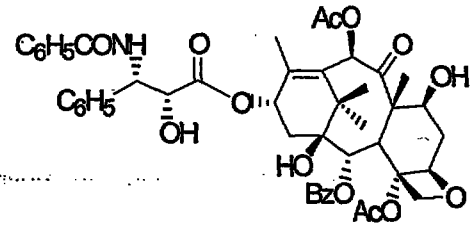
C7 ESTER SUBSTITUTED TAXANES

BACKGROUND OF THE INVENTION

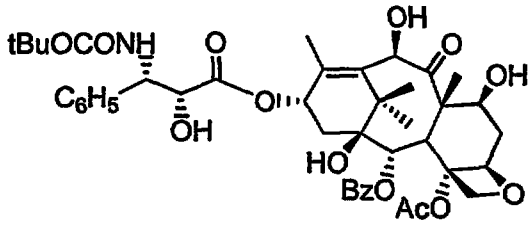
The present invention is directed to novel taxanes which have exceptional utility as antitumor agents.

The taxane family of terpenes, of which baccatin III and taxol are members, has been the subject of considerable interest in both the biological and chemical arts. Taxol itself is employed as a cancer chemotherapeutic agent and possesses a broad range of tumor-inhibiting activity. Taxol has a 2'R, 3'S configuration and the following structural formula:



wherein Ac is acetyl.

Colin et al. reported in U.S. Patent 4,814,470 that certain taxol analogs have an activity significantly greater than that of taxol. One of these analogs, commonly referred to as docetaxel, has the following structural formula:



Although taxol and docetaxel are useful chemotherapeutic agents, there are limitations on their effectiveness, including limited efficacy against certain types of cancers and toxicity to subjects when administered at various doses. Accordingly, a need remains for additional chemotherapeutic agents with improved efficacy and less toxicity.

SUMMARY OF THE INVENTION

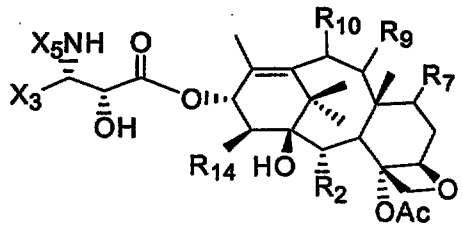
Among the objects of the present inventi on, therefore, is the provision of taxanes which compare favorably to taxol and docetaxel with respect to efficacy as anti-tumor agents and with respect to toxicity. In general, these taxanes possess an ester substituent other than formate, acetate and he terosubstituted acetate at C-7, a hydroxy substituent at C-10 and a range of C-3' substituents.

Briefly, therefore, the present invention is directed to the taxane composition, per se, to pharmaceutical compositions comprising the taxane and a pharmaceuti cally acceptable carrier, and to methods of administration.

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 one embodiment of the present inv ention, the taxanes of the present invention correspond to structure (1):



(1)

wherein

R_2 is acyloxy;

R_7 is $R_{7a}COO$-;

R_{7a} is hydrocarbyl, substituted hydrocarbyl, or heterocy clo wherein said hydrocarbyl or substituted hydrocarbyl contains carbon atoms in the alpha and beta positions relative to the carbon of which R_{7a} is a substituent;

R_9 is keto, hydroxy, or acyloxy;

R_{10} is hydroxy;

R_{14} is hydrido or hydroxy;

X_3 is substituted or unsubstituted alkyl, alkenyl, alkynyl, phenyl or heterocyclo;

X_5 is $-COX_{10}$, $-COOX_{10}$, or $-CONHX_{10}$;

X_{10} is hydrocarbyl, substituted hydrocarbyl, or heterocyclo;

Ac is acetyl; and

R_7, R_9, and R_{10} independently have the alpha or beta stereoc hemical configuration.

In one embodiment, R_2 is an ester ($R_{2a}C(O)O$-), a carbamate ($R_{2a}R_{2b}NC(O)O$-), a carbonate ($R_{2a}OC(O)O$-), or a thiocarbamate ($R_{2a}SC(O)O$-) wherein R_{2a} and R_{2b} are

independently hydrogen, hydrocarbyl, substituted hydrocarbyl or heterocycl o. In a preferred embodiment, R_2 is an ester ($R_{2a}C(O)O$-), wherein R_{2a} is aryl or heteroaromatic. In another preferred embodiment, R_2 is an ester ($R_{2a}C(O)O$-), wherein R_{2a} is substituted or unsubstituted phenyl, furyl, thienyl, or pyridyl. In one particu larly preferred embodiment, R_2 is benzoyloxy.

In one embodiment, R_7 is $R_{7a}COO$- wherein R_{7a} is (i) substituted or unsubstituted C_2 to C_8 alkyl (straight, branched or cyclic), such as ethyl, propyl, butyl, pentyl, or hexyl; (ii) substituted or unsub stituted C_2 to C_8 alkenyl (straight, branched or cyclic), such as ethenyl, propenyl, butenyl, pentenyl or hexenyl; (iii) substituted or unsubstituted C_2 to C_8 alkynyl (straight or branched) such as ethynyl, propynyl, butynyl, pentynyl, or hexynyl; (iv) sub stituted or unsubstituted phenyl; or (v) substituted or unsubstituted heteroaromatic such as furyl, thienyl, or pyridyl. The substituents may be hydrocarbyl or any of the heteroatom containing substituents identified elsewhere herein for substituted hydro carbyl. In a preferred embodiment, R_{7a} is ethyl, straight, branched or cyclic propyl, straight, branched or cyclic butyl, straight, branched or cyclic pentyl, straight, branched or cyclic hexyl, straight or branched propenyl, isobutenyl, furyl or thienyl. In another embodiment, R_{7a} is substituted ethyl, substituted propyl (straight, branched or cyclic), substituted propenyl (straight or branched), substituted isobutenyl, substituted furyl or substituted thienyl wherein the substituent(s) is/are selected f rom the group consisting of heterocyclo, alkoxy, alkenoxy, alkynoxy, aryloxy, hydroxy, protected hydroxy, keto, acyloxy, nitro, amino, amido, thiol, ketal, acetal, ester and ether moieties, but not phosphorous containing moieties.

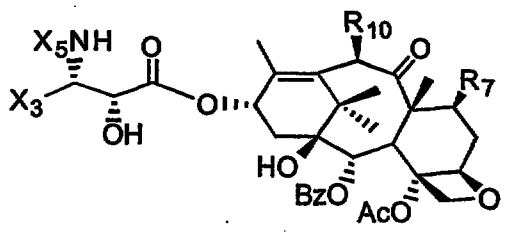
While R_9 is keto in one embodiment of the present invention, in other embodiments R_9 may have the alpha or beta stereochemical configuration, preferably the beta stereochemical configuration, and may be, for example, α- or β-hydroxy or α- or β-acyloxy. For example, when R_9 is acyloxy, it may be an ester ($R_{9a}C(O)O$-), a carbamate ($R_{9a}R_{9b}NC(O)O$-), a carbonate ($R_{9a}OC(O)O$-), or a thiocarbamate ($R_{9a}SC(O)O$-) wherein R_{9a} and R_{9b} are independently hydrogen, hydrocarbyl, substituted hydrocarbyl or heterocyclo. If R_9 is an ester ($R_{9a}C(O)O$-), R_{9a} is substituted or unsubstituted alkyl, substituted or unsubstituted alkenyl, substituted or unsubstituted aryl or substituted or unsubstituted heteroaromatic. Still more preferably, R_9 is an ester ($R_{9a}C(O)O$-), wherein R_{9a} is substituted or unsubst ituted phenyl, substituted or unsubstituted furyl, substituted or unsubstituted thienyl, or substituted or unsubstituted pyridyl. In one embodiment R_9 is ($R_{9a}C(O)O$-) wherein R_{9a} is methyl, ethyl, propyl (straight, branched or cyclic), butyl (straight, bra nched or cyclic), pentyl, (straight, branched or cyclic), or hexyl (straight, branched or cyclic). In another embodiment R_9 is ($R_{9a}C(O)O$-) wherein R_{9a} is substituted methyl, substituted ethyl, substituted propyl (straight, branched or cyclic), substituted butyl (straight,

branched or cyclic), substituted pentyl, (straight, branched or cyclic), or substituted hexyl (straight, branched or cyclic) wherein the substituent(s) is/are selected from the group consisting of heterocyclo, alkoxy, alkenoxy, alkynoxy, aryloxy, hydroxy, protected hydroxy, keto, acyloxy, nitro, amino, amido, thiol, ketal, acetal, ester and ether moieties, but not phosphorous containing moieties.

Exemplary X_3 substituents include substituted or unsubstituted C_2 to C_8 alkyl, substituted or unsubstituted C_2 to C_8 alkenyl, substituted or unsubstituted C_2 to C_8 alkynyl, substituted or unsubstituted heteroaromatics containing 5 or 6 ring atoms, and substituted or unsubstituted phenyl. Exemplary preferred X_3 substituents include substituted or unsubstituted ethyl, propyl, butyl, cyclopropyl, cyclobutyl, cyclohexyl, isobutenyl, furyl, thienyl, and pyridyl.

Exemplary X_5 substituents include $-COX_{10}$, $-COOX_{10}$ or $-CONHX_{10}$ wherein X_{10} is substituted or unsubstituted alkyl, alkenyl, phenyl or heteroa romatic. Exemplary preferred X_5 substituents include $-COX_{10}$, $-COOX_{10}$ or $-CONHX_{10}$ wherein X_{10} is (i) substituted or unsubstituted C_1 to C_8 alkyl such as substituted or unsubstituted methyl, ethyl, propyl (straight, branched or cyclic), butyl (straight, bra nched or cyclic), pentyl (straight, branched or cyclic), or hexyl (straight, branched or cyclic); (ii) substituted or unsubstituted C_2 to C_8 alkenyl such as substituted or unsubstituted ethenyl, propenyl (straight, branched or cyclic), butenyl (straight, b ranched or cyclic), pentenyl (straight, branched or cyclic) or hexenyl (straight, branched or cyclic); (iii) substituted or unsubstituted C_2 to C_8 alkynyl such as substituted or unsubstituted ethynyl, propynyl (straight or branched), butynyl (straight or b ranched), pentynyl (straight or branched), or hexynyl (straight or branched); (iv) substituted or unsubstituted phenyl, or (v) substituted or unsubstituted heteroaromatic such as furyl, thienyl, or pyridyl, wherein the substituent(s) is/are selected from t he group consisting of heterocyclo, alkoxy, alkenoxy, alkynoxy, aryloxy, hydroxy, protected hydroxy, keto, acyloxy, nitro, amino, amido, thiol, ketal, acetal, ester and ether moieties, but not phosphorous containing moieties.

In one preferred embodiment, the taxanes of the present invention correspond to the following structural formula (2):



(2)

wherein

R_7 is $R_{7a}COO$-;

R_{10} is hydroxy;

X_3 is substituted or unsubstituted alkyl, alkenyl, alkynyl, or heterocyclo;

X_5 is $-COX_{10}$, $-COOX_{10}$, or $-CONHX_{10}$;

X_{10} is hydrocarbyl, substituted hydrocarbyl, or heterocyclo;

R_{7a} is hydrocarbyl, substituted hydrocarbyl, or heterocyclo wherein said hydrocarbyl or substituted hydrocarbyl contains carbon atoms in the alpha and beta positions relative to the carbon of which R_{7a} is a substituent;

Bz is benzoyl; and

Ac is acetyl.

For example, in this preferred embodiment in which the taxane corresponds to structure (2), R_{7a} may be substituted or unsubstituted ethyl, propyl or butyl, more preferably substituted or unsubstituted ethyl or propyl, still more preferably substituted or unsubstituted ethyl, and still more preferably unsubstituted ethyl. While R_{7a} is selected from among these, in one embodiment X_3 is selected from substituted or unsubstituted alkyl, alkenyl, phenyl or heterocyclo, more preferably substituted or unsubstituted alkenyl, phenyl or heterocyclo, still more preferably substituted or unsubstituted phenyl or heterocyclo, and still more preferably heterocyclo such as furyl, thienyl or pyridyl. While R_{7a} and X_3 are selected from among these, in one embodiment X_5 is selected from $-COX_{10}$ wherein X_{10} is phenyl, alkyl or heterocyclo, more preferably phenyl. Alternatively, while R_{7a} and X_3 are selected from among these, in one embodiment X_5 is selected from $-COX_{10}$ wherein X_{10} is phenyl, alkyl or heterocyclo, more preferably phenyl, or X_5 is $-COOX_{10}$ wherein X_{10} is alkyl, preferably t-butyl. Among the more preferred embodiments, therefore, are taxanes corresponding to structure 2 in which (i) X_5 is $-COOX_{10}$ wherein X_{10} is tert-butyl or X_5 is $-COX_{10}$ wherein X_{10} is phenyl, (ii) X_3 is substituted or unsubstituted cycloalkyl, alkenyl, phenyl or heterocyclo, more preferably substituted or unsubstituted isobutenyl, phenyl, furyl, thienyl, or pyridyl, still more preferably unsubstituted isobutenyl, furyl, thienyl or pyridyl, and (iii) R_{7a} is unsubstituted ethyl or propyl, more preferably ethyl.

Among the preferred embodiments in which the taxane corresponds to structure (1) or (2) wherein R_7 is $R_{7a}COO$-, R_{7a} may be substituted or unsubstituted ethyl or propyl, and more preferably unsubstituted ethyl or propyl. While R_{7a} is selected from among these, in one embodiment X_3 is selected from substituted or unsubstituted cycloalkyl, phenyl or heterocyclo, more preferably substituted or unsubstituted cycloalkyl, phenyl, furyl, thienyl or pyridyl. While R_{7a} and X_3 are selected from among these, in one embodiment X_5 is selected from $-COOX_{10}$ wherein X_{10} is tert-butyl, tert-amyl, isobutyl, isopropyl or substituted or

unsubstituted cycloalkyl. R_2, R_9 and R_{14} are as defined in structures 1 and 2, and are preferably benzoyloxy, keto and hydrido, respectively. Among the more preferred embodiments, therefore, are taxanes corresponding to structure 2 in which (i) X_5 is $-COOX_{10}$ wherein X_{10} is tert-butyl, tert-amyl, isobutyl, isopropyl, or unsubstituted cycloalkyl, and more preferably tert -butyl, (ii) X_3 is substituted or unsubstituted cycloalkyl, phenyl, furyl, thienyl, or pyridyl, and more preferably unsubstituted cycloalkyl, phenyl, furyl, thienyl or pyridyl, and (iii) R_{7a} is unsubstituted ethyl or propyl. In each of the alternatives of this embodiment when the taxane has structure 1, R_7 and R_{10} may each have the beta stereochemical configuration, R_7 and R_{10} may each have the alpha stereochemical configuration, R_7 may have the alpha stereochemical configuration while R_{10} has the beta stereochemical configuration or R_7 may have the beta stereochemical configuration while R_{10} has the alpha stereochemical configuration.

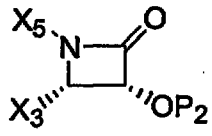
Among the preferred embodiments, therefore, are taxanes corresponding to structure 1 or 2 wherein R_7 is $R_{7a}COO-$ wherein R_{7a} is ethyl. In this embodiment, X_3 is preferably cycloalkyl, isobutenyl, phenyl, substituted phenyl such as p -nitrophenyl, or heterocyclo, more preferably heterocyclo, still more preferably furyl, thienyl or pyridyl; and X_5 is preferably benzoyl, alkoxycarbonyl, or heterocyclocarbonyl, more preferably benzoyl, t-butoxycarbonyl or t-amyloxycarbonyl. In one alternative of this embodiment, X_3 is heterocyclo; X_5 is benzoyl, alkoxycarbonyl, or heterocyclocarbonyl, more preferably benzoyl, t-butoxycarbonyl or t-amyloxycarbonyl, still more preferably t-butoxycarbonyl; R_2 is benzoyl, R_9 is keto and R_{14} is hydrido. In another alternative of this embodiment, X_3 is heterocyclo; X_5 is benzoyl, alkoxycarbonyl, or heterocyclocarbonyl, more preferably benzoyl, t -butoxycarbonyl or t-amyloxycarbonyl, still more preferably t-butoxycarbonyl; R_2 is benzoyl, R_9 is keto and R_{14} is hydrido. In another alternative of this embodiment, X_3 is heterocyclo; X_5 is benzoyl, alkoxycarbonyl, or heterocyclocarbonyl, more preferably benzoyl, t -butoxycarbonyl or t-amyloxycarbonyl, still more preferably t-butoxycarbonyl; R_2 is benzoyl, R_9 is keto and R_{14} is hydroxy. In another alternative of this embodiment, X_3 is heterocyclo; X_5 is benzoyl, alkoxycarbonyl, or heterocyclocarbonyl, more preferably benzoyl, t -butoxycarbonyl or t-amyloxycarbonyl, still more preferably t-butoxycarbonyl; R_2 is benzoyl, R_9 is hydroxy and R_{14} is hydroxy. In another alternative of this embodiment, X_3 is heterocyclo; X_5 is benzoyl, alkoxycarbonyl, or heterocyclocarbonyl, more preferably benzoyl, t-butoxycarbonyl or t-amyloxycarbonyl, still more preferably t-butoxycarbonyl; R_2 is benzoyl, R_9 is hydroxy and R_{14} is hydrido. In another alternative of this embodiment, X_3 is heterocyclo; X_5 is benzoyl, alkoxycarbonyl, or heterocyclocarbonyl, more preferably benzoyl, t -butoxycarbonyl or t-amyloxycarbonyl, still more preferably t-butoxycarbonyl; R_2 is benzoyl, R_9 is acyloxy and R_{14} is hydroxy. In another alternative of this embodiment, X_3 is heterocyclo; X_5 is benzoyl,

alkoxycarbonyl, or heterocyclocarbonyl, more preferably benzoy l, t-butoxycarbonyl or t-amyloxycarbonyl, still more preferably t -butoxycarbonyl; R_2 is benzoyl, R_9 is acyloxy and R_{14} is hydrido. In each of the alternatives of this embodiment when the taxane has structure 1, R_7 and R_{10} may each have the beta stereochem ical configuration, R_7 and R_{10} may each have the alpha stereochemical configuration, R_7 may have the alpha stereochemical configuration while R_{10} has the beta stereochemical configuration or R_7 may have the beta stereochemical configuration while R_{10} has the alpha stereochemical configuration.

Also among the preferred embodiments are taxanes corresponding to structure 1 or 2 wherein R_7 is $R_{7a}COO$- wherein R_{7a} is propyl. In this embodiment, X_3 is preferably cycloalkyl, isobutenyl, phenyl, substituted phenyl such as p-nitrophenyl, or heterocyclo, more preferably heterocyclo, still more preferably furyl, thienyl or pyridyl; and X_5 is preferably benzoyl, alkoxycarbonyl, or heterocyclocarbonyl, more preferably benzoyl, t-butoxycarbonyl or t-amyloxycarbonyl. In one alternative of this embodiment, X_3 is heterocyclo; X_5 is benzoyl, alkoxycarbonyl, or heterocyclocarbonyl, more preferably benzoyl, t-butoxycarbonyl or t-amyloxycarbonyl, still more preferably t-butoxycarbonyl; R_2 is benzoyl, R_9 is keto and R_{14} is hydrido. In another alternative of this embodiment, X_3 is heterocyclo; X_5 is benzoyl, alkoxycarbonyl, or heterocyclocarbonyl, more preferably benzoyl, t -butoxycarbonyl or t-amyloxycarbonyl, still more preferably t-butoxycarbonyl; R_2 is benzoyl, R_9 is keto and R_{14} is hydrido. In another alternative of this embodiment, X_3 is heterocyclo; X_5 is benzoyl, alkoxycarbonyl, or heterocyclocarbonyl, more preferably benzoyl, t -butoxycarbonyl or t-amyloxycarbonyl, still more preferably t -butoxycarbonyl; R_2 is benzoyl, R_9 is keto and R_{14} is hydroxy. In another alternative of this embodiment, X_3 is heterocyclo; X_5 is benzoyl, alkoxycarbonyl, or heterocyclocarbonyl, more preferably benzoyl, t -butoxycarbonyl or t-amyloxycarbonyl, still more preferably t -butoxycarbonyl; R_2 is benzoyl, R_9 is hydroxy and R_{14} is hydroxy. In another alternative of this embodiment, X_3 is heterocyclo; X_5 is benzoyl, alkoxycarbonyl, or heterocyclocarbonyl, more preferably benzoyl, t-butoxycarbonyl or t-amyloxycarbonyl, still more preferably t -butoxycarbonyl; R_2 is benzoyl, R_9 is hydroxy and R_{14} is hydrido. In another alternative of this embodiment, X_3 is heterocyclo; X_5 is benzoyl, alkoxycarbonyl, or heterocyclocarbonyl, more preferably benzoyl, t-butoxycarbonyl or t-amyloxycarbonyl, still more preferably t-butoxycarbonyl; R_2 is benzoyl, R_9 is acyloxy and R_{14} is hydroxy. In another alternative of this embodiment, X_3 is heterocyclo; X_5 is benzoyl, alkoxycarbonyl, or heterocyclocarbonyl, more preferably benzoyl, t -butoxycarbonyl or t-amyloxycarbonyl, still more preferably t-butoxycarbonyl; R_2 is benzoyl, R_9 is acyloxy and R_{14} is hydrido. In each of the alternatives of this embodiment when the taxane has structure 1, R_7 and R_{10} may each have the beta stereochemical configuration, R_7 and R_{10} may each have the alpha stereochemical configuration, R_7 may have the

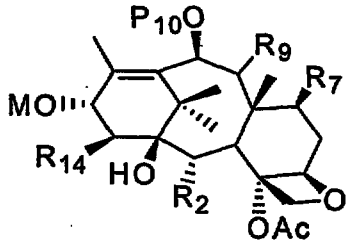
alpha stereochemical configuration while R_{10} has the beta stereochemical configuration or R_7 may have the beta stereochemical configuration while R_{10} has the alpha stereochemical configuration.

Taxanes having the general formula 1 may be obtained by treatment of a β-lactam with an alkoxide having the taxane tetracyclic nucleus and a C -13 metallic oxide substituent to form compounds having a β-amido ester substituent at C-13 (as described more fully in Holton U.S. Patent 5,466,834), followed by removal of the hydroxy protecting groups. The β-lactam has the following structural formula (3):



(3)

wherein P_2 is a hydroxy protecting group and X_3 and X_5 are as previously defined and the alkoxide has the structural formula (4):



(4)

wherein M is a metal or ammonium, P_{10} is a hydroxy protecting group and R_2, R_9, R_7 and R_{14} are as previously defined.

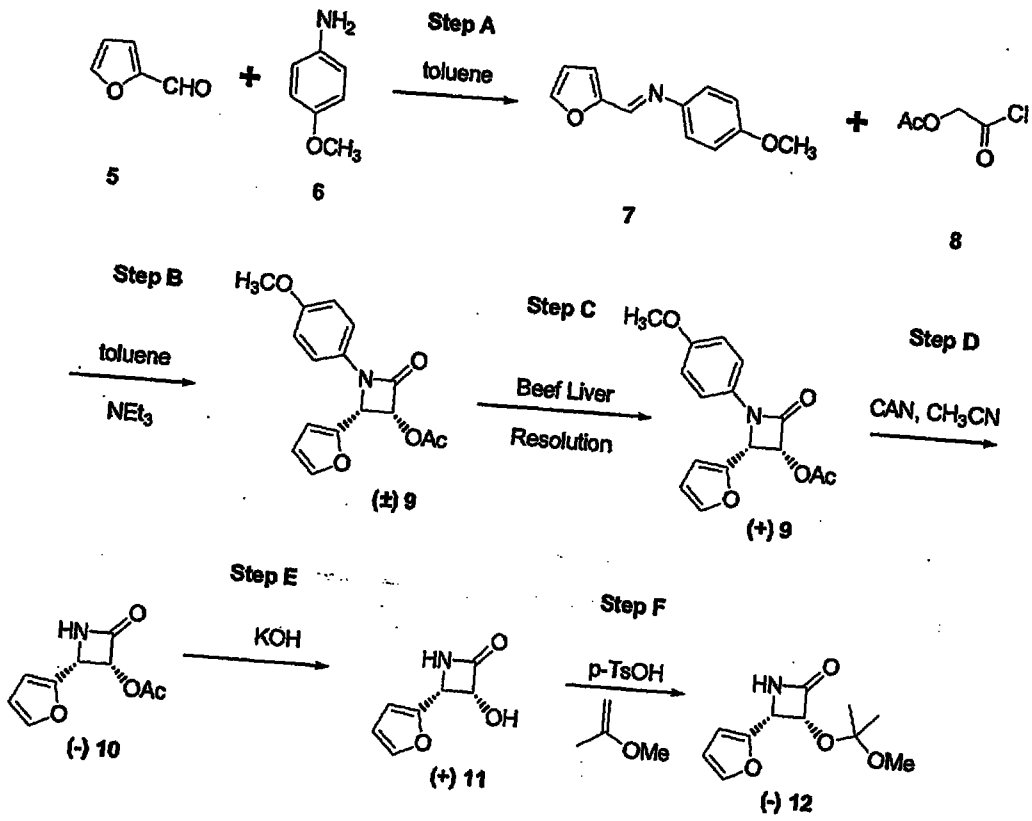
Alkoxide 4 may be prepared from 10-deacetylbaccatin III (or a derivative thereof) by selective protection of the C-10 hydroxyl group and then esterification of the C-7 hydroxyl group followed by treatment with a metallic amide. In one embodiment of the present invention, the C(10) hydroxyl group of 10-deacetylbaccatin III is selectively protected with a silyl group using, for example, a silylamide or bissilyamide as a silylating agent. Preferred silylating agents include tri(hydrocarbyl)silyl-trifluoromethylacetamides and bis tri(hydrocarbyl)-silyltrifluoromethylacetamides (with the hydrocarbyl moiety being substituted or unsubstituted alkyl or aryl) such as N,O-bis-(trimethylsilyl) trifluoroacetamide, N,O-bis-(triethylsilyl)trifluoroacetamide, N-methyl-N-triethylsilyltrifluoroacetamide, and N,O-

bis(t-butyldimethylsilyl)trifluoroacetamide. The silylating agents may be used either alone or in combination with a catalytic amount of a base such as an alkali metal base. Alkali metal amides, such as lithium amide catalysts, in general, and lithium hexamethyldisilazide, in particular, are preferred. The solvent for the selective silylation reaction is preferably an ethereal solvent such as tetrahydrofuran. Alternatively, however, other solvents such as ether or dimethoxyethane may be used. The temperature at which the C(10) selective silylation is carried out is not narrowly critical. In general, however, it is carried out at 0 °C or greater.

Selective esterification of the C(7) hydroxyl group of a C(10) protected taxane can be achieved using any of a variety of common acylating agents including, but not limited to, substituted and unsubstituted carboxylic acid derivatives, e.g., carboxylic acid halides, anhydrides, dicarbonates, isocyanates and haloformates. For example, the C(7) hydroxyl group of the 10 -protected-10-deacteyl baccatin III can be selectively acylated with dibenzyl dicarbonate, diallyl dicarbonate, 2,2,2 -trichloroethyl chloroformate, benzyl chloroformate or another common acylating agent. In general, acylation of the C(7) hydroxy group of a C(10) protected taxane are more efficient and more selective than are C(7) acylations of a 7,10 -dihydroxy taxane such as 10-DAB; stated another way, once the C(10) hydroxyl group has been protected, there is a significant difference in the reactivity of the remaining C(7), C(13), and C(1) hydroxyl groups. These acylation reactions may optionally be carried out in the presence or absence of an amine base.

Derivatives of 10-deacetylbaccatin III having alternative substit uents at C(2), C(9) and C(14) and processes for their preparation are known in the art. Taxane derivatives having acyloxy substituents other than benzoyloxy at C(2) may be prepared, for example, as described in Holton et al., U.S. Patent No. 5,728,725 or Kingston et al., U.S. Patent No. 6,002,023. Taxanes having acyloxy or hydroxy substituents at C(9) in place of keto may be prepared, for example as described in Holton et al., U.S. Patent No. 6,011,056 or Gunawardana et al., U.S. Patent No. 5,352,806. Taxanes having a beta hydroxy substituent at C(14) may be prepared from naturally occurring 14 -hydroxy-10-deacetylbaccatin III.

Processes for the preparation and resolution of the _ -lactam starting material are generally well known. For example, the β-lactam may be prepared as described in Holton, U.S. Patent No. 5,430,160 and the resulting enatiomeric mixtures of β-lactams may be resolved by a stereoselective hydrolysis using a lipase or enzyme as described, for example, in Patel, U.S. Patent No. 5,8 79,929 Patel U.S. Patent No. 5,567,614 or a liver homogenate as described, for example, in PCT Patent Application No. 00/41204. In a preferred embodiment in which the β-lactam is furyl substituted at the C(4) position, the β-lactam can be prepared as illu strated in the following reaction scheme:


Step A
toluene
Step B
toluene
NEt3
Step C
Beef Liver
Resolution
Step D
CAN, CH3CN
Step E
KOH
Step F
p-TsOH
5
6
7
8
(±) 9
(+) 9
(-) 10
(+) 11
(-) 12

wherein Ac is acetyl, NEt_3 is triethylamine, CAN is ceric ammonium nitrate, and p-TsOH is p-toluenesulfonic acid. The beef liver resolution may be carried out, for example, by combining the enatiomeric β-lactam mixture with a beef liver suspension (prepared, for example, by adding 20 g of frozen beef liver to a blender and then adding a pH 8 buffer to make a total volume of 1 L).

Compounds of formula 1 of the instant invention are useful for inhibiting t umor growth in mammals including humans and are preferably administered in the form of a pharmaceutical composition comprising an effective antitumor amount of a compound of the instant invention in combination with at least one pharmaceutically or pharmacologically acceptable carrier. The carrier, also known in the art as an excipient, vehicle, auxiliary, adjuvant, or diluent, is any substance which is pharmaceutically inert, confers a suitable consistency or form to the composition, and does not diminish the therapeutic efficacy of the antitumor compounds. The carrier is "pharmaceutically or pharmacologically acceptable" if it does not produce an adverse, allergic or other untoward reaction when administered to a mammal or human, as appropriate.

The pharmaceutical compositions containing the antitumor compounds of the present invention may be formulated in any conventional manner. Proper formulation is dependent upon the route of administration chosen. The compositions of the invention can be formulate d for any route of administration so long as the target tissue is available via that route. Suitable routes of administration include, but are not limited to, oral, parenteral (e.g., intravenous, intraarterial, subcutaneous, rectal, subcutaneous, intramus cular, intraorbital, intracapsular, intraspinal, intraperitoneal, or intrasternal), topical (nasal, transdermal, intraocular), intravesical, intrathecal, enteral, pulmonary, intralymphatic, intracavital, vaginal, transurethral, intradermal, aural, intramammary, buccal, orthotopic, intratracheal, intralesional, percutaneous, endoscopical, transmucosal, sublingual and intestinal administration.

Pharmaceutically acceptable carriers for use in the compositions of the present invention are well known to those o f ordinary skill in the art and are selected based upon a number of factors: the particular antitumor compound used, and its concentration, stability and intended bioavailability; the disease, disorder or condition being treated with the composition; the s ubject, its age, size and general condition; and the route of administration. Suitable carriers are readily determined by one of ordinary skill in the art (see, for example, J. G. Nairn, in: Remington's Pharmaceutical Science (A. Gennaro, ed.), Mack Publi shing Co., Easton, Pa., (1985), pp. 1492 -1517, the contents of which are incorporated herein by reference).

The compositions are preferably formulated as tablets, dispersible powders, pills, capsules, gelcaps, caplets, gels, liposomes, granules, solutions , suspensions, emulsions, syrups, elixirs, troches, dragees, lozenges, or any other dosage form

which can be administered orally. Techniques and compositions for making oral dosage forms useful in the present invention are described in the following refer ences: 7 Modern Pharmaceutics, Chapters 9 and 10 (Banker & Rhodes, Editors, 1979); Lieberman et al., Pharmaceutical Dosage Forms: Tablets (1981); and Ansel, Introduction to Pharmaceutical Dosage Forms 2nd Edition (1976).

The compositions of the invention for oral administration comprise an effective antitumor amount of a compound of the invention in a pharmaceutically acceptable carrier. Suitable carriers for solid dosage forms include sugars, starches, and other conventional substances including lactose, talc, sucrose, gelatin, carboxymethylcellulose, agar, mannitol, sorbitol, calcium phosphate, calcium carbonate, sodium carbonate, kaolin, alginic acid, acacia, corn starch, potato starch, sodium saccharin, magnesium carbonate, tragacanth, microcrystalline cellulose, colloidal silicon dioxide, croscarmellose sodium, talc, magnesium stearate, and stearic acid. Further, such solid dosage forms may be uncoated or may be coated by known techniques; e.g., to delay disintegration and absorption.

The antitumor compounds of the present invention are also preferably formulated for parenteral administration, e.g., formulated for injection via intravenous, intraarterial, subcutaneous, rectal, subcutaneous, intramuscular, intraorbital, intracapsular, intraspinal, in traperitoneal, or intrasternal routes. The compositions of the invention for parenteral administration comprise an effective antitumor amount of the antitumor compound in a pharmaceutically acceptable carrier. Dosage forms suitable for parenteral adminis tration include solutions, suspensions, dispersions, emulsions or any other dosage form which can be administered parenterally. Techniques and compositions for making parenteral dosage forms are known in the art.

Suitable carriers used in formulating liq uid dosage forms for oral or parenteral administration include nonaqueous, pharmaceutically -acceptable polar solvents such as oils, alcohols, amides, esters, ethers, ketones, hydrocarbons and mixtures thereof, as well as water, saline solutions, dextrose s olutions (e.g., DW5), electrolyte solutions, or any other aqueous, pharmaceutically acceptable liquid.

Suitable nonaqueous, pharmaceutically -acceptable polar solvents include, but are not limited to, alcohols (e.g., α-glycerol formal, β-glycerol formal, 1, 3-butyleneglycol, aliphatic or aromatic alcohols having 2 -30 carbon atoms such as methanol, ethanol, propanol, isopropanol, butanol, t -butanol, hexanol, octanol, amylene hydrate, benzyl alcohol, glycerin (glycerol), glycol, hexylene glycol, tetrahydrofurfuryl alcohol, lauryl alcohol, cetyl alcohol, or stearyl alcohol, fatty acid esters of fatty alcohols such as polyalkylene glycols (e.g., polypropylene glycol, polyethylene glycol), sorbitan, sucrose and cholesterol); amides (e.g., dimethylacetamide (DMA), benzyl benzoate DMA, dimethylformamide, N -(β-

hydroxyethyl)-lactamide, N, N-dimethylacetamide_amides, 2-pyrrolidinone, 1-methyl-2-pyrrolidinone, or polyvinylpyrrolidone); esters (e.g., 1 -methyl-2-pyrrolidinone, 2-pyrrolidinone, acetate esters such as monoa cetin, diacetin, and triacetin, aliphatic or aromatic esters such as ethyl caprylate or octanoate, alkyl oleate, benzyl benzoate, benzyl acetate, dimethylsulfoxide (DMSO), esters of glycerin such as mono, di, or tri -glyceryl citrates or tartrates, ethyl be nzoate, ethyl acetate, ethyl carbonate, ethyl lactate, ethyl oleate, fatty acid esters of sorbitan, fatty acid derived PEG esters, glyceryl monostearate, glyceride esters such as mono, di, or tri -glycerides, fatty acid esters such as isopropyl myristrate, fatty acid derived PEG esters such as PEG-hydroxyoleate and PEG-hydroxystearate, N-methyl pyrrolidinone, pluronic 60, polyoxyethylene sorbitol oleic polyesters such as poly(ethoxylated) $_{30\text{-}60}$ sorbitol poly(oleate)$_{2\text{-}4}$, poly(oxyethylene)$_{15\text{-}20}$ monooleate, poly(oxyethylene)$_{15\text{-}20}$ mono 12-hydroxystearate, and poly(oxyethylene) $_{15\text{-}20}$ mono ricinoleate, polyoxyethylene sorbitan esters such as polyoxyethylene -sorbitan monooleate, polyoxyethylene -sorbitan monopalmitate, polyoxyethylene -sorbitan monolaurate, polyoxyethy lene-sorbitan monostearate, and Polysorbate® 20, 40, 60 or 80 from ICI Americas, Wilmington, DE, polyvinylpyrrolidone, alkyleneoxy modified fatty acid esters such as polyoxyl 40 hydrogenated castor oil and polyoxyethylated castor oils (e.g., Cremophor® EL solution or Cremophor® RH 40 solution), saccharide fatty acid esters (i.e., the condensation product of a monosaccharide (e.g., pentoses such as ribose, ribulose, arabinose, xylose, lyxose and xylulose, hexoses such as glucose, fructose, galactose, mannose and sorbose, trioses, tetroses, heptoses, and octoses), disaccharide (e.g., sucrose, maltose, lactose and trehalose) or oligosaccharide or mixture thereof with a C_4-C_{22} fatty acid(s)(e.g., saturated fatty acids such as caprylic acid, capric acid, lauric a cid, myristic acid, palmitic acid and stearic acid, and unsaturated fatty acids such as palmitoleic acid, oleic acid, elaidic acid, erucic acid and linoleic acid)), or steroidal esters); alkyl, aryl, or cyclic ethers having 2 -30 carbon atoms (e.g., diethyl ether, tetrahydrofuran, dimethyl isosorbide, diethylene glycol monoethyl ether); glycofurol (tetrahydrofurfuryl alcohol polyethylene glycol ether); ketones having 3-30 carbon atoms (e.g., acetone, methyl ethyl ketone, methyl isobutyl ketone); aliphatic, cycloaliphatic or aromatic hydrocarbons having 4 -30 carbon atoms (e.g., benzene, cyclohexane, dichloromethane, dioxolanes, hexane, n -decane, n-dodecane, n-hexane, sulfolane, tetramethylenesulfon, tetramethylenesulfoxide, toluene, dimethylsulfoxide (DMSO), o r tetramethylenesulfoxide); oils of mineral, vegetable, animal, essential or synthetic origin (e.g., mineral oils such as aliphatic or wax-based hydrocarbons, aromatic hydrocarbons, mixed aliphatic and aromatic based hydrocarbons, and refined paraffin oil, vegetable oils such as linseed, tung, safflower, soybean, castor, cottonseed, groundnut, rapeseed, coconut, palm, olive, corn, corn germ, sesame, persic and peanut oil and glycerides such as mono -, di- or

triglycerides, animal oils such as fish, marine, s perm, cod-liver, haliver, squalene, squalane, and shark liver oil, oleic oils, and polyoxyethylated castor oil); alkyl or aryl halides having 1-30 carbon atoms and optionally more than one halogen substituent; methylene chloride; monoethanolamine; petrole um benzin; trolamine; omega-3 polyunsaturated fatty acids (e.g., alpha -linolenic acid, eicosapentaenoic acid, docosapentaenoic acid, or docosahexaenoic acid); polyglycol ester of 12 -hydroxystearic acid and polyethylene glycol (Solutol® HS -15, from BASF, Ludwigshafen, Germany); polyoxyethylene glycerol; sodium laurate; sodium oleate; or sorbitan monooleate.

Other pharmaceutically acceptable solvents for use in the invention are well known to those of ordinary skill in the art, and are identified in The Chemotherapy Source Book (Williams & Wilkens Publishing), The Handbook of Pharmaceutical Excipients, (American Pharmaceutical Association, Washington, D.C., and The Pharmaceutical Society of Great Britain, London, England, 1968), Modern Pharmaceutics, (G. Banker et al., eds., 3d ed.)(Marcel Dekker, Inc., New York, New York, 1995), The Pharmacological Basis of Therapeutics, (Goodman & Gilman, McGraw Hill Publishing), Pharmaceutical Dosage Forms, (H. Lieberman et al., eds.,)(Marcel Dekker, Inc., New York, New Yo rk, 1980), Remington's Pharmaceutical Sciences (A. Gennaro, ed., 19th ed.)(Mack Publishing, Easton, PA, 1995), The United States Pharmacopeia 24, The National Formulary 19, (National Publishing, Philadelphia, PA, 2000), A.J. Spiegel et al., and Use of Nona queous Solvents in Parenteral Products, JOURNAL OF PHARMACEUTICAL SCIENCES, Vol. 52, No. 10, pp. 917-927 (1963).

Preferred solvents include those known to stabilize the antitumor compounds, such as oils rich in triglycerides, for example, safflower oil, soybean oil or mixtures thereof, and alkyleneoxy modified fatty acid esters such as polyoxyl 40 hydrogenated castor oil and polyoxyethylated castor oils (e.g., Cremophor® EL solution or Cremophor® RH 40 solution). Commercially available triglycerides incl ude Intralipid® emulsified soybean oil (Kabi-Pharmacia Inc., Stockholm, Sweden), Nutralipid ® emulsion (McGaw, Irvine, California), Liposyn® II 20% emulsion (a 20% fat emulsion solution containing 100 mg safflower oil, 100 mg soybean oil, 12 mg egg phosphatides, and 25 mg glycerin per ml of solution; Abbott Laboratories, Chicago, Illinois), Liposyn® III 2% emulsion (a 2% fat emulsion solution containing 100 mg safflower oil, 100 mg soybean oil, 12 mg egg phosphatides, and 25 mg glycerin per ml of solution; Abbott Laboratories, Chicago, Illinois), natural or synthetic glycerol derivatives containing the docosahexaenoyl group at levels between 25% and 100% by weight based on the total fatty acid content (Dhasco® (from Martek Biosciences Corp., Columbia, MD), D HA Maguro® (from Daito Enterprises, Los Angeles, CA),

Soyacal®, and Travemulsion®. Ethanol is a preferred solvent for use in dissolving the antitumor compound to form solutions, emulsions, and the like.

Additional minor components can be included in the compositions of the invention for a variety of purposes well known in the pharmaceutical industry. These components will for the most part impart properties which enhance retention of the antitumor compound at the site of administration, protect the stabil ity of the composition, control the pH, facilitate processing of the antitumor compound into pharmaceutical formulations, and the like. Preferably, each of these components is individually present in less than about 15 weight % of the total composition, m ore preferably less than about 5 weight %, and most preferably less than about 0.5 weight % of the total composition. Some components, such as fillers or diluents, can constitute up to 90 wt.% of the total composition, as is well known in the formulation art. Such additives include cryoprotective agents for preventing reprecipitation of the taxane, surface active, wetting or emulsifying agents (e.g., lecithin, polysorbate -80, Tween® 80, pluronic 60, polyoxyethylene stearate), preservatives (e.g., ethyl -p-hydroxybenzoate), microbial preservatives (e.g., benzyl alcohol, phenol, m -cresol, chlorobutanol, sorbic acid, thimerosal and paraben), agents for adjusting pH or buffering agents (e.g., acids, bases, sodium acetate, sorbitan monolaurate), agents for adjusting osmolarity (e.g., glycerin), thickeners (e.g., aluminum monostearate, stearic acid, cetyl alcohol, stearyl alcohol, guar gum, methyl cellulose, hydroxypropylcellulose, tristearin, cetyl wax esters, polyethylene glycol), colorants, dyes, flow aids, non-volatile silicones (e.g., cyclomethicone), clays (e.g., bentonites), adhesives, bulking agents, flavorings, sweeteners, adsorbents, fillers (e.g., sugars such as lactose, sucrose, mannitol, or sorbitol, cellulose, or calcium phosphate), diluents (e.g., water, saline, electrolyte solutions), binders (e.g., starches such as maize starch, wheat starch, rice starch, or potato starch, gelatin, gum tragacanth, methyl cellulose, hydroxypropyl methylcellulose, sodium carboxymethyl cellulose, polyvinylpyrrolidone, sugars, polymers, acacia), disintegrating agents (e.g., starches such as maize starch, wheat starch, rice starch, potato starch, or carboxymethyl starch, cross-linked polyvinyl pyrrolidone, agar, alginic acid or a salt thereof such as sodium alginate, croscarmellose sodium or crospovidone), lubricants (e.g., silica, talc, stearic acid or salts thereof such as magnesium stearate, or polyethylene glycol), coating agents (e.g., concentrated sugar solutions including gum arabic, talc, polyvinyl pyrrolidone, carbopol gel, polyethylene glycol, or titanium dioxide), and antioxidants (e.g., sodium metabisulfite, sodium bisulfite, sodium sulfite, dextrose, phenols, and thiophenols).

In a preferred embodiment, a pharmaceutical composition of the invention comprises at least one nonaqueous, pharmaceutically acceptable solvent and an antitumor compound having a solubility in ethanol of at least about 100, 200, 300, 400,

500, 600, 700 or 800 mg/ml. While not being bound to a particular theory, it is believed that the ethanol solubility of the antitumor compound may be directly related to its efficacy. The antitumor compound can also be capable of being crystallized from a solution. In other words, a crystalline antitumor compound, such as compound 1393, can be dissolved in a solvent to form a solution and then recrystallized upon evaporation of the solvent without the formation of any amorphous antitumor compound. It is also preferred that the antitumor compound have an ID50 value (i.e, the drug concentration producing 50% inhibition of colony formation) of at least 4, 5, 6, 7, 8, 9, or 10 times less that of paclitaxel when measured according to the protocol set forth in the working examples.

Dosage form administration by these routes may be continuous or intermittent, depending, for example, upon the patient's physiological condition, whether the purpose of the administration is therapeutic or prophylactic, and other factors known to and assessable by a skilled practitioner.

Dosage and regimens for the administration of the pharmaceutical compositions of the invention can be readily determined by those with ordinary skill in treating cancer. It is understood that the dosage of the antitumor compounds will be dependent upon the age, sex, health, and weight of the recipient, kind of concurrent treatment, if any, frequency of treatment, and the nature of the effect desired. For any mode of administration, the actual amount of antitumor compound delivered, as well as the dosing schedule necessary to achieve the advantageous effects described herein, will also depend, in part, on such factors as the bioavailability of the antitumor compound, the disorder being treated, the desired therapeutic dose, and other factors that will be apparent to those of skill in the art. The dose administered to an animal, particularly a human, in the context of the present invention should be sufficient to effect the desired therapeutic response in the animal over a reasonable period of time. Preferably, an effective amount of the antitumor compound, whether administered orally or by another route, is any amount which would result in a desired therapeutic response when administered by that route. Preferably, the compositions for oral administration are prepared in such a way that a single dose in one or more oral preparations contains at least 20 mg of the antitumor compound per m^2 of patient body surface area, or at least 50, 100, 150, 200, 300, 400, or 500 mg of the antitumor compound per m^2 of patient body surface area, wherein the average body surface area for a human is 1.8 m^2. Preferably, a single dose of a composition for oral administration contains from about 20 to about 600 mg of the antitumor compound per m^2 of patient body surface area, more preferably from about 25 to about 400 mg/m^2, even more preferably, from about 40 to about 300 mg/m^2, and even more preferably from about 50 to about 200 mg/m^2. Preferably, the compositions for parenteral administration are prepared in such a way that a single dose contains at least 20 mg

of the antitumor compound per m^2 of patient body surface area, or at least 40, 50, 100, 150, 200, 300, 400, or 500 mg of the antitumor compound per m^2 of patient body surface area. Preferably, a single dose in one or more parenteral preparations contains from about 20 to about 500 mg of the antitumor compound per m^2 of patient body surface area, more preferably from about 40 to about 400 mg/m^2, and even more preferably, from about 60 to about 350 mg/m^2. However, the dosage may vary depending on the dosing schedule which can be adjusted as necessary to achieve the desired therapeutic effect. It should be noted that the ranges of effective doses provided herein are not intended to limit the invention and represent preferred dose ranges. The most preferred dosage will be tailored to the individual subject, as is understood and determinable by one of ordinary skill in the art without undue experimentation.

The concentration of the antitumor compound in a liquid pharmaceutical composition is preferably between about 0.01 mg and about 10 mg per ml of the composition, more preferably between about 0.1 mg and about 7 mg per ml, even more preferably between about 0.5 mg and about 5 mg per ml, and most preferably between about 1.5 mg and about 4 mg per ml. Relatively low concentrations are generally preferred because the antitumor compound is most soluble in the solution at low concentrations. The concentration of the antitumor compound in a solid pharmaceutical composition for oral administration is preferably between about 5 weight % and about 50 weight %, based on the total weight of the composition, more preferably between about 8 weight % and about 40 weight %, and most preferably between about 10 weight % and about 30 weight %.

In one embodiment, solutions for oral administration are prepared by dissolving an antitumor compound in any pharmaceutically acceptable solvent capable of dissolving the compound (e.g., ethanol or methylene chloride) to form a solution. An appropriate volume of a carrier which is a solution, such as Cremophor® EL solution, is added to the solution while stirring to form a pharmaceutically acceptable solution for oral administration to a patient. If desired, such solutions can be formulated to contain a minimal amount of, or to be free of, ethanol, which is known in the art to cause adverse physiological effects when administered at certain concentrations in oral formulations.

In another embodiment, powders or tablets for oral administration are prepared by dissolving an antitumor compound in any pharmaceutically acceptable solvent capable of dissolving the compound (e.g.,ethanol or methylene chloride) to form a solution. The solvent can optionally be capable of evaporating when the solution is dried under vacuum. An additional carrier can be added to the solution prior to drying, such as Cremophor® EL solution. The resulting solution is dried under vacuum to form a glass. The glass is then mixed with a binder to form a powder. The powder

can be mixed with fillers or other conventional tabletting agents and processed to form a tablet for oral administration to a patient. The powder can also be added to any liquid carrier as described above to form a solution, emulsion, suspension or the like for oral administration.

Emulsions for parenteral administration can be prepared by dissolving an antitumor compound in any pharmaceutically acceptable solvent capable of dissolving the compound (e.g., ethanol or methylene chloride) to form a solution. An appropriate volume of a carrier which is an emulsion, such as Liposyn® II or Liposyn® III emulsion, is added to the solution while stirring to form a pharmaceutically acceptable emulsion for parenteral administration to a patient. If desired, such emulsions can be formulated to contain a minimal amount of, or to be free of, ethanol or Cremophor® solution, which are known in the art to cause adverse physiological effects when administered at certain concentrations in parenteral formulations.

Solutions for parenteral administration can be prepared by dissolving an antitumor compound in any pharmaceutically acceptable solvent capable of dissolving the compound (e.g., ethanol or methylene chloride) to form a solution. An appropriate volume of a carrier which is a solution, such as Cremophor® solution, is added to the solution while stirring to form a pharmaceutically acceptable solution for parenteral administration to a patient. If desired, such solutions can be formulated to contain a minimal amount of, or to be free of, ethanol or Cremophor® solution, which are known in the art to cause adverse physiological effects when administered at certain concentrations in parenteral formulations.

If desired, the emulsions or solutions described above for oral or parenteral administration can be packaged in IV bags, vials or other conventional containers in concentrated form and diluted with any pharmaceutically acceptable liquid, such as saline, to form an acceptable taxane concentration prior to use as is known in the art.

Definitions

The terms "hydrocarbon" and "hydrocarbyl" as used herein describe organic compounds or radicals consisting exclusively of the elements carbon and hydrogen. These moieties include alkyl, alkenyl, alkynyl, and aryl moieties. These moieties also include alkyl, alkenyl, alkynyl, and aryl moieties substituted with other aliphatic or cyclic hydrocarbon groups, such as alkaryl, alkenaryl and alkynaryl. Unless otherwise indicated, these moieties preferably comprise 1 to 20 carbon atoms.

The "substituted hydrocarbyl" moieties described herein are hydrocarbyl moieties which are substituted with at least one atom other than carbon, including moieties in which a carbon chain atom is substituted with a hetero atom such as nitrogen, oxygen, silicon, phosphorous, boron, sulfur, or a halogen atom. These substituents include halogen, heterocyclo, alkoxy, alkenoxy, alkynoxy, aryloxy,

hydroxy, protected hydroxy, keto, acyl, acyloxy, nitro, amino, amido, nitro, cyano, thiol, ketals, acetals, esters and ethers.

The term "heteroatom" shall me an atoms other than carbon and hydrogen.

The "heterosubstituted methyl" moieties described herein are methyl groups in which the carbon atom is covalently bonded to at least one heteroatom and optionally with hydrogen, the heteroatom being, for example, a nitrogen, oxygen, silicon, phosphorous, boron, sulfur, or halogen atom. The heteroatom may, in turn, be substituted with other atoms to form a heterocyclo, alkoxy, alkenoxy, alkynoxy, aryloxy, hydroxy, protected hydroxy, oxy, acyloxy, nitro, amino, amido , thiol, ketals, acetals, esters or ether moiety.

The "heterosubstituted acetate" moieties described herein are acetate groups in which the carbon of the methyl group is covalently bonded to at least one heteroatom and optionally with hydrogen, the hetero atom being, for example, a nitrogen, oxygen, silicon, phosphorous, boron, sulfur, or halogen atom. The heteroatom may, in turn, be substituted with other atoms to form a heterocyclo, alkoxy, alkenoxy, alkynoxy, aryloxy, hydroxy, protected hydroxy, oxy, ac yloxy, nitro, amino, amido, thiol, ketals, acetals, esters or ether moiety.

Unless otherwise indicated, the alkyl groups described herein are preferably lower alkyl containing from one to eight carbon atoms in the principal chain and up to 20 carbon atoms. They may be straight or branched chain or cyclic and include methyl, ethyl, propyl, isopropyl, butyl, hexyl and the like.

Unless otherwise indicated, the alkenyl groups described herein are preferably lower alkenyl containing from two to eight carbon a toms in the principal chain and up to 20 carbon atoms. They may be straight or branched chain or cyclic and include ethenyl, propenyl, isopropenyl, butenyl, isobutenyl, hexenyl, and the like.

Unless otherwise indicated, the alkynyl groups described herei n are preferably lower alkynyl containing from two to eight carbon atoms in the principal chain and up to 20 carbon atoms. They may be straight or branched chain and include ethynyl, propynyl, butynyl, isobutynyl, hexynyl, and the like.

The terms "aryl" or "ar" as used herein alone or as part of another group denote optionally substituted homocyclic aromatic groups, preferably monocyclic or bicyclic groups containing from 6 to 12 carbons in the ring portion, such as phenyl, biphenyl, naphthyl, substituted phenyl, substituted biphenyl or substituted naphthyl. Phenyl and substituted phenyl are the more preferred aryl.

The terms "halogen" or "halo" as used herein alone or as part of another group refer to chlorine, bromine, fluorine, and iodine.

The terms "heterocyclo" or "heterocyclic" as used herein alone or as part of another group denote optionally substituted, fully saturated or unsaturated, monocyclic or bicyclic, aromatic or nonaromatic groups having at least one heteroatom in at least

one ring, and preferably 5 or 6 atoms in each ring. The heterocyclo group preferably has 1 or 2 oxygen atoms, 1 or 2 sulfur atoms, and/or 1 to 4 nitrogen atoms in the ring, and may be bonded to the remainder of the molecule through a carbon or heteroatom. Exemplary heterocyclo include heteroaromatics such as furyl, thienyl, pyridyl, oxazolyl, pyrrolyl, indolyl, quinolinyl, or isoquinolinyl and the like. Exemplary substituents include one or more of the following groups: hydrocarbyl, substituted hydrocarbyl, keto, hydroxy, protected hydroxy, acyl, acyloxy, alkoxy, alkenoxy, alkynoxy, aryloxy, halogen, amido, amino, nitro, cyano, thiol, ketals, acetals, esters and ethers.

The term "heteroaromatic" as used herein alone or as part of another group denote optionally substituted aromatic groups having at least one heteroatom in at least one ring, and preferably 5 or 6 atoms in each ring. The heteroaromatic group preferably has 1 or 2 oxygen atoms, 1 or 2 sulfur atoms, and/or 1 to 4 nitrogen atoms in the ring, and may be bonded to the remainder of the molecule through a carbon or heteroatom. Exemplary heteroaromatics include furyl, thienyl, pyridyl, oxazolyl, pyrrolyl, indolyl, quinolinyl, or isoquinolinyl and the like. Exemplary substituents include one or more of the following groups: hydrocarbyl, substituted hydrocarbyl, keto, hydroxy, protected hydroxy, acyl, acyloxy, alkoxy, alkenoxy, alkynoxy, aryloxy, halogen, amido, amino, nitro, cyano, thiol, ketals, acetals, esters and ethers.

The term "acyl," as used herein alone or as part of another group, denotes the moiety formed by removal of the hydroxyl group from the group --COOH of an organic carboxylic acid, e.g., RC(O)-, wherein R is R^1, R^1O-, R^1R^2N-, or R^1S-, R^1 is hydrocarbyl, heterosubstituted hydrocarbyl, or heterocyclo, and R^2 is hydrogen, hydrocarbyl or substituted hydrocarbyl.

The term "acyloxy," as used herein alone or as part of another group, denotes an acyl group as described above bonded through an oxygen linkage (--O--), e.g., RC(O)O- wherein R is as defined in connection with the term "acyl."

Unless otherwise indicated, the alkoxycarbonyloxy moieties described herein comprise lower hydrocarbon or substituted hydrocarbon or substituted hydrocarbon moieties.

Unless otherwise indicated, the carbamoyloxy moieties described herein are derivatives of carbamic acid in which one or both of the amine hydrogens is optionally replaced by a hydrocarbyl, substituted hydrocarbyl or heterocyclo moiety.

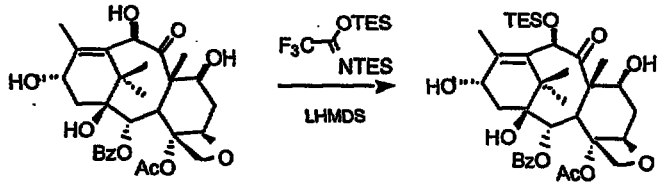
The terms "hydroxyl protecting group" and "hydroxy protecting group" as used herein denote a group capable of protecting a free hydroxyl group ("protected hydroxyl") which, subsequent to the reaction for which protection is employed, may be removed without disturbing the remainder of the molecule. A variety of protecting groups for the hydroxyl group and the synthesis thereof may be found in "Protective Groups in Organic Synthesis" by T. W. Greene, John Wiley and Sons, 1981, or Fieser

& Fieser. Exemplary hydroxyl protecting groups include methoxymethyl, 1 -ethoxyethyl, benzyloxymethyl, (.beta.-trimethylsilylethoxy)methyl, tetrahydropyranyl, 2,2,2-trichloroethoxycarbonyl, t-butyl(diphenyl)silyl, trialkylsilyl, trichloromethoxycarbonyl and 2,2,2 -trichloroethoxymethyl.

As used herein, "Ac" means acetyl; "Bz" means benzoyl; "Et" means ethyl; "Me" means methyl; "Ph" means phenyl; "Pr" means propyl; "Bu" means butyl; "Am" means amyl; "cpro" means cyclopropyl; "iPr" means isopropyl; "tBu" and "t -Bu" means tert-butyl; "R" means lower alkyl unless otherwise defined; "Py" means pyridine or pyridyl; "TES" means triethylsilyl; "TMS" means trimethylsilyl; "LAH" means lithium aluminum hydride; "10-DAB" means 10-desacetylbaccatin III"; "amine protecting group" includes, but is not limited to, carbamates, for example, 2,2,2 -trichloroethylcarbamate or tertbutylcarbamate; "protected hydroxy" means -OP wherein P is a hydroxy protecting group; "PhCO" means phenylcarbonyl; "tBuOCO" and "Boc" mean tert -butoxycarbonyl; "tAmOCO" means tert -amyloxycarbonyl; "2-FuCO" means 2-furylcarbonyl; "2-ThCO" means 2-thienylcarbonyl; "2-PyCO" means 2-pyridylcarbonyl; "3-PyCO" means 3-pyridylcarbonyl; "4-PyCO" means 4-pyridylcarbonyl; "C_4H_7CO" means butenylcarbonyl; "tC_3H_5CO" means *trans*-propenylcarbonyl; "EtOCO" means ethoxycarbonyl; "ibueCO" means iso butenylcarbonyl; "iBuCO" means isobutylcarbonyl; "iBuOCO" means isobutoxycarbonyl; "iPrOCO" means isopropyloxycarbonyl; "nPrOCO" means n -propyloxycarbonyl; "nPrCO" means n -propylcarbonyl; "ibue" means isobutenyl; "THF" means tetrahydrofuran; "DMAP" means 4-dimethylamino pyridine; "LHMDS" means Lithium HexamethylDiSilazanide.

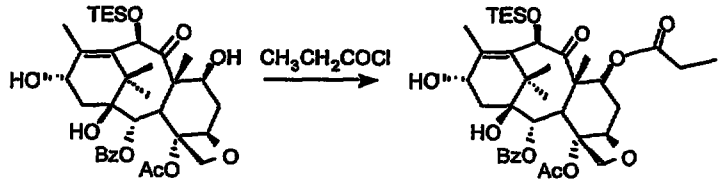
The following examples illustrate the invention.

Example 1



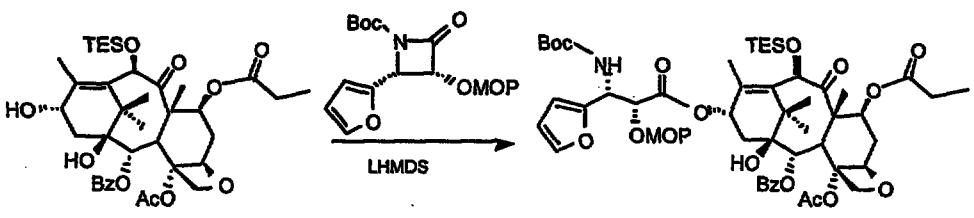
10-Triethylsilyl-10-deacetyl baccatin III. To a solution of 1.0 g (1.84 mmol) of 10-deacetyl baccatin III in 50 mL of THF at -10 °C under a nitrogen atmosphere was added 0.857 mL (2.76 mmol, 1.5 mol equiv) of *N,O*-(bis)-TES-trifluoroacetamide over a period of 3 min. This was followed by the addition of 0.062 mL of a 0.89 M THF solution of lithium bis(trimethylsilyl) amide (0.055 mmol,

0.03 mol equiv). After 10 min 0.038 mL (0.92 mmol, 0.5 mol equiv) of methanol was added, and after an additional 5 min 4 mL (0.055 mmol, 0.03 mol equiv) of acetic acid was added. The solution was diluted with 300 mL of ethyl acetate and washed two times with 100 mL of saturated aqueous sodium bicarbonate solution. The combined aqueous layers were extracted with 100 mL of ethyl acetate and the combined organic layers were washed with brine, dried over sodium sulfate, and concentrated under reduced pressure. To the residue was added 100 mL of hexane and the solid (1.23 g, 101%) was collected by filtration. Recrystallization of the solid by dissolving in boiling ethyl acetate (20 mL, 17 mL/g) and cooling to room temperature gave 1.132 g (94%) of a white solid. m.p. 242 °C; $[\alpha]_D^{25}$ -60.4 (c 0.7, $CHCl_3$); ^1H NMR ($CDCl_3$, 400MHz) δ (p.p.m): 8.10 (2H, d, *Jm* = 7.5Hz, Bz*o*), 7.60 (1H, t, *Jm* = 7.5Hz, Bz*p*), 7.47 (2H, t, *Jo* = 7.5Hz, Bz*m*), 5.64 (1H, d, *J*3 = 6.9Hz, H2), 5.26 (1H, s, H10), 4.97 (1H, d d, *J*6β = 2.2Hz, *J*6β = 9.9Hz, H5), 4.85 (1H, dd, *J*14α = 8.9Hz, *J*14β = 8.9Hz, H13), 4.30 (1H, d, *J*20β = 8.5Hz, H20α), 4.23 (1H, ddd, *J*7OH = 4.5Hz, *J*6α = 6.6Hz, *J*6β = 11.0Hz, H7), 4.15 (1H, d, *J*20α = 8.5Hz, H20β), 4.00 (1H, d, *J*2 = 6.9Hz, H3), 2.58 (1H, ddd, *J*7 = 6.6Hz, *J*5 = 9.9Hz, *J*6β = 14.5Hz, H6α), 2.28-2.25 (5H, m, 4Ac, H14α H14β), 2.02 (3H, s, 18Me), 1.97 (1H, d, *J*7 = 4.5Hz, H7OH), 1.78 (1H, ddd, *J*7 = 11.0Hz, *J*5 = 2.2Hz, *J*6α = 14.5Hz, H6β), 1.68 (3H, s, 19Me), 1.56 (1H, s, OH1), 1.32 (1H, d, *J*13 = 8.8Hz, OH13) , 1.18 (3H, s, 17Me), 1.06 (3H, s, 16Me), 0.98 (9H, t, JCH_2(TES) = 7.3Hz, CH_3(TES)), 0.65 (6H, dq, JCH_3(TES) = 7.3Hz, CH_2(TES)).

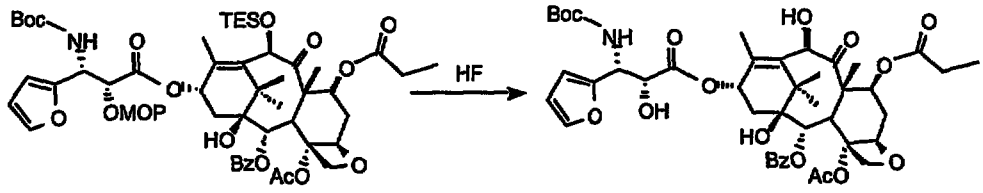


10-Triethylsilyl-10-deacetyl-7-propionyl baccatin III. To a solution of 1.0 g (1.517 mmol) of 10-triethylsilyl-10-deacetyl baccatin III and 37.0 mg (0.303 mmol) of DMAP in 20 mL of dichloromethane at room temperature under a nitrogen atmosphere was added 0.920 mL (11.381 mmol) of pyridine and 0.329 mL (3.794 mmol, 2.5 mol equiv) of propionyl chloride in that order. The mixture was stirred

at room temperature for 6 h, diluted with 350 mL of ethyl acetate and extracted with 50 mL of 10% aqueous copper sulfate solution. The organic layer was washed with 50 mL of saturated aqueous sodium bicarbonate solution, 50 mL of brine, dried over sodium sulfate and concentrated under reduced pressure. The crude product was dissolved in 75 mL of ethyl acetate, 100 mg of Norit A was added, the mixture was filtered through celite and concentrate d under reduced pressure to give 1.13 g of material. Recrystallization from ethyl acetate/hexanes (dissolved in 6.5 mL of refluxing ethyl acetate, then 24 mL of hexanes added, allowed to cool to room temperature, and left to stand for 17 h) afforded 787 m g (72.5%) of a white crystalline solid. A second recrystallization (*ca* 340 mg material dissolved in 2 mL of refluxing ethyl acetate, then 10 mL of hexanes added, allowed to cool to room temperature, and allowed to stand for 17 h) afforded 181 mg (16.7 %) of a white crystalline solid. The combined yield after recrystallization was 89.2%. m.p. 129 °C; $[\alpha]_D^{25}$ -47.9 (c 1.0, $CHCl_3$); NMR ^1H ($CDCl_3$, 300MHz) δ (ppm): 8.10 (2H, d, *Jm* = 7.4Hz, Bz*o*), 7.60 (1H, t, *Jm* = 7.4Hz, Bz*p*), 7.48 (2H, dd, *Jo* = 7.4Hz, *Jp* = 7.4Hz, Bz*m*), 5.64 (1H, d, *J*3 = 7.4Hz, H2), 5.47 (1H, dd, *J*6α = 7.4Hz, *J*6β = 10.1Hz, H7), 5.28 (1H, s, H10), 4.94 (1H, d, *J*6α = 9.4Hz, H5), 4.80 - 4.90 (1H, m, H13), 4.31 (1H, d, *J*20β = 8.1Hz, H20α), 4.16 (1H, d, *J*20α = 8.1Hz, H20β), 4.06 (1H, d, *J*2 = 7.4Hz, H3), 2.55 (1H, ddd, *J*7 = 7.4Hz, *J*5 = 9.4Hz, *J*6β = 14.8Hz, H6α), 2.28 (3H, s, 4Ac), 2.23 - 2.32 (4H, m, 7CH2, H14α, H14β), 2.07 (3H, s, 18Me), 2.02 (1H, d, *J*13 = 4.7Hz, OH13), 1.76 - 1.87 (4H, m, H6β, 19Me), 1.60 (1H, s, OH1), 1.17 (3H, s, 17Me), 1.09 (3H , t, *J* $7CH_2$ = 7.4Hz, $7CH_3$), 1.04 (3H, s, 16Me), 0.96 (9H, t, *J*CH_2(TES) = 8.0Hz, CH_3(TES)), 0.52 - 0.62 (6H, m, CH_2(TES)).



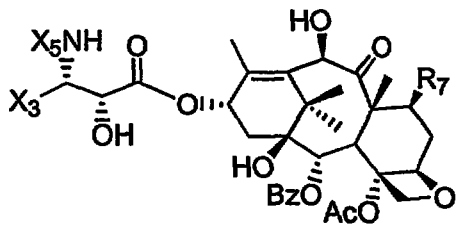
2'-O-MOP-3'-desphenyl-3'-(2-furyl)-10-triethylsilyl-7-propionyl taxotere. To a solution of 493 mg (0.690 m mol) of 10-triethylsilyl-10-deacetyl-7-propionyl baccatin III in 4 mL of anhydrous THF under a nitrogen atmosphere at -45 °C was added 0.72 mL (0.72 mmol) of a 1M solution of LiHMDS in THF. After 0.5 h a solution of 263 mg (0.814 mmol) of the -Lactam (predried as described above) in 2 mL of anhydrous THF was added. The mixture was warmed to 0 °C, and after 2 h 0.5 mL of saturated aqueous sodium bicarbonate solution was added. The mixture was diluted with 50 ml of ethyl acetate and washed two times wi th 5 mL of brine. The organic phase was dried over sodium sulfate and concentrated under reduced pressure to give 742 mg (104%) of a slightly yellow solid. The solid was recrystallized by dissolving it in 12 mL of a 1:5 mixture of ethyl acetate and hexane at reflux and then cooling to room temperature to give 627 mg (88%) of a white crystalline solid. Evaporation of the mother liquor gave 96 mg of material which was recrystallized as above from 2 mL of a 1:5 mixture of ethyl acetate and hexane to give an additional 46 mg (6%) of white crystalline solid. The total yield from recrystallization was 94%. Evaporation of the mother liquor gave 46 mg of material which was purified by column chromatography on silica gel to give an additional 20 mg (3%) of produc t. m.p. 207-209 °C; $[\alpha]_D^{25}$ -30.0 (c 5.0, methanol); ^{1}H NMR ($CDCl_3$, 400MHz) δ (ppm): 8.09-8.11 (m, 2H), 7.58-7.61 (m, 1H), 7.47-7.51(m, 2H), 7.39 (d, J = 0.8 Hz, 1H), 6.34 (dd, J = 3.2, 1.6 Hz, 1H), 6.26 (d, J = 3.2 Hz), 6.14 (dd, J = 8.8, 8.8 Hz, 1H), 5 .71 (d, J = 6.8 Hz, 1H), 5.47 (dd, J = 10.0, 7.2 Hz, 1H), 5.30-5.36 (m, 2H), 5.28 (s, 1H), 4.95 (d, J = 7.6 Hz, 1H), 4.76 (s, 1H), 4.33 (d, J= 8.0 Hz, 1H), 4,19 (d, J = 8.4 Hz, 1H), 4.03 (d, J = 6.8 Hz, 1H), 2.83 (s, 3H), 2.55 (ddd, J = 17.2, 9.6, 7.6, 1H) , 2.50 (s, 3H), 2.20-2.40 (m, 2H), 2.28 (q, J = 7.6 Hz, 2H), 1.95 (s, 3H), 1.84 (ddd, J = 14.8, 10.8, 2 Hz), 1.80 (s, 3H), 1.67 (s, 1H), 1.39 (s, 9H), 1.32 (s, 3H), 1.21 (s, 3H), 1.20 (s, 3H), 1.74 (s, 3H), 1.09 (t, J = 7.6 Hz, 3H), 0.93-0.99 (m, 9H), 0.50-0.65 (m, 6H).



3'-Desphenyl-3'-(2-furyl)-7-propionyl taxotere. (1393) To a solution of 206 mg (0.199 mmol) of 2'-O-MOP-3'-desphenyl-3'-(2-furyl)-10-triethylsilyl-7-propionyl taxotere in 1.7 mL of pyridine and 5.4 mL of acetoni trile at 0 °C was added 0.80 mL (2.0 mmol) of an aqueous solution containing 49% HF. The mixture was warmed to room temperature for 14 h and was then diluted with 20 mL of ethyl acetate and washed three times with 2 mL of saturated aqueous sodium bicarbonate and then with 8 mL of brine. The organic phase was dried over sodium sulfate and concentrated under reduced pressure to give 170 mg (100%) of a white solid. The crude product was crystallized with 2 mL of solvent (CH_2Cl_2:hexane=1:1.7) to give 155 mg (90.5%) of white crystals. Concentration of the mother liquor under reduced pressure gave 15 mg of material which was recrystallized using 0.2 mL of a 1:1.7 mixture of methylene chloride and hexane to give an additional 11 mg (7.5%) of white crystals. Th e total yield from recrystallization was 98%. m.p. 150-152 °C; $[\alpha]_D^{25}$ -27.0 (c 5.0, methanol); Anal. Calcd for $C_{44}H_{55}NO_{16}\bullet 0.5H_2O$: C, 61.18; H, 6.48. Found: C, 61.40; H, 6.65. ^1H NMR ($CDCl_3$, 500 MHz) δ (ppm): 8.11 (d, J = 7.5 Hz, 2H), 7.61 (dd, J = 7.5, 7.5 Hz, 1H), 7.50 (dd, J = 8.0, 7.5 Hz 2H), 7.41 (d, J = 1.0 Hz, 1H), 6.38 (dd, J = 3.0, 2.0 Hz, 1H), 6.33 (d, J = 3.5 Hz), 6.22 (dd, J = 9.5, 9.5 Hz, 1H), 5.69 (d, J = 7.0 Hz, 1H), 5.49 (dd, J = 11.0, 7.5 Hz, 1H), 5.35 (d, J = 9.5 Hz, 1H), 5.33 (d, J = 1 .5 Hz, 1H), 5.25 (d, J = 9.5 Hz, 1H), 4.94 (d, J = 8.5 Hz, 1H), 4.71 (dd, J = 5.5, 2.0 Hz, 1H), 4.33 (d, J= 8.5 Hz, 1H), 4,21 (d, J = 8.5 Hz, 1H), 4.01 (d, J = 6.5 Hz, 1H), 3.97 (d, J = 1.5 Hz, 1H), 3.30 (d, J = 5.5 Hz, 1H), 2.54 (ddd, J = 16.5, 9.5, 7.0, 1H), 2.41 (s, 3H), 2.37 (dd, J = 15.0, 9.0 Hz, 1H), 2.30 (dd, J = 17.5, 9.5 Hz, 1H), 2.25 (q, J = 7.5 Hz, 2H), 1.96 (s, 3H), 1.93 (ddd, J = 14.5, 11.0, 2.5 Hz), 1.85 (s, 3H), 1.64 (s, 1H), 1.36 (s, 9H), 1.23 (s, 3H), 1.10 (t, J = 7.5 Hz, 3H).

Example 2

The procedures described in Example 1 were repeated, but other suitably protected β-lactams were substituted for the β-lactam of Example 1 to prepare the series of compounds having structural formula (13) and the combinations of substituents identified in the following table.



(13)

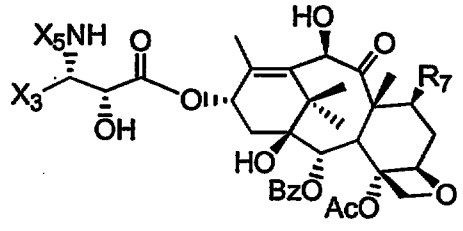
Compound	X_5	X_3	R_7
1351	tBuOCO-	ibue	EtCOO-
1364	tBuOCO-	2-pyridyl	EtCOO-
1372	tBuOCO-	3-pyridyl	EtCOO-
1386	tBuOCO-	4-pyridyl	EtCOO-
1393	tBuOCO-	2-furyl	EtCOO-
1401	tBuOCO-	3-furyl	EtCOO-
1418	tBuOCO-	2-thienyl	EtCOO-
1424	tBuOCO-	3-thienyl	EtCOO-
1434	tBuOCO-	Isopropyl	EtCOO-
1447	tBuOCO-	Cyclobutyl	EtCOO-
1458	tBuOCO-	Phenyl	EtCOO-
3069	2-FuCO-	2-thienyl	EtCOO-
3082	iPrOCO-	2-thienyl	EtCOO-
3171	nPrCO-	2-furyl	EtCOO-
3196	iBuOCO-	2-furyl	EtCOO-
3232	iBuOCO-	2-thienyl	EtCOO-
3327	nPrCO-	2-thienyl	EtCOO-
3388	PhCO-	3-thienyl	EtCOO-
3444	iPrOCO-	2-furyl	EtCOO-
3479	2-ThCO-	2-thienyl	EtCOO-
3555	C_4H_7CO-	2-thienyl	EtCOO-
3560	tC_3H_5CO-	2-thienyl	EtCOO-
3611	EtOCO-	2-furyl	EtCOO-
3629	2-FuCO-	2-furyl	EtCOO-
3632	2-ThCO-	2-furyl	EtCOO-
3708	tC_3H_5CO-	2-furyl	EtCOO-

3713	C_4H_7CO-	2-furyl	EtCOO-
4017	PhCO-	2-furyl	EtCOO-
4044	EtOCO-	2-thienyl	EtCOO-
4106	3-PyCO-	2-thienyl	EtCOO-
4135	iPrOCO-	2-thienyl	PrCOO-
4175	PhCO-	2-thienyl	PrCOO-
4219	2-FuCO-	2-thienyl	PrCOO-
4256	tBuOCO-	2-thienyl	PrCOO-
4283	ibueCO-	2-thienyl	PrCOO-
4290	ibuOCO-	2-thienyl	PrCOO-
4312	ibueCO-	2-thienyl	EtCOO-
4388	2-ThCO-	2-thienyl	PrCOO-
4394	tBuOCO-	3-furyl	PrCOO-
4406	tBuOCO-	Isobutenyl	PrCOO-
4446	tBuOCO-	3-thienyl	PrCOO-
4499	tBuOCO-	2-furyl	PrCOO-
4544	iBuOCO-	3-thienyl	EtCOO-
4600	iBuOCO-	3-thienyl	PrCOO-
4616	iBuOCO-	2-furyl	PrCOO-
4737	tC_3H_5CO-	2-furyl	PrCOO-
4757	tC_3H_5CO-	2-thienyl	PrCOO-
6171	ibueOCO-	2-furyl	EtCOO-
6131	ibueOCO-	2-furyl	iBuCOO-
5989	ibueOCO-	2-furyl	iPrCOO-
6141	ibueOCO-	2-furyl	nBuCOO-
6181	ibueOCO-	2-furyl	nPrCOO-
6040	ibuOCO-	2-furyl	ibueCOO-
6121	iPrCO-	2-furyl	iPrCOO-
6424	tAmOCO-	2-furyl	EtCOO-
6212	tAmOCO-	2-furyl	EtCOO-
6282	tAmOCO-	2-furyl	iBuCOO-
6252	tAmOCO-	2-furyl	iPrCOO-
6343	tAmOCO-	2-furyl	nBuCOO-
6272	tAmOCO-	2-furyl	nPrCOO-
6202	tC_3H_5CO-	2-furyl	iPrCOO-
4454	2-ThCO-	2-thienyl	nPrCOO-
4414	PhCO-	2-thienyl	nPrCOO-
6333	tBuOCO-	2-thienyl	iPrCOO-
6686	tBuOCO-	2-thienyl	tC_3H_5COO-
6363	tBuOCO-	2-thiazo	EtCOO-
4787	iBuOCO-	3-furyl	EtCOO-
4828	iBuOCO-	3-furyl	nPrCOO-
4898	tC_3H_5CO-	3-furyl	EtCOO-
4939	tC_3H_5CO-	3-furyl	nPrCOO-
5020	tC_3H_5CO-	3-thienyl	EtCOO-
5030	tC_3H_5CO-	3-thienyl	nPrCOO-
5191	iBuOCO-	Cpro	EtCOO-
5202	iBuOCO-	Cpro	nPrCOO-
5070	tBuOCO-	Cpro	EtCOO-

5080	tBuOCO-	Cpro	nPrCOO-
5121	iBuOCO-	Ibue	EtCOO-
5131	iBuOCO-	Ibue	nPrCOO-

Example 3

Following the processes described in Example 1 and elsewhere herein, the following specific taxanes having structural formula 14 may be prepared, wherein R_7 is as previously defined, including wherein R_7 is $R_{7a}COO$- and R_{7a} is (i) substituted or unsubstituted C_2 to C_8 alkyl (straight, branched or cyclic), such as ethyl, propyl, butyl, pentyl, or hexyl; (ii) substituted or unsubstituted C_2 to C_8 alkenyl (straight, branched or cyclic), such as ethenyl, propenyl, butenyl, pentenyl or hexenyl; (iii) substituted or unsubstituted C_2 to C_8 alkynyl (straight or branched) such as ethynyl, propynyl, butynyl, penty nyl, or hexynyl; (iv) substituted or unsubstituted phenyl; or (v) substituted or unsubstituted heterocyclo such as furyl, thienyl, or pyridyl. The substituents may be hydrocarbyl or any of the heteroatom containing substituents selected from the group con sisting of heterocyclo, alkoxy, alkenoxy, alkynoxy, aryloxy, hydroxy, protected hydroxy, keto, acyloxy, nitro, amino, amido, thiol, ketal, acetal, ester and ether moieties, but not phosphorous containing moieties.



(14)

X_5	X_3	R_7
tBuOCO-	2-furyl	R_aCOO-
tBuOCO-	3-furyl	R_aCOO-
tBuOCO-	2-thienyl	R_aCOO-
tBuOCO-	3-thienyl	R_aCOO-
tBuOCO-	2-pyridyl	R_aCOO-
tBuOCO-	3-pyridyl	R_aCOO-
tBuOCO-	4-pyridyl	R_aCOO-
tBuOCO-	Isobutenyl	R_aCOO-
tBuOCO-	Isopropyl	R_aCOO-
tBuOCO-	Cyclopropyl	R_aCOO-
tBuOCO-	Cyclobutyl	R_aCOO-
tBuOCO-	Cyclopentyl	R_aCOO-

tBuOCO-	Phenyl	R_aCOO-
benzoyl	2-furyl	R_aCOO-
benzoyl	3-furyl	R_aCOO-
benzoyl	2-thienyl	R_aCOO-
benzoyl	3-thienyl	R_aCOO-
benzoyl	2-pyridyl	R_aCOO-
benzoyl	3-pyridyl	R_aCOO-
benzoyl	4-pyridyl	R_aCOO-
benzoyl	Isobutenyl	R_aCOO-
benzoyl	Isopropyl	R_aCOO-
benzoyl	Cyclopropyl	R_aCOO-
benzoyl	Cyclobutyl	R_aCOO-
benzoyl	Cyclopentyl	R_aCOO-
benzoyl	Phenyl	R_aCOO-
2-FuCO-	2-furyl	R_aCOO-
2-FuCO-	3-furyl	R_aCOO-
2-FuCO-	2-thienyl	R_aCOO-
2-FuCO-	3-thienyl	R_aCOO-
2-FuCO-	2-pyridyl	R_aCOO-
2-FuCO-	3-pyridyl	R_aCOO-
2-FuCO-	4-pyridyl	R_aCOO-
2-FuCO-	Isobutenyl	R_aCOO-
2-FuCO-	Isopropyl	R_aCOO-
2-FuCO-	Cyclopropyl	R_aCOO-
2-FuCO-	Cyclobutyl	R_aCOO-
2-FuCO-	Cyclopentyl	R_aCOO-
2-FuCO-	Phenyl	R_aCOO-
2-ThCO-	2-furyl	R_aCOO-
2-ThCO-	3-furyl	R_aCOO-
2-ThCO-	2-thienyl	R_aCOO-
2-ThCO-	3-thienyl	R_aCOO-
2-ThCO-	2-pyridyl	R_aCOO-
2-ThCO-	3-pyridyl	R_aCOO-
2-ThCO-	4-pyridyl	R_aCOO-
2-ThCO-	Isobutenyl	R_aCOO-
2-ThCO-	Isopropyl	R_aCOO-
2-ThCO-	Cyclopropyl	R_aCOO-
2-ThCO-	Cyclobutyl	R_aCOO-
2-ThCO-	Cyclopentyl	R_aCOO-
2-ThCO-	Phenyl	R_aCOO-
2-PyCO-	2-furyl	R_aCOO-
2-PyCO-	3-furyl	R_aCOO-
2-PyCO-	2-thienyl	R_aCOO-
2-PyCO-	3-thienyl	R_aCOO-
2-PyCO-	2-pyridyl	R_aCOO-
2-PyCO-	3-pyridyl	R_aCOO-
2-PyCO-	4-pyridyl	R_aCOO-
2-PyCO-	Isobutenyl	R_aCOO-
2-PyCO-	Isopropyl	R_aCOO-

2-PyCO-	Cyclopropyl	R_aCOO-
2-PyCO-	Cyclobutyl	R_aCOO-
2-PyCO-	Cyclopentyl	R_aCOO-
2-PyCO-	Phenyl	R_aCOO-
3PyCO-	2-furyl	R_aCOO-
3-PyCO-	3-furyl	R_aCOO-
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3-PyCO-	Isopropyl	R_aCOO-
3-PyCO-	Cyclopropyl	R_aCOO-
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3-PyCO-	Phenyl	R_aCOO-
4-PyCO-	2-furyl	R_aCOO-
4-PyCO-	3-furyl	R_aCOO-
4-PyCO-	2-thienyl	R_aCOO-
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4-PyCO-	3-pyridyl	R_aCOO-
4-PyCO-	4-pyridyl	R_aCOO-
4-PyCO-	Isobutenyl	R_aCOO-
4-PyCO-	Isopropyl	R_aCOO-
4-PyCO-	Cyclopropyl	R_aCOO-
4-PyCO-	Cyclobutyl	R_aCOO-
4-PyCO-	Cyclopentyl	R_aCOO-
4-PyCO-	Phenyl	R_aCOO-
C_4H_7CO-	2-furyl	R_aCOO-
C_4H_7CO-	3-furyl	R_aCOO-
C_4H_7CO-	2-thienyl	R_aCOO-
C_4H_7CO-	3-thienyl	R_aCOO-
C_4H_7CO-	2-pyridyl	R_aCOO-
C_4H_7CO-	3-pyridyl	R_aCOO-
C_4H_7CO-	4-pyridyl	R_aCOO-
C_4H_7CO-	Isobutenyl	R_aCOO-
C_4H_7CO-	Isopropyl	R_aCOO-
C_4H_7CO-	Cyclopropyl	R_aCOO-
C_4H_7CO-	Cyclobutyl	R_aCOO-
C_4H_7CO-	Cyclopentyl	R_aCOO-
C_4H_7CO-	Phenyl	R_aCOO-
EtOCO-	2-furyl	R_aCOO-
EtOCO-	3-furyl	R_aCOO-
EtOCO-	2-thienyl	R_aCOO-
EtOCO-	3-thienyl	R_aCOO-
EtOCO-	2-pyridyl	R_aCOO-
EtOCO-	3-pyridyl	R_aCOO-

EtOCO-	4-pyridyl	R_aCOO-
EtOCO-	Isobutenyl	R_aCOO-
EtOCO-	Isopropyl	R_aCOO-
EtOCO-	Cyclopropyl	R_aCOO-
EtOCO-	Cyclobutyl	R_aCOO-
EtOCO-	Cyclopentyl	R_aCOO-
EtOCO-	Phenyl	R_aCOO-
ibueCO-	2-furyl	R_aCOO-
ibueCO-	3-furyl	R_aCOO-
ibueCO-	2-thienyl	R_aCOO-
ibueCO-	3-thienyl	R_aCOO-
ibueCO-	2-pyridyl	R_aCOO-
ibueCO-	3-pyridyl	R_aCOO-
ibueCO-	4-pyridyl	R_aCOO-
ibueCO-	Isobutenyl	R_aCOO-
ibueCO-	Isopropyl	R_aCOO-
ibueCO-	Cyclopropyl	R_aCOO-
ibueCO-	Cyclobutyl	R_aCOO-
ibueCO-	Cyclopentyl	R_aCOO-
ibueCO-	Phenyl	R_aCOO-
iBuCO-	2-furyl	R_aCOO-
iBuCO-	3-furyl	R_aCOO-
iBuCO-	2-thienyl	R_aCOO-
iBuCO-	3-thienyl	R_aCOO-
iBuCO-	2-pyridyl	R_aCOO-
iBuCO-	3-pyridyl	R_aCOO-
iBuCO-	4-pyridyl	R_aCOO-
iBuCO-	Isobutenyl	R_aCOO-
iBuCO-	Isopropyl	R_aCOO-
iBuCO-	Cyclopropyl	R_aCOO-
iBuCO-	Cyclobutyl	R_aCOO-
iBuCO-	Cyclopentyl	R_aCOO-
iBuCO-	Phenyl	R_aCOO-
iBuOCO-	2-furyl	R_aCOO-
iBuOCO-	3-furyl	R_aCOO-
iBuOCO-	2-thienyl	R_aCOO-
iBuOCO-	3-thienyl	R_aCOO-
iBuOCO-	2-pyridyl	R_aCOO-
iBuOCO-	3-pyridyl	R_aCOO-
iBuOCO-	4-pyridyl	R_aCOO-
iBuOCO-	Isobutenyl	R_aCOO-
iBuOCO-	Isopropyl	R_aCOO-
iBuOCO-	Cyclopropyl	R_aCOO-
iBuOCO-	Cyclobutyl	R_aCOO-
iBuOCO-	Cyclopentyl	R_aCOO-
iBuOCO-	Phenyl	R_aCOO-
iPrOCO-	2-furyl	R_aCOO-
iPrOCO-	3-furyl	R_aCOO-
iPrOCO-	2-thienyl	R_aCOO-

iPrOCO-	3-thienyl	R_aCOO-
iPrOCO-	2-pyridyl	R_aCOO-
iPrOCO-	3-pyridyl	R_aCOO-
iPrOCO-	4-pyridyl	R_aCOO-
iPrOCO-	Isobutenyl	R_aCOO-
iPrOCO-	Isopropyl	R_aCOO-
iPrOCO-	Cyclopropyl	R_aCOO-
iPrOCO-	Cyclobutyl	R_aCOO-
iPrOCO-	Cyclopentyl	R_aCOO-
iPrOCO-	Phenyl	R_aCOO-
nPrOCO-	2-furyl	R_aCOO-
nPrOCO-	3-furyl	R_aCOO-
nPrOCO-	2-thienyl	R_aCOO-
nPrOCO-	3-thienyl	R_aCOO-
nPrOCO-	2-pyridyl	R_aCOO-
nPrOCO-	3-pyridyl	R_aCOO-
nPrOCO-	4-pyridyl	R_aCOO-
nPrOCO-	Isobutenyl	R_aCOO-
nPrOCO-	Isopropyl	R_aCOO-
nPrOCO-	Cyclopropyl	R_aCOO-
nPrOCO-	Cyclobutyl	R_aCOO-
nPrOCO-	Cyclopentyl	R_aCOO-
nPrOCO-	Phenyl	R_aCOO-
nPrCO-	2-furyl	R_aCOO-
nPrCO-	3-furyl	R_aCOO-
nPrCO-	2-thienyl	R_aCOO-
nPrCO-	3-thienyl	R_aCOO-
nPrCO-	2-pyridyl	R_aCOO-
nPrCO-	3-pyridyl	R_aCOO-
nPrCO-	4-pyridyl	R_aCOO-
nPrCO-	Isobutenyl	R_aCOO-
nPrCO-	Isopropyl	R_aCOO-
nPrCO-	Cyclopropyl	R_aCOO-
nPrCO-	Cyclobutyl	R_aCOO-
nPrCO-	Cyclopentyl	R_aCOO-
nPrCO-	Phenyl	R_aCOO-
tBuOCO-	Cyclopentyl	EtCOO-
benzoyl	3-furyl	EtCOO-
benzoyl	2-thienyl	EtCOO-
benzoyl	2-pyridyl	EtCOO-
benzoyl	3-pyridyl	EtCOO-
benzoyl	4-pyridyl	EtCOO-
benzoyl	Isobutenyl	EtCOO-
benzoyl	Isopropyl	EtCOO-
benzoyl	Cyclopropyl	EtCOO-
benzoyl	Cyclobutyl	EtCOO-
benzoyl	Cyclopentyl	EtCOO-
benzoyl	Phenyl	EtCOO-
2-FuCO-	3-furyl	EtCOO-

2-FuCO-	3-thienyl	EtCOO-
2-FuCO-	2-pyridyl	EtCOO-
2-FuCO-	3-pyridyl	EtCOO-
2-FuCO-	4-pyridyl	EtCOO-
2-FuCO-	Isobutenyl	EtCOO-
2-FuCO-	Isopropyl	EtCOO-
2-FuCO-	Cyclopropyl	EtCOO-
2-FuCO-	Cyclobutyl	EtCOO-
2-FuCO-	Cyclopentyl	EtCOO-
2-FuCO-	Phenyl	EtCOO-
2-ThCO-	3-furyl	EtCOO-
2-ThCO-	3-thienyl	EtCOO-
2-ThCO-	2-pyridyl	EtCOO-
2-ThCO-	3-pyridyl	EtCOO-
2-ThCO-	4-pyridyl	EtCOO-
2-ThCO-	Isobutenyl	EtCOO-
2-ThCO-	Isopropyl	EtCOO-
2-ThCO-	Cyclopropyl	EtCOO-
2-ThCO-	Cyclobutyl	EtCOO-
2-ThCO-	Cyclopentyl	EtCOO-
2-ThCO-	Phenyl	EtCOO-
2-PyCO-	2-furyl	EtCOO-
2-PyCO-	3-furyl	EtCOO-
2-PyCO-	2-thienyl	EtCOO-
2-PyCO-	3-thienyl	EtCOO-
2-PyCO-	2-pyridyl	EtCOO-
2-PyCO-	3-pyridyl	EtCOO-
2-PyCO-	4-pyridyl	EtCOO-
2-PyCO-	Isobutenyl	EtCOO-
2-PyCO-	Isopropyl	EtCOO-
2-PyCO-	Cyclopropyl	EtCOO-
2-PyCO-	Cyclobutyl	EtCOO-
2-PyCO-	Cyclopentyl	EtCOO-
2-PyCO-	Phenyl	EtCOO-
3PyCO-	2-furyl	EtCOO-
3-PyCO-	3-furyl	EtCOO-
3-PyCO-	3-thienyl	EtCOO-
3-PyCO-	2-pyridyl	EtCOO-
3-PyCO-	3-pyridyl	EtCOO-
3-PyCO-	4-pyridyl	EtCOO-
3-PyCO-	Isobutenyl	EtCOO-
3-PyCO-	Isopropyl	EtCOO-
3-PyCO-	Cyclopropyl	EtCOO-
3-PyCO-	Cyclobutyl	EtCOO-
3-PyCO-	Cyclopentyl	EtCOO-
3-PyCO-	Phenyl	EtCOO-
4-PyCO-	2-furyl	EtCOO-
4-PyCO-	3-furyl	EtCOO-
4-PyCO-	2-thienyl	EtCOO-

4-PyCO-	3-thienyl	EtCOO-
4-PyCO-	2-pyridyl	EtCOO-
4-PyCO-	3-pyridyl	EtCOO-
4-PyCO-	4-pyridyl	EtCOO-
4-PyCO-	Isobutenyl	EtCOO-
4-PyCO-	Isopropyl	EtCOO-
4-PyCO-	Cyclopropyl	EtCOO-
4-PyCO-	Cyclobutyl	EtCOO-
4-PyCO-	Cyclopentyl	EtCOO-
4-PyCO-	Phenyl	EtCOO-
C_4H_7CO-	3-furyl	EtCOO-
C_4H_7CO-	3-thienyl	EtCOO-
C_4H_7CO-	2-pyridyl	EtCOO-
C_4H_7CO-	3-pyridyl	EtCOO-
C_4H_7CO-	4-pyridyl	EtCOO-
C_4H_7CO-	Isobutenyl	EtCOO-
C_4H_7CO-	Isopropyl	EtCOO-
C_4H_7CO-	Cyclopropyl	EtCOO-
C_4H_7CO-	Cyclobutyl	EtCOO-
C_4H_7CO-	Cyclopentyl	EtCOO-
C_4H_7CO-	Phenyl	EtCOO-
EtOCO-	3-furyl	EtCOO-
EtOCO-	3-thienyl	EtCOO-
EtOCO-	2-pyridyl	EtCOO-
EtOCO-	3-pyridyl	EtCOO-
EtOCO-	4-pyridyl	EtCOO-
EtOCO-	Isobutenyl	EtCOO-
EtOCO-	Isopropyl	EtCOO-
EtOCO-	Cyclopropyl	EtCOO-
EtOCO-	Cyclobutyl	EtCOO-
EtOCO-	Cyclopentyl	EtCOO-
EtOCO-	Phenyl	EtCOO-
ibueCO-	2-furyl	EtCOO-
ibueCO-	3-furyl	EtCOO-
ibueCO-	2-thienyl	EtCOO-
ibueCO-	3-thienyl	EtCOO-
ibueCO-	2-pyridyl	EtCOO-
ibueCO-	3-pyridyl	EtCOO-
ibueCO-	4-pyridyl	EtCOO-
ibueCO-	Isobutenyl	EtCOO-
ibueCO-	Isopropyl	EtCOO-
ibueCO-	Cyclopropyl	EtCOO-
ibueCO-	Cyclobutyl	EtCOO-
ibueCO-	Cyclopentyl	EtCOO-
ibueCO-	Phenyl	EtCOO-
iBuCO-	2-furyl	EtCOO-
iBuCO-	3-furyl	EtCOO-
iBuCO-	2-thienyl	EtCOO-
iBuCO-	3-thienyl	EtCOO-

iBuCO-	2-pyridyl	EtCOO-
iBuCO-	3-pyridyl	EtCOO-
iBuCO-	4-pyridyl	EtCOO-
iBuCO-	Isobutenyl	EtCOO-
iBuCO-	Isopropyl	EtCOO-
iBuCO-	Cyclopropyl	EtCOO-
iBuCO-	Cyclobutyl	EtCOO-
iBuCO-	Cyclopentyl	EtCOO-
iBuCO-	Phenyl	EtCOO-
iBuOCO-	2-pyridyl	EtCOO-
iBuOCO-	3-pyridyl	EtCOO-
iBuOCO-	4-pyridyl	EtCOO-
iBuOCO-	Isobutenyl	EtCOO-
iBuOCO-	Isopropyl	EtCOO-
iBuOCO-	Cyclobutyl	EtCOO-
iBuOCO-	Cyclopentyl	EtCOO-
iBuOCO-	Phenyl	EtCOO-
iPrOCO-	3-furyl	EtCOO-
iPrOCO-	3-thienyl	EtCOO-
iPrOCO-	2-pyridyl	EtCOO-
iPrOCO-	3-pyridyl	EtCOO-
iPrOCO-	4-pyridyl	EtCOO-
iPrOCO-	Isobutenyl	EtCOO-
iPrOCO-	Isopropyl	EtCOO-
iPrOCO-	Cyclopropyl	EtCOO-
iPrOCO-	Cyclobutyl	EtCOO-
iPrOCO-	Cyclopentyl	EtCOO-
iPrOCO-	Phenyl	EtCOO-
nPrOCO-	2-furyl	EtCOO-
nPrOCO-	3-furyl	EtCOO-
nPrOCO-	2-thienyl	EtCOO-
nPrOCO-	3-thienyl	EtCOO-
nPrOCO-	2-pyridyl	EtCOO-
nPrOCO-	3-pyridyl	EtCOO-
nPrOCO-	4-pyridyl	EtCOO-
nPrOCO-	Isobutenyl	EtCOO-
nPrOCO-	Isopropyl	EtCOO-
nPrOCO-	Cyclopropyl	EtCOO-
nPrOCO-	Cyclobutyl	EtCOO-
nPrOCO-	Cyclopentyl	EtCOO-
nPrOCO-	Phenyl	EtCOO-
nPrCO-	3-furyl	EtCOO-
nPrCO-	3-thienyl	EtCOO-
nPrCO-	2-pyridyl	EtCOO-
nPrCO-	3-pyridyl	EtCOO-
nPrCO-	4-pyridyl	EtCOO-
nPrCO-	Isobutenyl	EtCOO-
nPrCO-	Isopropyl	EtCOO-
nPrCO-	Cyclopropyl	EtCOO-

nPrCO-	Cyclobutyl	EtCOO-
nPrCO-	Cyclopentyl	EtCOO-
nPrCO-	Phenyl	EtCOO-

Example 4

Following the processes described in Example 1 and elsewhere herein, the following specific taxanes having structural formula 15 may be prepared, wherein R_{10} is hydroxy and R_7 in each of the series (that is, each of series "A" through "K") is as previously defined, including wherein R_7 is $R_{7a}COO$- and R_{7a} is (i) substituted or unsubstituted, preferably unsubstituted, C_2 to C_8 alkyl (straight, branched or cyclic), such as ethyl, propyl, butyl, pentyl, or hexyl; (ii) substituted or unsubstituted, preferably unsubstituted, C_2 to C_8 alkenyl (straight, branched or cyclic), such as ethenyl, propenyl, butenyl, pentenyl or hexenyl; (iii) substituted or unsubstituted, preferably unsubstituted, C_2 to C_8 alkynyl (straight or branched) such as ethynyl, propynyl, butynyl, pentynyl, or hexynyl; (iv) substituted or unsubstituted, preferably unsubstituted, phenyl; or (v) substituted or unsubstituted, preferably unsubstituted, heteroaromatic such as furyl, thienyl, or pyridyl.

In the "A" series of compounds, X_{10} is as otherwise as defined herein. Preferably, heterocyclo is substituted or unsubstituted furyl, thienyl, or pyridyl, X_{10} is substituted or unsubstituted furyl, thienyl, pyridyl, phenyl, or lower alkyl (e.g., tert-butyl), and R_7 and R_{10} each have the beta stereochemical configuration.

In the "B" series of compounds, X_{10} and R_{2a} are as otherwise as defined herein. Preferably, heterocyclo is preferably substituted or unsubstituted furyl, thienyl, or pyridyl, X_{10} is preferably substituted or unsubstituted furyl, thienyl, pyridyl, phenyl, or lower alkyl (e.g., tert-butyl), R_{2a} is preferably substituted or unsubstituted furyl, thienyl, pyridyl, phenyl, or lower alkyl, and R_7 and R_{10} each have the beta stereochemical configuration.

In the "C" series of compounds, X_{10} and R_{9a} are as otherwise as defined herein. Preferably, heterocyclo is preferably substituted or unsubstituted furyl, thienyl, or pyridyl, X_{10} is preferably substituted or unsubstituted furyl, thienyl, pyridyl, phenyl, or lower alkyl (e.g., tert-butyl), R_{9a} is preferably substituted or unsubstituted furyl, thienyl, pyridyl, phenyl, or lower alkyl, and R_7, R_9 and R_{10} each have the beta stereochemical configuration.

In the "D" and "E" series of compounds, X_{10} is as otherwise as defined herein. Preferably, heterocyclo is preferably substituted or unsubstituted furyl, thienyl, or pyridyl, X_{10} is preferably substituted or unsubstituted furyl, thienyl, pyridyl, phenyl, or lower alkyl (e.g., tert-butyl), and R_7, R_9 (series D only) and R_{10} each have the beta stereochemical configuration.

In the "F" series of compounds , X_{10}, R_{2a} and R_{9a} are as otherwise as defined herein. Preferably, heterocyclo is preferably substituted or unsubstituted furyl, thienyl, or pyridyl, X_{10} is preferably substituted or unsubstituted furyl, thienyl, pyridyl, phenyl, or lower alkyl (e.g., ter t-butyl), R_{2a} is preferably substituted or unsubstituted furyl, thienyl, pyridyl, phenyl, or lower alkyl, and R_7, R_9 and R_{10} each have the beta stereochemical configuration.

In the "G" series of compounds, X_{10} and R_{2a} are as otherwise as defined herein. Preferably, heterocyclo is preferably substituted or unsubstituted furyl, thienyl, or pyridyl, X_{10} is preferably substituted or unsubstituted furyl, thienyl, pyridyl, phenyl, or lower alkyl (e.g., tert -butyl), R_{2a} is preferably substituted or unsubstituted furyl, thienyl, pyridyl, phenyl, or lower alkyl, and R_7, R_9 and R_{10} each have the beta stereochemical configuration.

In the "H" series of compounds, X_{10} is as otherwise as defined herein. Preferably, heterocyclo is preferably substituted or unsubstitut ed furyl, thienyl, or pyridyl, X_{10} is preferably substituted or unsubstituted furyl, thienyl, pyridyl, phenyl, or lower alkyl (e.g., tert-butyl), R_{2a} is preferably substituted or unsubstituted furyl, thienyl, pyridyl, phenyl, or lower alkyl, and R_7 and R_{10} each have the beta stereochemical configuration.

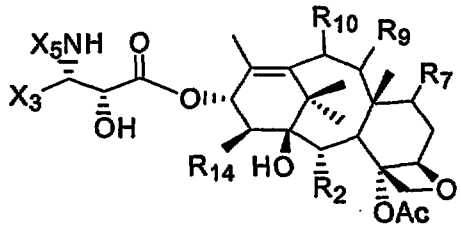
In the "I" series of compounds, X_{10} and R_{2a} are as otherwise as defined herein. Preferably, heterocyclo is preferably substituted or unsubstituted furyl, thienyl, or pyridyl, X_{10} is preferably substituted or unsubstituted furyl, thienyl, pyridyl, phenyl, or lower alkyl (e.g., tert -butyl), R_{2a} is preferably substituted or unsubstituted furyl, thienyl, pyridyl, phenyl, or lower alkyl, and R_7 and R_{10} each have the beta stereochemical configuration.

In the "J" series of compounds, X_{10} and R_{2a} are as otherwise as defined herein. Preferably, heterocyclo is preferably substituted or unsubstituted furyl, thienyl, or pyridyl, X_{10} is preferably substituted or unsubstituted furyl, thienyl, pyridyl, phenyl, or lower alkyl (e.g., tert-butyl), R_{2a} is preferably substituted or unsubstituted furyl, thienyl, pyridyl, phenyl, or lower alkyl, and R_7, R_9 and R_{10} each have the beta stereochemical configuration.

In the "K" series of compounds, X_{10}, R_{2a} and R_{9a} are as otherwise as defined herein. Preferably, heterocyclo is preferably substituted or unsubstituted furyl, thienyl, or pyridyl, X_{10} is preferably substituted or unsubstituted furyl, thienyl, pyridyl, phenyl, or lower alkyl (e.g., tert -butyl), R_{2a} is preferably substituted or unsubstituted furyl, thienyl, pyridyl, phenyl, or lower alkyl, and R_7, R_9 and R_{10} each have the beta stereochemical configuration.

Any substituents of each X_3, X_5, R_2, R_7, and R_9 may be hydrocarbyl or any of the heteroatom containing substitue nts selected from the group consisting of heterocyclo, alkoxy, alkenoxy, alkynoxy, aryloxy, hydroxy, protected hydroxy,

keto, acyloxy, nitro, amino, amido, thiol, ketal, acetal, ester and ether moieties, but not phosphorous containing moieties.



(15)

Series	X_5	X_3	R_7	R_2	R_9	R_{14}
A1	-$COOX_{10}$	Heterocyclo	$R_{7a}COO$-	C_6H_5COO-	O	H
A2	-COX_{10}	Heterocyclo	$R_{7a}COO$-	C_6H_5COO-	O	H
A3	-$CONHX_{10}$	Heterocyclo	$R_{7a}COO$-	C_6H_5COO-	O	H
A4	-$COOX_{10}$	optionally substituted C_2 to C_8 alkyl	$R_{7a}COO$-	C_6H_5COO-	O	H
A5	-COX_{10}	optionally substituted C_2 to C_8 alkyl	$R_{7a}COO$-	C_6H_5COO-	O	H
A6	-$CONHX_{10}$	optionally substituted C_2 to C_8 alkyl	$R_{7a}COO$-	C_6H_5COO-	O	H
A7	-$COOX_{10}$	optionally substituted C_2 to C_8 alkenyl	$R_{7a}COO$-	C_6H_5COO-	O	H
A8	-COX_{10}	optionally substituted C_2 to C_8 alkenyl	$R_{7a}COO$-	C_6H_5COO-	O	H
A9	-$CONHX_{10}$	optionally substituted C_2 to C_8 alkenyl	$R_{7a}COO$-	C_6H_5COO-	O	H
A10	-$COOX_{10}$	optionally substituted C_2 to C_8 alkynyl	$R_{7a}COO$-	C_6H_5COO-	O	H
A11	-COX_{10}	optionally substituted C_2 to C_8 alkynyl	$R_{7a}COO$-	C_6H_5COO-	O	H

A12	-CONHX$_{10}$	optionally substituted C_2 to C_8 alkynyl	$R_{7a}COO$-	C_6H_5COO-	O	H
B1	-COOX$_{10}$	heterocyclo	$R_{7a}COO$-	$R_{2a}COO$-	O	H
B2	-COX$_{10}$	heterocyclo	$R_{7a}COO$-	$R_{2a}COO$-	O	H
B3	-CONHX$_{10}$	heterocyclo	$R_{7a}COO$-	$R_{2a}COO$-	O	H
B4	-COOX$_{10}$	optionally substituted C_2 to C_8 alkyl	$R_{7a}COO$-	$R_{2a}COO$-	O	H
B5	-COX$_{10}$	optionally substituted C_2 to C_8 alkyl	$R_{7a}COO$-	$R_{2a}COO$-	O	H
B6	-CONHX$_{10}$	optionally substituted C_2 to C_8 alkyl	$R_{7a}COO$-	$R_{2a}COO$-	O	H
B7	-COOX$_{10}$	optionally substituted C_2 to C_8 alkenyl	$R_{7a}COO$-	$R_{2a}COO$-	O	H
B8	-COX$_{10}$	optionally substituted C_2 to C_8 alkenyl	$R_{7a}COO$-	$R_{2a}COO$-	O	H
B9	-CONHX$_{10}$	optionally substituted C_2 to C_8 alkenyl	$R_{7a}COO$-	$R_{2a}COO$-	O	H
B10	-COOX$_{10}$	optionally substituted C_2 to C_8 alkynyl	$R_{7a}COO$-	$R_{2a}COO$-	O	H
B11	-COX$_{10}$	optionally substituted C_2 to C_8 alkynyl	$R_{7a}COO$-	$R_{2a}COO$-	O	H
B12	-CONHX$_{10}$	optionally substituted C_2 to C_8 alkynyl	$R_{7a}COO$-	$R_{2a}COO$-	O	H
C1	-COOX$_{10}$	heterocyclo	$R_{7a}COO$-	C_6H_5COO-	$R_{9a}COO$-	H
C2	-COX$_{10}$	heterocyclo	$R_{7a}COO$-	C_6H_5COO-	$R_{9a}COO$-	H
C3	-CONHX$_{10}$	heterocyclo	$R_{7a}COO$-	C_6H_5COO-	$R_{9a}COO$-	H
C4	-COOX$_{10}$	optionally substituted C_2 to C_8 alkyl	$R_{7a}COO$-	C_6H_5COO-	$R_{9a}COO$-	H
C5	-COX$_{10}$	optionally substituted C_2 to C_8 alkyl	$R_{7a}COO$-	C_6H_5COO-	$R_{9a}COO$-	H

C6	-CONHX$_{10}$	optionally substituted C_2 to C_8 alkyl	$R_{7a}COO$-	C_6H_5COO-	$R_{9a}COO$-	H
C7	-COOX$_{10}$	optionally substituted C_2 to C_8 alkenyl	$R_{7a}COO$-	C_6H_5COO-	$R_{9a}COO$-	H
C8	-COX$_{10}$	optionally substituted C_2 to C_8 alkenyl	$R_{7a}COO$-	C_6H_5COO-	$R_{9a}COO$-	H
C9	-CONHX$_{10}$	optionally substituted C_2 to C_8 alkenyl	$R_{7a}COO$-	C_6H_5COO-	$R_{9a}COO$-	H
C10	-COOX$_{10}$	optionally substituted C_2 to C_8 alkynyl	$R_{7a}COO$-	C_6H_5COO-	$R_{9a}COO$-	H
C11	-COX$_{10}$	optionally substituted C_2 to C_8 alkynyl	$R_{7a}COO$-	C_6H_5COO-	$R_{9a}COO$-	H
C12	-CONHX$_{10}$	optionally substituted C_2 to C_8 alkynyl	$R_{7a}COO$-	C_6H_5COO-	$R_{9a}COO$-	H
D1	-COOX$_{10}$	heterocyclo	$R_{7a}COO$-	C_6H_5COO-	OH	H
D2	-COX$_{10}$	heterocyclo	$R_{7a}COO$-	C_6H_5COO-	OH	H
D3	-CONHX$_{10}$	heterocyclo	$R_{7a}COO$-	C_6H_5COO-	OH	H
D4	-COOX$_{10}$	optionally substituted C_2 to C_8 alkyl	$R_{7a}COO$-	C_6H_5COO-	OH	H
D5	-COX$_{10}$	optionally substituted C_2 to C_8 alkyl	$R_{7a}COO$-	C_6H_5COO-	OH	H
D6	-CONHX$_{10}$	optionally substituted C_2 to C_8 alkyl	$R_{7a}COO$-	C_6H_5COO-	OH	H
D7	-COOX$_{10}$	optionally substituted C_2 to C_8 alkenyl	$R_{7a}COO$-	C_6H_5COO-	OH	H
D8	-COX$_{10}$	optionally substituted C_2 to C_8 alkenyl	$R_{7a}COO$-	C_6H_5COO-	OH	H

D9	-CONHX$_{10}$	optionally substituted C_2 to C_8 alkenyl	$R_{7a}COO$-	C_6H_5COO-	OH	H
D10	-COOX$_{10}$	optionally substituted C_2 to C_8 alkynyl	$R_{7a}COO$-	C_6H_5COO-	OH	H
D11	-COX$_{10}$	optionally substituted C_2 to C_8 alkynyl	$R_{7a}COO$-	C_6H_5COO-	OH	H
D12	-CONHX$_{10}$	optionally substituted C_2 to C_8 alkynyl	$R_{7a}COO$-	C_6H_5COO-	OH	H
E1	-COOX$_{10}$	heterocyclo	$R_{7a}COO$-	C_6H_5COO-	O	OH
E2	-COX$_{10}$	heterocyclo	$R_{7a}COO$-	C_6H_5COO-	O	OH
E3	-CONHX$_{10}$	heterocyclo	$R_{7a}COO$-	C_6H_5COO-	O	OH
E4	-COOX$_{10}$	optionally substituted C_2 to C_8 alkyl	$R_{7a}COO$-	C_6H_5COO-	O	OH
E5	-COX$_{10}$	optionally substituted C_2 to C_8 alkyl	$R_{7a}COO$-	C_6H_5COO-	O	OH
E6	-CONHX$_{10}$	optionally substituted C_2 to C_8 alkyl	$R_{7a}COO$-	C_6H_5COO-	O	OH
E7	-COOX$_{10}$	optionally substituted C_2 to C_8 alkenyl	$R_{7a}COO$-	C_6H_5COO-	O	OH
E8	-COX$_{10}$	optionally substituted C_2 to C_8 alkenyl	$R_{7a}COO$-	C_6H_5COO-	O	OH
E9	-CONHX$_{10}$	optionally substituted C_2 to C_8 alkenyl	$R_{7a}COO$-	C_6H_5COO-	O	OH
E10	-COOX$_{10}$	optionally substituted C_2 to C_8 alkynyl	$R_{7a}COO$-	C_6H_5COO-	O	OH

E11	$-COX_{10}$	optionally substituted C_2 to C_8 alkynyl	$R_{7a}COO-$	C_6H_5COO-	O	OH
E12	$-CONHX_{10}$	optionally substituted C_2 to C_8 alkynyl	$R_{7a}COO-$	C_6H_5COO-	O	OH
F1	$-COOX_{10}$	heterocyclo	$R_{7a}COO-$	$R_{2a}COO-$	$R_{9a}COO-$	H
F2	$-COX_{10}$	heterocyclo	$R_{7a}COO-$	$R_{2a}COO-$	$R_{9a}COO-$	H
F3	$-CONHX_{10}$	heterocyclo	$R_{7a}COO-$	$R_{2a}COO-$	$R_{9a}COO-$	H
F4	$-COOX_{10}$	optionally substituted C_2 to C_8 alkyl	$R_{7a}COO-$	$R_{2a}COO-$	$R_{9a}COO-$	H
F5	$-COX_{10}$	optionally substituted C_2 to C_8 alkyl	$R_{7a}COO-$	$R_{2a}COO-$	$R_{9a}COO-$	H
F6	$-CONHX_{10}$	optionally substituted C_2 to C_8 alkyl	$R_{7a}COO-$	$R_{2a}COO-$	$R_{9a}COO-$	H
F7	$-COOX_{10}$	optionally substituted C_2 to C_8 alkenyl	$R_{7a}COO-$	$R_{2a}COO-$	$R_{9a}COO-$	H
F8	$-COX_{10}$	optionally substituted C_2 to C_8 alkenyl	$R_{7a}COO-$	$R_{2a}COO-$	$R_{9a}COO-$	H
F9	$-CONHX_{10}$	optionally substituted C_2 to C_8 alkenyl	$R_{7a}COO-$	$R_{2a}COO-$	$R_{9a}COO-$	H
F10	$-COOX_{10}$	optionally substituted C_2 to C_8 alkynyl	$R_{7a}COO-$	$R_{2a}COO-$	$R_{9a}COO-$	H
F11	$-COX_{10}$	optionally substituted C_2 to C_8 alkynyl	$R_{7a}COO-$	$R_{2a}COO-$	$R_{9a}COO-$	H
F12	$-CONHX_{10}$	optionally substituted C_2 to C_8 alkynyl	$R_{7a}COO-$	$R_{2a}COO-$	$R_{9a}COO-$	H
G1	$-COOX_{10}$	heterocyclo	$R_{7a}COO-$	$R_{2a}COO-$	OH	H
G2	$-COX_{10}$	heterocyclo	$R_{7a}COO-$	$R_{2a}COO-$	OH	H
G3	$-CONHX_{10}$	heterocyclo	$R_{7a}COO-$	$R_{2a}COO-$	OH	H

G4	$-COOX_{10}$	optionally substituted C_2 to C_8 alkyl	$R_{7a}COO-$	$R_{2a}COO-$	OH	H
G5	$-COX_{10}$	optionally substituted C_2 to C_8 alkyl	$R_{7a}COO-$	$R_{2a}COO-$	OH	H
G6	$-CONHX_{10}$	optionally substituted C_2 to C_8 alkyl	$R_{7a}COO-$	$R_{2a}COO-$	OH	H
G7	$-COOX_{10}$	optionally substituted C_2 to C_8 alkenyl	$R_{7a}COO-$	$R_{2a}COO-$	OH	H
G8	$-COX_{10}$	optionally substituted C_2 to C_8 alkenyl	$R_{7a}COO-$	$R_{2a}COO-$	OH	H
G9	$-CONHX_{10}$	optionally substituted C_2 to C_8 alkenyl	$R_{7a}COO-$	$R_{2a}COO-$	OH	H
G10	$-COOX_{10}$	optionally substituted C_2 to C_8 alkynyl	$R_{7a}COO-$	$R_{2a}COO-$	OH	H
G11	$-COX_{10}$	optionally substituted C_2 to C_8 alkynyl	$R_{7a}COO-$	$R_{2a}COO-$	OH	H
G12	$-CONHX_{10}$	optionally substituted C_2 to C_8 alkynyl	$R_{7a}COO-$	$R_{2a}COO-$	OH	H
H1	$-COOX_{10}$	heterocyclo	$R_{7a}COO-$	C_6H_5COO-	OH	OH
H2	$-COX_{10}$	heterocyclo	$R_{7a}COO-$	C_6H_5COO-	OH	OH
H3	$-CONHX_{10}$	heterocyclo	$R_{7a}COO-$	C_6H_5COO-	OH	OH
H4	$-COOX_{10}$	optionally substituted C_2 to C_8 alkyl	$R_{7a}COO-$	C_6H_5COO-	OH	OH
H5	$-COX_{10}$	optionally substituted C_2 to C_8 alkyl	$R_{7a}COO-$	C_6H_5COO-	OH	OH
H6	$-CONHX_{10}$	optionally substituted C_2 to C_8 alkyl	$R_{7a}COO-$	C_6H_5COO-	OH	OH
H7	$-COOX_{10}$	optionally substituted C_2 to C_8 alkenyl	$R_{7a}COO-$	C_6H_5COO-	OH	OH

H8	$-COX_{10}$	optionally substituted C_2 to C_8 alkenyl	$R_{7a}COO-$	C_6H_5COO-	OH	OH
H9	$-CONHX_{10}$	optionally substituted C_2 to C_8 alkenyl	$R_{7a}COO-$	C_6H_5COO-	OH	OH
H10	$-COOX_{10}$	optionally substituted C_2 to C_8 alkynyl	$R_{7a}COO-$	C_6H_5COO-	OH	OH
H11	$-COX_{10}$	optionally substituted C_2 to C_8 alkynyl	$R_{7a}COO-$	C_6H_5COO-	OH	OH
H12	$-CONHX_{10}$	optionally substituted C_2 to C_8 alkynyl	$R_{7a}COO-$	C_6H_5COO-	OH	OH
I1	$-COOX_{10}$	heterocyclo	$R_{7a}COO-$	$R_{2a}COO-$	O	OH
I2	$-COX_{10}$	heterocyclo	$R_{7a}COO-$	$R_{2a}COO-$	O	OH
I3	$-CONHX_{10}$	heterocyclo	$R_{7a}COO-$	$R_{2a}COO-$	O	OH
I4	$-COOX_{10}$	optionally substituted C_2 to C_8 alkyl	$R_{7a}COO-$	$R_{2a}COO-$	O	OH
I5	$-COX_{10}$	optionally substituted C_2 to C_8 alkyl	$R_{7a}COO-$	$R_{2a}COO-$	O	OH
I6	$-CONHX_{10}$	optionally substituted C_2 to C_8 alkyl	$R_{7a}COO-$	$R_{2a}COO-$	O	OH
I7	$-COOX_{10}$	optionally substituted C_2 to C_8 alkenyl	$R_{7a}COO-$	$R_{2a}COO-$	O	OH
I8	$-COX_{10}$	optionally substituted C_2 to C_8 alkenyl	$R_{7a}COO-$	$R_{2a}COO-$	O	OH
I9	$-CONHX_{10}$	optionally substituted C_2 to C_8 alkenyl	$R_{7a}COO-$	$R_{2a}COO-$	O	OH
I10	$-COOX_{10}$	optionally substituted C_2 to C_8 alkynyl	$R_{7a}COO-$	$R_{2a}COO-$	O	OH

I11	$-COX_{10}$	optionally substituted C_2 to C_8 alkynyl	$R_{7a}COO-$	$R_{2a}COO-$	O	OH
I12	$-CONHX_{10}$	optionally substituted C_2 to C_8 alkynyl	$R_{7a}COO-$	$R_{2a}COO-$	O	OH
J1	$-COOX_{10}$	heterocyclo	$R_{7a}COO-$	$R_{2a}COO-$	OH	OH
J2	$-COX_{10}$	heterocyclo	$R_{7a}COO-$	$R_{2a}COO-$	OH	OH
J3	$-CONHX_{10}$	heterocyclo	$R_{7a}COO-$	$R_{2a}COO-$	OH	OH
J4	$-COOX_{10}$	optionally substituted C_2 to C_8 alkyl	$R_{7a}COO-$	$R_{2a}COO-$	OH	OH
J5	$-COX_{10}$	optionally substituted C_2 to C_8 alkyl	$R_{7a}COO-$	$R_{2a}COO-$	OH	OH
J6	$-CONHX_{10}$	optionally substituted C_2 to C_8 alkyl	$R_{7a}COO-$	$R_{2a}COO-$	OH	OH
J7	$-COOX_{10}$	optionally substituted C_2 to C_8 alkenyl	$R_{7a}COO-$	$R_{2a}COO-$	OH	OH
J8	$-COX_{10}$	optionally substituted C_2 to C_8 alkenyl	$R_{7a}COO-$	$R_{2a}COO-$	OH	OH
J9	$-CONHX_{10}$	optionally substituted C_2 to C_8 alkenyl	$R_{7a}COO-$	$R_{2a}COO-$	OH	OH
J10	$-COOX_{10}$	optionally substituted C_2 to C_8 alkynyl	$R_{7a}COO-$	$R_{2a}COO-$	OH	OH
J11	$-COX_{10}$	optionally substituted C_2 to C_8 alkynyl	$R_{7a}COO-$	$R_{2a}COO-$	OH	OH
J12	$-CONHX_{10}$	optionally substituted C_2 to C_8 alkynyl	$R_{7a}COO-$	$R_{2a}COO-$	OH	OH
K1	$-COOX_{10}$	heterocyclo	$R_{7a}COO-$	$R_{2a}COO-$	$R_{9a}COO-$	OH
K2	$-COX_{10}$	heterocyclo	$R_{7a}COO-$	$R_{2a}COO-$	$R_{9a}COO-$	OH
K3	$-CONHX_{10}$	heterocyclo	$R_{7a}COO-$	$R_{2a}COO-$	$R_{9a}COO-$	OH

K4	$-COOX_{10}$	optionally substituted C_2 to C_8 alkyl	$R_{7a}COO-$	$R_{2a}COO-$	$R_{9a}COO-$	OH
K5	$-COX_{10}$	optionally substituted C_2 to C_8 alkyl	$R_{7a}COO-$	$R_{2a}COO-$	$R_{9a}COO-$	OH
K6	$-CONHX_{10}$	optionally substituted C_2 to C_8 alkyl	$R_{7a}COO-$	$R_{2a}COO-$	$R_{9a}COO-$	OH
K7	$-COOX_{10}$	optionally substituted C_2 to C_8 alkenyl	$R_{7a}COO-$	$R_{2a}COO-$	$R_{9a}COO-$	OH
K8	$-COX_{10}$	optionally substituted C_2 to C_8 alkenyl	$R_{7a}COO-$	$R_{2a}COO-$	$R_{9a}COO-$	OH
K9	$-CONHX_{10}$	optionally substituted C_2 to C_8 alkenyl	$R_{7a}COO-$	$R_{2a}COO-$	$R_{9a}COO-$	OH
K10	$-COOX_{10}$	optionally substituted C_2 to C_8 alkynyl	$R_{7a}COO-$	$R_{2a}COO-$	$R_{9a}COO-$	OH
K11	$-COX_{10}$	optionally substituted C_2 to C_8 alkynyl	$R_{7a}COO-$	$R_{2a}COO-$	$R_{9a}COO-$	OH
K12	$-CONHX_{10}$	optionally substituted C_2 to C_8 alkynyl	$R_{7a}COO-$	$R_{2a}COO-$	$R_{9a}COO-$	OH

Example 5

In Vitro cytotoxicity measured by the cell colony formation assay

Four hundred cells (HCT116) were plated in 60 mm Petri dishes containing 2.7 mL of medium (modified McCoy's 5a medium containing 10% fetal bovine serum and 100 units/mL penicillin and 100 mg/mL streptomyc in). The cells were incubated in a CO_2 incubator at 37 °C for 5 h for attachment to the bottom of Petri dishes. The compounds identified in Example 2 were made up fresh in medium at ten times the final concentration, and then 0.3 mL of this stock solution was added to the 2.7 mL of medium in the dish. The cells were then incubated with drugs for 72 h at 37 ° C. At the end of incubation the drug -containing media were

decanted, the dishes were rinsed with 4 mL of Hank's Balanc e Salt Solution (HBSS), 5 mL of fresh medium was added, and the dishes were returned to the incubator for colony formation. The cell colonies were counted using a colony counter after incubation for 7 days. Cell survival was calculated and the values of ID50 (the drug concentration producing 50% inhibition of colony formation) were determined for each tested compound.

Compound	IN VITRO ID 50 (nm) HCT116
taxol	2.1
docetaxel	0.6
1351	<1
1364	<10
1372	26.1
1386	<1
1393	<1
1401	<1
1418	<1
1424	<1
1434	<10
1447	<10
1458	<10
3069	<1
3082	<1
3171	<1
3196	<10
3232	<1
3327	<10
3388	<10
3444	<1
3479	<1
3555	<10
3560	<1
3611	<1
3629	<1
3632	<1
3708	<1
3713	<10
4017	<10
4044	<1
4106	<10
4135	<1
4175	<10
4219	29.0
4256	<1

4283	<1
4290	<10
4312	<1
4388	<1
4394	<1
4406	<1
4446	<1
4499	<1
4544	<10
4600	<10
4616	<1
4737	<1
4757	<1
6171	<10
6131	<1
5989	<10
6141	<1
6181	<1
6040	<10
6121	<10
6424	21.7
6212	<1
6282	<10
6252	<1
6343	<10
6272	<1
6202	<1
4454	<1
4414	<1
6333	<1
6686	<1
6363	<10
4787	<10
4828	<10
4898	<1
4939	<1
5020	<1
5030	<1
5191	<10
5202	<10
5070	<10
5080	<1
5121	21.1
5131	<10

Example 6

Preparation of Solutions for Oral Administration

Solution 1: Antitumor compound 1393 was dissolved in ethanol to form a solution containing 140 mg of the compound per ml of solution. An equal volume of Cremophor® EL solution was added to the solution while stirring to form a solution containing 70 mg of compound 1393 per ml. This soluti on was diluted using 9 parts by weight of saline to form a pharmaceutically acceptable solution for administration to a patient.

Solution 2: Antitumor compound 1458 was dissolved in ethanol to form a solution containing 310 mg of the compound per ml of so lution. An equal volume of Cremophor® EL solution was added to the solution while stirring to form a solution containing 155 mg of compound 1458 per ml. This solution was diluted using 9 parts by weight of saline to form a pharmaceutically acceptable sol ution for administration to a patient.

Solution 3: Antitumor compound 1351 was dissolved in ethanol to form a solution containing 145 mg of the compound per ml of solution. An equal volume of Cremophor® EL solution was added to the solution while stirri ng to form a solution containing 72.5 mg of compound 1351 per ml. This solution was diluted using 9 parts by weight of saline to form a pharmaceutically acceptable solution for administration to a patient.

Solution 4: Antitumor compound 4017 was dissolve d in ethanol to form a solution containing 214 mg of the compound per ml of solution. An equal volume of Cremophor® EL solution was added to the solution while stirring to form a solution containing 107 mg of compound 4017 per ml. This solution was dilut ed using 9 parts by weight of saline to form a pharmaceutically acceptable solution for administration to a patient.

Solution 5: Antitumor compound 1393 was dissolved in 100% ethanol then mixed with an equal volume of Cremophor® EL solution to form a sol ution containing 70 mg of compound 1393 per ml. This solution was diluted using 9 parts by weight of D%W (an aqueous solution containing 5 % weight by volume of dextrose) or 0.9% saline to form a pharmaceutically acceptable solution for administration to a patient.

Example 7

Preparation of a Suspension Containing Compound 1393 for Oral Administration

An oral composition of antitumor compound 1393 was prepared by suspending 25 mg of compound 1393 as a fine powder in one ml of carrier containing 1% carboxymethylcellulose (CMC) in deionized water.

Example 8

Preparation of a Tablet Containing Compound 1393 for Oral Administration

Antitumor compound 1393 (100 mg) was dissolved in methylene chloride (2 ml) and Cremophor® EL solution (100mg) was added. The methylene chloride was evaporated under vacuum to form a glass. Microcrystalline cellulose (600 mg) was added to the glass and mixed to form a powder which can be processed to form a tablet.

Example 9

Preparation of Emulsions Containing Compound 1393 for Parenteral Administration

Emulsion 1: Antitumor compound 1393 was dissolved in 100% ethanol to form a solution containing 40 mg of compound 1393 per ml of the solution. The solution was then diluted with 19 parts by weight of Liposyn® II (20%) with stirring to form an emulsion containing 2 mg of compound 1393 per ml for parenteral administration.

Emulsion 2: Antitumor compound 1393 was dissolved in 100% ethanol to form a solution containing 40 mg of compound 1393 per ml of the solution. The solution was then diluted with 19 parts by weight of Liposyn® III (2%) with stirring to form an emulsion containing 2 mg of compound 1393 per ml for parenteral administration.

Emulsion 3: Antitumor compound 1393 was dissolved in 100% ethanol to form a solution containing 40 mg of compound 1393 per ml of the solution. The solution was then diluted with 9 parts by weight of Liposyn® III (2%) with stirring to form an emulsion containing 4 mg of compound 1393 per ml for parenteral administration.

Example 10

Preparation of Solutions Containing Compound 1393 for Parenteral Administration

Solution 1: Antitumor compound 1393 was dissolved in 100% ethanol to form a solution containing 140 mg of compound 1393 per ml. The solution was then diluted with an equal volume of Cremophor® EL solution with stirring and was then diluted with 9 parts by weight of normal saline to form a solution containing 7 mg of compound 1393 per ml of solution for parenteral administration.

Solution 2: Antitumor compound 1393 was dissolved in 100% ethanol to form a solution containing 140 mg of compound 1393 per ml of the solution. The solution was then diluted with an equal volume of Cremophor® EL solution with stirring and was then diluted with 4 parts by weight of normal saline to form a solution containing 11.7 mg of compound 1393 per ml of solution for parenteral administration.

Solution 3: Antitumor compound 1393 was dissolved in 100% ethanol to form a solution containing 140 mg of compound 1393 per ml of the solution. The solution was then diluted with an equal volume of Cremophor® EL solution with stirring and was then diluted with 2.33 parts by weight of normal saline to form a solution containing 16.2 mg of compound 1393 per ml of solution for parenteral administration.

Example 11

In Vivo Evaluation of Antitumor Compounds Against Two Human Lung Carcinoma Xenografts

Two antitumor compounds were formulated for an i.v. dosing regime prepared in the following vehicle: 10% ethanol, 10% Cremophor and 80% isotonic saline. The formulation of antitumor compound 1393 as used in this evaluation is described as Solution 2 of Example 10. Other compounds were formulated similarly. Taxol (paclitaxel, Bristol Meyers Squibb), used as a control, was obtained as the marketed pharmaceutical drug.

The two lung tumor xenografts used in the studies were the SK -MES carcinoma, which is very sensitive to Taxol, and the NCI -H1299 (H1299) carcinoma, which is more resistant to Taxol as compared to the SK -MES neoplasm.

Female NCr-nude mice bearing either SK-MES or H1299 neoplasms (implanted subcutaneously in the flank with 1mm ^{3} human lung carcinoma fragments)

were pair-matched into groups of six mice each on Day 1, with the mean tumor size for the groups ranging from 241 -244 mg. Treatment groups consisted of: treatment with the vehicle (Group 1); treatment with Taxol (Group 2); and treatment with antitumor compound 1393 (Group 3).

Treatments of Taxol and the antitumor compound 1393, were administered intravenously at the maximum tolerated dose (MTD) appropriate for each compound, with half the dose being given one hour apart on the qd x 1 schedule. The MTDs for the antitumor compounds were calculated from earlier single dose data for mice receiving i.v. administration of these compounds. Taxol itself was given as a split i.v. dose of 36 mg/kg, with the two 18 mg/kg doses separated by one hour. Vehicle control animals were dosed twice intravenously with half the total volume being given separated by one hour. The study was terminated at Day 60.

The results are summarized in Table 1 and include mean days of survival (MDS), number of toxic deaths, number of survivors, number of complete or partial responses, and number with stable disease. The mean days of survival is the number of days after which a neoplasm reached a size of 1.5 g and the animal was euthanized. A complete response is obtained if the tumor is not palpable at the end of the study. A partial response is obtained if the tumor shrinks to a size smaller than its size on Day 1 of the study. "Stable disease" occurs when the treatment limits the growth of the neoplasm to a small size that does not reach 1.5 g in size by the termination of the study.

A tumor scoring system was designed to provide a more quantitative ranking of efficacy (therapeutic potential) among the antitumor agents evaluated against the different human solid tumor xenografts. Each mouse in a study was given a score of from 1 to 10 at the end of the study. The scores can be summarized as follows:

Score	Description
<1	Serious toxicity
2-3	Tumor reached the cut-off size but significant tumor growth delay was apparent
4-6	Tumor growth was significantly inhibited (Stable Disease)
7-9	Partial tumor shrinkage (Partial Response)
10	Complete Response (Perfect score)

The individual score for each mouse was averaged into a mean score for each treatment group. This tumor scoring system provided a better comparison of the different antitumor compounds by quantifying the treatment results (complete response versus partial response).

Table 1

Group	MDS (n)	Toxic Deaths	Survivors	Complete Response	Partial Response	Stable Disease	Mean Score
1	12.2 ± 1.3 (6)	0	0	0	0	0	1± 0
2	16 ± 2.0 (6)	0	0	0	0	0	1.3 ± 0.3
3	–	0	6	6	0	0	10 ± 0

An MDS value of 12.2 days was calculated for the vehicle-treated control Group 1. Taxol (36 mg/kg; Group 2) only produced a modest 30% survival extension (MDS of 16.0 days) compared to vehicle controls, with no recorded tumor regressions. In contrast, antitumor compound 1393 was highly active. Antitumor compound 1393 (72.1 mg/kg; Group 3) produced six complete responses, occurring between days 14 - 24, for a 100% complete response rate. All antitumor compounds, including Taxol, were well tolerated.

In the H1299 experiment, mice were pair-matched into groups of six animals each on Day 1, with the mean tumor size for the groups ranging from 229 -233 mg. The treatment protocol for the H1299 test was identical to the SK -MES test protocol. An MDS value of 24.5 days was calculated for the vehicle-treated control Group 1. Taxol (36 mg/kg; Group 2) was not active in the H1299 model, causing only a 10% survival extension (MDS of 27.0 days) in five animals compared to vehicle -treated animals (not statistically significant). One partial response was observed following Taxol treatment.

Table 2

Group	MDS (n)	Toxic Deaths	Survivors	Complete Response	Partial Response	Stable Disease	Mean Score
1	24.5 ± 3.3 (6)	0	0	0	0	0	1.2 ± 0.2
2	27.0 ± 4.6 (5)	0	1	0	1	0	2.7 ± 1.3
3	--	2	4	2	1	1	5.7 ± 1.9

Antitumor compound 1393 demonstrated significant efficacy against the Taxol - refractory H1299 neoplasm. Antitumor compound 1393 (72.1 mg/kg; Group 3) caused two complete responses in the H1299 test. Other mice treated with this compound experienced significantly increased survival times as compared to vehicle -treated or Taxol-treated animals.

Two mice died in the H1299 test from toxicity in the groups treated by the antitumor compound. Since the doses and schedule for compound were the same as in the SK-MES experiment where no toxic deaths occurred, the side effects experienced by the nude mice most likely were not due to systemic drug toxicity. One explanation based on the extreme reaction of the H1299 tumors to the antitumor compound including necrosis and hemorrhaging of the carcinomas is that the compound caused a destruction of the tumor architecture and stroma resulting in a release of toxic substance from the neoplasm to the host mice.

Antitumor compound 1393 was effective when given as a single dose against two upstaged (250 mg) human lung carcinoma xenografts.

Example 12

In Vivo Evaluation of Antitumor compounds Against the HCT116 Human Colon Carcinoma Xenograft

Antitumor compounds were formulated for an i.v. dosing regime and were prepared in the following vehicle: 5% ethanol, 5% Cremophor and 90% isotonic saline. The formulation of antitumor compound 1393 as used in this evaluation is described as Solution 1 of Example 10. Other compounds were similarly formulated. Taxol (paclitaxel, Bristol Meyers Squibb), used as a control, was obtained as the marketed pharmaceutical drug. The dosing volume was 0.3 ml per 20 g mouse.

The HCT116 carcinoma is representative of human colon tumors and is generally insensitive to chemotherapy drugs, thus, such neoplasms are not treated clinically with Taxol.

Female NCr-nude mice bearing HCT116 neoplasms (implanted subcutaneously in the flank with 1 mm^3 human carcinoma fragments) were pair - matched into groups of five mice each on Day 1, with the mean tumor size for three of the four groups ranging from 254 -260 mg. The mean tumor size for Group 3 (second Taxol control) was 104.8 mg on Day 1. Treatment groups consisted of : i.v. treatment with the vehicle (Group 1); i.v. treatment with Taxol in split doses on Day 1 (Group 2); intraperitoneal (i.p.) treatment with Taxol in non -split, qd x 5 doses over Days 1 -5 (Group 3); and i.v. treatment with antitumor compound 1393 (Group 4).

Antitumor compound 1393 was given intravenously in a single maximum tolerated dose (MTD) appropriate for each compound. The Taxol controls were administered to two separate groups: Group 2 was given as an i.v. split dose, qd x 1 on Day 1 and Group 3 was given as an i.p. non -split dose over five days (qd x 5). The MTD for antitumor compound 1393 was calculated from earlier single dose data for mice receiving i.v. administration of this compound. All vehicle control animals in the split dosing regimes were dosed twice intravenously with half of the total volume being given separated by one hour. The study was terminated on Day 60.

The results are summarized in Table 3 and include mean days of survival (MDS), number of toxic deaths, number of survivors, number of complete or partial responses, and number with stable di sease. The mean days of survival is the number of days after which a SKMES neoplasm reached a size of 2.0 g and the animal was euthanized. A complete response is obtained if the tumor is not palpable at the end of the study. A partial response is obtain ed if the tumor shrinks to a size smaller than its size on Day 1 of the study. "Stable disease" occurs when the treatment limits the growth of the neoplasm to a small size that does not reach 2.0 g in size by the termination of the study.

Table 3

Group	MDS (n)	Toxic Deaths	Survivors	Complete Response	Partial Response	Stable Disease	Mean Score
1	22.2 ± 2.0 (5)	0	0	0	0	0	1 ± 0
2	27.5 ± 1.7 (4)	0	1	0	0	1	2.2 ± 0.5
3	40.8 ± 3.6 (4)	0	1	0	1	0	3.6 ± 1.4
4	–	0	5	1	4	0	9.2 ± 0.2

All HCT116 carcinomas in the five mice in the vehicle control group (Group 1) grew progressively until the 2.0 g cut -off size was reached. An MDS value of 22.2 days was calculated for Group 1. Taxol given i.v. at a single dose of 36 mg/kg (Group 2) produced an MDS of 27.5 days in four mice and caused one case of stable disease (Table 3). This 24% increase in survival compared to animals in control Group 1 is statistically significant at $p = 0.048$ (unpaired *t* test). Taxol administered i.p. at a dose of 18 mg/kg on a daily x 5 schedule (Group 3) resulted in an MDS value of 40.8 days for four mice, with one animal experiencing a partial response at the end of the study (12 mg tumor on Day 60). The 84% survival extension compared to Group 1 control mice was significant ($p = 0.001$; unpaired *t* test). With compound 1393 (Group 4), no

tumor in any treated animal reached the 2.0 g endpoint. Mice treated with compound 1393 (73 mg/kg; Group 4) had 1 complete response and 4 partial responses.

On Day 60, the small tumors in the animals e xperiencing durable, partial HCT116 shrinkage (partial responses) were excised and weighed. A comparison of the actual weights of these small neoplasms with the weight estimated from caliper measurement translated into mg tumor weight demonstrated agreeme nt between the two sets of HCT116 weights on Day 60. All mice designated partial responses in Table 3 clearly experienced substantial tumor shrinkage from the Day 1 carcinoma starting size, as evidenced by the actual HCT116 weights on Day 60.

Antitumor compound 1393 was well tolerated in the study. No toxic deaths were reported, and group mean weight losses were generally in the 8% -12% range on Day 6. This is well within acceptable limits for side effects for cancer chemotherapy drugs set by the NCI. Taxol was well-tolerated on both schedules, causing only modest weight loss and no deaths. Antitumor compound 1393 demonstrated significant activity against upstaged (250 mg) HCT116 human colon cancer xenografts when administered in a single dose. Every an imal treated experienced a durable partial or complete shrinkage of its neoplasm.

The chemotherapy drug Taxol was included in the study as the positive drug control. Taxol itself on a qd x 1 schedule extended survival by a modest 24% over control mice, and produced no complete responses or partial responses. Taxol given on its optimal qd x 5 schedule caused an 84% survival extension compared to control animals, and produced one partial response. Therefore the efficacy achieved with Taxol administration was far less than that achieved with antitumor compound 1393.

Example 13

In Vivo Evaluation of Antitumor Compounds Against the MX-1 Human Breast Carcinoma Xenograft

Antitumor compounds were formulated for an i.v. dosing regime (single i.v. bolus on qd x 1 schedule) prepared in the following vehicle: 5% ethanol, 5% Cremophor and 90% isotonic saline. The formulation of antitumor compound 1393 as used in this evaluation is described as Solution 1 of Example 10. Other compounds were similarly formulated. Taxol (paclitaxel, Bristol Meyers Squibb), used as a control, was obtained as the marketed pharmaceutical drug. The dosing volume was 0.3 ml per 20 g mouse.

The MX-1 carcinoma is representative of estrogen -independent human breast carcinomas and is sensitive to a number of chemotherapy drugs including Taxol. In

fact, Taxol, on its optimal five day schedule, can produce tumor shrinkage in MX -1 bearing mice, but is not very effective on a qd x 1 schedule, as shown in this study.

Female NCr-nude mice bearing MX-1 neoplasms (implanted subcutaneously in the flank with 1 mm^3 MX-1 human breast carcinoma fragments) were pair -matched into three groups of six mice each on Day 1, with the mean tumor size ranging from 219-226 mg. Treatment groups consiste d of: treatment with the vehicle (Group 1); treatment with Taxol (36 mg/kg; Group 2); and treatment with antitumor compound 1393 (72.6 mg/kg; Group 3).

Antitumor compound 1393 was given intravenously in a single maximum tolerated dose (MTD) appropriate for each compound. The Taxol control was administered in a split dose (qd x 1 schedule) on Day 1. The MTDs for antitumor compound 1393 was calculated from earlier single dose data for mice receiving i.v. administration of this compound. All vehicle con trol animals in the split dosing regimes were dosed twice intravenously with half the total volume being given separated by one hour. The study was terminated on Day 60.

The results are summarized in Table 4 and include mean days of survival (MDS), number of toxic deaths, number of survivors, number of complete or partial responses, and number with stable disease. The mean days of survival is the number of days after which a neoplasm reached a size of 2.0 g and the animal was euthanized. A complete resp onse is obtained if the tumor is not palpable at the end of the study. A partial response is obtained if the tumor shrinks to a size smaller than its size on Day 1 of the study. "Stable disease" occurs when the treatment limits the growth of the neoplasm to a small size that does not reach 2.0 g in size by the termination of the study.

Table 4

Group	MDS (n)	Toxic Deaths	Survivors	Complete Response	Partial Response	Stable Disease	Mean Score
1	19.7 ± 3.5 (6)	0	0	0	0	0	1± 0
2	27.8 (1)	4	1	0	0	1	1.2 ± 0.8
3	--	0	6	5	1	0	9.8 ± 0.2

All MX-1 carcinomas grew rapidly and progressively in all six animals receiving vehicle (Group 1). The MDS for these mice to reach the 2.0 g tumor cut -off point was 19.7 days. Taxol given i.v. at a single d ose of 36 mg/kg (Group 2) was not well tolerated in this study; four toxic deaths were recorded. One mouse experienced a condition of stable disease and the other remaining animal achieved an MDS of 27.8

days (calculated). Therefore, Taxol demonstrated m oderate anti-tumor activity in the two mice that did not experience severe side effects.

Antitumor compound 1393 produced 5 complete responses and 1 partial response in the 6 treated mice. The total tumor regression response rate (complete responses and partial responses) of compound 1393 was 100%. No toxic deaths occurred in this group (Group 3).

Antitumor compound 1393 was well tolerated in the study. Mean body weight gains throughout the study were documented for mice receiving compound 1393. Taxol was not well-tolerated; 4 of 6 mice treated with the drug died during the course of the study.

A high tumor response rate was achieved in this MX -1 study with antitumor compound 1393 as compared with Taxol. Compound 1393 produced durable complete responses and partial responses in 100% of the treated animals.

Example 14

In Vivo Evaluation of Antitumor Compounds
Against DU 145 Human Prostate Carcinoma Xenografts

Antitumor compounds were prepared in a vehicle of 5% ethanol, 5% Cremophor and 90% isoto nic saline as described for antitumor compound 1393 in Solution 1 of Example 10. Other antitumor compounds were similarly formulated. Taxol (paclitaxel; Bristol Meyers Squibb) was obtained as the marketed pharmaceutical drug. The dosing volume was 0.3 m l per 20 g mouse.

Male NCr-nude mice (implanted subcutaneously with 1 mm^3 DU145 prostate carcinoma fragments in the flank) were sorted into treatment groups of five mice each. The DU145 group mean size range was 223 -228 mg. Dosing was initiated on Day 1. The antitumor compounds were given i.v. at an estimated maximum tolerated dose (MTD) appropriate for each agent on a qd x 1 schedule (single administration of compound). The i.v. Taxol was given on the qd x 1 schedule as two split doses (one hour between) of 12 mg/kg per split dose (total dose = 24 mg/kg). Taxol was also administered i.p. on a qd x 5 schedule at a daily dose of 18 mg/kg. The vehicle was administered i.v. to control mice in Group 1 on the qd x 1 schedule. The study was terminated on Day 91. Treatment groups are detailed in Table 5.

Table 5

Group	Compound	Mg/kg	Route	Schedule
1	Vehicle	---	i.v.	qd x 1
2	Taxol	24	i.v.	qd x 1
3	Taxol	18	i.p	qd x 5
4	1351	107.6	i.v.	qd x 1
5	1393	72.6	i.v.	qd x 1
6	1401	107.6	i.v.	qd x 1
7	1418	107.6	i.v.	qd x 1
8	1424	195.1	i.v.	qd x 1

The results are summarized in Table 6 and include mean days of survival (MDS), number of toxic deaths, number of survivors, number of complete or partial responses, and number with stable disease. The mean days of survival is the number of days after which a neoplasm reached a size of 1.5 g and the animal was euthanized. A complete response is obtained if the tumor is not palpable at the end of the study. A partial response is obtained if the tumor shrinks to a s ize smaller than its size on Day 1 of the study. "Stable disease" occurs when the treatment limits the growth of the neoplasm to a small size that does not reach 1.5 g in size by the termination of the study.

Table 6

Group	MDS (n)	Toxic Deaths	Survivors	Complete Response	Partial Response	Stable Disease	Mean Score
1	34.3 ± 9.4 (3)	1	1	1	0	0	2.8 ± 1.8
2	37.4 ± 8.9 (3)	1	1	0	0	1	2 ± 1
3	---	5	0	0	0	0	0 ± 0
4	62.6 ± 17.5 (2)	2	1	0	1	0	2.6 ± 1.5
5	55.1 (1)	0	4	3	1	0	8 ± 1.5
6	72.6 ± 8.7 (3)	1	1	1	0	0	3.6 ± 1.7
7	81.8 (1)	0	4	1	2	1	7.2 ± 1.2
8	76.0 ± 5.4 (4)	0	1	0	1	0	3.6 ± 1.1

DU145 tumors grew progressively in three of the five mice treated with vehicle (Group 1); an MDS value of 34.3 days was calculated for these animals. One mouse in Group 1 died of unknown causes on Day 40 and the carcinoma of another mouse in Group 1 regressed slowly from its 220 mg starting size of pair -match until the neoplasm was no longer palpable on Day 71. This latter case is most likely an example of a poor tumor take.

The prostate carcinomas in three of five animals receiving Taxol at 24 mg/kg (i.v.; qd x 1) grew steadily and reached the 1.5 g endpoint with an MDS of 37.4 days (Group 2). This 9% increase in survival compared to Group 1 controls is not statistically different ($p = 0.82$; unpaired t-test). One animal in Group 2 died on Day 32, possibly from drug-related side effects. The fifth mouse in Group 2 did not experience net tumor growth over the 91 day study; the carcinoma was the same size (196 mg) on Day 6 as on Day 91. Taxol administered i.p. at a dose of 18 mg/kg on a qd x 5 schedule (Group 3) was highly toxic. All five mice died of drug -related side effects including substantial (often more than 20%) weight loss.

Antitumor compounds 1393 and 1418 produced a total response rate of 50% or better in this experiment. Antitumor compound 1393 (Group 5) was the most efficacious compound in the entire study, causing 3 complete responses and 1 partial response out of five DU145-bearing mice (60% complete response rate). The other mouse receiving compound 1393 had its tumor reach the 1.5 g cut -off on (calculated) Day 55. Moreover, compound 1393 was well -tolerated, no toxic deaths were recorded, and the maximum mean weight loss for Group 5 was only 8.8% (Day 11).

Antitumor compound 1418 (Group 7) caused a mix of complete responses, partial responses, stable disease responses, and extended MDS values compared to Group 1 controls.

Antitumor compounds 1401 and 1424 gave a total response rate between 20% and 50%. These agents were quite active in the study but the efficacy they achieved was not as high as that produced by compounds in the first category. These compounds produced a mix of complete responses, partial responses, stable disease cases, and MDS values well extended compared to the Group 1 MDS of 34.3 days.

Compounds 1351 caused two toxic lethalities at the administered dose out of the five animals treated with each compound (40% mortality rate). This compound produced high weight loss (over 20%) in a number of the treated mice prior to their deaths.

The remaining compounds were well -tolerated in the experiment, each causing no or one toxic death, and producing 8 - 12% maximal mean weight losses in the second week of the test. These modest side effects are we ll within NCI guidelines for acceptable toxicity in mice caused by administration of chemotherapy drugs.

Example 15

In Vivo Evaluation of Antitumor Compounds Against A2780 Human Ovarian Carcinoma Xenografts

Antitumor compounds were prepared in a vehi cle of 5% ethanol, 5% Cremophor and 90% isotonic saline as described for antitumor compound 1393 in Solution 1 of Example 10. Other antitumor compounds were similarly formulated. Taxol (paclitaxel; Bristol Meyers Squibb) and Taxotere (docetaxel; Rhône -Poulenc Rorer) were obtained as the marketed pharmaceutical drugs. The dosing volume was 0.3 ml per 20 g mouse.

Female NCr-nude mice (implanted subcutaneously with 1 mm^3 A2780 ovarian carcinoma fragments in the flank) were sorted into treatment groups of five mice each, except for the Taxotere treatment group including six mice. The A2780 group mean size range was 237-243 mg. Dosing was initiated on Day 1. The antitumor compounds were given i.v. at an estimated maximum tolerated dose (MTD) appropriate for each agent on a qd x 1 schedule (single administration of compound). The i.v. Taxol was given on the qd x 1 schedule as two split doses (one hour between) of 12 mg/kg per split dose (total dose = 24 mg/kg). Taxol was also administered i.p. on a qd x 5 schedule at a daily dose of 15 mg/kg. Taxotere was given i.v. on a qd x 1 schedule at a dose of 70 mg/kg. The vehicle was administered i.v. to control mice in Group 1 on the qd x 1 schedule. Treatment groups are detailed in Table 7. The study was terminated on Day 60.

Table 7

Group	Agent	Mg/kg	Route	Schedule
1	Vehicle	---	i.v.	qd x 1
2	Taxol	24	i.v.	qd x 1
3	Taxol	15	i.p.	qd x 5
4	1351	75.3	i.v.	qd x 1
5	1401	107.6	i.v.	qd x 1
6	1418	107.6	i.v.	qd x 1
7	Taxotere	70	i.v.	qd x 1

The results are summarized in Table 8 and include mean days of survival (MDS), number of toxic deaths, number of survivors, number of complete or partial responses, and number with stable disease. The mean days of survival is the number of days after which a neoplasm r eached a size of 2.0 g and the animal was

euthanized. A complete response is obtained if the tumor is not palpable at the end of the study. A partial response is obtained if the tumor shrinks to a size smaller than its size on Day 1 of the study. "Stable disease" occurs when the treatment limits the growth of the neoplasm to a small size that does not reach 2.0 g in size by the termination of the study.

Table 8

Group	MDS (n)	Toxic Deaths	Survivors	Complete Response	Partial Response	Stable Disease	Mean Score
1	11.7 ± 2.5 (5)	0	0	0	0	0	1.2 ± 0.2
2	21.9 ± 5.5 (5)	0	1	0	0	0	1.8 ± 0.4
3	26.5 (1)	4	0	0	0	0	0.6 ± 0.6
4	23.0 ± 1.7 (4)	0	1	0	1	0	3.6 ± 1.1
5	32.1 ± 3.9 (4)	0	1	0	0	1	3.4 ± 0.4
6	32.0 ± 2.3 (5)	0	0	0	0	0	3 ± 0
7	27.4 ± 3.5 (5)	0	0	0	0	0	2.5 ± 0.3

The ovarian tumors in all five mice in Group 1 receiving vehicle grew progressively and reached the 2.0 g cut -off with an MDS value of 11.7 days. Thus, this ovarian carcinoma xenograft is a fast growing neoplasm that kills its host in a relatively short time period.

Taxol given on a qd x 1 schedule (Group 2) was moderately efficacious in this test. The MDS value of 21.9 days calculated for Group 2 mice represents a 87% increase in survival compared to Group 1 control animals, which is not si gnificant at p = 0.13; unpaired t-test). One animal in Group 2 was a recorded case of stable disease on Day 61. Taxol administered i.p. at a dose of 15 mg/kg on a qd x 5 schedule (Group 3) was highly toxic; four mice succumbed to drug -related side effects.

Taxotere (70 mg/kg; i.v.; qd x 1) was more active than Taxol in this experiment. The MDS of 27.4 days for all five mice in Group 7 gives a calculated survival extension of 134% compared to Group 1 controls, which is statistically significant at p = 0.007 (unpaired t-test).

One antitumor compound (1351) produced at least one complete response or partial response (Total response rate of at least 20%) in mice bearing A2780 ovarian carcinomas.

Compound 1401 produced stable disease and high MDS values but n o tumor shrinkage. One compound included in the A2780 experiment (1418) achieved significant MDS values, but did not cause any complete responses, partial responses, or cases of stable disease. Treatment with this compound resulted in approximately 300% survival extensions compared to Group 1 controls.

The groups treated with antitumor compounds experienced maximal mean group weight losses in the 3% to 19% range around Day 11, and the animal weights rebounded thereafter. The side effects recorded for al l antitumor compounds were within the NCI acceptable range, and indicated that the animals in the A2780 experiment received proper MTD dosages.

Example 16

In Vivo Evaluation of Antitumor Compounds Against A375 Human Melanoma Xenografts

Antitumor compounds were prepared in a vehicle of 5% ethanol, 5% Cremophor and 90% isotonic saline as described for antitumor compound 1393 in Solution 1 of Example 10. Other antitumor compounds were similarly formulated. Taxol (paclitaxel; Bristol Meyers Squibb) and T axotere (docetaxel; Rhône-Poulenc Rorer) were obtained as the marketed pharmaceutical drugs. The dosing volume was 0.3 ml per 20 g mouse.

Female NCr-nude mice (implanted subcutaneously with 1 mm^3 A375 melanoma in the flank) were sorted into treatment grou ps of six mice each, except for the Taxotere group having seven mice each. The tumor group mean size range was 206-212 mg. Dosing was initiated on Day 1. The antitumor compounds were given i.v. at an estimated maximum tolerated dose (MTD) appropriate fo r each agent on a qd x 1 schedule (single administration of compound). The i.v. taxol was given on the qd x 1 schedule as two split doses (one hour between) of 12 mg/kg per split dose (total dose = 24 mg/kg). Taxol was also administered i.p. on a qd x 5 schedule at a daily dose of 18 mg/kg. Taxotere was given i.v. on a qd x 1 schedule at a dose of 70 mg/kg. The vehicle was administered i.v. to control mice in Group 1 on the qd x 1 schedule. Treatment groups are detailed in Table 9. The study was termi nated on Day 60.

Table 9

Group	Agent	Mg/kg	Route	Schedule
1	Vehicle	---	i.v.	qd x 1
2	Taxol	24	i.v.	qd x 1
3	Taxol	18	i.p.	qd x 5
4	1351	107.6	i.v.	qd x 1
5	1393	72.6	i.v.	qd x 1
6	1401	107.6	i.v.	qd x 1
7	1418	107.6	i.v.	qd x 1
8	1424	195.1	i.v.	qd x 1
9	Taxotere	70	i.v.	qd x 1

The results are summarized in Table 10 and include mean days of survival (MDS), number of toxic deaths, number of survivors, number of complete or partial responses, and number with stable disease. The mean days of s urvival is the number of days after which a tumor reached a size of 2.0 g and the animal was euthanized. A complete response is obtained if the tumor is not palpable at the end of the study. A partial response is obtained if the tumor shrinks to a size s maller than its size on Day 1 of the study. "Stable disease" occurs when the treatment limits the growth of the tumor to a small size that does not reach 2.0 g in size by the termination of the study.

Table 10

Group	MDS (n)	Toxic Deaths	Survivors	Complete Response	Partial Response	Stable Disease	Mean Score
1	14.4 ± 0.9 (6)	0	0	0	0	0	1 ± 0
2	18.1 ± 0.6 (4)	2	0	0	0	0	0.8 ± 0.3
3	---	6	0	0	0	0	0 ± 0
4	---	6	0	0	0	0	0 ± 0
5	35.6 ± 3.2 (6)	0	0	0	0	0	3 ± 0
6	22.2 ± 1.1 (6)	0	0	0	0	0	2 ± 0
7	34.5 ± 3.1 (3)	1	2	0	1	1	4 ± 1.3
8	30.7 ± 1.1 (2)	4	0	0	0	0	1 ± 0.6
9	21.5 ± 0.5 (7)	0	0	0	0	0	2 ± 0

The A375 melanoma implants grew rapidly and progressively in all six mice treated with vehicle (Group 1). These neoplasm reached the 2.0 g cut -off with an MDS value of 14.4 days.

Animals (Group 2) administered Taxol on a qd x 1 schedule (24 mg/kg; i.v.) experienced a modest therapeutic benefit from the chemotherapy drug. The MDS

value of 18.1 days represented a 26% survival extension compared to Group 1 controls. This survival increase was statistically significant ($p = 0.016$; unpaired t - test).

Taxol given on a qd x 5 schedule (18 mg/kg; i.p.) was highly toxic to the mice. All six animals dosed at 18 mg/kg died of toxicity. Taxotere given i.v. at a dose o f 70 mg/kg (qd x 1; Group 9) produced an MDS of 21.5 days. This 49% survival extension was significant compared to Group 1 controls at $p < 0.0001$ (unpaired t -test).

Antitumor compound 1418 produced at least one case of partial response or stable disease on Day 60 (when the study was terminated), and excellent survival extensions in the other treated mice as evidenced by the MDS values for this agent. Antitumor compound 1418 (Group 7) produced 1 partial response, one case of stable disease, and an MDS of 34.5 days (140% survival extension over Group 1 controls; $p < 0.0001$; unpaired t-test). One animal receiving antitumor compound 1418 died of toxicity.

Two antitumor compounds produced good increases in life span compared to Group 1 controls, but treatment with these compounds (1393 and 1401) did not result in any 60-day survivors. (i.e., no complete responses, partial responses, or cases of stable disease). The MDS values for these two compounds ranged to 250% (antitumor compound 1393) greater than the MD S of 14.4 days calculated for Group 1 controls. These survival extensions are all significantly larger than the Group 1 animals at $p < 0.05$ (unpaired t -test).

Two antitumor compounds (1351 and 1424) caused at least three toxic deaths each among the six mice per group receiving these compounds. In general, 20 - 30% mean group weight losses were recorded for animals treated with these compounds. The side effect profile for other groups administered antitumor compounds was generally within NCI guidelines; mean weight losses for groups ranged between 5 - 19% early in the test, and then animal weights rebounded.

The acceptable level of weight losses seen with the efficacious agents in the A375 experiment indicates that these mice were treated with reasonable MTDs of these antitumor compounds.

Example 17

In Vivo Evaluation of Antitumor Compounds Against Panc-1 Human Pancreatic Carcinoma Xenografts

Antitumor compounds were prepared in a vehicle of 5% ethanol, 5% Cremophor and 90% isotonic saline as describe d for antitumor compound 1393 in Solution 1 of Example 10. Other antitumor compounds were similarly formulated. Taxol (paclitaxel; Bristol Meyer Squibb) was obtained as the marketed pharmaceutical drugs. The dosing volume was 0.3 mL per 20 g mouse.

Female NCr-nude mice (6-8 weeks of age, implanted subcutaneously with 1 mm^3 Panc-1 pancreatic carcinoma fragments in the flank) were sorted into treatment groups of six mice each. The Panc-1 pancreatic carcinoma groups had a mean tumor size range of 192-213 mg. Dosing was initiated on Day 1. The antitumor compounds were given i.v. at an estimated maximum tolerated dose (MTD) appropriate for each agent on a qd x 1 schedule (single administration of compound). The i.v Taxol was given in the qd x 1 schedule as tw o split doses one hour apart or two split doses of 12 mg/kg per split dose (total dose of 24 mg/kg). Taxol was also administered at a dose of 15 mg/kg i.p. on a qd x 5 schedule. Taxotere was given i.v. at a dose of 70 mg/kg on a qd x 1 schedule. The vehicle was given i.v. to control mice in Group 1 in each test on Day 1 (qd x 1) schedule. Treatment groups are detailed in Table 12. The study was terminated on Day 63.

Table 11

Group	Agent	Mg/kg	Route	Schedule
1	Vehicle	---	i.v.	qd x 1
2	Taxol	24	i.v.	qd x 1
3	Taxol	15	i.p.	qd x 5
4	1351	75.32	i.v.	qd x 1
5	1393	72.6	i.v.	qd x 1
6	1401	107.6	i.v.	qd x 1
7	1418	107.6	i.v.	qd x 1
8	1424	195.1	i.v.	qd x 1

The results are summarized in Table 12 and include mean days of survival (MDS), number of toxic deaths, number of survivors, number of complete or partial responses, and number with stable disease. The mean days of survival is the number of days after which a neoplasm reached a size of 1.5 g and the animal was

euthanized. A complete response is obtained if the tumor is not palpable at the end of the study. A partial response is obtained if the tumor shrinks to a size smaller than its size on Day 1 of the study. "Stable disease" occurs when the treatment limits the growth of the neoplasm to a small size that does not reach 1.5 g in size by the termination of the study.

Table 12

Group	MDS (n)	Toxic Deaths	Survivors	Complete Response	Partial Response	Stable Disease	Mean Score
1	23.0 ± 3.1	0	1	0	0	1	2 ± 0.8
2	34.7 ± 3.4	1	1	0	0	1	2.2 ± 0.8
3	—	4	1	0	1	0	1.2 ± 1.2
4	42.5 ± 10.2	0	4	1	1	2	5.7 ± 1.3
5	—	0	6	1	4	1	7.8 ± 1
6	—	0	6	0	3	3	6.8 ± 0.8
7	—	0	6	0	5	1	8 ± 0.6
8	—	6	0	0	0	0	0 ± 0

The Panc-1 neoplasms of mice receiving vehicle (Group 1) reached the 1.5 g cut-off with a calculated MDS of 23.0 days. One carcinoma in the vehicle control group did not grow out, presumably because of a poor tumor take.

Taxol (Group 2) administered i.v. at a dose of 24 mg/kg (qd x 1) produced one case of stable disease, and caused an MDS o f 34.7 days in four other mice (significantly different from Group 1 controls at $p = 0.038$; unpaired *t*-test). One mouse died from the toxicity caused by this dose of Taxol. Taxol given i.p. at a dose of 15 mg/kg (qd x 5) caused four toxic deaths among th e six animals in Group 3.

Five antitumor compounds were evaluated in the second Panc -1 experiment (1351, 1393, 1401, 1418 and 1424). Three of these compounds (1393, 1401 and 1418) produced overall response rates from 50% to 100%. Very high efficacy was obtained with antitumor compound 1393 (1 complete response, 4 partial responses and one case of stable disease out of six animals treated) and antitumor compound 1418 (5 partial responses and one case of stable disease among six treated mice). One compound (1424) was very toxic; all animals receiving this agent died from drug - related side effects.

Four of the five antitumor compounds (1351, 1393, 1401 and 1418) were well - tolerated, causing no toxic deaths and minimal mean group weight losses of 3% - 13%. Therefore, these compounds were administered at reasonable MTD dosages. As was stated above, antitumor compound 1424 was highly toxic at the doses given.

Example 18

In Vivo Evaluation of Antitumor Compounds Against VM46 Human Colon Carcinoma Xenograft s

Antitumor compounds were prepared in a vehicle of 5% ethanol, 5% Cremophor and 90% isotonic saline as described for antitumor compound 1393 in Solution 1 of Example 10. Other antitumor compounds were similarly formulated. Taxol (paclitaxel; Bristol Meyer Squibb) and Taxotere (docetaxel, Rhone- Poulenc Rorer) were obtained as the marketed pharmaceutical drugs. The dosing volume was 0.3 mL per 20 g mouse.

Female NCr-nude mice (6-8 weeks of age, implanted subcutaneously with 1 mm^3 VM46 colon carcinoma fragments in the flank) were sorted into treatment groups of six mice each. The VM46 colon carcinoma groups had a mean tumor size range of 181-188 mg. Dosing was initiated on Day 1. The antitumor compounds were given i.v. at an estimated maximum tolerated do se (MTD) appropriate for each agent on a qd x 1 schedule (single administration of compound). The i.v Taxol was given in the qd x 1 schedule as two split doses one hour apart. Taxotere was given i.v. at a dose of 70 mg/kg on a qd x 1 schedule. The vehicl e was given i.v. to control mice in Group 1 in each test on Day 1 (qd x 1) schedule. Treatment groups are detailed in Table 13. The VM46 study ended on Day 64.

Table 13

Group	Compound	mg/kg	Route	Schedule
1	Vehicle	---	i.v.	qd x 1
2	Taxol	24	i.v.	qd x 1
3	Taxol	15	i.p.	qd x 5
4	1351	107.6	i.v.	qd x 1
5	1393	72.6	i.v.	qd x 1
6	1401	107.6	i.v.	qd x 1
7	1418	107.6	i.v.	qd x 1
8	1424	195.1	i.v.	qd x 1
9	Taxotere	70	i.v.	qd x 1

The results are summarized in table 14 and include mean days of surviv al (MDS), number of toxic deaths, number of survivors, number of complete or partial responses, and number with stable disease. The mean days of survival is the number of days after which a neoplasm reached a size of 1.5 g and the animal was euthanized. A complete response is obtained if the tumor is not palpable at the end of the study. A partial response is obtained if the tumor shrinks to a size smaller than its size on Day 1 of the study. "Stable disease" occurs when the treatment limits the growth of the neoplasm to a small size that does not reach 1.5 g in size by the termination of the study.

Table 14

Group	MDS (n)	Toxic Deaths	Survivors	Complete Response	Partial Response	Stable Disease	Mean Score
1	31.0 ± 4.4 (6)	0	0	0	0	0	1.2 ± 0.2
2	43.3 ± 3.7 (4)	0	2	0	1	1	3.8 ± 1.4
3	36.1 ± 12.2 (2)	3	1	0	1	0	1.8 ± 1.3
4	43.7 ± 3.4 (3)	0	3	0	1	2	4.5 ± 1.4
5	46.2 ± 6.1 (5)	0	1	1	0	0	3.2 ± 1.4
6	46.1 ± 5.9 (4)	1	1	0	1	0	2.5 ± 1.3
7	41.7 ± 3.4 (3)	0	3	0	0	3	3.5 ± 0.8
8	45.4 ± 8.1 (3)	3	0	0	0	0	0.8 ± 0.4
9	45.3 ± 3.6 (6)	0	0	0	0	0	2 ± 0

The colon cancers in all six mice receiving vehicle (Group 1) grew progressively, and reached the 1.5 g endpoint with a calculated MDS value of 31.0 days.

Taxol (Group 2) given at 24 mg/kg (i.v.; qd x 1) caused one partial response, one case of stable disease, and an MDS of 43.3 days for the remaining four mice in the group (not significantly different from controls at p = 0.086; unpaired *t*-test). Taxol administered i.p. at a dose of 15 mg/kg (qd x 5) was excessivel y toxic, causing three mortalities among the six treated animals. Taxotere was quite active in this test, producing an MDS value of 45.3 days (significant at p 0.05 compared to Group 1 controls; unpaired *t*-test).

Three antitumor compounds (1351, 1393, and 1401) achieved response rates in the 16.7% - 20% range. The only complete response documented among this set of agents was recorded for antitumor compound 1393. Survival extensions in the range of 11 to 20 days longer than the MDS of 31.0 days calcu lated for the control group were obtained with 1351 and 1401.

Three of the five antitumor compounds (1351, 1393, and 1418) were quite well - tolerated in the VM46 study, causing no toxic deaths and maximal mean group weight losses in the 3% -14% range on Day 8. Acceptable toxicity (not more than one death per group, and maximal mean weight loss under 12%) was also reported for antitumor compound 1401. One compound, 1424, produced excessive toxicity causing the deaths of three animals in Group 8.

Example 19

In Vivo Evaluation of the Oral Administration of Antitumor Compounds Against the SKMES Human Lung Carcinoma Xenograft

Antitumor compounds were formulated for oral administration over a wide dose range in a study to investigate the efficacy of this comp ound against the SKMES human lung cancer xenograft. The antitumor compounds were prepared in the following vehicle: 5% ethanol, 5% Cremophor and 90% isotonic saline. The formulation of antitumor compound 1393 as used in this evaluation is described as Solution 1 of Example 10.

Female Nu/Nu mice (6-8 weeks of age; implanted with 1 mm^3 SKMES lung carcinoma fragments in the flank) were sorted into treatment groups of six mice each. SKMES size ranges and group mean SKMES size ranges were 126 -448 mg and 238-241 mg, respectively. Treatment groups consisted of: no treatment (Group 1), vehicle only (Group 2), Taxol (40 mg/kg; Group 3), antitumor compound 1418 (90 mg/kg; Group 4), and antitumor compound 1393 (dosages of 104 mg/kg, 73 mg/kg, 42 mg/kg, 20.8 mg/kg, 10.4 mg/kg and 5.2 mg/kg; Groups 5 -10 respectively). Treatments were administered as a single oral bolus on Day 1, and the study was terminated on Day 60.

The results are summarized in Table 15 and include mean days of survival (MDS), number of toxic deaths, number of survivors, number of complete or partial responses, and number with stable disease. The mean days of survival is the number of days after which a SKMES neoplasm reached a size of 2.0 g and the animal was euthanized. A complete response i s obtained if the tumor is not palpable at the end of the study. A partial response is obtained if the tumor shrinks to a size smaller than its size on Day 1 of the study. "Stable disease" occurs when the treatment limits the growth of the neoplasm to a small size that does not reach 2.0 g in size by the termination of the study.

Table 15

Group	MDS (n)	Toxic Deaths	Survivors	Complete Responses	Partial Responses	Stable Disease	% Total Response
1	14.5 ± 1.7 (5)	0	1	0	0	1	0
2	13.7 ± 1.4 (6)	0	0	0	0	0	0
3	13.2 ± 1.4 (6)	0	0	0	0	0	0
4	—	0	6	4	2	0	100
5	—	0	6	5	0	1	83.3
6	36.4 (1)	0	5	5	0	0	83.3
7	23.2 ± 4.8 (4)	0	2	2	0	0	33.3
8	16.0 ± 1.8 (6)	0	0	0	0	0	0
9	11.9 ± 1.0 (5)	0	1	1	0	0	16.7
10	14.9 ± 1.4 (5)	0	1	1	0	0	16.7

Antitumor compound 1393 demonstrated significant curative activity when administered orally at the two highest dosages of 104 and 73 mg/kg. Five complete responses and one case of stable disease were recorded in Group 5 (104 mg/kg). Five complete responses were also recorded for Group 6 (73 mg/kg). The MDS value for Group 7 of 23.2 days is not significantly different statistically from the Group 1 MDS value of 14.5 days (p=0.1002; unpaired t test). The MDS values for Groups 8 -10 were essentially the same as the MDS calculat ed for the Group 1 controls.

Antitumor compound 1418 (Group 4) was also highly active with a single oral administration. This compound recorded four complete responses and two partial responses. The total response rate was 100%. The total response rate is defined as the percentage of evaluable animals (excluding deaths due to procedure or toxicity) in a group that experience complete or partial responses at the termination of the study.

Example 20

In Vivo Evaluation of the Intravenous Administration of Antitumor Compound 1418 Against the SKMES Human Lung Carcinoma Xenograft

Antitumor compound 1418 was formulated for i.v. administration over a wide dose range in a study to investigate the efficacy of this compound against the SKMES human lung cancer xe nograft. The antitumor compound was prepared in the following vehicle: 10% ethanol and 90% Liposyn III.

Female Nu/Nu mice (6-8 weeks of age; implanted with 1 mm^3 SKMES lung carcinoma fragments in the flank) were sorted into treatment groups of six mice each. SKMES size ranges and group mean SKMES size ranges were 126 -448 mg and 238-241 mg, respectively. Treatment groups consisted of: vehicle only (Group 1), and antitumor compound 1418 (dosages of 154 mg/kg, 108 mg/kg, 62 mg/kg, and 15 mg/kg; Groups 2-5 respectively). Treatments were administered as a single i.v. bolus on Day 1, and the study was terminated on Day 60.

The results are summarized in Table 16 and include mean days of survival (MDS), number of toxic deaths, number of survivors, number of c omplete or partial responses, and number with stable disease. The mean days of survival is the number of days after which a SKMES neoplasm reached a size of 2.0 g and the animal was euthanized. A complete response is obtained if the tumor is not palpable at the end of the study. A partial response is obtained if the tumor shrinks to a size smaller than its size on Day 1 of the study. "Stable disease" occurs when the treatment limits the growth of the neoplasm to a small size that does not reach 2.0 g in size by the termination of the study.

Table 16

Group	MDS (n)	Toxic Deaths	Survivors	Complete Responses	Partial Responses	Stable Disease	% Total Response
1	17.4 ± 13 (6)	0	0	0	0	0	0
2	46.4 (1)	0	5	5	0	0	83.3
3	40.6 ± 2.9 (3)	0	3	1	2	0	50.0
4	35.3 ± 3.3 (6)	0	0	0	0	0	0
5	21.2 ± 2.9 (6)	0	0	0	0	0	0

Antitumor compound 1418 demonstrated significant curative activity when administered intravenously at the two highest dosages of 154 and 108 mg/kg. Five complete responses were recorded in Group 2 (154 mg/kg). One complete response and two partial responses were also recorded for Group 3 (108 mg/kg). The MDS value for Group 4 of 35.3 days is significantly different statistically from the Group 1 MDS value of 17.4 days ($p=0.0006$; unpaired t test). The MDS value for Group 5 was essentially the same as the MDS calculated for the Group 1 control.

Example 21

Oral vs. IV Administration of Antitumor Compound 1393

Antitumor compound 1393 was formulated as described in Emulsion 3 of Example 9 (i.e., a vehicle of 10% ethanol and 90% Liposyn III), and was administered as a single bolus by the oral route or the IV route over a wide dose range in a study to compare the efficacy of the administration route of this compound against the SKMES human lung cancer xenograft.

Female Nu/Nu mice (6-8 weeks of age; implanted with 1 mm^3 SKMES lung carcinoma fragments in the flank) were sorted into treatment groups of six mice each. SKMES tumor size ranges and group mean SKMES tumor size ranges were 126 -416 mg and 278-287 mg, respectively. Treatment groups consisted of: no treatment (Group 1), vehicle only by IV (Group 2), antitumor compound 1393 by IV (dosages of 104 mg/kg, 73 mg/kg, 42 mg/kg, 20.8 mg/kg, 10.4 mg/kg and 5.2 mg/kg; Groups 3 -8 respectively), vehicle only orally (Group 9), Taxol orally (40 mg/kg;Group 10), and antitumor compound 1393 orally (dosages of 104 mg/kg, 73 mg/kg, 42 mg/kg, 20.8 mg/kg, 10.4 mg/kg and 5.2 mg/kg; Groups 11 -16 respectively). Treatment was administered as a single bolus on Day 1, an d the study was terminated on Day 62.

The results are summarized in Table 17 and include mean days of survival (MDS), number of toxic deaths, number of survivors, number of complete or partial responses, and number with stable disease. The mean days of s urvival is the number of days after which a SKMES neoplasm reached a size of 2.0 g and the animal was euthanized. A complete response is obtained if the tumor is not palpable at the end of the study. A partial response is obtained if the tumor shrinks to a size smaller than its size on Day 1 of the study. "Stable disease" occurs when the treatment limits the growth of the neoplasm to a small size that does not reach 2.0 g in size by the termination of the study.

Table 17

Group	MDS (n)	Toxic Deaths	Survivors	Complete Responses	Partial Responses	Stable Disease	% Total Response
1	11.0 ± 1.7 (6)	0	0	0	0	0	0
2	8.9 ± 0.9 (6)	0	0	0	0	0	0
3	—	0	6	5	1	0	100
4	—	0	6	3	3	0	100
5	35.7 ± 1.2 (2)	0	4	3	1	0	66.7
6	23.2 ± 1.8 (6)	0	0	0	0	0	0

7	16.3 ± 1.3 (6)	0	0	0	0	0	0
8	10.5 ± 0.9 (6)	0	0	0	0	0	0
9	8.9 ± 0.5 (6)	0	0	0	0	0	0
10	9.2 ± 1.4 (5)	1	0	0	0	0	0
11	21.6 (1)	0	5	4	1	0	83.3
12	36.3 ± 1.5 (3)	1	2	2	0	0	40
13	14.5 ± 1.1 (6)	0	0	0	0	0	0
14	9.6 ± 0.6 (6)	0	0	0	0	0	0
15	9.1 ± 0.7 (6)	0	0	0	0	0	0
16	9.2 ± 0.8 (6)	0	0	0	0	0	0

Table 17 shows that antitumor compound 1393 has a clear dose response when administered as a single IV bolus. The top three doses resulted in six, six and four 62-day survivors (Groups 3-5). No 62-day survivors were recorded in the lower three dose groups (Groups 6-8), but the MDS values of 23.2 and 16.3 days calculated for Groups 6 and 7 are statistically different from the MDS of 11.0 days calculated for the Group 1 controls (no treatment) and the MDS of 8. 9 days calculated for the Group 2 controls (vehicle only by IV) at $p < 0.05$, unpaired t -test.

Oral administration of antitumor compound 1393 also showed a dose response, however it was much greater than the one obtained by IV administration. Five and two 62-day survivors were recorded in Groups 11 (104 mg/kg) and 12 (72.8 mg/kg) respectively. The MDS value of for the other four mice in Group 12 was 36.3 days, a survival extension of 230%, is statistically highly different from the Group 1 and Group 2 controls ($p<0.0001$; unpaired t test). The Group 13 (41.6 mg/kg) MDS of 14.5 days was not statistically significant ($p=0.1193$; unpaired t test). The lower doses of antitumor compound 1393 when given orally were not active in this test. Taxol was also not active when administered orally as a single bolus.

Example 22

In Vivo Evaluation of the Oral Administration of Antitumor Compound 1393 Against the MX-1 Human Breast Carcinoma Xenograft

Antitumor compounds were administered orally in a study to investigate whether such a formulation is efficacious against the MX -1 human breast carcinoma xenograft. The antitumor compounds were prepared in the following vehicle: 5% ethanol, 5% Cremophor and 90% isotonic saline. The formulation of antitumor compound 1393 as us ed in this evaluation is described as Solution 1 of Example 10.

Female Nu/Nu mice (12-13 weeks of age; implanted with 1 mm^3 MX-1 human breast carcinoma fragments in the flank) were sorted into treatment groups of six mice each (MX-1 tumor size ranges and group mean MX-1 tumor size ranges were 56-138 mg and 68-74 mg, respectively). Treatment groups consisted of: vehicle only (Group 1), Taxol (dosages of 40 mg/kg and 28 mg/kg; Groups 2 and 3), Taxotere (dosages of 100 mg/kg and 70 mg/kg; Groups 4 and 5), an d antitumor compound 1393 (dosages of 105 mg/kg and 73.4 mg/kg; Groups 6 and 7). All treatments were administered as a single oral bolus on Day 1, and the study was terminated on Day 60.

The results are summarized in Table 18 and include mean days of sur vival (MDS), number of toxic deaths, number of survivors, number of complete or partial responses, and number with stable disease. The mean days of survival is the number of days after which an MX-1 neoplasm reached a size of 1.5 g and the animal was euthanized. A complete response is obtained if the tumor is not palpable at the end of the study. A partial response is obtained if the tumor shrinks to a size smaller than its size on Day 1 of the study. "Stable disease" occurs when the treatment limits th e growth of the neoplasm to a small size that does not reach 1.5 g in size by the termination of the study.

Table 18

Group	MDS (n)	Toxic Deaths	Survivors	Complete Responses	Partial Responses	Stable Disease
1	20.4 ± 1.8 (5)	0	1	0	0	1
2	23.2 ± 1.3 (5)	0	1	0	1	0
3	23.1 ± 1.7 (5)	0	1	0	0	1
4	27.1 ± 3.5 (5)	0	1	0	1	0
5	27.9 ± 4.3 (6)	0	0	0	0	0
6	37.6 (1)	0	5	5	0	0
7	---	1	5	4	0	1

Nine mice of the twelve treated with antitumor compound 1393 were recorded as complete tumor regression s. Therefore, antitumor compound 1393 when administered orally was curative in the great majority of mice receiving single bolus dosages. This compares with the statistically insignificant increase in MDS for the Taxol and Taxotere groups over the control group. One partial response and one stable disease were recorded among the Taxol group. One partial response was recorded for the Taxotere group.

Example 23
Comparative Study regarding the Affect of Gender
in the Administration of Antitumor Compound 139 3

Antitumor compound 1393 was administered to male and female mice in a study to investigate the affect of gender on the efficacy of compound 1393 against the HCT116 human colon carcinoma xenograft.

The vehicles used to prepare compound 1393 for adminis tration were prepared as described in Emulsion 1 of Example 9 (Group 4)(i.e., a vehicle of 5% ethanol and 95% Liposyn II (Group 1)), Emulsion 2 of Example 9 (Group 5)(i.e, a vehicle of 5% ethanol and 95% Liposyn III (Group 2)), and Solution 1 of Example 6 (Group 6)(i.e., a vehicle of 5% ethanol, 5% Cremophor and 90% isotonic saline). Taxol was formulated in a vehicle of 15% ethanol, 15% Cremophor and 70% isotonic saline (Group 3).

Six groups consisting of ten mice in each group were made up of female Nu /Nu mice (8-9 weeks of age; implanted with 1 mm^3 HCT116 human breast carcinoma fragments in the flank). Another six groups consisting of ten mice in each group were made up of male Nu/Nu mice (6-7 weeks of age; implanted with 1 mm^3 HCT116 human breast carcinoma fragments in the flank). Treatment groups consisted of: Liposyn II-containing vehicle via i.v. route (Group 1), Liposyn III -containing vehicle via i.v. route (Group 2), Taxol (18mg/kg; i.v. qd x 5 schedule; Group 3), antitumor compound 1393 via i.v. route (104 mg/kg to females or 73 mg/kg to males; Groups 4 and 5), and antitumor compound 1393 via oral route (104 mg/kg to females or 73 mg/kg to males; Group 6). The study was terminated on Day 60.

The results are summarized in Table 19 for the femal e mice and Table 20 for the male mice. Included are mean days of survival (MDS), number of toxic deaths, number of survivors, number of complete or partial responses, and number with stable disease. The mean days of survival is the number of days after w hich an MX-1 neoplasm reached a size of 1.5 g and the animal was euthanized. A complete response is obtained if the tumor is not palpable at the end of the study. A partial response is obtained if the tumor shrinks to a size smaller than its size on Day 1 of the study. "Stable disease" occurs when the treatment limits the growth of the neoplasm to a small size that does not reach 1.5 g in size by the termination of the study.

Table 19
Female Mice Results

Group	MDS (n)	Toxic Deaths	Survivors	Complete Responses	Partial Responses	Stable Disease
1	17.8 ± 1.8 (8)	0	2	1	1	0
2	15.1 ± 1.1 (9)	0	1	1	0	0
3	42.3 ± 6.0 (3)	1	6	4	1	1
4	—	0	10	5	3	2
5	—	0	10	5	3	2
6	27.8 (1)	0	9	4	3	2

Table 20
Male Mice Results

Group	MDS (n)	Toxic Deaths	Survivors	Complete Responses	Partial Responses	Stable Disease
1	16.3 ± 0.6 (10)	0	0	0	0	0
2	16.7 ± 0.8 (10)	0	0	0	0	0
3	39.4 ± 2.5 (6)	0	4	1	2	1
4	—	0	10	7	1	2
5	—	2[a]	8	6	0	2
6	—	0	10	6	3	1

[a]One death due to an unknown reason.

The activity of antitumor compound 1393 was very similar in males compared to female mice, with the given condition that the female hosts received a higher dosage. Twenty-nine out of thirty males and twenty-eight out of thirty females were recorded as long term survivors at the end of the experiment. Antitumor compound 1393 produces approximately equivalent activity in male and female nude mice bearing HCT116 colon carcinoma xenografts.

Example 24
In Vivo Evaluation of the Oral Administration of Antitumor Compound 1393 Against A375 Human Melanoma Xenograft

Antitumor compound 1393 was formulated as Solution 1 in Example 6 in a study to investigate the efficacy of such a formulation when administered orally against the A375 human melanoma xenograft. Paclitaxel was simi larly formulated in a vehicle of 5% ethanol, 5% Cremophor and 90% isotonic saline.

Female *nu/nu* mice (6-8 weeks of age; implanted subcutaneously with 1 mm^3 A375 melanoma fragments in the flank) were sorted into one control and four treatment groups of ten mice each (group mean tumor size of 96 -98 mg). Treatment groups were treated with a single oral bolus, unless otherwise specified, as follows: vehicle only (Group 1); paclitaxel (40 mg/kg; Group 2); antitumor compound 1393 (104 mg/kg; Group 3); antitumor compound 1393 (73 mg/kg on Day 1, followed by doses of 21.9 mg/kg on Days 11, 21, 31 and 41 for a cumulative dose of 160.6 mg/kg ; Group 4); and antitumor compound 1393 (36.5 mg/kg on Days 1, 15, 29 and 43 (a q14dx3 schedule) for a cumulative dose of 109. 5 mg/kg; Group 5). The study was terminated on Day 60.

The results are summarized in Table 21 and include mean days of survival (MDS), number of toxic deaths, number of survivors, number of complete or partial responses, and number with stable disease. The mean days of survival is the number of days after which a neoplasm reached a size of 2.0 g and the animal was euthanized. A complete response is obtained if the tumor is not palpable at the end of the study. A partial response is obtained if the tumo r shrinks to a size smaller than its size on Day 1 of the study. "Stable disease" occurs when the treatment limits the growth of the neoplasm to a small size that does not reach 2.0 g in size by the termination of the study.

Table 21

Group	MDS (n)	Toxic Deaths	Survivors	Complete Response	Partial Response	Stable Disease
1	22.9 ± 3.6 (7)	0	3	1	0	2
2	23.7 ± 3.0 (8)	0	2	0	1	1
3	37.8 (1)	0	9	9	0	0
4	--	1	9	8	1	0
5	33.5 ± 5.6 (6)	0	4	0	1	3

The insignificant difference between the mean survival data f or the vehicle (Group 1) and paclitaxel (Group 2) indicates that paclitaxel was not active in this study. Administration of 104 mg/kg of antitumor compound 1393 as a single oral bolus (Group 3) resulted in nine complete regression responses. This highly curative response was expressed in the majority of Group 3 mice by Day 21. The oral administration of 73 mg/kg of antitumor compound 1393 on Day 1, followed by 21.9 mg/kg doses on Days 11, 21, 31 and 41 (Group 4) was equally efficacious; eight complete regression responses and one partial regression response were recorded. As with the Group 3 mice, the majority of Group 4 mice experienced complete regression responses by Day 21. The only difference between the Group 3 and Group 4 treatments was a transie nt, greater earlier reduction in mean tumor volume for Group 3 as compared to Group 4 (46 mg vs. 120 mg, respectively by Day 11). The 60 day results were not statistically different between Groups 3 and 4. The administration of 36.5 mg/kg of antitumor co mpound 1393 on a q14d x 3 schedule beginning Day 1 (Group 5) was less efficacious than the treatments given to Groups 3 and 4. Three cases of stable disease and one partial response resulted for Group 5 mice. The melanomas in the remaining six mice reach ed 2.0 g in size (study endpoint) with a 33.5 mean day of survival.

Example 25

In Vivo Evaluation of the Oral Administration of Antitumor Compounds Against MX-1 Human Breast Carcinoma Xenograft

This study investigated the efficacy of various antitumor c ompounds when administered orally against the MX-1 human breast carcinoma xenograft. Antitumor compound 1351 was formulated as Solution 3 in Example 6. Antitumor compound 1458 was formulated as Solution 2 in Example 6. Antitumor compound 4017 was formulated as Solution 4 in Example 6. Other antitumor compounds were formulated similarly in a vehicle of 5% ethanol, 5% Cremophor and 90% isotonic saline.

Female *nu/nu* mice (11-12 weeks of age; implanted subcutaneously with 1 mm^3 MX-1 human breast carcinoma fragments in the flank) were sorted into one control (n=10) and treatment (n=6) groups (group mean tumor size of 47 -49 mg). Treatment groups were treated with a single oral bolus as summarized in Table 22. The study was terminated on Day 63.

The results are summarized in Table 22 and include mean days of survival (MDS), number of toxic deaths, number of survivors, number of complete or partial responses, and number with stable disease. The mean days of survival is the number of days after which a neopl asm reached a size of 1.5 g and the animal was euthanized. A complete response is obtained if the tumor is not palpable at the end of

the study. A partial response is obtained if the tumor shrinks to a size smaller than its size on Day 1 of the study. "Stable disease" occurs when the treatment limits the growth of the neoplasm to a small size that does not reach 1.5 g in size by the termination of the study.

Table 22

Group	Antitumor Compound	Dose (mg/kg)	Mean Day of Survival (n)	Maximum Weight Loss (Day)	Toxic Deaths	Complete Response	Partial Response	Stable Disease
1	vehicle	n/a	21.5 ± 0.7 (8)	n/a	0	0	0	2
2	1351	107	46.2 ± 5.1 (5)	-9.1% (5)	0	0	0	1
3	1458	233	46.0 ± 1.6 (5)	-5.8% (5)	0	1	0	0
4	4017	160	39.4 ± 4.6 (5)	-4.3% (5)	1	0	0	0

The majority of the antitumor compounds evaluated are active in the MX -1 human breast carcinoma xenograft model, at well tolerated doses. The responses produced by antitumor compounds 1351, 1458, and 4017 were characterized by significant survival extensions compared to vehicle control mice.

In addition to survival and tumor regression responses, the effect of treatment on blood cell populations was assessed. The major effect of these antitumor compounds on blood cell populations was a marked reduction in the neutrophil cell number. As well, monocyte depletion correlated fairly well with neutrophil reduction for each antitumor compound. These antitumor compounds did not affect the general white blood cell population, lymphocytes, and p latelets. There was a correlation between antitumor activity and reduced neutrophil count. In general, toxicity (as determined by neutrophil depletion) and weight loss correlated with efficacy. Importantly, the toxicities observed with the very efficaci ous antitumor compounds were manageable and reversible; neutrophil count and body weight rebounded from their low points in just a few days. Table 23 summarizes the weight reduction, neutrophil and monocyte measurements on Day 4, with tumor weight reducti on calculated at Day 18:

Table 23

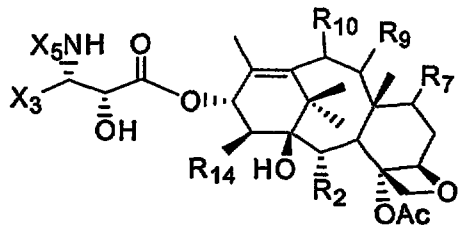
Group	Antitumor Compound	Dose (mg/kg)	Weight (mg)	% Reduction	Neutrophils (K/µL)	% Reduction	Monocytes (K/µL)	% Reduction
1	vehicle	n/a	868.5	-	0.9115		0.096	-
2	1351	107	122.1	85.9%	0.408	55.2%	0.088	8.3%
3	1458	233	21.8	97.5%	0.232	74.5%	0.057	40.6%
4	4017	160	256.5	70.5%	0.228	75.0%	0.073	24.0%

Summary of Results for Tumor Scoring System

In the animal studies described in the examples above, antitumor compounds 1393 and 1418 consistently demonstrated excellent efficacy scores for the tumors that they were tested against. The 75 percentile score for all antitumor compounds against a given tumor model was calculated. These two antitumor compounds scored at or above the 75 percentile score. Antitumor compound 1351 also demonstrated good scores in the models in which it was tested.

Claims

1. A taxane having the formula



wherein

R_2 is acyloxy;

R_7 is $R_{7a}COO$-;

R_{7a} is hydrocarbyl, substituted hydrocarbyl, or heterocyclo w herein said hydrocarbyl or substituted hydrocarbyl contains carbon atoms in the alpha and beta positions relative to the carbon atom of which R_{7a} is a substituent;

R_9 is keto, hydroxy, or acyloxy;

R_{10} is hydroxy;

R_{14} is hydrido or hydroxy;

X_3 is substituted or unsubstituted alkyl, alkenyl, alkynyl, phenyl or heterocyclo;

X_5 is $-COX_{10}$, $-COOX_{10}$, or $-CONHX_{10}$;

X_{10} is hydrocarbyl, substituted hydrocarbyl, or heterocyclo; and

Ac is acetyl.

2. The taxane of claim 1 wherein R_{7a} is substituted or unsubstituted C_2 - C_8 alkyl, C_2 - C_8 alkenyl or C_2 - C_8 alkynyl.

3. The taxane of claim 2 wherein X_3 is 2-furyl, 3-furyl, 2-thienyl, 3-thienyl, 2-pyridyl, 3-pyridyl, 4-pyridyl, C_1 - C_8 alkyl, C_2 - C_8 alkenyl, or C_2 - C_8 alkynyl.

4. The taxane of claim 2 wherein X_5 is $-COX_{10}$ and X_{10} is substituted or unsubstituted phenyl, 2-furyl, 3-furyl, 2-thienyl, 3-thienyl, 2-pyridyl, 3-pyridyl, 4-

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pyridyl, C_1 - C_8 alkyl, C_2 - C_8 alkenyl, or C_2 - C_8 alkynyl, or X_5 is -$COOX_{10}$ and X_{10} is substituted or unsubstituted C_1 - C_8 alkyl, C_2 - C_8 alkenyl, or C_2 - C_8 alkynyl.

5. The taxane of claim 2 wherein X_5 is -COX_{10} and X_{10} is phenyl, or X_5 is -$COOX_{10}$ and X_{10} is t-butyl.

6. The taxane of claim 2 wherein R_{14} is hydrido.

7. The taxane of claim 6 wherein X_3 is 2-furyl, 3-furyl, 2-thienyl, 3-thienyl, 2-pyridyl, 3-pyridyl, 4-pyridyl, C_1 - C_8 alkyl, C_2 - C_8 alkenyl, or C_2 - C_8 alkynyl.

8. The taxane of claim 6 wherein X_5 is -COX_{10} and X_{10} is substituted or unsubstituted phenyl, 2-furyl, 3-furyl, 2-thienyl, 3-thienyl, 2-pyridyl, 3-pyridyl, 4-pyridyl, C_1 - C_8 alkyl, C_2 - C_8 alkenyl, or C_2 - C_8 alkynyl or X_5 is -$COOX_{10}$ and X_{10} is substituted or unsubstituted C_1 - C_8 alkyl, C_2 - C_8 alkenyl, or C_2 - C_8 alkynyl.

9. The taxane of claim 6 wherein X_5 is -COX_{10} and X_{10} is phenyl, or X_5 is -$COOX_{10}$ and X_{10} is t-butyl.

10. The taxane of claim 2 wherein R_2 is benzoyloxy.

11. The taxane of claim 10 wherein X_3 is 2-furyl, 3-furyl, 2-thienyl, 3-thienyl, 2-pyridyl, 3-pyridyl, 4-pyridyl, C_1 - C_8 alkyl, C_2 - C_8 alkenyl, or C_2 - C_8 alkynyl.

12. The taxane of claim 10 wherein X_5 is -COX_{10} and X_{10} is substituted or unsubstituted phenyl, 2-furyl, 3-furyl, 2-thienyl, 3-thienyl, 2-pyridyl, 3-pyridyl, 4-pyridyl, C_1 - C_8 alkyl, C_2 - C_8 alkenyl, or C_2 - C_8 alkynyl or X_5 is -$COOX_{10}$ and X_{10} is substituted or unsubstituted C_1 - C_8 alkyl, C_2 - C_8 alkenyl, or C_2 - C_8 alkynyl.

13. The taxane of claim 10 wherein X_5 is -COX_{10} and X_{10} is phenyl, or X_5 is -$COOX_{10}$ and X_{10} is t-butyl.

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14. The taxane of claim 2 wherein R_{14} is hydrido and R_9 is keto.

15. The taxane of claim 14 wherein X_3 is 2-furyl, 3-furyl, 2-thienyl, 3-thienyl, 2-pyridyl, 3-pyridyl, 4-pyridyl, C_1 - C_8 alkyl, C_2 - C_8 alkenyl, or C_2 - C_8 alkynyl.

16. The taxane of claim 14 wherein X_5 is $-COX_{10}$ and X_{10} is substituted or unsubstituted phenyl, 2-furyl, 3-furyl, 2-thienyl, 3-thienyl, 2-pyridyl, 3-pyridyl, 4-pyridyl, C_1 - C_8 alkyl, C_2 - C_8 alkenyl, or C_2 - C_8 alkynyl or X_5 is $-COOX_{10}$ and X_{10} is substituted or unsubstituted C_1 - C_8 alkyl, C_2 - C_8 alkenyl, or C_2 - C_8 alkynyl.

17. The taxane of claim 14 wherein X_5 is $-COX_{10}$ and X_{10} is phenyl, or X_5 is $-COOX_{10}$ and X_{10} is t-butyl.

18. The taxane of claim 2 wherein R_2 is benzoyloxy and R_9 is keto.

19. The taxane of claim 18 wherein X_3 is 2-furyl, 3-furyl, 2-thienyl, 3-thienyl, 2-pyridyl, 3-pyridyl, 4-pyridyl, C_1 - C_8 alkyl, C_2 - C_8 alkenyl, or C_2 - C_8 alkynyl.

20. The taxane of claim 18 wherein X_5 is $-COX_{10}$ and X_{10} is substituted or unsubstituted phenyl, 2-furyl, 3-furyl, 2-thienyl, 3-thienyl, 2-pyridyl, 3-pyridyl, 4-pyridyl, C_1 - C_8 alkyl, C_2 - C_8 alkenyl, or C_2 - C_8 alkynyl or X_5 is $-COOX_{10}$ and X_{10} is substituted or unsubstituted C_1 - C_8 alkyl, C_2 - C_8 alkenyl, or C_2 - C_8 alkynyl.

21. The taxane of claim 18 wherein X_5 is $-COX_{10}$ and X_{10} is phenyl, or X_5 is $-COOX_{10}$ and X_{10} is t-butyl.

22. The taxane of claim 2 wherein R_{14} is hydrido and R_2 is benzoyloxy.

23. The taxane of claim 22 wherein X_3 is 2-furyl, 3-furyl, 2-thienyl, 3-thienyl, 2-pyridyl, 3-pyridyl, 4-pyridyl, C_1 - C_8 alkyl, C_2 - C_8 alkenyl, or C_2 - C_8 alkynyl.



24. The taxane of claim 22 wherein X_5 is $-COX_{10}$ and X_{10} is substituted or unsubstituted phenyl, 2-furyl, 3-furyl, 2-thienyl, 3-thienyl, 2-pyridyl, 3-pyridyl, 4-pyridyl, C_1 - C_8 alkyl, C_2 - C_8 alkenyl, or C_2 - C_8 alkynyl or X_5 is $-COOX_{10}$ and X_{10} is substituted or unsubstituted C_1 - C_8 alkyl, C_2 - C_8 alkenyl, or C_2 - C_8 alkynyl.

25. The taxane of claim 22 wherein X_5 is $-COX_{10}$ and X_{10} is phenyl, or X_5 is $-COOX_{10}$ and X_{10} is t-butyl.

26. The taxane of claim 2 wherein R_{14} is hydrido, R_9 is keto, and R_2 is benzoyloxy.

27. The taxane of claim 26 wherein X_3 is 2-furyl, 3-furyl, 2-thienyl, 3-thienyl, 2-pyridyl, 3-pyridyl, 4-pyridyl, C_1 - C_8 alkyl, C_2 - C_8 alkenyl, or C_2 - C_8 alkynyl.

28. The taxane of claim 26 wherein X_5 is $-COX_{10}$ and X_{10} is substituted or unsubstituted phenyl, 2-furyl, 3-furyl, 2-thienyl, 3-thienyl, 2-pyridyl, 3-pyridyl, 4-pyridyl, C_1 - C_8 alkyl, C_2 - C_8 alkenyl, or C_2 - C_8 alkynyl or X_5 is $-COOX_{10}$ and X_{10} is substituted or unsubstituted C_1 - C_8 alkyl, C_2 - C_8 alkenyl, or C_2 - C_8 alkynyl.

29. The taxane of claim 26 wherein X_5 is $-COX_{10}$ and X_{10} is phenyl, or X_5 is $-COOX_{10}$ and X_{10} is t-butyl.

30. The taxane of claim 1 wherein R_{7a} is C_2 - C_8 alkyl.

31. The taxane of claim 30 wherein X_3 is 2-furyl, 3-furyl, 2-thienyl, 3-thienyl, 2-pyridyl, 3-pyridyl, 4-pyridyl, C_1 - C_8 alkyl, C_2 - C_8 alkenyl, or C_2 - C_8 alkynyl.

32. The taxane of claim 30 wherein X_5 is $-COX_{10}$ and X_{10} is substituted or unsubstituted phenyl, 2-furyl, 3-furyl, 2-thienyl, 3-thienyl, 2-pyridyl, 3-pyridyl, 4-pyridyl, C_1 - C_8 alkyl, C_2 - C_8 alkenyl, or C_2 - C_8 alkynyl, or X_5 is $-COOX_{10}$ and X_{10} is substituted or unsubstituted C_1 - C_8 alkyl, C_2 - C_8 alkenyl, or C_2 - C_8 alkynyl.

33. The taxane of claim 30 wherein X_5 is -COX_{10} and X_{10} is phenyl, or X_5 is -$COOX_{10}$ and X_{10} is t-butyl.

34. The taxane of claim 30 wherein R_{14} is hydrido.

35. The taxane of claim 34 wherein X_3 is 2-furyl, 3-furyl, 2-thienyl, 3-thienyl, 2-pyridyl, 3-pyridyl, 4-pyridyl, C_1 - C_8 alkyl, C_2 - C_8 alkenyl, or C_2 - C_8 alkynyl.

36. The taxane of claim 34 wherein X_5 is -COX_{10} and X_{10} is substituted or unsubstituted phenyl, 2-furyl, 3-furyl, 2-thienyl, 3-thienyl, 2-pyridyl, 3-pyridyl, 4-pyridyl, C_1 - C_8 alkyl, C_2 - C_8 alkenyl, or C_2 - C_8 alkynyl or X_5 is -$COOX_{10}$ and X_{10} is substituted or unsubstituted C_1 - C_8 alkyl, C_2 - C_8 alkenyl, or C_2 - C_8 alkynyl.

37. The taxane of claim 34 wherein X_5 is -COX_{10} and X_{10} is phenyl, or X_5 is -$COOX_{10}$ and X_{10} is t-butyl.

38. The taxane of claim 30 wherein R_2 is benzoyloxy.

39. The taxane of claim 38 wherein X_3 is 2-furyl, 3-furyl, 2-thienyl, 3-thienyl, 2-pyridyl, 3-pyridyl, 4-pyridyl, C_1 - C_8 alkyl, C_2 - C_8 alkenyl, or C_2 - C_8 alkynyl.

40. The taxane of claim 38 wherein X_5 is -COX_{10} and X_{10} is substituted or unsubstituted phenyl, 2-furyl, 3-furyl, 2-thienyl, 3-thienyl, 2-pyridyl, 3-pyridyl, 4-pyridyl, C_1 - C_8 alkyl, C_2 - C_8 alkenyl, or C_2 - C_8 alkynyl or X_5 is -$COOX_{10}$ and X_{10} is substituted or unsubstituted C_1 - C_8 alkyl, C_2 - C_8 alkenyl, or C_2 - C_8 alkynyl.

41. The taxane of claim 38 wherein X_5 is -COX_{10} and X_{10} is phenyl, or X_5 is -$COOX_{10}$ and X_{10} is t-butyl.

42. The taxane of claim 30 wherein R_{14} is hydrido and R_9 is keto.

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43. The taxane of claim 42 wherein X_3 is 2-furyl, 3-furyl, 2-thienyl, 3-thienyl, 2-pyridyl, 3-pyridyl, 4-pyridyl, C_1 - C_8 alkyl, C_2 - C_8 alkenyl, or C_2 - C_8 alkynyl.

44. The taxane of claim 42 wherein X_5 is $-COX_{10}$ and X_{10} is substituted or unsubstituted phenyl, 2-furyl, 3-furyl, 2-thienyl, 3-thienyl, 2-pyridyl, 3-pyridyl, 4-pyridyl, C_1 - C_8 alkyl, C_2 - C_8 alkenyl, or C_2 - C_8 alkynyl or X_5 is $-COOX_{10}$ and X_{10} is substituted or unsubstituted C_1 - C_8 alkyl, C_2 - C_8 alkenyl, or C_2 - C_8 alkynyl.

45. The taxane of claim 42 wherein X_5 is $-COX_{10}$ and X_{10} is phenyl, or X_5 is $-COOX_{10}$ and X_{10} is t-butyl.

46. The taxane of claim 30 wherein R_2 is benzoyloxy and R_9 is keto.

47. The taxane of claim 46 wherein X_3 is 2-furyl, 3-furyl, 2-thienyl, 3-thienyl, 2-pyridyl, 3-pyridyl, 4-pyridyl, C_1 - C_8 alkyl, C_2 - C_8 alkenyl, or C_2 - C_8 alkynyl.

48. The taxane of claim 46 wherein X_5 is $-COX_{10}$ and X_{10} is substituted or unsubstituted phenyl, 2-furyl, 3-furyl, 2-thienyl, 3-thienyl, 2-pyridyl, 3-pyridyl, 4-pyridyl, C_1 - C_8 alkyl, C_2 - C_8 alkenyl, or C_2 - C_8 alkynyl or X_5 is $-COOX_{10}$ and X_{10} is substituted or unsubstituted C_1 - C_8 alkyl, C_2 - C_8 alkenyl, or C_2 - C_8 alkynyl.

49. The taxane of claim 46 wherein X_5 is $-COX_{10}$ and X_{10} is phenyl, or X_5 is $-COOX_{10}$ and X_{10} is t-butyl.

50. The taxane of claim 30 wherein R_{14} is hydrido and R_2 is benzoyloxy.

51. The taxane of claim 50 wherein X_3 is 2-furyl, 3-furyl, 2-thienyl, 3-thienyl, 2-pyridyl, 3-pyridyl, 4-pyridyl, C_1 - C_8 alkyl, C_2 - C_8 alkenyl, or C_2 - C_8 alkynyl.

52. The taxane of claim 50 wherein X_5 is $-COX_{10}$ and X_{10} is substituted or unsubstituted phenyl, 2-furyl, 3-furyl, 2-thienyl, 3-thienyl, 2-pyridyl, 3-pyridyl, 4-

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pyridyl, C_1 - C_8 alkyl, C_2 - C_8 alkenyl, or C_2 - C_8 alkynyl or X_5 is -$COOX_{10}$ and X_{10} is substituted or unsubstituted C_1 - C_8 alkyl, C_2 - C_8 alkenyl, or C_2 - C_8 alkynyl.

53. The taxane of claim 50 wherein X_5 is -COX_{10} and X_{10} is phenyl, or X_5 is -$COOX_{10}$ and X_{10} is t-butyl.

54. The taxane of claim 30 wherein R_{14} is hydrido, R_9 is keto, and R_2 is benzoyloxy.

55. The taxane of claim 54 wherein X_3 is 2-furyl, 3-furyl, 2-thienyl, 3-thienyl, 2-pyridyl, 3-pyridyl, 4-pyridyl, C_1 - C_8 alkyl, C_2 - C_8 alkenyl, or C_2 - C_8 alkynyl.

56. The taxane of claim 54 wherein X_5 is -COX_{10} and X_{10} is substituted or unsubstituted phenyl, 2-furyl, 3-furyl, 2-thienyl, 3-thienyl, 2-pyridyl, 3-pyridyl, 4-pyridyl, C_1 - C_8 alkyl, C_2 - C_8 alkenyl, or C_2 - C_8 alkynyl or X_5 is -$COOX_{10}$ and X_{10} is substituted or unsubstituted C_1 - C_8 alkyl, C_2 - C_8 alkenyl, or C_2 - C_8 alkynyl.

57. The taxane of claim 54 wherein X_5 is -COX_{10} and X_{10} is phenyl, or X_5 is -$COOX_{10}$ and X_{10} is t-butyl.

58. The taxane of claim 1 wherein R_{7a} is ethyl.

59. The taxane of claim 58 wherein X_3 is 2-furyl, 3-furyl, 2-thienyl, 3-thienyl, 2-pyridyl, 3-pyridyl, 4-pyridyl, C_1 - C_8 alkyl, C_2 - C_8 alkenyl, or C_2 - C_8 alkynyl.

60. The taxane of claim 58 wherein X_5 is -COX_{10} and X_{10} is substituted or unsubstituted phenyl, 2-furyl, 3-furyl, 2-thienyl, 3-thienyl, 2-pyridyl, 3-pyridyl, 4-pyridyl, C_1 - C_8 alkyl, C_2 - C_8 alkenyl, or C_2 - C_8 alkynyl, or X_5 is -$COOX_{10}$ and X_{10} is substituted or unsubstituted C_1 - C_8 alkyl, C_2 - C_8 alkenyl, or C_2 - C_8 alkynyl.

61. The taxane of claim 58 wherein X_5 is -COX_{10} and X_{10} is phenyl, or X_5 is -$COOX_{10}$ and X_{10} is t-butyl.

62. The taxane of claim 58 wherein R_{14} is hydrido.

63. The taxane of claim 62 wherein X_3 is 2-furyl, 3-furyl, 2-thienyl, 3-thienyl, 2-pyridyl, 3-pyridyl, 4-pyridyl, C_1 - C_8 alkyl, C_2 - C_8 alkenyl, or C_2 - C_8 alkynyl.

64. The taxane of claim 62 wherein X_5 is $-COX_{10}$ and X_{10} is substituted or unsubstituted phenyl, 2-furyl, 3-furyl, 2-thienyl, 3-thienyl, 2-pyridyl, 3-pyridyl, 4-pyridyl, C_1 - C_8 alkyl, C_2 - C_8 alkenyl, or C_2 - C_8 alkynyl or X_5 is $-COOX_{10}$ and X_{10} is substituted or unsubstituted C_1 - C_8 alkyl, C_2 - C_8 alkenyl, or C_2 - C_8 alkynyl.

65. The taxane of claim 62 wherein X_5 is $-COX_{10}$ and X_{10} is phenyl, or X_5 is $-COOX_{10}$ and X_{10} is t-butyl.

66. The taxane of claim 58 wherein R_2 is benzoyloxy.

67. The taxane of claim 66 wherein X_3 is 2-furyl, 3-furyl, 2-thienyl, 3-thienyl, 2-pyridyl, 3-pyridyl, 4-pyridyl, C_1 - C_8 alkyl, C_2 - C_8 alkenyl, or C_2 - C_8 alkynyl.

68. The taxane of claim 66 wherein X_5 is $-COX_{10}$ and X_{10} is substituted or unsubstituted phenyl, 2-furyl, 3-furyl, 2-thienyl, 3-thienyl, 2-pyridyl, 3-pyridyl, 4-pyridyl, C_1 - C_8 alkyl, C_2 - C_8 alkenyl, or C_2 - C_8 alkynyl or X_5 is $-COOX_{10}$ and X_{10} is substituted or unsubstituted C_1 - C_8 alkyl, C_2 - C_8 alkenyl, or C_2 - C_8 alkynyl.

69. The taxane of claim 66 wherein X_5 is $-COX_{10}$ and X_{10} is phenyl, or X_5 is $-COOX_{10}$ and X_{10} is t-butyl.

70. The taxane of claim 58 wherein R_{14} is hydrido and R_9 is keto.

71. The taxane of claim 70 wherein X_3 is 2-furyl, 3-furyl, 2-thienyl, 3-thienyl, 2-pyridyl, 3-pyridyl, 4-pyridyl, C_1 - C_8 alkyl, C_2 - C_8 alkenyl, or C_2 - C_8 alkynyl.

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72. The taxane of claim 70 wherein X_5 is $-COX_{10}$ and X_{10} is substituted or unsubstituted phenyl, 2-furyl, 3-furyl, 2-thienyl, 3-thienyl, 2-pyridyl, 3-pyridyl, 4-pyridyl, C_1 - C_8 alkyl, C_2 - C_8 alkenyl, or C_2 - C_8 alkynyl or X_5 is $-COOX_{10}$ and X_{10} is substituted or unsubstituted C_1 - C_8 alkyl, C_2 - C_8 alkenyl, or C_2 - C_8 alkynyl.

73. The taxane of claim 70 wherein X_5 is $-COX_{10}$ and X_{10} is phenyl, or X_5 is $-COOX_{10}$ and X_{10} is t-butyl.

74. The taxane of claim 58 wherein R_2 is benzoyloxy and R_9 is keto.

75. The taxane of claim 74 wherein X_3 is 2-furyl, 3-furyl, 2-thienyl, 3-thienyl, 2-pyridyl, 3-pyridyl, 4-pyridyl, C_1 - C_8 alkyl, C_2 - C_8 alkenyl, or C_2 - C_8 alkynyl.

76. The taxane of claim 74 wherein X_5 is $-COX_{10}$ and X_{10} is substituted or unsubstituted phenyl, 2-furyl, 3-furyl, 2-thienyl, 3-thienyl, 2-pyridyl, 3-pyridyl, 4-pyridyl, C_1 - C_8 alkyl, C_2 - C_8 alkenyl, or C_2 - C_8 alkynyl or X_5 is $-COOX_{10}$ and X_{10} is substituted or unsubstituted C_1 - C_8 alkyl, C_2 - C_8 alkenyl, or C_2 - C_8 alkynyl.

77. The taxane of claim 74 wherein X_5 is $-COX_{10}$ and X_{10} is phenyl, or X_5 is $-COOX_{10}$ and X_{10} is t-butyl.

78. The taxane of claim 58 wherein R_{14} is hydrido and R_2 is benzoyloxy.

79. The taxane of claim 78 wherein X_3 is 2-furyl, 3-furyl, 2-thienyl, 3-thienyl, 2-pyridyl, 3-pyridyl, 4-pyridyl, C_1 - C_8 alkyl, C_2 - C_8 alkenyl, or C_2 - C_8 alkynyl.

80. The taxane of claim 78 wherein X_5 is $-COX_{10}$ and X_{10} is substituted or unsubstituted phenyl, 2-furyl, 3-furyl, 2-thienyl, 3-thienyl, 2-pyridyl, 3-pyridyl, 4-pyridyl, C_1 - C_8 alkyl, C_2 - C_8 alkenyl, or C_2 - C_8 alkynyl or X_5 is $-COOX_{10}$ and X_{10} is substituted or unsubstituted C_1 - C_8 alkyl, C_2 - C_8 alkenyl, or C_2 - C_8 alkynyl.

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81. The taxane of claim 78 wherein X_5 is -COX_{10} and X_{10} is phenyl, or X_5 is -$COOX_{10}$ and X_{10} is t-butyl.

82. The taxane of claim 58 wherein R_{14} is hydrido, R_9 is keto, and R_2 is benzoyloxy.

83. The taxane of claim 82 wherein X_3 is 2-furyl, 3-furyl, 2-thienyl, 3-thienyl, 2-pyridyl, 3-pyridyl, 4-pyridyl, C_1 - C_8 alkyl, C_2 - C_8 alkenyl, or C_2 - C_8 alkynyl.

84. The taxane of claim 82 wherein X_5 is -COX_{10} and X_{10} is substituted or unsubstituted phenyl, 2-furyl, 3-furyl, 2-thienyl, 3-thienyl, 2-pyridyl, 3-pyridyl, 4-pyridyl, C_1 - C_8 alkyl, C_2 - C_8 alkenyl, or C_2 - C_8 alkynyl or X_5 is -$COOX_{10}$ and X_{10} is substituted or unsubstituted C_1 - C_8 alkyl, C_2 - C_8 alkenyl, or C_2 - C_8 alkynyl.

85. The taxane of claim 82 wherein X_5 is -COX_{10} and X_{10} is phenyl, or X_5 is -$COOX_{10}$ and X_{10} is t-butyl.

86. The taxane of claim 82 wherein X_5 is -$COOX_{10}$ and X_{10} is t-butyl.

87. The taxane of claim 86 wherein X_3 is 2-furyl, 3-furyl, 2-thienyl, 3-thienyl, 2-pyridyl, 3-pyridyl, 4-pyridyl, C_1 - C_8 alkyl, C_2 - C_8 alkenyl, or C_2 - C_8 alkynyl.

88. The taxane of claim 86 wherein X_3 is furyl or thienyl.

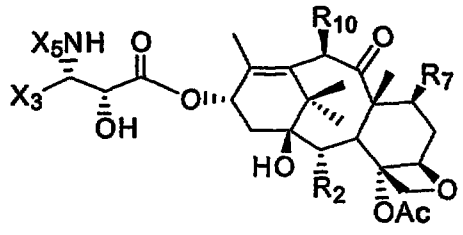
89. The taxane of claim 86 wherein X_3 is 2-furyl.

90. The taxane of claim 86 wherein X_3 is 2- thienyl.

91. The taxane of claim 86 whe rein X_3 is cycloalkyl.



92. A taxane having the formula



wherein

R_2 is benzoyloxy;

R_7 is $R_{7a}COO$-;

R_{10} is hydroxy;

X_3 is substituted or unsubstituted alkyl, alkenyl, alkynyl, or heterocyclo;

X_5 is $-COX_{10}$, $-COOX_{10}$, or $-CONHX_{10}$;

X_{10} is hydrocarbyl, substituted hydrocarbyl, or heterocyclo; and

R_{7a} is hydrocarbyl, substituted hydrocarbyl, or heterocyclo wherein said hydrocarbyl or substituted hydrocarbyl contains carbon atoms in the alpha and beta positions relative to the carbon of which R_{7a} is a substituent; and

Ac is acetyl.

93. The taxane of claim 92 wherein X_3 is 2-furyl, 3-furyl, 2-thienyl, 3-thienyl, 2-pyridyl, 3-pyridyl, 4-pyridyl, C_1 - C_8 alkyl, C_2 - C_8 alkenyl, or C_2 - C_8 alkynyl.

94. The taxane of claim 93 wherein X_5 is $-COX_{10}$ and X_{10} is substituted or unsubstituted phenyl, 2-furyl, 3-furyl, 2-thienyl, 3-thienyl, 2-pyridyl, 3-pyridyl, 4-pyridyl, C_1 - C_8 alkyl, C_2 - C_8 alkenyl, or C_2 - C_8 alkynyl, or X_5 is $-COOX_{10}$ and X_{10} is substituted or unsubstituted C_1 - C_8 alkyl, C_2 - C_8 alkenyl, or C_2 - C_8 alkynyl.

95. The taxane of claim 93 wherein X_5 is $-COX_{10}$ and X_{10} is phenyl, or X_5 is $-COOX_{10}$ and X_{10} is t-butyl.

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96. The taxane of claim 92 wherein X_3 is furyl or thienyl.

97. The taxane of claim 96 wherein X_5 is $-COX_{10}$ and X_{10} is substituted or unsubstituted phenyl, 2-furyl, 3-furyl, 2-thienyl, 3-thienyl, 2-pyridyl, 3-pyridyl, 4-pyridyl, C_1 - C_8 alkyl, C_2 - C_8 alkenyl, or C_2 - C_8 alkynyl, or X_5 is $-COOX_{10}$ and X_{10} is substituted or unsubstituted C_1 - C_8 alkyl, C_2 - C_8 alkenyl, or C_2 - C_8 alkynyl.

98. The taxane of claim 96 wherein X_5 is $-COX_{10}$ and X_{10} is phenyl, or X_5 is $-COOX_{10}$ and X_{10} is t-butyl.

99. The taxane of claim 93 wherein X_3 is cycloalkyl.

100. The taxane of claim 99 wherein X_5 is $-COX_{10}$ and X_{10} is substituted or unsubstituted phenyl, 2-furyl, 3-furyl, 2-thienyl, 3-thienyl, 2-pyridyl, 3-pyridyl, 4-pyridyl, C_1 - C_8 alkyl, C_2 - C_8 alkenyl, or C_2 - C_8 alkynyl, or X_5 is $-COOX_{10}$ and X_{10} is substituted or unsubstituted C_1 - C_8 alkyl, C_2 - C_8 alkenyl, or C_2 - C_8 alkynyl.

101. The taxane of claim 99 wherein X_5 is $-COX_{10}$ and X_{10} is phenyl, or X_5 is $-COOX_{10}$ and X_{10} is t-butyl.

102. The taxane of claim 93 wherein X_3 is isobutenyl.

103. The taxane of claim 102 wherein X_5 is $-COX_{10}$ and X_{10} is substituted or unsubstituted phenyl, 2-furyl, 3-furyl, 2-thienyl, 3-thienyl, 2-pyridyl, 3-pyridyl, 4-pyridyl, C_1 - C_8 alkyl, C_2 - C_8 alkenyl, or C_2 - C_8 alkynyl, or X_5 is $-COOX_{10}$ and X_{10} is substituted or unsubstituted C_1 - C_8 alkyl, C_2 - C_8 alkenyl, or C_2 - C_8 alkynyl.

104. The taxane of claim 102 wherein X_5 is $-COX_{10}$ and X_{10} is phenyl, or X_5 is $-COOX_{10}$ and X_{10} is t-butyl.

105. The taxane of claim 92 wherein R_{7a} is ethyl or propyl.

106. The taxane of claim 105 wherein X_3 is 2-furyl, 3-furyl, 2-thienyl, 3-thienyl, 2-pyridyl, 3-pyridyl, 4-pyridyl, C_1 - C_8 alkyl, C_2 - C_8 alkenyl, or C_2 - C_8 alkynyl.

107. The taxane of claim 106 wherein X_5 is $-COX_{10}$ and X_{10} is substituted or unsubstituted phenyl, 2-furyl, 3-furyl, 2-thienyl, 3-thienyl, 2-pyridyl, 3-pyridyl, 4-pyridyl, C_1 - C_8 alkyl, C_2 - C_8 alkenyl, or C_2 - C_8 alkynyl, or X_5 is $-COOX_{10}$ and X_{10} is substituted or unsubstituted C_1 - C_8 alkyl, C_2 - C_8 alkenyl, or C_2 - C_8 alkynyl.

108. The taxane of claim 106 wherein X_5 is $-COX_{10}$ and X_{10} is phenyl, or X_5 is $-COOX_{10}$ and X_{10} is t-butyl.

109. The taxane of claim 105 wherein X_3 is furyl or thienyl.

110. The taxane of claim 109 wherei n X_5 is $-COX_{10}$ and X_{10} is substituted or unsubstituted phenyl, 2-furyl, 3-furyl, 2-thienyl, 3-thienyl, 2-pyridyl, 3-pyridyl, 4-pyridyl, C_1 - C_8 alkyl, C_2 - C_8 alkenyl, or C_2 - C_8 alkynyl, or X_5 is $-COOX_{10}$ and X_{10} is substituted or unsubstituted C_1 - C_8 alkyl, C_2 - C_8 alkenyl, or C_2 - C_8 alkynyl.

111. The taxane of claim 109 wherein X_5 is $-COX_{10}$ and X_{10} is phenyl, or X_5 is $-COOX_{10}$ and X_{10} is t-butyl.

112. The taxane of claim 105 wherein X_3 is cycloalkyl.

113. The taxane of claim 112 wherein X_5 is $-COX_{10}$ and X_{10} is substituted or unsubstituted phenyl, 2-furyl, 3-furyl, 2-thienyl, 3-thienyl, 2-pyridyl, 3-pyridyl, 4-pyridyl, C_1 - C_8 alkyl, C_2 - C_8 alkenyl, or C_2 - C_8 alkynyl, or X_5 is $-COOX_{10}$ and X_{10} is substituted or unsubstituted C_1 - C_8 alkyl, C_2 - C_8 alkenyl, or C_2 - C_8 alkynyl.

114. The taxane of claim 112 wherein X_5 is $-COX_{10}$ and X_{10} is phenyl, or X_5 is $-COOX_{10}$ and X_{10} is t-butyl.

115. The taxane of claim 105 wherein X_3 is isobutenyl.

116. The taxane of claim 115 wherein X_5 is $-COX_{10}$ and X_{10} is substituted or unsubstituted phenyl, 2-furyl, 3-furyl, 2-thienyl, 3-thienyl, 2-pyridyl, 3-pyridyl, 4-pyridyl, C_1 - C_8 alkyl, C_2 - C_8 alkenyl, or C_2 - C_8 alkynyl, or X_5 is $-COOX_{10}$ and X_{10} is substituted or unsubstituted C_1 - C_8 alkyl, C_2 - C_8 alkenyl, or C_2 - C_8 alkynyl.

117. The taxane of claim 115 wherein X_5 is $-COX_{10}$ and X_{10} is phenyl, or X_5 is $-COOX_{10}$ and X_{10} is t-butyl.

118. The taxane of claim 92 wherein X_3 is furyl or thienyl, R_{7a} is ethyl, and X_5 is $-COX_{10}$ and X_{10} is phenyl, or X_5 is $-COOX_{10}$ and X_{10} is t-butyl.

119. The taxane of claim 92 wherein X_3 is substituted or unsubstituted furyl, R_{7a} is ethyl, and X_5 is $-COX_{10}$ and X_{10} is phenyl, or X_5 is $-COOX_{10}$ and X_{10} is t-butyl.

120. The taxane of claim 92 wherein X_3 is substituted or unsubstituted thienyl, R_{7a} is ethyl, and X_5 is $-COX_{10}$ and X_{10} is phenyl, or X_5 is $-COOX_{10}$ and X_{10} is t-butyl.

121. The taxane of claim 92 wherein X_3 is isobutenyl, R_{7a} is ethyl, and X_5 is $-COX_{10}$ and X_{10} is phenyl, or X_5 is $-COOX_{10}$ and X_{10} is t-butyl.

122. The taxane of claim 92 wherein X_3 is alkyl, R_{7a} is ethyl, and X_5 is $-COX_{10}$ and X_{10} is phenyl, or X_5 is $-COOX_{10}$ and X_{10} is t-butyl.

123. The taxane of claim 92 wherein X_3 is 2-furyl or 2-thienyl, R_{7a} is ethyl, X_5 is $-COOX_{10}$ and X_{10} is t-butyl.

124. The taxane of claim 92 wherein X_3 is 2-furyl, R_{7a} is ethyl, X_5 is $-COOX_{10}$ and X_{10} is t-butyl.

125. The taxane of claim 92 wherein X_3 is 2-thienyl, R_{7a} is ethyl, X_5 is $-COOX_{10}$ and X_{10} is t-butyl.



126. The taxane of claim 92 wherein X_3 is isobutenyl, X_5 is $-COOX_{10}$ and X_{10} is t-butyl.

127. The taxane of claim 92 wherein X_3 is cycloalkyl, R_{7a} is ethyl, X_5 is $-COOX_{10}$ and X_{10} is t-butyl.

128. A pharmaceutical composition comprising the taxane of claim 1 and at least one pharmaceutically acceptable carrier.

129. The pharmaceutical composition of claim 128 wherein X_3 is 2-furyl, 3-furyl, 2-thienyl, 3-thienyl, 2-pyridyl, 3-pyridyl, 4-pyridyl, C_1 - C_8 alkyl, C_2 - C_8 alkenyl, or C_2 - C_8 alkynyl.

130. The pharmaceutical composition of claim 129 wherein X_5 is $-COX_{10}$ and X_{10} is substituted or unsubstituted phenyl, 2- furyl, 3-furyl, 2-thienyl, 3-thienyl, 2-pyridyl, 3-pyridyl, 4-pyridyl, C_1 - C_8 alkyl, C_2 - C_8 alkenyl, or C_2 - C_8 alkynyl, or X_5 is $-COOX_{10}$ and X_{10} is substituted or unsubstituted C_1 - C_8 alkyl, C_2 - C_8 alkenyl, or C_2 - C_8 alkynyl.

131. The pharmaceutical composition of claim 129 wherein X_5 is $-COX_{10}$ and X_{10} is phenyl, or X_5 is $-COOX_{10}$ and X_{10} is t-butyl.

132. The pharmaceutical composition of claim 128 wherein R_{7a} is ethyl or propyl.

133. The pharmaceutical composition of claim 132 wherein X_3 is 2-furyl, 3-furyl, 2-thienyl, 3-thienyl, 2-pyridyl, 3-pyridyl, 4-pyridyl, C_2 - C_8 alkyl, C_2 - C_8 alkenyl, or C_2 - C_8 alkynyl.

134. The pharmaceutical composition of claim 133 wherein X_5 is $-COX_{10}$ and X_{10} is substituted or unsubstituted phenyl, 2- furyl, 3-furyl, 2-thienyl, 3-thienyl, 2-pyridyl, 3-pyridyl, 4-pyridyl, C_1 - C_8 alkyl, C_2 - C_8 alkenyl, or C_2 - C_8 alkynyl, or X_5 is $-COOX_{10}$ and X_{10} is substituted or unsubstituted C_1 - C_8 alkyl, C_2 - C_8 alkenyl, or C_2 - C_8 alkynyl.

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135. The pharmaceutical composition of claim 133 wherein X_5 is $-COX_{10}$ and X_{10} is phenyl, or X_5 is $-COOX_{10}$ and X_{10} is t-butyl.

136. The pharmaceutical composition of claim 129 wherein X_3 is furyl or thienyl, R_{7a} is ethyl, and X_5 is $-COX_{10}$ and X_{10} is phenyl, or X_5 is $-COOX_{10}$ and X_{10} is t-butyl.

137. The pharmaceutical composition of claim 129 wherein X_3 is substituted or unsubstituted furyl, R_{7a} is ethyl, and X_5 is $-COX_{10}$ and X_{10} is phenyl, or X_5 is $-COOX_{10}$ and X_{10} is t-butyl.

138. The pharmaceutical composition of claim 129 wherein X_3 is substituted or unsubstituted thienyl, R_{7a} is ethyl, and X_5 is $-COX_{10}$ and X_{10} is phenyl, or X_5 is $-COOX_{10}$ and X_{10} is t-butyl.

139. The pharmaceutical composition of claim 129 wherein X_3 is isobutenyl, R_{7a} is ethyl, and X_5 is $-COX_{10}$ and X_{10} is phenyl, or X_5 is $-COOX_{10}$ and X_{10} is t-butyl.

140. The pharmaceutical composition of claim 129 wherein X_3 is alkyl, R_{7a} is ethyl, and X_5 is $-COX_{10}$ and X_{10} is phenyl, or X_5 is $-COOX_{10}$ and X_{10} is t-butyl.

141. The pharmaceutical composition of claim 129 wherein X_3 is 2-furyl or 2-thienyl, R_{7a} is ethyl, X_5 is $-COOX_{10}$ and X_{10} is t-butyl.

142. The pharmaceutical composition of claim 129 wherein X_3 is 2-furyl, R_{7a} is ethyl, X_5 is $-COOX_{10}$ and X_{10} is t-butyl.

143. The pharmaceutical composition of claim 129 wherein X_3 is 2-thienyl, R_{7a} is ethyl, X_5 is $-COOX_{10}$ and X_{10} is t-butyl.

144. The pharmaceutical composition of claim 129 wherein X_3 is isobutenyl, X_5 is $-COOX_{10}$ and X_{10} is t-butyl.

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145. The pharmaceutical composition of claim 129 wherein X_3 is cycloalkyl, R_{7a} is ethyl, X_5 is $-COOX_{10}$ and X_{10} is t-butyl.

146. A composition for oral administration comprising the taxane of claim 1 and at least one pharmaceutically acceptable car rier.

147. The composition of claim 146 wherein X_3 is 2-furyl, 3-furyl, 2-thienyl, 3-thienyl, 2-pyridyl, 3-pyridyl, 4-pyridyl, C_1 - C_8 alkyl, C_2 - C_8 alkenyl, or C_2 - C_8 alkynyl.

148. The composition of claim 146 wherein X_5 is $-COX_{10}$ and X_{10} is phenyl, or X_5 is $-COOX_{10}$ and X_{10} is t-butyl.

149. The composition of claim 146 wherein R_{7a} is ethyl or propyl.

150. The composition of claim 149 wherein X_3 is 2-furyl, 3-furyl, 2-thienyl, 3-thienyl, 2-pyridyl, 3-pyridyl, 4-pyridyl, C_2 - C_8 alkyl, C_2 - C_8 alkenyl, or C_2 - C_8 alkynyl.

151. The composition of claim 150 wherein X_5 is $-COX_{10}$ and X_{10} is phenyl, or X_5 is $-COOX_{10}$ and X_{10} is t-butyl.

152. The composition of claim 150 wherein X_3 is furyl, thienyl or isobutenyl, R_{7a} is ethyl, and X_5 is $-COX_{10}$ wherein X_{10} is phenyl, or X_5 is $-COOX_{10}$ wherein X_{10} is t-butyl.

153. The composition of claim 146 wherein X_3 is alkyl, R_{7a} is ethyl, and X_5 is $-COX_{10}$ and X_{10} is phenyl, or X_5 is $-COOX_{10}$ and X_{10} is t-butyl.

154. The composition of claim 152 wherein X_3 is 2-furyl or 2-thienyl, R_{7a} is ethyl, X_5 is $-COOX_{10}$ and X_{10} is t-butyl or X_5 is $-COX_{10}$ and X_{10} is phenyl.

155. The composition of claim 154 wherein X_3 is 2-furyl, R_{7a} is ethyl, X_5 is $-COX_{10}$ and X_{10} is phenyl.



156. The composition of claim 154 wherein X_3 is 2-thienyl, R_{7a} is ethyl, X_5 is $-COOX_{10}$ and X_{10} is t-butyl.

157. The composition of claim 152 wherein X_3 is isobutenyl, R_{7a} is ethyl, and X_5 is $-COX_{10}$ and X_{10} is phenyl, or X_5 is $-COOX_{10}$ and X_{10} is t-butyl.

158. The composition of claim 157 wherein X_3 is isobutenyl, R_{7a} is ethyl, X_5 is $-COOX_{10}$ and X_{10} is t-butyl.

159. The composition of claim 152 wherein X_3 is phenyl, R_{7a} is ethyl, X_5 is $-COOX_{10}$ and X_{10} is t-butyl.

160. A method of inhibiting tumor growth in a mammal, said method comprising orally administering a therapeutically effective amount of a pharmaceutical composition containing the taxane of claim 1 and at least one pharmaceutically acceptable carrier.

161. The method of claim 160 wherein X_3 is 2-furyl, 3-furyl, 2-thienyl, 3-thienyl, 2-pyridyl, 3-pyridyl, 4-pyridyl, C_1 - C_8 alkyl, C_2 - C_8 alkenyl, or C_2 - C_8 alkynyl.

162. The method of claim 161 wherein X_5 is $-COX_{10}$ and X_{10} is phenyl, or X_5 is $-COOX_{10}$ and X_{10} is t-butyl.

163. The method of claim 160 wherein R_{7a} is ethyl or propyl.

164. The method of claim 163 wherein X_3 is 2-furyl, 3-furyl, 2-thienyl, 3-thienyl, 2-pyridyl, 3-pyridyl, 4-pyridyl, C_1 - C_8 alkyl, C_2 - C_8 alkenyl, or C_2 - C_8 alkynyl.

165. The method of claim 164 wherein X_5 is $-COX_{10}$ and X_{10} is phenyl, or X_5 is $-COOX_{10}$ and X_{10} is t-butyl.

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166. The method of claim 160 wherein X_3 is furyl, thienyl or isobutenyl, R_{7a} is ethyl, and X_5 is $-COX_{10}$ and X_{10} is phenyl, or X_5 is $-COOX_{10}$ and X_{10} is t-butyl.

167. The method of claim 166 wherein X_3 is alkyl, R_{7a} is ethyl, and X_5 is $-COX_{10}$ and X_{10} is phenyl, or X_5 is $-COOX_{10}$ and X_{10} is t-butyl.

168. The method of claim 166 wherein X_3 is 2-furyl or 2-thienyl, R_{7a} is ethyl, X_5 is $-COOX_{10}$ and X_{10} is t-butyl or X_5 is $-COX_{10}$ and X_{10} is phenyl.

169. The method of claim 168 wherein X_3 is 2-furyl, R_{7a} is ethyl, X_5 is $-COX_{10}$ and X_{10} is phenyl.

170. The method of claim 166 wherein X_3 is 2-thienyl, R_{7a} is ethyl, X_5 is $-COOX_{10}$ and X_{10} is t-butyl.

171. The method of claim 166 wherein X_3 is isobutenyl, R_{7a} is ethyl, and X_5 is $-COX_{10}$ and X_{10} is phenyl, or X_5 is $-COOX_{10}$ and X_{10} is t-butyl.

172. The method of claim 171 wherein X_3 is isobutenyl, R_{7a} is ethyl, X_5 is $-COOX_{10}$ and X_{10} is t-butyl.

173. The method of claim 166 wherein X_3 is phenyl, R_{7a} is ethyl, X_5 is $-COOX_{10}$ and X_{10} is t-butyl.

174. A method of inhibiting tumor growth in a mammal, said method comprising orally administering a therapeutically effective amount of a pharmaceutical composition containing the taxane of claim 92 and at least one pharmaceutically acceptable carrier.

175. The method of claim 174 wherein X_3 is phenyl, isobutenyl, furyl or thienyl, R_{7a} is ethyl, X_5 is $-COOX_{10}$ and X_{10} is t-butyl or X_5 is $-COOX_{10}$ and X_{10} is t-butyl.



176. A pharmaceutical composition comprising the taxane of claim 92 and at least one pharmaceutically acceptable carrier.

177. A pharmaceutical composition comprising the taxane of claim 96 and at least one pharmaceutically acceptable carrier.

