653247 27/23/92

AUSTRALIA
Patents Act 1990

Patent Request/Notice of Entitlement

We, FLORIDA STATE UNIVERSITY, of 2035 East Paul Dirac Drive, Tallahassee, Florida 32310, United States of America, being the Applicant and Nominated Person, request the grant of a patent for an invention entitled:

"NOVEL ALKOXY SUBSTITUTED TAXANES AND PHARMACEUTICAL COMPOSITIONS CONTAINING THEM",

which is described in the accompanying standard complete specification.

Convention priority is claimed from the following basic applications:

Application Number	Country	Country Code	Date of Application
07/763,805	United States of America	U.S.	23rd September 1991
07/863,198	United States of America	U.S.	3rd April 1992

The basic applications were filed in the joint names of Robert A. Holton and Ronald J. Beidiger, who are the actual inventors of the invention.

We have entitlement from the actual inventors, as well as from the applicants of the basic applications, by assignment.

The basic applications were the first applications made in a Convention country in respect of the invention.

Our address for service is care of E. F. WELLINGTON & CO., Patent Attorneys, 312 St. Kilda Road, Melbourne, Victoria 3004, Australia.

DATED this 4th day of September 1992

For and on behalf of
FLORIDA STATE UNIVERSITY,
By:

BRUCE S. WELLINGTON
Patent Attorneys for Applicant
and Nominated Person

To: The Commissioner of Patents,
Commonwealth of Australia
C/KA/6973/3

M 039205 040992

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(12) PATENT ABRIDGMENT (11) Document No. AU-B-22123/92
(19) AUSTRALIAN PATENT OFFICE (10) Acceptance No. 653247

(54) Title
NOVEL ALKOXY SUBSTITUTED TAXANES AND PHARMACEUTICAL COMPOSITIONS CONTAINING THEM

International Patent Classification(s)
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763805	23.09.91	US UNITED STATES OF AMERICA
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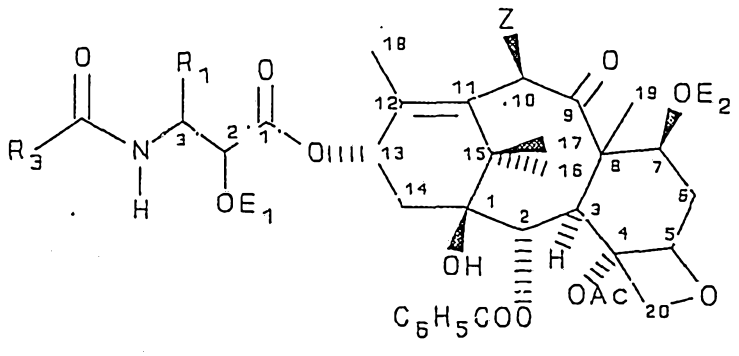
(56) Prior Art Documents
AU 22124/92 C07D 305/14

(57)

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

CLAIMS

1. A taxane derivative of the formula



(3)

including physiologically acceptable salts thereof, wherein

R_1 is phenyl or substituted phenyl,

R_3 is CH_3O-, or CH_3CH_2O-,

.../2

Z is $-OCOT_2$,

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, and functional groups which increase the water solubility of the taxane derivative, the functional groups having the formula $-COGCOR^1$ wherein:

G is ethylene, propylene, CHCH, 1,2-cyclohexylene, or 1,2-phenylene;

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

R^2 = hydrogen or methyl;

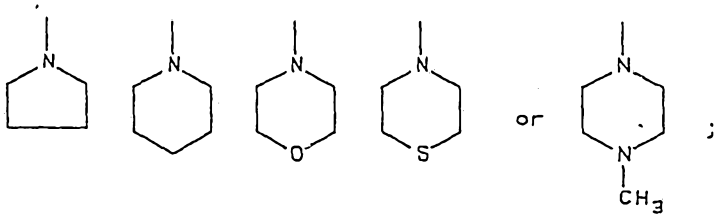
R^3 = $(CH_2)_nNR^6R^7$ or $(CH_2)_nNR^{\oplus 5}R^7R^8X^{\ominus}$;

n = 1 to 3;

R^4 = hydrogen or lower alkyl containing 1 to 4 carbons;

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

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



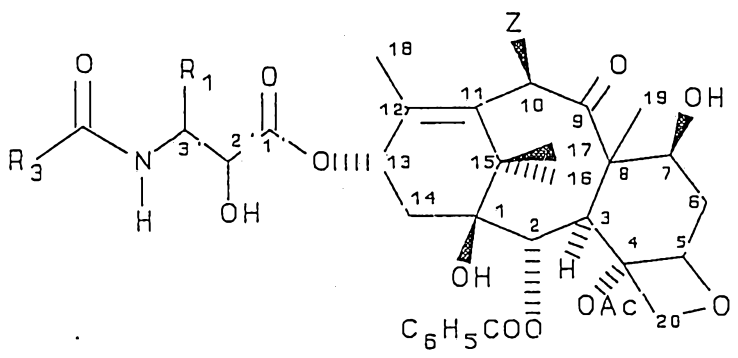
;

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

$X^{\ominus}$ = halide; and

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, or KOH.

4. A taxane derivative of the formula



(3)

including physiologically acceptable salts thereof, wherein

R_1 is phenyl or substituted phenyl,

R_3 is CH_3O-,

Z is $-OT_1$,

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, and

Ac is acetyl.

AUSTRALIA

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REGULATION 3.2

653247

FSUB 9815

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312 St. Kilda Road,
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Invention Title:

"NOVEL ALKOXY SUBSTITUTED TAXANES AND PHARMACEUTICAL COMPOSITIONS CONTAINING THEM"

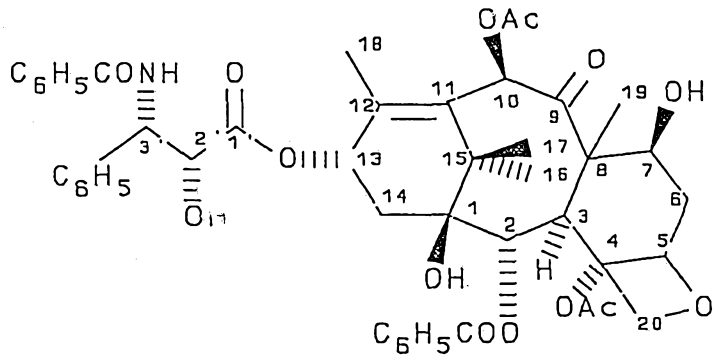
Details of Associated Provisional Applications Nos:

The following statement is a full description of this invention including the best method of performing it known to us.

BACKGROUND OF THE INVENTION

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

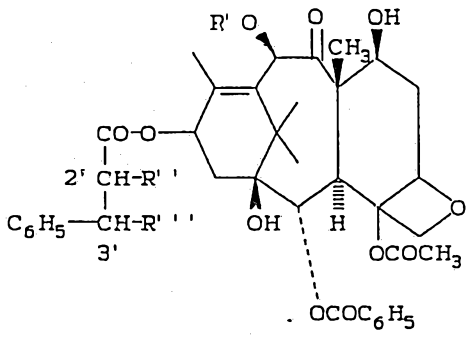
The taxane family of terpenes, of which taxol is a member, has attracted considerable interest in both the biological and chemical arts. Taxol is a promising cancer chemotherapeutic agent with a broad spectrum of antileukemic and tumor-inhibiting activity. Taxol has a 2'R, 3'S configuration and the following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



(2)

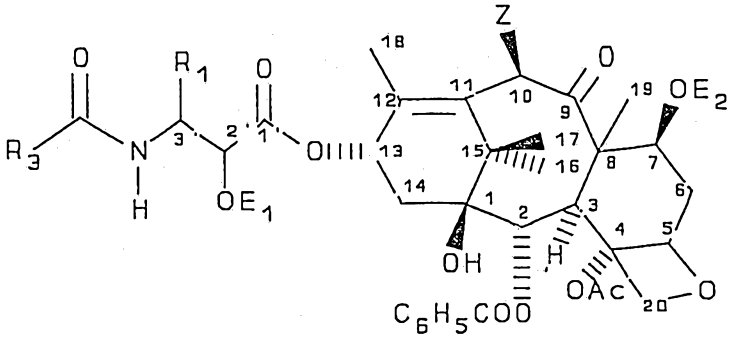
R' represents hydrogen or acetyl and one of R'' and R''' represents hydroxy and the other represents tert-butoxycarbonylamino and their stereoisomeric forms, and mixtures thereof. The compound of formula (2) in which R'' is hydroxy, R''' is tert-butoxycarbonylamino having the 2'R, 3'S configuration is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

including physiologically acceptable salts thereof, wherein

R_1 is phenyl or substituted phenyl,

R_3 is CH_3O-, or CH_3CH_2O-,

Z is $-OT_1$,

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.

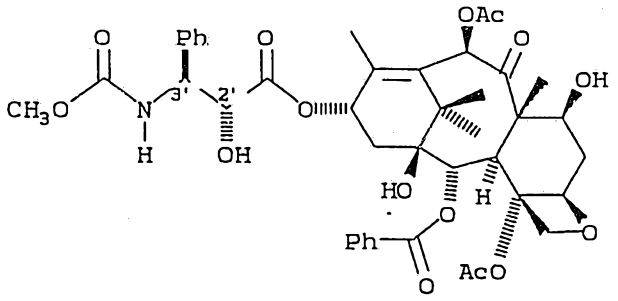
Other objects and features of this invention will be in part apparent and in part pointed out hereinafter.

DETAILED DESCRIPTION OF THE PREFERRED EMBODIMENTS

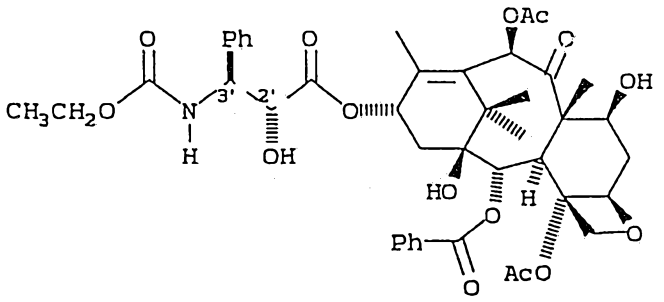
In accordance with the present invention, it has been discovered that compounds having structural formula (3), in general, and structural formulas (4) and (5), in particular show remarkable properties, in vitro, and are valuable antileukemia and antitumor agents. Their biological activity has been determined in vitro, using tubulin assays according to the method of Parness et al.,

AUSTRALIA PATENT OFFICE

J. Cell Biology, 91: 479-487 (1981) and human cancer cell lines, and is comparable to that exhibited by taxol and taxotere.

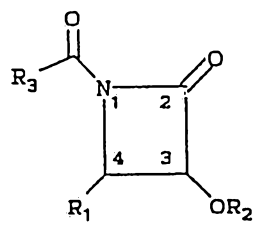


(4)



(5)

Taxanes having formulas (4) and (5) 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:



(6)

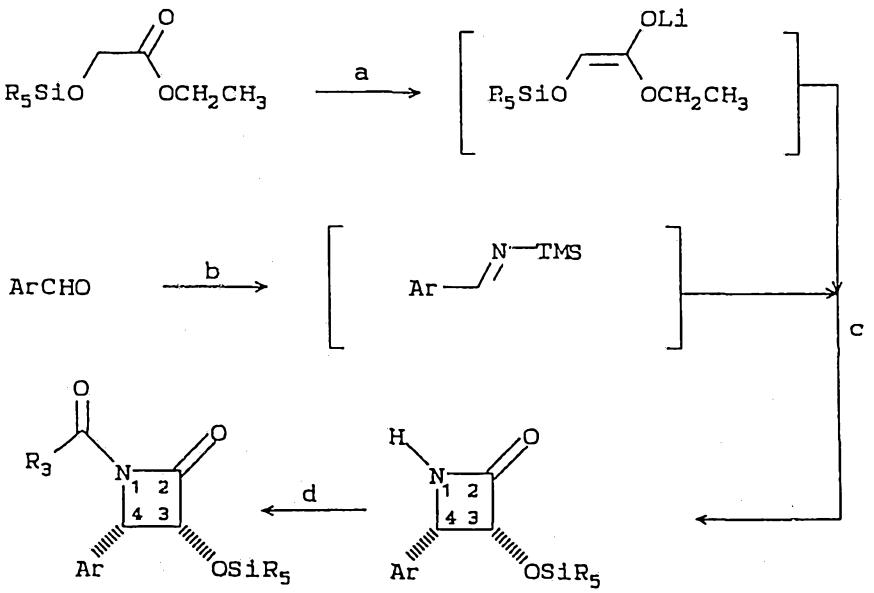
wherein

R_1 is phenyl or substituted phenyl,

R_2 is a hydroxy protecting group,

R_3 is CH_3O- or CH_3CH_2O-.

ß-lactams **(6)** can be prepared from readily available starting materials, as is illustrated by the following reaction scheme:



reagents

(a) LDA, THF, -78°C to -50°C;

(b) LHMDS, THF, -78°C to 0°C;

(c) THF, -78°C to 25°C, (2h); and

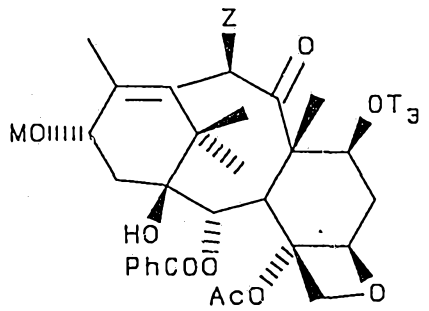
(d) treithylamine and an alkyl chloroformate (R_3 = alkoxycarbonyl).

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-ethoxy-ethyl, 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:



(7)

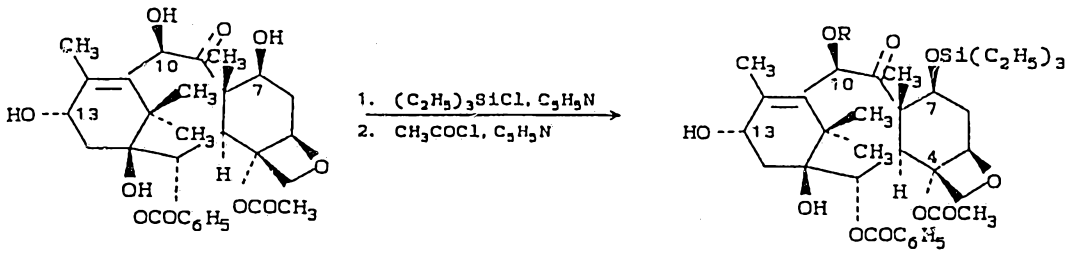
wherein Z is $-OT_1$; T_1 is hydrogen, hydroxyl protecting group, or $-COT_2$; T_2 is H, C_1-C_6 alkyl, C_2-C_6 alkenyl, C_2-C_6 alkynyl or monocylic aryl; T_3 is hydrogen or a hydroxy protecting group; and M is a metal, preferably selected from the group comprising Group IA, Group IIA and transition 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

AUSTRALIA PATENT OFFICE

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:

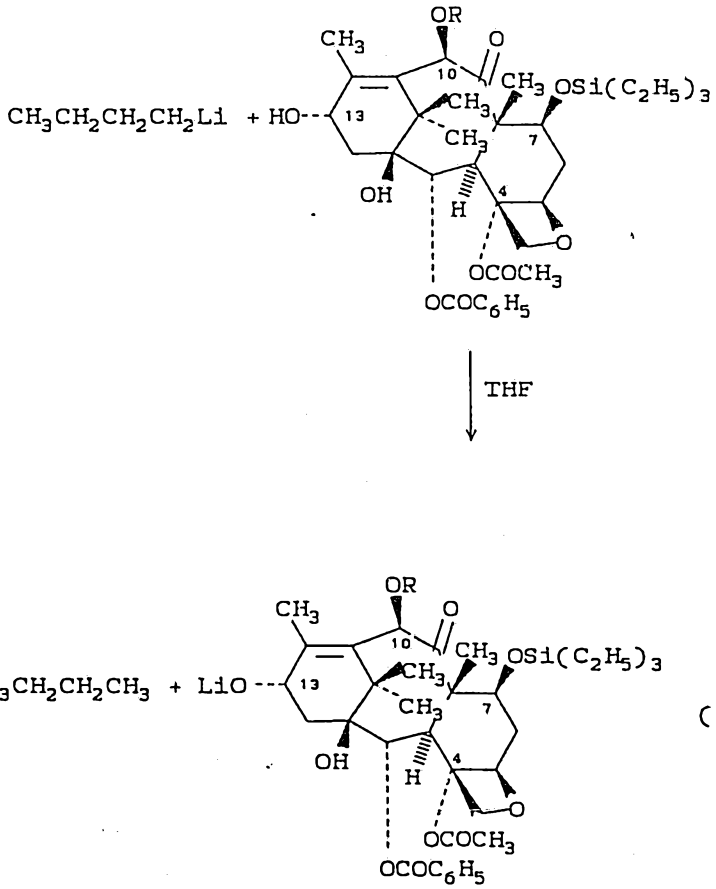


(8) (9) a, T_1=H b, T_1=$COCH_3$

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 **(9a)** 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 **9a** at 0 °C under an argon atmosphere for 48 hours to provide 86% yield of 7-O-triethylsilyl baccatin III **(9b)**. Greene, et al. in JACS 110, 5917 at 5918 (1988).

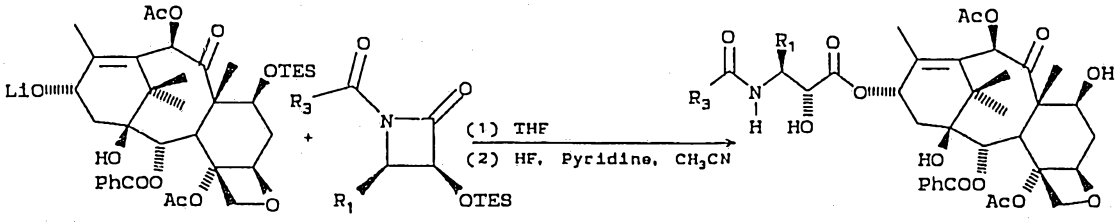
The 7-O-triethylsilyl baccatin III **(9b)** is reacted with an organometallic compound such as

n-butyllithium in a solvent such as tetrahydrofuran (THF), to form the metal alkoxide 13-O-lithium-7-O-triethylsilyl baccatin III **(10)** as shown in the following reaction scheme:



(10)

As shown in the following reaction scheme, 13-O-lithium-7-O-triethylsilyl baccatin III **(10)** reacts with ß-lactam **(6)** 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 triethylsilyl groups are then hydrolyzed under mild conditions so as not to disturb the ester linkage or the taxane substituents.



10

wherein

R_1 is phenyl or substituted phenyl,

R_3 is CH_3O- or CH_3CH_2O-.

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.

The present invention also provides pharmaceutical compositions containing a compound of formula **(3)**, in general, and the compounds of formulas **(4)** and **(5)** in particular, in combination with one or more pharmaceutically acceptable, inert or physiologically active, diluents or adjuvants.

These compositions may be presented in any form appropriate for the administration route envisaged. The parental route, and especially the intravenous route, is the preferential route for administration.

The compositions according to the invention for parenteral administration may be aqueous or nonaqueous sterile solutions, suspensions or emulsions. Propylene glycol, vegetable oils, especially olive oil, and

injectable organic esters, e.g. ethyl oleate, may be used as the solvent or the vehicle. These compositions may also contain adjuvants, especially wetting agents, emulsifiers or dispersants. The sterilization may be carried out in several ways, e.g. using a bacteriological filter, by incorporating sterilizing agents into the composition, by irradiation or by heating. They may also be in the form of sterile solid compositions which may be dissolved or dispersed in sterile water or any other injectable sterile medium.

The products of general formula (3) are more particularly used in the treatment of acute leukemias and solid tumors, at daily doses which are generally between 1 and 2 mg/kg by the intravenous (perfusion) route for an adult.

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, CHCH, 1,2-cyclohexylene, or 1,2-phenylene;

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

R^2 = hydrogen or methyl;

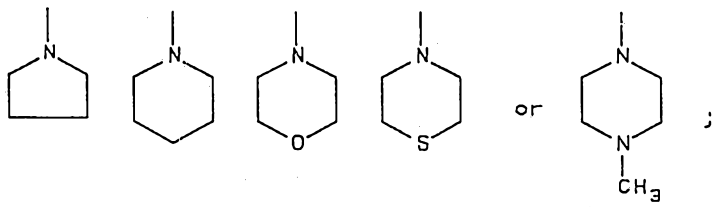
R^3 = $(CH_2)_nNR^6R^7$ or $(CH_2)_nNR^{\oplus 6}R^7R^8X^{\ominus}$;

n = 1 to 3;

R^4 = hydrogen or lower alkyl containing 1 to 4 carbons;

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

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



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

X^e = halide; and

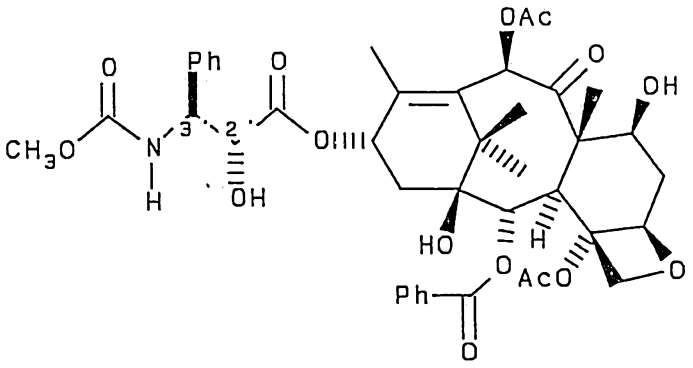
base = NH_3, $(HOC_2H_4)_3N$, $N(CH_3)_3$, $CH_3N(C_2H_4OH)_2$, $NH_2(CH_2)_6NH_2$, N-methylglucamine, NaOH, or KOH.

The preparation of compounds in which E_1 or E_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

Preparation of N-debenzoyl-N-methoxycarbonyl taxol.



(4)

To a solution of 7-triethylsilyl baccatin III (100 mg, 0.143 mmol)) in 1 mL of THF at -45°C was added dropwise 0.087 mL of a 1.63M solution of nBuLi in hexane. After 0.5 h at -45°C, a solution of cis-1-methoxycarbonyl

-3-triethylsilyloxy-4-phenylazetidin-2-one (252 mg, 0.715 mmol) in 1 mL of THF was added dropwise to the mixture. The solution was warmed to 0°C and kept at that temperture 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 129 mg of a mixture containing (2'R,3'S)-2',7-(bis)triethylsilyl-N-debenzoyl-N-methoxycarbonyl taxol and a small amount of the (2'S,3'R) isomer.

To a solution of 129 mg (0.112 mmol) of the mixture obtained from the previous reaction in 6 mL of acetonitrile and 0.3 mL of pyridine at 0°C was added 0.9 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 108 mg of material which was purified by flash chromatography to give 90 mg (76%) of N-debenzoyl-N-methoxycarbonyl taxol, which was recrystallized from methanol/water.

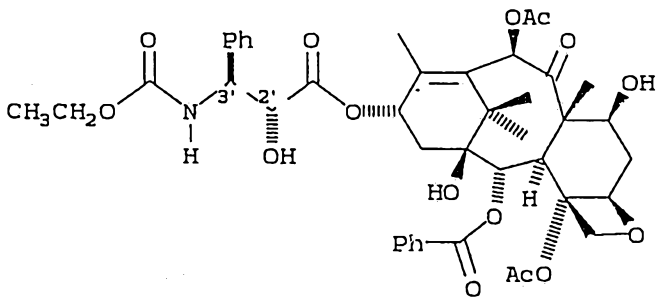
m.p. 169-171°C; $[\alpha]^{25}_{Na}$-63.7° (c 1.1, $CHCl_3$).

^1H NMR ($CDCl_3$, 300 MHz) δ 8.12 (d, J = 7.1 Hz, 2H, benzoate ortho), 7.65-7.3 (m, 8H, aromatic), 6.28 (m, 2H, H10, H13), 5.66 (d, J = 7.1 Hz, 1H, H2ß), 5.58 (d, J = 9.4 Hz, 1H, H3'), 5.30 (d, J = 9.4 Hz, 1H, NH), 4.93 (dd, J = 9.3, 1.7 Hz, 1H, H5), 4.65 (br s, 1H, H2'), 4.40 (m, 1H, H7), 4.29 (d, J = 8.8 Hz, 1H, H20α), 4.17 (d, J = 8.8 Hz, 1H, H20ß), 3.79 (d, J = 7.1 Hz, 1H, H3), 3.58 (s, 3H, COO<u>Me</u>), 3.34 (d, J = 5 Hz, 1H, 2'OH), 2.54 (m, 1H, H6α), 2.47 (d, J = 3.8 Hz 1H, 7OH), 2.36 (s, 3H, 4Ac), 2.24 (s, 3H, 10Ac), 2.22 (m,

2H, H14α, H14ß), 1.88 (m, 1H, H6α), 1.82 (br s, 3H, Me18), 1.73 (s, 1H, 10H), 1.68 (s, 3H, Me19), 1.27 (s, 3H, Me17), 1.14 (s, 3H, Me16).

EXAMPLE 2

Preparation of N-debenzoyl-N-ethoxycarbonyl taxol.



(5)

To a solution of 7-triethylsilyl baccatin III (155 mg, 0.221 mmol)) in 2 mL of THF at -45°C was added dropwise 0.136 mL of a 1.63M solution of nBuLi in hexane. After 0.5 h at -45°C, a solution of cis-1-ethoxycarbonyl-3-triethylsilyloxy-4-phenylazetidin-2-one (386 mg, 1.11 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. Evaportation of the organic layer gave a residue which was purified by filtration through silica gel to give 252 mg of a mixture containing (2'R,3'S)-2',7-(bis)triethylsilyl-N-debenzoyl-N-ethoxycarbonyl taxol and a small amount of the (2'S,3'R) isomer.

To a solution of 252 mg (0.112 mmol) of the mixture obtained from the previous reaction in 12 mL of

acetonitrile and 0.6 mL of pyridine at 0°C was added 1.8 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 216 mg of material which was purified by flash chromatography to give 155 mg (85%) of N-debenzoyl-N-ethoxycarbonyl taxol, which was recrystallized from methanol/water.

m.p. 161.5-162.5°C; $[\alpha]^{25}_{Na}$-62.2° (c 0.51, $CHCl_3$).

^1H NMR ($CDCl_3$, 300 MHz) δ 8.12 (d, J = 7.7 Hz, 2H, benzoate ortho), 7.65-7.3 (m, 8H, aromatic), 6.28 (m, 1H, H10) 6.27 (m, 1H, H13), 5.67 (d, J = 7.1 Hz, 1H, H2ß), 5.53 (d, J = 9.3 Hz, 1H, H3'), 5.29 (d, J = 9.3 Hz, 1H, NH), 4.94 (dd, J = 9.3, 2.2 Hz, 1H, H5), 4.64 (dd, J = 5.0, 2.8 Hz, 1H, H2'), 4.41 (m, 1H, H7), 4.29 (d, J = 8.5 Hz, 1H, H20α), 4.17 (d, J = 8.5 Hz, 1H, H20ß), 4.01 (q, J = 7.1 Hz, 2H, $COO\underline{CH_2}CH_3$), 3.79 (d, J = 7.1 Hz, 1H, H3), 3.45 (d, J = 5 Hz, 1H, 2'OH), 2.54 (m, 1H, H6α), 2.47 (d, J = 3.9 Hz 1H, 7OH), 2.36 (s, 3H, 4Ac), 2.24 (s, 3H, 10Ac), 2.22 (m, 2H, H14α, H14ß), 1.87 (m, 1H, H6α), 1.83 (br s, 3H, Mel8), 1.77 (s, 1H, 1OH), 1.68 (s, 3H, Mel9), 1.27 (s, 3H, Mel7), 1.15 (s, 3H, Mel6), 1.14 (t, J = 7.1 Hz, 2H, $COOCH_2\underline{CH_3}$).

EXAMPLE 3

Tubulin binding assays were performed using compounds (4) and (5) 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	64	
5	44	78
Taxol	100	98
Taxotere	100	___

EXAMPLE 4

IC_{50} data were obtained in vitro on a human cancer cell line (HCT 116) which is available from the National Cancer Institute, and a multidrug resistant cell line (HCT/VM46), which is resistant to a variety of hydrophobic agents, including 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-[(phenylamino)carbonyl]-2H-tetrazolium 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	0.093	n.d.
5	0.007	0.206
Taxol	0.004	0.536
Taxotere	0.007	0.246

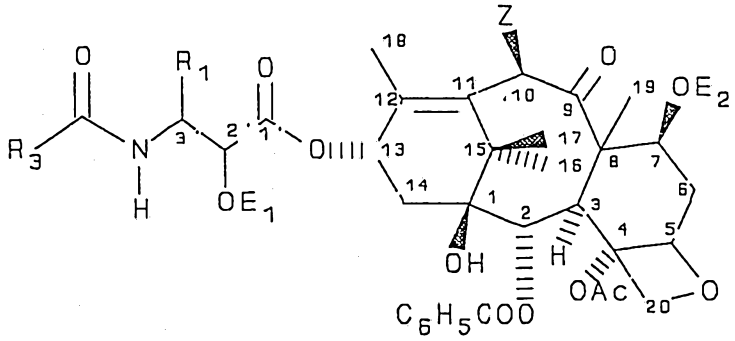
In view of the above, it will be seen that the several objects of the invention are achieved.

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.

The matter contained in each of the following claims is to be read as part of the general description of the present invention.

The claims defining the invention are as follows:

1. A taxane derivative of the formula



(3)

including physiologically acceptable salts thereof, wherein

R_1 is phenyl or substituted phenyl,

R_3 is CH_3O-, or CH_3CH_2O-,

Z is $-OCOT_2$,

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, and functional groups which increase the water solubility of the taxane derivative, the functional groups having the formula $-COGCOR^1$ wherein:

G is ethylene, propylene, CHCH, 1,2-cyclohexylene, or 1,2-phenylene;

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

R^2 = hydrogen or methyl;

R^3 = $(CH_2)_nNR^6R^7$ or $(CH_2)_nNR^{\oplus 5}R^7R^8X^{\ominus}$;

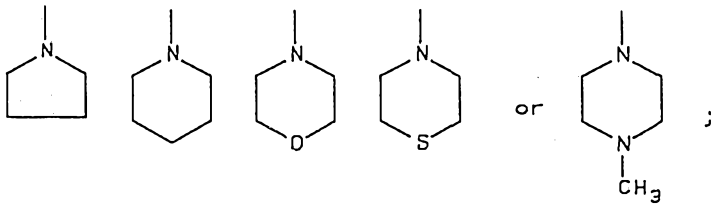
n = 1 to 3;

R^4 = hydrogen or lower alkyl containing 1 to 4 carbons;



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

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



;

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

X^e = halide; and

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, or KOH.

2. A taxane derivative of claim 1 wherein R_1 is phenyl, R_3 is CH_3O-, Z is $-OCOCH_3$, and the taxane derivative has the 2'R, 3'S configuration.

3. A taxane derivative of claim 1 wherein R_1 is phenyl, R_3 is CH_3CH_2O-, Z is $-OCOCH_3$, and the taxane derivative has the 2'R, 3'S configuration.

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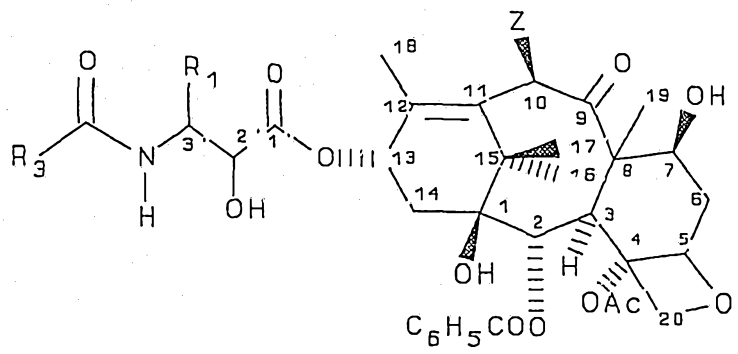
4. A taxane derivative of the formula



(3)

including physiologically acceptable salts thereof, wherein

R_1 is phenyl or substituted phenyl,

R_3 is CH_3O-,

Z is $-OT_1$,

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, and

Ac is acetyl.

5. A pharmaceutical composition which contains a taxane derivative of claim 1 or 4 and one or more pharmacologically acceptable, inert or physiologically active diluents or adjuvants.

6. A composition of claim 5 which contains a taxane derivative of claim 1 wherein Z is $-OCOCH_3$, and E_1 and E_2 are hydrogen.

7. A composition of claim 5 which contains a taxane derivative of claim 1 wherein R_1 is phenyl, R_3 is CH_3O-, Z is $-OCOCH_3$, and the taxane derivative has the 2'R, 3'S configuration.

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8. A composition of claim 5 which contains a taxane derivative of claim 1 wherein R_1 is phenyl and R_3 is CH_3CH_2O-.

9. A composition of claim 5 which contains a taxane derivative of claim 1 wherein E_1 and E_2 are hydrogen.

10. A composition of claim 5 which contains a taxane derivative of claim 1 wherein R_1 is phenyl, R_3 is CH_3CH_2O-, Z is $-OCOCH_3$, and the taxane derivative has the 2'R, 3'S configuration.

11. A taxane derivative of claim 1, substantially as hereinbefore described with reference to any one of the practical Examples.

12. The use of a taxane derivative of any one of claims 1 to 4 or 11, or of a composition of any one of claims 5 to 10, as an antileukemia or antitumor agent.

DATED this 14th day of April, 1994

FLORIDA STATE UNIVERSITY
By its Patent Attorneys,
E. F. WELLINGTON & CO.,
By:

(B. S. Wellington)

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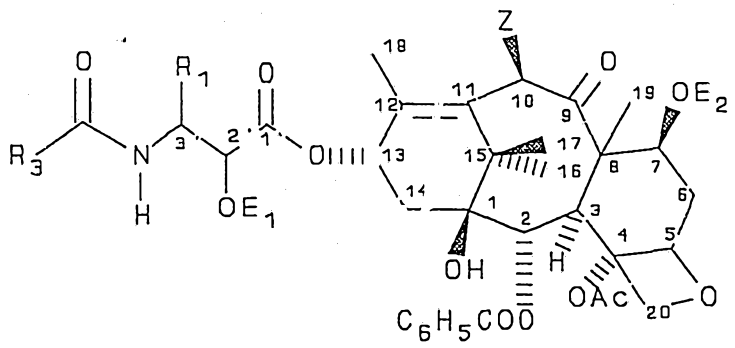
ABSTRACT

A taxane derivative of the formula



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

R^2 = hydrogen or methyl;

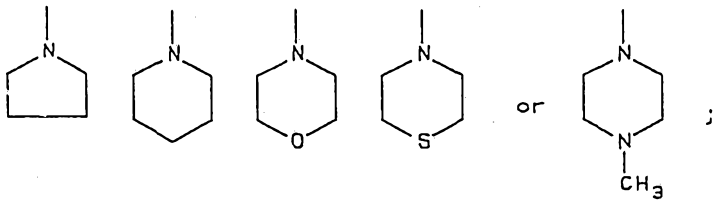
R^3 = $(CH_2)_nNR^6R^7$ or $(CH_2)_nNR^{\oplus 6}R^7R^8X^{\ominus}$;

n = 1 to 3;

R^4 = hydrogen or lower alkyl containing 1 to 4 carbons;

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

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



;

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

$X^{\ominus}$ = halide; and

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, or KOH, are useful as antitumor agents.

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