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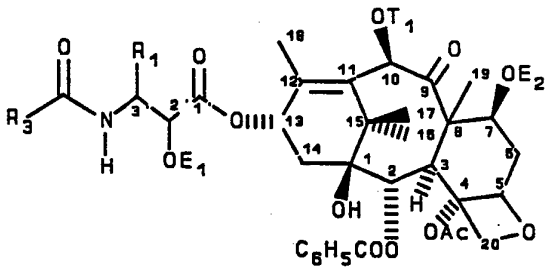
(54) Title: FURYL OR THIENYL CARBONYL SUBSTITUTED TAXANES AND PHARMACEUTICAL COMPOSITIONS CONTAINING THEM



(3)

(57) Abstract

Taxane derivatives of formula (3) wherein R_1 is phenyl or p-nitrophenyl, R_3 is furyl or thienyl, T_1 is hydrogen, hydroxyl protecting group, or $-COT_2$, T_2 is H, C_1-C_6 alkyl, C_2-C_6 alkenyl, C_2-C_6 alkynyl or monocyclic aryl, Ac is acetyl, and E_1 and E_2 are independently selected from hydrogen and functional groups which increase the water solubility of the taxane derivative are useful as antitumor agents.

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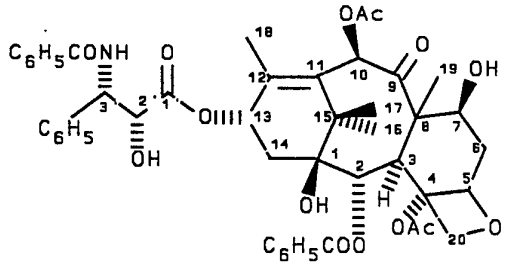
FURYL OR THIENYL CARBONYL SUBSTITUTED TAXANES AND PHARMACEUTICAL COMPOSITIONS CONTAINING THEM

BACKGROUND OF THE INVENTION

The present invention is directed to novel taxanes which have utility as antileukemia and antitumor agents.

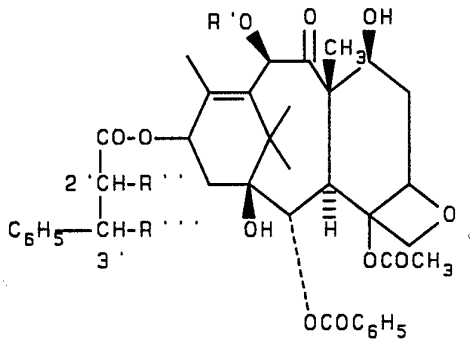
The taxane family of terpenes, of which taxol is a member, has attracted considerable interest in both the biological and chemical arts. Taxol is a promising cancer chemotherapeutic agent with a broad spectrum of antileukemic and tumor-inhibiting activity. Taxol has a 2'R, 3'S configuration and the following structural formula:



(1)

wherein Ac is acetyl. Because of this promising activity, taxol is currently undergoing clinical trials in both France and the United States.

Colin et al. reported in U.S. Patent No. 4,814,470 that taxol derivatives having structural formula **(2)** below, have an activity significantly greater than that of taxol **(1)**.



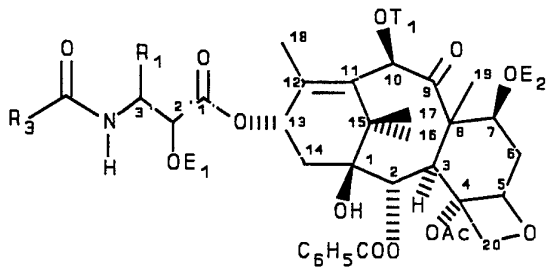
R' represents hydrogen or acetyl and one of R'' and R''' represents hydroxy and the other represents tert-butoxy-carbonylamino and their stereoisomeric forms, and mixtures thereof. The compound of formula **(2)** in which R'' is hydroxy, R''' is tert-butoxycarbonylamino having the 2'R, 3'S configuration is commonly referred to as taxotere.

Although taxol and taxotere are promising chemotherapeutic agents, they are not universally effective. Accordingly, a need remains for additional chemotherapeutic agents.

SUMMARY OF THE INVENTION

Among the objects of the present invention, therefore, is the provision of novel taxane derivatives which are valuable antileukemia and antitumor agents.

Briefly, therefore, the present invention is directed to taxane derivatives of the formula:



(3)

wherein

R_1 is phenyl or p-nitrophenyl-,

R_3 is furyl or thienyl,

T_1 is hydrogen, hydroxyl protecting group, or $-COT_2$,

T_2 is H, C_1-C_6 alkyl, C_2-C_6 alkenyl, C_2-C_6 alkynyl or monocylic aryl,

Ac is acetyl, and

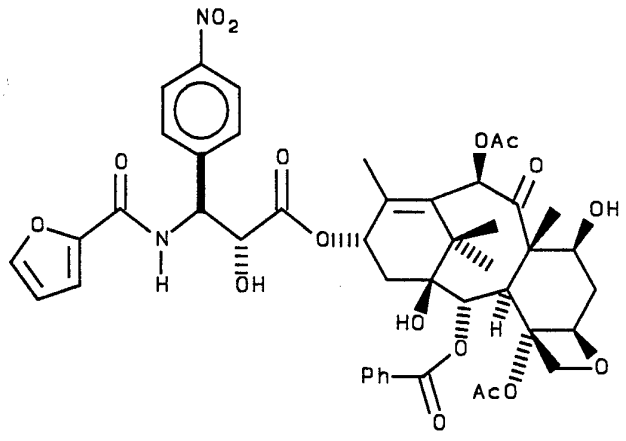
E_1 and E_2 are independently selected from hydrogen, hydroxy protecting groups and functional groups

which increase the water solubility of the taxane derivative.

Other objects and features of this invention will be in part apparent and in part pointed out hereinafter.

DETAILED DESCRIPTION OF THE PREFERRED EMBODIMENTS

In accordance with the present invention, it has been discovered that compounds having structural formula **(3)**, in general, and structural formulas **(4)**, **(5)**, and **(6)**, in particular show remarkable properties, in vitro, and are valuable antileukemia and antitumor agents. Their biological activity has been determined in vitro, using tubulin assays according to the method of Parness et al., J. Cell Biology, 91: 479-487 (1981) and human cancer cell lines, and is comparable to that exhibited by taxol and taxotere.



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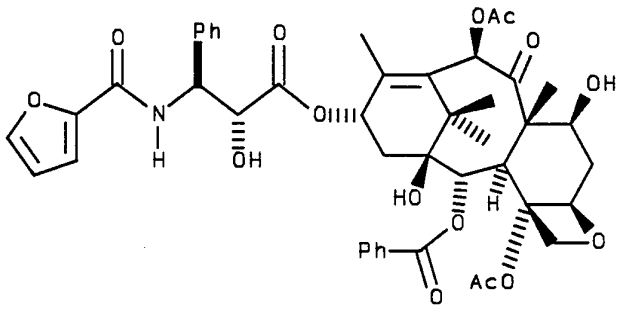

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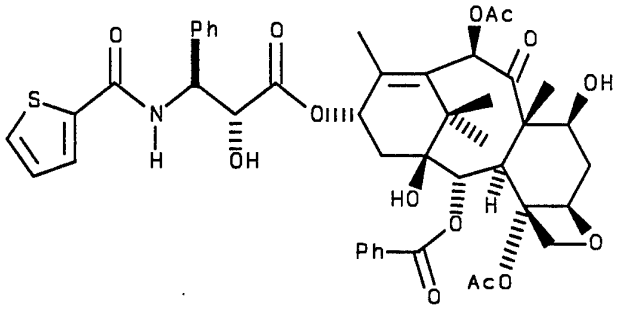
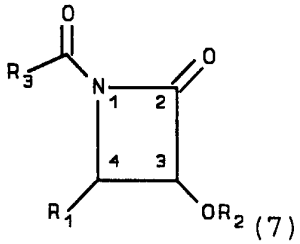


(6)

Taxanes having formulas **(4)**, **(5)** and **(6)** which have the 2'R, 3'S configuration may be obtained by reacting a ß-lactam with metal alkoxides having the taxane tetracyclic nucleus and a C-13 metallic oxide substituent to form compounds having a ß-amido ester substituent at C-13. The ß-lactams have the following structural formula:



(7)

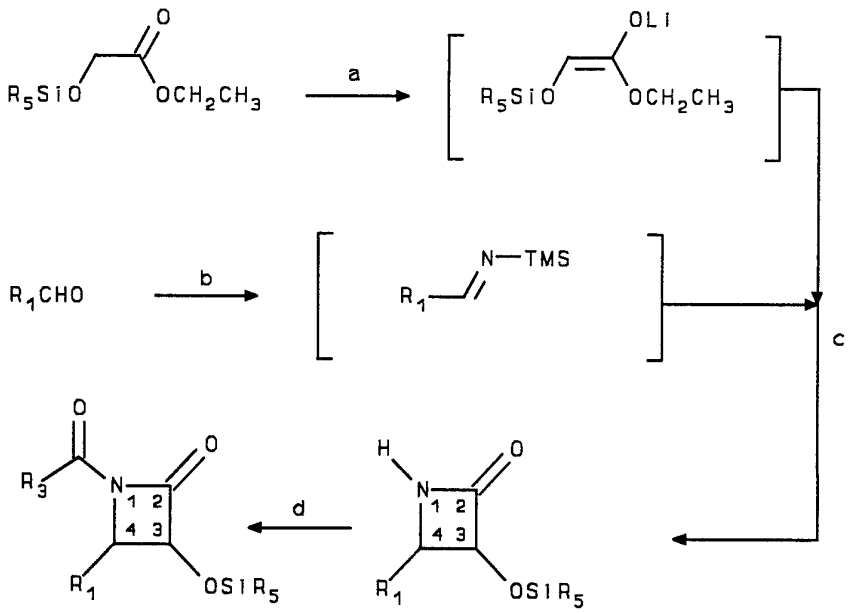
wherein

R_1 is phenyl or p-nitrophenyl,

R_2 is a hydroxy protecting group, and

R_3 is furyl or thienyl.

ß-lactams **(7)** can be prepared from readily available starting materials, as is illustrated by the following reaction scheme:



reagents

(a) lithium diisopropyl amide, tetrahydrofuran ("THF"), -78°C to -50°C;

(b) lithium hexamethyl disilazane, THF, -78°C to 0°C;

(c) THF, -78°C to 25°C, (2h); and

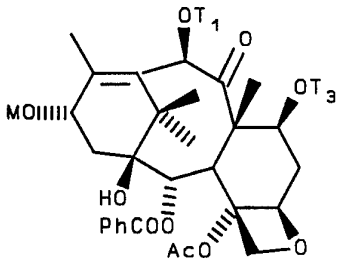
(d) triethylamine and an acyl chloride.

The 3-hydroxyl protecting group shown in the above reaction scheme is $-SiR_5$ wherein R_5 is trialkyl or triaryl such as triethyl. The 3-hydroxyl may be protected with other standard protecting groups such as 1-ethoxyethyl, or 2,2,2-trichloroethoxymethyl. Additional hydroxy protecting groups and the synthesis thereof may be found in "Protective groups in Organic Synthesis" by T.W. Greene, John Wiley & Sons, 1981.

The racemic ß-lactams may be resolved into the pure enantiomers prior to protection by recrystallization of the corresponding 2-methoxy-2-(trifluoromethyl) phenylacetic esters. However, the reaction described hereinbelow in which the ß-amido ester side chain is attached has the advantage of being highly diastereo-

selective, thus permitting the use of a racemic mixture of side chain precursor.

The metal alkoxides having the taxane tetracyclic nucleus and a C-13 metallic oxide substituent have the following structural formula:

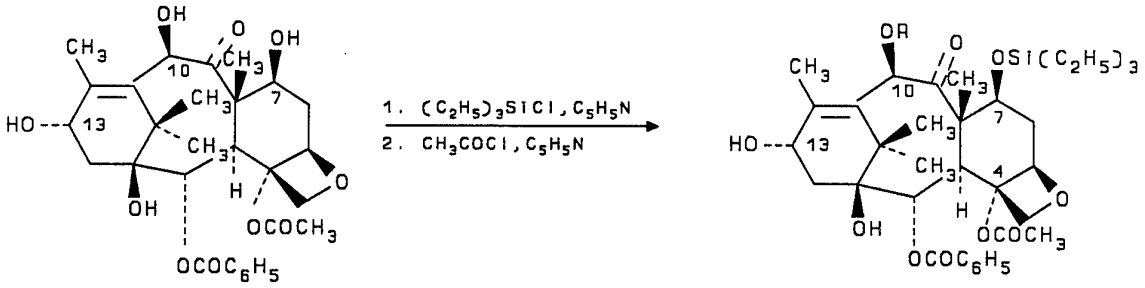


(8)

wherein T_1 is hydrogen, hydroxyl protecting group, or $-COT_2$; T_2 is H, C_1-C_6 alkyl, C_2-C_6 alkenyl, C_2-C_6 alkynyl or monocylic aryl; T_3 is hydrogen or a hydroxy protecting group; and M is a metal, preferably selected from the group comprising Group IA, Group IIA and transition metals, most preferably, Li, Mg, Na, K or Ti.

Preferably, the metal alkoxides are prepared by reacting an alcohol having the taxane tetracyclic nucleus and a C-13 hydroxyl group with an organometallic compound in a suitable solvent. Most preferably, the alcohol is a protected baccatin III, in particular, 7-O-triethylsilyl baccatin III (which can be obtained as described by Greene, et al. in JACS 110: 5917 (1988) or by other routes) or 7,10-bis-O-triethylsilyl baccatin III.

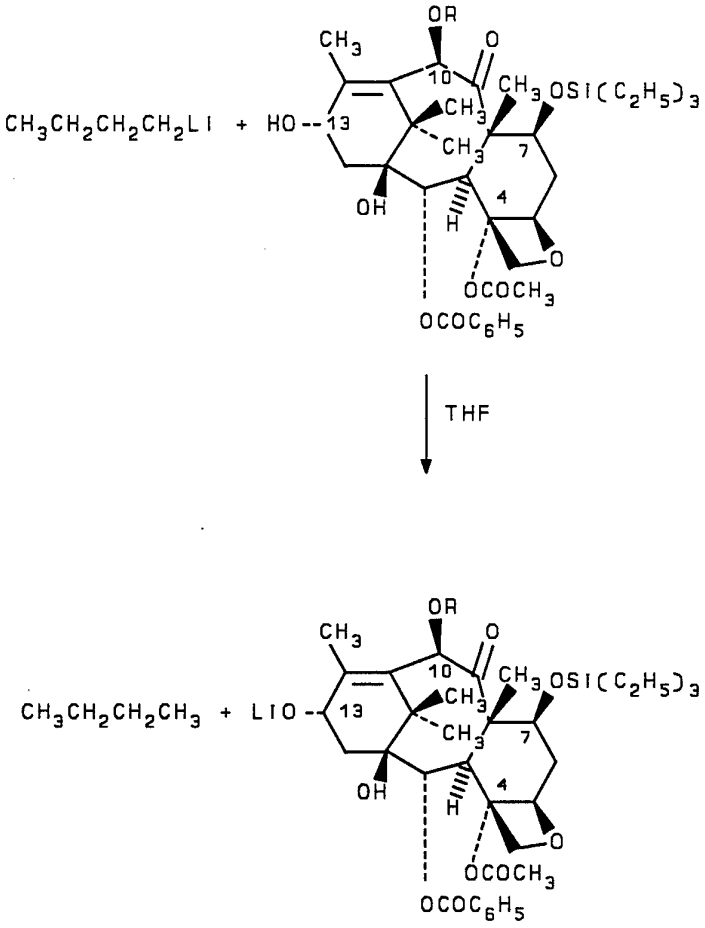
As reported in Greene et al., 10-deacetyl baccatin III is converted to 7-O-triethylsilyl-10-deacetyl baccatin III according to the following reaction scheme:



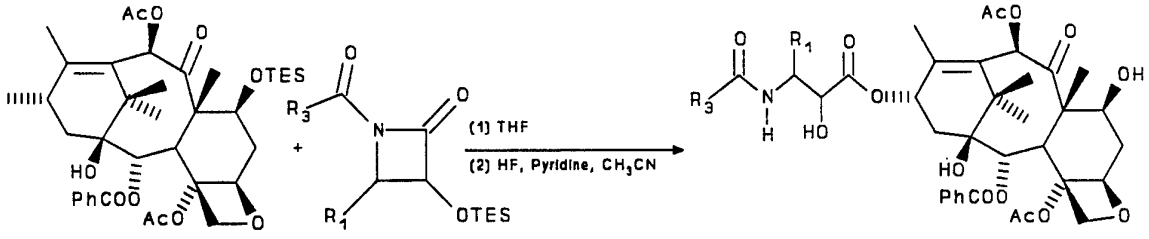
(9) **(10)** a, T_1=H
b, T_1=$COCH_3$

Under what is reported to be carefully optimized conditions, 10-deacetyl baccatin III is reacted with 20 equivalents of $(C_2H_5)_3SiCl$ at 23°C under an argon atmosphere for 20 hours in the presence of 50 ml of pyridine/mmol of 10-deacetyl baccatin III to provide 7-triethylsilyl-10-deacetyl baccatin III **(10a)** as a reaction product in 84-86% yield after purification. The reaction product may then optionally be acetylated with 5 equivalents of CH_3COCl and 25 mL of pyridine/mmol of **10a** at 0 °C under an argon atmosphere for 48 hours to provide 86% yield of 7-O-triethylsilyl baccatin III **(10b)**. Greene, et al. in JACS 110, 5917 at 5918 (1988).

The 7-O-triethylsilyl baccatin III **(10b)** is reacted with an organometallic compound such as n-butyllithium in a solvent such as tetrahydrofuran (THF), to form the metal alkoxide 13-O-lithium-7-O-triethylsilyl baccatin III **(11)** as shown in the following reaction scheme:



As shown in the following reaction scheme, 13-O-lithium-7-O-triethylsilyl baccatin III **(11)** reacts with ß-lactam **(7)** in which R_2 is triethyl silyl to provide an intermediate in which the C-7 and C-2' hydroxyl groups are protected with a triethylsilyl group. The triethyl-silyl groups are then hydrolyzed under mild conditions so as not to disturb the ester linkage or the taxane substituents.



wherein

R_1 is phenyl or p-nitrophenyl, and

R_3 is phenyl.

Both the conversion of the alcohol to the metal alkoxide and the ultimate synthesis of the taxane derivative can take place in the same reaction vessel. Preferably, the ß-lactam is added to the reaction vessel after formation therein of the metal alkoxide.

Compounds of formula (1) of the instant invention are useful for inhibiting tumor growth in animals including humans and are preferably administered in the form of a pharmaceutical composition comprising an effective antitumor amount of compound of the instant invention in combination with a pharmaceutically acceptable carrier or diluent.

Antitumor compositions herein may be made up in any suitable form appropriate for desired use; e.g., oral, parenteral or topical administration. Examples of parenteral administration are intramuscular, intravenous, intraperitoneal, rectal and subcutaneous administration.

The diluent or carrier ingredients should not be such as to diminish the therapeutic effects of the antitumor compounds.

Suitable dosage forms for oral use include tablets, dispersible powders, granules, capsules, suspensions, syrups, and elixirs. Inert diluents and carriers for tablets include, for example, calcium carbonate, sodium carbonate, lactose and talc. Tablets may also contain granulating and disintegrating agents such as starch and alginic acid, binding agents such as starch, gelatin and acacia, and lubricating agents such as magnesium stearate, stearic acid and talc. Tablets may be uncoated or may be coated by unknown techniques; e.g., to delay disintegration and absorption. Inert diluents and carriers which may be used in capsules include, for example, calcium carbonate, calcium phosphate and kaolin.

Suspensions, syrups and elixirs may contain conventional excipients, for example, methyl cellulose, tragacanth, sodium alginate; wetting agents, such as lecithin and polyoxyethylene stearate; and preservatives, e.g., ethyl-p-hydroxybenzoate.

Dosage forms suitable for parenteral administration include solutions, suspensions, dispersions, emulsions and the like. They may also be manufactured in the form of sterile solid compositions which can be dissolved or suspended in sterile injectable medium immediately before use. They may contain suspending or dispersing agents known in the art.

The water solubility of compounds of formula **(3)** may be improved by modification of the C2′ and/or C7 substituents to incorporate appropriate functional groups, E_1 and E_2. For increased water solubility, E_1 and E_2 may independently be hydrogen and $-COGCOR^1$ wherein

G is ethylene, propylene, -CH=CH-, 1,2-cyclohexane, or 1,2-phenylene,

R^1 = OH base, NR^2R^3, OR^3, SR^3, $OCH_2CONR^4R^5$, or OH

R^2 = hydrogen, methyl

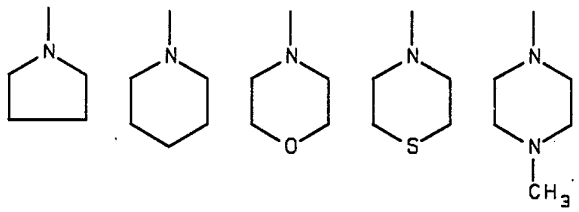
R^3 = $(CH_2)_nNR^6R^7$; $(CH_2)_n\overset{\oplus}{N}R^6R^7R^8X^{\ominus}$

n = 1 to 3

R^4 = hydrogen, lower alkyl containing 1 to 4 carbons

R^5 = hydrogen, lower alkyl containing 1 to 4 carbons, benzyl, hydroxyethyl, CH_2CO_2H, dimethylaminoethyl

R^6R^7 = lower alkyl containing 1 or 2 carbons, benzyl or R^6 and R^7 together with the nitrogen atom of NR^6R^7 form the following rings



R^8 = lower alkyl containing 1 or 2 carbons, benzyl

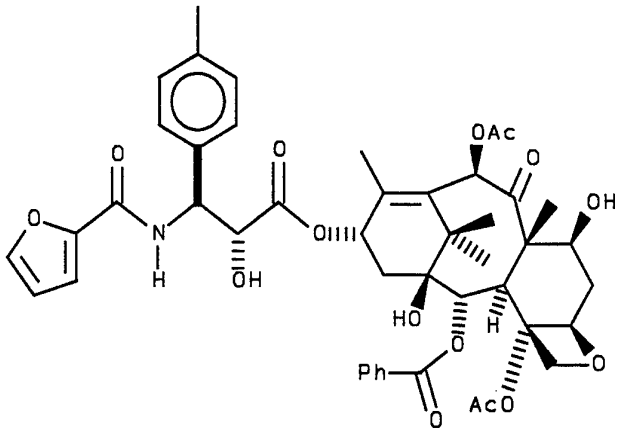
X^{δ} = halide

base = NH_3, $(HOC_2H_4)_3N$, $N(CH_3)_3$, $CH_3N(C_2H_4OH)_2$, $NH_2(CH_2)_6NH_2$, N-methylglucamine, NaOH, KOH.

The preparation of compounds in which X_1 or X_2 is $-COGCOR^1$ is set forth in Hangwitz U.S. Patent 4,942,184 which is incorporated herein by reference.

The following examples illustrate the invention.

EXAMPLE 1



(4)

Preparation of N-debenzoyl-N-(furoyl)-3'-desphenyl-3'-(4-nitrophenyl) taxol.

To a solution of 7-triethylsilyl baccatin III (200 mg, 0.286 mmol) in 2 mL of THF at -45 °C was added dropwise 0.174 mL of a 1.63M solution of nBuLi in hexane. After 0.5 h at -45 °C, a solution of cis-1-(furoyl)-3-triethylsilyloxy-4-(4-nitrophenyl)azetidin-2-one (596 mg, 1.43 mmol) in 2 mL of THF was added dropwise to the mixture. The solution was warmed to 0 °C and kept at that

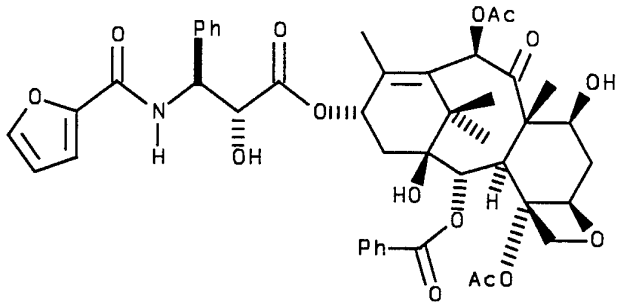
temperature for 1 h before 1 mL of a 10% solution of AcOH in THF was added. The mixture was partitioned between saturated aqueous $NaHCO_3$ and 60/40 ethyl acetate/hexane. Evaporation of the organic layer gave a residue which was purified by filtration through silica gel to give 320 mg of a mixture containing (2'R,3'S)-2',7-(bis)triethylsilyl-N-debenzoyl-N-(furoyl)-3'-desphenyl-3'-(4-nitrophenyl) taxol and a small amount of the (2'S,3'R) isomer.

To a solution of 320 mg (0.286 mmol) of the mixture obtained from the previous reaction in 18 mL of acetonitrile and 0.93 mL of pyridine at 0 °C was added 2.8 mL of 48% aqueous HF. The mixture was stirred at 0 °C for 3 h, then at 25 °C for 13 h, and partitioned between saturated aqueous sodium bicarbonate and ethyl acetate. Evaporation of the ethyl acetate solution gave 254 mg of material which was purified by flash chromatography to give 187 mg (74%)N-debenzoyl-N-(furoyl)-3'-desphenyl-3'-(4-nitrophenyl) taxol, which was recrystallized from methanol/water.

m.p.184-185 °C; $[\alpha]^{25}_{Na}$-60.0° (c 0.006, $CHCl_3$).

^1H NMR ($CDCl_3$, 300 MHz) δ 8.26 (d, J = 8.79 Hz, 2H, Ar-NO_2), 8.12 (d, J=7.2 Hz, 2H, benzoate ortho), 7.68 (d, J=8.8 Hz 2H, benzamide ortho), 7.7-7.47 (m, 6 H, aromatic), 7.3 (d, J = 9.3 Hz, 1H, NH), 7.02(d, J=3.3 Hz, 1H, furyl), 6.48(dd, J=3.3 Hz, 1.65 Hz, 1H, furyl), 6.27 (s, 1H Hz, H10), 6.26 (dd, J = 8.5, 8.5 Hz, 1H, H13), 5.87 (dd, J = 8.8, 1.65 Hz, 1H, H3'), 5.65 (d, J = 6.6 Hz, 1H, H2β), 4.93 (d, J = 8.2 Hz, 1H, H5), 4.79 (dd, J = 2.7, 1.4 Hz, 1H, H2'), 4.38 (m, 1H, H7), 4.29 (d, J = 8.4 Hz, 1H, H20α), 4.18 (d, J = 8.4 Hz, 1H, H20β), 3.97 (d, J=3.3 Hz, 1H, 2'OH), 3.79 (d, J = 6.6 Hz, 1H, H3), 2.5 (m, 1H, H6α), 2.4(m, 1H, 7OH), 2.38 (s, 3H, 4Ac), 2.27 (m, 2H, H14), 2.22 (s, 3H, 10Ac), 1.88 (m, 1H, H6β), 1.81 (br s, 3H, Me18), 1.78 (s, 1H, 1OH), 1.68 (s, 3H, Me19), 1.21 (s, 3H, Me17), 1.13(s, 3H, Me16).

EXAMPLE 2



Preparation of N-debenzoyl-N-(2-furoyl) taxol.

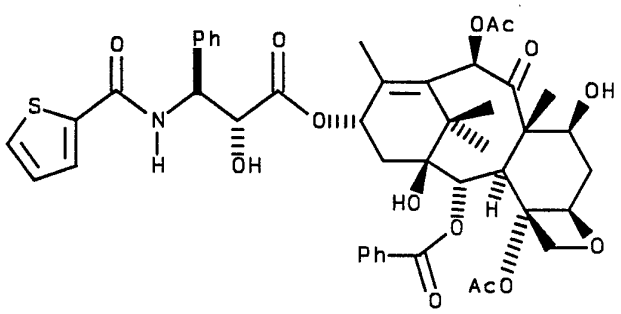
To a solution of 7-triethylsilyl baccatin III (200 mg, 0.286 mmol) in 2 mL of THF at -45 °C was added dropwise 0.174 mL of a 1.63M solution of nBuLi in hexane. After 0.5 h at -45 °C, a solution of cis-1-(2-furoyl)-3-triethylsilyloxy-4-phenylazetidin-2-one (531 mg, 1.43 mmol) in 2 mL of THF was added dropwise to the mixture. The solution was warmed to 0 °C and kept at that temperature for 1 h before 1 mL of a 10% solution of AcOH in THF was added. The mixture was partitioned between saturated aqueous $NaHCO_3$ and 60/40 ethyl acetate/hexane. Evaporation of the organic layer gave a residue which was purified by filtration through silica gel to give 306 mg of a mixture containing (2'R,3'S)-2',7-(bis)triethylsilyl-N-debenzoyl-N-(2-furoyl) taxol and a small amount of the (2'S,3'R) isomer.

To a solution of 306 mg (0.286 mmol) of the mixture obtained from the previous reaction in 18 mL of acetonitrile and 0.93 mL of pyridine at 0 °C was added 2.8 mL of 48% aqueous HF. The mixture was stirred at 0 °C for 3 h, then at 25 °C for 13 h, and partitioned between saturated aqueous sodium bicarbonate and ethyl acetate. Evaporation of the ethyl acetate solution gave 240 mg of material which was purified by flash chromatography to give 192 mg (80%) of N-debenzoyl-N-(2-furoyl) taxol, which was recrystallized from methanol/water.

m.p.172-174 °C; $[\alpha]^{25}_{Na}$-49.6° (c 0.0103, $CHCl_3$).

^{1}H NMR ($CDCl_3$, 300 MHz) δ 8.12 (d, J = 7.1 Hz, 2H, benzoate ortho), 7.64-7.33 (m,9H, aromatic), 7.19 (d, J = 8.8 Hz, 1H, NH), 7.01 (d,J= 3.3 Hz, 1H, furyl), 6.45 (dd,1H, furyl),6.26(s, 1H, H10), 6.21 (dd, J = 8.8, 8.8 Hz, 1H, H13), 5.72 (dd, J = 8.8, 1.7 Hz, 1H, H3'), 5.66 (d, J = 7.1 Hz, 1H, H2ß), 4.92 (d, J = 8.2 Hz, 1H, H5), 4.75 (br s,1H, H2'), 4.40 (m, 1H, H7), 4.28 (d, J = 8.2 Hz, 1H, H20α), 4.18 (d, J = 8.2 Hz, 1H, H20ß), 3.78 (d, J = 6.6 Hz, 1H, H3), 3.69 (d,J = 3.8 Hz,1H, 2'OH), 2.53 (m, 1H, H6α), 2.47 (br s,1H, 7OH), 2.36 (s, 3H, 4Ac), 2.32 (m, 2H, H14), 2.22 (s, 3H, 10Ac), 1.84 (m, 1H, H6ß), 1.79 (br s, 3H, Me18), 1.67 (s, 3H, Me19), 1.22 (s, 3H, Me17), 1.13 (s, 3H, Me16).

EXAMPLE 3



Preparation of N-debenzoyl-N-(2-thienoyl) taxol.

To a solution of 7-triethylsilyl baccatin III (200 mg, 0.286 mmol) in 2 mL of THF at -45 °C was added dropwise 0.174 mL of a 1.63M solution of nBuLi in hexane. After 0.5 h at -45 °C, a solution of cis-1-(2-thienoyl)-3-triethylsilyloxy-4-phenylazetidin-2-one (554 mg, 1.43 mmol) in 2 mL of THF was added dropwise to the mixture. The solution was warmed to 0 °C and kept at that temperature for 1 h before 1 mL of a 10% solution of AcOH in THF was added. The mixture was partitioned between

saturated aqueous $NaHCO_3$ and 60/40 ethyl acetate/hexane. Evaporation of the organic layer gave a residue which was purified by filtration through silica gel to give 311 mg of a mixture containing (2'R,3'S)-2',7-(bis)triethylsilyl-N-debenzoyl-N-(2-thienoyl) taxol and a small amount of the (2'S,3'R) isomer.

To a solution of 311 mg (0.286 mmol) of the mixture obtained from the previous reaction in 18 mL of acetonitrile and 0.93 mL of pyridine at 0 °C was added 2.8 mL of 48% aqueous HF. The mixture was stirred at 0 °C for 3 h, then at 25 °C for 13 h, and partitioned between saturated aqueous sodium bicarbonate and ethyl acetate. Evaporation of the ethyl acetate solution gave 246 mg of material which was purified by flash chromatography to give 195 mg (80%) of N-debenzoyl-N-(2-thienoyl) taxol, which was recrystallized from methanol/water. m.p.218-219 °C; $[\alpha]^{25}_{Na}$-47.6° (c 0.0103, $CHCl_3$).

^{1}H NMR ($CDCl_3$, 300 MHz) δ 8.12 (d, J = 7.1 Hz, 2H, benzoate ortho), 7.64-7.31 (m, 10H, aromatic), 7.05 (dd, 1H, thienyl ring), 6.86 (d, J = 9.3 Hz, 1H, NH), 6.23 (s, 1H, H10), 6.21 (dd, J = 8.8, 8.8 Hz, 1H, H13), 5.75 (dd, J = 8.8, 2.2 Hz, 1H, H3'), 5.66 (d, J = 7.1 Hz, 1H, H2ß), 4.93 (dd, J = 9.3, 1.65 Hz, 1H, H5), 4.78 (dd,J = 5.0, 2.7 Hz,1H, H2'), 4.41 (m, 1H, H7), 4.28 (d, J = 8.2 Hz, 1H, H20α), 4.18 (d, J = 8.2 Hz, 1H, H20ß), 3.78 (d, J = 6.6 Hz, 1H, H3), 3.63 (d, J = 4.9 Hz,1H, 2'OH), 2.53 (m, 1H, H6α), 2.48 (d, J = 4.4 Hz,1H, 7OH), 2.36 (s, 3H, 4Ac), 2.30 (m, 2H, H14), 2.23 (s, 3H, 10Ac), 1.85 (m, 1H, H6ß), 1.78 (br s, 3H, Me18), 1.68 (s, 3H, Me19), 1.23 (s, 3H, Me17), 1.13 (s, 3H, Me16).

EXAMPLE 4

Tubulin binding assays were performed using compounds **(4)**, **(5)**, **(6)** and substantially as set forth in Parness et al., J. Cell Biology 91: 479-487 (1981) and

compared to taxol and taxotere. The results are presented in Table 1.

TABLE 1

Compound Name/Formula	Tubulin Assay Init. Peak	Rel. Rate
4	219	
5	92	
6	114	
Taxol	100	98
Taxotere	100	___

EXAMPLE 5

Taxanes 4, 5 and 6 was evaluated in in vitro cytotoxicity activity against human colon carcinoma cells HCT-116 and HCT-116/VM46. The HCT116/VM cells are cells that have been selected for teniposide resistance and express the multidrug resistance phenotype, including resistance to taxol. Cytotoxicity was assessed in HCT116 and HCT VM46 human colon carcinoma cells by XTT (2,3-bis(2-methoxy-4-nitro-5-sulfophenyl)-5-[(phenyl-amino)carbonyl]-2H-t etrazolium hydroxide) assay (Scudiero et al, "Evaluation of a soluble tetrazolium/formazan assay for cell growth and drug sensitivity in culture using human and other tumor cell lines", Cancer Res. 48:4827-4833, 1988). Cells were plated at 4000 cells/well in 96 well microtiter plates and 24 hours later drugs were added and serial diluted. The cells were incubated at 37°C for 72 hours at which time the tetrazolium dye, XTT, was added. A dehydrogenase enzyme in live cells reduces the XTT to a form that absorbs light at 450 nm which can be quantitated spectrophotometrically. The greater the absorbance the greater the number of live cells. The results are expressed as an IC_{50} which is the drug

concentration required to inhibit cell proliferation (i.e. absorbance at 450 nm) to 50% of that of untreated control cells. The results are presented in Table 2. Lower numbers indicate greater activity.

TABLE 2

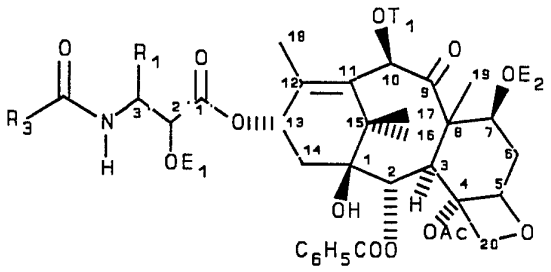
Compound Name/Formula	IC_{50} HCT 116	HCT VM46
4	0.002	0.883
5	0.003	0.300
6	0.002	0.202
Taxol	0.004	0.536
Taxotere	0.007	0.246

In view of the above, it will be seen that the several objects of the invention are achieved.

As various changes could be made in the above compositions without departing from the scope of the invention, it is intended that all matter contained in the above description be interpreted as illustrative and not in a limiting sense.

WHAT I CLAIM IS:

1. A taxane derivative of the formula



wherein

R_1 is phenyl or p-nitrophenyl,

R_3 is furyl or thienyl,

T_1 is hydrogen, hydroxyl protecting group, or $-COT_2$,

T_2 is H, C_1-C_6 alkyl, C_2-C_6 alkenyl, C_2-C_6 alkynyl or monocylic aryl,

Ac is acetyl, and

E_1 and E_2 are independently selected from hydrogen, hydroxyl protecting groups, and functional groups which increase the water solubility of the taxane derivative.

2. The taxane derivative of claim 1 wherein T_1 is $-COCH_3$, and E_1 and E_2 are hydrogen.

3. The taxane derivative of claim 1 wherein the taxane derivative has the 2'R, 3'S configuration.

4. The taxane derivative of claim 1 wherein R_1 is phenyl, T_1 is $-OCOCH_3$, and at least one of E_1 and E_2 is $-COGCOR^1$ wherein

G is ethylene, propylene, CH=CH, 1,2-cyclohexane, or 1,2-phenylene,

R^1 = OH base, NR^2R^3, OR^3, SR^3, $OCH_2CONR^4R^5$, OH

R^2 = hydrogen, methyl

R^3 = $(CH_2)_nNR^6R^7$; $(CH_2)_nN^{\oplus}R^6R^7R^8X^{\ominus}$

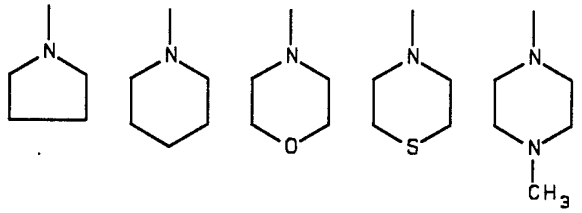
n = 1 to 3

R^4 = hydrogen, lower alkyl containing 1 to 4 carbons

R^5 = hydrogen, lower alkyl containing 1 to 4 carbons, benzyl, hydroxyethyl, CH_2CO_2H, dimethylaminoethyl

R^6R^7 = lower alkyl containing 1 or 2 carbons, benzyl or R^6 and

R^7 together with the nitrogen atom of NR^6R^7 form the following rings



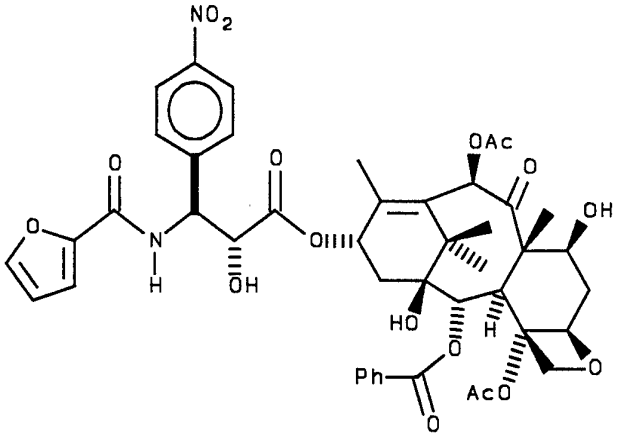
R^8 = lower alkyl containing 1 or 2 carbons, benzyl

$X^{\ominus}$ = halide

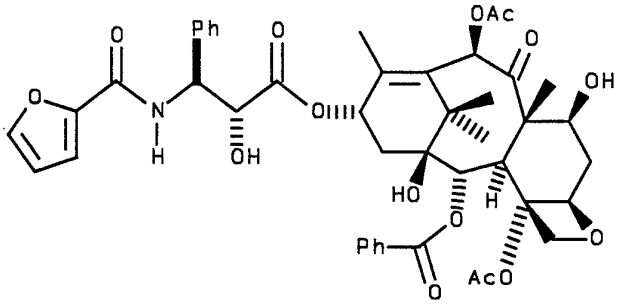
base = NH_3, $(HOC_2H_4)_3N$, $N(CH_3)_3$, $CH_3N(C_2H_4OH)_2$, $NH_2(CH_2)_6NH_2$, N-methylglucamine, NaOH, KOH.

5. The taxane derivative of claim 1 wherein T_1 is H or $-COT_2$, T_2 is C_1-C_6 alkyl, and E_1 and E_2 are hydrogen.

6. A taxane derivative of the formula

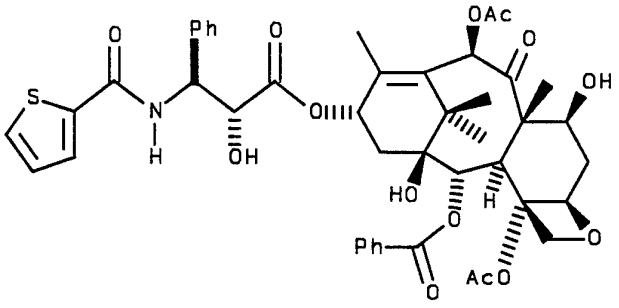


(4)



(5)

or



(6)

wherein

Ph is phenyl, and

Ac is acetyl.

7. A pharmaceutical composition which contains the taxane derivative of claim 1 and one or more pharmacologically acceptable, inert or physiologically active diluents or adjuvants.

INTERNATIONAL SEARCH REPORT

International application No.
PCT/US93/10473

A. CLASSIFICATION OF SUBJECT MATTER

IPC(5) :C07D 333/10,307/12,305/14; A61K 31/34,31/38,31/335
US CL :549/60,473,510,511; 514/444,449,471
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)

U.S. : 549/60,473,510,511; 514/444,449,471

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)

CAS Online

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	US,A, 4,942,184 (HAUGWITZ ET AL) 17 JULY 1990, ENTIRE DOCUMENT.	1-7

☐ Further documents are listed in the continuation of Box C. ☐ See patent family annex.

*	Special categories of cited documents:	"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
"A"	document defining the general state of the art which is not considered to be part of particular relevance	"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
"E"	earlier document published on or after the international filing date	"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
"L"	document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)	"&"	document member of the same patent family
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