TITLE OF THE INVENTION

CONJUGATES USEFUL IN THE TREATMENT OF PROSTATE CANCER

BACKGROUND OF THE INVENTION

In 1994 cancer of the prostate gland is expected to be diagnosed in 200,000 men in the U.S. and 38,000 American males will die from this disease (Garnick, M.B. (1994). The Dilemmas of Prostate Cancer. Scientific American, April:72-81). Thus, prostate cancer is the most frequently diagnosed malignancy (other than that of the skin) in U.S. men and the second leading cause of cancer-related deaths (behind lung cancer) in that group.

Prostate specific Antigen (PSA) is a single chain 33 kDa glycoprotein that is produced almost exclusively by the human prostate epithelium and occurs at levels of 0.5 to 2.0 mg/ml in human seminal fluid (Nadji, M., Taber, S.Z., Castro, A., et al. (1981) Cancer 48:1229; Papsidero, L., Kuriyama, M., Wang, M., et al. (1981). JNCI 66:37; Qui, S.D., Young, C.Y.F., Bihartz, D.L., et al. (1990), J. Urol. 144:1550; Wang, M.C., Valenzuela, L.A., Murphy, G.P., et al. (1979). Invest. Urol. 17:159). The single carbohydrate unit is attached at asparagine residue number 45 and accounts for 2 to 3 kDa of the total molecular mass. PSA is a protease with chymotrypsin-like specificity (Christensson, A., Laurell, C.B., Lilja, H. (1990). Eur. J. Biochem. 194:755-763). It has been shown that PSA is mainly responsible for dissolution of the gel structure formed at ejaculation by proteolysis of the major proteins in the sperm entrapping gel, Semenogelin I and Semenogelin II, and fibronectin (Lilja, H. (1985). J. Clin. Invest. 76:1899; Lilja, H., Oldbring, J., Rannevik, G., et al. (1987). J. Clin. Invest. 80:281; McGee, R.S., Herr, J.C. (1988). Biol. Reprod. 39:499). The PSA mediated proteolysis of the gel-forming proteins generates several soluble Semenogelin I and Semenogelin II fragments and soluble fibronectin fragments with liquefaction of the ejaculate and release of progressively motile spermatoza (Lilja, H., Laurell, C.B. (1984). Scand. J. Clin. Lab. Invest. 44:447; McGee, R.S., Herr, J.C. (1987).

Biol. Reprod. 37:431). Furthermore, PSA may proteolytically degrade IGFBP-3 (insulin-like growth factor binding protein 3) allowing IGF to stimulate specifically the growth of PSA secreting cells (Cohen et al., (1992) J. Clin. Endo. & Meta. 75:1046-1053).

PSA complexed to alpha 1 - antichymotrypsin is the predominant molecular form of serum PSA and may account for up to 95% of the detected serum PSA (Christensson, A., Björk, T., Nilsson, O., et al. (1993). J. Urol. 150:100-105; Lilja, H., Christensson, A., Dahlén, U. (1991). Clin. Chem. 37:1618-1625; Stenman, U.H., Leinoven, J., Alfthan, H., et al. (1991). Cancer Res. 51:222-226). The prostatic tissue (normal, benign hyperplastic, or malignant tissue) is implicated to predominantly release the mature, enzymatically active form of PSA, as this form is required for complex formation with alpha 1 - antichymotrypsin (Mast, A.E., Enghild, J.J., Pizzo, S.V., et al. (1991). Biochemistry 30:1723-1730; Perlmutter, D.H., Glover, G.I., Rivetna, M., et al. (1990). Proc. Natl. Acad. Sci. USA 87:3753-3757). Therefore, in the microenvironment of prostatic PSA secreting cells the PSA is believed to be processed and secreted in its mature enzymatically active form not complexed to any inhibitory molecule. PSA also forms stable complexes with alpha 2 - macroglobulin, but as this results in encapsulation of PSA and complete loss of the PSA epitopes, the in vivo significance of this complex formation is unclear. A free, noncomplexed form of PSA constitutes a minor fraction of the serum PSA (Christensson, A., Björk, T., Nilsson, O., et al. (1993). J. Urol. 150:100-105; Lilja, H., Christensson, A., Dahlén, U. (1991). Clin. Chem. 37:1618-1625). The size of this form of serum PSA is similar to that of PSA in seminal fluid (Lilja, H., Christensson, A., Dahlén, U. (1991). Clin. Chem. 37:1618-1625) but it is yet unknown as to whether the free form of serum PSA may be a zymogen; an internally cleaved, inactive form of mature PSA; or PSA manifesting enzyme activity. However, it seems unlikely that the free form of serum PSA manifests enzyme activity, since there is considerable (100 to 1000 fold) molar excess of both unreacted alpha

1 - antichymotrypsin and alpha 2 - macroglobulin in serum as compared with the detected serum levels of the free 33 kDa form of PSA (Christensson, A., Björk, T., Nilsson, O., et al. (1993). J. Urol. 150:100-105; Lilja, H., Christensson, A., Dahlén, U. (1991). Clin. Chem. 37:1618-1625).

Serum measurements of PSA are useful for monitoring the treatment of adenocarcinoma of the prostate (Duffy, M.S. (1989). Ann. Clin. Biochem. 26:379-387; Brawer, M.K. and Lange, P.H. (1989). Urol. Suppl. 5:11-16; Hara, M. and Kimura, H. (1989). J. Lab. Clin. Med. 113:541-548), although above normal serum concentrations of PSA have also been reported in benign prostatic hyperplasia and subsequent to surgical trauma of the prostate (Lilja, H., Christensson, A., Dahlén, U. (1991). Clin. Chem. 37:1618-1625). Prostate metastases are also known to secrete immunologically reactive PSA since serum PSA is detectable at high levels in prostatectomized patients showing widespread metatstatic prostate cancer (Ford, T.F., Butcher, D.N., Masters, R.W., et al. (1985). Brit. J. Urology 57:50-55). Therefore, a cytotoxic compound that could be activated by the proteolytic activity of PSA should be prostate cell specific as well as specific for PSA secreting prostate metastases.

It is the object of this invention to provide a novel anti-cancer composition useful for the treatment of prostate cancer which comprises oligopeptides, that are selectively proteolytically cleaved by free prostate specific antigen (PSA) and that include a cyclic amino acid having a hydrophilic substituent, in conjugation with a cytotoxic agent.

Another object of this invention is to provide a method of treating prostate cancer which comprises administration of the novel anti-cancer composition.

SUMMARY OF THE INVENTION

Chemical conjugates which comprise oligopeptides, having amino acid sequences that are selectively proteolytically cleaved by free prostate specific antigen (PSA) and that include a cyclic amino acid having a hydrophilic substituent, and known cytotoxic agents are

disclosed. Such conjugates are useful in the treatment of prostatic cancer and benign prostatic hyperplasia (BPH).

DETAILED DESCRIPTION OF THE INVENTION

The instant invention relates to novel anti-cancer compositions useful for the treatment of prostate cancer. Such compositions comprise the oligopeptides covalently bonded directly, or through a chemical linker, to a cytotoxic agent. The oligopeptides are chosen from oligomers that are selectively recognized by the free prostate specific antigen (PSA) and are capable of being proteolytically cleaved by the enzymatic activity of the free prostate specific antigen. Such a combination of an oligopeptide and cytotoxic agent may be termed a conjugate.

The conjugates of the instant invention are further characterized by incorporation of a cyclic amino acid having a hydrophilic substituent as part of the oligopeptides, said cyclic amino acid which contributes to the aqueous solubility of the conjugate. Examples of such hydrophilic cyclic amino acids include but are not limited to hydroxylated, polyhydroxylated and alkoxylated proline and pipecolic acid moieties.

Ideally, the cytotoxic activity of the cytotoxic agent is greatly reduced or absent when the oligopeptide containing the PSA proteolytic cleavage site is bonded directly, or through a chemical linker, to the cytotoxic agent and is intact. Also ideally, the cytotoxic activity of the cytotoxic agent increases significantly or returns to the activity of the unmodified cytotoxic agent upon proteolytic cleavage of the attached oligopeptide at the cleavage site.

Furthermore, it is preferred that the oligopeptide is selected from oligopeptides that are not cleaved or are cleaved at a much slower rate in the presence of non-PSA proteolytic enzymes when compared to the cleavage of the oligopeptides in the presence of free enzymatically active PSA.

For the reasons above, it is desireable for the oligopeptide to comprise a short peptide sequence, preferably less than ten amino acids. Most preferably the oligopeptide comprises seven or six amino

acids. Because the conjugate preferably comprises a short amino acid sequence, the solubility of the conjugate may be influenced to a greater extent by the generally hydrophobic character of the cytotoxic agent component. Therefore, the hydrophilic substituents on the cyclic amino acid of the instant conjugates are selected to offset or diminish such a hydrophobic contribution by the cytotoxic agent.

While it is not necessary for practicing this aspect of the invention, a preferred embodiment of this invention is a conjugate wherein the oligopeptide, and the chemical linker if present, are detached from the cytotoxic agent by the proteolytic activity of the free PSA and any other native proteolytic enzymes present in the tissue proximity, thereby presenting the cytotoxic agent, or a cytotoxic agent that retains part of the oligopeptide/linker unit but remains cytotoxic, into the physiological environment at the place of proteolytic cleavage. Pharmaceutically acceptable salts of the conjugates are also included.

It is understood that the oligopeptide that is conjugated to the cytotoxic agent, whether through a direct covalent bond or through a chemical linker, does not need to be the oligopeptide that has the greatest recognition by free PSA and is most readily proteolytically cleaved by free PSA. Thus, the oligopeptide that is selected for incorporation in such an anti-cancer composition will be chosen both for its selective, proteolytic cleavage by free PSA and for the cytotoxic activity of the cytotoxic agent-proteolytic residue conjugate (or, in what is felt to be an ideal situation, the unmodified cytotoxic agent) which results from such a cleavage. The term "selective" as used in connection with the proteolytic PSA cleavage means a greater rate of cleavage of an oligopeptide component of the instant invention by free PSA relative to cleavage of an oligopeptide which comprises a random sequence of amino acids. Therefore, the oligopeptide component of the instant invention is a prefered substrate of free PSA. The term "selective" also indicates that the oligopeptide is proteolytically cleaved by free PSA between two specific amino acids in the oligopeptide.

The oligopeptide components of the instant invention are selectively recognized by the free prostate specific antigen (PSA) and are capable of being proteolytically cleaved by the enzymatic activity of the free prostate specific antigen. Such oligopeptides comprise an oligomer selected from:

a) HaaXaaSerTyrGlnlSerSer (SEQ.ID.NO.: 1);

b) HaaTyrGlnlSerSer (SEQ.ID.NO.: 2);

c) HaaXaaLysTyrGlnlSerSer (SEQ.ID.NO.: 3);

d) HaaXaaLysTyrGlnlSerSer (SEQ.ID.NO.: 4);

e) HaaXaahArgTyrGlnlSerSer (SEQ.ID.NO.: 5);

f) HaaXaahArgChaGlnlSerSer (SEQ.ID.NO.: 6);

g) HaaXaaSerTyrGlnlSerXaa (SEQ.ID.NO.: 7);

h) HaaTyrGlnlSerXaa (SEQ.ID.NO.: 8);

i) HaaXaaSerChgGlnlSerXaa (SEQ.ID.NO.: 9);

j) HaaChgGlnlSerXaa (SEQ.ID.NO.: 10);

wherein Haa is a cyclic amino acid substituted with a hydrophilic moiety, Xaa is any amino acid, hArg is homoarginine, Cha is cyclohexylalanine and Chg is cyclohexylglycine.

In an embodiment of the instant invention, the oligopeptide comprises an oligomer that is selected from:

a) HaaTyrGlnlSerSerSerLeu (SEQ.ID.NO.: 11),

b) HaaXaaSerTyrGlnlSerAla (SEQ.ID.NO.: 12),

c) AlaHaaXaaSerTyrTyrlSer (SEQ.ID.NO.: 13),

d) AlaAsnHaaXaaSerTyrGlnlSer (SEQ.ID.NO.: 14),

e) HaaXaaSerTyrGlnlSerSerThr (SEQ.ID.NO.: 15),

f) HaaTyrGlnlSerSerThr (SEQ.ID.NO.: 16),

g) HaaXaaSerTyrGlnlSerSerSer (SEQ.ID.NO.: 17),

h) HaaTyrGlnlSerSerSer (SEQ.ID.NO.: 18),

i) HaaXaaLysTyrGlnlSerSerSer (SEQ.ID.NO.: 19),

j) HaaXaahArgTyrGlnlSerSerSer (SEQ.ID.NO.: 20),

k) HaaXaaSerTyrGlnlSerSerLeu (SEQ.ID.NO.: 21);

l) HaaTyrGlnlSerSerLeu (SEQ.ID.NO.: 22);

m) HaaXaaSerTyrGlnlSerLeu (SEQ.ID.NO.: 23);

n) HaaTyrGlnlSerLeu (SEQ.ID.NO.: 24);

p) HaaXaaSerTyrGlnlSerNle (SEQ.ID.NO.: 25);

q) HaaTyrGlnlSerNle (SEQ.ID.NO.: 26);

r) HaaXaaSerTyrGlnlSerTIC (SEQ.ID.NO.: 27);

s) HaaTyrGlnlSerTIC (SEQ.ID.NO.: 28);

t) HaaXaaSerChgGlnlSerLeu (SEQ.ID.NO.: 29);

u) HaaChgGlnlSerLeu (SEQ.ID.NO.: 30);

v) HaaXaaSerChgGlnlSerNle (SEQ.ID.NO.: 31);

w) HaaChgGlnlSerNle (SEQ.ID.NO.: 32);

x) HaaXaaSerChgGlnlSerTIC (SEQ.ID.NO.: 33);

y) HaaChgGlnlSerTIC (SEQ.ID.NO.: 34);

z) hArgChgGlnlSerLeu (SEQ.ID.NO.: 35); and

aa) hArgTyrGlnlSerLeu (SEQ.ID.NO.: 36).

In a more preferred embodiment of the instant invention, the oligopeptide comprises an oligomer selected from:

a) 4-HypXaaSerTyrGlnlSerSer (SEQ.ID.NO.: 37),

b) 4-HypXaaSerTyrGlnlSerAla (SEQ.ID.NO.: 38),

c) Ala-4-HypXaaSerTyrTyrlSer (SEQ.ID.NO.: 39),

d) AlaAsn4-HypXaaSerTyrGlnlSer (SEQ.ID.NO.: 40),

e) 4-HypXaaSerTyrGlnlSerSerThr (SEQ.ID.NO.: 41),

f) 4-HypTyrGlnlSerSerThr (SEQ.ID.NO.: 42),

g) 4-HypXaaSerTyrGlnlSerSerSer (SEQ.ID.NO.: 43),

h) 4-HypTyrGlnlSerSerSer (SEQ.ID.NO.: 44),

i) 4-HypXaaLysTyrGlnlSerSerSer (SEQ.ID.NO.: 45),

j) 4-HypXaahArgTyrGlnlSerSerSer (SEQ.ID.NO.: 46),

k) 4-HypXaaSerTyrGlnlSerSerLeu (SEQ.ID.NO.: 47);

l) 4-HypTyrGlnlSerSerLeu (SEQ.ID.NO.: 48);

m) 4-HypXaaSerTyrGlnlSerLeu (SEQ.ID.NO.: 49);

n) 4-HypTyrGlnlSerLeu (SEQ.ID.NO.: 50);

p) 4-HypXaaSerTyrGlnlSerNle (SEQ.ID.NO.: 51);

q) 4-HypTyrGlnlSerNle (SEQ.ID.NO.: 52);

r) 4-HypXaaSerTyrGlnlSerTIC (SEQ.ID.NO.: 53);

s) 4-HypTyrGlnlSerTIC (SEQ.ID.NO.: 54);

t) 4-HypXaaSerChgGlnlSerLeu (SEQ.ID.NO.: 55);

u) 4-HypChgGlnlSerLeu (SEQ.ID.NO.: 56);

v) 4-HypXaaSerChgGlnlSerNle (SEQ.ID.NO.: 57);

w) 4-HypChgGlnlSerNle (SEQ.ID.NO.: 58);

x) 4-HypXaaSerChgGlnlSerTIC (SEQ.ID.NO.: 59);

y) 4-HypChgGlnlSerTIC (SEQ.ID.NO.: 60);

wherein 4-Hyp is 4-hydroxyproline, Xaa is any amino acid, hArg is homoarginine, Cha is cyclohexylalanine and Chg is cyclohexylglycine.

Preferably Xaa in the more preferred embodiment is selected from Ala, Ser and Ile.

The phrase "oligomers that comprise an amino acid sequence" as used hereinabove, and elsewhere in the Detailed Description of the Invention, describes oligomers of from about 3 to about 100 amino acids residues which include in their amino acid sequence the specific amino acid sequence decribed and which are therefore proteolytically cleaved within the amino acid sequence described by free PSA. Preferably, the oligomer is from 5 to 10 amino acid residues. Thus, for example, the following oligomer:
hArgSer4-HypChgGlnlSerLeu (SEQ.ID.NO.: 61);
comprises the amino acid sequence:
4-HypChgGlnlSerLeu (SEQ.ID.NO.: 56);
and would therefore come within the instant invention.

A person of ordinary skill in the peptide chemistry art would readily appreciate that certain amino acids in a biologically active oligopeptide may be replaced by other homologous, isosteric and/or isoelectronic amino acids wherein the biological activity of the original oligopeptide has been conserved in the modified oligopeptide. Certain unnatural and modified natural amino acids may also be utilized to replace the corresponding natural amino acid in the oligopeptides of the instant invention. Thus, for example, tyrosine may be replaced by 3-iodotyrosine, 2-methyltyrosine, 3-fluorotyrosine, 3-methyltyrosine and the like. Further for example, lysine may be replaced with N'-(2-imidazolyl)lysine and the like. The following list of amino acid replacements is meant to be illustrative and is not limiting:

Original Amino Acid	Replacement Amino Acid(s)
Ala	Gly
Arg	Lys, Ornithine
Asn	Gln
Asp	Glu

Glu	Asp
Gln	Asn
Gly	Ala
Ile	Val, Leu, Met, Nle
Leu	Ile, Val, Met, Nle
Lys	Arg, Ornithine
Met	Leu, Ile, Nle, Val
Ornithine	Lys, Arg
Phe	Tyr, Trp
Ser	Thr
Thr	Ser
Trp	Phe, Tyr
Tyr	Phe, Trp
Val	Leu, Ile, Met, Nle

Thus, for example, the following oligopeptides may be synthesized by techniques well known to persons of ordinary skill in the art and would be expected to be proteolytically cleaved by free PSA when incorporated in a conjugate of this invention:

Asn4-HypIleSerTyrGlnlSer (SEQ.ID.NO.: 62)
Asn4-HypValSerTyrGlnlSer (SEQ.ID.NO.: 63)
4-HypAlaSerTyrGlnlSerSer (SEQ.ID.NO.: 64)
(3,4-dihydroxyproline)AlaSerTyrGln lSerSer (SEQ.ID.NO.: 65)
3-hydroxyprolineSerChgGlnlSer (SEQ.ID.NO.: 66)
4-HypAlaSerChgGlnlSerSer (SEQ.ID.NO.: 67).

The inclusion of the symbol "l" within an amino acid sequence indicates the point within that sequence where the oligopeptide is proteolytically cleaved by free PSA.

The compounds of the present invention may have asymmetric centers and occur as racemates, racemic mixtures, and as individual diastereomers, with all possible isomers, including optical isomers, being included in the present invention. Unless otherwise

specified, named amino acids are understood to have the natural "L" stereoconfiguration

The following abbreviations are utilized in the specification and tables to denote the indicated amino acids and moieties:

hR or hArg:	homoarginine
hY or hTyr:	homotyrosine
Cha:	cyclohexylalanine
Amf:	4-aminomethylphenylalanine
DPL:	2-(4,6-dimethylpyrimidinyl)lysine
(imidazolyl)K:	N'-(2-imidazolyl)lysine
Me_2PO_3-Y:	O-dimethylphosphotyrosine
O-Me-Y:	O-methyltyrosine
TIC:	1,2,3,4-tetrahydro-3-isoquinoline carboxylic acid
DAP:	1,3-diaminopropane
TFA:	trifluoroacetic acid
AA:	acetic acid
3PAL	3-pyridyl-alanine
4-Hyp	4-hydroxyproline
Abu	alpha-aminobutyric acid
Thi	thienylalanine

It is well known in the art, and understood in the instant invention, that peptidyl therapeutic agents such as the instant oligopeptide-cytotoxic agent conjugates preferably have the terminal amino moiety of any oligopeptide substituent protected with a suitable protecting group, such as acetyl, benzoyl, pivaloyl and the like. Such protection of the terminal amino group reduces or eliminates the enzymatic degradation of such peptidyl therapeutic agents by the action of amino peptidases which are present in the blood plasma of warm blooded animals.

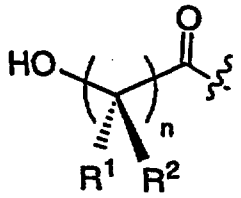
Such protecting groups also include a hydrophilic

blocking groups, which are chosen based upon the presence of hydrophilic functionality. Blocking groups that increase the hydrophilicity of the conjugates and therefore increase the aqueous solubility of the conjugates include but are not limited to hydroylated alkanoyl, polyhydroxylated alkanoyl, hydroylated aroyl, polyhydroxylated aroyl, polyethylene glycol, glycosylates, sugars and crown ethers. N-Terminus unnatural amino acid moieties may also ameleorate such enzymatic degradation by amino peptidases.

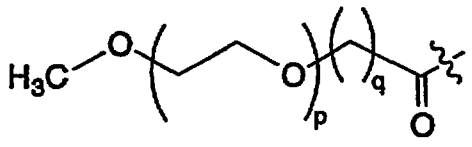
Preferably the N-terminus protecting group is selected from

a) acetyl;

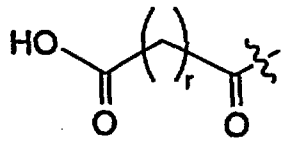
b)



c)



d)



wherein:

R^1 and R^2 are independently selected from:

a) hydrogen,

b) unsubstituted or substituted aryl, unsubstituted or substituted heterocycle, C_3-C_{10} cycloalkyl, C_2-C_6 alkenyl, C_2-C_6 alkynyl, halogen, C_1-C_6 perfluoroalkyl, R^3O-,

$R^3C(O)NR^3$-, $(R^3)_2NC(O)$-, $R^3{}_2N$-$C(NR^3)$-, $R^4S(O)_mNH$, CN, NO_2, $R^3C(O)$-, N_3, -$N(R^3)_2$, or $R^4OC(O)NR^3$-,

c) unsubstituted C_1-C_6 alkyl,

d) substituted C_1-C_6 alkyl wherein the substituent on the substituted C_1-C_6 alkyl is selected from unsubstituted or substituted aryl, unsubstituted or substituted heterocyclic, C_3-C_{10} cycloalkyl, C_2-C_6 alkenyl, C_2-C_6 alkynyl, R^3O-, $R^4S(O)_mNH$, $R^3C(O)NR^3$-, $(R^3)_2NC(O)$-, $R^3{}_2N$-$C(NR^3)$-, CN, $R^3C(O)$-, N_3, -$N(R^3)_2$, and $R^4OC(O)$-NR^3-; or

R^1 and R^2 are combined to form - $(CH_2)_s$ - wherein one of the carbon atoms is optionally replaced by a moiety selected from: O, $S(O)_m$, -NC(O)-, NH and -$N(COR^4)$- ;

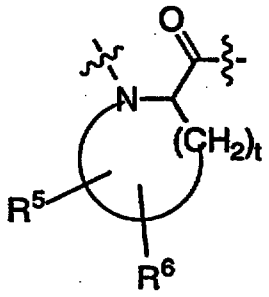
R^3 is selected from: hydrogen, aryl, substituted aryl, heterocycle, substituted heterocycle, C_1-C_6 alkyl and C_3-C_{10} cycloalkyl;

R^4 is selected from: aryl, substituted aryl, heterocycle, substituted heterocycle, C_1-C_6 alkyl and C_3-C_{10} cycloalkyl;

m is 0, 1 or 2;
n is 1, 2, 3 or 4;
p is zero or an integer between 1 and 100;
q is 0 or 1, provided that if p is zero, q is 1;
r is an integer between 1 and 10; and
s is 3, 4 or 5.

Preferably, r is 1, 2 or 3.

The oligopeptides of the instant conjugates comprise a cyclic amino acid substituted with a hydrophilic moiety, previously represented by the term "Haa", which may also be represented by the formula:



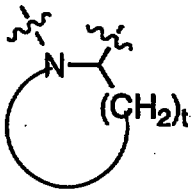
wherein:

R5 is selected from HO- and C1-C6 alkoxy;

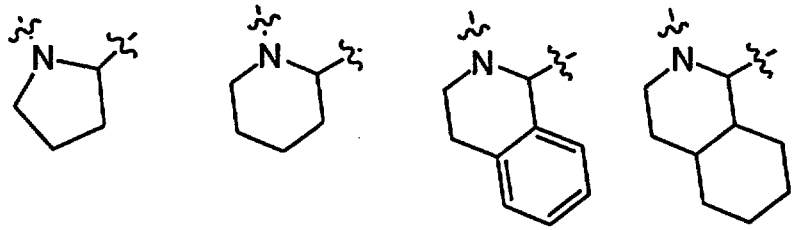
R6 is selected from hydrogen, halogen, C1-C6 alkyl, HO- and C1-C6 alkoxy; and

t is 3 or 4.

The structure



represents a cyclic amine moiety having 5 or 6 members in the ring, such a cyclic amine which may be optionally fused to a phenyl or cyclohexyl ring. Examples of such a cyclic amine moiety include, but are not limited to, the following specific structures:



The conjugates of the present invention may have asymmetric centers and occur as racemates, racemic mixtures, and as individual diastereomers, with all possible isomers, including optical

isomers, being included in the present invention. When any variable (e.g. aryl, heterocycle, R^3 etc.) occurs more than one time in any constituent, its definition on each occurence is independent of every other occurence. For example, $HO(CR^1R^2)_2$- represents $HOCH_2CH_2$-, $HOCH_2CH(OH)$-, $HOCH(CH_3)CH(OH)$-, etc. Also, combinations of substituents and/or variables are permissible only if such combinations result in stable compounds.

As used herein, "alkyl" and the alkyl portion of aralkyl and similar terms, is intended to include both branched and straight-chain saturated aliphatic hydrocarbon groups having the specified number of carbon atoms; "alkoxy" represents an alkyl group of indicated number of carbon atoms attached through an oxygen bridge.

As used herein, "cycloalkyl" is intended to include non-aromatic cyclic hydrocarbon groups having the specified number of carbon atoms. Examples of cycloalkyl groups include cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl and the like.

"Alkenyl" groups include those groups having the specified number of carbon atoms and having one or several double bonds. Examples of alkenyl groups include vinyl, allyl, isopropenyl, pentenyl, hexenyl, heptenyl, cyclopropenyl, cyclobutenyl, cyclopentenyl, cyclohexenyl, 1-propenyl, 2-butenyl, 2-methyl-2-butenyl, isoprenyl, farnesyl, geranyl, geranylgeranyl and the like.

"Alkynyl" groups include those groups having the specified number of carbon atoms and having one triple bonds. Examples of alkynyl groups include acetylene, 2-butynyl, 2-pentynyl, 3-pentynyl and the like.

"Halogen" or "halo" as used herein means fluoro, chloro, bromo and iodo.

As used herein, "aryl," and the aryl portion of aralkyl and aroyl, is intended to mean any stable monocyclic or bicyclic carbon ring of up to 7 members in each ring, wherein at least one ring is aromatic. Examples of such aryl elements include phenyl, naphthyl, tetrahydro-naphthyl, indanyl, biphenyl, phenanthryl, anthryl or acenaphthyl.

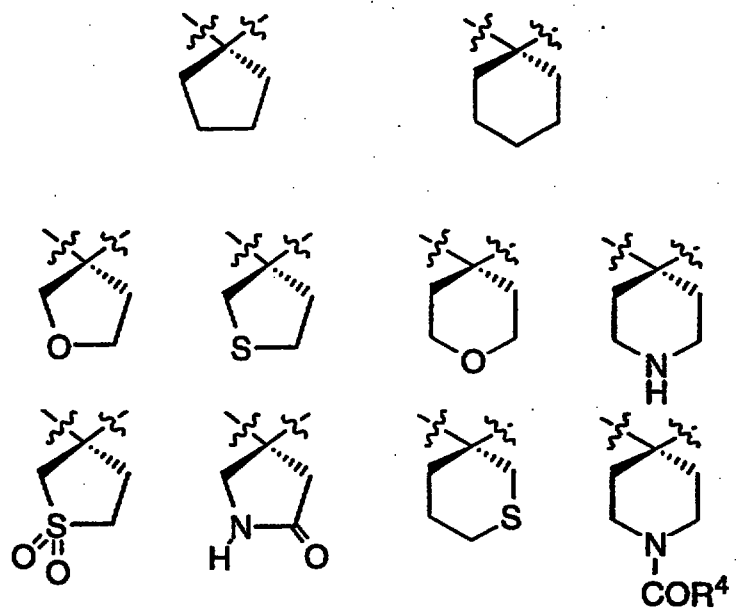
The term heterocycle or heterocyclic, as used herein, represents a stable 5- to 7-membered monocyclic or stable 8- to 11-membered bicyclic heterocyclic ring which is either saturated or unsaturated, and which consists of carbon atoms and from one to four heteroatoms selected from the group consisting of N, O, and S, and including any bicyclic group in which any of the above-defined heterocyclic rings is fused to a benzene ring. The heterocyclic ring may be attached at any heteroatom or carbon atom which results in the creation of a stable structure. Examples of such heterocyclic elements include, but are not limited to, azepinyl, benzimidazolyl, benzisoxazolyl, benzofurazanyl, benzopyranyl, benzothiopyranyl, benzofuryl, benzothiazolyl, benzothienyl, benzoxazolyl, chromanyl, cinnolinyl, dihydrobenzofuryl, dihydrobenzothienyl, dihydrobenzothiopyranyl, dihydrobenzothiopyranyl sulfone, furyl, imidazolidinyl, imidazolinyl, imidazolyl, indolinyl, indolyl, isochromanyl, isoindolinyl, isoquinolinyl, isothiazolidinyl, isothiazolyl, isothiazolidinyl, morpholinyl, naphthyridinyl, oxadiazolyl, 2-oxoazepinyl, oxazolyl, 2-oxopiperazinyl, 2-oxopiperdinyl, 2-oxopyrrolidinyl, piperidyl, piperazinyl, pyridyl, pyrazinyl, pyrazolidinyl, pyrazolyl, pyridazinyl, pyrimidinyl, pyrrolidinyl, pyrrolyl, quinazolinyl, quinolinyl, quinoxalinyl, tetrahydrofuryl, tetrahydroisoquinolinyl, tetrahydroquinolinyl, thiamorpholinyl, thiamorpholinyl sulfoxide, thiazolyl, thiazolinyl, thienofuryl, thienothienyl, and thienyl.

As used herein in the terms "substituted C_{1-8} alkyl", "substituted aryl" and "substituted heterocycle" include moieties containing from 1 to 3 substituents in addition to the point of attachment to the rest of the compound. Such additional substituents are selected from F, Cl, Br, CF_3, NH_2, $N(C_1\text{-}C_6$ alkyl$)_2$, NO_2, CN, (C_1-C_6 alkyl)O-, -OH, (C_1-C_6 alkyl)$S(O)_m$-, (C_1-C_6 alkyl)C(O)NH-, H_2N-C(NH)-, (C_1-C_6 alkyl)C(O)-, (C_1-C_6 alkyl)OC(O)-, N_3, (C_1-C_6 alkyl)OC(O)NH- and C_1-C_{20} alkyl.

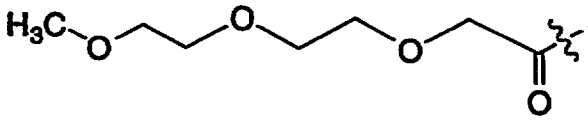
The term "an integer between 1 and 10" represents the numbers 1 and 10 as well as those integers between those numbers. The term "an integer between 1 and 100" represents the numbers 1

and 100 as well as those integers between those numbers.

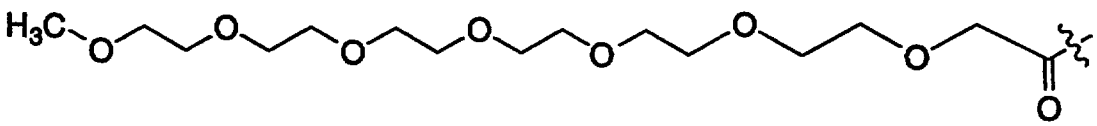
When R^1 and R^2 are combined to form - $(CH_2)_s$ -, the cyclic moieties and heteroatom-containing cyclic moieties so defined include, but are not limited to:



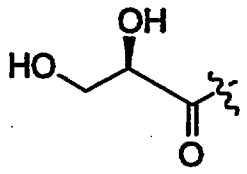
As used herein, the term "PEG" represents certain polyethylene glycol containing substituents having the designated number of ethyleneoxy subunits. Thus the term PEG(2) represents



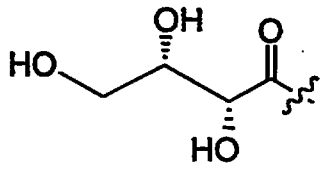
and the term PEG(6) represents



As used herein, the term "(2R)(2,3-dihydroxypropionyl)" represents the following structure:



As used herein, the term "(2R,3S) 2,3,4-trihydroxybutanoyl" represents the following structure:



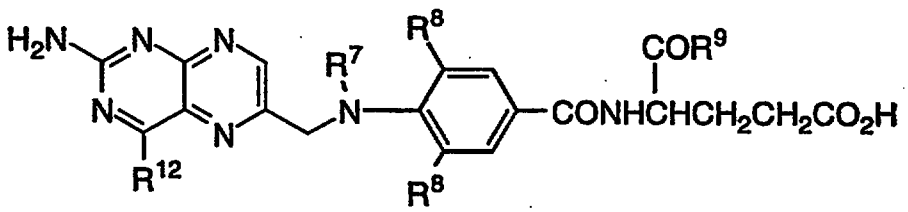
Because the conjugates of the invention can be used for modifying a given biological response, cytotoxic agent is not to be construed as limited to classical chemical therapeutic agents. For example, the cytotoxic agent may be a protein or polypeptide possessing a desired biological activity. Such proteins may include, for example, a toxin such as abrin, ricin A, pseudomonas exotoxin, or diphtheria toxin; a protein such as tumor necrosis factor, α-interferon, β-interferon, nerve growth factor, platelet derived growth factor, tissue plasminogen activator; or, biological response modifiers such as, for example, lymphokines, interleukin-1 ("IL-1"), interleukin-2 ("IL-2"), interleukin-6 ("IL-6"), granulocyte macrophage colony stimulating factor ("GM-CSF"), granulocyte colony stimulating factor ("G-CSF"), or other growth factors.

The preferred cytotoxic agents include, in general, alkylating agents, antiproliferative agents, tubulin binding agents and the like. Preferred classes of cytotoxic agents include, for example, the anthracycline family of drugs, the vinca drugs, the mitomycins, the bleomycins, the cytotoxic nucleosides, the taxanes, the pteridine family of drugs, diynenes and the podophyllotoxins. Particularly useful members of those classes include, for example, doxorubicin, carminomycin, daunorubicin, aminopterin, methotrexate, methopterin, dichloro-methotrexate, mitomycin C, porfiromycin, 5-fluorouracil,

6-mercaptopurine, cytosine arabinoside, podophyllotoxin, or podophyllotoxin derivatives such as etoposide or etoposide phosphate, melphalan, vinblastine, vincristine, leurosidine, vindesine, leurosine, taxol and the like. Other useful cytotoxic agents include estramustine, cisplatin and cyclophosphamide. One skilled in the art may make chemical modifications to the desired cytotoxic agent in order to make reactions of that compound more convenient for purposes of preparing conjugates of the invention.

A highly preferred group of cytotoxic agents for the present invention include drugs of the following formulae:

THE METHOTREXATE GROUP OF FORMULA(1):

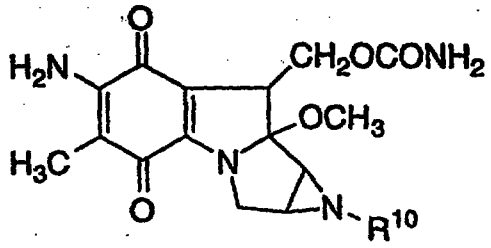


(1)

in which

R^{12} is amino or hydroxy;
R^7 is hydrogen or methyl;
R^8 is hydrogen, fluoro, chloro, bromo or iodo;
R^9 is hydroxy or a moiety which completes a salt of the carboxylic acid;

THE MITOMYCIN GROUP OF FORMULA (2):

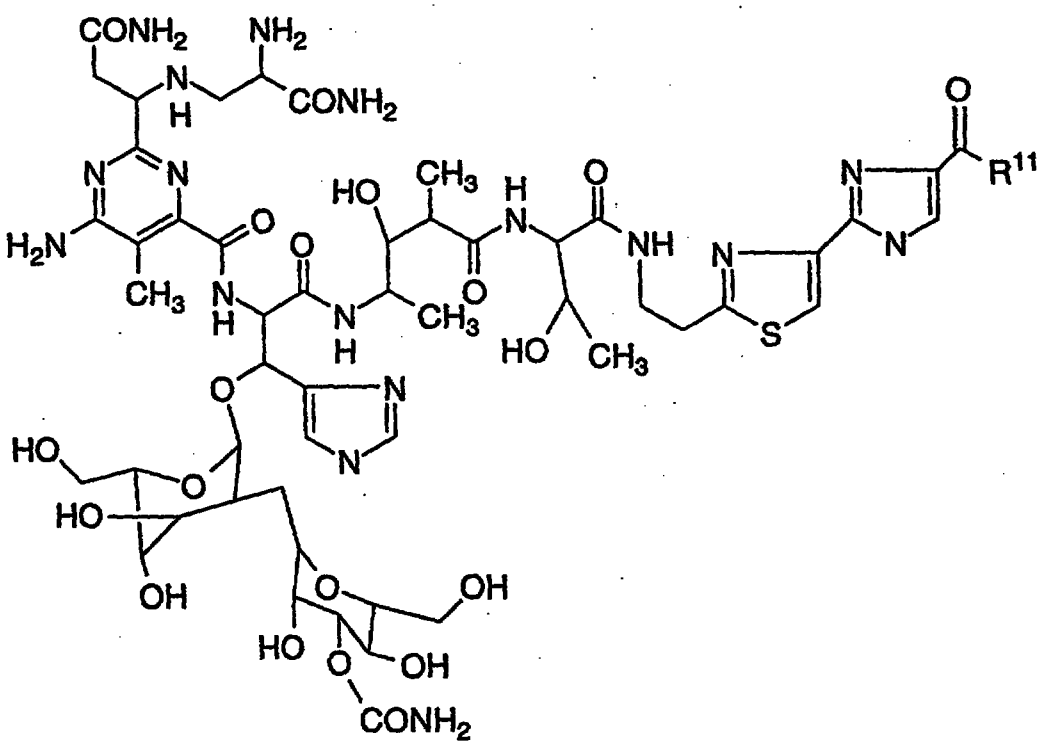


(2)

in which

R^{10} is hydrogen or methyl;

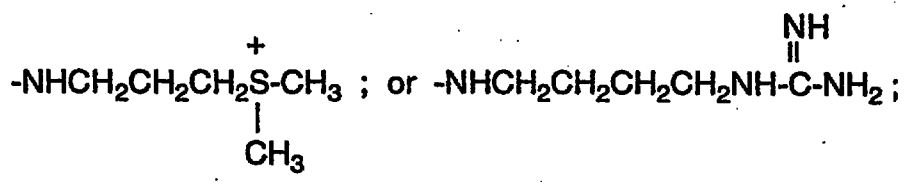
THE BLEOMYCIN GROUP OF FORMULA (3)



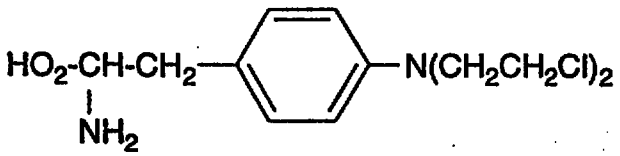
(3)

in which

R^{11} is hydroxy, amino, C_1-C_3 alkylamino, di(C_1-C_3 alkyl)amino, C_4-C_6 polymethylene amino,

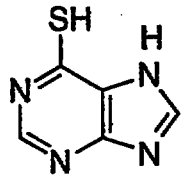


MELPHALAN OF FORMULA (4):



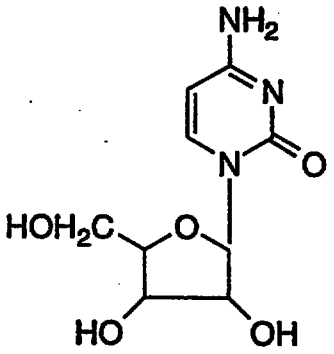
(4)

6-MERCAPTOPURINE OF FORMULA (5):



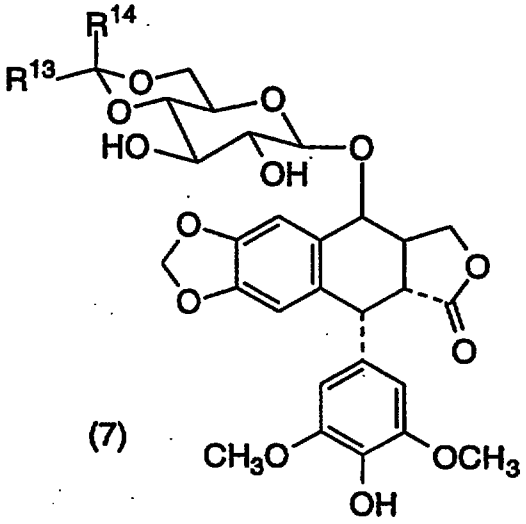
(5)

A CYTOSINE ARABINOSIDE OF FORMULA (6):



(6)

THE PODOPHYLLOTOXINS OF FORMULA(7):



(7)

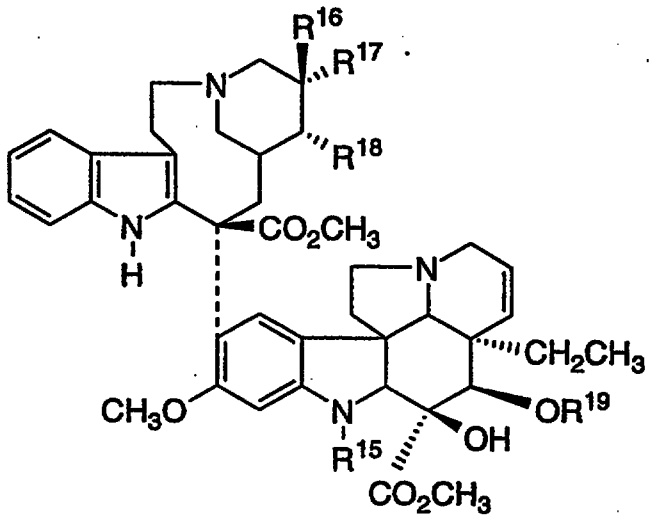
in which

R^{13} is hydrogen or methyl;

R^{14} is methyl or thienyl;

or a phosphate salt thereof;

THE VINCA ALKALOID GROUP OF DRUGS OF FORMULA (8):



(8)

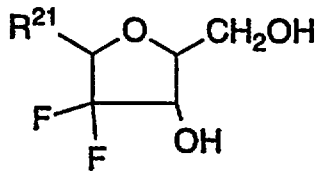
in which

R^{15} is H, CH_3 or CHO; when R^{17} and R^{18} are taken singly;

R^{18} is H, and one of R^{16} and R^{17} is ethyl and the other is H or OH; when R^{17} and R^{18} are taken together with the carbons to which they are attached, they form an oxirane ring in which case R^{16} is ethyl;

R^{19} is hydrogen, (C_1-C_3 alkyl)-CO, or chlorosubstituted (C_1-C_3 alkyl)-CO;

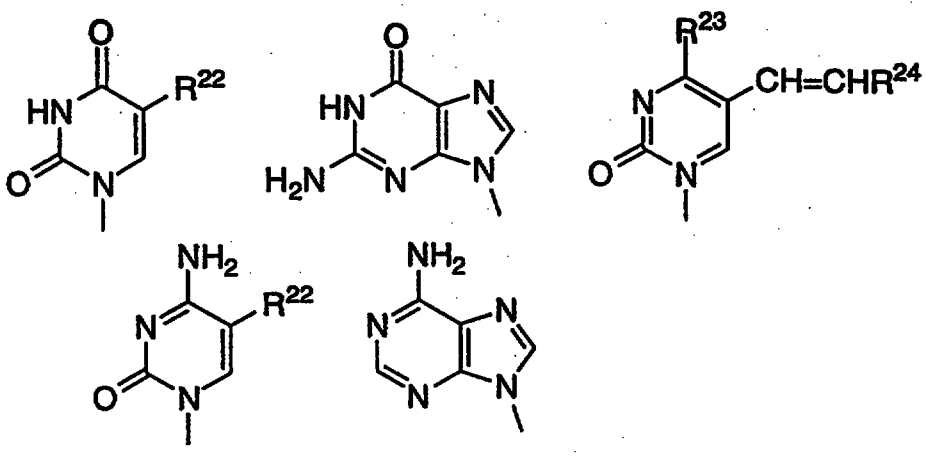
DIFLUORONUCLEOSIDES OF FORMULA (9):



(9)

in which

R^{21} is a base of one of the formulae:



in which

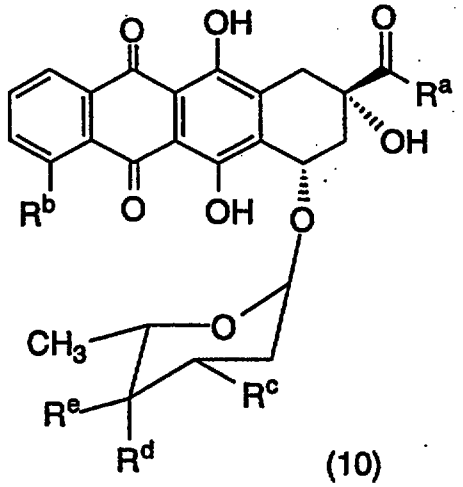
R^{22} is hydrogen, methyl, bromo, fluoro, chloro or iodo;

R^{23} is -OH or $-NH_2$;

R^{24} is hydrogen, bromo, chloro or iodo;

or,

THE ANTHRACYCLINES ANTIBIOTICS OF FORMULA (10):



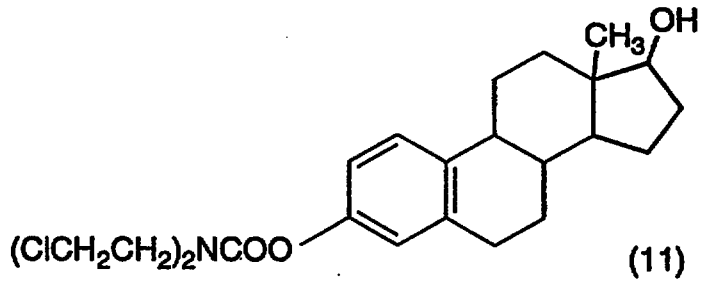
(10)

wherein

R^a is $-CH_3$, $-CH_2OH$, $-CH_2OCO(CH_2)_3CH_3$, or $-CH_2OCOCH(OC_2H_5)_2$;

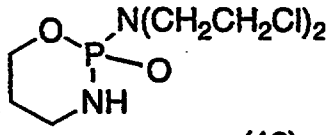
R^b is -OCH_3, -OH or -H;
R^c is -NH_2, -$NHCOCF_3$, 4-morpholinyl, 3-cyano-4-morpholinyl, 1-piperidinyl, 4-methoxy-1-piperidinyl, benzylamine, dibenzylamine, cyanomethylamine, or 1-cyano-2-methoxyethyl amine;
R^d is -OH -OTHP or -H; and
R^e is -OH or -H provided that
R^6 is not -OH when R^5 is -OH or -OTHP.

ESTRAMUSTINE (11)



(11)

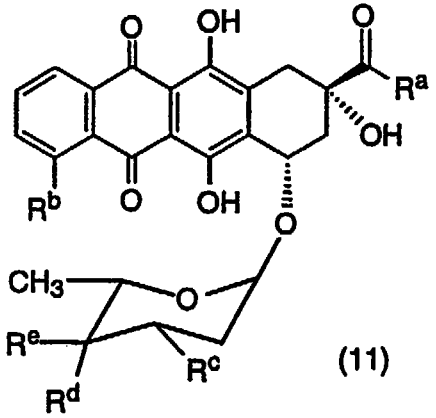
CYCLOPHOSPHAMIDE (12)



(12)

The most highly preferred drugs are the anthracycline antiobiotic agents of Formula (10), described previously. One skilled in the art understands that this structural formula includes compounds which are drugs, or are derivatives of drugs, which have acquired in the art different generic or trivial names. Table 1, which follows, represents a number of anthracycline drugs and their generic or trivial names and which are especially preferred for use in the present invention.

Table 1



(11)

Compound	R^a	R^b	R^c	R^d	R^e
daunorubicin[a]	CH_3	OCH_3	NH_2	OH	H
doxorubicin[b]	CH_2OH	OCH_3	NH_2	OH	H
detorubicin	$CH_2OCOCH(OC_2H_5)2$	OCH_3	NH_2	OH	H
carminomycin	CH_3	OH	NH_2	OH	H
idarubicin	CH_3	H	NH_2	OH	H
epirubicin	CH_2OH	OCH_3	NH_2	OH	OH
esorubicin	CH_2OH	OCH_3	NH_2	H	H
THP	CH_2OH	OCH_3	NH_2	OTHP	H
AD-32	$CH_2OCO(CH_2)3CH_3$	OCH_3	$NHCOCF_3$	OH	H

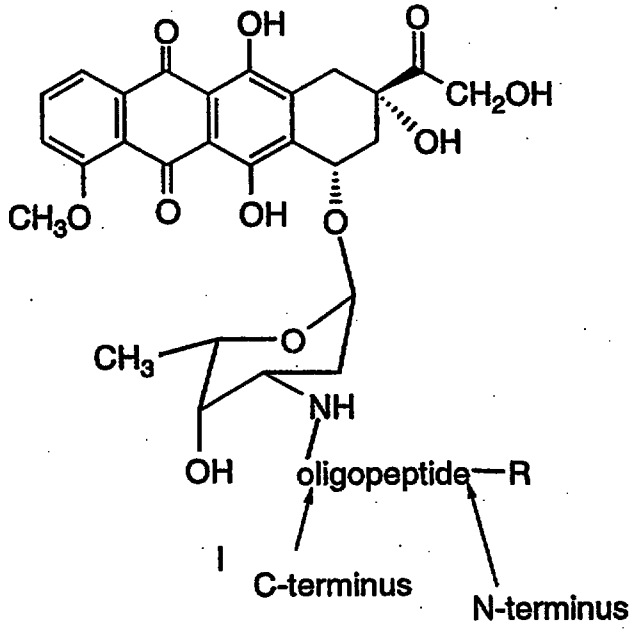
[a]"daunomycin" is an alternative name for daunorubicin

[b]"adriamycin" is an alternative name for doxorubicin

SUBSTITUTE SHEET (RULE 26)

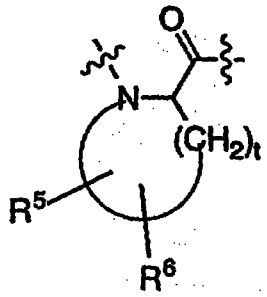
Of the compounds shown in Table 1, the most highly preferred cytotoxic agents are doxorubicin, vinblastine and desacetylvinblastine. Doxorubicin (also referred to herein as "DOX") is that anthracycline of Formula (10) in which R^a is $-CH_2OH$, R^b is $-OCH_3$, R^c is $-NH_2$, R^d is -OH, and R^e is -H.

The oligopeptide-cytotoxic agent conjugate of the instant invention wherein the cytotoxic agent is the preferred cytotoxic agent doxorubicin may be described by the general formula I below:



wherein:

oligopeptide is an oligopeptide which is selectively recognized by the free prostate specific antigen (PSA) and is capable of being proteolytically cleaved by the enzymatic activity of the free prostate specific antigen, wherein the oligopeptide comprises a cyclic amino acid of the formula:



and wherein

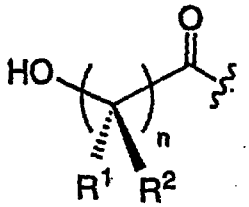
the C-terminus carbonyl is covalently bound to the amine of doxorubicin;

R is selected from

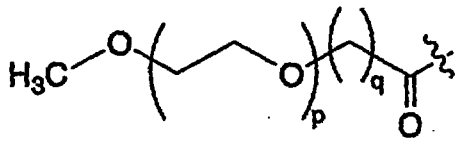
a) hydrogen,

b) -(C=O)R^{1a},

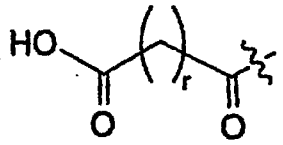
c)



d)



e)



R^1 and R^2 are independently selected from: hydrogen, OH, C_1-C_6 alkyl, C_1-C_6 alkoxy, C_1-C_6 aralkyl and aryl;

R^{1a} is C_1-C_6-alkyl, hydroxylated aryl, polyhydroxylated aryl or aryl,

R5 is selected from HO- and C_1-C_6 alkoxy;

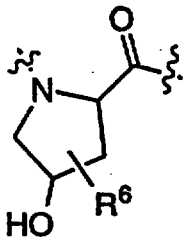
R6 is selected from hydrogen, halogen, C_1-C_6 alkyl, HO- and C_1-C_6 alkoxy; and

n is		1, 2, 3 or 4;
p is		zero or an integer between 1 and 100;
q is		0 or 1, provided that if p is zero, q is 1;
r is		an integer between 1 and 10; and
t is		3 or 4;

or a pharmaceutically acceptable salt thereof.

In a preferred embodiment of the oligopeptide-cytotoxic agent conjugate:

the cyclic amino acid is

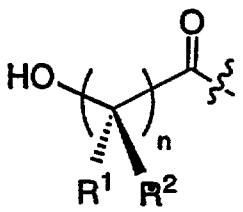


R is selected from

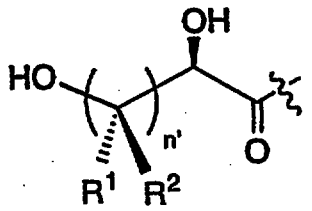
a) hydrogen,

b) -(C=O)R^{1a},

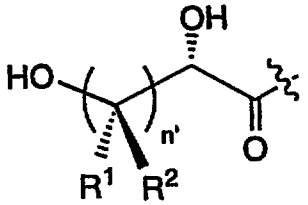
c)



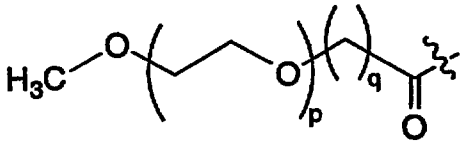
d)



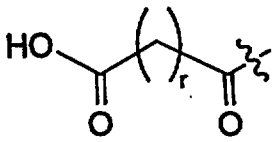
e)



f)



g)



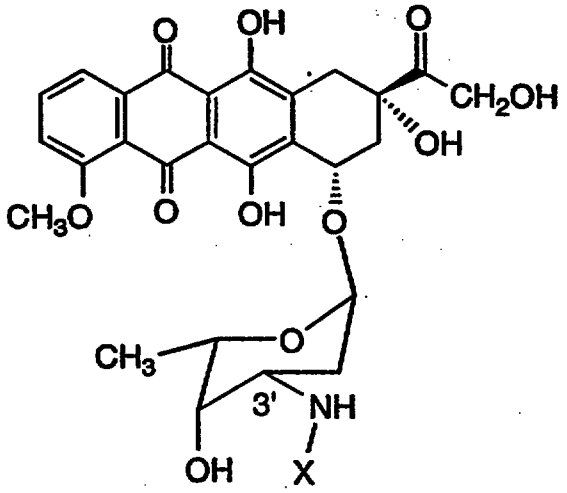
R^1 and R^2 are independently selected from: hydrogen, C_1-C_6 alkyl and aryl;

R^{1a} is C_1-C_6-alkyl or aryl,

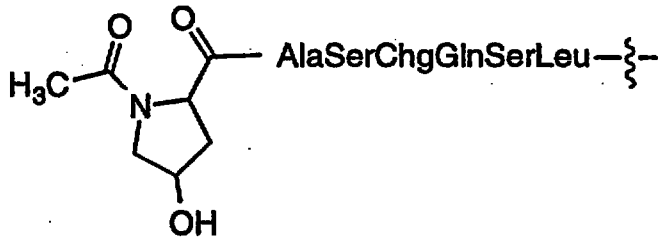
n is	1, 2, 3 or 4;
n' is	0, 1, 2 or 3;
p is	zero or an integer between 1 and 14;
q is	0 or 1, provided that if p is zero, q is 1;
r is	an integer between 1 and 10; and
t is	3;

or an optical isomer or a pharmaceutically acceptable salt thereof.

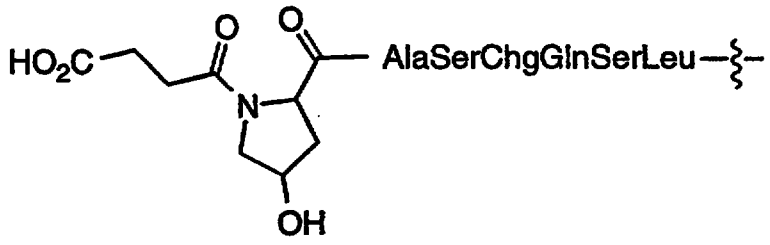
The following compounds are specific examples of the oligopeptide-cytotoxic agent conjugate of the instant invention:



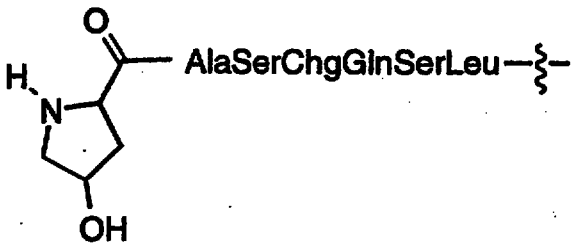
wherein X is:



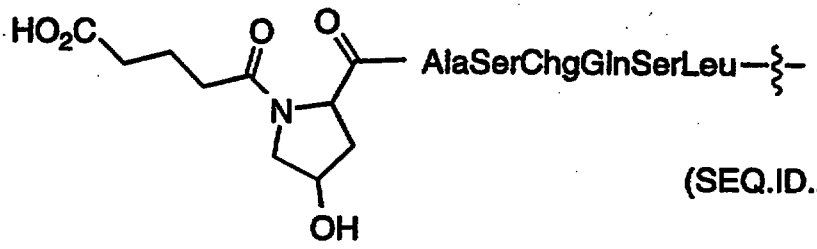
AlaSerChgGlnSerLeu—{- (SEQ.ID.NO.: 68),



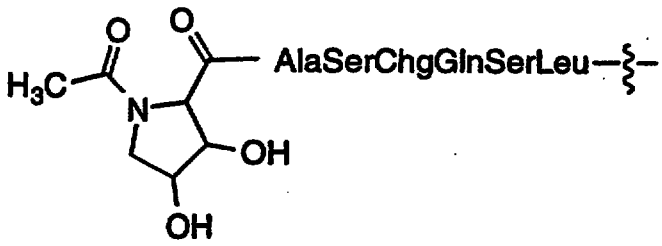
AlaSerChgGlnSerLeu—{- (SEQ.ID.NO.: 69),



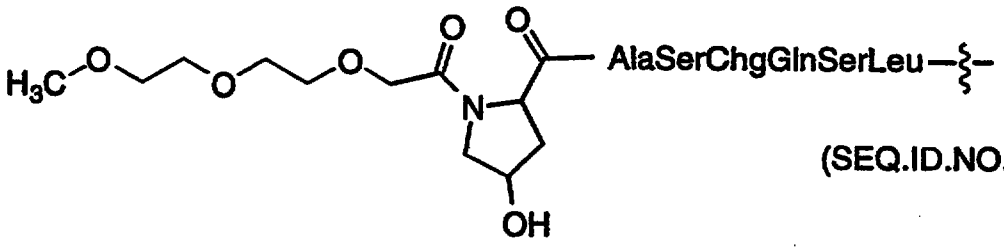
(SEQ.ID.NO.: 70),



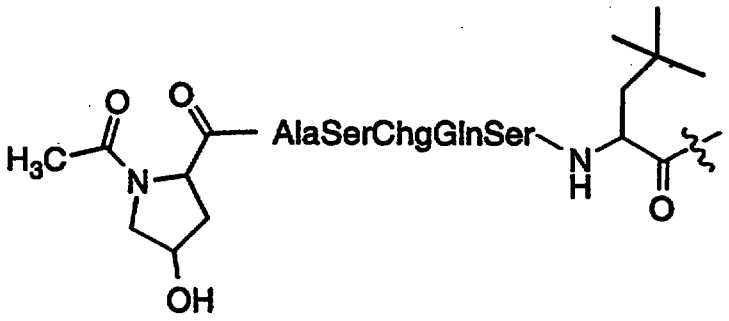
(SEQ.ID.NO.: 71),



(SEQ.ID.NO.: 72),



(SEQ.ID.NO.: 73),



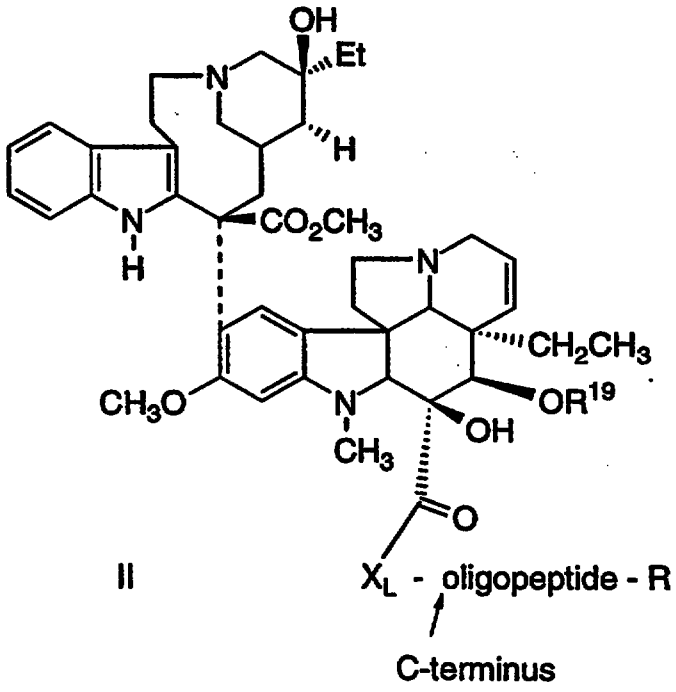
(SEQ.ID.NO.: 74),

	SEQ. ID. NO.
Succinyl-(4-Hyp)ASChgQ-SV-DOX (3')	75
Glutaryl-(4-Hyp)ASChgQ-SV-DOX (3')	76
Glutaryl-(4-Hyp)ASChgQ-SI-DOX (3')	77
Succinyl-(4-Hyp)SSChgQ-SI-DOX (3')	78

Succinyl-(4-Hyp)ASChgQ-SI-DOX (3')	79
Succinyl-(4-Hyp)ASChgQ-SAbu-DOX (3')	80
Glutaryl-(4-Hyp)SSChgQ-SI-DOX (3')	81
Glutaryl-(4-Hyp)SSChgQ-SL-DOX (3')	82
PEG(2)-(4-Hyp)SSChgQ-SL-DOX (3')	83
Succinyl-(4-Hyp)ASChgQ-SThi-DOX (3')	84
PEG(4)-(4-Hyp)-SSChgQ-SL-DOX (3')	85
PEG(2)-(4-Hyp)ASChgQ-SThi-DOX(3')	86
Succinyl-3,4-(diOH)PASChgQ-SL-DOX (3')	87
Malonyl-(4-Hyp)ASChgQ-SL-DOX (3')	88

or an optical isomer or pharmaceutically acceptable salt thereof.

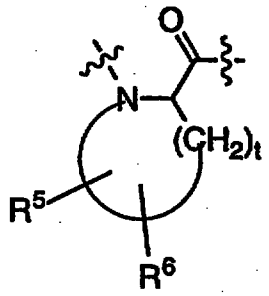
The oligopeptide-cytotoxic agent conjugate of the instant invention wherein the cytotoxic agent is the preferred cytotoxic agent vinblastine or desacetylvinblastine may be described by the general formula II below:



wherein:

oligopeptide is an oligopeptide which is specifically recognized by the free prostate specific antigen (PSA) and is capable of being proteolytic-

ally cleaved by the enzymatic activity of the free prostate specific antigen, and the oligopeptide comprises a cyclic amino acid of the formula:



;

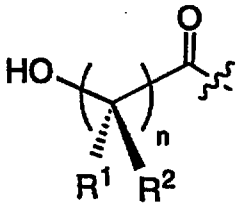
XL is - NH - (CH2)u - NH -

R is selected from

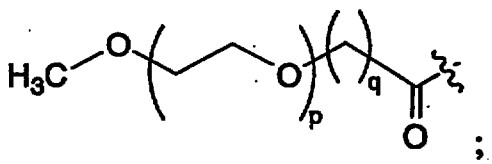
a) hydrogen,

b) -(C=O)R1a,

c)

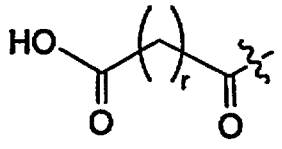


d)



;

e)



;

R1 and R2 are independently selected from: hydrogen, OH, C1-C6 alkyl, C1-C6 alkoxy, C1-C6 aralkyl and aryl;

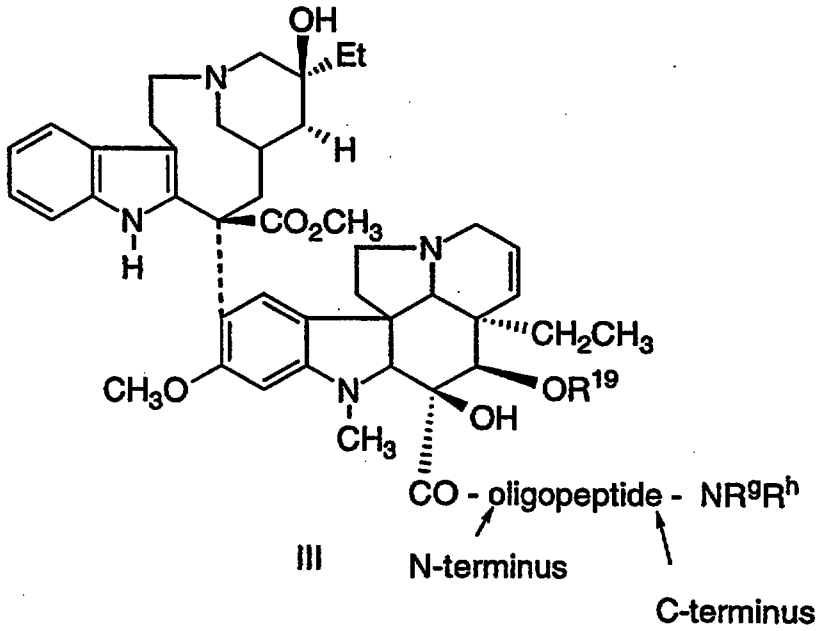
R^{1a} is C_1-C_6-alkyl, hydroxylated aryl, polyhydroxylated aryl or aryl,

R^{19} is hydrogen, (C_1-C_3 alkyl)-CO, or chlorosubstituted (C_1-C_3 alkyl)-CO;

n is	1, 2, 3 or 4;
p is	zero or an integer between 1 and 100;
q is	0 or 1, provided that if p is zero, q is 1;
r is	1, 2 or 3;
t is	3 or 4;
u is	1, 2, 3, 4 or 5,

or the pharmaceutically acceptable salt thereof.

Another embodiment of the oligopeptide-cytotoxic agent conjugate of the instant invention wherein the cytotoxic agent is the preferred cytotoxic agent vinblastine or desacetylvinblastine may be described by the general formula III below:

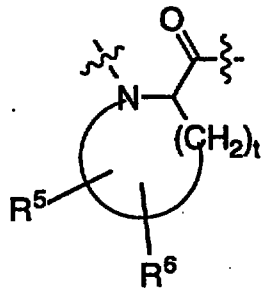


III

wherein:

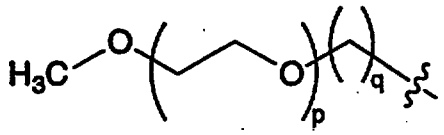
oligopeptide is an oligopeptide which is specifically recognized

by the free prostate specific antigen (PSA) and is capable of being proteolytically cleaved by the enzymatic activity of the free prostate specific antigen, and the oligopeptide comprises a cyclic amino acid of the formula:



;

R^g and R^h are independently selected from: hydrogen, C_1-C_6-alkyl, -C_1-C_6-alkyl-OH, -C_1-C_6-alkyl-di-OH, -C_1-C_6-alkyl-tri-OH and



provided that at least one R^d and R^e are not hydrogen or C_1-C_6-alkyl, or

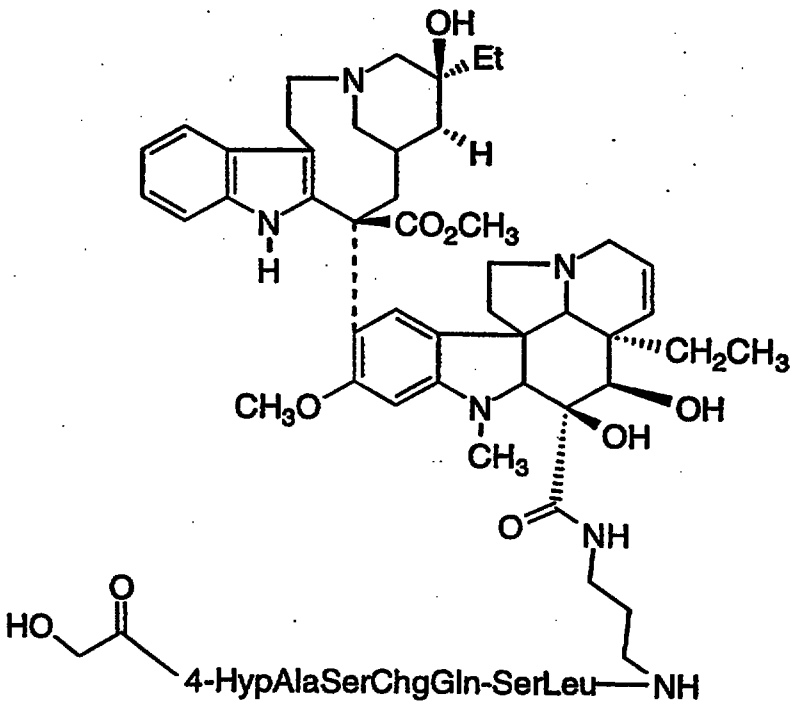
R^g and R^h are combined to form a -$CH_2CH_2OCH_2CH_2$- diradical;

R^{19} is hydrogen, (C_1-C_3 alkyl)-CO, or chlorosubstituted (C_1-C_3 alkyl)-CO;

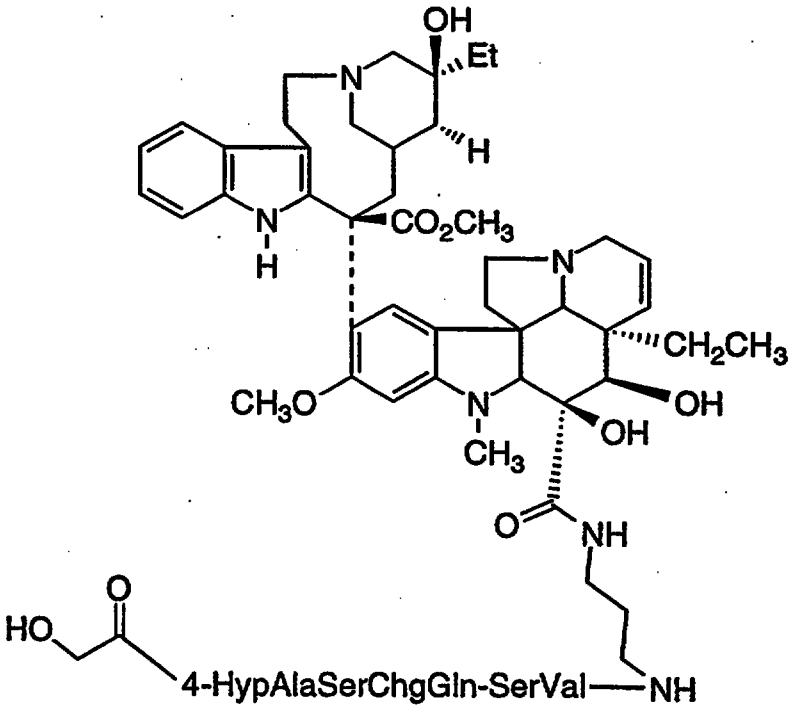
p is zero or an integer between 1 and 100;
q is 0 or 1, provided that if p is zero, q is 1;

or the pharmaceutically acceptable salt thereof.

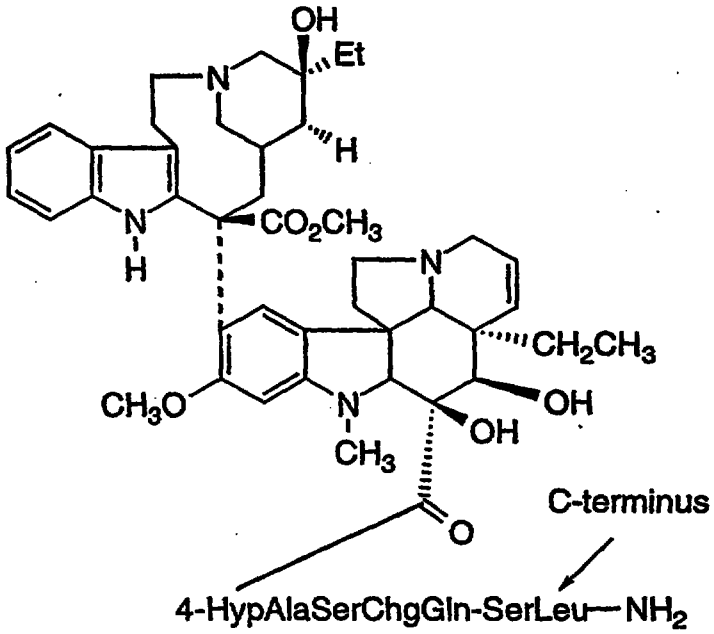
The following compounds are specific examples of the oligopeptide-desacetylvinblastine conjugate of the instant invention:



(SEQ.ID.NO.: 89),



(SEQ.ID.NO.: 90),



(SEQ.ID.NO.: 91),

or an optical isomer or pharmaceutically acceptable salt thereof.

The oligopeptides, peptide subunits and peptide derivatives (also termed "peptides") of the present invention can be synthesized from their constituent amino acids by conventional peptide synthesis techniques, preferably by solid-phase technology. The peptides are then purified by reverse-phase high performance liquid chromatography (HPLC).

Standard methods of peptide synthesis are disclosed, for example, in the following works: Schroeder *et al.*, "The Peptides", Vol. I, Academic Press 1965; Bodansky *et al.*, "Peptide Synthesis", Interscience Publishers, 1966; McOmie (ed.) "Protective Groups in Organic Chemistry", Plenum Press, 1973; Barany *et al.*, "The Peptides: Analysis, Synthesis, Biology" 2, Chapter 1, Academic Press, 1980, and Stewart *et al.*, *"Solid Phase Peptide Synthesis"*, Second Edition, Pierce Chemical Company, 1984. The teachings of these works are hereby incorporated by reference.

The suitably substituted cyclic amino acid having a hydrophilic substituent, which may be incorporated into the instant conjugates by standard peptide synthesis techniques, is itself either

commercially available or is readily synthesized by techniques well known in the art or described herein. Thus syntheses of suitably substituted prolines are described in the following articles and references cited therein: J. Ezquerra et al., *J. Org. Chem.* 60:2925-2930 (1995); P. Gill and W. D. Lubell, *J. Org. Chem.*, 60:2658-2659 (1995); and M. W. Holladay et al., *J. Med. Chem.*, 34:457-461 (1991). The teachings of these works are hereby incorporated by reference.

The pharmaceutically acceptable salts of the compounds of this invention include the conventional non-toxic salts of the compounds of this invention as formed, e.g., from non-toxic inorganic or organic acids. For example, such conventional non-toxic salts include those derived from inorganic acids such as hydrochloric, hydrobromic, sulfuric, sulfamic, phosphoric, nitric and the like: and the salts prepared from organic acids such as acetic, propionic, succinic, glycolic, stearic, lactic, malic, tartaric, citric, ascorbic, pamoic, maleic, hydroxymaleic, phenylacetic, glutamic, benzoic, salicylic, sulfanilic, 2-acetoxybenzoic, fumaric, toluenesulfonic, methanesulfonic, ethane disulfonic, oxalic, isethionic, trifluoroacetic and the like.

The conjugates of the instant invention which comprise the oligopeptide containing the PSA cleavage site and a cytotoxic agent may similarly be synthesized by techniques well known in the medicinal chemistry art. For example, a free amine moiety on the cytotoxic agent may be covalently attached to the oligopeptide at the carboxyl terminus such that an amide bond is formed. Similarly, an amide bond may be formed by covalently coupling an amine moiety of the oligopeptide and a carboxyl moiety of the cytotoxic agent. For these purposes a reagent such as 2-(1H-benzotriazol-1-yl)-1,3,3-tetramethyluronium hexafluorophosphate (known as HBTU) and 1-hyroxybenzotriazole hydrate (known as HOBT), dicyclohexylcarbodiimide (DCC), N-ethyl-N-(3-dimethylaminopropyl)- carbodiimide (EDC), diphenylphosphorylazide (DPPA), benzotriazol-1-yl-oxy-tris-(dimethylamino)phosphonium

hexafluorophosphate (BOP) and the like, used in combination or singularly, may be utilized.

Furthermore, the instant conjugate may be formed by a non-peptidyl bond between the PSA cleavage site and a cytotoxic agent. For example, the cytotoxic agent may be covalently attached to the carboxyl terminus of the oligopeptide via a hydroxyl moiety on the cytotoxic agent, thereby forming an ester linkage. For this purpose a reagent such as a combination of HBTU and HOBT, a combination of BOP and imidazole, a combination of DCC and DMAP, and the like may be utilized. The carboxylic acid may also be activated by forming the nitrophenyl ester or the like and reacted in the presence of DBU (1,8-diazabicyclo[5,4,0]undec-7-ene).

The instant conjugate may also be formed by attachment of the oligopeptide to the cytotoxic agent via a linker unit. Such linker units include, for example, a biscarbonyl alkyl diradical whereby an amine moiety on the cytotoxic agent is connected with the linker unit to form an amide bond and the amino terminus of the oligopeptide is connected with the other end of the linker unit also forming an amide bond. Conversely, a diaminoalkyl diradical linker unit, whereby a carbonyl moiety on the cyctotoxic agent is covalently attacted to one of the amines of the linker unit while the other amine of the linker unit is covalently attached to the C terminus of the oligopeptide, may also be uselful. Other such linker units which are stable to the physiological environment when not in the presence of free PSA, but are cleavable upon the cleavage of the PSA proteolytic cleavage site, are also envisioned. Furthermore, linker units may be utilized that, upon cleavage of the PSA proteolytic cleavage site, remain attached to the cytotoxic agent but do not significantly decrease the cytotoxic activity of such a post-cleavage cytotoxic agent derivative when compared with an unmodified cytotoxic agent.

One skilled in the art understands that in the synthesis of compounds of the invention, one may need to protect various reactive functionalities on the starting compounds and intermediates while a desired reaction is carried out on other portions of the molecule. After

the desired reactions are complete, or at any desired time, normally such protecting groups will be removed by, for example, hydrolytic or hydrogenolytic means. Such protection and deprotection steps are conventional in organic chemistry. One skilled in the art is referred to Protective Groups in Organic Chemistry, McOmie, ed., Plenum Press, NY, NY (1973); and, Protective Groups in Organic Synthesis, Greene, ed., John Wiley & Sons, NY, NY (1981) for the teaching of protective groups which may be useful in the preparation of compounds of the present invention.

By way of example only, useful amino-protecting groups may include, for example, C_1-C_{10} alkanoyl groups such as formyl, acetyl, dichloroacetyl, propionyl, hexanoyl, 3,3-diethylhexanoyl, γ-chlorobutryl, and the like; C_1-C_{10} alkoxycarbonyl and C_5-C_{15} aryloxycarbonyl groups such as tert-butoxycarbonyl, benzyloxycarbonyl, allyloxycarbonyl, 4-nitrobenzyloxycarbonyl, fluorenylmethyloxycarbonyl and cinnamoyloxycarbonyl; halo-(C_1-C_{10})-alkoxycarbonyl such as 2,2,2-trichloroethoxycarbonyl; and C_1-C_{15} arylalkyl and alkenyl group such as benzyl, phenethyl, allyl, trityl, and the like. Other commonly used amino-protecting groups are those in the form of enamines prepared with β-keto-esters such as methyl or ethyl acetoacetate.

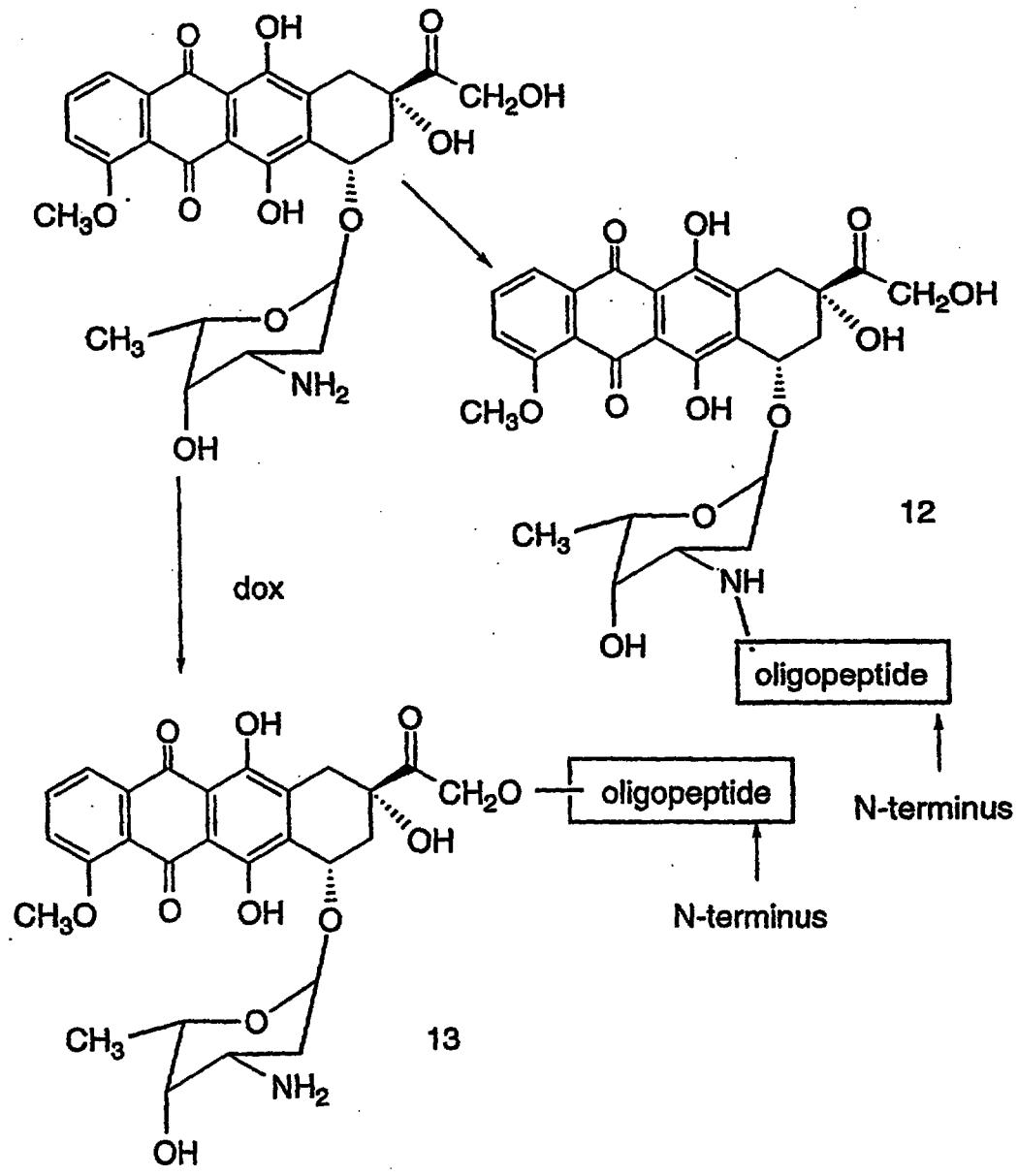
Useful carboxy-protecting groups may include, for example, C_1-C_{10} alkyl groups such as methyl, tert-butyl, decyl; halo-C_1-C_{10} alkyl such as 2,2,2-trichloroethyl, and 2-iodoethyl; C_5-C_{15} arylalkyl such as benzyl, 4-methoxybenzyl, 4-nitrobenzyl, triphenylmethyl, diphenylmethyl; C_1-C_{10} alkanoyloxymethyl such as acetoxymethyl, propionoxymethyl and the like; and groups such as phenacyl, 4-halophenacyl, allyl, dimethylallyl, tri-(C_1-C_3 alkyl)silyl, such as trimethylsilyl, β-p-toluenesulfonylethyl, β-p-nitrophenylthio-ethyl, 2,4,6-trimethylbenzyl, β-methylthioethyl, phthalimidomethyl, 2,4-dinitro-phenylsulphenyl, 2-nitrobenzhydryl and related groups.

Similarly, useful hydroxy protecting groups may include, for example, the formyl group, the chloroacetyl group, the benzyl group, the benzhydryl group, the trityl group, the 4-nitrobenzyl group,

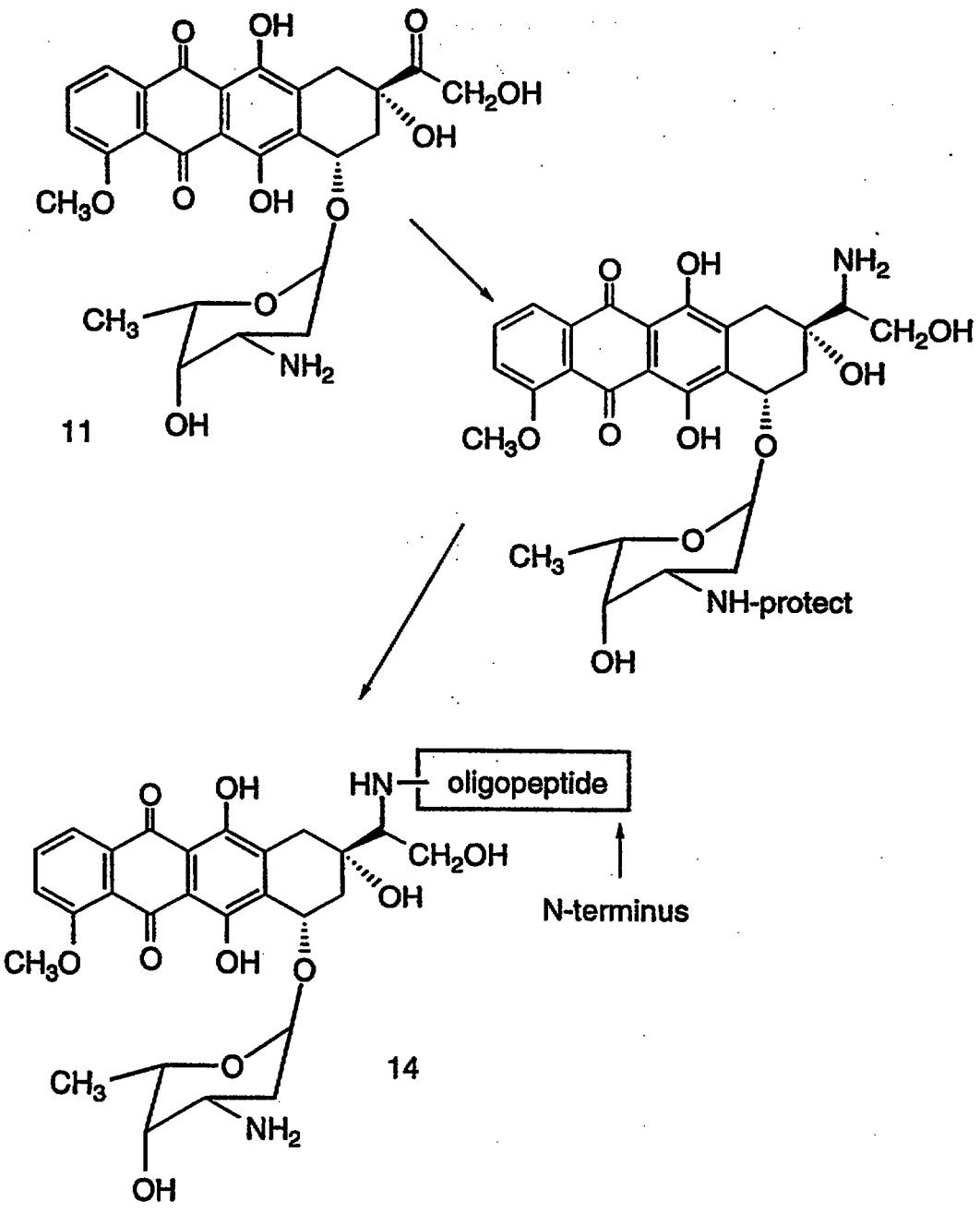
the trimethylsilyl group, the phenacyl group, the tert-butyl group, the methoxymethyl group, the tetrahydropyranyl group, and the like.

With respect to the preferred embodiment of an oligopeptide combined with the anthracycline antibiotic doxorubicin, the following Reaction Schemes illustrate the synthsis of the conjugates of the instant invention.

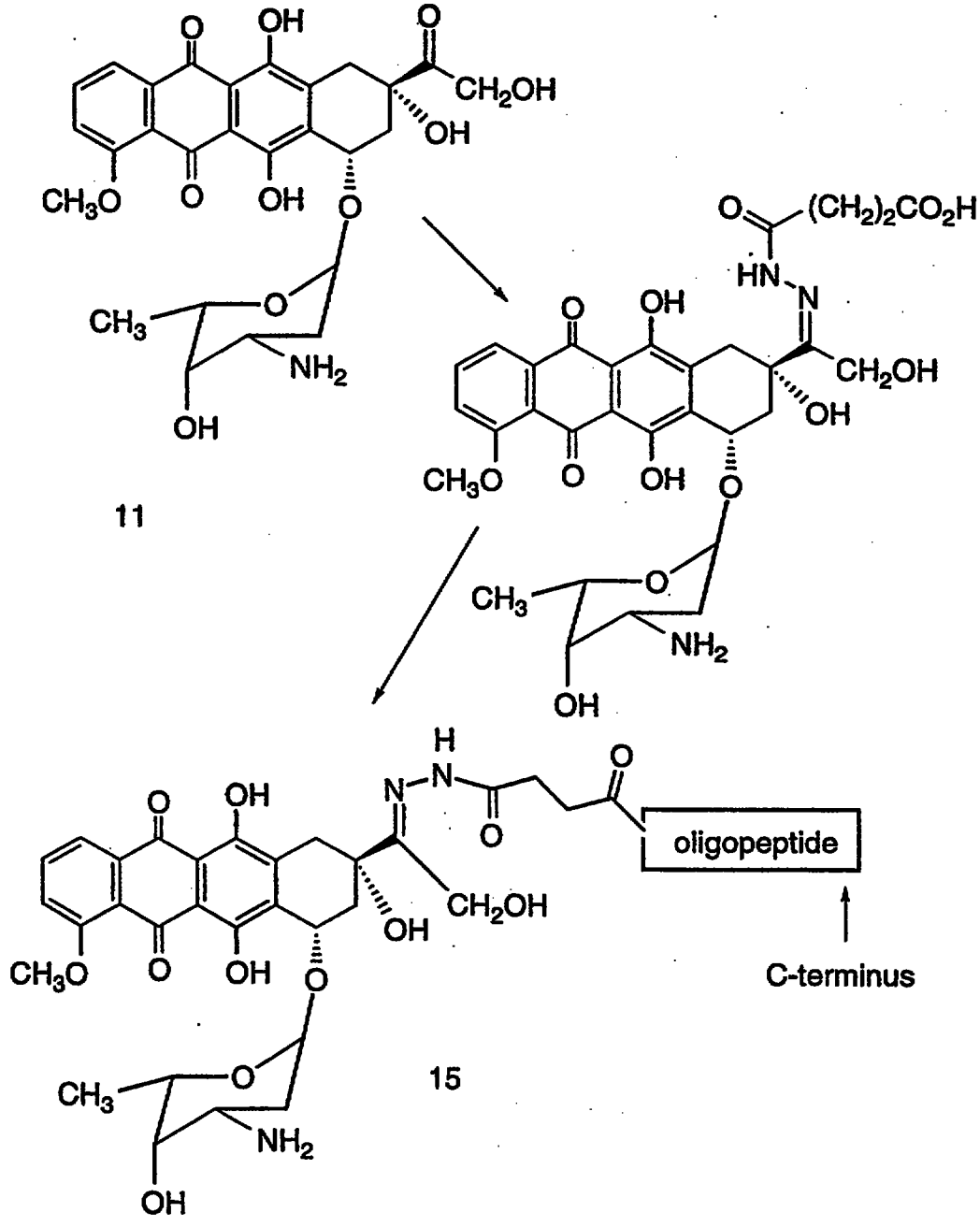
REACTION SCHEME I



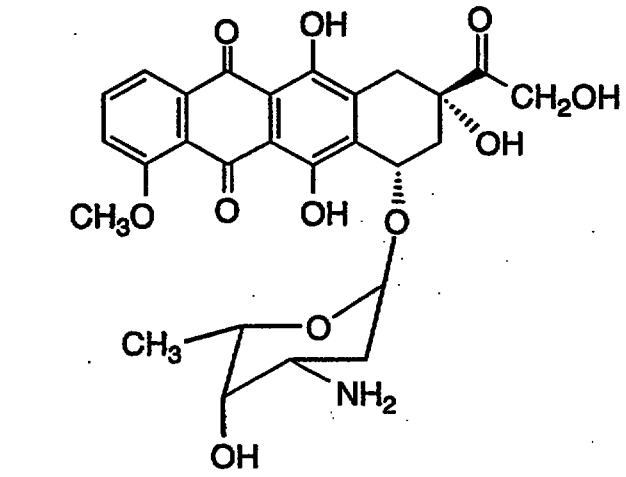
REACTION SCHEME II



REACTION SCHEME III

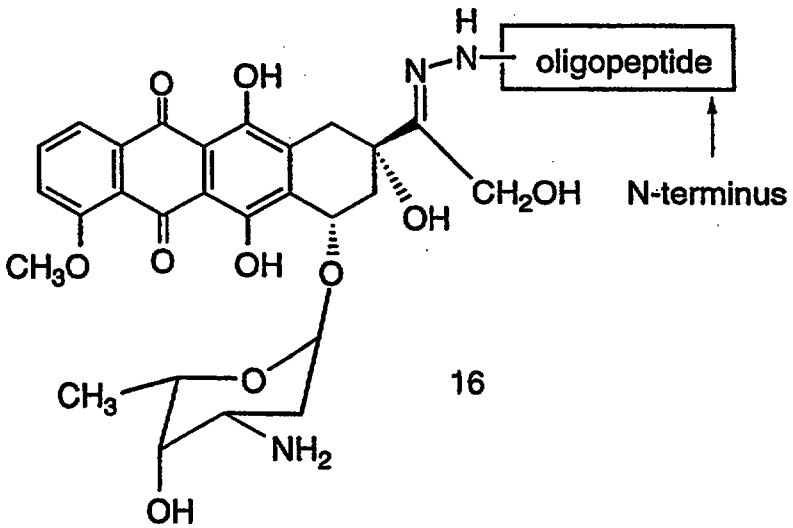


REACTION SCHEME IV



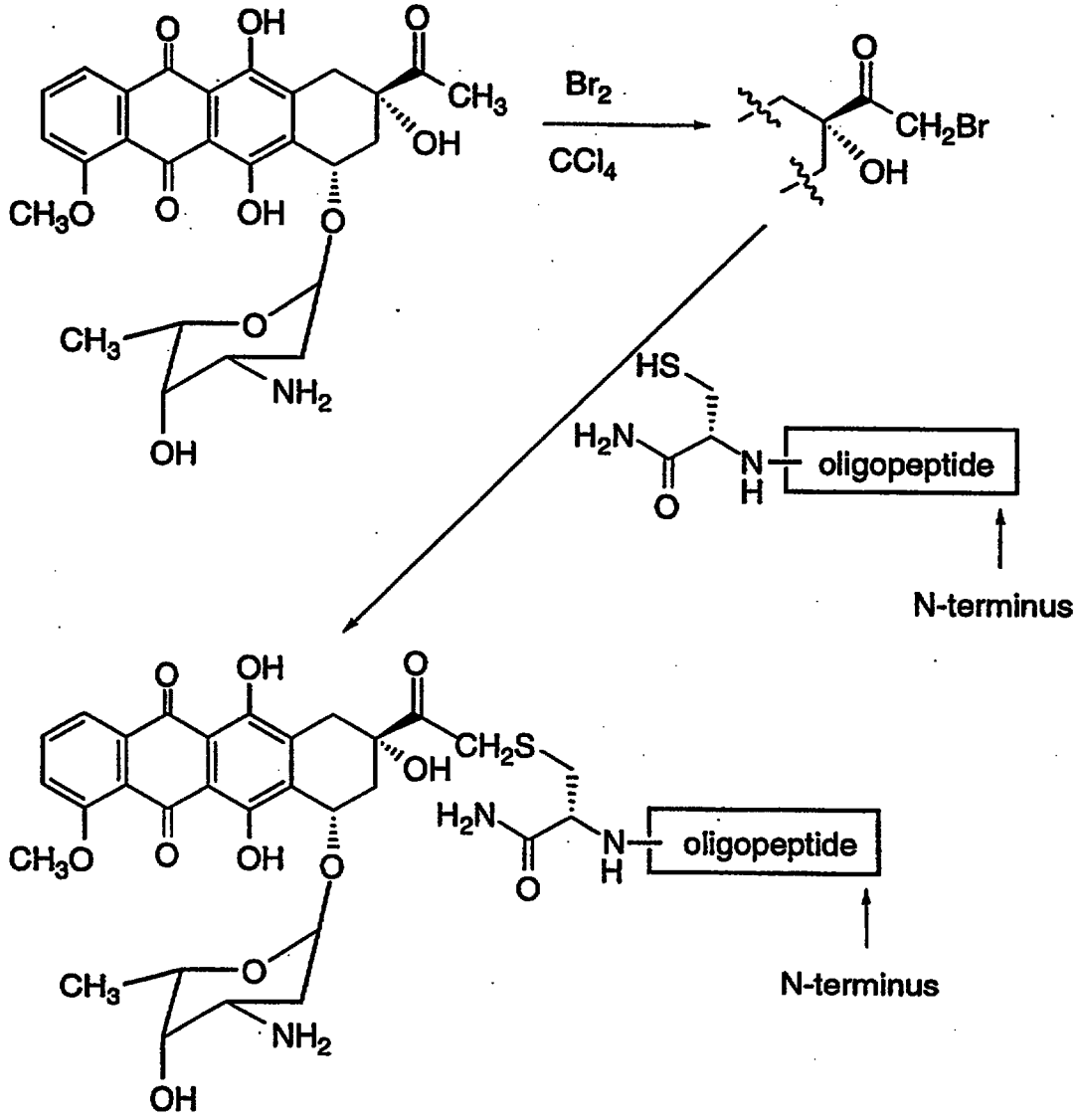
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REACTION SCHEME V



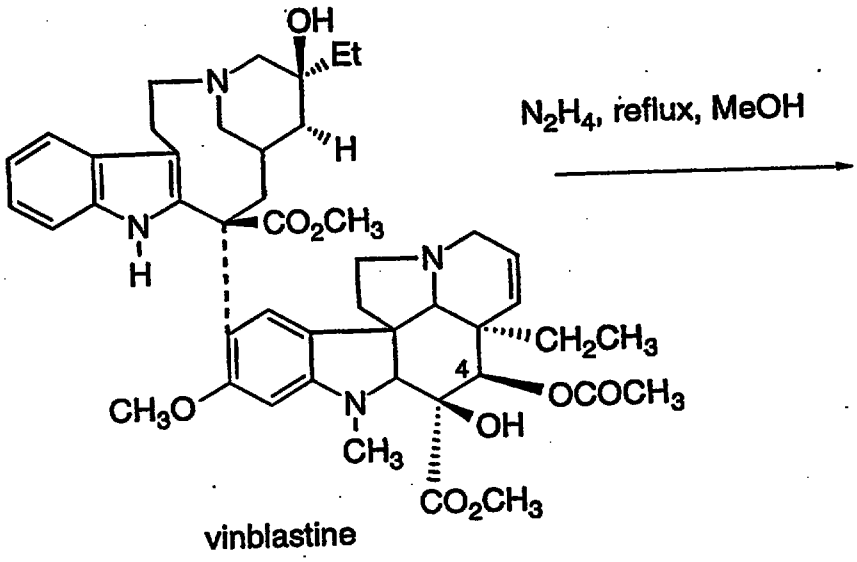
Reaction Scheme VI illustrates preparation of conjugates utilized in the instant method of treatment wherein the oligopeptides are combined with the vinca alkaloid cytotoxic agent vinblastine. Attachment of the N-terminus of the oligopeptide to vinblastine is illustrated (S.P. Kandukuri et al. J. Med. Chem. 28:1079-1088 (1985)).

Reaction Scheme VII illustrates preparation of conjugates of the oligopeptides of the instant invention and the vinca alkaloid

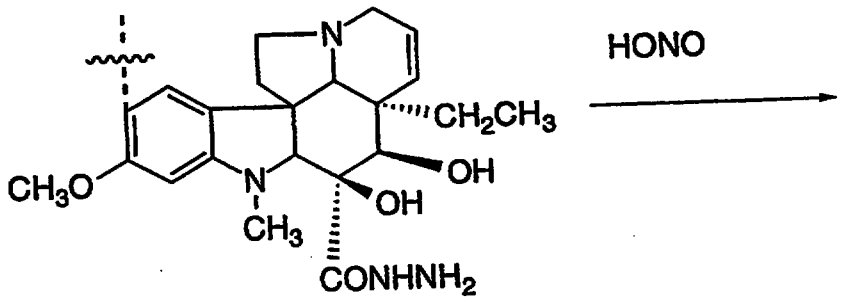
cytotoxic agent vinblastine wherein the attachment of vinblastine is at the C-terminus of the oligopeptide. The use of the 1,3-diaminopropane linker is illustrative only; other spacer units between the carbonyl of vinblastine and the C-terminus of the oligopeptide are also envisioned. Furthermore, Scheme VII illustrates a synthesis of conjugates wherein the C-4-position hydroxy moiety is reacetylated following the addition of the linker unit. Applicants have discovered that the desacetyl vinblastine conjugate is also efficacious and may be prepared by eliminating the steps shown in Reaction Scheme VII of protecting the primary amine of the linker and reacting the intermediate with acetic anhydride, followed by deprotection of the amine. Conjugation of the oligopeptide at other positions and functional groups of vinblastine may be readily accomplished by one of ordinary skill in the art and is also expected to provide compounds useful in the treatment of prostate cancer.

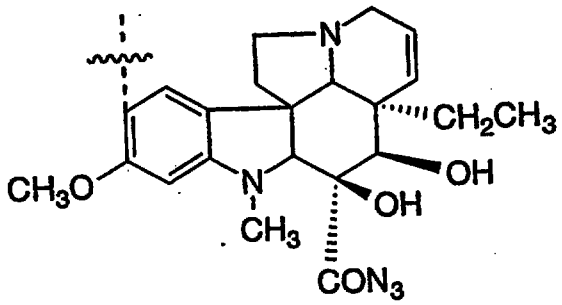
It is also understood that conjugates may be prepared wherein the N-terminus of the oligopeptide, which comprises a cyclic amino acid having a hydrophilic substituent, utilized in the instant method of treatment is combined with one cytotoxic agent, such as vinblastine, while the C-terminus is simultaneously attached to another cytotoxic agent, which is the same or different cytotoxic agent, such as doxorubicin. Reaction Scheme VIII illustrates the synthesis of such a polycytotoxic agent conjugate. Such a polycytotoxic conjugate may offer advantages over a conjugate containing only one cytotoxic agent.

REACTION SCHEME VI

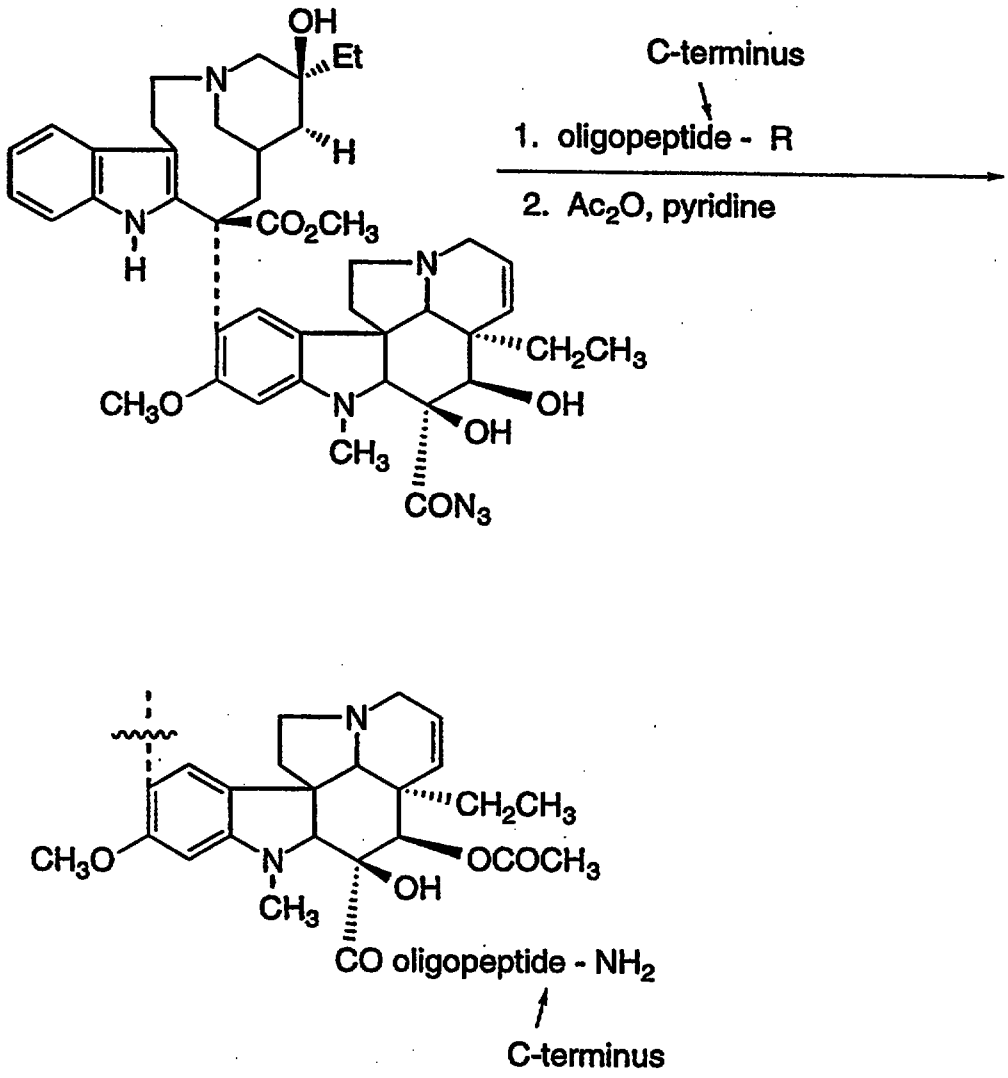


vinblastine





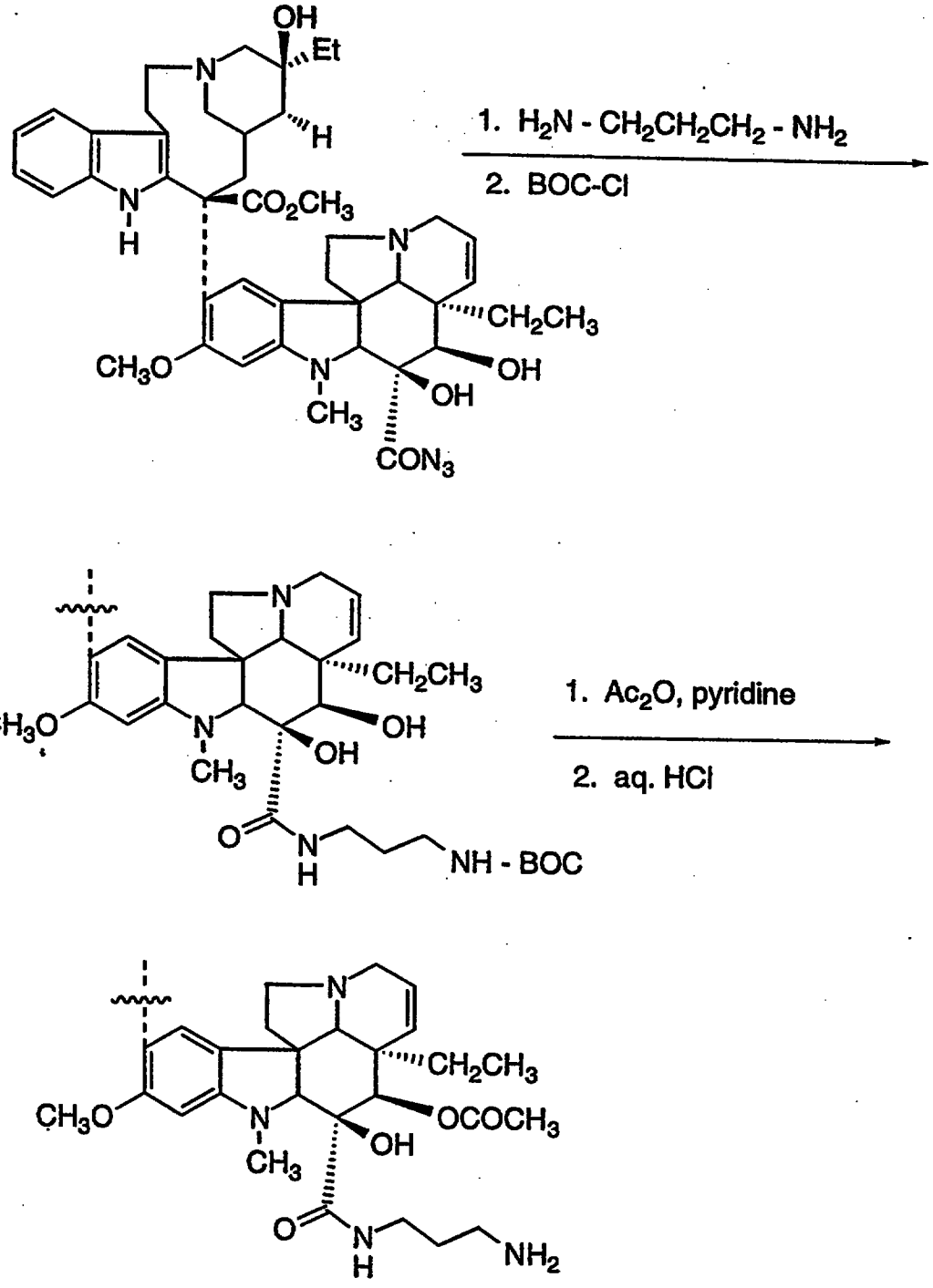
REACTION SCHEME VI (Continued)



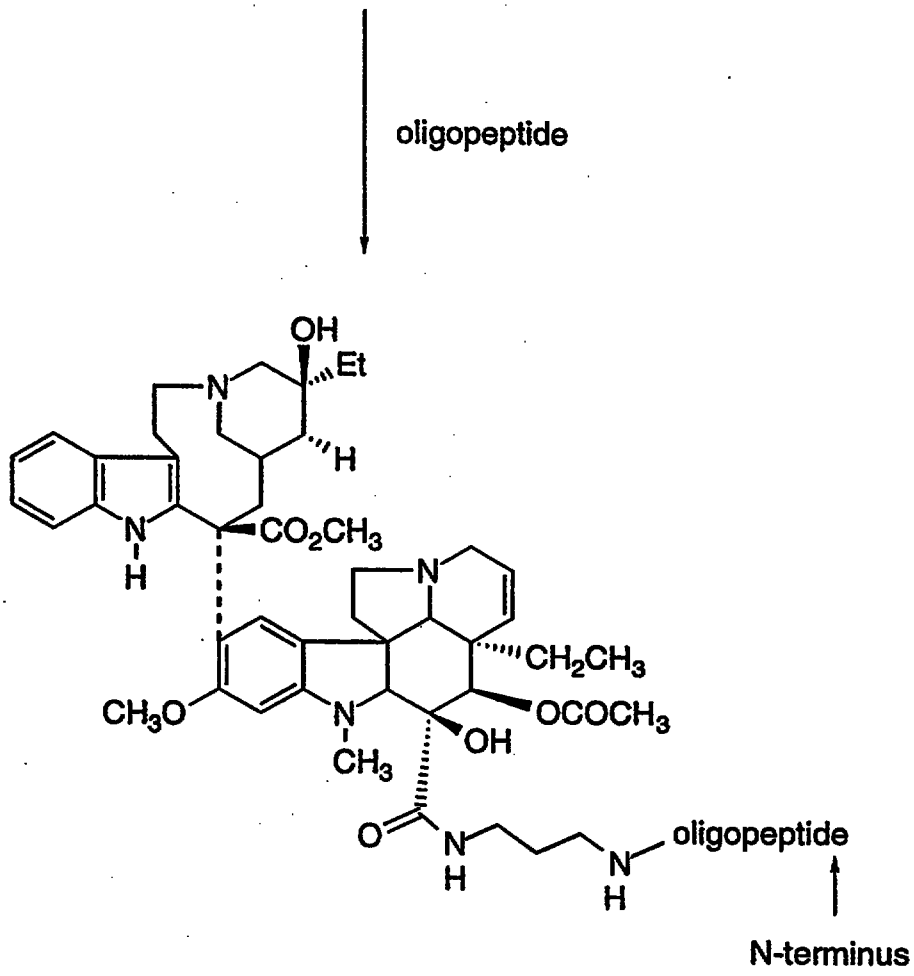
wherein R is -NH_2, -O-alkyl and the like

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REACTION SCHEME VII

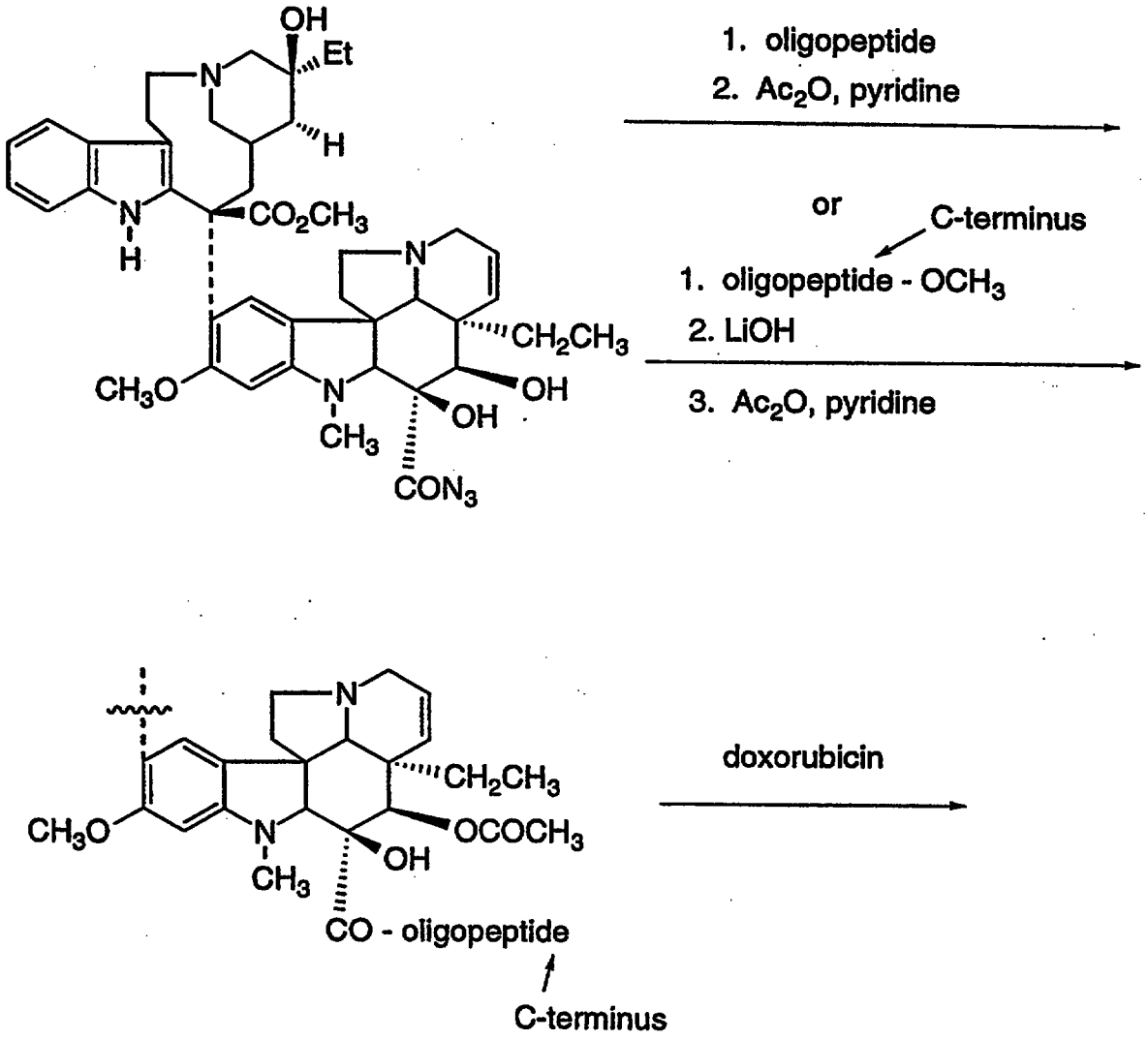


REACTION SCHEME VII (Continued)

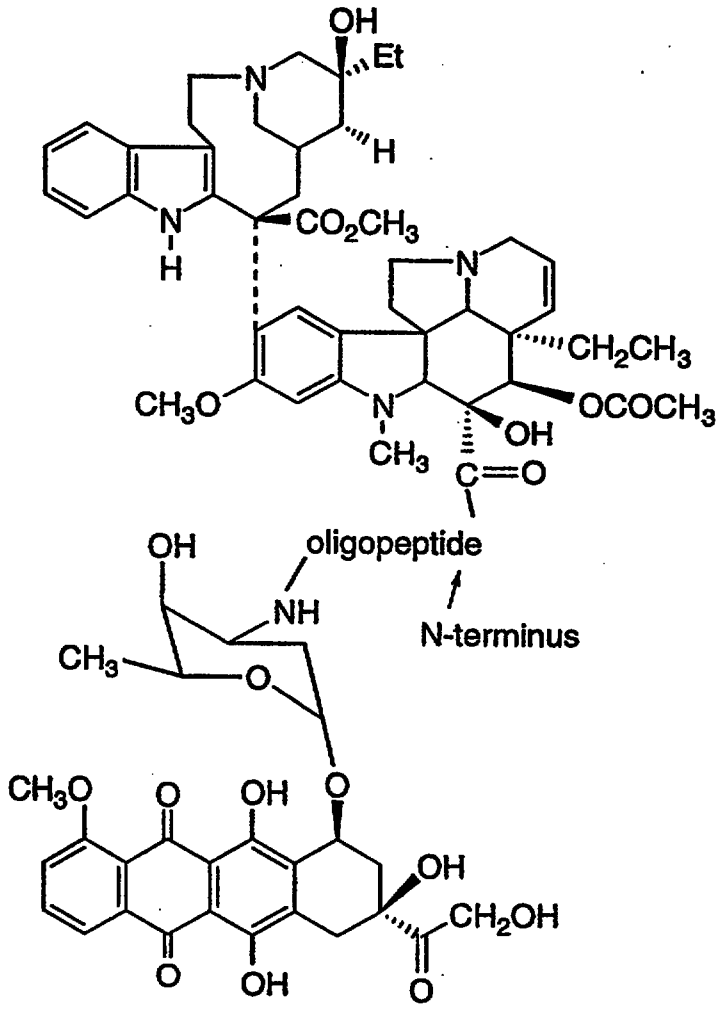


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REACTION SCHEME VIII



REACTION SCHEME VIII (Continued)



The oligopeptide-cytotoxic agent conjugates of the invention are administered to the patient in the form of a pharmaceutical composition which comprises a conjugate of of the instant invention and a pharmaceutically acceptable carrier, excipient or diluent therefor. As used, "pharmaceutically acceptable" refers to those agents which are useful in the treatment or diagnosis of a warm-blooded animal including, for example, a human, equine, procine, bovine, murine, canine, feline, or other mammal, as well as an avian or other warm-blooded

animal. The preferred mode of administration is parenterally, particularly by the intravenous, intramuscular, subcutaneous, intraperitoneal, or intralymphatic route. Such formulations can be prepared using carriers, diluents or excipients familiar to one skilled in the art. In this regard, See, e.g. Remington's Pharmaceutical Sciences, 16th ed., 1980, Mack Publishing Company, edited by Osol et al. Such compositions may include proteins, such as serum proteins, for example, human serum albumin, buffers or buffering substances such as phosphates, other salts, or electrolytes, and the like. Suitable diluents may include, for example, sterile water, isotonic saline, dilute aqueous dextrose, a polyhydric alcohol or mixtures of such alcohols, for example, glycerin, propylene glycol, polyethylene glycol and the like. The compositions may contain preservatives such as phenethyl alcohol, methyl and propyl parabens, thimerosal, and the like. If desired, the composition can include about 0.05 to about 0.20 percent by weight of an antioxidant such as sodium metabisulfite or sodium bisulfite.

As used herein, the term "composition" is intended to encompass a product comprising the specified ingredients in the specific amounts, as well as any product which results, directly or indirectly, from combination of the specific ingredients in the specified amounts.

For intravenous administration, the composition preferably will be prepared so that the amount administered to the patient will be from about 0.01 to about 1 g of the conjugate. Preferably, the amount administered will be in the range of about 0.2 g to about 1 g of the conjugate. The conjugates of the invention are effective over a wide dosage range depending on factors such as the disease state to be treated or the biological effect to be modified, the manner in which the conjugate is administered, the age, weight and condition of the patient as well as other factors to be determined by the treating physician. Thus, the amount administered to any given patient must be determined on an individual basis.

One skilled in the art will appreciate that although specific reagents and reaction conditions are outlined in the following examples, modification can be made which are meant to be encompassed by the

spirit and scope of the invention. The following preparations and examples, therefore, are provided to further illustrate the invention, and are not limiting.

EXAMPLES

EXAMPLE 1

Preparation of Oligopeptides which Comprise the PSA Mediated Cleavage Site:

Blocked oligopeptides were prepared by solid-phase synthesis, using a double coupling protocol for the introduction of amino acids on the Applied Biosystems model 430A automated peptide synthesizer. Deprotection and removal of the oligopeptide from the resin support were achieved by treatment with liquid hydrofluoric acid. The oligopeptides were purified by preparative high pressure liquid chromatography on reverse phase C18 silica columns using an aqueous 0.1% trifluoroacetic acid/acetonitrile gradient. Identity and homogeneity of the oligopeptides were confirmed by amino acid composition analysis, high pressure liquid chromatography, and fast atom bombardment mass spectral analysis. The oligopeptides that were prepared by this method are shown in Table 2.

TABLE 2

SEQ.ID.NO.	PEPTIDE / PEPTIDE-DOX CONJUGATE	Time to 50% Substrate Cleavage by PSA (Min)
73	Ac-PSSChgQ-SV-acid	120
74	Ac-PASChgQ-SL-acid	150
75	Ac-(Dehydro-Pro)-ASChgQ-SL-acid	3 HOURS = 28%
68	Ac-(4-trans-L-Hyp)ASChgQ-SL-acid	75
76	Ac-(4-trans-L-Hyp)ChgQ-SSSL-acid	3 HOURS = 0% n=2
77	Ac-(4-trans-L-Hyp)ASChgQ-SThi-acid	20
78	Ac-(4-trans-L-Hyp)ASChgQ-S(TIC)-acid	3 HOURS = 16%
68	PEG(2)-(4-trans-L-Hyp)-ASChgQ-SL-acid	3 HOURS = 44%

4-trans-L-Hyp is *trans*-4-hydroxy-L-proline
Dehydro-Pro is 3,4-dehydro-L-proline

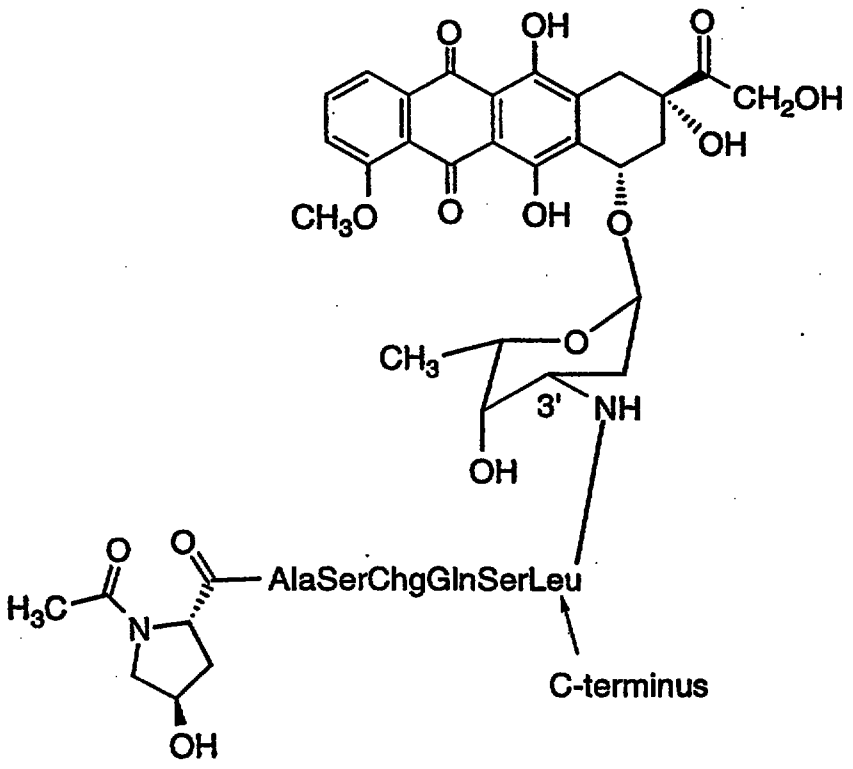
EXAMPLE 2

Assessment of the Recognition of Oligopeptides by Free PSA :

The oligopeptides prepared as described in Example 1 were individually dissolved in PSA digestion buffer (12 mM tris(hydroxymethyl)-aminomethane pH8.0, 25 mM NaCl, 0.5 mM $CaCl_2$) and the solution added to PSA at a molar ration of 100 to 1. Alternatively, the PSA digestion buffer utilized is 50 mM tris(hydroxymethyl)-aminomethane pH7.4, 140 mM NaCl. The reaction is quenched after various reaction times by the addition of trifluoroacetic acid (TFA) to a final 1% (volume/volume). Alternatively the reaction is quenched with 10mM ZnCl2. The quenched reaction was analyzed by HPLC on a reversed-phase C18 column using an aqueous 0.1%TFA/acetonitrile gradient. The results of the assessment are shown in Table 2. Table 2 shows the amount of time (in minutes) required for 50% cleavage of the noted oligopeptides with enzymatically active free PSA. Oligopeptides containing free amine moieties (ie. comprising hArg, Orn, Lys and or 3PAL) were tested as TFA salts. All other oligopeptides were tested as neutral compounds.

EXAMPLE 3

Preparation of [N-Ac-(4-trans-L-Hyp)]-Ala-Ser-Chg-Gln-Ser-Leu-Dox (SEQ.ID.NO.: 68)



Step A: [N-Ac-(4-trans-L-Hyp(Bzl))]-Ala-Ser(Bzl)Chg-Gln-Ser(Bzl)Leu-PAM Resin (3-1).

Starting with 0.5 mmol (0.67g) Boc-Leu-PAM resin, the protected peptide was synthesized on a 430A ABI peptide synthesizer. The protocol used a 4 fold excess (2 mmol) of each of the following protected amino acids: Boc-Ser(Bzl), Boc-Gln, Boc-Chg, Boc-Ala, N-Boc-(4-trans-L-Hyp(Bzl)). Coupling was achieved using DCC and HOBT activation in methyl-2-pyrrolidinone. Acetic acid was used for the introduction of the N terminal acetyl group. Removal of the Boc group was performed using 50% TFA in methylene chloride and the TFA salt neutralized with diisopropylethylamine. At the completion of the synthesis the peptide resin was dried to yield Intermediate 3-1.

Step B: [N-Ac-(4-trans-L-Hyp)]-Ala-Ser-Chg-Gln-Ser-Leu-OH (3-2)

The protected peptide resin (3-1), 1.2 g, was treated with HF (20 ml) for 1 hr at 0°C in the presence of anisole (2 ml). After evaporation of the HF, the residue was washed with ether, filtered and extracted with H_2O (200 ml). The filtrate was lyophilyzed to yield Intermediate 3-2.

Step C: [N-Ac-(4-trans-L-Hyp)]-Ala-Ser-Chg-Gln-Ser-Leu-Dox

The above described intermediate (3-2), 1.157 g (1.45 mmol) was dissolved in DMSO (30 ml) and diluted with DMF (30 ml). To the solution was added doxorubicin hydrochloride, 516 mg (0.89 mmol) followed by 0.310 ml of diisopropylethylamine (1.78 mmol). The stirred solution was cooled (0°C) and 0.276 ml of diphenyl-phosphoryl azide (1.28 mmol) added. After 30 minutes, an additional 0.276 ml (1.28 mmol) of DPPA was added and the pH adjusted to ~7.5 (pH paper) with diisopropylethylamine (DIEA). The pH of the cooled reaction (0°C) was maintained at ~7.5 with DIEA for the next 3 hrs. and the reaction stirred at 0-4°C overnight. After 18 hrs., the reaction (found to be complete by analytical HPLC, system A) was concentrated to an oil. Purification of the crude product was achieved by preparative HPLC, Buffer A = 0.1% NH_4OAc-H_2O; B=CH_3CN. The crude product was dissolved in 400 ml of 100% A buffer, filtered and purified on a C-18 reverse phase HPLC radial compression column (Waters, Delta-Pak, 15μM, 100Å). A step gradient of 100% A to 60% A was used at a flow rate of 75 ml/min (UV = 214nm). Homogeneous product fractions (evaluated by HPLC, system A) were pooled and freeze-dried. The product was dissolved in H_2O (300 ml), filtered and freeze-dried to provide the purified title compound.

HPLC conditions, system A

Column: Vydac 15 cm #218TP5415, C18
Eluant: Gradient 95:5 (A:B) to 5:95 (A:B) over 45 min.
A=0.1% TFA/H_2O, B=0.1% TFA/Acetonitrile
Flow: 1.5 ml/min.
Wavelength: 214 nM, 254 nM
Retention times: Doxorubicin = 13.66 min.
Ac-Hyp-Ala-Ser-Chg-Gln-Ser-Leu-OH = 10.8 min.
Ac-Hyp-Ala-Ser-Chg-Gln-Ser-Leu-Dox = 18.2 min.

PHYSICAL PROPERTIES

The physical/chemical properties of the product of Step C are shown below:

Molecular Formula:	$C_{62}H_{85}N_9O_{23}$
Molecular Weight:	1323.6
High Resolution ES Mass Spec:	1341.7 (NH_4^+)
HPLC:	System A
Column:	Vydac 15 cm #218TP5415, C18
Eluant:	Gradient 95:5 (A:B) to 5:95 (A:B) over 45 min. A=0.1% TFA/H_2O, B=0.1% TFA/Acetonitrile
Flow:	1.5 ml/min.
Wavelength:	214 nm, 254 nm
Retention Time:	18.2 min.

Amino Acid Compositional Analysis[1]:

Theory	Found
Ala (1)	1.00
Ser (2)	1.88
Chg (1)	0.91
Gln[2] (1)	1.00 (as Glu)
Hyp (1)	0.80

Leu (1) 1.01
Peptide Content: 0.657 µmol/mg
Note: [1]20 hr., 100°C, 6N HCl
[2]Gln converted to Glu

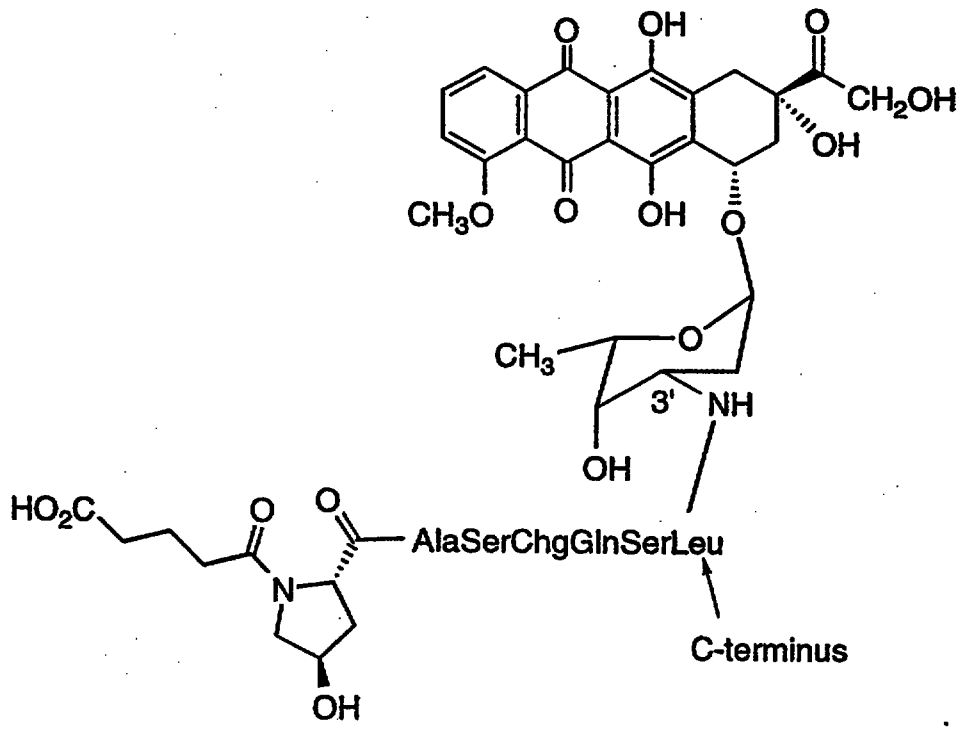
Table 3 shows other peptide-doxorubicin conjugates that were prepared by the procedures described in Example 3, but utilizing the appropriate amino acid residues and blocking group acylation.

TABLE 3

SEQ. ID.NO.	PEPTIDE / PEPTIDE-DOX CONJUGATE	Time to 50% Substrate Cleavage by PSA (Min)
89	Ac-(4-trans-L-Hyp)ASChgQ-SThi-DOX (3')	INSOLUBLE
74	Ac-(4-trans-L-Hyp)ASChgQ-StBuAla-DOX (3')	25
73	PEG(2)-(4-trans-L-Hyp)ASChgQ-SL-DOX (3')	20
68	Ac-(4-trans-L-Hyp)ASChgQ-SL-DOX (3')	20

EXAMPLE 4

Preparation of [N-Glutaryl-(4-trans-L-Hyp)]-Ala-Ser-Chg-Gln-Ser-Leu-Dox (SEQ.ID.NO.: 71)



Step A: [N-Glutaryl(OFm)-(4-trans-L-Hyp)]-Ala-Ser-Chg-Gln-Ser-Leu-PAM Resin

Starting with 0.5mmol (0.67g) Boc-Leu-PAM resin, the protected peptide was synthesized on a 430A ABI peptide synthesizer. The protocol used a 4 fold excess (2 mmol) of each of the following protected amino acids: Fmoc-Ser(tBu), Fmoc-Gln(Trt), Fmoc-Chg, Fmoc-Ala, Boc-(4-trans-L-Hyp). Coupling was achieved using DCC and HOBT activation in methyl-2-pyrrolidinone. The intermediate mono fluorenylmethyl ester of glutaric acid [Glutaryl(OFm)] was used for the introduction of the N-terminal glutaryl group. Removal of the Fmoc group was performed using 20% piperidine. The acid sensitive protecting groups, Boc, Trt and tBu, were removed with 50% TFA in methylene chloride. Neutralization of the TFA salt was with

diisopropylethylamine. At the completion of the synthesis, the peptide resin was dried to yield the title compound.

Step B: [N-Glutaryl(OFm)-(4-trans-L-Hyp)]-Ala-Ser-Chg-Gln-Ser-Leu-OH

The protected peptide resin from Step A, 1.2 g, was treated with HF (20 ml) for 1 hr at 0°C in the presence of anisole (2 ml). After evaporation of the HF, the residue was washed with ether, filtered and extracted with DMF. The DMF filtrate (75 ml) was concentrated to dryness and triturated with H_2O. The insoluble product was filtered and dried to provide the title compound.

Step C: [N-Glutaryl(OFm)-(4-trans-L-Hyp)]-Ala-Ser-Chg-Gln-Ser-Leu-Dox

The above prepared intermediate from Step B, (1.33g, 1.27mmol) was dissolved in DMSO (6 ml) and DMF (69 ml). To the solution was added doxorubicin hydrochloride, 599 mg (1.03 mmol) followed by 376µl of diisopropylethylamine (2.16 mmol). The stirred solution was cooled (0°C) and 324 µl of diphenylphosphoryl azide (1.5mmol) added. After 30 minutes, an additional 324 µl of DPPA was added and the pH adjusted to ~7.5 (pH paper) with diisopropylethylamine (DIEA). The pH of the cooled reaction (0°C) was maintained at ~7.5 with DIEA for the next 3 hrs and the reaction stirred at 0-4°C overnight. After 18 hrs., the reaction (found to be complete by analytical HPLC, system A) was concentrated to provide the title compound as an oil.

Step D: [N-Glutaryl-(4-trans-L-Hyp)]-Ala-Ser-Chg-Gln-Ser-Leu-Dox

The above product from Step C was dissolved in DMF (54 ml), cooled (0°C) and 14 ml of piperidine added. The solution was concentrated to dryness and purified by preparative HPLC. (A=0.1% NH_4OAc-H_2O; B=CH_3CN.) The crude product was dissolved in 100 ml of 80% A buffer, filtered and purified on a C-18 reverse phase HPLC

radial compression column (Waters, Delta-Pak, 15µ, 100Å). A step gradient of 80% A to 67% A was used at a flow rate of 75 ml/min (uv = 214nm). Homogeneous product fractions (evaluated by HPLC, system A) were pooled and freeze-dried. The product was further purified using the above HPLC column. Buffer A = 15% acetic acid-H_2O; B=15% acetic acid-methanol. The product was dissolved in 100 ml of 20% B/80% A buffer and purified. A step gradient of 20% B to 80% B was used at a flow rate of 75 ml/min (uv = 260nm). Homogeneous product fractions (evaluated by HPLC, system A) were pooled, concentrated and freeze-dried from H_2O to yield the purified title compound.

HPLC conditions, system A

Column:	Vydac 15 cm #218TP5415, C18
Eluant:	Gradient 95:5 (A:B) to 5:95 (A:B) over 45 min. A=0.1% TFA/H_2O, B=0.1% TFA/Acetonitrile
Flow:	1.5 ml/min.
Wavelength:	214 nm, 254 nm

Retention times: Doxorubicin = 13.66 min.

[N-Glutaryl(OFm) - (4-trans-L-Hyp)]-Ala-Ser-Chg-Gln-Ser-Leu-OH = 19.66 min.

[N-Glutaryl(OFm) - (4-trans-L-Hyp)]-Ala-Ser-Chg-Gln-Ser-Leu-Dox = 24.8 min.

[N-Glutaryl-(4-trans-L-Hyp)]-Ala-Ser-Chg-Gln-Ser-Leu-Dox = 18.3 min.

High Resolution ES Mass Spec: 1418.78 (Na^+)

HPLC:	System A
Column:	Vydac 15 cm #218TP5415, C18
Eluant:	Gradient 95:5 (A:B) to 5:95 (A:B) over 45 min. A=0.1% TFA/H_2O, B=0.1% TFA/Acetonitrile
Flow:	1.5 ml/min.
Wavelength:	214 nm, 254 nm
Retention Time:	18.3 min.

Amino Acid Compositional Analysis[1]:

Theory	Found
Ala(1)	0.99
Ser (2)	2.02
Chg (1)	1.00
Gln[2] (1)	1.01 (as Glu)
Hyp (1)	0.99
Leu (1)	1.00

Peptide Content: 0.682 μmol/mg

Note: [1]20 hr., 100°C, 6N HCl

[2]Gln converted to Glu

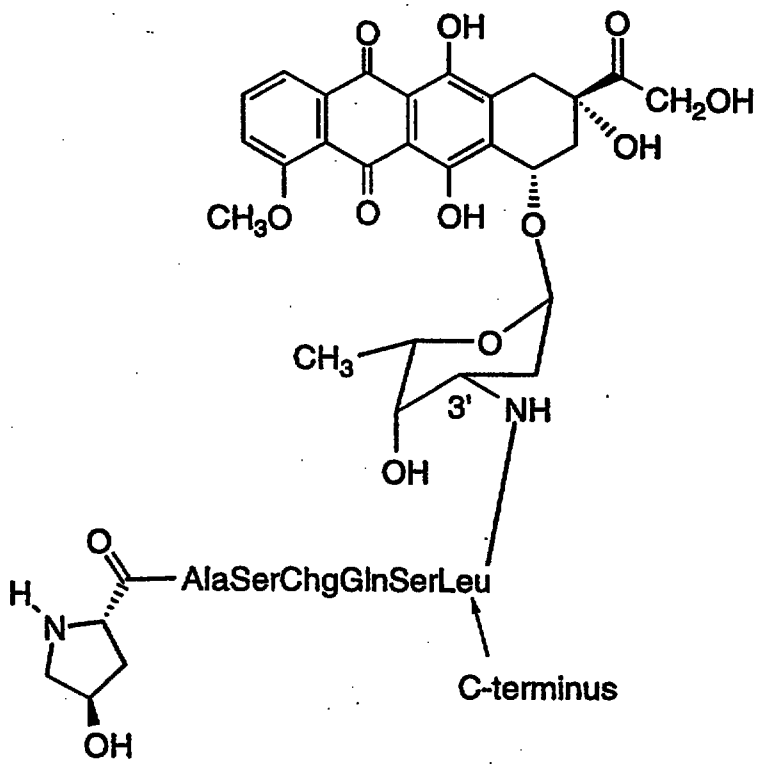
Table 4 shows other peptide-doxorubicin conjugates that were prepared by the procedures described in Example 4, but utilizing the appropriate amino acid residues and blocking group acylation.

TABLE 4

	SEQ. ID. NO.
Succinyl-(4-trans-L-Hyp)ASChgQ-SV-DOX (3')	75
Glutaryl-(4-trans-L-Hyp)ASChgQ-SV-DOX (3')	76
Glutaryl-(4-trans-L-Hyp)ASChgQ-SI-DOX (3')	77
Succinyl-(4-trans-L-Hyp)SSChgQ-SI-DOX (3')	78
Succinyl-(4-trans-L-Hyp)ASChgQ-SI-DOX (3')	79
Succinyl-(4-trans-L-Hyp)ASChgQ-SAbu-DOX (3')	80
Glutaryl-(4-trans-L-Hyp)SSChgQ-SI-DOX (3')	81
Glutaryl-(4-trans-L-Hyp)SSChgQ-SL-DOX (3')	82
PEG(2)-(4-trans-L-Hyp)SSChgQ-SL-DOX (3')	83
Succinyl-(4-trans-L-Hyp)ASChgQ-SThi-DOX (3')	84
PEG(4)-(4-trans-L-Hyp)-SSChgQ-SL-DOX (3')	85
PEG(2)-(4-trans-L-Hyp)ASChgQ-SThi-DOX(3')	86
Succinyl-3,4-(diOH)PASChgQ-SL-DOX (3')	87
Malonyl-(4-trans-L-Hyp)ASChgQ-SL-DOX (3')	88

EXAMPLE 5

Preparation of (4-trans-L-Hyp)-Ala-Ser-Chg-Gln-Ser-Leu-Dox_ (SEQ.ID.NO.: 70)



Step A: Fmoc-(4-trans-L-Hyp(Bzl))-Ala-Ser(Bzl)Chg-Gln-Ser(Bzl)Leu-PAM Resin

Starting with 0.5 mmol (0.67g) Boc-Leu-PAM resin, the protected peptide was synthesized on a 430A ABI peptide synthesizer. The protocol used a 4 fold excess (2 mmol) of each of the following protected amino acids: Boc-Ser(Bzl), Boc-Gln, Boc-Chg, Boc-Ala, N-Boc-(4-trans-L-Hyp(Bzl)). Coupling was achieved using DCC and HOBT activation in methyl-2-pyrrolidinone. Fmoc-OSu (succinamidyl ester of Fmoc) was used for the introduction of the N-terminal protecting group. Removal of the Boc group was performed using

50% TFA in methylene chloride and the TFA salt neutralized with diisopropylethylamine. At the completion of the synthesis the peptide resin was dried to yield the title intermediate.

Step B: Fmoc-(4-trans-L-Hyp)-Ala-Ser-Chg-Gln-Ser-Leu-OH

The protected peptide resin from Step A, 1.1 g, was treated with HF (20 ml) for 1 hr at 0°C in the presence of anisole (2 ml). After evaporation of the HF, the residue was washed with ether, filtered and extracted with H_2O (200 ml). The filtrate was lyophilyzed to yield the title intermediate.

Step C: Fmoc-(4-trans-L-Hyp)-Ala-Ser-Chg-Gln-Ser-Leu-Dox

The intermediate from Step B, 0.274 g, was dissolved in DMSO (10 ml) and diluted with DMF (10 ml). To the solution was added doxorubicin hydrochloride, 104 mg followed by 62 µL of diisopropylethylamine. The stirred solution was cooled (0°C) and 56 µL of diphenylphosphoryl azide added. After 30 minutes, an additional 56 µL of DPPA was added and the pH adjusted to ~7.5 (pH paper) with diisopropylethylamine (DIEA). The pH of the cooled reaction (0°C) was maintained at ~7.5 with DIEA. After 4 hrs., the reaction (found to be complete by analytical HPLC, system A) was concentrated to an oil. HPLC conditions, system A

Step D: (4-trans-L-Hyp)-Ala-Ser-Chg-Gln-Ser-Leu-Dox

The above product from Step C was dissolved in DMF (10 ml), cooled (0°C) and 4 ml of piperidine added. The solution was concentrated to dryness and purified by preparative HPLC. (A=0.1% NH_4OAc-H_2O; B=CH_3CN.) The crude product was dissolved in 100 ml of 90% A buffer, filtered and purified on a C-18 reverse phase HPLC radial compression column (Waters, Delta-Pak, 15µ, 100Å). A step gradient of 90% A to 65% A was used at a flow rate of 75 ml/min (uv = 214nm). Homogeneous product fractions (evaluated by HPLC, system A) were pooled and freeze-dried.

HPLC conditions, system A

Column: Vydac 15 cm #218TP5415, C18
Eluant: Gradient 95:5 (A:B) to 5:95 (A:B) over 45 min.
A=0.1% TFA/H_2O, B=0.1% TFA/Acetonitrile
Flow: 1.5 ml/min.
Wavelength: 214 nm, 254 nm
Retention times: Doxorubicin = 13.66 min.
Fmoc - (4-trans-L-Hyp)-Ala-Ser-Chg-Gln-Ser-Leu-OH = 18.6 min.
Fmoc - (4-trans-L-Hyp)-Ala-Ser-Chg-Gln-Ser-Leu-Dox = 23.8 min.
(4-trans-L-Hyp)-Ala-Ser-Chg-Gln-Ser-Leu-Dox = 17.6 min.

Molecular Formula: $C_{60}H_{83}N_9O_{22}$
Molecular Weight: 1281.56
High Resolution ES Mass Spec: 1282.59 (MH^+)
HPLC: System A
Column: Vydac 15 cm #218TP5415, C18
Eluant: Gradient 95:5 (A:B) to 5:95 (A:B) over 45 min.
A=0.1% TFA/H_2O, B=0.1% TFA/Acetonitrile
Flow: 1.5 ml/min.
Wavelength: 214 nm, 254 nm
Retention Time: 17.6 min.

Amino Acid Compositional Analysis[1]:

Theory	Found
Ala (1)	1.00
Ser (2)	1.94
Chg (1)	0.94
Gln[2] (1)	1.05 (as Glu)
Hyp (1)	0.96
Leu (1)	1.03

Peptide Content: 0.690 µmol/mg
Note: [1]20 hr., 100°C, 6N HCl
[2]Gln converted to Glu

EXAMPLE 6

Assessment of the Recognition of Oligopeptide-Doxorubicin Conjugates by Free PSA :

The conjugates prepared as described in Examples 3-5 were individually dissolved in PSA digestion buffer (12 mM tris(hydroxymethyl)-aminomethane pH8.0, 25 mM NaCl, 0.5 mM $CaCl_2$) and the solution added to PSA at a molar ration of 100 to 1. Alternatively, the PSA digestion buffer utilized is 50 mM tris(hydroxymethyl)-aminomethane pH7.4, 140 mM NaCl. The reaction is quenched after various reaction times by the addition of trifluoroacetic acid (TFA) to a final 1% (volume/volume). Alternatively the reaction is quenched with 10mM ZnCl2. The quenched reaction was analyzed by HPLC on a reversed-phase C18 column using an aqueous 0.1%TFA/acetonitrile gradient. The results of the assessment are shown in Table 3. Table 3 shows the amount of time (in minutes) required for 50% cleavage of the noted oligopeptide-cytotoxic agent conjugates with enzymatically active free PSA. If no salt is indicated for the conjugate, the free conjugate was tested. The oligopeptide-cytotoxic agent conjugates described in Examples 4 and 5 were assessed for the amount of time (in minutes) required for 50% cleavage of the oligopeptide with enzymatically active free PSA and 50% cleavage occurred in less than 2 hours for those conjugates.

EXAMPLE 7

In vitro Assay of Cytotoxicity of Peptidyl Derivatives of Doxorubicin:

The cytotoxicities of the cleaveable oligopeptide-doxorubicin conjugates, prepared as described in Examples 3 and 4, against a line of cells which is known to be killed by unmodified doxorubicin were assessed with an Alamar Blue assay. Specifically, cell cultures of LNCap prostate tumor cells (which express enzymatically active PSA) or DuPRO cells in 96 well plates was diluted with medium

(Dulbecco's Minimum Essential Medium-α [MEM-α]) containing various concentrations of a given conjugate (final plate well volume of 200µl). The cells were incubated for 3 days at 37°C, 20µl of Alamar Blue is added to the assay well. The cells were further incubated and the assay plates were read on a EL-310 ELISA reader at the dual wavelengths of 570 and 600 nm at 4 and 7 hours after addition of Alamar Blue. Relative percentage viability at the various concentration of conjugate tested was then calculated versus control (no conjugate) cultures. Some results of this assessment are shown in Table 5. If no salt is indicated, the free conjugate was tested.

TABLE 5

SEQ. ID.NO.	PEPTIDE / PEPTIDE-DOX CONJUGATE	LNCaP Cell Kill in 72 HRS EC 50 (µM)
74	Ac-(4-trans-L-Hyp)ASChgQ-StBuAla-DOX (3')	100 (DuPRO > 100) n =2
68	Ac-(4-trans-L-Hyp)ASChgQ-SL-DOX (3')	4.5 (DuPRO = 90)

EXAMPLE 8

In vivo Efficacy of Peptidyl -Cytotoxic Agent Conjugates

LNCaP.FGC or DuPRO-1 cells are trypsinized, resuspended in the growth medium and centifuged for 6 mins. at 200xg. The cells are resuspended in serum-free MEM-α and counted. The appropriate volume of this solution containing the desired number of cells is then transferred to a conical centrifuge tube, centrifuged as before and resuspended in the appropriate volume of a cold 1:1 mixture of MEM-α Matrigel (Collaborative Biomedical Products, New Bedford, Mass.). The suspension is kept on ice until the animals are inoculated.

Harlan Sprague Dawley male nude mice (10-12 weeks old) are restrained without anesthesia and are inoculated with 0.5 mL of cell suspension on the left flank by subcutaneous injection using a 22G

needle. Mice are either given approximately 5x105 DuPRO cells or 1.5x107 LNCaP.FGC cells.

Following inoculation with the tumor cells the mice are treated under one of two protocols:

Protocol A:

One day after cell inoculation the animals are dosed by interperitoneal administration with a 0.1-0.5 mL volume of test conjugate, doxorubicin or vehicle control (sterile water). Dosages of the conjugate and doxorubicin are initially the maximum non-lethal amount, but may be subsequently titrated lower. Identical doses are administered at 24 hour intervals for 5 days. After 10 days, blood samples are removed from the mice and the serum level of PSA is determined. Similar serum PSA levels are determined at 5-10 day intervals. At the end of 5.5 weeks the mice are sacrificed and weights of any tumors present are measured and serum PSA again determined.The animals' weights are determined at the beginning and end of the assay.

Protocol B:

Ten days after cell inoculation,blood samples are removed from the animals and serum levels of PSA are determined. Animals are then grouped according to their PSA serum levels. At 14-15 days after cell inoculation, the animals are dosed by interperitoneal administration with a 0.1-0.5 mL volume of test conjugate, doxorubicin or vehicle control (sterile water). Dosages of the conjugate and doxorubicin are initially the maximum non-lethal amount, but may be subsequently titrated lower. Identical doses are administered at 24 hour intervals for 5 days. Serum PSA levels are determined at 5-10 day intervals. At the end of 5.5 weeks the mice are sacrificed, weights of any tumors present are measured and serum PSA again determined. The animals' weights are determined at the beginning and end of the assay.

Protocol C:

One day after cell inoculation,the animals are dosed by interperitoneal administration with a 0.1-0.5 mL volume of test conjugate, doxorubicin or vehicle control (sterile water). Dosages of the conjugate and doxorubicin are initially the maximum non-lethal amount, but may be subsequently titrated lower. Identical doses are administered at 7 day intervals for 5 consecutive weeks. Serum PSA levels are determined immediately prior to or at the time of sacrificing the mice. At the end of 5.5 weeks the mice are sacrificed and weights of any tumors present are measured. The animals' weights are determined at the beginning and end of the assay.

EXAMPLE 9

In vitro determination of proteolytic cleavage of conjugates by endogenous non-PSA proteases

Step A: Preparation of proteolytic tissue extracts

All procedures are carried out at 4°C. Appropriate animals are sacrificed and the relevant tissues are isolated and stored in liquid nitrogen. The frozen tissue is pulverized using a mortar and pestle and the pulverized tissue is transfered to a Potter-Elvejeh homogenizer and 2 volumes of Buffer A (50 mM Tris containing 1.15% KCl, pH 7.5) are added. The tissue is then disrupted with 20 strokes using first a lose fitting and then a tight fitting pestle. The homogenate is centrifuged at 10,000 x g in a swinging bucket rotor (HB4-5), the pellet is discarded and the supernatant centrifuged at 100,000 x g (Ti 70). The supernatant (cytosol) is saved.

The pellet is resuspended in Buffer B (10 mM EDTA containing 1.15% KCl, pH 7.5) using the same volume as used above with Buffer A. The suspension is homogenized in a dounce homogenizer and the solution centrifuged at 100,000x g. The supernatant is discarded and the pellet (membrane)resuspended in Buffer C (10 mM potassium phosphate buffer containing 0.25 M

sucrose, pH 7.4), using 1/2 the volume used above, and homogenized with a dounce homogenizer.

Protein content of the two solutions (cytosol and membrane) is determine using the Bradford assay. Assay aliquots are then removed and frozen in liquid N_2. The aliquots are stored at -70°C.

Step B: Proteolytic cleavage assay

For each time point, 20 microgram of peptide-doxorubicin conjugate and 150 micrograms of tissue protein, prepared as described in Step A and as determined by Bradford in reaction buffer are placed in solution of final volume of 200 microliters in buffer (50 mM TRIS, 140 mM NaCl, pH 7.2). Assay reactions are run for 0, 30, 60, 120, and 180 minutes and are then quenched immediately in boiling water for 90 seconds. Reaction products are analyzed by HPLC using a VYDAC C18 15 cm column in water / acetonitrile (5% to 50% acetonitrile over 30 minutes).

SEQUENCE LISTING

(1) GENERAL INFORMATION

(i) APPLICANT: Garsky, Victor M.
Feng, Dong-Mei
DeFeo-Jones, Deborah

(ii) TITLE OF THE INVENTION: CONJUGATES USEFUL IN THE TREATMENT
OF PROSTATE CANCER

(iii) NUMBER OF SEQUENCES: 97

(iv) CORRESPONDENCE ADDRESS:
(A) ADDRESSEE: Merck & Co., Inc.
(B) STREET: P.O. Box 2000, 126 E. Lincoln Ave.
(C) CITY: Rahway
(D) STATE: NJ
(E) COUNTRY: USA
(F) ZIP: 07065-0900

(v) COMPUTER READABLE FORM:
(A) MEDIUM TYPE: Diskette
(B) COMPUTER: IBM Compatible
(C) OPERATING SYSTEM: DOS
(D) SOFTWARE: FastSEQ for Windows Version 2.0

(vi) CURRENT APPLICATION DATA:
(A) APPLICATION NUMBER:
(B) FILING DATE:
(C) CLASSIFICATION:

(vii) PRIOR APPLICATION DATA:
(A) APPLICATION NUMBER: 60/029,224
(B) FILING DATE: 30-OCT-1996

(A) APPLICATION NUMBER: 60/042,921
(B) FILING DATE: 04-APR-1997

(viii) ATTORNEY/AGENT INFORMATION:
(A) NAME: Muthard, David A
(B) REGISTRATION NUMBER: 35,297
(C) REFERENCE/DOCKET NUMBER: 19821Y

(ix) TELECOMMUNICATION INFORMATION:
(A) TELEPHONE: 908-594-3903
(B) TELEFAX: 908-594-4720
(C) TELEX:

(2) INFORMATION FOR SEQ ID NO:1:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 7 amino acids
(B) TYPE: amino acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: peptide
(ix) FEATURE:

(A) NAME/KEY: Other
(B) LOCATION: 1...1
(D) OTHER INFORMATION: cyclic amino acid substituted with a hydrophilic moiety

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:1:

Xaa Xaa Ser Tyr Gln Ser Ser
1 5

(2) INFORMATION FOR SEQ ID NO:2:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 5 amino acids
(B) TYPE: amino acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: peptide
(ix) FEATURE:

(A) NAME/KEY: Other
(B) LOCATION: 1...1
(D) OTHER INFORMATION: cyclic amino acid substituted with a hydrophilic moiety

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:2:

Xaa Tyr Gln Ser Ser
1 5

(2) INFORMATION FOR SEQ ID NO:3:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 7 amino acids
(B) TYPE: amino acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: peptide
(ix) FEATURE:

(A) NAME/KEY: Other
(B) LOCATION: 1...1
(D) OTHER INFORMATION: cyclic amino acid substituted with a hydrophilic moiety

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:3:

Xaa Xaa Lys Tyr Gln Ser Ser
1 5

(2) INFORMATION FOR SEQ ID NO:4:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 7 amino acids
(B) TYPE: amino acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: peptide
(ix) FEATURE:

(A) NAME/KEY: Other
(B) LOCATION: 1...1
(D) OTHER INFORMATION: cyclic amino acid substituted with a hydrophilic moiety

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:4:

Xaa Xaa Lys Tyr Gln Ser Ser
1 5

(2) INFORMATION FOR SEQ ID NO:5:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 7 amino acids
(B) TYPE: amino acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: peptide
(ix) FEATURE:

(A) NAME/KEY: Other
(B) LOCATION: 1...1
(D) OTHER INFORMATION: cyclic amino acid substituted with a hydrophilic moiety

(A) NAME/KEY: Other
(B) LOCATION: 3...3
(D) OTHER INFORMATION: homoarginine

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:5:

Xaa Xaa Xaa Tyr Gln Ser Ser
1 5

(2) INFORMATION FOR SEQ ID NO:6:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 7 amino acids
(B) TYPE: amino acid

(C) STRANDEDNESS: single
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: peptide
(ix) FEATURE:

(A) NAME/KEY: Other
(B) LOCATION: 1...1
(D) OTHER INFORMATION: cyclic amino acid substituted with a hydrophilic moiety

(A) NAME/KEY: Other
(B) LOCATION: 3...3
(D) OTHER INFORMATION: homoarginine

(A) NAME/KEY: Other
(B) LOCATION: 4...4
(D) OTHER INFORMATION: cyclohexylalanine

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:6:

Xaa Xaa Xaa Xaa Gln Ser Ser
1 5

(2) INFORMATION FOR SEQ ID NO:7:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 7 amino acids
(B) TYPE: amino acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: peptide
(ix) FEATURE:

(A) NAME/KEY: Other
(B) LOCATION: 1...1
(D) OTHER INFORMATION: cyclic amino acid substituted with a hydrophilic moiety

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:7:

Xaa Xaa Ser Tyr Gln Ser Xaa
1 5

(2) INFORMATION FOR SEQ ID NO:8:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 5 amino acids
(B) TYPE: amino acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: peptide
(ix) FEATURE:

(A) NAME/KEY: Other
(B) LOCATION: 1...1
(D) OTHER INFORMATION: cyclic amino acid substituted with a hydrophilic moiety

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:8:

Xaa Tyr Gln Ser Xaa
1 5

(2) INFORMATION FOR SEQ ID NO:9:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 7 amino acids
(B) TYPE: amino acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: peptide
(ix) FEATURE:

(A) NAME/KEY: Other
(B) LOCATION: 1...1
(D) OTHER INFORMATION: cyclic amino acid substituted with a hydrophilic moiety

(A) NAME/KEY: Other
(B) LOCATION: 4...4
(D) OTHER INFORMATION: cyclohexylglycine

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:9:

Xaa Xaa Ser Xaa Gln Ser Xaa
1 5

(2) INFORMATION FOR SEQ ID NO:10:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 5 amino acids
(B) TYPE: amino acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: peptide
(ix) FEATURE:

(A) NAME/KEY: Other
(B) LOCATION: 1...1
(D) OTHER INFORMATION: cyclic amino acid substituted with a hydrophilic moiety

(A) NAME/KEY: Other
(B) LOCATION: 2...2
(D) OTHER INFORMATION: cyclohexylglycine

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:10:

Xaa Xaa Gln Ser Xaa
1 5

(2) INFORMATION FOR SEQ ID NO:11:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 7 amino acids
(B) TYPE: amino acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: peptide
(ix) FEATURE:

(A) NAME/KEY: Other
(B) LOCATION: 1...1
(D) OTHER INFORMATION: cyclic amino acid substituted with a hydrophilic moiety

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:11:

Xaa Tyr Gln Ser Ser Ser Leu
1 5

(2) INFORMATION FOR SEQ ID NO:12:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 7 amino acids
(B) TYPE: amino acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: peptide
(ix) FEATURE:

(A) NAME/KEY: Other
(B) LOCATION: 1...1
(D) OTHER INFORMATION: cyclic amino acid substituted with a hydrophilic moiety

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:12:

Xaa Xaa Ser Tyr Gln Ser Ala
1 5

(2) INFORMATION FOR SEQ ID NO:13:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 7 amino acids
(B) TYPE: amino acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: peptide
(ix) FEATURE:

(A) NAME/KEY: Other
(B) LOCATION: 2...2
(D) OTHER INFORMATION: cyclic amino acid substituted with a hydrophilic moiety

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:13:

Ala Xaa Xaa Ser Tyr Tyr Ser
1 5

(2) INFORMATION FOR SEQ ID NO:14:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 8 amino acids
(B) TYPE: amino acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: peptide
(ix) FEATURE:

(A) NAME/KEY: Other
(B) LOCATION: 3...3
(D) OTHER INFORMATION: cyclic amino acid substituted with a hydrophilic moiety

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:14:

Ala Asn Xaa Xaa Ser Tyr Gln Ser
1 5

(2) INFORMATION FOR SEQ ID NO:15:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 8 amino acids
(B) TYPE: amino acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: peptide
(ix) FEATURE:

(A) NAME/KEY: Other
(B) LOCATION: 1...1
(D) OTHER INFORMATION: cyclic amino acid substituted with a hydrophilic moiety

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:15:

Xaa Xaa Ser Tyr Gln Ser Ser Thr
1 5

(2) INFORMATION FOR SEQ ID NO:16:

(i) SEQUENCE CHARACTERISTICS:

(A) LENGTH: 6 amino acids
(B) TYPE: amino acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: peptide
(ix) FEATURE:

(A) NAME/KEY: Other
(B) LOCATION: 1...1
(D) OTHER INFORMATION: cyclic amino acid substituted with a hydrophilic moiety

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:16:

Xaa Tyr Gln Ser Ser Thr
1 5

(2) INFORMATION FOR SEQ ID NO:17:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 8 amino acids
(B) TYPE: amino acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: peptide
(ix) FEATURE:

(A) NAME/KEY: Other
(B) LOCATION: 1...1
(D) OTHER INFORMATION: cyclic amino acid substituted with a hydrophilic moiety

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:17:

Xaa Xaa Ser Tyr Gln Ser Ser Ser
1 5

(2) INFORMATION FOR SEQ ID NO:18:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 6 amino acids
(B) TYPE: amino acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: peptide
(ix) FEATURE:

(A) NAME/KEY: Other
(B) LOCATION: 1...1
(D) OTHER INFORMATION: cyclic amino acid substituted with a hydrophilic moiety

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:18:

Xaa Tyr Gln Ser Ser Ser
1 5

(2) INFORMATION FOR SEQ ID NO:19:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 8 amino acids
(B) TYPE: amino acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: peptide
(ix) FEATURE:

(A) NAME/KEY: Other
(B) LOCATION: 1...1
(D) OTHER INFORMATION: cyclic amino acid substituted with a hydrophilic moiety

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:19:

Xaa Xaa Lys Tyr Gln Ser Ser Ser
1 5

(2) INFORMATION FOR SEQ ID NO:20:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 8 amino acids
(B) TYPE: amino acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: peptide
(ix) FEATURE:

(A) NAME/KEY: Other
(B) LOCATION: 1...1
(D) OTHER INFORMATION: cyclic amino acid substituted with a hydrophilic moiety

(A) NAME/KEY: Other
(B) LOCATION: 3...3
(D) OTHER INFORMATION: homoarginine

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:20:

Xaa Xaa Xaa Tyr Gln Ser Ser Ser
1 5

(2) INFORMATION FOR SEQ ID NO:21:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 8 amino acids
(B) TYPE: amino acid
(C) STRANDEDNESS: single

(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: peptide
(ix) FEATURE:

(A) NAME/KEY: Other
(B) LOCATION: 1...1
(D) OTHER INFORMATION: cyclic amino acid substituted with a hydrophilic moiety

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:21:

Xaa Xaa Ser Tyr Gln Ser Ser Leu
1 5

(2) INFORMATION FOR SEQ ID NO:22:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 6 amino acids
(B) TYPE: amino acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: peptide
(ix) FEATURE:

(A) NAME/KEY: Other
(B) LOCATION: 1...1
(D) OTHER INFORMATION: cyclic amino acid substituted with a hydrophilic moiety

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:22:

Xaa Tyr Gln Ser Ser Leu
1 5

(2) INFORMATION FOR SEQ ID NO:23:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 7 amino acids
(B) TYPE: amino acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: peptide
(ix) FEATURE:

(A) NAME/KEY: Other
(B) LOCATION: 1...1
(D) OTHER INFORMATION: cyclic amino acid substituted with a hydrophilic moiety

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:23:

Xaa Xaa Ser Tyr Gln Ser Leu
1 5

(2) INFORMATION FOR SEQ ID NO:24:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 5 amino acids
(B) TYPE: amino acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: peptide
(ix) FEATURE:

(A) NAME/KEY: Other
(B) LOCATION: 1...1
(D) OTHER INFORMATION: cyclic amino acid substituted with a hydrophilic moiety

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:24:

Xaa Tyr Gln Ser Leu
1 5

(2) INFORMATION FOR SEQ ID NO:25:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 7 amino acids
(B) TYPE: amino acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: peptide
(ix) FEATURE:

(A) NAME/KEY: Other
(B) LOCATION: 1...1
(D) OTHER INFORMATION: cyclic amino acid substituted with a hydrophilic moiety

(A) NAME/KEY: Other
(B) LOCATION: 7...7
(D) OTHER INFORMATION: norleucine

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:25:

Xaa Xaa Ser Tyr Gln Ser Leu
1 5

(2) INFORMATION FOR SEQ ID NO:26:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 5 amino acids
(B) TYPE: amino acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: peptide

(ix) FEATURE:

(A) NAME/KEY: Other
(B) LOCATION: 1...1
(D) OTHER INFORMATION: cyclic amino acid substituted with a hydrophilic moiety

(A) NAME/KEY: Other
(B) LOCATION: 5...5
(D) OTHER INFORMATION: norleucine

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:26:

Xaa Tyr Gln Ser Leu
1 5

(2) INFORMATION FOR SEQ ID NO:27:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 7 amino acids
(B) TYPE: amino acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: peptide
(ix) FEATURE:

(A) NAME/KEY: Other
(B) LOCATION: 1...1
(D) OTHER INFORMATION: cyclic amino acid substituted with a hydrophilic moiety

(A) NAME/KEY: Other
(B) LOCATION: 7...7
(D) OTHER INFORMATION: 1,2,3,4-tetrahydroisoquinoline 3-carboxylic acid

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:27:

Xaa Xaa Ser Tyr Gln Ser Xaa
1 5

(2) INFORMATION FOR SEQ ID NO:28:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 5 amino acids
(B) TYPE: amino acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: peptide
(ix) FEATURE:

(A) NAME/KEY: Other
(B) LOCATION: 1...1

(D) OTHER INFORMATION: cyclic amino acid substituted with a hydrophilic moiety

(A) NAME/KEY: Other
(B) LOCATION: 5...5
(D) OTHER INFORMATION: 1,2,3,4-tetrahydroisoquinoline 3-carboxylic acid

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:28:

Xaa Tyr Gln Ser Xaa
1 5

(2) INFORMATION FOR SEQ ID NO:29:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 7 amino acids
(B) TYPE: amino acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: peptide
(ix) FEATURE:

(A) NAME/KEY: Other
(B) LOCATION: 1...1
(D) OTHER INFORMATION: cyclic amino acid substituted with a hydrophilic moiety

(A) NAME/KEY: Other
(B) LOCATION: 4...4
(D) OTHER INFORMATION: cyclohexylglycine

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:29:

Xaa Xaa Ser Xaa Gln Ser Leu
1 5

(2) INFORMATION FOR SEQ ID NO:30:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 5 amino acids
(B) TYPE: amino acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: peptide
(ix) FEATURE:

(A) NAME/KEY: Other
(B) LOCATION: 1...1
(D) OTHER INFORMATION: cyclic amino acid substituted with a hydrophilic moiety

(A) NAME/KEY: Other
(B) LOCATION: 2...2

(D) OTHER INFORMATION: cyclohexylglycine

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:30:

Xaa Xaa Gln Ser Leu
1 5

(2) INFORMATION FOR SEQ ID NO:31:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 7 amino acids
(B) TYPE: amino acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: peptide
(ix) FEATURE:

(A) NAME/KEY: Other
(B) LOCATION: 1...1
(D) OTHER INFORMATION: cyclic amino acid substituted with a hydrophilic moiety

(A) NAME/KEY: Other
(B) LOCATION: 4...4
(D) OTHER INFORMATION: cyclohexylglycine

(A) NAME/KEY: None
(B) LOCATION: 7...7
(D) OTHER INFORMATION: norleucine

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:31:

Xaa Xaa Ser Xaa Gln Ser Leu
1 5

(2) INFORMATION FOR SEQ ID NO:32:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 5 amino acids
(B) TYPE: amino acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: peptide
(ix) FEATURE:

(A) NAME/KEY: Other
(B) LOCATION: 1...1
(D) OTHER INFORMATION: cyclic amino acid substituted with a hydrophilic moiety

(A) NAME/KEY: Other
(B) LOCATION: 2...2
(D) OTHER INFORMATION: cyclohexylglycine

(A) NAME/KEY: Other
(B) LOCATION: 5...5
(D) OTHER INFORMATION: norleucine

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:32:

Xaa Xaa Gln Ser Leu
1 5

(2) INFORMATION FOR SEQ ID NO:33:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 7 amino acids
(B) TYPE: amino acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: peptide
(ix) FEATURE:

(A) NAME/KEY: Other
(B) LOCATION: 1...1
(D) OTHER INFORMATION: cyclic amino acid substituted with a hydrophilic moiety

(A) NAME/KEY: Other
(B) LOCATION: 4...4
(D) OTHER INFORMATION: cyclohexylglycine

(A) NAME/KEY: Other
(B) LOCATION: 7...7
(D) OTHER INFORMATION: 1,2,3,4-tetrahydroisoquinoline 3-carboxylic acid

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:33:

Xaa Xaa Ser Xaa Gln Ser Xaa
1 5

(2) INFORMATION FOR SEQ ID NO:34:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 5 amino acids
(B) TYPE: amino acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: peptide
(ix) FEATURE:

(A) NAME/KEY: Other
(B) LOCATION: 1...1
(D) OTHER INFORMATION: cyclic amino acid substituted with a hydrophilic moiety

(A) NAME/KEY: Other

(B) LOCATION: 2...2
(D) OTHER INFORMATION: cyclohexylglycine

(A) NAME/KEY: Other
(B) LOCATION: 5...5
(D) OTHER INFORMATION: 1,2,3,4-tetrahydroisoquinoline 3-carboxylic acid

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:34:

Xaa Xaa Gln Ser Xaa
1 5

(2) INFORMATION FOR SEQ ID NO:35:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 6 amino acids
(B) TYPE: amino acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: peptide
(ix) FEATURE:

(A) NAME/KEY: Other
(B) LOCATION: 1...1
(D) OTHER INFORMATION: cyclic amino acid substituted with a hydrophilic moiety

(A) NAME/KEY: Other
(B) LOCATION: 2...2
(D) OTHER INFORMATION: homoarginine

(A) NAME/KEY: Other
(B) LOCATION: 3...3
(D) OTHER INFORMATION: cyclohexylglycine

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:35:

Xaa Xaa Xaa Gln Ser Leu
1 5

(2) INFORMATION FOR SEQ ID NO:36:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 6 amino acids
(B) TYPE: amino acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: peptide
(ix) FEATURE:

(A) NAME/KEY: Other
(B) LOCATION: 1...1

(D) OTHER INFORMATION: cyclic amino acid substituted with a hydrophilic moiety

(A) NAME/KEY: Other
(B) LOCATION: 2...2
(D) OTHER INFORMATION: homoarginine

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:36:

Xaa Xaa Tyr Gln Ser Leu
1 5

(2) INFORMATION FOR SEQ ID NO:37:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 7 amino acids
(B) TYPE: amino acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: peptide
(ix) FEATURE:

(A) NAME/KEY: Other
(B) LOCATION: 1...1
(D) OTHER INFORMATION: 4-hydroxyproline

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:37:

Pro Xaa Ser Tyr Gln Ser Ser
1 5

(2) INFORMATION FOR SEQ ID NO:38:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 7 amino acids
(B) TYPE: amino acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: peptide
(ix) FEATURE:

(A) NAME/KEY: None
(B) LOCATION: 1...1
(D) OTHER INFORMATION: 4-hydroxyproline

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:38:

Pro Xaa Ser Tyr Gln Ser Ala
1 5

(2) INFORMATION FOR SEQ ID NO:39:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 7 amino acids

(B) TYPE: amino acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: peptide
(ix) FEATURE:

(A) NAME/KEY: Other
(B) LOCATION: 2...2
(D) OTHER INFORMATION: 4-hydroxyproline

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:39:

Ala Pro Xaa Ser Tyr Tyr Ser
1 5

(2) INFORMATION FOR SEQ ID NO:40:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 8 amino acids
(B) TYPE: amino acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: peptide
(ix) FEATURE:

(A) NAME/KEY: Other
(B) LOCATION: 3...3
(D) OTHER INFORMATION: 4-hydroxyproline

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:40:

Ala Asn Pro Xaa Ser Tyr Gln Ser
1 5

(2) INFORMATION FOR SEQ ID NO:41:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 8 amino acids
(B) TYPE: amino acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: peptide
(ix) FEATURE:

(A) NAME/KEY: Other
(B) LOCATION: 1...1
(D) OTHER INFORMATION: 4-hydroxyproline

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:41:

Pro Xaa Ser Tyr Gln Ser Ser Thr
1 5

(2) INFORMATION FOR SEQ ID NO:42:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 6 amino acids
(B) TYPE: amino acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: peptide
(ix) FEATURE:

(A) NAME/KEY: Other
(B) LOCATION: 1...1
(D) OTHER INFORMATION: 4-hydroxyproline

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:42:

Pro Tyr Gln Ser Ser Thr
1 5

(2) INFORMATION FOR SEQ ID NO:43:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 8 amino acids
(B) TYPE: amino acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: peptide
(ix) FEATURE:

(A) NAME/KEY: Other
(B) LOCATION: 1...1
(D) OTHER INFORMATION: 4-hydroxyproline

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:43:

Pro Xaa Ser Tyr Gln Ser Ser Ser
1 5

(2) INFORMATION FOR SEQ ID NO:44:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 6 amino acids
(B) TYPE: amino acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: peptide
(ix) FEATURE:

(A) NAME/KEY: Other
(B) LOCATION: 1...1
(D) OTHER INFORMATION: 4-hydroxyproline

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:44:

Pro Tyr Gln Ser Ser Ser
1 5

(2) INFORMATION FOR SEQ ID NO:45:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 8 amino acids
(B) TYPE: amino acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: peptide
(ix) FEATURE:

(A) NAME/KEY: Other
(B) LOCATION: 1...1
(D) OTHER INFORMATION: 4-hydroxyproline

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:45:

Pro Xaa Lys Tyr Gln Ser Ser Ser
1 5

(2) INFORMATION FOR SEQ ID NO:46:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 8 amino acids
(B) TYPE: amino acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: peptide
(ix) FEATURE:

(A) NAME/KEY: Other
(B) LOCATION: 1...1
(D) OTHER INFORMATION: 4-hydroxyproline

(A) NAME/KEY: Other
(B) LOCATION: 3...3
(D) OTHER INFORMATION: homoarginine

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:46:

Pro Xaa Xaa Tyr Gln Ser Ser Ser
1 5

(2) INFORMATION FOR SEQ ID NO:47:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 8 amino acids
(B) TYPE: amino acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: peptide
(ix) FEATURE:

(A) NAME/KEY: Other
(B) LOCATION: 1...1
(D) OTHER INFORMATION: 4-hydroxyproline

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:47:

Pro Xaa Ser Tyr Gln Ser Ser Leu
1 5

(2) INFORMATION FOR SEQ ID NO:48:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 6 amino acids
(B) TYPE: amino acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: peptide
(ix) FEATURE:

(A) NAME/KEY: Other
(B) LOCATION: 1...1
(D) OTHER INFORMATION: 4-hydroxyproline

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:48:

Pro Tyr Gln Ser Ser Leu
1 5

(2) INFORMATION FOR SEQ ID NO:49:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 7 amino acids
(B) TYPE: amino acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: peptide
(ix) FEATURE:

(A) NAME/KEY: Other
(B) LOCATION: 1...1
(D) OTHER INFORMATION: 4-hydroxyproline

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:49:

Pro Xaa Ser Tyr Gln Ser Leu
1 5

(2) INFORMATION FOR SEQ ID NO:50:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 5 amino acids

(B) TYPE: amino acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: peptide
(ix) FEATURE:

(A) NAME/KEY: Other
(B) LOCATION: 1...1
(D) OTHER INFORMATION: 4-hydroxyproline

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:50:

Pro Tyr Gln Ser Leu
1 5

(2) INFORMATION FOR SEQ ID NO:51:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 7 amino acids
(B) TYPE: amino acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: peptide
(ix) FEATURE:

(A) NAME/KEY: Other
(B) LOCATION: 1...1
(D) OTHER INFORMATION: 4-hydroxyproline

(A) NAME/KEY: Other
(B) LOCATION: 7...7
(D) OTHER INFORMATION: norleucine

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:51:

Pro Xaa Ser Tyr Gln Ser Leu
1 5

(2) INFORMATION FOR SEQ ID NO:52:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 5 amino acids
(B) TYPE: amino acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: peptide
(ix) FEATURE:

(A) NAME/KEY: Other
(B) LOCATION: 1...1
(D) OTHER INFORMATION: 4-hydroxyproline

(A) NAME/KEY: Other

(B) LOCATION: 5...5
(D) OTHER INFORMATION: norleucine

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:52:

Pro Tyr Gln Ser Leu
1 5

(2) INFORMATION FOR SEQ ID NO:53:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 7 amino acids
(B) TYPE: amino acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: peptide
(ix) FEATURE:

(A) NAME/KEY: Other
(B) LOCATION: 1...1
(D) OTHER INFORMATION: 4-hydroxyproline

(A) NAME/KEY: Other
(B) LOCATION: 7...7
(D) OTHER INFORMATION: 1,2,3,4-tetrahydroisoquinoline 3-carboxylic acid

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:53:

Pro Xaa Ser Tyr Gln Ser Xaa
1 5

(2) INFORMATION FOR SEQ ID NO:54:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 5 amino acids
(B) TYPE: amino acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: peptide
(ix) FEATURE:

(A) NAME/KEY: Other
(B) LOCATION: 1...1
(D) OTHER INFORMATION: 4-hydroxyproline

(A) NAME/KEY: Other
(B) LOCATION: 5...5
(D) OTHER INFORMATION: 1,2,3,4-tetrahydroisoquinoline 3-carboxylic acid

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:54:

Pro Tyr Gln Ser Xaa

1 5

(2) INFORMATION FOR SEQ ID NO:55:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 7 amino acids
(B) TYPE: amino acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: peptide
(ix) FEATURE:

(A) NAME/KEY: Other
(B) LOCATION: 1...1
(D) OTHER INFORMATION: 4-hydroxyproline

(A) NAME/KEY: Other
(B) LOCATION: 4...4
(D) OTHER INFORMATION: cyclohexylglycine

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:55:

Pro Xaa Ser Xaa Gln Ser Leu
1 5

(2) INFORMATION FOR SEQ ID NO:56:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 5 amino acids
(B) TYPE: amino acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: peptide
(ix) FEATURE:

(A) NAME/KEY: Other
(B) LOCATION: 1...1
(D) OTHER INFORMATION: 4-hydroxyproline

(A) NAME/KEY: Other
(B) LOCATION: 2...2
(D) OTHER INFORMATION: cyclohexylglycine

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:56:

Pro Xaa Gln Ser Leu
1 5

(2) INFORMATION FOR SEQ ID NO:57:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 7 amino acids
(B) TYPE: amino acid
(C) STRANDEDNESS: single

(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: peptide
(ix) FEATURE:

(A) NAME/KEY: Other
(B) LOCATION: 1...1
(D) OTHER INFORMATION: 4-hydroxyproline

(A) NAME/KEY: Other
(B) LOCATION: 4...4
(D) OTHER INFORMATION: cyclohexylglycine

(A) NAME/KEY: Other
(B) LOCATION: 7...7
(D) OTHER INFORMATION: norleucine

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:57:

Pro Xaa Ser Xaa Gln Ser Leu
1 5

(2) INFORMATION FOR SEQ ID NO:58:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 5 amino acids
(B) TYPE: amino acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: peptide
(ix) FEATURE:

(A) NAME/KEY: Other
(B) LOCATION: 1...1
(D) OTHER INFORMATION: 4-hydroxyproline

(A) NAME/KEY: Other
(B) LOCATION: 2...2
(D) OTHER INFORMATION: cyclohexylglycine

(A) NAME/KEY: Other
(B) LOCATION: 5...5
(D) OTHER INFORMATION: norleucine

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:58:

Pro Xaa Gln Ser Leu
1 5

(2) INFORMATION FOR SEQ ID NO:59:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 7 amino acids
(B) TYPE: amino acid
(C) STRANDEDNESS: single

(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: peptide
(ix) FEATURE:

(A) NAME/KEY: Other
(B) LOCATION: 1...1
(D) OTHER INFORMATION: 4-hydroxyproline

(A) NAME/KEY: Other
(B) LOCATION: 4...4
(D) OTHER INFORMATION: cyclohexylglycine

(A) NAME/KEY: Other
(B) LOCATION: 7...7
(D) OTHER INFORMATION: 1,2,3,4-tetrahydroisoquinoline 3-carboxylic acid

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:59:

Pro Xaa Ser Xaa Gln Ser Xaa
1 5

(2) INFORMATION FOR SEQ ID NO:60:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 5 amino acids
(B) TYPE: amino acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: peptide
(ix) FEATURE:

(A) NAME/KEY: Other
(B) LOCATION: 1...1
(D) OTHER INFORMATION: 4-hydroxyproline

(A) NAME/KEY: Other
(B) LOCATION: 2...2
(D) OTHER INFORMATION: cyclohexylglycine

(A) NAME/KEY: Other
(B) LOCATION: 5...5
(D) OTHER INFORMATION: 1,2,3,4-tetrahydroisoquinoline 3-carboxylic acid

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:60:

Pro Xaa Gln Ser Xaa
1 5

(2) INFORMATION FOR SEQ ID NO:61:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 7 amino acids

(B) TYPE: amino acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: peptide
(ix) FEATURE:

(A) NAME/KEY: Other
(B) LOCATION: 1...1
(D) OTHER INFORMATION: homoarginine

(A) NAME/KEY: Other
(B) LOCATION: 3...3
(D) OTHER INFORMATION: 4-hydroxyproline

(A) NAME/KEY: Other
(B) LOCATION: 4...4
(D) OTHER INFORMATION: cyclohexylglycine

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:61:

Xaa Ser Pro Xaa Gln Ser Leu
1 5

(2) INFORMATION FOR SEQ ID NO:62:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 7 amino acids
(B) TYPE: amino acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: peptide
(ix) FEATURE:

(A) NAME/KEY: Other
(B) LOCATION: 2...2
(D) OTHER INFORMATION: 4-hydroxyproline

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:62:

Asn Pro Ile Ser Tyr Gln Ser
1 5

(2) INFORMATION FOR SEQ ID NO:63:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 7 amino acids
(B) TYPE: amino acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: peptide
(ix) FEATURE:

(A) NAME/KEY: Other

(B) LOCATION: 2...2
(D) OTHER INFORMATION: 4-hydroxyproline

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:63:

Asn Pro Val Ser Tyr Gln Ser
1 5

(2) INFORMATION FOR SEQ ID NO:64:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 7 amino acids
(B) TYPE: amino acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: peptide
(ix) FEATURE:

(A) NAME/KEY: Other
(B) LOCATION: 1...1
(D) OTHER INFORMATION: 4-hydroxyproline

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:64:

Pro Ala Ser Tyr Gln Ser Ser
1 5

(2) INFORMATION FOR SEQ ID NO:65:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 7 amino acids
(B) TYPE: amino acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: peptide
(ix) FEATURE:

(A) NAME/KEY: Other
(B) LOCATION: 1...1
(D) OTHER INFORMATION: 3,4-dihydroxyproline

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:65:

Xaa Ala Ser Tyr Gln Ser Ser
1 5

(2) INFORMATION FOR SEQ ID NO:66:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 5 amino acids
(B) TYPE: amino acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: peptide
(ix) FEATURE:

(A) NAME/KEY: Other
(B) LOCATION: 1...1
(D) OTHER INFORMATION: 3-hydroxyproline

(A) NAME/KEY: Other
(B) LOCATION: 3...3
(D) OTHER INFORMATION: cyclohexylglycine

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:66:

Xaa Ser Xaa Gln Ser
1 5

(2) INFORMATION FOR SEQ ID NO:67:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 7 amino acids
(B) TYPE: amino acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: peptide
(ix) FEATURE:

(A) NAME/KEY: Other
(B) LOCATION: 1...1
(D) OTHER INFORMATION: 4-hydroxyproline

(A) NAME/KEY: Other
(B) LOCATION: 4...4
(D) OTHER INFORMATION: cyclohexylglycine

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:67:

Pro Ala Ser Xaa Gln Ser Ser
1 5

(2) INFORMATION FOR SEQ ID NO:68:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 7 amino acids
(B) TYPE: amino acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: peptide
(ix) FEATURE:

(A) NAME/KEY: Other
(B) LOCATION: 1...1
(D) OTHER INFORMATION: N-acetyl-4-hydroxyproline

(A) NAME/KEY: Other

(B) LOCATION: 4...4
(D) OTHER INFORMATION: cyclohexylglycine

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:68:

Xaa Ala Ser Xaa Gln Ser Leu
1 5

(2) INFORMATION FOR SEQ ID NO:69:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 7 amino acids
(B) TYPE: amino acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: peptide
(ix) FEATURE:

(A) NAME/KEY: Other
(B) LOCATION: 1...1
(D) OTHER INFORMATION: N-succinyl-4-hydroxyproline

(A) NAME/KEY: Other
(B) LOCATION: 4...4
(D) OTHER INFORMATION: cyclohexylglycine

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:69:

Xaa Ala Ser Xaa Gln Ser Leu
1 5

(2) INFORMATION FOR SEQ ID NO:70:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 7 amino acids
(B) TYPE: amino acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: peptide
(ix) FEATURE:

(A) NAME/KEY: Other
(B) LOCATION: 1...1
(D) OTHER INFORMATION: 4-hydroxyproline

(A) NAME/KEY: Other
(B) LOCATION: 4...4
(D) OTHER INFORMATION: cyclohexylglycine

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:70:

Pro Ala Ser Xaa Gln Ser Leu
1 5

(2) INFORMATION FOR SEQ ID NO:71:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 7 amino acids
(B) TYPE: amino acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: peptide
(ix) FEATURE:

(A) NAME/KEY: Other
(B) LOCATION: 1...1
(D) OTHER INFORMATION: N-glutaryl-4-hydroxyproline

(A) NAME/KEY: Other
(B) LOCATION: 4...4
(D) OTHER INFORMATION: cyclohexylglycine

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:71:

Xaa Ala Ser Xaa Gln Ser Leu
1 5

(2) INFORMATION FOR SEQ ID NO:72:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 7 amino acids
(B) TYPE: amino acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: peptide
(ix) FEATURE:

(A) NAME/KEY: Other
(B) LOCATION: 1...1
(D) OTHER INFORMATION: N-acetyl-3,4-dihydroxyproline

(A) NAME/KEY: Other
(B) LOCATION: 4...4
(D) OTHER INFORMATION: cyclohexylglycine

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:72:

Xaa Ala Ser Xaa Gln Ser Leu
1 5

(2) INFORMATION FOR SEQ ID NO:73:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 7 amino acids
(B) TYPE: amino acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: peptide
(ix) FEATURE:

(A) NAME/KEY: Other
(B) LOCATION: 1...1
(D) OTHER INFORMATION: N-(PEG-2)-4-hydroxyproline

(A) NAME/KEY: Other
(B) LOCATION: 4...4
(D) OTHER INFORMATION: cyclohexylglycine

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:73:

Xaa Ala Ser Xaa Gln Ser Leu
1 5

(2) INFORMATION FOR SEQ ID NO:74:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 7 amino acids
(B) TYPE: amino acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: peptide
(ix) FEATURE:

(A) NAME/KEY: Other
(B) LOCATION: 1...1
(D) OTHER INFORMATION: N-acetyl-4-hydroxyproline

(A) NAME/KEY: Other
(B) LOCATION: 4...4
(D) OTHER INFORMATION: cyclohexylglycine

(A) NAME/KEY: Other
(B) LOCATION: 7...7
(D) OTHER INFORMATION: 2-amino-4,4-dimethylpropanoic acid

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:74:

Xaa Ala Ser Xaa Gln Ser Xaa
1 5

(2) INFORMATION FOR SEQ ID NO:75:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 7 amino acids
(B) TYPE: amino acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: peptide
(ix) FEATURE:

(A) NAME/KEY: Other

(B) LOCATION: 1...1
(D) OTHER INFORMATION: N-succinyl-4-hydroxyproline

(A) NAME/KEY: Other
(B) LOCATION: 4...4
(D) OTHER INFORMATION: cyclohexylglycine

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:75:

Xaa Ala Ser Xaa Gln Ser Val
1 5

(2) INFORMATION FOR SEQ ID NO:76:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 7 amino acids
(B) TYPE: amino acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: peptide
(ix) FEATURE:

(A) NAME/KEY: Other
(B) LOCATION: 1...1
(D) OTHER INFORMATION: N-glutaryl-4-hydroxyproline

(A) NAME/KEY: Other
(B) LOCATION: 4...4
(D) OTHER INFORMATION: cyclohexylglycine

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:76:

Xaa Ala Ser Xaa Gln Ser Val
1 5

(2) INFORMATION FOR SEQ ID NO:77:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 7 amino acids
(B) TYPE: amino acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: peptide
(ix) FEATURE:

(A) NAME/KEY: Other
(B) LOCATION: 1...1
(D) OTHER INFORMATION: N-glutaryl-4-hydroxyproline

(A) NAME/KEY: Other
(B) LOCATION: 4...4
(D) OTHER INFORMATION: cyclohexylglycine

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:77:

Xaa Ala Ser Xaa Gln Ser Ile
1 5

(2) INFORMATION FOR SEQ ID NO:78:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 7 amino acids
(B) TYPE: amino acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: peptide
(ix) FEATURE:

(A) NAME/KEY: Other
(B) LOCATION: 1...1
(D) OTHER INFORMATION: N-succinyl-4-hydroxyproline

(A) NAME/KEY: Other
(B) LOCATION: 4...4
(D) OTHER INFORMATION: cyclohexylglycine

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:78:

Xaa Ser Ser Xaa Gln Ser Ile
1 5

(2) INFORMATION FOR SEQ ID NO:79:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 7 amino acids
(B) TYPE: amino acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: peptide
(ix) FEATURE:

(A) NAME/KEY: Other
(B) LOCATION: 1...1
(D) OTHER INFORMATION: N-succinyl-4-hydroxyproline

(A) NAME/KEY: Other
(B) LOCATION: 4...4
(D) OTHER INFORMATION: cyclohexylglycine

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:79:

Xaa Ala Ser Xaa Gln Ser Ile
1 5

(2) INFORMATION FOR SEQ ID NO:80:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 7 amino acids

(B) TYPE: amino acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: peptide
(ix) FEATURE:

(A) NAME/KEY: Other
(B) LOCATION: 1...1
(D) OTHER INFORMATION: N-succinyl-4-hydroxyproline

(A) NAME/KEY: Other
(B) LOCATION: 4...4
(D) OTHER INFORMATION: cyclohexylglycine

(A) NAME/KEY: Other
(B) LOCATION: 7...7
(D) OTHER INFORMATION: 2-aminobutyric acid

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:80:

Xaa Ala Ser Xaa Gln Ser Xaa
1 5

(2) INFORMATION FOR SEQ ID NO:81:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 7 amino acids
(B) TYPE: amino acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: peptide
(ix) FEATURE:

(A) NAME/KEY: Other
(B) LOCATION: 1...1
(D) OTHER INFORMATION: N-glutaryl-4-hydroxyproline

(A) NAME/KEY: Other
(B) LOCATION: 4...4
(D) OTHER INFORMATION: cyclohexylglycine

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:81:

Xaa Ser Ser Xaa Gln Ser Ile
1 5

(2) INFORMATION FOR SEQ ID NO:82:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 7 amino acids
(B) TYPE: amino acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: peptide
(ix) FEATURE:

(A) NAME/KEY: Other
(B) LOCATION: 1...1
(D) OTHER INFORMATION: N-glutaryl-4-hydroxyproline

(A) NAME/KEY: Other
(B) LOCATION: 4...4
(D) OTHER INFORMATION: cyclohexylglycine

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:82:

Xaa Ser Ser Xaa Gln Ser Leu
1 5

(2) INFORMATION FOR SEQ ID NO:83:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 7 amino acids
(B) TYPE: amino acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: peptide
(ix) FEATURE:

(A) NAME/KEY: Other
(B) LOCATION: 1...1
(D) OTHER INFORMATION: N-(PEG-2)-4-hydroxyproline

(A) NAME/KEY: Other
(B) LOCATION: 4...4
(D) OTHER INFORMATION: cyclohexylglycine

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:83:

Xaa Ser Ser Xaa Gln Ser Leu
1 5

(2) INFORMATION FOR SEQ ID NO:84:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 7 amino acids
(B) TYPE: amino acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: peptide
(ix) FEATURE:

(A) NAME/KEY: Other
(B) LOCATION: 1...1
(D) OTHER INFORMATION: N-succinyl-4-hydroxyproline

(A) NAME/KEY: Other

(B) LOCATION: 4...4
(D) OTHER INFORMATION: cyclohexylglycine

(A) NAME/KEY: Other
(B) LOCATION: 7...7
(D) OTHER INFORMATION: thienylalanine

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:84:

Xaa Ala Ser Xaa Gln Ser Xaa
1 5

(2) INFORMATION FOR SEQ ID NO:85:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 7 amino acids
(B) TYPE: amino acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: peptide
(ix) FEATURE:

(A) NAME/KEY: Other
(B) LOCATION: 1...1
(D) OTHER INFORMATION: N-(PEG-4)-4-hydroxyproline

(A) NAME/KEY: Other
(B) LOCATION: 4...4
(D) OTHER INFORMATION: cyclohexylglycine

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:85:

Xaa Ser Ser Xaa Gln Ser Leu
1 5

(2) INFORMATION FOR SEQ ID NO:86:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 7 amino acids
(B) TYPE: amino acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: peptide
(ix) FEATURE:

(A) NAME/KEY: Other
(B) LOCATION: 1...1
(D) OTHER INFORMATION: N-(PEG-4)-4-hydroxyproline

(A) NAME/KEY: Other
(B) LOCATION: 4...4
(D) OTHER INFORMATION: cyclohexylglycine

(A) NAME/KEY: Other

(B) LOCATION: 7...7
(D) OTHER INFORMATION: thienylalanine

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:86:

Xaa Ala Ser Xaa Gln Ser Xaa
1 5

(2) INFORMATION FOR SEQ ID NO:87:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 7 amino acids
(B) TYPE: amino acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: peptide
(ix) FEATURE:

(A) NAME/KEY: Other
(B) LOCATION: 1...1
(D) OTHER INFORMATION: N-succinyl-3,4-dihydroxyproline

(A) NAME/KEY: Other
(B) LOCATION: 4...4
(D) OTHER INFORMATION: cyclohexylglycine

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:87:

Xaa Ala Ser Xaa Gln Ser Leu
1 5

(2) INFORMATION FOR SEQ ID NO:88:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 7 amino acids
(B) TYPE: amino acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: peptide
(ix) FEATURE:

(A) NAME/KEY: Other
(B) LOCATION: 1...1
(D) OTHER INFORMATION: N-malonyl-4-hydroxyproline

(A) NAME/KEY: Other
(B) LOCATION: 4...4
(D) OTHER INFORMATION: cyclohexylglycine

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:88:

Xaa Ala Ser Xaa Gln Ser Leu
1 5

(2) INFORMATION FOR SEQ ID NO:89:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 7 amino acids
(B) TYPE: amino acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: peptide
(ix) FEATURE:

(A) NAME/KEY: Other
(B) LOCATION: 1...1
(D) OTHER INFORMATION: N-acetylproline

(A) NAME/KEY: Other
(B) LOCATION: 4...4
(D) OTHER INFORMATION: cyclohexylglycine

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:89:

Xaa Ser Ser Xaa Gln Ser Val
1 5

(2) INFORMATION FOR SEQ ID NO:90:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 7 amino acids
(B) TYPE: amino acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: peptide
(ix) FEATURE:

(A) NAME/KEY: Other
(B) LOCATION: 1...1
(D) OTHER INFORMATION: N-acetylproline

(A) NAME/KEY: Other
(B) LOCATION: 4...4
(D) OTHER INFORMATION: cyclohexylglycine

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:90:

Xaa Ala Ser Xaa Gln Ser Leu
1 5

(2) INFORMATION FOR SEQ ID NO:91:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 7 amino acids
(B) TYPE: amino acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: peptide
(ix) FEATURE:

(A) NAME/KEY: Other
(B) LOCATION: 1...1
(D) OTHER INFORMATION: N-acetyl-3,4-dehydroproline

(A) NAME/KEY: Other
(B) LOCATION: 4...4
(D) OTHER INFORMATION: cyclohexylglycine

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:91:

Xaa Ala Ser Xaa Gln Ser Leu
1 5

(2) INFORMATION FOR SEQ ID NO:92:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 7 amino acids
(B) TYPE: amino acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: peptide
(ix) FEATURE:

(A) NAME/KEY: Other
(B) LOCATION: 1...1
(D) OTHER INFORMATION: N-acetyl-4-hydroxyproline

(A) NAME/KEY: Other
(B) LOCATION: 2...2
(D) OTHER INFORMATION: cyclohexylglycine

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:92:

Xaa Xaa Gln Ser Ser Ser Leu
1 5

(2) INFORMATION FOR SEQ ID NO:93:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 7 amino acids
(B) TYPE: amino acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: peptide
(ix) FEATURE:

(A) NAME/KEY: Other
(B) LOCATION: 1...1
(D) OTHER INFORMATION: N-acetyl-4-hydroxyproline

(A) NAME/KEY: Other

(B) LOCATION: 4...4
(D) OTHER INFORMATION: cyclohexylglycine

(A) NAME/KEY: Other
(B) LOCATION: 7...7
(D) OTHER INFORMATION: thienylalanine

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:93:

Xaa Ala Ser Xaa Gln Ser Xaa
1 5

(2) INFORMATION FOR SEQ ID NO:94:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 7 amino acids
(B) TYPE: amino acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: peptide
(ix) FEATURE:

(A) NAME/KEY: Other
(B) LOCATION: 1...1
(D) OTHER INFORMATION: N-acetyl-4-hydroxyproline

(A) NAME/KEY: Other
(B) LOCATION: 4...4
(D) OTHER INFORMATION: cyclohexylglycine

(A) NAME/KEY: Other
(B) LOCATION: 7...7
(D) OTHER INFORMATION: 1,2,3,4-tetrahydroisoquinoline 3-carboxylic acid

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:94:

Xaa Ala Ser Xaa Gln Ser Xaa
1 5

(2) INFORMATION FOR SEQ ID NO:95:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 7 amino acids
(B) TYPE: amino acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: peptide
(ix) FEATURE:

(A) NAME/KEY: Other
(B) LOCATION: 1...1
(D) OTHER INFORMATION: N-(hydroxyacetyl)-4-hydroxyproline

(A) NAME/KEY: Other
(B) LOCATION: 4...4
(D) OTHER INFORMATION: cyclohexylglycine

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:95:

Xaa Ala Ser Xaa Gln Ser Val
1 5

(2) INFORMATION FOR SEQ ID NO:96:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 7 amino acids
(B) TYPE: amino acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: peptide
(ix) FEATURE:

(A) NAME/KEY: Other
(B) LOCATION: 1...1
(D) OTHER INFORMATION: 4-hydroxyproline

(A) NAME/KEY: Other
(B) LOCATION: 4...4
(D) OTHER INFORMATION: cyclohexylglycine

(A) NAME/KEY: Other
(B) LOCATION: 7...7
(D) OTHER INFORMATION: leucinamide

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:96:

Pro Ala Ser Xaa Gln Ser Xaa
1 5

(2) INFORMATION FOR SEQ ID NO:97:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 7 amino acids
(B) TYPE: amino acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: peptide
(ix) FEATURE:

(A) NAME/KEY: Other
(B) LOCATION: 1...1
(D) OTHER INFORMATION: N-(hydroxyacetyl)-4-hydroxyproline

(A) NAME/KEY: Other
(B) LOCATION: 4...4
(D) OTHER INFORMATION: cyclohexylglycine

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:97:

Xaa Ala Ser Xaa Gln Ser Leu
1 5

WHAT IS CLAIMED IS:

1. A conjugate which is useful for the treatment of prostate cancer which comprises a cytotoxic agent attached to an oligopeptide, wherein the oligopeptide comprises a sequence of amino acids that is selectively proteolytically cleaved by free prostate specific antigen and wherein the means of attachment is a covalent bond or through a chemical linker, said sequence of amino acids which comprises at least one cyclic amino acid having a hydrophilic substituent;

or the pharmaceutically acceptable salt thereof.

2. The conjugate according to Claim 1 wherein the cytotoxic agent is a member of a class of cytotoxic agents selected from the following classes:

a) anthracycline family of drugs,
b) the vinca alkaloid drugs,
c) the mitomycins,
d) the bleomycins,
e) the cytotoxic nucleosides,
f) the pteridine family of drugs,
g) diynenes,
h) estramustine,
i) cyclophosphamide,
j) the taxanes and
k) the podophyllotoxins,

or the pharmaceutically acceptable salt thereof.

3. The conjugate according to Claim wherein the cytotoxic agent is selected from the following cytotoxic agents:

a) doxorubicin,
b) carminomycin,

c) daunorubicin,
d) aminopterin,
e) methotrexate,
f) methopterin,
g) dichloro-methotrexate,
h) mitomycin C,
i) porfiromycin,
j) 5-fluorouracil,
k) 6-mercaptopurine,
l) cytosine arabinoside,
m) podophyllotoxin,
n) etoposide,
o) etoposide phosphate,
p) melphalan,
q) vinblastine,
r) vincristine,
s) leurosidine,
t) vindesine,
u) estramustine,
v) cisplatin,
w) cyclophosphamide,
x) taxol, and
y) leurosine,

or the pharmaceutically acceptable salt thereof.

4. The conjugate according to Claim 2 wherein the cytotoxic agent is selected from doxorubicin and vinblastine or a cytotoxic derivative thereof.

5. The conjugate according to Claim 2 wherein the cytotoxic agent is doxorubicin or a cytotoxic derivative thereof.

6. The conjugate according to Claim 1 wherein the oligopeptide comprises an oligomer selected from:

a) HaaXaaSerTyrGlnlSerSer (SEQ.ID.NO.: 1);

b) HaaTyrGlnlSerSer (SEQ.ID.NO.: 2);

c) HaaXaaLysTyrGlnlSerSer (SEQ.ID.NO.: 3);

d) HaaXaaLysTyrGlnlSerSer (SEQ.ID.NO.: 4);

e) HaaXaahArgTyrGlnlSerSer (SEQ.ID.NO.: 5);

f) HaaXaahArgChaGlnlSerSer (SEQ.ID.NO.: 6);

g) HaaXaaSerTyrGlnlSerXaa (SEQ.ID.NO.: 7);

h) HaaTyrGlnlSerXaa (SEQ.ID.NO.: 8);

i) HaaXaaSerChgGlnlSerXaa (SEQ.ID.NO.: 9);

j) HaaChgGlnlSerXaa (SEQ.ID.NO.: 10);

wherein Haa is a cyclic amino acid substituted with a hydrophilic moiety, Xaa is any amino acid, hArg is homoarginine, Cha is cyclohexylalanine and Chg is cyclohexylglycine.

7. The conjugate according to Claim 1 wherein the oligopeptide comprises an oligomer selected from:

a) HaaXaaSerTyrGlnlSerSer (SEQ.ID.NO.: 11),

b) HaaXaaSerTyrGlnlSerAla (SEQ.ID.NO.: 12),

c) AlaHaaXaaSerTyrTyrIlSer (SEQ.ID.NO.: 13),

d) AlaAsnHaaXaaSerTyrGlnlSer (SEQ.ID.NO.: 14),

e) HaaXaaSerTyrGlnlSerSerThr (SEQ.ID.NO.: 15),

f) HaaTyrGlnlSerSerThr (SEQ.ID.NO.: 16),

g) HaaXaaSerTyrGlnlSerSerSer (SEQ.ID.NO.: 17),

h) HaaTyrGlnlSerSerSer (SEQ.ID.NO.: 18),

i) HaaXaaLysTyrGlnlSerSerSer (SEQ.ID.NO.: 19),

j) HaaXaahArgTyrGlnlSerSerSer (SEQ.ID.NO.: 20),

k) HaaXaaSerTyrGlnlSerSerLeu (SEQ.ID.NO.: 21);

l) HaaTyrGlnlSerSerLeu (SEQ.ID.NO.: 22);

m) HaaXaaSerTyrGlnlSerLeu (SEQ.ID.NO.: 23);

n) HaaTyrGlnlSerLeu (SEQ.ID.NO.: 24);

p) HaaXaaSerTyrGlnlSerNle (SEQ.ID.NO.: 25);

q) HaaTyrGlnlSerNle (SEQ.ID.NO.: 26);

r) HaaXaaSerTyrGlnlSerTIC (SEQ.ID.NO.: 27);

s) HaaTyrGlnlSerTIC (SEQ.ID.NO.: 28);

t) HaaXaaSerChgGlnlSerLeu (SEQ.ID.NO.: 29);

* C L M S *

u) HaaChgGln|SerLeu (SEQ.ID.NO.: 30);

v) HaaXaaSerChgGln|SerNle (SEQ.ID.NO.: 31);

w) HaaChgGln|SerNle (SEQ.ID.NO.: 32);

x) HaaXaaSerChgGln|SerTIC (SEQ.ID.NO.: 33);

y) HaaChgGln|SerTIC (SEQ.ID.NO.: 34);

z) hArgChgGln|SerLeu (SEQ.ID.NO.: 35); and

aa) hArgTyrGln|SerLeu (SEQ.ID.NO.: 36).

8. The conjugate according to Claim 1 wherein the oligopeptide comprises an oligomer selected from:

a) 4-HypXaaSerTyrGln|SerSer (SEQ.ID.NO.: 37),

b) 4-HypXaaSerTyrGln|SerAla (SEQ.ID.NO.: 38),

c) Ala4-HypXaaSerTyrTyr|Ser (SEQ.ID.NO.: 39),

d) AlaAsn4-HypXaaSerTyrGln|Ser (SEQ.ID.NO.: 40),

e) 4-HypXaaSerTyrGln|SerSerThr (SEQ.ID.NO.: 41),

f) 4-HypTyrGln|SerSerThr (SEQ.ID.NO.: 42),

g) 4-HypXaaSerTyrGln|SerSerSer (SEQ.ID.NO.: 43),

h) 4-HypTyrGln|SerSerSer (SEQ.ID.NO.: 44),

i) 4-HypXaaLysTyrGln|SerSerSer (SEQ.ID.NO.: 45),

j) 4-HypXaahArgTyrGlnlSerSerSer (SEQ.ID.NO.: 46),

k) 4-HypXaaSerTyrGlnlSerSerLeu (SEQ.ID.NO.: 47);

l) 4-HypTyrGlnlSerSerLeu (SEQ.ID.NO.: 48);

m) 4-HypXaaSerTyrGlnlSerLeu (SEQ.ID.NO.: 49);

n) 4-HypTyrGlnlSerLeu (SEQ.ID.NO.: 50);

p) 4-HypXaaSerTyrGlnlSerNle (SEQ.ID.NO.: 51);

q) 4-HypTyrGlnlSerNle (SEQ.ID.NO.: 52);

r) 4-HypXaaSerTyrGlnlSerTIC (SEQ.ID.NO.: 53);

s) 4-HypTyrGlnlSerTIC (SEQ.ID.NO.: 54);

t) 4-HypXaaSerChgGlnlSerLeu (SEQ.ID.NO.: 55);

u) 4-HypChgGlnlSerLeu (SEQ.ID.NO.: 56);

v) 4-HypXaaSerChgGlnlSerNle (SEQ.ID.NO.: 57);

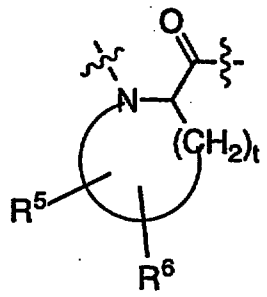
w) 4-HypChgGlnlSerNle (SEQ.ID.NO.: 58);

x) 4-HypXaaSerChgGlnlSerTIC (SEQ.ID.NO.: 59);

y) 4-HypChgGlnlSerTIC (SEQ.ID.NO.: 60);

wherein 4-Hyp is 4-hydroxyproline, Xaa is any amino acid, hArg is homoarginine, Cha is cyclohexylalanine and Chg is cyclohexylglycine.

9. The conjugate according to Claim 1 wherein the cyclic amino acid having a hydrophilic substituent is selected from:

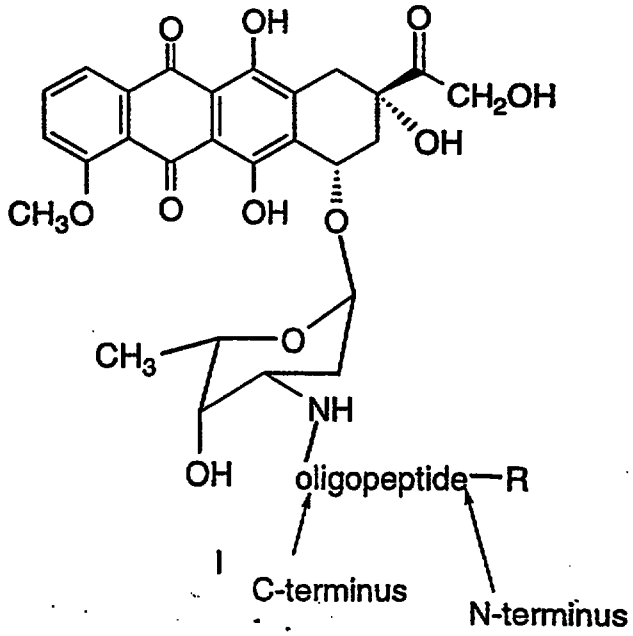


wherein:
R^5 is selected from HO- and C1-C6 alkoxy;

R6 is selected from hydrogen, halogen, C1-C6 alkyl, HO- and C1-C6 alkoxy; and

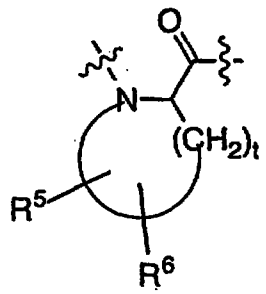
t is 3 or 4.

10. A conjugate which is useful for the treatment of prostate cancer of the formula I:



wherein:

oligopeptide is an oligopeptide which is selectively recognized by the free prostate specific antigen (PSA) and is capable of being proteolytically cleaved by the enzymatic activity of the free prostate specific antigen, wherein the oligopeptide comprises a cyclic amino acid of the formula:



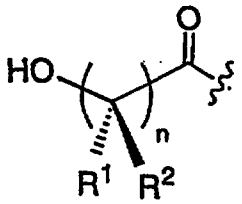
and wherein the C-terminus carbonyl is covalently bound to the amine of doxorubicin;

R is selected from

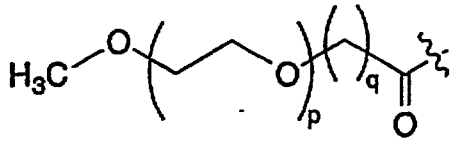
a) hydrogen,

b) -(C=O)R^{1a},

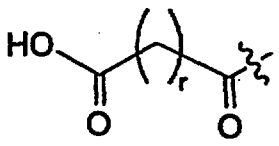
c)



d)



e)



R^1 and R^2 are independently selected from: hydrogen, OH, C_1-C_6 alkyl, C_1-C_6 alkoxy, C_1-C_6 aralkyl and aryl;

R^{1a} is C_1-C_6-alkyl, hydroxylated aryl, polyhydroxylated aryl or aryl,

R^5 is selected from HO- and C1-C6 alkoxy;

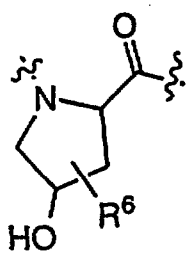
R^6 is selected from hydrogen, halogen, C_1-C_6 alkyl, HO- and C_1-C_6 alkoxy; and

n is		1, 2, 3 or 4;
p is		zero or an integer between 1 and 100;
q is		0 or 1, provided that if p is zero, q is 1;
r is		an integer between 1 and 10; and
t is		3 or 4;

or a pharmaceutically acceptable salt thereof.

11. The conjugate according to Claim 10 wherein:

the cyclic amino acid is



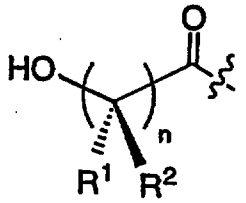
R is selected from

* C L M S *

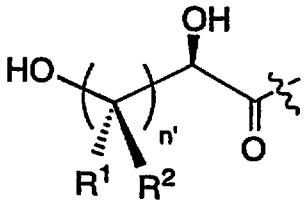
a) hydrogen,

b) -(C=O)R^{1a},

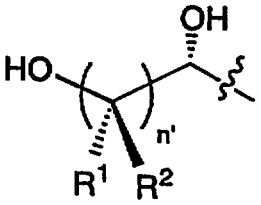
c)



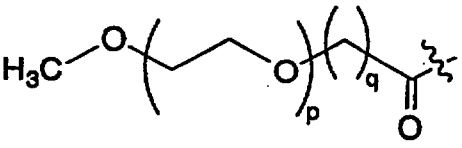
d)



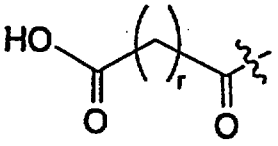
e)



f)



g)



R^1 and R^2 are independently selected from: hydrogen, C_1-C_6 alkyl and aryl;

R^{1a} is C_1-C_6-alkyl or aryl,

n is 1, 2, 3 or 4;
n' is 0, 1, 2 or 3;
p is zero or an integer between 1 and 14;
q is 0 or 1, provided that if p is zero, q is 1;
r is an integer between 1 and 10;
t is 3;

or a optical isomer or pharmaceutically acceptable salt thereof.

12. The conjugate according to Claim 10 wherein: oligopeptide is an oligomer that comprises an amino acid sequence selected from:

a) 4-HypXaaSerTyrGlnlSerSer (SEQ.ID.NO.: 37),

b) 4-HypXaaSerTyrGlnlSerAla (SEQ.ID.NO.: 38),

c) Ala-4-HypXaaSerTyrTyrlSer (SEQ.ID.NO.: 39),

d) AlaAsn4-HypXaaSerTyrGlnlSer (SEQ.ID.NO.: 40),

e) 4-HypXaaSerTyrGlnlSerSerThr (SEQ.ID.NO.: 41),

f) 4-HypTyrGlnlSerSerThr (SEQ.ID.NO.: 42),

g) 4-HypXaaSerTyrGlnlSerSerSer (SEQ.ID.NO.: 43),

h) 4-HypTyrGlnlSerSerSer (SEQ.ID.NO.: 44),

i) 4-HypXaaLysTyrGlnlSerSerSer (SEQ.ID.NO.: 45),

j) 4-HypXaahArgTyrGlnlSerSerSer (SEQ.ID.NO.: 46),

k) 4-HypXaaSerTyrGlnlSerSerLeu (SEQ.ID.NO.: 47);

l) 4-HypTyrGlnlSerSerLeu (SEQ.ID.NO.: 48);

m) 4-HypXaaSerTyrGlnlSerLeu (SEQ.ID.NO.: 49);

n) 4-HypTyrGlnlSerLeu (SEQ.ID.NO.: 50);

p) 4-HypXaaSerTyrGlnlSerNle (SEQ.ID.NO.: 51);

q) 4-HypTyrGlnlSerNle (SEQ.ID.NO.: 52);

r) 4-HypXaaSerTyrGlnlSerTIC (SEQ.ID.NO.: 53);

s) 4-HypTyrGlnlSerTIC (SEQ.ID.NO.: 54);

t) 4-HypXaaSerChgGlnlSerLeu (SEQ.ID.NO.: 55);

u) 4-HypChgGlnlSerLeu (SEQ.ID.NO.: 56);

v) 4-HypXaaSerChgGlnlSerNle (SEQ.ID.NO.: 57);

w) 4-HypChgGlnlSerNle (SEQ.ID.NO.: 58);

x) 4-HypXaaSerChgGlnlSerTIC (SEQ.ID.NO.: 59);

y) 4-HypChgGlnlSerTIC (SEQ.ID.NO.: 60);

wherein 4-Hyp is 4-hydroxyproline, Xaa is any amino acid, hArg is homoarginine, Cha is cyclohexylalanine and Chg is cyclohexylglycine;

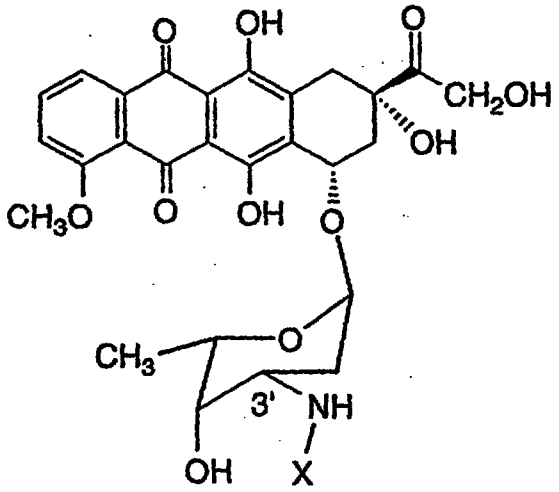
or an optical isomer or pharmaceutically acceptable salt thereof.

13. The conjugate according to Claim 12 wherein:

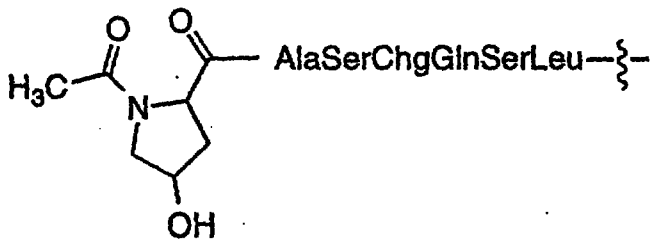
Xaa is alanine or isoleucine;

or an optical isomer or pharmaceutically acceptable salt thereof.

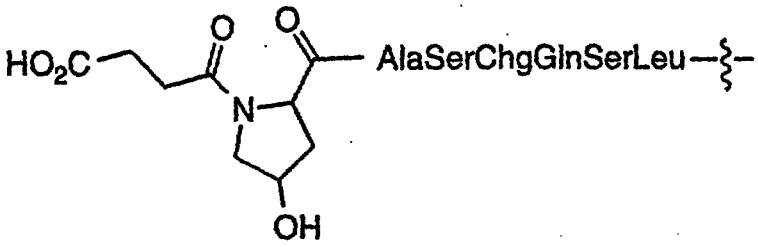
14. The conjugate according to Claim 10 which is selected from:



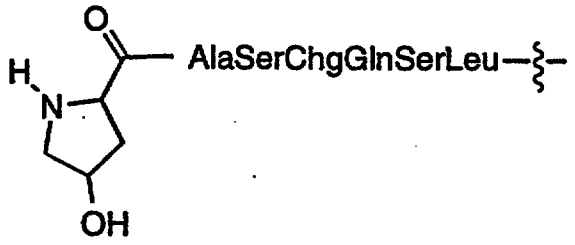
wherein X is:



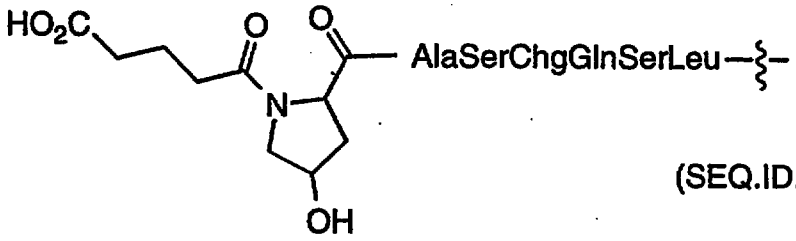
(SEQ.ID.NO.: 68),



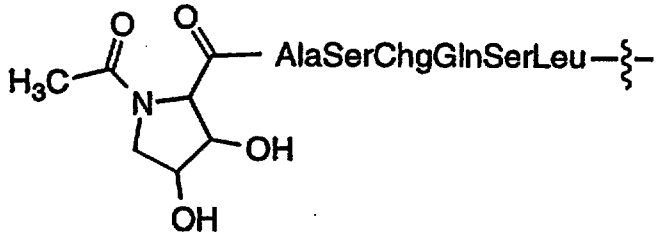
(SEQ.ID.NO.: 69),



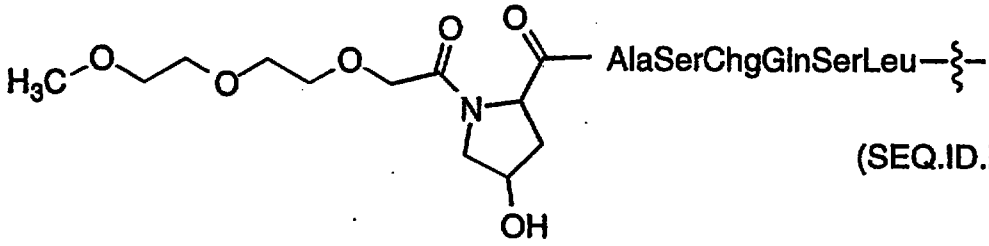
(SEQ.ID.NO.: 70),



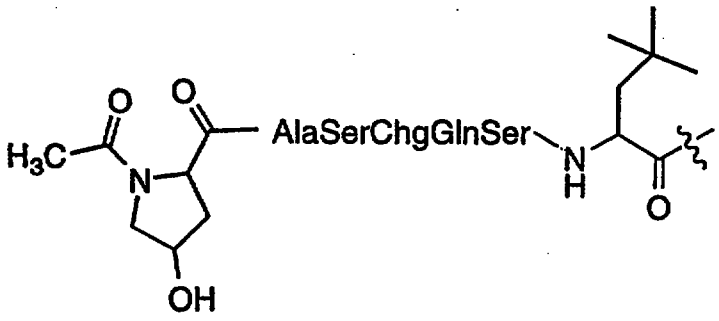
(SEQ.ID.NO.: 71),



(SEQ.ID.NO.: 72),



(SEQ.ID.NO.: 73),



(SEQ.ID.NO.: 74),

	SEQ. ID. NO.
Succinyl-(4-Hyp)ASChgQ-SV-DOX (3')	75
Glutaryl-(4-Hyp)ASChgQ-SV-DOX (3')	76
Glutaryl-(4-Hyp)ASChgQ-SI-DOX (3')	77
Succinyl-(4-Hyp)SSChgQ-SI-DOX (3')	78

* C L M S *

Succinyl-(4-Hyp)ASChgQ-SI-DOX (3')	79
Succinyl-(4-Hyp)ASChgQ-SAbu-DOX (3')	80
Glutaryl-(4-Hyp)SSChgQ-SI-DOX (3')	81
Glutaryl-(4-Hyp)SSChgQ-SL-DOX (3')	82
PEG(2)-(4-Hyp)SSChgQ-SL-DOX (3')	83
Succinyl-(4-Hyp)ASChgQ-SThi-DOX (3')	84
PEG(4)-(4-Hyp)-SSChgQ-SL-DOX (3')	85
PEG(2)-(4-Hyp)ASChgQ-SThi-DOX(3')	86
Succinyl-3,4-(diOH)PASChgQ-SL-DOX (3')	87
Malonyl-(4-Hyp)ASChgQ-SL-DOX (3')	88

or an optical isomer or pharmaceutically acceptable salt thereof.

15. The conjugate according to Claim 10 which is:

	SEQ. ID. NO.
Succinyl-(4-trans-L-Hyp)ASChgQ-SV-DOX (3')	75
Glutaryl-(4-trans-L-Hyp)ASChgQ-SV-DOX (3')	76
Glutaryl-(4-trans-L-Hyp)ASChgQ-SI-DOX (3')	77
Succinyl-(4-trans-L-Hyp)SSChgQ-SI-DOX (3')	78
Succinyl-(4-trans-L-Hyp)ASChgQ-SI-DOX (3')	79
Succinyl-(4-trans-L-Hyp)ASChgQ-SAbu-DOX (3')	80
Glutaryl-(4-trans-L-Hyp)SSChgQ-SI-DOX (3')	81
Glutaryl-(4-trans-L-Hyp)SSChgQ-SL-DOX (3')	82
PEG(2)-(4-trans-L-Hyp)SSChgQ-SL-DOX (3')	83
Succinyl-(4-trans-L-Hyp)ASChgQ-SThi-DOX (3')	84
PEG(4)-(4-trans-L-Hyp)-SSChgQ-SL-DOX (3')	85
PEG(2)-(4-trans-L-Hyp)ASChgQ-SThi-DOX(3')	86
Succinyl-3,4-(diOH)PASChgQ-SL-DOX (3')	87
Malonyl-(4-trans-L-Hyp)ASChgQ-SL-DOX (3')	88

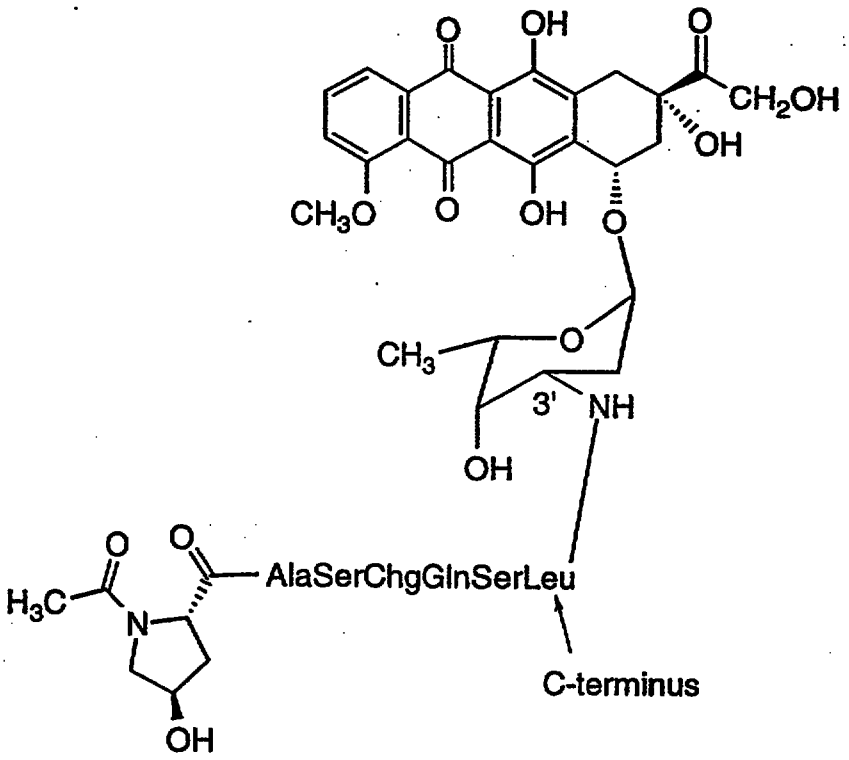
or an optical isomer or pharmaceutically acceptable salt thereof.

16. The conjugate according to Claim 10 which is:

[N-Ac-(4-trans-L-Hyp)]-Ala-Ser-Chg-Gln-Ser-Leu-Dox



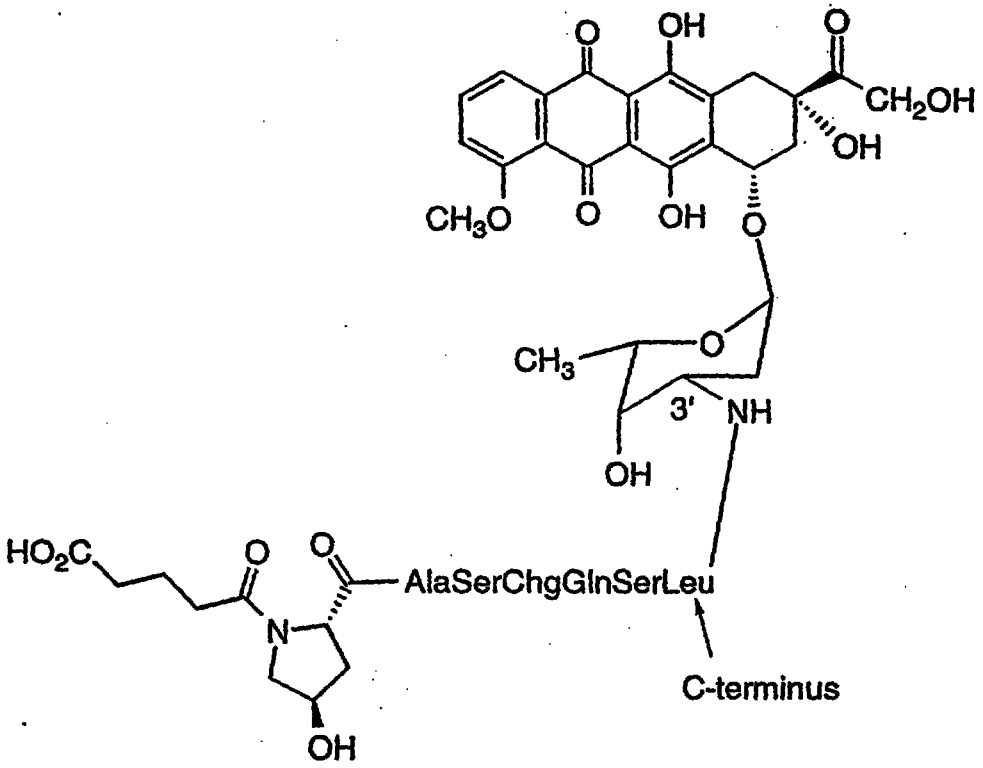
(SEQ.ID.NO.: 68)



or an optical isomer or pharmaceutically acceptable salt thereof.

5

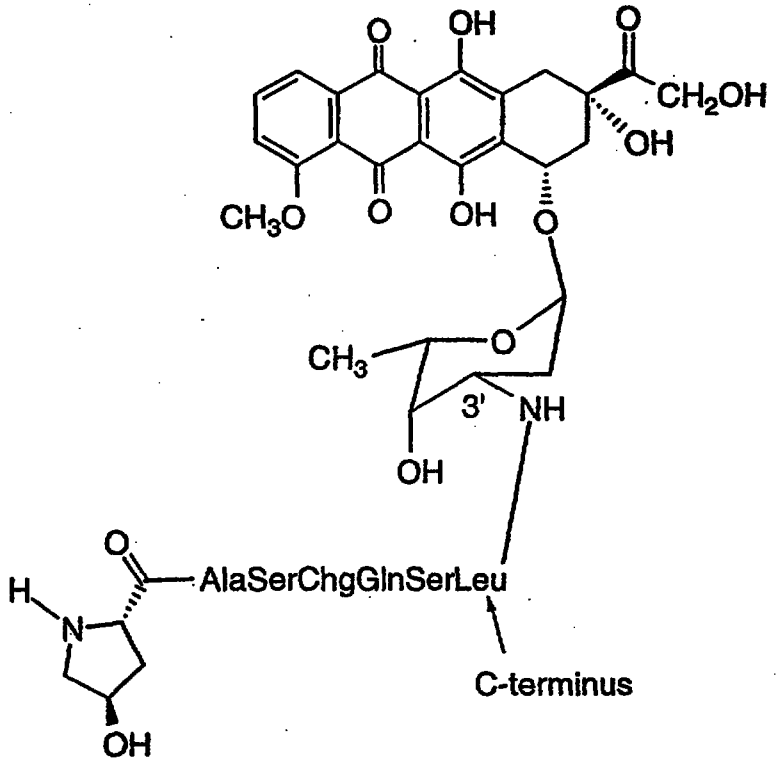
17. The conjugate according to Claim 10 which is:



(SEQ.ID.NO.: 71)
or an optical isomer or pharmaceutically acceptable salt thereof.

5

18. The conjugate according to Claim 10 which is:

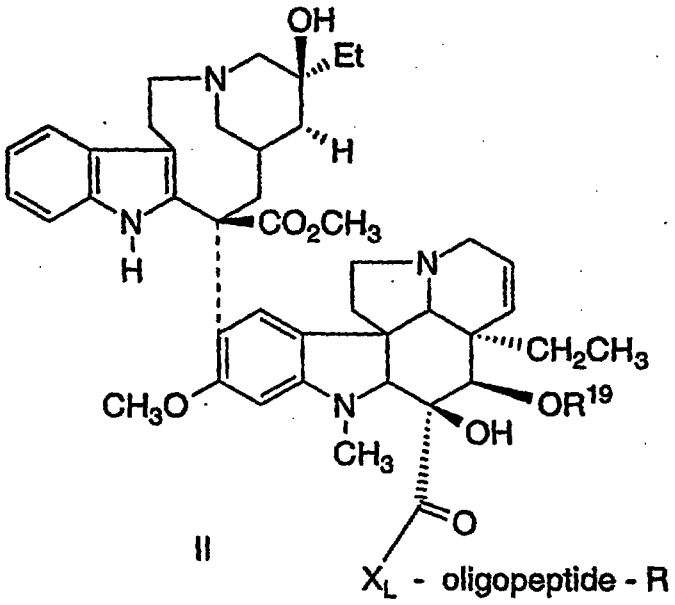


(SEQ.ID.NO.: 70)

or an optical isomer or pharmaceutically acceptable salt thereof.

19. The conjugate according to Claim 1 of the formula II:

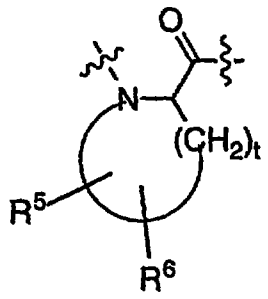
* C L M S *



II

wherein:

oligopeptide is an oligopeptide which is specifically recognized by the free prostate specific antigen (PSA) and is capable of being proteolytically cleaved by the enzymatic activity of the free prostate specific antigen, and the oligopeptide comprises a cyclic amino acid of the formula:



;

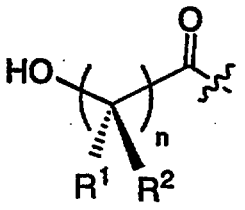
XL is - NH - (CH2)u - NH -

R is selected from

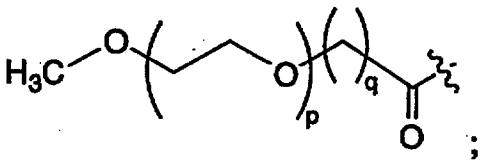
a) hydrogen,

b) -(C=O)R1a,

c)

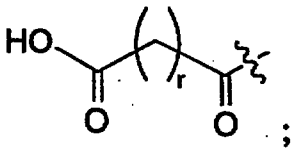


d)



;

e)



;

R1 and R2 are independently selected from: hydrogen, OH, C1-C6 alkyl, C1-C6 alkoxy, C1-C6 aralkyl and aryl;

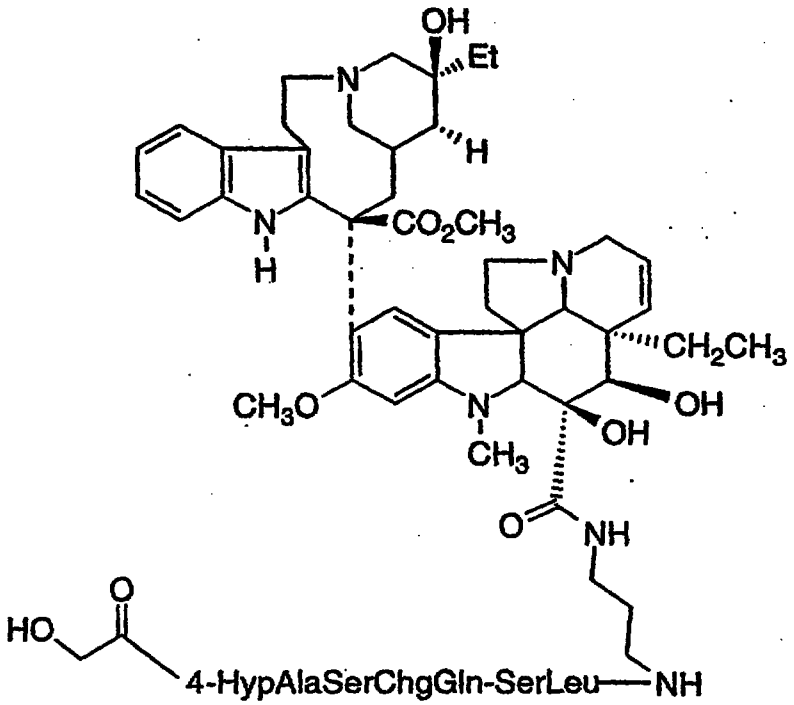
R1a is C1-C6-alkyl, hydroxylated aryl, polyhydroxylated aryl or aryl,

R19 is hydrogen, (C1-C3 alkyl)-CO, or chlorosubstituted (C1-C3 alkyl)-CO;

n is	1, 2, 3 or 4;
p is	zero or an integer between 1 and 100;
q is	0 or 1, provided that if p is zero, q is 1;
r is	1, 2 or 3;
t is	3 or 4;
u is	1, 2, 3, 4 or 5,

or a pharmaceutically acceptable salt thereof.

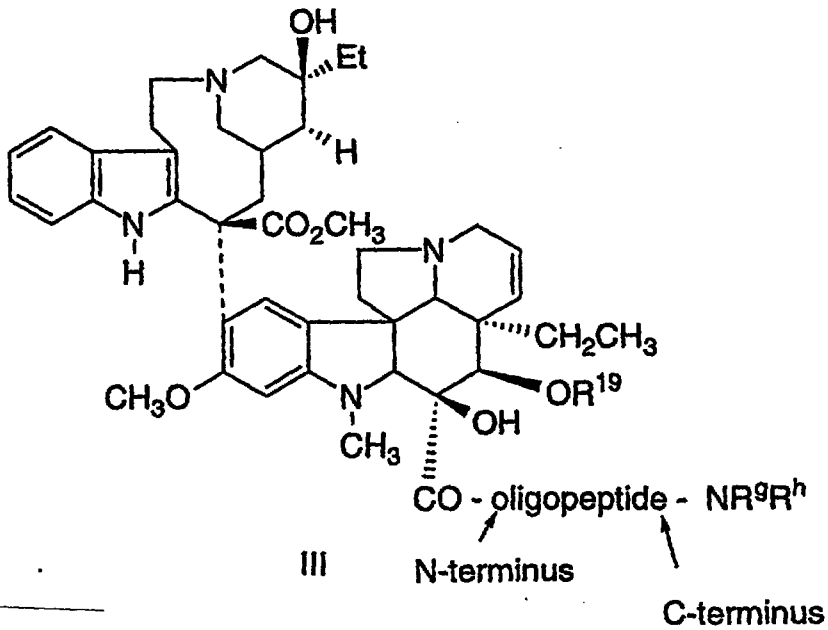
20. The conjugate according to Claim 16 which is selected from:



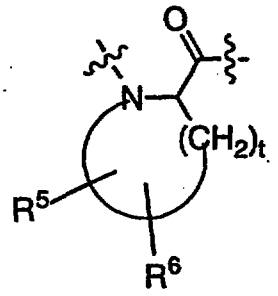
(SEQ.ID.NO.: 89),

or a pharmaceutically acceptable salt or optical isomer thereof.

21. The conjugate according to Claim 1 of the formula III:

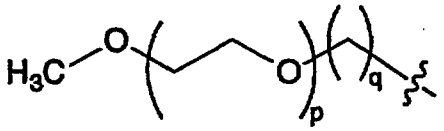


wherein:
oligopeptide is an oligopeptide which is specifically recognized by the free prostate specific antigen (PSA) and is capable of being proteolytically cleaved by the enzymatic activity of the free prostate specific antigen, and the oligopeptide comprises a cyclic amino acid of the formula:



;

R^g and R^h are independently selected from: hydrogen, C_1-C_6-alkyl, -C_1-C_6-alkyl-OH, -C_1-C_6-alkyl-di-OH, -C_1-C_6-alkyl-tri-OH and



provided that at least one R^d and R^e are not hydrogen or C_1-C_6-alkyl, or

R^g and R^h are combined to form a -$CH_2CH_2OCH_2CH_2$- diradical;

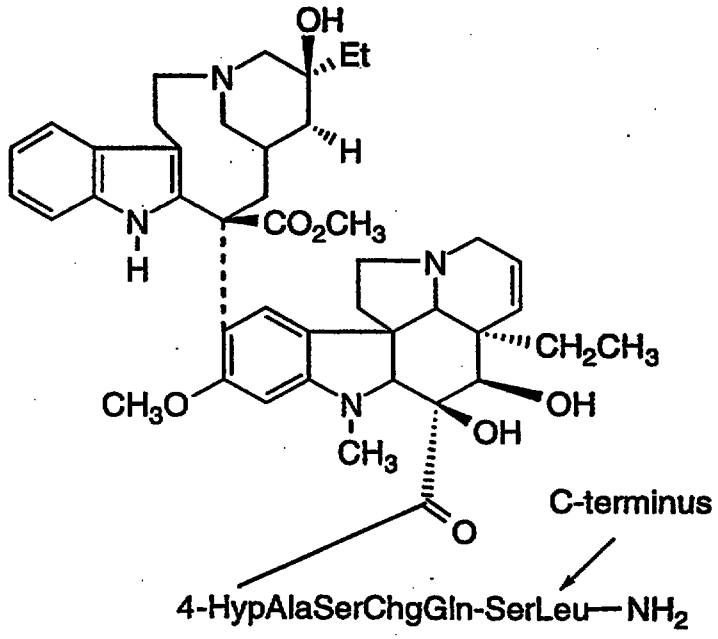
R^{19} is hydrogen, (C_1-C_3 alkyl)-CO, or chloro-substituted (C_1-C_3 alkyl)-CO;

p is zero or an integer between 1 and 100;
q is 0 or 1, provided that if p is zero, q is 1;

or a pharmaceutically acceptable salt thereof.

* C L M S *

22. The conjugate according to Claim 18 which is:



(SEQ.ID.NO.: 91),

or a pharmaceutically acceptable salt or optical isomer thereof.

23. A pharmaceutical composition comprising a pharmaceutical carrier, and dispersed therein, a therapeutically effective amount of a compound of Claim 1.

24. A pharmaceutical composition comprising a pharmaceutical carrier, and dispersed therein, a therapeutically effective amount of a compound of Claim 10.

25. A pharmaceutical composition comprising a pharmaceutical carrier, and dispersed therein, a therapeutically effective amount of a compound of Claim 14.

26. A pharmaceutical composition comprising a pharmaceutical carrier, and dispersed therein, a therapeutically effective amount of a compound of Claim 17.

27. A method for treating prostate cancer which comprises administering to a mammal in need thereof a therapeutically effective amount of a composition of Claim 23.

28. A method for treating prostate cancer which comprises administering to a mammal in need thereof a therapeutically effective amount of a composition of Claim 24.

29. A method for treating prostate cancer which comprises administering to a mammal in need thereof a therapeutically effective amount of a composition of Claim 25.

30. A method for treating prostate cancer which comprises administering to a mammal in need thereof a therapeutically effective amount of a composition of Claim 26.

31. A method for treating benign prostatic hyperplasia which comprises administering to a mammal in need thereof a therapeutically effective amount of a composition of Claim 23.

32. A method for treating benign prostatic hyperplasia which comprises administering to a mammal in need thereof a therapeutically effective amount of a composition of Claim 24.

33. A method for treating benign prostatic hyperplasia which comprises administering to a mammal in need thereof a therapeutically effective amount of a composition of Claim 25.

34. A method for treating benign prostatic hyperplasia which comprises administering to a mammal in need thereof a therapeutically effective amount of a composition of Claim 26.

35. A pharmaceutical composition made by combining the compound of Claim 1 and a pharmaceutically acceptable carrier.

THIS SHEET HAS BEEN REPLACED

36. A process for making a pharmaceutical composition comprising combining a compound of Claim 1 and a pharmaceutically acceptable carrier.

This Sheet Has Been Replaced



