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PATENTS ACT 1990

NOTICE OF ENTITLEMENT

WE, INDENA S.p.A. of Viale Ortles, 12, I-20139, Milano, Italy being the applicant in respect to the attached application state the following:-

The inventor of the invention is as follows:

Bombardelli, Ezio of Viale Ortles, 12, I-20139, Milano, Italy;

The person nominated for the grant of the patent INDENA S.p.A. has entitlement from the inventor by virtue of a verbal arrangement of May 19, 1995.

The basic application listed in the declaration made under Article 8 of the PCT was filed in the name of the applicant, INDENA S.p.A.

The basic application listed in the declaration made under Article 8 of the PCT is the first application made in a convention country in respect of the invention.

DATED THIS 1ST DAY OF AUGUST, 1997

INDENA S.p.A.
By their Patent Attorneys
LORD & COMPANY
PERTH, WESTERN AUSTRALIA.

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10-DEACETYL-14BETA-HYDROXYBACCATINE III DERIVATIVES, A PROCESS FOR THE PREPARATION THEREOF AND FORMULATIONS CONTAINING THEM

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(71) Applicant(s)
INDENA S.P.A.

(72) Inventor(s)
EZIO BOMBARDELLI

(74) Attorney or Agent
LORD & COMPANY , 4 Douro Place, WEST PERTH WA 6005

(56) Prior Art Documents
WO 94/22856
EP 0559019

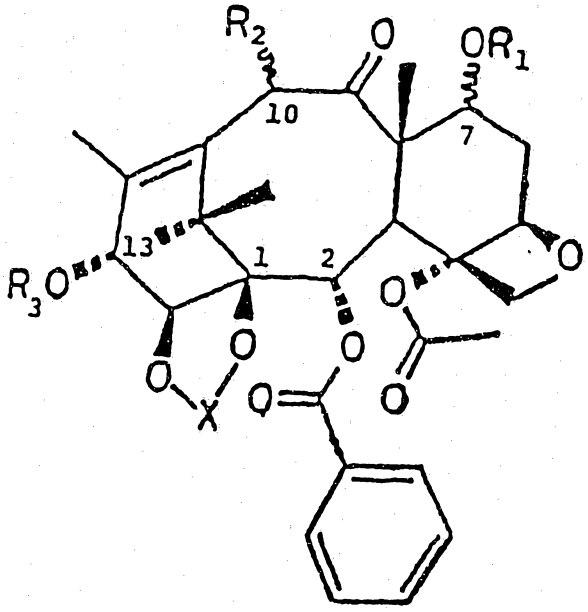
(57)

EP-A-559019 describes 14-β-hydroxy-10-deacetyl baccatine III derivatives.

Now it has been found that the compounds having the above reported formula 1, in addition to having a remarkable cytotoxic and antitumour activity, are free from the drawbacks of paclitaxel mentioned above.

Claim

1. Compounds of formula 1:



(1)

wherein

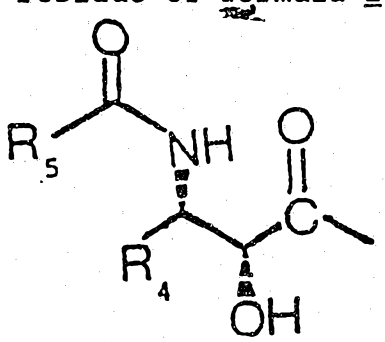
.../2

X is a >C = S, >C = NH or >S = O group;

OR_1, which can be α or β oriented, is a hydroxy, alkylsilyloxy (preferably triethylsilyloxy, O-TES), dichloromethoxycarbonyl group,

R_2 is an α or β oriented hydroxy group, or a Troc group (Troc= Cl_3CCH_2COO-), or, with the carbon atom to which is connected, it forms a keto group;

R_3 is a isoserine residue of formula 2:



(2)

R_4 is a straight or branched alkyl or alkenyl group, having 1-5 carbon atoms, or an aryl group;

R_5 is an alkyl or alkenyl group, having 1-5 carbon atoms, or an aryl group, or a tert-butoxy group.

atoms, or an aryl group, or a tert-butoxy group.

5. Pharmaceutical compositions with antitumour activity, having a reduced cardiotoxicity, containing one or more compounds of formula 1.

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(71) Applicant (*for all designated States except US*): INDENA S.P.A. [IT/IT]; Viale Ortles, 12, I-20139 Milano (IT).

(72) Inventor; and
(75) Inventor/Applicant (*for US only*): BOMBARDELLI, Ezio [IT/IT]; Viale Ortles, 12, I-20139 Milano (IT).

(74) Agent: MINOJA, Fabrizio; Studio Consulenza Brevettuale, Via Rossini, 8, I-20122 Milano (IT).

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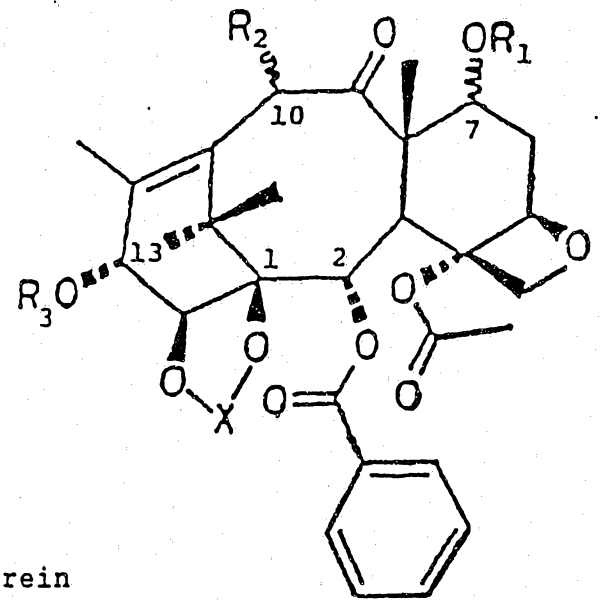
(54) Title: 10-DEACETYL-14BETA-HYDROXYBACCATINE III DERIVATIVES, A PROCESS FOR THE PREPARATION THEREOF AND FORMULATIONS CONTAINING THEM

(57) Abstract

The present invention relates to novel 10-deacetyl-14β-hydroxybaccatine III derivatives. The novel derivatives, having cytotoxic and antitumour activity, are prepared from this synton after functionalization of the hydroxyls at 1-, 14- as thiocarbonate, iminocarbonate and sulfite and possible oxidation of the hydroxyl at C_{10}. These derivatives are subjected to a subsequent esterification at position 13- with a variously substituted isoserine chain. The products of the invention can be administered by the injective or oral route, when suitably formulated.

10-DEACETYL-14BETA-HYDROXYBACCATINE III DERIVATIVES, A PROCESS FOR THE PREPARATION THEREOF AND FORMULATIONS CONTAINING THEM

The present invention relates to 10-deacetyl-14β-hydroxybaccatine III of formula 1:



(1)

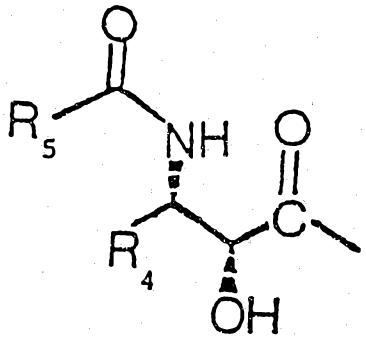
wherein

X is a >C = S, >C = NH or >S = O group;

OR_1, which can be α or β oriented, is a hydroxy, alkylsilyloxy (preferably triethylsilyloxy, O-TES), dichloromethoxycarbonyl group,

R_2 is an α or β oriented hydroxy group, or a Troc (TrOC= Cl_3CCH_2COO-) group, or, with the carbon atom to which is connected, it forms a keto group;

R_3 is a isoserine residue of formula 2:



(2)

R_4 is a straight or branched alkyl or alkenyl group, having 1-5 carbon atoms, or an aryl group;

R_5 is an alkyl or alkenyl group, having 1-5 carbon atoms, or an aryl group, or a tert-butoxy group.

Paclitaxel (taxol), as it is already well-known, is a diterpenoid extracted from plants of the Taxus genus having anticancerogenic activity on different forms of human tumours. Its clinical use still involves some drawbacks such as cardiotoxicity and a poor water solubility, which makes its administration complex. Moreover, paclitaxel induces resistance quickly. Due to these reasons, researches have been in progress for some years aiming at synthesizing novel paclitaxel analogues which cause less adverse effects compared with the parent molecule.

WO 94/22856 generically describes compounds similar to the present compounds in which the substituent of C_1 and C_{14} can be connected to form a cyclic structure. J. Med. Chem. 1994, 37: 1408-1410 describes 14β OH-deacetylbaccatine-1, 14-carbonate-Biorganic & Medicinal Chemistry Letters, Vol. 4 NO. 13: 1571-1576, reports the preparation of 14β hydroxy-docetaxel-1, 14-acetonide, whereas the same journal on page 1565-1570, discloses synthesis intermediates, bearing an orthoformiate bound to C_1 and C_{14} hydroxyls.

Tetrahedron Letters Vol. 5 NO. 13 pages 3063-3064 and Tetrahedron Letters Vol 35 NO 15 pages 2349-2352 discloses two processes for the synthesis of Docetaxel.

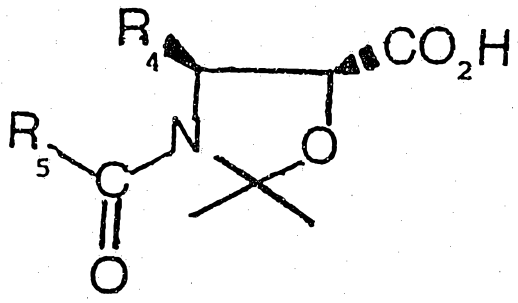
EP-A-559019 describes 14-β-hydroxy-10-deacetyl baccatine III derivatives.

Now it has been found that the compounds having the above reported formula 1, in addition to having a remarkable cytotoxic and antitumour activity, are free from the drawbacks of paclitaxel mentioned above.

According to the invention, the compounds of formula 1 are obtained by semisynthesis, starting from 10-deacetyl-14β-hydroxybaccatine III which, upon protection of the hydroxyls at 7- and 10-, is reacted a) with thiophosgene in pyridine, thereby obtaining the corresponding 1,14-thiocarbonate, (1, with X = >C = S) or b) with thionyl chloride in the presence of tertiary bases (in which case a 1,14-sulfite will be obtained), (1, with X = >S = O) or c) with cyanogen bromide (after conversion of the hydroxyls at 1- and 14- into the corresponding lithium alkoxides), in order to obtain the iminocarbonate (1, with X = >C = NH). The operative

details will be reported in the examples, and of course those skilled in the art will make use of well known variations when carrying out the process, without however departing from the original inventive scope.

The resulting thiocarbonates, sulfites and iminocarbonates are esterified at the hydroxyl at C_{13} with the suitably activated isoserine chains of formula 2, according to what reported in literature for the semisynthesis of paclitaxel and analogues thereof (see, for ex. EP-A 400,971; Fr. Dem. 86, 10400; E. Didier et al. Tetrahedron Letters 35, 2349 (1994); E. Didier et al., ibid. 35, 3063 (1994)). Preferably the isoserine chains are used in the oxazolinedicarboxylic acid activated form corresponding to the formula 3:



(3)

wherein R_4 and R_5 have the meanings defined above.

Alternatively to this synton, the analogous compound wherein the ketalizing acetone can be replaced by 1,3-bromoacetone, hexachloroacetone, chloral or an aromatic aldehyde, preferably p-methoxy benzaldehyde or o,p-dimethoxy benzaldehyde, can be used. The esterification of the oxazolidinecarboxylic acids with the taxane syntons and the subsequent elimination of the protecting groups are carried out as described in literature for the synthesis of paclitaxel and the analogues thereof.

The compounds of formula 1 wherein R_2 forms a keto group with C_{10} can be obtained analogously, starting from 14β-hydroxy-10-dehydrobaccatine III.

Among the compounds of formula 1, particularly active proved to be 13-[(2R,3S)-3-tert-butoxycarbonylamino-2-hydroxy-3-isobutyl-propanoyl]-14β-hydroxybaccatine III 1,14-thiocarbonate (5), 13-[(2R,3S)-3-tert-butoxycarbonylamino-2-hydroxy-3-isobutenyl-propanoyl]-14β-hydroxybaccatine III 1,14-thiocarbonate (6), 13-[(2R,3S)-3-caproylamino-2-hydroxy-3-isobutenyl-propanoyl]-14β-hydroxybaccatine III 1,14-thiocarbonate III (7); active and with a different solubility in water proved to be the analogous derivatives having as substituents at the 1,14 hydroxyls the >C = NH group or the >S = O group. The compounds 13-[(2R,3S)-3-caproylamino-2-hydroxy-3-isobutenyl-propanoyl]-14β-hydroxybaccatine III 1,14-iminocarbonate (8) and 13-[(2R,3S)-3-caproylamino-2-hydroxy-3-isobutenyl-propanoyl]-14β-hydroxybaccatine-III 1,14-sulfite (9) showed advantages compared with the compounds of the prior art in terms of both activity and tolerability.

The cytotoxicity data of the compounds 5, 8 and 9 compared with those of paclitaxel are reported in the following Table, by way of example.

Table. - IC_{50} of the compounds 5, 8 and of paclitaxel on six tumour cell lines.

Cell line	Exposure time (h)	Paclitaxel	IC_{50} (nM) 5	8	9
L1210 (murine leukemia)	72	7.5 ± 2.0	0.5 ± 0.1	2.4 ± 0.1	1.8 ± 0.1
A121 (Human ovarian)	72	4.7 ± 0.3	0.8 ± 0.3	1.9 ± 0.2	1.1 ± 0.1
A549 (Human NSCLC)	72	5.7 ± 0.5	2.3 ± 0.3	2.1 ± 0.3	1.8 ± 0.2
HT-29 (Human colon)	72	6.9 ± 0.4	0.3 ± 0.1	0.5 ± 0.1	0.5 ± 0.1
MCF7 (Human breast)	72	4.8 ± 0.1	1.2 ± 0.2	0.8 ± 0.2	1.0 ± 0.3
MCF7-ADR (resistant)	72	395 ± 8.7	18 ± 2.2	21 ± 6.2	16 ± 4.9

Standard conditions: basal medium = RPMI 1640 + 20 mM HEPES + 2 mM L-glutamine.

The compounds of formula 1 show surprising advantages compared with paclitaxel on cell lines resistant to other anti-tumour substances, such as adriamycin or cis-platinum. The differences between paclitaxel and these products are even more evident in in vivo models, such as the athymic nude mouse with human tumour implant. The products of the invention can be incorporated in suitable pharmaceutical formulations for the administration of the products both parenterally

and orally. For the intravenous administration, mixtures of Chremoform L and ethanol, polysorbates or liposomial preparations prepared with natural or synthetic phosphatidylcholine, or mixtures of natural phospholipids in the presence of cholesterol, are mainly used, furthermore formulations with micronized compounds with particle size below 300 nm are used. The compounds are administered to the man at concentrations ranging from 30 to 500 mg/m^2.

The examples reported below further illustrated the invention.

Example 1 - Preparation of 7,10-DiTroc-14β-hydroxy-10-deacetylbaccatine III 1,14-iminocarbonate.

A solution of 205 mg of 7,10-DiTroc-14β-hydroxy-10-deacetyl baccatine III (prepared according to US 5,254,591) in 5 ml of tetrahydrofuran is added with 336 µl of a 1.6M solution of butyl-lithium in n-hexane at 0°C, followed by the addition 45.6 mg of cyanogen bromide. After stirring for 10 minutes at 0°C the reaction mixture is left under stirring at room temperature for 20 minutes, during which time the reaction products disappear; the reaction mixture is treated with a $NaHCO_3$ saturated solution in the presence of methylene chloride. The organic phase is washed with cold water and concentrated after drying over Na_2SO_4. The residue is purified through a silica gel column, eluting the desired compound with a chloroform/acetone 3:1 mixture. 140 mg of iminocarbonate are obtained.

Example 2 - Preparation of 7,10-DiTroc-14β-hydroxy-10-deacetylbaccatine III 1,14-sulfite.

A solution of 100 mg of 7,10-DiTroc-14β-

hydroxydeacetylbaccatine III in 1.5 ml of methylene chloride is added with 63 µl (46 mg) of triethylamine and subsequently 12 µl (19.6 mg) of $SOCl_2$ diluted in 200 µl of methylene chloride; the reaction mixture is stirred at 0°C for 10 minutes, then is diluted with 10 vol. of methylene chloride and shaken with water in the presence of ice, washing thoroughly to neutrality.

The organic phase is concentrated to dryness and the residue is chromatographed on silica gel, eluting the reaction product with an hexane/ethyl acetate 1:1 mixture. 74 mg of cyclic sulfite are obtained, which is a mixture of diastereomers at the sulfur atom.

Example 3 - Preparation of 7-O-Tes-14β-hydroxybaccatine III 1,14-sulfite.

A solution of 100 mg of 7-O-Tes-14β-hydroxy-10-deacetylbaccatine III (U.S. 5,264,591) in 1.5 ml of methylene chloride is added with 63 µl (46 mg) of triethylamine and subsequently 12 µl (19.6 mg) of $SOCl_2$ diluted in 200 µl of methylene chloride; the reaction mixture is stirred at 0°C for 10 minutes, then is diluted with 10 vol. of methylene chloride and shaken with water in the presence of ice, washing thoroughly to neutrality.

The organic phase is concentrated to dryness and the residue is chromatographed on silica gel, eluting the reaction product with a methylene chloride/methanol 95:5 mixture. 81 mg of 7-O-Tes-14β-hydroxy-10-deacetylbaccatine III cyclic sulfite are obtained, which is a mixture of diastereomers at the sulfur atom.

50 mg of reaction product are dissolved in 1 ml of anhydrous pyridine and added with 30 µl of acetyl

chloride at 0°C under strong stirring. After 5h at 0°C the reaction mixture is poured into 10 ml of water and is immediately extracted for three times with 10 ml each of ethyl acetate. The organic phase is washed with diluted HCl to remove pyridine and finally with a NaCl saturated solution to neutrality; the organic phase is dried and concentrated to dryness. 46 mg of 14-β-hydroxy-baccatine III 7-O-Tes-1,14-sulfite are obtained.

Example 4 - Preparation of 14β-hydroxy-10-deacetyl-baccatine III 7-O-Tes-1,14-thiocarbonate.

a) A suspension of 2.8 g of 14β-hydroxy-10-deacetyl-baccatine III in 25 ml of methylene chloride is added with 8.3 ml of anhydrous pyridine; the resulting solution is cooled at -15°C and is added dropwise with 26.6 ml of a 1.9M thiophosgene solution, under nitrogen atmosphere and with stirring, during 10 minutes. A precipitate forms; the reaction mixture, after checking by TLC (hexane/ethyl acetate 7:3), is treated with a $NaHCO_3$ solution to completely destroy phosgene. After dilution with water, the mixture is extracted with methylene chloride. The yellowish organic phase is washed with diluted HCl and then with water to neutrality. The organic phase, after drying over Na_2SO_4, is concentrated to dryness. 2.7 g of 14β-hydroxy-10-deacetyl-baccatine III 1,14-thiocarbonate are obtained.

b) 500 mg of 14β-hydroxy-10-deacetylbaccatine III 1,14-thiocarbonate are dissolved in 5 ml of DMF and treated with 287 µl of Tes-chloride and 116 mg of imidazole, adding the silylating agent dropwise

under stirring. After 2 h, the reaction mixture is added with celite and poured onto ice. The precipitate, after thorough washing with water, is washed with hexane to remove the silanol and then is extracted with methylene chloride. By concentration of the organic phase, 14β-hydroxy-10-deacetylbaccatine III 7-O-Tes-1,14-thiocarbonate is obtained, having a sufficient purity for the subsequent reactions. Alternatively, the residue is chromatographed over 10 g of silica gel, eluting with an hexane/ethyl acetate 1:1 mixture. 490 mg of product are obtained, M^+a m/z 602.

Example 5 - Preparation of 14β-hydroxybaccatine III 7-O-Tes-1,14-thiocarbonate.

500 mg of 14β-hydroxy-10-deacetyl-baccatine III 7-O-Tes-1,14-thiocarbonate are dissolved in 10 ml of anhydrous pyridine and added with 200 µl of acetyl chloride at 0°C under strong stirring. After 5h at 0°C, the reaction mixture is poured into 100 ml of water and is immediately extracted for three times with 50 ml each of ethyl acetate. The organic phase is washed with diluted HCl to remove pyridine and finally with a NaCl saturated solution to neutrality; the organic phase is dried and concentrated to dryness. 501 mg of 14β-hydroxybaccatine III 7-O-Tes-1,14-thiocarbonate are obtained.

Example 6 - Preparation of 13-[(2R,3S)-3-terbutoxy-carbonyl-amino-2-hydroxy-3-isobutyl-propanoyl]-14β-hydroxybaccatine III 1,14-thiocarbonate.

0.5 g of 7-O-triethylsilyl-14β-hydroxybaccatine III 1,14-thiocarbonate are dissolved in 60 ml of toluene.

The solution is added with 800 mg of (4S,5R)-N-(tert-butoxycarbonyl)-2,2-dimethyl-4-isobutyl-5-oxazolidine-carboxylic acid, 400 mg of cyclohexylcarbodiimide and 40 mg of N,N-dimethylaminopyridine. The reaction mixture is kept at 80°C for two hours, then is filtered and washed with water; the organic phase is then concentrated to dryness. The residue is treated with methanol containing 0.1% of H_2SO_4, at 10°C. The methanol solution is diluted with water and the product is extracted with ethyl acetate; the organic phase is concentrated to dryness and the residue is chromatographed on silica gel, eluting with acetone/hexane 4:6. Are obtained 580 mg of 5, M^+a m/z 887.

Example 7 - Preparation of 13-[(2R,3S)-3-tert-butoxy-carbonyl-amino-2-hydroxy-3-isobutyl-propanoyl]-14β-hydroxybaccatine III 1,14-iminocarbonate.

0.7 g of 7,10-of-Troc-14β-hydroxybaccatine III 1,14-iminocarbonate are dissolved in 80 ml of toluene. The solution is added with 750 mg of (4S,5R)-N-(tert-butoxycarbonyl)-2,2-dimethyl-4-isobutyl-5-oxazolidine-carboxylic acid, 400 mg of cyclohexylcarbodiimide and 40 mg of N,N-dimethylaminopyridine. The reaction mixture is kept at 80°C for two hours. The reaction mixture is filtered and washed with water and the organic phase is then concentrated to dryness. The residue is treated with methanol containing 0.1% of H_2SO_4 at 10°C; after partial dilution with water and further acidification with acetic acid, the solution is treated with Zn to remove Troc. The hydromethanol solution is diluted with water and the product is extracted with ethyl acetate; the organic phase is concentrated to dryness and the

residue is chromatographed on silica gel, eluting with acetone/hexane 4:6. 480 mg of product are obtained, M^+a m/z 841.

Example 8 - Preparation of 13-[(2R,3S)-3-caproyl-amino-2-hydroxy-3-isobutyl-propanoyl]-14β-hydroxybaccatine III 1,14-thiocarbonate.

0.5 g of 7-O-triethylsilyl-14β-hydroxybaccatine III 1,14-thiocarbonate are dissolved in 60 ml of toluene. The solution is added with 750 mg of (4S,5R)-N-(caproyl)-2,2-dimethyl-4-isobutyl-5-oxazolidine-carboxylic acid, 400 mg of cyclohexylcarbodiimide and 40 mg of N,N-dimethylaminopyridine. The reaction mixture is kept at 80°C for two hours, filtered and washed with water, and the organic phase is then concentrated to dryness. The residue is treated with methanol containing 0.1% of H_2SO_4 at 10°C. The methanol solution is diluted with water and the product is extracted with ethyl acetate; the organic phase is concentrated to dryness and the residue is chromatographed on silica gel, eluting with acetone/hexane 4:6. 502 mg of desired product are obtained.

Example 9 - Preparation of 13-[(2R,3S)-3-caproyl-amino-2-hydroxy-3-isobutyl-propanoyl]-14β-hydroxybaccatine III 1,14-sulfite.

0.5 g of 7-O-triethylsilyl-14β-hydroxybaccatine III 1,14-sulfite are dissolved in 60 ml of toluene. The solution is added with 750 mg of (4S,5R)-N-(caproyl)-2,2-dimethyl-4-isobutyl-5-oxazolidine-carboxylic acid, 400 mg of cyclohexylcarbodiimide and 40 mg of N,N-dimethylaminopyridine. The reaction mixture is kept at 80°C for two hours, filtered and washed with water, and

the organic phase is then concentrated to dryness. The residue is treated with methanol containing 0.1% of H_2SO_4 at 10°C. The methanol solution is diluted with water and the product is extracted with ethyl acetate; the organic phase is concentrated to dryness and the residue is chromatographed on silica gel, eluting with acetone/hexane 4:6. 502 mg of desired product are obtained.

Example 10 - Preparation of 13-[(2R,3S)-3-caproyl-amino-2-hydroxy-3-isobutenyl-propanoyl]-14β-hydroxybaccatine III 1,14-thiocarbonate.

0.5 g of 7-O-triethylsilyl-14β-hydroxybaccatine III 1,14-thiocarbonate are dissolved in 60 ml of toluene. The solution is added with 750 mg of (4S,5R)-N-(caproyl)-2,2-dimethyl-4-isobutenyl-5-oxazolidine-carboxylic acid, 400 mg of cyclohexylcarbodiimide and 40 mg of N,N-dimethylaminopyridine. The reaction mixture is kept at 80°C for two hours. The reaction mixture is filtered and washed with water and the organic phase is then concentrated to dryness. The residue is treated with methanol containing 0.1% of H_2SO_4 at 10°C. The methanol solution is diluted with water and the product is extracted with ethyl acetate; the organic phase is concentrated to dryness and the residue is chromatographed on silica gel, eluting with acetone/hexane 3:7. 445 mg of desired product are obtained.

Example 11 - Preparation of 13-[(2R,3S)-3-caproyl-amino-2-hydroxy-3-isobutenyl-propanoyl]-14β-hydroxybaccatine III 1,14-sulfite.

0.5 g of 7-O-triethylsilyl-14β-hydroxybaccatine III

1,14-sulfite are dissolved in 60 ml of toluene. The solution is added with 750 mg of (4S,5R)-N-(caproyl)-2,2-dimethyl-4-isobutenyl-5-oxazolidine-carboxylic acid, 400 mg of cyclohexylcarbodiimide and 40 mg of N,N-dimethylaminopyridine. The reaction mixture is kept at 80°C for two hours. The reaction mixture is filtered and washed with water and the organic phase is then concentrated to dryness. The residue is treated with methanol containing 0.1% of H_2SO_4 at 10°C. The methanol solution is diluted with water and the product is extracted with ethyl acetate; the organic phase is concentrated to dryness and the residue is chromatographed on silica gel, eluting with acetone/hexane 7:3. 495 mg of desired product are obtained.

Example 12 - <u>Preparation of 13-[(2R,3S)-3-caproyl-amino-2-hydroxy-3-crotonyl-propanoyl]-14β-hydroxybaccatine III 1,14-thiocarbonate.</u>

0.5 g of 7-O-triethylsilyl-14β-hydroxybaccatine III 1,14-thiocarbonate are dissolved in 60 ml of toluene. The solution is added with 760 mg of (4S,5R)-N-(caproyl)-2,2-dimethyl-4-crotonyl-5-oxazolidine-carboxylic acid, 400 mg of cyclohexylcarbodiimide and 40 mg of N,N-dimethylaminopyridine. The reaction mixture is kept at 80°C for two hours. The reaction mixture is filtered and washed with water and the organic phase is then concentrated to dryness. The residue is treated with methanol containing 0.1% of H_2SO_4 at 10°C. The methanol solution is diluted with water and the product is extracted with ethyl acetate; the organic phase is concentrated to dryness and the residue is

chromatographed on silica gel, eluting with acetone/hexane 2:8. 430 mg of desired product are obtained.

Example 13 - Preparation of 7-O-Tes-10-dehydro-14β-hydroxybaccatine III 1,14-thiocarbonate

a) 14β-Hydroxy-10-dehydrobaccatine III

10 g of 10-deacetyl-14β-hydroxybaccatine III are suspended in 350 ml of methanol and added with 65 g of $Cu(OAc)_2$. The suspension is stirred at room temperature for 120 h. The salts are filtered off, the solution is evaporated to dryness and the residue is chromatographed on 100 g of silica gel, eluting with an hexane/ethyl acetate 6:4 mixture. After crystallization from ligroin, 9.3 g of 6 are obtained, M^+a m/z 558.

b) Title compound

0.5 g of 14β-hydroxy-10-dehydrobaccatine are treated according to the procedure of Example 4 a). 350 mg of the desired product are obtained.

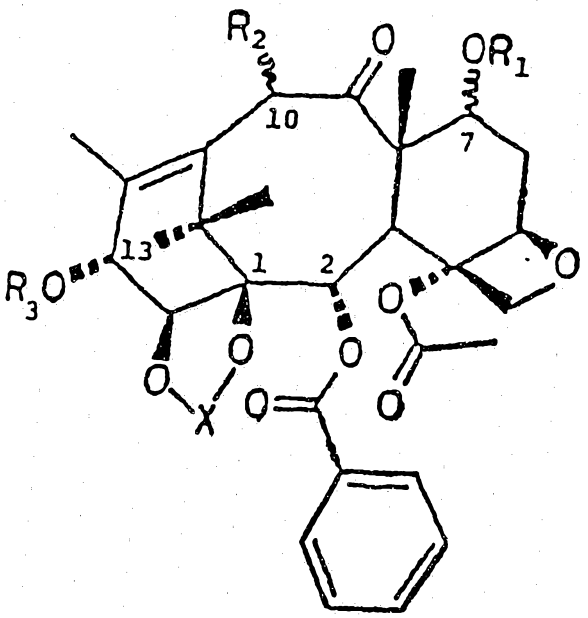
Example 14 - Preparation of 13-[(2R,3S)-3-caproyl-amino-2-hydroxy-3-crotonyl-propanoyl]10-dehydro-14β-hydroxy-baccatine III 1,14-thiocarbonate.

0.5 g of 7-O-triethylsilyl-10-dehydro-14β-hydroxy-baccatine III 1,14-thiocarbonate are dissolved in 60 ml of toluene. The solution is added with 760 mg of (4S,5R)-N-(caproyl)-2,2-dimethyl-4-crotonyl-5-oxazolidine-carboxylic acid, 400 mg of cyclohexylcarbodiimide and 40 mg of N,N-dimethylaminopyridine. The reaction mixture is kept at 80°C for two hours. The reaction mixture is filtered and washed with water and the organic phase is then concentrated to dryness. The residue is treated with methanol containing 0.1% of H_2SO_4 at 10°C. The

methanol solution is diluted with water and the product is extracted with ethyl acetate; the organic phase is concentrated to dryness and the residue is chromatographed on silica gel, eluting with acetone/hexane 2:8. 430 mg of desired product are obtained.

CLAIMS

1. Compounds of formula 1:



(1)

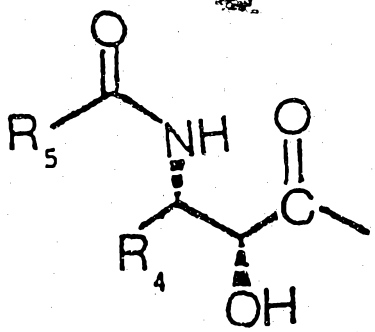
wherein

X is a >C = S, >C = NH or >S = O group;

OR_1, which can be α or β oriented, is a hydroxy, alkylsilyloxy (preferably triethylsilyloxy, O-TES), dichloromethoxycarbonyl group,

R_2 is an α or β oriented hydroxy group, or a Troc group (Troc= Cl_3CCH_2COO-), or, with the carbon atom to which is connected, it forms a keto group;

R_3 is a isoserine residue of formula 2:



(2)

R_4 is a straight or branched alkyl or alkenyl group, having 1-5 carbon atoms, or an aryl group;

R_5 is an alkyl or alkenyl group, having 1-5 carbon atoms, or an aryl group, or a tert-butoxy group.

atoms, or an aryl group, or a tert-butoxy group.

2. A compound of formula 1, selected from the group consisting of:

- 7,10-DiTroc-14β-hydroxy-10-deacetylbaccatine III 1,14-iminocarbonate;
- 7,10-DiTroc-14β-hydroxy-10-deacetylbaccatine III 1,14-sulfite;
- 7-O-Tes-14β-hydroxybaccatine III 1,14-sulfite;
- 14β-hydroxy-10-deacetylbaccatine III 7-O-Tes-1,14-thiocarbonate;
- 14β-hydroxybaccatine III 7-O-Tes-1,14-thiocarbonate;
- 13-[(2R,3S)-3-tert-butoxy-carbonyl-amino-2-hydroxy-3-isobutylpropanoyl]-14β-hydroxybaccatine III 1,14-thiocarbonate;
- 13-[(2R,3S)-3-tert-butoxy-carbonyl-amino-2-hydroxy-3-isobutylpropanoyl]-14β-hydroxybaccatine III 1,14-iminocarbonate;
- 13-[(2R,3S)-3-caproyl-amino-2-hydroxy-3-isobutyl-propanoyl]-14β-hydroxybaccatine III 1,14-thiocarbonate;
- 13-[(2R,3S)-3-caproyl-amino-2-hydroxy-3-isobutyl-propanoyl]-14β-hydroxybaccatine III 1,14-sulfite;
- 13-[(2R,3S)-3-caproyl-amino-2-hydroxy-3-isobutenyl-propanoyl]-14β-hydroxybaccatine III 1,14-thiocarbonate;
- 13-[(2R,3S)-3-caproyl-amino-2-hydroxy-3-isobutenyl-propanoyl]-14β-hydroxybaccatine III 1,14-sulfite;
- 13-[(2R,3S)-3-caproyl-amino-2-hydroxy-3-crotonyl-propanoyl]-14β-hydroxybaccatine III 1,14-thiocarbonate;

- 7-O-Tes-10-dehydro-14β-hydroxybaccatine III 1,14-thiocarbonate;
- 13-[(2R,3S)-3-caproyl-amino-2-hydroxy-3-crotonyl-propanoyl]10-dehydro-14β-hydroxybaccatine III 1,14-thiocarbonate;
- 13-[(2R,3S)-3-tert-butoxycarbonylamino-2-hydroxy-3-isobutenyl-propanoyl]-14β-hydroxybaccatine III 1,14-thiocarbonate;
- 13-[(2R,3S)-3-caproylamino-2-hydroxy-3-isobutenyl-propanoyl]-14β-hydroxybaccatine III 1,14-iminocarbonate.

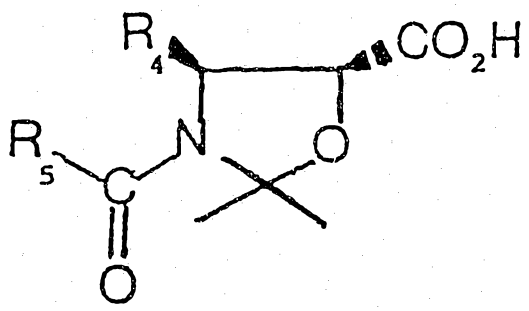
3. A process for the preparation of the compounds of formula 1, which process comprises the following steps:

i) reacting 10-deacetyl-14β-hydroxybaccatine III (respectively 10-dehydro-14β-hydroxybaccatine III), upon protection of the hydroxyls at 7- and 10- (respectively of the hydroxyl at 7-): a) with thiophosgene in pyridine, to form the corresponding 1,14-thiocarbonate, or b) with thionyl chloride in the presence of tertiary bases, to form the corresponding 1,14-sulfite, or c) with butyl lithium and cyanogen bromide, to form the corresponding 1,14-iminocarbonate;

ii) esterifying the resulting intermediates at 13 with activated isoserines; and

iii) finally deprotecting the hydroxy groups.

4. A process according to claim 3, in which process the esterification at 13 is carried out with activated isoserines of formula 3:



(3)

wherein R4 and R5 have the meanings defined above or with corresponding ketals with 1,3-bromoacetone, hexachloroacetone, chloral, p-methoxy- or o,p-dimethoxy benzaldehyde.

5. Pharmaceutical compositions with antitumour activity, having a reduced cardiotoxicity, containing one or more compounds of formula 1.

6. The use of the compounds of formula 1 for the preparation of pharmaceutical compositions with antitumour activity, having a reduced cardiotoxicity.

7. Compounds of formula 1 substantially as hereinbefore described in the accompanying Examples 1 to 13.

8. A process for the preparation of the compounds of formula 1 substantially as hereinbefore described in the accompanying Examples 1 to 13.

9. Pharmaceutical compositions with antitumour activity substantially as hereinbefore described in the accompanying Examples 1 to 13.

INTERNATIONAL SEARCH REPORT

International application No.
PCT/EP 96/01919

A. CLASSIFICATION OF SUBJECT MATTER

IPC6: C07D 305/14
According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

IPC6: C07D

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)

WPI, IFIPAT, CA

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	WO, A, 9422856 (THE RESEARCH FOUNDATION OF THE STATE UNIVERSITY OF NEW YORK), 13 October 1994 (13.10.94) --	1-6
X	J. Med. Chem., Volume 37, 1994, I. Ojima et al, "Structure-Activity Relationships of New Taxoids Derived From 14-beta-Hydroxy-10-deacetylbaccatin III" page 1408 - page 1410 --	1-6
X	Bioorg. Med. Chem. Lett., Volume 4, No 13, 1994, I. Ojima et al, "Synthesis and Biological Activity of 14-hydroxydocetaxel" page 1571 - page 1576 --	1-6

[X] Further documents are listed in the continuation of Box C. [X] See patent family annex.

* Special categories of cited documents:
"A" document defining the general state of the art which is not considered to be of particular relevance
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"O" document referring to an oral disclosure, use, exhibition or other means
"P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention
"X" document of particular relevance: the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone
"Y" document of particular relevance: the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art
"&" document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
24 Sept 1996	18. 10. 96
Name and mailing address of the ISA/ European Patent Office, P.B. 5818 Patentlaan 2 NL-2280 HV Rijswijk Tel. (+31-70) 340-2040, Tx. 31 651 epo nl, Fax: (+31-70) 340-3016	Authorized officer TEDDY ERCEGOVIC

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INTERNATIONAL SEARCH REPORT

International application No.
PCT/EP 96/01919

C (Continuation). DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	Bioorg. Med. Chem. Lett., Volume 4, No 13, 1994, J. Kant et al, "Synthesis and Antitumor Properties of Novel 14-betahydroxytaxol and Related Analogues" page 1565 - page 1570	1-6
A	EP, A1, 0559019 (INDENA S.P.A), 8 Sept 1993 (08.09.93)	1-6
A	Tetrahedron Lett., Volume 35, No 15, 1994, E. Didier et al, "2-Monosubstituted-1, 3-Oxazolidines as Improved Protective Groups of N-Boc-Phenylisoserine in Docetaxel Preparation" page 2349 - page 2352	1-6
A	Tetrahedron Lett., Volume 35, No 19, 1994, E. Didier et al, "Expeditious Semisynthesis of Docetaxel Using 2-Trichloromethyl-1,3-Oxazolidine as Side-Chain Protection" page 3063 - page 3064	1-6

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INTERNATIONAL SEARCH REPORT

05/09/96

International application No.
PCT/EP 96/01919

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		CA-A- 2158147	13/10/94
		CZ-A- 9502480	13/03/96
		EP-A- 0690856	10/01/96
		HU-D- 9502642	00/00/00
		NO-A- 953796	15/11/95
		PL-A- 310827	08/01/96
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