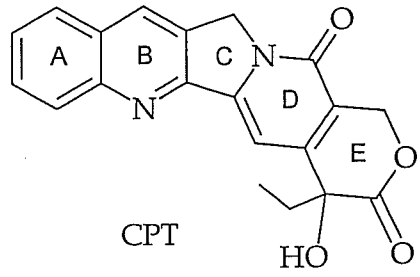
NEW CAMPTOTHECIN ANALOGUE COMPOUNDS, A PROCESS FOR THEIR PREPARATION AND PHARMACEUTICAL COMPOSITIONS CONTAINING THEM

The present invention relates to new camptothecin analogue compounds having a ketonic E ring with an aminoalkylcarbonyloxy substituent or derivative of said substituent, to a process for their preparation and to pharmaceutical compositions containing them.

Camptothecin (CPT), an alkaloid isolated from *Camptotheca accuminata*, is an anti-cancer agent having a broad spectrum of activity. Its insoluble nature has for a long time directed research towards the soluble salts of the compound, which have proved to be inactive and toxic.



CPT

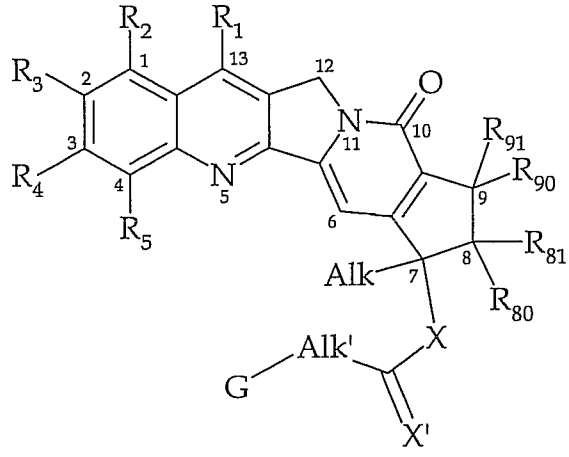
Another problem comes from the lack of stability of the E ring. In fact, in physiological media, the lactone function of the E ring is in equilibrium with the open hydroxy-acid form. The latter is inactive and seems to have a particular intrinsic toxicity [*Cancer Research.*, 49, 1465 (1989); ibid, 49, 5077 (1989)]. Attempts at modifying this ring in order to make it more stable have been carried out; in particular, the cyclic oxygen atom has been replaced by a nitrogen or sulphur atom, but in each case there is loss of pharmacological activity, so confirming the importance of the lactone [*Journal of Medicinal Chemistry*, 32, 715 (1989)]. Other structural modifications of the E ring of CPT have been subsequently described, in particular in the patent specification EP 1 101 765. Those newer compounds are characterised by replacement of the lactone by a cyclic ketone function.

The present invention relates to camptothecin analogues having a ketone function on a five-membered E ring and having on that same ring an aminoalkylcarbonyloxy group or a derivative thereof, which substitutes the hydroxyl function alpha to the ketone.

This modification provides the compounds of the invention with enhanced pharmacological activity, especially in respect of their cytotoxicity.

It will accordingly be possible to use them in the manufacture of medicaments for use in the treatment of cancer diseases.

The invention relates to compounds of formula (I) :



(I),

wherein :

- Alk represents an alkyl group,

- R_1, R_2, R_3, R_4 and R_5 are independently selected from a hydrogen atom, a halogen atom, an alkyl group, an alkenyl group, an alkynyl group, a polyhaloalkyl group, an optionally substituted cycloalkyl group, an optionally substituted cycloalkylalkyl group, an optionally substituted aryl group, a hydroxy group, a hydroxyalkyl group, an alkoxy group, an alkoxyalkyl group, a nitro group, a cyano group, an acyloxy group, a -C(O)-R group, and the groups $-(CH_2)_p-NR_aR_b$ and $-O-C(O)-N-R_aR_b$, wherein R represents an alkyl group, an alkoxy group or an amino group (optionally substituted on the nitrogen atom by one or two alkyl groups), p is an integer from 0 to 6, and R_a and R_b independently represent a hydrogen atom, an alkyl group, a cycloalkyl group, a cycloalkylalkyl group, an acyl group, an optionally substituted aryl group or an optionally substituted arylalkyl group, or R_a and R_b form together with the nitrogen

atom carrying them a pyrrolyl, piperidyl or piperazinyl group, it being possible for each of those cyclic groups to be optionally substituted,
or two adjacent groups from R_2, R_3, R_4 and R_5 form together with the carbon atoms carrying them a group -T-$(CR_cR_d)_t$-T'-, wherein T and T', which are the same or different, represent an oxygen atom, a sulphur atom or a group N-R_e; R_c and R_d, which are the same or different, represent a hydrogen atom or a halogen atom; t is an integer from 1 to 3 inclusive; and Re represents a hydrogen atom, an alkyl group or a benzyl group,

- R_{80} and R_{90} independently represent a hydrogen atom, a hydroxy group, an alkyl group or an alkoxy group,

- R_{81} and R_{91} independently represent a hydrogen atom, an alkyl group, an alkenyl group or an alkynyl group, or, taken in pairs on adjacent carbon atoms, together form a bond or an oxirane group, or two geminal groups (R_{80} and R_{81}) and/or (R_{90} and R_{91}) together form an oxo group or a group -O-$(CH_2)_{t1}$-O-, t_1 being an integer from 1 to 3 inclusive,

- X and X', which are the same or different, represent an oxygen atom, a sulphur atom, an amino group or an alkylamino group,

- Alk' represents an alkylene, alkenylene or alkynylene chain,

- G represents a group NR_6R_7 wherein:

i) either R_6 and R_7 represent, each independently of the other, a hydrogen atom, an alkyl group, a cycloalkyl group, an optionally substituted aryl group, an optionally substituted arylalkyl group, an optionally substituted cycloalkyl group, an optionally substituted cycloalkylalkyl group, an optionally substituted heteroaryl group or an optionally substituted heteroarylalkyl group,

ii) or R_6 and R_7 form together with the nitrogen atom a 5- to 8-membered monocyclic

heterocycloalkyl group  or a 5- to 11-membered bicyclic heterocyclo-

alkyl group  , wherein:

- Y represents a nitrogen atom, an oxygen atom or a CH_2 group and
- R_8 represents a hydrogen atom, an alkyl group, an optionally substituted cycloalkyl group, an optionally substituted cycloalkylalkyl group, an optionally substituted aryl group, an optionally substituted arylalkyl group, an optionally substituted heterocycloalkyl group, an optionally substituted heterocycloalkylalkyl group, an optionally substituted heteroaryl group or an optionally substituted heteroarylalkyl group,

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

it being understood that:

- the term alkyl denotes a linear or branched chain of from 1 to 6 carbon atoms,
- the term alkenyl denotes a linear or branched chain of from 2 to 6 carbon atoms containing from 1 to 3 double bonds,
- the term alkynyl denotes a linear or branched chain of from 2 to 6 carbon atoms containing from 1 to 3 triple bonds,
- the term alkylene denotes a linear or branched divalent radical containing from 1 to 6 carbon atoms,
- the term alkenylene denotes a linear or branched divalent radical containing from 2 to 6 carbon atoms and from 1 to 3 double bonds,
- the term alkynylene denotes a linear or branched divalent radical containing from 2 to 6 carbon atoms and from 1 to 3 triple bonds,
- the term acyl denotes a linear or branched alkyl-carbonyl radical containing from 1 to 6 carbon atoms,

- the term alkoxy denotes an alkyl-oxy radical, the alkyl group of which is linear or branched and contains from 1 to 6 carbon atoms,
- the term acyloxy denotes an acyl-oxy radical, the acyl group of which is a linear or branched alkylcarbonyl radical,
- the term aryloxyalkyl denotes an aryl-oxy-alkyl group, the alkyl group of which is linear or branched and contains from 1 to 6 carbon atoms,
- the terms arylalkyl, cycloalkylalkyl, heteroarylalkyl and heterocycloalkylalkyl denote aryl-alkyl, cycloalkyl-alkyl, heteroaryl-alkyl and heterocycloalkyl-alkyl radicals, the alkyl groups of which denote a linear or branched chain of from 1 to 6 carbon atoms,
- the term polyhaloalkyl denotes a linear or branched carbon chain containing from 1 to 3 carbon atoms and from 1 to 7 halogen atoms,
- the term halogen denotes fluorine, chlorine, bromine or iodine atoms,
- the term aryl denotes a phenyl, naphthyl, indanyl, indenyl, dihydronaphthyl or tetrahydronaphthyl group,
- the term cycloalkyl denotes a monocyclic or bicyclic hydrocarbon group containing from 3 to 11 carbon atoms and optionally being unsaturated with 1 or 2 unsaturated bonds,
- the term heteroaryl denotes a monocyclic or bicyclic group wherein at least one of the rings is aromatic, containing from 5 to 11 ring members and containing from 1 to 4 hetero atoms selected from nitrogen, oxygen and sulphur,
- the term heterocycloalkyl denotes a mono- or bi-cyclic group which is saturated or unsaturated with 1 or 2 unsaturated bonds, containing from 4 to 11 ring members and containing from 1 to 4 hetero atoms selected from nitrogen, oxygen and sulphur,
- the expression "optionally substituted" when used in relation to aryl or arylalkyl, cycloalkyl or cycloalkylalkyl, heteroaryl or heteroarylalkyl, and heterocycloalkyl or heterocycloalkylalkyl groups means that the respective aryl, cycloalkyl, heteroaryl and heterocycloalkyl groups may be substituted by from 1 to 3 identical or different substituents selected from a halogen atom and the groups alkyl, alkoxy, alkylthio, alkylsulphinyl, alkylsulphonyl, hydroxy, mercapto, cyano, nitro, amino (optionally substituted by one or two alkyl groups), acyl, formyl, aminocarbonyl (optionally substituted on the nitrogen atom by one or two alkyl groups), acylamino (optionally

substituted on the nitrogen atom by an alkyl group), alkoxycarbonyl, carboxy and sulpho,

- the expression "optionally substituted" when used in relation to the groups pyrrolyl, piperidyl or piperazinyl means that the groups concerned may be substituted by from 1 to 3 identical or different groups selected from alkyl, alkoxy, aryl, arylalkyl, aryloxy and aryloxyalkyl.

An advantageous aspect of the invention relates to compounds of formula (I) wherein Alk represents an ethyl group.

Another advantageous aspect of the invention relates to compounds of formula (I) wherein R_{80} and R_{81} together form an oxo group, or wherein R_{90} and R_{91} together form an oxo group, or wherein R_{80} and R_{81} and also R_{90} and R_{91} form two oxo groups. More advantageously, R_{80} and R_{81} together form an oxo group and R_{90} and R_{91} each represent a hydrogen atom.

Preferred compounds of formula (I) are those wherein R_5 represents a hydrogen atom.

Other preferred compounds of formula (I) are those wherein R_2, R_3 and R_4 are selected from a hydrogen atom, a halogen atom, an alkyl group and an alkoxy group.

Other preferred compounds of formula (I) are those wherein R_3 and R_4 together form a methylenedioxy or ethylenedioxy (preferably methylenedioxy) group.

Advantageous compounds of formula (I) are those wherein R_2 represents a hydrogen atom.

An especially advantageous aspect of the invention relates to compounds of formula (I) wherein R_1 represents an alkyl, cycloalkyl or cycloalkylalkyl (preferably cycloalkyl) group.

Another advantageous aspect of the invention relates to compounds of formula (I) wherein R_1 represents an optionally substituted aryl (preferably phenyl) group.

Another likewise advantageous aspect of the invention relates to compounds of formula (I) wherein G represents an NR_6R_7 group wherein R_6 and R_7 form together with the nitrogen atom a 5- to 8-membered (more advantageously 6-membered), monocyclic (advantageously saturated) heterocycloalkyl group:



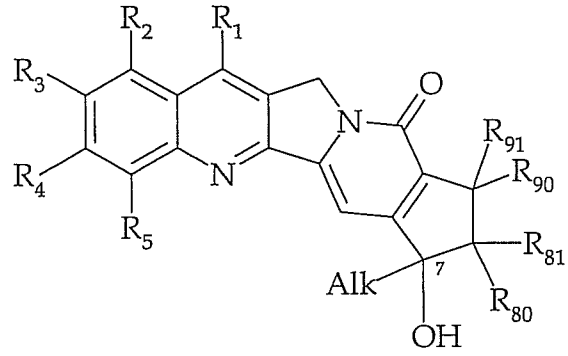
, wherein Y represents a nitrogen atom, an oxygen atom or a CH_2 group (more advantageously CH_2) and R_8 represents a hydrogen atom or an alkyl group (more advantageously hydrogen).

Other preferred compounds are those belonging to the general formula (I) wherein Alk' represents an alkylene group (more advantageously $-CH_2-CH_2-$).

Other preferred compounds of the invention are those wherein X and X', which are the same or different, represent an oxygen atom or a sulphur atom (more advantageously oxygen).

Especially interesting compounds of the invention are 7-ethyl-2,3-methylenedioxy-13-methyl-8,10-dioxo-8,9,10,12-tetrahydro-7*H*-cyclopenta-[6,7]indolizino[1,2-*b*]quinolin-7-yl 3-piperidinopropanoate; 7-ethyl-2,3-methylenedioxy-13-cyclobutyl-8,10-dioxo-8,9,10,12-tetrahydro-7*H*-cyclopenta[6,7]indolizino[1,2-*b*]quinolin-7-yl 3-piperidinopropanoate; and 7-ethyl-2,3-methylenedioxy-13-cyclobutyl-8,10-dioxo-8,9,10,12-tetrahydro-7*H*-cyclopenta[6,7]indolizino[1,2-*b*]quinolin-7-yl 3-hexahydrocyclopenta[*c*]pyrrol-2(1*H*)-yl-propanoate.

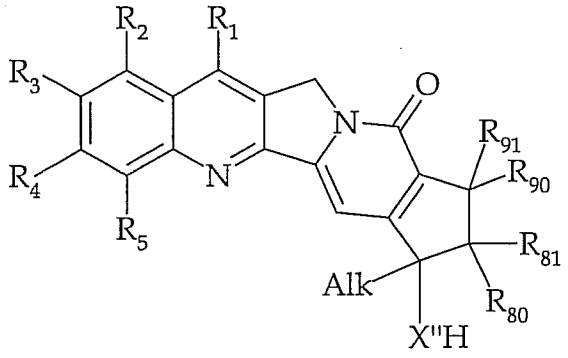
The present invention relates also to a process for the preparation of compounds of formula (I), which process is characterised in that there is used as starting material a compound of formula (II) synthesised as described in EP 1 101 765:



(II),

wherein Alk, R_1, R_2, R_3, R_4, R_5, R_{80}, R_{81}, R_{90} and R_{91} are as defined for formula (I),

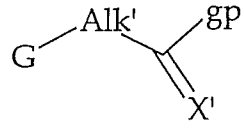
wherein the hydroxy group at C_7 is converted into X"H wherein X" represents an SH, amino or alkylamino group to yield the compound of formula (III)



(III),

wherein Alk, R_1, R_2, R_3, R_4, R_5, R_{80}, R_{81}, R_{90} and R_{91} are as defined for formula (I) and X" is as defined hereinbefore,

which compounds of formula (II) or (III) are condensed with the reagent (IV) :



(IV),

wherein G, Alk' and X' are as defined for formula (I) and gp is a leaving group such as Hal, OH, SH, NR'R" or OC(O)R' wherein R' and R" represent alkyl groups,

to yield the compound of formula (I),

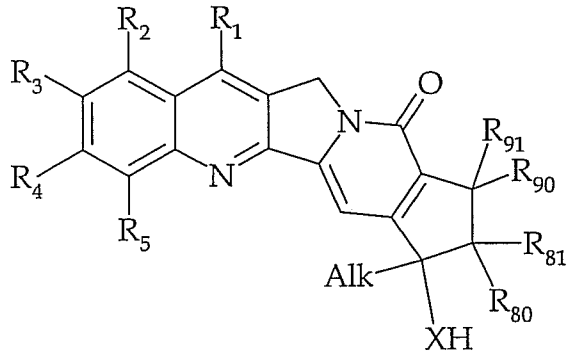
it being understood, for the purpose of simplifying the above process, that the reactive groups present in R_{80}, R_{81}, R_{90} and R_{91} may be protected by conventional protecting groups

and deprotected at the appropriate point in time, that the hydroxy groups present in those same positions may be oxidised to oxo groups by conventional chemistry methods, and, conversely, the oxo groups present in those same positions may be reduced by conventional reducing agents at any appropriate point in time during synthesis, and that, when two of those groups together form a bond, the latter can be introduced at any point in time deemed useful by the person skilled in the art in order to facilitate synthesis,

which compounds of formula (I) :

- may be purified, if necessary, according to a conventional purification technique,
- are separated, where appropriate, into their stereoisomers according to a conventional separation technique,
- are converted, if desired, into addition salts thereof with a pharmaceutically acceptable acid or base.

The present invention relates also to the synthesis intermediates (III'):



(III'),

wherein:

- Alk represents an alkyl group,
- R_1, R_2, R_3, R_4 and R_5 are independently selected from a hydrogen atom, a halogen atom, an alkyl group, an alkenyl group, an alkynyl group, a polyhaloalkyl group, an optionally substituted cycloalkyl group, an optionally substituted cycloalkylalkyl group, a hydroxy group, a hydroxyalkyl group, an alkoxy group, an alkoxyalkyl group, a nitro group, a cyano group, an acyloxy group, a -C(O)-R group, and the groups $-(CH_2)_p-NR_aR_b$ and $-O-C(O)-N-R_aR_b$, wherein R represents an alkyl group, an

alkoxy group or an amino group (optionally substituted on the nitrogen atom by one or two alkyl groups), p is an integer from 0 to 6, and R_a and R_b independently represent a hydrogen atom, an alkyl group, a cycloalkyl group, a cycloalkylalkyl group, an acyl group, an optionally substituted aryl group or an optionally substituted arylalkyl group, or R_a and R_b form together with the nitrogen atom carrying them a pyrrolyl, piperidyl or piperazinyl group, it being possible for each of those cyclic groups to be optionally substituted, and at least two adjacent groups from R_2, R_3, R_4 and R_5 form together with the carbon atoms carrying them a group $-T-(CR_cR_d)_t-T'-$, wherein T and T', which are the same or different, represent an oxygen atom, a sulphur atom or a group $N-R_e$; R_c and R_d, which are the same or different, represent a hydrogen atom or a halogen atom; t is an integer from 1 to 3 inclusive; and Re represents a hydrogen atom, an alkyl group or a benzyl group, it being understood that at least one of the two groups R_c or R_d represents a halogen atom when T and T' each represent an oxygen atom and X represents an oxygen atom,

- R_{80} and R_{90} independently represent a hydrogen atom, a hydroxy group, an alkyl group or an alkoxy group,

- R_{81} and R_{91} independently represent a hydrogen atom, an alkyl group, an alkenyl group or an alkynyl group, or, taken in pairs on adjacent carbon atoms, together form a bond or an oxirane group, or two geminal groups (R_{80} and R_{81}) and/or (R_{90} and R_{91}) together form an oxo group or a group $-O-(CH_2)_{t1}-O-$, t_1 being an integer from 1 to 3 inclusive,

- X represents an oxygen atom, a sulphur atom, an amino group or an alkylamino group,

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

Among the pharmaceutical compositions according to the invention, there may be mentioned more especially those that are suitable for oral, parenteral or nasal

administration, tablets or dragées, sublingual tablets, capsules, lozenges, suppositories, creams, ointments, dermal gels etc..

The useful dosage varies according to the age and weight of the patient, the nature and severity of the disorder and the route of administration, which may be oral, nasal, rectal or parenteral (especially intravenous). The unit dose generally ranges from 0.1 to 500 mg per 24 hours for treatment in from 1 to 3 administrations.

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

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

The starting compounds of formulae (II) and (III') wherein X represents an oxygen atom were synthesised under test conditions described in the patent specification EP 1 101 765 and adapted to the compounds of the invention using prior art documents known to the skilled person. By way of example, Preparations 1 to 6 serve to illustrate, without implying limitation in any way, the manner in which the synthesis described in the patent specification EP 1 101 765 is adapted to the compounds of the invention.

PREPARATION 1 : 7-Ethyl-7-hydroxy-2,3-methylenedioxy-13-methyl-9,12-dihydro-7*H*-cyclopenta[6,7]indolizino[1,2-*b*]quinoline-8,10-dione

The title compound is prepared according to the method described in Example 11 of the patent specification EP 1 101 765, replacing the 2-bromo-3-bromomethyl-6,7-methylenedioxyquinoline by 2-bromo-3-bromomethyl-4-methyl-6,7-methylenedioxyquinoline.

PREPARATION 2 : 7-Ethyl-7-hydroxy-2,3-methylenedioxy-13-cyclobutyl-9,12-dihydro-7*H*-cyclopenta[6,7]indolizino[1,2-*b*]quinoline-8,10-dione

The title compound is prepared according to the method described in Example 11 of the patent specification EP 1 101 765, replacing the 2-bromo-3-bromomethyl-6,7-methylenedioxyquinoleine by 2-bromo-3-bromomethyl-4-cyclobutyl-6,7-methylenedioxyquinoline.

PREPARATION 3 : 7-Ethyl-2,3-difluoromethylenedioxy-7-hydroxy-13-[3-piperidinopropyl]-9,12-dihydro-7*H*-cyclopenta[6,7]-indolizino[1,2-*b*]quinoline-8,10-dione

The title compound is prepared according to the method described in Example 11 of the patent specification EP 1 101 765, replacing the 2-bromo-3-bromomethyl-6,7-methylenedioxyquinoline by 2-bromo-3-bromomethyl-4-piperidinopropyl-6,7-difluoromethylenedioxyquinoline.

Elemental microanalysis:

	C %	H %	N %
Calculated:	64.80	5.44	7.82
Found:	64.29	4.48	7.70

PREPARATION 4 : 7-Ethyl-7-hydroxy-2,3-difluoromethylenedioxy-13-cyclobutyl-9,12-dihydro-7*H*-cyclopenta[6,7]indolizino[1,2-*b*]quinoline-8,10-dione

The title compound is prepared according to the method described in Example 11 of the patent specification EP 1 101 765, replacing the 2-bromo-3-bromomethyl-6,7-methylenedioxyquinoline by 2-bromo-3-bromomethyl-4-cyclobutyl-6,7-difluoromethylenedioxyquinoline.

Elemental microanalysis:

	C %	H %	N %
Calculated:	64.38	4.32	6.01
Found:	63.15	4.46	5.76

PREPARATION 5 : 7-Ethyl-7-hydroxy-2,3-difluoromethylenedioxy-13-isopropyl-9,12-dihydro-7*H*-cyclopenta[6,7]indolizino[1,2-*b*]quinoline-8,10-dione

The title compound is prepared according to the method described in Example 11 of the patent specification EP 1 101 765, replacing the 2-bromo-3-bromomethyl-6,7-methylene-

dioxyquinoline by 2-bromo-3-bromomethyl-4-isopropyl-6,7-difluoromethylenedioxy-quinoline.

Elemental microanalysis:

	C %	H %	N %
Calculated:	64.43	4.44	6.16
Found:	63.50	4.70	6.29

PREPARATION 6 : 7-Ethyl-7-hydroxy-2,3-difluoromethylenedioxy-9,12-dihydro-7*H*-cyclopenta[6,7]indolizino[1,2-*b*]quinoline-8,10-dione

The title compound is prepared according to the method described in Example 11 of the patent specification EP 1 101 765, replacing the 2-bromo-3-bromomethyl-6,7-methylene-dioxyquinoline by 2-bromo-3-bromomethyl-6,7-difluoromethylenedioxyquinoline.

Elemental microanalysis:

	C %	H %	N %
Calculated:	61.17	3.42	6.79
Found:	59.78	3.30	6.58

EXAMPLE 1 : 7-Ethyl-2,3-methylenedioxy-13-methyl-8,10-dioxo-8,9,10,12-tetrahydro-7*H*-cyclopenta[6,7]indolizino[1,2-*b*]quinolin-7-yl 3-piperidinopropanoate hydrochloride

To a suspension of 0.8 g (2 mmol) of the compound of Preparation 1 in 150 ml of dichloromethane there are added, in succession, 1.13 g (7.2 mmol) of 3-piperidin-1-ylpropanoic acid, 2.28 g (12.7 mmol) of 1-(3-dimethylaminopropyl)-3-ethylcarbodiimide hydrochloride and 0.34 g (2.78 mmol) of 4-dimethylaminopyridine. The reaction mixture is stirred for 24 hours at ambient temperature and then filtered. The filtrate is washed with sodium bicarbonate solution and then with water and is dried over magnesium sulphate. After concentrating the solvent *in vacuo*, the residue is dissolved in a solution of dichloromethane containing 30 % ethanol. 0.57 ml of 1N hydrochloric acid is added and the precipitate formed is filtered off and recrystallised from acetonitrile to yield the expected compound.

EXAMPLE 2 : 7-Ethyl-2,3-methylenedioxy-13-cyclobutyl-8,10-dioxo-8,9,10,12-tetrahydro-7*H*-cyclopenta[6,7]indolizino[1,2-*b*]quinolin-7-yl 3-piperidinopropanoate hydrochloride

The title compound was synthesised as described in Example 1, replacing the starting material: the compound of Preparation 1 being replaced by that of Preparation 2.

Mass spectrum : (MH^+) m/z = 570.3

EXAMPLE 3 : 2,3-Difluoromethylenedioxy-7-ethyl-8,10-dioxo-13-[3-(1-piperidyl)-propyl]-8,9,10,12-tetrahydro-7*H*-cyclopenta[6,7]indolizino[1,2-*b*]-quinolin-7-yl 3-piperidinopropanoate

The title compound was synthesised as described in Example 1, replacing the starting material: the compound of Preparation 1 being replaced by that of Preparation 3.

EXAMPLE 4 : 2,3-Difluoromethylenedioxy-7-ethyl-8,10-dioxo-13-cyclobutyl-8,9,10,12-tetrahydro-7*H*-cyclopenta[6,7]indolizino[1,2-*b*]quinolin-7-yl 3-piperidinopropanoate

The title compound was synthesised as described in Example 1, replacing the starting material: the compound of Preparation 1 being replaced by that of Preparation 4.

EXAMPLE 5 : 2,3-Difluoromethylenedioxy-7-ethyl-8,10-dioxo-13-isopropyl-8,9,10,12-tetrahydro-7*H*-cyclopenta[6,7]indolizino[1,2-*b*]quinolin-7-yl 3-piperidinopropanoate

The title compound was synthesised as described in Example 1, replacing the starting material: the compound of Preparation 1 being replaced by that of Preparation 5.

EXAMPLE 6 : **2,3-Difluoromethylenedioxy-7-ethyl-8,10-dioxo-8,9,10,12-tetrahydro-7*H*-cyclopenta[6,7]indolizino[1,2-*b*]quinolin-7-yl 3-piperidino-butanoate**

The title compound was synthesised as described in Example 1, replacing the 3-piperidinopropanoic acid by 4-piperidinobutanoic acid and replacing the starting material: the compound of Preparation 1 being replaced by that of Preparation 6.

The compounds of Examples 7 to 21 (see hereinbelow) were obtained by adapting experimental procedures 1 to 6, using suitable substrates.

EXAMPLE 7 : **7-Ethyl-2,3-difluoro-13-isopropyl-8,10-dioxo-8,9,10,12-tetrahydro-7*H*-cyclopenta[6,7]indolizino[1,2-*b*]quinolin-7-yl 3-piperidino-propanoate**

EXAMPLE 8 : **7-Ethyl-2,3-difluoro-8-[2-(1,3-dioxolan)yl]-13-isopropyl-10-oxo-8,9,10,12-tetrahydro-7*H*-cyclopenta[6,7]indolizino[1,2-*b*]quinolin-7-yl 3-piperidinopropanoate**

EXAMPLE 9 : **13-{3-[Benzyl(methyl)amino]propyl}-7-ethyl-2,3-difluoro-8,10-dioxo-8,9,10,12-tetrahydro-7*H*-cyclopenta[6,7]indolizino[1,2-*b*]-quinolin-7-yl 3-morpholinopropanoate**

EXAMPLE 10 : **2,3-(Difluoromethylenedioxy)-7-ethyl-8,10-dioxo-13-cyclobutyl-8,9,10,12-tetrahydro-7*H*-cyclopenta[6,7]indolizino[1,2-*b*]quinolin-7-yl 3-dimethylaminopropanoate**

EXAMPLE 11 : **2,3-Ethylenedioxy-7-ethyl-8,10-dioxo-13-methoxyethyl-8,9,10,12-tetrahydro-7*H*-cyclopenta[6,7]indolizino[1,2-*b*]quinolin-7-yl 3-piperidinobutanoate**

EXAMPLE 12 : 2,3-Ethylenedioxy-7-ethyl-8,10-dioxo-13-dimethylaminomethyl-8,9,10,12-tetrahydro-7*H*-cyclopenta[6,7]indolizino[1,2-*b*]quinolin-7-yl 3-piperidinopropanoate

EXAMPLE 13 : 2,3-Methylenedioxy-7-ethyl-8,10-dioxo-13-methyl-8,9,10,12-tetrahydro-7*H*-cyclopenta[6,7]indolizino[1,2-*b*]quinolin-7-yl 3-piperidinopropanoate

EXAMPLE 14 : 3-Chloro-7-ethyl-2-fluoro-8,9,10-trioxo-8,9,10,12-tetrahydro-7*H*-cyclopenta[6,7]indolizino[1,2-*b*]quinolin-7-yl 3-(4-methyl-piperazino)propanoate

EXAMPLE 15 : 3-Chloro-7-ethyl-2-fluoro-8,9,10-trioxo-8,9,10,12-tetrahydro-7*H*-cyclopenta[6,7]indolizino[1,2-*b*]quinolin-7-yl 3-(4-methyl-piperazino)propanoate

EXAMPLE 16 : 2,3-Methylenedioxy-7-ethyl-8,10-dioxo-13-cyclohexyl-8,9,10,12-tetrahydro-7*H*-cyclopenta[6,7]indolizino[1,2-*b*]quinolin-7-yl 3-piperidinopropanoate

EXAMPLE 17 : 13-Cyclobutyl-7-ethyl-2-fluoro-8,10-dioxo-3-(1-piperidyl)-8,9,10,12-tetrahydro-7*H*-cyclopenta[6,7]indolizino[1,2-*b*]quinolin-7-yl 3-(4-methylpiperazino)propanoate

EXAMPLE 18 : 13-(4-Methylpiperazinomethyl)-7-ethyl-2,3-ethylenedioxy-8,10-dioxo-8,9,10,12-tetrahydro-7*H*-cyclopenta[6,7]indolizino[1,2-*b*]-quinolin-7-yl 3-(4-methylpiperazino)propanoate

EXAMPLE 19 : 3-Chloro-7-ethyl-2-methyl-8,9,10-trioxo-8,9,10,12-tetrahydro-7*H*-cyclopenta[6,7]indolizino[1,2-*b*]quinolin-7-yl 3-piperidino-propanoate

EXAMPLE 20 : 7-Ethyl-2-hydroxy-8,10-dioxo-8,9,10,12-tetrahydro-7*H*-cyclopenta-[6,7]indolizino[1,2-*b*]quinolin-7-yl 3-piperidinopropanoate

EXAMPLE 21 : 7-Ethyl-2,3-methylenedioxy-13-(2-methyl-1-propenyl)-8,10-dioxo-8,9,10,12-tetrahydro-7*H*-cyclopenta[6,7]indolizino[1,2-*b*]quinolin-7-yl 3-piperidinopropanoate

EXAMPLE 22 : 7-Ethyl-2,3-methylenedioxy-13-cyclobutyl-8,10-dioxo-8,9,10,12-tetrahydro-7*H*-cyclopenta[6,7]indolizino[1,2-*b*]quinolin-7-yl 3-hexahydrocyclopenta[*c*]pyrrol-2(1*H*)-ylpropanoate hydrochloride

The title compound was synthesised as described in Example 1, replacing the 3-piperidinopropanoic acid by 3-hexahydrocyclopenta[*c*]pyrrol-2(1*H*)-ylpropanoic acid and replacing the starting material: the compound of Preparation 1 being replaced by that of Preparation 2.

EXAMPLE 23 : 7-Ethyl-2,3-methylenedioxy-13-cyclobutyl-8,10-dioxo-8,9,10,12-tetrahydro-7*H*-cyclopenta[6,7]indolizino[1,2-*b*]quinolin-7-yl 3-[(4aR,8aS)-octahydroisoquinolin-2(1*H*)-yl]propanoate hydrochloride

The title compound was synthesised as described in Example 1, replacing the 3-piperidin-1-ylpropanoic acid by 3-[(4aR,8aS)-octahydroisoquinolin-2(1*H*)-yl]propanoic acid and replacing the starting material: the compound of Preparation 1 being replaced by that of Preparation 2.

EXAMPLE 24 : 7-Ethyl-2,3-methylenedioxy-13-cyclobutyl-8,10-dioxo-8,9,10,12-tetrahydro-7*H*-cyclopenta[6,7]indolizino[1,2-*b*]quinolin-7-yl 3-[(6,7-dimethoxy-3,4-dihydroisoquinolin-2(1H)-yl]propanoate hydrochloride

The title compound was synthesised as described in Example 1, replacing the 3-piperidin-1-ylpropanoic acid by 3-(6,7-dimethoxy-3,4-dihydroisoquinolin-2(1*H*)-yl)propanoic acid

and replacing the starting material: the compound of Preparation 1 being replaced by that of Preparation 2.

PHARMACOLOGICAL STUDY

EXAMPLE A : ***In vitro* activity**

The murine leukaemia L1210 and the human colon carcinomas HCT116 and HT29 were used *in vitro*. The cells are cultured in RPMI 1640 complete culture medium containing 10 % foetal calf serum, 2mM glutamine, 50 units/ml of penicillin, 50 µg/ml of streptomycin and 10mM Hepes, pH = 7.4. The cells are distributed on microplates and are exposed to the cytotoxic compounds for 4 doubling times, that is to say 48 hours (L1210) or 96 hours (HCT116 and HT29). The number of viable cells is then quantified by a colorimetric assay, the Microculture Tetrazolium Assay (J. Carmichael *et al.*, Cancer Res. ; 47, 936-942, (1987)). The results are expressed in terms of the IC_{50} (the concentration of cytotoxic agent which inhibits proliferation of the treated cells by 50 %).

The compounds of the invention appear to be powerful cytotoxic agents, the IC_{50} values being substantially below 1µM.

***In vitro* activity**			
	IC_{50} (nM)		
	L1210	**HCT116**	**HT29**
Example 1	4.2	-	-
Example 2	-	1.5	3.7
Example 23	7.3	1.1	2.4
Example 24	7.9	0.7	2.6

EXAMPLE B : ***In vivo* toxicity**

The compounds are formulated in a Tween/water mixture and administered by the intravenous (i.v.) route (administration over three weeks at the rate of once per week, the

injection volume being 0.2 ml/mouse with increasing doses of compounds of 6.25, 12.5, 25 and 50 mg/kg) to nude mice (bab/c supplied by Iffa Credo) weighing about 20 g. The maximum tolerated dose (MTD) is the largest dose causing neither death nor a weight loss of more than 20 %.

By way of example, the compound of Example 2 has an MTD of 25 mg/kg (intravenous administration once per week for 3 weeks) or two times less toxic than its "non-esterified" close structural homologue (the compound of Preparation 2) for the same *in vivo* activity with respect to HCT116.

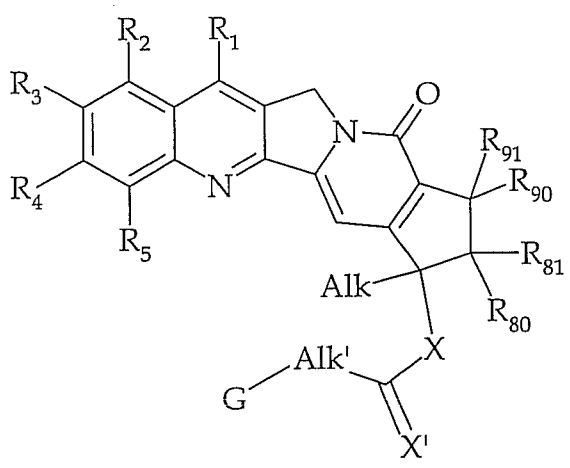
EXAMPLE C : Pharmaceutical composition

Preparation formula for 1000 tablets each containing 10 mg of active ingredient:

Compound of Example 2	10 g
Hydroxypropylcellulose	2 g
Wheat starch	10 g
Lactose	100 g
Magnesium stearate	3 g
Talc	3 g

CLAIMS

1. Compounds of formula (I) :



(I),

wherein :

- Alk represents an alkyl group,

- R_1, R_2, R_3, R_4 and R_5 are independently selected from a hydrogen atom, a halogen atom, an alkyl group, an alkenyl group, an alkynyl group, a polyhaloalkyl group, an optionally substituted cycloalkyl group, an optionally substituted cycloalkylalkyl group, an optionally substituted aryl group, a hydroxy group, a hydroxyalkyl group, an alkoxy group, an alkoxyalkyl group, a nitro group, a cyano group, an acyloxy group, a -C(O)-R group, and the groups $-(CH_2)_p-NR_aR_b$ and $-O-C(O)-N-R_aR_b$, wherein R represents an alkyl group, an alkoxy group or an amino group (optionally substituted on the nitrogen atom by one or two alkyl groups), p is an integer from 0 to 6, and R_a and R_b independently represent a hydrogen atom, an alkyl group, a cycloalkyl group, a cycloalkylalkyl group, an acyl group, an optionally substituted aryl group or an optionally substituted arylalkyl group, or R_a and R_b form together with the nitrogen atom carrying them a pyrrolyl, piperidyl or piperazinyl group, it being possible for each of those cyclic groups to be optionally substituted,

or two adjacent groups from R_2, R_3, R_4 and R_5 form together with the carbon atoms carrying them a group -T-$(CR_cR_d)_t$-T'-, wherein T and T', which are the same or different, represent an oxygen atom, a sulphur atom or a group N-R_e; R_c and R_d, which are the same or different, represent a hydrogen atom or a halogen atom; t is an integer from 1 to 3 inclusive; and Re represents a hydrogen atom, an alkyl group or a benzyl group,

- R_{80} and R_{90} independently represent a hydrogen atom, a hydroxy group, an alkyl group or an alkoxy group,

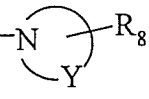
- R_{81} and R_{91} independently represent a hydrogen atom, an alkyl group, an alkenyl group or an alkynyl group, or, taken in pairs on adjacent carbon atoms, together form a bond or an oxirane group, or two geminal groups (R_{80} and R_{81}) and/or (R_{90} and R_{91}) together form an oxo group or a group -O-$(CH_2)_{t1}$-O-, t_1 being an integer from 1 to 3 inclusive,

- X and X', which are the same or different, represent an oxygen atom, a sulphur atom, an amino group or an alkylamino group,

- Alk' represents an alkylene, alkenylene or alkynylene chain,

- G represents a group NR_6R_7 wherein:

i) either R_6 and R_7 represent, each independently of the other, a hydrogen atom, an alkyl group, a cycloalkyl group, an optionally substituted aryl group, an optionally substituted arylalkyl group, an optionally substituted cycloalkyl group, an optionally substituted cycloalkylalkyl group, an optionally substituted heteroaryl group or an optionally substituted heteroarylalkyl group,

ii) or R_6 and R_7 form together with the nitrogen atom a 5- to 8-membered monocyclic heterocycloalkyl group  or a 5- to 11-membered bicyclic heterocyclo-

alkyl group , wherein:

- Y represents a nitrogen atom, an oxygen atom or a CH_2 group and
- R_8 represents a hydrogen atom, an alkyl group, an optionally substituted cycloalkyl group, an optionally substituted cycloalkylalkyl group, an optionally substituted aryl group, an optionally substituted arylalkyl group, an optionally substituted heterocycloalkyl group, an optionally substituted heterocycloalkylalkyl group, an optionally substituted heteroaryl group or an optionally substituted heteroarylalkyl group,

their enantiomers and diastereoisomers, and addition salts thereof with a pharmaceutically acceptable acid or base,

it being understood that:

- the term alkyl denotes a linear or branched chain of from 1 to 6 carbon atoms,
- the term alkenyl denotes a linear or branched chain of from 2 to 6 carbon atoms containing from 1 to 3 double bonds,
- the term alkynyl denotes a linear or branched chain of from 2 to 6 carbon atoms containing from 1 to 3 triple bonds,
- the term alkylene denotes a linear or branched divalent radical containing from 1 to 6 carbon atoms,
- the term alkenylene denotes a linear or branched divalent radical containing from 2 to 6 carbon atoms and from 1 to 3 double bonds,
- the term alkynylene denotes a linear or branched divalent radical containing from 2 to 6 carbon atoms and from 1 to 3 triple bonds,
- the term acyl denotes a linear or branched alkyl-carbonyl radical containing from 1 to 6 carbon atoms,
- the term alkoxy denotes an alkyl-oxy radical, the alkyl group of which is linear or branched and contains from 1 to 6 carbon atoms,

- the term acyloxy denotes an acyl-oxy radical, the acyl group of which is a linear or branched alkylcarbonyl radical,
- the term aryloxyalkyl denotes an aryl-oxy-alkyl group, the alkyl group of which is linear or branched and contains from 1 to 6 carbon atoms,
- the terms arylalkyl, cycloalkylalkyl, heteroarylalkyl and heterocycloalkylalkyl denote aryl-alkyl, cycloalkyl-alkyl, heteroaryl-alkyl and heterocycloalkyl-alkyl radicals, the alkyl groups of which denote a linear or branched chain of from 1 to 6 carbon atoms,
- the term polyhaloalkyl denotes a linear or branched carbon chain containing from 1 to 3 carbon atoms and from 1 to 7 halogen atoms,
- the term halogen denotes fluorine, chlorine, bromine or iodine atoms,
- the term aryl denotes a phenyl, naphthyl, indanyl, indenyl, dihydronaphthyl or tetrahydronaphthyl group,
- the term cycloalkyl denotes a monocyclic or bicyclic hydrocarbon group containing from 3 to 11 carbon atoms and optionally being unsaturated with 1 or 2 unsaturated bonds,
- the term heteroaryl denotes a monocyclic or bicyclic group wherein at least one of the rings is aromatic, containing from 5 to 11 ring members and containing from 1 to 4 hetero atoms selected from nitrogen, oxygen and sulphur,
- the term heterocycloalkyl denotes a mono- or bi-cyclic group which is saturated or unsaturated with 1 or 2 unsaturated bonds, containing from 4 to 11 ring members and containing from 1 to 4 hetero atoms selected from nitrogen, oxygen and sulphur,
- the expression "optionally substituted" when used in relation to aryl or arylalkyl, cycloalkyl or cycloalkylalkyl, heteroaryl or heteroarylalkyl, and heterocycloalkyl or heterocycloalkylalkyl groups means that the respective aryl, cycloalkyl, heteroaryl and heterocycloalkyl groups may be substituted by from 1 to 3 identical or different substituents selected from a halogen atom and the groups alkyl, alkoxy, alkylthio, alkylsulphinyl, alkylsulphonyl, hydroxy, mercapto, cyano, nitro, amino (optionally substituted by one or two alkyl groups), acyl, formyl, aminocarbonyl (optionally substituted on the nitrogen atom by one or two alkyl groups), acylamino (optionally substituted on the nitrogen atom by an alkyl group), alkoxycarbonyl, carboxy and sulpho,

– the expression "optionally substituted" when used in relation to the groups pyrrolyl, piperidyl or piperazinyl means that the groups concerned may be substituted by from 1 to 3 identical or different groups selected from alkyl, alkoxy, aryl, arylalkyl, aryloxy and aryloxyalkyl.

2. Compounds of formula (I) according to claim 1, wherein Alk represents an ethyl group, their enantiomers and diastereoisomers, and addition salts thereof with a pharmaceutically acceptable acid or base.

3. Compounds of formula (I) according to claim 1, wherein R_{80} and R_{81} together form an oxo group, or wherein R_{90} and R_{91} together form an oxo group, or wherein R_{80} and R_{81} and also R_{90} and R_{91} form two oxo groups, their enantiomers and diastereoisomers, and addition salts thereof with a pharmaceutically acceptable acid or base.

4. Compounds of formula (I) according to claim 1, wherein R_5 represents a hydrogen atom, their enantiomers and diastereoisomers, and addition salts thereof with a pharmaceutically acceptable acid or base.

5. Compounds of formula (I) according to claim 1, wherein R_2, R_3 and R_4 are selected from a hydrogen atom, a halogen atom, an alkyl group and an alkoxy group, their enantiomers and diastereoisomers, and addition salts thereof with a pharmaceutically acceptable acid or base.

6. Compounds of formula (I) according to claim 1, wherein R_3 and R_4 together form a methylenedioxy or ethylenedioxy group, their enantiomers and diastereoisomers, and addition salts thereof with a pharmaceutically acceptable acid or base.

7. Compounds of formula (I) according to claim 1, wherein R_2 represents a hydrogen atom, their enantiomers and diastereoisomers, and addition salts thereof with a pharmaceutically acceptable acid or base.

8. Compounds of formula (I) according to claim 1, wherein R_1 represents an alkyl, cycloalkyl or cycloalkylalkyl group, their enantiomers and diastereoisomers, and addition salts thereof with a pharmaceutically acceptable acid or base.

9. Compounds of formula (I) according to claim 1, wherein R_1 represents an optionally substituted aryl group, their enantiomers and diastereoisomers, and addition salts thereof with a pharmaceutically acceptable acid or base.

10. Compounds of formula (I) according to claim 1, wherein G represents a group NR_6R_7 wherein R_6 and R_7 form together with the nitrogen atom a 5- to-8-membered monocyclic heterocycloalkyl group , wherein Y represents a nitrogen atom, an oxygen atom or a group CH_2 and R_8 represents a hydrogen atom or an alkyl group, their enantiomers and diastereoisomers, and addition salts thereof with a pharmaceutically acceptable acid or base.

11. Compounds of formula (I) according to claim 1, wherein Alk' represents an alkylene group, their enantiomers and diastereoisomers, and addition salts thereof with a pharmaceutically acceptable acid or base.

12. Compounds of formula (I) according to claim 1, wherein X and X', which are the same or different, represent an oxygen atom or a sulphur atom, their enantiomers and diastereoisomers, and addition salts thereof with a pharmaceutically acceptable acid or base.

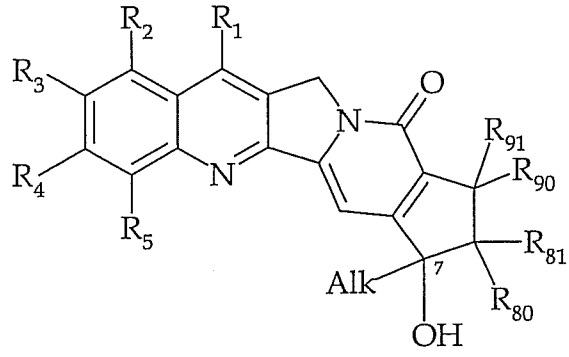
13. Compound of formula (I) according to claim 1, which is 7-ethyl-2,3-methylenedioxy-13-methyl-8,10-dioxo-8,9,10,12-tetrahydro-7*H*-cyclopenta[6,7]-indolizino[1,2-*b*]quinolin-7-yl 3-piperidinopropanoate, its enantiomers and addition salts thereof with a pharmaceutically acceptable acid or base.

14. Compound of formula (I) according to claim 1, which is 7-ethyl-2,3-methylenedioxy-13-cyclobutyl-8,10-dioxo-8,9,10,12-tetrahydro-7*H*-cyclopenta[6,7]-

indolizino[1,2-*b*]quinolin-7-yl 3-piperidinopropanoate, its enantiomers and addition salts thereof with a pharmaceutically acceptable acid or base.

15. Compound of formula (I) according to claim 1, which is 7-ethyl-2,3-methylene-dioxy-13-cyclobutyl-8,10-dioxo-8,9,10,12-tetrahydro-7*H*-cyclopenta[6,7]indolizino-[1,2-*b*]quinolin-7-yl 3-hexahydrocyclopenta[*c*]pyrrol-2(1*H*)-ylpropanoate, its enantiomers and addition salts thereof with a pharmaceutically acceptable acid or base.

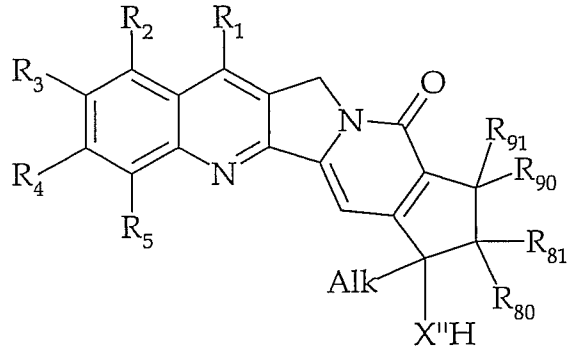
16. Process for the preparation of compounds of formula (I) according to claim 1, characterised in that there is used as starting material a compound of formula (II) synthesised as described in EP 1 101 765 :



(II),

wherein Alk, R_1, R_2, R_3, R_4, R_5, R_{80}, R_{81}, R_{90} and R_{91} are as defined for formula (I),

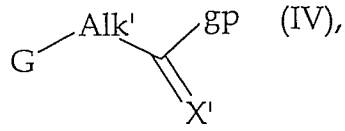
wherein the hydroxy group at C_7 is converted into X"H wherein X" represents an SH, amino or alkylamino group to yield the compound of formula (III)



(III),

wherein Alk, R_1, R_2, R_3, R_4, R_5, R_{80}, R_{81}, R_{90} and R_{91} are as defined for formula (I) and X" is as defined hereinbefore,

which compounds of formula (II) or (III) are condensed with the reagent (IV) :



(IV),

wherein G, Alk' and X' are as defined for formula (I) and gp is a leaving group such as Hal, OH, SH, NR'R" or OC(O)R' wherein R' and R" represent alkyl groups,

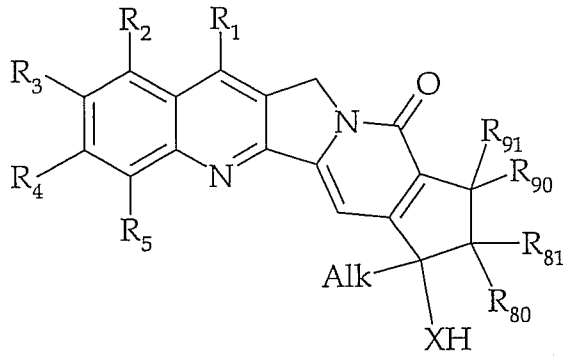
to yield the compound of formula (I),

it being understood, for the purpose of simplifying the above process, that the reactive groups present in R_{80}, R_{81}, R_{90} and R_{91} may be protected by conventional protecting groups and deprotected at the appropriate point in time, that the hydroxy groups present in those same positions may be oxidised to oxo groups by conventional chemistry methods, and, conversely, the oxo groups present in those same positions may be reduced by conventional reducing agents at any appropriate point in time during synthesis, and that, when two of those groups together form a bond, the latter can be introduced at any point in time deemed useful by the person skilled in the art in order to facilitate synthesis,

which compounds of formula (I) :

- may be purified, if necessary, according to a conventional purification technique,
- are separated, where appropriate, into their stereoisomers according to a conventional separation technique,
- are converted, if desired, into addition salts thereof with a pharmaceutically acceptable acid or base.

17. Compounds of formula (III'):



(III'),

wherein:

- Alk represents an alkyl group,
- R_1, R_2, R_3, R_4 and R_5 are independently selected from a hydrogen atom, a halogen atom, an alkyl group, an alkenyl group, an alkynyl group, a polyhaloalkyl group, an optionally substituted cycloalkyl group, an optionally substituted cycloalkylalkyl group, a hydroxy group, a hydroxyalkyl group, an alkoxy group, an alkoxyalkyl group, a nitro group, a cyano group, an acyloxy group, a -C(O)-R group, and the groups $-(CH_2)_p-NR_aR_b$ and $-O-C(O)-N-R_aR_b$, wherein R represents an alkyl group, an alkoxy group or an amino group (optionally substituted on the nitrogen atom by one or two alkyl groups), p is an integer from 0 to 6, and R_a and R_b independently represent a hydrogen atom, an alkyl group, a cycloalkyl group, a cycloalkylalkyl group, an acyl group, an optionally substituted aryl group or an optionally substituted arylalkyl group, or R_a and R_b form together with the nitrogen atom carrying them a pyrrolyl, piperidyl or piperazinyl group, it being possible for each of those cyclic groups to be optionally substituted, and at least two adjacent groups from R_2, R_3, R_4 and R_5 form together with the carbon atoms carrying them a group $-T-(CR_cR_d)_t-T'-$, wherein T and T', which are the same or different, represent an oxygen atom, a sulphur atom or a group $N-R_e$; R_c and R_d, which are the same or different, represent a hydrogen atom or a halogen atom; t is an integer from 1 to 3 inclusive; and R_e represents a hydrogen atom, an alkyl group or a benzyl group, it being understood that at least one of the two groups R_c or R_d represents a halogen atom when T and T' each represent an oxygen atom and X represents an oxygen atom,

- R_{80} and R_{90} independently represent a hydrogen atom, a hydroxy group, an alkyl group or an alkoxy group,

- R_{81} and R_{91} independently represent a hydrogen atom, an alkyl group, an alkenyl group or an alkynyl group, or, taken in pairs on adjacent carbon atoms, together form a bond or an oxirane group, or two geminal groups (R_{80} and R_{81}) and/or (R_{90} and R_{91}) together form an oxo group or a group $-O-(CH_2)_{t1}-O-$, t_1 being an integer from 1 to 3 inclusive,
- X represents an oxygen atom, a sulphur atom, an amino group or an alkylamino group,

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

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

19. Pharmaceutical compositions according to claim 18 comprising at least one active ingredient according to any one of claims 1 to 15 for use in the manufacture of medicaments for use in the treatment of cancer diseases.