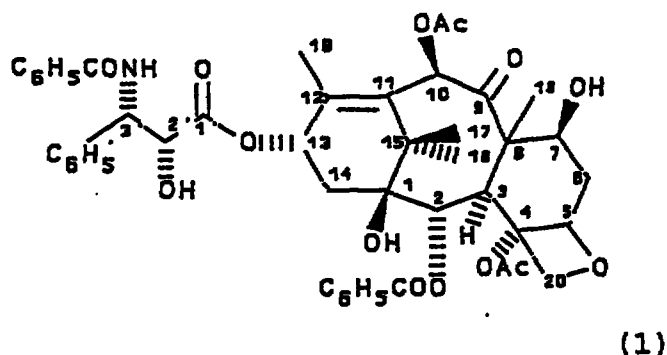


Description**BACKGROUND OF THE INVENTION**

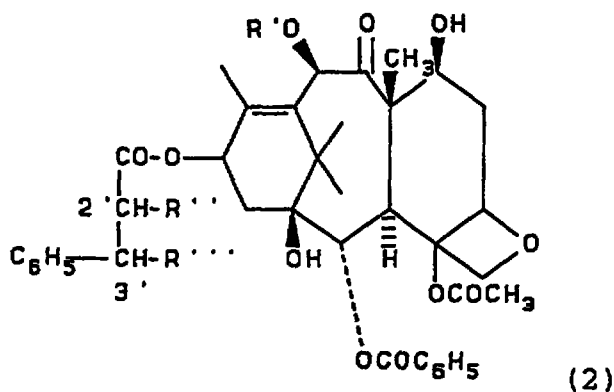
The present invention is directed to novel taxanes which have utility as antileukemia and antitumor agents.

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:



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 US-A-4,814,470 that taxol derivatives having structural formula (2) below, have an activity significantly greater than that of taxol (1).



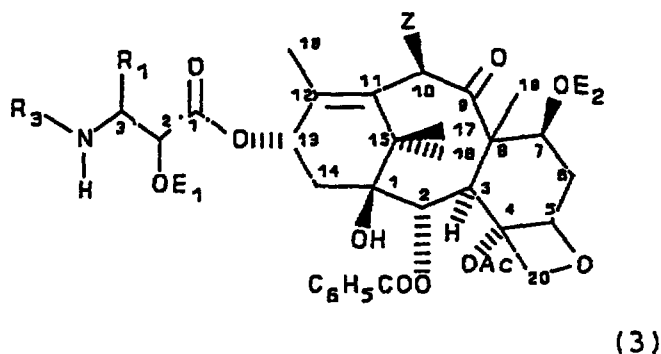
R' represents hydrogen or acetyl and one of R'' and R''' represents hydroxy and the other represents tert-butoxycarbonylamino and their stereoisomeric forms, and mixtures thereof. The compound of formula (2) in which R' is hydrogen, R'' is hydroxy, R''' is tert-butoxycarbonylamino having the 2'R, 3'S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

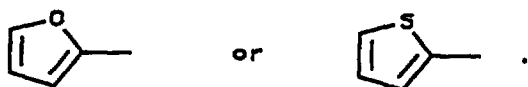
SUMMARY OF THE INVENTION

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

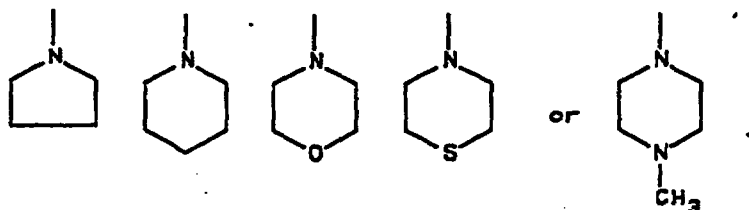
Briefly, therefore, the present invention is directed to taxane derivatives of the formula:



wherein
R₁ is



- Z is -OT₁,
T₁ is hydrogen, hydroxyl protecting group, or -COT₂,
T₂ is H, C₁-C₆ alkyl, alkenyl up to C₆, alkynyl up to C₆ or monocyclic aryl,
R₃ is benzoyl, substituted benzoyl or C₁-C₆ alkoxy carbonyl,
Ac is acetyl, and
E₁ and E₂ are independently selected from hydrogen and functional groups which increase the water solubility of the taxane derivative, the functional groups having the formula -COG COR' wherein
G is ethylene, propylene, -CH=CH-, 1,2-cyclohexylene, or 1,2-phenylene;
R¹ = OH base, NR²R³, OR³, SR³, OCH₂CONR⁴R⁵, or OH;
R² = hydrogen or methyl;
R³ = (CH₂)_nNR⁶R⁷ or (CH₂)_nN⁺R⁶R⁷R⁸X⁹;
n = 1 to 3;
R⁴ = hydrogen or lower alkyl containing 1 to 4 carbons;
R⁵ = hydrogen, lower alkyl containing 1 to 4 carbons, benzyl, hydroxyethyl, CH₂CO₂H, or dimethylaminoethyl;
R⁶ and R⁷ = independently selected from lower alkyl containing 1 or 2 carbons or benzyl, or R⁶ and R⁷ together with the nitrogen atom of NR⁶R⁷ forms one of the following rings

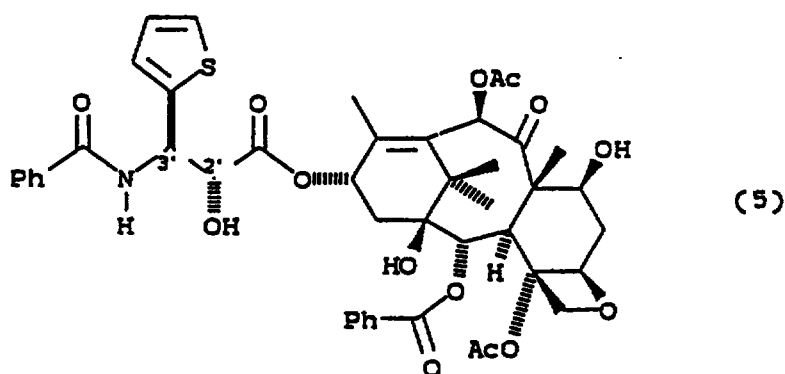
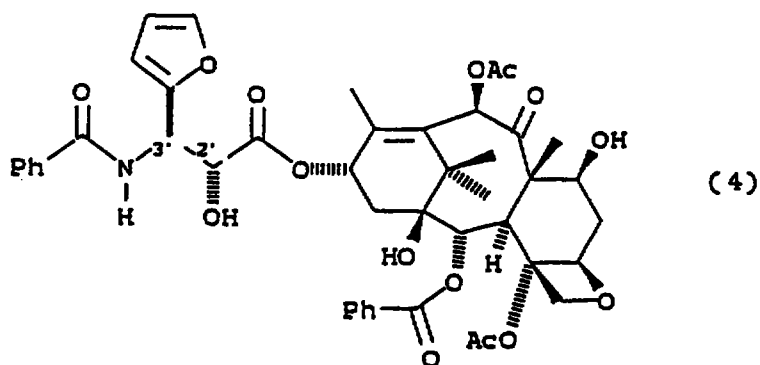


- R⁸ = lower alkyl containing 1 or 2 carbons or benzyl;
X⁹ = halide; and
base = NH₃, (HOC₂H₄)₃N, N(CH₃)₃, CH₃N(C₂H₄OH)₂, NH₂(CH₂)₆NH₂, N-methylglucamine, NaOH, or KOH.

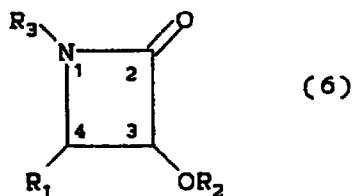
Other objects and features of this invention will be in part apparent and in part pointed out hereinafter.

DETAILED DESCRIPTION OF THE PREFERRED EMBODIMENTS

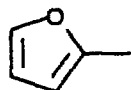
In accordance with the present invention, it has been discovered that compounds having structural formula (3), in general, and structural formulae (4) and (5), in particular, show remarkable properties, in vitro, and are valuable antileukemia and antitumor agents. Their biological activity has been determined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



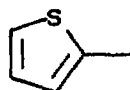
Taxanes having formulae (4) and (5) which have the 2'R, 3'S configuration may be obtained by reacting a β -lactam with metal alkoxides having the taxane tetracyclic nucleus and a C-13 metallic oxide substituent to form compounds having a β -amido ester substituent at C-13. The β -lactams have, for example,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



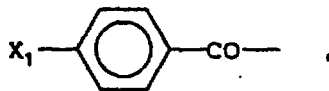
wherein
R₁ is



or

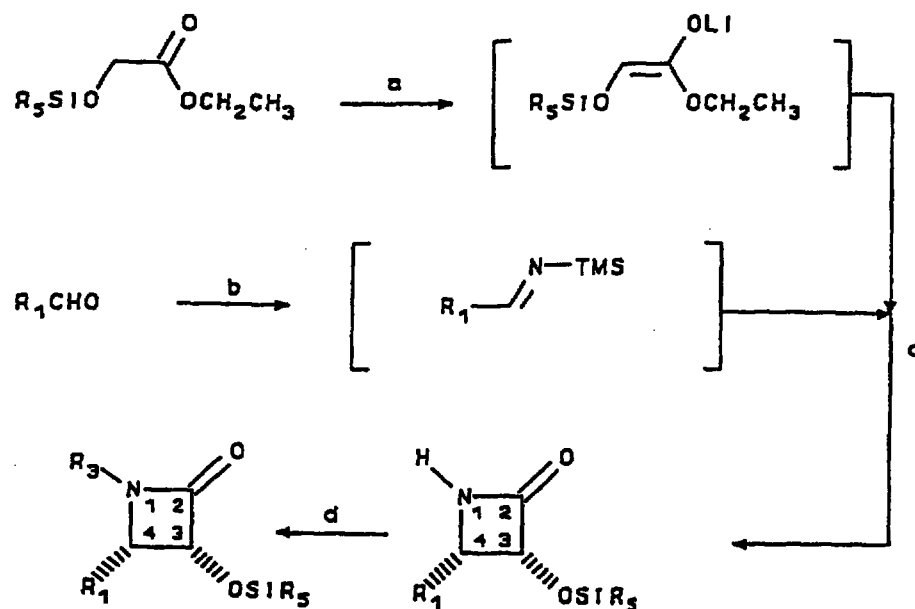


R_2 is a hydroxy protecting group,
 R_3 is benzoyl, $C_1 - C_6$ alkoxy carbonyl, or



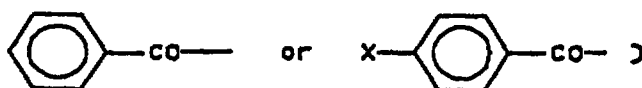
and

X_1 is Cl, Br, F, NO_2 -, or CH_3O -.
 β -lactams (6) can be prepared from readily available starting materials, as is illustrated by the following reaction scheme:



reagents

- (a) LDA, THF, $-78^\circ C$ to $-50^\circ C$;
 (b) LHMDS, THF, $-78^\circ C$ to $0^\circ C$;
 (c) THF, $-78^\circ C$ to $25^\circ C$, (2h); and
 (d) triethylamine and an acyl chloride
 ($R_3 =$



or alkyl chloroformate ($R_3 =$ alkoxy carbonyl).

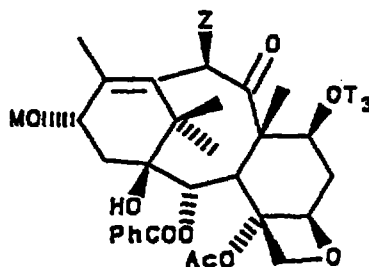
(LDA is lithium diisopropylamide and LHMDS is lithium hexamethyldisilazane).

The 3-hydroxy 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 β -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 β -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.

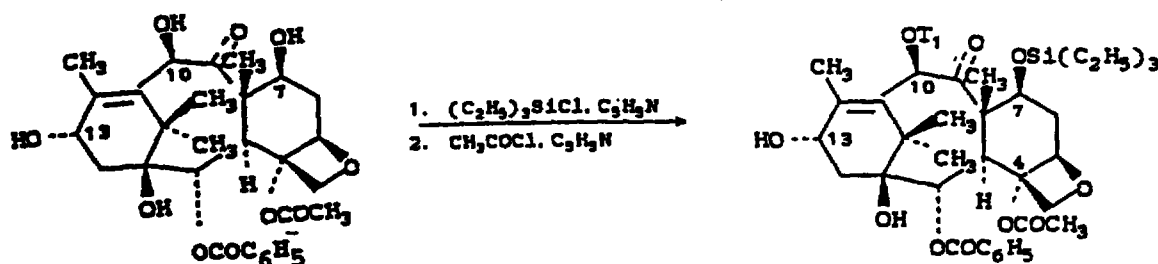
The metal alkoxides having the taxane tetracyclic nucleus and a C-13 metallic oxide substituent have the following structural formula:



wherein Z is $-\text{OT}_1$; T_1 is hydrogen, hydroxyl protecting group, or $-\text{COT}_2$; T_2 is H, C_1 - C_6 alkyl, alkenyl up to C_6 , alkynyl up to C_6 or monocyclic aryl; T_3 is a hydroxy protecting group; and M is a metal, preferably selected from the group comprising Group IA, Group IIA and transition metals, and most preferably, Li, Mg, Na, K or Ti.

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. 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:

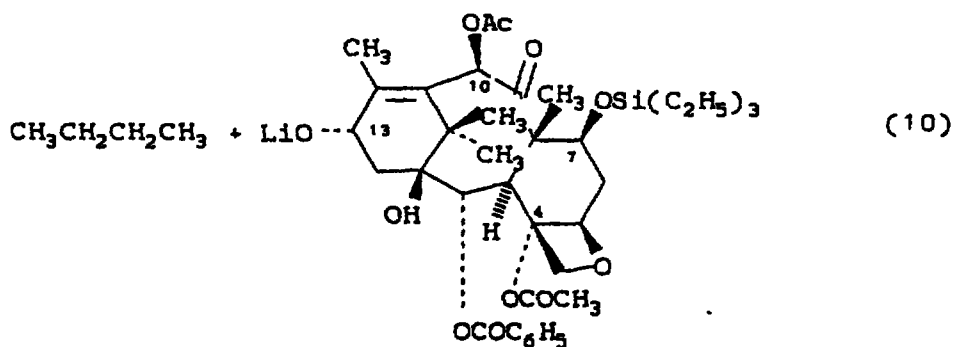
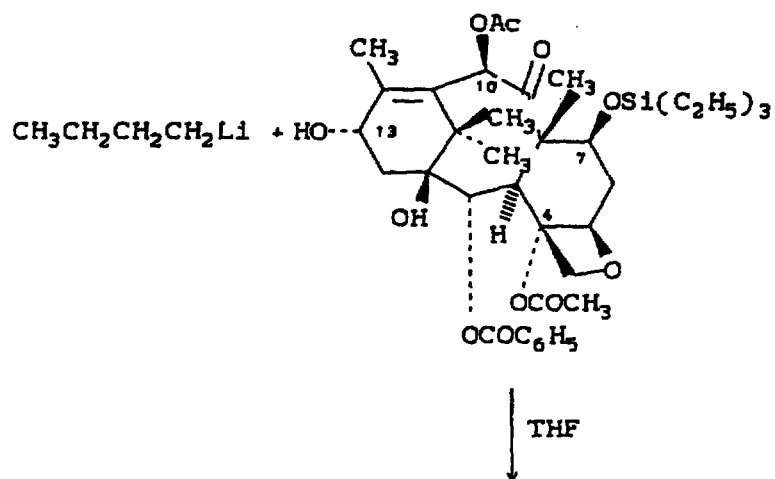


(8)

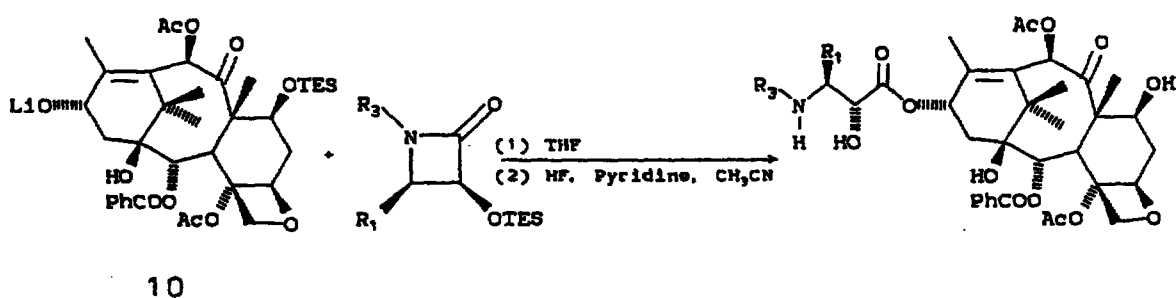
(9) a, $\text{T}_1 = \text{H}$
b, $\text{T}_1 = \text{COCH}_3$

Under what are reported to be carefully optimized conditions, 10-deacetyl baccatin III is reacted with 20 equivalents of $(\text{C}_2\text{H}_5)_3\text{SiCl}$ 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); see Greene, et al. in JACS 110, 5917 at 5918 (1988).

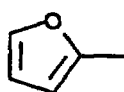
The 7-O-triethylsilyl baccatin III (9b) is reacted with an organometallic compound such as n-butyllithium in a solvent such as tetrahydrofuran (THF), to form the metal alkoxide 13-O-lithium-7-O-triethylsilyl baccatin III (10) as shown in the following reaction scheme:



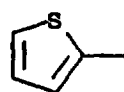
As shown in the following reaction scheme, 13-O-lithium-7-O-triethylsilyl baccatin III (10) reacts with β -lactam (6) in which R_2 is triethyl silyl to provide an intermediate in which the C-7 and C-2' hydroxyl groups are protected with a triethylsilyl group. The triethylsilyl groups are then hydrolyzed under mild conditions so as not to disturb the ester linkage or the taxane substituents.



wherein
 R_1 is



or



R₃ is benzoyl, C₁-C₆ alkoxy carbonyl, or



X₁ is Cl, Br, F, NO₂-, or CH₃O-.

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 β -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 formulae (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 non-aqueous 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.

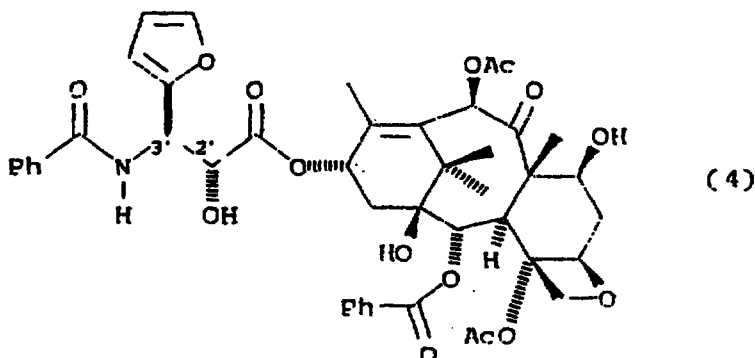
The products of general formula (3) are more particularly used in the treatment of acute leukemias and solid tumors, at daily doses which are generally between 1 and 2 mg/kg by the intravenous (perfusion) route for an adult.

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, E₁ and E₂. For increased water solubility, E₁ and E₂ may independently be hydrogen or -COGCOR¹ wherein G and R, are as defined above.

The preparation of compounds in which E₁ or E₂ is -COGCOR¹ is set forth in US-A-4942184.

The following Examples illustrate the invention.

EXAMPLE 1



Preparation of 3'-desphenyl-3'-(2-furyl) taxol.

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-benzoyl-3-triethylsilyloxy-4-(2-furyl)azetidin-2-one (266 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 temperature for 1 h before 1 mL of a 10% solution of AcOH in THF was added. The mixture was partitioned between saturated aqueous NaHCO₃ and 80/40 ethyl acetate/hexane. Evaporation of the organic layer gave a residue which was purified by filtration through silica gel to give 143 mg of a mixture containing (2'R,3'S)-2',7-(bis)triethylsilyl-

3'-desphenyl-3'-(2-furyl) taxol and a small amount of the (2'S,3'R) isomer.

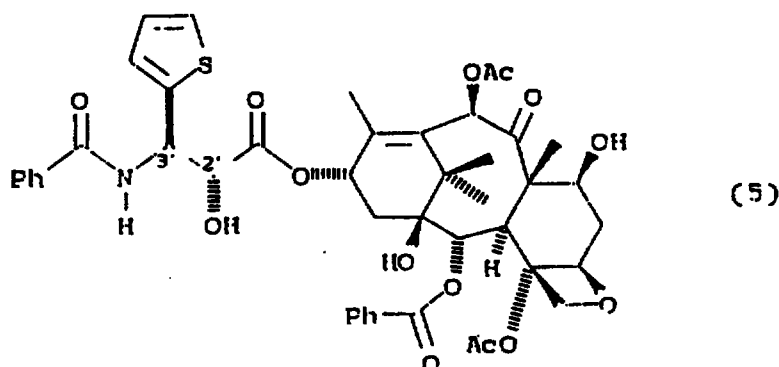
To a solution of 143 mg of the mixture obtained from the previous reaction in 6 mL of acetonitrile and 0.3 mL of pyridine at 0 °C was added 0.9 mL of 48% aqueous HF. The mixture was stirred at 0 °C for 3 h, then at 25 °C for 13 h, and partitioned between saturated aqueous sodium bicarbonate and ethyl acetate.

Evaporation of the ethyl acetate solution gave 115 mg of material which was purified by flash chromatography to give 98 mg (81%) of 3'-desphenyl-3'-(2-furyl) taxol, which was recrystallized from methanol/water.

m.p. 174-176 °C; $[\alpha]_D^{25}$ Na -47.8° (c 0.045, CHCl₃).

¹H NMR (CDCl₃, 300 MHz) δ 8.14 (d, *J* = 7.0 Hz, 2H, benzoate ortho), 7.74 (m, 2H, aromatic), 7.51 (m, 7H, aromatic), 6.86 (d, *J* = 9.2 Hz, 1H, NH), 6.40 (d, *J* = 1.2 Hz, 2H, furyl), 6.29 (s, 1H, H10), 6.24 (dd, *J* = 9.2, 9.2 Hz, 1H, H13), 5.89 (dd, *J* = 9.2, 2.4 Hz, 1H, H3'), 5.69 (d, *J* = 7.0 Hz, 1H, H2β), 4.96 (dd, *J* = 9.5, 1.8 Hz, 1H, H5), 4.83 (d, *J* = 2.4 Hz, 1H, H2'), 4.42 (dd, *J* = 10.7, 6.7 Hz, 1H, H7), 4.31 (d, *J* = 8.6 Hz, 1H, H20α), 4.20 (d, *J* = 8.6 Hz, 1H, H20β), 3.83 (d, *J* = 7.0 Hz, 1H, H3), 2.56 (m, 1H, H6α), 2.43 (s, 3H, 4Ac), 2.35 (m, 2H, H14), 2.24 (s, 3H, 10Ac), 1.89 (m, 1H, H6β), 1.87 (br s, 3H, Me18), 1.87 (s, 1H, 1OH), 1.69 (s, 3H, Me19), 1.25 (s, 3H, Me17), 1.15 (s, 3H, Me16).

EXAMPLE 2



Preparation of 3'-Desphenyl-3'-(2-thienyl)taxol.

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-(4-benzoyl)-3-triethylsilyloxy-4-(2-thienyl)azetidin-2-one (277 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 temperature for 1 h before 1 mL of a 10% solution of AcOH in THF was added. The mixture was partitioned between saturated aqueous NaHCO₃ and 60/40 ethyl acetate/hexane. Evaporation of the organic layer gave a residue which was purified by filtration through silica gel to give 169 mg of a mixture containing (2'R,3'S)-2',7-(bis)triethylsilyl-3'-desphenyl-3'-(2-thienyl) taxol and a small amount of the (2'S,3'R) isomer.

To a solution of 169 mg 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 140 mg of material which was purified by flash chromatography to give 93 mg (76%) of 3'-desphenyl-3'-(2-thienyl) taxol, which was recrystallized from methanol/water.

m.p. 173-175 °C; $[\alpha]_D^{25}$ Na -42.1° (c 0.515, CHCl₃).

¹H NMR (CDCl₃, 300 MHz) δ 8.14 (d, *J* = 7.1 Hz, 2H, benzoate ortho), 7.72 (d, *J* = 8.7 Hz, 2H, benzamide ortho), 7.65-7.35 (m, 6H, aromatic), 7.31 (dd, *J* = 5.5, 1.1 Hz, 1H, thienyl), 7.19 (dd, *J* = 3.9, 1.1 Hz, 1H, thienyl), 7.03 (dd, *J* = 5.5, 3.9 Hz, 1H, thienyl), 6.96 (d, *J* = 8.8 Hz, 1H, NH), 6.28 (s, 1H, H10), 6.24 (dd, *J* = 8.8, 7.7 Hz, 1H, H13), 6.05 (dd, *J* = 8.8, 1.7 Hz, 1H, H3'), 5.68 (d, *J* = 7.1 Hz, 1H, H2), 4.95 (dd, *J* = 9.3, 1.7 Hz, 1H, H5), 4.78 (d, *J* = 2.2 Hz, 1H, H2'), 4.40 (dd, *J* = 11.0, 6.6 Hz, 1H, H7), 4.31 (d, *J* = 8.5 Hz, 1H, H20α), 4.20 (d, *J* = 8.5 Hz, 1H, H20β), 3.81 (d, *J* = 7.1 Hz, 1H, H3), 3.72 (br s, 1H, 2'OH), 2.54 (m, 1H, H6α), 2.41 (s, 3H, 4Ac), 2.37 (m, 2H, H14α, H14β), 2.23 (s, 3H, 10Ac), 1.88 (m, 1H, H6β), 1.82 (br s, 3H, Me18), 1.68 (s, 3H, Me19), 1.23 (s, 3H, Me17), 1.14 (s, 3H, Me16).

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	83	98
5	75	
Taxol	100	
Taxotere	100	

EXAMPLE 4

IC₅₀ 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 serially 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 IC₅₀ 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

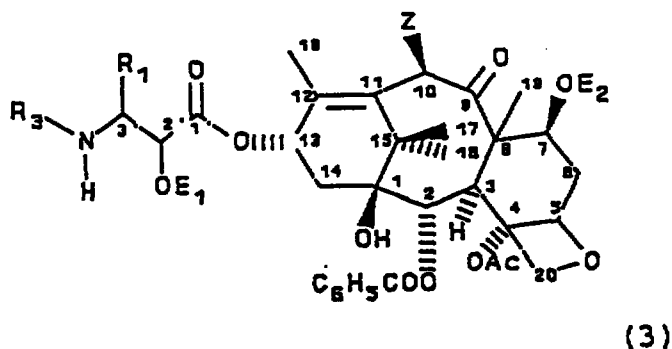
Compound Name/Formula	IC ₅₀	
	HCT 116	HCT VM46
4	0.004	0.079
5	0.006	0.110
Taxol	0.004	0.536
Taxotere	0.007	0.246

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



Claims

1. A taxane derivative of the formula



wherein
R₁ is



Z is -OT₁,

T₁ is hydrogen, hydroxyl protecting group, or -COT₂,

T₂ is H, C₁-C₆ alkyl, alkenyl up to C₆, alkynyl up to C₆ or monocyclic aryl.

R₃ is benzoyl, substituted benzoyl or C₁-C₆ alkoxy carbonyl,

Ac is acetyl, and

E₁ and E₂ are independently selected from hydrogen and functional groups which increase the water solubility of the taxane derivative, the functional groups having the formula -COG COR¹ wherein:

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

R¹ = OH base, NR²R³, OR³, SR³, OCH₂CONR⁴R⁵, or OH;

R² = hydrogen or methyl;

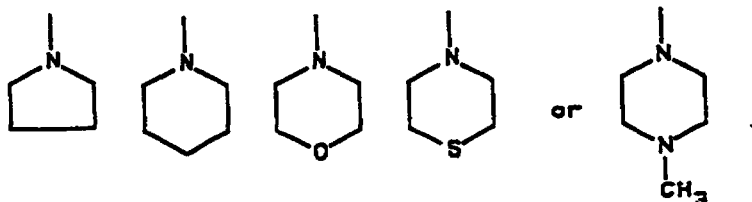
R³ = (CH₂)_nNR⁶R⁷ or (CH₂)_nN⁸R⁶R⁷R⁸X⁹;

n = 1 to 3;

R⁴ = hydrogen or lower alkyl containing 1 to 4 carbons;

R⁵ = hydrogen, lower alkyl containing 1 to 4 carbons, benzyl, hydroxyethyl, CH₂CO₂H, or dimethylaminoethyl;

R⁶ and R⁷ = independently selected from lower alkyl containing 1 or 2 carbons or benzyl, or R⁶ and R⁷ together with the nitrogen atom of NR⁶R⁷ forms one of the following rings



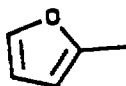
R⁸ = lower alkyl containing 1 or 2 carbons or benzyl;

X⁹ = halide; and

base = NH₃, (HOC₂H₄)₃N, N(CH₃)₃, CH₃N(C₂H₄OH)₂, NH₂(CH₂)₆NH₂, N-methylglucamine, NaOH, or KOH.

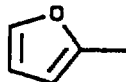


2. A taxane derivative according to claim 1, wherein R_1 is



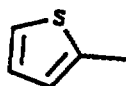
and the taxane has the 2'R, 3'S configuration.

3. A taxane derivative according to claim 1, wherein R_1 is



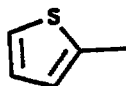
and E_1 is $-\text{COGCOR}^1$ wherein G and R^1 are as defined in claim 1.

4. A taxane derivative according to claim 1, wherein R_1 is



and the taxane derivative has the 2'R, 3'S configuration.

5. A taxane derivative according to claim 1, wherein R_1 is

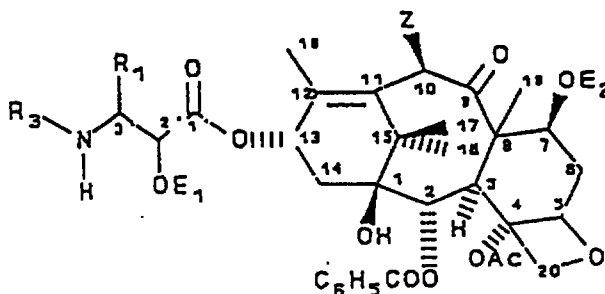


and E_1 is $-\text{COGCOR}^1$ wherein G and R^1 are as defined in claim 1.

6. A pharmaceutical composition which contains a taxane derivative according to any one of claims 1 to 5, and one or more pharmacologically acceptable, inert or physiologically active diluents or adjuvants.

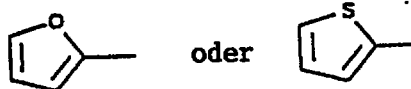
Patentansprüche

1. Taxan-Derivat der Formel



(3)

worin
 $R_1 =$



ist;

Z = -OT₁ ist;

T₁ = Wasserstoff, Wasserstoff-Schutzgruppe oder -COT₂ ist;

T₂ = H, C₁-C₆-Alkyl, Alkenyl mit bis zu C₆, Alkynyl mit bis zu C₆ oder monocyclisches Aryl ist;

R₃ = Benzoyl, substituiertes Benzoyl oder C₁-C₆-Alkoxy-carbonyl ist,

Ac = Acetyl ist, und

E₁ und E₂ unabhängig voneinander unter Wasserstoff und funktionellen Gruppen ausgewählt sind, die die Löslichkeit des Taxan-Derivats in Wasser erhöhen, wobei die funktionellen Gruppen die Formel -COGCOR¹ haben, worin

G = Ethylen, Propylen, -CH=CH-, 1,2-Cyclohexylen oder 1,2-Phenylene ist;

R¹ = OH-Base, NR²R³, OR³, SR³, OCH₂CONR⁴R⁵ oder OH ist;

R² = Wasserstoff oder Methyl ist;

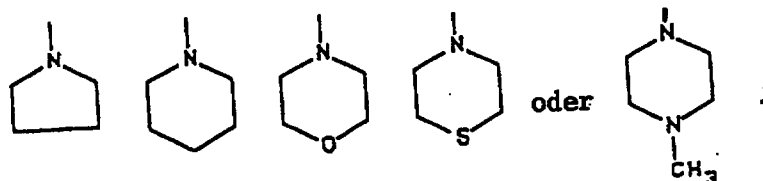
R³ = (CH₂)_nNR⁶R⁷ oder (CH₂)_nN⁶R⁶R⁷R⁸X⁹ ist;

n = 1 bis 3; ist;

R⁴ = Wasserstoff oder niederes Alkyl mit 1 bis 4 Kohlenstoff-Atomen ist;

R⁵ = Wasserstoff, niederes Alkyl mit 1 bis 4 Kohlenstoff-Atomen, Benzyl, Hydroxyethyl, CH₂CO₂H oder Dimethylaminoethyl ist;

R⁶ und R⁷ = unter niederem Alkyl mit 1 oder 2 Kohlenstoff-Atomen unabhängig ausgewählt dem Stickstoff-Atom des NR⁶R⁷ einen der folgenden Ringe

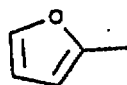


R⁸ = niederes Alkyl mit 1 oder 2 Kohlenstoff-Atomen oder Benzyl ist;

X⁹ = Halid ist; und

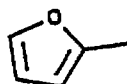
Base = NH₃, (HOC₂H₄)₃N, N(CH₃)₃, CH₃N(C₂H₄OH)₂, NH₂(CH₂)₆NH₂, N-Methylglucamin, NaOH oder KOH ist.

2. Taxan-Derivat nach Anspruch 1, bei dem R₁



ist und das Taxan die Konfiguration 2'R, 3'S hat.

3. Taxan-Derivat nach Anspruch 1, bei der R₁

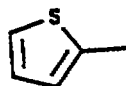


ist und E₁ gleich -COGCOR¹ ist, worin G und R¹ wie in Anspruch 1 definiert sind.



4. Taxan-Dérivat nach Anspruch 1, in dem R₁

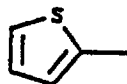
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ist und das Taxan-Dérivat die Konfiguration 2'R, 3'S hat.

10 5. Taxan-Dérivat nach Anspruch 1, in dem R₁

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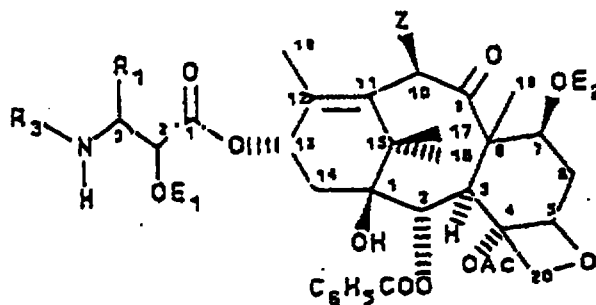
ist und E₁ gleich -COGCOR¹ ist, worin G und R¹ wie in Anspruch 1 definiert sind.

20 6. Pharmazeutische Zusammensetzung, die ein Taxan-Dérivat nach einem der Ansprüche 1 bis 5 und ein oder mehrere pharmakologisch zulässige, inerte oder physiologisch aktive Verdünnungsmittel oder Hilfsstoffe enthält.

Revendications

25 1. Dérivé taxane de formule :

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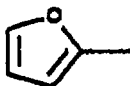
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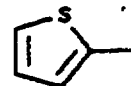
dans lequel :

- R₁ est un groupe ;

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ou



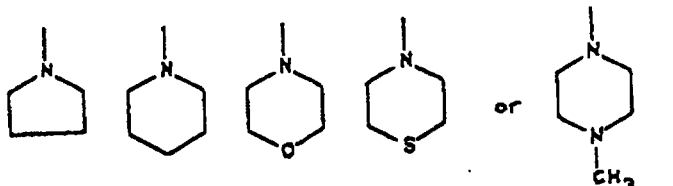
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- Z est un groupe -OT₁,
- T₁ représente un atome d'hydrogène, un groupe hydroxyle protecteur, ou un groupe -COT₂,
- T₂ représente un atome d'hydrogène, un groupe alkyl C₁₋₆, un groupe alkenyle comportant jusqu'à 6 atomes de carbone, un groupe alkynyle comportant jusqu'à 6 atomes de carbone, ou un groupe aryle monocyclique,
- Ac représente un groupe acétyle, et
- E₁ et E₂ sont choisis indépendamment parmi l'hydrogène, et les groupes fonctionnels qui augmentent la solubilité dans l'eau, du dérivé taxane, les groupes fonctionnels ayant la formule -COGCOR¹ dans laquelle :
- G représente l'éthylène, le propylène, le groupe -CH=CH-, le 1,2-cyclohexylène, ou le 1,2-phénylène;

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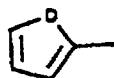


- R¹ représente un groupe base OH, NR²R³, OR³, SR³, OCH₂CONR⁴R⁵, ou OH;
- R² représente un atome d'hydrogène ou un groupe méthyle;
- R³ représente un groupe (CH₂)_nNR⁶R⁷, ou (CH₂)_nN⁺R⁶R⁷R⁸X⁻;
- n est égal à 1, 2, ou 3;
- R⁴ représente un atome d'hydrogène ou un groupe alkyl inférieur comportant 1 à 4 atomes de carbone;
- R⁵ représente un atome d'hydrogène, un groupe alkyle inférieur comportant 1 à 4 atomes de carbone, benzyle, hydroxyéthyle, CH₂COOH, ou diméthylaminoéthyle;
- R⁶ et R⁷ sont choisis indépendamment parmi les groupes alkyle inférieurs comportant 1 ou 2 atomes de carbone, ou benzyle, ou R⁶ ou R⁷ ensemble, avec l'atome d'azote du group NR⁶R⁷, forment l'un des cycles suivants ;



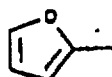
- R⁸ représente un groupe alkyl inférieur comportant 1 ou 2 atomes de carbone, ou un groupe benzyle;
- X⁺ représente un halogénure; et
- base représente NH₃, (HOC₂H₄)₃N, N(CH₃)₃, CH₃N(C₂H₄OH)₂, NH₂(CH₂)₆NH₂, N-méthylglucamine, NaOH, ou KOH.

2. Dérivé taxane selon la revendication 1, dans lequel R₁ est un groupe :



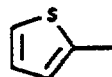
et le dérivé taxane à la configuration 2'R,3'S.

3. Dérivé taxane selon la revendication 1, dans lequel R₁ est un groupe :



et E₁ est un groupe -COGCOR¹, dans lequel G et R¹ sont tels que définis dans la revendication 1.

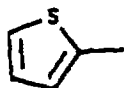
4. Dérivé taxane selon la revendication 1, dans lequel R₁ est un groupe :



et le dérivé taxane à la configuration 2'R,3'S.



5. Dérivé taxane selon la revendication 1, dans lequel R_1 est un groupe :



et E_1 est un groupe $-\text{COGCOR}'$, dans lequel G et R' sont tels que définis dans la revendication 1.

6. Composition pharmaceutique qui contient un dérivé taxane selon l'une quelconque des revendications 1 à 5, et un ou plusieurs diluants ou adjuvants pharmacologiquement acceptables, inertes, ou physiologiquement actifs.