) and triethylamine (30.6 ml; 0.22 mol) are mixed together in acetonitrile (520 ml). Ethylmalonyl chloride (28.1 ml; 0.22 mol) is added at ambient temperature and under an argon atmosphere. The mixture obtained is agitated for 3 hours. Sodium ethanolate (prepared by the dissolution of 3 g, i.e. 0.13 mol, of sodium in 140 ml of absolute ethanol) is then added dropwise and the resultant mixture is agitated at ambient temperature for 16 hours. The precipitate is collected by filtration, washed successively with ethanol, water, ethanol and ether. It is then dried under reduced pressure at 70°C over phosphorus pentoxide in order to produce the product in the title (28.6 g; 83 % yield) in the form of a whitish powder.

NMR ^{1}H (DMSO): 1.30 (t, 3H); 2.40 (s, 3H); 4.35 (q, 2H); 4.85 (s, 2H); 7.41 (s, 1H); 7.91 (s, 1H); 12.15 (wide peak, 1H).

IR (KBr): 879, 1108, 1250, 1288, 1483, 1664, 1721 cm^{-1}.

3.c. Ethyl 2,7-dichloro-4-chloromethyl-6-methyl-3-quinolinecarboxylate:

The product of Stage 3.b (28.4 g; 90 mmol) is heated for 4 hours at reflux in phosphorus oxychloride (400 ml). The mixture obtained is concentrated under reduced pressure (20 mm Hg) at 80°C. The residue is taken up in diisopropylether (400 ml). The resultant precipitate is collected by filtration, washed with ether and petroleum ether, then dried under reduced pressure in order to produce the product in the title (25.4 g; 85 % yield) in the form of a whitish powder (M.p. 126-127°C).

NMR ^{1}H (DMSO): 1.37 (t, 3H); 2.58 (s, 3H); 4.49 (q, 2H); 5.14 (s, 2H); 8.16 (s, 1H); 8.35 (s, 1H).

IR (KBr): 874, 1006, 1163, 1243, 1278, 1577, 1723 cm^{-1}.

3.d. 2,7-dichloro-4-chloromethyl-6-methyl-3-quinolylmethanol:

The product of Stage 3.c (25.2 g; 76.5 mmol) is mixed under an argon atmosphere with dichloroethane (630 ml). Diisobutylaluminium hydride (1M in dichloromethane; 307 ml; 307 mmol) is added dropwise while the reaction mixture is agitated and the temperature is maintained below 20°C. The reaction mixture is then agitated at ambient temperature for 3 hours, then poured into an aqueous solution of potassium tartrate (concentrated to 20 % by weight; 1.5 l). The emulsion thus obtained is agitated vigorously for 1 hour, filtered on celite and the two phases are then separated. The aqueous phase is extracted with ethyl acetate (200 ml) and the combined organic phases are washed with an aqueous solution of sodium chloride (concentrated to 20 % by weight; 500 ml). The organic phase obtained is dried over magnesium sulphate, filtered and concentrated under reduced pressure. The residue is taken up in diethylether (50 ml) and the resultant precipitate is collected by filtration. By drying under reduced pressure, the product in the title is obtained (18.3 g; 93 % yield) in the form of a whitish powder (M.p. 169-170°C).

NMR ^{1}H (DMSO): 2.57 (t, 3H); 4.84 (s, 2H); 5.36 (s, 2H); 8.06 (s, 1H); 8.27 (s, 1H).

IR (KBr): 870, 1022, 1102, 1304, 1482, 1567 cm^{-1}.

3.e. 2,7-dichloro-6-methyl-4-(4-methylpiperidinomethyl)-3-quinolylmethanol:

A solution of the product of Stage 3.d (16.2 g; 55.7 mmol) in THF (70 ml) is treated with a solution of 4-methylpiperidine (23 ml; 195 mmol). The mixture obtained is agitated at ambient temperature for 2 hours. Water (200 ml) and dichloroethane (200 ml) are added. The organic phase is washed with an aqueous solution of sodium chloride (concentrated to 20 % by weight; 100 ml), dried over magnesium sulphate and concentrated under reduced pressure. By crystallization of the residue from diethylether, the product in the title is obtained (18.3 g; 93 % yield) in the form of a white crystalline solid (M.p. 170-171.5°C).

NMR ^{1}H ($CDCl_3$): 0.88 (d, 3H); 1.17 (m, 2H); 1.42 (m, 1H); 1.60 (m, 2H); 2.19 (t, 2H); 2.56 (s, 3H); 2.82 (d, 2H); 4.02 (s, 2H); 4.93 (s, 2H); 6.36 (wide peak, 1H); 7.95 (s, 1H); 8.02 (s, 1H).

IR (KBr): 971, 1013, 1105, 1293, 1479, 1559 cm^{-1}.

3.f. (+)-8-[2,7-dichloro-6-methyl-4-(4-methylpiperidinomethyl)-3-quinolylmethyl]-5-ethyl-5-hydroxy-1,3,4,5,8,9-hexahydrooxepino[3,4-c]pydidine-3,9-dione:

A suspension of (+)-**EHHOPD** (obtained in Stage 1.c.; 1.56 g; 7,0 mmol) in anhydrous dioxane (70 ml) is treated successively, under an argon atmosphere, with the product of

Stage 3.e (2.47 g; 7.0 mmol), triphenylphosphine (2.02 g; 7.7 mmol) and diisopropyl azodicarboxylate (1.07 ml; 10.5 mmol). The mixture is agitated at ambient temperature for 16 hours. The volatile substances are then evaporated off under reduced pressure. The residue is purified by chromatography on a silica column (eluant: ethyl acetate). The solid obtained is taken up in diethylether, filtered and dried in order to produce the product in the title (1.96 g; 50 % yield) in the form of a whitish solid (M.p. 182°C).

NMR ^{1}H (DMSO): 0.89 (m, 8H); 1.23 (m, 1H); 1.41 (t, 2H); 1.64 (m, 2H); 2.09 (q, 2H); 2.59 (m, 5H); 3.15 (dd, 2H); 4.06 (dd, 2H); 5.31 (dd, 2H); 5.35 (dd, 2H); 5.75 (s, 1H); 6.29 (d, 1H); 7.17 (d, 1H); 8.06 (s, 1H); 8.46 (s, 1H).

IR (KBr): 878, 1053, 1275, 1474, 1572, 1648, 1747 cm^{-1}.

3.g. (+)-9-chloro-5-ethyl-5-hydroxy-10-methyl-12-(4-methylpiperidinomethyl)-4,5,13,15-tetrahydro-1H,3H-oxepino[3',4':6,7]indolizino[1,2-c]quinoline-3,15-dione:

A mixture of the product of Stage 3.f (3.80 g; 6.80 mmol), tetrabutylammonium bromide (2.42 g; 7.5 mmol), potassium acetate (1.00 g; 10.2 mmol), triphenylphosphine (890 mg; 3.4 mmol) and palladium (II) acetate (220 mg; 0,68 mmol) is agitated under an argon atmosphere in anhydrous acetonitrile (85 mg) at reflux for 24 hours. After cooling down to ambient temperature, the resultant precipitate is collected by filtration and washed successively with acetonitrile, water, acetone and diethylether in order to produce, after drying under reduced pressure, the product in the title (2.5 g; 70 % yield) in the form of a whitish powder.

NMR ^{1}H (DMSO): 0.86 (m, 6H); 1.12 (q, 2H); 1.36 (m, 1H); 1.56 (d, 2H); 1.84 (q, 2H); 2.12 (t, 2H); 2.56 (s, 3H); 2.83 (dd, 2H); 3.26 (dd, 2H); 4.03 (dd, 2H); 5.28 (dd, 2H); 5.45 (dd, 2H); 6.04 (s, 1H); 7.34 (s, 1H); 8.14 (s, 1H); 8.38 (s, 1H).

IR (KBr): 870, 1058, 1208, 1280, 1477, 1593, 1655, 1749 cm^{-1}.

3.h. (+) 1-[(5R)-9-chloro-5-ethyl-5-hydroxy-10-methyl-3,15-dioxo-4,5,13,15-tetrahydro-1H,3H-oxepino[3',4':6,7]indolizino[1,2-c]quinolin-12-ylmethyl]-4-methyl-hexahydropyridinium chloride:

A mixture of the product of Stage 3.g (2.3 g; 7.7 mmol) and absolute ethanol (300 ml) is subjected to ultrasound for 2 minutes. The milky suspension obtained is agitated and treated with hydrochloric acid (1N solution; 13.2 ml; 13.2 mmol) in order to produce a light yellow solution which, at rest, forms a gel-type precipitate. The precipitate is collected by filtration on a Büchner and washed successively with ethanol and ether, then dried under reduced pressure in order to produce the product in the title (2.1 g; 85 % yield).

NMR ^{1}H (DMSO): 0.87 (m, 6H); 1.59 (m, 5H); 1.84 (q, 2H); 2.64 (s, 3H); 3.28 (dd, 2H); 3.45 (s, 2H); 4.93 (s, 2H); 5.47 (dd, 2H); 5.61 (s, 2H); 6.04 (wide peak, 1H); 7.41 (s, 1H); 8.28 (s, 1H); 8.63 (s, 1H); 10.30 (wide peak, 1H).

IR (KBr): 1043, 1212, 1479, 1585, 1655, 1751 cm^{-1}.

5

PHARMACOLOGICAL STUDY OF THE PRODUCTS OF THE INVENTION

Test on cell proliferation.

Five tumoral cell lines are used in this study: SW620 (human colon adenocarcinoma), OVCAR-5 (human ovary adenocarcinoma), PC-3 and DU 145 (cell line of human prostate) and NCI-H69 (human lung adenocarcinoma). These lines are obtained from the NCI/Frederick Cancer Research and Development Center (Frederick, MD). They are cultured in complete medium containing RMPI-1640 medium enriched with 10 % of foetal calf serum and 2 mM of L-Glutamine. They are incubated at 37°C in a humidified atmosphere with 5 % of CO_2. The adherent cells are detached by a treatment with a solution with 0,25 % trypsine and 0.2% EDTA (Worthington Biochemical Corp., Freehold, NJ) for 5 minutes at 37°C. Counting the cells is carried out using a Coulter Z1 counter (Coulter Corp., Hialeah, FL). The viability is evaluated by staining the cells with propidium iodide then they are counted with an EPICS Elite flow cytometer (Coulter).

The compound of Examples 2 and 3 to be tested is dissolved at 5 mM in a solution of N,N-dimethylacetamine (DMA, Aldrich). Subsequent dilutions are carried out with culture medium. The tested final molar concentrations are: 1.10^{-6}, 2.10^{-7}, 4.10^{-8}, 8.10^{-9}, $1{,}6.10^{-9}$, $3{,}2.10^{-10}$, $6{,}4.10^{-11}$, $1{,}28.10^{-11}$, $2{,}56.10^{-12}$, and $5{,}12.10^{-13}$. Each concentration is tested on eight wells. Checks on the influence of DMA are carried out on all the cell lines. The result of these checks is that at the maximum concentration used (0.02 %) the DMA has no effect. Doxorubicin at concentrations of 1.10^{-7} M and 2.10^{-7} M is used as a positive control.

The cells are seeded at 5.10^{3} cells per well on a microplate with 96 wells (Costar Corporation, Cambridge, MA). The cells are incubated for 24 hours at 37°C in order to allow a repeat of the cell multiplication. The compound of Examples 2 and 3 to be tested is then added at the concentrations indicated above and the cells are incubated at 37°C in a humidified atmosphere with 5 % CO_2, for 3 days for the adherent cells (SW620, OVCAR-5, PC-3 and DU 145) and for 5 days for the cells in suspension (NCI-H69).

The adherent cells are tested by the SRB method (described by L.V. Rubenstein, R.H. Shoemaker, K.D. Paull, R.M. Simon, S. Tosini, P. Skehan, D.A Scudiero, A. Monks, and M.R. Boyd "Comparison of in vitro anticancer-drug-screening data generated with tetrazolium assay versus a protein assay against a diverse panel of human tumor cell lines", *J. Nat. Cancer Inst.*, **82**:1113-1118, 1990). After incubation for 3 days the supernatant is eliminated and 200 µl RPMI-1640 free from foetal calf serum is added.

The cells are fixed by the addition of 50 µl of 50% trichloroacetic (final concentration of trichloroacetic acid 10 %) and incubated at 4°C for 1 hour. The wells are washed 5 times with water then stained with 50 µl of a solution with 0.4 % sulphorhodamine B (SRB, Sigma) in acetic acid at 1 % at ambient temperature for 10 minutes. The stain is solubilized with 100 µl of TRIS buffer at 10 mM, pH 10, for about 5 minutes with agitation, the microplates are read using spectrophotometry at 570 nm.

The cells in suspension are tested by the XTT method (described by D.A. Scudiero, R.H. Shoemaker, K.D. Paull, A. Monks, S. Tierney, T.H. Nofziger, M.J. Currens, D. Seniff and M.R. Boyd: "Evaluation of a soluble tetrazolium/formazan assay for cell growth and drug sensitivity in culture using human and other tumor cell lines", *Cancer Research* **48**:4827-4833, 1988). After incubation in the presence of the compound of Examples 2 and 3 to be tested, XTT [sodium salt of 2,3-bis(2-methoxy-4-nitro-5-sulphophenyl)-2H-tetrazolium-5-carboxanilide, (Sigma)] and phenazine methosulphate (PMS, Sigma) in solution in saline phosphate buffer are added to the cultures, and the cells are incubated for 4 hours at 37°C in an atmosphere with 5 % CO_2. The final concentrations of XTT and PMS are 50 and 0.38 µg/well respectively. The production de formazan is stopped by the addition of 10 µl of sodium dodecylsulphate at 10 % (Sigma) and the absorbance is read using spectrophotometry at 450 nm with a reference filter at 600-650 nm.

Results:

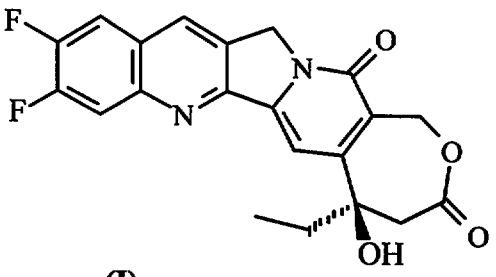
The molar concentrations of the compounds of Examples 2 and 3 inhibiting the cell proliferation by 50% are compiled in the following table:

Cell line	Example 2	Example 3
SW620	5.10^{-9}	3.10^{-8}
OVCAR-5	8.10^{-9}	4.10^{-8}
PC-3	1.10^{-8}	3.10^{-8}
DU 145	1.10^{-9}	7.10^{-9}
NCI-H69	3.10^{-10}	1.10^{-9}

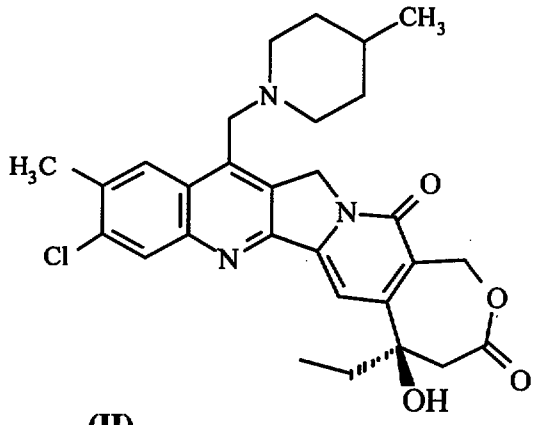
* C L M S *

CLAIMS

1. Product characterized in that its formula is one of formulae **(I)** or **(II)** represented below

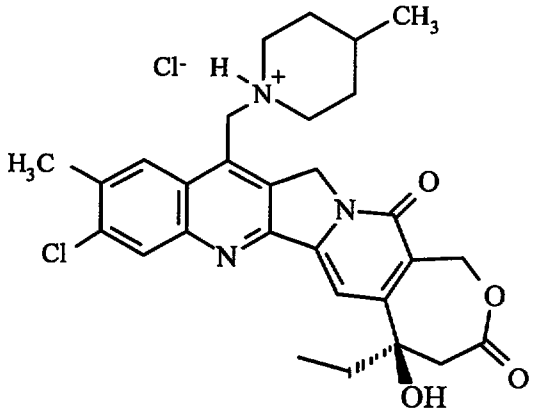


(I)



(II)

or in that it is the salts of the compound of formula **(II)** such as for example that of formula **(III)** represented below

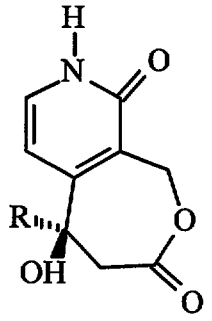


(III)

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* C L M S *

2. As a new industrial product, a product of general formula **M** represented below

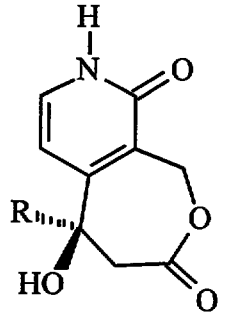


M

in which R represents a linear or branched alkyl radical containing from 1 to 10 carbon atoms.

3. Product according to claim 2, characterized in that R represents an ethyl radical.

4. Preparation process for a product of general formula **M** represented below,

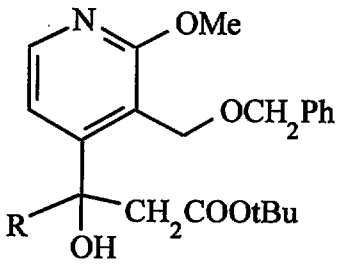


M

in which R represents a linear or branched alkyl radical containing from 1 to 10 carbon atoms,

characterized in that it is constituted by the following successive stages:

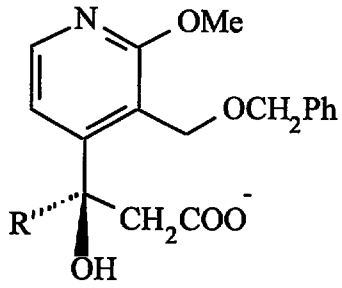
- the racemic *t*-butyl ester represented below



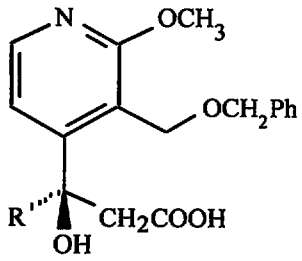
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is treated with trifluoroacetic acid for 18 hours at ambient temperature in order to produce the corresponding carboxylic acid;

- then the quinidine salt of the acid obtained previously is heated in isopropyl alcohol at a temperature greater than 30°C, and preferably at about 50°C, before leaving the reaction medium to cool down to ambient temperature, so that the salt of one of the enantiomers of the above-mentioned acid crystallizes while the salt of the other enantiomer, the anion of which is represented below, remains in solution

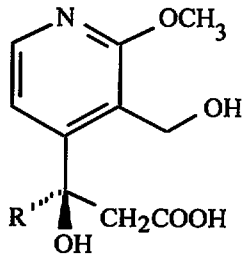


- the solution in isopropyl alcohol of the salt of the enantiomer which has not crystallized is concentrated and treated with hydrochloric acid and agitated, producing the compound of general formula **A** represented below



A

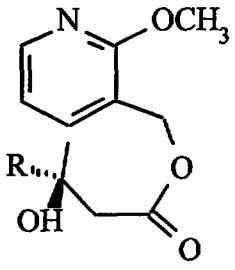
- the compound of general formula **A** is then put in contact with palladium on damp carbon, then ammonium formate or formic acid is added to the mixture in order to produce the debenzylated product of general formula **B** represented below



B

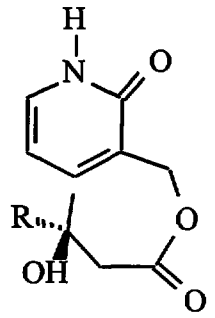
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- then the compound of general formula **B** is cyclized by the action of dicyclohexylcarbodiimide in order to obtain the lactonic compound of general formula **C** represented below



C

-finally, the -OCH_3 group of the lactonic compound of general formula **C** is converted into carbonyl, by the action of sodium iodide and trimethylsilyl chloride, in order to obtain a compound of general formula **M** represented below.

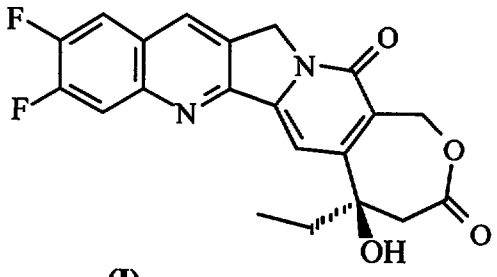


M

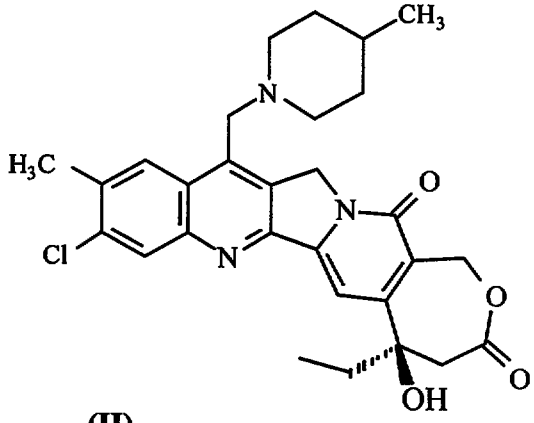
5. Process according to claim 4, characterized in that R represents the ethyl group.

6. As a medicament, a product characterized in that its formula is one of the formulae **(I)** or **(II)** represented below

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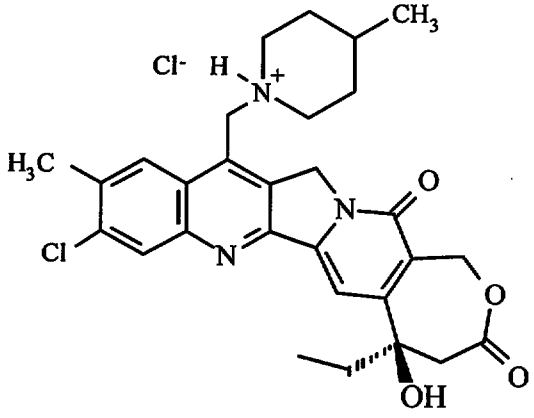


(I)



(II)

or in that it is an addition salt with pharmaceutically acceptable mineral or organic acids of the product of formula **(II)** such as for example that of formula **(III)** represented below



(III)

or also any mixture of the last-named.

7. Pharmaceutical composition containing, as active ingredient, at least one of the compounds of claim 6.

8. Use of a compound according to claim 1 for the preparation of antitumoral medicaments.

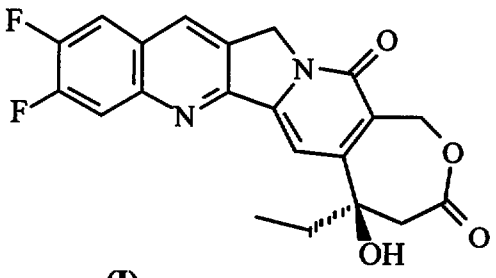
9. Use of a compound according to claim 1 for the preparation of antiviral medicaments.

10. Use of a compound according to claim 1 for the preparation of antiparasitic medicaments.

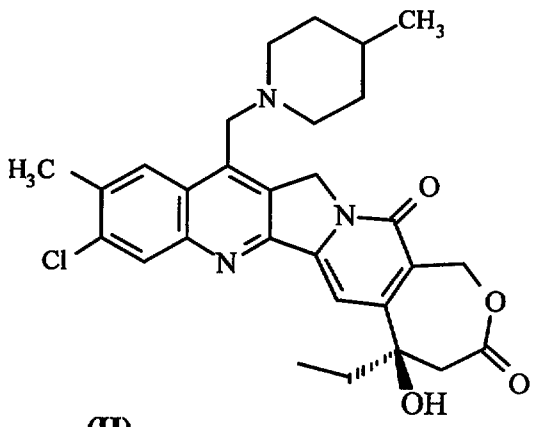
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CLAIMS

1. Product characterized in that its formula is one of formulae **(I)** or **(II)** represented below

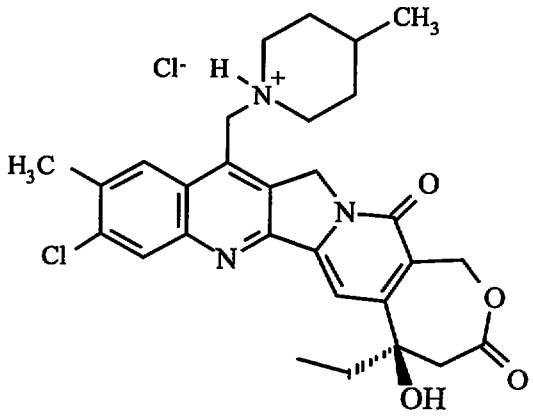


(I)



(II)

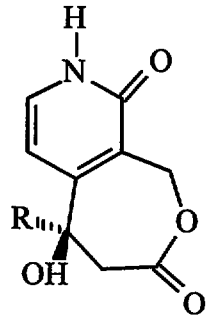
or in that it is the salts of the compound of formula **(II)** such as for example that of formula **(III)** represented below



(III)

* C L M S *

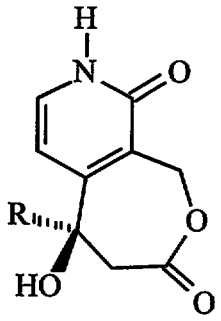
2. As a new industrial product, a product of general formula **M** represented below



M

in which R represents an ethyl radical.

3. Preparation process for a product of general formula **M** represented below,

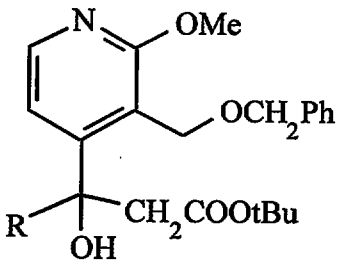


M

in which R represents an ethyl radical,

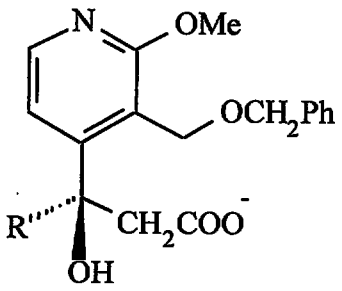
characterized in that it is constituted by the following successive stages:

- the racemic *t*-butyl ester represented below

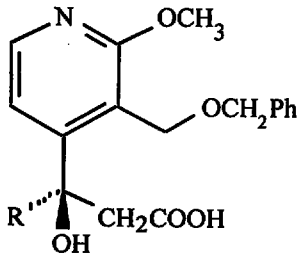


is treated with trifluoroacetic acid for 18 hours at ambient temperature in order to produce the corresponding carboxylic acid;

- then the quinidine salt of the acid obtained previously is heated in isopropyl alcohol at a temperature greater than 30°C, and preferably at about 50°C, before leaving the reaction medium to cool down to ambient temperature, so that the salt of one of the enantiomers of the above-mentioned acid crystallizes while the salt of the other enantiomer, the anion of which is represented below, remains in solution

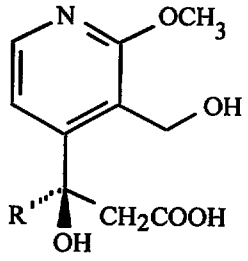


- the solution in isopropyl alcohol of the salt of the enantiomer which has not crystallized is concentrated and treated with hydrochloric acid and agitated, producing the compound of general formula **A** represented below



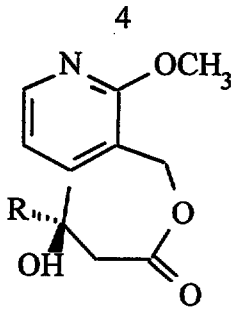
A

- the compound of general formula **A** is then put in contact with palladium on damp carbon, then ammonium formate or formic acid is added to the mixture in order to produce the debenzylated product of general formula **B** represented below



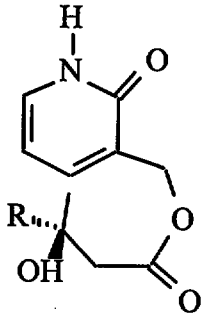
B

- then the compound of general formula **B** is cyclized by the action of dicyclohexylcarbodiimide in order to obtain the lactonic compound of general formula **C** represented below



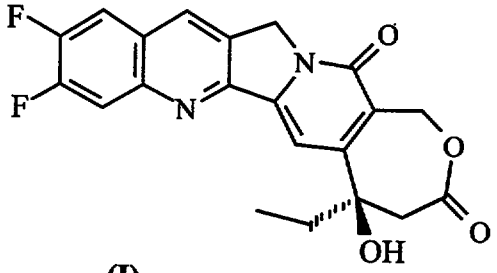
C

-finally, the -OCH_3 group of the lactonic compound of general formula **C** is converted into carbonyl, by the action of sodium iodide and trimethylsilyl chloride, in order to obtain a compound of general formula **M** represented below.

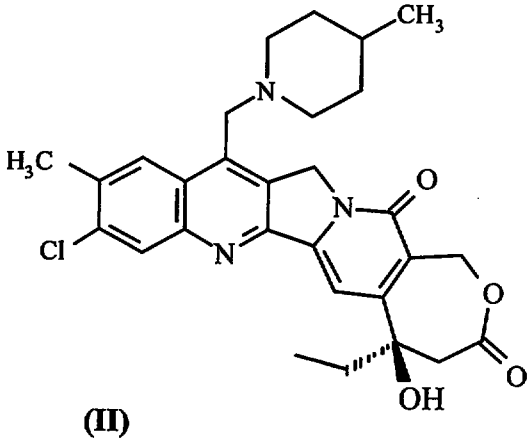


M

4. As a medicament, a product characterized in that its formula is one of the formulae **(I)** or **(II)** represented below

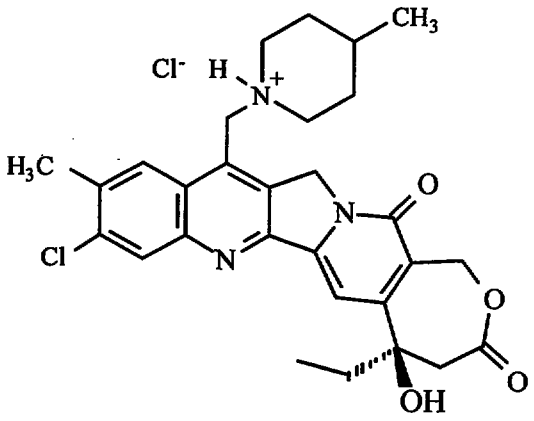


(I)



(II)

or in that it is an addition salt with pharmaceutically acceptable mineral or organic acids of the product of formula **(II)** such as for example that of formula **(III)** represented below



(III)

or also any mixture of the last-named.

5. Pharmaceutical composition containing, as active ingredient, at least one of the compounds of claim 4.

6. Use of a compound according to claim 1 for the preparation of antitumoral medicaments.

7. Use of a compound according to claim 1 for the preparation of antiviral medicaments.

8. Use of a compound according to claim 1 for the preparation of antiparasitic medicaments.