(19) Europäisches Patentamt
European Patent Office
Office européen des brevets

(11) Publication number: **0 604 910 A1**

(12) # EUROPEAN PATENT APPLICATION

(21) Application number: **93120801.1**

(22) Date of filing: **23.12.93**

(51) Int. Cl.[5]: **C07F 9/655**, A61K 31/675, C07F 9/6558, C07D 305/14, C07D 407/12, C07F 7/18

A request for correction of the description has been filed pursuant to Rule 88 EPC. A decision on the request will be taken during the proceedings before the Examining Division (Guidelines for Examination in the EPO, A-V, 2.2).

(30) Priority: **24.12.92 US 996455**
17.08.93 US 108015
24.11.93 US 154840

(43) Date of publication of application:
06.07.94 Bulletin 94/27

(84) Designated Contracting States:
AT BE CH DE DK ES FR GB GR IE IT LI LU MC NL PT SE

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(54) **Phosphonooxymethyl ethers of taxane derivatives.**

(57) The present invention concerns novel water-soluble phosphonooxymethyl ethers of taxane derivatives, their use as antitumor agents, and pharmaceutical compositions containing the novel compounds.

EP 0 604 910 A1

BACKGROUND OF THE INVENTION

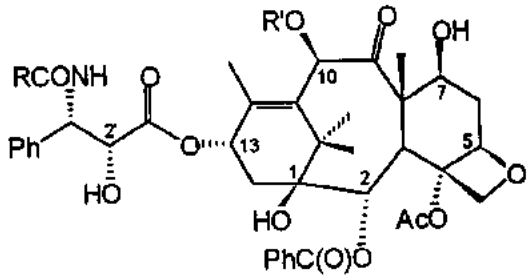
1. Field of the Invention

The present invention concerns antitumor compounds. More particularly, the invention provides novel taxane derivatives, pharmaceutical compositions thereof, and their use as antitumor agents.

2. Background Art

Taxol® (paclitaxel) is a natural product extracted from the bark of Pacific yew trees, Taxus brevifolia. It has been shown to have excellent antitumor activity in in vivo animal models, and recent studies have elucidated its unique mode of action, which involves abnormal polymerization of tubulin and disruption of mitosis. It is currently undergoing clinical trials against ovarian, breast and other types of cancer in the United States and France and preliminary results have confirmed it as a most promising chemotherapeutic agent. The results of paclitaxel clinical studies are reviewed in Rowinsky and Donehower, "The Clinical Pharmacology and Use of Antimicrotubule Agents in Cancer Chemotherapeutics" Pharmac. Ther., 52:35-84, 1991.

Recently, a semi-synthetic analog of paclitaxel named Taxotere® has also been found to have good antitumor activity in animal models. Taxotere® is also currently undergoing clinical trials in Europe and the United States. The structures of paclitaxel and Taxotere® are shown below; the conventional numbering system of the paclitaxel molecule is provided.



Taxol®: R = Ph; R' = acetyl

Taxotere®: R = t-butoxy; R' = hydrogen

One drawback of paclitaxel is its very limited water solubility requiring it to be formulated in nonaqueous pharmaceutical vehicles. One commonly used carrier is Cremophor EL which may itself have undesirable side effects in man. Accordingly, a number of research teams have prepared water-soluble derivatives of paclitaxel which are disclosed in the following references:

(a) Haugwitz et al, U.S. Patent No. 4,942,184;

(b) Kingston et al, U.S. Patent No. 5,059,699;

(c) Stella et al, U.S. Patent No. 4,960,790;

(d) European Patent Application 0,558,959 A1 published September 8, 1993.

(e) Vyas et al, Bioorganic & Medicinal Chemistry Letters, 1993, 3:1357-1360.

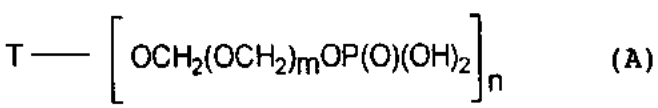
and

(f) Nicolaou et al, Nature, 1993, 364:464-466

Compounds of the present invention are phosphonooxymethyl ethers of taxane derivatives and pharmaceutically acceptable salts thereof. The water solubility of the salts facilitates preparation of pharmaceutical formulations.

SUMMARY OF THE INVENTION

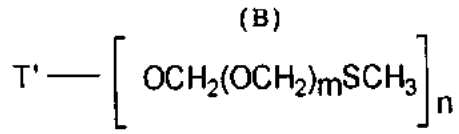
The present invention relates to taxane derivatives having the formula (A):



(A)

wherein T is a taxane moiety bearing on the C13 carbon atom a substituted 3-amino-2-hydroxypropanoyloxy group; n is 1, 2 or 3; m is 0 or an integer from 1 to 6 inclusive; or a pharmaceutically acceptable salt thereof.

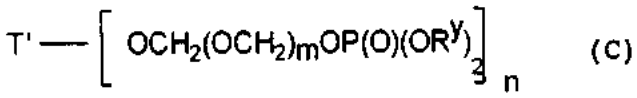
Another aspect of the present invention provides taxane derivatives having the formula (B):



(B)

wherein **T'** is T in which non-reacting hydroxy groups have been blocked, m and n are as defined under formula (A).

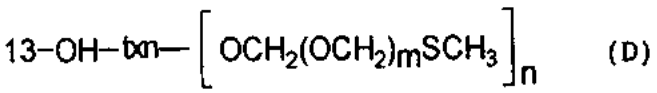
Yet another aspect of the present invention provides intermediates having the formula (C):



(C)

wherein T', m and n are as defined under formula (A), and R^y is a phosphono protecting group.

Another aspect of the present invention provides compounds of the formula (D):



(D)

wherein m and n are as defined above; and txn is a taxane moiety; or a C13 metal alkoxide thereof.

Another aspect of the present invention provides a method for inhibiting tumor in a mammalian host which comprises administering to said mammalian host an antitumor effective amount of a compound of formula (A).

Yet another aspect of the present invention provides a pharmaceutical composition which comprises an antitumor effective amount of a compound of formula (A) and a pharmaceutically acceptable carrier.

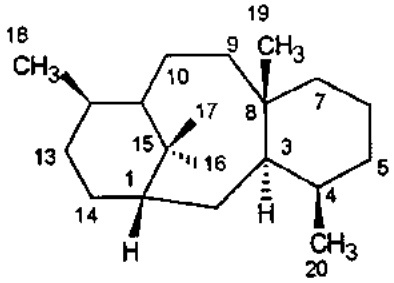
DETAILED DESCRIPTION OF THE INVENTION

In the application, unless otherwise specified explicitly or in context, the following definitions apply. "Alkyl" means a straight or branched saturated carbon chain having from one to six carbon atoms; examples include methyl, ethyl, n-propyl, isopropyl, n-butyl, sec-butyl, isobutyl, t-butyl, n-pentyl, sec-pentyl, isopentyl, and n-hexyl. "Alkenyl" means a straight or branched carbon chain having at least one carbon-carbon double bond, and having from two to six carbon atoms; examples include ethenyl, propenyl, isopropenyl, butenyl, isobutenyl, pentenyl, and hexenyl. "Alkynyl" means a straight or branched carbon chain having at least one carbon-carbon triple bond, and from two to six carbon atoms; examples include ethynyl, propynyl, butynyl, and hexynyl.

"Aryl" means aromatic hydrocarbon having from six to ten carbon atoms; examples include phenyl and naphthyl. "Substituted aryl" means aryl substituted with at least one group selected from C_{1-6} alkanoyloxy, hydroxy, halogen, C_{1-6} alkyl, trifluoromethyl, C_{1-6} alkoxy, aryl, C_{2-6} alkenyl, C_{1-6} alkanoyl, nitro, amino, and amido. "Halogen" means fluorine, chlorine, bromine, and iodine.

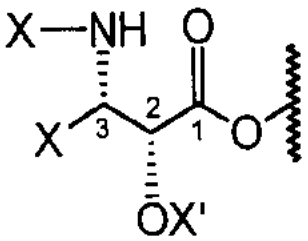
"Phosphono-" means the group $-P(O)(OH)_2$ and "phosphonooxymethoxy" or "phosphonooxymethyl ether" means generically the group $-OCH_2(OCH_2)_mOP(O)(OH)_2$. "(Methylthio)thiocarbonyl" means the group $-C(S)SCH_3$. "Methylthiomethyl" (also abbreviated as MTM) generically refers to the group $-CH_2SCH_3$.

"Taxane moiety" (also abbreviated as txn) denotes moieties containing the twenty carbon taxane core framework represented by the structural formula shown below with the absolute configuration.



The numbering system shown above is one used in conventional taxane nomenclature, and is followed throughout the application. For example, the notation C1 refers to the carbon atom labelled as "1"; C5-C20 oxetane refers to an oxetane ring formed by the carbon atoms labelled as 4, 5 and 20 with an oxygen atom; and C9 oxy refers to an oxygen atom attached to the carbon atom labelled as "9", said oxygen atom may be an oxo group, α- or β-hydroxy, or α- or β-acyloxy.

"Substituted 3-amino-2-hydroxypropanoyloxy" denotes a residue represented by the formula



(X is a nonhydrogen group and X' is hydrogen or a non-hydrogen group.) The stereochemistry of this residue is the same as the paclitaxel sidechain. This group is sometimes referred to in the application as the "C13 sidechain."

"Taxane derivative" (abbreviated as T) refers to a compound having a taxane moiety bearing a C13 sidechain.

"Heteroaryl" means a five- or six-membered aromatic ring containing at least one and up to four non-carbon atoms selected from oxygen, sulfur and nitrogen. Examples of heteroaryl include thienyl, furyl, pyrrolyl, imidazolyl, pyrazolyl, thiazolyl, isothiazolyl, oxazolyl, isoxazolyl, triazolyl, thiadiazolyl, oxadiazolyl, tetrazolyl, thiatriazolyl, oxatriazolyl, pyridyl, pyrimidyl, pyrazinyl, pyridazinyl, triazinyl, tetrazinyl, and like rings.

"Phosphono protecting groups" means moieties which can be employed to block or protect the phosphono functional group; preferably such protecting groups are those that can be removed by methods that do not appreciably affect the rest of the molecule. Suitable phosphonooxy protecting groups are well known to those skilled in the art and include for example benzyl and allyl groups.

"Hydroxy protecting groups" include, but is not limited to, ethers such as methyl, t-butyl, benzyl, p-methoxybenzyl, p-nitrobenzyl, allyl, trityl, methoxymethyl, methoxyethoxymethyl, ethoxyethyl, tetrahydropyranyl, tetrahydrothiopyranyl, and trialkylsilyl ethers such as trimethylsilyl ether and t-butyl-dimethylsilyl ether; esters such as benzoyl, acetyl, phenylacetyl, formyl, mono-, di-, and trihaloacetyl such as chloroacetyl, dichloroacetyl, trichloroacetyl, trifluoroacetyl; and carbonates such as methyl, ethyl, 2,2,2-trichloroethyl, allyl, benzyl, and p-nitrophenyl.

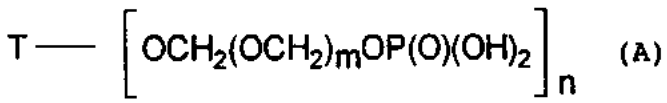
Additional examples of hydroxy and phosphono protecting groups may be found in standard reference works such as Greene and Wuts, Protective Groups in Organic Synthesis, 2d Ed., 1991, John Wiley & Sons, and McOmie, Protective Groups in Organic Chemistry, 1975, Plenum Press. Methods for introducing and removing protecting groups are also found in such textbooks.

"Pharmaceutically acceptable salt" means a metal or an amine salt of the acidic phosphono group in which the cation does not contribute significantly to the toxicity or biological activity of the active compound. Suitable metal salts include lithium, sodium, potassium, calcium, barium, magnesium, zinc, and aluminum salts. Preferred metal salts are sodium and potassium salts. Suitable amine salts are for example, ammonia, tromethamine (TRIS), triethylamine, procaine, benzathine, dibenzylamine, chloroprocaine, choline, diethanolamine, triethanolamine, ethylenediamine, glucamine, N-methylglucamine, lysine, arginine,

ethanolamine, to name but a few. Preferred amine salts are lysine, arginine and N-methylglucamine salts.

In the specification and in the claims, the term $-OCH_2(OCH_2)_mOP(O)(OH)_2$ is intended to emcompass both the free acid and its pharmaceutically acceptable salts, unless the context indicates specifically that the free acid is meant.

One aspect of the present invention provides taxane derivatives of the formula (A)

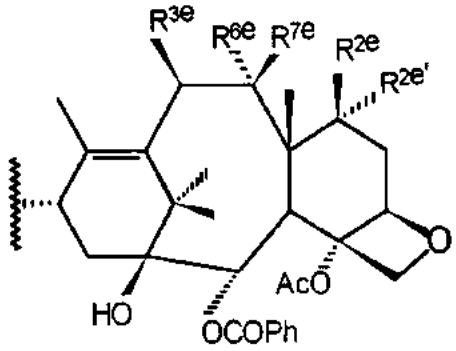


(A)

wherein T is a taxane moiety bearing on the C13 carbon atom a substituted 3-amino-2-hydroxypropanoyloxy group; n is an 1, 2 or 3; m is 0, or an integer from 1 to 6 inclusive, or a pharmaceutically acceptable salt thereof.

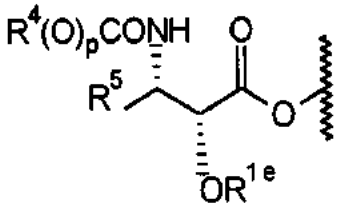
In one embodiment the taxane moiety contains at least the following functionalities: C1-hydroxy, C2-benzoyloxy, C4-acetyloxy, C5-C20 oxetane, C9-oxy, and C11-C12 double bond.

In a preferred embodiment the taxane moiety is derived from a residue having the formula



wherein $R^{2e'}$ is hydrogen and R^{2e} is hydrogen, hydroxy, - $OC(O)R^x$, or $-OC(O)OR^x$; or R^{2e} is hydrogen and $R^{2e'}$ is fluoro; R^{3e} is hydrogen, hydroxy, $-OC(O)R^x$, C_{1-6}alkyloxy, or $-OC(O)OR^x$; one of R^{6e} or R^{7e} is hydrogen and the other is hydroxy or $-OC(O)R^x$; or R^{6e} and R^{7e} together form an oxo group; R^x is as defined below.

In another embodiment, the C13 sidechain is derived from a residue having the formula



wherein R^{1e} is hydrogen or $-C(O)R^x$, $-C(O)OR^x$; R^4 and R^5 are independently C_{1-6} alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, or -Z-R^5; Z is a direct bond, C_{1-6} alkyl or C_{2-6} alkenyl; R^6 is aryl, substituted aryl, C_{3-6} cycloalkyl, or heteroaryl; and R^x is C_{1-6} alkyl optionally substituted with one to six same or different halogen atoms, C_{3-6} cycloalkyl, C_{2-6} alkenyl, or a radical of the formula

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