

(12) **United States Patent**
Bouchard et al.

(10) **Patent No.:** **US 6,372,780 B2**
(45) **Date of Patent:** **Apr. 16, 2002**

- (54) **METHODS OF TREATING CELL LINES EXPRESSING MULTIDRUG RESISTANCE P-GLYCOPROTEIN**
- (75) Inventors: **Hervé Bouchard**, Ivry-sur-Seine;
Jean-Dominique Bourzat, Vincennes;
Alain Commerçon, Vitry-sur-Seine, all of (FR)
- (73) Assignee: **Aventis Pharma S.A.**, Antony Cedex (FR)
- (*) Notice: Subject to any disclaimer, the term of this patent is extended or adjusted under 35 U.S.C. 154(b) by 0 days.
- (21) Appl. No.: **09/752,779**
- (22) Filed: **Jan. 3, 2001**

Related U.S. Application Data

- (63) Continuation of application No. 09/066,929, filed on Apr. 28, 1998, which is a continuation of application No. 08/622,011, filed on Mar. 26, 1996, now Pat. No. 5,847,170.
- (60) Provisional application No. 60/010,144, filed on Jan. 17, 1996.

(30) Foreign Application Priority Data

Mar. 27, 1995	(FR)	95 03545
Dec. 22, 1995	(FR)	95 15381

- (51) **Int. Cl.⁷** **A61K 31/337**
- (52) **U.S. Cl.** **514/449**
- (58) **Field of Search** **514/449**

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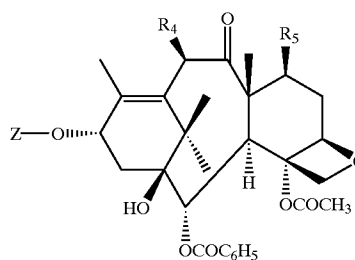
English language Derwent Abstract of FR 2 771 092, 1999.

Primary Examiner—Ba K. Trinh
(74) *Attorney, Agent, or Firm*—Finnegan, Henderson, Farabow, Garrett & Dunner LLP

(57) ABSTRACT

Now taxoids of general formula (I)

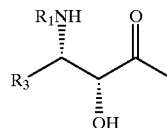
(I)



their preparation and pharmaceutical compositions containing them.

The new products of general formula (I) in which Z represents a radical of general formula (II):

(II)



display noteworthy antitumor and antileukaemic properties.

14 Claims, No Drawings

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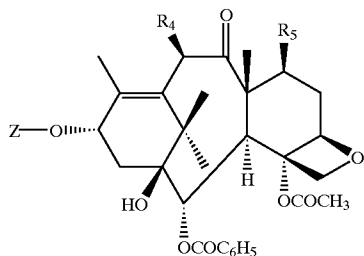
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**METHODS OF TREATING CELL LINES
EXPRESSING MULTIDRUG RESISTANCE
P-GLYCOPROTEIN**

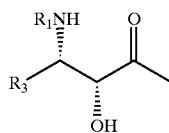
This is a continuation of application Ser. No. 09/066,929, 5
filed Apr. 28, 1998, allowed which is a continuation of
application Ser. No. 08/622,011, filed Mar. 26, 1996, now
U.S. Pat. No. 5,847,170, which claims benefit of provisional
application No. 60/010,144, dated Jan. 17, 1996, all of
which are specifically incorporated herein by reference. 10

The present invention relates to new taxoids of general
formula (I)



in which

Z represents a hydrogen atom or a radical of general
formula (II).



in which:

R₁ represents

a benzoyl radical optionally substituted with one or more
identical or different atoms or radicals selected from
halogen atoms, alkyl radicals containing 1 to 4 carbon
atoms, alkoxy radicals containing 1 to 4 carbon atoms
and trifluoromethyl radicals,

a thenoyl or furoyl radical or

a radical R₂—O—CO— in which R₂ represents:

an alkyl radical containing 1 to 8 carbon atoms,
an alkenyl radical containing 2 to 8 carbon atoms,
an alkynyl radical containing 3 to 8 carbon atoms,
a cycloalkyl radical containing 3 to 6 carbon atoms,
a cycloalkenyl radical containing 4 to 6 carbon atoms
or

a bicycloalkyl radical containing 7 to 10 carbon atoms,
these radicals being optionally substituted with one or 55
more substituents selected from halogen atoms,
hydroxyl radicals, alkoxy radicals containing 1 to 4
carbon atoms, dialkylamino radicals in which each
alkyl portion contains 1 to 4 carbon atoms, piperi-
dino radicals, morpholino radicals, 1-piperazinyl
radicals, said piperazinyl radicals being optionally
substituted at position 4 with an alkyl radical con-
taining 1 to 4 carbon atoms or with a phenylalkyl
radical in which the alkyl portion contains 1 to 4
carbon atoms, cycloalkyl radicals containing 3 to 6
carbon atoms, cycloalkenyl radicals containing 4 to 65
carbon atoms, phenyl radicals, said phenyl radicals

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being optionally substituted with one or more atoms
or radicals selected from halogen atoms, alkyl radi-
cals containing 1 to 4 carbon atoms, and alkoxy
radicals containing 1 to 4 carbon atoms, cyano
radicals, carboxyl radicals and alkoxy carbonyl radi-
cals in which the alkyl portion contains 1 to 4 carbon
atoms,

a phenyl or α - or β -naphthyl radical optionally
substituted with one or more atoms or radicals
selected from halogen atoms, alkyl radicals con-
taining 1 to 4 carbon atoms, and alkoxy radicals
containing 1 to 4 carbon atoms,

a 5-membered aromatic heterocyclic radical prefer-
ably selected from furyl and thienyl radicals,
or a saturated heterocyclic radical containing 4 to 6
carbon atoms, optionally substituted with one or
more alkyl radicals containing 1 to 4 carbon
atoms,

R₃ represents

an unbranched or branched alkyl radical containing 1 to 8
carbon atoms,

an unbranched or branched alkenyl radical containing 2 to
8 carbon atoms,

an unbranched or branched alkynyl radical containing 2 to
8 carbon atoms,

a cycloalkyl radical containing 3 to 6 carbon atoms,

a phenyl or α - or β -naphthyl radical optionally substituted
with one or more atoms or radicals selected from
halogen atoms, alkyl, alkenyl, alkynyl, aryl, aralkyl,
alkoxy, alkylthio, aryloxy, arylthio, hydroxyl,
hydroxyalkyl, mercapto, formyl, acyl, acylamino,
aroylamino, alkoxy carbonylamino, amino, alkylamino,
dialkylamino, carboxyl, alkoxy carbonyl, carbamoyl,
alkylcarbamoyl, dialkylcarbamoyl, cyano, nitro and
trifluoromethyl radicals,

or a 5-membered aromatic heterocycle containing one or
more identical or different hetero atoms selected from
nitrogen, oxygen and sulphur atoms and optionally
substituted with one or more identical or different
substituents selected from halogen atoms, alkyl, aryl,
amino, alkylamino, dialkylamino,
alkoxy carbonylamino, acyl, aryl carbonyl, cyano,
carboxyl, carbamoyl, alkylcarbamoyl, dialkylcarbam-
oyl and alkoxy carbonyl radicals,

with the understanding that, in the substituents of the
phenyl, α - or β -naphthyl and aromatic heterocyclic
radicals, the alkyl radicals and the alkyl portions of the
other radicals contain 1 to 4 carbon atoms, the alkenyl
and alkynyl radicals contain 2 to 8 carbon atoms, and
the aryl radicals are phenyl or α - or β -naphthyl radicals,

R₄ represents

an alkoxy radical containing 1 to 6 carbon atoms in an
unbranched or branched chain,

an alkenyloxy radical containing 3 to 6 carbon atoms in an
unbranched or branched chain,

an alkynyloxy radical containing 3 to 6 carbon atoms in an
unbranched or branched chain,

a cycloalkyloxy radical containing 3 to 6 carbon atoms or
a cycloalkenyloxy radical containing 4 to 6 carbon atoms,
these radicals being optionally substituted with one or
more substituents selected from halogen atoms, an
alkoxy radical containing 1 to 4 carbon atoms, an
alkylthio radical containing 1 to 4 carbon atoms, a
carboxyl radical, an alkyloxycarbonyl radical in which

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the alkyl portion contains 1 to 4 carbon atoms, a cyano radical, a carbamoyl radical, an N-alkylcarbamoyl radical and a N,N-dialkylcarbamoyl radical in which each alkyl portion contains 1 to 4 carbon atoms, or both alkyl portions, together with the nitrogen atom to which they are linked, form a saturated 5- or 6-membered heterocyclic radical optionally containing a second hetero atom selected from oxygen, sulphur and nitrogen atoms, said saturated 5- or 6-membered heterocyclic radical optionally being substituted with a substituent selected from an alkyl radical containing 1 to 4 carbon atoms, a phenyl radical, and a phenylalkyl radical in which the alkyl portion contains 1 to 4 carbon atoms,

R_5 represents

an alkoxy radical containing 1 to 6 carbon atoms in an unbranched or branched chain,

an alkenyloxy radical containing 3 to 6 carbon atoms,

an alkynyloxy radical containing 3 to 6 carbon atoms,

a cycloalkyloxy radical containing 3 to 6 carbon atoms or

a cycloalkenyloxy radical containing 3 to 6 carbon atoms,

these radicals being optionally substituted with at least

one substituent selected from halogen atoms, an alkoxy radical containing 1 to 4 carbon atoms, an alkylthio radical containing 2 to 4 carbon atoms, a carboxyl radical, an alkoxy carbonyl radical in which the alkyl portion contains 1 to 4 carbon atoms, a cyano radical, a carbamoyl radical, an N-alkylcarbamoyl radical, and a N,N-dialkylcarbamoyl radical in which each alkyl portion contains 1 to 4 carbon atoms or, with the nitrogen atom to which it is linked, forms a saturated 5- or 6-membered heterocyclic radical optionally containing a second hetero atom selected from oxygen, sulphur and nitrogen atoms, optionally substituted with a substituent selected from an alkyl radical containing 1 to 4 carbon atoms, a phenyl radical and a phenylalkyl radical in which the alkyl portion contains 1 to 4 carbon atoms.

Preferably, the aryl radicals which can be represented by R_3 are phenyl or α - or β -naphthyl radicals optionally substituted with one or more atoms or radicals selected from halogen atoms (fluorine, chlorine, bromine, iodine) alkyl, alkenyl, alkynyl, aryl, arylalkyl, alkoxy, alkylthio, aryloxy, arylthio, hydroxyl, hydroxyalkyl, mercapto, formyl, acyl, acylamino, aroylamino, alkoxy carbonylamino, amino, alkylamino, dialkylamino, carboxyl, alkoxy carbonyl, carbamoyl, dialkylcarbamoyl, cyano, nitro and trifluoromethyl radicals, on the understanding that the alkyl radicals and the alkyl portions of the other radicals contain 1 to 4 carbon atoms, that the alkenyl and alkynyl radicals contain 2 to 8 carbon atoms and that the aryl radicals are phenyl or α - or β -naphthyl radicals.

Preferably, the heterocyclic radicals which can be represented by R_3 are 5-membered aromatic heterocyclic radicals containing one or more identical or different atoms selected from nitrogen, oxygen and sulphur atoms, optionally substituted with one or more identical or different substituents selected from halogen atoms (fluorine, chlorine, bromine, iodine), alkyl radicals containing 1 to 4 carbon atoms, aryl radicals containing 6 or 10 carbon atoms, alkoxy radicals containing 1 to 4 carbon atoms, aryloxy radicals containing 6 or 10 carbon atoms, amino radicals, alkylamino radicals containing 1 to 4 carbon atoms, dialkylamino radicals in which each alkyl portion contains 1 to 4 carbon atoms, acylamino radicals in which the acyl portion contains 1 to 4 carbon atoms, alkoxy carbonylamino radicals containing 1 to 4 carbon atoms, acyl radicals containing 1 to 4 carbon atoms,

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arylcarbonyl radicals in which the aryl portion contains 6 or 10 carbon atoms, cyano radicals, carboxyl radicals, carbamoyl radicals, alkylcarbamoyl radicals in which the alkyl portion contains 1 to 4 carbon atoms, dialkylcarbamoyl radicals in which each alkyl portion contains 1 to 4 carbon atoms, and alkoxy carbonyl radicals in which the alkoxy portion contains 1 to 4 carbon atoms.

Preferably, the radicals R_4 and R_5 , which may be identical or different, represent unbranched or branched alkoxy radicals containing 1 to 6 carbon atoms, optionally substituted with a methoxy, ethoxy, ethylthio, carboxyl, methoxy carbonyl, ethoxy carbonyl, cyano, carbamoyl, N-methylcarbamoyl, N-ethylcarbamoyl, N,N-dimethylcarbamoyl, N,N-diethylcarbamoyl, N-pyrrolidinocarbonyl or N-piperidinocarbonyl radical.

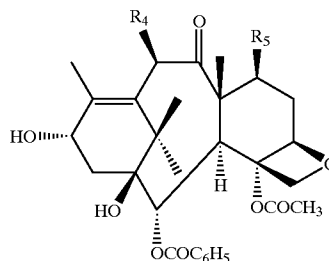
More particularly, the present invention relates to the products of general formula (I) in which Z represents a hydrogen atom or a radical of general formula (II) in which R_1 represents a benzoyl radical or a radical $R_2-O-CO-$ in which R_2 represents a tert-butyl radical and R_3 represents a n alkyl radical containing 1 to 6 carbon atoms, an alkenyl radical containing 2 to 6 carbon atoms, a cycloalkyl radical containing 3 to 6 carbon atoms a phenyl radical optionally substituted with one or more identical or different atoms or radicals selected from halogen atoms (fluorine, chlorine), alkyl (methyl), alkoxy (methoxy), dialkylamino (dimethylamino), acylamino (acetylamino), alkoxy carbonylamino (tert-butoxycarbonylamino), trifluoromethyl, a 2-furyl radical, a 3-furyl radical, a 2-thienyl radical, a 3-thienyl radical, a 2-thiazolyl radical, a 4-thiazolyl radical, and a 5-thiazolyl radical, and R_4 and R_5 , which may be identical or different, each represent an unbranched or branched alkoxy radical containing 1 to 6 carbon atoms.

Still more particularly, the present invention relates to the products of general formula (I) in which Z represents a hydrogen atom or a radical of general formula (II) in which R_1 represents a benzoyl radical or a radical $R_2-O-CO-$ in which R_2 represents a tert-butyl radical and R_3 represents an isobutyl, isobutenyl, butenyl, cyclohexyl, phenyl, 2-furyl, 3-furyl, 2-thienyl, 3-thienyl, 2-thiazolyl, 4-thiazolyl or 5-thiazolyl radical, and R_4 and R_5 , which may be identical or different, each represent a methoxy, ethoxy or propoxy radical.

The products of general formula (I) in which Z represents a radical of general formula (II) display noteworthy antitumor and antileukaemic properties.

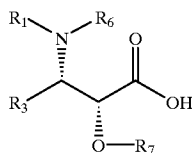
According to the present invention, the new products of general formula (I) in which Z represents a radical of general formula (II) may be obtained by esterification of a product of general formula (III):

(III)

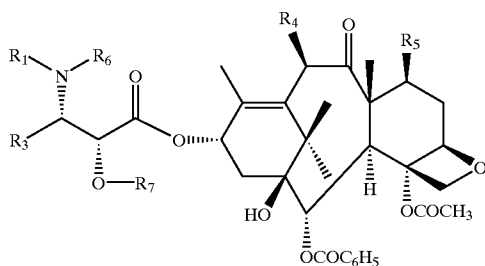


in which R_4 and R_5 are defined as above, by means of an acid of general formula (IV):

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in which R_1 and R_3 are defined as above, and either R_6 represents a hydrogen atom and R_7 represents a group protecting the hydroxyl function, or R_6 and R_7 together form a saturated 5- or 6-membered heterocycle, or by means of a derivative of this acid, to obtain an ester of general formula (V):



in which R_1 , R_3 , R_4 , R_5 , R_6 and R_7 are defined as above, followed by replacement of the protective groups represented by R_7 and/or R_6 and R_7 by hydrogen atoms.

The esterification by means of an acid of general formula (IV) may be performed in the presence of a condensing agent (carbodiimide, reactive carbonate) and an activating agent (aminopyridines) in an organic solvent (ether, ester, ketones, nitriles, aliphatic hydrocarbons, halogenated aliphatic hydrocarbons, aromatic hydrocarbons) at a temperature from -10 to 90°C .

The esterification may also be carried out using the acid of general formula (IV) in the form of the symmetrical anhydride, working in the presence of an activating agent (aminopyridines) in an organic solvent (ethers, esters, ketones, nitriles, aliphatic hydrocarbons, halogenated aliphatic hydrocarbons, aromatic hydrocarbons) at a temperature of from 0 to 90°C .

The esterification may also be carried out using the acid of general formula (IV) in halide form or in the form of a mixed anhydride with an aliphatic or aromatic acid, optionally prepared in situ, in the presence of a base (tertiary aliphatic amine), working in an organic solvent (ethers, esters, ketones, nitriles, aliphatic hydrocarbons, halogenated aliphatic hydrocarbons, aromatic hydrocarbons) at a temperature of from 0 to 80°C .

Preferably, R_6 represents a hydrogen atom and R_7 represents a group protecting the hydroxyl function, or alternatively R_6 and R_7 together form a saturated 5- or 6-membered heterocycle.

When R_6 represents a hydrogen atom, R_7 preferably represents a methoxymethyl, 1-ethoxyethyl, benzoyloxymethyl, trimethylsilyl, triethylsilyl, β -trimethylsilylethoxymethyl, benzyloxycarbonyl or tetrahydropyranyl radical.

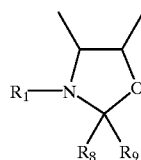
When R_6 and R_7 together form a heterocycle, the latter is preferably an oxazolidine ring optionally monosubstituted or gem-disubstituted at position 2.

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Replacement of the protective groups R_7 and/or R_6 and R_7 by hydrogen atoms may be performed, depending on their nature, in the following manner:

- 1) when R_6 represents a hydrogen atom and R_7 represents a group protecting the hydroxyl function, replacement of the protective groups by hydrogen atoms is performed by means of an inorganic acid (hydrochloric acid, sulphuric acid, hydrofluoric acid) or organic acid (acetic acid, methanesulphonic acid, trifluoromethanesulphonic acid, p-toluenesulphonic acid) used alone or mixed, working in an organic solvent chosen from alcohols, ethers, esters, aliphatic hydrocarbons, halogenated aliphatic hydrocarbons, aromatic hydrocarbons or nitriles at a temperature of from -10 to 60°C ., or by means of a source of fluoride ions such as a hydrofluoric acid/triethylamine complex, or by catalytic hydrogenation,

- 2) when R_6 and R_7 together form a saturated 5- or 6-membered heterocycle, and more especially an oxazolidine ring of general formula (VI):



in which R_1 is defined as above and R_6 and R_9 , which may be identical or different, represent a hydrogen atom or an alkyl radical containing 1 to 4 carbon atoms, or an aralkyl radical in which the alkyl portion contains 1 to 4 carbon atoms and the aryl portion preferably represents a phenyl radical optionally substituted with one or more alkoxy radicals containing 1 to 4 carbon atoms, or an aryl radical preferably representing a phenyl radical optionally substituted with one or more alkoxy radicals containing 1 to 4 carbon atoms, or alternatively R_6 represents an alkoxy radical containing 1 to 4 carbon atoms or a trihalomethyl radical such as trichloromethyl or a phenyl radical substituted with a trihalomethyl radical such as trichloromethyl and R_9 represents a hydrogen atom, or alternatively R_6 and R_9 , together with the carbon atom to which they are linked, form a 4- to 7-membered ring, replacement of the protective group formed by R_6 and R_7 by hydrogen atoms may be performed, depending on the meanings of R_1 , R_8 and R_9 , in the following manner:

- a) when R_1 represents a tert-butoxycarbonyl radical and R_8 and R_9 , which may be identical or different, represent an alkyl radical or an aralkyl (benzyl) or aryl (phenyl) radical, or alternatively R_8 represents a trihalomethyl radical or a phenyl radical substituted with a trihalomethyl radical and R_9 represents a hydrogen atom, or alternatively R_8 and R_9 together form a 4- to 7-membered ring, treatment of the ester of general formula (V) with an inorganic or organic acid, where appropriate in an organic solvent such as an alcohol, yields the product of general formula (VII).

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