DOLASTATIN-15 DERIVATIVES IN COMBINATION WITH TAXANES

BACKGROUND OF THE INVENTION

Cancer is a disease for which many potentially effective treatments are available. However, due to the prevalence of cancers of various types and the serious effects it can have, more effective treatments, especially those with fewer adverse side effects than currently available forms of treatment, are needed.

SUMMARY OF THE INVENTION

This invention relates to pharmaceutical compositions useful in treating cancer in a mammal. The pharmaceutical compositions of the present invention comprise two compounds: a first compound which is paclitaxel, taxotere or a modified taxane or taxoid analog and a second compound, which is a compound of Formula I:

$$R^1\ R^2\ N\text{-}CHX\text{-}CO\text{-}A\text{-}B\text{-}D\text{-}(E)_s\text{-}(F)_t\text{-}(G)_u\text{-}K \qquad (I)$$

Formula I is discussed in detail below. Some examples of compounds of Formula I are specifically presented herein. For example, compounds of Formula I can be those in which R^1 and R^2 are each methyl or ethyl; X is isopropyl, sec-butyl or tert-butyl; s is 1; t and u are each 0; A is valyl, isoleucyl or 2-tert-butylglycyl; B is N-methylvalyl, 1-isoleucyl or 2-tert-butylglycyl; D is thiazolidinyl-carbonyl, 3,4-dehydroprolyl or prolyl; E is prolyl, thiazolidinyl-4-carbonyl, homoprolyl, hydroxyprolyl or 3,4-dehydroprolyl; and K is a substituted amino moiety having the formula $R^5\text{-}N\text{-}R^6$, wherein R^5 is hydrogen or $C_1\text{-}C_4$-alkoxy and R^6 is a monovalent radical such as (1)- or (2)-

adamantyl; (CH_2)v-phenyl with v=1; α,α-dimethylbenzyl; a C_1-C_{12} linear or branched hydroxyalkyl group, such as -$C(CH_3)_2$-CH_2-CH_2-OH, also referred to as 3-hydroxy-1,1-dimethylpropyl; a C_3-C_{10} cycloalkyl group, such as bicyclo[3.3.0]octa-1-yl, 1-methylcyclopentyl or 1-methylcyclohexyl; or a C_1-C_{12} linear or branched alkyl group, such as

$-C(CH_3)_3$, also referred to as tert-butyl;

$-\underset{(CH_3)_2}{C}-CH_2-CH_3$, also referred to as 1,1-dimethylpropyl;

$-\underset{CH_3}{C}(CH_2-CH_3)_2$, also referred to as 1-methyl-1-ethylpropyl;

$-\underset{CH_3}{CH}-C(CH_3)_3$, also referred to as (S)- or (R)-1-methyl-2,2-dimethyl-propyl;

$-\underset{C_2H_5}{CH}-CH(CH_3)_2$, also referred to as (S)- or (R)-1-ethyl-2-methylpropyl;

$-\underset{CH(CH_3)_2}{CH}-CH(CH_3)_2$, also referred to as 1-isopropyl-2-methyl-propyl; or

$-C(CH_3)_2-CH(CH_3)_2$, also referred to as 1,1-dimethyl-2-methylpropyl;

$-CH(CH_3)_2$, also referred to as isopropyl;

$-CH(CH_3)CH_2CH_3$, sec-butyl [(S) or (R)]; or

$-CH(CH_3)CH(CH_3)_2$, also referred to as 1,2-dimethylpropyl.

Each compound is present in the pharmaceutical composition in an effective amount. The pharmaceutical composition can include one or more of each type of compound (e.g., one or more of the first type of compound, such as paclitaxel or paclitaxel and taxotere and one or more compounds of Formula I).

This invention also relates to methods of treating cancer in a mammal in which the pharmaceutical compounds described herein are used. In the method of the present invention, the two compounds are administered in the

pharmaceutical composition or as individual/separate compounds which are given sufficiently close in time to have the desired effect.

It has been discovered that, surprisingly the combination of paclitaxel, taxotere or a modified taxane or taxoid analog as described herein and a compound having Formula I as described herein provides enhanced or therapeutically synergistic anticancer effects *in vivo*. For purposes of this invention, two drugs are considered therapeutically synergistic if a combination regimen produces a significantly better tumor cell kill than the best constituent when it is administered alone at optimal or maximum tolerated doses. Differences in tumor cell kill less than half a decade are not considered signficant.

BRIEF DESCRIPTION OF THE DRAWINGS

The Figure depicts compounds i-xvii, as examples of compounds of Formula I.

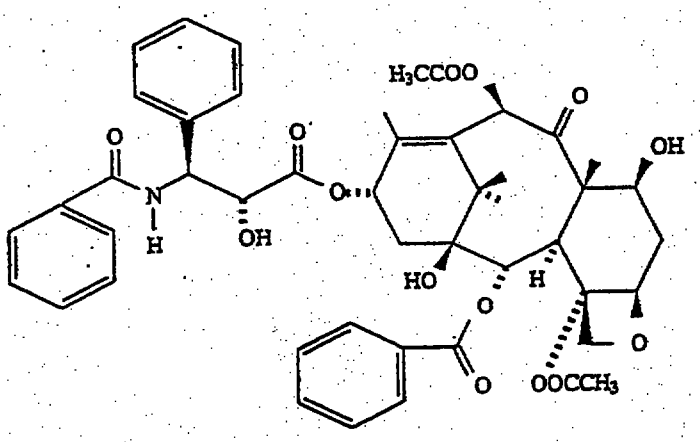
DETAILED DESCRIPTION OF THE INVENTION

The present invention relates to pharmaceutical compositions useful in treating cancer in a mammal. The pharmaceutical composition of the present invention comprises two compounds: a first compound which is paclitaxel, taxotere or a modified taxane or taxoid analog and a second compound of Formula I as further described below. Each compound is present in the pharmacuetical composition in an effective amount. One or more of each type of compound can be present in the pharmaceutical composition or administered in the present method. As used herein the term "an effective amount" refers to an amount sufficient to elicit the desired biological response. In the instant invention, the desired biological response is inhibition (partial or total) of formation of a tumor or a hematological malignancy, reversal of the development of a

solid tumor or other malignancy or prevention or reduction of its further progression.

PACLITAXEL, TAXOTERE OR A MODIFIED TAXANE OR TAXOID ANALOG

Paclitaxel (Taxol®), which is one example of a first compound of the pharmaceutical composition, is a diterpene isolated from the bark of the Western (Pacific) yew, *Taxus brevifolia* and is representative of a class of therapeutic agent having a taxane ring system. For purposes of this invention any therapeutic agent which has a taxane ring system is defined as a "taxane". The formula for paclitaxel is:



Paclitaxel and its analogs have been produced by partial synthesis from 10-deacetylbaccatin III, a precursor obtained from yew needles and twigs, and by total synthesis. See Holton, *et al.*, *J. Am. Chem. Soc. 116*:1597-1601 (1994) and Nicolaou, *et al.*, *Nature 367*:630 (1994). Paclitaxel has been demonstrated to possess antineoplastic activity. More recently, it was shown that the antitumor activity of paclitaxel is due to a promotion of microtubule polymerization. See Kumar, N., *J. Biol. Chem. 256*:10435-10441 (1981); Rowinsky, *et al.*, *J. Natl. Cancer Inst. 82*:1247-1259 (1990); and Schiff, *et al.*, *Nature 277*:655-667 (1979). Paclitaxel has now demonstrated efficacy in several human tumors in clinical trials. See McGuire, *et*

al., *Ann. Int. Med.* *111*:237-279 (1989); Holmes, *et al.*, *J. Natl. Cancer Inst.* *83*:1797-1805 (1991); Kohn *et al.*, *J. Natl. Cancer Inst.* *86*:18-24 (1994); and Kohn, *et al.*, *American Society for Clinical Oncology* *12* (1993). Paclitaxel is available from Bristol-Myers Squibb Company, New York, NY by the registered tradename Taxol®.

The first compound in the pharmaceutical composition is typically paclitaxel (Taxol ®), taxotere or a modified taxane or taxoid analog. The modified taxane or taxoid analogs are those compounds having a taxane ring bearing modified side chains. A number of these analogs have improved properties, such as greater water solubility and stability than that of naturally occurring paclitaxel. For example, RPR109881 is a new oral and iv active taxoid analog under development by Rhone-Poulenc Rhorer and currently in Phase I Clinical Trials. These analogs are known to those of skill in the art and are disclosed, for example, in U.S. Patent Nos. 5,278,324; 5,272,171; 5,254,580; 5,250,683; 5,248,796; and 5,227,400, the disclosures of which are incorporated herein by reference. Taxotere can be prepared by the method in WO 93/18210, the disclosure of which is incorporated herein by reference. In particular embodiments, the first compound in the pharmaceutical composition is paclitaxel or taxotere.

COMPOUNDS OF FORMULA I

A number of short peptides with significant activity as inhibitors of cell growth have been isolated from the Indian Ocean sea hare *Dolabella auricularia* (Bai, *et al.*, *Biochem. Pharmacology*, *40*: 1859-1864 (1990); Beckwith *et al.*, *J. Natl. Cancer Inst.*, *85*: 483-488 (1993) and references cited therein). These include Dolastatins 1-10 (U.S. Patent No. 4,816,444, issued to Pettit *et al.*) and Dolastatin-15 (European Patent Application No. 398558). Dolastatin-15, for example, markedly inhibits the growth of

the National Cancer Institute's P388 lymphocytic leukemia cell line, a strong predictor of efficacy against various types of human malignancies. This compound, however, is present only in trace quantities in the sea hare and is difficult to isolate, expensive to synthesize and suffers from poor aqueous solubility.

The compounds of Formula I are derivatives of Dolastatin-15, which overcome the above-mentioned disadvantages of Dolastatin-15 while retaining antineoplastic activity or exhibiting greater antineoplastic activity than the natural product. The Dolastatin-15 derivatives of Formula I, which are employed in combination with paclitaxel, taxotere or a modified taxane or taxoid analog in the present invention, can be synthesized, as described herein and in related copending application U.S.S.N. 08/472,453, filed June 7, 1995, the teachings of which are incorporated herein in their entirety.

The Dolastatin-15 derivatives of Formula I generally comprise L-amino acids, but they can also contain one or more D-amino acids, as described in related copending application U.S.S.N. 08/472,453 filed on June 7, 1995. The compounds of Formula I can also be present as salts with physiologically-compatible acids, such as, but not limited to, hydrochloric acid, citric acid, tartaric acid, lactic acid, phosphoric acid, methanesulfonic acid, acetic acid, formic acid, maleic acid, fumaric acid, malic acid, succinic acid, malonic acid, sulfuric acid, L-glutamic acid, L-aspartic acid, pyruvic acid, mucic acid, benzoic acid, glucuronic acid, oxalic acid, ascorbic acid and acetylglycine.

For purposes of the present invention, the term "monovalent radical" is intended to mean an electrically neutral molecular fragment capable of forming one covalent bond with a second neutral molecular fragment. Monovalent

radicals include the hydrogen atom, alkyl groups (e.g. methyl, ethyl, propyl and tert-butyl groups), cycloalkyl groups, hydroxy alkyl groups, adamantyl groups, halogen atoms (e.g. fluorine, chlorine and bromine atoms), aryl groups (e.g. phenyl, benzyl and naphthyl groups) and alkoxy groups (e.g. methoxy and ethoxy groups). Two monovalent radicals on adjacent sigma-bonded atoms can also form a pi bond between the adjacent atoms. Two monovalent radicals may also be linked together, for example, by a polymethylene unit to form a cyclic structure. For example, the unit -N(R)R', wherein R and R' are monovalent radicals, can, together with the nitrogen atom, form a heterocyclic ring. In addition, two monovalent radicals bonded to the same atom can also form a divalent radical, such as an alkylidene group, for example, a propylidene group, or an oxygen atom.

More specifically, for the compounds of Formula I:

R^1 is alkyl, such as C_1-C_3; cycloalkyl, such as cyclopropyl; alkylsulfonyl, such as C_1-C_3; fluoroalkyl, such as fluoroethyl, difluoroethyl, fluoroisopropyl; aminosulfonyl which may be substituted by alkyl, such as methyl;

R^2 is hydrogen; alkyl, such as C_1-C_3; fluoroalkyl, such as fluoroethyl, difluoroethyl, fluoroisopropyl; cycloalkyl, such as cyclopropyl;

R^1-N-R^2 together may be a pyrrolidino or piperidino residue;

A is a valyl, isoleucyl, leucyl, allo-isoleucyl, 2,2-dimethylglycyl, 2-cyclopropylglycyl, 2-cyclopentylglycyl, 3-tert-butylalanyl, 2-tert-butylglycyl, 3-cyclohexylalanyl, 2-ethylglycyl,

2-cyclohexylglycyl, norleucyl or norvalyl residue;

B is a N-alkyl-valyl, -norvalyl, -leucyl, -isoleucyl, -2-tert-butylglycyl, -3-tert-butylalanyl, -2-ethylglycyl, -2-cyclopropylglycyl, -2-cyclopentylglycyl, norleucyl or -2-cyclohexylglycyl residue where N-alkyl is preferably N-methyl or N-ethyl;

D is a prolyl, homoprolyl, hydroxyprolyl, 3,4-dehydroprolyl, 4-fluoroprolyl, 3-methylprolyl, 4-methylprolyl, 5-methylprolyl, azetidine-2-carbonyl, 3,3-dimethylprolyl, 4,4-difluoroprolyl, oxazolidine-4-carbonyl or thiazolidine-4-carbonyl residue;

E is a prolyl, homoprolyl, hydroxyprolyl, 3,4-dehydroprolyl, 4-fluoroprolyl, 3-methylprolyl, 4-methylprolyl, 5-methylprolyl, azetidine-2-carbonyl, 3,3-dimethylprolyl, 4,4-difluoroprolyl, oxazolidine-4-carbonyl or thiazolidine-4-carbonyl residue;

F and G are independently selected from the group consisting of prolyl, homoprolyl, hydroxyprolyl, thiazolidinyl-4-carbonyl, 1-aminopentyl-1-carbonyl, valyl, 2-tert-butylglycyl, isoleucyl, leucyl, 3-cyclohexylalanyl, phenylalanyl, N-methylphenylalanyl, tetrahydrosioquinolyl-2-histidyl, 1-aminoindyl-1-carbonyl, 3-pyridylalanyl, 2-cyclohexylglycyl, norleucyl, norvalyl, neopentylglycyl, trytophanyl, glycyl, 2,2-dimethylglycyl alanyl, ß-alanyl and 3-naphthylalanyl residues;

X is hydrogen, alkyl (such as C_1-C_5), cycloalkyl (such as C_3-C_7), -CH_2-cyclohexyl or arylalkyl (such as benzyl or phenethyl);

s, t and u are independently 0 or 1; and

K is hydroxy, alkoxy (such as C_1-C_4), phenoxy, benzyloxy or a substituted or unsubstituted amino moiety.

In addition, the compounds of Formula I can be present as a salt thereof with physiologically tolerated acids.

One subclass of compounds of this invention includes compounds of Formula I wherein R^1-N-R^2 is a pyrrolidinyl or piperidinyl residue.

Another subclass of compounds of this invention includes compounds of Formula I wherein K is an amino moiety of the formula R^5-N-R^6, wherein:

R^5 is hydrogen, or hydroxy, or C_{1-7} alkoxy, or benzyloxy, or phenyloxy or C_{1-12} linear or branched hydroxyalkyl, such as 3-hydroxy-1,1-dimethylpropyl, or C_{1-7} linear or branched alkyl (which may be substituted by one or more fluoro atoms), or C_{3-10}-cycloalkyl, such as, bicyclo[3.3.0]octa-1yl, 1-methylcyclopentyl or 1-methylcylcohexyl; or benzyl (which may be substituted by up to three substituents which may independently be CF_3, nitro, C_{1-7} alkylsulfonyl, C_{1-4} alkoxy, phenoxy, benzoxy, halogen, C_{1-4}-alkyl, cyano, hydroxy, $N(CH_3)_2$, COOMe, COOEt, COOiPr, or $COONH_2$);

R^6 is hydrogen, or C_{1-12} linear or branched alkyl (which may be substituted by one or more fluoro atoms), or C_{1-12} linear or branched hydroxyalkyl, such as 3-hydroxy-1,1-dimethylpropyl, or C_{3-10}-cycloalkyl, such

as bicyclo[3.3.0]octa-1-yl, or 1-methylcyclopentyl or 1-methylcyclohexyl; or -$(CH_2)_v$-C_{3-7}- cycloalkyl (v=0,1,2, or 3), or norephedryl, or norpseudoephedryl, or quinolyl, or pyrazyl, or -CH_2-benzimidazolyl, or (1)-adamantyl, or (2)-adamantyl- -CH_2-adamantyl, or alpha-methyl-benzyl, or alpha-dimethylbenzyl, or -$(CH_2)_v$-phenyl (v=0,1,2, or 3; which may be substituted by up to two substituents which may independently be CF_3, nitro, C_{1-7} alkylsulfonyl, C_{1-4} alkoxy, phenoxy, benzoxy, halogen, C_{1-4}-alkyl which may form a cyclic system, cyano, hydroxy, $N(CH_3)_2$, COOMe, COOEt, COOiPr, or $COONH_2$), or -$(CH_2)_m$-naphthyl (m=0 or 1); or -$(CH_2)_w$-benzhydryl (w=0,1, or 2); or biphenyl or picolyl or benzothiazolyl or benzoisothiazolyl or benzopyrazolyl or benzoxazolyl or -$(CH_2)_m$-fluorenyl (m=0 or 1); or pyrimidyl or -(CH_2)m-indanyl (m=0 or 1); or -$(CH_2CH_2O)_y$-CH_3 (y=0,1,2,3,4, or 5), or -$(CH_2CH_2O)_y$-CH_2CH_3 (y=0,1,2,3,4, or 5), or NH-C_6H_5 (which may be substituted by up to two substituents which may independently be CF_3, nitro, C_{1-7} alkylsulfonyl, C_{1-4} alkoxy, halogen, C_{1-4} alkyl which may form a cyclic system, cyano, hydroxy, COOMe, COOEt, COOiPr, or $COONH_2$), or -NCH_3-C_6H_5 or -NH-CH_2-C_6H_5 or -NCH_3-CH_2-C_6H_5 or 5-membered heteroaryl which may be substituted by up to two substituents which may independently be CF_3, nitro, thiomethyl, thioethyl, C_{3-6}-cycloalkyl, -CH_2-COOEt, C_{3-4}-alkylene group forming a bicyclic system with the heterocycle, phenyl; or -CHR^7-5-membered heteroaryl (which may be substituted by up to two substituents which may independently be CF_3, nitro, cyano, halogen, COOMe, COOEt, COOiPr, $CONH_2$, C_{1-4}-alkyl, C_{1-4}-alkoxy, phenyl, benzyl, naphthyl, or C_{1-7}-alkylsulfonyl [R^7 = hydrogen, linear or branched C_{1-5} alkyl, benzyl; or R^7 and R^5 together form a group -$(CH_2)_3$- or -$(CH_2)_4$-).

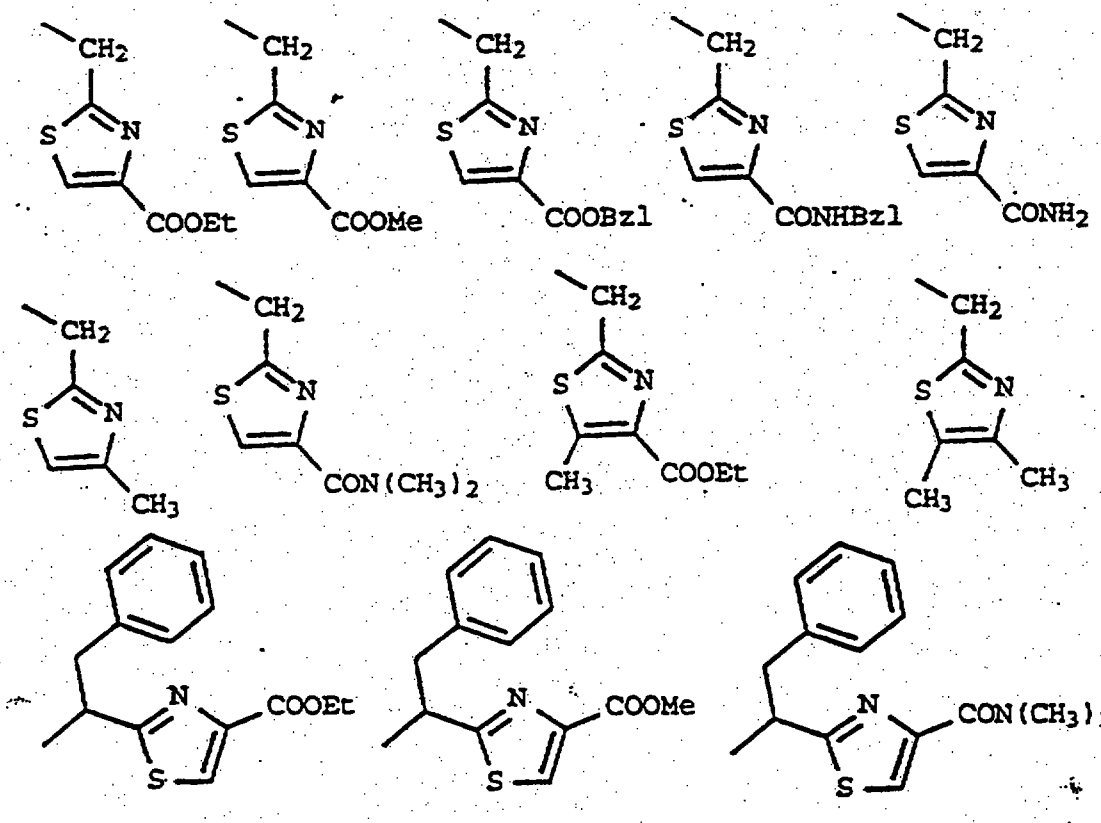
This subclass includes compounds of Formula I wherein s, t and u are independently 0 or 1; R^1, R^2 and X are lower alkyl, A is a lower alkyl amino acid, B is a N-loweralkylated lower alkyl amino acid; D,E,F,G and K are as previously defined. With the foregoing in mind, three sets of such compounds can thus be depicted by the following formulas II, III, and IV:

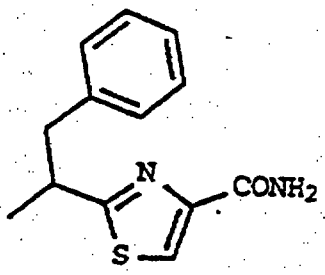
R^1R^2N-CXH-CO-A-B-Pro-Pro-F-G-K II

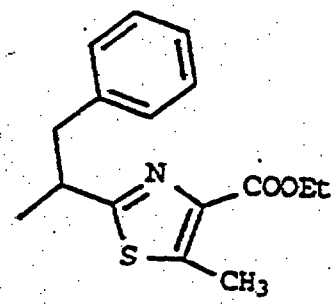
R^1R^2N-CXH-CO-A-B-Pro-Pro-F-K III

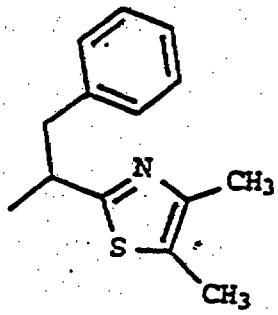
R^1R^2N-CXH-CO-A-B-Pro-Pro-K IV

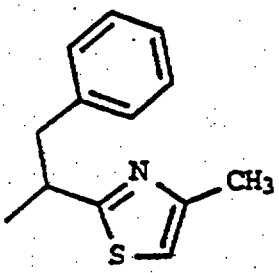
-CHR^7-5-membered heteroaryl may, for example, be represented by one of the following residues:

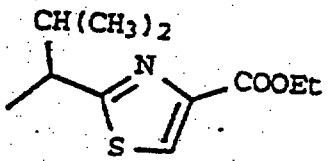


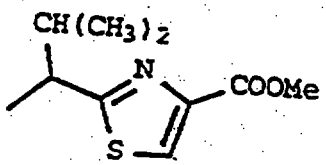

CONH2

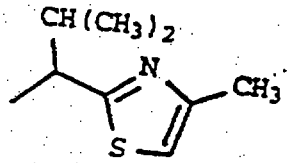

COOEt
CH3

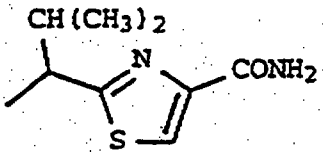

CH3
CH3

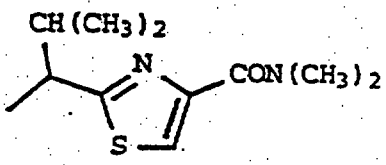

CH3

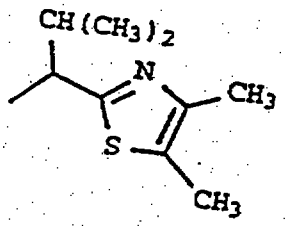

CH(CH3)2
COOEt

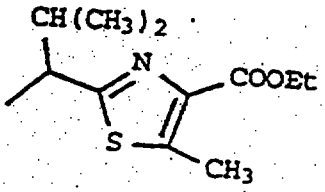

CH(CH3)2
COOMe

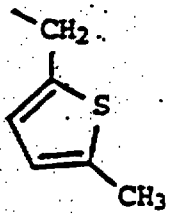

CH(CH3)2
CH3

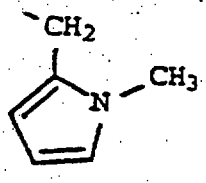

CH(CH3)2
CONH2

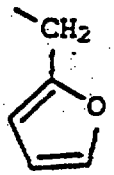

CH(CH3)2
CON(CH3)2

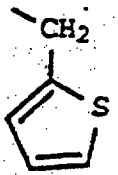

CH(CH3)2
CH3
CH3

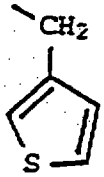

CH(CH3)2
COOEt
CH3

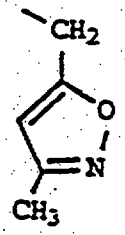

CH2
CH3


CH2
CH3

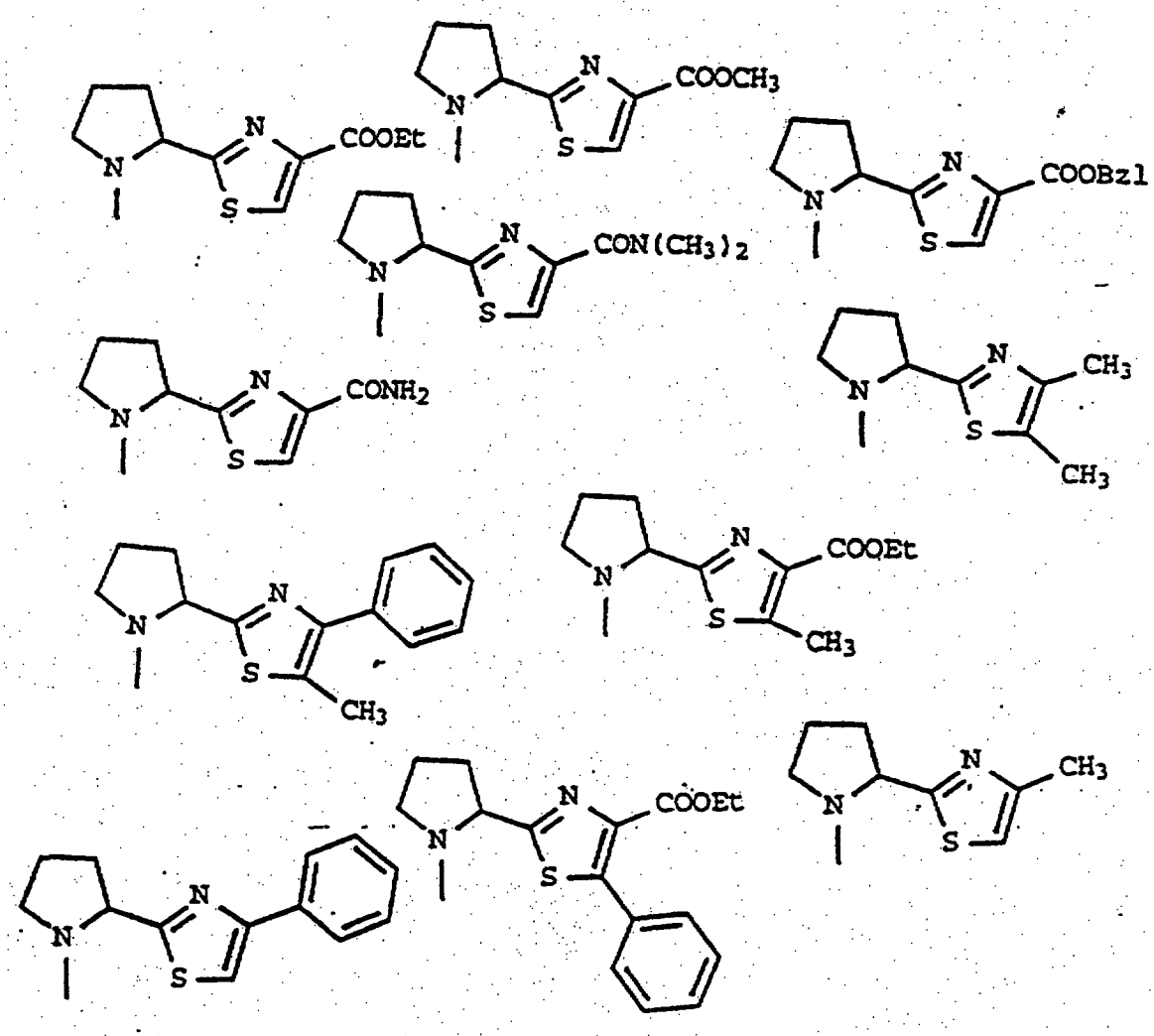

CH2


CH2

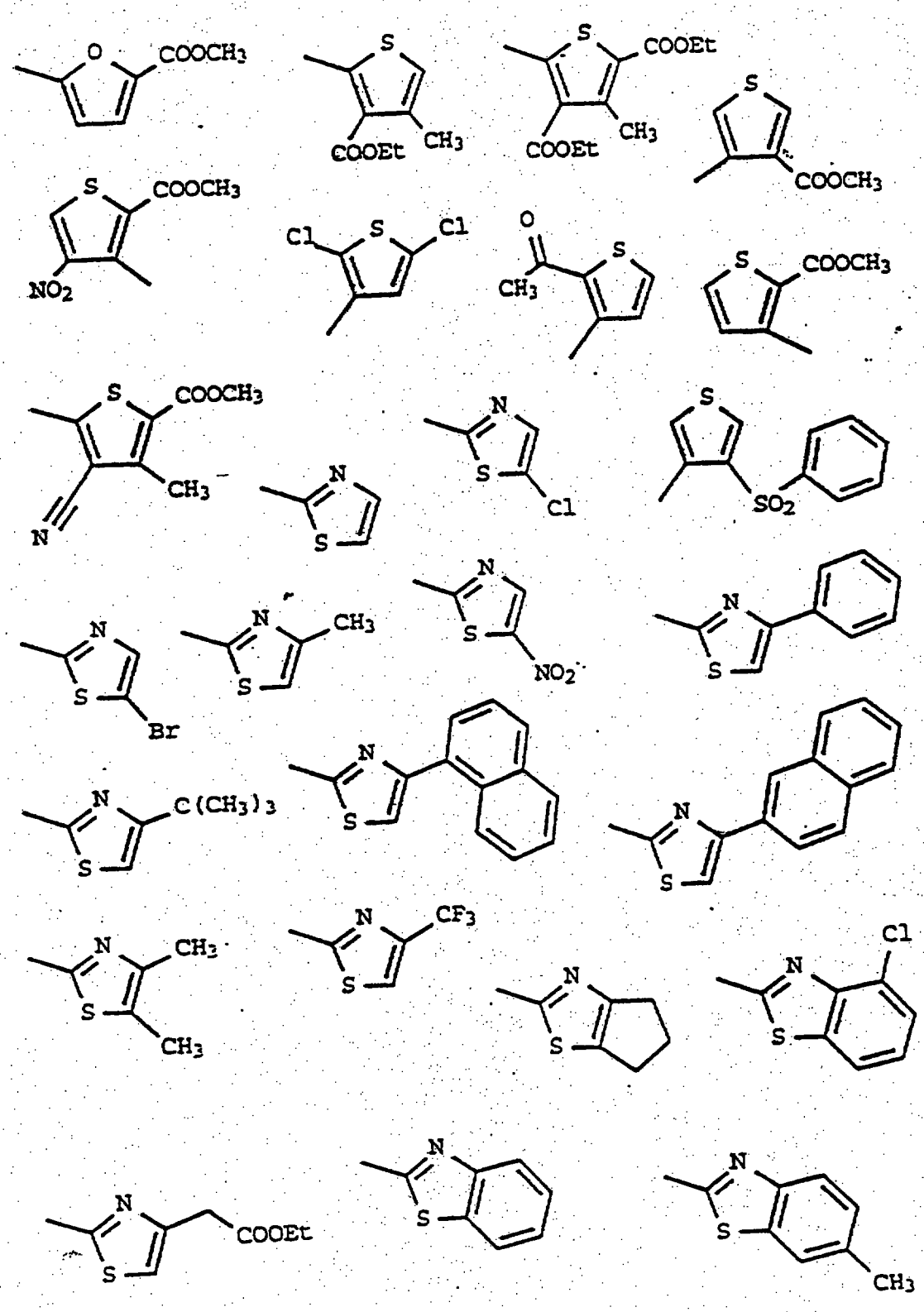

CH2

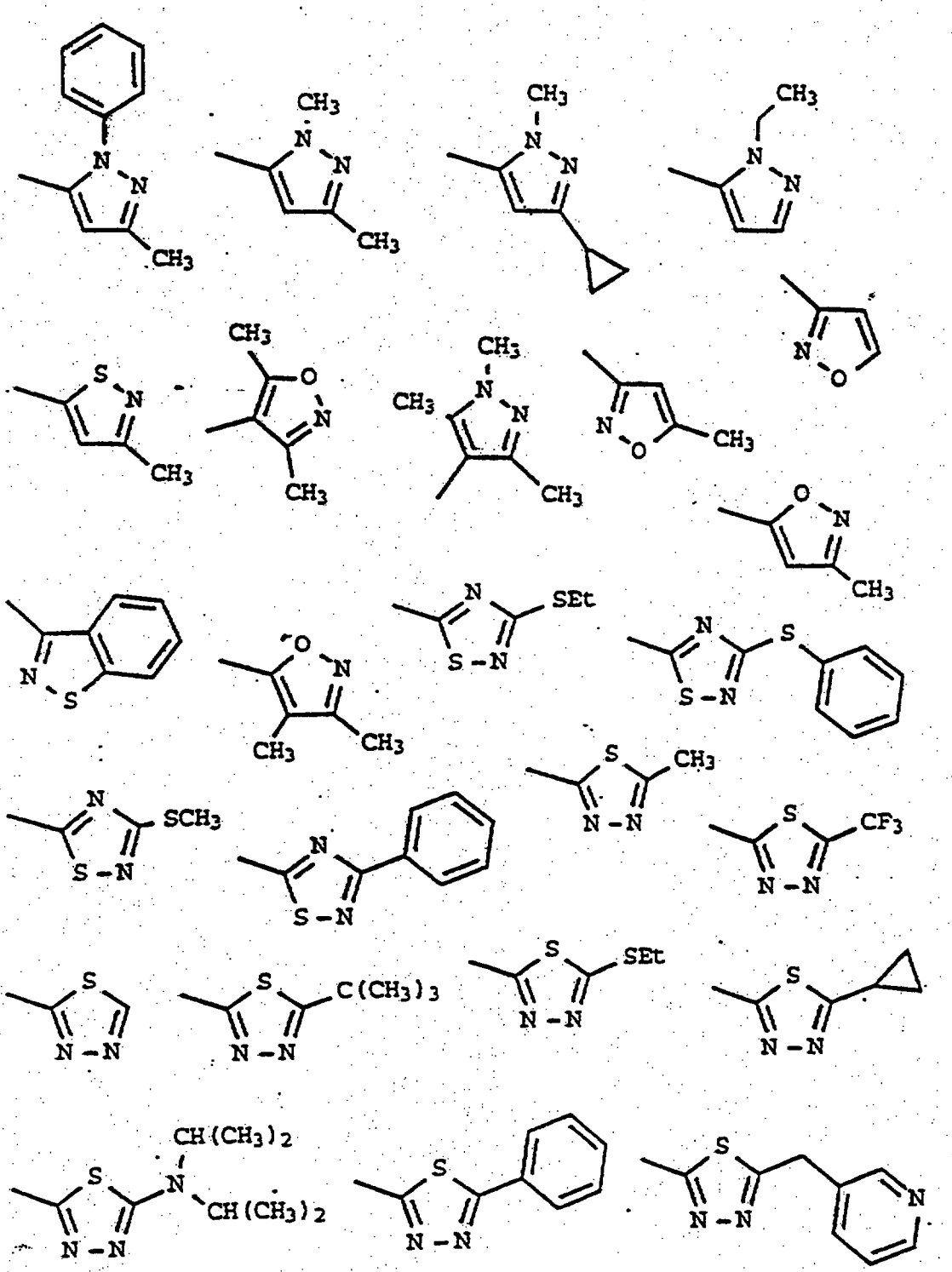

CH2
CH3

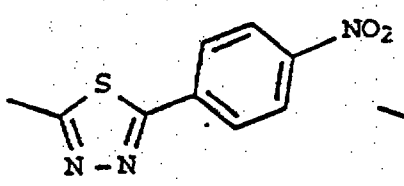
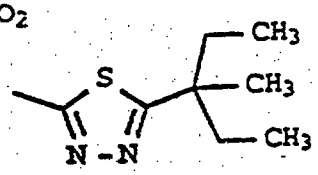
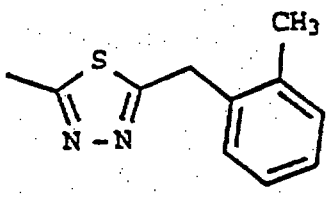
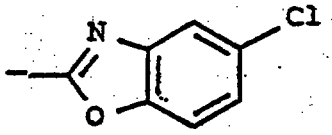
-NR^5CHR^7-5-membered heteroaryl may, for example, be represented by the following residues:



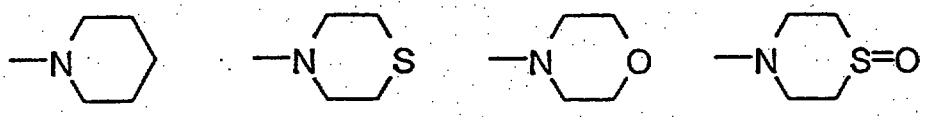
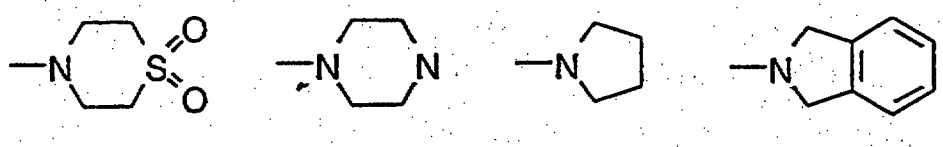
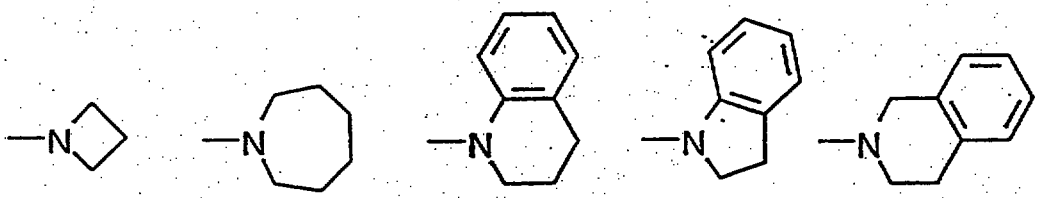
5-membered heteroaryl may, for example, be represented by the following residues:





In another subclass of compounds of this invention R^5-N-R^6 together may form structures selected from the group consisting of:

Still another subclass of compounds of this invention includes, for example, compounds of Formula I wherein s, t and u are 1 and K is a hydroxy, alkoxy, phenoxy or benzyloxy moiety.

Yet another subclass of compounds of this invention includes, for example, compounds of Formula I wherein s and t are 1, u is 0 and K is a hydroxy, alkoxy, phenoxy or benzyloxy moiety.

Another subclass of compounds of this invention includes, for example, compounds of Formula I wherein s is 1, t and u are 0 and K is a hydroxy, alkoxy, phenoxy or benzyloxy moiety.

In particular embodiments, the second compound in the pharmaceutical composition of the invention is a compound of Formula I in which R^1 and R^2 are each methyl or ethyl; X is isopropyl, sec-butyl or tert-butyl; s is 1; t and u are each 0; A is valyl, isoleucyl or 2-tert-butylglycyl; B is N-methylvalyl, 1-isoleucyl or -2-tert-butylglycyl; D is prolyl, thiazolidinyl-4-carbonyl or 3,4 dehydroprolyl; E is prolyl, thiazolidinyl-4-carbonyl, homoprolyl, 3,4-dehydroprolyl or hydroxyprolyl; and K is a substituted or unsubstituted amino moiety having the formula R^5-N-R^6.

In a further embodiment, the second compound in the pharmaceutical composition is a compound of Formula I in which R^1 and R^2 are each methyl or ethyl; X is isopropyl, sec-butyl or tert-butyl; s is 1; t and u are each 0; A is valyl, isoleucyl or 2-tert-butylglycyl; B is N-methylvalyl, 1-isoleucyl or 2-tertbutylglycyl; D is prolyl, thiazolidinyl-4-carbonyl, or 3,4-dehydroprolyl; E is prolyl, thiazolidinyl-4-carbonyl, homoprolyl, 3,4-dehydroprolyl or hydroxyprolyl; and K is a substituted amino moiety having the formula R^5-N-R^6 wherein R^5 is hydrogen or C_1-C_4 alkoxy and R^6 is a C_1-C_{12} linear or branched alkyl group or a C_1-C_{12} linear or branched

hydroxyalkyl group represented, for example, by the following monovalent radicals:

$-C(CH_3)_2-CH_2-CH_2-OH$, also referred to as 3-hydroxy-1,1-dimethylpropyl;

$-C(CH_3)_3$, also referred to as tert-butyl;

$-\underset{(CH_3)_2}{C}-CH_2-CH_3$, also referred to as 1,1-dimethyl propyl;

$-\underset{CH_3}{C}(CH_2-CH_3)_2$, also referred to as 1-methyl-1-ethyl propyl;

$-\underset{CH_3}{CH}-C(CH_3)_3$, also referred to as (S)- or (R)-1-methyl-2,2-dimethyl propyl;

$-\underset{C_2H_5}{CH}-CH(CH_3)_2$, also referred to as (S)- or (R)-1-ethyl-2-methyl propyl;

$-\underset{CH(CH_3)_2}{CH}-CH(CH_3)_2$, also referred to as 1-isopropyl-2-methyl butyl; or

$-C(CH_3)_2-CH(CH_3)_2$, also referred to as 1,1-dimethyl-2-methyl propyl

$-CH(CH_3)_2$, also referred to as isopropyl

$-CH(CH_3)CH_2CH_3$, also referred to as sec-butyl, (S)- or (R)-

$-CH(CH_3)CH(CH_3)_2$, also referred to as 1,2-dimethylpropyl.

In another embodiment, the second compound in the pharmaceutical composition of the invention is a compound of Formula I in which R^1 and R^2 are each methyl or ethyl; X is isopropyl, sec-butyl or tert-butyl; s is 1; t and u are each 0; A is valyl, isoleucyl or 2-tert-butylglycyl; B is N-methylvalyl, 1-isoleucyl or 2-tert-butylglycyl; D is prolyl, thiazolidinyl-4-carbonyl, 3,4-dehydroprolyl; E is prolyl, thiazolidinyl-4-carbonyl, homoprolyl, 3,4-dehydroprolyl or hydroxyprolyl; and K is a substituted amino moiety having the formula R^5-N-R^6 wherein R^5 is hydrogen or C_1-C_4 alkoxy and R^6 is a monovalent radical such as a C_3-C_{10} cycloalkyl group (e.g. cyclobutyl, cyclopentyl, cyclohexyl, or 1-methylcyclopentyl, or 1-

methylcyclohexyl or bicyclo[3.3.0]octa-1-yl); a (1)- or (2)-adamantyl group; (CH_2)v-phenyl with v=1 or α,α-dimethylbenzyl.

In a further embodiment, the second compound in the pharmaceutical composition of the invention is a compound of Formula I in which R^1 and R^2 are each methyl; X is isopropyl; s is 1; t and u are each 0; A is valyl; B is N-methylvalyl; D is prolyl; E is prolyl; and K is a substituted amino moiety having the formula R^5-N-R^6 wherein R^5 is benzyl and R^6 is hydrogen. This compound corresponds to compound (xvii) depicted in the Figure. The results of the use of compound (xvii) of Formula I, in combination with paclitaxel are presented in Tables 1-4.

The pharmaceutical compositions of the present invention may optionally contain a pharmaceutically acceptable carrier. Pharmaceutically acceptable carriers are well known to those who are skilled in the art. The choice of a carrier will be determined in part by the particular compounds in the combination, as well as by the particular method used to administer the pharmaceutical composition. Accordingly, there is a wide variety of suitable formulations of the pharmaceutical compositions of the present invention. For example, paclitaxel (Taxol®) is available as a sterile nonpyrogenic solution which includes polyoxyethylated castor oil (Cremophor® EL) and dehydrated alcohol, USP.

In another aspect, the present invention comprises a method for partially or totally inhibiting formation of, or otherwise treating (e.g., reversing or inhibiting the further development of) solid tumors (e.g., tumors of the lung, breast, colon, prostate, bladder, rectum, or endometrium) or hematological malignancies (e.g., leukemias, lymphomas) in a mammal, for example, a human, by administering to the mammal an effective amount of a first compound which is paclitaxel, taxotere or a modified taxane

or taxoid analog and administering an effective amount of a second compound, which is a compound of Formula I.

The two compounds are administered in combination according to the invention. The term in combination in this context means that the drugs are given either simultaneously or sequentially. If given sequentially, one of the two compounds is usually detectable in the serum of the subject at the onset of administration of the other compound. In one embodiment, a compound of Formula I is administered first, followed by administration of the above described first compound, such as paclitaxel. In a specific embodiment, paclitaxel is administered about one hour after administration of a compound of Formula I. Alternatively, the first compound and the second compound can be administered simultaneously, or the first compound could be administered first, followed by administration of a second compound, which is a compound of Formula I.

The first and the second compounds may be administered alone or with a pharmaceutically accepted carrier or diluent appropriate for the desired route of administration. Administration can be by any of the means which are conventional for pharmaceutical, preferably oncological, agents, including oral and parenteral means such as subcutaneously, intravenously, intramuscularly, intraperitoneally, nasally or rectally. Such pharmaceutical compositions may also contain other therapeutically active ingredients.

The dosage administered to the mammal, such as a human, includes a combination of an effective amount of a compound of Formula I and an effective amount of paclitaxel, taxotere or modified taxane or taxoid analog, as described herein. For a particular condition or method of treatment, the dosage can be determined empirically, using known methods, and will depend upon factors such as the biological activity, mechanism of action, cross

resistance, overlapping toxicity and toxicity profile of the particular compounds employed; the means of administration; the age, health and body weight of the recipient; the nature and extent of the symptoms; the frequency of treatment; the administration of other therapies; and the effect desired.

A typical daily dose of the compounds of Formula I will be from about 5 to about 250 milligrams per kilogram of body weight by oral administration and from about 1 to about 100 milligrams per kilogram of body weight by parenteral administration. A typical daily dose of paclitaxel, taxotere or a modified taxane or taxoid analog will generally be from 5 to about 250 milligrams per kilogram.

The first and the second compounds of the present invention can be administered in conventional solid or liquid pharmaceutical administration forms, for example, uncoated or (film)coated tablets, capsules, powders, granules, suppositories or solutions. These are produced in a conventional manner. The active substances can for this purpose be processed with conventional pharmaceutical aids such as tablet binders, fillers, preservatives, tablet disintegrants, flow regulators, plasticizers, wetting agents, dispersants, emulsifiers, solvents, sustained release compositions, antioxidants and/or propellant gases (cf. H. Sücker *et al.*: Pharmazeutische Technologie, Thieme-Verlag, Stuttgart, 1978). The administration forms obtained in this way typically contain from about 1 to about 90% by weight of the active substance.

The compounds of Formula I are described in detail above. In a particular embodiment, the method of the invention uses a compound of Formula I in which R^1 and R^2 are each methyl or ethyl; X is isopropyl, sec-butyl or tert-butyl; s is 1; t and u are each 0; A is valyl, isoleucyl or 2-tert-butylglycyl; B is N-methylvalyl, 1-

isoleucyl or 2-tert-butylglycyl; D is prolyl, thiazolidinyl-4-carbonyl or 3,4-dehydroprolyl; E is prolyl, thiazolidinyl-4-carbonyl, homoprolyl, 3,4-dehydroprolyl or hydroxyprolyl; and K is a substituted or unsubstituted amino moiety having the formula R^5-N-R^6.

In a further embodiment, the method of the invention uses a compound of Formula I in which R^1 and R^2 are each methyl or ethyl ; X is isopropyl, sec-butyl or tert-butyl; s is 1; t and u are each 0; A is valyl, isoleucyl or 2-tert-butylglycyl; B is N-methylvalyl, 1-isoleucyl or 2-tert-butylglycyl; D is prolyl, thiazolidinyl-4-carbonyl or 3,4-dehydroprolyl; E is prolyl, thiazolidinyl-4-carbonyl, homoprolyl, 3,4-dehydroprolyl or hydroxyprolyl; and K is a substituted amino moiety having the formula R^5-N-R^6 wherein R^5 is hydrogen or C_1-C_4 alkoxy and R^6 is a C_1-C_{12} linear or branched alkyl group or C_1-C_{12} linear or branched hydroxyalkyl group represented, for example, by the following monovalent radicals:

$-C(CH_3)_2-CH_2-CH_2-OH$, also referred to as 3-hydroxy-1,1-dimethylpropyl;

$-C(CH_3)_3$, also referred to as tert-butyl;

$-\underset{(CH_3)_2}{C}-CH_2-CH_3$, also referred to as 1,1-dimethyl propyl;

$-\underset{CH_3}{C}(CH_2-CH_3)_2$, also referred to as 1-methyl-1-ethyl propyl;

$-\underset{CH_3}{CH}-C(CH_3)_3$, also referred to as (S)- or (R)-1-methyl-2,2-dimethyl propyl;

$-\underset{CH_2H_5}{CH}-CH(CH_3)_2$, also referred to as (S)- or (R)-1-ethyl-2-methyl propyl;

$-\underset{CH(CH_3)_2}{CH}-CH(CH_3)_2$, also referred to as 1-isopropyl-2-methyl butyl; or

$-C(CH_3)_2-CH(CH_3)_2$, also referred to as 1,1-dimethyl-2-methyl propyl

$-CH(CH_3)_2$, also referred to as isopropyl

$-CH(CH_3)CH_2CH_3$, also referred to as sec-butyl, (S)- or (R)-

$-CH(CH_3)CH(CH_3)_2$, also referred to as 1,2-dimethylpropyl.

In another embodiment, the method of the invention uses a compound of Formula I in which R^1 and R^2 are each methyl or ethyl; X is isopropyl, sec-butyl or tert-butyl; s is 1; t and u are each 0; A is valyl, isoleucyl or 2-tert-butylglycyl; B is N-methylvalyl, 1-isoleucyl or 2-tert-butylglycyl; D is prolyl, thiazolidinyl-4-carbonyl, 3,4-dehydroprolyl; E is prolyl, thiazolidinyl-4-carbonyl, homoprolyl, 3,4-dehydroprolyl or hydroxyprolyl; and K is a substituted amino moiety having the formula R^5-N-R^6 wherein R^5 is hydrogen or C_1-C_4 alkoxy and R^6 is a monovalent radical such as a C_3-C_{10} cycloalkyl group (e.g. cyclobutyl, cyclopentyl, cyclohexyl, 1-methylcyclopentyl, 1-methylcyclohexyl or bicyclo[3.3.0]octa-1-yl); a (1)- or (2)-adamantyl group; $(CH_2)v$-phenyl with v=1 or α,α-dimethylbenzyl.

In a further embodiment, the method of the invention uses a compound of Formula I in which R^1 and R^2 are each methyl; X is isopropyl; s is 1; t and u are each 0; A is valyl; B is N-methylvalyl; D is prolyl; E is prolyl; and K is a substituted amino moiety having the formula R^5-N-R^6 wherein R^5 is benzyl and R^6 is hydrogen. This compound corresponds to compound (xvii) depicted in the Figure. The results of the use of compound (xvii) of Formula I, in combination with paclitaxel are presented in Tables 1-4.

SYNTHETIC METHODS

The compounds of Formula I can be prepared by known methods of peptide synthesis such as those described herein and, in U.S. Patent Application Serial No. 08/470,453 filed June 7, 1995, the teachings of which are incorporated herein by reference. The peptides can be assembled sequentially from individual amino acids or by linking

suitable small peptide fragments. In sequential assembly, the peptide chain is extended stepwise, starting at the C-terminus, by one amino acid per step. In fragment coupling, fragments of different lengths can be linked together, and the fragments can also be obtained by sequential assembly from amino acids or by fragment coupling of still shorter peptides.

In both sequential assembly and fragment coupling it is necessary to link the units by forming an amide linkage, which can be accomplished via a variety of enzymatic and chemical methods. The methods described herein for formation of peptidic amide linkages, are also suitable for the formation of non-peptidic amide linkages.

Chemical methods for forming the amide linkage are described in detail in standard references on peptide chemistry, including Müller, Methoden der organischen Chemie Vol. XV/2, 1-364, Thieme Verlag, Stuttgart, (1974); Stewart and Young, Solid Phase Peptide Synthesis, 31-34 and 71-82, Pierce Chemical Company, Rockford, IL (1984); Bodanszky *et al.*, Peptide Synthesis, 85-128, John Wiley & Sons, New York, (1976); Practice of Peptide Synthesis, M. Bodansky, A. Bodansky, Springer-Verlag, 1994 and other standard works in peptide chemistry. Preferred methods include the azide method, the symmetric and mixed anhydride method, the use of *in situ* generated or preformed active esters, the use of urethane protected N-carboxy anhydrides of amino acids and the formation of the amide linkage using coupling reagents, such as dicyclohexylcarbodiimide (DCC), diisopropylcarbodiimide (DIC), 1-ethoxycarbonyl-2-ethoxy-1,2-dihydroquinoline (EEDQ), pivaloyl chloride, 1-ethyl-3-(3-dimethylaminopropyl)carbodiimide hydrochloride (EDCI), n-propane-phosphonic anhydride (PPA), N,N-bis (2-oxo-3-oxazolidinyl)amido phosphoryl chloride (BOP-Cl), bromo-tris-pyrrolidinophosphonium hexafluorophosphate (PyBrop), diphenylphosphoryl azide (DPPA), Castro's reagent

(BOP, PyBop), O-benzotriazolyl-N,N,N',N'-tetramethyluronium salts (HBTU), O-azabenzotriazolyl-N,N,N',N'-tetramethyluronuim salts (TATU), diethylphosphoryl cyanide (DEPCN), 2,5-diphenyl-2,3-dihydro-3-oxo-4-hydroxythiophene dioxide (Steglich's reagent; HOTDO), and 1,1'-carbonyldiimidazole (CDI). The coupling reagents can be employed alone or in combination with additives such as N,N-dimethyl- 4-aminopyridine (DMAP), N-hydroxy-benzotriazole (HOBt), N-hydroxybenzotriazine (HOOBt), N-hydroxysuccinimide (HOSu) or 2-hydroxypyridine.

Although the use of protecting groups is generally not necessary in enzymatic peptide synthesis, reversible protection of reactive groups not involved in formation of the amide linkage is necessary for both reactants in chemical synthesis. Three conventional protective group techniques typically used for chemical peptide synthesis are: the benzyloxycarbonyl (Z), the t-butoxycarbonyl (Boc) and the 9-fluorenylmethoxycarbonyl (Fmoc) techniques. Identified in each case is the protective group on the α-amino group of the chain-extending unit. A detailed review of amino-acid protective groups is given by Müller, Methoden der organischen Chemie Vol. XV/1, pp 20-906, Thieme Verlag, Stuttgart (1974).

The units employed for assembling the peptide chain can be reacted in solution, in suspension or by a method similar to that described by Merrifield in *J. Amer. Chem. Soc. 85* (1963) 2149. In one method, peptides are assembled sequentially or by fragment coupling using the Z, Boc or Fmoc protective group technique, with one of the reactants in the Merrifield technique being bonded to an insoluble polymeric support (also called resin hereinafter). This typically entails assembling the peptide sequentially on the polymeric support using the Boc or Fmoc protective group technique, with the growing peptide chain covalently bonded at the C terminus to the insoluble resin particles.

This procedure allows the removal of reagents and by-products by filtration, eliminating the need to recrystallize intermediates.

The protected amino acids can be linked to any suitable polymer, which must be insoluble in the solvents used and have a stable physical form which permits filtration. The polymer must contain a functional group to which the first protected amino acid can be covalently attached. A wide variety of polymers are suitable for this purpose, for example, cellulose, polyvinyl alcohol, polymethacrylate, sulfonated polystyrene, chloromethylated styrene/divinylbenzene copolymer (Merrifield resin), 4-methylbenzhydrylamine resin (MBHA-resin), phenylacetamidomethyl resin (Pam-resin), p-benzyloxy-benzyl-alcohol-resin, benzhydryl-amine-resin (BHA-resin), 4-(hydroxymethyl)-benzoyl-oxymethyl-resin, the resin of Breipohl *et al.* (*Tetrahedron Letters 28* (1987) 565; supplied by BACHEM), 4-(2,4-dimethoxyphenylaminomethyl) phenoxy resin (supplied by Novabiochem) or o-chlorotrityl-resin (supplied by Biohellas).

Solvents suitable for peptide synthesis include any solvent which is inert under the reaction conditions, for example, water, N,N-dimethylformamide (DMF), dimethyl sulfoxide (DMSO), acetonitrile, dichloromethane (DCM), 1,4-dioxane, tetrahydrofuran (THF), N-methyl-2-pyrrolidone (NMP) and mixtures of these solvents.

Peptide synthesis on the polymeric support can be carried out in a suitable inert organic solvent in which the amino acid derivatives and starting materials employed are soluble. Particularly useful solvents are, for example, DMF, DCM, NMP, acetonitrile, DMSO and mixtures thereof, due to their resin swelling properties.

Following synthesis, the peptide is removed (commonly referred to as cleaved) from the polymeric support. The conditions under which this cleavage is accomplished are

well known in the art of peptide synthesis and depend in part on the type of resin employed. The cleavage reactions most commonly used are acid- or palladium-catalyzed, the acid catalyzed cleavage being conducted in, for example, liquid anhydrous hydrogen fluoride, anhydrous trifluoromethanesulfonic acid, dilute or concentrated trifluoroacetic acid, and acetic acid/dichloromethane/ trifluoroethanol mixtures. The palladium-catalyzed cleavage can be carried out in THF or THF-DCM-mixtures in the presence of a weak base such as morpholine. Certain protecting groups are also cleaved off under these conditions.

Partial deprotection of the peptide may also be necessary prior to certain derivatization reactions. For example, peptides dialkylated at the N-terminus can be prepared either by coupling the appropriate N,N-di-alkylamino acid to the peptide in solution or on the polymeric support or by reductive alkylation of the resin-bound peptide in DMF/1% acetic acid with $NaCNBH_3$ and the appropriate aldehyde or by hydrogenation of the peptide in solution in the presence of aldehyde or ketone and Pd/C.

The various non-naturally occurring amino acids as well as the various non-amino acid moieties disclosed herein may be obtained from commercial sources or synthesized from commercially-available materials using methods known in the art. For example, amino acid building blocks with R^1 and R^2 moieties can be prepared according to E. Wüensch, Huben Weyl, Methoden der organischen Chemie Vol. XV/1, p. 306, Thieme Verlag, Stuttgart (1974) and literature cited therein. Peptides with gamma-or delta-lactam bridges can be prepared by incorporating the appropriate lactam-bridged dipeptide units (R. Freidinger, *J. Org. Chem.* (1982) 104-109) into the peptide chain. Peptides with thiazole-, oxazol-, thiazolin- or oxazolin-containing dipeptide building blocks can be prepared by

incorporating the appropriate dipeptidic units (P. Jouin *et al.*, *Tetrahedron Letters* (1992), pp. 2087-2810; P. Wipf *et al.*, *Tetrahedon Letters* (1992), pp. 907-910; W.R. Tully, *J. Med. Chem.* (1991), p 2065; *Synthesis* (1987), p 235) into the peptide chain.

The following procedures are intended to illustrate methods useful for preparation of compounds of Forumla I. When applicable, amino acids are abbreviated using the known three letter codes. Other meanings used are: Me_2Val=N,N-dimethylvaline, MeVal=N-methylvaline, TFA = triffluoroacetic acid, Ac = acetic acid, Bu = butyl, Et = ethyl, Me = methyl, Bzl = benzyl, Nal = 3-naphthylalanine, Cha = 3-cyclohexylalanine, Npg = neopentyl glycine, Abu = 2-amino butyryl, Dab = 2,4-diaminobutyryl, iPr = isopropyl

GENERAL SYNTHETIC PROCEDURES

I. Compounds of Formula I of the present invention are either synthesized by classical solution synthesis using standard Z- and Boc-methodology as described above or by standard methods of solid-phase synthesis on a completely automatic model 431A synthesizer supplied by APPLIED BIOSYSTEMS. The apparatus uses different synthetic cycles for the Boc and Fmoc protective group techniques.

In the case of solid phase synthesis, the N,N-dialkyl-penta- or hexapeptide acids are liberated from the solid support and further coupled with the corresponding C-terminal amines in solution. BOP-Cl and PyBrop were used as reagents for coupling of the amino acid following the N-methylamino acids. The reaction times were correspondingly increased. For reductive alkylation of the N-terminus, the peptide-resin was deprotected at the N terminus and then reacted with a 3-fold molar excess of aldehyde or

ketone in DMF/1% acetic acid with addition of 3 equivalents of $NaCNBH_3$. After the reaction was complete (negative Kaiser test) the resin was washed several times with water, isopropanol, DMF and dichloromethane.

In solution synthesis, the use of either Boc-protected amino acid NCAs (N-tert-butyloxycarbonyl-amino acid-N-carboxy-anhydrides), Z-protected amino acid NCAs (N-benzyloxycarbonyl-amino acid-N-carboxy-anhydrides), or the use of pivaloylchloride as condensing agent respectively is most advantageous for coupling of the amino acid following the N-methylamino acids. Reductive alkylation of the N terminus can, for example, be achieved by reaction of the N-terminally deprotected peptides or amino acids with the corresponding aldehydes or ketones using $NaCNBH_3$ or hydrogen, Pd/C.

a) Synthetic cycle for the Boc protective group technique:

1.	30% trifluoroacetic acid in DCM	1 x 3 min
2.	50% trifluoroacetic acid in DCM	1 x 1 min
3.	DCM washing	
4.	5% diisopropylethylamine in DCM	5 x 1 min
5.	5% diisopropylethylamine in NMP	1 x 1 min
6.	NMP washing	5 x 1 min
7.	Addition of preactivated protected amino acid (DCC and 1 equivalent of HOBt in NMP/DCM); Peptide coupling (1st part)	1 x 30 min
8.	Addition of DMSO to the reaction mixture until it contains 20% DMSO by volume; Peptide coupling (2nd part)	1 x 16 min

9.	Addition of 3.8 equivalents of diisopropylethylamine to the reaction mixture;	
	Peptide coupling (3rd part)	1 x 7 min
10.	DCM washing	3 x 1 min
11.	If conversion is incomplete, repetition of coupling (back to 6)	
12.	10% acetic anydride, 5% diisopropylethylamine in DCM	1 x 2 min
13.	10% acetic anhydride in DCM	1 x 4 min
14.	DCM washing	4 x 1 min
15.	Back to 1.	

BOP-Cl and PyBrop were used as reagents for coupling of the amino acid following N-methylamino acids. The reaction times were correspondingly increased. In solution synthesis, the use of either Boc-protected amino acid NCAs (N-tert-butyloxycarbonyl-amino acid-N-carboxy-anhydrides) or Z-protected amino acids NCAs respectively is most advantageous for this type of coupling.

b) Synthetic cycle for the Fmoc protective group technique:

1.	DMF washing	1 x 1 min
2.	20% piperidine in DMF	1 x 4 min
3.	20% piperidine in DMF	1 x 16 min
4.	DMF washing	5 x 1 min
5.	Addition of the preactivated protected amino acid (activation by 1 equivalent of TBTU and 5 equivalents of DIPEA in DMF);	
	Peptide coupling	1 x 61 min
6.	DMF washing	3 x 1 min
7.	If conversion is incomplete, repetition of coupling (back to 5)	

8.	10% acetic anhydride in DMF	1 x 8 min
9.	DMF washing	3 x 1 min
10.	Back to 2.	

BOP-Cl and PyBrop were used as reagents for coupling on the amino acid following the N-methylamino acids. The reaction times were correspondingly increased.

II. Reductive Alkylation of the N-terminus

The peptide-resin prepared in Ia or Ib above was deprotected at the N-terminus (steps 2-4 in Ib or 1-6 in 1a) and then reacted with a 3-fold molar excess of aldehyde or ketone in DMF/1% acetic acid with addition of 3 equivalents of $NaCNBH_3$. After reaction was complete (negative Kaiser test) the resin was washed several times with water, isopropanol, DMF and dichloromethane.

III. Workup of the peptide-resins obtained as in Ia and II

The peptide-resin was dried under reduced pressure and transferred into a reaction vessel of a TEFLON HF apparatus (supplied by PENINSULA). Addition of a scavenger, for example, anisole (1ml/g of resin), and in the case of tryptophan-containing peptides of a thiol to remove the indolic formyl group, for example, ethanedithiol (0.5 ml/g of resin), was followed by condensing in hydrogen fluoride (10 ml/g of resin) while cooling with liquid N_2. The mixture was allowed to warm to 0°C and stirred at this temperature for 45 minutes. The hydrogen fluoride was then stripped off under reduced pressure, and the residue was washed with ethyl acetate in order to remove remaining scavenger. The peptide was extracted with 30% acetic acid and filtered, and the filtrate was lyophilized.

IV. Work-up of the peptide-resins obtained as in Ib and II

The peptide-resin was dried under reduced pressure and then subjected to one of the following cleavage procedures, depending on the amino acid composition (Wade, Tregear, Howard Florey Fmoc Workshop Manual, Melbourne 1985).

Cleavage conditions:

	TFA	Scavenger	Reaction time
1.	95%	5% water	1.5 h
2.	95%	5% ethanethiol/ anisole (1:3)	1.5 h

The suspension of the peptide-resin in the suitable TFA mixture was stirred at room temperature for the stated time and then the resin was filtered off and washed with TFA and DCM. The filtrate and the washings were concentrated, and the peptide was precipitated by addition of the diethyl ether. After cooling in an ice bath, the precipitate was filtered off, taken up in 30% acetic acid and lyophilized.

V. When an o-chlorotrityl-resin (supplied by Biohellas) is used, the suspension of the peptide-resin in an acetic acid/ trifluoroethanol/ dichloromethane mixture (1:1:3) is stirred at room temperature for 1 h. The resin is then filtered off with suction and thoroughly washed with the cleavage solution. The combined filtrates are concentrated in vacuo and treated with water. The precipitated solid is removed by filtration or centrifugation, washed with diethyl ether and dried under reduced pressure.

VI. Purification and characterization of the peptides

Purification was carried out by gel chromatography (SEPHADEX G-10, G-15/10% HOAc, SEPHADEX LH20/MeOH) medium pressure chromatography (stationary phase: HD-SIL C-18, 20-45 micron, 100 Angstrom; mobile phase: gradient with A=0.1% TFA/MeOH, B=0.1% TFA/water) or preparative HPLC (stationary phase: water Delta-Pak C-18, 15 micron, 100 Angstrom; mobile phase: gradient with A= 0.1% TFA/MeOH, B= 0.1% TFA/water).

The purity of the resulting products was determined by analytical HPLC (stationary phase: 100 2.1 mm VYDAC C-18, 51, 300 Angstrom; mobile phase: acetonitrile-water gradient, buffered with 0.1% TFA, 40°C).

Characterization was by amino acid analysis and fast atom bombardment mass spectroscopy.

SPECIFIC SYNTHETIC PROCEDURES

EXAMPLE 1A: N,N-dimethyl-Val-Val-N-methyl-Val-Pro-Pro-Val-Phe-NH_2

1.98 g of Fmoc-RINK-resin (substitution 0.46 mmol/g), corresponding to a batch size of 0.84 mmol, were reacted as in Ib above with 1.26 mmol each of

Fmoc-Phe-OH
Fmoc-Val-OH
Fmoc-Pro-OH
Fmoc-Pro-OH
Fmoc-N-methyl-Val-OH
Fmoc-Val-OH
Fmoc-Val-OH

The amino acid following the N-methyl amino acid was coupled on with PyBrop as coupling reagent. After the iterative synthetic cycles were completed, the peptide-resin underwent N-terminal deprotection (steps 2-4 in Ib),

and was further reacted with aqueous formaldehyde solution as in II and then dried under reduced pressure. The resulting resin was subjected to TFA cleavage as in IV. The crude product (590 mg) was purified by gel filtration (SEPHADEX-LH-20). The yield was 295 mg.

EXAMPLE 1A:

Example 1 can also be prepared via classical solution phase methodology. The synthesis of N,N-dimethyl-Val-Val-N-methyl-Val-Pro-Pro-Val-Phe-NH_2 and its associated intermediates is described in the following paragraph.

a) Z-MeVal-Pro-OMe

66.25 g (250 mmol) of Z-MeVal-OH were dissolved in 250 ml of dry dichloromethane. After addition of 36.41 ml (262.5 mmol) of triethylamine, the reaction mixture was cooled to -25°C and 32.37 ml (262.5 mmol) pivaloyl chloride were added. After stirring for 2.5 hours, 41.89g (250 mmol) of H-Pro-OMe-HCl in 250 ml of dichloromethane, neutralized with 36.41 ml (262.5 mmol) triethylamine at 0°C, were added to the reaction mixture. Stirring was continued for 2h at -25°C and overnight at room temperature. The reaction mixture was diluted with dichloromethane and thoroughly washed with saturated aqueous $NaHCO_3$ solution (3X), water (1X), 5% citric acid (3X) and saturated NaCl solution. The organic phase was dried over sodium sulfate, filtered and evaporated to dryness. The residue (91.24 g) was stirred with petroleum ether overnight and filtered. 62.3 g of product were obtained.

b) H-MeVal-Pro-OMe

48.9 g (130 mmol) Z-MeVal-Pro-OMe were dissolved in 490 ml of methanol. After addition of 10.9 ml (130 mmol) concentrated hydrochloric acid and 2.43 g of 10% palladium/charcoal, the reaction mixture was hydrogenated. Filtration and evaporation to dryness yielded 36.43 g of product.

c) Z-Val-MeVal-Pro-OMe

18.1 g (65 mmol) of H-MeVal-Pro-OMe, 21.6 g (78 mmol) Z-Val-N-carboxyanhydride and 22.8 ml (130 mmol) diisopropylethylamine were stirred in 110 ml of DMF at 40°C for 2 days. After evaporation of DMF, dichloromethane was added and the organic phase washed with saturated aqueous $NaHCO_3$ solution (3X), water (1X) 5% citric acid (3X) and saturated NaCl solution. The organic phase was dried over sodium sulfate, filtered and evaporated to dryness. The product (29.3 g) was obtained as a viscous oil.

d) H-Val-MeVal-Pro-OMe

29.3 g (61.6 mmol) of Z-Val-MeVal-Pro-OMe were dissolved in 230 ml of methanol. After addition of 1.15 g of 10% palladium/charcoal, the reaction mixture was hydrogenated. Filtration and evaporation to dryness yielded 21.96 g of product.

e) Z-Val-Val-MeVal-Pro-OMe

15.29 g (61 mmol) of Z-Val-OH and 21.96 g (61 mmol) of H-Val-MeVal-Pro-OMe were dissolved in 610 ml of dichloromethane and cooled to 0°C. After addition of

8.16 mol(73.2 mmol) of N-methylmorpholine, 2.77 g (20.3 mmol) of HOBt and 11.74g (61 mmol) of EDCI, the reaction mixture was stirred overnight at room temperature, diluted with dichloromethane and thoroughly washed with saturated aqueous $NaHCO_3$ solution (3X), water (1X), 5% citric acid (3X) and saturated NaCl solution. The organic phase was dried over sodium sulfate, filtered and evaporated to dryness to yield 31.96 g of the product.

f) Z-Val-Val-MeVal-Pro-OH

31.96 g (57 mmol) of Z-Val-Val-MeVal-Pro-OMe were dissolved in 250 ml of methanol. 102.6 ml of a 1N LiOH solution was added and the mixture stirred overnight at room temperature. After addition of 500 ml of water, the aqueous phase was washed three times with ethyl acetate. The organic phase was dried over sodium sulfate, filtered and evaporated to dryness yielding 30.62 g of the desired product as a white solid.

g) Z-Val-Val-MeVal-Pro-Pro-Val-Phe-NH_2

25 g (43.3 mmol) of Z-Val-Val-MeVal-Pro-OH and 15.59 g (43.3 mmol) of H-Pro-Val-Phe-NH_2 were suspended in 430 ml of dry dichloromethane. After cooling to 0°C, 5.81 ml (52 mmol) N-methylmorpholine, 1.97 g (15 mmol) of HOBt and 8.33 g (43.3 mmol) of EDCI were added and the reaction mixture stirred overnight at room temperature. The solvents were evaporated, the residue dissolved in 640 ml of dichloromethane and thoroughly washed with saturated aqueous $NaHCO_3$ solution (4X), water (1X), 5% citric acid (3X) and saturated NaCl solution. The organic phase was dried

over sodium sulfate, filtered and evaporated to dryness to yield 33.04 g of the product. The crude product was chromatographed on a silica gel column with 20% MeOH/hexane. 18.32 g of the desired product were obtained.

h) N,N-dimethyl-Val-Val-MeVal-Pro-Pro-Val-Phe-NH_2

18.32 g of Z-Val-Val-MeVal-Pro-Pro-Val-Phe-NH_2 were dissolved in 80 ml of methanol. 0.4 g of 10% palladium/carbon were added under nitrogen atmosphere and the reaction mixture hydrogenated at room temperature for 4 hours. After addition of 6.22 ml (81.24 mmol) of a 37% aqueous formaldehyde solution, hydrogenation was continued for 5 hours. Filtration and evaporation of the solvent gave rise to 15.6 g of crude product. Further purification was achieved by dissolving the peptide in water, adjusting the pH to 2 and extracting the aqueous phase three times with ethyl acetate. The aqueous phase was then adjusted to pH 8-9 and extracted four times with ethyl acetate. The organic phase was washed with water and dried over sodium sulfate, filtered and evaporated to yield 11.3 g of purified product as a white powder. The compound was characterized by fast atom bombardment mass spectrometry ($[M+H]^+$ = 797).

EXAMPLE 2A: N,N-dimethyl-Val-Val-NMe-Val-Pro-{1-[thiazol-(2)-yl]-2-phenyl}-ethylamide

4.11 g of Fmoc-Pro-p-alkoxybenzyl-alcohol-resin (substitution 0.73 mmol/g), corresponding to a batch size of 3 mmol, were reacted as in Ib with 4.5 mmol each of

Fmoc-N-MeVal-OH

Fmoc-Val-OH

Fmoc-Val-OH

The amino acid following the N-methylamino acid was in this case reacted with double coupling using PyBrop or Bop-Cl with increased reaction times. After the synthesis was complete, the peptide-resin underwent N-terminal deprotection (Steps 2-4 in Ib), and was further reacted with aqueous formaldehyde solution as in II and then dried under reduced pressure. The resin obtained in this way was subjected to TFA cleavage as in IV. The crude product (750 mg) was employed directly for the next coupling. 100 mg of this compound were reacted with 45 mg of (S)-2-[1-amino-2-phenylethyl]thiazole and 230 mg of PyBop with the addition of 192 microliters of DIPEA in DMF at room temperature for 2 days. The reaction mixture was purified by gel chromatography (SEPHADEX LH-20, methanol) and the product fractions were combined. 83 mg of product were obtained.

EXAMPLE 1B

Me_2Val-Val-MeVal-Pro-Pro-NHCH$(CH_3)_2$

a) Z-MeVal-Pro-OMe

66.25 g (250 mmol) Z-MeVal-OH were dissolved in 250 ml dry dichloromethane. After addition of 36.41 ml (262.5 mmol) triethylamine, the reaction mixture was cooled to -25°C and 32.27 ml (262.5 mmol) pivaloyl chloride were added. After stirring for 2.5 h, 41.89 g (250 mmol) H-Pro-OMe x HCl in 250 ml dichloromethane, neutralized with 36.41 ml (262.5 mmol) triethylamine at 0°C, were added to the reaction mixture. Stirring continued for 2 h at -25°C and overnight at room temperature. The reaction mixture was diluted with dichloromethane and thoroughly washed with saturated aqueous $NaHCO_3$ solution (3x), water (1x), 5% citric acid (3x) and saturated NaCl solution. The organic phase was dried over sodium sulfate, filtered and evaporated to dryness. The residue (91.24 g) was stirred with petroleum ether overnight and filtered. 62.3 g of product were obtained.

b) H-MeVal-Pro-OMe

48.9 g (130 mmol) Z-MeVal-Pro-OMe were dissolved in 490 ml methanol. After addition of 10.9 ml (130 mmol) concentrated hydrochloric acid and 2.43 g 10 % Palladium/charcoal, the reaction mixture was hydrogenated. Filtration and evaporation to dryness yielded 36.43 g of the product.

c) Z-Val-MeVal-Pro-OMe

18.1 g (65 mmol) H-MeVal-Pro-OMe, 21.6 g (78 mmol) Z-Val-N-carboxyanhydride and 22.8 ml (130 mmol) diisopropylethylamine were stirred in 110 ml DMF at 40°C for 2 d. After evaporation of DMF, dichloromethane was added and the organic phase washed with saturated aqueous $NaHCO_3$ solution (3x), water (1x), 5% citric acid (3x) and saturated NaCl solution. The organic phase was dried over sodium sulfate and evaporated to dryness. The product (29.3 g) was obtained as a viscous oil.

d) H-Val-MeVal-Pro-OMe

29.3 g (61.6 mmol) of Z-Val-MeVal-Pro-OMe were dissolved in 230 ml methanol. After addition of 1.15 g 10% Palladium/charcoal, the reaction mixture was hydrogenated. Filtration and evaporation to dryness yielded 21.96 g of the product.

e) Z-Val-Val-MeVal-Pro-OMe

15.29 g (61 mmol) Z-Val-OH and 21.96 g (61 mmol) H-Val-MeVal-Pro-OMe were dissolved in 610 ml dichloromethane and cooled to 0°C. After addition of

8.16 ml (73.2 mmol) N-Methylmoropholine, 2.77 g (20.3 mmol) HOBt and 11.74 g (61 mmol) EDCI, the reaction mixture was stirred overnight at room temperature, diluted with dichloromethane and thoroughly washed with saturated aqueous $NaHCO_3$ solution (3x), water (1x), 5% citric acid (3x) and saturated NaCl solution. The organic phase was dried over sodium sulfate, filtered and evaporated to dryness to yield 31.96 g of the product.

f) Z-Val-Val-MeVal-Pro-OH

31.96 g (57 mmol) Z-Val-Val-MeVal-Pro-OMe were dissolved in 250 ml methanol. 102.6 ml of a 1 N LiOH solution was added and the mixture stirred overnight at room temperature. After addition of 500 ml water, the aqueous phase was washed three times with ethyl acetate, adjusted to pH 2 at 0°C and extracted three times with ethyl acetate. The organic phase was dried over sodium sulfate, filtered and evaporated to dryness yielding 30.62 g of the desired product as a white solid.

g) Z-Val-Val-MeVal-Pro-Pro-$NHCH(CH_3)_2$

2 g (3.35 mmol) Z-Val-Val-MeVal-Pro-OH and 0.664 g (3.35 mmol) H-Pro-$NHCH(CH_3)_2$ were dissolved in 34 ml of dry dichloromethane. After cooling to 0°C, 1.35 ml (12.1 mmol) N-methylmorpholine, 0.114 g (0.84 mmol) HOBt and 0.645 g (3.35 mmol) EDCI were added and the reaction mixture stirred overnight at room temperature. 80 ml dichloromethane were added and the organic phase thoroughly washed with saturated aqueous $NaHCO_3$ solution (3x), water (1x), 5% citric acid (3x) and saturated NaCl solution (1x). The organic phase

was dried over sodium sulfate, filtered and evaporated to dryness to yield 1.96 g of the product which was used in the next reaction without further purification.

h) Me_2Val-Val-MeVal-Pro-Pro-NHCH$(CH_3)_2$

1.96 g Z-Val-Val-MeVal-Pro-Pro-NHCH$(CH_3)_2$ were dissolved in 11 ml methanol. 0.054 g 10% Pd/C were added under nitrogen atmosphere and the reaction mixture hydrogenated at room temperature for 4 h. After addition of 0.86 ml (11.24 mmol) of a 37% aqueous formaldehyde solution and 0.281 g 10% Pd/C, hydrogenation was continued for 5 h. Filtration and evaporation of the solvent gave rise to 2.77 g of crude product. Further purification was achieved by dissolving the peptide in water, adjusting the pH to 2 and extracting the aqueous phase three times with ethyl acetate. The aqueous phase was then adjusted to pH 8-9 and extracted four times with dichloromethane. The organic phase was dried over sodium sulfate, filtered and evaporated to yield 1.37 g of purified product as a white foam. The compound was further purified using medium pressure liquid chromatography (10-50% A in 10 min.; 50-90% A in 320 min.). Fractions containing the product were combined, lyophilized, redissolved in water and the pH adjusted to 9 with 1 N LiOH. After extraction with dichloromethane, the organic phase was dried over sodium sulfate, filtered and evaporated to dryness. Lyophilization led to 500 mg of pure product, which was characterized by fast atom bombardment mass spectrometry ($[M+H]^+$ = 593).

EXAMPLE 2B

Me_2Val-Val-MeVal-Pro-Pro-NHC$(CH_3)_3$

a) Z-Val-Val-MeVal-Pro-Pro-NHC$(CH_3)_3$

2 g (3.35 mmol) Z-Val-Val-MeVal-Pro-OH and 0.692 g (3.35 mmol) H-Pro-NHC$(CH_3)_3$ were dissolved in 34 ml of dry dichloromethane. After cooling to 0°C, 1.35 ml (12.1 mmol) N-methylmorpholine, 0.114 g (0.84 mmol) HOBt and 0.645 g (3.35 mmol) EDCI were added and the reaction mixture stirred overnight at room temperature. 80 ml dichloromethane were added and the organic phase thoroughly washed with saturated aqueous $NaHCO_3$ solution (3x), water (1x), 5% citric acid (3x) and saturated NaCl solution (1x). The organic phase was dried over sodium sulfate, filtered and evaporated to dryness to yield 1.8 g of the product which was used in the next reaction without further purification.

b) Me_2Val-Val-MeVal-Pro-Pro-NHC$(CH_3)_3$

1.8 g Z-Val-Val-MeVal-Pro-Pro-NHC$(CH_3)_3$ were dissolved in 10 ml methanol. 0.045 g 10% Pd/C were added under nitrogen atmosphere and the reaction mixture hydrogenated at room temperature for 4 h. After addition of 0.86 ml (11.24 mmol) of a 37% aqueous formaldehyde solution and 0.252 g 10% Pd/C, hydrogenation was continued for 5 h. Filtration and evaporation of the solvent gave rise to 1.82 g of crude product. The compound was further purified using medium pressure liquid chromatography (10-50% A in 10 min.; 50-90% A in 320 min.). Fractions containing the product were combined, lyophilized, redissolved in water and the pH adjusted to 9 with 1 N LiOH. After extraction with dichloromethane, the

organic phase was dried over sodium sulfate and evaporated to dryness. Lyophilization led to 547 mg of pure product, which was characterized by fast atom bombardment mass spectrometry ($[M+H]^+$ = 607).

EVALUATION OF BIOLOGICAL ACTIVITY

In vivo Methodology

The combination of a compound of Formula I and paclitaxel, taxotere or a modified taxane or taxoid analog was further tested in various preclinical assays for *in vivo* activity, which are indicative of clinical utility. The P388 (ascites model), LX-1, CX-1 and PC-3 (human tumor xenograft models for lung, colon and prostate) tumor models are all suitable for use in this invention.

In general, any dosing regimen which appears to provide an acceptable level of antitumor activity for both agents is suitable. Any acceptable method of drug administration can be used in the combination therapy of this invention and can be determined using techniques well known to those of skill in the art. In addition, the drugs can be administered either simultaneously or sequentially, in any order.

P388 MODEL

The P388 tumor model employs a murine lymphocytic leukemia cell line (See Schabel *et al.*, *Pharmac. Ther. A*, 1:411-435). The P388 tumor cells used in this invention, were harvested from donor mice by peritoneal lavage at day 7 post transplant. $1x10^6$ P388 tumor cells were then implanted intraperitoneally in a volume of 0.5 ml in mice.

A typical dosing regimen includes initiation of treatment approximately one day post transplant followed by treatment on days 5 and 9 post transplant. Generally the compounds of Formula I are administered intravenously (i.v.) and the paclitaxel, taxotere or modified taxane or taxoid analog is administered intraperitoneally (i.p.).

Therapeutic results of the combinations of the invention against P388 cells, are presented in terms of increase in lifespan reflected by the relative median survival time (MST) of treated (T) versus control (C) group (survival period for untreated mice is generally in the range of 11 to 13 days) and is represented as %T/C values. According to the National Cancer Institute guidelines a %T/C in the range or 128-190% indicates a drug with moderate to good activity. In addition, the Net log Cell Kill is used to compare efficacy of different schedules and combinations, and is calculated as follows:

$$\text{Net log Cell Kill} = \frac{[(T-C) - \text{duration of treatment}] \times 0.332}{\text{Doubling Time}}$$

Where,
Doubling Time = time required for control tumors to double once (0.4 days).
T and C = the median survival time (days) for the control (C) and treated (T) mice.
Duration of treatment with drug
0.332 = Derived constant

A positive Net log Cell Kill number indicates that fewer tumor cells are present at the end of treatment. A negative number indicates that the tumor was still growing during treatment.

EXAMPLE 3: Combination Treatment Using Compound (xvii) and Paclitaxel in the P388 Tumor Model

1×10^6 P388 tumor cells were transplanted intraperitoneally in a volume of 0.5 ml in mice. Treatment was initiated approximately 1 day later followed by treatment on both day 5 and day 9, post transplant. Compound (xvii) was administered IV while paclitaxel was administered IP. Compound (xvii) was administered at either 20, 40 or 60 mg/kg and paclitaxel at either 10, 20

or 30 mg/kg. The dosing was sequential with compouond (xvii) being administered first followed by paclitaxel one hour later.

RESULTS:

The results from Example 3 are shown in Table 1. The data in Table 1 shows that single drug treatment resulted in an optimal %T/C of 175% for compound (xvii) corresponding to a Net log Cell Killing (NlCK) of 0.66 when administered intravenously at a dose of 60 mg/kg and an optimal %T/C of 183% corresponding to a NlCK of 1.33 for paclitaxel when administered intraperitoneally at a dose of 10 mg/kg. For combination drug treatment the data of Table 1 show that the combination of 60 mg/kg (xvii) and 20 mg/kg of paclitaxel resulted in a significant increase in life span (P Value less than 0.001, as determined by the Mann-Whitney Test) and an optimal %T/C value of 242% corresponding to a NlCK of 5.98 with 38% of the animals surviving more than 60 days.

HUMAN TUMOR XENOGRAFTS MODEL

Human tumors from lung (LX-1), colon (CX-1) and prostate (PC-3) which had been grown in athymic nude mice were transplanted (xenografted) into new recipient mice, as is well known in the art. The transplanted tumor fragments were approximately 50 mg in size. The day of transplantation was designated as day 0. The combination therapy of the present invention was evaluated for anti-tumor efficacy following administration to the xenograft-bearing mice.

Combination therapy was accomplished by intravenous administration of both drugs. The Q2dx3; 5, 12 and 19 injection schedule was followed with paclitaxel being administered one hour after Compound (xvii). In other words, treatment consisted of 3 cycles, starting on days 5, 12 and 19 post tumor implantation. One cycle of treatment consisted of treatment every other day for a total of three

times. The optimal dose for single dose administration of both Compound (xvii) and paclitaxel used in the LX-1 and CX-1 types of human xenograft models tested, can be found in Tables 2-3, with no optimal dose determined with the PC-3 model.

Tumor diameters and body weights were measured twice weekly. Tumor volumes were calculated using the diameters measured with Vernier calipers, and the formula:

$$(\text{length} \times \text{width}^2) / 2 = \text{mg of tumor weight}$$

Mean tumor weights (MTW) were calculated for each treatment group, and T/C values determined for each group relative to the untreated control tumors.

Results are also presented as Net log Cell Kill and are calculated as follows:

$$\text{Net log Cell Kill} = \frac{[(T-C) - \text{duration of treatment}] \times 0.332}{\text{Doubling Time}}$$

T and C = The median days required for the control and treated tumors to reach a specified tumor size, in this instance 2000 mm^3.

Doubling Time = Time required for control tumors to double in size.

0.332 = Derived constant

EXAMPLE 4: Combination Treatment Using Compound 103793 and Paclitaxel in the LX-1 Human Tumor Xenograft Model

The Q2dx3; 5, 12 and 19 dosing regimen described above was used in this example. Paclitaxel was administered IV one hour after Compound (xvii) was administered IV. The optimal single dose of both paclitaxel and Compound (xvii) can be determined from Table 2.

TABLE 1

DOSE RESPONSE OF COMPOUND (xvii) WITH AND WITHOUT PACLITAXEL AGAINST THE P388 *IN VIVO* TUMOR MODEL

DRUGS Dose (mg/kg) (xvii) IV	Paclitaxel IP	% Toxic Death	% T/C	Net Log Cell Kill	% 60 Day Cures	Total # Animals
0	30	8	204	2.99	3	36
0	20	0	175	0.66	4	24
0	10	0	183	1.33		24
60	0	0	175	0.66		42
40	0	0	158	-0.66	2	42
20	0	0	158	-0.66		42
60	30	25	217	3.98	25	24
60	20	4	242	5.98	38	24
60	10	0	204	2.99		24
40	30	21	212	3.65	8	24
40	20	0	212	3.65	12	24
40	10	0	183	1.33		24
20	30	8	217	3.98	25	24
20	20	0	217	3.98	14	22
20	10	0	183	1.33	4	24

Q4Dx3;1 Paclitaxel injected one hour after (xvii)

EXAMPLE 5: Combination Treatment Using Compound 103793 and Paclitaxel in the CX-1 Human Tumor Xenograft Model

The Q2dx3; 5, 12 and 19 dosing regimen described above was used in this example. Paclitaxel was administered IV one hour after Compound (xvii) was administered IV. The optimal single dose of both paclitaxel and Compound (xvii) can be determined from Table 3.

EXAMPLE 6: Combination Treatment Using Compound 103793 and Paclitaxel in the PC-3 Human Tumor Xenograft Model

The Q2dx3; 5, 12 and 19 dosing regimen described above was used in this example. Paclitaxel was administered IP one hour after Compound (xvii) was administered IV. The optimal single dose of both paclitaxel and Compound (xvii) was not determined.

RESULTS:

The results obtained using the Human Xenograft Model to assess anti-tumor efficacy of the combination therapy of the present invention are presented in Tables 2-4. The data presented represents results from preliminary experiments. The data in Table 2 show that the optimal combination of compound (xvii) and paclitaxel was 15 mg/kg and 10 mg/kg respectively, in the LX-1 model. The combination resulted in some regressions and tumor growth delay. However, the same combination schedule in the CX-1 model did not result in any advantage over the single drug treatment as shown in Table 3.

In the PC-3 model, there was no beneficial effect of the combination as compared to single drug treatment. However, the optimal dose for single dose administration was not determined.

TABLE 2

DOSE RESPONSE OF COMPOUND (xvii) WITH AND WITHOUT PACLITAXEL AGAINST THE LX-1 *IN VIVO* TUMOR MODEL. LX-1#16								
DRUGS						REGRESSIONS		
Compound (xvii) (IV)	Paclitaxel (IV)	% Toxic Death	MTW d27 % T/C	Net Log Cell Kill	Total # Animals	PARTIAL	COMPLETE	CURE
Dose (mg/kg)								
0	10	0	10.5	-0.374	6	2		
25	0	0	3.94	-0.042	6			
15	0	0	12.24	-0.465	6			
7.5	0	0	19.06	-0.581	6			
25	10	0	1.28	0.382	6	4		
15	10	17	1.92	0.589	6	1		
7.5	10		4.57	-0.033	6			

*Q2Dx3;5,12,19 Paclitaxel injected one hour after Compound (xvii).

TABLE 3

DOSE RESPONSE OF COMPOUND (xvii) WITH AND WITHOUT PACLITAXEL AGAINST THE CX-1 *IN VIVO* TUMOR MODEL. CX-1#9

DRUGS						REGRESSIONS		
Compound (xvii) (IV)	Paclitaxel (IV)	% Toxic Death	MTW d55 % T/C	Net Log Cell Kill	Total # Animals	PARTIAL	COMPLETE	CURE
Dose (mg/kg)								
0	10		38.12	-0.124	6	2		
25	0	83			6			
15	0		52.87	-0.313	6			
7.5	0		109.7	-0.763	6			
25	10		47.64	-0.354	6	2		
15	10		51.61	-0.39	6	2		
7.5	10		73.85	-0.531	6	1		

*Q2Dx3;5,12,19 Paclitaxel injected one hour after Compound (xvii).

TABLE 4

DOSE RESPONSE OF COMPOUND (xvii) WITH AND WITHOUT PACLITAXEL AGAINST THE PC-3 *IN VIVO* TUMOR MODEL. PC-3#8

DRUGS						REGRESSIONS		
Compound (xvii) (IV)	Paclitaxel (IP)	% Toxic Death	MTW d35 % T/C	Net Log Cell Kill	Total # Animals	PARTIAL	COMPLETE	CURE
Dose (mg/kg)								
0	30	17	2	toxic	6	5		
0	20	0	2.86	1.98	6	5	1	
0	10	0	55.12	-0.672	6	2		
30	0	33	0.09	0.967	6	3	1	
30	30	33	0.09	0.603	6	4		
30	20	0	0.09	1.07	6	4		2
30	10	17	0.09	1.98	6	3	2	

*Q2Dx3;5,12,19 Paclitaxel injected one hour after Compound (xvii).

The following compounds were prepared and can be prepared according to the Examples:

3. Xaa Val Xab Pro Xac
4. Xaa Val Xab Pro Xad
5. Xaa Val Xab Pro Xae
6. Xaa Val Xab Pro Xaf
7. Xaa Val Xab Pro Xag
8. Xaa Val Xab Pro Xah
9. Xaa Val Xab Pro Xai
10. Xaa Val Xab Pro Xak
11. Xaa Val Xab Pro Xal
12. Xaa Val Xab Pro Xam
13. Xaa Val Xab Pro Xan
14. Xaa Val Xab Pro Xao
15. Xaa Val Xab Pro Xap
16. Xaa Val Xab Pro Xaq
17. Xaa Val Xab Pro Xar
18. Xaa Val Xab Pro Xas
19. Xaa Val Xab Pro Xat
20. Xaa Val Xab Pro Xau
21. Xaa Val Xab Pro Xav
22. Xaa Val Xab Pro Xaw
23. Xaa Val Xab Pro Xax
24. Xaa Val Xab Pro Xay
25. Xaa Val Xab Pro Xaz
26. Xaa Val Xab Pro Xba
27. Xaa Val Xab Pro Xbb
28. Xaa Val Xbc Pro Xay
29. Xaa Val Xab Pro Xbd
30. Xaa Val Xab Pro Xbe
31. Xaa Val Xab Pro Xbf
32. Xaa Val Xab Pro Xbg
33. Xaa Val Xab Pro Xbh
34. Xaa Val Xab Pro Xbi

35. Xaa Val Xab Pro Xbk
36. Xaa Val Xab Pro Xbl
37. Xaa Val Xab Pro Xbm
38. Xaa Val Xab Pro Xbn
39. Xaa Val Xab Pro Xbo
40. Xaa Val Xab Pro Xbp
41. Xaa Val Xab Pro Xbq
42. Xaa Val Xab Pro Xbr
43. Xaa Val Xab Pro Xbs
44. Xaa Val Xab Pro Xbt
45. Xaa Val Xab Pro Xbu
46. Xaa Val Xab Pro Xbv
47. Xaa Val Xab Pro Xbw
48. Xaa Val Xab Pro Xbx
49. Xaa Val Xab Pro Xby
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72. Xcx Val Xab Pro Xcv
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125. Xab Val Xab Pro Xbn
126. Xab Val Xab Pro Xbo
127. Xab Val Xab Pro Xch
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129. Xaa Val Xab Pro Xdu
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146. Xaa Val Xab Pro Xen
147. Xaa Val Xab Pro Xeo
148. Xaa Val Xab Pro Xep
149. Xaa Val Xab Pro Xeq
150. Xaa Val Xab Pro Xer
151. Xaa Val Xab Pro Xcq
152. Xaa Val Xab Pro Pro Val Phe
153. Xaa Val Xab Pro Xet Val Phe NH_2
154. Xaa Val Xer Pro Pro Val Phe NH_2
155. Xaa Val Xbc Pro Pro Val Phe NH_2
156. Xaa Ile Xab Pro Pro Val Phe NH_2
157. Xaa Leu Xab Pro Pro Val Phe NH_2
158. Xde Val Xab Pro Pro Val Phe NH_2
159. Xdd Val Xab Pro Pro Val Phe NH_2
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161. Xeu Val Xab Pro Pro Val Phe NH_2
162. Xaa Val Xab Pro Pro Phe Phe NH_2
163. Xaa Val Xab Pro Pro Val NH_2
163. Xaa Val Xab Pro Xev
165. Xaa Val Xab Pro Pro NH_2
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169. Xdd Val Xab Pro Pro NH_2
170. Xaa Xdf Xab Pro Pro NH_2
171. Xaa Val Xab Pro Xey
172. Xaa Val Xab Pro Xez
173. Xfa Val Xab Pro Pro Val Phe NH_2
174. Xaa Val Xab Pro Pro Xfb

175. Xaa Val Xab Pro Xfc
176. Xaa Val Xab Pro Xfd
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178. Xaa Val Xab Pro Xff
179. Xaa Val Xab Pro Xfg
180. Xaa Val Xab Pro Xfh
181. Xaa Val Xab Pro Xfi
182. Xaa Val Xab Pro Xfj
183. Xaa Val Xdl Pro Pro NH_2
184. Xaa Val Xfk Pro Pro NH_2
185. Xaa Val Xfl Pro Xfh
186. Xaa Val Xfk Pro Xfh
187. Xcx Val Xab Pro Xfh
188. Xaa Val Xab Pro Pro Xdf Phe NH_2
189. Xaa Val Xab Pro Pro Leu Phe NH_2
190. Xaa Val Xab Pro Pro Ile Phe NH_2

Examples for the MS-characterization of the synthesized novel compounds are listed below:

EXAMPLE	Fast atom bombardment MS analysis
3.	565
4.	579
5.	593
6.	607
7.	621
8.	635
11.	607
12.	607
13.	621
14.	649
15.	635
16.	635
17.	635
18	635
19.	621

This Sheet Has Been Replaced

THIS SHEET HAS BEEN REPLACED

20.	621
21.	635
22.	635
25.	633
26.	647
27.	661
31.	623
32.	671
33.	667
34.	681
35.	655
36.	655
37.	669
38.	621
39.	635
41.	649
42.	621
43.	633
44.	667
45.	607
46.	647
47.	668
48.	655
49.	669
50.	685
51.	629
52.	625
53.	721
55.	579
58.	623
61.	597
62.	621
63.	609
64.	625
65.	635

66.	591
67.	715
68.	685
69.	685
70.	591
71.	607
72.	621
74.	706
75.	579
76.	579
77.	579
78.	607
79.	607
80.	607
81.	607
82.	637
83.	692
84.	706
85.	706
86.	706
87.	607
90.	635
92.	659
93.	617
94.	636
95.	678
128.	671
131.	625
139.	625
151.	637
152.	798
153.	810
154.	812
155.	812
156.	812

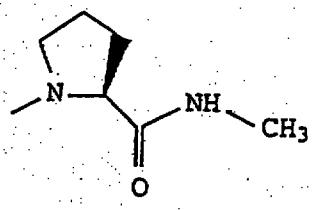
157.	812
258.	812
159.	811
160.	825
161.	881
162.	845
163.	649
164.	737
165.	550
166.	551
167.	731
168.	550
169.	566
170.	566
171.	635
172.	704
173.	853
174.	740
175.	619
176.	845
177.	649
178.	691
179.	717
180.	641
181.	579
182.	595
183.	566
184.	566
185.	669
186.	656
187.	669
188.	811
189.	812
190.	812

The symbols used in the description of the compounds of Formula I have the following meanings:

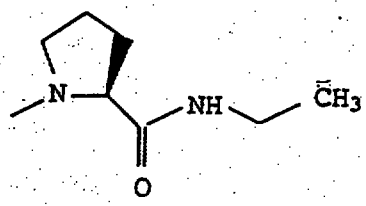
Xaa: N,N-Dimethylvaline

Xab: N-Methylvaline

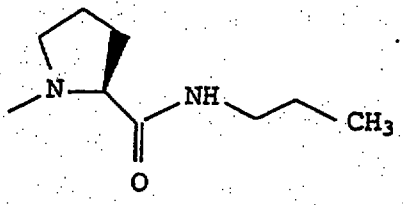
Xac:



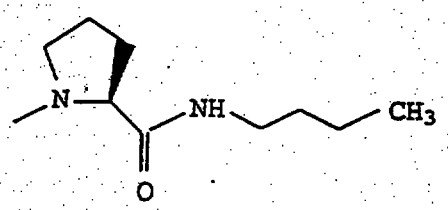
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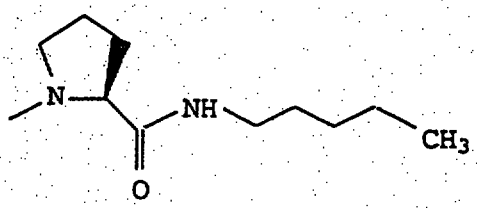
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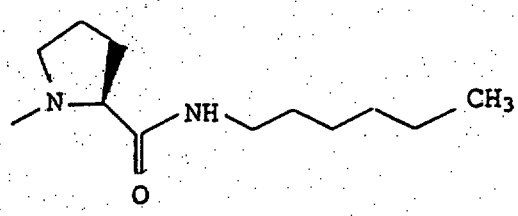
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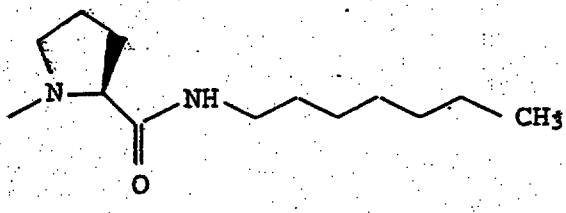
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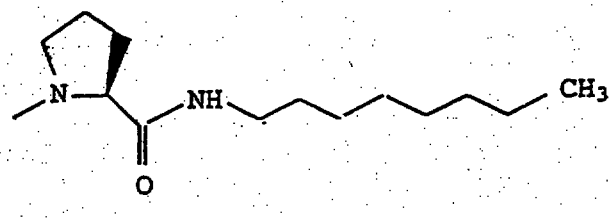
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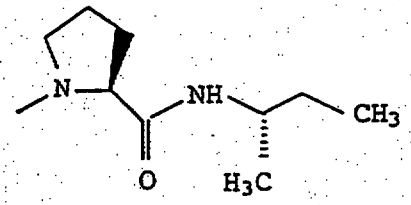
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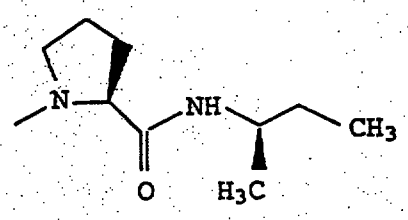
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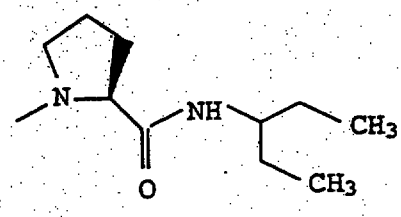
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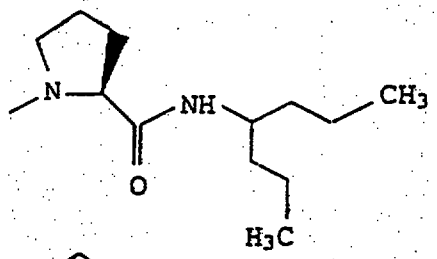
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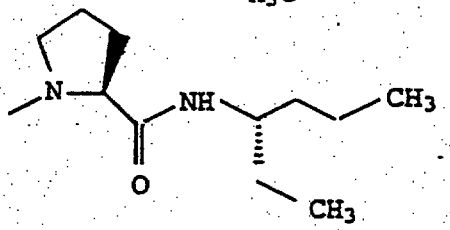
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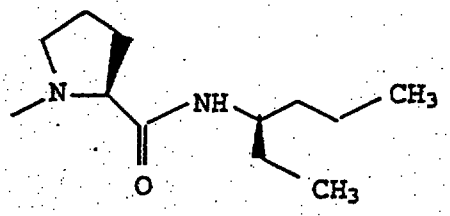
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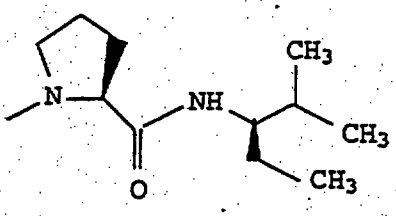
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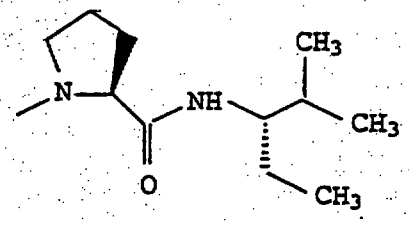
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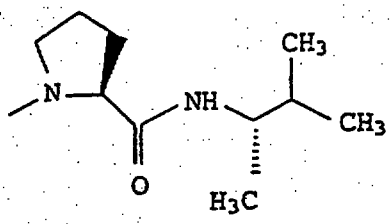
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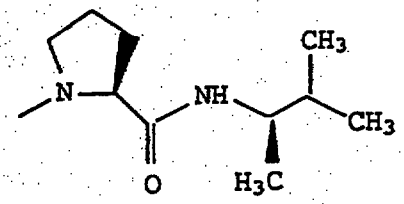
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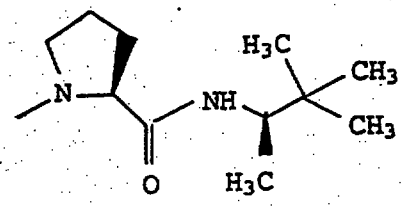
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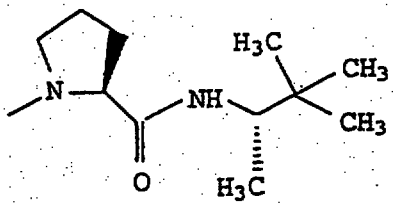
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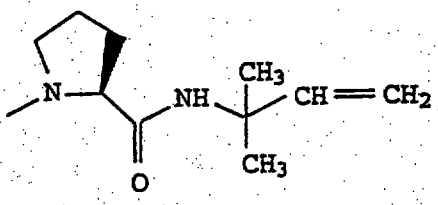
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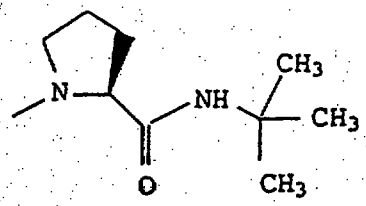
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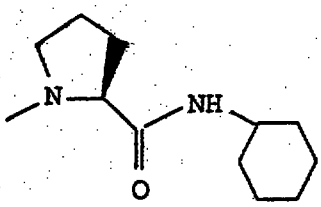
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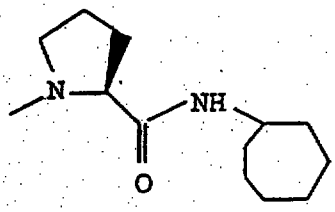
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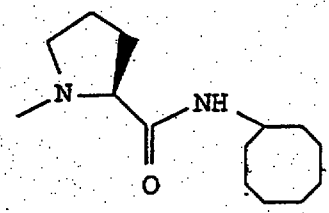
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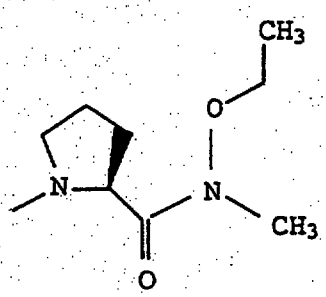


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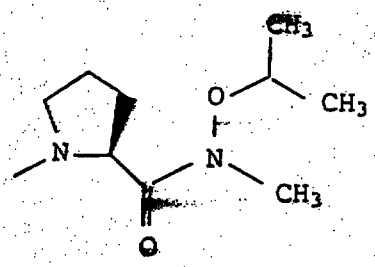


Xbc: N-Methyl-isoleucine

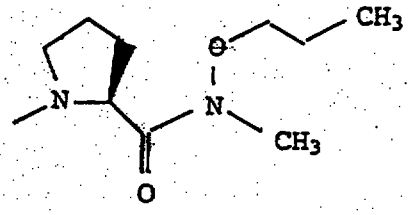
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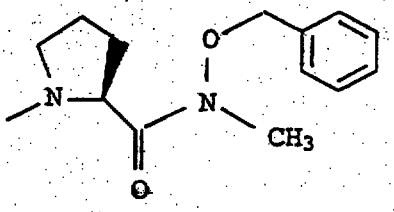
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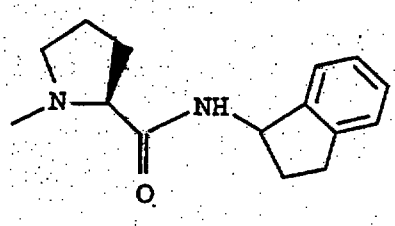
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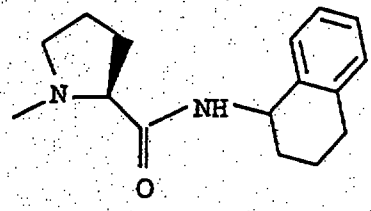
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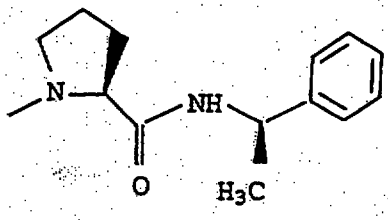
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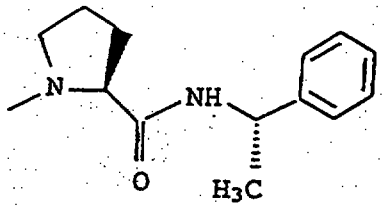
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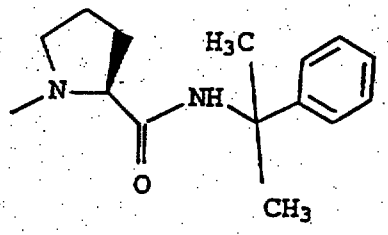
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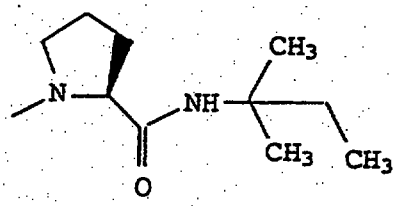
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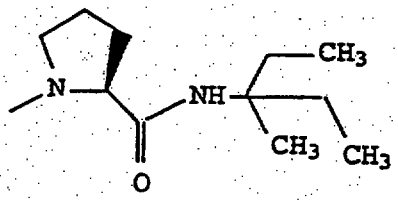
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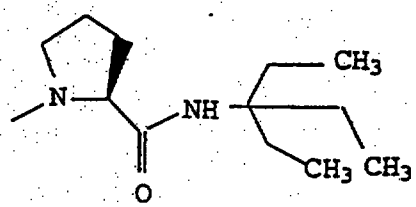
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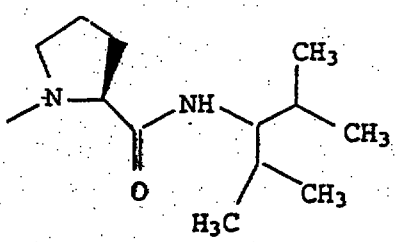
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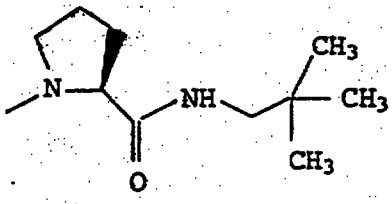
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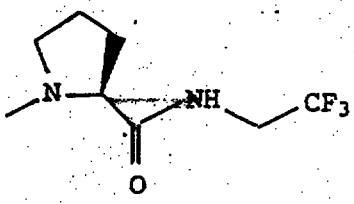
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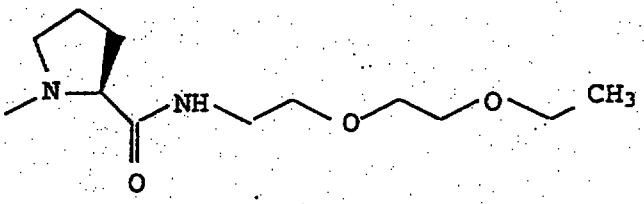
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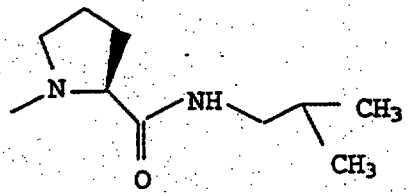
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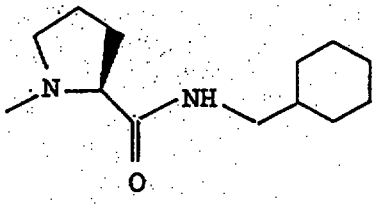
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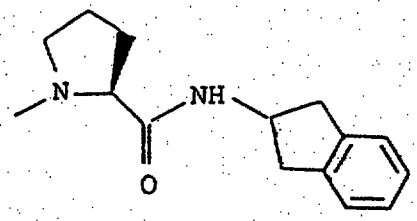
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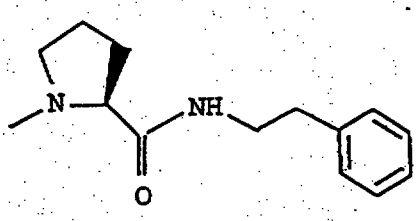
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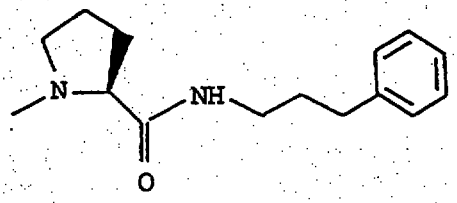
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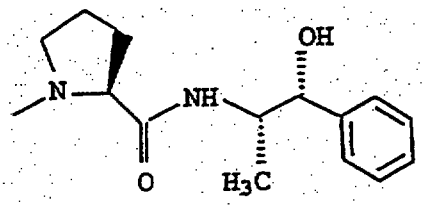
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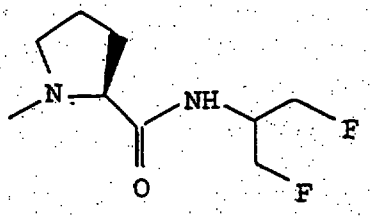
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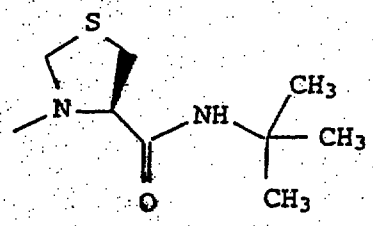
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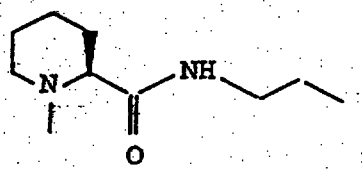


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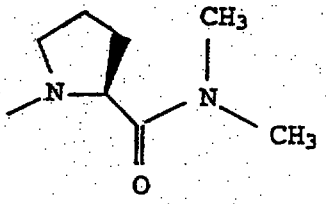


Xcc: Proline adamantyl(1)amide

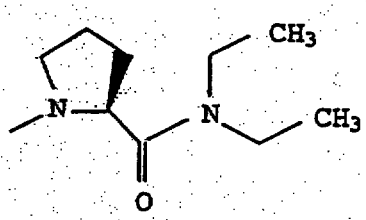
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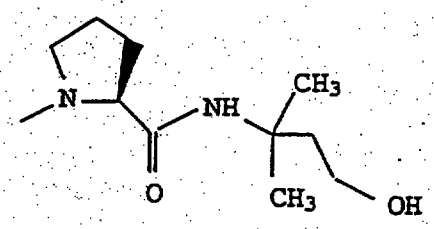
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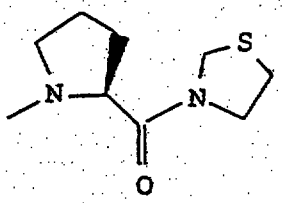
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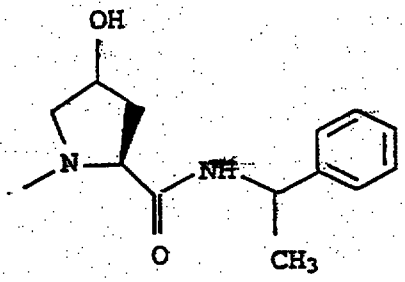
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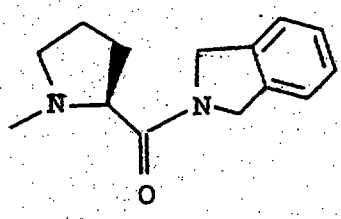
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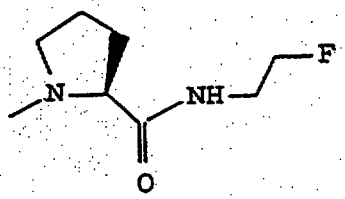
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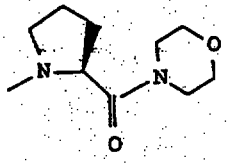
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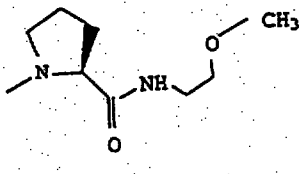
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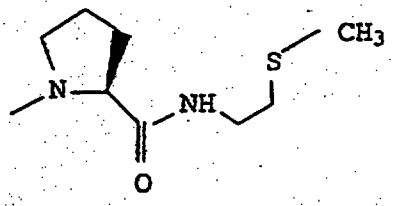
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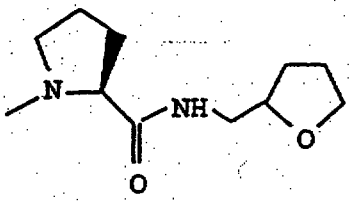
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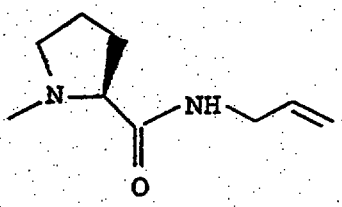
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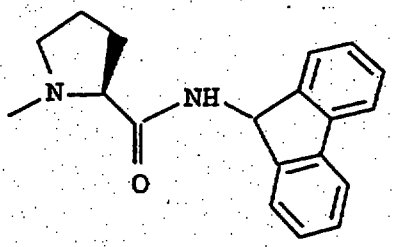
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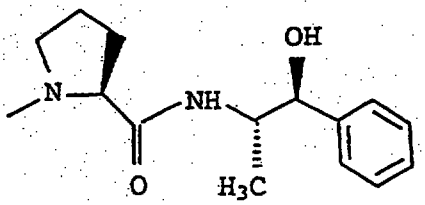
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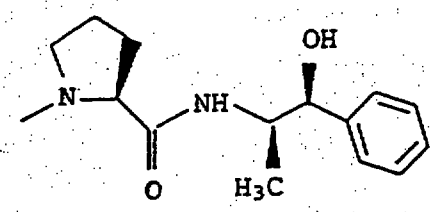
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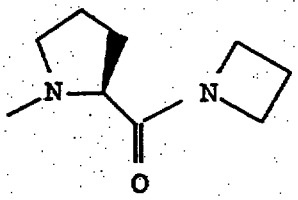
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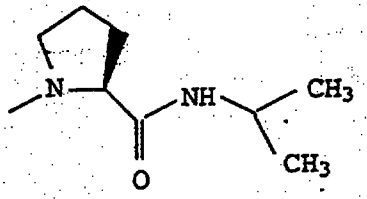
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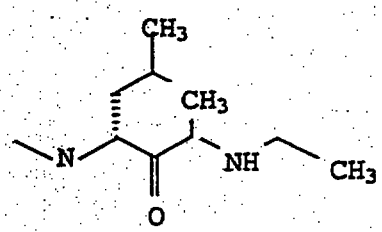
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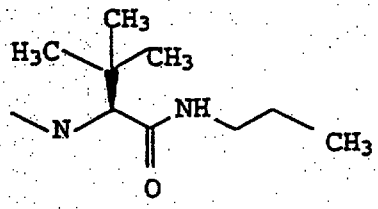
Xcw: N-Methyl-N-ethyl-valine

Xcx: N,N-Diethylvaline

Xcy:



Xcz:



Xda: N-Methyl-2-aminobutyroyl

Xdb: 2-aminobutyroyl

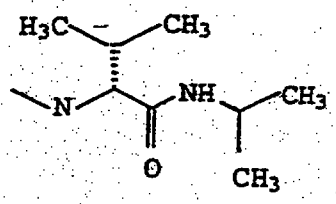
Xdc: N,N-Dimethyl-2-aminobutyroyl

Xdd: N,N-Dimethyl-2-tert.butylglycine

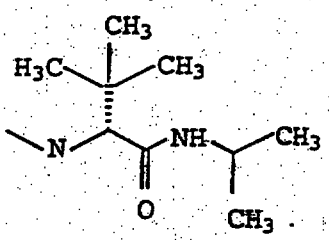
Xde: N,N-Dimethyl-isoleucine

Xdf: 2-tert.butylglycine

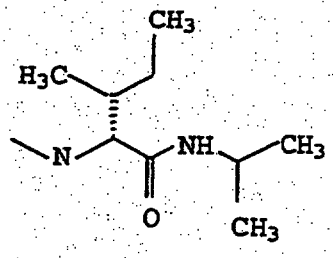
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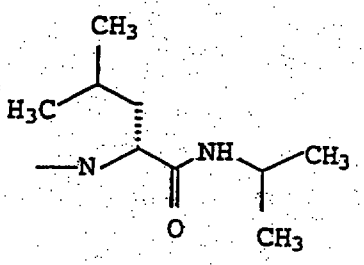
Xdh:



Xdi:

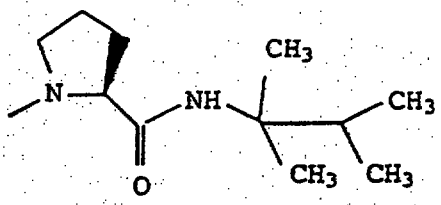


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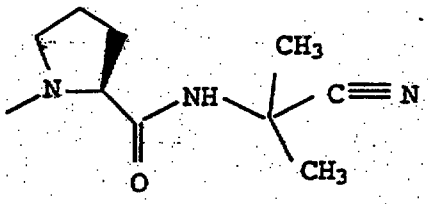


Xdl: N-Methyl-2-tert.butylglycine

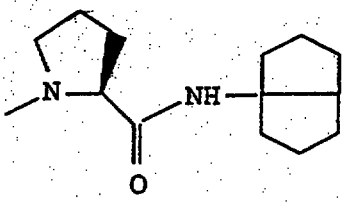
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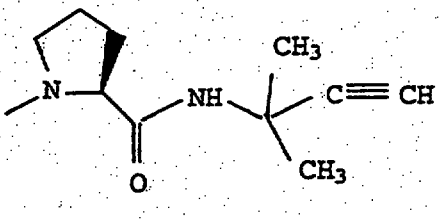
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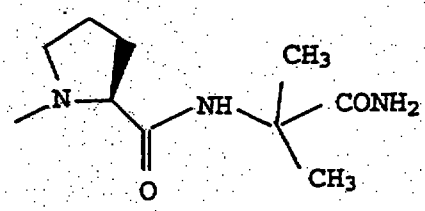
Xdo:



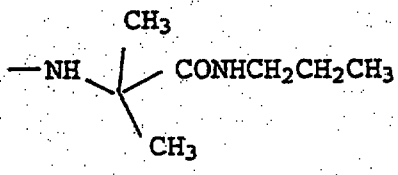
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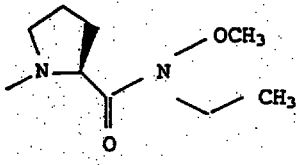
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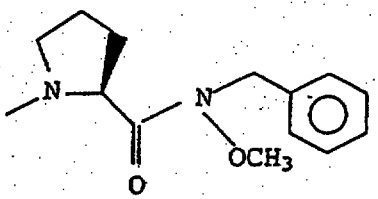
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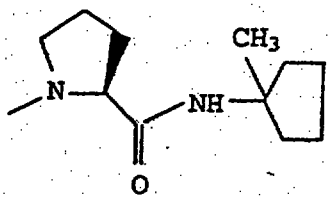
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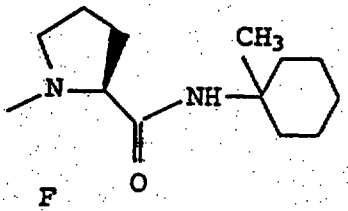
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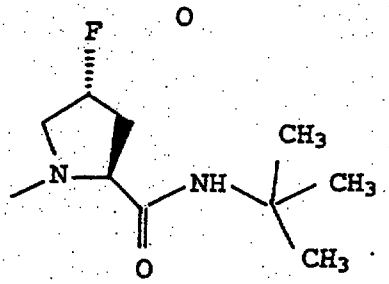
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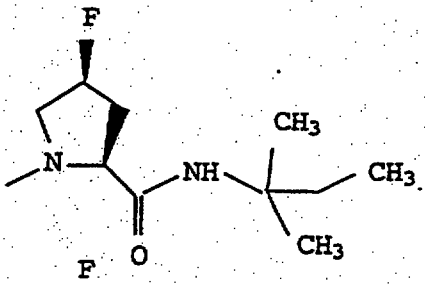
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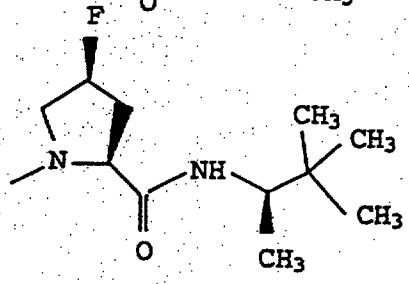
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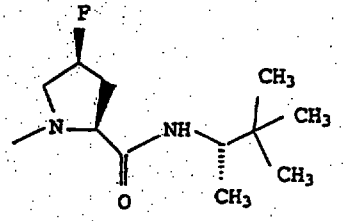
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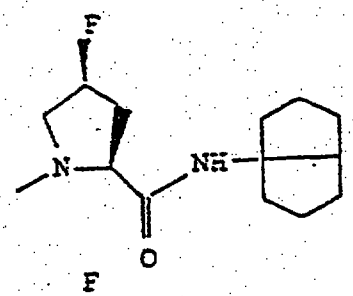
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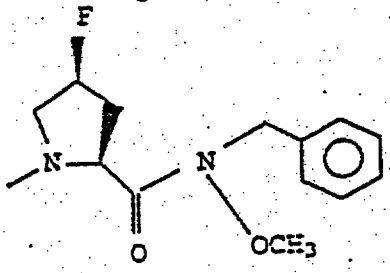
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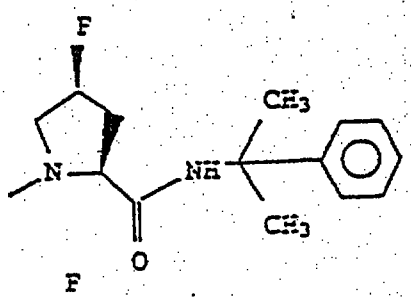
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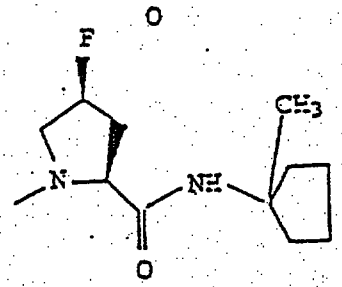
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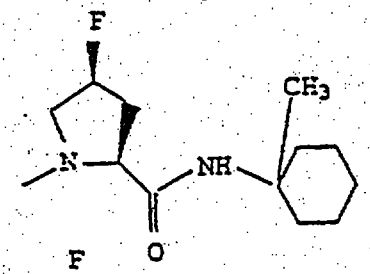
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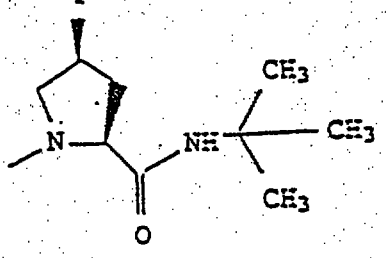
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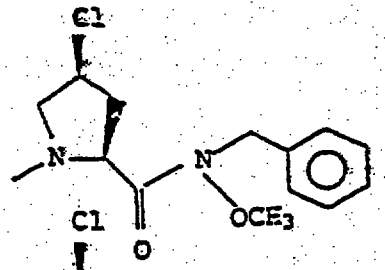
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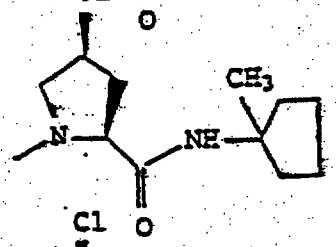
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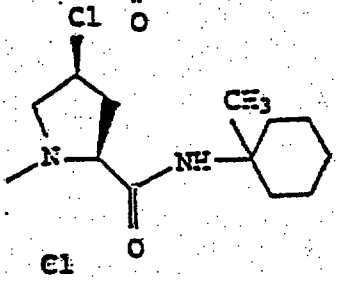
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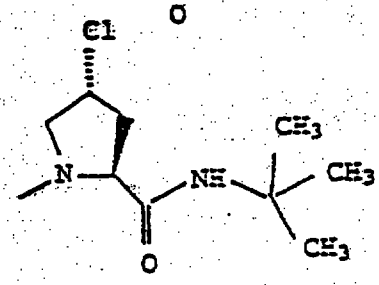
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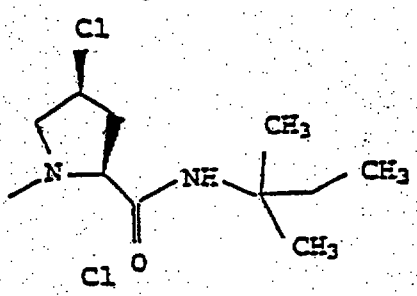
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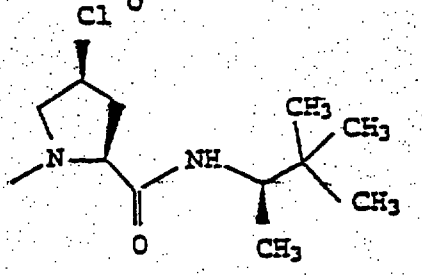
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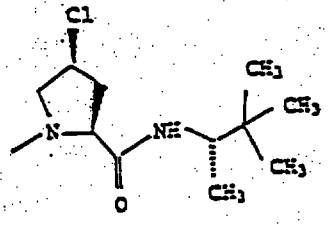
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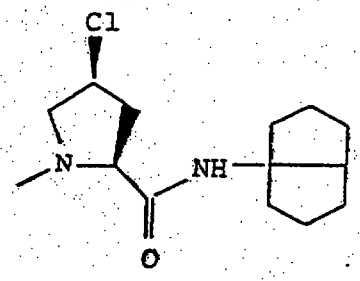
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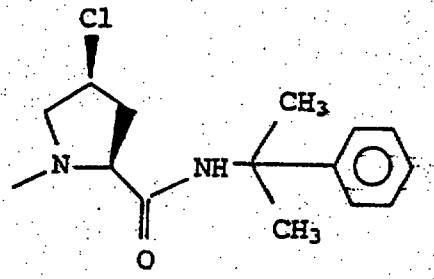
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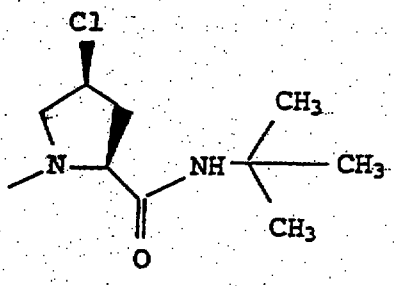
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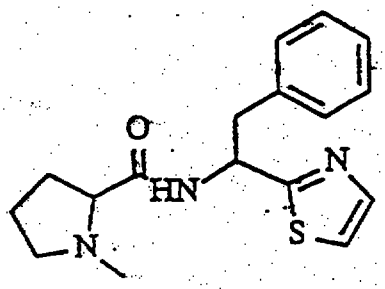
Xer: N-Methylleucine

Xes: N-Acetyl-N-methylvaline

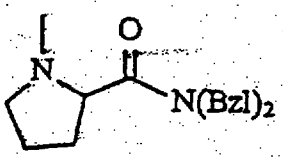
Xet: pipecolinic acid

Xeu: N,N-Dibutylvaline

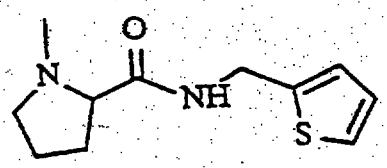
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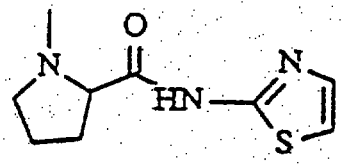


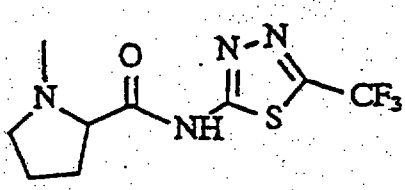
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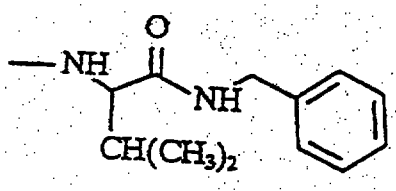
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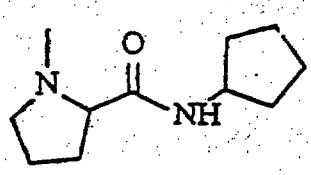
Xey: 

Xez: 

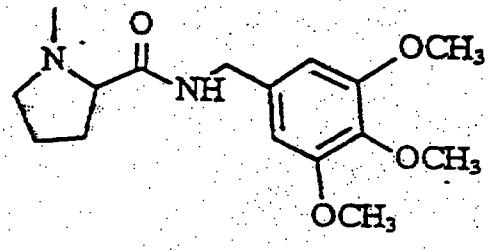
Xfa: N,N-dipropylvaline

Xfb: 

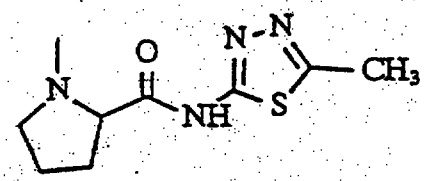
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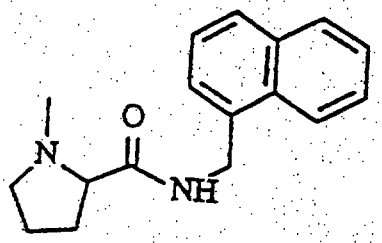
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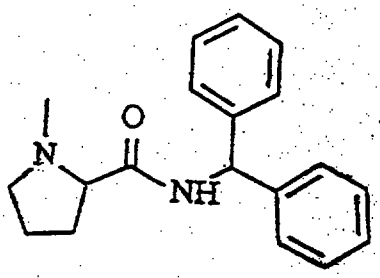
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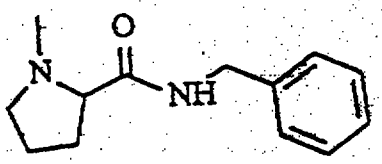
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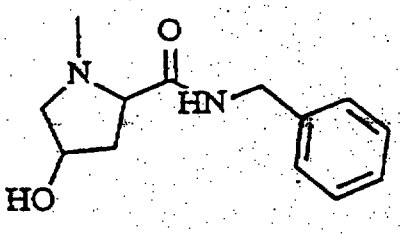
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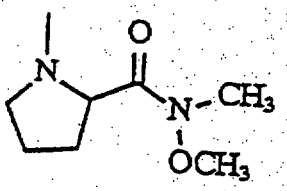
Xfh:



Xfi:



Xfj:



Xfk: N-Ethylvaline

Xfl: N-Methyl-3-tert-butylalanine

EQUIVALENTS

Those skilled in the art will recognize or be able to ascertain using no more than routine experimentation many equivalents to the specific embodiments of the invention described herein. Such equivalents are intended to be encompassed in the scope of the following claims.

REPLACED SHEETS SG
☐ Description : paged ..... to paged .....
☑ Claim(s) : paged 86 to paged 104
☐ Drawing(s) : paged ..... to paged .....
☐ Abstract : paged ..... to paged .....

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☐ Claim(s) : paged ..... to paged .....
☐ Drawing(s) : paged ..... to paged .....
☐ Abstract : paged ..... to paged .....

CLAIMS

What is claimed is:

1. A pharmaceutical composition comprising:

an effective amount of a first compound selected from the group consisting of paclitaxel, taxotere and modified taxane or taxoid analogs; and

an effective amount of a second compound, wherein the second compound is of Formula I

$$R^1\ R^2\ N\text{-}CHX\text{-}CO\text{-}A\text{-}B\text{-}D\text{-}(E)_s\text{-}(F)_t\text{-}(G)_u\text{-}K \qquad (I)$$

wherein:

R^1 is alkyl, cycloalkyl, alkylsulfonyl, fluoroalkyl, or aminosulfonyl;

R^2 is hydrogen, alkyl, fluoroalkyl or cycloalkyl;

$R^1\text{-}N\text{-}R^2$ together may be a pyrrolidino or piperidino residue;

A is a valyl, isoleucyl, leucyl, allo-isoleucyl, 2,2-dimethylglycyl, 2-cyclopropylglycyl, 2-cyclopentylglycyl, 3-tert-butylalanyl, 2-tert-butylglycyl, 3-cyclohexylalanyl, 2-ethylglycyl, 2-cyclohexylglycyl, norleucyl or norvalyl residue;

B is a N-alkyl-valyl, -norvalyl, -leucyl, -isoleucyl, -2-tert-butylglycyl, -3-tert-

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butylalanyl, -2-ethylglycyl, -2-cyclopropylglycyl, -2-cyclopentylglycyl, norleucyl or -2-cyclohexylglycyl residue;

D is a prolyl, homoprolyl, hydroxyprolyl, 3,4-dehydroprolyl, 4-fluoroprolyl, 3-methylprolyl, 4-methylprolyl, 5-methylprolyl, azetidine-2-carbonyl, 3,3-dimethylprolyl, 4,4-difluoroprolyl, oxazolidine-4-carbonyl or thiazolidine-4-carbonyl residue;

E is a prolyl, homoprolyl, hydroxyprolyl, 3,4-dehydroprolyl, 4-fluoroprolyl, 3-methylprolyl, 4-methyl prolyl, 5-methylprolyl, azetidine-2-carbonyl, 3,3-dimethylprolyl, 4,4-difluoroprolyl, oxazolidine-4-carbonyl or thiazolidine-4-carbonyl residue;

F and G are independently selected from the group consisting of prolyl, homoprolyl, hydroxyprolyl, thiazolidinyl-4-carbonyl, 1-aminopentyl-1-carbonyl, valyl, 2-tert-butylglycyl, isoleucyl, leucyl, 3-cyclohexylalanyl, phenylalanyl, N-methylphenylalanyl, tetrahydrosioquinolyl-2-histidyl, 1-aminoindyl-1-carbonyl, 3-pyridylalanyl, 2-cyclohexylglycyl, norleucyl, norvalyl, neopentylglycyl, trytophanyl, glycyl, 2,2-dimethylglycyl, alanyl, ß-alanyl and 3-naphthylalanyl residues;

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X is hydrogen, alkyl, cycloalkyl, $-CH_2$-cyclohexyl or arylalkyl;

s, t and u are independently 0 or 1; and

K is hydroxy, alkoxy, phenoxy, benzyloxy or a substituted or unsubstituted amino moiety;

and the salts thereof with physiologically tolerated acids.

2. The pharmaceutical composition of Claim 1 further comprising a pharmaceutically acceptable carrier.

3. A composition of Claim 1 wherein for the compound of Formula I, K is a substituted amino moiety having the formula R^5-N-R^6 wherein:

R^5 is hydrogen, or hydroxy, or C_{1-7} alkoxy, or benzyloxy, or phenyloxy, or C_{1-7}- linear or branched alkyl (which may be substituted by one or more fluoro atoms), or C_{1-12} linear or branched hydroxyalkyl, or C_{3-10}-cycloalkyl, or benzyl (which may be substituted by up to three substituents which may independently be CF_3, nitro, C_{1-7} alkylsulfonyl, C_{1-4} alkoxy, phenoxy, benzoxy, halogen, C_{1-4}-alkyl, cyano, hydroxy, $N(CH_3)_2$, COOMe, COOEt, COOiPr, or $COONH_2$);

R^6 is hydrogen, C_{1-12} linear or branched alkyl (which may be substituted by one or more fluoro atoms), or C_{1-12} linear or branched hydroxyalkyl, or C_{3-10}-cycloalkyl, or

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$-(CH_2)_v-C_{3-7}-$ cycloalkyl (v=0,1,2, or 3), or norephedryl, or norpseudoephedryl, or quinolyl, or pyrazyl, or $-CH_2-$benzimidazolyl, or (1)-adamantyl or (2)-adamantyl or $-CH_2-$adamantyl, or alpha-methyl-benzyl, or alpha-dimethylbenzyl, or $-(CH_2)_v-$phenyl (v=0,1,2, or 3) which may be substituted by up to two substituents which may independently be CF_3, nitro, C_{1-7} alkylsulfonyl, C_{1-4} alkoxy, phenoxy, benzoxy, halogen, $C_{1-4}-$alkyl which may form a cyclic system, cyano, hydroxy, $N(CH_3)_2$, COOMe, COOEt, COOiPr, or $COONH_2$); or $-(CH_2)_m-$naphthyl (m=0 or 1); or $-(CH_2)_w-$benzhydryl (w=0,1, or 2); or biphenyl or picolyl or benzothiazolyl or benzoisothiazolyl or benzopyrazolyl or benzoxazolyl or $-(CH_2)_m-$fluorenyl (m=0 or 1); or pyrimidyl or $-(CH_2)_m-$indanyl (m=0 or 1); or $-(CH_2CH_2O)_y-CH_3$ (y=0,1,2,3,4, or 5), or $-(CH_2CH_2O)_y-CH_2CH_3$ (y=0,1,2,3,4, or 5), or $NH-C_6H_5$ (which may be substituted by up to two substituents which may independently be CF_3, nitro, C_{1-7} alkylsulfonyl, C_{1-4} alkoxy, halogen, C_{1-4} alkyl which may form a cyclic system, cyano, hydroxy, COOMe, COOEt, COOiPr, or $COONH_2$), or $-NCH_3-C_6H_5$, or $-NH-CH_2-C_6H_5$, or $-NCH_3-CH_2-C_6H_5$, or 5-membered heteroaryl (which may be substituted by up to two substituents which may independently be CF_3, nitro, thiomethyl, thioethyl, $C_{3-6}-$cycloalkyl, $-CH_2-$COOEt, $C_{3-4}-$alkylene group forming a bicyclic system with the

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heterocycle), or phenyl, or -CHR^7-5-membered heteroaryl (which may be substituted by up to two substituents which may independently be CF_3, nitro, cyano, halogen, COOMe, COOEt, COOiPr, $CONH_2$, C_{1-4}-alkyl, C_{1-4}-alkoxy, phenyl, benzyl, naphthyl, or C_{1-7}-alkylsulfonyl [R^7 = hydrogen, linear or branched C_{1-5} alkyl, benzyl; or R^7 and R^5 together form a group $-(CH_2)_3-$ or $-(CH_2)_4-$).

4. A composition of Claim 3 wherein for the compound of Formula I R^1 and R^2 are each methyl or ethyl; X is isopropyl, sec-butyl or tert-butyl; s is 1; t and u are each 0; A is valyl, 2-ethylglycyl, isoleucyl or 2-tert-butylglycyl; B is N-methylvalyl, 2-ethylglycyl, 1-isoleucyl or 2-tertbutylglycyl; D is prolyl, 4-fluoroprolyl, thiazolidinyl-4-carbonyl, or 3,4-dehydroprolyl; E is prolyl, 4-fluoroprolyl, thiazolidinyl-4-carbonyl, homoprolyl, 3,4-dehydroprolyl or hydroxyprolyl; and K is a substituted amino moiety having the formula R^5-N-R^6 wherein R^5 is hydrogen or C_1-C_4 alkoxy and R^6 is a C_1-C_{12} linear or branched alkyl group selected from the group of monovalent radicals consisting of:

$-C(CH_3)_3$, also referred to as tert-butyl;

$-\underset{(CH_3)_2}{\overset{|}{C}}-CH_2-CH_3$, also referred to as 1,1-dimethyl propyl;

$-\underset{CH_3}{\overset{|}{C}}(CH_2-CH_3)_2$, also referred to as 1-methyl-1-ethyl propyl

$-\underset{CH_3}{\overset{|}{CH}}-C(CH_3)_3$, also referred to as (S)- or (R)-1-methyl-2,2-dimethyl propyl;

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$-CH(C_2H_5)-CH(CH_3)_2$, also referred to as (S)- or (R)-1-ethyl-2-methyl propyl;

$-CH(CH(CH_3)_2)-CH(CH_3)_2$, also referred to as 1-isopropyl-2-methyl butyl; or

$-C(CH_3)_2-CH(CH_3)_2$, also referred to as 1,1-dimethyl-2-methylpropyl

$-CH(CH_3)_2$, also referred to as isopropyl

$-CH(CH_3)CH_2CH_3$, also referred to as sec-butyl, (S)- or (R)-

$-CH(CH_3)CH(CH_3)_2$, also referred to as 1,2-dimethylpropyl.

5. A composition of Claim 4 wherein the monovalent radical is $-C(CH_3)_3$, also referred to as tert-butyl.

6. A composition of Claim 3 wherein for the compound of Formula I R^1 and R^2 are each methyl or ethyl; X is isopropyl, sec-butyl or tert-butyl; s is 1; t and u are each 0; A is valyl, 2-ethylglycyl, isoleucyl or 2-tert-butylglycyl; B is N-methylvalyl, 2-ethylglycyl, 1-isoleucyl or 2-tertbutylglycyl; D is prolyl, 4-fluoroprolyl, thiazolidinyl-4-carbonyl, or 3,4-dehydroprolyl; E is prolyl, 4-fluoroprolyl, thiazolidinyl-4-carbonyl, homoprolyl, 3,4-dehydroprolyl or hydroxyprolyl; and K is a substituted amino moiety having the formula R^5-N-R^6 wherein R^5 is hydrogen or C_1-C_4 alkoxy and R^6 is selected from the group of monovalent radicals consisting of: (CH_2)v-phenyl (wherein v is 1) and α,α-dimethylbenzyl.

7. A composition of Claim 3 wherein for the compound of Formula I R^1 and R^2 are each methyl or ethyl; X is

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isopropyl, sec-butyl or tert-butyl; s is 1; t and u are each 0; A is valyl, 2-ethylglycyl, isoleucyl or 2-tert-butylglycyl; B is N-methylvalyl, 2-ethylglycyl, 1-isoleucyl or 2-tertbutylglycyl; D is prolyl, 4-fluoroprolyl, thiazolidinyl-4-carbonyl, or 3,4-dehydroprolyl; E is prolyl, 4-fluoroprolyl, thiazolidinyl-4-carbonyl, homoprolyl, 3,4-dehydroprolyl or hydroxyprolyl; and K is a substituted amino moiety having the formula R^5-N-R^6 wherein R^5 is hydrogen or C_1-C_4 alkoxy and R^6 is a C_1-C_{12} linear or branched hydroxyalkyl.

8. A composition of Claim 7 wherein R^6 is 3-hydroxy-1,1-dimethylpropyl.

9. A composition of Claim 3 wherein for the compound of Formula I R^1 and R^2 are each methyl or ethyl; X is isopropyl, sec-butyl or tert-butyl; s is 1; t and u are each 0; A is valyl 2-ethylglycyl, isoleucyl or 2-tert-butylglycyl; B is N-methylvalyl, 2-ethylglycyl, 1-isoleucyl or 2-tertbutylglycyl; D is prolyl, 4-fluoroprolyl, thiazolidinyl-4-carbonyl, or 3,4-dehydroprolyl; E is prolyl, 4-fluoroprolyl, thiazolidinyl-4-carbonyl, homoprolyl, 3,4-dehydroprolyl or hydroxyprolyl; and K is a substituted amino moiety having the formula R^5-N-R^6 wherein R^5 is hydrogen or C_1-C_4 alkoxy and R^6 is a C_{3-10} cycloalkyl selected from the group consisting of: (1)-adamantyl, (2)-adamantyl, cyclobutyl, cyclopentyl, cyclohexyl, 1-methylcyclopentyl, 1-methylcyclohexyl and [3.3.0]octa-1-yl.

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10. A composition of Claim 3 wherein for the compound of Formula I R^1 and R^2 are each methyl; X is isopropyl; s is 1; t and u are each 0; A is valyl; B is N-methylvalyl; D is prolyl; E is prolyl; R^5 is benzyl and R^6 is hydrogen.

11. A method for treating cancer in a mammal, selected from the group consisting of: lung, breast, colon, prostate, bladder, rectal, endometrial and hematological (e.g., leukemias, lymphomas) cancers, comprising:
administering to said mammal an effective amount of a first compound selected from the group consisting of paclitaxel, taxotere and modified taxane or taxoid analogs; and
administering to said mammal an effective amount of a second compound of Formula I:

$$R^1\ R^2\ N\text{-}CHX\text{-}CO\text{-}A\text{-}B\text{-}D\text{-}(E)_s\text{-}(F)_t\text{-}(G)_u\text{-}K \qquad (I)$$

wherein:

R^1 is alkyl, cycloalkyl, alkylsulfonyl, fluoroalkyl, or aminosulfonyl;

R^2 is hydrogen, alkyl, fluoroalkyl or cycloalkyl;

$R^1\text{-}N\text{-}R^2$ together may be a pyrrolidino or piperidino residue;

A is a valyl, isoleucyl, leucyl, allo-isoleucyl, 2,2-dimethylglycyl, 2-cyclopropylglycyl, 2-cyclopentylglycyl, 3-tert-butylalanyl, 2-tert-butylglycyl, 3-

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cyclohexylalanyl, 2-ethylglycyl, 2-cyclohexylglycyl, norleucyl or norvalyl residue;

B is a N-alkyl-valyl, -norvalyl, -leucyl, -isoleucyl, -2-tert-butylglycyl, -3-tert-butylalanyl, -2-ethylglycyl, -2-cyclopropylglycyl, -2-cyclopentylglycyl, norleucyl or -2-cyclohexylglycyl residue;

D is a prolyl, homoprolyl, hydroxyprolyl, 3,4-dehydroprolyl, 4-fluoroprolyl, 3-methylprolyl, 4-methylprolyl, 5-methylprolyl, azetidine-2-carbonyl, 3,3-dimethylprolyl, 4,4-difluoroprolyl, oxazolidine-4-carbonyl or thiazolidine-4-carbonyl residue;

E is a prolyl, homoprolyl, hydroxyprolyl, 3,4-dehydroprolyl, 4-fluoroprolyl, 3-methylprolyl, 4-methyl prolyl, 5-methylprolyl, azetidine-2-carbonyl, 3,3-dimethylprolyl, 4,4-difluoroprolyl, oxazolidine-4-carbonyl or thiazolidine-4-carbonyl residue;

F and G are independently selected from the group consisting of prolyl, homoprolyl, hydroxyprolyl, thiazolidinyl-4-carbonyl, 1-aminopentyl-1-carbonyl, valyl, 2-tert-butylglycyl, isoleucyl, leucyl, 3-cyclohexylalanyl, phenylalanyl, N-methylphenylalanyl, tetrahydrosioquinolyl-2-histidyl,

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1-aminoindyl-1-carbonyl, 3-pyridylalanyl, 2-cyclohexylglycyl, norleucyl, norvalyl, neopentylglycyl, trytophanyl, glycyl, 2,2-dimethylglycyl, alanyl, ß-alanyl and 3-naphthylalanyl residues;

X is hydrogen, alkyl, cycloalkyl, $-CH_2$-cyclohexyl or arylalkyl;

s, t and u are independently 0 or 1; and

K is hydroxy, alkoxy, phenoxy, benzyloxy or a substituted or unsubstituted amino moiety;

and the salts thereof with physiologically tolerated acids.

12. A method of Claim 11 wherein the compound of Formula I is administered first followed by administration of the first compound.

13. A method of Claim 11 wherein the first compound is administered first followed by administration of the compound of Formula I.

14. A method of Claim 11 wherein the first compound and the compound of Formula I are administered simultaneously.

15. A method of Claim 11 wherein said mammal is human.

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16. A method of Claim 15 wherein for the compound of Formula I K is a substituted amino moiety having the formula R^5-N-R^6

wherein:

R^5 is hydrogen, or hydroxy, or C_{1-7} alkoxy, or benzyloxy, or phenyloxy, or C_{1-7}- linear or branched alkyl (which may be substituted by one or more fluoro atoms), or C_{1-12} linear or branched hydroxyalkyl, or C_{3-10}-cycloalkyl, or benzyl (which may be substituted by up to three substituents which may independently be CF_3, nitro, C_{1-7} alkylsulfonyl, C_{1-4} alkoxy, phenoxy, benzoxy, halogen, C_{1-4}-alkyl, cyano, hydroxy, $N(CH_3)_2$, COOMe, COOEt, COOiPr, or $COONH_2$);

R^6 is hydrogen, C_{1-12} linear or branched alkyl (which may be substituted by one or more fluoro atoms), or C_{1-12} linear or branched hydroxyalkyl, or C_{3-10}-cycloalkyl, or $-(CH_2)_v-C_{3-7}$- cycloalkyl (v=0,1,2, or 3), or norephedryl, or norpseudoephedryl, or quinolyl, or pyrazyl; or $-CH_2$-benzimidazolyl, or (1)-adamantyl or (2)-adamantyl or $-CH_2$-adamantyl, or alpha-methyl-benzyl, or alpha-dimethylbenzyl, or $-(CH_2)_v$-phenyl (v=0,1,2, or 3; which may be substituted by up to two substituents which may independently be CF_3, nitro, C_{1-7} alkylsulfonyl, C_{1-4} alkoxy, phenoxy, benzoxy, halogen, C_{1-4}-alkyl which may form

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a cyclic system, cyano, hydroxy, $N(CH_3)_2$, COOMe, COOEt, COOiPr, or $COONH_2$), or -$(CH_2)_m$-naphthyl (m=0 or 1); or -$(CH_2)_w$-benzhydryl (w=0,1, or 2); or biphenyl or picolyl or benzothiazolyl or benzoisothiazolyl or benzopyrazolyl or benzoxazolyl or -$(CH_2)_m$-fluorenyl (m=0 or 1); or pyrimidyl or -$(CH_2)_m$-indanyl (m=0 or 1); or -$(CH_2CH_2O)_y$-CH_3 (y=0,1,2,3,4, or 5), or -$(CH_2CH_2O)_y$-CH_2CH_3 (y=0,1,2,3,4, or 5), or NH-C_6H_5 (which may be substituted by up to two substituents which may independently be CF_3, nitro, C_{1-7} alkylsulfonyl, C_{1-4} alkoxy, halogen, C_{1-4} alkyl which may form a cyclic system, cyano, hydroxy, COOMe, COOEt, COOiPr, or $COONH_2$), or -NCH_3-C_6H_5, or -NH-CH_2-C_6H_5, or-NCH_3-CH_2-C_6H_5, or 5-membered heteroaryl (which may be substituted by up to two substituents which may independently be CF_3, nitro, thiomethyl, thioethyl, C_{3-6}-cycloalkyl, -CH_2-COOEt, C_{3-4}-alkylene group forming a bicyclic system with the heterocycle), or phenyl, or -CHR^7-5-membered heteroaryl (which may be substituted by up to two substituents which may independently be CF_3, nitro, cyano, halogen, COOMe, COOEt, COOiPr, $CONH_2$, C_{1-4}-alkyl, C_{1-4}-alkoxy, phenyl, benzyl, naphthyl, or C_{1-7}- alkylsulfonyl [R^7 = hydrogen, linear or branched C_{1-5} alkyl, benzyl; or R^7 and R^5 together form a group -$(CH_2)_3$- or -$(CH_2)_4$-).

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17. A method of Claim 16 wherein for the compound of Formula I R^1 and R^2 are each methyl or ethyl; X is isopropyl, sec-butyl or tert-butyl; s is 1; t and u are each 0; A is valyl, 2-ethylglycyl, isoleucyl or 2-tert-butylglycyl; B is N-methylvalyl, 2-ethylglycyl, isoleucyl or 2-tertbutylglycyl; D is prolyl, 4-fluoroprolyl, thiazolidinyl-4-carbonyl, or 3,4-dehydroprolyl; E is prolyl, 4-fluoroprolyl, thiazolidinyl-4-carbonyl, homoprolyl, 3,4-dehydroprolyl or hydroxyprolyl; and K is a substituted amino moiety having the formula R^5-N-R^6 wherein R^5 is hydrogen or C_1-C_4 alkoxy and R^6 is a C_1-C_{12} linear or branched alkyl group selected from the group of monovalent radicals consisting of:

$-C(CH_3)_3$, also referred to as tert-butyl;

$-\underset{(CH_3)_2}{\overset{|}{C}}-CH_2-CH_3$, also referred to as 1,1-dimethyl propyl;

$-\underset{CH_3}{\overset{|}{C}}(CH_2-CH_3)_2$, also referred to as 1-methyl-1-ethyl propyl;

$-\underset{CH_3}{\overset{|}{C}}H-C(CH_3)_3$, also referred to as (S)- or (R)-1-2,2-dimethyl propyl;

$-\underset{C_2H_5}{\overset{|}{C}}H-CH(CH_3)_2$, also referred to as (S)- or (R)-1-ethyl-2-methyl propyl;

$-\underset{CH(CH_3)_2}{\overset{|}{C}}H-CH(CH_3)_2$, also referred to as 1-isopropyl-2-methyl butyl; or

$-C(CH_3)_2-CH(CH_3)_2$, also referred to as 1,1-dimethyl-2-methyl propyl

$-CH(CH_3)_2$, also referred to as isopropyl

$-CH(CH_3)CH_2CH_3$, also referred to as sec-butyl, (S)- or (R)-

$-CH(CH_3)CH(CH_3)_2$, also referred to as 1,2-dimethylpropyl.

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18. A method of Claim 17 wherein said monovalent radical is $-(CH_3)_3$, also referred to as tert butyl.

19. A method of Claim 16 wherein for the compound of Formula I R^1 and R^2 are each methyl or ethyl; X is isopropyl, sec-butyl or tert-butyl; s is 1; t and u are each 0; A is valyl, 2-ethylglycyl, isoleucyl or 2-tert-butylglycyl; B is N-methylvalyl, 2-ethylglycyl, 1-isoleucyl or 2-tertbutylglycyl; D is prolyl, 4-fluoroprolyl, thiazolidinyl-4-carbonyl, or 3,4-dehydroprolyl; E is prolyl, 4-fluoroprolyl, thiazolidinyl-4-carbonyl, homoprolyl, 3,4-dehydroprolyl or hydroxyprolyl; and K is a substituted amino moiety having the formula R^5-N-R^6 wherein R^5 is hydrogen or C_1-C_4 alkoxy and R^6 is selected from the group of monovalent radicals consisting of: (CH_2)v-phenyl (wherein v is 1), and α,α-dimethylbenzyl.

20. A method of Claim 16 wherein for the compound of Formula I R^1 and R^2 are each methyl or ethyl; X is isopropyl, sec-butyl or tert-butyl; s is 1; t and u are each 0; A is valyl, 2-ethylglycyl, isoleucyl or 2-tert-butylglycyl; B is N-methylvalyl, 2-ethylglycyl, 1-isoleucyl or 2-tertbutylglycyl; D is prolyl, 4-fluoroprolyl, thiazolidinyl-4-carbonyl, or 3,4-dehydroprolyl; E is prolyl, 4-fluoroprolyl, thiazolidinyl-4-carbonyl, homoprolyl, 3,4-dehydroprolyl or hydroxyprolyl; and K is a substituted amino moiety having the formula R^5-N-R^6 wherein R^5 is hydrogen or C_1-C_4 alkoxy and R^6 is a C_1-C_{12} linear or branched hydroxyalkyl.

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21. A method of Claim 20 wherein R^6 is 3-hydroxy-1,1-dimethylpropyl.

22. A method of Claim 16 wherein for the compound of Formula I R^1 and R^2 are each methyl or ethyl; X is isopropyl, sec-butyl or tert-butyl; s is 1; t and u are each 0; A is valyl, 2-ethylglycyl, isoleucyl or 2-tert-butylglycyl; B is N-methylvalyl, 2-ethylglycyl, isoleucyl or 2-tertbutylglycyl; D is prolyl, 4-fluoroprolyl, thiazolidinyl-4-carbonyl, or 3,4-dehydroprolyl; E is prolyl, 4-fluoroprolyl, thiazolidinyl-4-carbonyl, homoprolyl, 3,4-dehydroprolyl or hydroxyprolyl; and K is a substituted amino moiety having the formula R^5-N-R^6 wherein R^5 is hydrogen or C_1-C_4 alkoxy and R^6 is a C_{3-10} cycloalkyl selected from the group consisting of: (1)-adamantyl, (2)-adamantyl, cyclobutyl, cyclopentyl, cyclohexyl, 1-methylcyclopentyl, 1-methylcyclohexyl and [3.3.0]octa-1-yl.

23. A method of Claim 16 wherein for the compound of Formula I R^1 and R^2 are each methyl; X is isopropyl; s is 1; t and u are each 0; A is valyl; B is N-methylvalyl; D is prolyl; E is prolyl; R^5 is benzyl and R^6 is hydrogen.

24. A method of Claim 16 wherein for the compound of Formula I R^1 and R^2 are each methyl; X is isopropyl; s is 1; t and u are each 0; A is valyl; B is N-methylvalyl; D is prolyl; E is prolyl; R^5 is benzyl and R^6 is hydrogen and the first compound is paclitaxel.

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25. A composition of Claim 3 wherein the first compound is paclitaxel and wherein for the second compound of Formula I, R^1 and R^2 are each methyl; X is isopropyl; s is 1; t and u are each 0; A is valyl; B is N-methylvalyl; D ~~is~~ prolyl; E is prolyl; R^5 is benzyl and R^6 is hydrogen.

26. A composition of Claim 3 wherein for the compound of Formula I R^1 and R^2 are each methyl or ethyl; X is isopropyl, sec-butyl or tert-butyl; s is 1; t and u are each 0; A is valyl, isoleucyl, 2-ethylglycyl, or 2-tertbutylglycyl; B is N-methylvalyl, 1-isoleucyl, 2-ethylglycyl or 2-tertbutylglycyl; D is prolyl, 4-fluoroprolyl, thiazolidinyl-4-carbonyl, or 3,4-dehydroprolyl; and E is prolyl, 3-methylprolyl, 4-fluoroprolyl, thiazolidinyl-4-carbonyl, homoprolyl, 3,4-dehydroprolyl or hydroxyprolyl.

27. A method of Claim 16 wherein for the compound of Formula I R^1 and R^2 are each methyl or ethyl; X is isopropyl, sec-butyl or tert-butyl; s is 1; t and u are each 0; A is valyl, isoleucyl, 2-ethylglycyl, or 2-tertbutylglycyl; B is N-methylvalyl, 1-isoleucyl, 2-ethylglycyl or 2-tertbutylglycyl; D is prolyl, 4-fluoroprolyl, thiazolidinyl-4-carbonyl, or 3,4-dehydroprolyl; and E is prolyl, 3-methylprolyl, 4-fluoroprolyl, thiazolidinyl-4-carbonyl, homoprolyl, 3,4-dehydroprolyl or hydroxyprolyl.

28. The use of a first compound selected from paclitaxel, taxotere and modified taxane or taxoid

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analogs and a second compound which is a compound of the Formula I as defined in any one of Claims 1 to 27 for the manufacture of a medicament for the treatment of cancer in a mammal, the cancer for example being selected from lung, breast, colon, prostate, bladder, rectal, endometrial, an haematological (e.g., leukemias, lymphomas) cancer.

29. The use of a compound of the Formula I as defined in any one of Claims 1 to 27 for the manufacture of a medicament for combination therapy in conjunction with a compound selected from paclitaxel, taxotere and modified taxane or taxoid analogs in the treatment of cancer in a mammal, the cancer for example being selected from lung, breast, colon, prostate, bladder, rectal, endometrial and haematological (e.g., leukemias, lymphomas) cancers.

30. The use of a first compound selected from paclitaxel, taxotere and modified taxane or taxoid analogs for the manufacture of a medicament for combination therapy in conjunction with a second compound, the second compound being a compound of the Formula I as defined in any one of Claims 1 to 27 in the treatment of cancer in a mammal, the cancer for example being selected from lung, breast, colon, prostate, bladder, rectal, endometrial and haematological (e.g., leukemias, lymphomas) cancers.

31. A process for the manufacture of a medicament for the treatment of cancer in a mammal, the cancer for example being selected from lung, breast, colon,

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prostate, bladder, rectal, endometrial and haematological (e.g., leukemias, lymphomas) cancers; the process being characterized in the use, as essential constituents of said medicament of a first compound selected from paclitaxel, taxotere and modified taxane or taxoid analogs and a second compound which is a compound of the Formula I as defined in any one of Claims 1 to 27.

32. A process for the manufacture of a medicament for the treatment of cancer in a mammal, said mammal being one of a population which is also being treated with a first compound selected from paclitaxel, taxotere and modified taxane or taxoid analogs, the cancer for example being selected from lung, breast, colon, prostate, bladder, rectal, endometrial and haematological (e.g., leukemias, lymphomas) cancers; the process being characterized in the use, as an essential constituent of said medicament of a second compound which is a compound of the Formula I as defined in any one of Claims 1 to 27.

33. A process for the manufacture of a medicament for the treatment of cancer in a mammal, said mammal being one of a population which is also being treated with a compound of the Formula I as defined in any one of Claims 1 to 27, the cancer for example being selected from lung, breast, colon, prostate, bladder, rectal, endometrial and haematological (e.g., leukemias, lymphomas) cancers; the process being characterized in the use, as an essential constituent of said medicament

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of a compound which is a compound selected from paclitaxel, taxotere and modified taxane or taxoid analogs.

34. The use according to Claim 29 or Claim 30 or the process according to Claim 32 or Claim 33 wherein the treatment of combination therapy involves administration of a first compound selected from paclitaxel, taxotere, and modified taxane or taxoid analogs, first followed by administration of the compound of the Formula I

35. The use according to Claim 29 or Claim 30 or the process according to Claim 32 or Claim 33 wherein the treatment or combination therapy involves administration of the compound of the Formula I, first followed by administration of a first compound selected from paclitaxel, taxotere, and modified taxane or taxoid analogs.

36. The use or process according to any one of Claims 28 to 35 wherein the treatment or combination therapy involves administration of the compound of the Formula I and a first compound selected frompaclitaxel, taxotere, and modified taxane or taxoid analogs, simultaneously.

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