The invention relates to fluorotaxoid-fatty acid conjugates and pharmaceutical compositions thereof. The conjugates have the following formula:

\[
\text{(1)}
\]
The invention described in this application was made with funds from the National Institutes of Health, Grant Number ROI CA1033 14. The United States Government has certain rights in this invention.

BACKGROUND OF THE INVENTION

First generation taxoid compounds such as paclitaxel (Taxol®) and docetaxel (Taxotere®) have gained prominence as anticancer drugs. See E. K. Rowinsky, Annual Review of Medicine 1997, 48, 353; M. Suffness, Taxol Science and Applications; CRC Press: New York, 1995.

U.S. Patent Nos. 5,795,909; 5,919,815 and 6,080,877 disclose the omega-3 fatty acid DHA conjugated to first generation taxane anticancer agents such as paclitaxel and docetaxel. The DHA-paclitaxel conjugate has shown antitumor activity in animal studies, and is effective in reducing undesirable side effects because of its selective targeting to tumor cells and lower doses. See also Bradley, et al. Clinical Cancer Research (2000) 7, 3229-3238.


While these and other second generation taxoids have shown a high degree of efficacy in the treatment of various forms of cancer, there is a continuing need for improving the activity, metabolic stability, and mode of action of these compounds.
SUMMARY OF THE INVENTION

These, and other objectives as will be apparent to those of ordinary skill in the art, have been achieved by providing a compound having the formula:

![Chemical Structure]

wherein:

FA is an omega-3 fatty acid residue;

R¹ represents an alkyl, alkenyl, alkylamino, dialkylamino, or alkoxy group having one to six carbon atoms; a non-aromatic carbocyclic alkyl or alkenyl group having three to seventeen ring carbon atoms; a carbocyclic aryl group having six to eighteen ring carbon atoms; a non-aromatic heterocyclic group having three to seventeen ring carbon atoms or a heterocyclic aryl group having five to seventeen ring carbon atoms, wherein said cyclic groups can be unfused or fused, and unsubstituted or substituted;

R² represents a hydrogen; alkyl, alkenyl, alkoxy, alkenyloxy, acyloxy, alkylthio, alkenylthio, alkylamino or dialkylamino having one to six carbon atoms; halogen; fluoroalkyl group having one to three fluorine atoms and one to three carbon atoms; hydroxy; carboxyl; amino or azido;
R³ and R⁵ both represent hydrogen, or R³ and R⁵ are linked as a cyclic carbonate;

R⁴ represents an alkyl or alkenyl group having one to six carbon atoms; or a cycloalkyl or cycloalkenyl group having three to seven ring carbon atoms; and

R⁶ represents a fluoro vinyl, difluoro vinyl, or trifluoro vinyl group having the formula

\[
\begin{align*}
  & \text{R}^7 & \text{R}^8 & \text{R}^9 \\
  & \text{R}^8 & \text{R}^7 & \text{R}^9 \\
\end{align*}
\]

wherein R⁷, R⁸, and R⁹ each independently represent a hydrogen or fluoro group, provided that at least one of R⁷, R⁸, and R⁹ represents a fluoro group.

In another embodiment, the invention provides a pharmaceutical composition comprising the fluorotaxoid-omega-3 fatty acid conjugate.

In yet another embodiment, the invention provides a method for treating cancer in a human in need thereof. The method includes administering to the human an effective amount of the fluorotaxoid and omega-3 fatty acid conjugate.

**DETAILED DESCRIPTION OF THE INVENTION**

In one aspect of the invention, conjugates of fluorotaxoids and omega-3 fatty acids are provided. The fluorotaxoid contains a fluoro vinyl, difluoro vinyl, or trifluoro vinyl group at the C3' position of a taxoid compound.

In a preferred embodiment, the fluorotaxoid conjugates of the invention are represented by the formula:
In formula (1), FA represents the omega-3 fatty acid residue and the remainder represents the fluorotaxoid.

\[ R^1 \] represents a hydrocarbon group selected from an alkyl, alkenyl, alkylamino, dialkylamino, or alkoxy group having one to six carbon atoms; a non-aromatic carbocyclic alkyl or alkenyl group having three to seventeen ring carbon atoms; an aryl group having six to eighteen ring carbon atoms; or a non-aromatic heterocyclic group having three to seventeen ring carbon atoms; or a heteroaryl group having five to seventeen ring carbon atoms. These acyclic and cyclic hydrocarbon groups may be attached to the fluorotaxoid at any carbon position.

Some examples of suitable straight-chained alkyl groups include methyl, ethyl, \( n \)-propyl, \( n \)-butyl, \( n \)-pentyl, and \( n \)-hexyl.

Some examples of suitable branched alkyl groups include iro-propyl, iro-butyl, \( n \)-isobutyl, \( n \)-butyl, \( 1 \)-methylbutyl, \( 2 \)-methylbutyl, \( 3 \)-methylbutyl (isopentyl), \( 1,1 \)-dimethylpropyl, \( 1,2 \)-dimethylpropyl, \( 2,2 \)-dimethylpropyl (neopentyl), \( 1 \)-methylpentyl, \( 2 \)-methylpentyl, \( 3 \)-methylpentyl, and \( 4 \)-methylpentyl.
Some examples of suitable straight-chained alkenyl groups include vinyl, 2-propen-1-yl, 2-buten-1-yl, 3-buten-1-yl, 2-penten-1-yl, 3-penten-1-yl, 1,3-pentadien-1-yl, 4-penten-1-yl, 2-hexen-1-yl, 3-hexenyl, 4-hexen-1-yl, and 5-hexen-1-yl.

Some examples of suitable branched alkenyl groups include propen-2-yl, 1-butene-2-yl, 2-butene-2-yl, 1-butene-3-yl, 1-pentene-2-yl, 1-pentene-3-yl, 1-pentene-4-yl, 2-pentene-2-yl, 2-pentene-3-yl, 2-pentene-4-yl, 1-butene-3-methyl-2-yl, 1-butene-3-methyl-3-yl, 2-butene-2-methyl-1-yl, 2-butene-2-methyl-3-yl, 2-butene-2-methyl-4-yl, 2-butene-2-methylene, 2-butene-2,3-dimethyl-1-yl, 1-hexene-2-yl, 1-hexene-3-yl, 1-hexene-4-yl, 1-hexene-5-yl, 2-hexene-2-yl, 2-hexene-3-yl, 2-hexene-4-yl, 2-hexene-5-yl, 3-hexene-2-yl, 3-hexene-3-yl, 1-pentene-3-methyl-2-yl, 1-pentene-3-methyl-3-yl, 1-pentene-3-methyl-4-yl, 2-pentene-3-methyl-2-yl, and 2-pentene-3-methyl-4-yl.

Some examples of suitable alkylamino groups include methylamino, ethylamino, n-propylamino, iso-propylamino, ra-butylamino, sec-butylamino, iso-butylamino, tert-butylamino, w-pentylamino, wo-pentylamino, neo-pentylamino, «-hexylamino, 2,3-dimethylbutylamino, cyclopropylamino, cyclobutylamino, cyclopentylamino, cyclohexylamino, cycloheptylamino, 2-hydroxyethylamino, 2-(2-hydroxyethylenoxy)ethylamino, 2-methoxyethylamino, 2-ethoxyethylamino, and 3-hydroxypropylamino.

Some examples of suitable dialkylamino groups include dimethylamino, methylethylamino, methyl(/?-propyl)amino, methyl(wo-propyl)amino, methyl(«-butyl)amino, methyl(50-butyl)amino, methyl(«-pentyl)amino, methyl(50-pentyl)amino, methyl(neopentyl)amino, diethylamino, ethyl(«-propyl)amino, ethyl(wo-propyl)amino, ethyl(n-butyl)amino, ethyl(wo-butyl)amino, di(«-propyl)amino, and di(50-propyl)amino.

Some examples of suitable alkoxy groups include methoxy, ethoxy, n-propoxy, iso-propoxy, «-butoxy, wo-butoxy, sec-butoxy, »-butoxy, «-pentoxy, 1-methylbutoxy, 2-methylbutoxy, 3-methylbutoxy, «-hexoxy, 1,1-dimethylbutoxy, 1,2-dimethylbutoxy, 2,2-dimethylbutoxy, 2,3-dimethylbutoxy, 1-ethylbutoxy, 2-ethylbutoxy, cyclopropoxy, cyclobutyloxy, 2,4-dimethylcyclobutyloxy, cyclohexyloxy, cyclopropylmethylxoy, cyclohexymethoxy, and phenoxy.

The non-aromatic carboxylic alkyl or alkenyl groups of R¹ have three to seventeen ring carbon atoms. Some examples of suitable non-aromatic carboxylic alkyl groups include cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl, and cycloheptyl. Some examples of
suitable non-aromatic carboxylic alkenyl groups include cyclobutenyl, cyclobutadienyl, cyclopentenyl, cyclohexenyl, cyclohexadienyl, cycloheptenyl, and cycloheptadienyl.

The cyclic groups described above can be fused or unfused. The total number of carbon atoms include carbon atoms from fused rings.

A preferred unfused carbocyclic aryl group is phenyl. Some examples of suitable fused aryl groups include naphthyl, phenanthryl, anthracenyl, triphenylenyl, chrysenyl, and pyrenyl.

The heterocyclic aryl groups have five to seventeen atoms in the ring with one or more heteroatoms, preferably nitrogen, sulfur, or oxygen atoms. Some examples of suitable heteroaryl groups include pyridinyl, pyrimidinyl, triazinyl, imidazolyl, benzimidazolyl, pyrrolyl, cinnolinyl, phthalazinyl, quinazolinyl, purinyl, 2,6-naphthyridinyl, 1,8-naphthyridinyl, quinolinyl, isoquinolinyl, carbazolyl, oxazolyl, thiophenyi, thiazolyl, furyl, pyridazinyl, pyrazolyl, 1,4-diazanaphthalenyl, indolyl, pyrazinyl, 4,5-diazaphenanthrene, and benzoazole.

$R^1$ can also be a non-aromatic heterocyclic group. Some examples of suitable non-aromatic heterocyclic groups include piperidinyl, piperidinyl-$N$-oxide, $N$-methylpiperidinyl, piperazinyl, 1-methylpiperazinyl, piperazinyl-$N$-oxide, 1-acetylpiperazinyl, 1-(o-tolyl)piperazinyl, homopiperazinyl, and morpholino.

The cycloalkyl, cycloalkenyl, aryl, heteroaryl and non-aromatic heterocyclic rings described above for $R'$ can be substituted with any of the hydrocarbon groups thus far described.

Some examples of hydrocarbyl-substituted cycloalkyl groups include 2-methylcyclopropyl, 2-ethylcyclopropyl, 2-methylcyclobutyl, 3-methylcyclobutyl, 2-methylcyclopentyl, 2,3-dimethylcyclopentyl, 3-/so-propylocyclopentyl, 2,6-dimethylcyclohexyl, 4-(f-butyl)cyclohexyl, 2-vinylcyclohexyl, 2,6-diallylcyclopentyl, 3,4-diallylcyclopentyl, 1-(4-pyridinyl)piperidinyl, 1-(4-pyridinylmethyl)piperidinyl, 4-(4-pyridinyl)piperidinyl, 4-(4-pyridinyl)piperazin-1-yl, and bicyclohexyl groups.

Some examples of hydrocarbyl-substituted cycloalkenyl groups include 3-methyl-3-cyclopenten-1-yl, 3,4-dimethyl-3-cyclopenten-1-yl, 2-/so-propyl-2-cyclopenten-1-yl, 2,3-
diethyl-2-cyclopenten-1-yl, 4-vinyl-1-cyclohexen-1-yl, S^-diethyl-S-cyclopenten-1-yl, and 3,4-diallyl-3-cyclopenten-1-yl groups.

Some examples of hydrocarbyl-substituted aryl groups include tolyl, mesityl, xylyl, cumenyl, cymenyl, 3,5-di(=butyl)phenyl, 2-methylnaphthyl, 2-vinylphenyl, 2-vinylbenzyl, 2-vinylnaphthyl, 4-cyclohexylphenyl, biphenyl, 4-(4-piperidinyl)pyridinyl, and /?-terphenyl groups.

Some examples of hydrocarbyl-substituted heteroaryl groups include 2-methylpyridin-1-yl, 2-ethylpyridin-1-yl, 3-vinylimidazol-1-yl, 2-methylimidazol-1-yl, 2-methylquinoxalin-1-yl, 1-allylbenzotriazolyl, 2,2'-bipyridyl, 4,4'-bipyridyl, 4-methylpyrazinyl, 4-(pyridinylmethyl)pyridinyl, 4-benzylpyrazinyl, nicotinamidyl, 2-methylfuranyl, 5-methylfurfurylamino, 2-methylthiophenyl, 4-methyloxazolyl, 2,5-diphenyl-4-methyloxazolyl, and 4-methylthiazolyl groups.

Alternatively, the cycloalkyl, cycloalkenyl, aryl, heteroaryl and non-aromatic heterocyclic rings described above for R^1 can be substituted with a halogen, nitro, hydroxyl carboxyl, amino or azido group.

In formula (1), R^2 can also represent any of the hydrocarbon groups described above with regard to R^1. For example, R^2 can represent alkyl, such as methyl; alkenyl; alkoxy, such as methoxy; alkenyloxy; acyloxy; alkylthio; alkenylthio; alkylamino; or dialkylamino having one to six carbon atoms. Preferably, the hydrocarbon group contains a maximum of two carbon atoms. Alternatively, R^2 can also represent hydrogen; a halogen, such as iodo, bromo, chloro or fluoro; or fluoroalkyl having one to three fluorine atoms and one to three carbon atoms, for example, trichloromethyl; hydroxyl; amino; carboxyl; or azido.

R^3 and R^5 both preferably represent hydrogen, or R^3 and R^5 together represent a cyclic carbonate (i.e., -O-C(=O)-O-).

R^4 represents any of the alkyl, alkenyl, cycloalkyl, or cycloalkenyl groups described above for R^1. Preferably, R^4 is a ter/-butyl group.

In formula (1), R^6 represents a fluorinated vinyl group having the formula
In formula (2), R\textsuperscript{7}, R\textsuperscript{8}, and R\textsuperscript{9} each independently represent a hydrogen or fluoro group provided that at least one of R\textsuperscript{7}, R\textsuperscript{8}, and R\textsuperscript{9} represents a fluoro group. The fluorinated vinyl group can be a fluorovinyl, difluorovinyl, or trifluorovinyl group.

The fluorovinyl group can be a 2-fluorovinyl group (-CH=CH\textsubscript{2}) or a 2-fluorovinyl group (-CF=CH\textsubscript{2}). In addition, the 2-fluorovinyl group can be in a cis- or trans-configuration.

The difluorovinyl group can be a 2,2-difluorovinyl group (-CH=CF\textsubscript{2}) or a 1,2-difluorovinyl group (-CF=CH\textsubscript{F}). The 1,2-difluorovinyl group can have the fluoro substituents in either a cis- or trans-configuration with respect to each other.

The trifluorovinyl group can be a 1,2,2-trifluorovinyl group (-CF=CF\textsubscript{2}).

In a preferred embodiment, the fluorotaxoids in the conjugate of the present invention are represented by the formula:

\begin{center}
\textbf{(3)}
\end{center}
In formula (3), $R_1$ and $R_2$ are independently as described above. For example, $R_1$ can be methyl, ethyl, methoxy, dimethylamino or cyclopropyl and $R_2$ can be hydrogen, methyl, methoxy, chloro, fluoro or azido. More preferably, $R_1$ represents methyl, ethyl, methoxy, or cyclopropyl, and $R_2$ represents hydrogen, methoxy, or azido.

Some particularly preferred fluorotaxoid compounds for the conjugates of the present invention include those listed in the table below. These taxoids have shown particular potency for the inhibition of the growth of cancer cells as shown in the following table. The results were obtained according to the methods of Skehan et al (See Skehan et al., J. Nat. Cancer Inst., 82, 1107 (1990)), as more fully described in the Examples. The resistance factor (R/S) shown in the table is a measure of the degree of resistance of a cell line against a taxoid compound. The resistance factor is a ratio of the cytotoxicity of a taxoid compound against a drug-resistant cell line (R) as compared to its cytotoxicity against a drug-sensitive cell line (S).
Highly Potent Difluorovinyl-taxoids (IC50 nM)

\[
\begin{align*}
\text{Taxoid} & & R^1 & & R^2 & & \text{MCF7 (breast)} & & \text{MCF7-R (breast)} & & R/S \\
\text{Paclitaxel} & & \text{Me} & & \text{H} & & 1.2 & & 300 & & 250 \\
\text{SB-T-12851} & & \text{Me} & & \text{H} & & 0.099 & & 0.95 & & 9.6 \\
\text{SB-T-12852-1} & & \text{cyc/o-Pr} & & \text{MeO} & & 0.092 & & 0.48 & & 5.2 \\
\text{SB-T-12853-1} & & \text{Et} & & \text{MeO} & & 0.34 & & 0.57 & & 1.7 \\
\text{SB-T-12855-1} & & \text{MeO} & & \text{MeO} & & 0.078 & & 0.50 & & 6.4 \\
\text{SB-T-12851-3} & & \text{Me} & & \text{N}_3 & & 0.092 & & 0.34 & & 3.7 \\
\text{SB-T-12852-3} & & \text{cyc/o-Pr} & & \text{N}_3 & & 0.092 & & 0.45 & & 4.9 \\
\text{SB-T-12855-3} & & \text{MeO} & & \text{N}_3 & & 0.076 & & 0.40 & & 5.3 \\
\end{align*}
\]

The conjugates of the present invention are formed by conjugating the fluorotaxoid and an omega-3 fatty acid. Any omega-3 fatty acid can be used in accordance with the present invention. Examples of omega-3 fatty acids include docosahexaenoic acid (DHA), eicosapentaenoic acid (EPA), and \(\alpha\)-linolenic acid (LNA). The structures of these fatty acids are shown below (see formula (4), (5) and (6)): 
(4): Docosahexaenoic acid (DHA)

(5): Eicosapentanoic acid (EPA)

(6): α-Linolenic acid (LNA)
DHA can be isolated, for example, from fish oil, or can be chemically synthesized. Preferably, DHA is produced by biological synthesis, such as by the methods disclosed in U.S. Patent Numbers 5,374,657; 5,492,938; 5,407,957 and 5,397,591, the specifications of which are hereby incorporated by reference. DHA can also be purchased from, for example, Martek Biosciences Corporation, Columbia, MD.

EPA can be isolated from, for example, marine oils (i.e., fish and shellfish). Marine oils are produced from the body of fatty fish, livers of lean fish, as well as from blubber of marine mammals, such as whales and seals. Commercial fish oils include inter alia the oils of anchovy (Engraulis spp.), capelin (Mallotus spp.), cod and cod liver (fiadus spp.), herring (Cupea spp.), horse mackerel (Scomber spp.), tuna (Euthynnus spp.), menhaden (revoortia spp.), salmon (Salmo salar, syn. Oncorhynchiiis spp.), rainbow trout (Oncorhynchus mykiss), and sardine (Salāina spp.). Marine oils form a significant proportion (2-3%) of the world's edible oil production. The relative amount of EPA and DHA varies from 5-20 and 3-26% of fatty acids.


Alternatively, the omega-3 fatty acid can be synthesized by any method known in the art. For instance, EPA can be synthesized through desaturation and elongation of dietary LNA (A. Kamal-Eldin and N. V. Yanishlieva, Eur. J. Lipid Sci. Technol. (2002), 104, 825-836). EPA can also be commercially obtained from, for example, Sigma-Aldrich Chemicals Co. (St. Louis, MO).

A fluorotaxoid-omega-3 fatty acid conjugate can be prepared by coupling an omega-3 fatty acid to the C-2' hydroxyl group of a fluorotaxoid by any method known to those in the art. The coupling reaction can occur in one or more steps. For example, selective covalent
coupling of an omega-3 fatty acid to the C-2' hydroxyl of a fluorotaxoid can be achieved in a single step by using any dehydrating agent known to those in the art.

Examples of suitable dehydrating agents include dicyclohexylcarbodiimide (DCC) and diisopropylcarbodiimide (DIC). The dehydrating agent can be used in the presence or absence of an amine base such as, for instance, 4-\(\text{N,\text{N}}\)-dimethylaminopyridine (DMAP).

A general scheme for preparing omega-3 fatty acid-fluorotaxoid conjugates is shown below. In this scheme, DHA is used as the omega-3 fatty acid. Other omega-3 fatty acids, such as those described above, can be coupled to the C-2' hydroxyl group of a fluorotaxoid in the same manner.

![Diagram](image)

Omega-3 fatty acids can be unstable in the presence of oxygen. Measures can be taken to stabilize the fluorotaxoid-fatty acid conjugates. For example, anti-oxidants can be added to the conjugates after synthesis. Examples of suitable anti-oxidants include, but are not limited to, ascorbic acid, ascorbyl palmitate, dilauryl ascorbate, hydroquinone, butylated
hydroxyanisole, sodium meta bisulfite, t-β-carotene and α-tocopherol. Heavy metal chelators, such as ethylenediamine tetraacetic acid (EDTA) can also be used.

The fluorotaxoid compounds in the conjugate are either uncharged or in the form of pharmaceutically acceptable salts. The term "pharmaceutically acceptable salt" refers to a salt prepared from a suitable taxoid conjugate and, for example, an acid or a base. The salt is acceptably non-toxic and has acceptable pharmacokinetics. Such salts are formed by well known procedures.

Suitable acids for producing salts of the fluorotaxoids used in the invention include mineral acids and organic acids. Some examples of mineral acids include hydrochloric, hydriodic, hydrobromic, phosphoric, metaphosphoric, nitric and sulfuric acids. Some examples of organic acids include tartaric, acetic, citric, maleic, malic, benzoic, glycollic, gluconic, gulonic, succinic, arenesulfonic, e.g. p-toluenesulfonic acids, and the like.

Suitable bases for producing salts of the compounds of the invention include inorganic bases and organic bases. Some examples of inorganic bases include ammonia and the hydroxides of lithium, sodium, potassium, magnesium and calcium. Some examples of organic bases include primary, secondary, and tertiary alkyl amines.

In another aspect, the invention is directed to a pharmaceutical composition comprising a conjugate according to formula (1) or formula (3) and a pharmaceutically acceptable carrier. Compositions may, for example, be pills, capsules, solutions, creams, etc.

In this specification, a pharmaceutically acceptable carrier is considered to be synonymous with a vehicle or an excipient as understood by practitioners in the art. Examples of carriers include starch, milk, sugar, certain types of clay, gelatin, stearic acid or salts thereof, magnesium or calcium stearate, talc, vegetable fats or oils, gums and glycols.

The pharmaceutical formulation may also include one or more of the following: a stabilizer, a surfactant, preferably a nonionic surfactant, and optionally a salt and/or a buffering agent.

The stabilizer may, for example, be an amino acid, such as for instance, glycine, alanine, or leucine; or an oligosaccharide, such as for example, sucrose, tetralose, lactose or a dextran. Alternatively, the stabilizer may be a sugar alcohol, such as for instance, mannitol;
or a combination thereof. Preferably the stabilizer or combination of stabilizers constitutes from about 0.1% to about 10% weight for weight of the fluorotaxoid fatty acid conjugate.

The surfactant may be, for example, an ionic surfactant, such as a polyacrylate. Alternatively, the surfactant may be a nonionic surfactant, such as a polyethylene glycol, polyoxyethylene polyoxypropylene glycol, or polysorbate. Some examples of such non-ionic surfactants include Tween 20, Tween 80, and Pluronic F-68 at from about 0.001% (w/v) to about 10% (w/v).

The salt or buffering agent may be any salt or buffering agent, such as, for example, sodium chloride; sodium or potassium phosphates; citric acid; sodium or potassium citrates; or a mixture thereof. The buffering agent is useful for maintaining the pH of the compounds of the invention. The salt and/or buffering agent is also useful to maintain the osmolality at a level suitable for administration to a mammal. For example, the salt or buffering agent can be present at a roughly isotonic concentration of about 150 mM to about 300 mM.

The pharmaceutical compositions of the invention may additionally contain one or more conventional additives. Some examples of such additives include a solubilizer, such as, for example, glycerol; an antioxidant such as, for example, benzalkonium chloride (a mixture of quaternary ammonium compounds, known as "quart"), benzyl alcohol, chloretone or chlorobutanol; an anaesthetic agent such as, for example, a morphine derivative; or an isotonic agent, etc. As a further precaution against oxidation or other spoilage, the pharmaceutical compositions of the invention may be stored under nitrogen gas in vials sealed with impermeable stoppers.

When aqueous suspensions are used for oral administration, emulsifying and/or suspending agents are commonly added. In addition, coloring, sweetening and/or flavoring agents may be added to the oral compositions.

Pharmaceutical compositions are preferably sterile. The pH of the solutions can be suitably adjusted and buffered. For intravenous use, the total concentration of the solute(s) can be controlled in order to render the preparation isotonic.

Carrier compositions deemed to be suited for topical use include gels, salves, lotions, creams, ointments and the like. The compounds can also be incorporated with a support base or matrix or the like which can be directly applied to skin.
In another aspect, the invention is directed to inhibiting the growth of cancer cells in a mammal in need thereof. In the method, an effective amount of a conjugate of fluorotaxoid and omega-3 fatty acid is administered to a mammal.

The cancer cells can be any type of cancer treatable by the taxoid compounds. For example, the cancer can be breast, ovary, lung, head, neck, colon, pancreatic, melanoma, brain, prostate, or renal cancer.

Any mammal in need thereof can be treated in accordance with the present invention. Mammals include, for example, humans, baboons, and other primates, as well as pet animals such as dogs and cats, laboratory animals such as rats and mice, and farm animals such as horses, sheep, and cows.

The method of the invention comprises administering an effective amount of the fluorotaxoid/omega-3 fatty acid conjugate. An effective amount of the conjugate is any amount effective in treating cancer or for inhibiting the growth of cancer cells in a mammal in need thereof.

The actual administered amount of the conjugate will vary according to various factors well known in the art, e.g., the type of cancer, the particular fluorotaxoid being administered, the mode of administration, and the particular subject being treated. The amount required for effective treatment is governed by pharmacological standards and by the discretion of medical practitioners in the art. For example, the effective amount can be determined during clinical and pre-clinical trials by methods familiar to physicians and clinicians.

The minimum amount of a conjugate administered to a human is the lowest amount capable of inhibiting the growth of cancer cells. The maximum amount is the highest effective amount that does not cause undesirable or intolerable side effects. The minimum amount can be, for example, 0.01, 0.05, or 0.1 milligrams per kilogram body weight per day. The maximum amount can be, for example, 10, 50, or 100 milligrams per kilogram body weight per day. Higher doses may be employed to treat the cancer to the extent patient tolerance permits.

The fluorotaxoid/omega-3 fatty acid conjugates may be administered alone or as an adjunct with other conventional drugs for treating cancer. The adjunctive drugs can be, for
example, chemotherapy drugs. Some examples of chemotherapy drugs include methotrexate (Abitrexate®), fluorouracil (Adrucil®), hydroxyurea (Hydrea®), and mercaptopurine (Purinethol®).

The conjugates may be administered by any suitable method known in the art. Some examples of suitable modes of administration include oral, systemic, and topical administration.

For oral administration, liquid or solid oral formulations can be used, as known in the art. Some examples of formulations suitable for oral administration include tablets, capsules, pills, troches, elixirs, suspensions, and syrups.

Systemic administration includes enteral or parenteral modes of administration, e.g., intravenous; intramuscular; subcutaneous; or intraperitoneal modes of administration. For example, the conjugates may be administered by injection of a solution or suspension; or intranasally, in the form of, for example, a nebulizer, liquid mist, or intranasal spray; or transdermally, in the form of, for example, a patch; or rectally, in the form of, for example, a suppository; or intrabronchially, in the form of, for example, an inhaler spray.

Suitable carrier compositions for topical use include gels, salves, lotions, creams, ointments, and the like. The compounds can also be incorporated with a support base or matrix or the like which can be directly applied to skin.

The timing of the administration of the conjugates may also be modified. For example, the conjugates may be administered intermittently or by controlled release. Controlled release administration is a method of drug delivery to achieve a certain level of the drug over a particular period of time. See, for example, U.S. Patent Publication No. 2004/01 15261, incorporated herein by reference.

The following non-limiting examples are illustrative of the present invention. It should be noted that various changes would be made in the above examples and processes therein without departing from the scope of the present invention. For this reason, it is intended that the illustrative embodiments of the present application should be interpreted as being illustrative and not limiting in any sense.
EXAMPLES

Example 1. Synthesis of 4-difluorovinyl β-lactam

(3R,4S)-3-AcO-β-lactam was prepared through [2+2] ketene-imine cycloaddition, followed by enzymatic optical resolution of racemic β-lactam (Scheme 111-20).

Scheme HI-20. Synthesis of (3J?,4S)-3-AcO-β-lactam

The protecting group of the 3-acetoxamo moiety of (3/?,4S)-3-AcO-β-lactam was changed to triisopropylsilyl (TIPS). The resulting (3/?,4S)-l-PMP-3-TIPSO-4-(2-methyl-1-propenyl)azetidin-2-one II-(-+) was subjected to ozonolysis to give (3/?,4S)-l-PMP-3-TIPSO-4-formylazetidin-2-one 111-147 (Scheme 111-21).

Scheme HI-21. Synthesis of (3J?,4S)-l-PMP-3-TIPSO-4-formylazetidin-2-one

Enantiopure (3/?,4S)-l-PMP-3-TIPSO-4-formylazetidin-2-one 111-147 was transformed to (3R,4S)-l-PMP-3-TIPSO-4-difluorovinyl-2-one 111-48 using CBπF2, hexamethyldiphosphorous triamide (HMPA), and Zn in THF (Scheme 111-22).
Finally the PMP group was removed using cerium ammonium nitrate (CAN) to give enantiopure (3R,4S)-3-TIPS-4-difluorovinylazetidin-2-one III-49(+) followed by carbalkoxylation with di-f-butyl dicarbonate (BOC₂O) to give desired (3R,4S)-N-Boc-3-TIPS-4-difluorovinylazetidin-2-one III-50 in excellent yields (Scheme 111-24).

**Example 2. Synthesis of C-3' Difluorovinyl Second-Generation Taxoids**

The synthesis of baccatin core was performed using literature methods starting from 10-DAB, yielding III-41 or III-43 in high yields (Scheme III-25).
The ring-opening coupling of β-lactams with modified baccatins was carried out at -40°C in THF using LiHMDS. The subsequent removal of the silyl protecting groups by HF/pyridine gave the corresponding new difluorovinyl-taxoids III-51 in fairly good overall yields (Scheme 111-26).

Example 3. 1-(4-Methoxyphenyl)-3-triisopropylsilanyloxy-4-(2,2-difluorovinyl)azetidin-2-one (111-48)

To a solution of dibromodifluoromethane (1.97 mL, 12.79 mmol) in THF (85 mL)
were added hexamethylphosphorous triamide (4.79 mL, 25.56 mmol) and Zn (1.67 g, 25.56 mmol) at -78 °C. The mixture was allowed to warm slowly to -10 °C. The mixture was stirred for additional 30 min at -10 °C and ether was added to the reaction mixture. The ether layer was decanted and the residue was washed with dichloromethane and water. The combined organic layers were washed with saturated copper sulfate solution until the blue color stayed, and dried over MgSO4. The filtrate was concentrated under reduced pressure to give yellow oil. Crude material was purified by flash chromatography on silica gel to yield 111-48 (688 mg, 68%): 1H NMR (CDCl3, 300 MHz): δ 1.08-1.15 (21 H, m), 3.79 (3 H, s), 4.54 (1 H, ddd, J = 1.5, 6.3, 16.5 Hz), 4.83 (1 H, m), 5.14 (1 H, d, J = 5.1 Hz), 6.87 (2H, d, J = 9.0 Hz). 7.32 (2H, d, J = 9.0 Hz); 13C NMR (CDCl3, 75.5 MHz): δ 12.1, 17.9, 54.1 (d, J = 8.5 Hz), 55.8, 75.8 (dd, J = 5.0, 22.1 Hz), 76.9, 77.4, 114.8, 118.6, 130.9, 156.7, 164.9; 19F NMR (282 MHz, CDCl3): δ -80.80 (d, IF, J = 32.7 Hz), -86.34 (dd, IF, J = 2.8 Hz, J = 28.2). LRMS (FAB+, m/z): Calcd. for C2iH3iF2NO:Si+H+, 412.21; Found, 412.217.

Example 4. 3-Triisopropylsiloxy-4-(2,2-difluorovinyl)azetidin-2-one (HI-49)

To a solution of N-PMP-β-lactam (688 mg, 1.67 mmol) in acetonitrile (50 mL) and water (10 mL), was added dropwise a solution of eerie ammonium nitrate (3.74 g, 6.69 mmol) in water (40 mL). The reaction mixture was stirred for 2 h. Work up with water and saturated Na2SU3 solution. The aqueous layer was extracted with EtOAc, and the combined organic layer was washed with water, dried over MgSO4 and concentrated. The crude product was purified on a silica gel column to yield the β-lactam 111-49 as a pale yellow oil (469 mg, 92% yield): 1H NMR (CDCl3, 400 MHz): δ 1.03-1.18 (21 H, m), 4.44-4.54 (2 H, m), 5.04 (1 H, dd, J = 1.6, 2.4 Hz), 6.59 (1 H, bs); 13C NMR (CDCl3, 100 MHz): δ 12.1, 17.8 (d, J = 4.6 Hz), 50.4 (d, J = 7.6 Hz), 77.1 (dd, J = 15.9, 23.5 Hz), 79.3, 157.6 (t, J = 289.9 Hz), 169.4; 19F NMR (282 MHz, CDCl3): δ -82.33 (d, IF, J = 34.7 Hz), -87.50 (dd, IF, J = 9.3, 25.7 Hz).

Example 5. 1-(ferf-Butoxycarbonyl)-3-triisopropylosiloxy-4-(2,2-difluorovinyl)azetidin-2-one (π i-50)

To a solution of 4-(2,2-difluorovinyl)-β-lactam III-49 (469 mg, 1.54 mmol), triethylamine (0.75 mL, 4.62 mmol), and DMAP (43 mg, 0.35 mmol) in CH2Ch(9 mL), was
added Boc2Θ (398 mg, 1.77 mmol) at room temperature. The reaction mixture was stirred for 18 hours and quenched with water. The reaction mixture was diluted with ethylacetate (EtOAc) and the organic layer was washed with brine, dried over MgSO₄ and concentrated under reduced pressure. Crude material was purified by flash chromatography on silica gel to give 1-Boc-4-(2,2-difluorovinyl)-β-lactam 111-50 as yellow oil (599 mg, 96% yield): [α]D²⁰ +24.17 (c 14.4, CHCl₃); ¹H NMR (CDCl₃, 400 MHz): δ 1.04-1.17 (21 H, m), 1.49 (9 H, s), 4.49 (1 H, ddd, J = 1.6, 13.8, 23.7 Hz), 4.75 (1 H, dddd, J = 0.9, 2.4, 5.1, 9.0 Hz), 5.04 (1 H, d, J = 5.7 Hz), 6.59 (1 H, bs); ¹³C NMR (CDCl₃, 100 MHz): δ 12.0, 17.8 (d, J = 5.3 Hz), 28.2, 53.6 (d, J = 8.4 Hz), 74.5 (dd, J = 10.6, 26.5 Hz), 77.2, 83.9, 147.9, 158.5 (t, J = 292.2 Hz), 165.3; ¹⁹F NMR (282 MHz, CDCl₃): δ -81.20 (d, IF, J = 31.0 Hz), -85.83 (dd, IF, J = 5.6 Hz, J = 29.3). HRMS (FAB+, m/z): Calcd. for C₄₁H₃₃F₂N₂O₁₅H⁺, 836.3300; Found, 836.3278.

Example 6. 10-Acetyl-3'-dephenyl-3'-(2,2-difluorovinyl)docetaxel, SB-T-12851 (Ill-Sla)

Yield 83 %; white solid; mp 155-160 °C; [α]D²⁰ -74.83 (c 2.86, CHCl₃); ¹H NMR (CDCl₃, 400 MHz): δ 1.15 (3H, s, C-16), 1.25 (3H, m, C-17), 1.30 (9H, s, Boc), 1.68 (3H, s, H-19), 1.75 (bs, 1H, OH), 1.88 (4H, m, H-6b), 2.24 (3H, s, 10-OAc), 2.33 (2H, m, H-14), 2.39 (3H, s, 4-OAc), 2.49 (IH, d, J = 3.6 Hz, OH), 2.55 (IH, d, J = 6.4, 9.6, 14.8 Hz, H-6a), 3.52 (IH, d, J = 5.6 Hz, OH), 3.81 (IH, d, J = 7.2 Hz, H-3), 4.17 (IH, d, J = 8.4 Hz, H-20b), 4.28 (1H, s, J = 2.8 Hz, H-2'), 4.31 (IH, d, J = 8.4 Hz, H-20a), 4.44 (IH, m, H-7), 4.58 (IH, d, J = 1.2, 9.6, 24.8 Hz, H-3'-vinyl), 4.87 (IH, t, J = 8.8 Hz, H-3'), 4.96 (2H, d, J = 9.6, H-5, NH-3'), 5.66 (1H, d, J = 7.2 Hz, H-2), 6.24 (1H, t, J = 8.8 Hz, H-13), 6.30 (IH, s, H-IO), 7.49 (2H, t, J = 7.6 Hz), 7.61 (IH, t, J = 7.2 Hz), 8.11 (2H, d, J = 7.6 Hz); uC NMR (CDCl₃, 100 MHz) δ 9.8, 14.4, 15.1, 21.1, 22.1, 22.5, 26.9, 28.3, 35.7 (d, J = 13.7 Hz), 43.5, 45.7, 48.2, 58.8, 72.4, 72.9, 75.8, 76.7, 79.3, 80.7, 81.3, 84.6, 128.9, 129.3, 130.4, 133.4, 133.9, 142.4, 155.1, 156.7, 158.0, 167.3, 170.5, 171.5, 172.7, 203.9; ¹⁹F NMR, (CDCl₃, 282 MHz) δ -84.29 (1F, dd, J = 25.7, 36.4 Hz), -86.22 (1F, dd, J = 34.7 Hz); HRMS (FAB+, m/z): Calcd. for C₄₁H₃₃F₂N₂O₁₅-H⁺, 836.3300; Found, 836.3278.
Example 7. 3'-dephenyl-3'-(2,2-difluorovinyl)-10-cyclopropanecarbonyl-docetaxel, SB-T-12852 (UI-51b)

Yield 88 %; white solid; mp 171-177 °C; [α]D20 73.71 (c 5.44, CHCb); 1H NMR (CDCl3, 400 MHz): δ 0.98 (2 H, m, CHs-c-Pr), 1.13 (2 H, m, CFb-c-Pr), 1.15 (3H, s, C-16), 1.26 (3H, m, C-17), 1.30 (9H, s, Boc), 1.66 (3H, m, H-19), 1.78 (2 H, m, OCH-c-Pr), 1.87 (4H, m, H-6b, H-18), 2.31 (2H, m, H-14), 2.38 (3H, s, 4-OAc), 2.53 (IH, ddd, J = 6.8, 10.0, 15.2 Hz, H-6a), 2.59 (IH, d, J = 3.2 Hz, OH), 3.57 (IH, bs, OH), 3.80 (IH, d, J = 6.8 Hz, H-3), 4.17 (IH, d, J = 8.4 Hz, H-20b), 4.28 (2 H, m, H-2'), H-20a), 4.40 (IH, m, H-7), 4.58 (IH, ddd, J = 1.6, 9.6, 24.8 Hz, H-3'-vinyl), 4.87 (IH, t, J = 8.8 Hz, H-3'), 4.97 (2H, m, H-5', NH'), 5.66 (IH, d, J = 7.2 Hz, H-2), 6.24 (1H, t, J = 8.0 Hz, H-13), 6.29 (IH, s, H-IO), 7.49 (2H, t, J = 7.6 Hz), 7.60 (IH, t, J = 7.6 Hz), 8.11 (2H, d, J = 7.2 Hz); 13C NMR (CDCl3, 100 MHz) δ 9.4, 9.6, 9.8, 13.2, 22.5, 27.0, 28.3, 35.7, (d, J = 5.3 Hz), 43.5, 45.9, 48.2, 58.8, 72.4, 72.9, 73.3, 75.3, 75.6, 76.6, 79.3, 80.7, 81.3, 84.7, 128.9, 129.3, 130.4, 133.4, 133.9, 142.4, 155.1, 156.7, 167.3, 170.5, 172.6, 175.3, 204.0; 19F NMR, (CDCl3, 282 MHz) δ -84.32 (1 F, dd, J = 25A, 36.4 Hz), -86.30 (1 F, dd, J = 36.7 Hz); HRMS (FAB +, m/z): Calcd. for C43H53F2NO15-H+, 862.3456; Found, 862.3445.

Example 8. 3'-Dephenyl-3'-(2,2-difluorovinyl)-10-propanoyl-docetaxel, SB-T-12853 (III-Sle)

Yield 64 %; white solid; mp 175-181 °C; [α]D20 -82.83 (c 5.01, CHCb); 1HNMR(CDCl3, 400 MHz): δ 1.14 (3H, s, H-16), 1.24 (6H, m, H-17, H-IO-CH3), 1.30 (9H, s, Boc), 1.67 (3H, s, H-19), 1.78 (1 H, m, OH), 1.87 (4H, m, H-6b, H-18), 2.31 (2H, m, H-14), 2.38 (3H, s, 4-OAc), 2.53 (4H, m, H-6a, H-10, CH2, OH), 3.55 (IH, bs, OH), 3.81 (IH, d, J = 6.8 Hz, H-3), 4.17 (IH, d, J = 8.4 Hz, H-20b), 4.29 (2H, m, H-2', H-20a), 4.39 (IH, m, H-7), 4.56 (IH, ddd, J = 1.6, 9.6, 24.8 Hz, H-3'-vinyl), 4.86 (IH, t, J = 8.8 Hz, H-3'), 4.96 (2H, m, H-5, NH'), 5.66 (IH, d, J = 7.2 Hz, H-2), 6.25 (1H, t, J = 8.4 Hz, H-13), 6.30 (IH, s, H-10), 7.49 (2H, t, J = 7.6 Hz), 7.60 (IH, t, J = 7.2 Hz), 8.11 (2H, d, J = 7.2 Hz); 13C NMR (CDCl3, 100 MHz) δ 9.2, 9.8, 15.1, 22.1, 22.5, 26.9, 27.8, 28.4, 35.7 (d, J = 12.9 Hz), 43.5, 45.9, 48.2, 58.8, 72.2, 72.4, 72.9, 73.3, 75.3, 75.6, 76.6, 77.4, 79.3, 80.7, 81.3, 84.6, 128.9, 129.3, 130.4, 133.5, 133.9, 142.2, 155.1, 156.7, 167.3, 170.5, 172.6, 174.8, 203.9; 19F NMR, (CDCl3, 282 MHz) δ -84.31 (1 F, dd, J = 23.7, 34.7 Hz), -86.23 (1 F, dd, J = 36.4 Hz); HRMS (FAB +, m/z):
$m/z$: Calcd. For C42H53F2NOis-H+, 850.3456; Found 850.3450.

**Example 9.** 3'-Dephenyl-3'-(2^-difluorovinyl)-10-dimethylcarbamoyldocetaxel,

**SB-T-12854 (π i-51d)**

Yield 84%; white solid; mp 166-170 0°C; [α]$_D^{20}$ -70.48 (c 6.3, CHCb); 1H NMR (CDCb, 400 MHz): δ 1.15 (3H, s, H-16), 1.25 (3H, m, H-17), 1.30 (9H, s, Boc), 1.67 (3H, s, H-19), 1.84 (1H, m, OH), 1.89 (4H, m, H-6b, H-18), 2.31 (2H, m, H-14), 2.38 (3H, s, 4-OAc), 2.53 (1H, ddd, J = 6.8, 9.6, 15.2 Hz, H-6a), 3.64 (1H, d, J = 5.6 Hz, OH), 3.80 (IH, d, J = 6.8 Hz, H-3), 4.17 (IH, d, J = 8.4 Hz, H-20b), 4.29 (2H, m, H-20a), 4.44 (IH, m, H-7), 4.57 (IH, dd, J = 10.0, 25.2 Hz, H-3’-vinyl), 4.86 (IH, t, J = 8.8 Hz, H-3’), 4.97 (1H, d, J = 9.2 Hz, NH-3’), 5.02 (1H, m, H-5), 5.66 (IH, d, J = 7.2 Hz, H-2), 6.24 (2H, m, H-13, H-IO), 7.49 (2H, t, J = 7.6 Hz), 7.59 (IH, t, J = 7.2 Hz), 8.10 (2H, d, J = 7.6 Hz); 13C NMR (CDCb, 100 MHz) δ 9.6, 15.1, 22.1, 34.2, 35.6 (d, J = 12.1 Hz), 36.3, 36.8, 43.5, 45.8, 48.2, 58.7, 72.6, 72.9, 73.3, 75.4, 76.3, 76.7, 77.4, 79.4, 80.6, 81.3, 84.6, 128.9, 129.4, 130.4, 133.7, 133.9, 142.7, 151.5, 156.3, 167.3, 170.4, 171.3, 203.9; 19F NMR, (CDCb, 282 MHz) δ -84.31 (1F, dd, J = 25.7, 37.2 Hz), -86.23 (1F, dd, J = 36.4 Hz); HRMS (FAB +,

**Example 10.** 3’-Dephenyl-3’-(2^-difluorovinyl)-10-methoxycarbonyldocetaxel,

**SB-T-12855 (iπ -51e)**

Yield 90%; white solid; mp 144-148 0°C; [α]$_D^{20}$ -77.06 (c 6.8, CHCb); iH NMR (CDCb, 400 MHz): δ 1.15 (3H, s, H-16), 1.24 (3H, m, H-17), 1.29 (9H, s, Boc), 1.68 (3H, s, H-19), 1.78 (1H, m, OH), 1.88 (1H, m, H-6b), 1.91 (3H, s, H-18), 2.31 (2H, m, H-14), 2.39 (3H, s, 4-OAc), 2.53 (2H, m, H-6a, OH), 3.55 (1H, d, J = 5.6 Hz, OH), 3.78 (IH, d, J = 7.2 Hz, H-3), 3.86 (3H, s, H-IO-MeO), 4.17 (IH, d, J = 8.4 Hz, H-20b), 4.29 (2H, m, H-2’, H-20a), 4.38 (IH, m, H-7), 4.57 (IH, ddd, J = 1.6, 9.6, 24.8 Hz, H-3’-vinyl), 4.86 (IH, t, J = 8.8 Hz, H-3’), 4.96 (2H, m, H-5, NH), 5.66 (IH, d, J = 6.8 Hz, H-2), 6.11 (IH, s, H-10), 6.23 (2H, t, J = 8.0 Hz, H-13), 7.49 (2H, t, J = 7.6 Hz), 7.60 (1H, t, J = 7.2 Hz), 8.10 (2H, d, J = 7.2 Hz); 13C NMR (CDCb, 100 MHz) δ 9.7, 15.2, 22.1, 22.5, 26.8, 28.3, 35.8 (d, J = 23.5 Hz), 43.4, 45.9, 48.2, 55.8, 58.8, 72.1, 72.3, 72.8, 73.3, 75.2, 76.7, 77.4, 78.4, 79.2, 80.7, 81.2, 84.6, 128.9, 129.3, 130.4, 133.0, 133.9, 143.2, 155.1, 155.9, 156.5, 167.3, 170.6, 172.3, 204.1; 19F NMR,
(CDCl₃, 282 MHz) δ -84.30 (1 F, dd, J = 23.7, 34.7 Hz), -86.22 (1 F, dd, J = 34.7 Hz);
HRMS (FAB+, m/z): Calcd. for C₄₃H₄₇F₂NO₆-H⁺, 852.3249; Found 852.3227.

**Example 11.** 3'-Dephenyl-3-(2^-difluorovinyl)-2-debenzoyl-2-(3-fluorobenzoyl)-10-acetyldocetaxel, SB-T-12851-2 (IH-Slf)

Yield 72%; white solid; [α]D°²⁰ -73.29 (c 7.0 CHCl₃); ¹H NMR (CDCl₃, 400 MHz): δ 1.15 (3H, s, C-16), 1.26 (3H, m, C-17), 1.31 (9H, s, Boc), 1.68 (4H, s, H-19, OH), 1.89 (4H, m, H-6b, H-18), 2.24 (3H, s, 10-OAc), 2.33 (2H, m, H-14), 2.39 (3H, s, 4-OAc), 2.47 (IH, bs, OH), 2.56 (IH, ddd, J = 7.0, 9.5, 15.0 Hz, H-6a), 3.46 (IH, bs, OH), 3.82 (IH, d, J = 7.0 Hz, H-3), 4.16 (IH, d, J = 8.5 Hz, H-20b), 4.28 (1 H, s, H-2'), 4.31 (IH, d, J = 8.5 Hz, H-20a), 4.42 (IH, dd, J = 6.5, 11.0 Hz, H-7), 4.58 (IH, ddd, J = 1.0, 9.0, 26.0 Hz, H-3'vinyl), 4.90 (2H, m, H-3', NH-3'), 4.97 (1 H, dd, J = 2.0, 9.0 Hz, H-5), 5.64 (IH, d, J = 7.0 Hz, H-2), 6.23 (1 H, t, J = 8.0 Hz, H-13), 6.30 (IH, s, H-IO), 7.31 (IH, dt, J = 2.0, 8.0 Hz), 7.49 (IH, ddd, J = 6.0, 8.5, 13.5 Hz), 7.80 (IH, d, J = 9.0 Hz), 7.91 (IH, d, J = 7.5 Hz); ¹³C NMR (CDCl₃, 100 MHz) δ 9.5, 14.8, 20.8, 21.8, 22.2, 26.7, 28.1, 35.5 (d, J = 11.8 Hz), 43.2, 45.6, 58.5, 72.1, 72.5, 73.1, 75.5, 76.3, 79.1, 80.4, 80.9, 84.4, 117.0 (J = 23.2 Hz), 120.8 (J = 21 Hz), 125.9, 129.4 (J = 13.1 Hz), 131.2 (J = 7.4 Hz), 132.9, 142.2, 154.9, 156.7, 160.9, 164.2, 165.9, 170.2, 171.2, 203.5; ¹⁹F NMR (CDCl₃, 282 MHz) δ -84.23 (1 F, dd, J = 25.7, 34.7 Hz), -86.21 (1 F, dd, J = 36.7 Hz), -111.7 (1 F, dd, J = 9.3, 14.6 Hz); HRMS (FAB+, m/z): Calcd. for C₄₃H₄₇F₂NO₆H₂⁺, 854.3205; Found, 854.3207.

**Example 12.** 3'-Dephenyl-3-(2,2-difluorovinyl)-2-debenzoyl-2-(3-fluorobenzoyl)-10-cyclopropanecarbonyldocetaxel, SB-T-12852-2 (IH-Slg)

Yield 78%; white solid; [α]D°²⁰ -77.04 (c 7.1, CHCl₃); ¹H NMR (CDCl₃, 500 MHz): δ 0.99 (2 H, m, CH₂-C-Pr), 1.12 (2 H, m, CH₂-C-Pr), 1.15 (3H, s, C-16), 1.26 (3H, m, C-17), 1.30 (9H, s, Boc), 1.63 (3H, s, H-19), 1.75(2 H, m, OH, CH-c-Pr). 1.86 (IH, m, H-6b), 1.87 (3H, s, H-18), 2.33 (2H, m, H-14), 2.39 (3H, s, 4-OAc), 2.53 (IH, ddd, J = 7.0, 9.5, 15.5 Hz, H-6a), 2.61 (IH, bs, OH), 3.55 (IH, bs, OH), 3.80 (IH, d, J = 7.0 Hz, H-3), 4.17 (IH, d, J = 8.0 Hz, H-20b), 4.28 (IH, s, H-2'), 4.29 (1 H, d, J = 8.0 Hz, H-20a), 4.40 (IH, dd, J = 7.0, 10.5 Hz, H-7), 4.58 (IH, ddd, J = 8.5, 23.5 Hz, H-3'vinyl), 4.86 (IH, m, H-3'), 4.97 (2 H, m, H-5, NH), 5.63 (IH, d, J = 7.0 Hz, H-7), 6.24 (1 H, t, J = 9.5 Hz, H-13), 6.29 (IH, s, H-10), 7.49 (2H,
Example 13. 3’-Dephenyl-3’-(2’,2-difluorovinyl)-2-debenzoyl-2-(3-fluorobenzoyl)-10-
propanoyl-docetaxel, SB-T-12853-2 (III-51h)

Yield 71%; white solid; [α]D20 -71.57(c 8.3, CHCl3); 1H NMR (CDCl3, 500 MHz): δ 1.14 (3H, s, H-16), 1.24 (6H, m, H-17, H-IO-CH3), 1.31 (9H, s, Boc), 1.67 (3H, s, H-19), 1.72 (1H, bs, OH), 1.88 (4H, m, H-6b, H-18), 2.32 (2H, m, H-14), 2.39 (3H, s, 4-OAc), 2.53 (3H, m, H-6a, H-IO, CH2), 3.51 (IH, bs, OH), 3.82 (IH, d, J = 7.0 Hz, H-3), 4.16 (IH, d, J = 8.5 Hz, H-20b), 4.28 (IH, d, J = 1.5 Hz, H-2’), 4.30 (1H, t, J = 8.5 Hz, H-20a), 4.42 (IH, dd, J = 6.5, 10.5 Hz, H-7), 4.58 (IH, ddd, J = 1.5, 9.0, 24.5 Hz, H-3’), 4.87 (IH, m, H-3’), 4.96 (2H, m, H-5, NH-3’), 5.64 (IH, d, J = 6.5 Hz, H-2), 6.23 (1H, t, J = 8.0 Hz, H-13), 6.31 (IH, s, H-10), 7.31 (IH, dt, J = 2.0, 7.0 Hz), 7.48 (IH, ddd, J = 5.5, 7.5, 13.0 Hz), 7.80 (IH, d, J = 8.5 Hz), 7.91 (IH, d, J = 7.5 Hz); 13C NMR (CDCl3, 125 MHz) δ 8.9, 9.5, 14.8, 21.9, 22.2, 26.7, 27.5, 28.1, 35.5 (d, J = 10.3 Hz), 43.2, 45.6, 58.5, 72.1, 72.5, 73.1, 75.3, 75.4, 76.3, 79.1, 80.9, 84.4, 116.9 (d, J = 23.8 Hz), 120.8 (d, J = 21.2 Hz), 125.9, 130.4 (d, J = 7.5 Hz), 131.3 (d, J = 7.4 Hz), 133.0, 142.1, 154.6, 160.9, 164.2, 165.8, 170.2, 174.6, 203.6; 19F NMR, (CDCl3, 282 MHz) δ -84.24 (IF, dd, J = 23.9, 34.9 Hz), -86.22 (IF, d, J = 36.4 Hz); HRMS (FAB+, m/z): Calcd. for C43Hs2F3NOi5-H+, 868.3362; Found, 868.3352.

Example 14. 3’-Dephenyl-3’-(2,2-difluorovinyl)-2-debenzoyl-2-(3-fluorobenzoyl)-10-
dimethylcarbamoyl-docetaxel, SB-T-128S4-2 (III-5H)

Yield 71%; white solid; [α]D20 -85.33 (c 1.5, CHCl3); 1H NMR (CDCl3, 500 MHz): δ 1.16 (3H, s, H-16), 1.26 (3H, m, H-17), 1.31 (9H, s, Boc), 1.60 (IH, OH), 1.67 (3H, s, H-19), 1.84 (1H, m, OH), 1.89 (IH, m, H-6b), 1.91 (3H, s, H-18), 2.33 (2H, m, H-14), 2.40 (3H, s, 4-
OAc), 2.55 (1H, ddd, J = 6.0, 9.5, 14.5 Hz, H-6a), 2.97 (3H, s, NMe), 3.05 (3H, s, N-Me), 3.40 (1H, s, OH), 3.82 (IH, d, J = 7.0 Hz, H-3), 4.17 (IH, d, J = 7.5 Hz, H-20b), 4.29 (IH, s, H-2\'), 4.31 (1H, d, J = 7.5 Hz, H-20a), 4.45 (IH, dd, J = 6.0, 10.5 Hz, H-7), 4.58 (IH, m, H-3' vinyl), 4.87 (2H, bs, H-3', NH-3'), 4.99 (IH, d, J = 8.0 Hz, H-5), 5.64 (IH, d, J = 7.0 Hz, H-2), 6.26 (2H, m, H-13, H-IO), 7.32 (2H, dt, J = 2.0, 8.0 Hz), 7.49 (IH, ddd, J = 6.0, 8.5, 13.5 Hz), 7.81 (1H, d, J = 9.5 Hz), 7.92 (1H, d, J = 8.0 Hz); 13C NMR (CDCl$_3$, 125 MHz) δ 9.3, 14.7, 22.3, 26.9, 28.1, 35.4 (d, J= 6.0 Hz), 36.0, 36.6, 43.2, 45.5, 58.5, 72.4, 72.7, 73.1, 75.6, 76.1, 76.4, 77.2, 79.3, 80.4, 81.1, 84.6, 110.7 (d, J = 15.1 Hz), 120.8 (d, J = 21.2 Hz), 125.9, 130.4 (d, J = 7.7 Hz), 131.3 (d, J = 7.5 Hz), 133.9, 142.7, 155.1, 157.4, 161.2, 164.1, 166.1, 170.2, 172.3, 205.5; 19F NMR, (CDCl$_3$, 282 MHz) δ -84.13 (1F, dd, J = 25.4, 36.4 Hz), -86.13 (1F, d, J = 36.6 Hz), -111.73 (IF, dd, J = 9.3, 14.6 Hz); HRMS (FAB+, m/z): Calcd. for C$_{41}$H$_{35}$F$_3$N$_2$O$_{16}$H$^+$, 883.3471; Found 883.3433.

**Example IS.** 3'-Dephenyl-3'-(2^-difluorovinyl)-2-debenzoyl-2-(3-fluorobenzoyl)-10-methoxycarbonyldoctaxel, SB-T-12855-2 (III-SI)j

Yield 72% ; white solid; [$\alpha$]$_D^{20}$ -70.31 (c 6.5, CHCl$_3$); 1H NMR (CDCl$_3$, 500 MHz): δ 1.15 (3H, s, H-16), 1.25 (3H, m, H-17), 1.29 (9H, s, Boc), 1.65 (IH, bs, OH), 1.69 (3H, s, H-19), 1.88 (1H, m, H-6b), 1.92 (3H, s, H-18), 2.31 (2H, m, H-14), 2.39 (3H, s, 4-OAc), 2.46 (IH, bs, OH), 2.57 (1H, ddd, J = 6.0, 9.0, 15 Hz, H-6a), 3.48 (IH, bs, OH), 3.79 (IH, d, J = 7.5 Hz, H-3), 3.87 (3H, s, H-IO-MeO), 4.16 (IH, d, J = 8.5 Hz, H-20b), 4.28 (IH, s, H-2\'), 4.31 (1H, d, J = 8.5 Hz, H-20a), 4.39 (IH, dd, J = 7.0, 10.5 Hz, H-7), 4.58 (IH, dd, J = 9.0, 24.5 Hz, H-3' vinyl), 4.87-4.94 (2H, m, H-3', NH-3'), 4.97 (IH, d, J = 8.0 Hz, H-5), 5.65 (IH, d, J = 7.0 Hz, H-2), 6.12 (1H, s, H-IO), 6.23 (2H, t, J = 9.0 Hz, H-13), 7.31 (1H, dt, J = 2.5, 8.5 Hz), 7.49 (IH, ddd, J = 5.0, 7.5, 13.5 Hz), 7.79 (1H, d, J = 8.5 Hz), 7.91 (1H, d, J = 8.0 Hz); 13C NMR (CDCl$_3$, 125 MHz) δ 9.4, 14.9, 21.8, 22.2, 26.6, 28.1, 35.3, 35.6, 43.1, 45.6, 47.9, 55.6, 58.5, 72.1, 72.5, 73.1, 75.4, 76.3, 78.2, 79.2, 80.5, 81.0, 84.6, 117.1 (d, J = 23.5 Hz), 120.8 (d, J = 21.4 Hz), 126.0, 130.4 (d, J = 8.0 Hz), 131.3 (d, J= 7.5 Hz), 132.7, 143.1, 154.9, 155.7, 160.9, 164.2, 165.9, 170.3, 203.8; 19F NMR, (CDCl$_3$, 282 MHz) δ -84.15 (IF, dd, J = 25.4, 36.4 Hz), -86.17 (IF, d, J = 36.7 Hz), -111.71 (1F, dd, J = 9.3, 14.6 Hz); HRMS (FAB+, m/z): Calcd. for C$_{41}$H$_{35}$F$_3$N$_2$O$_{16}$H$^+$, 870.3154; Found 870.3146.
Example 16. 3′-Dephenyl-3′-(2 2-difluorovinyl)-2-debenzoyl-2-(3-chlorobenzoyl)-10-acetyldocetaxel, SB-T-12851-4 (π i-Slk)

Yield 57%; white solid; mp 0°C; [α]D²⁰ 72.93 (c 4.1, CHCl₃); ¹H NMR (CDCl₃, 500 MHz): δ 1.14 (3H, s, C-16), 1.25 (3H, m, C-17), 1.31 (9H, s, Boc), 1.67 (3H, s, H-19), 1.73 (IH, s, OH), 1.89 (4H, m, H-6b, H-18), 2.24 (3H, s, 10-OAc), 2.33 (2H, d, J = 8.5 Hz, H-14), 2.39 (3H, s, 4-OAc), 2.51 (IH, d, J = 3.5 Hz, OH), 2.55 (IH, ddd, J = 6.5, 9.0, 15.0 Hz, H-6a), 3.51 (IH, bs, OH), 3.81 (IH, d, J = 7.5 Hz, H-3), 4.15 (IH, d, J = 8.5 Hz, H-20b), 4.29 (2H, m, H-2′, H-20a), 4.41 (IH, ddd, J = 6.5, 11.0 Hz, H-7), 4.58 (IH, ddd, J = 10.0, 24.5 Hz, H-3′vinyl), 4.86 (IH, m, H-3′), 4.93 (IH, d, J = 9.0 Hz, NH-3′), 4.98 (1H, d, J = 7.5, H-5), 5.62 (IH, d, J = 7.5 Hz, H-2), 6.21 (1H, t, J = 9.5 Hz, H-13), 6.30 (IH, s, H-IO), 7.45 (IH, t, J = 7.5 Hz), 7.58 (IH, ddd, J = 1.5, 8.5 Hz), 8.00 (IH, d, J = 7.5 Hz), 8.12 (1H, s); ¹³C NMR (CDCl₃, 125 MHz) δ 9.5, 14.8, 20.8, 21.8, 22.1, 26.7, 28.1, 35.4 (d, J = 16.7 Hz), 43.1, 45.6, 58.5, 72.1, 72.5, 73.1, 75.5, 76.3, 79.2, 80.4, 80.9, 84.3, 128.2, 130.0, 130.3, 130.9, 132.9, 134.8, 142.2, 154.8, 165.7, 170.2, 171.2, 203.5; ¹⁹F NMR, (CDCl₃, 282 MHz) δ -84.15 (IF, dd, J = 25.7, 36.7Hz), -86.12 (1F, dd, J=36.7 Hz); HRMS (FAB+, m/z): Calcd. for C₄H₅F₂NO₃⁻H⁺, 870.2910; Found, 870.2891.

Example 17. 3′-Dephenyl-3′-(2^difluorovinyl)-2-debenzoyl-2-(3-chlorobenzoyl)-10-cyclopropanecarboxyldocetaxel, SB-T-12852-4 (III-511)

Yield 73%; white solid; mp 0°C; [α]D²⁰ 78.97 (c 5.8, CHCl₃); ¹H NMR (CDCl₃, 400 MHz): δ 1.02 (2H, m, CH₂-C-Pr), 1.15 (2H, m, CH²-C-Pr), 1.16 (3H, s, C-16), 1.28 (3H, m, C-17), 1.32 (9H, s, Boc), 1.68 (3H, s, H-19), 1.70 (1H, bs, OH), 1.80(1H, m, CH-c-Pr), 1.86-1.89 (IH, m, H-6b), 1.89 (3H, s, H-18), 2.33 (2H, m, H-14), 2.41 (3H, s, 4-OAc), 2.56 (IH, ddd, J = 7.0, 9.0, 15.0 Hz, H-6a), 2.59 (IH, bs, OH), 3.51 (IH, bs, OH), 3.82 (IH, d, J = 7.0 Hz, H-3), 4.16 (IH, d, J = 8.5 Hz, H-20b), 4.29 (IH, s, H-2′), 4.31 (IH, d, J = 8.5 Hz, H-20a), 4.41 (IH, ddd, J = 7.0, 10.5 Hz, H-7), 4.59 (IH, dd, J = 9.0, 25.0 Hz, H-3′vinyl), 4.89 (IH, m, H-3′), 4.98 (2H, m, H-5, NH), 5.63 (IH, d, J = 7.0 Hz, H-7), 6.24 (1H, t, J = 9.0 Hz, H-13), 6.31 (IH, s, H-10), 7.46 (2H, x J = 8.5 Hz), 7.60 (IH, dd, J = 1.0, 7.0 Hz), 8.01 (IH, d, J = 7.5 Hz), 8.13 (IH, s); ¹³C NMR (CDCl₃, 100 MHz) δ 9.2, 9.4, 13.0, 14.9, 21.9, 22.2, 26.7, 28.1, 35.4, (d, J = 7.9 Hz), 43.2, 45.6, 48.0, 58.5, 72.1, 72.6, 73.1, 75.3, 75.5, 76.3, 77.2, 79.2, 80.4, 81.0, 84.4, 128.3, 130.0, 130.3, 130.9, 133.0, 133.7, 134.8, 142.3, 154.8, 165.7, 170.2, 175.1,
203.7; \(^{19}\)F NMR (CDCl\(_3\), 282 MHz) \(\delta \) -84.15 (IF, dd, \(J = 25.7, 34.7\) Hz), -86.16 (IF, d, \(J = 36.7\) Hz); HRMS (FAB*, \(m/\ell\)): Calcd. for \(C_{43}H_{52}ClF_2NO, \delta^H\) 896.3066; Found, 896.3036.

**Example 18.** 3'-Dephenyl-3'-(2^-difluorovinyl)-2-debenzoyl-2-(3-chlorobenzoyl)-10-propanoyldocetaxel, SB-T-12853-4 (III-51m)

Yield 72%; white solid; \([\alpha]_D^{20}\) -76.73 (c 4.9, CHCl\(_3\)); \(^1\)H NMR (CDCl\(_3\), 500 MHz): \(\delta \) 1.14 (3H, s, H-16), 1.22-1.25 (6H, m, H-17, H-IO-CH\(_3\)), 1.31 (9H, s, Boc), 1.67 (3H, s, H-19), 1.71 (1H, s, OH), 1.86-1.91 (4H, m, H-6b, H-18), 2.32 (2H, m, H-14), 2.39 (3H, s, 4-OAc), 2.40-2.59 (3H, m, H-6a, H-IO, CH\(_2\)), 3.49 (IH, bs, OH), 3.82 (IH, d, \(J = 7.0\) Hz, H-3), 4.15 (2H, d, \(J = 8.5\) Hz, H-20b), 4.29 (2H, H-2\'), 4.40 (IH, dd, \(J = 6.0, 10.5\) Hz, H-7), 4.58 (IH, ddd, \(J = 1.5, 9.0, 24.5\) Hz, H-3'), 4.87 (IH, m, H-3'), 4.92 (1H, d, \(J = 9.0\) Hz, NH-3'), 4.98 (1H, d, \(J = 1.5, 9.5\) Hz, H-5), 5.62 (IH, d, \(J = 7.5\) Hz, H-2), 6.22 (1H, t, \(J = 9.5\) Hz, H-13), 6.31 (IH, s, H-10), 7.45 (IH, m, H-10), 7.45 (IH, ddd, \(J = 1.0, 2.0, 8.0\) Hz), 8.00 (IH, d, \(J = 7.5\) Hz), 8.12 (IH, s); \(^1\)C NMR (CDCl\(_3\), 125 MHz) \(\delta \) 8.9, 9.5, 14.9, 21.8, 22.2, 26.7, 27.5, 28.1, 35.5 (d, \(J = 15.9\) Hz), 43.2, 45.7, 58.5, 72.2, 72.6, 73.1, 75.3, 75.5, 76.3, 79.2, 80.4, 81.0, 84.4, 128.3, 130.1, 130.3, 130.9, 133.1, 133.7, 134.8, 142.1, 154.8, 165.7, 170.2, 174.6, 203.6; \(^{19}\)F NMR (CDCl\(_3\), 282 MHz) \(\delta \) -84.14 (1F, dd, \(J = 23.7, 34.7\) Hz), -86.13 (1F, d, \(J = 36.7\) Hz); HRMS (FAB*, \(m/\ell\)): Calcd. for \(C_{42}H_{32}ClF_2NO, \delta^H\) 884.3066; Found 884.3057.

**Example 19.** 3'-Dephenyl-3'-(2^-difluorovinyl)-2-debenzoyl-2-(3-chlorobenzoyl)-10-dimethylcarbamoyldocetaxel, SB-T-128S4-4 (III-51n)

Yield 91%; white solid; mp \(^0\)C; \([\alpha]_D^{20}\) -88.09 (c 2.1, CHCl\(_3\)); \(^1\)H NMR (CDCl\(_3\), 500 MHz): \(\delta \) 1.17 (3H, s, H-16), 1.27 (3H, m, H-17), 1.33 (9H, s, Boc), 1.62 (IH, bs, OH), 1.69 (3H, s, H-19), 1.84 (1H, m, OH), 1.90 (IH, ddd, \(J = 2.5, 11.5, 17.5\) Hz, H-6b), 1.93 (3H, s, H-18), 2.34 (2H, m, H-14), 2.42 (3H, s, 4-OAc), 2.56 (1H, ddd, \(J = 6.0, 9.0, 15.0\) Hz, H-6a), 2.98 (3H, s, N-Me), 3.06 (3H, s, N-Me), 3.25 (1H, d, \(J = 2.5\) Hz, OH), 3.52 (IH, d, \(J = 5.5\) Hz, OH), 3.83 (IH, d, \(J = 7.0\) Hz, H-3), 4.18 (IH, d, \(J = 8.5\) Hz, H-20b), 4.29 (IH, s, H-2'), 4.32 (1H, d, \(J = 8.5\) Hz, H-20a), 4.46 (IH, dd, \(J = 6.5, 11.0\) Hz, H-7), 4.58 (IH, ddd, \(J = 1.5, 10.0, 24.5\) Hz, H-3'vinyl), 4.93 (2H, m, H-3', NH-3'), 5.01 (IH, d, \(J = 7.0\) Hz, H-5), 5.63 (IH, d, \(J = 7.5\) Hz, H-2), 6.25 (1H, t, \(J = 9.0\) Hz, H-13), 6.27 (1H, s, H-10), 7.47 (2H, t, \(J = 7.5\) Hz), 7.49 (IH,
dd, $J = 1.0, 9.5$ Hz), 7.82 ($1$ H, d, $J = 8.0$ Hz), 8.15 ($1$ H, s); $^{13}$C NMR (CDCl$_3$, 125 MHz) $\delta$
9.3, 14.9, 22.2, 26.9, 28.1, 35.4 (d, $J = 6.0$ Hz), 36.0, 36.6, 43.2, 45.5, 58.5, 72.4, 72.6, 73.1,
75.6, 76.1, 76.3, 79.3, 80.4, 81.1, 84.6, 128.3, 130.1, 130.4, 130.9, 133.3, 133.7, 134.8, 142.6,
154.8, 156.1, 165.7, 171.1, 205.5; $^{19}$F NMR, (CDCl$_3$, 282 MHz) $\delta$-84.16 (IF, dd, $J = 23.9,$
34.9 Hz), -86.17 (IF, d, $J = 36.7$ Hz); HRMS (FAB+, $m/z$): Calced. for C$_{42}$H$_{33}$ClF$_2$N$_2$O$_{15}$H$^+$,
899.3175; Found 899.3151.

**Example 20.** 3'-Dephenyl-3'-(2,2-difluorovinyl)-2-debenzoyl-2-(3-chlorobenzoyl)-10-
methoxycarbonyldocetaxel, SB-T-12855-4  (III-510)

Yield 70%; white solid; [\alpha]$_D^{20}$ -72.09 (c 4.3, CHCl$_3$); $^1$H NMR (CDCl$_3$, 500 MHz): $\delta$ 1.16
(3H, s, H-16), 1.26 (3H, m, H-17), 1.32 (9H$_5$, s, Boc), 1.63 (IH, bs, OH), 1.71 (3H, s, H-19),
1.91 (1H, m, H-6b), 1.94 (3H, s, H-18), 2.33 (2H, d, $J = 9.0$ Hz, H-14), 2.42 (3H, s, 4-OAc),
2.46 (IH, d, $J = 4.0$ Hz, OH), 2.59 (1H, ddd, $J = 7.5, 10.0, 15.5$ Hz, H-6a), 3.46 (IH, $J = 6.0$
Hz, OH), 3.81 (IH, d, $J = 7.0$ Hz, H-3), 3.87 (3H, s, H-IO-MeO), 4.17 (IH, d, $J = 8.5$ Hz, H-
20b), 4.29 (IH, d, $J = 5.5$ Hz, H-2'), 4.32 (1H, d, $J = 8.5$ Hz, H-20a), 4.39 (IH, m, H-7), 4.59
(IH, d, $J = 8.0, 24.5$ Hz, H-3'), 4.89 (2H, m, H-3', NH-3'), 5.00 (IH, d, $J = 8.5$ Hz, H-
5), 5.64 (IH, d, $J = 7.5$ Hz, H-2), 6.13 (1H, s, H-IO), 6.23 (2H, t, $J = 8.5$ Hz, H-13), 7.49 (1
H, t, $J = 8.0$ Hz), 7.60 (IH, d, $J = 7.5$ Hz), 8.01 (1H, d, $J = 8.0$ Hz), 8.14 (1H, s); $^{13}$C NMR
(CDCl$_3$, 125 MHz) $\delta$ 9.4, 14.9, 21.7, 22.2, 26.6, 28.1, 35.3, 35.6, 43.1, 45.6, 55.6, 58.5, 72.1,
72.5, 73.2, 75.4, 76.3, 78.2, 79.2, 80.5, 80.9, 84.4, 128.3, 130.1, 130.3, 130.9, 132.6, 133.7,
134.9, 143.1, 154.9, 155.7, 165.7, 170.2, 203.8; $^{19}$F NMR (CDCl$_3$, 282 MHz) $\delta$-84.16 (IF, dd,
$J = 23.7, 34.7$ Hz), -86.17 (IF, dd, $J = 34.9$ Hz); HRMS (FAB+, $m/z$): Calcd. for C$_{41}$H$_{30}$ClF$_2$N$_2$O$_{16}$H$^+$,
886.2859; Found 886.2845.

**Example 21.** 3'-Dephenyl-3'-(2,2-difluorovinyl)-2-debenzoyl-2-(3-methoxybenzoyl)-10-
acetyldocetaxel, SB-T-12851-1  (III-S1p)

Yield 76%; white solid; [\alpha]$_D^{20}$ -74.42 (c 2.15, CHCl$_3$); $^1$H NMR (CDCl$_3$, 400 MHz): $\delta$ 1.15
(3H, s, C-16), 1.26 (3H, m, C-17), 1.30 (9H, s, Boc), 1.68 (3H, s, H-19), 1.76 (IH, s, OH),
1.88 (4H, m, H-6b, H-18), 2.24 (3H, s, 10-OAc), 2.33 (2H, m, H-14), 2.38 (3H, s, 4-OAc),
2.49 (IH, d, $J = 3.5$ Hz, OH), 2.56 (IH, ddd, $J = 6.5, 9.5, 15.0$ Hz, H-6a), 3.47 (IH, $J = 4.5$
Hz, OH), 3.81 (IH, d, $J = 7.5$ Hz, H-3), 3.90 (3H, s, 2-m-MeO), 4.15 (IH, d, $J = 8.0$ Hz, H-
Example 22. 3'-Dephenyl-3'(2,2-difluorovinyl)-2-debenzoyl-2-(3-methoxybenzoyl)-10-cyclopropanecarbonyldocetaxel, SB-T-12852-1 (III-51q)

Yield 99%; white solid; [α]D20 -77.03 (c 5.79, CHCl3); 1H NMR (CDCl3, 500 MHz): δ 0.99 (2 H, m, CH2-C-Pr), 1.10 (2 H, m, CH2-C-Pr), 1.15 (3H, s, C-16), 1.25 (3H, m, C-17), 1.28 (9H, s, Boc), 1.66 (3H, s, H-19), 1.74-1.81 (2 H, m, CH-c-Pr, OH), 1.83-1.89 (IH, m, H-6b), 1.87 (3H, s, H-18), 2.31 (2H, m, H-14), 2.37 (3H, s, 4-OAc), 2.53 (IH, ddd, J = 6.5, 9.5, 15.0 Hz, H-6a), 2.59 (IH, dd, J = 3.5 Hz, OH), 3.55 (IH, bs, OH), 3.79 (IH, d, J = 7.5 Hz, H-3), 3.88 (3H, s, m-MeO-H-2), 4.16 (IH, d, J = 8.5 Hz, H-20b), 4.26 (IH, d, J = 2.5 Hz, H-2'), 4.34 (1 H, d, J = 8.5 Hz, H-20a), 4.40 (IH, m, H-7), 4.57 (IH, dd, J = 10.0, 24.5 Hz, H-3' vinyl), 4.86 (IH, t, J = 8.5 Hz, H-3'), 4.96 (2 H, m, H-5, NH′), 5.65 (IH, d, J = 7.0 Hz, H-7), 6.23 (1 H, t, J = 9.0 Hz, H-13), 6.28 (IH, s, H-10), 7.13 (IH, ddd, J = 2.0, 3.0, 8.0 Hz), 7.38 (2H, t, J = 7.5 Hz), 7.63 (IH, s), 7.79 (IH, d, J = 7.5 Hz); 13C NMR (CDCl3, 125 MHz) δ 9.2, 9.4, 9.5, 13.0, 14.8, 22.0, 22.3 (d, J = 2.9 Hz), 26.7, 28.1, 35.5, (d, J = 4.3 Hz), 43.2, 45.6, 55.3, 58.5, 72.1, 72.6, 73.1, 75.1, 75.3, 75.5, 76.4, 77.2, 79.0, 80.4, 81.0, 84.4, 114.0, 120.6, 122.7, 129.7, 130.3, 133.2, 142.1, 154.8, 156.4, 159.7, 166.9, 170.2, 172.4, 175.1, 203.8; 19F NMR (CDCl3, 282 MHz) δ -84.62 (IF, dd, J = 25.7, 36.7 Hz), -86.29 (IF, d, J = 36.4 Hz); HRMS (FAB+, m/z): Calcd. for C42H33F2NO9H+, 866.3405; Found, 866.3439.

Example 23. 3'-Dephenyl-3'(2,2-difluorovinyl)-2-debenzoyl-2-(3-methoxybenzoyl)-10-propanoyldocetaxel. SB-T-12853-1 (ID-Sir)

Yield 58%; white solid; [α]D20 -79.78 (c 3.66, CHCl3); 1H NMR (CDCl3, 500 MHz): δ 1.15
(3H, s, H-16), 1.22-1.25 (6H, m, H-17, H-10-CH3), 1.30 (9H, s, Boc), 1.67 (3H, s, H-19), 1.71 (1H, s, OH), 1.79 (IH, s, OH), 1.86-1.91 (4H, m, H-6b, H-18), 2.32 (2H, m, H-14), 2.38 (3H, s, 4-OAc), 2.38-2.59 (3H, m, H-6a, H-IO, CH2), 3.52 (IH, bs, OH), 3.82 (IH, d, J = 7.0 Hz, H-3), 3.89 (H, /w-MeO-H2), 4.18 (2H, d, J = 8.5 Hz, H-20b), 4.27 (IH, H-2'), 4.35 (IH, d, J = 8.5 Hz, H-20a), 4.40 (IH, dd, J = 6.5, 11.0 Hz, H-7), 4.58 (1H, ddd, J = 1.5, 10.0, 25.0 Hz, H-3'), 4.87 (IH, t, J = 9.0 Hz, H-3'), 4.96 (2H, m, NH-3', H-5), 5.66 (IH, d, J = 6.5 Hz, H-2), 6.24 (1H, t, J = 9.0 Hz, H-13), 6.31 (IH, s, H-IO), 7.15 (IH, ddd, J = 1.0, 2.5, 8.5 Hz), 7.39 (1H, t, J = 7.5 Hz), 7.65 (IH, s), 7.71 (IH, d, J = 8.0 Hz); 13C NMR (CDCl3, 125 MHz) δ 9.0, 9.5, 14.8, 21.9, 22.3, 26.7, 27.5, 28.1, 35.4 (d, J = 15.9 Hz), 43.2, 45.6, 55.3, 58.3, 72.1, 72.6, 73.1, 75.1, 75.3, 76.4, 77.2, 79.0, 81.1, 84.4, 114.0, 122.7, 129.7, 130.3, 133.2, 141.9, 154.8, 159.7, 166.9, 170.2, 174.6, 203.7; 19F NMR, (CDCl3, 282 MHz) δ -84.58 (IF, d, J = 25.7, 36.7 Hz), -86.26 (IF, d, J = 36.7 Hz); HRMS (FAB+, m/z): Calcd. for C43H52F2NO16·H+, 880.3562; Found 880.3578.

**Example 24.** 3'-dephenyl-3'-(2,2-difluorovinyl)-2-debenzoyl-2-(3-methoxybenzoyl)-10-dimethylcarbamate-docetaxel, ST-T-12854-1 (III-SIs)

Yield 74%; white solid; 1H NMR (CDCl3, 500 MHz): δ 1.15 (3H, s, H-16), 1.25 (3H, s, H-17), 1.29 (9H, s, Boc), 1.67 (3H, s, H-19), 1.76 (IH, bs, OH), 1.88 (IH, m, H-6b), 1.89 (3H, s, H-18), 2.31 (2H, m, H-14), 2.38 (3H, s, 4-OAc), 2.53 (1H, ddd, J = 6.5, 10.0, 15.0 Hz, H-6a), 2.96 (3H, s, N-Me), 3.04 (3H, s, N-Me), 3.52 (1H, bs, OH), 3.81 (IH, d, J = 7.0 Hz, H-3), 3.90 (3H, s, m-MeO-H2), 4.17 (IH, d, J = 8.0 Hz, H-20b), 4.27 (IH, s, H-2'), 4.35 (1H, d, J = 8.0 Hz, H-20a), 4.45 (IH, dd, J = 6.0, 10.5 Hz, H-7), 4.58 (IH, ddd, J = 1.5, 10.0, 25.0 Hz, H-3'vinyl), 4.87 (IH, t, J = 8.5 Hz, H-3'), 4.97 (IH, m, H-5, NH-3'), 5.65 (IH, d, J = 7.0 Hz, H-2), 6.25 (2H, m, H-10, H-13), 7.14 (IH, dd, J = 1.5, 7.5 Hz), 7.39 (2H, t, J = 8.0 Hz), 7.65 (1H, s), 7.71 (1H, d, J = 7.5 Hz); 13C NMR (CD+Cl3, 125 MHz) δ 9.3, 14.9, 22.3, 26.9, 28.1, 35.4 (d, J = 12.9 Hz), 36.0, 36.6, 43.2, 45.5, 55.3, 58.5, 72.4, 72.7, 73.1, 75.2, 76.1, 76.4, 79.2, 80.4, 81.2, 84.6, 114.0, 120.7, 122.7, 129.7, 130.3, 133.5, 133.7, 142.4, 154.8, 156.1, 159.7, 166.9, 171.0, 205.6; 19F NMR (CDCl3, 282 MHz) δ -84.60 (IF, dd, J = 23.9, 34.9 Hz), -86.30 (IF, d, J = 36.4 Hz); HRMS (FAB+, m/z): Calcd. For C43H52F2NO16·H+, 895.3671; Found 895.3676.
Example 25. 3’-Dephenyl-3’-(2,2-difluorovinyl)-2-debenzy1-2-(3-methoxybenzoyl)-10-methoxycarbonyldocetaxel, SB-T-12855-1 (Ill-Sit)

Yield 89%; white solid; \([\alpha]_D^{20} = 68.98\text{ (c 4.61, CHCl}_3)\); \(^1^H\) NMR (CDCl\(_3\), 500 MHz): \(\delta\) 1.15 (3H, s, H-16), 1.24 (3H, m, H-17), 1.29 (9H, s, Boc), 1.69 (3H, s, H-19), 1.78 (IH, bs, OH), 1.88 (1H, m, H-6b), 1.91 (3H, s, H-18), 2.32 (2H, m, H-14), 2.38 (3H, s, 4-OAc), 2.49 (IH, d, \(J = 4.5\text{ Hz, OH})\), 2.56 (1H, ddd, \(J \approx 7.0, 9.5, 15.0\text{ Hz, H-6a})\), 3.53 (IH, \(J = 5.5\text{ Hz, OH})\), 3.78 (IH, d, \(J = 6.5\text{ Hz, H-3})\), 3.87 (3H, s, H-IO-MeO), 3.89 (3H, s, \(n\text{-MeO-H2})\), 4.18 (IH, d, \(J = 8.5\text{ Hz, H-2b})\), 4.27 (IH, d, \(J = 3.0\text{ Hz, H-2'})\), 4.36 (1H, d, \(J = 8.5\text{ Hz, H-20a})\), 4.41 (IH, m, H-7), 4.59 (IH, ddd, \(J = 9.5, 24.5\text{ Hz, H-3'}\) vinyl), 4.86 (IH, \(\chi_J = 9.0\text{ Hz, H-3'})\), 4.95 (2H, m, H-5, NH-3'), 5.66 (IH, d, \(J = 7.5\text{ Hz, H-2})\), 6.12 (1H, s, H-IO), 6.24 (1H, t, \(J = 8.5\text{ Hz, H-13})\), 7.15 (IH, d, \(J = 2.0, 7.5\text{ Hz})\), 7.39 (1H, t, \(J = 8.0\text{ Hz})\), 7.64 (1H, s), 7.71 (1H, d, \(J = 7.0\text{ Hz})\); \(^{13}C\) NMR (CDCl\(_3\), 125 MHz) \(\delta\) 9.5, 14.9, 21.8, 22.3, 26.6, 28.1, 35.3 (d, \(J = 22.0\text{ Hz})\), 43.1, 45.6, 55.6, 55.6, 58.5, 72.0, 72.6, 73.1, 75.0, 77.2, 78.2, 79.0, 80.5, 81.1, 84.4, 114.0, 120.7, 129.7, 130.3, 132.8, 142.9, 154.8, 155.7, 159.7, 166.9, 170.3, 203.9; \(^{19}F\) NMR (CDCl\(_3\), 282 MHz) \(\delta\) -84.60 (IF, ddd, \(J = 25.7, 36.7\text{ Hz})\), -86.27 (IF, ddd, \(J = 36.7\text{ Hz})\); HRMS (FAB\(^-\), m/z): Calcd. for \(C_{42}H_{53}F_2NO_{17}\) \(4^+\), 882.3354; Found 882.3353.

Example 26. 3’-Dephenyl-3’-(2,2-difluorovinyl)-2-debenzy1-2-(3-azidobenzoyl)-10-acetyldocetaxel, SB-T-12851-3 (111-51 u)

Yield 49%; white solid; \([\alpha]_D^{20} = -70.59\text{ (c 3.23, CHCl}_3)\); \(^1^H\) NMR (CDCl\(_3\), 400 MHz): \(\delta\) 1.15 (3H, s, C-16), 1.26 (3H, s, C-17), 1.30 (9H, s, Boc), 1.67 (3H, s, H-19), 1.69 (IH, bs, OH), 1.88 (4H, m, H-6b, H-18), 2.24 (3H, s, 10-OAc), 2.32 (2H, m, H-14), 2.39 (3H, s, 4-OAc), 2.49 (IH, bs, OH), 2.56 (IH, ddd, \(J = 7.0, 9.5, 15.0\text{ Hz, H-6a})\), 3.48 (IH, \(J = 4.0\text{ Hz, OH})\), 3.82 (IH, d, \(J = 7.0\text{ Hz, H-3})\), 4.16 (IH, d, \(J = 8.5\text{ Hz, H-20b})\), 4.26 (1H, s, H-2'), 4.33 (IH, d, \(J = 8.5\text{ Hz, H-20a})\), 4.42 (IH, ddd, \(J = 6.5, 10.5\text{ Hz, H-7})\), 4.57 (IH, ddd, \(J = 1.5, 9.5, 25.0\text{ Hz, H-3'vinyl})\), 4.85 (IH, t, \(J = 8.5\text{ Hz, H-3'})\), 4.93 (IH, d, \(J = 9.5\text{ Hz, NH-3'})\), 4.98 (1H, d, \(J = 7.5, 8.0\text{ Hz, H-5})\), 5.66 (IH, d, \(J = 7.5\text{ Hz, H-2})\), 6.22 (1H, t, \(J = 9.0\text{ Hz, H-13})\), 6.29 (IH, s, H-10), 7.23 (IH, dd, \(J = 1.5, 8.0\text{ Hz})\), 7.48 (IH, t, \(J = 8.0\text{ Hz})\), 7.81 (1H, s), 7.89 (IH, d, \(J = 8.0\text{ Hz})\); \(^{13}C\) NMR (CDCl\(_3\), 100 MHz) \(\delta\) 9.5, 14.9, 20.8, 21.9, 22.4, 26.7, 28.1, 35.5 (d, \(J = 15.1\text{ Hz})\), 43.2, 45.6, 58.5, 72.1, 72.6, 73.1, 75.4, 75.5, 76.4, 79.1, 80.4, 81.0, 84.4, 120.1, 124.4, 126.7, 130.2, 133.0, 140.9, 142.2, 154.8, 166.1, 170.3, 171.2, 203.6; \(^{19}F\) NMR, (CDCl\(_3\), 282 MHz) \(\delta\)
Example 27. 3'-Dephenyl-3'-(2,2-difluorovinyl)-2-debenzoyl-2-(3-azidobenzoyl)-10-cyclopropanecarbonyldocetaxel, SB-T-12852-3 (III-51w)

Yield 78%; white solid; [α]D20 -67.39 (c 5.09, CHCl₃); 1H NMR (CDCl₃, 400 MHz): δ 1.02 (2H, m, CH₂-C-Pr), 1.15 (2H, m, CH₂-C-Pr), 1.17 (3H, s, C-16), 1.28 (3H, m, C-17), 1.32 (9H, s, Boc), 1.68 (3H, s, H-19), 1.76 (IH, bs, OH), 1.79 (1H, m, CH-c-Pr), 1.86-1.91 (IH, m, H-6b), 1.90 (3H, s, H-18), 2.34 (2H, m, H-14), 2.41 (3H, s, 4-OAc), 2.56 (IH, ddd, J = 6.5, 9.5, 15.0 Hz, H-6a), 2.62 (IH, bs, OH), 3.54 (IH, d, J = 5.5 Hz, OH), 3.83 (IH, d, J = 5.5 Hz, H-3). 4.18 (IH, d, J = 8.5 Hz, H-20b), 4.28 (IH, d, J = 3.0 Hz, H-2'), 4.35 (1H, d, J = 8.5 Hz, H-20a), 4.43 (IH, dd, J = 6.5, 10.0 Hz, H-7), 4.58 (IH, ddd, J = 1.5, 9.0, 24.5 Hz, H-3' vinyl), 4.87 (IH, t, J = 8.5 Hz, H-3'), 4.98 (2H, m, H-5 ', NH-3'), 5.67 (IH, d, J = 7.0 Hz, H-7), 6.24 (1H, t, J = 8.0 Hz, H-13), 6.31 (1H, s, H-IO), 7.25 (IH, d, J = 1.5, 8.0 Hz), 7.49 (2H, t, J = 8.0 Hz), 7.82 (IH, s), 7.90 (IH, d, J = 8.0 Hz); 13C NMR (CDCl₃, 100 MHz) δ 9.2, 9.4, 9.5, 13.0, 14.9, 22.0, 22.3, 26.7, 28.1, 35.5, (d, J = 7.6 Hz), 43.2, 45.6, 58.5, 72.1, 72.6, 73.1, 75.3, 75.5, 76.4, 79.1, 80.4, 81.0, 84.5, 120.1, 124.4, 126.7, 130.2, 130.8, 133.1, 140.9, 142.3, 154.8, 166.1, 170.3, 175.1, 203.7; 19F NMR (CDCl₃, 282 MHz) δ -84.02 (IF, dd, J = 25.7, 34.9 Hz), -86.14 (IF, d, J = 34.9 Hz); HRMS (FAB+, m/z): Calcd. for C₄₁H₅₃F₄N₄O₁₅⁻C-H⁺, 877.3314; Found, 877.3351.

Example 28. 3'-Dephenyl-3'-(2,2-difluorovinyl)-2-debenzoyl-2-(3-azidobenzoyl)-10-propanoyldocetaxel, SB-T-12853-3 (III-51x)

Yield 93%; white solid; [α]D20 -67.77 (c 3.32, CHCl₃); 1H NMR (CDCl₃, 500 MHz): δ 1.14 (3H, s, H-16), 1.22-1.25 (6H, m, H-17, H-10-CH3), 1.30 (9H, s, Boc), 1.67 (3H, s, H-19), 1.71 (1H, s, OH), 1.69 (IH, s, OH), 1.85-1.91 (4H, m, H-6b, H-18), 2.32 (2H, m, H-14), 2.39 (3H, s, 4-OAc), 2.47-2.59 (3H, m, H-6a, H-10, CH2), 3.48 (IH, d, J = 4.5 Hz, OH), 3.82 (IH, d, J = 7.5 Hz, H-3), 4.16 (IH, d, J = 8.5 Hz, H-20b), 4.26 (IH, H-2'), 4.33 (IH, d, J = 8.5 Hz, H-20a), 4.43 (IH, dd, J = 7.0, 11.0 Hz, H-7), 4.56 (IH, ddd, J = 1.5, 9.0, 24.5 Hz, H-3'), 4.86 (1H, t, J = 8.0 Hz, H-3'), 4.92 (1H, d, J = 9.5 Hz, NH-3'), 4.98 (IH, d, J = 8.0 Hz, H-5), 5.66 (IH, d, J = 7.5 Hz, H-2), 6.22 (1H, t, J = 8.0 Hz, H-13), 6.31 (IH, s, H-10), 7.23 (IH, dd, J
Example 29. 3'-Dephenyl-3'-(2,2-difluorovinyl)-2-debenzoyl-2-(3-azidobenzoyl)-10-dimethylcarbamoyldocetaxel, SB-T-12854-3 (Ill-Sly)

Yield 79%; white solid; [α]D20 -75.39 (c 4.51, CHCl3); 1H NMR (CDCl3, 500 MHz): δ 1.15 (3H, s, H-16), 1.25 (3H, s, H-17), 1.30 (9H, s, Boc), 1.66 (3H, s, H-19), 1.75 (IH, bs, OH), 1.87 (IH, m, H-6b), 1.90 (3H, s, H-18), 2.31 (2H, m, H-14), 2.39 (3H, s, 4-OAc), 2.54 (1H, ddd, J = 7.0, 10.0, 15.5 Hz, H-6a), 2.96 (3H, s, N-Me), 3.04 (3H, s, N-Me), 3.56 (1H, bs, OH), 3.81 (IH, d, J = 7.0 Hz, H-3'), 4.16 (IH, d, J = 8.5 Hz, H-20b), 4.27 (IH, s, H-2'), 4.32 (1H, d, J = 8.5 Hz, H-20a), 4.45 (IH, d, J = 6.5, 10.5 Hz, H-7), 4.57 (IH, ddd, J = 1.0, 9.0, 24.0 Hz, H-3'vinyl), 4.85 (IH, t, J = 8.0 Hz, H-3'), 4.97 (2H, m, H-5, NH-3'), 5.65 (IH, d, J = 7.0 Hz, H-2), 6.23 (1H, t, J = 9.5 Hz, H-13), 6.25 (IH, s, H-10), 7.23 (IH, ddd, J = 1.5, 8.5 Hz), 7.47 (IH, t, J = 8.0 Hz), 7.80 (1H, s), 7.89 (1H, d, J = 8.0 Hz); 13C NMR (CDCl3, 125 MHz) δ 9.3, 14.9, 22.3, 26.9, 28.1, 35.4 (d, J = 6.6 Hz), 36.0, 36.6, 43.2, 58.5, 72.4, 72.6, 73.1, 75.6, 76.1, 76.3, 79.2, 80.1, 84.7, 120.7, 120.2, 124.3, 126.7, 130.2, 130.9, 133.4, 140.9, 142.6, 154.9, 156.1, 166.1, 170.3, 205.5; 19F NMR (CDCl3, 282 MHz) δ -84.06 (IF, ddd, J = 25.7, 34.7 Hz), -86.12 (IF, d, J = 36.7 Hz); HRMS (FAB+, m/z): Calcd. for C42H53F2N4O15H+: 906.3579; Found 906.3588.

Example 30. 3'-Dephenyl-3'-(2,2-difluorovinyl)-2-debenzoyl-2-(3-azidobenzoyl)-10-methoxycarbonyldocetaxel, SB-T-12855-3 (III-Sllz)

Yield 77%; white solid; [α]D20 -66.67 (c 3.9, CHCl3); 1H NMR (CDCl3, 400 MHz): δ 1.15 (3H, s, H-16), 1.24 (3H, s, H-17), 1.29 (9H, s, Boc), 1.69 (3H, s, H-19), 1.71 (IH, bs, OH), 1.89 (1H, m, H-6b), 1.92 (3H, s, H-18), 2.32 (2H, m, H-14), 2.39 (3H, s, 4-OAc), 2.49 (IH, bs, OH), 2.56 (1H, ddd, J = 6.5, 9.5, 14.5 Hz, H-6a), 3.51 (IH, bs, OH), 3.79 (IH, d, J = 7.0 Hz, t, J = 7.5 Hz), 7.48 (IH, s), 7.89 (IH, d, J = 8.0 Hz); 13C NMR (CDCl3, 125 MHz) δ 9.0, 9.5, 14.9, 21.7, 22.4, 26.7, 27.5, 28.1, 35.5 (d, J = 11.5 Hz), 43.2, 45.6, 58.5, 72.1, 72.6, 73.1, 75.1, 75.3, 75.4, 76.4, 79.1, 81.0, 84.5, 120.1, 124.4, 126.7, 130.2, 130.8, 133.2, 140.9, 154.8, 159.7, 166.1, 170.3, 174.6, 203.7; 19F NMR (CDCl3, 282 MHz) δ -83.99 (IF, dd, J = 25.7, 34.7 Hz), -86.12 (IF, d, J = 36.7 Hz); HRMS (FAB+, m/z): Calcd. for C42H52F2N4O15H+: 906.3470; Found 901.3473.
Hz, H-3), 3.87 (3 H, s, H-IO-MeO), 4.17 (IH, d, J= 8.5 Hz, H-20b), 4.26 (IH, s, H-2'), 4.33 (1 H, d, J= 8.5 Hz, H-20a), 4.40 (IH, dd, J= 7.0, 11.0 Hz, H-7), 4.57 (IH, ddd, J= 1.0, 9.0, 24.5 Hz, H-3' vinyl), 4.85 (1H, t, J= 8.5 Hz, H-3'), 4.96 (2H, m, H-5 , NH-3'), 5.66 (IH, d, J= 7.5 Hz, H-2), 6.12 (1 H, s, H-IO), 6.22 (1 H, t, J= 9.0 Hz, H-13), 7.23 (IH, dd, J= 1.5, 6.5 Hz), 7.48 (1 H, t, J= 7.5 Hz), 7.81 (1 H, s), 7.89 (1 H, d, J= 8.0 Hz); 13C NMR (CDCl3, 100 MHz) δ 9.5, 14.9, 21.8, 22.4, 26.6, 28.1, 35.4 (d, J= 18.6 Hz), 43.1, 45.6, 55.6, 55.6, 58.5, 72.0, 72.5, 73.1, 75.4, 76.3, 78.2, 79.1, 80.4, 81.0, 84.3, 120.1, 124.4, 126.7, 130.2, 130.8, 132.7, 140.9, 143.0, 154.7, 155.7, 166.1, 170.4, 203.8; 19F NMR (CDCl3, 282 MHz) δ -84.01 (IF, dd, J= 25.7, 36.7 Hz), -86.13 (IF, d, J= 36.7 Hz); HRMS (FAB +, m/z): Calcd. for C41H39F2N4O6·H+: 893.3263; Found 893.3269.

Example 31. Tumor Growth Inhibitory Activity of Fluorotaxoids

Fluorotaxoids were evaluated in their tumor growth inhibitory activities against human tumor cell lines, MCF7 (mammary carcinoma) or MCF7-R (mammary carcinoma cells 250-fold resistant to paclitaxel), after 72 h drug exposure according to literature methods. Results are shown for some selected compounds in the tables below.

In the tables, lower numbers indicate higher potency (or greater activity). Paclitaxel was used as the standard for comparison. The data represent the mean values of at least three separate experiments.
Example 31a

Cytotoxicity (IC$_{50}$ nM) of CF$_2$=CH-Taxoids (1)

\[
\begin{array}{cccccc}
\text{CF$_2$=CH-Taxoid} & \text{R'} & \text{R''} & \text{MCF7 (breast)} & \text{MCF7-R (breast)} & \text{R/S} \\
\hline
\text{Paclitaxel} & \text{Me} & \text{H} & 1.2 & 300 & 250 \\
\text{SB-T-12851} & \text{Me} & \text{H} & 0.099 & 0.95 & 9.6 \\
\text{SB-T-12852} & \text{cyc/o-Pr} & \text{H} & 0.12 & 6.03 & 53 \\
\text{SB-T-12853} & \text{Et} & \text{H} & 0.12 & 1.2 & 10 \\
\text{SB-T-12854} & \text{Me}_2\text{N} & \text{H} & 0.13 & 4.27 & 33 \\
\text{SB-T-12855} & \text{MeO} & \text{H} & 0.14 & 1.29 & 9.2 \\
\end{array}
\]
Cytotoxicity (IC$_{50}$ nM) of CF$_2$=CH-Taxoids (2)

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<tr>
<th>CF$_2$=CH-Taxoid</th>
<th>R$^1$</th>
<th>R$^2$</th>
<th>MCF7 (breast)</th>
<th>MCF7-R (breast)</th>
<th>R/S</th>
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<tbody>
<tr>
<td>Paclitaxel</td>
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<td>H</td>
<td>1.2</td>
<td>300</td>
<td>250</td>
</tr>
<tr>
<td>SB-T-12851-1</td>
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<td>MeO</td>
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<tr>
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</tr>
<tr>
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<tr>
<td>SB-T-12854-1</td>
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<tr>
<td>SB-T-12855-1</td>
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<td>MeO</td>
<td>0.078</td>
<td>0.50</td>
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</tbody>
</table>
Example 31c

Cytotoxicity (IC$_{50}$ nM) of CF$_2$=CH-Taxoids (3)

![Chemical Structure](image)

<table>
<thead>
<tr>
<th>CF$_2$=CH-Taxoid</th>
<th>R'</th>
<th>R''</th>
<th>MCF7 (breast)</th>
<th>MCF7-R (breast)</th>
<th>R/S</th>
</tr>
</thead>
<tbody>
<tr>
<td>Paclitaxel</td>
<td>Me</td>
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<td>1.2</td>
<td>300</td>
<td>250</td>
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<tr>
<td>SB-T-12851-2</td>
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<tr>
<td>SB-T-12852-2</td>
<td>cyc/o-Pr</td>
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<td>23</td>
</tr>
<tr>
<td>SB-T-12853-2</td>
<td>Et</td>
<td>F</td>
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<td>2.54</td>
<td>11</td>
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<tr>
<td>SB-T-12854-2</td>
<td>Me$_2$N</td>
<td>F</td>
<td>0.17</td>
<td>2.25</td>
<td>9.4</td>
</tr>
<tr>
<td>SB-T-12855-2</td>
<td>MeO</td>
<td>F</td>
<td>0.12</td>
<td>1.85</td>
<td>11</td>
</tr>
</tbody>
</table>
**Example 31d**

Cytotoxicity (IC$_{50}$ nM) of CF$_2$=CH-Taxoids (4)

![Chemical structure](image)

<table>
<thead>
<tr>
<th>CF$_2$=CH-Taxoid</th>
<th>$R^1$</th>
<th>$R^2$</th>
<th>MCF7 (breast)</th>
<th>MCF7-R (breast)</th>
<th>R/S</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pacitaxel</td>
<td>Me</td>
<td>H</td>
<td>1.2</td>
<td>300</td>
<td>250</td>
</tr>
<tr>
<td>SB-T-12851-3</td>
<td>Me</td>
<td>$N_3$</td>
<td>0.092</td>
<td>0.34</td>
<td>3.7</td>
</tr>
<tr>
<td>SB-T-12852-3</td>
<td>cyc/o-Pr</td>
<td>$N_3$</td>
<td>0.092</td>
<td>0.45</td>
<td>4.9</td>
</tr>
<tr>
<td>SB-T-12853-3</td>
<td>Et</td>
<td>$N_3$</td>
<td>0.13</td>
<td>0.38</td>
<td>2.9</td>
</tr>
<tr>
<td>SB-T-12854-3</td>
<td>$Me_2N$</td>
<td>$N_3$</td>
<td>0.13</td>
<td>0.45</td>
<td>3.7</td>
</tr>
<tr>
<td>SB-T-12855-3</td>
<td>MeO</td>
<td>$N_3$</td>
<td>0.076</td>
<td>0.40</td>
<td>5.3</td>
</tr>
</tbody>
</table>
Example 31e

Cytotoxicity (IC$_{50}$ nM) of CF$_2$=CH-Taxoids (5)

Assessment of cell growth inhibition was determined according to the methods of Skehan et al (See Skehan et al., J. Nat. Cancer Inst., 82, 1107 (1990)). Briefly, cells were plated between 400 and 1200 cells/well in 96 well plates and incubated at 37°C for 15-18 h prior to drug addition to allow attachment of cells. Compounds tested were solubilized in 100% DMSO and further diluted in RPMI-1640 containing 10 mM HEPES. Each cell line was treated with 10 concentrations of compounds (5 log range). After a 72 h incubation, 100 µL of ice-cold 50% TCA was added to each well and incubated for 1 h at 4°C. Plates were then washed 5 times with tap water to remove TCA, low-molecular-weight metabolites and serum proteins. Sulforhodamine B (SRB) (0.4%, 50 µL) was added to each well. Following a 5 minute incubation at room temperature, plates were rinsed 5 times with 0.1% acetic acid and air dried. Bound dye was solubilized with 10 mM Tris Base (pH 10.5) for 5 min on a gyratory shaker. Optical density was measured at 570 nm.
Data were fit with the Sigmoid-Emax concentration-effect model with non-linear regression, weighted by the reciprocal of the square of the predicted response (see Holford, N. H. G.; Scheiner, L. B., "Understanding the dose-effect relationship: Clinical applications of pharmaco-kinetic-pharmacodynamic models," *Clin. Pharmacokinet.*, 6, 429-453 (1981)). The fitting software was developed by the Roswell Park Cancer Institute with Microsoft FORTRAN, and uses the Marquardt algorithm (see Marquardt, D. W., "An algorithm for least squares estimation of nonlinear parameters," *J. Soc. Ind. Appl. Math.*, 11, 431-441 (1963)) as adopted by Nash for the non-linear regression (see Nash, J. C., "Compact numerical method for computers: Linear algebra and function minimization." John Wiley & Sons, New York, 1979). The concentration of drug which resulted in 50% growth inhibition (ICso) was calculated.

### Example 32

**Experimental procedure for the preparation of conjugate DHA-SB-T-12851**

To a solution of SB-T-12851 (23.9 mg, 0.0286 mmol) and 4-dimethylaminopyridine (DMAP, 3.49 mg; 0.0286 mmol) in dichloromethane (1.73 mL) under nitrogen were added 1,3-diisopropylcarbodiimide (DIC, 8.85 μL, 0.0572 mmol), and docosahexaenoic acid (DHA, 10.9 μL; 0.0314 mmol). The mixture was stirred at ambient temperature for 0.5 h. Then, the reaction mixture was concentrated in vacuo. The crude product was purified by column chromatography on silica gel (ethyl acetate/hexanes = 1/4 tol/2) to give DHA-SB-T-12851 as a white solid (24.3 mg, 74 % yield).

m.p. 60-62 °C, [α]D 21° -56.0 (c 1.2, CHCl3); H NMR (CDC13, 400 MHz): δ 0.97 (t, J = 7.6 Hz, 3 H), 1.14 (s, 3 H), 1.25 (s, 3 H), 1.32 (s, 9 H), 1.62 (s, 1 H), 1.67 (s, 3 H), 1.88 (m, 1 H), 1.93 (s, 3 H), 2.07 (t, J = 7.6 Hz, 2 H), 2.23 (s, 3 H), 2.25 (m, 2 H), 2.32 (m, 1 H), 2.44 (s, 4 H), 2.45 (2, 1 H), 2.48 (m, 3 H), 2.55 (m, 2 H), 2.65 (m, 10 H), 3.82 (d, J = 6.8 Hz, 1 H), 4.18 (d, J = 8.4 Hz, 1 H), 4.32 (d, J = 8.4 Hz, 1 H), 4.40 (m, 1 H), 4.44 (m, 1 H), 4.98 (m, 4 H), 5.40 (m, 12 H), 5.68 (d, J = 6.8 Hz, 1 H), 6.26 (t, J = 9.2 Hz, 1 H), 6.29 (s, 1 H), 7.50 (t, J = 7.6 Hz, 2 H), 9.64 (t, J = 7.6 Hz, 1 H), 8.13 (d, J = 7.6 Hz, 2 H); 13C NMR (CDC13, 75.5 MHz): δ 9.8, 14.6, 15.1, 20.8, 21.1, 21.1, 22.4, 22.5, 22.7, 25.8, 25.9, 27.0, 28.4, 30.0, 33.8, 35.7, 35.8, 43.5, 45.9, 58.8, 72.0, 72.4, 74.3, 75.4, 75.9, 76.7, 79.5, 80.9, 81.2, 84.7, 127.3, 127.6, 128.1, 128.3, 128.6, 128.7, 128.9, 129.0, 129.4, 130.1, 130.5, 132.3, 133.0, 133.9, 143.3, 154.0, 154.9, 156.9, 159.8, 167.4, 167.6, 170.1, 171.5, 172.2, 204.1; 18F NMR, (CDCl3, 282 MHz) δ
-85.3 (d, J = 36.7 Hz, 1 F), -83.6 (dd, J = 33.6, 24.5 Hz, 1 F); MALDI-TOF/MS (m/z): 1168.756 ([NB-Na]+, calcd 1168.54); C_{63}H_{80}F_{2}NO_{16} (1145.55).

Other DHA-conjugates of fluorotaxods were synthesized in the same manner.

**Example 33**

**2'-Docosahexaenoyl-3'-dephenyl-3'-difluorovinyl-10-cyclopropanecarboxyldocetaxel (DHA-SB-T-12852):**

White solid, 78% yield, m.p. 55-57 °C, [α]_{D}^{21} -54.8 (c 0.8, CHCl_{3}); H NMR (CDCl_{3}, 400 MHz): δ 0.97 (t, J = 7.6 Hz, 3 H), 1.01 (t, J = 4.4 Hz, 2 H), 1.12 (t, J = 1.0 Hz, 3 H), 1.14 (s, 3 H), 1.28 (t, J = 9.0 Hz, 3 H), 1.32 (s, 9 H), 1.59 (s, 1 H), 1.67 (s, 3 H), 1.77 (m, 1 H), 1.87 (m, 1 H), 1.93 (s, 3 H), 2.08 (m, 2 H), 2.23 (m, 1 H), 2.39 (s, 4 H), 2.51 (m, 6 H), 2.85 (m, 10 H), 3.82 (d, J = 12 Hz, 1 H), 4.18 (d, J = 8.4 Hz, 1 H), 4.30 (d, J = 8.4 Hz, 1 H), 4.44 (m, 2 H), 5.03 (m, 4 H), 5.38 (m, 12 H), 5.68 (d, J = 7.2 Hz, 1 H), 6.27 (t, J = 8.8 Hz, 1 H), 6.29 (s, 1 H), 7.50 (t, J = 7.6 Hz, 2 H), 7.61 (t, J = 7.6 Hz, 1 H), 8.13 (d, J = 7.2 Hz, 2 H); ^{13} C NMR (CDCl_{3}, 75.5 MHz): δ 9.35, 9.58, 9.76, 13.20, 14.48, 15.02, 20.77, 22.44, 22.68, 25.76, 25.86, 27.00, 28.33, 29.92, 33.79, 35.66, 34.24, 45.82, 58.74, 71.96, 72.43, 74.25, 75.39, 75.60, 76.63, 79.51, 80.80, 81.21, 84.71, 127.22, 127.55, 128.07, 128.26, 128.54, 128.80, 129.94, 129.38, 130.03, 130.42, 132.26, 132.97, 133.87, 143.23, 153.9, 154.79, 156.78, 159.69, 167.36, 167.50, 170.04, 172.11, 175.30, 204.23; ^{19}F NMR, (CDCl_{3}, 282 MHz) δ -85.3 (d, J = 33.6 Hz, 1 F), -83.6 (dd, J = 36.7, 24.5 Hz, 1 F); MALDI-TOF/MS (m/z): 1194.546 ([M+Na]^{+}, calcd 1194.56); C_{65}H_{83}F_{2}NO_{16} (1171.57).

**Example 34**

**2'-Docosahexaenoyl-3'-dephenyl-3'-difluorovinyl-10-propionyldocetaxel (DHA-SB-T-12853):**

White solid, 78% yield, m.p. 57-58 °C; [α]_{D}^{22} -57.6 (c 2.5, CHCl_{3}); ^{1} H NMR (500 MHz, CDCl_{3}) δ 0.97 (t, J = 7.5 Hz, 3 H), 1.14 (s, 3 H), 1.24 (m, 6 H), 1.32 (s, 9 H), 1.67 (s, 3 H), 1.88 (m, 1 H), 1.93 (s, 3 H), 2.11 (m, 2 H), 2.22-2.40 (m, 2 H), 2.39 (s, 3 H), 2.41-2.61 (m, 5 H), 2.85 (m, 10 H), 3.82 (d, J = 7.0 Hz, 1 H), 4.18 (d, J = 8.0 Hz, 1 H), 4.31 (d, J = 8.0 Hz, 1 H), 4.38-4.47 (m, 2 H), 4.93-5.07 (m, 4 H), 5.30-5.46 (m, 12 H), 5.67 (d, J = 7.5 Hz, 1 H), 6.26 (t, J = 8.0 Hz, 1 H), 6.31 (s, 1 H), 7.50 (x, J = 7.0 Hz, 2 H), 7.61 (x, J = 7.0 Hz, 1 H), 8.12
Example 35

2'-Docosahexaenoyl-3'-dephenyl-3'-difluorovinyl-10-(7V,9N-dimethyl-carnainoyl)

docetaxel (DHA-SB-T-12854):

White solid, 77% yield, m.p. 53-55 °C; [α]D22 57.6 (c 2.5, CHCl3); 1H NMR (500 MHz, CDCl3) δ 0.97 (t, J= 7.5 Hz, 3 H), 1.14 (s, 3 H), 1.24 (m, 6 H), 1.31 (s, 9 H), 1.67 (s, 3 H), 1.88 (m, 1 H), 1.95 (s, 3 H), 2.07 (m, 2 H), 2.22-2.40 (m, 2 H), 2.39 (s, 3 H), 2.41-2.61 (m, 3 H), 2.85 (m, 10 H), 2.95 (s, 3 H), 3.02 (s, 3 H), 3.23 (d, J = 2.4 Hz, 1 H), 3.81 (d, J = 7.6 Hz, 1 H), 4.18 (d, J = 8.4 Hz, 1 H), 4.31 (d, J = 8.4 Hz, 1 H), 4.37-4.50 (m, 2 H), 4.93-5.07 (m, 4 H), 5.30-5.46 (m, 12 H), 5.67 (d, J = 7.5 Hz, 1 H), 6.25 (s, 1 H), 6.28 (t, J = 9.2 Hz, 1 H), 7.50 (t, J = 7.6 Hz, 2 H), 7.61 (t, J = 7.2 Hz, 1 H), 8.12 (d, J = 7.2 Hz, 2 H); 13C NMR (75.45 MHz, CDCl3) δ 9.0, 9.6, 14.3, 14.7, 20.8, 22.1, 22.2, 22.4, 25.5, 25.6, 25.7, 26.7, 27.5, 28.1, 33.6, 35.3, 35.4, 35.5, 43.2, 45.6, 58.4, 71.8, 72.4, 74.0, 75.3, 76.1, 76.4, 77.2, 79.4, 80.6, 81.0, 84.7, 126.9, 127.3, 127.7, 127.8, 128.0, 128.1, 128.2, 128.3, 128.4, 128.6, 128.7, 129.2, 129.4, 129.8, 130.2, 132.0, 133.0, 133.6, 143.3, 156.1, 167.2, 167.3, 169.8, 171.8, 205.8; 19F NMR, (CDCl3, 376 MHz) δ -83.55 (1 F, dd, J= 24.0, 34.9 Hz), -85.34 (1 F, d, J= 34.7 Hz). LRMS (ESI) m/z calcd for C64H83F2NO16H+ 1175.6, found 1175.6; (MALDI) m/z calcd for C64H83F2NO16Na+ 1197.568, found 1197.662.

Thus, while there have been described what are presently believed to be the preferred embodiments of the present invention, those skilled in the art will realize that other and further embodiments can be made without departing from the spirit of the invention, and it is intended to include all such further modifications and changes as come within the true scope of the claims set forth herein.
What is Claimed is:

1. A conjugate comprising a fluorotaxoid and an omega-3 fatty acid, represented by the formula:

   \[
   \text{FA} - \text{R}^1 - \text{R}^2 - \text{R}^3 - \text{R}^4 - \text{R}^5 - \text{R}^6
   \]

   wherein:

   FA is an omega-3 fatty acid residue;

   R\(^1\) represents an alkyl, alkenyl, alkylamino, dialkylamino, or alkoxy group having one to six carbon atoms; a non-aromatic carbocyclic alkyl or alkenyl group having three to seventeen ring carbon atoms; a carbocyclic aryl group having six to eighteen ring carbon atoms; a non-aromatic heterocyclic group having three to seventeen ring carbon atoms or a heterocyclic aryl group having five to seventeen ring carbon atoms, wherein said cyclic groups can be unfused or fused, and unsubstituted or substituted;

   R\(^2\) represents a hydrogen; alkyl, alkenyl, alkoxy, alkenyloxy, acyloxy, alkylthio, alkenylthio, alkylamino or dialkylamino having one to six carbon atoms; halogen; fluoroalkyl group having one to three fluorine atoms and one to three carbon atoms; hydroxyl; carboxyl; amino or azido;

   R\(^3\) and R\(^5\) both represent hydrogen, or R\(^3\) and R\(^5\) are linked as a cyclic carbonate;
R⁴ represents an alkyl or alkenyl group having one to six carbon atoms; or a cycloalkyl or cycloalkenyl group having three to seven ring carbon atoms; and

R⁶ represents a fluorovinyl, difluorovinyl, or trifluorovinyl group having the formula

\[ \text{(2)} \]

wherein R⁷, R⁸, and R⁹ each independently represent a hydrogen or fluoro group, provided that at least one of R⁷, R⁸, and R⁹ represents a fluoro group.

2. A conjugate according to claim 1, wherein R⁷ represents hydrogen and each of R⁸ and R⁹ represents a fluoro group.

3. A conjugate according to claim 1, wherein R⁴ represents tert-butyl.

4. A conjugate according to claim 3, wherein the fluorotaxoid is represented by the formula:

\[ \text{(3)} \]

wherein R¹ represents an alkyl, alkenyl, alkylamino, dialkylamino, or alkoxy group having one to six carbon atoms; a non-aromatic carbocyclic alkyl or alkenyl group having
three to seventeen ring carbon atoms; a carbocyclic aryl group having six to eighteen ring carbon atoms; a non-aromatic heterocyclic group having three to seventeen ring carbon atoms or a heterocyclic aryl group having five to seventeen ring carbon atoms, wherein said cyclic groups can be unfused or fused, and unsubstituted or substituted; and

wherein $R^2$ represents a hydrogen; alkyl, alkenyl, alkoxy, alkenyloxy, acyloxy, alkylthio, alkenylthio, alkylamino or dialkylamino having one to six carbon atoms; halogen; fluoroalkyl group having one to three fluorine atoms and one to three carbon atoms; hydroxyl; carboxyl; amino or azido.

5. A conjugate according to claim 4, wherein $R^1$ represents methyl, ethyl, methoxy, dimethylamino or cyclopropyl and $R^2$ represents hydrogen, methyl, methoxy, chloro, fluoro or azido.

6. A conjugate according to claim 4, wherein $R^1$ represents methyl, ethyl, methoxy, dimethylamino or cyclopropyl and $R^2$ represents methoxy.

7. A conjugate according to claim 4, wherein $R^1$ represents methyl, ethyl, methoxy, dimethylamino or cyclopropyl and $R^2$ represents azido.

8. A conjugate according to claim 4, wherein $R^1$ represents methyl, ethyl, methoxy, dimethylamino or cyclopropyl and $R^2$ represents chloro.

9. A conjugate according to claim 4, wherein $R^1$ represents methyl, ethyl, methoxy, dimethylamino or cyclopropyl and $R^2$ represents fluoro.

10. A conjugate according to claim 1, wherein the omega-3 fatty acid is selected from the group consisting of docosahexanoic acid, eicosapentaenoic acid, and $\alpha$-linolenic acid.

11. A pharmaceutical composition comprising a conjugate, said conjugate comprising a fluorotaxoid and an omega-3 fatty acid represented by the formula:
wherein:

FA is an omega-3 fatty acid residue;

R\textsuperscript{1} represents an alkyl, alkenyl, alkylamino, dialkylamino, or alkoxy group having one to six carbon atoms; a non-aromatic carbocyclic alkyl or alkenyl group having three to seventeen ring carbon atoms; a carbocyclic aryl group having six to eighteen ring carbon atoms; a non-aromatic heterocyclic group having three to seventeen ring carbon atoms or a heterocyclic aryl group having five to seventeen ring carbon atoms, wherein said cyclic groups can be unfused or fused, and unsubstituted or substituted;

R\textsuperscript{2} represents a hydrogen; alkyl, alkenyl, alkoxy, alkenyloxy, acyloxy, alkylthio, alkenylthio, alkylamino or dialkylamino having one to six carbon atoms; halogen; fluoroalkyl group having one to three fluorine atoms and one to three carbon atoms; hydroxyl; carboxyl; amino or azido;

R\textsuperscript{3} and R\textsuperscript{5} both represent hydrogen, or R\textsuperscript{3} and R\textsuperscript{5} are linked as a cyclic carbonate;

R\textsuperscript{4} represents an alkyl or alkenyl group having one to six carbon atoms; or a cycloalkyl or cycloalkenyl group having three to seven ring carbon atoms; and

R\textsuperscript{6} represents a fluorovinyl, difluorovinyl, or trifluorovinyl group having the formula
wherein $R_7$, $R_8$, and $R_9$ each independently represent a hydrogen or fluoro group, provided that at least one of $R_7$, $R_8$, and $R_9$ represents a fluoro group.

12. A method for treating cancer in a human in need thereof, the method comprising administering to the human an effective amount of a conjugate comprising a fluorotaxoid and an omega-3 fatty acid represented by the formula:

$$
\text{FA} \quad \text{R}^1 \quad \text{R}^2
$$

wherein:

FA is an omega-3 fatty acid residue;

$R^1$ represents an alkyl, alkenyl, alkylamino, dialkylamino, or alkoxy group having one to six carbon atoms; a non-aromatic carbocyclic alkyl or alkenyl group having three to seventeen ring carbon atoms; a carbocyclic aryl group having six to eighteen ring carbon atoms; a non-aromatic heterocyclic group having three to seventeen ring carbon atoms or a heterocyclic aryl group having five to seventeen ring carbon atoms, wherein said cyclic groups can be unfused or fused, and unsubstituted or substituted;
$R^2$ represents a hydrogen; alkyl, alkenyl, alkoxy, alkenyloxy, acyloxy, alkylthio, alkenylthio, alkylamino or dialkylamino having one to six carbon atoms; halogen; fluoroalkyl group having one to three fluorine atoms and one to three carbon atoms; hydroxyl; carboxyl; amino or azido;

$R^3$ and $R^5$ both represent hydrogen, or $R^3$ and $R^5$ are linked as a cyclic carbonate;

$R^4$ represents an alkyl or alkenyl group having one to six carbon atoms; or a cycloalkyl or cycloalkenyl group having three to seven ring carbon atoms; and

$R^6$ represents a fluorovinyl, difluorovinyl, or trifluorovinyl group having the formula

\[ \begin{array}{c}
R^9 \\
\text{---} \\
R^8
\end{array} \]

\[ \text{(2)} \]

wherein $R^7$, $R^8$, and $R^9$ each independently represent a hydrogen or fluoro group, provided that at least one of $R^7$, $R^8$, and $R^9$ represents a fluoro group.