LIGAND-DRUG CONJUGATES

FIELD OF THE INVENTION

The present invention generally relates to novel small molecule PSMA ligand containing drug conjugates that selectively target PSMA expressing tumor cells and cause their death through release of a toxic drug payload. Furthermore, the invention generally relates to the use of such drug conjugates for the treatment of cancer.

BACKGROUND OF THE INVENTION:

Prostate cancer is the most common cancer in men and is one among the leading causes of cancer mortality in spite of recent technologies of early diagnosis and treatments. Metastatic prostate cancer further reduces the probabilities of survival of the patient. Androgen deprivation therapy has long been used for the treatment of metastatic prostate cancer. The patient initially responds well to this treatment, however later progresses from castration-sensitive to castration-resistant phase as the response towards androgen deprivation therapy is reduced. There have been several drugs used in combination with androgen deprivation therapy to reduce or stop the progression to castration-resistant phase. However, there are very few effective therapies for advanced prostate cancer including metastatic castration-resistant prostate cancer, androgen-independent prostate cancer or relapsing prostate cancer.

Prostate-specific membrane antigen (PSMA), also known as *N*-acetyl-L-aspartyl-L-glutamate (NAAG) peptidase or glutamate carboxypeptidase II, is a zinc containing metal-enzyme transmembrane glycoprotein normally expressed in healthy human tissues and normal prostate epithelium. It is overexpressed in the prostatic adenocarcinoma cells as compared to benign prostatic tissue. The degree of overexpression of PSMA directly correlates with the stage and grade of tumor progression and malignancy in prostate cancer patients [see Silver, David A., *et al.*, Wright Jr, George L., *et al.*, Bostwick, David G., *et al.* and Mannweiler, Sebastian, *et al.*]. It is often observed that increased PSMA expression correlates with the development of advanced stage cancer such as metastatic prostate cancer or castration-resistant prostate cancer (CRPC) and also confirms the risk of recurrence after surgical intervention [see Wright Jr, George L., *et al.*, Ross, Jeffrey S., *et al.*, Mitsiades, Constantine S., *et al.*]. PSMA upon binding with an antibody or a ligand has high propensity to internalize. This aspect has been leveraged for the development of radiopharmaceuticals as well as antibody drug conjugates (ADCs) for diagnostics and therapeutics purpose [see Liu, He, *et al.*].

Some of the PSMA-targeted ADCs reported are MLN2704 (PSMA-antibody MLN591-maytansine conjugate) [see Galsky, Matthew D., *et al.*], PSMA-ADC (PSMA-antibody-monomethyl auristatin E (MMAE)) conjugate [Ma, Dangshe, *et al.*], and MEDI3726 (ADCT-401) [see Song Cho, *et al*].

PSMA ligand conjugated to small molecule have strongly surfaced on the horizon of clinical landscape as PSMA-targeting imaging agents, therapies, and/or theranostic agents offering distinctive advantages over ADCs due to their faster *in vivo* distribution, kinetics, more efficient penetration into solid tumors, and less adverse immunogenic responses. Moreover, they are single synthetic entities with robust reproducibility and low manufacturing cost [see Xiankai Sun *et al.*]. Some of the PSMA ligands conjugated to small molecules have been reported in U.S. patent no 6,479,470 B1, Kozikowski *et al*, International Published Patent Application No. WO 2006093991 A1 and U.S. Patent No. 6,528,499.

For diagnostic purpose the ligands have been radiolabelled and used as imaging agents to detect PSMA expressing cancers. Such imaging agents have been reported in U.S. Patent No. 7,408,079 B2 and U.S. Patent No. 8,487,129 B2. Further there are several reports wherein the PSMA binding ligands have been conjugated with a radiolabelled molecules *via* linkers. U.S. Patent No. 10,398,791 discloses among others ^{177}Lu Vipivotide tetraxetan (PLUVICTO®), which has been recently approved by US Food and Drug Administration (FDA) for the treatment of adult patients with prostate-specific membrane antigen (PSMA)-positive metastatic castration-resistant prostate cancer (mCRPC) who have been treated with androgen receptor (AR) pathway inhibition and taxane-based chemotherapy. Gallium Ga-68 Gozetotide (LOCAMETZ®) is disclosed in U.S. Patent No. 11,369,590 B2 and Sung-Hyun Moon *et al* discloses another radiolabelled compound comprising PSMA binding ligand, a linker and a radioactive isotope of Gallium coordinated to a chelating group. These Gallium based compounds are used as diagnostic agent for positron emission tomography (PET) imaging of PSMA-positive lesions in men with prostate cancer with suspected metastasis or recurrence. Piflufolastat F-18 (PYLARIFY®) disclosed in U.S. Patent No. 8,487,129 B2 is yet another radioactive diagnostic agent similar to LOCAMETZ®.

U.S. Patent No. 10,016,519 B2, European Patent Application No. EP2862857 A1, U.S. Patent No. 9,056,841 B2, International Published Patent Application No. WO 2020083853 A1 and U.S. Patent No. 9,861,713 B2 are some of the other patents/applications disclosing radioactive isotope of metals that are coordinated to the chelating groups linked to the PSMA binding ligands.

Even though PSMA targeted radiopharmaceuticals for diagnostic and therapeutic purposes are currently aiding the prostate cancer treatment regimen, they suffer from serious drawbacks like off target toxicities, and the requirement of a specialized setup or facility for handling and administering of radioactive substances, besides manufacturability issues.

International Published Patent Application No. WO 2022108992 discloses a non-radioactive compound with PSMA-targeting ligand, a cleavable linker, and a cytotoxic chemotherapeutic *viz*. Monomethyl Auristatin E (MMAE). Such ligand-linker conjugates are also reported in International Published Patent Application No. WO 2021101407 A1, Russian Patent No. RU2697519 C1, U.S. Patent Application Nos. 11,202,836 B2 and 9,193,763 B2.

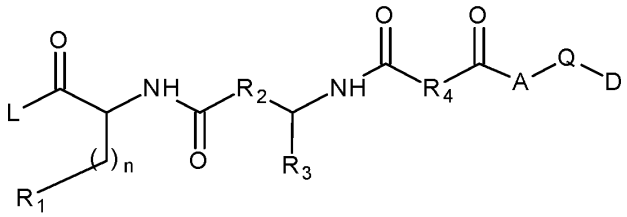
Therefore, a need remains to develop an agent that is highly selective towards cancerous cells expressing PSMA and is therapeutically effective in the treatment of such cancers. The object of the present invention is to provide an option to develop and fulfill these needs.

SUMMARY OF THE INVENTION

2-(3-((*S*)-5-amino-1-carboxypentyl)ureido) pentanedioic acid, 2-[3-(1,3-dicarboxypropyl)ureido]pentanedioic acid or 2-[3-(1-carboxy-2-mercapto-ethyl)ureido]pentanedioic acid are known as PSMA binding ligands.

The present invention generally relates to compounds comprising a PSMA binding ligands conjugated to a cytotoxic or therapeutic agent through a linker.

In a first aspect of the present invention, there is provided a compound of Formula I



Formula I

or pharmaceutically acceptable salt, stereoisomer or isotope thereof; wherein,

n is 0, 1, 2, 3 or 4;

L is a Ligand;

R_1 is selected from a 6 to 14 membered aryl or a 5 to 13 membered heteroaryl containing one, two or three heteroatoms independently selected from nitrogen, oxygen or sulfur;

R_1 is unsubstituted or substituted with one or more R_5;

R_5, at each occurrence, is independently selected from halogen, —C(O)NH_2, —C(O)OR_6, —C_{1-3} alkyl, —OR_7, and a 6 to 10 membered aryl; wherein,

R_6 is hydrogen or C_{1-3} alkyl;

R_7 is hydrogen or C_{1-3} alkyl;

R_2 is absent or is selected from a 6 to 10 membered cycloalkyl or a 6 to 10 membered aryl;

R_3 is hydrogen or —C_1-C_5COOH;

R_4 is selected from a group consisting of —C_{1-10} alkyl-, —C_{2-6} alkenyl-, —C_{1-3} alkyl-O-C_{1-3} alkyl—, —C_{2-6} alkyl-N(R_8)—, —C_{2-6} alkyl(N(R_8)($R_{8'}$))—, —N(R_8)-C_{2-6} alkyl—, a 3 to 6 membered cycloalkyl and —C_{1-2} alkyl-(-OC_2H_4)$_{1-8}$-OC_{1-2} alkyl—; wherein,

R_8 and $R_{8'}$ are independently selected from hydrogen, C_{1-6} alkyl, -C(O)-C_{1-4}alkyl-aryl or -C(O)-(-C_2H_4O)$_{1-8}$-C_{1-2} alkyl-N(R)(R'), wherein said aryl is selected from 6 to 14 membered aryl and is optionally substituted by -C_{1-3}alkyl or -OC_{1-3}alkyl; wherein

R and R' are independently selected from hydrogen, -C_{1-6} alkyl or -C(O)-C_{1-4}alkyl-aryl, wherein said aryl is selected from 6 to 14 membered aryl and is optionally substituted by -C_{1-3}alkyl or -OC_{1-3}alkyl;

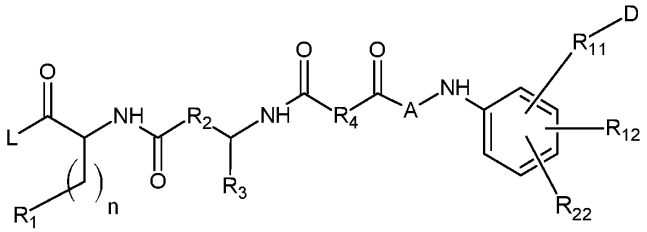
A is an amino acid or a peptide comprising 2-5 amino acids;

A is attached to Q through its C terminal;

Q is a self-immolative group; and

D is a cytotoxic agent or a therapeutic agent.

In a second aspect of the present invention, there is provided a compound of Formula II



Formula II

or pharmaceutically acceptable salt, stereoisomer or isotope thereof; wherein,

n is 0, 1, 2, 3 or 4;

L is a Ligand;

R_1 is selected from a 6 to 14 membered aryl or a 5 to 13 membered heteroaryl containing one, two or three heteroatoms independently selected from nitrogen, oxygen or sulfur;

R_1 is unsubstituted or substituted with one or more R_5;

R_5, at each occurrence, is independently selected from halogen, —C(O)NH_2, —C(O)OR_6, —C_{1-3} alkyl, —OR_7, and 6 to 10 membered aryl; wherein,

R_6 is hydrogen or C_{1-3} alkyl;

R_7 is hydrogen or C_{1-3} alkyl;

R_2 is absent or is selected from 6 to 10 membered cycloalkyl or a 6 to 10 membered aryl;

R_3 is hydrogen, or —C_1-C_5COOH;

R_4 is selected from a group consisting of —C_{1-10} alkyl-, —C_{2-6} alkenyl-, —C_{1-3} alkyl-O-C_{1-3} alkyl—, —C_{2-6} alkyl-N(R_8)—, —C_{2-6} alkyl(N(R_8)($R_{8'}$))—, —N(R_8)-C_{2-6} alkyl—, a 3 to 6 membered cycloalkyl and —C_{1-2} alkyl-(-OC_2H_4)$_{1-8}$-OC_{1-2} alkyl—; wherein,

R_8 and $R_{8'}$ are independently selected from hydrogen, C_{1-6} alkyl, -C(O)-C_{1-4}alkyl-aryl or -C(O)-(-C_2H_4O)$_{1-8}$-C_{1-2} alkyl-N(R)(R'), wherein said aryl is selected from 6 to 14 membered aryl and is optionally substituted by -C_{1-3}alkyl or -OC_{1-3}alkyl; wherein

R and R' are independently selected from hydrogen, -C_{1-6} alkyl or -C(O)-C_{1-4}alkyl-aryl, wherein said aryl is selected from 6 to 14 membered aryl and is optionally substituted by -C_{1-3}alkyl or -OC_{1-3}alkyl;

A is an amino acid or a peptide comprising 2-5 amino acids;

R_{11} is selected from —C_{1-3} alkyl-OC(O)—**,

—C_{1-3} alkyl-O-C(O)-N(R_{19})-C_{1-5} alkyl-N(R_{19})-C(O)—**,

—C_{1-3} alkyl-O-C(O)-N[C_{1-5} alkyl-N($R_{20}R_{21}$)]-C_{1-3} alkyl—**, or

—C_{1-3} alkyl-O-C(O)-Het_2-C_{1-3} alkyl-N(R_{19})-C(O)—**,

wherein ** indicates point of attachment to D;

R_{19} is selected from H, —C_{1-3} alkyl or —C_{1-3} alkyl-O-C_{1-3} alkyl-OH;

R_{20} is H or —C_{1-3} alkyl;

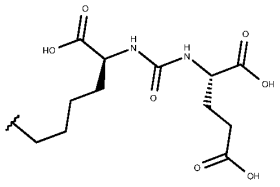
R_{21} is H or —C_1-C_3 alkyl; and

Het_2 is a 5 to 10 membered heterocyclic ring containing one, two or three heteroatoms independently selected from nitrogen, oxygen or sulfur;

R_{12} is selected from hydrogen, —C(O)N(R_{13})(R_{14}) or —(-OC_2H_4)$_{1-10}$-CH_3

R_{13} is hydrogen;

R_{14} is selected from —C_{1-5} alkyl, —C_{2-5} alkenyl, —C_{2-5} alkynyl, —C_{1-5} alkyl-N(R_{15})(R_{16}), —C_{1-5} alkyl-O-C_{1-3} alkyl, —(-C_2H_4O)$_{1-10}$$C_2H_5$, —(-$C_2H_4O$)$_{1-10}$-$C_2H_4$-$R_{17}$, —$C_{1-3}$ alkyl-Het_3-(-C_2H_4O)$_{1-10}$-C_2H_4-R_{18} or



; wherein:

R_{15} is hydrogen or C_{1-3} alkyl;

R_{16} is hydrogen or C_{1-3} alkyl; or

R_{15} and R_{16} along with the nitrogen atom to which they are attached form a 5 to 6 membered heterocyclic ring, wherein 1 or 2 carbon atoms in the heterocyclic ring are optionally replaced with additional heteroatoms independently selected from nitrogen, oxygen and sulfur and wherein the 5 to 6 membered heterocyclic ring is unsubstituted or substituted with C_{1-3} alkyl, halogen or –OH;

R_{17} is selected from hydrogen or —C(O)NH-C_{2-5} alkyl-$N(CH_3)_2$;

R_{18} is selected from hydrogen or —C(O)NH-C_{2-5} alkyl-$N(CH_3)_2$;

Het_3 is a 5 to 10 membered heterocyclic ring containing one, two or three heteroatoms independently selected from nitrogen, oxygen and sulfur;

OR

R_{13} and R_{14} along with the nitrogen atom to which they are attached form a 4 to 6 membered heterocyclic ring, wherein 1 or 2 carbons in the heterocyclic ring are optionally replaced with additional heteroatoms independently selected from nitrogen, oxygen and sulfur, and wherein the 4 to 6 membered heterocyclic ring is unsubstituted or substituted with C_{1-3} alkyl, —$N(CH_3)_2$ or —$CH_2N(CH_3)_2$;

R_{22} is selected from hydrogen, —C(O)N(R_{23})(R_{24}) or —(-OC_2H_4)$_{1-10}$-CH_3

R_{23} is hydrogen;

R_{24} is selected from —C_{1-5} alkyl, —C_{2-5} alkenyl, —C_{2-5} alkynyl, —C_{1-5} alkyl-N(R_{25})(R_{26}), —C_{1-5} alkyl-O-C_{1-3} alkyl, —(-C_2H_4O)$_{1-10}C_2H_5$, —(-C_2H_4O)$_{1-10}$-C_2H_4-R_{27}, —C_{1-3} alkyl-Het_3-(-C_2H_4O)$_{1-10}$-C_2H_4-R_{28} or

; wherein

R_{25} is hydrogen or C1 to C3 alkyl;

R_{26} is hydrogen or C1 to C3 alkyl; or

R_{25} and R_{26} along with the nitrogen atom to which they are attached form a 5 to 6 membered heterocyclic ring, wherein 1 or 2 carbon atoms in the heterocyclic ring are optionally replaced with additional heteroatoms independently selected from nitrogen,

oxygen and sulfur and wherein the 5 to 6 membered heterocyclic ring is unsubstituted or substituted with C_{1-3} alkyl, halogen or –OH;

R_{27} is selected from hydrogen or —C(O)NH-C_{2-5} alkyl-$N(CH_3)_2$;

R_{28} is selected from hydrogen or —C(O)NH-C_{2-5} alkyl-$N(CH_3)_2$;

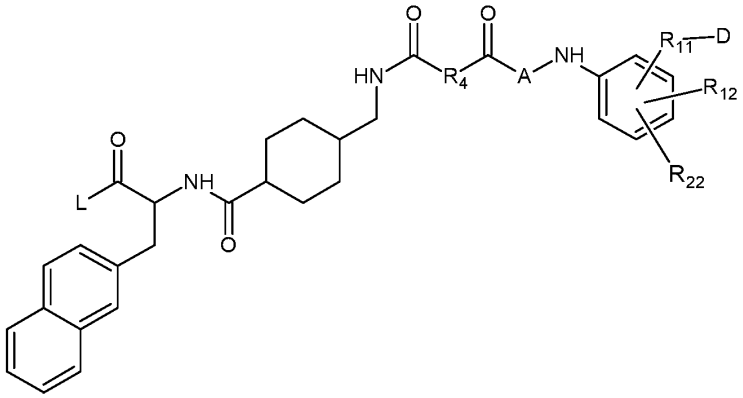
Het_3 is a 5 to 10 membered heterocyclic ring containing one, two or three heteroatoms independently selected from nitrogen, oxygen and sulfur;

OR

R_{23} and R_{24} along with the nitrogen atom to which they are attached form a 4 to 6 membered heterocyclic ring, wherein 1 or 2 carbons in the heterocyclic ring are optionally replaced with additional heteroatoms independently selected from nitrogen, oxygen and sulfur, and wherein the 4 to 6 membered heterocyclic ring is unsubstituted or substituted with C_{1-3} alkyl, —$N(CH_3)_2$ or —$CH_2N(CH_3)_2$; and

D is a cytotoxic agent or therapeutic agent.

In a third aspect of the present invention, there is provided a compound of Formula III



Formula III

or pharmaceutically acceptable salt, stereoisomer or isotope thereof; wherein,

L is a Ligand;

R_4 is selected from a group consisting of —C_{1-10} alkyl-, —C_{2-6} alkenyl-, —C_{1-3} alkyl-O-C_{1-3} alkyl—, —C_{2-6} alkyl-N(R_8)—, —C_{2-6} alkyl(N(R_8)($R_{8'}$))—, —N(R_8)-C_{2-6} alkyl—, a 3 to 6 membered cycloalkyl and —C_{1-2} alkyl-(-OC_2H_4)$_{1-8}$-OC_{1-2} alkyl—; wherein,

R_8 and $R_{8'}$ are independently selected from hydrogen, C_{1-6} alkyl, -C(O)-C_{1-4}alkyl-aryl or -C(O)-(-C_2H_4O)$_{1-8}$-C_{1-2} alkyl-N(R)(R'), wherein said aryl is selected from 6 to 14 membered aryl and is optionally substituted by -C_{1-3}alkyl or -OC_{1-3}alkyl; wherein

R and R' are independently selected from hydrogen, -C_{1-6} alkyl or -C(O)-C_{1-4}alkyl-aryl, wherein said aryl is selected from 6 to 14 membered aryl and is optionally substituted by -C_{1-3}alkyl or -OC_{1-3}alkyl;

A is an amino acid or a peptide comprising 2-5 amino acids;

R_{11} is selected from —C_{1-3} alkyl-OC(O)—**,

—C_{1-3} alkyl-O-C(O)-N(R_{19})-C_{1-5} alkyl-N(R_{19})-C(O)—**,

—C_{1-3} alkyl-O-C(O)-N[C_{1-5} alkyl-N($R_{20}R_{21}$)]-C_{1-3} alkyl—**, or

—C_{1-3} alkyl-O-C(O)-Het_2-C_{1-3} alkyl-N(R_{19})-C(O)—**,

wherein ** indicates point of attachment to D;

R_{19} is selected from H, CH_3 or –C_2H_4-O-C_2H_4-OH;

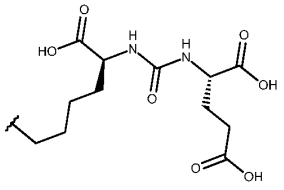
R_{20} is CH_3; R_{21} is CH_3; and

Het_2 is pyrrolidinyl;

R_{12} is selected from hydrogen, —C(O)N(R_{13})(R_{14}) or —(-OC_2H_4)$_{1-10}$-CH_3

R_{13} is hydrogen;

R_{14} is selected from —C_{1-5} alkyl, —C_{2-5} alkenyl, —C_{2-5} alkynyl, —C_{1-5} alkyl-N(R_{15})(R_{16}), —C_{1-5} alkyl-O-C_{1-3} alkyl, —(-C_2H_4O)$_{1-10}C_2H_5$, —(-C_2H_4O)$_{1-10}$-C_2H_4-R_{17}, —C_{1-3} alkyl-Het_3-(-C_2H_4O)$_{1-10}$-C_2H_4-R_{18} or



; wherein:

R_{15} is —CH_3 or —C_2H_5; R_{16} is —CH_3 or —C_2H_5;

or

R_{15} and R_{16} along with the nitrogen atom to which they are attached form a 5 to 6 membered heterocyclic ring, wherein 1 or 2 carbon atoms in the heterocyclic ring are optionally replaced with additional heteroatoms independently selected from nitrogen, oxygen and sulfur and wherein the 5 to 6 membered heterocyclic ring is unsubstituted or substituted with —CH_3.

R_{17} is —C(O)N$HC_2H_4N(CH_3)_2$;

R_{18} is —C(O)N$HC_2H_4N(CH_3)_2$.

or

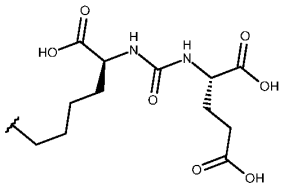
R_{13} and R_{14} along with the nitrogen atom to which they are attached form a 4 to 6 membered heterocyclic ring, wherein 1 or 2 carbons in the heterocyclic ring are optionally replaced

with additional heteroatoms independently selected from nitrogen, oxygen and sulfur, and wherein the 4 to 6 membered heterocyclic ring is unsubstituted or substituted with C_{1-3} alkyl, —$N(CH_3)_2$ or —$CH_2N(CH_3)_2$;

R_{22} is selected from hydrogen, —$C(O)N(R_{23})R_{24}$ or —$(-OC_2H_4)_{1-10}$-CH_3;

R_{23} is hydrogen;

R_{24} is selected from —C_{1-5} alkyl, —C_{2-5} alkenyl, —C_{2-5} alkynyl, —C_{1-5} alkyl-$N(R_{25})(R_{26})$, —C_{1-5} alkyl-O-C_{1-3} alkyl, —$(-C_2H_4O)_{1-10}C_2H_5$, —$(-C_2H_4O)_{1-10}$-C_2H_4-R_{27}, —C_{1-3} alkyl-Het_3-$(-C_2H_4O)_{1-10}$-C_2H_4-R_{28} or



; wherein:

R_{25} is —CH_3 or —C_2H_5;

R_{26} is —CH_3 or —C_2H_5; or

R_{25} and R_{26} along with the nitrogen atom to which they are attached form a 5 to 6 membered heterocyclic ring, wherein 1 or 2 carbon atoms in the heterocyclic ring are optionally replaced with additional heteroatoms independently selected from nitrogen, oxygen and sulfur and wherein the 5 to 6 membered heterocyclic ring is unsubstituted or substituted with —CH_3;

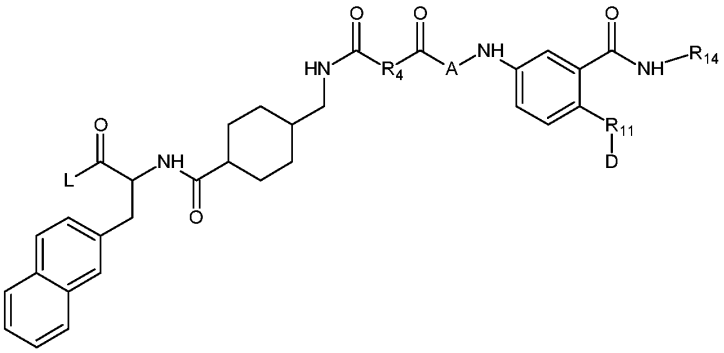
R_{27} is —$C(O)NH$-C_{2-5} alkyl-$N(CH_3)_2$;

R_{28} is —$C(O)NH$-C_{2-5} alkyl-$N(CH_3)_2$;

OR

R_{23} and R_{24} along with the nitrogen to which they are attached form a 4 to 6 membered heterocyclic ring, wherein 1 or 2 carbons in the heterocyclic ring are optionally replaced with additional heteroatoms independently selected from nitrogen, oxygen and sulfur, and wherein the 4 to 6 membered heterocyclic ring is unsubstituted or substituted with C_{1-3} alkyl, —$N(CH_3)_2$ or —$CH_2N(CH_3)_2$; and D is a cytotoxic agent or therapeutic agent.

In a fourth aspect of the present invention, there is provided a compound of Formula IV



Formula IV

or pharmaceutically acceptable salt, stereoisomer or isotope thereof; wherein,

L is a Ligand;

R_4 is selected from a group consisting of —C_{1-10} alkyl-, —C_{2-6} alkenyl-, —C_{1-3} alkyl-O-C_{1-3} alkyl—, —C_{2-6} alkyl-N(R_8)—, —C_{2-6} alkyl(N(R_8)($R_{8'}$))—, —N(R_8)-C_{2-6} alkyl—, a 3 to 6 membered cycloalkyl and —C_{1-2} alkyl-(-OC_2H_4)$_{1-8}$-OC_{1-2} alkyl—; wherein,

R_8 and $R_{8'}$ are independently selected from hydrogen, C_{1-6} alkyl, -C(O)-C_{1-4}alkyl-aryl or -C(O)-(-C_2H_4O)$_{1-8}$-C_{1-2} alkyl-N(R)(R'), wherein said aryl is selected from 6 to 14 membered aryl and is optionally substituted by -C_{1-3}alkyl or -OC_{1-3}alkyl; wherein

R and R' are independently selected from hydrogen, -C_{1-6} alkyl or -C(O)-C_{1-4}alkyl-aryl, wherein said aryl is selected from 6 to 14 membered aryl and is optionally substituted by -C_{1-3}alkyl or -OC_{1-3}alkyl;

A is an amino acid or a peptide comprising 2-5 amino acids;

R_{11} is selected from —C_{1-3} alkyl-OC(O)—**,

—C_{1-3} alkyl-O-C(O)-N(R_{19})-C_{1-5} alkyl-N(R_{19})-C(O)—**,

—C_{1-3} alkyl-O-C(O)-N[C_{1-5} alkyl-N($R_{20}R_{21}$)]-C_{1-3} alkyl—**, or

—C_{1-3} alkyl-O-C(O)-Het_2-C_{1-3} alkyl-N(R_{19})-C(O)—**,

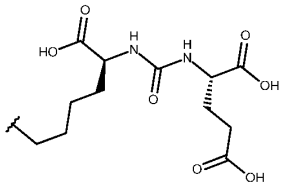
wherein ** indicates point of attachment to D;

R_{19} is selected from H, -CH_3 or –C_2H_4-O-C_2H_4-OH;

R_{20} is -CH_3; R_{21} is -CH_3;

Het_2 is pyrrolidinyl;

R_{14} is selected from —C_1-C_5 alkyl, —C_1 to C_5 alkyl-N(R_{15})(R_{16}), —C_1-C_5 alkyl-OCH_3, (-C_2H_4O)$_{1-10}$ CH_2-CH_3 or,

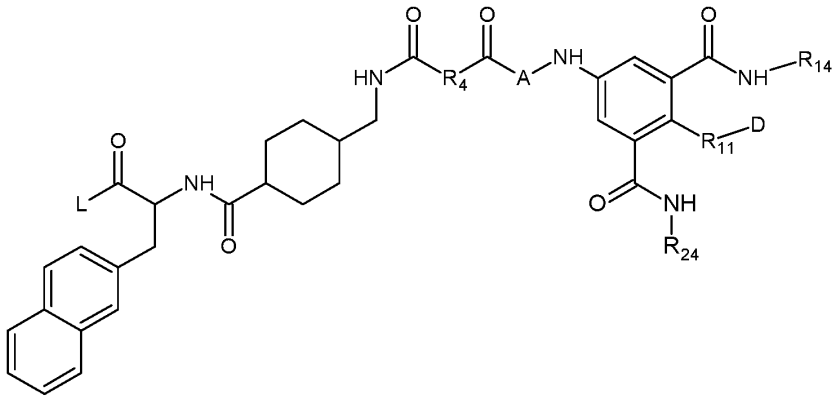


; wherein

R_{15} is C_{1-3} alkyl; and

R_{16} is C_{1-3} alkyl.

In a fifth aspect, there is provided a compound of Formula V



Formula V

or pharmaceutically acceptable salt, stereoisomer or isotope thereof; wherein,

L is a Ligand;

R_4 is selected from a group consisting of —C_{1-10} alkyl-, —C_{2-6} alkenyl-, —C_{1-3} alkyl-O-C_{1-3} alkyl—, —C_{2-6} alkyl-N(R_8)—, —C_{2-6} alkyl(N(R_8)($R_{8'}$))—, —N(R_8)-C_{2-6} alkyl—, a 3 to 6 membered cycloalkyl and —C_{1-2} alkyl-(-OC_2H_4)$_{1-8}$-OC_{1-2} alkyl—; wherein,

R_8 and $R_{8'}$ are independently selected from hydrogen, C_{1-6} alkyl, -C(O)-C_{1-4}alkyl-aryl or -C(O)-(-C_2H_4O)$_{1-8}$-C_{1-2} alkyl-N(R)(R'), wherein said aryl is selected from 6 to 14 membered aryl and is optionally substituted by -C_{1-3}alkyl or -OC_{1-3}alkyl; wherein

R and R' are independently selected from hydrogen, -C_{1-6} alkyl or -C(O)-C_{1-4}alkyl-aryl, wherein said aryl is selected from 6 to 14 membered aryl and is optionally substituted by -C_{1-3}alkyl or -OC_{1-3}alkyl;

A is an amino acid or a peptide comprising 2-5 amino acids;

R_{11} is selected from —C_{1-3} alkyl-OC(O)—**,

—C_{1-3} alkyl-O-C(O)-N(R_{19})-C_{1-5} alkyl-N(R_{19})-C(O)—**,

—C_{1-3} alkyl-O-C(O)-N[C_{1-5} alkyl-N($R_{20}R_{21}$)]-C_{1-3} alkyl—**, or

—C_{1-3} alkyl-O-C(O)-Het_2-C_{1-3} alkyl-N(R_{19})-C(O)—**,

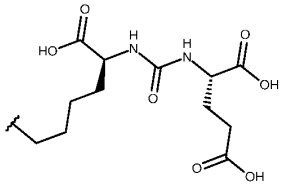
wherein ** indicates point of attachment to D;

R_{19} is selected from H, -CH_3 or –C_2H_4-O-C_2H_4-OH;

R_{20} is -CH_3; R_{21} is -CH_3; and

Het_2 is pyrrolidinyl;

R_{14} is selected from —C_1-C_5 alkyl, —C_1 to C_5 alkyl-N(R_{15})(R_{16}), —C_1-C_5 alkyl-OCH_3, (-C_2H_4O)$_{1-10}$ CH_2-CH_3 or

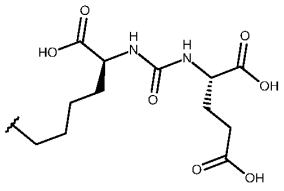


, wherein

R_{15} is C_{1-3} alkyl;

R_{16} is C_{1-3} alkyl;

R_{24} is selected from —C_{1-5} alkyl, —C_{1-5} alkyl-N(R_{25})(R_{26}), —C_{1-5} alkyl-OCH_3, (-C_2H_4O)$_{1-10}$$CH_2$-$CH_3$ or

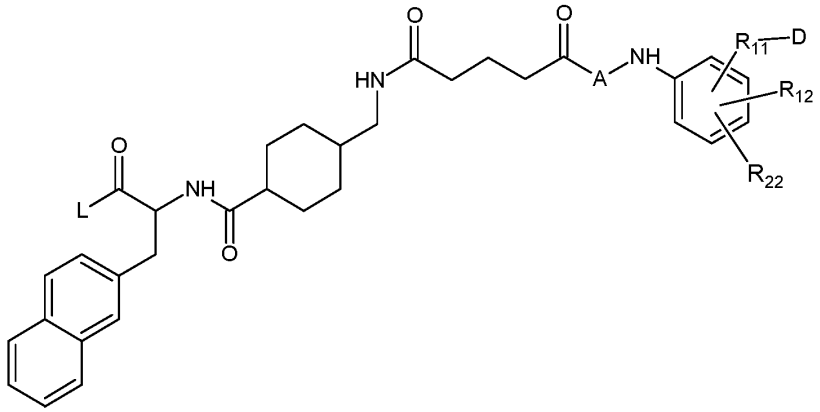


; wherein

R_{25} is hydrogen or C_{1-3} alkyl; and

R_{26} is hydrogen or C_{1-3} alkyl.

In a sixth aspect, there is provided a compound of Formula VI



Formula VI

or pharmaceutically acceptable salt, stereoisomer or isotope thereof; wherein,

L is a Ligand;

A is an amino acid or a peptide comprising 2-5 amino acids;

R_{11} is selected from —C_{1-3} alkyl-OC(O)—**,

—C_{1-3} alkyl-O-C(O)-N(R_{19})-C_{1-5} alkyl-N(R_{19})-C(O)—**,

—C_{1-3} alkyl-O-C(O)-N[C_{1-5} alkyl-N($R_{20}R_{21}$)]-C_{1-3} alkyl—**, or

—C_{1-3} alkyl-O-C(O)-Het_2-C_{1-3} alkyl-N(R_{19})-C(O)—**,

wherein ** indicates point of attachment to D;

R_{19} is selected from H, CH_3 or –C_2H_4-O-C_2H_4-OH;

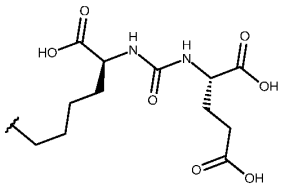
R_{20} is CH_3; R_{21} is CH_3; and

Het_2 is pyrrolidinyl;

R_{12} is selected from hydrogen, —C(O)N(R_{13})R_{14} or —(-OC_2H_4)$_{1-10}$-CH_3;

R_{13} is hydrogen;

R_{14} is —CH_3, —CH_2-C≡CH, —C_{1-3} alkyl-N(R_{15})(R_{16}), —$C_2H_4OCH_3$, —(-C_2H_4O)$_{3-8}$-C_2H_5, —(-C_2H_4O)$_{5-10}$-C_2H_4-R_{17}, —CH_2-triazole-(-C_2H_4O)4-C_2H_4-R_{18} or



; wherein

R_{15} is —CH_3 or —C_2H_5;

R_{16} is —CH_3 or —C_2H_5; or

R_{15} and R_{16} along with the nitrogen atom to which they are attached form a 5 to 6 membered heterocyclic ring, wherein 1 or 2 carbon atoms in the heterocyclic ring are optionally replaced with additional heteroatoms independently selected from nitrogen, oxygen and sulfur and wherein the 5 to 6 membered heterocyclic ring is unsubstituted or substituted with —CH_3;

R_{17} is —$C(O)NHC_2H_4N(CH_3)_2$;

R_{18} is —$C(O)NHC_2H_4N(CH_3)_2$;

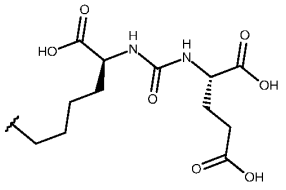
OR

R_{13} and R_{14} along with the nitrogen atom to which they are attached form a 4 to 6 membered heterocyclic ring, wherein 1 or 2 carbons in the heterocyclic ring are optionally replaced with additional heteroatoms independently selected from nitrogen, oxygen and sulfur, and wherein the 4 to 6 membered heterocyclic ring is unsubstituted or substituted with C_{1-3} alkyl, —$N(CH_3)_2$ or —$CH_2N(CH_3)_2$;

R_{22} is selected from hydrogen, —$C(O)N(R_{23})(R_{24})$ or —$(-OC_2H_4)_{1-10}$-CH_3;

R_{23} is hydrogen;

R_{24} is —CH_3, —CH_2-C≡CH, —C_{1-3} alkyl-$N(R_{25})(R_{26})$, —$C_2H_4OCH_3$, —$(-C_2H_4O)_{3-8}$-C_2H_5, —$(-C_2H_4O)_{5-10}$-C_2H_4-R_{27}, —CH_2-triazole-$(-C_2H_4O)4$-C_2H_4-R_{28} or



; wherein

R_{25} is —CH_3 or —C_2H_5;

R_{26} is —CH_3 or —C_2H_5; or

R_{25} and R_{26} along with the nitrogen atom to which they are attached form a 5 to 6 membered heterocyclic ring, wherein 1 or 2 carbon atoms in the heterocyclic ring are optionally replaced with additional heteroatoms independently selected from nitrogen, oxygen and sulfur and wherein the 5 to 6 membered heterocyclic ring is unsubstituted or substituted with —CH_3;

R_{27} is —$C(O)NHC_2H_4N(CH_3)_2$;

R_{28} is —$C(O)NHC_2H_4N(CH_3)_2$;

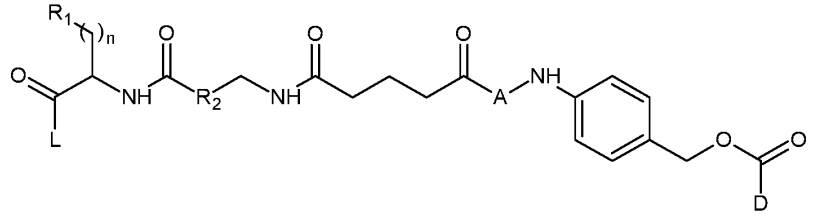
OR

R_{23} and R_{24} along with the nitrogen atom to which they are attached form a 4 to 6 membered heterocyclic ring, wherein 1 or 2 carbons in the heterocyclic ring are

optionally replaced with additional heteroatoms independently selected from nitrogen, oxygen and sulfur, and wherein the 4 to 6 membered heterocyclic ring is unsubstituted or substituted with C_{1-3} alkyl, —$N(CH_3)_2$ or —$CH_2N(CH_3)_2$; and

D is a cytotoxic agent or therapeutic agent.

In a seventh aspect, there is provided a compound of Formula VI,



Formula VII

or pharmaceutically acceptable salt, stereoisomer or isotope thereof;

wherein:

L is a ligand and D is a cytotoxic agent or therapeutic agent;

n is 0, 1, or 2;

R_1 is selected from the group consisting of phenyl, indolyl, thiophenyl, quinolinyl and isoquinolinyl;

R_1 is unsubstituted or substituted with one or more R_5;

R_5 is selected from halogen, —OH, or a 6 to 10 membered aryl ring;

R_2 is cyclohexyl or phenyl;

A is a peptide val-cit.

In an eighth aspect, there is provided a method of treatment of a disease associated with the PSMA expressing cells, wherein the method comprises administering a compound according to any one of the preceding aspects or a medicament comprised thereof.

In a ninth aspect, the present invention provides a method of treatment of cancer by administering a medicament comprising a compound selected from the group consisting of a compound of Formula I, a compound of Formula II, a compound of Formula III, a compound of Formula IV, a compound of Formula V, a compound of Formula VI and a compound of Formula VII and a pharmaceutically acceptable excipient.

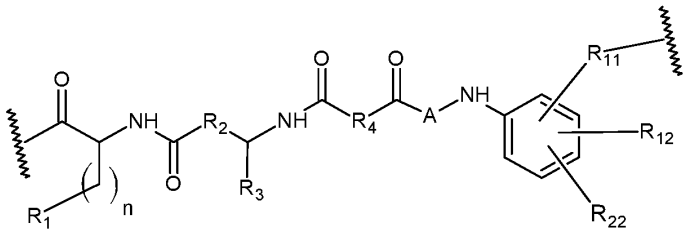
In a tenth aspect, the present invention provides a method of treatment of cancer involving cells that are positive for expression of PSMA, wherein the method comprises administering a compound or a medicament comprising a compound selected from the group consisting of a compound of Formula I, a compound of Formula II, a compound of Formula III, a compound

of Formula IV, a compound of Formula V, a compound of Formula VI and a compound of Formula VII.

In an eleventh aspect, the present invention provides the use of a compound selected from the group consisting of a compound of Formula I, a compound of Formula II, a compound of Formula III, a compound of Formula IV, a compound of Formula V, a compound of Formula VI and a compound of Formula VII for the preparation of a medicament used in the treatment of a disease associated with the PSMA expressing cells.

In a twelfth aspect, the present invention provides a pharmaceutical composition comprising a compound selected from the group consisting of a compound of Formula I, a compound of Formula II, a compound of Formula III, a compound of Formula IV, a compound of Formula V, a compound of Formula VI and a compound of Formula VII and a pharmaceutically acceptable carrier.

In a thirteenth aspect, the present invention provides a ligand-drug conjugate, wherein the ligand L and the drug D is conjugated via linker of Formula VIII:



Formula VIII

wherein:

n is 0, 1, 2, 3 or 4;

R_1 is selected from a 6 to 14 membered aryl or a 5 to 13 membered heteroaryl containing one, two or three heteroatoms independently selected from nitrogen, oxygen or sulfur;

R_1 is unsubstituted or substituted with one or more R_5;

R_5, at each occurrence, is independently selected from halogen, —$C(O)NH_2$, —$C(O)OR_6$, —$C_{1\text{-}3}$ alkyl, —OR_7, and a 6 to 10 membered aryl; wherein,

R_6 is hydrogen or $C_{1\text{-}3}$ alkyl;

R_7 is hydrogen or $C_{1\text{-}3}$ alkyl;

R_2 is absent or is selected from a 6 to 10 membered cycloalkyl or a 6 to 10 membered aryl;

R_3 is hydrogen or —C_1-C_5COOH;

R_4 is selected from a group consisting of —C_{1-10} alkyl-, —C_{2-6} alkenyl-, —C_{1-3} alkyl-O-C_{1-3} alkyl—, —C_{2-6} alkyl-N(R_8)—, —C_{2-6} alkyl(N(R_8)($R_{8'}$))—, —N(R_8)-C_{2-6} alkyl—, a 3 to 6 membered cycloalkyl and —C_{1-2} alkyl-(-OC_2H_4)$_{1-8}$-OC_{1-2} alkyl—; wherein,

R_8 and $R_{8'}$ are independently selected from hydrogen, C_{1-6} alkyl, -C(O)-C_{1-4}alkyl-aryl or -C(O)-(-C_2H_4O)$_{1-8}$-C_{1-2} alkyl-N(R)(R'), wherein said aryl is selected from 6 to 14 membered aryl and is optionally substituted by -C_{1-3}alkyl or -OC_{1-3}alkyl; wherein

R and R' are independently selected from hydrogen, -C_{1-6} alkyl or -C(O)-C_{1-4}alkyl-aryl, wherein said aryl is selected from 6 to 14 membered aryl and is optionally substituted by -C_{1-3}alkyl or -OC_{1-3}alkyl;

A is an amino acid or a peptide comprising 2-5 amino acids;

A is attached to NH through its C terminal;

R_{11} is selected from a group consisting of —C_{1-3} alkyl-OC(O)—**,

—C_{1-3} alkyl-O-C(O)-N(R_{19})-C_{1-5} alkyl-N(R_{19})-C(O)—**,

—C_{1-3} alkyl-O-C(O)-N[C_{1-5} alkyl-N($R_{20}R_{21}$)]-C_{1-3} alkyl—**, or

—C_{1-3} alkyl-O-C(O)-Het_2-C_{1-3} alkyl-N(R_{19})-C(O)—**,

wherein:

R_{19} is selected from hydrogen, —C_{1-3} alkyl or —C_{1-3} alkyl-O-C_{1-3} alkyl-OH;

R_{20} is hydrogen or —C_{1-3} alkyl;

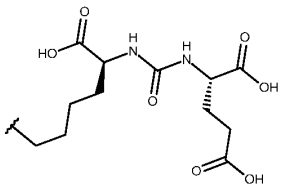
R_{21} is hydrogen or —C_{1-3} alkyl; and

Het_2 is a 5 to 10 membered heterocyclic ring containing one, two or three heteroatoms independently selected from nitrogen, oxygen or sulfur;

R_{12} is selected from hydrogen, —C(O)N(R_{13})(R_{14}) or —(-OC_2H_4)$_{1-10}$-CH_3;

R_{13} is hydrogen;

R_{14} is selected from —C_{1-5} alkyl, —C_{2-5} alkenyl, —C_{2-5} alkynyl, —C_{1-5} alkyl-N(R_{15})(R_{16}), —C_{1-5} alkyl-O-C_{1-3} alkyl, —(-C_2H_4O)$_{1-10}C_2H_5$, —(-C_2H_4O)$_{1-10}$-C_2H_4-R_{17}, —C_{1-3} alkyl-Het_3-(-C_2H_4O)$_{1-10}$-C_2H_4-R_{18} or



; wherein:

R_{15} is hydrogen or C1 to C3 alkyl;

R_{16} is hydrogen or C1 to C3 alkyl; or

R_{15} and R_{16} along with the nitrogen atom to which they are attached form a 5 to 6 membered heterocyclic ring, wherein 1 or 2 carbon atoms in the heterocyclic ring are optionally replaced with additional heteroatoms independently selected from nitrogen, oxygen and sulfur and wherein the 5 to 6 membered heterocyclic ring is unsubstituted or substituted with C_{1-3} alkyl, halogen or –OH;

R_{17} is selected from hydrogen or —C(O)NH-C_{2-5} alkyl-$N(CH_3)_2$;

R_{18} is selected from hydrogen or —C(O)NH-C_{2-5} alkyl-$N(CH_3)_2$;

Het_3 is a 5 to 10 membered heterocyclic ring containing one, two or three heteroatoms independently selected from nitrogen, oxygen and sulfur;

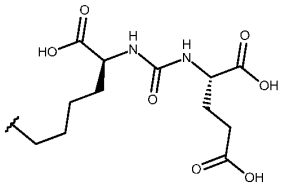
OR

R_{13} and R_{14} along with the nitrogen atom to which they are attached form a 4 to 6 membered heterocyclic ring, wherein 1 or 2 carbons in the heterocyclic ring are optionally replaced with additional heteroatoms independently selected from nitrogen, oxygen and sulfur, and wherein the 4 to 6 membered heterocyclic ring is unsubstituted or substituted with C_{1-3} alkyl, —$N(CH_3)_2$ or —$CH_2N(CH_3)_2$;

R_{22} is selected from hydrogen, —C(O)N(R_{23})(R_{24}) or —$(-OC_2H_4)_{1-10}$-CH_3

R_{23} is hydrogen;

R_{24} is selected from —C_{1-5} alkyl, —C_{2-5} alkenyl, —C_{2-5} alkynyl, —C_{1-5} alkyl-N(R_{25})(R_{26}), —C_{1-5} alkyl-O-C_{1-3} alkyl, —$(-C_2H_4O)_{1-10}C_2H_5$, —$(-C_2H_4O)_{1-10}$-C_2H_4-R_{27}, —C_{1-3} alkyl-Het_3-$(-C_2H_4O)_{1-10}$-C_2H_4-R_{28} or



; wherein

R_{25} is hydrogen or C1 to C3 alkyl;

R_{26} is hydrogen or C1 to C3 alkyl; or

R_{25} and R_{26} along with the nitrogen atom to which they are attached form a 5 to 6 membered heterocyclic ring, wherein 1 or 2 carbon atoms in the heterocyclic ring are optionally replaced with additional heteroatoms independently selected from nitrogen, oxygen and sulfur and wherein the 5 to 6 membered heterocyclic ring is unsubstituted or substituted with C_{1-3} alkyl, halogen or –OH;

R_{27} is selected from hydrogen or —C(O)NH-C_{2-5} alkyl-$N(CH_3)_2$;

R_{28} is selected from hydrogen or —C(O)NH-C_{2-5} alkyl-$N(CH_3)_2$;

Het_3 is a 5 to 10 membered heterocyclic ring containing one, two or three heteroatoms independently selected from nitrogen, oxygen and sulfur;

OR

R_{23} and R_{24} along with the nitrogen atom to which they are attached form a 4 to 6 membered heterocyclic ring, wherein 1 or 2 carbons in the heterocyclic ring are optionally replaced with additional heteroatoms independently selected from nitrogen, oxygen and sulfur, and wherein the 4 to 6 membered heterocyclic ring is unsubstituted or substituted with $C_{1\text{-}3}$ alkyl, —$N(CH_3)_2$ or —$CH_2N(CH_3)_2$.

DETAILED DESCRIPTION

Definitions:

As used herein, "pharmaceutically acceptable salts" refer to derivatives of the disclosed compounds wherein the parent compound is modified by making non-toxic acid or base salts thereof. Examples of pharmaceutically acceptable salts include, but are not limited to, mineral acid or organic acid salts of basic residues such as amines; alkali or organic salts of acidic residues such as carboxylic acids; and the like. The pharmaceutically acceptable salts include the conventional non-toxic salts or the quaternary ammonium salts of the parent compound formed, for example, from non-toxic inorganic or organic acids. For example, conventional non-toxic acid 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, glycolic, stearic, lactic, malic, tartaric, citric, ascorbic, pamoic, malefic, hydroxymaleic, phenylacetic, glutamic, aspartic, benzoic, salicylic, mesylic, sulfanilic, 2-acetoxybenzoic, fumaric, toluenesulfonic, methanesulfonic, ethane disulfonic, oxalic, malonic, succinic, glutaric, adipic, isethionic and the like. The pharmaceutically acceptable acid addition salts also include salts formed with the addition of one or more equivalents of acids, for example, monohydrochloride, and dihydrochloride salts.

The term "isotope" as used herein refers to the analog of a compound wherein at least one atom in the compound is replaced by its isotope. For example, when at least one hydrogen atom is replaced by a deuterium atom, the compound formed is called an isotope of the original compound. In particular, when a hydrogen atom in original compound is replaced by a deuterium atom, the resulting compound is called as "deuterated analog". The isotope may be a fully or partially isotope substituted derivative.

The term "stereoisomers" as used herein refers to compounds that have identical chemical constitution, but differ with regard to the arrangement of their atoms or groups in space. The

compounds of the present invention may contain asymmetric or chiral centers and, therefore, exist in different stereoisomeric forms. It is intended, unless specified otherwise, that all stereoisomeric forms of the compounds of Formula I to Formula VIII as well as mixtures thereof, including racemic mixtures, form part of the present invention. In addition, all geometric and positional isomers (including *E* and *Z*-forms) as well as mixtures thereof, are also embraced within the scope of the invention. In general, a reference to a compound is intended to cover its stereoisomers and mixture of various stereoisomers.

The term "alkyl" as used herein refers to a saturated hydrocarbon chain radical that includes solely carbon and hydrogen atoms in the backbone, either linear or branched, having from 1 to 10 carbon atoms, both inclusive unless defined otherwise. Suitable non-limiting examples of alkyl groups include, for example, methyl, ethyl, n-propyl, 1-methylethyl (isopropyl), n-pentyl, n-hexyl.

The numerical in phrases like "C_{1-4}" or "C1 to C4", refers to the number of carbon atoms in the chain. For example, the phrase "C_{1-4} alkyl" or "C1 to C4 alkyl" refers to an alkyl chain having 1 to 4 carbon atoms.

The term "alkenyl" as used herein refers to a hydrocarbon chain containing at least one carbon-carbon double bond, and may have (*E*) or (*Z*) configuration. An alkenyl group may contain 2 to 8 carbon atoms unless specified otherwise. Unless set forth or recited to the contrary, all alkenyl groups described herein may form part of a straight or branched chain. Suitable non-limiting examples of alkenyl groups include, e.g., ethylene, 2-propenyl (allyl), 2-methyl-2-propenyl and 2-butenyl. Unless set forth or recited to the contrary, all alkenyl groups described herein may be unsubstituted or substituted.

The term "alkynyl: as used herein refers to a hydrocarbon chain containing at least one carbon-carbon triple bond. Such group may contain 2 to 5 carbon atoms unless specified otherwise. Unless set forth or recited to the contrary, all alkenyl groups described herein may form part of a straight or branched chain. Non-limiting examples of alkynyl groups are: ethynyl, 2-propynyl, 1-propynyl, 2-butynyl. The alkynyl group of the present invention may be further substituted with the akenyl or alkyl groups as defined above.

The term "aryl" as used herein refers to an aromatic radical having 6 to 14 carbon atoms, including monocyclic, bicyclic or tricyclic aromatic systems. A bicyclic aryl group includes an aromatic ring fused to a saturated, partially unsaturated ring, or aromatic ring. The bicyclic aryl group may be attached to the rest of the molecule at any suitable position including the position on the aromatic ring or saturated or partially unsaturated ring. Typical aryl groups include, but are not limited to, phenyl, naphthyl, indanyl (for e.g. 1-indanyl, 5-indanyl), indenyl,

anthracenyl and phenanthrenyl. Unless set forth or recited to the contrary, all aryl groups described herein may be unsubstituted or substituted. For example, an aryl group can be substituted with one or more groups independently selected from:

C_{1-4} alkyl (for example, methyl, ethyl, propyl and butyl) optionally substituted with one more halogen (for example, chloro, fluoro, iodo or bromo);

phenyl; 5 to 10 membered heteroaryl ring optionally substituted with one or more groups selected from C_{1-4} alkyl; amino group, optionally further substituted with a substituted heteroaryl group; and COOH.

The term "heteroaryl ring" refers to a 5 to 14 membered aromatic heterocyclic ring containing one or more (such as 1, 2 or 3) heteroatoms, each independently selected from nitrogen, oxygen and sulfur. The heteroaryl ring may be a mono-, bi- or tri-cyclic ring system and includes fused ring systems (at least one of which is aromatic). The heteroaryl ring radical may be attached to the main structure at any heteroatom or carbon atom that results in the creation of a stable structure. Suitable examples of heteroaryl rings include, but are not limited to, oxazolyl, isoxazolyl, imidazolyl, furyl, indolyl, isoindolyl, pyrrolyl, triazolyl, triazinyl, tetrazoyl, thienyl, thiazolyl, isothiazolyl, pyridyl, pyrimidinyl, pyrazinyl, pyridazinyl, benzofuranyl, benzothiazolyl, benzoxazolyl, benzimidazolyl, benzothienyl, benzopyranyl, carbazolyl, quinolinyl, isoquinolinyl, quinazolinyl, purinyl, quinoxalinyl, quinolinyl, isoquinolinyl, thiadiazolyl, indolizinyl, imidazo[1,2-a]pyridyl and phthalazinyl. Unless set forth or recited to the contrary, all heteroaryl groups described or claimed herein may be unsubstituted or substituted.

The terms "heterocycloalkyl" or "heterocyclic ring" are used interchangeably and refer to an aromatic or non-aromatic cyclic ring containing one, two or three heteroatoms, each independently selected from nitrogen, sulphur or oxygen. Suitable non-limiting examples of heterocycloalkyl groups include those listed under "heteroaryl ring". Heterocycloalkyl group may further include but are not limited to, pyrrolidinyl, piperidine, piperazinyl, morpholinyl, thiomorpholine and 1,3-oxazine. Unless set forth or recited to the contrary, a heterocycloalkyl ring described herein may be unsubstituted or substituted.

As used herein the term "self-immolative group" is a group that has a tendency undergo a cascade of disassembly reactions ultimately leading to release of the active molecule. Such cascade of disassembly reactions are usually triggered due to enzymatic activation of the amino acid or the peptide (A) next to a self-immolative group (Q). Enzymes such as cathepsins and plasmin are non-limiting examples of enzymes that trigger self-immolation of Q of the present invention.

The term “cytotoxic agent” as used herein refers to any agent that exerts a cytotoxic effect on a cell upon contact. Such cytotoxic agents are well known to a person skilled in the art. Examples of cytotoxic agents that may be used in the of the invention include, but are not limited to, alkylating drugs, anthracyclines, pyrimidine derivatives, vinca alkaloids, photodynamic drugs, platinum- containing compounds, taxanes, topoisomerase inhibitors, ribosome inactivating agents (e.g., gelonin), agents that induce DNA damage (e.g., calicheamicin), tubulin inhibitors (e.g., emtansine), anti-mitotic agents (e.g., monomethyl auristatin), or bacterial toxins. The cytotoxic agents may also be radioisotopes or cytotoxic antibodies.

The terms “therapeutic agent”, “active ingredient”, “active agent” as used herein refer to an agent that is administered to treat a condition, disease or illness or the symptoms thereof. For the purpose of present invention, a therapeutic agent is an anget known for the treatment of a disease or illness involving cells expressing PSMA.

The terms "subject" or "patient" are used interchangeably and refer to a subject that may benefit from the present invention such as a mammal (e.g., canine, feline, ovine, porcine, equine, bovine, or human). In one specific embodiment, the patient is human. Diagnosis of a disease or disorder associated with expression of PSMA may be performed by a skilled physician by methods known in the art.

The term “subject in need thereof” in the context of the present invention inter alia refers to mammals, particularly human subjects, suffering from a disease or disorder associated with expression of PSMA.

The terms “disease” and “disorder” are used interchangeably.

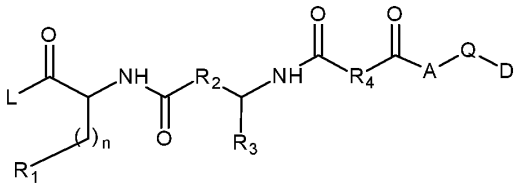
The term “cancer” as used herein refers to the diseases caused by uncontrolled cell division and the ability of cells to metastasize, or to establish new growth in additional sites. The terms “malignant”, “malignancy”, “neoplasm”, “tumor”, “cancer” and variations thereof refer to cancerous cells or groups of cancerous cells. For the purpose of the present invention, the cancer is associated with the expression of PSMA in the cancerous cells or the cancer is associated with the expression of PSMA in the cells that are in a close proximity of cancerous cells.

It is to be understood that the terms ‘treat’, ‘treating’, ‘treatment’ or forms thereof, as used herein, mean reducing, preventing, curing, reversing, ameliorating, attenuating, alleviating, minimizing, suppressing, or halting the deleterious effects of a disease or a condition or delaying the onset of one or more clinical indications of a disease or disorder.

A "therapeutically effective amount" of a compound is an amount which is sufficient to reduce or ameliorate the progression, severity and/or duration of a disease or disorder or ameliorate one or more symptoms of a disease or disorder, prevent the recurrence of a disease or disorder, prevent the development or onset of a disease or disorder, or one or more symptoms thereof. For the purpose of the present invention, a therapeutically effective amount is an amount of the compound of the present invention administered to the subject to reduce or ameliorate the progression, severity, duration or symptoms of the diseases associated with the expression of PSMA.

The terms "pharmaceutical composition", "medicament" and "dosage form" are used interchangeably and mean a pharmaceutical preparation consisting of drug substance(s) and/or excipient(s) to facilitate dosing or administration and delivery of the content of the drug product to the subject. The drug substance is an active ingredient or a compound containing active ingredient/s. For the purpose of present invention, the compounds of Formula I to VII are the drug substances.

According to the first aspect of the present invention, there is provided a compound of Formula I



Formula I

or pharmaceutically acceptable salt, stereoisomer or isotope thereof,

wherein: n is 0, 1, 2, 3 or 4;

L is a ligand;

R_1 is selected from a 6 to 14 membered aryl or a 5 to 13 membered heteroaryl containing one, two or three heteroatoms independently selected from nitrogen, oxygen or sulfur;

R_1 is unsubstituted or substituted with one or more R_5;

R_5, at each occurrence, is independently selected from halogen, —$C(O)NH_2$, —$C(O)OR_6$, —$C_{1\text{-}3}$ alkyl, —OR_7, and a 6 to 10 membered aryl; wherein,

R_6 is hydrogen or $C_{1\text{-}3}$ alkyl;

R_7 is hydrogen or $C_{1\text{-}3}$ alkyl;

R_2 is absent or is selected from a 6 to 10 membered cycloalkyl or a 6 to 10 membered aryl;

R_3 is hydrogen or —C_1-C_5COOH;

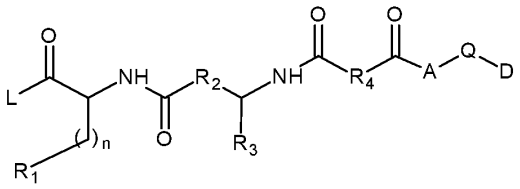
A is an amino acid or a peptide comprising 2-5 amino acids;

A is attached to Q through its C terminal;

Q is a self-immolative group; and

D is a cytotoxic agent or a therapeutic agent.

According to one aspect of the present invention, there is provided a compound of Formula I



Formula I

or pharmaceutically acceptable salt, stereoisomer or isotope thereof,

wherein: n is 0, 1, 2, 3 or 4;

L is a ligand;

R_1 is selected from a 6 to 14 membered aryl or a 5 to 13 membered heteroaryl containing one, two or three heteroatoms independently selected from nitrogen, oxygen or sulfur;

R_1 is unsubstituted or substituted with one or more R_5;

R_5, at each occurrence, is independently selected from halogen, —$C(O)NH_2$, —$C(O)OR_6$, —C_{1-3} alkyl, —OR_7, and a 6 to 10 membered aryl; wherein,

R_6 is hydrogen or C_{1-3} alkyl;

R_7 is hydrogen or C_{1-3} alkyl;

R_2 is absent or is selected from a 6 to 10 membered cycloalkyl or a 6 to 10 membered aryl;

R_3 is hydrogen or —C_1-C_5COOH;

R_4 is selected from a group consisting of —C_{1-10} alkyl-, —C_{2-6} alkenyl-, —C_{1-3} alkyl-O-C_{1-3} alkyl—, —C_{2-6} alkyl-N(R_8)—, —C_{2-6} alkyl(N(R_8)($R_{8'}$))—, —N(R_8)-C_{2-6} alkyl—, a 3 to 6 membered cycloalkyl and —C_{1-2} alkyl-(-OC_2H_4)$_{1-8}$-OC_{1-2} alkyl—; wherein,

R_8 and $R_{8'}$ are independently selected from hydrogen, C_{1-6} alkyl, -C(O)-C_{1-4}alkyl-aryl or -C(O)-(-C_2H_4O)$_{1-8}$-C_{1-2} alkyl-N(R)(R'), wherein said aryl is selected from 6 to 14 membered aryl and is optionally substituted by -C_{1-3}alkyl or -OC_{1-3}alkyl; wherein

R and R' are independently selected from hydrogen, -C_{1-6} alkyl or -C(O)-C_{1-4}alkyl-aryl, wherein said aryl is selected from 6 to 14 membered aryl and is optionally substituted by -C_{1-3}alkyl or -OC_{1-3}alkyl;

A is an amino acid or a peptide comprising 2-5 amino acids;

A is attached to Q through its C terminal;

Q is a self-immolative group; and

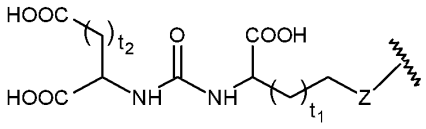
D is a cytotoxic agent or a therapeutic agent.

The compounds of Formula I may be described in one or more embodiments. It is to be understood that the embodiments described herein are illustrative of the present invention and are not intended to be limiting. It is also to be understood that the embodiments described herein may be used independently or in conjunction with any definition, or any other embodiment defined herein. Thus, the invention contemplates all possible combinations and permutations of the various independently described embodiments.

According to an embodiment n is 0, wherein R_1 is directly attached to the carbon next to –CO. According to another embodiment, n is 1, 2, 3 or 4, wherein R_1 is attached to the carbon next to –CO through 1 or 2 or 3 or 4 methylene groups.

According to an embodiment, L is an antigen binding ligand. According to a preferred embodiment, the ligand is prostate specific membrane antigen (PSMA) binding ligand.

According to an embodiment, L is a ligand of Formula L_1:



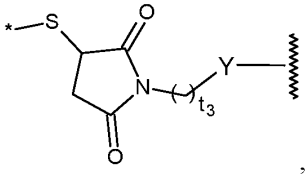
Formula L_1

wherein,

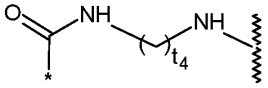
t_1 is 0, 1, 2, 3, or 4;

t_2 is 1, 2, 3 or 4;

Z is selected from the group consisting of $N(R_9)$, Formula Z_1 and Formula Z_2:



Formula Z_1



Formula Z_2

wherein:

t_3 is selected from 1, 2, 3, 4, 5 or 6;

t_4 is selected from 1, 2, 3, 4, 5 or 6;

Y is $-CH_2-$ or –NH- and

‘ wwwww ’ indicates attachment of Formula L_1 to the rest of the compound of Formula I;

R_9 is selected from the group consisting of hydrogen, C_{1-5} alkyl, a 6 to 10 membered aryl, a 5 to 10 membered heterocyclyl ring wherein the heterocyclyl ring contains one, two or three heteroatoms independently selected from nitrogen, oxygen or sulfur; and wherein R_9 is unsubstituted or substituted with halogen.

In an embodiment, t_1 is 3; t_2 is 2; and Z is $N(R_9)$, wherein R_9 is hydrogen.

In an embodiment, t_1 is 3; t_2 is 2; and Z is $N(R_9)$, wherein R_9 is phenyl.

In another embodiment, t_1 is 3; t_2 is 2; and Z is $N(R_9)$, wherein phenyl substituted with Cl, Br, or I.

In an embodiment, t_1 is 0; t_2 is 2; and Z is Z_1, wherein t_3 is 1, 2, 3, 4, 5 or 6 and Y is —NH—.

In an embodiment, t_1 is 1; t_2 is 2 and Z is a compound of Formula Z_2.

In an embodiment, R_1 is selected from phenyl, a fused bicyclic or a fused tricyclic aromatic ring. In an embodiment, R_1 is selected from a monocyclic or a fused bicyclic heteroaromatic ring containing at least one heteroatom independently selected from nitrogen, oxygen or sulfur. In an embodiment, R_1 is unsubstituted.

In an embodiment, R_1 is substituted with Cl, Br, I, —OH, $—C(O)NH_2$, —C(O)OH, $—C(O)OCH_3$, $—C(O)OC_2H_5$, $—CH_3$, $—CH_2CH_3$, $—OCH_3$, $—OCH_2CH_3$ or phenyl.

In an embodiment, R_2 is absent. In an embodiment, R_2 is selected from a monocyclic or a fused bicyclic aromatic or non-aromatic ring. In an embodiment, R_2 is a monocyclic aromatic ring. In an embodiment, R_2 is a monocyclic non-aromatic ring.

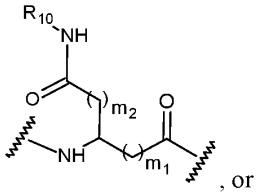
In an embodiment, when R_2 is absent and R_3 is H. In another embodiment, when R_2 is absent R_3 is $—C_{1-5}COOH$. The skilled person would appreciated that in the absence of R_2, the carbon atom with R_3 is directly attached to —CO.

In an embodiment, when R_2 is selected from a 6 to 10 membered cycloalkyl or a 6 to 10 membered aryl, R_3 is H.

According to an embodiment of the present invention, the A is an amino acid or a peptide comprising two or more same or different amino acids. The amino acids used for the present invention can be selected from natural or non-natural amino acids. It can be racemic or a stereoisomer. In a particular embodiment, the amino acids used in the present invention are stereoisomers. In another particular embodiment, the amino acids used in the present invention are dextro- rotatory or levo-rotatory.

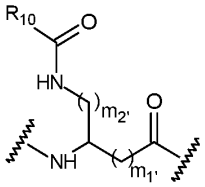
In an embodiment, at each occurrence, the amino acid is independently selected from the group consisting of alanine (ala), arginine (arg), aspartic acid (asp), cysteine (cys), glutamic acid (glu), glycine (gly), lysine (lys), phenylalanine (phe), serine (ser), threonine (thr), tryptophan

(trp), valine (val), ornithine (orn), citrulline (cit), homocitrulline (hct), lanthionine (lan), homocysteine (hcy) or an amino acid having Formula A_1 or Formula A2



, or

Formula A_1



Formula A_2

wherein

m_1 and m_1' are 0, 1, 2 or 3;

m_2 and m_2' are is 0, 1, 2, 3 or 4;

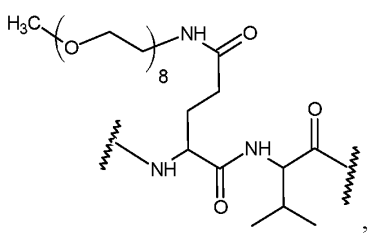
R_{10} is selected from $(-C_2H_4O)_{1-24}CH_3$, $(-C_2H_4O)_{1-24}C_{1-2}$ alkyl($N(R_{10'})(R_{10''})$)—, C_{1-3} alkyl-aryl or —C_{1-3} alkyl-Het_1-$(-C_2H_4O)_{1-24}CH_3$, wherein Het_1 is a 5 to 10 membered heterocyclic ring containing one, two or three heteroatoms independently selected from nitrogen, oxygen or sulfur and wherein said aryl is selected from 6 to 14 membered aryl and is optionally substituted by -C_{1-3}alkyl or -OC_{1-3}alkyl; wherein

$R_{10'}$ and $R_{10''}$ are independently selected from hydrogen, C_{1-6} alkyl or -C(O)-C_{1-4}alkyl-aryl wherein said aryl is selected from 6 to 14 membered aryl and is optionally substituted by -C_{1-3}alkyl or -OC_{1-3}alkyl.

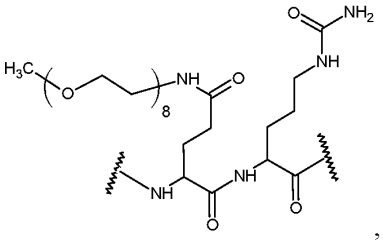
In a particular embodiment, the amino acid is independently selected from alanine (ala), arginine (arg), aspartic acid (asp), cysteine (cys), glutamic acid (glu), glycine (gly), lysine (lys), phenylalanine (phe), serine (ser), threonine (thr), tryptophan (trp), valine (val), citrulline (cit), homocitrulline (hct), homocysteine (hcy) or amino acid having the Formula A_1 or Formula A_2 wherein:

m_1 m_1' are 0, 1 or 2; m_2 is 2; m_2' is 4; R_{10} is selected from $(-C_2H_4O)_{6-8}CH_3$, $(-C_2H_4O)_3C_2H_4(NH(C(O)C_3H_6$-aryl))—, C_3H_6-aryl or —CH_2-Het_1-$(-C_2H_4O)_8CH_3$, wherein Het_1 is triazolyl and aryl is 4-methyl phenyl or 4-methoxy phenyl.

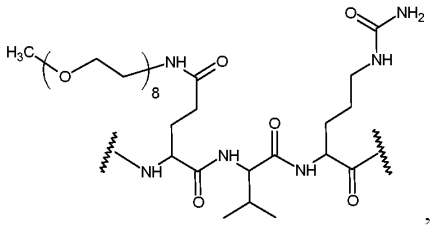
In an embodiment, at each occurrence, a peptide is independently selected from ala-ala, ala-ala-ala, ala-phe, val-ala, val-cit, ala-val-cit, ala(beta)-val-cit, glu-val-cit, glu-cit, glu-val, gly-gly, gly-gly-phe, gly-gly-phe-gly, asp-cit, asp-val-cit and asp-val; or a peptide is selected from the group of compounds having following formula:



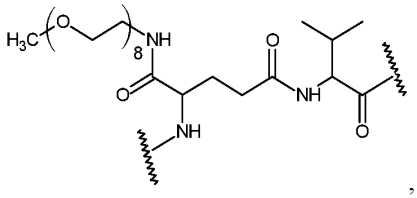
Formula P_1



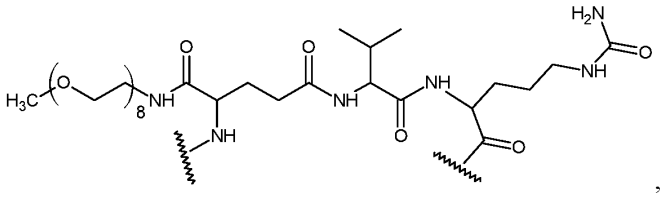
Formula P_2



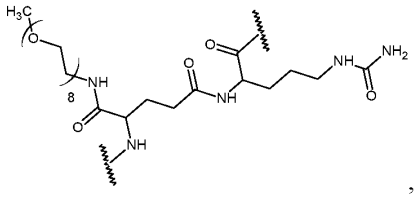
Formula P_3



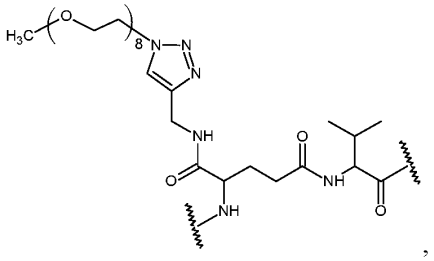
Formula P_4



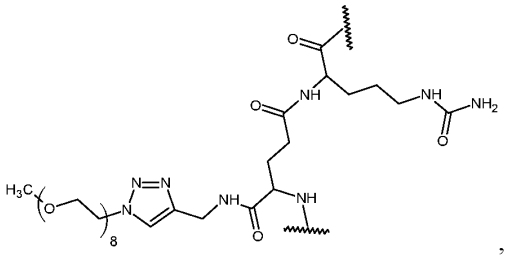
Formula P_5



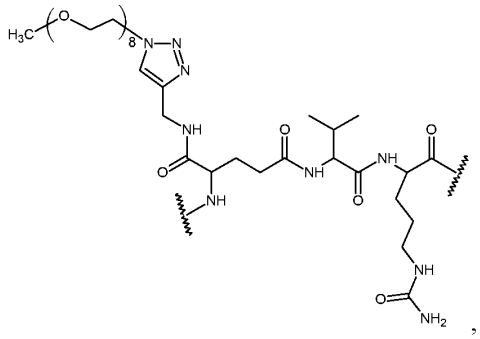
Formula P_6



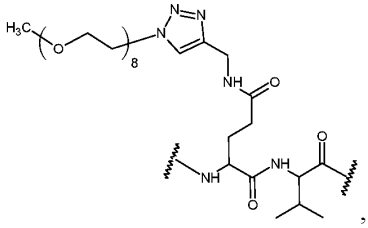
Formula P_7



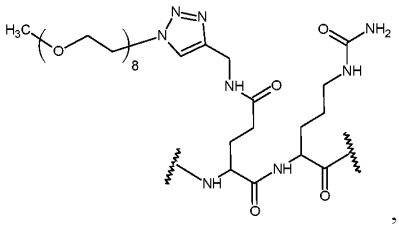
Formula P_8



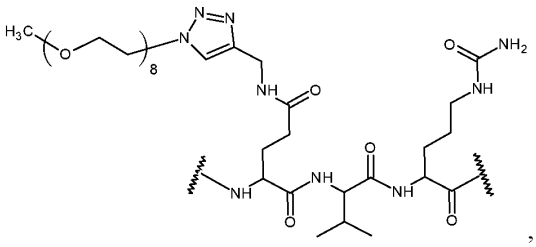
Formula P_9



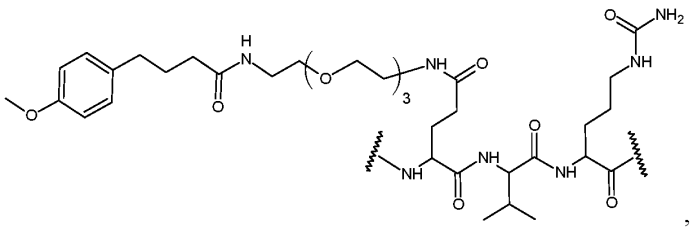
Formula P_{10}



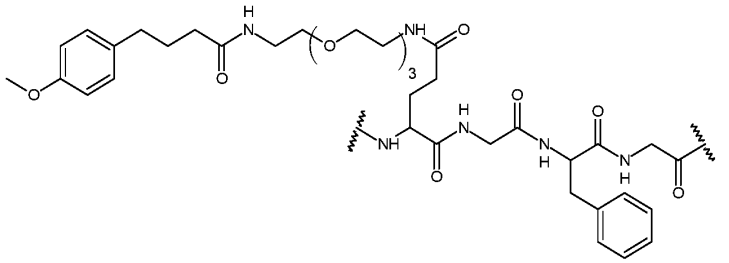
Formula P_{11}



Formula P_{12}

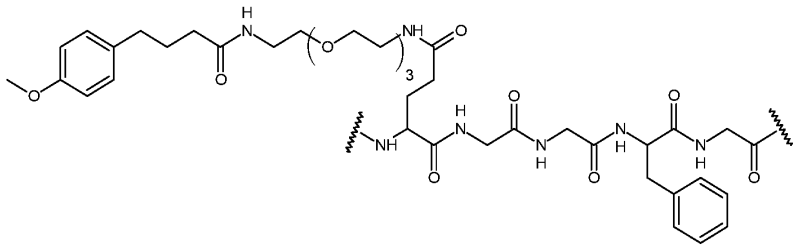


Formula P_{13}



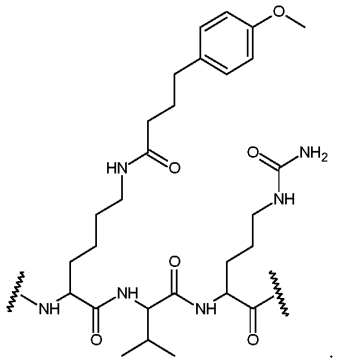
,

Formula P_{14}



, and

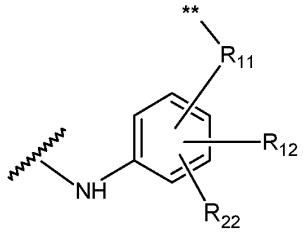
Formula P_{15}



.

Formula P_{16}

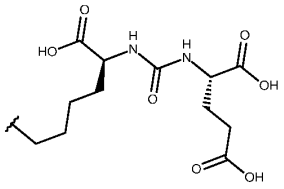
According to an embodiment of the present invention, the self-immolative group Q is of the Formula Q_1:



Formula Q_1

wherein,

R_{11} is selected from a group consisting of —C_{1-3} alkyl-OC(O)—**,
—C_{1-3} alkyl-O-C(O)-N(R_{19})-C_{1-5} alkyl-N(R_{19})-C(O)—**,
—C_{1-3} alkyl-O-C(O)-N[C_{1-5} alkyl-N($R_{20}R_{21}$)]-C_{1-3} alkyl—**, and
—C_{1-3} alkyl-O-C(O)-Het_2-C_{1-3} alkyl-N(R_{19})-C(O)—**,
wherein
R_{19} is selected from hydrogen, —C_{1-3} alkyl or —C_{1-3} alkyl-O-C_{1-3} alkyl-OH;
R_{20} is hydrogen or —C_{1-3} alkyl;
R_{21} is hydrogen or —C_{1-3} alkyl; and
Het_2 is a 5 to 10 membered heterocyclic ring containing one, two or three heteroatoms independently selected from nitrogen, oxygen or sulfur;
R_{12} is selected from hydrogen, —C(O)N(R_{13})(R_{14}) or —(-OC_2H_4)$_{1-10}$-CH_3
R_{13} is hydrogen;
R_{14} is selected from —C_{1-5} alkyl, —C_{2-5} alkenyl, —C_{2-5} alkynyl, —C_{1-5} alkyl-N(R_{15})(R_{16}), —C_{1-5} alkyl-O-C_{1-3} alkyl, —(-C_2H_4O)$_{1-10}$$C_2H_5$, —(-$C_2H_4O$)$_{1-10}$-$C_2H_4$-$R_{17}$, —$C_{1-3}$ alkyl-Het_3-(-C_2H_4O)$_{1-10}$-C_2H_4-R_{18} or



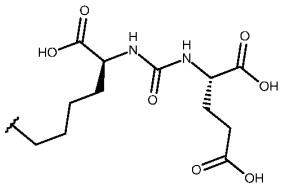
; wherein:
R_{15} is hydrogen or C1 to C3 alkyl;
R_{16} is hydrogen or C1 to C3 alkyl; or
R_{15} and R_{16} along with the nitrogen atom to which they are attached form a 5 to 6 membered heterocyclic ring, wherein 1 or 2 carbon atoms in the heterocyclic ring are optionally replaced with additional heteroatoms independently selected from nitrogen, oxygen and sulfur and wherein the 5 to 6 membered heterocyclic ring is unsubstituted or substituted with C_{1-3} alkyl, halogen or –OH;
R_{17} is selected from hydrogen or —C(O)NH-C_{2-5} alkyl-N(CH_3)$_2$;
R_{18} is selected from hydrogen or —C(O)NH-C_{2-5} alkyl-N(CH_3)$_2$;
Het_3 is a 5 to 10 membered heterocyclic ring containing one, two or three heteroatoms independently selected from nitrogen, oxygen and sulfur;
OR
R_{13} and R_{14} along with the nitrogen atom to which they are attached form a 4 to 6 membered heterocyclic ring, wherein 1 or 2 carbons in the heterocyclic ring are

optionally replaced with additional heteroatoms independently selected from nitrogen, oxygen and sulfur, and wherein the 4 to 6 membered heterocyclic ring is unsubstituted or substituted with C_{1-3} alkyl, —$N(CH_3)_2$ or —$CH_2N(CH_3)_2$;

R_{22} is selected from hydrogen, —$C(O)N(R_{23})(R_{24})$ or —$(-OC_2H_4)_{1-10}$-CH_3

R_{23} is hydrogen;

R_{24} is selected from —C_{1-5} alkyl, —C_{2-5} alkenyl, —C_{2-5} alkynyl, —C_{1-5} alkyl-$N(R_{25})(R_{26})$, —C_{1-5} alkyl-O-C_{1-3} alkyl, —$(-C_2H_4O)_{1-10}C_2H_5$, —$(-C_2H_4O)_{1-10}$-C_2H_4-R_{27}, —C_{1-3} alkyl-Het_3-$(-C_2H_4O)_{1-10}$-C_2H_4-R_{28} or



; wherein

R_{25} is hydrogen or C1 to C3 alkyl;

R_{26} is hydrogen or C1 to C3 alkyl; or

R_{25} and R_{26} along with the nitrogen atom to which they are attached form a 5 to 6 membered heterocyclic ring, wherein 1 or 2 carbon atoms in the heterocyclic ring are optionally replaced with additional heteroatoms independently selected from nitrogen, oxygen and sulfur and wherein the 5 to 6 membered heterocyclic ring is unsubstituted or substituted with C_{1-3} alkyl, halogen or –OH;

R_{27} is selected from hydrogen or —$C(O)NH$-C_{2-5} alkyl-$N(CH_3)_2$;

R_{28} is selected from hydrogen or —$C(O)NH$-C_{2-5} alkyl-$N(CH_3)_2$;

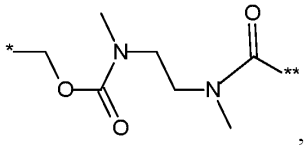
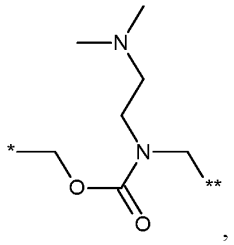
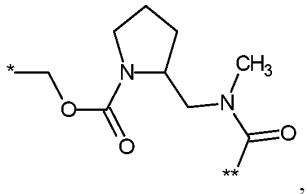
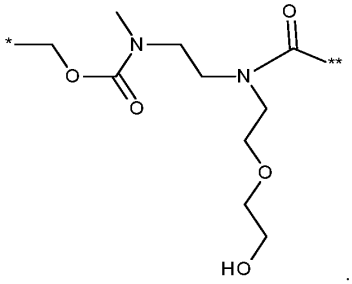
Het_3 is a 5 to 10 membered heterocyclic ring containing one, two or three heteroatoms independently selected from nitrogen, oxygen and sulfur;

OR

R_{23} and R_{24} along with the nitrogen atom to which they are attached form a 4 to 6 membered heterocyclic ring, wherein 1 or 2 carbons in the heterocyclic ring are optionally replaced with additional heteroatoms independently selected from nitrogen, oxygen and sulfur, and wherein the 4 to 6 membered heterocyclic ring is unsubstituted or substituted with C_{1-3} alkyl, —$N(CH_3)_2$ or —$CH_2N(CH_3)_2$; and

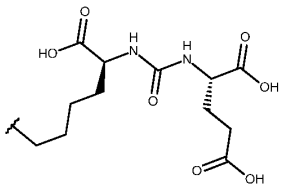
'wwwww' indicates the point of attachment of Q to C terminal of A and ** indicates point of attachment of Q to D.

In an embodiment, in the compound of Formula I, R_{11} is selected from:

*–$CH_2OC(O)$-**,  ,  ,  , or  .

In an embodiment, in the compound of Formula VIII, R_{13} is hydrogen and

R_{14} is selected from —$C_{1\text{-}5}$ alkyl, —$C_{2\text{-}5}$ alkenyl, —$C_{2\text{-}5}$ alkynyl, —$C_{1\text{-}5}$ alkyl-$N(R_{15})(R_{16})$, —$C_{1\text{-}5}$ alkyl-O-$C_{1\text{-}3}$ alkyl, —$(\text{-}C_2H_4O)_{1\text{-}10}C_2H_5$, —$(\text{-}C_2H_4O)_{1\text{-}10}$-$C_2H_4$-$R_{17}$, —$C_{1\text{-}3}$ alkyl-Het_3-$(\text{-}C_2H_4O)_{1\text{-}10}$-$C_2H_4$-$R_{18}$ or

 ; wherein:

R_{15} is selected from H, —CH_3 or —C_2H_5;

R_{16} is selected from H, —CH_3 or —C_2H_5;

R_{15} and R_{16} along with the nitrogen atom to which they are attached form a 5 to 6 membered heterocyclic ring, wherein 1 or 2 carbon atoms in the heterocyclic ring are optionally replaced with additional heteroatoms independently selected from nitrogen, oxygen and sulfur and wherein the 5 to 6 membered heterocyclic ring is unsubstituted or substituted with $C_{1\text{-}3}$ alkyl, halogen or –OH;

R_{17} is selected from hydrogen or —$C(O)NH$-C_2H_5-$N(CH_3)_2$;

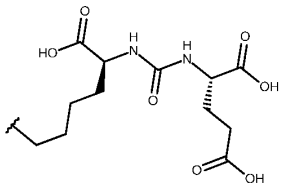
R_{18} is selected from hydrogen or —$C(O)NH$-C_2H_5-$N(CH_3)_2$;

Het_3 is triazolyl;

In an embodiment, in the compound of Formula VIII, R_{13} and R_{14} along with the nitrogen atom to which they are attached form a 4 to 6 membered heterocyclic ring, wherein 1 or 2 carbons in the heterocyclic ring are optionally replaced with additional heteroatoms independently selected from nitrogen, oxygen and sulfur, and wherein the 4 to 6 membered heterocyclic ring is unsubstituted or substituted with C_{1-3} alkyl, —$N(CH_3)_2$ or —$CH_2N(CH_3)_2$.

In an embodiment, in the compound of Formula VIII, R_{23} is hydrogen and

R_{24} is selected from —C_{1-5} alkyl, —C_{2-5} alkenyl, —C_{2-5} alkynyl, —C_{1-5} alkyl-$N(R_{25})(R_{26})$, —C_{1-5} alkyl-O-C_{1-3} alkyl, —$(-C_2H_4O)_{1-10}C_2H_5$, —$(-C_2H_4O)_{1-10}$-C_2H_4-R_{27}, —C_{1-3} alkyl-Het_3-$(-C_2H_4O)_{1-10}$-C_2H_4-R_{28} or



; wherein

R_{25} is selected from H, —CH_3 or —C_2H_5;

R_{26} is selected from H, —CH_3 or —C_2H_5;

R_{25} and R_{26} along with the nitrogen atom to which they are attached form a 5 to 6 membered heterocyclic ring, wherein 1 or 2 carbon atoms in the heterocyclic ring are optionally replaced with additional heteroatoms independently selected from nitrogen, oxygen and sulfur and wherein the 5 to 6 membered heterocyclic ring is unsubstituted or substituted with C_{1-3} alkyl, halogen or –OH;

R_{27} is selected from hydrogen or —C(O)NH-C_2H_5-$N(CH_3)_2$;

R_{28} is selected from hydrogen or —C(O)NH-C_2H_5-$N(CH_3)_2$;

Het_4 is triazolyl;

In an embodiment, in the compound of Formula VIII, R_{23} and R_{24} along with the nitrogen atom to which they are attached form a 4 to 6 membered heterocyclic ring, wherein 1 or 2 carbons in the heterocyclic ring are optionally replaced with additional heteroatoms independently selected from nitrogen, oxygen and sulfur, and wherein the 4 to 6 membered heterocyclic ring is unsubstituted or substituted with C_{1-3} alkyl, —$N(CH_3)_2$ or —$CH_2N(CH_3)_2$.

According to an embodiment of the present invention, D is an active ingredient with cytotoxic or therapeutic effect.

One of the objects of the present invention is to provide an option for the selective treatment of a disease associated with the PSMA expressing cells or tissues. The compounds of the present invention are designed in such a way that the selectivity of these compounds is due to

the ligands and the efficacy for the treatment of disease is arrived at using the drug D. Thus D, for the present invention can be any active ingredient that is known or being investigated for the treatment of the pathology associated with PSMA hyperproliferation of cells. Along with the several prostate tissues, PSMA is expressed in various parts of the body, including but not limited to brain cells, renal cells, bladder cells, colon cells and breast cells. Diseases, especially tumours or cancers, more specifically solid tumours, associated with these cells are targeted by the therapeutic agent (D) of the present invention.

In some embodiments, the therapeutic agent is a drug that is known for the treatment of cancer. In some other embodiments the therapeutic agent is a drug known or being investigated for the treatment of cancer associated with expression of PSMA cells. In some other embodiments, the therapeutic agent is a drug known or being investigated in the treatment of prostate cancer, lung cancer, renal cell cancer, glioblastoma, pancreatic cancer, bladder cancer, breast cancer, colon cancer, oesophageal cancer, stomach cancer head cancer, neck cancer, head and neck cancer, colorectal cancer, leukaemia/lymphoma, uterine cancer, skin cancer, endocrine cancer, urinary cancer, gastrointestinal cancer, ovarian cancer or cervical cancer. Non-limiting examples of such therapeutic agents are olaparib, rucaparib, talazoparib, niraparib, vellparib; irinotecan, topotecan, exatecan, etoposide, teniposide, dabrafenib, entrectinib, larotrectinib, trametinib, selpercatinib, docetaxel, mobocertinib, infigratinib, tivozanib, tepotinib, pralsetinib, capmatinib, pemigatinib, tucatinib, neratinib, osimertinib, ceritinib, abemaciclib, ribociclib, palbociclib, ripretinib, selumetinib, avapritinib, erdafitinib, lorlatinib, dacomitinib, encorafenib, brigatinib, alectinib, lenvatinib, cabozantinib, regorafenib, axitinib, alpelisib, tazemetostat, relugolix, darolutamide, apalutamide, sonidegib, enzalutamide, vismodegib, mitomycin, trabectedin, giredestrant, pemrametostat and adavosertib.

In an embodiment, D is a cytotoxic agent as defined above. Some of the non-limiting examples of cytotoxic agents are microtubule disrupting agents, such as auristatin, for example monomethyl auristatin E (MMAE), monomethyl auristatin F (MMAF), and auristatin F (AF); maytansinoids, for example DM1, DM3, and DM4; DNA damaging agents, such as calicheamicins, duocarmycins, SN-38, and pyrrolo[2,1-c][1,4]benzodi-azepines (PBDs); amanitins, anthracyclines, baccatins, camptothecins, cemadotins, colchicines, colcimids, combretastatins, cryptophycins, discodermolides, doxorubicin, echinomycins, eleutherobins, epothilones, estramustines, lexitropsins, maytansines, methotrexate, netropsins, puromycins, rhizoxins, taxanes, tubulysins, or vinca alkaloids.

According to an embodiment, the present invention provides a compound of Formula I, wherein:

n is 0, 1 or 2

R_1 is selected from a 6 to 10 membered aryl or a 5 to 13 membered heteroaryl containing one, two or three heteroatoms independently selected from nitrogen, oxygen or sulfur;

R_1 is unsubstituted or substituted with one or more R_5;

R_5, at each occurrence, is independently selected from halogen, —OH, —OCH_3, —OC_2H_5 or a 6 to 10 membered aryl;

R_2 is selected from a group consisting of a 5 to 6 membered cycloalkyl and 6 to 10 membered aryl;

R_3 is hydrogen;

R_4 is selected from a group consisting of —C_{1-10} alkyl-, —C_{2-6} alkenyl-, —C_{1-3} alkyl-O-C_{1-3} alkyl—, —C_{2-6} alkyl-N(R_8)—, —C_{2-6} alkyl(N(R_8)($R_{8'}$))—, —N(R_8)-C_{2-6} alkyl—, a 3 to 6 membered cycloalkyl and —C_{1-2} alkyl-(-OC_2H_4)$_{1-8}$-OC_{1-2} alkyl—; wherein,

R_8 and $R_{8'}$ are independently selected from hydrogen, C_{1-6} alkyl, -C(O)-C_{1-4}alkyl-aryl or -C(O)-(- C_2H_4O)$_{1-8}$-C_{1-2} alkyl-N(R)(R'), wherein said aryl is selected from 6 to 14 membered aryl and is optionally substituted by -C_{1-3}alkyl or -OC_{1-3}alkyl; wherein

R and R' are independently selected from hydrogen, -C_{1-6} alkyl or -C(O)-C_{1-4}alkyl-aryl, wherein said aryl is selected from 6 to 14 membered aryl and is optionally substituted by -C_{1-3}alkyl or -OC_{1-3}alkyl;

A is selected from the group consisting of cit, ala-ala, ala-ala-ala, ala-phe, val-ala, val-cit, ala-val-cit, ala(beta)-val-cit, glu-val-cit, glu-cit, glu-val, gly-gly, gly-gly-phe, gly-gly-phe-gly, Formula P_3, Formula P_5, Formula P_9, Formula P_{12}, Formula P_{13}, Formula P_{14}, Formula P_{15} and Formula P_{16}.

According to an embodiment, the present invention provides a compound of Formula I, wherein:

n is 1;

R_1 is naphthyl;

R_2 is cyclohexyl or phenyl;

R_3 is hydrogen;

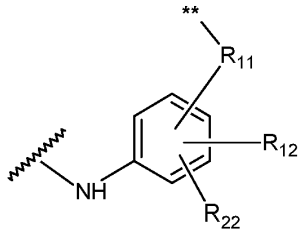
R_4 is selected from a group consisting of —C_{1-10} alkyl-, —C_{2-6} alkenyl-, —C_{1-3} alkyl-O-C_{1-3} alkyl—, —C_{2-6} alkyl-N(R_8)—, —C_{2-6} alkyl(N(R_8)($R_{8'}$))—, —N(R_8)-C_{2-6} alkyl—, a 3 to 6 membered cycloalkyl and —C_{1-2} alkyl-(-OC_2H_4)$_{1-8}$-OC_{1-2} alkyl—; wherein,

R_8 and $R_{8'}$ are independently selected from hydrogen, C_{1-6} alkyl, -C(O)-C_{1-4}alkyl-aryl or -C(O)-(-C_2H_4O)$_{1-8}$-C_{1-2} alkyl-N(R)(R'), wherein said aryl is selected from 6 to 14 membered aryl and is optionally substituted by -C_{1-3}alkyl or -OC_{1-3}alkyl; wherein

R and R' are independently selected from hydrogen, -C_{1-6} alkyl or -C(O)-C_{1-4}alkyl-aryl, wherein said aryl is selected from 6 to 14 membered aryl and is optionally substituted by -C_{1-3}alkyl or -OC_{1-3}alkyl;

A is selected from the group consisting of cit, ala-ala, ala-ala-ala, ala-phe, val-ala, val-cit, ala-val-cit, ala(beta)-val-cit, glu-val-cit, glu-cit, glu-val, gly-gly, gly-gly-phe, gly-phe-gly, gly-gly-phe-gly, Formula P_3, Formula P_5, Formula P_9, Formula P_{12}, Formula P_{13}, Formula P_{14}, Formula P_{15} and Formula P_{16};

Q is of Formula Q1,



Formula Q_1

wherein:

** indicates point of attachment of Q to D.

R_{11} is selected from —C_{1-3} alkyl-OC(O)—**,

—C_{1-3} alkyl-O-C(O)-N(R_{19})-C_{1-5} alkyl-N(R_{19})-C(O)—**,

—C_{1-3} alkyl-O-C(O)-N[C_{1-5} alkyl-N($R_{20}R_{21}$)]-C_{1-3} alkyl—**, or

—C_{1-3} alkyl-O-C(O)-Het_2-C_{1-3} alkyl-N(R_{19})-C(O)—**,

R_{19} is selected from H, CH_3 or –C_2H_4-O-C_2H_4-OH;

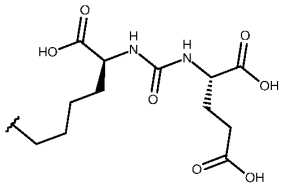
R_{20} is CH_3; R_{21} is CH_3; and

Het_2 is pyrrolidinyl;

R_{12} is selected from hydrogen, —C(O)N(R_{13})(R_{14}) or —$(-OC_2H_4)_{1-10}$-CH_3

R_{13} is hydrogen;

R_{14} is selected from —C_{1-5} alkyl, —C_{2-5} alkenyl, —C_{2-5} alkynyl, —C_{1-5} alkyl-N(R_{15})(R_{16}), —C_{1-5} alkyl-O-C_{1-3} alkyl, —$(-C_2H_4O)_{1-10}C_2H_5$, —$(-C_2H_4O)_{1-10}$-C_2H_4-R_{17}, —C_{1-3} alkyl-Het_3-$(-C_2H_4O)_{1-10}$-C_2H_4-R_{18} or



wherein:

R_{15} is —CH_3 or —C_2H_5; R_{16} is —CH_3 or —C_2H_5;

or

R_{15} and R_{16} along with the nitrogen atom to which they are attached form a 5 to 6 membered heterocyclic ring, wherein 1 or 2 carbon atoms in the heterocyclic ring are optionally replaced with additional heteroatoms independently selected from nitrogen, oxygen and sulfur and wherein the 5 to 6 membered heterocyclic ring is unsubstituted or substituted with —CH_3;

R_{17} is —$C(O)NHC_2H_4N(CH_3)_2$;

R_{18} is —$C(O)NHC_2H_4N(CH_3)_2$;

Het_3 is triazolyl;

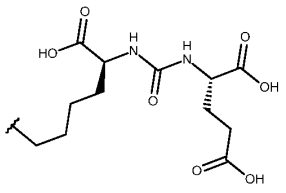
OR

R_{13} and R_{14} along with the nitrogen atom to which they are attached form a 4 to 6 membered heterocyclic ring, wherein 1 or 2 carbons in the heterocyclic ring are optionally replaced with additional heteroatoms independently selected from nitrogen, oxygen and sulfur, and wherein the 4 to 6 membered heterocyclic ring is unsubstituted or substituted with C_{1-3} alkyl, —$N(CH_3)_2$ or —$CH_2N(CH_3)_2$;

R_{22} is selected from hydrogen, —$C(O)N(R_{23})(R_{24})$ or —$(-OC_2H_4)_{1-10}$-CH_3

R_{23} is hydrogen;

R_{24} is selected from —C_{1-5} alkyl, —C_{2-5} alkenyl, —C_{2-5} alkynyl, —C_{1-5} alkyl-$N(R_{25})(R_{26})$, —C_{1-5} alkyl-O-C_{1-3} alkyl, —$(-C_2H_4O)_{1-10}C_2H_5$, —$(-C_2H_4O)_{1-10}$-C_2H_4-R_{27}, —C_{1-3} alkyl-Het_3-$(-C_2H_4O)_{1-10}$-C_2H_4-R_{28} or



; wherein

R_{25} is hydrogen or C1 to C3 alkyl;

R_{26} is hydrogen or C1 to C3 alkyl; or

R_{25} and R_{26} along with the nitrogen atom to which they are attached form a 5 to 6 membered heterocyclic ring, wherein 1 or 2 carbon atoms in the heterocyclic ring are optionally replaced with additional heteroatoms independently selected from nitrogen, oxygen and sulfur and wherein the 5 to 6 membered heterocyclic ring is unsubstituted or substituted with C_{1-3} alkyl, halogen or –OH;

R_{27} is selected from hydrogen or —$C(O)NH$-C_{2-5} alkyl-$N(CH_3)_2$;

R_{28} is selected from hydrogen or —C(O)NH-C_{2-5} alkyl-$N(CH_3)_2$;

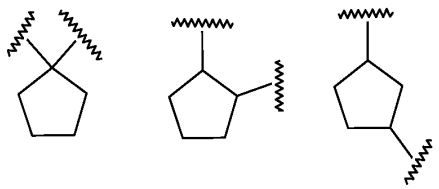
Het_3 is a 5 to 10 membered heterocyclic ring containing one, two or three heteroatoms independently selected from nitrogen, oxygen and sulfur;

OR

R_{23} and R_{24} along with the nitrogen atom to which they are attached form a 4 to 6 membered heterocyclic ring, wherein 1 or 2 carbons in the heterocyclic ring are optionally replaced with additional heteroatoms independently selected from nitrogen, oxygen and sulfur, and wherein the 4 to 6 membered heterocyclic ring is unsubstituted or substituted with C_{1-3} alkyl, —$N(CH_3)_2$ or —$CH_2N(CH_3)_2$; and

'wwwww' indicates point of attachment of Q to C terminal of A and ** indicates point of attachment of Q to D.

It will be appreciated by the skilled person that when R_4 is a 3 to 6 membered cycloalkyl group, it is attached to the adjacent group on both sides through either the same carbon or though different carbons. For example when R_4 is a 5 membered cycloalkyl group, it may be attached to the adjacent groups as below:



According to some of the previous embodiments, the present invention provides a compound of Formula I, wherein R_4 is selected from a group consisting of —C_{2-5} alkyl, —CH_2=CH_2—, —CH_2-O-CH_2—, —$CH_2(-OC_2H_4)_2$-OCH_2— and cyclobutyl; and A is selected from the group consisting of cit, val-ala, val-cit, gly-gly-phe-gly, or the peptide selected from the group consisting of Formula P_3, Formula P_5, Formula P_9 and Formula P_{12}. In an embodiment, the present invention provides a compound of Formula I, wherein R_4 is selected from a group consisting of —C_{2-5} alkyl and a 3 to 6 membered cycloalkyl; and A is selected from the group consisting of cit, val-ala, val-cit, glu-val-cit, gly-gly-phe-gly.

According to an embodiments, the present invention provides a compound of Formula I, wherein:

n is 0, 1 or 2;

R_1 is selected from the group consisting of phenyl, indolyl, thiophenyl, quinolinyl, and isoquinolinyl;

R_1 is unsubstituted or substituted with one or more R_5;

R_5 is selected from halogen, —OH, or 6 to 10 membered aryl ring;

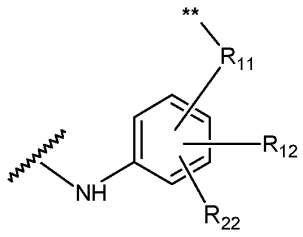
R_2 is cyclohexyl or phenyl;

R_3 is hydrogen;

R_4 is —$C_{1\text{-}10}$ alkyl;

A is val-cit; and

Q is of Formula Q_1,



Formula Q_1

wherein:

R_{11} is —$CH_2OC(O)$—; and

R_{12} is hydrogen; and R_{22} is hydrogen.

According to an embodiments, the present invention provides a compound of Formula I, wherein:

n is 0, 1 or 2;

R_1 is selected from a 6 to 10 membered aryl;

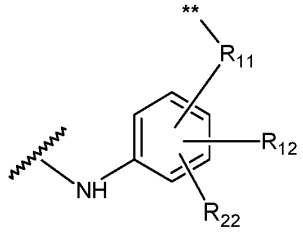
R_2 is absent;

R_3 is —CH_2COOH, —CH_2CH_2COOH;

R_4 is 3 to 6 membered cycloalkyl;

A is Cit;

Q is of Formula Q_1,



Formula Q_1

wherein:

R_{11} is —CH_2-O-C(O)-N(CH_3)-C_2H_4-N(CH_3)-C(O)—; and

R_{12} is hydrogen; and R_{22} is hydrogen.

According to an embodiment, the present invention provides a compound of Formula I, wherein:

n is 0, 1 or 2;

R_1 is selected from a 6 to 10 membered aryl;

R_2 is cyclohexyl or phenyl;

R_3 is hydrogen;

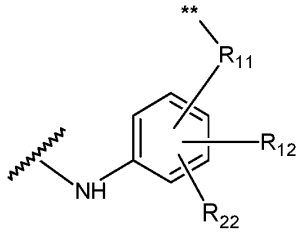
R_4 is selected from a group consisting of —$C_{1\text{-}10}$ alkyl- and —$C_{2\text{-}6}$ alkyl($N(R_8)(R_{8'})$)—; wherein,

R_8 and $R_{8'}$ are independently selected from hydrogen, $C_{1\text{-}6}$ alkyl, -C(O)-$C_{1\text{-}4}$alkyl-aryl or -C(O)-(-$C_2H_4O)_{1\text{-}8}$-$C_{1\text{-}2}$ alkyl-N(R)(R'), wherein said aryl is selected from 6 to 14 membered aryl and is optionally substituted by -$C_{1\text{-}3}$alkyl or -$OC_{1\text{-}3}$alkyl; wherein

R and R' are independently selected from hydrogen, -$C_{1\text{-}6}$ alkyl or -C(O)-$C_{1\text{-}4}$alkyl-aryl, wherein said aryl is selected from 6 to 14 membered aryl and is optionally substituted by -$C_{1\text{-}3}$alkyl or -$OC_{1\text{-}3}$alkyl;

A is selected from the group consisting of val-cit, gly-gly-phe-gly, Formula P_2, Formula P_{13}, Formula P_{14}, Formula P_{15} and Formula P_{16};

Q is of Formula Q_1,

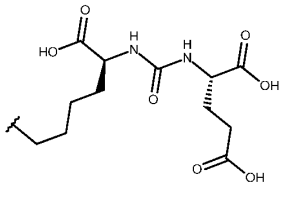


Formula Q_1

wherein:

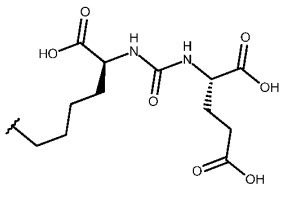
R_{11} is —CH_2-O-C(O)—; and

R_{12} is selected from hydrogen or —C(O)$N(R_{13})(R_{14})$, wherein R_{13} is hydrogen; R_{14} is selected from —$C_{1\text{-}5}$ alkyl-$N(R_{15})(R_{16})$ or



; wherein R_{15} and R_{16} are independently selected from hydrogen and —C_{1-5} alkyl;

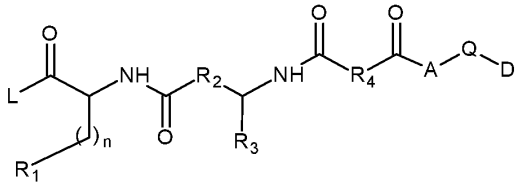
R_{22} is selected from hydrogen or —$C(O)N(R_{23})(R_{24})$, wherein R_{23} is hydrogen and R_{24} is selected from —C_{1-5} alkyl-$N(R_{25})(R_{26})$ or



; wherein R_{23} and R_{24} are independently selected from hydrogen and —C_{1-5} alkyl;

wherein at least one of R_{12} and R_{22} is hydrogen.

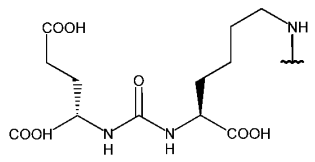
In another aspect, the present disclosure relates to a compound of Formula I:



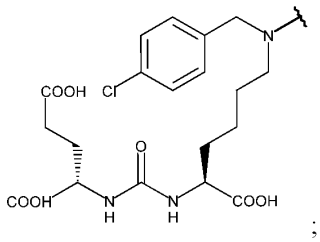
Formula I

or pharmaceutically acceptable salt, stereoisomer or isotope thereof; wherein:

L is a ligand, selected from:

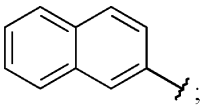
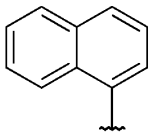
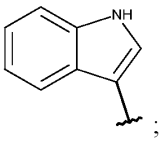


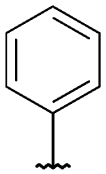
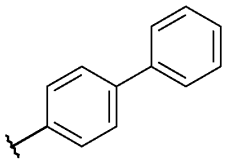
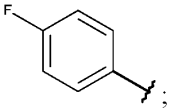
; and

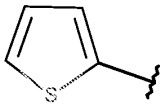


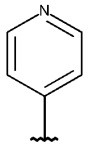
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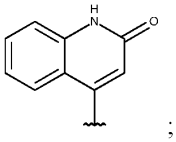
R_1 is selected from:


;

;


;

;

;


;


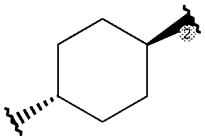
;


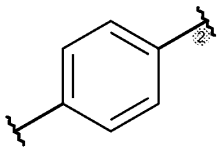
; and


;

n is selected from 0, 1 and 2;

R_2 is absent or selected from:

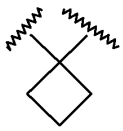


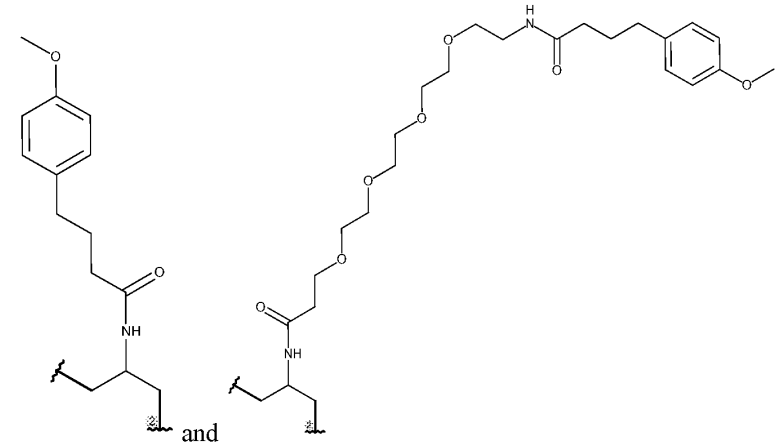
; and


;

R_3 is selected from hydrogen and $-C_2H_4COOH$;

R_4 is selected from

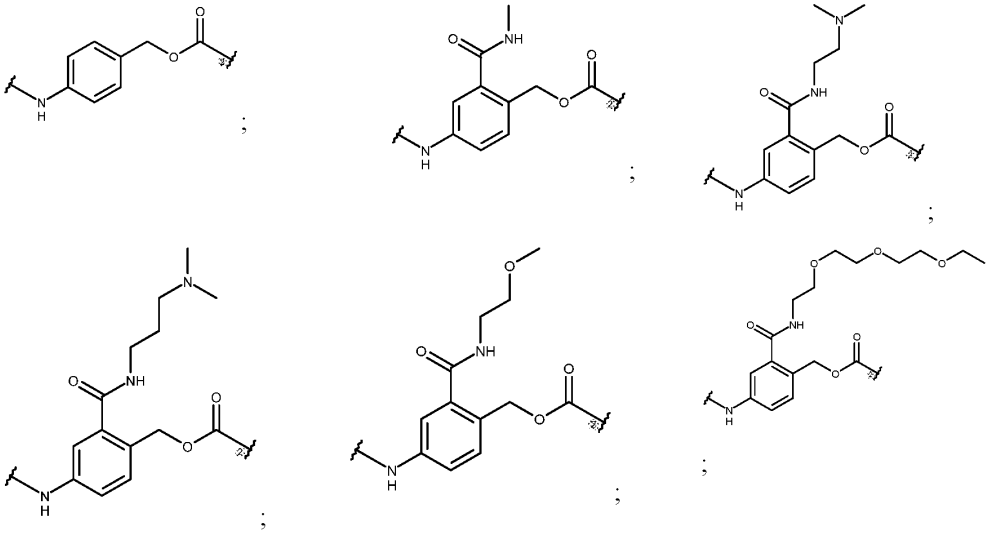

; $—C_{2-5}$ alkyl, —CH=CH—, $—CH_2-O-CH_2—$, $—CH_2(-OC_2H_4)_{2-8}-OCH_2—$,

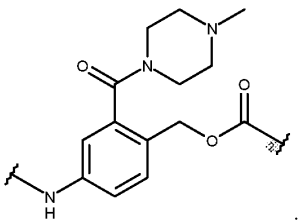
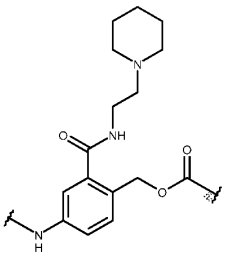
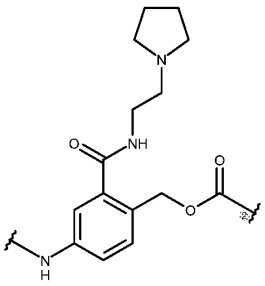
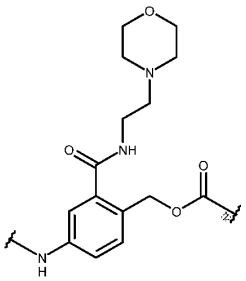
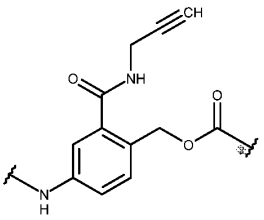
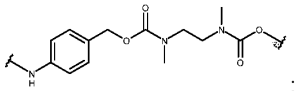
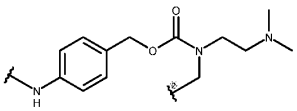
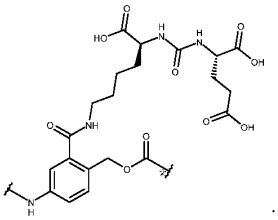
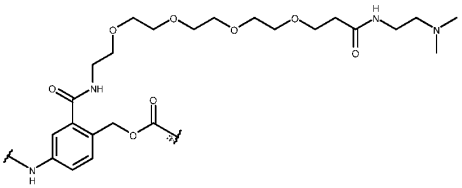
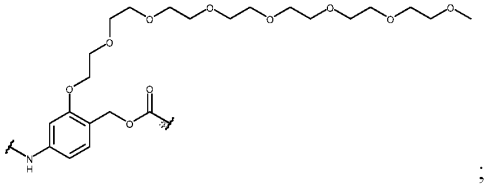
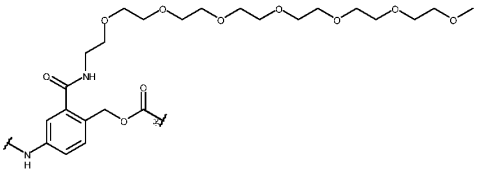
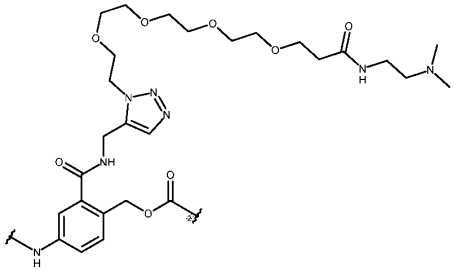


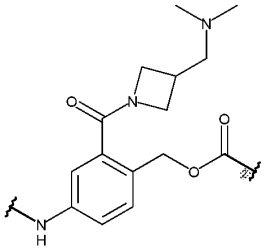
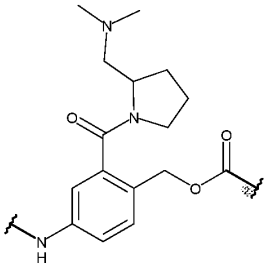
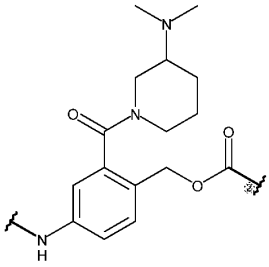
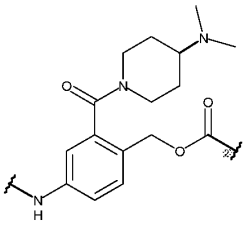
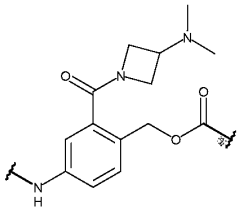
and ;

A is selected from cit, val-cit, val-ala, gly-gly-phe-gly, glu-val-cit, gly-gly-phe, gly-phe-gly, Formula P1-ala, Formula P3, Formula P4-ala, Formula P5, Formula P9, Formula P12, Formula P13 and Formula P16;

Q is selected from:



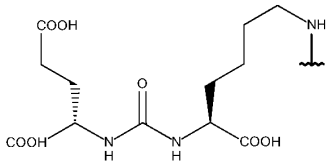

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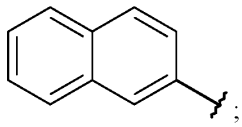

;

;

;

; and

;

D is a cytotoxic agent or a therapeutic agent selected from Monomethyl auristatin E (MMAE), Rucaparib, Talazoparib, Niraparib, SN-38, Exatecan, Belotecan, Mitomycin C etc.

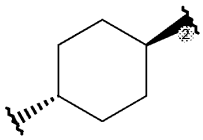
In one embodiment, the present disclosure relates to a compound of Formula I or pharmaceutically acceptable salt, stereoisomer or isotope thereof, wherein:

L is a ligand of formula:



R_1 is  ;

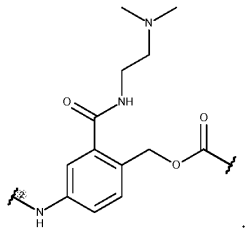
n is 1;

R_2 is  ;

R_3 is hydrogen;

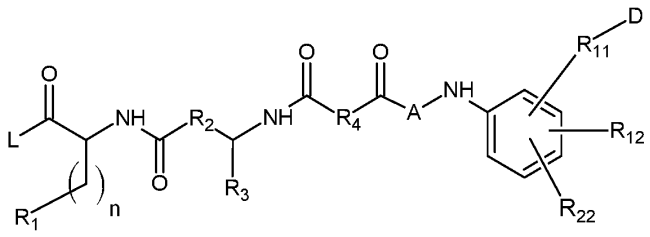
R_4 is $-C_3H_6-$

A is val-cit;

Q is  ;

D is Monomethyl auristatin E (MMAE).

In a second aspect of the present invention, there is provided a compound of Formula II



Formula II

or pharmaceutically acceptable salt, stereoisomer or isotope thereof; wherein,

n is 0, 1, 2, 3 or 4;

L is a Ligand;

R_1 is selected from a 6 to 14 membered aryl or a 5 to 13 membered heteroaryl containing one, two or three heteroatoms independently selected from nitrogen, oxygen or sulfur;

R_1 is unsubstituted or substituted with one or more R_5;

R_5, at each occurrence, is independently selected from halogen, —C(O)NH_2, —C(O)OR_6, —C_{1-3} alkyl, —OR_7, and 6 to 10 membered aryl; wherein,

R_6 is hydrogen or C_{1-3} alkyl;

R_7 is hydrogen or C_{1-3} alkyl;

R_2 is absent or is selected from 6 to 10 membered cycloalkyl or a 6 to 10 membered aryl;

R_3 is hydrogen, or —C_1-C_5COOH;

R_4 is selected from a group consisting of —C_{1-10} alkyl, —C_{2-6} alkenyl, —C_{1-3} alkyl-O-C_{1-3} alkyl—, —C_{2-6} alkyl-N(R_8)—, —N(R_8)-C_{2-6} alkyl—, a 3 to 6 membered cycloalkyl and —C_{1-2} alkyl $(-OC_2H_4)_{1-8}$-OC_{1-2} alkyl—; wherein,

R_8 is hydrogen or C_{1-6} alkyl;

A is an amino acid or a peptide comprising 2-5 amino acids;

R_{11} is selected from —C_{1-3} alkyl-OC(O)—**,

—C_{1-3} alkyl-O-C(O)-N(R_{19})-C_{1-5} alkyl-N(R_{19})-C(O)—**,

—C_{1-3} alkyl-O-C(O)-N[C_{1-5} alkyl-N($R_{20}R_{21}$)]-C_{1-3} alkyl—**, or

—C_{1-3} alkyl-O-C(O)-Het_2-C_{1-3} alkyl-N(R_{19})-C(O)—**;

wherein ** indicates point of attachment to D;

R_{19} is selected from H, —C_{1-3} alkyl or —C_{1-3} alkyl-O-C_{1-3} alkyl-OH;

R_{20} is H or —C_{1-3} alkyl;

R_{21} is H or —C_1-C_3 alkyl; and

Het_2 is a 5 to 10 membered heterocyclic ring containing one, two or three heteroatoms independently selected from nitrogen, oxygen or sulfur;

R_{12} is selected from hydrogen, —C(O)N(R_{13})R_{14} or —$(-OC_2H_4)_{1-10}$-CH_3

R_{13} is hydrogen;

R_{14} is selected from —C_{1-5} alkyl, —C_{2-5} alkenyl, —C_{2-5} alkynyl, —C_{1-5} alkyl-N(R_{15})R_{16}, —C_{1-5} alkyl-O-C_{1-3} alkyl, —$(-C_2H_4O)_{1-10}C_2H_5$, —$(-C_2H_4O)_{1-10}$-C_2H_4-R_{17} or —C_{1-3} alkyl-Het_3-$(-C_2H_4O)_{1-10}$-C_2H_4-R_{18}; wherein:

R_{15} is hydrogen or C_{1-3} alkyl;

R_{16} is hydrogen or C_{1-3} alkyl; or

R_{15} and R_{16} along with the nitrogen atom to which they are attached form a 5 to 6 membered heterocyclic ring, wherein 1 or 2 carbon atoms in the heterocyclic ring are optionally replaced with additional heteroatoms independently selected from nitrogen,

oxygen and sulfur and wherein the 5 to 6 membered heterocyclic ring is unsubstituted or substituted with C_{1-3} alkyl, halogen or –OH;

R_{17} is selected from hydrogen or —C(O)NH-C_{2-5} alkyl-$N(CH_3)_2$;

R_{18} is selected from hydrogen or —C(O)NH-C_{2-5} alkyl-$N(CH_3)_2$;

Het_3 is a 5 to 10 membered heterocyclic ring containing one, two or three heteroatoms independently selected from nitrogen, oxygen and sulfur;

OR

R_{13} and R_{14} along with the nitrogen atom to which they are attached form a 4 to 6 membered heterocyclic ring, wherein 1 or 2 carbons in the heterocyclic ring are optionally replaced with additional heteroatoms independently selected from nitrogen, oxygen and sulfur, and wherein the 4 to 6 membered heterocyclic ring is unsubstituted or substituted with C_{1-3} alkyl, —$N(CH_3)_2$ or —$CH_2N(CH_3)_2$;

R_{22} is selected from hydrogen, —C(O)N(R_{23})R_{24} or —$(-OC_2H_4)_{1-10}$-CH_3

R_{23} is hydrogen;

R_{24} is selected from —C_{1-5} alkyl, —C_{2-5} alkenyl, —C_{2-5} alkynyl, —C_{1-5} alkyl-N(R_{25})R_{26}, —C_{1-5} alkyl-O-C_{1-3} alkyl, —$(-C_2H_4O)_{1-10}C_2H_5$, —$(-C_2H_4O)_{1-10}$-C_2H_4-R_{27} or —C_{1-3} alkyl-Het_3-$(-C_2H_4O)_{1-10}$-C_2H_4-R_{28}; wherein

R_{25} is hydrogen or C1 to C3 alkyl;

R_{26} is hydrogen or C1 to C3 alkyl; or

R_{25} and R_{26} along with the nitrogen atom to which they are attached form a 5 to 6 membered heterocyclic ring, wherein 1 or 2 carbon atoms in the heterocyclic ring are optionally replaced with additional heteroatoms independently selected from nitrogen, oxygen and sulfur and wherein the 5 to 6 membered heterocyclic ring is unsubstituted or substituted with C_{1-3} alkyl, halogen or –OH;

R_{27} is selected from hydrogen or —C(O)NH-C_{2-5} alkyl-$N(CH_3)_2$;

R_{28} is selected from hydrogen or —C(O)NH-C_{2-5} alkyl-$N(CH_3)_2$;

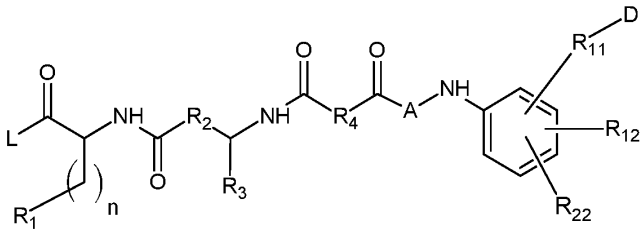
Het_3 is a 5 to 10 membered heterocyclic ring containing one, two or three heteroatoms independently selected from nitrogen, oxygen and sulfur;

OR

R_{23} and R_{24} along with the nitrogen atom to which they are attached form a 4 to 6 membered heterocyclic ring, wherein 1 or 2 carbons in the heterocyclic ring are optionally replaced with additional heteroatoms independently selected from nitrogen, oxygen and sulfur, and wherein the 4 to 6 membered heterocyclic ring is unsubstituted or substituted with C_{1-3} alkyl, $—N(CH_3)_2$ or $—CH_2N(CH_3)_2$; and

D is a cytotoxic agent or therapeutic agent.

In one embodiment of the present invention, there is provided a compound of Formula II



Formula II

or pharmaceutically acceptable salt, stereoisomer or isotope thereof; wherein:

n is 0, 1, 2, 3 or 4;

L is a Ligand;

R_1 is selected from a 6 to 14 membered aryl or a 5 to 13 membered heteroaryl containing one, two or three heteroatoms independently selected from nitrogen, oxygen or sulfur;

R_1 is unsubstituted or substituted with one or more R_5;

R_5, at each occurrence, is independently selected from halogen, $—C(O)NH_2$, $—C(O)OR_6$, $—C_{1-3}$ alkyl, $—OR_7$, and a 6 to 10 membered aryl; wherein:

R_6 is hydrogen or C_{1-3} alkyl;

R_7 is hydrogen or C_{1-3} alkyl;

R_2 is absent or is selected from a 6 to 10 membered cycloalkyl or a 6 to 10 membered aryl;

R_3 is hydrogen, or $—C_1$-C_5COOH;

R_4 is selected from a group consisting of —C_{1-10} alkyl-, —C_{2-6} alkenyl-, —C_{1-3} alkyl-O-C_{1-3} alkyl—, —C_{2-6} alkyl-N(R_8)—, —C_{2-6} alkyl(N(R_8)($R_{8'}$))—, —N(R_8)-C_{2-6} alkyl—, a 3 to 6 membered cycloalkyl and —C_{1-2} alkyl-(-OC_2H_4)$_{1-8}$-OC_{1-2} alkyl—; wherein,

R_8 and $R_{8'}$ are independently selected from hydrogen, C_{1-6} alkyl, -C(O)-C_{1-4}alkyl-aryl or -C(O)-(-C_2H_4O)$_{1-8}$-C_{1-2} alkyl-N(R)(R'), wherein said aryl is selected from 6 to 14 membered aryl and is optionally substituted by -C_{1-3}alkyl or -OC_{1-3}alkyl; wherein

R and R' are independently selected from hydrogen, -C_{1-6} alkyl or -C(O)-C_{1-4}alkyl-aryl, wherein said aryl is selected from 6 to 14 membered aryl and is optionally substituted by -C_{1-3}alkyl or -OC_{1-3}alkyl;

A is an amino acid or a peptide comprising 2-5 amino acids;

R_{11} is selected from —C_{1-3} alkyl-OC(O)—**,

—C_{1-3} alkyl-O-C(O)-N(R_{19})-C_{1-5} alkyl-N(R_{19})-C(O)—**,

—C_{1-3} alkyl-O-C(O)-N[C_{1-5} alkyl-N($R_{20}R_{21}$)]-C_{1-3} alkyl—**, or

—C_{1-3} alkyl-O-C(O)-Het_2-C_{1-3} alkyl-N(R_{19})-C(O)—**,

wherein ** indicates point of attachment to D;

R_{19} is selected from H, —C_{1-3} alkyl or —C_{1-3} alkyl-O-C_{1-3} alkyl-OH;

R_{20} is H or —C_{1-3} alkyl;

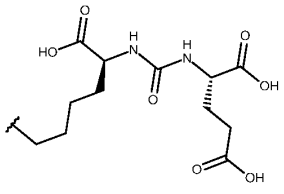
R_{21} is H or —C_1-C_3 alkyl; and

Het_2 is a 5 to 10 membered heterocyclic ring containing one, two or three heteroatoms independently selected from nitrogen, oxygen or sulfur;

R_{12} is selected from hydrogen, —C(O)N(R_{13})(R_{14}) or —(-OC_2H_4)$_{1-10}$-CH_3;

R_{13} is hydrogen;

R_{14} is selected from —C_{1-5} alkyl, —C_{2-5} alkenyl, —C_{2-5} alkynyl, —C_{1-5} alkyl-N(R_{15})(R_{16}), —C_{1-5} alkyl-O-C_{1-3} alkyl, —(-C_2H_4O)$_{1-10}C_2H_5$, —(-C_2H_4O)$_{1-10}$-C_2H_4-R_{17} or —C_{1-3} alkyl-Het_3-(-C_2H_4O)$_{1-10}$-C_2H_4-R_{18} or



; wherein:

R_{15} is hydrogen or C_{1-3} alkyl;

R_{16} is hydrogen or C_{1-3} alkyl; or

R_{15} and R_{16} along with the nitrogen atom to which they are attached form a 5 to 6 membered heterocyclic ring, wherein 1 or 2 carbon atoms in the heterocyclic ring are

optionally replaced with additional heteroatoms independently selected from nitrogen, oxygen and sulfur and wherein the 5 to 6 membered heterocyclic ring is unsubstituted or substituted with C_{1-3} alkyl, halogen or –OH;

R_{17} is selected from hydrogen or —C(O)NH-C_{2-5} alkyl-$N(CH_3)_2$;

R_{18} is selected from hydrogen or —C(O)NH-C_{2-5} alkyl-$N(CH_3)_2$;

Het_3 is a 5 to 10 membered heterocyclic ring containing one, two or three heteroatoms independently selected from nitrogen, oxygen and sulfur;

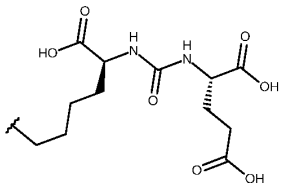
OR

R_{13} and R_{14} along with the nitrogen atom to which they are attached form a 4 to 6 membered heterocyclic ring, wherein 1 or 2 carbons in the heterocyclic ring are optionally replaced with additional heteroatoms independently selected from nitrogen, oxygen and sulfur, and wherein the 4 to 6 membered heterocyclic ring is unsubstituted or substituted with C_{1-3} alkyl, —$N(CH_3)_2$ or —$CH_2N(CH_3)_2$;

R_{22} is selected from hydrogen, —C(O)N(R_{23})(R_{24}) or —(-$OC_2H_4)_{1-10}$-CH_3 , wherein:

R_{23} is hydrogen;

R_{24} is selected from —C_{1-5} alkyl, —C_{2-5} alkenyl, —C_{2-5} alkynyl, —C_{1-5} alkyl-N(R_{25})(R_{26}), —C_{1-5} alkyl-O-C_{1-3} alkyl, —(-$C_2H_4O)_{1-10}C_2H_5$, —(-$C_2H_4O)_{1-10}$-C_2H_4-R_{27} or —C_{1-3} alkyl-Het_3-(-$C_2H_4O)_{1-10}$-C_2H_4-R_{28} or



; wherein:

R_{25} is hydrogen or C1 to C3 alkyl;

R_{26} is hydrogen or C1 to C3 alkyl; or

R_{25} and R_{26} along with the nitrogen atom to which they are attached form a 5 to 6 membered heterocyclic ring, wherein 1 or 2 carbon atoms in the heterocyclic ring are optionally replaced with additional heteroatoms independently selected from nitrogen, oxygen and sulfur and wherein the 5 to 6 membered heterocyclic ring is unsubstituted or substituted with C_{1-3} alkyl, halogen or –OH;

R_{27} is selected from hydrogen or —C(O)NH-C_{2-5} alkyl-$N(CH_3)_2$;

R_{28} is selected from hydrogen or —C(O)NH-C_{2-5} alkyl-$N(CH_3)_2$;

Het_3 is a 5 to 10 membered heterocyclic ring containing one, two or three heteroatoms independently selected from nitrogen, oxygen and sulfur;

OR

R_{23} and R_{24} along with the nitrogen atom to which they are attached form a 4 to 6 membered heterocyclic ring, wherein 1 or 2 carbons in the heterocyclic ring are optionally replaced with additional heteroatoms independently selected from nitrogen, oxygen and sulfur, and wherein the 4 to 6 membered heterocyclic ring is unsubstituted or substituted with C_{1-3} alkyl, —$N(CH_3)_2$ or —$CH_2N(CH_3)_2$; and

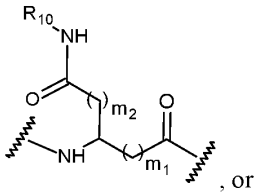
D is a cytotoxic agent or therapeutic agent as defined above.

According to an embodiment, the ligand in Formula II is of Formula L_1, wherein t_1 is 3; t_2 is 2; and Z is $N(R_9)$, wherein R_9 is hydrogen. In an embodiment, L is a ligand of Formula L_1, wherein t_1 is 3; t_2 is 2; and Z is $N(R_9)$, wherein R_9 is phenyl. In another embodiment, L is a ligand of Formula L_1, wherein t_1 is 3; t_2 is 2; and Z is $N(R_9)$, wherein phenyl substituted with Cl, Br, or I.

In an embodiment, the ligand in Formula II is of Formula L_1, wherein t_1 is 0; t_2 is 2; and Z is Z_1, wherein t_3 is 1, 2, 3, 4, 5 or 6 and Y is —NH—.

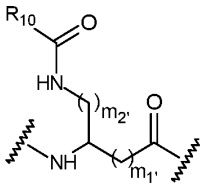
In an embodiment, the ligand in Formula II is of Formula L_1, wherein t_1 is 1; t_2 is 2 and Z is the compound of Formula Z_2.

Further according to an embodiment, in Formula II, A is an amino acid selected from the group of consisting of alanine (ala), arginine (arg), aspartic acid (asp), cysteine (cys), glutamic acid (glu), glycine (gly), lysine (lys), phenylalanine (phe), serine (ser), threonine (thr), tryptophan (trp), valine (val), ornithine (orn), citrulline (cit), homocitrulline (hct), lanthionine (lan), homocysteine (hcy) or an amino acid having Formula A_1 or Formula A_2



, or

Formula A_1



Formula A_2

wherein:

m_1 and m_1' are 0, 1, 2 or 3;

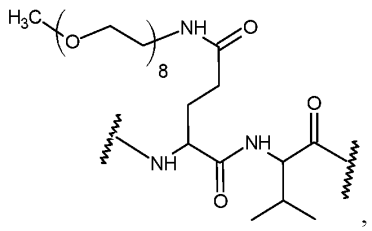
m_2 and m_2' are is 0, 1, 2, 3 or 4;

R_{10} is selected from $(-C_2H_4O)_{1-24}CH_3$, $(-C_2H_4O)_{1-24}C_{1-2}$ alkyl($N(R_{10'})(R_{10''})$)—, C_{1-3} alkyl-aryl or —C_{1-3} alkyl-Het_1-$(-C_2H_4O)_{1-24}CH_3$, wherein Het_1 is a 5 to 10 membered heterocyclic ring containing one, two or three heteroatoms independently selected from nitrogen, oxygen or

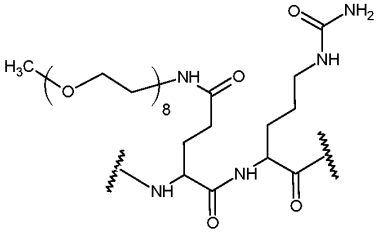
sulfur and wherein said aryl is selected from 6 to 14 membered aryl and is optionally substituted by -C_{1-3}alkyl or -OC_{1-3}alkyl; wherein

$R_{10'}$ and $R_{10''}$ are independently selected from hydrogen, C_{1-6} alkyl or -C(O)-C_{1-4}alkyl-aryl wherein said aryl is selected from 6 to 14 membered aryl and is optionally substituted by -C_{1-3}alkyl or -OC_{1-3}alkyl..

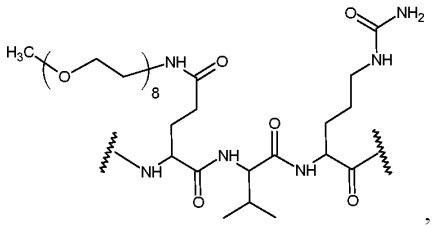
In another embodiment, in Formula II, A is a peptide selected from the group consisting of ala-ala, ala-ala-ala, ala-phe, val-ala, val-cit, ala-val-cit, ala(beta)-val-cit, glu-val-cit, glu-cit, glu-val, gly-gly, gly-gly-phe, gly-phe-gly, gly-gly-phe-gly, asp-cit, asp-val-cit and asp-val; or the peptide is selected from a group of compounds having following formula:



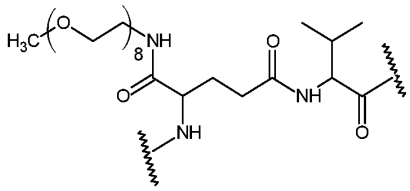
Formula P_1



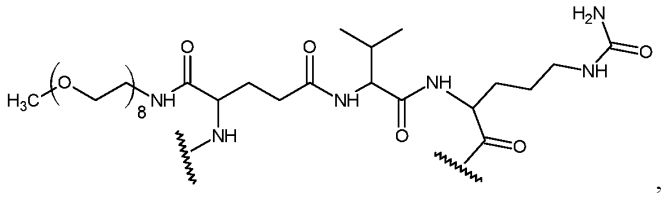
Formula P_2



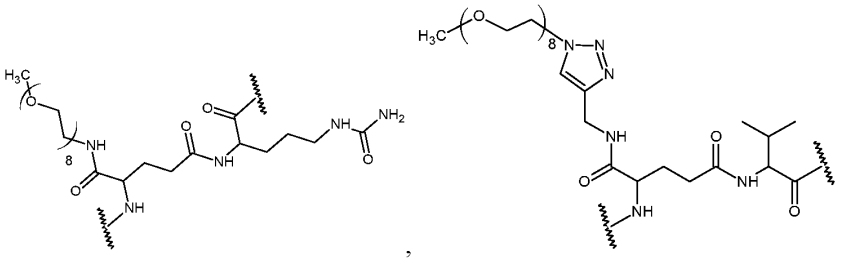
Formula P_3



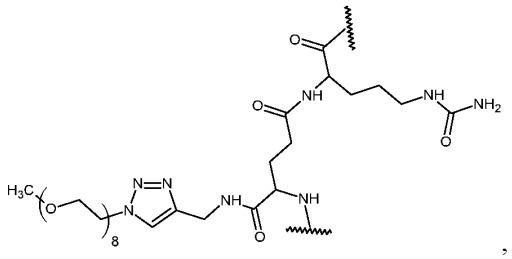
Formula P_4



Formula P_5

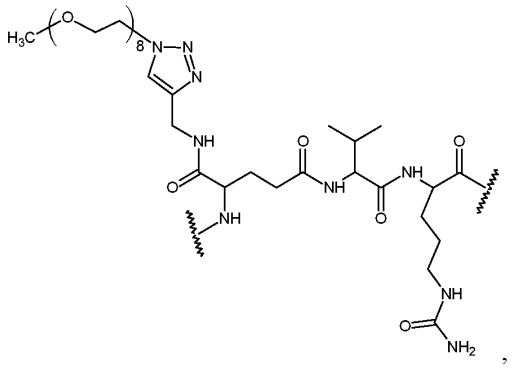


Formula P_6



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Formula P_7

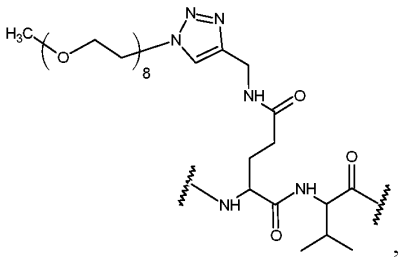


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Formula P_8

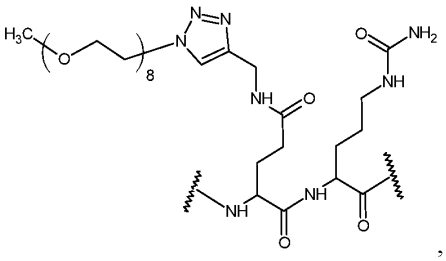
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Formula P_9



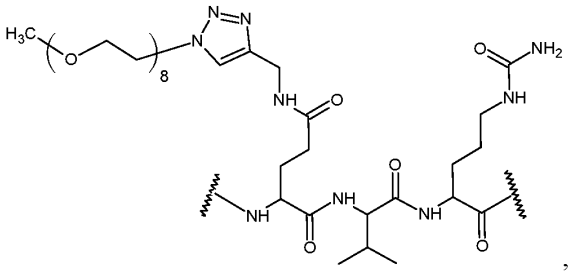
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Formula P_{10}



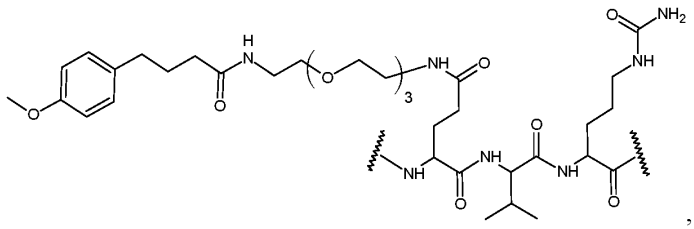
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Formula P_{11}

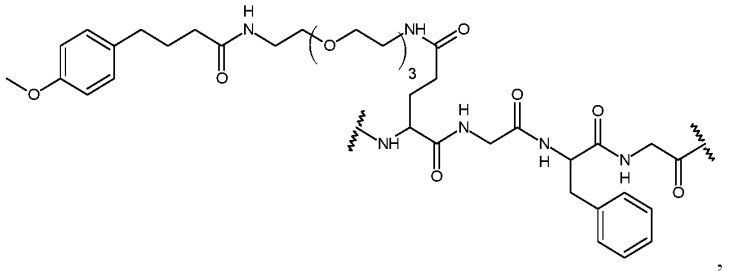


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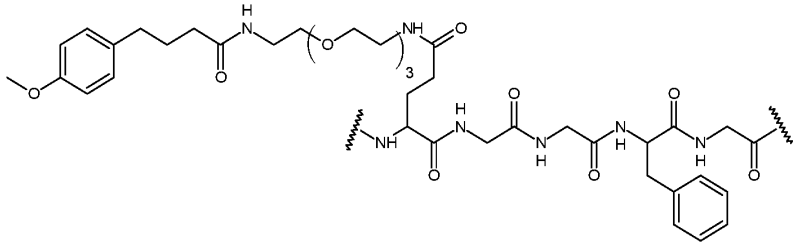
Formula P_{12}



Formula P_{13}

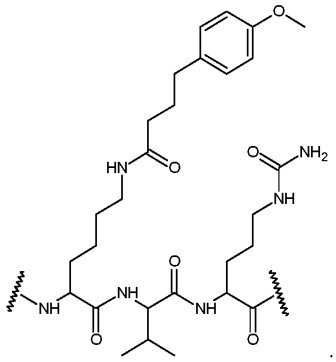


Formula P_{14}



, and

Formula P_{15}



Formula P_{16}

In an embodiment, the present invention provides a compound of Formula II, wherein:

L is of Formula L_1, wherein t_1 is 3; t_2 is 2; and Z is $N(R_9)$, wherein R_9 is hydrogen. In an embodiment, L is a ligand of Formula L_1, wherein t_1 is 3; t_2 is 2; and Z is $N(R_9)$, wherein R_9 is

phenyl. In another embodiment, L is a ligand of Formula L_1, wherein t_1 is 3; t_2 is 2; and Z is $N(R_9)$, wherein phenyl substituted with Cl, Br, or I;

R_1 is naphthyl;

R_2 is a 6 to 10 membered cycloalkyl;

R_3 is hydrogen;

R_4 is selected from —C_{1-10} alkyl- or a 3 to 6 membered cycloalkyl;

A is an amino acid or peptide as mentioned in previous embodiments;

R_{12} is —$C(O)N(R_{13})(R_{14})$, wherein:

R_{13} is hydrogen; and

R_{14} is —C_{1-5} alkyl-$N(R_{15})(R_{16})$,

wherein:

R_{15} is C1 to C3 alkyl;

R_{16} is C1 to C3 alkyl; and

R_{22} is hydrogen.

In an embodiment, the present invention provides a compound of Formula II, wherein:

L is a ligand of Formula L_1, wherein t_1 is 3; t_2 is 2; and Z is $N(R_9)$, wherein R_9 is hydrogen. In an embodiment, L is a ligand of Formula L_1, wherein t_1 is 3; t_2 is 2; and Z is $N(R_9)$, wherein R_9 is phenyl. In another embodiment, L is a ligand of Formula L_1, wherein t_1 is 3; t_2 is 2; and Z is $N(R_9)$, wherein phenyl substituted with Cl, Br, or I;

R_1 is naphthyl;

R_2 is a 6 to 10 membered cycloalkyl;

R_3 is hydrogen;

R_4 is selected from —C_{1-10} alkyl- or a 3 to 6 membered cycloalkyl;

A is an amino acid or peptide as mentioned in previous embodiments;

R_{12} is —$C(O)N(R_{13})(R_{14})$, wherein:

R_{13} is hydrogen; and

R_{14} is —C_{1-5} alkyl-$N(R_{15})(R_{16})$,

wherein:

R_{15} is C1 to C3 alkyl; and

R_{16} is C1 to C3 alkyl;

R_{22} is —$C(O)N(R_{23})(R_{24})$, wherein:

R_{23} is hydrogen; and

R_{24} is —C_{1-5} alkyl-$N(R_{25})(R_{26})$,

wherein:

R_{25} is C_{1-3} alkyl; and

R_{26} is C_{1-3} alkyl.

In an embodiment, the present invention provides a compound of Formula II, wherein:

L is of Formula L_1, wherein t_1 is 3; t_2 is 2; and Z is $N(R_9)$, wherein R_9 is hydrogen. In an embodiment, L is a ligand of Formula L_1, wherein t_1 is 3; t_2 is 2; and Z is $N(R_9)$, wherein R_9 is phenyl. In another embodiment, L is a ligand of Formula L_1, wherein t_1 is 3; t_2 is 2; and Z is $N(R_9)$, wherein phenyl substituted with Cl, Br, or I;

R_1 is naphthyl;

R_2 is a 6 to 10 membered cycloalkyl;

R_3 is hydrogen;

R_4 is selected from —C_{1-10} alkyl- or —C_{2-6} alkyl($N(R_8)(R_{8'})$)—; wherein

R_8 and $R_{8'}$ are independently selected from hydrogen, -C(O)-C_{1-4}alkyl-aryl or -C(O)-(-$C_2H_4O)_{1-8}$-C_{1-2} alkyl-N(R)(R'), wherein said aryl is selected from 6 to 14 membered aryl and is optionally substituted by -C_{1-3}alkyl or -OC_{1-3}alkyl, wherein both R_8 and $R_{8'}$ are not hydrogen; wherein

R and R' are independently selected from hydrogen or -C(O)-C_{1-4}alkyl-aryl, wherein said aryl is selected from 6 to 14 membered aryl and is optionally substituted by -C_{1-3}alkyl or -OC_{1-3}alkyl, wherein both R and R' are not hydrogen;

A is an amino acid or peptide as mentioned in previous embodiments;

R_{11} is selected from —C_{1-3} alkyl-OC(O)—**, wherein ** indicates point of attachment to D;

R_{12} is —C(O)$N(R_{13})(R_{14})$, wherein:

R_{13} is hydrogen; and

R_{14} is —C_{1-5} alkyl-$N(R_{15})(R_{16})$,

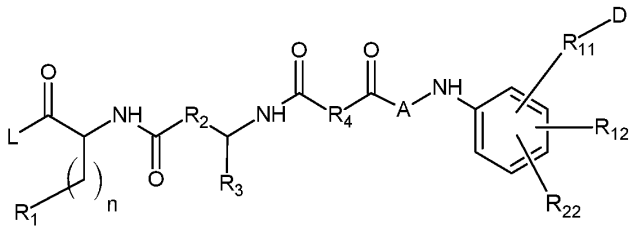
wherein:

R_{15} is C1 to C3 alkyl;

R_{16} is C1 to C3 alkyl; and

R_{22} is hydrogen.

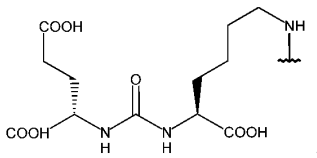
In another aspect, the present disclosure relates to a compound of Formula II:



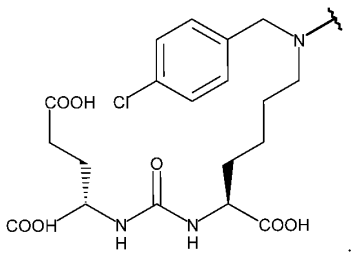
Formula II

or pharmaceutically acceptable salt, stereoisomer or isotope thereof; wherein:

L is a ligand, selected from:

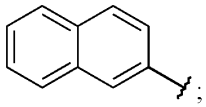


; and

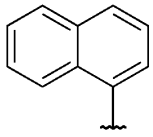


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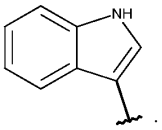
R_1 is selected from:



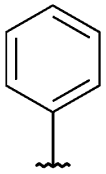
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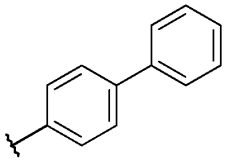
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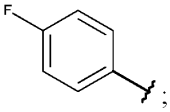
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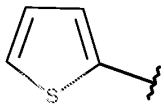
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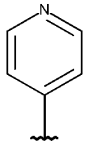
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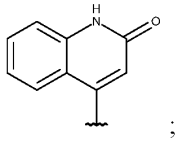
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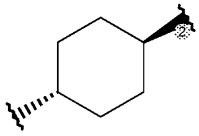
; and



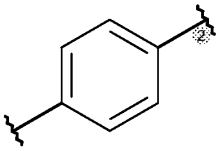
;

n is selected from 0, 1 and 2;

R_2 is absent or selected from:



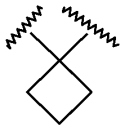
; and



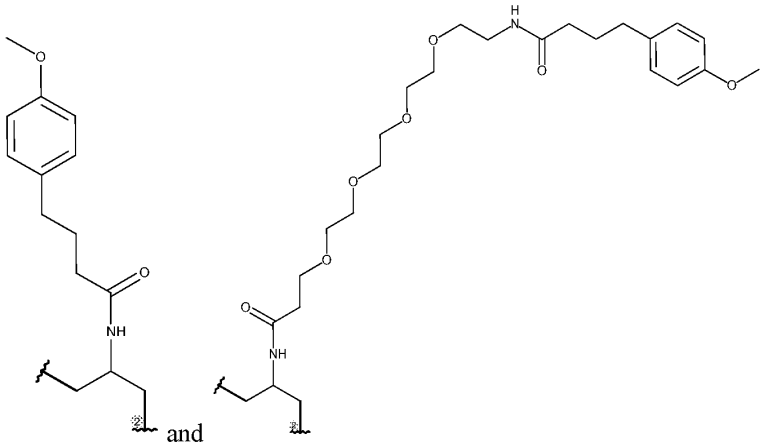
;

R_3 is selected from hydrogen and $-C_2H_4COOH$;

R_4 is selected from

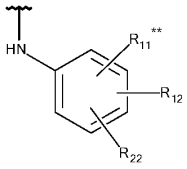


; —C_{2-5} alkyl, —CH=CH—, —CH_2-O-CH_2—, —$CH_2(-OC_2H_4)_{2-8}$-OCH_2—,

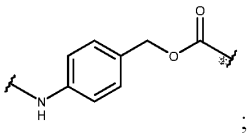


and ;

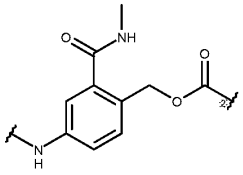
A is selected from cit, val-ala, val-cit, gly-gly-phe-gly, glu-val-cit, gly-gly-phe, gly-phe-gly, Formula P1-ala, Formula P3, Formula P4-ala, Formula P5, Formula P9, Formula P12, Formula P13 and Formula P16;



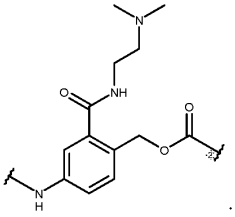
is selected from:



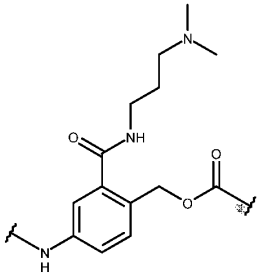
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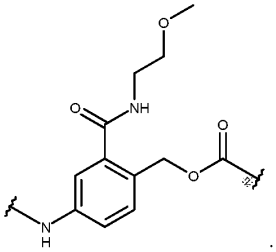


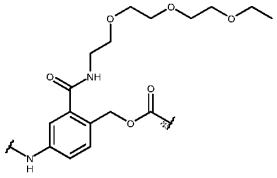
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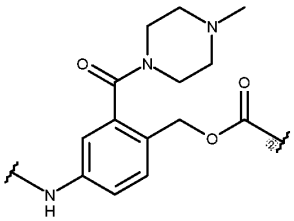


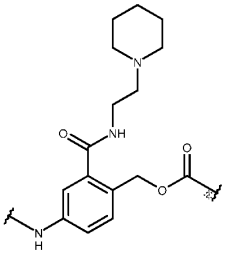
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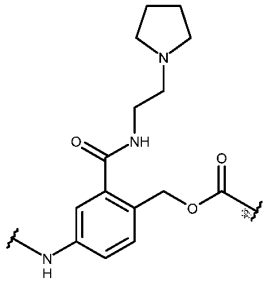

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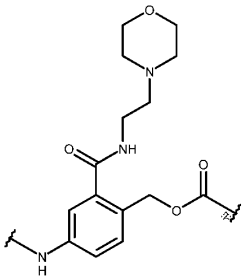

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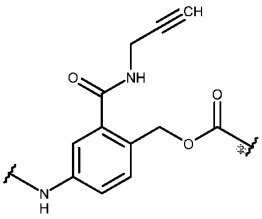

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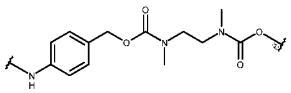

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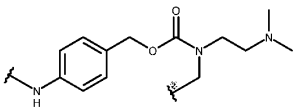

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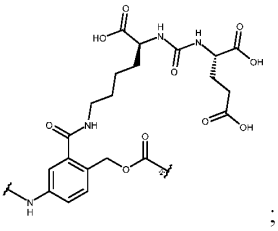

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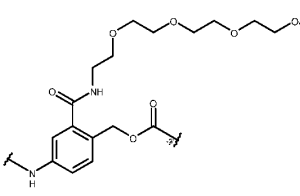

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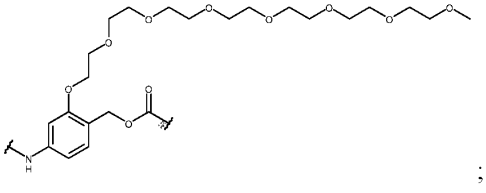

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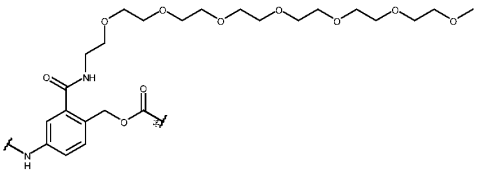
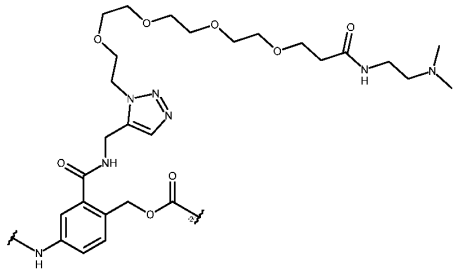
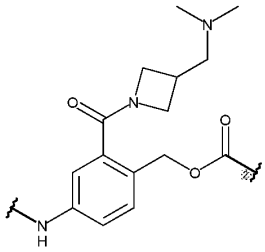
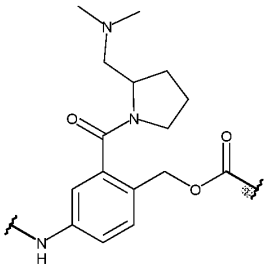
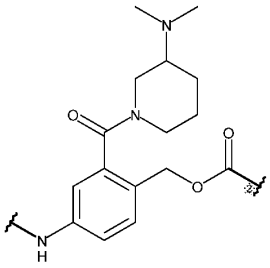
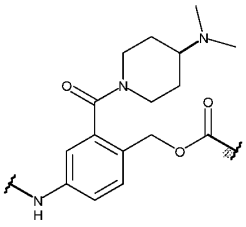
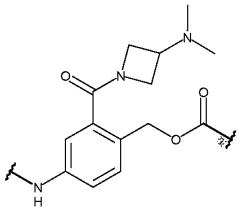

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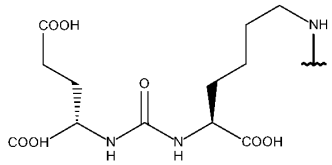

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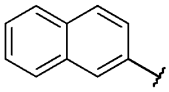

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; and

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D is a cytotoxic agent or a therapeutic agent selected from Monomethyl auristatin E (MMAE), Rucaparib, Talazoparib, Niraparib, SN-38, Exatecan, Belotecan, Mitomycin C.

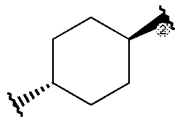
In one embodiment, the present disclosure relates to a compound of Formula II or pharmaceutically acceptable salt, stereoisomer or isotope thereof, wherein:

L is a ligand of formula:



R_1 is  ;

n is 1;

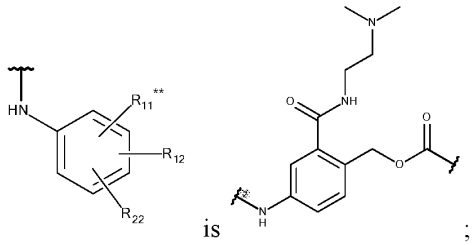


R_2 is ;

R_3 is hydrogen;

R_4 is $-C_3H_6-$

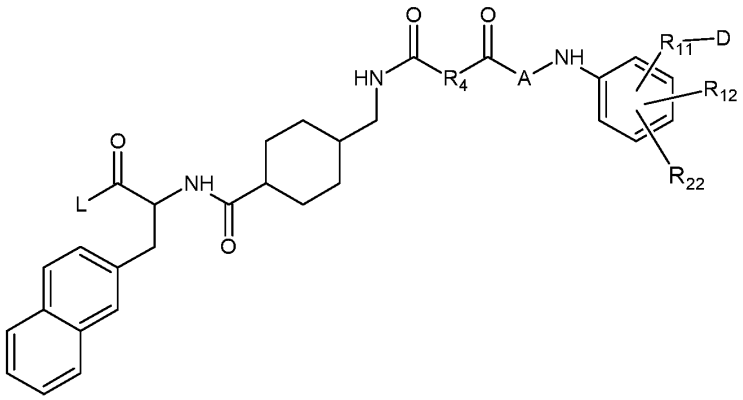
A is val-cit;



is ;

D is Monomethyl auristatin E (MMAE).

In a third aspect of the present invention, there is provided a compound of Formula III



Formula III

or pharmaceutically acceptable salt, stereoisomer or isotope thereof; wherein,

L is a Ligand;

R_4 is selected from a group consisting of —C_{1-10} alkyl, —C_{2-6} alkenyl, —C_{1-3} alkyl-O-C_{1-3} alkyl—, —C_{2-6} alkyl-N(R_8)—, —N(R_8)-C_{2-6} alkyl—, a 3 to 6 membered cycloalkyl and —C_{1-2} alkyl $(-OC_2H_4)_{1-8}$-OC_{1-2} alkyl—; wherein,

R_8 is hydrogen or C_{1-6} alkyl;

A is an amino acid or a peptide comprising 2-5 amino acids;

R_{11} is selected from —C_{1-3} alkyl-OC(O)—**,
—C_{1-3} alkyl-O-C(O)-N(R_{19})-C_{1-5} alkyl-N(R_{19})-C(O)—**,
—C_{1-3} alkyl-O-C(O)-N[C_{1-5} alkyl-N($R_{20}R_{21}$)]-C_{1-3} alkyl—**, or
—C_{1-3} alkyl-O-C(O)-Het_2-C_{1-3} alkyl-N(R_{19})-C(O)—**,
wherein ** indicates point of attachment to D;
R_{19} is selected from H, CH_3 or –C_2H_4-O-C_2H_4-OH;
R_{20} is CH_3; R_{21} is CH_3; and
Het_2 is pyrrolidinyl;
R_{12} is selected from hydrogen, —C(O)N(R_{13})R_{14} or —(-OC_2H_4)$_{1-10}$-CH_3
R_{13} is hydrogen;
R_{14} is —CH_3, —CH_2-C≡CH, —C_{1-3} alkyl-N(R_{15})R_{16}, —$C_2H_4OCH_3$, —(-C_2H_4O)$_{3-8}$-C_2H_5, —(-C_2H_4O)$_{5-10}$-C_2H_4-R_{17}, —CH_2-triazole-(-C_2H_4O)4-C_2H_4-R_{18};
R_{15} is —CH_3 or —C_2H_5; R_{16} is —CH_3 or —C_2H_5;
or
R_{15} and R_{16} along with the nitrogen atom to which they are attached form a 5 to 6 membered heterocyclic ring, wherein 1 or 2 carbon atoms in the heterocyclic ring are optionally replaced with additional heteroatoms independently selected from nitrogen, oxygen and sulfur and wherein the 5 to 6 membered heterocyclic ring is unsubstituted or substituted with —CH_3.
R_{17} is —C(O)N$HC_2H_4N(CH_3)_2$;
R_{18} is —C(O)N$HC_2H_4N(CH_3)_2$.
or
R_{13} and R_{14} along with the nitrogen atom to which they are attached form a 4 to 6 membered heterocyclic ring, wherein 1 or 2 carbons in the heterocyclic ring are optionally replaced with additional heteroatoms independently selected from nitrogen, oxygen and sulfur, and wherein the 4 to 6 membered heterocyclic ring is unsubstituted or substituted with C_{1-3} alkyl, —$N(CH_3)_2$ or —$CH_2N(CH_3)_2$;
R_{22} is selected from hydrogen, —C(O)N(R_{23})R_{24} or —(-OC_2H_4)$_{1-10}$-CH_3;
R_{23} is hydrogen;
R_{24} is selected from —CH_3, —CH_2-C≡CH, —C_{1-3} alkyl-N(R_{25})R_{26}, —$C_2H_4OCH_3$, —(-C_2H_4O)$_{3-8}$-C_2H_5, —(-C_2H_4O)$_{5-10}$-C_2H_4-R_{27}, —CH_2-triazole-(-C_2H_4O)$_4$-C_2H_4-R_{28}; wherein:
R_{25} is —CH_3 or —C_2H_5;
R_{26} is —CH_3 or —C_2H_5; or

R_{25} and R_{26} along with the nitrogen atom to which they are attached form a 5 to 6 membered heterocyclic ring, wherein 1 or 2 carbon atoms in the heterocyclic ring are optionally replaced with additional heteroatoms independently selected from nitrogen, oxygen and sulfur and wherein the 5 to 6 membered heterocyclic ring is unsubstituted or substituted with —CH_3;

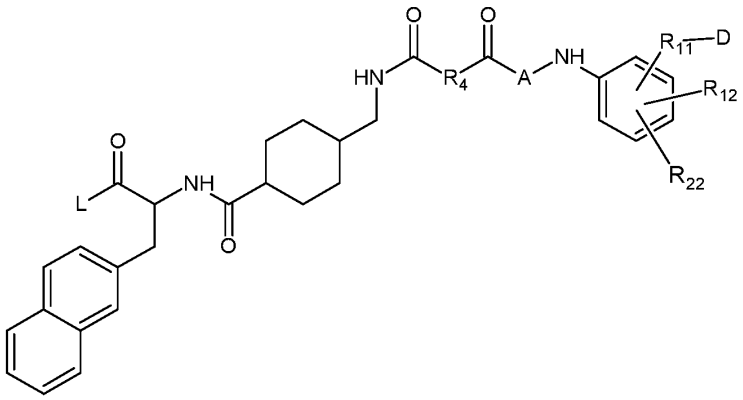
R_{27} is —C(O)NH-C_{2-5} alkyl-$N(CH_3)_2$;

R_{28} is —C(O)NH-C_{2-5} alkyl-$N(CH_3)_2$;

OR

R_{23} and R_{24} along with the nitrogen to which they are attached form a 4 to 6 membered heterocyclic ring, wherein 1 or 2 carbons in the heterocyclic ring are optionally replaced with additional heteroatoms independently selected from nitrogen, oxygen and sulfur, and wherein the 4 to 6 membered heterocyclic ring is unsubstituted or substituted with C_{1-3} alkyl, —$N(CH_3)_2$ or —$CH_2N(CH_3)_2$; and D is a cytotoxic agent or therapeutic agent.

In one embodiment of the present invention, there is provided a compound of Formula III



Formula III

or pharmaceutically acceptable salt, stereoisomer or isotope thereof; wherein:

L is a Ligand;

R_4 is selected from a group consisting of —C_{1-10} alkyl, —C_{2-6} alkenyl, —C_{1-3} alkyl-O-C_{1-3} alkyl—, —C_{2-6} alkyl-$N(R_8)$—, —C_{2-6} alkyl($N(R_8)(R_{8'})$)—, —$N(R_8)$-C_{2-6} alkyl—, a 3 to 6 membered cycloalkyl and —C_{1-2} alkyl $(-OC_2H_4)_{1-8}$-OC_{1-2} alkyl—; wherein:

R_8 and $R_{8'}$ are independently selected from hydrogen, C_{1-6} alkyl, -C(O)-C_{1-4}alkyl-aryl or -C(O)-$(-C_2H_4O)_{1-8}$-C_{1-2} alkyl-N(R)(R'), wherein said aryl is selected from 6 to 14 membered aryl and is optionally substituted by -C_{1-3}alkyl or -OC_{1-3}alkyl; wherein

R and R' are independently selected from hydrogen, -C_{1-6} alkyl or -C(O)-C_{1-4}alkyl-aryl, wherein said aryl is selected from 6 to 14 membered aryl and is optionally substituted by -C_{1-3}alkyl or -OC_{1-3}alkyl;

A is an amino acid or a peptide comprising 2-5 amino acids;

R_{11} is selected from —C_{1-3} alkyl-OC(O)—**,

—C_{1-3} alkyl-O-C(O)-N(R_{19})-C_{1-5} alkyl-N(R_{19})-C(O)—**,

—C_{1-3} alkyl-O-C(O)-N[C_{1-5} alkyl-N($R_{20}R_{21}$)]-C_{1-3} alkyl—**, or

—C_{1-3} alkyl-O-C(O)-Het_2-C_{1-3} alkyl-N(R_{19})-C(O)—**,

wherein ** indicates point of attachment to D;

R_{19} is selected from H, CH_3 or –C_2H_4-O-C_2H_4-OH;

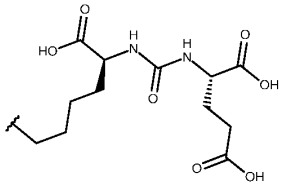
R_{20} is CH_3; R_{21} is CH_3; and

Het_2 is pyrrolidinyl.

R_{12} is selected from hydrogen, —C(O)N(R_{13})(R_{14}) or —(-OC_2H_4)$_{1-10}$-CH_3;

R_{13} is hydrogen;

R_{14} is —CH_3, —CH_2-C≡CH, —C_{1-3} alkyl-N(R_{15})(R_{16}), —$C_2H_4OCH_3$, —(-C_2H_4O)$_{3-8}$-C_2H_5, —(-C_2H_4O)$_{5-10}$-C_2H_4-R_{17}, —CH_2-triazole-(-C_2H_4O)4-C_2H_4-R_{18} or



;

R_{15} is —CH_3 or —C_2H_5; R_{16} is —CH_3 or —C_2H_5;

or

R_{15} and R_{16} along with the nitrogen atom to which they are attached form a 5 to 6 membered heterocyclic ring, wherein 1 or 2 carbon atoms in the heterocyclic ring are optionally replaced with additional heteroatoms independently selected from nitrogen, oxygen and sulfur and wherein the 5 to 6 membered heterocyclic ring is unsubstituted or substituted with —CH_3;

R_{17} is —C(O)N$HC_2H_4N(CH_3)_2$;

R_{18} is —C(O)N$HC_2H_4N(CH_3)_2$;

or

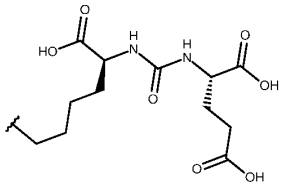
R_{13} and R_{14} along with the nitrogen atom to which they are attached form a 4 to 6 membered heterocyclic ring, wherein 1 or 2 carbons in the heterocyclic ring are optionally replaced with additional heteroatoms independently selected from nitrogen, oxygen and sulfur, and

wherein the 4 to 6 membered heterocyclic ring is unsubstituted or substituted with C_{1-3} alkyl, —$N(CH_3)_2$ or —$CH_2N(CH_3)_2$;

R_{22} is selected from hydrogen, —$C(O)N(R_{23})(R_{24})$ or —$(-OC_2H_4)_{1-10}$-CH_3;

R_{23} is hydrogen;

R_{24} is selected from —CH_3, —CH_2-C≡CH, —C_{1-3} alkyl-$N(R_{25})(R_{26})$, —$C_2H_4OCH_3$, —$(-C_2H_4O)_{3-8}$-C_2H_5, —$(-C_2H_4O)_{5-10}$-C_2H_4-R_{27}, —CH_2-triazole-$(-C_2H_4O)_4$-C_2H_4-R_{28} or



; wherein:

R_{25} is —CH_3 or —C_2H_5;

R_{26} is —CH_3 or —C_2H_5; or

R_{25} and R_{26} along with the nitrogen atom to which they are attached form a 5 to 6 membered heterocyclic ring, wherein 1 or 2 carbon atoms in the heterocyclic ring are optionally replaced with additional heteroatoms independently selected from nitrogen, oxygen and sulfur and wherein the 5 to 6 membered heterocyclic ring is unsubstituted or substituted with —CH_3;

R_{27} is —$C(O)NH$-C_{2-5} alkyl-$N(CH_3)_2$;

R_{28} is —$C(O)NH$-C_{2-5} alkyl-$N(CH_3)_2$;

OR

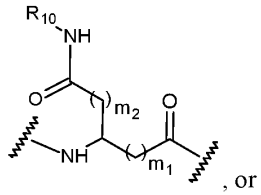
R_{23} and R_{24} along with the nitrogen to which they are attached form a 4 to 6 membered heterocyclic ring, wherein 1 or 2 carbons in the heterocyclic ring are optionally replaced with additional heteroatoms independently selected from nitrogen, oxygen and sulfur, and wherein the 4 to 6 membered heterocyclic ring is unsubstituted or substituted with C_{1-3} alkyl, —$N(CH_3)_2$ or —$CH_2N(CH_3)_2$; and D is a cytotoxic agent or therapeutic agent as defined above.

According to an embodiment, ligand in Formula III is a lignad of Formula L_1, wherein t_1 is 3; t_2 is 2; and Z is $N(R_9)$, wherein R_9 is hydrogen. In an embodiment, L is a ligand of Formula L_1, wherein t_1 is 3; t_2 is 2; and Z is $N(R_9)$, wherein R_9 is phenyl. In another embodiment, L is a ligand of Formula L_1, wherein t_1 is 3; t_2 is 2; and Z is $N(R_9)$, wherein phenyl substituted with Cl, Br, or I.

In an embodiment, the ligand in Formula III is a ligand of Formula L_1, wherein t_1 is 0; t_2 is 2; and Z is Z_1, wherein t_3 is 1, 2, 3, 4, 5 or 6 and Y is —NH—.

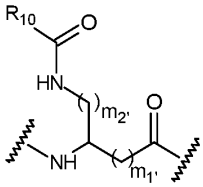
In an embodiment, the ligand in Formula III is a ligand of Formula L_1, wherein t_1 is 1; t_2 is 2 and Z is the compound of Formula Z_2.

Further according to an embodiment, in Formula III, A is an amino acid selected from the group consisting of alanine (ala), arginine (arg), aspartic acid (asp), cysteine (cys), glutamic acid (glu), glycine (gly), lysine (lys), phenylalanine (phe), serine (ser), threonine (thr), tryptophan (trp), valine (val), ornithine (orn), citrulline (cit), homocitrulline (hct), lanthionine (lan), homocysteine (hcy) or an amino acid having Formula A_1 or Formula A2



, or

Formula A_1



Formula A_2

wherein:

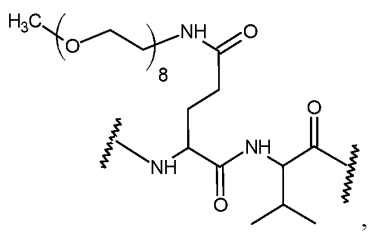
m_1 and m_1' are 0, 1, 2 or 3;

m_2 and m_2' are is 0, 1, 2, 3 or 4;

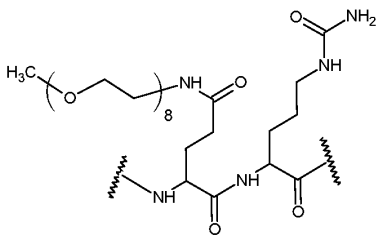
R_{10} is selected from $(-C_2H_4O)_{1-24}CH_3$, $(-C_2H_4O)_{1-24}C_{1-2}$ alkyl$(N(R_{10'})(R_{10''}))$—, C_{1-3} alkyl-aryl or —C_{1-3} alkyl-Het_1-$(-C_2H_4O)_{1-24}CH_3$, wherein Het_1 is a 5 to 10 membered heterocyclic ring containing one, two or three heteroatoms independently selected from nitrogen, oxygen or sulfur and wherein said aryl is selected from 6 to 14 membered aryl and is optionally substituted by -C_{1-3}alkyl or -OC_{1-3}alkyl; wherein

$R_{10'}$ and $R_{10''}$ are independently selected from hydrogen, C_{1-6} alkyl or -C(O)-C_{1-4}alkyl-aryl wherein said aryl is selected from 6 to 14 membered aryl and is optionally substituted by -C_{1-3}alkyl or -OC_{1-3}alkyl.

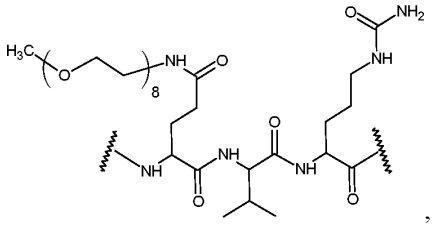
In another embodiment, in Formula III, A is a peptide selected from the group consisting of ala-ala, ala-ala-ala, ala-phe, val-ala, val-cit, ala-val-cit, ala(beta)-val-cit, glu-val-cit, glu-cit, glu-val, gly-gly, gly-gly-phe, gly-phe-gly, gly-gly-phe-gly, asp-cit, asp-val-cit and asp-val; or the peptide is selected from a group of compounds having the following formula:



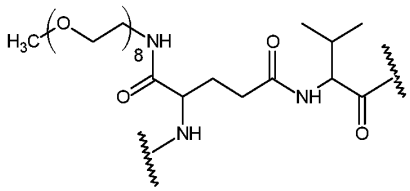
,



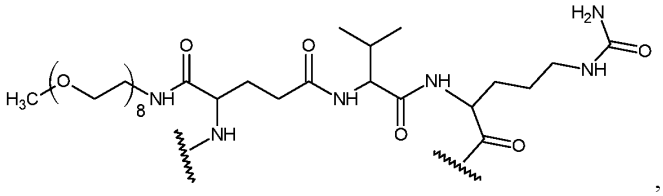
Formula P_1



Formula P_2

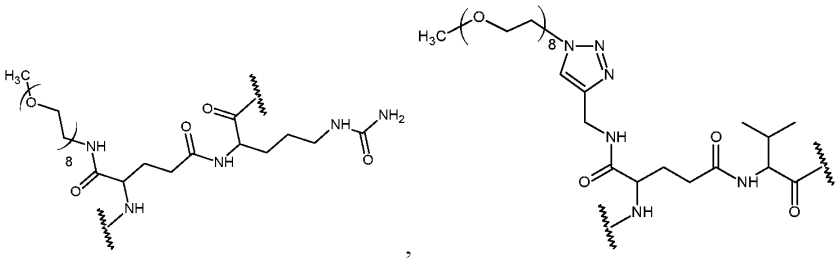


Formula P_3



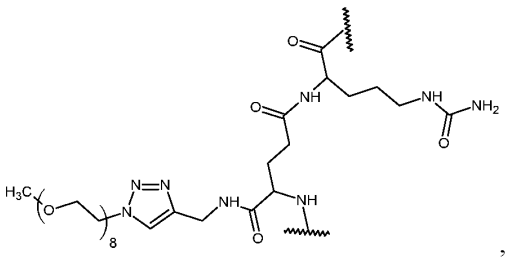
Formula P_4

Formula P_5

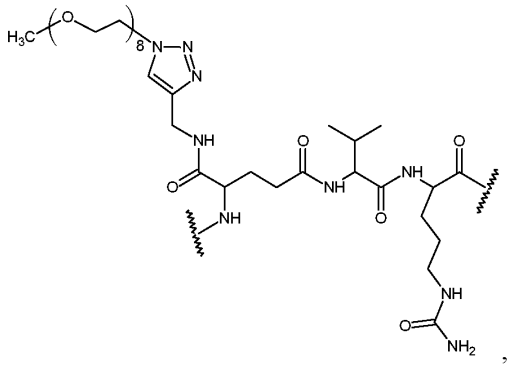


Formula P_6

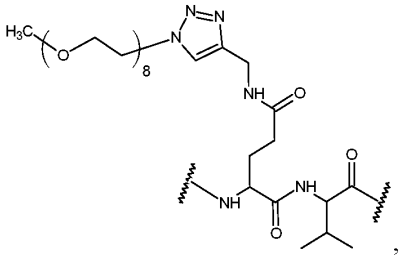
Formula P_7



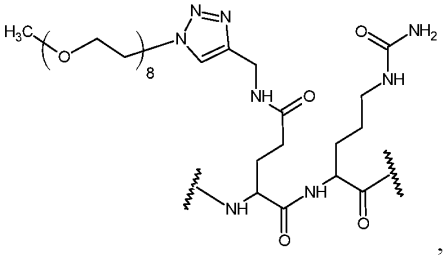
Formula P_8



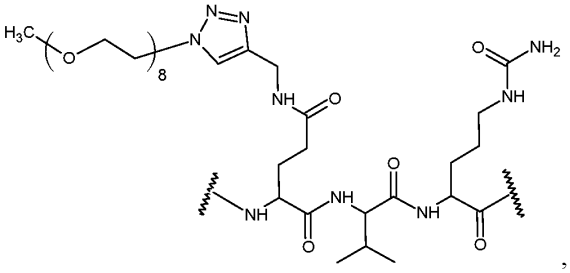
Formula P_9



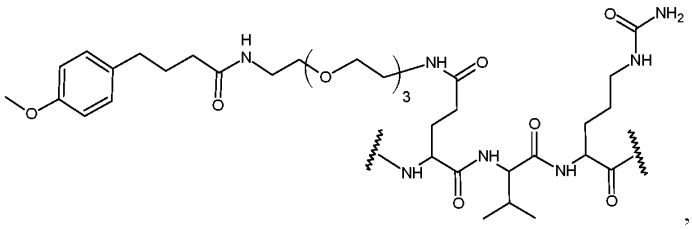
Formula P_{10}



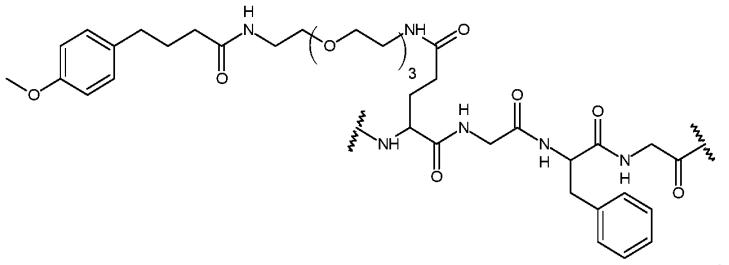
Formula P_{11}



Formula P_{12}

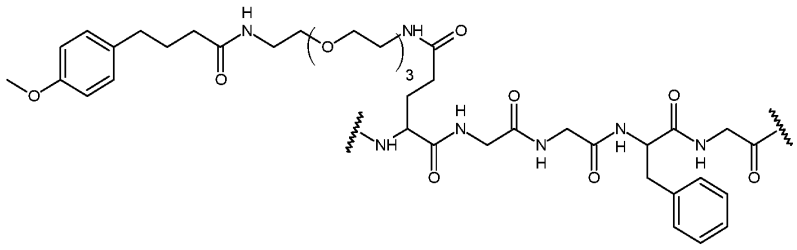


Formula P_{13}



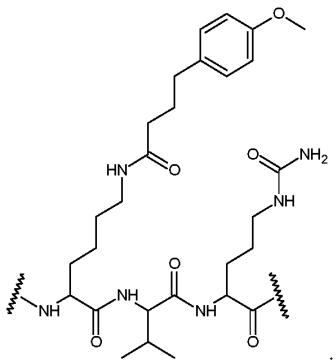
,

Formula P_{14}



, and

Formula P_{15}



.

Formula P_{16}

In an embodiment, the present invention provides a compound of Formula III, wherein:

L is of Formula L_1, wherein t_1 is 3; t_2 is 2; and Z is N(R_9), wherein R_9 is hydrogen. In an embodiment, L is ligand of Formula L_1, wherein t_1 is 3; t_2 is 2; and Z is N(R_9), wherein R_9 is phenyl. In another embodiment, L is ligand of Formula L_1, wherein t_1 is 3; t_2 is 2; and Z is N(R_9), wherein phenyl substituted with Cl, Br, or I;

R_4 is selected from —C_{1-10} alkyl- and 3 to 6 membered cycloalkyl;

A is selected from the group consisting of cit, val-ala, val-cit, gly-gly-phe-gly, Formula P_3, Formula P_5, Formula P_9, Formula P_{12}, Formula P_{13} Formula P_{14} Formula P_{15} and Formula P_{16};

R_{11} is —C_{1-3} alkyl-OC(O)—**

wherein ** indicates point of attachment to D;

R_{12} is —C(O)N(R_{13})(R_{14}),

wherein:

R_{13} is hydrogen;

R_{14} is —C_{1-5} alkyl-N(R_{15})(R_{16}),

R_{15} is C_{1-3} alkyl;

R_{16} is C_{1-3} alkyl; and

R_{22} is hydrogen.

In an embodiment, the present invention provides a compound of Formula III, wherein:

L is of Formula L_1, wherein t_1 is 3; t_2 is 2; and Z is N(R_9), wherein R_9 is hydrogen. In an embodiment, L is ligand of Formula L_1, wherein t_1 is 3; t_2 is 2; and Z is N(R_9), wherein R_9 is phenyl. In another embodiment, L is ligand of Formula L_1, wherein t_1 is 3; t_2 is 2; and Z is N(R_9), wherein phenyl substituted with Cl, Br, or I;

R_4 is selected from —C_{1-10} alkyl- and 3 to 6 membered cycloalkyl;

A is selected from the group consisting of cit, val-ala, val-cit, gly-gly-phe-gly, Formula P_3, Formula P_5, Formula P_9, Formula P_{12}, Formula P_{13} Formula P_{14} Formula P_{15} and Formula P_{16};

R_{11} is —C_{1-3} alkyl-OC(O)—**

wherein ** indicates point of attachment to D;

R_{12} is —C(O)N(R_{13})(R_{14}),

wherein:

R_{13} is hydrogen;

R_{14} is —C_{1-5} alkyl-N(R_{15})(R_{16}),

R_{15} is C_{1-3} alkyl;

R_{16} is C_{1-3} alkyl; and

R_{22} is —C(O)N(R_{23})(R_{24}),

wherein:

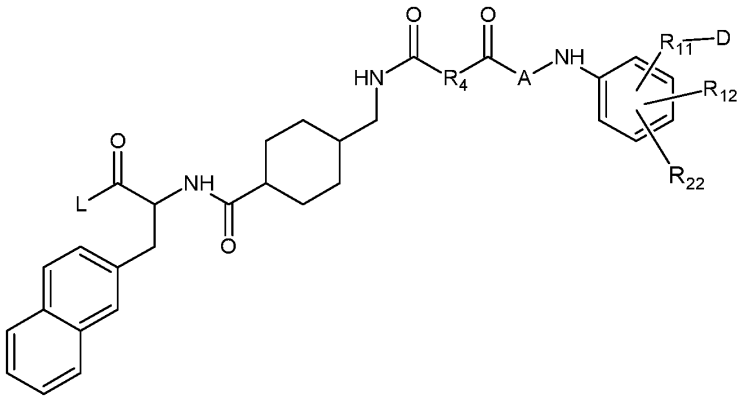
R_{23} is hydrogen;

R_{24} is —C_{1-5} alkyl-N(R_{25})(R_{26}), wherein:

R_{25} is C_{1-3} alkyl; and

R_{26} is C_{1-3} alkyl.

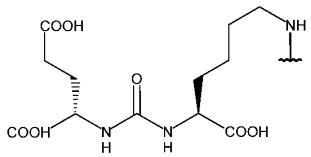
In another aspect, the present disclosure relates to a compound of Formula III:



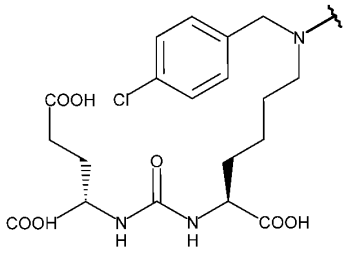
Formula III

or pharmaceutically acceptable salt, stereoisomer or isotope thereof; wherein:

L is a ligand, selected from:

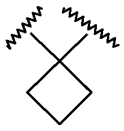


; and

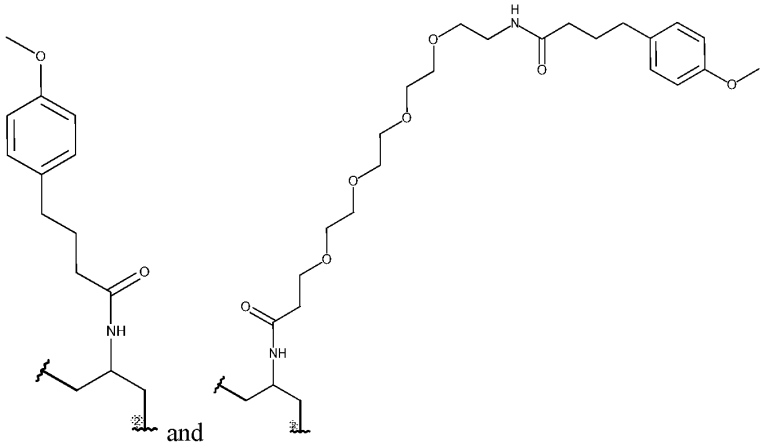


;

R_4 is selected from

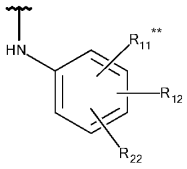


; —$C_{2\text{-}5}$ alkyl, —CH=CH—, —CH_2-O-CH_2—, —$CH_2(-OC_2H_4)_{2\text{-}8}$-$OCH_2$—,

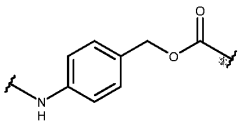
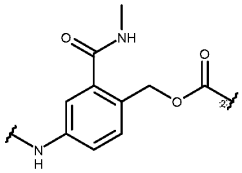
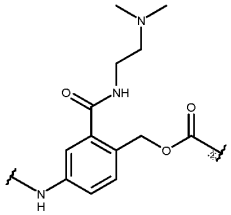
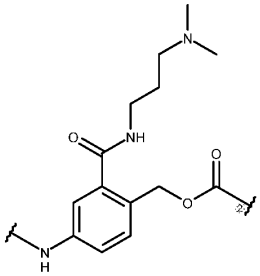
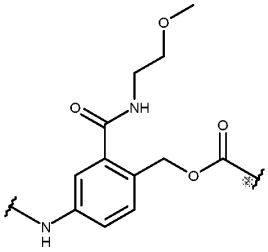
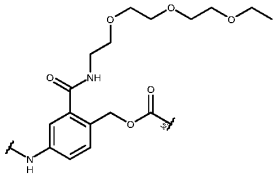
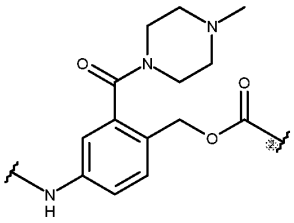
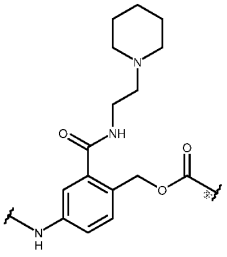
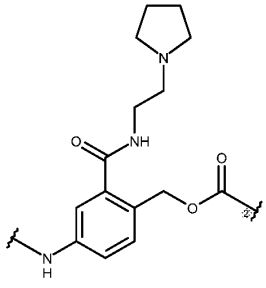


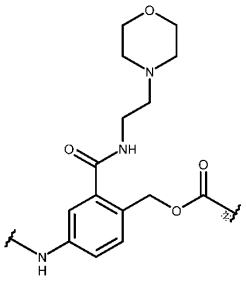
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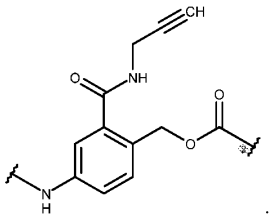
A is selected from cit, val-cit, val-ala, gly-gly-phe-gly, glu-val-cit, gly-gly-phe, gly-phe-gly, Formula P1-ala, Formula P3, Formula P4-ala, Formula P5, Formula P9, Formula P12, Formula P13 and Formula P16;

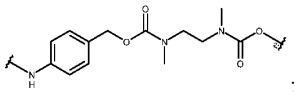


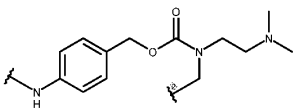
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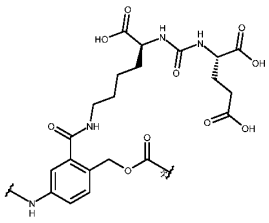

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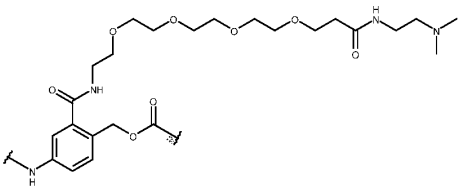

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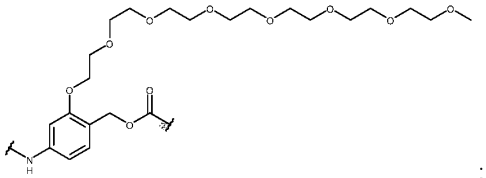

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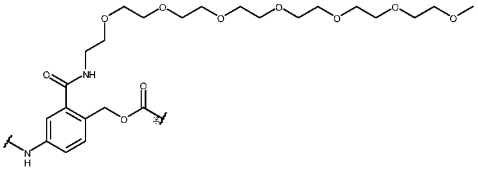

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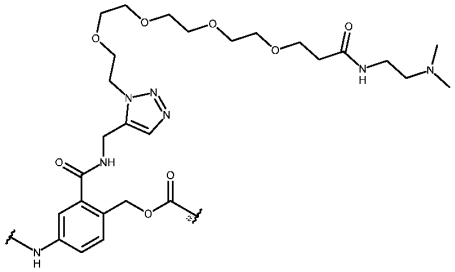

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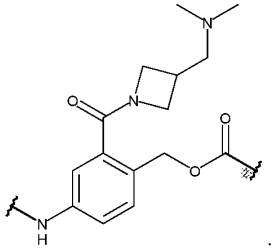

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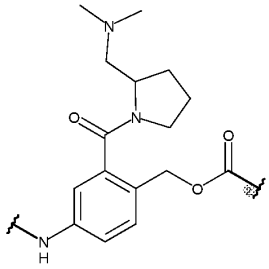

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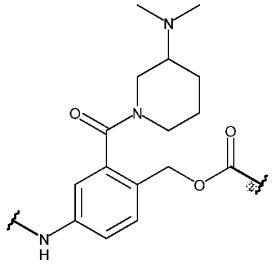

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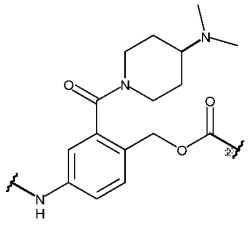
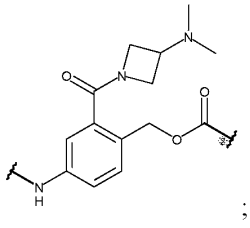

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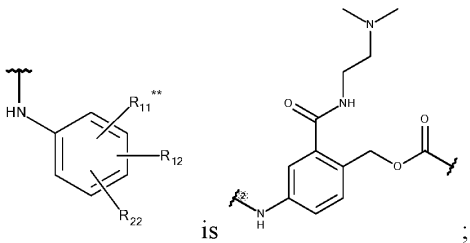

; and 
;

D is a cytotoxic agent or a therapeutic agent selected from Monomethyl auristatin E (MMAE), Rucaparib, Talazoparib, Niraparib, SN-38, Exatecan, Belotecan, Mitomycin C.

In one embodiment, the present disclosure relates to a compound of Formula III or pharmaceutically acceptable salt, stereoisomer or isotope thereof, wherein:

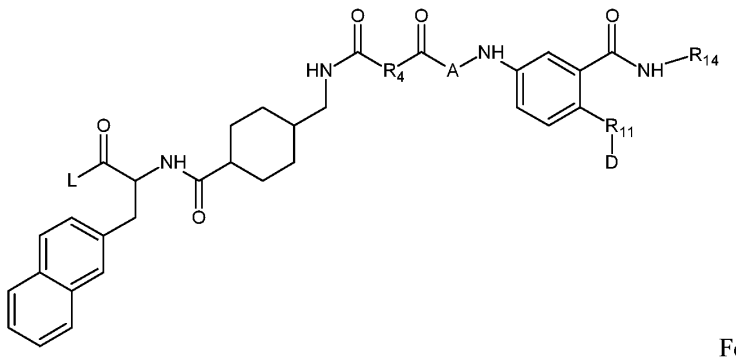
R_4 is $-C_3H_6-$;

A is val-cit;


is ;

D is Monomethyl auristatin E (MMAE).

In a fourth aspect of the present invention, there is provided a compound of Formula IV



Formula IV

or pharmaceutically acceptable salt, stereoisomer or isotope thereof; wherein,

L is a Ligand;

R_4 is selected from a group consisting of —C_{1-10} alkyl, —C_{2-6} alkenyl, —C_{1-3} alkyl-O-C_{1-3} alkyl—, —C_{2-6} alkyl-N(R_8)—, —N(R_8)-C_{2-6} alkyl—, a 3 to 6 membered cycloalkyl and —C_{1-2} alkyl $(-OC_2H_4)_{1-8}$-OC_{1-2} alkyl—; wherein,

R_8 is hydrogen or C_{1-6} alkyl;

A is an amino acid or a peptide comprising 2-5 amino acids;

R_{11} is selected from —C_{1-3} alkyl-OC(O)—**,

—C_{1-3} alkyl-O-C(O)-N(R_{19})-C_{1-5} alkyl-N(R_{19})-C(O)—**,

—C_{1-3} alkyl-O-C(O)-N[C_{1-5} alkyl-N($R_{20}R_{21}$)]-C_{1-3} alkyl—**, or

—C_{1-3} alkyl-O-C(O)-Het_2-C_{1-3} alkyl-N(R_{19})-C(O)—**;

wherein ** indicates point of attachment to D;

R_{19} is selected from H, -CH_3 or –C_2H_4-O-C_2H_4-OH;

R_{20} is -CH_3; R_{21} is -CH_3;

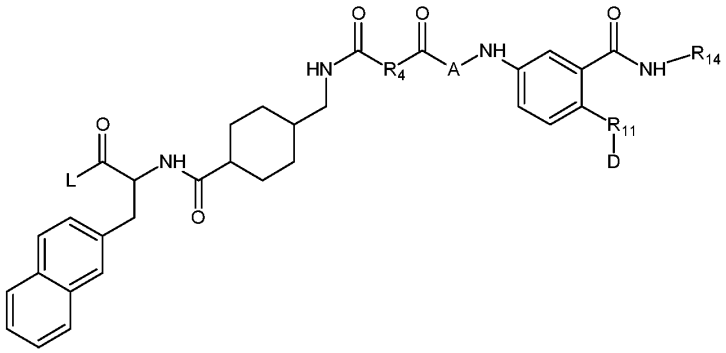
Het_2 is pyrrolidinyl;

R_{14} is selected from —C_1-C_5 alkyl, —C_1 to C_5 alkyl-N(R_{15})R_{16}, —C_1-C_5 alkyl-OCH_3, $(-C_2H_4O)_{1-10}$ CH_2-CH_3, wherein

R_{15} is C_{1-3} alkyl; and

R_{16} is C_{1-3} alkyl.

In one embodiment of the present invention, there is provided a compound of Formula IV



Formula IV

or pharmaceutically acceptable salt, stereoisomer or isotope thereof; wherein:

L is a Ligand; D is a cytotoxic or therapeutic agent as defined above;

R_4 is selected from a group consisting of —C_{1-10} alkyl, —C_{2-6} alkenyl, —C_{1-3} alkyl-O-C_{1-3} alkyl—, —C_{2-6} alkyl-N(R_8)—, —C_{2-6} alkyl(N(R_8)($R_{8'}$))—, —N(R_8)-C_{2-6} alkyl—, 3 to 6 membered cycloalkyl and —C_{1-2} alkyl $(-OC_2H_4)_{1-8}$-OC_{1-2} alkyl—; wherein:

R_8 and $R_{8'}$ are independently selected from hydrogen, C_{1-6} alkyl, -C(O)-C_{1-4}alkyl-aryl or -C(O)-$(-C_2H_4O)_{1-8}$-C_{1-2} alkyl-N(R)(R'), wherein said aryl is selected from 6 to 14 membered aryl and is optionally substituted by -C_{1-3}alkyl or -OC_{1-3}alkyl; wherein

R and R' are independently selected from hydrogen, -C_{1-6} alkyl or -C(O)-C_{1-4}alkyl-aryl, wherein said aryl is selected from 6 to 14 membered aryl and is optionally substituted by -C_{1-3}alkyl or -OC_{1-3}alkyl;

A is an amino acid or a peptide comprising 2-5 amino acids;

R_{11} is selected from —C_{1-3} alkyl-OC(O)—**,

—C_{1-3} alkyl-O-C(O)-N(R_{19})-C_{1-5} alkyl-N(R_{19})-C(O)—**,

—C_{1-3} alkyl-O-C(O)-N[C_{1-5} alkyl-N($R_{20}R_{21}$)]-C_{1-3} alkyl—**, or

—C_{1-3} alkyl-O-C(O)-Het_2-C_{1-3} alkyl-N(R_{19})-C(O)—**,

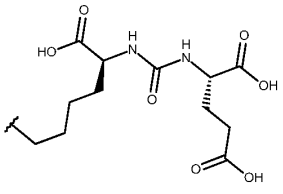
wherein ** indicates point of attachment to D and

R_{19} is selected from H, -CH_3 or –C_2H_4-O-C_2H_4-OH;

R_{20} is -CH_3; R_{21} is -CH_3;

Het_2 is pyrrolidine;

R_{14} is selected from —C_1-C_5 alkyl, —C_1 to C_5 alkyl-N(R_{15})(R_{16}), —C_1-C_5 alkyl-OCH_3, $(-C_2H_4O)_{1-10}$ CH_2-CH_3, or



wherein:

R_{15} is C_{1-3} alkyl; and

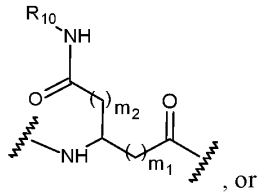
R_{16} is C_{1-3} alkyl.

According to an embodiment, ligand in Formula IV is of Formula L_1, wherein t_1 is 3; t_2 is 2; and Z is N(R_9), wherein R_9 is hydrogen. In an embodiment, L is ligand of Formula L_1, wherein t_1 is 3; t_2 is 2; and Z is N(R_9), wherein R_9 is phenyl. In another embodiment, L is ligand of Formula L_1, wherein t_1 is 3; t_2 is 2; and Z is N(R_9), wherein phenyl substituted with Cl, Br, or I.

In an embodiment, ligand in Formula IV is of Formula L_1, wherein t_1 is 0; t_2 is 2; and Z is Z_1, wherein t_3 is 1, 2, 3, 4, 5 or 6 and Y is —NH—.

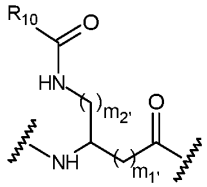
In an embodiment, ligand in Formula IV is of Formula L_1, wherein t_1 is 1; t_2 is 2 and Z is the compound of Formula Z_2.

Further according to an embodiment, in Formula IV, A is an amino acid rom the group of consisting of alanine (ala), arginine (arg), aspartic acid (asp), cysteine (cys), glutamic acid (glu), glycine (gly), lysine (lys), phenylalanine (phe), serine (ser), threonine (thr), tryptophan (trp), valine (val), ornithine (orn), citrulline (cit), homocitrulline (hct), lanthionine (lan), homocysteine (hcy) or an amino acid having Formula A_1 or Formula A_2



, or

Formula A_1



Formula A_2

wherein:

m_1 and m_1' are 0, 1, 2 or 3;

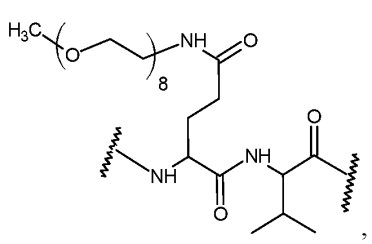
m_2 and m_2' are is 0, 1, 2, 3 or 4;

R_{10} is selected from $(-C_2H_4O)_{1-24}CH_3$, $(-C_2H_4O)_{1-24}C_{1-2}$ alkyl$(N(R_{10'})(R_{10''}))$—, C_{1-3} alkyl-aryl or —C_{1-3} alkyl-Het_1-$(-C_2H_4O)_{1-24}CH_3$,

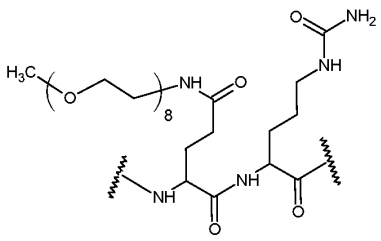
wherein Het_1 is a 5 to 10 membered heterocyclic ring containing one, two or three heteroatoms independently selected from nitrogen, oxygen or sulfur and wherein said aryl is selected from 6 to 14 membered aryl and is optionally substituted by -C_{1-3}alkyl or -OC_{1-3}alkyl; wherein

$R_{10'}$ and $R_{10''}$ are independently selected from hydrogen, C_{1-6} alkyl or -C(O)-C_{1-4}alkyl-aryl wherein said aryl is selected from 6 to 14 membered aryl and is optionally substituted by -C_{1-3}alkyl or -OC_{1-3}alkyl.

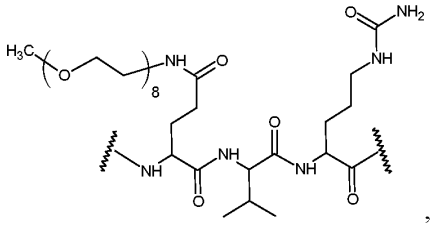
In another embodiment in Formula IV, A is a peptide selected from the group consisting of ala-ala, ala-ala-ala, ala-phe, val-ala, val-cit, ala-val-cit, ala(beta)-val-cit, glu-val-cit, glu-cit, glu-val, gly-gly, gly-gly-phe, gly-phe-gly, gly-gly-phe-gly, asp-cit, asp-val-cit and asp-val; or the peptide is selected from a group of compounds having the following formula:



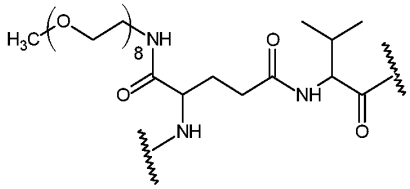
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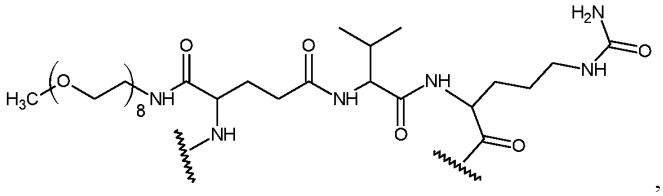
Formula P_1



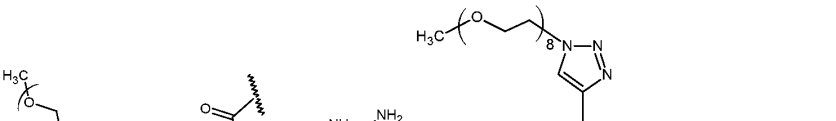
Formula P_2



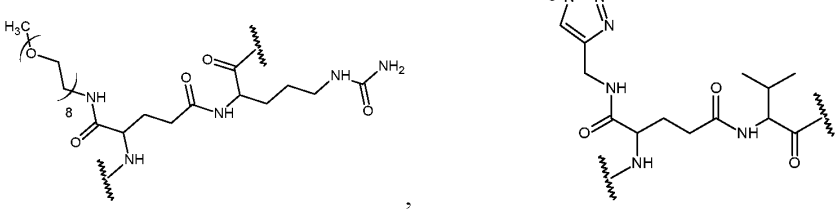
Formula P_3



Formula P_4



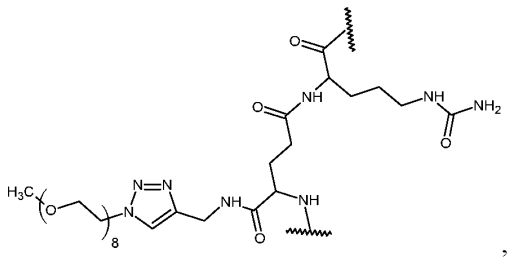
Formula P_5

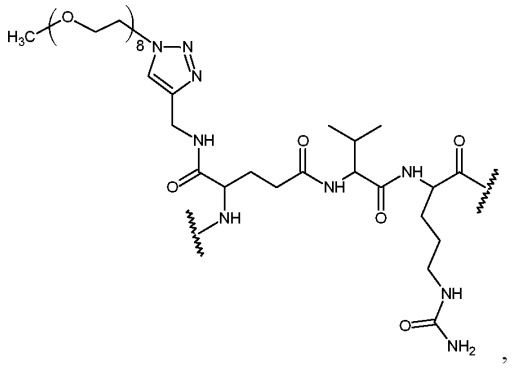


Formula P_6

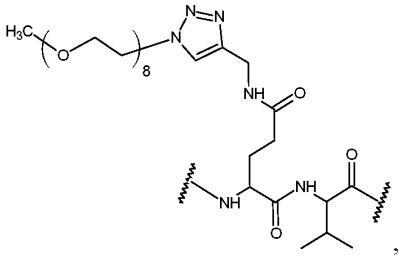
Formula P_7

Formula P_8

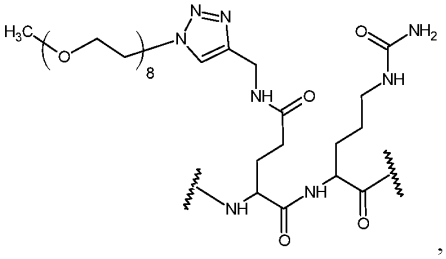




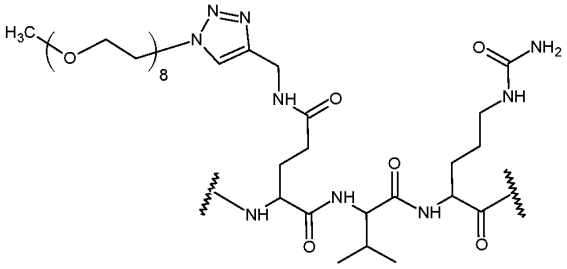
Formula P_9



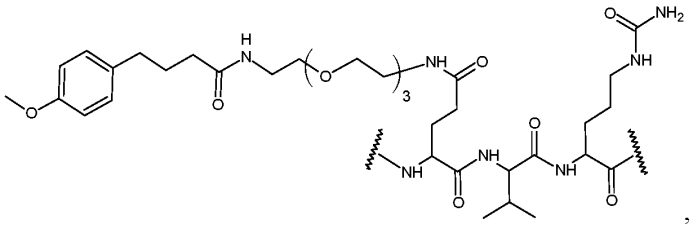
Formula P_{10}



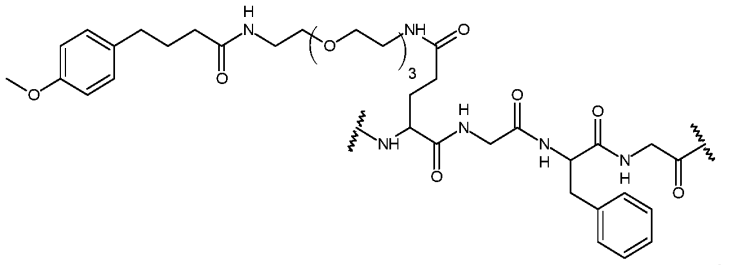
Formula P_{11}



Formula P_{12}

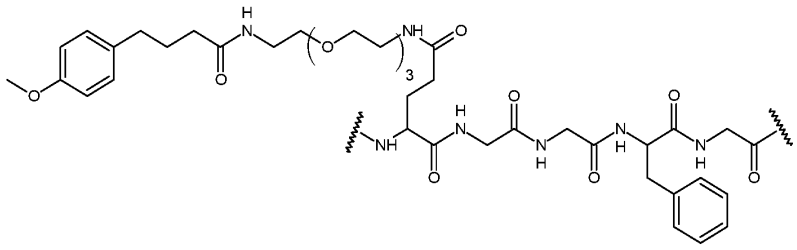


Formula P_{13}



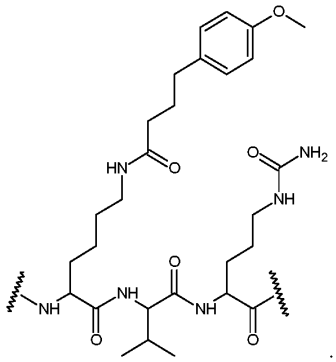
,

Formula P_{14}



, and

Formula P_{15}



.

Formula P_{16}

In an embodiment, the present invention provides a compound of Formula IV, wherein:

L is a ligand of Formula L_1, wherein t_1 is 3; t_2 is 2; and Z is $N(R_9)$, wherein R_9 is hydrogen. In an embodiment, L is a ligand of Formula L_1, wherein t_1 is 3; t_2 is 2; and Z is $N(R_9)$, wherein R_9 is phenyl. In another embodiment, L is a ligand of Formula L_1, wherein t_1 is 3; t_2 is 2; and Z is $N(R_9)$, wherein phenyl substituted with Cl, Br, or I;

R_4 is selected from —$C_{2\text{-}5}$ alkyl, —$C_{2\text{-}5}$ alkyl($N(R_8)(R_{8'})$)— and 3 to 6 membered cycloalkyl;

R_8 and $R_{8'}$ are independently selected from hydrogen, -C(O)-$C_{1\text{-}4}$alkyl-aryl or -C(O)-(-$C_2H_4O)_{2\text{-}6}$-$C_{1\text{-}2}$ alkyl-N(R)(R'), , wherein said aryl is selected from 6 to 14 membered aryl and is optionally substituted by -$C_{1\text{-}3}$alkyl or -O$C_{1\text{-}3}$alkyl; wherein

R and R' are independently selected from hydrogen or -C(O)-C_{1-4}alkyl-aryl, wherein said aryl is selected from 6 to 14 membered aryl and is optionally substituted by -C_{1-3}alkyl or -OC_{1-3}alkyl;

A is selected from the group consisting of cit, val-ala, val-cit, glu-val-cit, gly-gly-phe-gly, Formula P_3, Formula P_5, Formula P_9, Formula P_{12}, Formula P_{13}, Formula P_{14}, Formula P_{15} and Formula P_{16};

R_{11} is —C_{1-3} alkyl-OC(O)—**

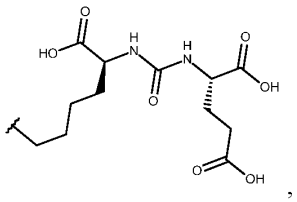
wherein ** indicates the point of attachment to D;

R_{12} is —C(O)N(R_{13})(R_{14}),

wherein:

R_{13} is hydrogen;

R_{14} is selected from —C_{1-5} alkyl-N(R_{15})(R_{16}) and

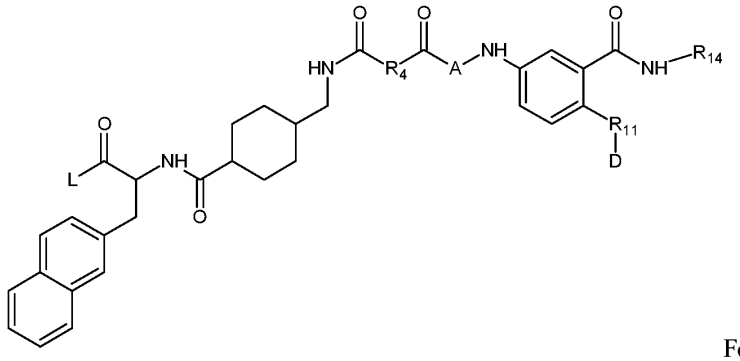


,

R_{15} is C_{1-3} alkyl; and

R_{16} is C_{1-3} alkyl.

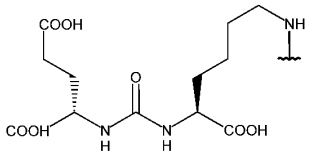
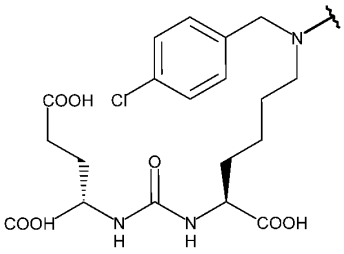
In another aspect, the present disclosure relates to a compound of Formula IV:



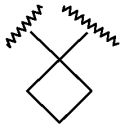
Formula IV

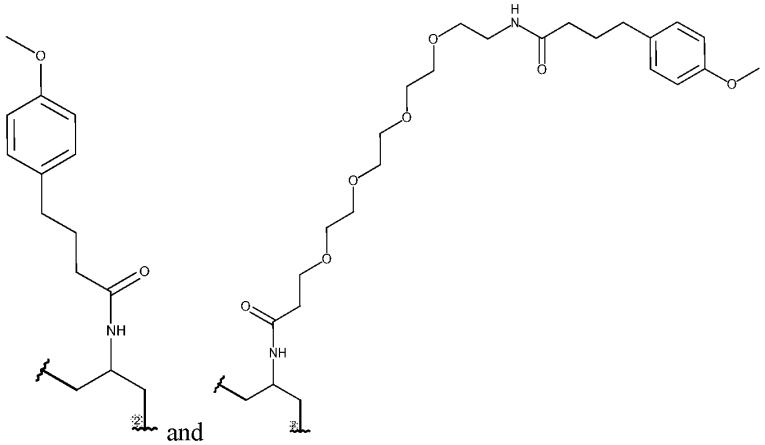
or pharmaceutically acceptable salt, stereoisomer or isotope thereof; wherein:

L is a ligand, selected from:


; and

;

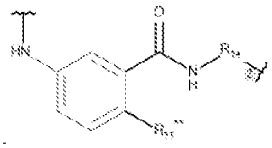
R_4 is selected from

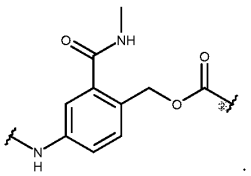

; —C_{2-5} alkyl, —CH_2=CH_2—, —CH_2-O-CH_2—, —$CH_2(-OC_2H_4)_{2-8}$-OCH_2—,

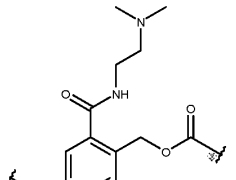

and ;

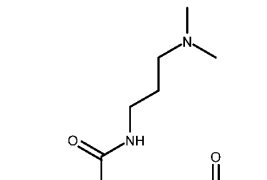
A is selected from cit, val-cit, val-ala, gly-gly-phe-gly, glu-val-cit, gly-gly-phe, gly-phe-gly, Formula P1-ala, Formula P3, Formula P4-ala, Formula P5, Formula P9, Formula P12, Formula P13 and Formula P16;

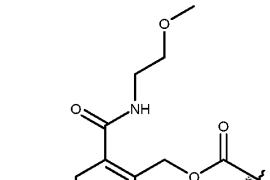
R_{11} is selected from -CH_2-O-C(O)-;

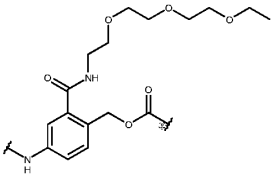

is selected from:

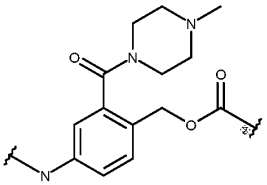

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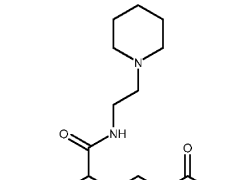

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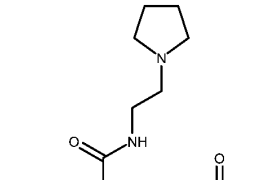

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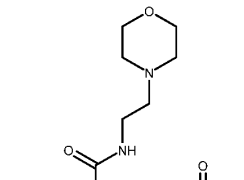

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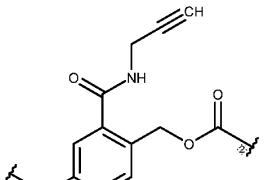

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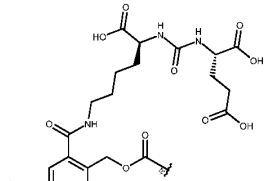

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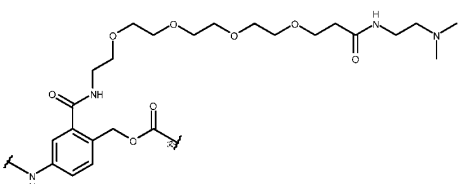

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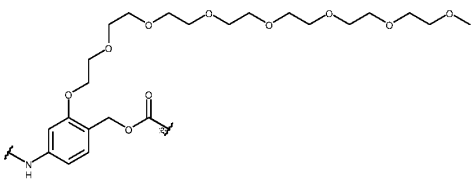

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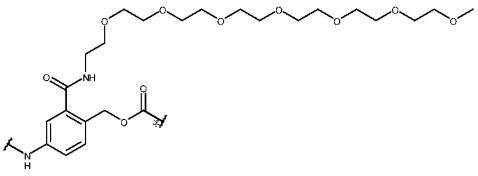
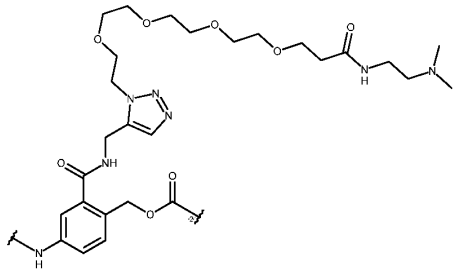
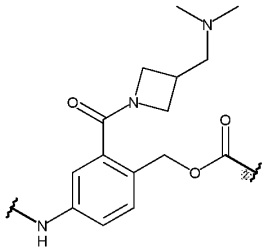
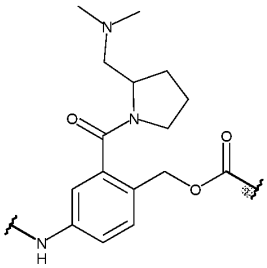
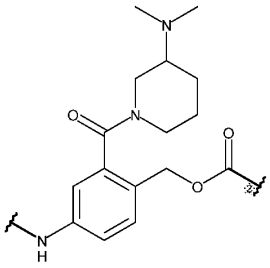
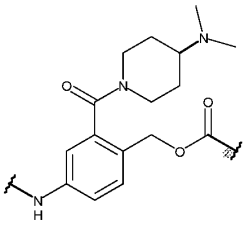
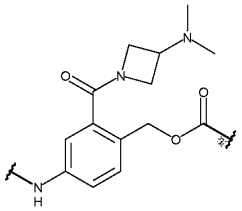

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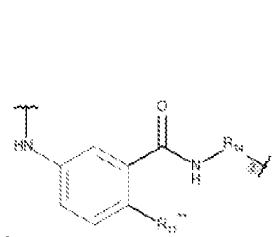
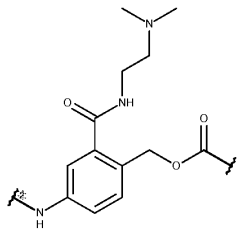

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;

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; and

;

D is a cytotoxic agent or a therapeutic agent selected from Monomethyl auristatin E (MMAE), Rucaparib, Talazoparib, Niraparib, SN-38, Exatecan, Belotecan, Mitomycin C etc.

In one embodiment, the present disclosure relates to a compound of Formula IV or pharmaceutically acceptable salt, stereoisomer or isotope thereof, wherein:

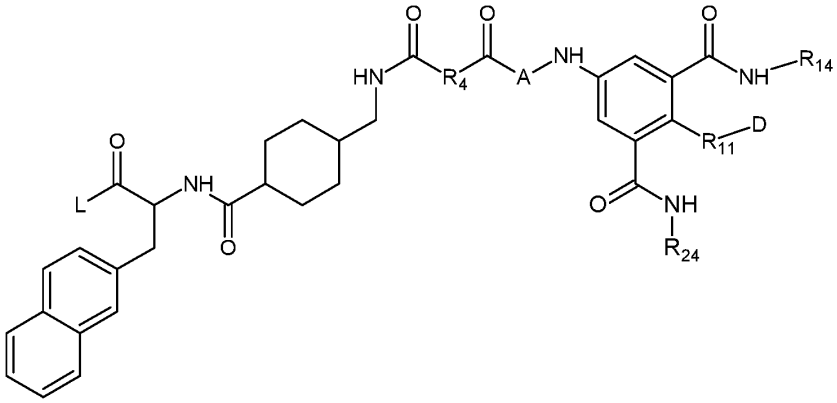
R_4 is $-C_3H_6-$;

A is val-cit;


is

;

D is Monomethyl auristatin E (MMAE).

In a fifth aspect, there is provided a compound of Formula V



Formula V

or pharmaceutically acceptable salt, stereoisomer or isotope thereof; wherein,

L is a Ligand;

R_4 is selected from a group consisting of —$C_{1\text{-}10}$ alkyl, —$C_{2\text{-}6}$ alkenyl, —$C_{1\text{-}3}$ alkyl-O-$C_{1\text{-}3}$ alkyl—, —$C_{2\text{-}6}$ alkyl-N(R_8)—, —N(R_8)-$C_{2\text{-}6}$ alkyl—, a 3 to 6 membered cycloalkyl and —$C_{1\text{-}2}$ alkyl $(\text{-OC}_2\text{H}_4)_{1\text{-}8}$-O$C_{1\text{-}2}$ alkyl—; wherein,

R_8 is hydrogen or $C_{1\text{-}6}$ alkyl;

A is an amino acid or a peptide comprising 2-5 amino acids;

R_{11} is selected from —$C_{1\text{-}3}$ alkyl-OC(O)—**,

—$C_{1\text{-}3}$ alkyl-O-C(O)-N(R_{19})-$C_{1\text{-}5}$ alkyl-N(R_{19})-C(O)—**,

—$C_{1\text{-}3}$ alkyl-O-C(O)-N[$C_{1\text{-}5}$ alkyl-N($R_{20}R_{21}$)]-$C_{1\text{-}3}$ alkyl—**,

—$C_{1\text{-}3}$ alkyl-O-C(O)-Het_2-$C_{1\text{-}3}$ alkyl-N(R_{19})-C(O)—**, or

—$C_{1\text{-}3}$ alkyl-O-C(O)-N(R_{19})-$C_{1\text{-}5}$ alkyl-N(R_{19})-C(O)—**;

wherein ** indicates point of attachment to D;

R_{19} is selected from H, -CH_3 or –C_2H_4-O-C_2H_4-OH;

R_{20} is -CH_3; R_{21} is -CH_3; and

Het_2 is pyrrolidinyl;

R_{14} is selected from —C_1-C_5 alkyl, —C_1 to C_5 alkyl-N(R_{15})R_{16}, —C_1-C_5 alkyl-OCH_3, $(\text{-C}_2\text{H}_4\text{O})_{1\text{-}10}\text{CH}_2\text{-CH}_3$, wherein

R_{15} is $C_{1\text{-}3}$ alkyl;

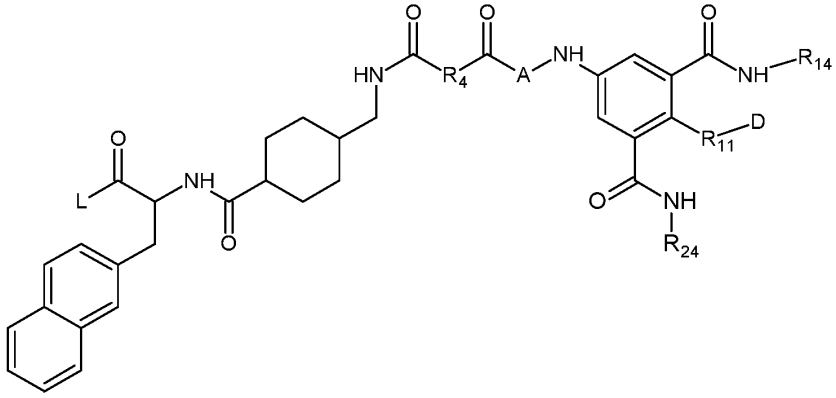
R_{16} is $C_{1\text{-}3}$ alkyl;

R_{24} is selected from —$C_{1\text{-}5}$ alkyl, —$C_{1\text{-}5}$ alkyl-N(R_{25})R_{26}, —$C_{1\text{-}5}$ alkyl-OCH_3, (-$C_2H_4O)_{1\text{-}10}CH_2$-$CH_3$; wherein

R_{25} is hydrogen or $C_{1\text{-}3}$ alkyl; and

R_{26} is hydrogen or $C_{1\text{-}3}$ alkyl.

In one embodiment, there is provided a compound of Formula V



Formula V

or pharmaceutically acceptable salt, stereoisomer or isotope thereof; wherein:

L and A is as defined in previous embodiments;

R_4 is selected from a group consisting of —$C_{1\text{-}10}$ alkyl, —$C_{2\text{-}6}$ alkenyl, —$C_{1\text{-}3}$ alkyl-O-$C_{1\text{-}3}$ alkyl—, —$C_{2\text{-}6}$ alkyl-N(R_8)—, —N(R_8)-$C_{2\text{-}6}$ alkyl—, a 3 to 6 membered cycloalkyl and —$C_{1\text{-}2}$ alkyl $(-OC_2H_4)_{1\text{-}8}$-$OC_{1\text{-}2}$ alkyl—; wherein:

R_8 is hydrogen or $C_{1\text{-}6}$ alkyl;

R_{11} is selected from —$C_{1\text{-}3}$ alkyl-OC(O)—**,

—$C_{1\text{-}3}$ alkyl-O-C(O)-N(R_{19})-$C_{1\text{-}5}$ alkyl-N(R_{19})-C(O)—**,

—$C_{1\text{-}3}$ alkyl-O-C(O)-N[$C_{1\text{-}5}$ alkyl-N($R_{20}R_{21}$)]-$C_{1\text{-}3}$ alkyl—**, or

—$C_{1\text{-}3}$ alkyl-O-C(O)-Het_2-$C_{1\text{-}3}$ alkyl-N(R_{19})-C(O)—**,

wherein ** indicates point of attachment to D;

R_{19} is selected from H, -CH_3 or –C_2H_4-O-C_2H_4-OH;

R_{20} is -CH_3; R_{21} is -CH_3; and

Het_2 is pyrrolidinyl;

R_{14} is selected from —C_1-C_5 alkyl, —C_1 to C_5 alkyl-N(R_{15})(R_{16}), —C_1-C_5 alkyl-OCH_3, (-$C_2H_4O)_{1\text{-}10}$ CH_2-CH_3 wherein:

R_{15} is $C_{1\text{-}3}$ alkyl;

R_{16} is $C_{1\text{-}3}$ alkyl;

R_{24} is selected from —C_{1-5} alkyl, —C_{1-5} alkyl-N(R_{25})(R_{26}), —C_{1-5} alkyl-OCH_3, (-C_2H_4O)$_{1-10}$$CH_2$-$CH_3$ wherein:

R_{25} is hydrogen or C_{1-3} alkyl; and

R_{26} is hydrogen or C_{1-3} alkyl.

In an embodiment, the present invention provides a compound of Formula V, wherein:

L is a ligand of Formula L_1, wherein t_1 is 3; t_2 is 2; and Z is N(R_9), wherein R_9 is hydrogen. In an embodiment, L is a ligand of Formula L_1, wherein t_1 is 3; t_2 is 2; and Z is N(R_9), wherein R_9 is phenyl. In another embodiment, L is a ligand of Formula L_1, wherein t_1 is 3; t_2 is 2; and Z is N(R_9), wherein R_9 is phenyl substituted with Cl, Br, or I;

R_4 is selected from —C_{2-5} alkyl and 3 to 6 membered cycloalkyl;

A is selected from the group consisting of cit, val-ala, val-cit, glu-val-cit, gly-gly-phe-gly;

R_{11} is —C_{1-3} alkyl-OC(O)—**

wherein ** indicates point of attachment to D;

R_{12} is —C(O)N(R_{13})(R_{14}),

wherein:

R_{13} is hydrogen;

R_{14} is —C_{1-5} alkyl-N(R_{15})(R_{16}),

R_{15} is C_{1-3} alkyl;

R_{16} is C_{1-3} alkyl; and

R_{22} is —C(O)N(R_{23})R_{24},

wherein:

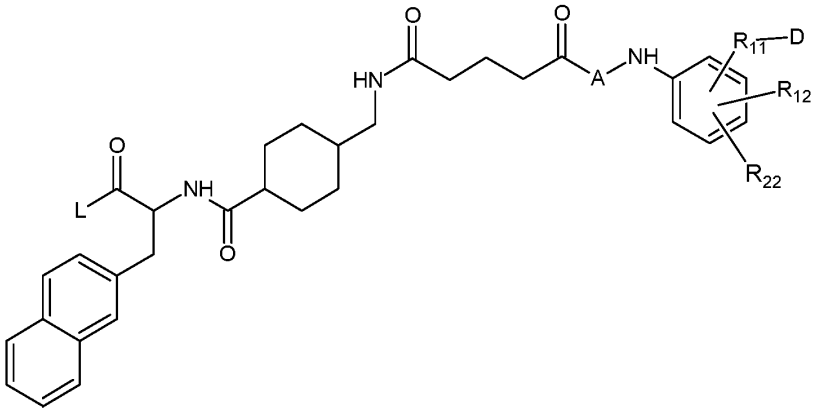
R_{23} is hydrogen;

R_{24} is —C_{1-5} alkyl-N(R_{25})(R_{26}),

R_{25} is C_{1-3} alkyl; and

R_{26} is C_{1-3} alkyl.

In a sixth aspect, there is provided a compound of Formula VI



Formula VI

or pharmaceutically acceptable salt, stereoisomer or isotope thereof; wherein,

L is a Ligand;

A is an amino acid or a peptide comprising 2-5 amino acids;

R_{11} is selected from —C_{1-3} alkyl-OC(O)—**,

—C_{1-3} alkyl-O-C(O)-N(R_{19})-C_{1-5} alkyl-N(R_{19})-C(O)—**,

—C_{1-3} alkyl-O-C(O)-N[C_{1-5} alkyl-N($R_{20}R_{21}$)]-C_{1-3} alkyl—**,

—C_{1-3} alkyl-O-C(O)-Het_2-C_{1-3} alkyl-N(R_{19})-C(O)—**, or

—C_{1-3} alkyl-O-C(O)-N(R_{19})-C_{1-5} alkyl-N(R_{19})-C(O)—**;

wherein ** indicates point of attachment to D;

R_{19} is selected from H, CH_3 or –C_2H_4-O-C_2H_4-OH;

R_{20} is CH_3; R_{21} is CH_3; and

Het_2 is pyrrolidinyl;

R_{12} is selected from hydrogen, —C(O)N(R_{13})R_{14} or —(-OC_2H_4)$_{1-10}$-CH_3;

R_{13} is hydrogen;

R_{14} is —CH_3, —CH_2-C≡CH, —C_{1-3} alkyl-N(R_{15})R_{16}, —$C_2H_4OCH_3$, —(-C_2H_4O)$_{3-8}$-C_2H_5, —(-C_2H_4O)$_{5-10}$-C_2H_4-R_{17}, —CH_2-triazole-(-C_2H_4O)4-C_2H_4-R_{18};

R_{15} is —CH_3 or —C_2H_5;

R_{16} is —CH_3 or —C_2H_5; or

R_{15} and R_{16} along with the nitrogen atom to which they are attached form a 5 to 6 membered heterocyclic ring, wherein 1 or 2 carbon atoms in the heterocyclic ring are optionally replaced with additional heteroatoms independently selected from

nitrogen, oxygen and sulfur and wherein the 5 to 6 membered heterocyclic ring is unsubstituted or substituted with —CH_3;

R_{17} is —$C(O)NHC_2H_4N(CH_3)_2$;

R_{18} is —$C(O)NHC_2H_4N(CH_3)_2$;

OR

R_{13} and R_{14} along with the nitrogen atom to which they are attached form a 4 to 6 membered heterocyclic ring, wherein 1 or 2 carbons in the heterocyclic ring are optionally replaced with additional heteroatoms independently selected from nitrogen, oxygen and sulfur, and wherein the 4 to 6 membered heterocyclic ring is unsubstituted or substituted with C_{1-3} alkyl, —$N(CH_3)_2$ or —$CH_2N(CH_3)_2$;

R_{22} is selected from hydrogen, —$C(O)N(R_{23})R_{24}$ or —$(-OC_2H_4)_{1-10}$-CH_3;

R_{23} is hydrogen;

R_{24} is —CH_3, —CH_2-C≡CH, —C_{1-3} alkyl-$N(R_{25})R_{26}$, —$C_2H_4OCH_3$, —$(-C_2H_4O)_{3-8}$-C_2H_5, —$(-C_2H_4O)_{5-10}$-C_2H_4-R_{27}, —CH_2-triazole-$(-C_2H_4O)4$-C_2H_4-R_{28};

R_{25} is —CH_3 or —C_2H_5;

R_{26} is —CH_3 or —C_2H_5; or

R_{25} and R_{26} along with the nitrogen atom to which they are attached form a 5 to 6 membered heterocyclic ring, wherein 1 or 2 carbon atoms in the heterocyclic ring are optionally replaced with additional heteroatoms independently selected from nitrogen, oxygen and sulfur and wherein the 5 to 6 membered heterocyclic ring is unsubstituted or substituted with —CH_3;

R_{27} is —$C(O)NHC_2H_4N(CH_3)_2$;

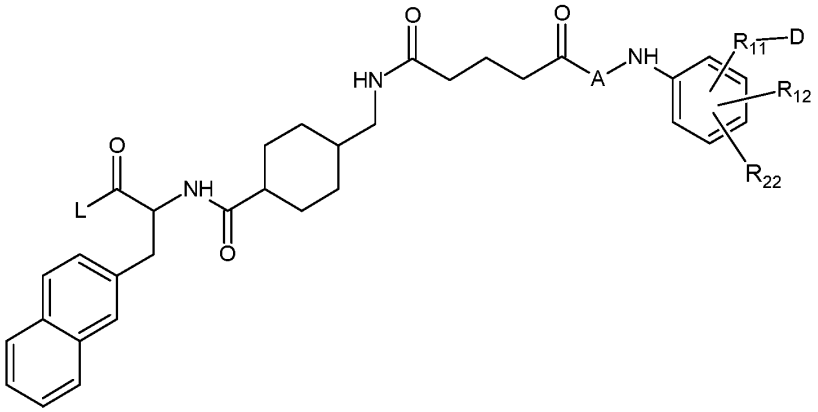
R_{28} is —$C(O)NHC_2H_4N(CH_3)_2$;

OR

R_{23} and R_{24} along with the nitrogen atom to which they are attached form a 4 to 6 membered heterocyclic ring, wherein 1 or 2 carbons in the heterocyclic ring are optionally replaced with additional heteroatoms independently selected from nitrogen, oxygen and sulfur, and wherein the 4 to 6 membered heterocyclic ring is unsubstituted or substituted with C_{1-3} alkyl, —$N(CH_3)_2$ or —$CH_2N(CH_3)_2$; and

D is a cytotoxic agent or therapeutic agent.

In one embodiment, there is provided a compound of Formula VI



Formula VI

or pharmaceutically acceptable salt, stereoisomer or isotope thereof; wherein:

L and A is as defined in previous embodiments;

R_{11} is selected from —C_{1-3} alkyl-OC(O)—**,

—C_{1-3} alkyl-O-C(O)-N(R_{19})-C_{1-5} alkyl-N(R_{19})-C(O)—**,

—C_{1-3} alkyl-O-C(O)-N[C_{1-5} alkyl-N($R_{20}R_{21}$)]-C_{1-3} alkyl—**, or

—C_{1-3} alkyl-O-C(O)-Het_2-C_{1-3} alkyl-N(R_{19})-C(O)—**,

wherein ** indicates point of attachment to D;

R_{19} is selected from H, CH_3 or –C_2H_4-O-C_2H_4-OH;

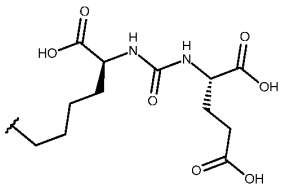
R_{20} is CH_3; R_{21} is CH_3; and

Het_2 is pyrrolidinyl;

R_{12} is selected from hydrogen, —C(O)N(R_{13})(R_{14}) or —(-OC_2H_4)$_{1-10}$-CH_3;

R_{13} is hydrogen;

R_{14} is —CH_3, —CH_2-C≡CH, —C_{1-3} alkyl-N(R_{15})(R_{16}), —$C_2H_4OCH_3$, —(-C_2H_4O)$_{3-8}$-C_2H_5, —(-C_2H_4O)$_{5-10}$-C_2H_4-R_{17}, —CH_2-triazole-(-C_2H_4O)4-C_2H_4-R_{18} or



, wherein:

R_{15} is —CH_3 or —C_2H_5;

R_{16} is —CH_3 or —C_2H_5; or

R_{15} and R_{16} along with the nitrogen atom to which they are attached form a 5 to 6 membered heterocyclic ring, wherein 1 or 2 carbon atoms in the heterocyclic ring

are optionally replaced with additional heteroatoms independently selected from nitrogen, oxygen and sulfur and wherein the 5 to 6 membered heterocyclic ring is unsubstituted or substituted with —CH_3;

R_{17} is —$C(O)NHC_2H_4N(CH_3)_2$;

R_{18} is —$C(O)NHC_2H_4N(CH_3)_2$;

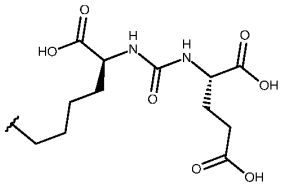
OR

R_{13} and R_{14} along with the nitrogen atom to which they are attached form a 4 to 6 membered heterocyclic ring, wherein 1 or 2 carbons in the heterocyclic ring are optionally replaced with additional heteroatoms independently selected from nitrogen, oxygen and sulfur, and wherein the 4 to 6 membered heterocyclic ring is unsubstituted or substituted with C_{1-3} alkyl, —$N(CH_3)_2$ or —$CH_2N(CH_3)_2$;

R_{22} is selected from hydrogen, —$C(O)N(R_{23})(R_{24})$ or —$(-OC_2H_4)_{1-10}$-CH_3;

R_{23} is hydrogen;

R_{24} is —CH_3, —CH_2-C≡CH, —C_{1-3} alkyl-$N(R_{25})(R_{26})$, —$C_2H_4OCH_3$, —$(-C_2H_4O)_{3-8}$-C_2H_5, —$(-C_2H_4O)_{5-10}$-C_2H_4-R_{27}, —CH_2-triazolyl-$(-C_2H_4O)4$-C_2H_4-R_{28} or



, wherein:

R_{25} is —CH_3 or —C_2H_5;

R_{26} is —CH_3 or —C_2H_5; or

R_{25} and R_{26} along with the nitrogen atom to which they are attached form a 5 to 6 membered heterocyclic ring, wherein 1 or 2 carbon atoms in the heterocyclic ring are optionally replaced with additional heteroatoms independently selected from nitrogen, oxygen and sulfur and wherein the 5 to 6 membered heterocyclic ring is unsubstituted or substituted with —CH_3;

R_{27} is —$C(O)NHC_2H_4N(CH_3)_2$;

R_{28} is —$C(O)NHC_2H_4N(CH_3)_2$;

OR

R_{23} and R_{24} along with the nitrogen atom to which they are attached form a 4 to 6 membered heterocyclic ring, wherein 1 or 2 carbons in the heterocyclic ring are optionally replaced with additional heteroatoms independently selected from nitrogen,

oxygen and sulfur, and wherein the 4 to 6 membered heterocyclic ring is unsubstituted or substituted with C_{1-3} alkyl, —$N(CH_3)_2$ or —$CH_2N(CH_3)_2$; and

D is a cytotoxic agent or therapeutic agent as defined above.

In an embodiment, the present invention provides a compound of Formula VI, wherein:

L is a ligand of Formula L_1, wherein t_1 is 3; t_2 is 2; and Z is $N(R_9)$, wherein R_9 is hydrogen. In an embodiment, L is a ligand of Formula L_1, wherein t_1 is 3; t_2 is 2; and Z is $N(R_9)$, wherein R_9 is phenyl. In another embodiment, L is a ligand of Formula L_1, wherein t_1 is 3; t_2 is 2; and Z is $N(R_9)$, wherein R_9 is phenyl substituted with Cl, Br, or I;

A is selected from the group consisting of cit, val-ala, val-cit, gly-gly-phe-gly, Formula P_3, Formula P_5, Formula P_9 and Formula P_{12};

R_{11} is —C_{1-3} alkyl-OC(O)—**

wherein ** indicates the point of attachment to D;

R_{12} is —$C(O)N(R_{13})(R_{14})$,

wherein:

R_{13} is hydrogen;

R_{14} is —C_{1-5} alkyl-$N(R_{15})(R_{16})$,

R_{15} is C_{1-3} alkyl;

R_{16} is C_{1-3} alkyl; and

R_{22} is hydrogen.

In an embodiment, the present invention provides a compound of Formula VI, wherein:

L is a lignad of Formula L_1, wherein t_1 is 3; t_2 is 2; and Z is $N(R_9)$, wherein R_9 is hydrogen. In an embodiment, L is a ligand of Formula L_1, wherein t_1 is 3; t_2 is 2; and Z is $N(R_9)$, wherein R_9 is phenyl. In another embodiment, L is a ligand of Formula L_1, wherein t_1 is 3; t_2 is 2; and Z is $N(R_9)$, wherein R_9 is phenyl substituted with Cl, Br, or I;

A is selected from the group consisting of cit, val-ala, val-cit, gly-gly-phe-gly, Formula P_3, Formula P_5, Formula P_9 and Formula P_{12};

R_{11} is —C_{1-3} alkyl-OC(O)—**

wherein ** indicates the point of attachment to D;

R_{12} is —$C(O)N(R_{13})(R_{14})$,

wherein:

R_{13} is hydrogen;

R_{14} is —C_{1-5} alkyl-$N(R_{15})(R_{16})$,

R_{15} is C_{1-3} alkyl;

R_{16} is C_{1-3} alkyl; and

R_{22} is —C(O)N(R_{23})(R_{24}),

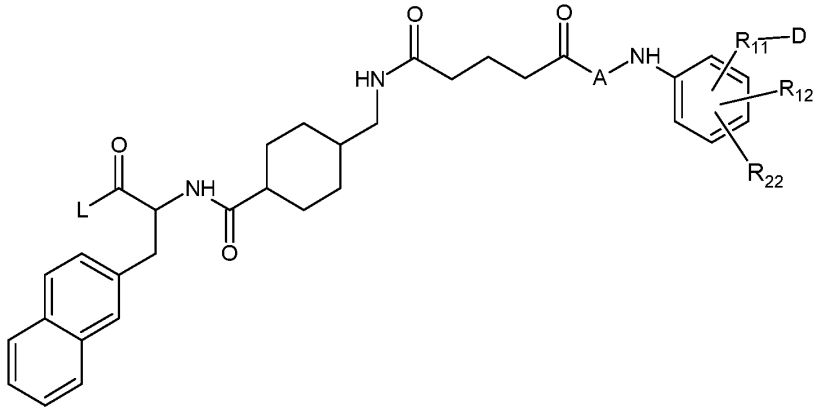
R_{23} is hydrogen;

R_{24} is —C_{1-5} alkyl-N(R_{25})(R_{26}),

R_{25} is C_{1-3} alkyl; and

R_{26} is C_{1-3} alkyl.

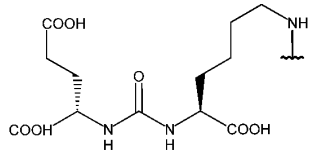
In another aspect, the present disclosure relates to a compound of Formula VI:



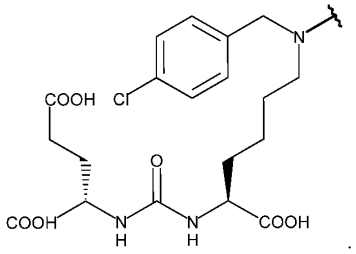
Formula VI

or pharmaceutically acceptable salt, stereoisomer or isotope thereof; wherein:

L is a ligand, selected from:

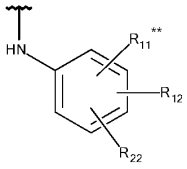


; and

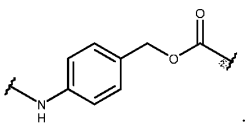


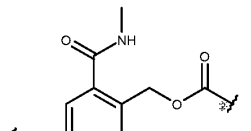
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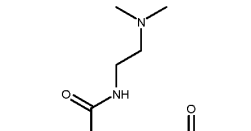
A is selected from cit, val-cit, val-ala, gly-gly-phe-gly, glu-val-cit, gly-gly-phe, gly-phe-gly, Formula P1-ala, Formula P3, Formula P4-ala, Formula P5, Formula P9, Formula P12, Formula P13 and Formula P16;

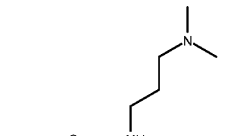


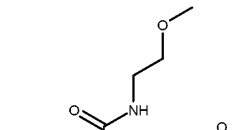
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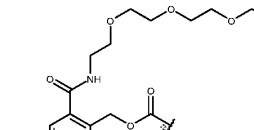

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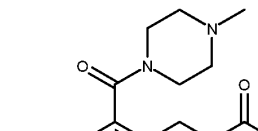

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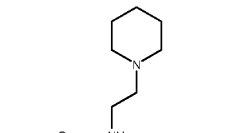

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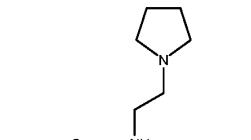

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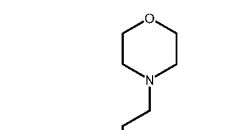

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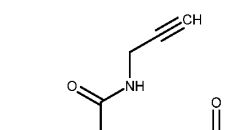

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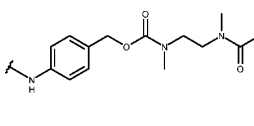

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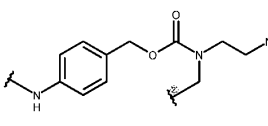

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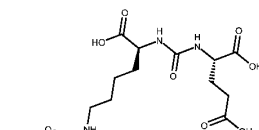

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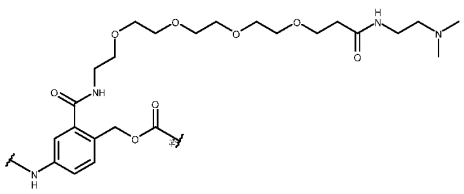
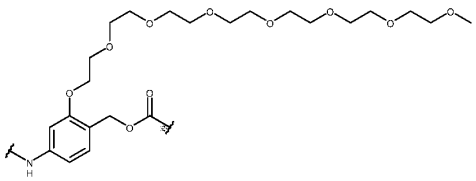
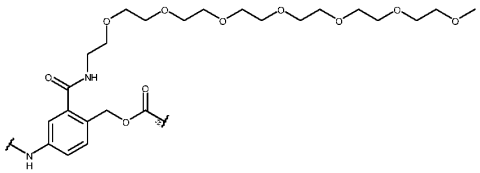
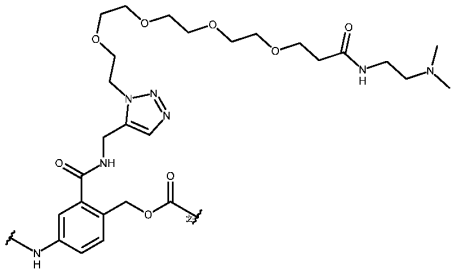
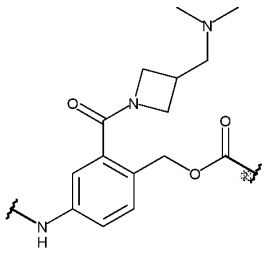
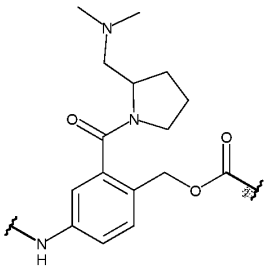
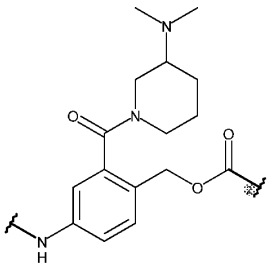
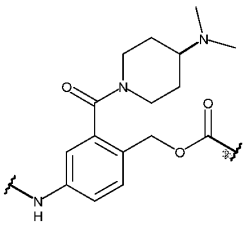
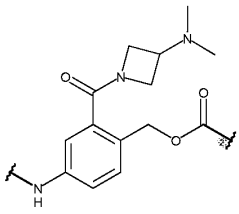

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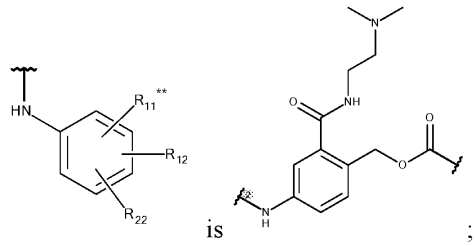
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D is a cytotoxic agent or a therapeutic agent selected from Monomethyl auristatin E (MMAE), Rucaparib, Talazoparib, Niraparib, SN-38, Exatecan, Belotecan, Mitomycin C etc.

In one embodiment, the present disclosure relates to a compound of Formula VI or pharmaceutically acceptable salt, stereoisomer or isotope thereof, wherein:

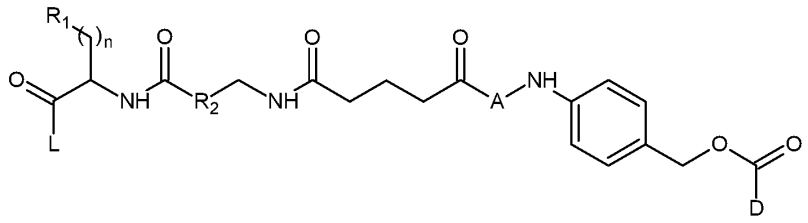
A is val-cit;



is ;

D is Monomethyl auristatin E (MMAE).

In a seventh aspect, there is provided a compound of Formula VII,



Formula VII

or pharmaceutically acceptable salt, stereoisomer or isotope thereof;

wherein:

L is a ligand and D is a cytotoxic agent or therapeutic agent;

n is 0, 1, or 2;

R_1 is selected from the group consisting of phenyl, indolyl, thiophenyl, quinolinyl and isoquinolinyl;

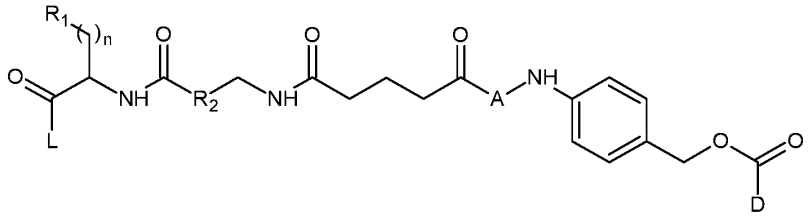
R_1 is unsubstituted or substituted with one or more R_5;

R_5 is selected from halogen, —OH, or a 6 to 10 membered aryl ring;

R_2 is cyclohexyl or phenyl;

A is a peptide val-cit.

In another embodiment, there is provided a compound of Formula VII,



Formula VII

or pharmaceutically acceptable salt, stereoisomer or isotope thereof;

wherein:

L and D are as defined above;

n is 0, 1, or 2;

R_1 is selected from the group consisting of phenyl, indolyl, thiophenyl, quinolinyl and isoquinolinyl;

R_1 is unsubstituted or substituted with one or more R_5;

R_5 is selected from halogen, —OH, or a 6 to 10 membered aryl ring;

R_2 is cyclohexyl or phenyl; and

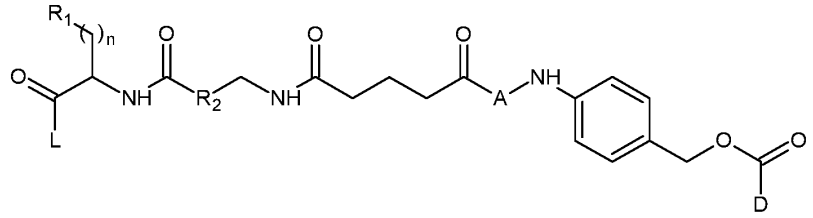
A is a peptide val-cit.

In an embodiment, in the compound is a compound of Formula VII, wherein:

L is a ligand of Formula L_1, wherein t_1 is 3; t_2 is 2; and Z is $N(R_9)$, wherein R_9 is hydrogen. In an embodiment, L is a ligand of Formula L_1, wherein t_1 is 3; t_2 is 2; and Z is $N(R_9)$, wherein R_9 is phenyl. In another embodiment, L is a ligand of Formula L_1, wherein t_1 is 3; t_2 is 2; and Z is $N(R_9)$, wherein R_9 is phenyl substituted with Cl, Br, or I; and

R_2 is a 6 to 10 membered cycloalkyl.

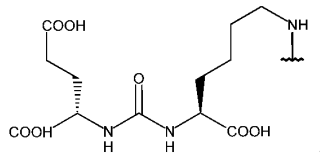
In another aspect, the present disclosure relates to a compound of Formula VII:



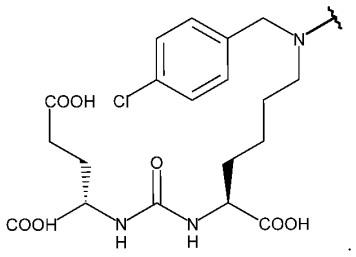
Formula VII

or pharmaceutically acceptable salt, stereoisomer or isotope thereof; wherein:

L is a ligand, selected from:

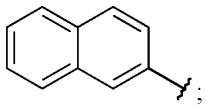
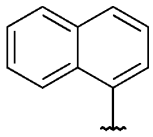
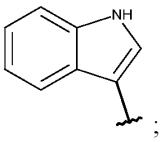


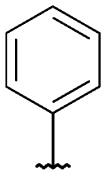
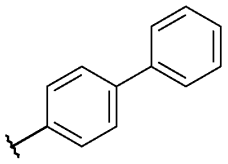
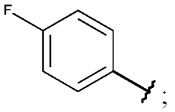
; and

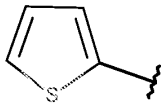


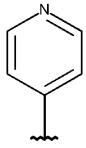
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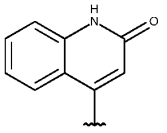
R_1 is selected from:


;

;


;

;

;


;


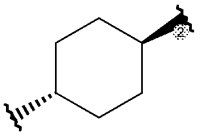
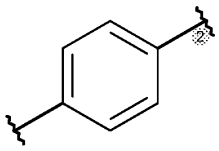
;


; and


;

n is selected from 0, 1 and 2;

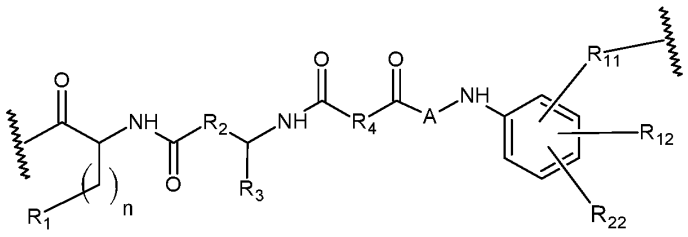
R_2 is absent or selected from:


; and

;

A is selected from val-cit, val-ala, gly-gly-phe-gly, glu-val-cit and Formula P3;

D is a cytotoxic agent or a therapeutic agent selected from Monomethyl auristatin E (MMAE), Rucaparib, Talazoparib, Niraparib, SN-38, Exatecan, Belotecan, Mitomycin C etc.

In one aspect, the present invention provides a ligand-drug conjugate, wherein the ligand L and the drug D is conjugated via linker of Formula VIII:



Formula VIII

wherein:

n is 0, 1, 2, 3 or 4;

R_1 is selected from a 6 to 14 membered aryl or a 5 to 13 membered heteroaryl containing one, two or three heteroatoms independently selected from nitrogen, oxygen or sulfur;

R_1 is unsubstituted or substituted with one or more R_5;

R_5, at each occurrence, is independently selected from halogen, —$C(O)NH_2$, —$C(O)OR_6$, —C_{1-3} alkyl, —OR_7, and a 6 to 10 membered aryl; wherein,

R_6 is hydrogen or C_{1-3} alkyl;

R_7 is hydrogen or C_{1-3} alkyl;

R_2 is absent or is selected from a 6 to 10 membered cycloalkyl or a 6 to 10 membered aryl;

R_3 is hydrogen or —C_1-C_5COOH;

R_4 is selected from a group consisting of —C_{1-10} alkyl-, —C_{2-6} alkenyl-, —C_{1-3} alkyl-O-C_{1-3} alkyl—, —C_{2-6} alkyl-N(R_8)—, —N(R_8)-C_{2-6} alkyl—, 3 to 6 membered cycloalkyl and —C_{1-2} alkyl-$(-OC_2H_4)_{1-8}$-OC_{1-2} alkyl—; wherein,

R_8 is hydrogen or C_{1-6} alkyl;

A is an amino acid or a peptide comprising 2-5 amino acids;

A is attached to NH through its C terminal;

R_{11} is selected from a group consisting of —C_{1-3} alkyl-OC(O)—**,

—C_{1-3} alkyl-O-C(O)-N(R_{19})-C_{1-5} alkyl-N(R_{19})-C(O)—**,

—C_{1-3} alkyl-O-C(O)-N[C_{1-5} alkyl-N($R_{20}R_{21}$)]-C_{1-3} alkyl—**,

—C_{1-3} alkyl-O-C(O)-Het_2-C_{1-3} alkyl-N(R_{19})-C(O)—**, and

—C_{1-3} alkyl-O-C(O)-N(R_{19})-C_{1-5} alkyl-N(R_{19})-C(O)—**;

wherein:

R_{19} is selected from hydrogen, —C_{1-3} alkyl or —C_{1-3} alkyl-O-C_{1-3} alkyl-OH;

R_{20} is hydrogen or —C_{1-3} alkyl;

R_{21} is hydrogen or —C_{1-3} alkyl; and

Het_2 is a 5 to 10 membered heterocyclic ring containing one, two or three heteroatoms independently selected from nitrogen, oxygen or sulfur;

R_{12} is selected from hydrogen, —C(O)N(R_{13})R_{14} or —$(-OC_2H_4)_{1-10}$-CH_3;

R_{13} is hydrogen;

R_{14} is selected from —C_{1-5} alkyl, —C_{2-5} alkenyl, —C_{2-5} alkynyl, —C_{1-5} alkyl-N(R_{15})R_{16}, —C_{1-5} alkyl-O-C_{1-3} alkyl, —$(-C_2H_4O)_{1-10}C_2H_5$, —$(-C_2H_4O)_{1-10}$-C_2H_4-R_{17} or —C_{1-3} alkyl-Het_3-$(-C_2H_4O)_{1-10}$-C_2H_4-R_{18}; wherein:

R_{15} is hydrogen or C1 to C3 alkyl;

R_{16} is hydrogen or C1 to C3 alkyl; or

R_{15} and R_{16} along with the nitrogen atom to which they are attached form a 5 to 6 membered heterocyclic ring, wherein 1 or 2 carbon atoms in the heterocyclic ring are optionally replaced with additional heteroatoms independently selected from nitrogen, oxygen and sulfur and wherein the 5 to 6 membered heterocyclic ring is unsubstituted or substituted with C_{1-3} alkyl, halogen or –OH;

R_{17} is selected from hydrogen or —C(O)NH-C_{2-5} alkyl-$N(CH_3)_2$;

R_{18} is selected from hydrogen or —C(O)NH-C_{2-5} alkyl-$N(CH_3)_2$;

Het_3 is a 5 to 10 membered heterocyclic ring containing one, two or three heteroatoms independently selected from nitrogen, oxygen and sulfur;

OR

R_{13} and R_{14} along with the nitrogen atom to which they are attached form a 4 to 6 membered heterocyclic ring, wherein 1 or 2 carbons in the heterocyclic ring are optionally replaced with additional heteroatoms independently selected from nitrogen, oxygen and sulfur, and wherein the 4 to 6 membered heterocyclic ring is unsubstituted or substituted with C_{1-3} alkyl, —$N(CH_3)_2$ or —$CH_2N(CH_3)_2$;

R_{22} is selected from hydrogen, —$C(O)N(R_{23})R_{24}$ or —$(-OC_2H_4)_{1-10}$-CH_3;

R_{23} is hydrogen;

R_{24} is selected from —C_{1-5} alkyl, —C_{2-5} alkenyl, —C_{2-5} alkynyl, —C_{1-5} alkyl-$N(R_{25})R_{26}$, —C_{1-5} alkyl-O-C_{1-3} alkyl, —$(-C_2H_4O)_{1-10}C_2H_5$, —$(-C_2H_4O)_{1-10}$-C_2H_4-R_{27} or —C_{1-3} alkyl-Het_3-$(-C_2H_4O)_{1-10}$-C_2H_4-R_{28}; wherein:

R_{25} is hydrogen or C1 to C3 alkyl;

R_{26} is hydrogen or C1 to C3 alkyl; or

R_{25} and R_{26} along with the nitrogen atom to which they are attached form a 5 to 6 membered heterocyclic ring, wherein 1 or 2 carbon atoms in the heterocyclic ring are optionally replaced with additional heteroatoms independently selected from nitrogen, oxygen and sulfur and wherein the 5 to 6 membered heterocyclic ring is unsubstituted or substituted with C_{1-3} alkyl, halogen or –OH;

R_{27} is selected from hydrogen or —C(O)NH-C_{2-5} alkyl-$N(CH_3)_2$;

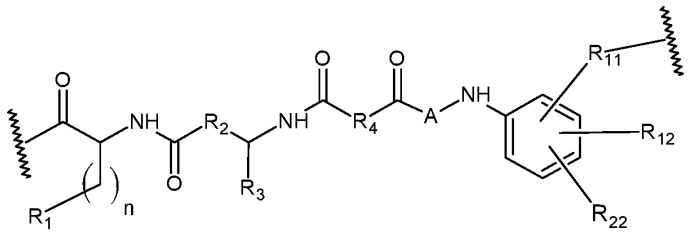
R_{28} is selected from hydrogen or —C(O)NH-C_{2-5} alkyl-$N(CH_3)_2$;

Het_3 is a 5 to 10 membered heterocyclic ring containing one, two or three heteroatoms independently selected from nitrogen, oxygen and sulfur;

OR

R_{23} and R_{24} along with the nitrogen atom to which they are attached form a 4 to 6 membered heterocyclic ring, wherein 1 or 2 carbons in the heterocyclic ring are optionally replaced with additional heteroatoms independently selected from nitrogen, oxygen and sulfur, and wherein the 4 to 6 membered heterocyclic ring is unsubstituted or substituted with C_{1-3} alkyl, —$N(CH_3)_2$ or —$CH_2N(CH_3)_2$.

In yet another aspect, the present invention provides a ligand-drug conjugate; wherein the ligand L and the drug D is conjugated via a linker of Formula VIII:



Formula VIII

wherein:

n is 0, 1, 2, 3 or 4;

R_1 is selected from a 6 to 14 membered aryl or a 5 to 10 membered heteroaryl containing one, two or three heteroatoms independently selected from nitrogen, oxygen or sulfur;

R_1 is unsubstituted or substituted with one or more R_5;

R_5, at each occurrence, is independently selected from halogen, —$C(O)NH_2$, —$C(O)OR_6$, —C_{1-3} alkyl, —OR_7, and a 6 to 10 membered aryl; wherein:

R_6 is hydrogen or C_{1-3} alkyl;

R_7 is hydrogen or C_{1-3} alkyl;

R_2 is absent or is selected from a 6 to 10 membered cycloalkyl or a 6 to 10 membered aryl;

R_3 is hydrogen or —C_1-C_5COOH;

R_4 is selected from a group consisting of —C_{1-10} alkyl-, —C_{2-6} alkenyl-, —C_{1-3} alkyl-O-C_{1-3} alkyl—, —C_{2-6} alkyl-N(R_8)—, —C_{2-6} alkyl(N(R_8)($R_{8'}$))—, —N(R_8)-C_{2-6} alkyl—, a 3 to 6 membered cycloalkyl and —C_{1-2} alkyl-(-OC_2H_4)$_{1-8}$-OC_{1-2} alkyl—; wherein:

R_8 and $R_{8'}$ are independently selected from hydrogen, C_{1-6} alkyl, -C(O)-C_{1-4}alkyl-aryl or -C(O)-(-C_2H_4O)$_{1-8}$-C_{1-2} alkyl-N(R)(R'), wherein said aryl is selected from 6 to 14 membered aryl and is optionally substituted by -C_{1-3}alkyl or -OC_{1-3}alkyl; wherein

R and R' are independently selected from hydrogen, -C_{1-6} alkyl or -C(O)-C_{1-4}alkyl-aryl, wherein said aryl is selected from 6 to 14 membered aryl and is optionally substituted by -C_{1-3}alkyl or -OC_{1-3}alkyl;

A is an amino acid or a peptide comprising 2-5 amino acids;

A is attached to NH through its C terminal;

R_{11} is selected from a group consisting of —C_{1-3} alkyl-OC(O)—**,

—C_{1-3} alkyl-O-C(O)-N(R_{19})-C_{1-5} alkyl-N(R_{19})-C(O)—**,

—C_{1-3} alkyl-O-C(O)-N[C_{1-5} alkyl-N($R_{20}R_{21}$)]-C_{1-3} alkyl—**, and

—C_{1-3} alkyl-O-C(O)-Het_2-C_{1-3} alkyl-N(R_{19})-C(O)—**,

wherein:

R_{19} is selected from hydrogen, —C_{1-3} alkyl or —C_{1-3} alkyl-O-C_{1-3} alkyl-OH;

R_{20} is hydrogen or —C_{1-3} alkyl;

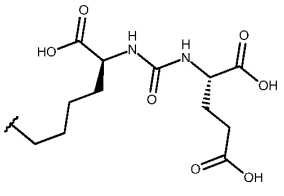
R_{21} is hydrogen or —C_{1-3} alkyl; and

Het_2 is a 5 to 10 membered heterocyclic ring containing one, two or three heteroatoms independently selected from nitrogen, oxygen or sulfur;

R_{12} is selected from hydrogen, —C(O)N(R_{13})(R_{14}) or —(-OC_2H_4)$_{1-10}$-CH_3;

R_{13} is hydrogen;

R_{14} is selected from —C_{1-5} alkyl, —C_{2-5} alkenyl, —C_{2-5} alkynyl, —C_{1-5} alkyl-N(R_{15})(R_{16}), —C_{1-5} alkyl-O-C_{1-3} alkyl, —(-C_2H_4O)$_{1-10}C_2H_5$, —(-C_2H_4O)$_{1-10}$-C_2H_4-R_{17} or —C_{1-3} alkyl-Het_3-(-C_2H_4O)$_{1-10}$-C_2H_4-R_{18} or



, wherein:

R_{15} is hydrogen or C1 to C3 alkyl;

R_{16} is hydrogen or C1 to C3 alkyl; or

R_{15} and R_{16} along with the nitrogen atom to which they are attached form a 5 to 6 membered heterocyclic ring, wherein 1 or 2 carbon atoms in the heterocyclic ring are optionally replaced with additional heteroatoms independently selected from nitrogen, oxygen and sulfur and wherein the 5 to 6 membered heterocyclic ring is unsubstituted or substituted with C_{1-3} alkyl, halogen or –OH;

R_{17} is selected from hydrogen or —C(O)NH-C_{2-5} alkyl-N(CH_3)$_2$;

R_{18} is selected from hydrogen or —C(O)NH-C_{2-5} alkyl-N(CH_3)$_2$;

Het_3 is a 5 to 10 membered heterocyclic ring containing one, two or three heteroatoms independently selected from nitrogen, oxygen and sulfur;

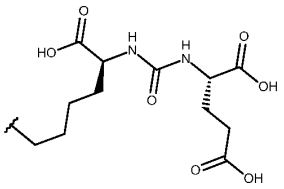
OR

R_{13} and R_{14} along with the nitrogen atom to which they are attached form a 4 to 6 membered heterocyclic ring, wherein 1 or 2 carbons in the heterocyclic ring are optionally replaced with additional heteroatoms independently selected from nitrogen, oxygen and sulfur, and wherein the 4 to 6 membered heterocyclic ring is unsubstituted or substituted with C_{1-3} alkyl, $—N(CH_3)_2$ or $—CH_2N(CH_3)_2$;

R_{22} is selected from hydrogen, $—C(O)N(R_{23})(R_{24})$ or $—(-OC_2H_4)_{1-10}-CH_3$;

R_{23} is hydrogen;

R_{24} is selected from $—C_{1-5}$ alkyl, $—C_{2-5}$ alkenyl, $—C_{2-5}$ alkynyl, $—C_{1-5}$ alkyl-$N(R_{25})(R_{26})$, $—C_{1-5}$ alkyl-O-C_{1-3} alkyl, $—(-C_2H_4O)_{1-10}C_2H_5$, $—(-C_2H_4O)_{1-10}-C_2H_4-R_{27}$ or $—C_{1-3}$ alkyl-Het_3-$(-C_2H_4O)_{1-10}-C_2H_4-R_{28}$ or



, wherein:

R_{25} is hydrogen or C1 to C3 alkyl;

R_{26} is hydrogen or C1 to C3 alkyl; or

R_{25} and R_{26} along with the nitrogen atom to which they are attached form a 5 to 6 membered heterocyclic ring, wherein 1 or 2 carbon atoms in the heterocyclic ring are optionally replaced with additional heteroatoms independently selected from nitrogen, oxygen and sulfur and wherein the 5 to 6 membered heterocyclic ring is unsubstituted or substituted with C_{1-3} alkyl, halogen or –OH;

R_{27} is selected from hydrogen or $—C(O)NH-C_{2-5}$ alkyl-$N(CH_3)_2$;

R_{28} is selected from hydrogen or $—C(O)NH-C_{2-5}$ alkyl-$N(CH_3)_2$;

Het_3 is a 5 to 10 membered heterocyclic ring containing one, two or three heteroatoms independently selected from nitrogen, oxygen and sulfur;

OR

R_{23} and R_{24} along with the nitrogen atom to which they are attached form a 4 to 6 membered heterocyclic ring, wherein 1 or 2 carbons in the heterocyclic ring are optionally replaced with additional heteroatoms independently selected from nitrogen, oxygen and sulfur, and

wherein the 4 to 6 membered heterocyclic ring is unsubstituted or substituted with C_{1-3} alkyl, —$N(CH_3)_2$ or —$CH_2N(CH_3)_2$.

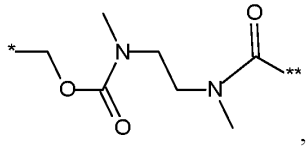
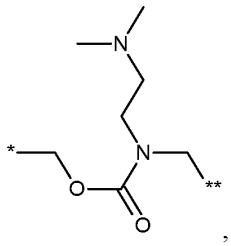
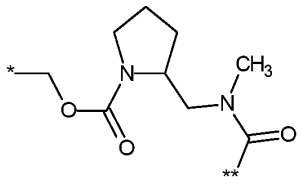
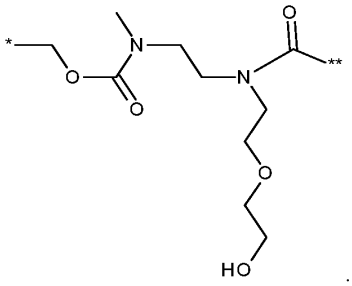
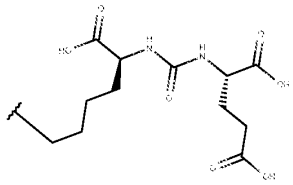
According to an embodiment, of the present invention, the A is an amino acid or a peptide comprising two or more of the same or different amino acids. A is as defined in the first aspect.

According to an embodiment, L is an antigen binding ligand. According to a preferred embodiment the ligand is prostate specific membrane antigen (PSMA) binding ligand.

According to an embodiment, L is a ligand of Formula L_1.

In an embodiment, t_1 is 3; t_2 is 2; and Z is $N(R_9)$, wherein R_9 is hydrogen. In an embodiment, t_1 is 3; t_2 is 2; and Z is $N(R_9)$, wherein R_9 is phenyl. In another embodiment, t_1 is 3; t_2 is 2; and Z is $N(R_9)$, wherein R_9 is phenyl substituted with Cl, Br, or I. In an embodiment, t_1 is 0; t_2 is 2; and Z is Z_1, wherein t_3 is 1, 2, 3, 4, 5 or 6 and Y is —NH—. In an embodiment, t_1 is 1; t_2 is 2 and Z is the compound of Formula Z_2.

In an embodiment, the compound is compound of Formula VIII, wherein R_{11} is selected from:

*–$CH_2OC(O)$-**,  ,  ,  ,  , or  , wherein:

In an embodiment, the compound is a compound of Formula VIII, wherein: R_{13} is hydrogen and R_{14} is selected from —C_{1-5} alkyl, —C_{1-5} alkyl-$N(R_{15})(R_{16})$, —C_{1-5} alkyl-O-C_{1-3} alkyl, —$(-C_2H_4O)_{1-5}C_2H_5$, —$(-C_2H_4O)_{1-10}$-C_2H_4-R_{17} or —C_{1-3} alkyl-Het_3-$(-C_2H_4O)_{1-10}$-C_2H_4-R_{18} or

, wherein:

R_{15} is selected from H, —CH_3 or —C_2H_5;

R_{16} is selected from H, —CH_3 or —C_2H_5;

R_{15} and R_{16} along with the nitrogen atom to which they are attached form a 5 to 6 membered heterocyclic ring, wherein 1 or 2 carbon atoms in the heterocyclic ring are optionally replaced with additional heteroatoms independently selected from nitrogen, oxygen and sulfur and wherein the 5 to 6 membered heterocyclic ring is unsubstituted or substituted with C_{1-3} alkyl, halogen or –OH;

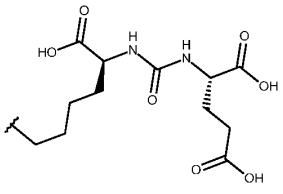
R_{17} is selected from hydrogen or —C(O)NH-C_2H_5-$N(CH_3)_2$;

R_{18} is selected from hydrogen or —C(O)NH-C_2H_5-$N(CH_3)_2$; and

Het_3 is triazolyl;

In an embodiment, the compound is a compound of Formula VIII, wherein R_{13} and R_{14} along with the nitrogen atom to which they are attached form a 4 to 6 membered heterocyclic ring, wherein 1 or 2 carbons in the heterocyclic ring are optionally replaced with additional heteroatoms independently selected from nitrogen, oxygen and sulfur, and wherein the 4 to 6 membered heterocyclic ring is unsubstituted or substituted with C_{1-3} alkyl, —$N(CH_3)_2$ or —$CH_2N(CH_3)_2$.

In an embodiment, the compound is a compound of Formula VIII, wherein R_{23} is hydrogen and R_{24} is selected from —C_{1-5} alkyl, —C_{1-5} alkyl-$N(R_{25})(R_{26})$, —C_{1-5} alkyl-O-C_{1-3} alkyl, —(-$C_2H_4O)_{1-5}C_2H_5$, —(-$C_2H_4O)_{1-10}$-C_2H_4-R_{27} or —C_{1-3} alkyl-Het_4-(-$C_2H_4O)_{1-10}$-C_2H_4-R_{28} or



, wherein:

R_{25} is selected from H, —CH_3 or —C_2H_5;

R_{26} is selected from H, —CH_3 or —C_2H_5; or

R_{25} and R_{26} along with the nitrogen atom to which they are attached form a 5 to 6 membered heterocyclic ring, wherein 1 or 2 carbon atoms in the heterocyclic ring are optionally replaced with additional heteroatoms independently selected from nitrogen, oxygen and sulfur and wherein the 5 to 6 membered heterocyclic ring is unsubstituted or substituted with C_{1-3} alkyl, halogen or –OH;

R_{27} is selected from hydrogen or —C(O)NH-C_2H_5-$N(CH_3)_2$;

R_{28} is selected from hydrogen or —C(O)NH-C_2H_5-$N(CH_3)_2$; and

Het_4 is triazolyl;

In an embodiment, the compound is a in compound of Formula VIII, wherein R_{23} and R_{24} along with the nitrogen atom to which they are attached form a 4 to 6 membered heterocyclic ring, wherein 1 or 2 carbons in the heterocyclic ring are optionally replaced with additional heteroatoms independently selected from nitrogen, oxygen and sulfur, and wherein the 4 to 6 membered heterocyclic ring is unsubstituted or substituted with C_{1-3} alkyl, —$N(CH_3)_2$ or —$CH_2N(CH_3)_2$.

According to an embodiment of the present invention, D is an active ingredient with cytotoxic or therapeutic effect as defined above.

According to an embodiment, the present invention provides a compound of Formula VIII, wherein:

n is 0, 1 or 2;

R_1 is selected from a 6 to 10 membered aryl or a 5 to 10 membered heteroaryl containing one, two or three heteroatoms independently selected from nitrogen, oxygen or sulfur;

R_1 is unsubstituted or substituted with one or more R_5;

R_5, at each occurrence, is independently selected from halogen, —OH, —OCH_3, —OC_2H_5 or a 6 to 10 membered aryl;

R_2 is selected from a group consisting of a 5 to 6 membered cycloalkyl and a 6 to 10 membered aryl;

R_3 is hydrogen;

R_4 is selected from a group consisting of —C_{1-10} alkyl, —C_{2-6} alkenyl, —C_{1-3} alkyl-O-C_{1-3} alkyl—, —C_{2-6}-alkyl-N(H)—, —C_{2-6} alkyl($N(R_8)(R_{8'})$)—, a 3 to 6 membered cycloalkyl and —C_{1-2} alkyl $(-OC_2H_4)_{1-8}$-OC_{1-2} alkyl—, wherein

R_8 and $R_{8'}$ are independently selected from hydrogen, C_{1-6} alkyl, -C(O)-C_{1-4}alkyl-aryl or -C(O)-$(-C_2H_4O)_{1-8}$-C_{1-2} alkyl-N(R)(R'), wherein said aryl is selected from 6 to 14 membered aryl and is optionally substituted by -C_{1-3}alkyl or -OC_{1-3}alkyl; wherein

R and R' are independently selected from hydrogen, -C_{1-6} alkyl or -C(O)-C_{1-4}alkyl-aryl, wherein said aryl is selected from 6 to 14 membered aryl and is optionally substituted by -C_{1-3}alkyl or -OC_{1-3}alkyl; and

A is selected from the group consisting of cit, ala-ala, ala-ala-ala, ala-phe, val-ala, val-cit, ala-val-cit, ala(beta)-val-cit, glu-val-cit, glu-cit, glu-val, gly-gly, gly-gly-phe, gly-phe-gly, gly-gly-phe-gly, Formula P_3, Formula P_5, Formula P_9, Formula P_{12}, Formula P_{13}, Formula P_{14}, Formula P_{15} and Formula P_{16}.

According to an embodiment, the present invention provides a compound of Formula VIII, wherein:

n is 1;

R_1 is naphthyl;

R_2 is cyclohexyl or phenyl;

R_3 is hydrogen;

R_4 is selected from a group consisting of —C_{1-10} alkyl, —C_{2-6} alkenyl, —C_{1-3} alkyl-O-C_{1-3} alkyl—, —C_{2-6} alkyl($N(R_8)(R_{8'})$)—, a 3 to 6 membered cycloalkyl and —C_{1-2} alkyl$(-OC_2H_4)_{1-8}$-O-C_{1-2}alkyl—, wherein

R_8 and $R_{8'}$ are independently selected from hydrogen, C_{1-6} alkyl, -C(O)-C_{1-4}alkyl-aryl or -C(O)-$(-C_2H_4O)_{1-8}$-C_{1-2} alkyl-N(R)(R'), wherein said aryl is selected from 6 to 14 membered aryl and is optionally substituted by -C_{1-3}alkyl or -OC_{1-3}alkyl; wherein

R and R' are independently selected from hydrogen, -C_{1-6} alkyl or -C(O)-C_{1-4}alkyl-aryl, wherein said aryl is selected from 6 to 14 membered aryl and is optionally substituted by -C_{1-3}alkyl or -OC_{1-3}alkyl;

A is selected from the group consisting of cit, ala-ala, ala-ala-ala, ala-phe, val-ala, val-cit, ala-val-cit, ala(beta)-val-cit, glu-val-cit, glu-cit, glu-val, gly-gly, gly-gly-phe, gly-phe-gly, gly-gly-phe-gly, Formula P_3, Formula P_5, Formula P_9, Formula P_{12}, Formula P_{13}, Formula P_{14}, Formula P_{15} and Formula P_{16};

R_{11} is selected from —C_{1-3} alkyl-OC(O)—**,

—C_{1-3} alkyl-O-C(O)-$N(R_{19})$-C_{1-5} alkyl-$N(R_{19})$-C(O)—**,

—C_{1-3} alkyl-O-C(O)-$N[C_{1-5}$ alkyl-$N(R_{20}R_{21})]$-C_{1-3} alkyl—**, or

—C_{1-3} alkyl-O-C(O)-Het_2-C_{1-3} alkyl-$N(R_{19})$-C(O)—**,

R_{19} is selected from H, CH_3 or $–C_2H_4$-O-C_2H_4-OH;

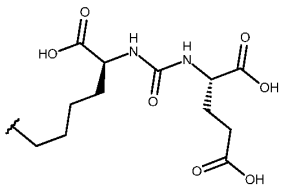
R_{20} is CH_3; R_{21} is CH_3; and

Het_2 is pyrrolidinyl;

R_{12} is selected from hydrogen, —C(O)$N(R_{13})(R_{14})$ or —$(-OC_2H_4)_{1-10}$-CH_3;

R_{13} is hydrogen;

R_{14} is selected from —C_{1-5} alkyl, —C_{2-5} alkenyl, —C_{2-5} alkynyl, —C_{1-5} alkyl-$N(R_{15})(R_{16})$, —C_{1-5} alkyl-O-C_{1-3} alkyl, —$(-C_2H_4O)_{1-10}C_2H_5$, —$(-C_2H_4O)_{1-10}$-C_2H_4-R_{17} or —C_{1-3} alkyl-Het_3-$(-C_2H_4O)_{1-10}$-C_2H_4-R_{18} or



, wherein:

R_{15} is —CH_3 or —C_2H_5; R_{16} is —CH_3 or —C_2H_5;

or

R_{15} and R_{16} along with the nitrogen atom to which they are attached form a 5 to 6 membered heterocyclic ring, wherein 1 or 2 carbon atoms in the heterocyclic ring are optionally replaced with additional heteroatoms independently selected from nitrogen, oxygen and sulfur and wherein the 5 to 6 membered heterocyclic ring is unsubstituted or substituted with —CH_3;

R_{17} is —$C(O)NHC_2H_4N(CH_3)_2$;

R_{18} is —$C(O)NHC_2H_4N(CH_3)_2$;

Het_3 is triazolyl;

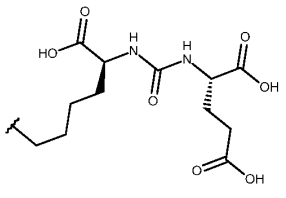
OR

R_{13} and R_{14} along with the nitrogen atom to which they are attached form a 4 to 6 membered heterocyclic ring, wherein 1 or 2 carbons in the heterocyclic ring are optionally replaced with additional heteroatoms independently selected from nitrogen, oxygen and sulfur, and wherein the 4 to 6 membered heterocyclic ring is unsubstituted or substituted with $C_{1\text{-}3}$ alkyl, —$N(CH_3)_2$ or —$CH_2N(CH_3)_2$;

R_{22} is selected from hydrogen, —$C(O)N(R_{23})(R_{24})$ or —$(\text{-}OC_2H_4)_{1\text{-}10}\text{-}CH_3$;

R_{23} is hydrogen;

R_{24} is selected from —$C_{1\text{-}5}$ alkyl, —$C_{2\text{-}5}$ alkenyl, —$C_{2\text{-}5}$ alkynyl, —$C_{1\text{-}5}$ alkyl-$N(R_{25})(R_{26})$, —$C_{1\text{-}5}$ alkyl-O-$C_{1\text{-}3}$ alkyl, —$(\text{-}C_2H_4O)_{1\text{-}10}C_2H_5$, —$(\text{-}C_2H_4O)_{1\text{-}10}\text{-}C_2H_4\text{-}R_{27}$ or —$C_{1\text{-}3}$ alkyl-Het_3-$(\text{-}C_2H_4O)_{1\text{-}10}\text{-}C_2H_4\text{-}R_{28}$ or



, wherein:

R_{25} is hydrogen or C1 to C3 alkyl;

R_{26} is hydrogen or C1 to C3 alkyl; or

R_{25} and R_{26} along with the nitrogen atom to which they are attached form a 5 to 6 membered heterocyclic ring, wherein 1 or 2 carbon atoms in the heterocyclic ring are optionally replaced with additional heteroatoms independently selected from nitrogen, oxygen and sulfur and wherein the 5 to 6 membered heterocyclic ring is unsubstituted or substituted with $C_{1\text{-}3}$ alkyl, halogen or –OH;

R_{27} is selected from hydrogen or —$C(O)NH\text{-}C_{2\text{-}5}$ alkyl-$N(CH_3)_2$;

R_{28} is selected from hydrogen or —C(O)NH-C_{2-5} alkyl-$N(CH_3)_2$;

Het_3 is a 5 to 10 membered heterocyclic ring containing one, two or three heteroatoms independently selected from nitrogen, oxygen and sulfur;

OR

R_{23} and R_{24} along with the nitrogen atom to which they are attached form a 4 to 6 membered heterocyclic ring, wherein 1 or 2 carbons in the heterocyclic ring are optionally replaced with additional heteroatoms independently selected from nitrogen, oxygen and sulfur, and wherein the 4 to 6 membered heterocyclic ring is unsubstituted or substituted with C_{1-3} alkyl, —$N(CH_3)_2$ or —$CH_2N(CH_3)_2$.

According to one embodiment, the present invention provides a compound of Formula VIII, wherein:

R_4 is selected from a group consisting of —C_{2-5} alkyl, —CH_2=CH_2—, —CH_2-O-CH_2—, —$CH_2(-OC_2H_4)_2$-OCH_2— and cyclobutyl; and

A is selected from the group consisting of cit, val-ala, val-cit, gly-gly-phe-gly, or the peptide selected from the group consisting of Formula P_3, Formula P_5, Formula P_9, Formula P_{12}, Formula P_{13}, Formula P_{14}, Formula P_{15} and Formula P_{16}.

In an embodiment, the present invention provides a compound of Formula VIII, wherein:

R_4 is selected from a group consisting of —C_{2-5} alkyl and a 3 to 6 membered cycloalkyl; and

A is selected from the group consisting of cit, val-ala, val-cit, glu-val-cit, gly-gly-phe-gly, Formula P_1, Formula P_{13}, Formula P_{14}, Formula P_{15} and Formula P_{16}.

According to another embodiments, the present invention provides a compound of Formula VIII, wherein:

n is 0, 1 or 2;

R_1 is selected from the group consisting of phenyl, indolyl, thiophenyl, quinolinyl, and isoquinolinyl;

R_1 is unsubstituted or substituted with one or more R_5;

R_5, at each occurrence, is independently selected from halogen, —OH, or a 6 to 10 membered aryl ring;

R_2 is cyclohexyl or phenyl;

R_3 is hydrogen;

R_4 is —C_{1-10} alkyl;

A is val-cit;

R_{11} is —$CH_2OC(O)$—; R_{12} is hydrogen; and R_{22} is hydrogen.

According to an embodiment, the present invention provides a compound of Formula VIII, wherein:

n is 0, 1 or 2

R_1 is a 6 to 10 membered aryl;

R_2 is absent;

R_3 is —CH_2COOH, —CH_2CH_2COOH;

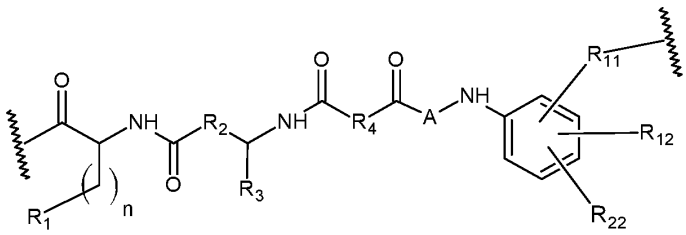
R_4 is a 3 to 6 membered cycloalkyl;

A is Cit;

R_{11} is —CH_2-O-C(O)-N(CH_3)-C_2H_4-N(CH_3)-C(O)—;

R_{12} is hydrogen; and R_{22} is hydrogen.

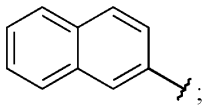
In another aspect, the present disclosure relates to a compound of Formula VIII:

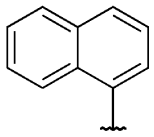


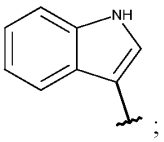
Formula VIII

or pharmaceutically acceptable salt, stereoisomer or isotope thereof; wherein:

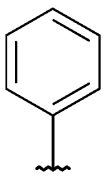
R_1 is selected from:

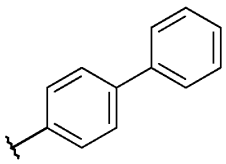

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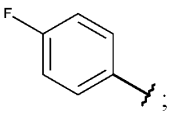

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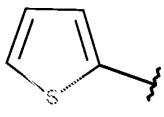
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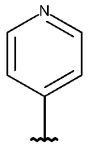

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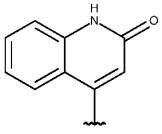
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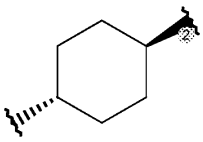
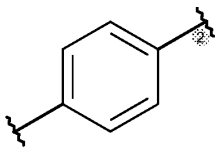
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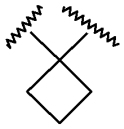
n is selected from 0, 1 and 2;

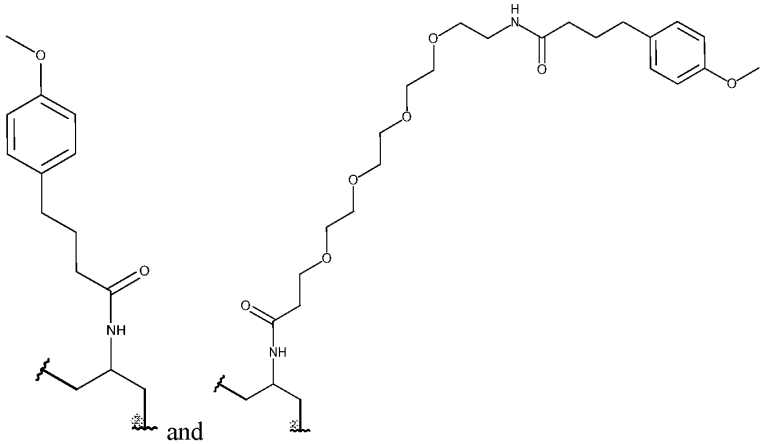
R_2 is absent or selected from:


; and

;

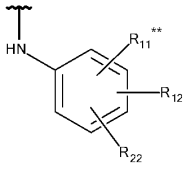
R_3 is selected from hydrogen and $-C_2H_4COOH$;

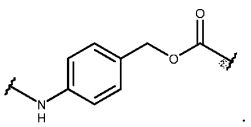
R_4 is selected from

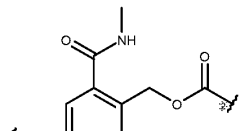

; $—C_{2-5}$ alkyl, —CH=CH—, $—CH_2-O-CH_2—$, $—CH_2(-OC_2H_4)_{2-8}-OCH_2—$,

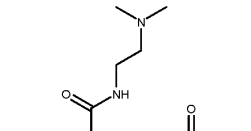

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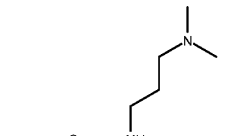
A is selected from cit, val-cit, val-ala, gly-gly-phe-gly, glu-val-cit, gly-gly-phe, gly-phe-gly, Formula P1-ala, Formula P3, Formula P4-ala, Formula P5, Formula P9, Formula P12, Formula P13 and Formula P16;

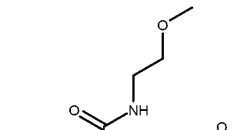

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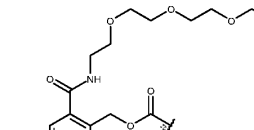

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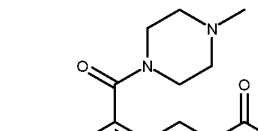

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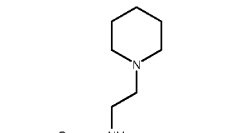

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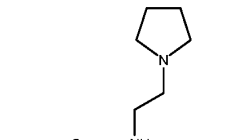

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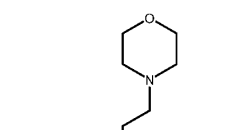

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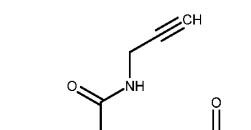

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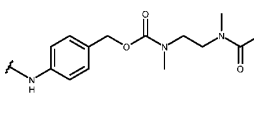

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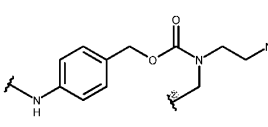

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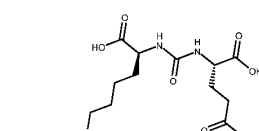

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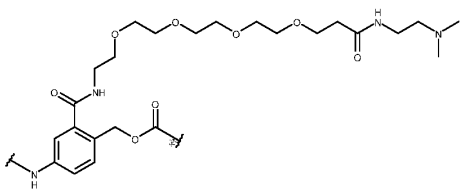
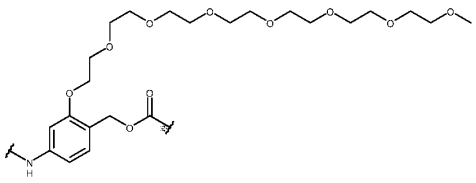
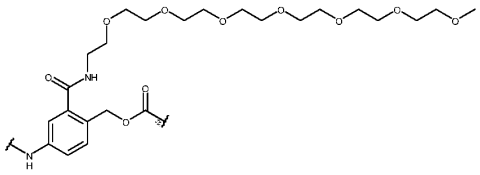
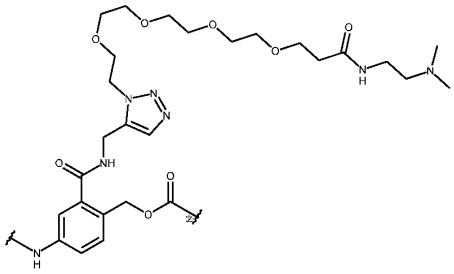
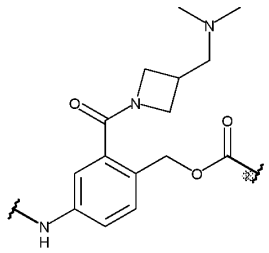
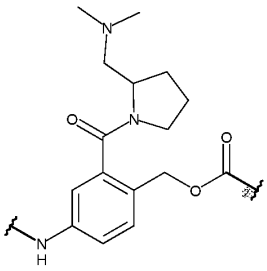
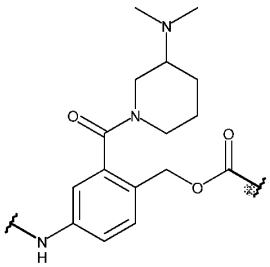
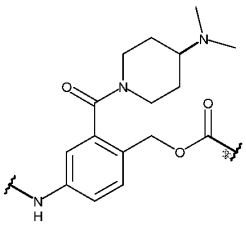
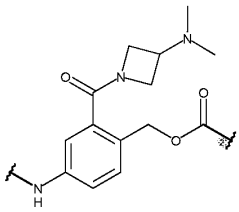

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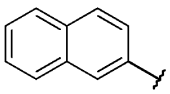
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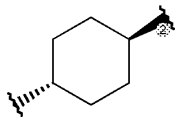

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; and

;

D is a cytotoxic agent or a therapeutic agent selected from Monomethyl auristatin E (MMAE), Rucaparib, Talazoparib, Niraparib, SN-38, Exatecan, Belotecan, Mitomycin C etc.

In one embodiment, the present disclosure relates to a compound of Formula II or pharmaceutically acceptable salt, stereoisomer or isotope thereof, wherein:

R_1 is  ;

n is 1;

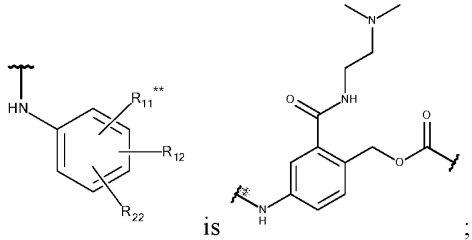


R_2 is ;

R_3 is hydrogen;

R_4 is $-C_3H_6-$

A is val-cit;

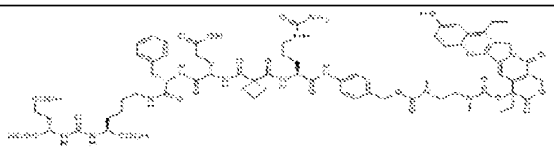


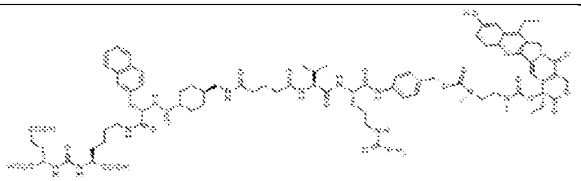
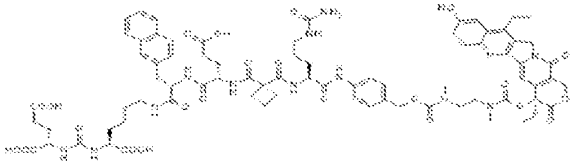
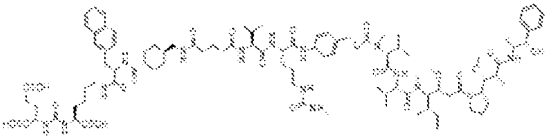
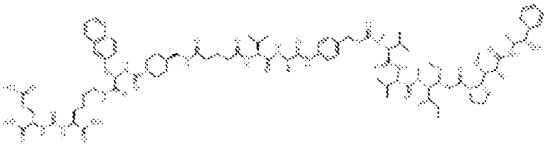
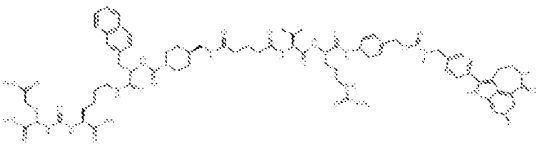
is ;

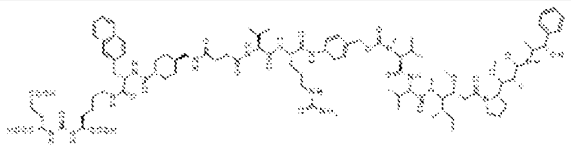
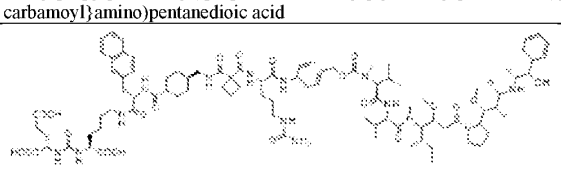
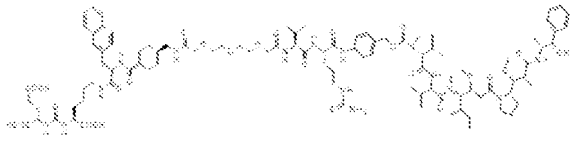
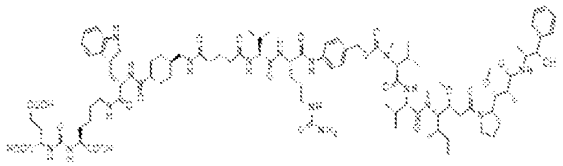
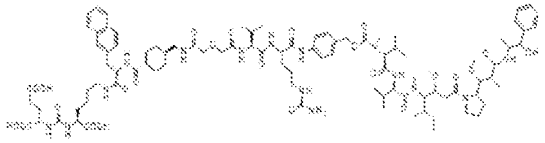
D is Monomethyl auristatin E (MMAE).

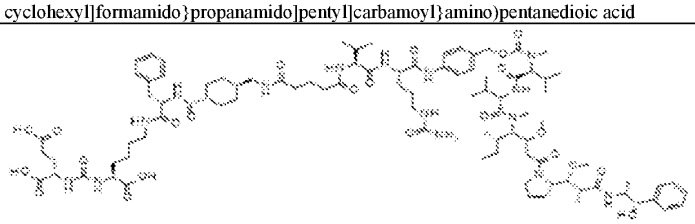
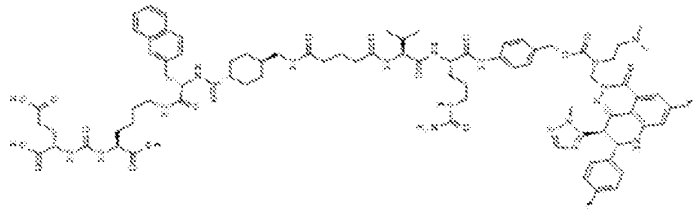
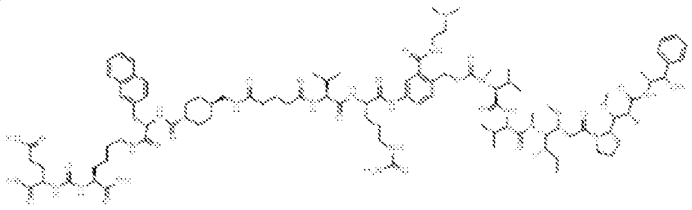
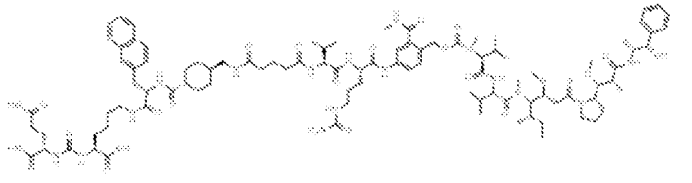
Some examples of the compounds of present invention are as listed in Table 1 below. It would be appreciated by those skilled in the art that the compounds listed in Table 1 are limited and depending on the definitions of the variables in the embodiments discussed above, a skilled person can arrive at several such compounds. All such compounds envisioned by the skilled person are included in the present invention. Further, in the specification wherever the IUPAC name of the compound and the structure is mentioned, the structure should be preferred over the name. Any error in the IUPAC name is unintentional.

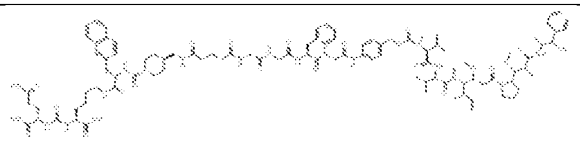
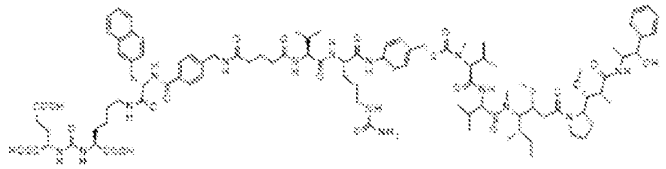
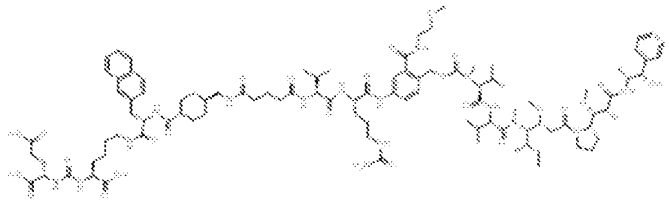
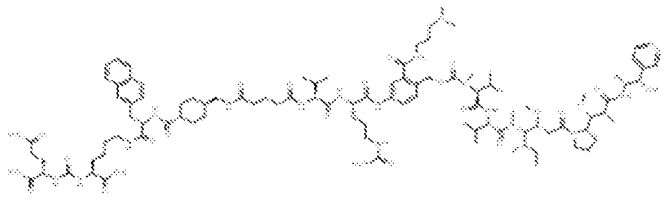
Table 1: Compounds

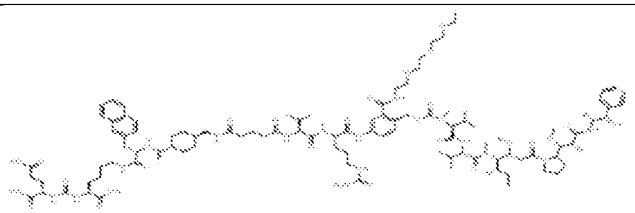
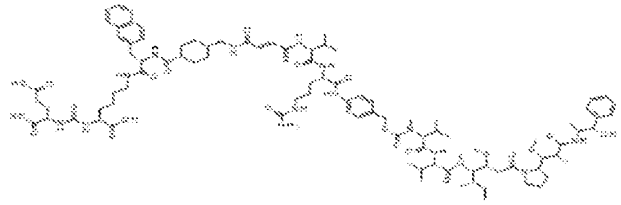
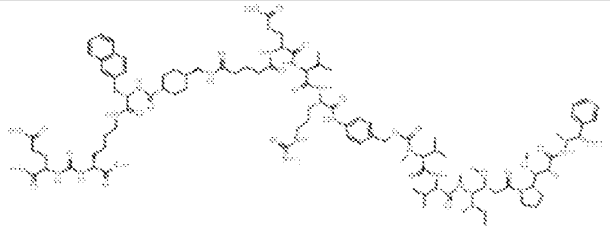
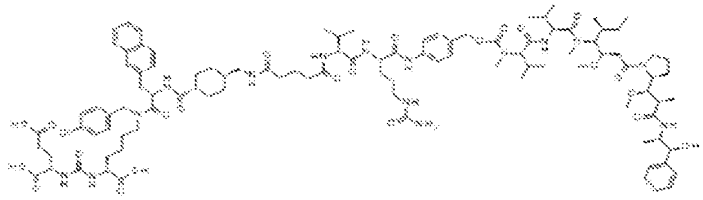
Sr No	Compound No	Structure/Name
1.	1.1	 (2*S*)-2-({[(1*S*)-5-[(2*S*)-2-[(2*S*)-2-[(1-{[(1*S*)-4-(carbamoylamino)-1-[(4-{[({2-[({[(19*S*)-10,19-diethyl-7-hydroxy-14,18-dioxo-17-oxa-3,13-diazapentacyclo[11.8.0.0^{2,11}.0^{4,9}.0^{15,20}] henicosa-1(21),2(11),3,5,7,9,15(20)-heptaen-19-yl]oxy}carbonyl)(methyl)amino]ethyl} (methyl) carbamoyl) oxy]methyl}phenyl)carbamoyl]butyl]carbamoyl}cyclobutyl)formamido]-4-carboxybutanamido]-3-phenylpropanamido]-1-arboxypentyl]carbamoyl}amino) pentanedioic acid

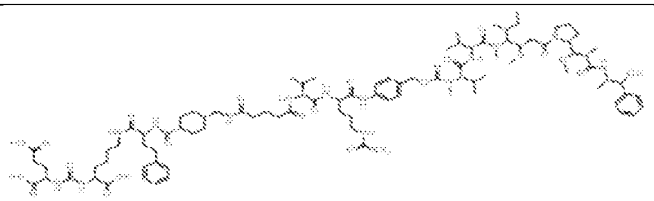
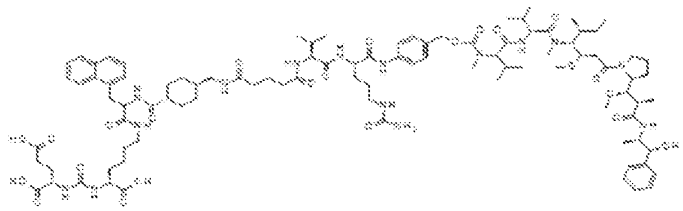
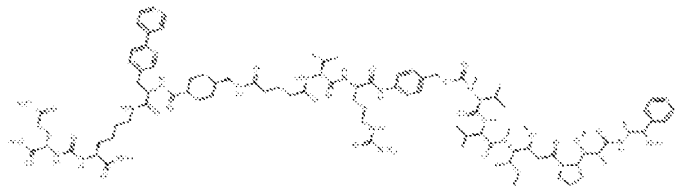
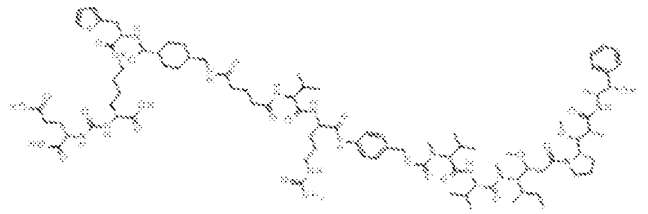
2.	1.2	 (2*S*)-2-({[(1*S*)-1-carboxy-5-[(2*S*)-3-(naphthalen-2-yl)-2-{[(1*R*,4*R*)-4-[(4-{[(1*S*)-1-{[(1*S*)-4-(carbamoylamino)-1-[(4-{[({2-[({[(19*S*)-10,19-diethyl-7-hydroxy-14,18-dioxo-17-oxa-3,13-diazapentacyclo[11.8.0.02,11.04,9.015,20]henicosa-1(21),2(11),3,5,7,9,15(20)-heptaen-19-yl]oxy}carbonyl)(methyl)amino]ethyl}(methyl)carbamoyl)oxy]methyl}phenyl)carbamoyl]butyl]carbamoyl}-2-methylpropyl]carbamoyl}butanamido)methyl]cyclohexyl]formamido}propanamido]pentyl]carbamoyl}amino) pentanedioic acid
3.	1.3	 (2*S*)-2-({[(1*S*)-5-[(2*S*)-2-[(2*S*)-2-[(1-{[(1*S*)-4-(carbamoylamino)-1-[(4-{[({2-[({[(19*S*)-10,19-diethyl-7-hydroxy-14,18-dioxo-17-oxa-3,13-diazapentacyclo[11.8.0.$0^{2,11}$.$0^{4,9}$.$0^{15,20}$] henicosa-1(21),2(11),3,5,7,9,15(20)-heptaen-19-yl]oxy}carbonyl)(methyl)amino]ethyl} (methyl) carbamoyl)oxy]methyl}phenyl)carbamoyl]butyl]carbamoyl}cyclobutyl)formamido]-4-carboxybutanamido]-3-(naphthalen-2-yl)propanamido]-1-carboxypentyl]carbamoyl}amino) pentanedioic acid
4.	1.4	 (2*S*)-2-({[(1*S*)-1-carboxy-5-[(2*S*)-3-(naphthalen-2-yl)-2-{[(1*R*,4*R*)-4-[(4-{[(1*S*)-1-{[(1*S*)-4-(carbamoylamino)-1-({4-[({[(1*S*)-1-{[(1*S*)-1-{[(3*R*,4*S*,5*S*)-1-[(2*S*)-2-[(1*R*,2*R*)-2-{[(1*S*,2*R*)-1-hydroxy-1-phenylpropan-2-yl]carbamoyl}-1-methoxy-2-methylethyl]pyrrolidin-1-yl]-3-ethoxy-5-methyl-1-oxoheptan-4-yl](methyl)carbamoyl}-2-methylpropyl]carbamoyl}-2-methylpropyl](methyl)carbamoyl}oxy)methyl]phenyl}carbamoyl)butyl]carbamoyl}-2-methylpropyl]carbamoyl}butanamido)methyl]cyclohexyl]formamido}propanamido]pentyl]carbamoyl}amino)pentanedioic acid
5.	1.5	 (2*S*)-2-({[(1*S*)-1-carboxy-5-[(2*S*)-3-(naphthalen-2-yl)-2-{[(1*R*,4*R*)-4-[(4-{[(1*S*)-1-{[(1*S*)-1-({4-[({[(1*S*)-1-{[(1*S*)-1-{[(3*R*,4*S*,5*S*)-1-[(2*S*)-2-[(1*R*,2*R*)-2-{[(1*S*,2*R*)-1-hydroxy-1-phenylpropan-2-yl]carbamoyl}-1-methoxy-2-methylethyl]pyrrolidin-1-yl]-3-methoxy-5-methyl-1-oxoheptan-4-yl](methyl)carbamoyl}-2-methylpropyl]carbamoyl}-2-methylpropyl](methyl)carbamoyl}oxy)methyl]phenyl}carbamoyl)ethyl]carbamoyl}-2-methylpropyl]carbamoyl}butanamido)methyl]cyclohexyl]formamido}propanamido]pentyl]carbamoyl}amino)pentanedioic acid
6.	1.6	 (2*S*)-2-({[(1*S*)-1-carboxy-5-[(2*S*)-3-(naphthalen-2-yl)-2-{[(1*R*,4*R*)-4-[(4-{[(1*S*)-1-{[(1*S*)-4-(carbamoylamino)-1-({4-[({[(4-{6-fluoro-9-oxo-3,10-diazatricyclo[6.4.1.04,13]trideca-1,4,6,8(13)-tetraen-2-yl}phenyl)methyl](methyl)carbamoyl}oxy)methyl]phenyl}carbamoyl)butyl]carbamoyl}-2-methylpropyl]carbamoyl}butanamido)methyl]cyclohexyl]formamido}propanamido]pentyl]carbamoyl}amino)pentanedioic acid

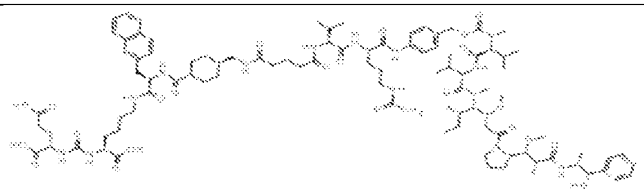
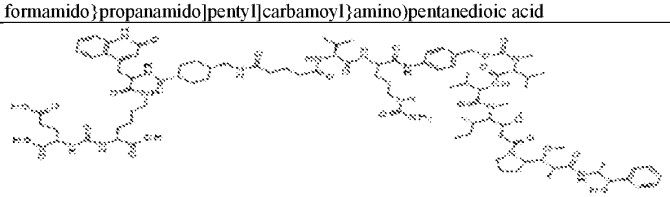
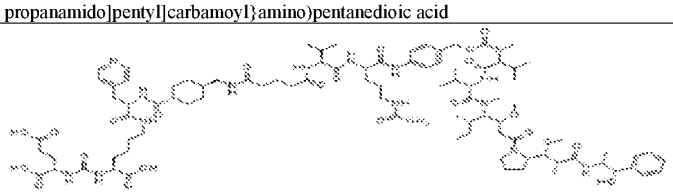
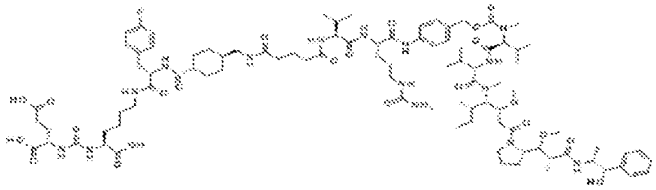
7.	1.7	 (2*S*)-2-({[(1*S*)-1-carboxy-5-[(2*S*)-3-(naphthalen-2-yl)-2-{[(1*R*,4*R*)-4-[(3-[(1*S*)-1-{[(1*S*)-4-(carbamoylamino)-1-({4-[({[(1*S*)-1-{[(1*S*)-1-{[(3*R*,4*S*,5*S*)-1-[(2*S*)-2-[(1*R*,2*R*)-2-{[(1*S*,2*R*)-1-hydroxy-1-phenylpropan-2-yl]carbamoyl}-1-methoxy-2-methylethyl]pyrrolidin-1-yl]-3-ethoxy-5-methyl-1-oxoheptan-4-yl](methyl)carbamoyl}-2-methylpropyl]carbamoyl}-2-methylpropyl](methyl)carbamoyl}oxy)methyl]phenyl}carbamoyl)butyl]carbamoyl}-2-methylpropyl]carbamoyl}propanamido)methyl]cyclohexyl]formamido}propanamido]pentyl]carbamoyl}amino)pentanedioic acid
8.	1.8	 (2*S*)-2-({[(1*S*)-1-carboxy-5-[(2*S*)-3-(naphthalen-2-yl)-2-{[(1*R*,4*R*)-4-{[(1-{[(1*S*)-4-(carbamoylamino)-1-({4-[({[(1*S*)-1-{[(1*S*)-1-{[(3*R*,4*S*,5*S*)-1-[(2*S*)-2-[(1*R*,2*R*)-2-{[(1*S*,2*R*)-1-hydroxy-1-phenylpropan-2-yl]carbamoyl}-1-methoxy-2-methylethyl]pyrrolidin-1-yl]-3-methoxy-5-methyl-1-oxoheptan-4-yl](methyl)carbamoyl}-2-methylpropyl]carbamoyl}-2-methylpropyl](methyl)carbamoyl}oxy)methyl]phenyl}carbamoyl)butyl]carbamoyl}cyclobutyl)formamido]methyl}cyclohexyl]formamido}propanamido]pentyl]carbamoyl}amino)pentanedioic acid
9.	1.9	 (2*S*)-2-({[(1*S*)-1-carboxy-5-[(2*S*)-3-(naphthalen-2-yl)-2-{[(1*R*,4*R*)-4-[(2-{2-[2-({[(1*S*)-1-{[(1*S*)-4-(carbamoylamino)-1-({4-[({[(1*S*)-1-{[(1*S*)-1-{[(3*R*,4*S*,5*S*)-1-[(2*S*)-2-[(1*R*,2*R*)-2-{[(1*S*,2*R*)-1-hydroxy-1-phenylpropan-2-yl]carbamoyl}-1-methoxy-2-methylethyl]pyrrolidin-1-yl]-3-methoxy-5-methyl-1-oxoheptan-4-yl](methyl)carbamoyl}-2-methylpropyl]carbamoyl}-2-methylpropyl](methyl)carbamoyl}oxy)methyl]phenyl}carbamoyl)butyl]carbamoyl}-2-methylpropyl]carbamoyl}methoxy)ethoxy]ethoxy}acetamido)methyl]cyclohexyl]formamido}propanamido]pentyl]carbamoyl}amino)pentanedioic acid
10.	1.10	 (2*S*)-2-({[(1*S*)-1-carboxy-5-[(2*S*)-3-(1*H*-indol-3-yl)-2-{[(1*R*,4*R*)-4-[(4-{[(1*S*)-1-{[(1*S*)-4-(carbamoylamino)-1-({4-[({[(1*S*)-1-{[(1*S*)-1-{[(3*R*,4*S*,5*S*)-1-[(2*S*)-2-[(1*R*,2*R*)-2-{[(1*S*,2*R*)-1-hydroxy-1-phenylpropan-2-yl]carbamoyl}-1-methoxy-2-methylethyl]pyrrolidin-1-yl]-3-methoxy-5-methyl-1-oxoheptan-4-yl](methyl)carbamoyl}-2-methylpropyl]carbamoyl}-2-methylpropyl](methyl)carbamoyl}oxy)methyl]phenyl} carbamoyl)butyl]carbamoyl}-2-methylpropyl]carbamoyl}butanamido)methyl] cyclohexyl]formamido}propanamido]pentyl]carbamoyl}amino)pentanedioic acid
11.	1.11	 (2*S*)-2-({[(1*S*)-1-carboxy-5-[(2*S*)-3-(naphthalen-2-yl)-2-{[(1*R*,4*R*)-4-{[2-({[(1*S*)-1-{[(1*S*)-4-(carbamoylamino)-1-({4-[({[(1*S*)-1-{[(1*S*)-1-{[(3*R*,4*S*,5*S*)-1-[(2*S*)-2-[(1*R*,2*R*)-2-{[(1*S*,2*R*)-1-hydroxy-1-phenylpropan-2-yl]carbamoyl}-1-methoxy-2-methylethyl]pyrrolidin-1-yl]-3-methoxy-5-methyl-1-oxoheptan-4-yl](methyl)carbamoyl}-2-methylpropyl]carbamoyl}-2-

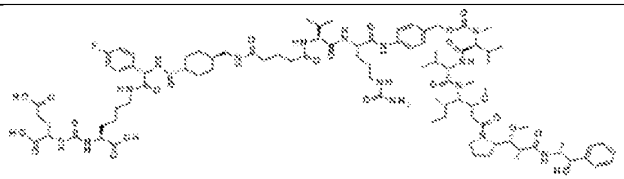
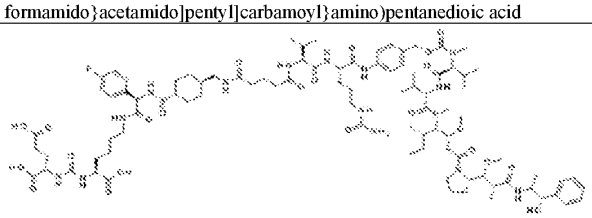
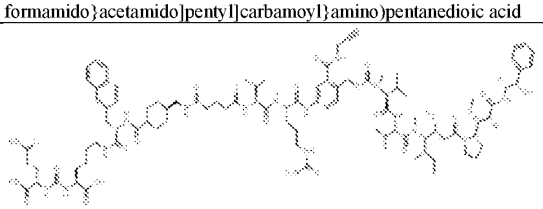
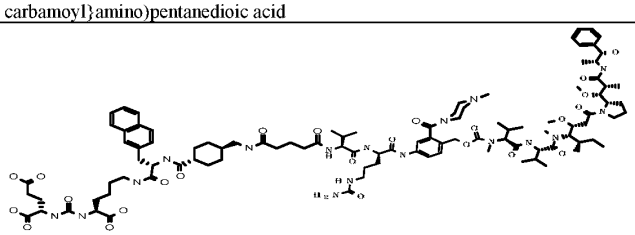
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12.	1.12	 (2*S*)-2-({[(1*S*)-1-carboxy-5-[(2*S*)-3-phenyl-2-{[(1*R*,4*R*)-4-[(4-{[(1*S*)-1-{[(1*S*)-4-(carbamoylamino)-1-({4-[({[(1*S*)-1-{[(1*S*)-1-{[(3*R*,4*S*,5*S*)-1-[(2*S*)-2-[(1*R*,2*R*)-2-{[(1*S*,2*R*)-1-hydroxy-1-phenylpropan-2-yl]carbamoyl}-1-methoxy-2-methylethyl]pyrrolidin-1-yl]-3-methoxy-5-methyl-1-oxoheptan-4-yl](methyl)carbamoyl}-2-methylpropyl]carbamoyl}-2-methylpropyl](methyl)carbamoyl}oxy)methyl]phenyl}carbamoyl)butyl]carbamoyl}-2-methylpropyl]carbamoyl}butanamido)methyl]cyclohexyl]formamido}propanamido]pentyl]carbamoyl}amino)pentanedioic acid
13.	1.13	 (2*S*)-2-({[(1*S*)-1-carboxy-5-[(2*S*)-3-(naphthalen-2-yl)-2-{[(1*R*,4*R*)-4-[(4-{[(1*S*)-1-{[(1*S*)-4-(carbamoylamino)-1-({4-[({[2-(dimethylamino)ethyl]({[(11*S*,12*R*)-7-fluoro-11-(4-fluorophenyl)-12-(1-methyl-1*H*-1,2,4-triazol-5-yl)-4-oxo-2,3,10-triazatricyclo[7.3.1.0^{5,13}]trideca-1,5,7,9(13)-tetraen-3-yl]methyl})carbamoyl}oxy)methyl] phenyl}carbamoyl)butyl]carbamoyl}-2-methylpropyl]carbamoyl}butanamido)methyl] cyclohexyl]formamido}propanamido]pentyl]carbamoyl}amino)pentanedioic acid
14.	1.14	 (2*S*)-2-({[(1*S*)-1-carboxy-5-[(2*S*)-3-(naphthalen-2-yl)-2-{[(1*R*,4*R*)-4-[(4-{[(1*S*)-1-{[(1*S*)-4-(carbamoylamino)-1-[(3-{[2-(dimethylamino)ethyl]carbamoyl}-4-[({[(1*S*)-1-{[(1*S*)-1-{[(3*R*,4*S*,5*S*)-1-[(2*S*)-2-[(1*R*,2*R*)-2-{[(1*S*,2*R*)-1-hydroxy-1-phenylpropan-2-yl]carbamoyl}-1-methoxy-2-methylethyl]pyrrolidin-1-yl]-3-methoxy-5-methyl-1-oxoheptan-4-yl](methyl)carbamoyl}-2-methylpropyl]carbamoyl}-2-methylpropyl](methyl)carbamoyl}oxy)methyl]phenyl)carbamoyl]butyl]carbamoyl}-2-methylpropyl]carbamoyl}butanamido)methyl] cyclohexyl]formamido}propanamido]pentyl]carbamoyl}amino)pentanedioic acid
15.	1.15	 (2*S*)-2-({[(1*S*)-1-carboxy-5-[(2*S*)-3-(naphthalen-2-yl)-2-{[(1*R*,4*R*)-4-[(4-{[(1*S*)-1-{[(1*S*)-4-(carbamoylamino)-1-({4-[({[(1*S*)-1-{[(1*S*)-1-{[(3*R*,4*S*,5*S*)-1-[(2*S*)-2-[(1*R*,2*R*)-2-{[(1*S*,2*R*)-1-hydroxy-1-phenylpropan-2-yl]carbamoyl}-1-methoxy-2-methylethyl]pyrrolidin-1-yl]-3-methoxy-5-methyl-1-oxoheptan-4-yl](methyl)carbamoyl}-2-methylpropyl]carbamoyl}-2-methylpropyl](methyl)carbamoyl}oxy)methyl]-3-(methylcarbamoyl)phenyl}carbamoyl)butyl]carbamoyl}-2-methylpropyl]carbamoyl}butanamido)methyl]cyclohexyl]formamido}propanamido]pentyl]carbamoyl}amino)pentanedioic acid

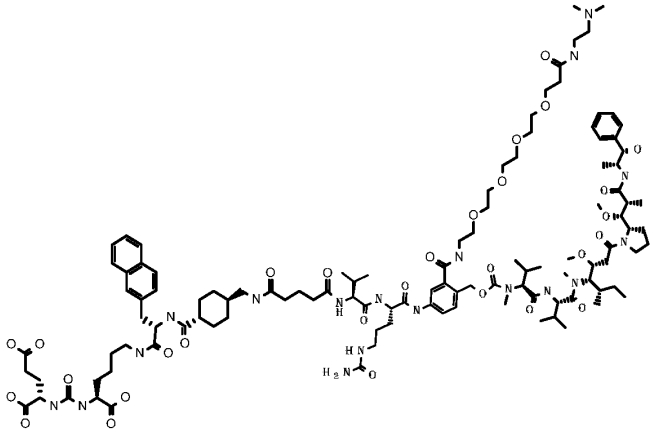
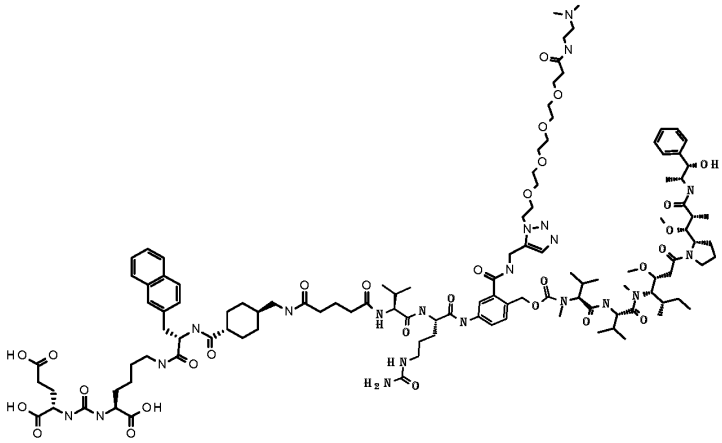
16.	1.16	 (2*S*)-2-({[(1*S*)-1-carboxy-5-[(2*S*)-3-(naphthalen-2-yl)-2-{[(1*R*,4*R*)-4-{[4-({[({[(1*S*)-1-{[({4-[({[(1*S*)-1-{[(1*S*)-1-{[(3*R*,4*S*,5*S*)-1-[(2*S*)-2-[(1*R*,2*R*)-2-{[(1*S*,2*R*)-1-hydroxy-1-phenylpropan-2-yl]carbamoyl}-1-methoxy-2-methylethyl]pyrrolidin-1-yl]-3-methoxy-5-methyl-1-oxoheptan-4-yl](methyl)carbamoyl}-2-methylpropyl]carbamoyl}-2-methylpropyl](methyl)carbamoyl}oxy)methyl]phenyl}carbamoyl)methyl]carbamoyl}-2-phenylethyl]carbamoyl}methyl)carbamoyl]methyl}carbamoyl)butanamido]methyl}cyclohexyl]formamido}propanamido]pentyl]carbamoyl}amino)pentanedioic acid
17.	1.17	 (2*S*)-2-({[(1*S*)-5-[(2*S*)-2-({4-[(4-{[(1*S*)-1-{[(1*S*)-4-(carbamoylamino)-1-({4-[({[(1*S*)-1-{[(1*S*)-1-{[(3*R*,4*S*,5*S*)-1-[(2*S*)-2-[(1*R*,2*R*)-2-{[(1*S*,2*R*)-1-hydroxy-1-phenylpropan-2-yl]carbamoyl}-1-methoxy-2-methylethyl]pyrrolidin-1-yl]-3-methoxy-5-methyl-1-oxoheptan-4-yl](methyl)carbamoyl}-2-methylpropyl]carbamoyl}-2-methylpropyl](methyl) carbamoyl}oxy)methyl]phenyl}carbamoyl)butyl]carbamoyl}-2-methylpropyl] carbamoyl}butanamido)methyl]phenyl}formamido)-3-(naphthalen-2-yl)propanamido]-1-carboxypentyl]carbamoyl}amino)pentanedioic acid
18.	1.18	 (2*S*)-2-({[(1*S*)-1-carboxy-5-[(2*S*)-3-(naphthalen-2-yl)-2-{[(1*R*,4*R*)-4-[(4-{[(1*S*)-1-{[(1*S*)-4-(carbamoylamino)-1-({4-[({[(1*S*)-1-{[(1*S*)-1-{[(3*R*,4*S*,5*S*)-1-[(2*S*)-2-[(1*R*,2*R*)-2-{[(1*S*,2*R*)-1-hydroxy-1-phenylpropan-2-yl]carbamoyl}-1-methoxy-2-methylethyl]pyrrolidin-1-yl]-3-methoxy-5-methyl-1-oxoheptan-4-yl](methyl)carbamoyl}-2-methylpropyl]carbamoyl}-2-methylpropyl](methyl)carbamoyl}oxy)methyl]-3-[(2-methoxyethyl)carbamoyl] phenyl} carbamoyl)butyl]carbamoyl}-2-methylpropyl]carbamoyl}butanamido)methyl]cyclohexyl] formamido}propanamido]pentyl]carbamoyl}amino) pentanedioic acid
19.	1.19	 (2*S*)-2-({[(1*S*)-1-carboxy-5-[(2*S*)-3-(naphthalen-2-yl)-2-{[(1*R*,4*R*)-4-[(4-{[(1*S*)-1-{[(1*S*)-4-(carbamoylamino)-1-[(3-{[3-(dimethylamino)propyl]carbamoyl}-4-[({[(1*S*)-1-{[(1*S*)-1-{[(3*R*,4*S*,5*S*)-1-[(2*S*)-2-[(1*R*,2*R*)-2-{[(1*S*,2*R*)-1-hydroxy-1-phenylpropan-2-yl]carbamoyl}-1-methoxy-2-methylethyl]pyrrolidin-1-yl]-3-methoxy-5-methyl-1-oxoheptan-4-yl](methyl)carbamoyl}-2-methylpropyl]carbamoyl}-2-methylpropyl](methyl)carbamoyl} oxy)methyl]phenyl)carbamoyl]butyl]carbamoyl}-2-methylpropyl]carbamoyl}butanamido) methyl]cyclohexyl]formamido}propanamido]pentyl]carbamoyl}amino)pentanedioic acid

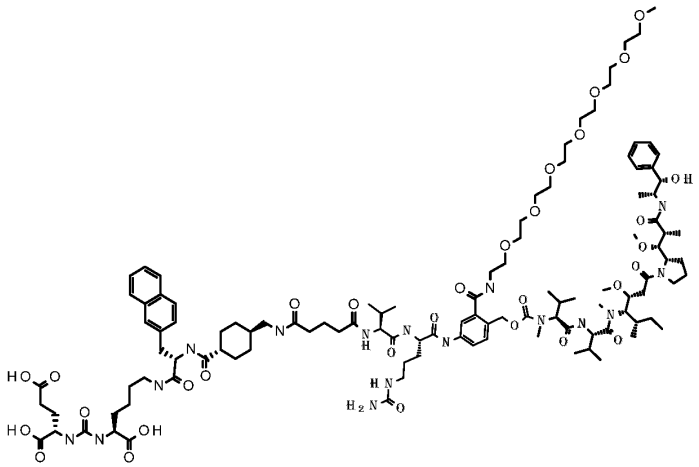
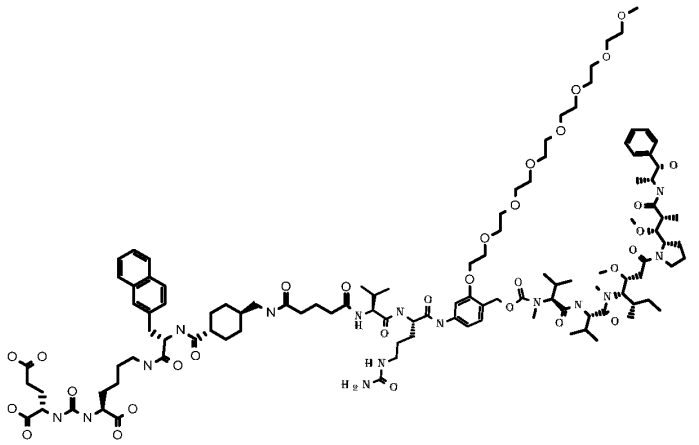
20.	1.20	 (2*S*)-2-({[(1*S*)-1-carboxy-5-[(2*S*)-3-(naphthalen-2-yl)-2-{[(1*R*,4*R*)-4-[(4-{[(1*S*)-1-{[(1*S*)-4-(carbamoylamino)-1-{[3-({2-[2-(2-ethoxyethoxy)ethoxy]ethyl}carbamoyl)-4-[({[(1*S*)-1-{[(1*S*)-1-{[(3*R*,4*S*,5*S*)-1-[(2*S*)-2-[(1*R*,2*R*)-2-{[(1*S*,2*R*)-1-hydroxy-1-phenylpropan-2-yl]carbamoyl}-1-methoxy-2-methylethyl]pyrrolidin-1-yl]-3-methoxy-5-methyl-1-oxoheptan-4-yl](methyl)carbamoyl}-2-methylpropyl]carbamoyl}-2-methylpropyl](methyl)carbamoyl}oxy)methyl]phenyl}carbamoyl)butyl]carbamoyl}-2-methylpropyl]carbamoyl}butanamido)methyl]cyclohexyl]formamido}propanamido]pentyl]carbamoyl}amino)pentanedioic acid
21.	1.21	 (2*S*)-2-({[(1*S*)-1-carboxy-5-[(2*S*)-3-(naphthalen-2-yl)-2-{[(1*R*,4*R*)-4-{[(2*E*)-3-{[(1*S*)-1-{[(1*S*)-4-(carbamoylamino)-1-({4-[({[(1*S*)-1-{[(1*S*)-1-{[(3*R*,4*S*,5*S*)-1-[(2*S*)-2-[(1*R*,2*R*)-2-{[(1*S*,2*R*)-1-hydroxy-1-phenylpropan-2-yl]carbamoyl}-1-methoxy-2-methylethyl]pyrrolidin-1-yl]-3-methoxy-5-methyl-1-oxoheptan-4-yl](methyl)carbamoyl}-2-methylpropyl]carbamoyl}-2-methylpropyl](methyl)carbamoyl}oxy)methyl]phenyl}carbamoyl)butyl]carbamoyl}-2-methylpropyl]carbamoyl}prop-2-enamido]methyl}cyclohexyl]formamido}propanamido]pentyl]carbamoyl}amino)pentanedioic acid
22.	1.22	 (2*S*)-2-({[(1*S*)-1-carboxy-5-[(2*S*)-3-(naphthalen-2-yl)-2-{[(1*R*,4*R*)-4-({4-[(1-{[(1*S*)-1-{[(1*S*)-4-(carbamoylamino)-1-({4-[({[(1*S*)-1-{[(1*S*)-1-{[(3*R*,4*S*,5*S*)-1-[(2*S*)-2-[(1*R*,2*R*)-2-{[(1*S*,2*R*)-1-hydroxy-1-phenylpropan-2-yl]carbamoyl}-1-methoxy-2-methylethyl]pyrrolidin-1-yl]-3-methoxy-5-methyl-1-oxoheptan-4-yl](methyl)carbamoyl}-2-methylpropyl]carbamoyl}-2-methylpropyl](methyl)carbamoyl}oxy)methyl]phenyl}carbamoyl)butyl]carbamoyl}-2-methylpropyl]carbamoyl}-3-carboxypropyl)carbamoyl]butanamido}methyl)cyclohexyl]formamido}propanamido]pentyl]carbamoyl}amino)pentanedioic acid
23.	1.23	 (2*S*)-2-({[(1*S*)-1-carboxy-5-[(2*S*)-*N*-[(4-chlorophenyl)methyl]-3-(naphthalen-2-yl)-2-{[(1*R*,4*R*)-4-[(4-{[(1*S*)-1-{[(1*S*)-4-(carbamoylamino)-1-({4-[({[(1*S*)-1-{[(1*S*)-1-[(3*R*,4*S*,5*S*)-1-[(2*S*)-2-[(1*R*,2*R*)-2-{[(1*S*,2*R*)-1-hydroxy-1-phenylpropan-2-yl]carbamoyl}-1-methoxy-2-methylethyl]pyrrolidin-1-yl]-3-methoxy-5-methyl-1-oxoheptan-4-yl](methyl)carbamoyl}-2-methylpropyl]carbamoyl}-2-methylpropyl](methyl)carbamoyl}oxy)methyl]phenyl}carbamoyl)butyl]carbamoyl}-2-methylpropyl]carbamoyl}butanamido)methyl]cyclohexyl]formamido}propanamido]pentyl]carbamoyl}amino)pentanedioic acid

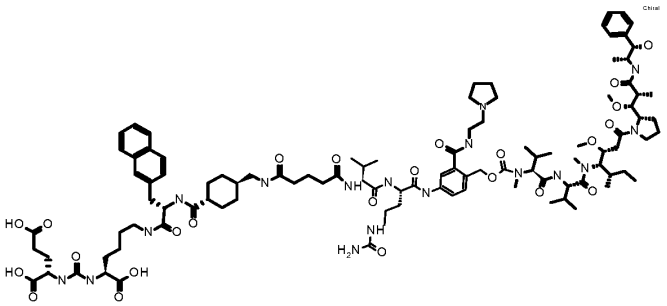
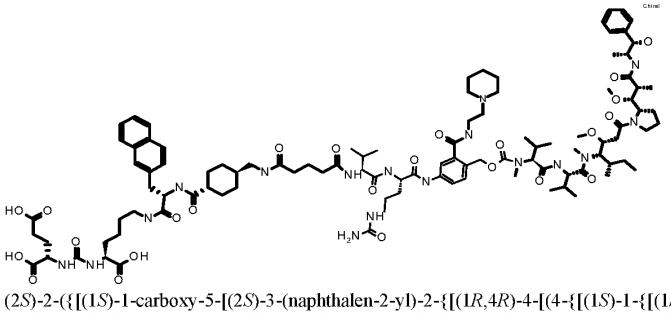
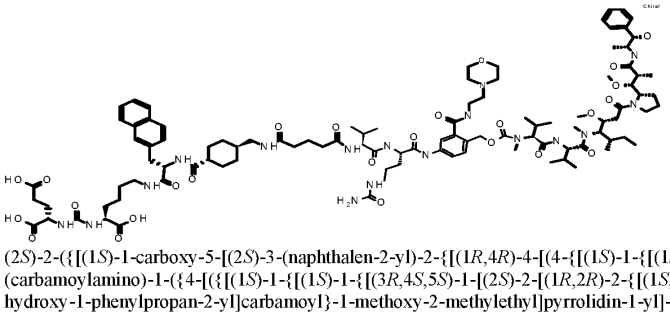
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25.	1.25	 (2*S*)-2-({[(1*S*)-1-carboxy-5-[3-(naphthalen-1-yl)-2-{[(1*R*,4*R*)-4-[(4-{[(1*S*)-1-{[(1*S*)-4-(carbamoylamino)-1-({4-[({[(1*S*)-1-{[(1*S*)-1-{[(3*R*,4*S*,5*S*)-1-[(2*S*)-2-[(1*R*,2*R*)-2-{[(1*S*,2*R*)-1-hydroxy-1-phenylpropan-2-yl]carbamoyl}-1-methoxy-2-methylethyl]pyrrolidin-1-yl]-3-methoxy-5-methyl-1-oxoheptan-4-yl](methyl)carbamoyl}-2-methylpropyl]carbamoyl}-2-methylpropyl](methyl)carbamoyl}oxy)methyl]phenyl}carbamoyl)butyl]carbamoyl}-2-methylpropyl]carbamoyl}butanamido)methyl]cyclohexyl]formamido}propanamido]pentyl]carbamoyl}amino)pentanedioic acid
26.	1.26	 (2*S*)-2-({[(1*S*)-5-[(2*S*)-3-{[1,1'-biphenyl]-4-yl}-2-{[(1*R*,4*R*)-4-[(4-{[(1*S*)-1-{[(1*S*)-4-(carbamoylamino)-1-({4-[({[(1*S*)-1-{[(1*S*)-1-{[(3*R*,4*S*,5*S*)-1-[(2*S*)-2-[(1*R*,2*R*)-2-{[(1*S*,2*R*)-1-hydroxy-1-phenylpropan-2-yl]carbamoyl}-1-methoxy-2-methylethyl]pyrrolidin-1-yl]-3-methoxy-5-methyl-1-oxoheptan-4-yl](methyl)carbamoyl}-2-methylpropyl]carbamoyl}-2-methylpropyl](methyl)carbamoyl}oxy)methyl]phenyl}carbamoyl)butyl]carbamoyl}-2-methylpropyl]carbamoyl}butanamido)methyl]cyclohexyl]formamido}propanamido]-1-carboxypentyl]carbamoyl}amino)pentanedioic acid
27.	1.27	 (2*S*)-2-({[(1*S*)-1-carboxy-5-[(2*S*)-2-{[(1*R*,4*R*)-4-[(4-{[(1*S*)-1-{[(1*S*)-4-(carbamoylamino)-1-({4-[({[(1*S*)-1-{[(1*S*)-1-{[(3*R*,4*S*,5*S*)-1-[(2*S*)-2-[(1*R*,2*R*)-2-{[(1*S*,2*R*)-1-hydroxy-1-phenylpropan-2-yl]carbamoyl}-1-methoxy-2-methylethyl]pyrrolidin-1-yl]-3-methoxy-5-methyl-1-oxoheptan-4-yl](methyl)carbamoyl}-2-methylpropyl]carbamoyl}-2-methylpropyl](methyl)carbamoyl}oxy)methyl] phenyl}carbamoyl)butyl]carbamoyl}-2-methylpropyl]carbamoyl}butanamido)methyl] cyclohexyl]formamido}-3-(thiophen-2-yl)propanamido]pentyl]carbamoyl}amino) pentanedioic acid

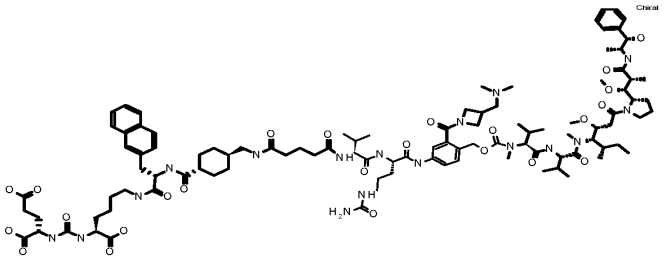
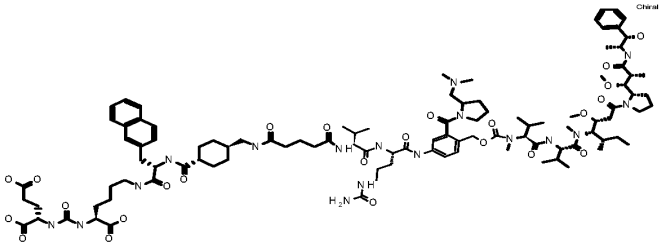
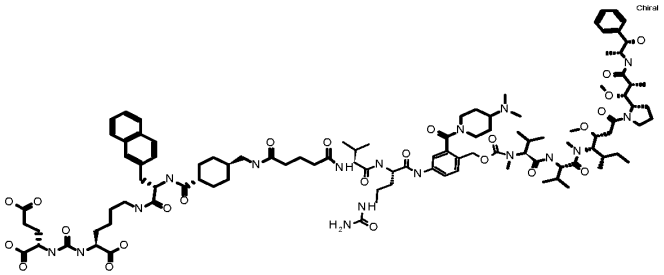
28.	1.28	 (2*S*)-2-({[(1*S*)-1-carboxy-5-[(2*R*)-3-(naphthalen-2-yl)-2-{[(1*R*,4*R*)-4-[(4-{[(1*S*)-1-{[(1*S*)-4-(carbamoylamino)-1-({4-[({[(1*S*)-1-{[(1*S*)-1-{[(3*R*,4*S*,5*S*)-1-[(2*S*)-2-[(1*R*,2*R*)-2-{[(1*S*,2*R*)-1-hydroxy-1-phenylpropan-2-yl]carbamoyl}-1-methoxy-2-methylethyl]pyrrolidin-1-yl]-3-methoxy-5-methyl-1-oxoheptan-4-yl](methyl)carbamoyl}-2-methylpropyl]carbamoyl}-2-methylpropyl](methyl)carbamoyl}oxy)methyl]phenyl} carbamoyl)butyl]carbamoyl}-2-methylpropyl]carbamoyl}butanamido)methyl]cyclohexyl]formamido}propanamido]pentyl]carbamoyl}amino)pentanedioic acid
29.	1.29	 (2*S*)-2-({[(1*S*)-1-carboxy-5-[3-(2-oxo-1,2-dihydroquinolin-4-yl)-2-{[(1*R*,4*R*)-4-[(4-{[(1*S*)-1-{[(1*S*)-4-(carbamoylamino)-1-({4-[({[(1*S*)-1-{[(1*S*)-1-{[(3*R*,4*S*,5*S*)-1-[(2*S*)-2-[(1*R*,2*R*)-2-{[(1*S*,2*R*)-1-hydroxy-1-phenylpropan-2-yl]carbamoyl}-1-methoxy-2-methylethyl]pyrrolidin-1-yl]-3-methoxy-5-methyl-1-oxoheptan-4-yl](methyl)carbamoyl}-2-methylpropyl]carbamoyl}-2-methylpropyl](methyl)carbamoyl}oxy)methyl]phenyl}carbamoyl)butyl]carbamoyl}-2-methylpropyl]carbamoyl}butanamido)methyl]cyclohexyl]formamido}propanamido]pentyl]carbamoyl}amino)pentanedioic acid
30.	1.30	 (2*S*)-2-({[(1*S*)-1-carboxy-5-[3-(pyridin-4-yl)-2-{[(1*R*,4*R*)-4-[(4-{[(1*S*)-1-{[(1*S*)-4-(carbamoylamino)-1-({4-[({[(1*S*)-1-{[(1*S*)-1-{[(3*R*,4*S*,5*S*)-1-[(2*S*)-2-[(1*R*,2*R*)-2-{[(1*S*,2*R*)-1-hydroxy-1-phenylpropan-2-yl]carbamoyl}-1-methoxy-2-methylethyl]pyrrolidin-1-yl]-3-methoxy-5-methyl-1-oxoheptan-4-yl](methyl)carbamoyl}-2-methylpropyl]carbamoyl}-2-methylpropyl](methyl)carbamoyl}oxy)methyl]phenyl}carbamoyl)butyl]carbamoyl}-2-methylpropyl]carbamoyl}butanamido)methyl]cyclohexyl]formamido}propanamido]pentyl]carbamoyl}amino)pentanedioic acid
31.	1.31	 (2*S*)-2-({[(1*S*)-1-carboxy-5-[(2*S*)-3-(4-fluorophenyl)-2-{[(1*R*,4*R*)-4-[(4-{[(1*S*)-1-{[(1*S*)-4-(carbamoylamino)-1-({4-[({[(1*S*)-1-{[(1*S*)-1-{[(3*R*,4*S*,5*S*)-1-[(2*S*)-2-[(1*R*,2*R*)-2-{[(1*S*,2*R*)-1-hydroxy-1-phenylpropan-2-yl]carbamoyl}-1-methoxy-2-methylethyl]pyrrolidin-1-yl]-3-methoxy-5-methyl-1-oxoheptan-4-yl](methyl)carbamoyl}-2-methylpropyl]carbamoyl}-2-methylpropyl](methyl)carbamoyl}oxy)methyl]phenyl} carbamoyl)butyl]carbamoyl}-2-methylpropyl]carbamoyl}butanamido)methyl]cyclohexyl]formamido}propanamido]pentyl]carbamoyl}amino)pentanedioic acid

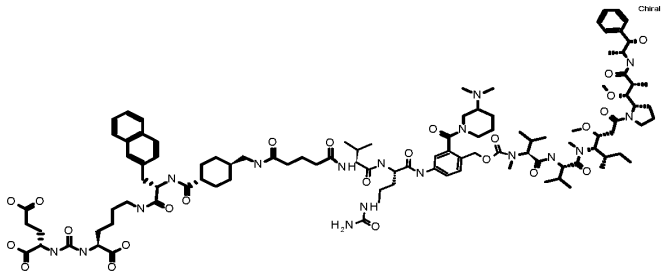
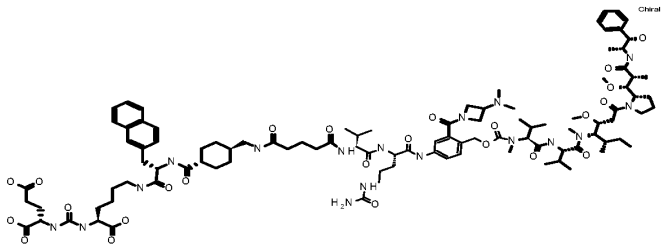
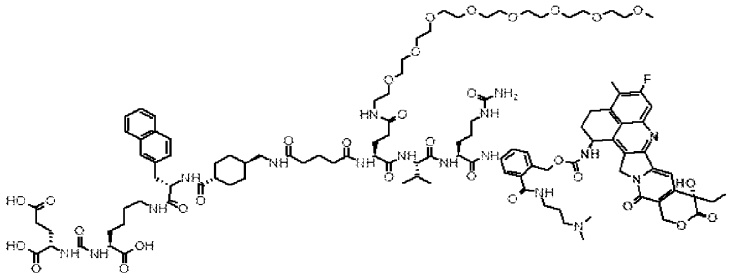
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33.	1.33	 (2*S*)-2-({[(1*S*)-1-carboxy-5-[(2*R*)-2-(4-fluorophenyl)-2-{[(1*R*,4*R*)-4-[(4-{[(1*S*)-1-{[(1*S*)-4-(carbamoylamino)-1-({4-[({[(1*S*)-1-{[(1*S*)-1-{[(3*R*,4*S*,5*S*)-1-[(2*S*)-2-[(1*R*,2*R*)-2-{[(1*S*,2*R*)-1-hydroxy-1-phenylpropan-2-yl]carbamoyl}-1-methoxy-2-methylethyl]pyrrolidin-1-yl]-3-methoxy-5-methyl-1-oxoheptan-4-yl](methyl)carbamoyl}-2-methylpropyl]carbamoyl}-2-methylpropyl](methyl)carbamoyl}oxy)methyl]phenyl} carbamoyl)butyl]carbamoyl}-2-methylpropyl]carbamoyl}butanamido)methyl]cyclohexyl] formamido}acetamido]pentyl]carbamoyl}amino)pentanedioic acid
34.	1.34	 (2*S*)-2-({[(1*S*)-1-carboxy-5-[(2*S*)-3-(naphthalen-2-yl)-2-{[(1*R*,4*R*)-4-[(4-{[(1*S*)-1-{[(1*S*)-4-(carbamoylamino)-1-({4-[({[(1*S*)-1-{[(1*S*)-1-{[(3*R*,4*S*,5*S*)-1-[(2*S*)-2-[(1*R*,2*R*)-2-{[(1*S*,2*R*)-1-hydroxy-1-phenylpropan-2-yl]carbamoyl}-1-methoxy-2-methylethyl]pyrrolidin-1-yl]-3-methoxy-5-methyl-1-oxoheptan-4-yl](methyl)carbamoyl}-2-methylpropyl]carbamoyl}-2-methylpropyl](methyl)carbamoyl}oxy)methyl]-3-(*N*-(prop-2-yn-1-yl)benzamide)}carbamoyl)butyl]carbamoyl}-2-methylpropyl]carbamoyl}butanamido)methyl]cyclohexyl]formamido}propanamido]pentyl] carbamoyl}amino)pentanedioic acid
35.	1.35	 (2*S*)-2-({[(1*S*)-1-carboxy-5-[(2*S*)-3-(naphthalen-2-yl)-2-{[(1*R*,4*R*)-4-[(4-{[(1*S*)-1-{[(1*S*)-4-(carbamoylamino)-1-({4-[({[(1*S*)-1-{[(1*S*)-1-{[(3*R*,4*S*,5*S*)-1-[(2*S*)-2-[(1*R*,2*R*)-2-{[(1*S*,2*R*)-1-hydroxy-1-phenylpropan-2-yl]carbamoyl}-1-methoxy-2-methylethyl]pyrrolidin-1-yl]-3-methoxy-5-methyl-1-oxoheptan-4-yl](methyl)carbamoyl}-2-methylpropyl]carbamoyl}-2-methylpropyl](methyl)carbamoyl}oxy)methyl]-3-(4-methylpiperazine-1-carbonyl)phenyl} carbamoyl)butyl]carbamoyl}-2-methylpropyl]carbamoyl}butanamido)methyl] cyclohexyl]formamido}propanamido]pentyl]carbamoyl}amino)pentanedioic acid

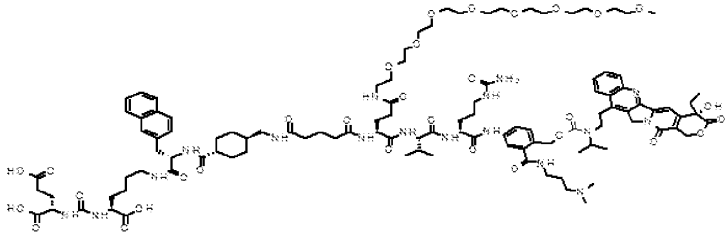
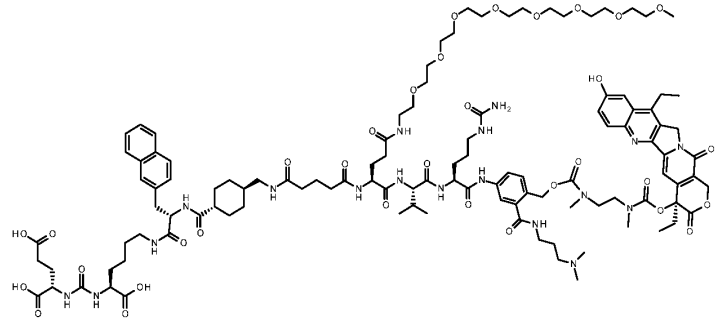
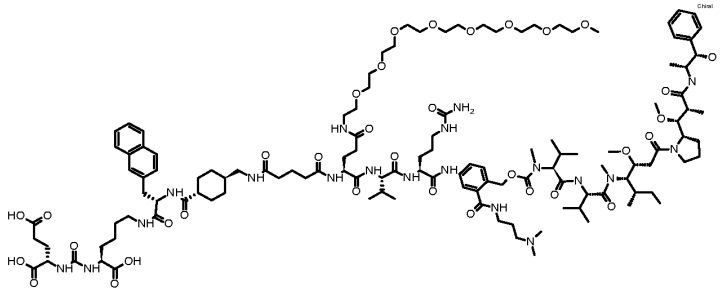
36.	1.36	 (2*S*)-2-({[(1*S*)-1-carboxy-5-[(2*S*)-3-(naphthalen-2-yl)-2-{[(1*R*,4*R*)-4-[(4-{[(1*S*)-1-{[(1*S*)-4-(carbamoylamino)-1-({3-[(14-{[2-(dimethylamino)ethyl]carbamoyl}-3,6,9,12-tetraoxatetradecan-1-yl)carbamoyl]-4-[({[(1*S*)-1-{[(1*S*)-1-{[(3*R*,4*S*,5*S*)-1-[(2*S*)-2-[(1*R*,2*R*)-2-{[(1*S*,2*R*)-1-hydroxy-1-phenylpropan-2-yl]carbamoyl}-1-methoxy-2-methylethyl]pyrrolidin-1-yl]-3-methoxy-5-methyl-1-oxoheptan-4-yl](methyl)carbamoyl}-2-methylpropyl]carbamoyl}-2-methylpropyl](methyl)carbamoyl}oxy)methyl]phenyl}carbamoyl)butyl]carbamoyl}-2-methylpropyl]carbamoyl}butanamido)methyl]cyclohexyl]formamido}propanamido]pentyl]carbamoyl}amino)pentanedioic acid
37.	1.37	 (2*S*)-2-({[(1*S*)-1-carboxy-5-[(2*S*)-3-(naphthalen-2-yl)-2-{[(1*R*,4*R*)-4-[(4-{[(1*S*)-1-{[(1*S*)-4-(carbamoylamino)-1-{[3-({[1-(14-{[2-(dimethylamino)ethyl]carbamoyl}-3,6,9,12-tetraoxatetradecan-1-yl)-1*H*-1,2,3-triazol-4-yl]methyl}carbamoyl)-4-[({[(1*S*)-1-{[(1*S*)-1-{[(3*R*,4*S*,5*S*)-1-[(2*S*)-2-[(1*R*,2*R*)-2-{[(1*S*,2*R*)-1-hydroxy-1-phenylpropan-2-yl]carbamoyl}-1-methoxy-2-methylethyl]pyrrolidin-1-yl]-3-methoxy-5-methyl-1-oxoheptan-4-yl](methyl)carbamoyl}-2-methylpropyl]carbamoyl}-2-methylpropyl](methyl)carbamoyl}oxy)methyl]phenyl]carbamoyl}butyl]carbamoyl}-2-methylpropyl]carbamoyl}butanamido)methyl]cyclohexyl]formamido}propanamido]pentyl]carbamoyl}amino)pentanedioic acid

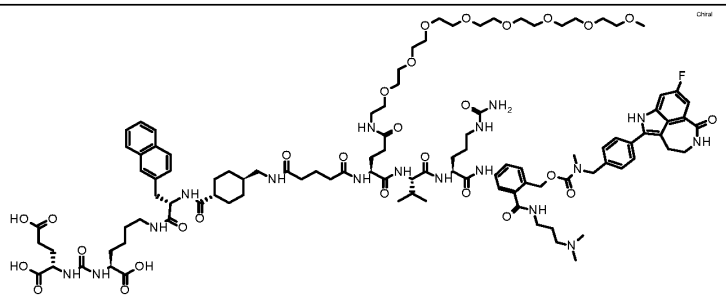
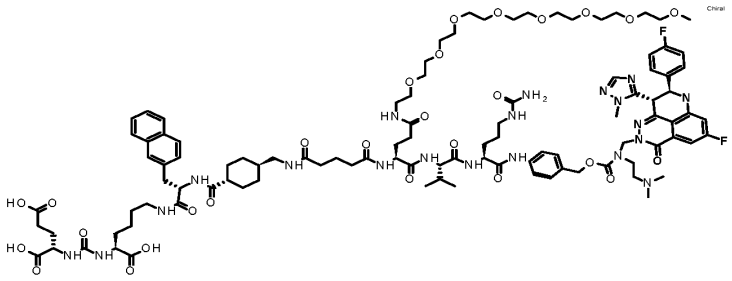
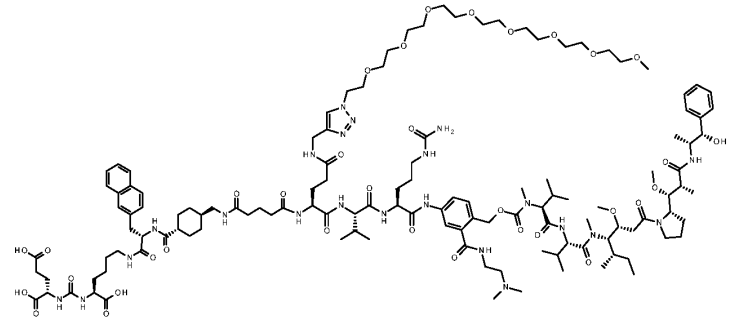
38.	1.38	 (2*S*)-2-({[(1*S*)-1-carboxy-5-[(2*S*)-3-(naphthalen-2-yl)-2-{[(1*R*,4*R*)-4-[(4-{[(1*S*)-1-{[(1*S*)-4-(carbamoylamino)-1-({4-[({[(1*S*)-1-{[(1*S*)-1-{[(3*R*,4*S*,5*S*)-1-[(2*S*)-2-[(1*R*,2*R*)-2-{[(1*S*,2*R*)-1-hydroxy-1-phenylpropan-2-yl]carbamoyl}-1-methoxy-2-methylethyl]pyrrolidin-1-yl]-3-methoxy-5-methyl-1-oxoheptan-4-yl](methyl)carbamoyl}-2-methylpropyl]carbamoyl}-2-methylpropyl](methyl)carbamoyl}oxy)methyl]-3-[(2,5,8,11,14,17,20,23-octaoxapentacosan-25-yl)carbamoyl]phenyl}carbamoyl)butyl]carbamoyl}-2-methylpropyl]carbamoyl} butanamido)methyl]cyclohexyl]formamido}propanamido]pentyl] carbamoyl}amino)pentanedioic acid
39.	1.39	 (2S)-2-[[(1S)-1-carboxy-5-[[(2S)-2-[[4-[[[5-[[(1S)-1-[[(1S)-1-[[4-[[[(1S)-1-[[(1S)-1-[[(1S,2R)-4-[(2S)-2-[(1R,2R)-3-[[(1R,2S)-2-hydroxy-1-methyl-2-phenyl-ethyl]amino]-1-methoxy-2-methyl-3-oxo-propyl]pyrrolidin-1-yl]-2-methoxy-1-[(1S)-1-methylpropyl]-4-oxo-butyl]-methyl-carbamoyl]-2-methyl-propyl]carbamoyl]-2-methyl-propyl]-methyl-carbamoyl]oxymethyl]-3-[2-[2-[2-[2-[2-[2-(2-methoxyethoxy)ethoxy]ethoxy]ethoxy]ethoxy]ethoxy]phenyl]carbamoyl]-4-ureido-butyl]carbamoyl]-2-methyl-propyl]amino]-5-oxo-pentanoyl]amino]methyl]cyclohexanecarbonyl]amino]-3-(2-naphthyl)propanoyl]amino]pentyl]carbamoylamino]pentanedioic acid

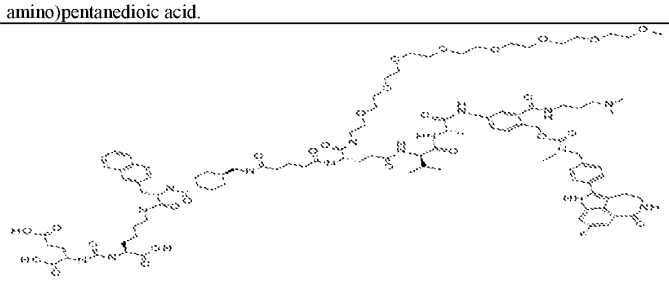
40.	1.40	 (2*S*)-2-({[(1*S*)-1-carboxy-5-[(2*S*)-3-(naphthalen-2-yl)-2-{[(1*R*,4*R*)-4-[(4-{[(1*S*)-1-{[(1*S*)-4-(carbamoylamino)-1-({4-[({[(1*S*)-1-{[(1*S*)-1-{[(3*R*,4*S*,5*S*)-1-[(2*S*)-2-[(1*R*,2*R*)-2-{[(1*S*,2*R*)-1-hydroxy-1-phenylpropan-2-yl]carbamoyl}-1-methoxy-2-methylethyl]pyrrolidin-1-yl]-3-methoxy-5-methyl-1-oxoheptan-4-yl](methyl)carbamoyl}-2-methylpropyl]carbamoyl}-2-methylpropyl](methyl)carbamoyl}oxy)methyl]-3-{[2-(pyrrolidin-1-yl)ethyl]carbamoyl}phenyl}carbamoyl)butyl]carbamoyl}-2-methylpropyl]carbamoyl}butanamido)methyl]cyclohexyl]formamido}propanamido]pentyl]carbamoyl}amino)pentanedioic acid
41.	1.41	 (2*S*)-2-({[(1*S*)-1-carboxy-5-[(2*S*)-3-(naphthalen-2-yl)-2-{[(1*R*,4*R*)-4-[(4-{[(1*S*)-1-{[(1*S*)-4-(carbamoylamino)-1-({4-[({[(1*S*)-1-{[(1*S*)-1-{[(3*R*,4*S*,5*S*)-1-[(2*S*)-2-[(1*R*,2*R*)-2-{[(1*S*,2*R*)-1-hydroxy-1-phenylpropan-2-yl]carbamoyl}-1-methoxy-2-methylethyl]pyrrolidin-1-yl]-3-methoxy-5-methyl-1-oxoheptan-4-yl](methyl)carbamoyl}-2-methylpropyl]carbamoyl}-2-methylpropyl](methyl)carbamoyl}oxy)methyl]-3-{[2-(piperidin-1-yl)ethyl]carbamoyl}phenyl}carbamoyl)butyl]carbamoyl}-2-methylpropyl]carbamoyl}butanamido)methyl]cyclohexyl]formamido}propanamido]pentyl]carbamoyl}amino)pentanedioic acid
42.	1.42	 (2*S*)-2-({[(1*S*)-1-carboxy-5-[(2*S*)-3-(naphthalen-2-yl)-2-{[(1*R*,4*R*)-4-[(4-{[(1*S*)-1-{[(1*S*)-4-(carbamoylamino)-1-({4-[({[(1*S*)-1-{[(1*S*)-1-{[(3*R*,4*S*,5*S*)-1-[(2*S*)-2-[(1*R*,2*R*)-2-{[(1*S*,2*R*)-1-hydroxy-1-phenylpropan-2-yl]carbamoyl}-1-methoxy-2-methylethyl]pyrrolidin-1-yl]-3-methoxy-5-methyl-1-oxoheptan-4-yl](methyl)carbamoyl}-2-methylpropyl]carbamoyl}-2-methylpropyl](methyl)carbamoyl}oxy)methyl]-3-{[2-(morpholin-4-yl)ethyl]carbamoyl}phenyl}carbamoyl)butyl]carbamoyl}-2-methylpropyl]carbamoyl}butanamido)methyl]cyclohexyl]formamido}propanamido]pentyl]carbamoyl}amino)pentanedioic acid

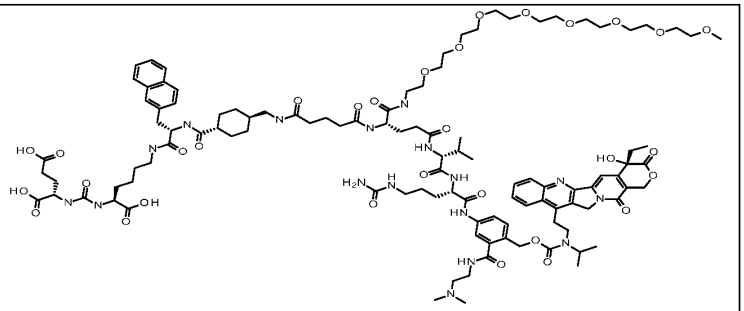
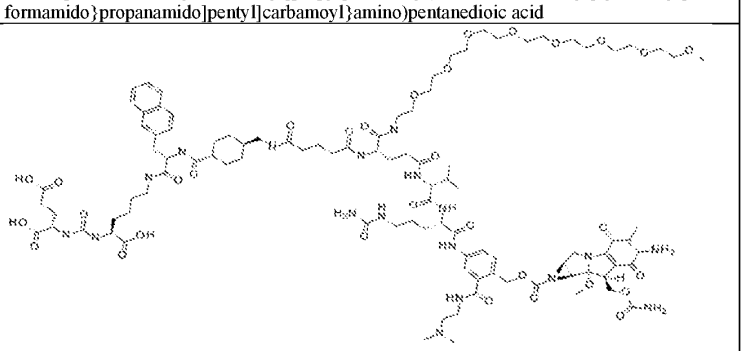
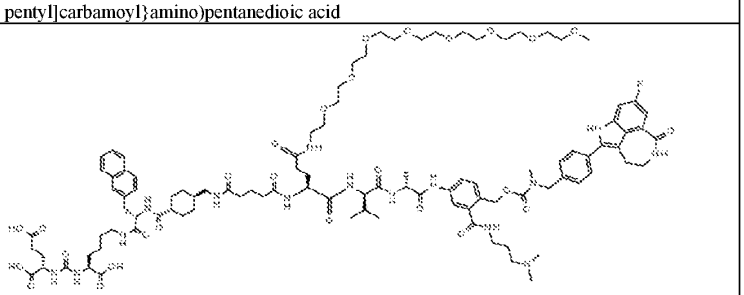
43.	1.43	 (2*S*)-2-({[(1*S*)-1-carboxy-5-[(2*S*)-3-(naphthalen-2-yl)-2-{[(1*R*,4*R*)-4-[(4-{[(1*S*)-1-{[(1*S*)-4-(carbamoylamino)-1-[(3-{3-[(dimethylamino)methyl]azetidine-1-carbonyl}-4-[({[(1*S*)-1-{[(1*S*)-1-{[(3*R*,4*S*,5*S*)-1-[(2*S*)-2-[(1*R*,2*R*)-2-{[(1*S*,2*R*)-1-hydroxy-1-phenylpropan-2-yl]carbamoyl}-1-methoxy-2-methylethyl]pyrrolidin-1-yl]-3-methoxy-5-methyl-1-oxoheptan-4-yl](methyl)carbamoyl}-2-methylpropyl]carbamoyl}-2-methylpropyl](methyl)carbamoyl}oxy)methyl]phenyl)carbamoyl]butyl]carbamoyl}-2-methylpropyl]carbamoyl}butanamido)methyl]cyclohexyl]formamido}propanamido]pentyl]carbamoyl}amino)pentanedioic acid
44.	1.44	 (2*S*)-2-({[(1*S*)-1-carboxy-5-[(2*S*)-3-(naphthalen-2-yl)-2-{[(1*R*,4*R*)-4-[(4-{[(1*S*)-1-{[(1*S*)-4-(carbamoylamino)-1-[(3-{2-[(dimethylamino)methyl]pyrrolidine-1-carbonyl}-4-[({[(1*S*)-1-{[(1*S*)-1-{[(3*R*,4*S*,5*S*)-1-[(2*S*)-2-[(1*R*,2*R*)-2-{[(1*S*,2*R*)-1-hydroxy-1-phenylpropan-2-yl]carbamoyl}-1-methoxy-2-methylethyl]pyrrolidin-1-yl]-3-methoxy-5-methyl-1-oxoheptan-4-yl](methyl)carbamoyl}-2-methylpropyl]carbamoyl}-2-methylpropyl](methylcarbamoyl}oxy)methyl]phenyl)carbamoyl]butyl]carbamoyl}-2-methylpropyl]carbamoyl}butanamido)methyl]cyclohexyl]formamido}propanamido]pentyl]carbamoyl}amino)pentanedioic acid
45.	1.45	 (2*S*)-2-({[(1*S*)-1-carboxy-5-[(2S)-3-(naphthalen-2-yl)-2-{[(1*R*,4*R*)-4-[(4-{[(1*S*)-1-{[(1*S*)-4-(carbamoylamino)-1-({3-[4-(dimethylamino)piperidine-1-carbonyl]-4-[({[(1*S*)-1-{[(1*S*)-1-{[(3*R*,4*S*,5*S*)-1-[(2*S*)-2-[(1*R*,2*R*)-2-{[(1*S*,2*R*)-1-hydroxy-1-phenylpropan-2-yl]carbamoyl}-1-methoxy-2-methylethyl]pyrrolidin-1-yl]-3-methoxy-5-methyl-1-oxoheptan-4-yl](methyl)carbamoyl}-2-methylpropyl]carbamoyl}-2-methylpropyl](methyl)carbamoyl}oxy)methyl] phenyl}carbamoyl)butyl]carbamoyl}-2-methylpropyl]carbamoyl}butanamido)methyl] cyclohexyl]formamido}propanamido]pentyl]carbamoyl}amino)pentanedioic acid

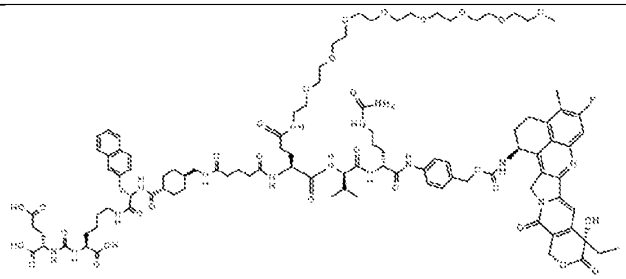
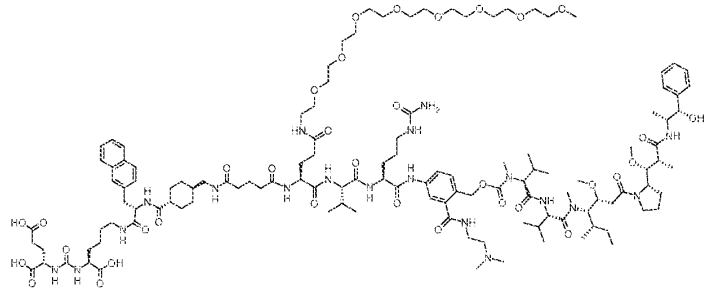
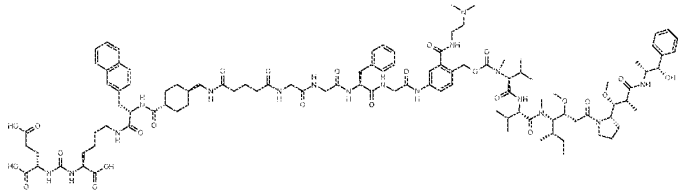
46.	1.46	 (2*S*)-2-({[(1*S*)-1-carboxy-5-[(2*S*)-3-(naphthalen-2-yl)-2-{[(1*R*,4*R*)-4-[(4-{[(1*S*)-1-{[(1*S*)-4-(carbamoylamino)-1-({3-[3-(dimethylamino)piperidine-1-carbonyl]-4-[({[(1*S*)-1-{[(1*S*)-1-{[(3*R*,4*S*,5*S*)-1-[(2*S*)-2-[(1*R*,2*R*)-2-{[(1*S*,2*R*)-1-hydroxy-1-phenylpropan-2-yl]carbamoyl}-1-methoxy-2-methylethyl]pyrrolidin-1-yl]-3-methoxy-5-methyl-1-oxoheptan-4-yl](methyl)carbamoyl}-2-methylpropyl]carbamoyl}-2-methylpropyl](methyl)carbamoyl}oxy)methyl]phenyl}carbamoyl)butyl]carbamoyl}-2-methylpropyl]carbamoyl}butanamido)methyl]cyclohexyl]formamido}propanamido]pentyl]carbamoyl}amino)pentanedioic acid
47.	1.47	 (2*S*)-2-({[(1*S*)-1-carboxy-5-[(2*S*)-3-(naphthalen-2-yl)-2-{[(1*R*,4*R*)-4-[(4-{[(1*S*)-1-{[(1*S*)-4-(carbamoylamino)-1-({3-[3-(dimethylamino)azetidine-1-carbonyl]-4-[({[(1*S*)-1-{[(1*S*)-1-{[(3*R*,4*S*,5*S*)-1-[(2*S*)-2-[(1*R*,2*R*)-2-{[(1*S*,2*R*)-1-hydroxy-1-phenylpropan-2-yl]carbamoyl}-1-methoxy-2-methylethyl]pyrrolidin-1-yl]-3-methoxy-5-methyl-1-oxoheptan-4-yl](methyl)carbamoyl}-2-methylpropyl]carbamoyl}-2-methylpropyl](methyl)carbamoyl}oxy)methyl]phenyl}carbamoyl)butyl]carbamoyl}-2-methylpropyl]carbamoyl}butanamido)methyl]cyclohexyl]formamido}propanamido]pentyl]carbamoyl}amino)pentanedioic acid
48.	1.48	 (2*S*)-2-({[(1*S*)-1-carboxy-5-[(2*S*)-3-(naphthalen-2-yl)-2-{[(1*R*,4*R*)-4-[(4-{[(1*S*)-1-{[(1*S*)-1-{[(1*S*)-4-(carbamoylamino)-1-({4-[({[(10*S*,23*S*)-10-ethyl-18-fluoro-10-hydroxy-19-methyl-5,9-dioxo-8-oxa-4,15-diazahexacyclo[14.7.1.0^{2,14}.0^{4,13}.0^{6,11}.0^{20,24}]tetracosa-1,6(11),12,14,16,18,20(24)-heptaen-23-yl]carbamoyl}oxy)methyl]phenyl}carbamoyl)butyl]carbamoyl}-2-methylpropyl]carbamoyl}-3-[(2,5,8,11,14,17,20,23-octaoxapentacosan-25-yl)carbamoyl]propyl]carbamoyl}butanamido)methyl]cyclohexyl]formamido}propanamido]pentyl]carbamoyl}amino)pentanedioic acid

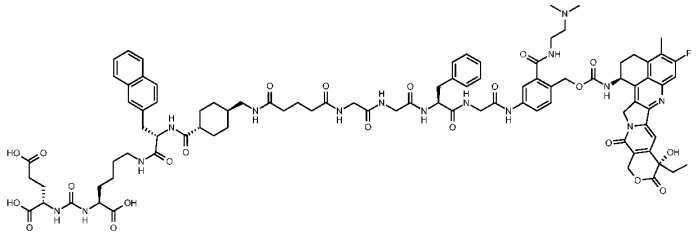
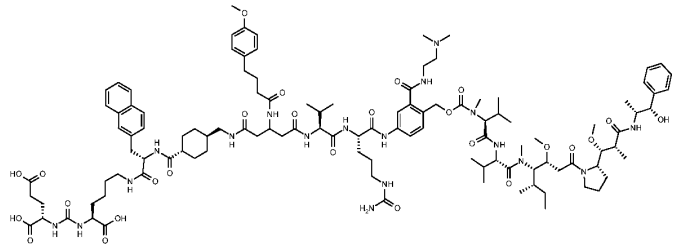
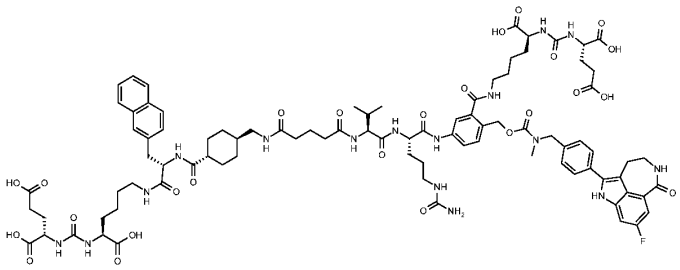
49.	1.49	 (2*S*)-2-({[(1*S*)-1-carboxy-5-[(2*S*)-3-(naphthalen-2-yl)-2-{[(1*R*,4*R*)-4-[(4-{[(1*S*)-1-{[(1*S*)-1-{[(1*S*)-4-(carbamoylamino)-1-[(3-{[3-(dimethylamino)propyl]carbamoyl}-4-{[({2-[(19*S*)-19-ethyl-19-hydroxy-14,18-dioxo-17-oxa-3,13-diazapentacyclo[11.8.0.0^{2},^{11}.0^{4},^{9}.0^{15},^{20}]henicosa-1(21),2,4(9),5,7,10,15(20)-heptaen-10-yl]ethyl}(propan-2-yl)carbamoyl)oxy]methyl}phenyl)carbamoyl]butyl]carbamoyl}-2-methylpropyl]carbamoyl}-3-[(2,5,8,11,14,17,20,23-octaoxapentacosan-25-yl)carbamoyl]propyl]carbamoyl}butanamido)methyl]cyclohexyl]formamido}propanamido]pentyl]carbamoyl}amino)pentanedioic acid
50.	1.50	 (2*S*)-2-({[(1*S*)-5-[(2*S*)-2-({4-[(4-{[(1*S*)-1-{[(1*S*)-1-{[(1*S*)-4-(carbamoylamino)-1-[(4-{[({2-[({[(19*S*)-10,19-diethyl-7-hydroxy-14,18-dioxo-17-oxa-3,13-diazapentacyclo[11.8.0.0^{2},^{11}.0^{4},^{9}.0^{15},^{20}]henicosa-1(21),2(11),3,5,7,9,15(20)-heptaen-19-yl]oxy}carbonyl)(methyl)amino]ethyl}(methyl)carbamoyl)oxy]methyl}phenyl)carbamoyl]butyl]carbamoyl}-2-methylpropyl]carbamoyl}-4-(2,5,8,11,14,17,20,23-octaoxapentacosan-25-yloxy)-4-oxobutyl]carbamoyl}butanamido)methyl]cyclohexyl}formamido)-3-(naphthalen-2-yl)propanamido]-1-carboxypentyl]carbamoyl}amino)pentanedioic acid
51.	1.51	 (2*S*)-2-({[(1*S*)-1-carboxy-5-[(2*S*)-3-(naphthalen-2-yl)-2-{[(1*R*,4*R*)-4-[(4-{[(1*S*)-1-{[(1*S*)-1-{[(1*S*)-4-(carbamoylamino)-1-[(3-{[3-(dimethylamino)propyl]carbamoyl}-4-[({[(1*S*)-1-{[(1*S*)-1-{[(3*R*,4*S*,5*S*)-1-[(2*S*)-2-[(1*R*,2*R*)-2-{[(1*S*,2*R*)-1-hydroxy-1-phenylpropan-2-yl]carbamoyl}-1-methoxy-2-methylethyl]pyrrolidin-1-yl]-3-methoxy-5-methyl-1-oxoheptan-4-yl](methyl)carbamoyl}-2-methylpropyl]carbamoyl}-2-methylpropyl](methyl)carbamoyl}oxy)methyl]phenyl)carbamoyl]butyl]carbamoyl}-2-methylpropyl]carbamoyl}-3-[(2,5,8,11,14,17,20,23-octaoxapentacosan-25-yl)carbamoyl]propyl]carbamoyl}butanamido)methyl]cyclohexyl]formamido}propanamido]pentyl]carbamoyl}amino)pentanedioic acid

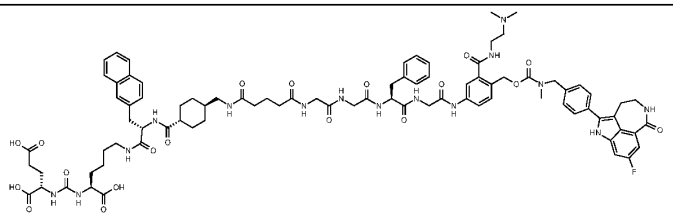
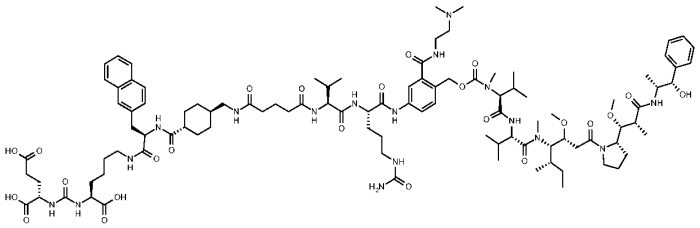
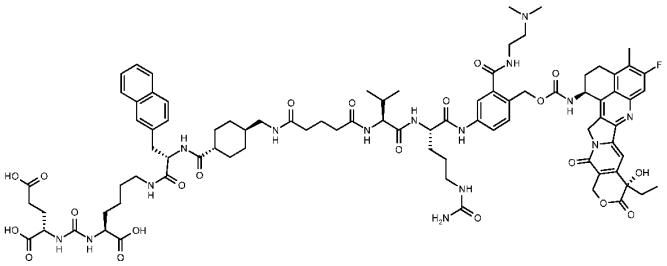
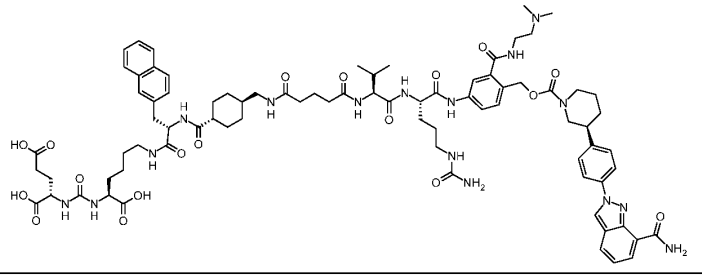
52.	1.52	 (2*S*)-2-({[(1*S*)-1-carboxy-5-[(2*S*)-3-(naphthalen-2-yl)-2-{[(1*R*,4*R*)-4-[(4-{[(1*S*)-1-{[(1*S*)-1-{[(1*S*)-4-(carbamoylamino)-1-[(3-{[3-(dimethylamino)propyl]carbamoyl}-4-[({[(4-{6-fluoro-9-oxo-3,10-diazatricyclo[6.4.1.0^{4,13}]trideca-1,4,6,8(13)-tetraen-2-yl}phenyl)methyl](methyl)carbamoyl}oxy)methyl]phenyl)carbamoyl]butyl]carbamoyl}-2-methylpropyl]carbamoyl}-3-[(2,5,8,11,14,17,20,23-octaoxapentacosan-25-yl)carbamoyl]propyl]carbamoyl}butanamido)methyl]cyclohexyl]formamido}propanamido]pentyl]carbamoyl}amino)pentanedioic acid
53.	1.53	 (2*S*)-2-({[(1*S*)-1-carboxy-5-[(2*S*)-3-(naphthalen-2-yl)-2-{[(1*R*,4*R*)-4-[(4-{[(1*S*)-1-{[(1*S*)-1-{[(1*S*)-4-(carbamoylamino)-1-({4-[({[2-(dimethylamino)ethyl]({[(11*S*,12*R*)-7-fluoro-11-(4-fluorophenyl)-12-(1-methyl-1*H*-1,2,4-triazol-5-yl)-4-oxo-2,3,10-triazatricyclo[7.3.1.0^{5,13}]trideca-1,5,7,9(13)-tetraen-3-yl]methyl})carbamoyl}oxy)methyl]phenyl}carbamoyl)butyl]carbamoyl}-2-methylpropyl]carbamoyl}-3-[(2,5,8,11,14,17,20,23-octaoxapentacosan-25-yl)carbamoyl]propyl]carbamoyl}butanamido)methyl]cyclohexyl]formamido}propanamido]pentyl]carbamoyl}amino)pentanedioic acid
54.	1.54	 (2*S*)-2-({[(1*S*)-1-carboxy-5-[(2*S*)-3-(naphthalen-2-yl)-2-{[(1*R*,4*R*)-4-[(4-{[(1*S*)-1-{[(1*S*)-1-{[(1S)-4-(carbamoylamino)-1-[(3-{[2-(dimethylamino)ethyl]carbamoyl}-4-[({[(1*S*)-1-{[(1*S*)-1-{[(3*R*,4*S*,5*S*)-1-[(2*S*)-2-[(1*R*,2*R*)-2-{[(1*S*,2*R*)-1-hydroxy-1-phenylpropan-2-yl]carbamoyl}-1-methoxy-2-methylethyl]pyrrolidin-1-yl]-3-methoxy-5-methyl-1-oxoheptan-4-yl](methyl)carbamoyl}-2-methylpropyl]carbamoyl}-2-methylpropyl](methyl)carbamoyl}oxy)methyl]phenyl)carbamoyl]butyl]carbamoyl}-2-methylpropyl]carbamoyl}-3-({[1-(2,5,8,11,14,17,20,23-octaoxapentacosan-25-yl)-1*H*-1,2,3-triazol-4-yl]methyl}carbamoyl)propyl]carbamoyl}butanamido)methyl]cyclohexyl]formamido}propanamido]pentyl]carbamoyl}amino)pentanedioic acid

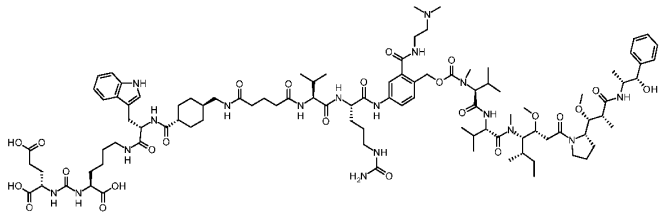
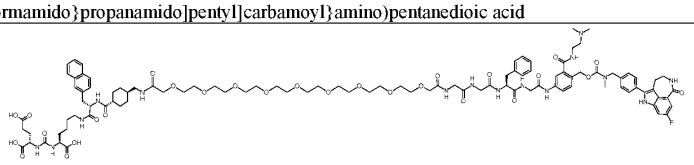
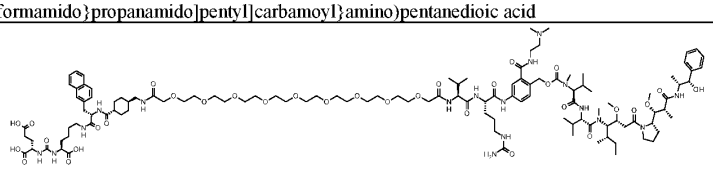
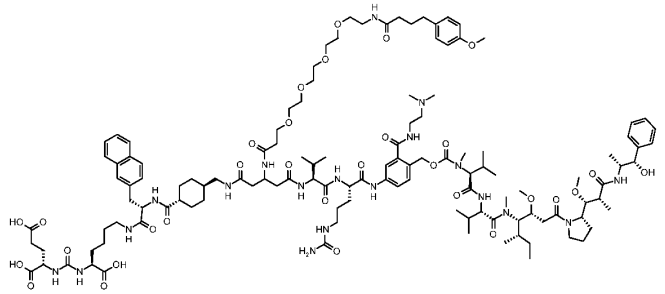
55.	1.55	(2*S*)-2-({[(1*S*)-1-carboxy-5-[(2*S*)-3-(naphthalen-2-yl)-2-{[(1*R*,4*R*)-4-[(4-{[(1*S*)-3-{[(1*S*)-1-{[(1*S*)-4-(carbamoylamino)-1-[(3-{[2-(dimethylamino)ethyl]carbamoyl}-4-[({[(1*S*)-1-{[(1*S*)-1-{[(3*R*,4*S*,5*S*)-1-[(2*S*)-2-[(1*R*,2*R*)-2-{[(1*S*,2*R*)-1-hydroxy-1-phenylpropan-2-yl]carbamoyl}-1-methoxy-2-methylethyl]pyrrolidin-1-yl]-3-methoxy-5-methyl-1-oxoheptan-4-yl](methyl)carbamoyl}-2-methylpropyl]carbamoyl}-2-methylpropyl](methyl)carbamoyl}oxy)methyl]phenyl)carbamoyl]butyl]carbamoyl}-2-methylpropyl]carbamoyl}-1-({[1-(2,5,8,11,14,17,20,23-octaoxapentacosan-25-yl)-1*H*-1,2,3-triazol-4-yl]methyl}carbamoyl)propyl]carbamoyl}butanamido)methyl]cyclohexyl]formamido}propanamido]pentyl]carbamoyl}amino)pentanedioic acid
56.	1.56	(2*S*)-2-({[(1*S*)-1-carboxy-5-[(2*S*)-3-(naphthalen-2-yl)-2-{[(1*R*,4*R*)-4-[(4-{[(1*S*)-3-{[(1*S*)-1-{[(1*S*)-4-(carbamoylamino)-1-[(3-{[3-(dimethylamino)propyl]carbamoyl}-4-[({[(4-{6-fluoro-9-oxo-3,10-diazatricyclo[6.4.1.0^{4,13}]trideca-1,4,6,8(13)-tetraen-2-yl}phenyl)methyl](methyl)carbamoyl}oxy)methyl]phenyl)carbamoyl]butyl]carbamoyl}-2-methylpropyl]carbamoyl}-1-[(2,5,8,11,14,17,20,23-octaoxapentacosan-25-yl)carbamoyl]propyl]carbamoyl}butanamido)methyl]cyclohexyl]formamido}propanamido]pentyl]carbamoyl}amino)pentanedioic acid.
57.	1.57	 (2*S*)-2-({[(1*S*)-1-carboxy-5-[(2*S*)-3-(naphthalen-2-yl)-2-{[(1*R*,4*R*)-4-[(4-{[(1*S*)-1-{[(1*S*)-1-[(3-{[3-(dimethylamino)propyl]carbamoyl}-4-[({[(4-{6-fluoro-9-oxo-3,10-diazatricyclo[6.4.1.0^{4,13}]trideca-1,4,6,8(13)-tetraen-2-yl}phenyl)methyl](methyl)carbamoyl}oxy)methyl]phenyl)carbamoyl]ethyl]carbamoyl}-2-methylpropyl]carbamoyl}-3-[(2,5,8,11,14,17,20,23-octaoxapentacosan-25-yl)carbamoyl]propyl]carbamoyl}butanamido)methyl]cyclohexyl]formamido}propanamido]pentyl]carbamoyl}amino)pentanedioic acid

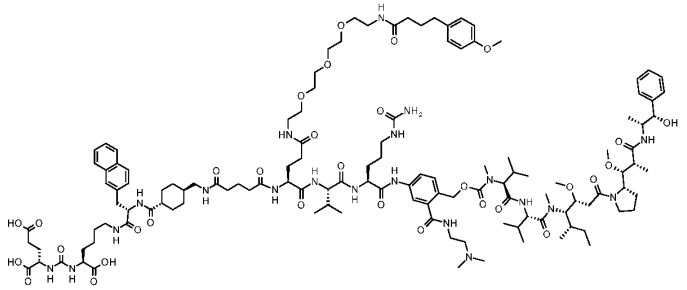
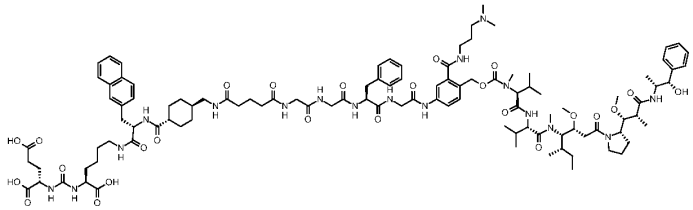
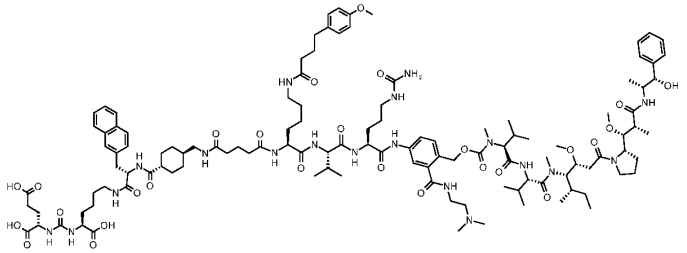
58.	1.58	 (2*S*)-2-({[(1*S*)-1-carboxy-5-[(2*S*)-3-(naphthalen-2-yl)-2-{[(1*R*,4*R*)-4-[(4-{[(1*S*)-3-{[(1*S*)-1-{[(1*S*)-4-(carbamoylamino)-1-[(3-{[2-(dimethylamino)ethyl]carbamoyl}-4-{[({2-[(19*S*)-19-ethyl-19-hydroxy-14,18-dioxo-17-oxa-3,13-diazapentacyclo[11.8.0.0^{2,11}.0^{4,9}.0^{15,20}]henicosa-1(21),2(11),3,5,7,9,15(20)-heptaen-10-yl]ethyl}(propan-2-yl)carbamoyl)oxy]methyl}phenyl)carbamoyl]butyl]carbamoyl}-2-methylpropyl]carbamoyl}-1-[(2,5,8,11,14,17,20,23-octaoxapentacosan-25-yl)carbamoyl]propyl]carbamoyl}butanamido)methyl]cyclohexyl]formamido}propanamido]pentyl]carbamoyl}amino)pentanedioic acid
59.	1.59	 (2*S*)-2-({[(1*S*)-1-carboxy-5-[(2*S*)-3-(naphthalen-2-yl)-2-{[(1*R*,4*R*)-4-[(4-{[(1*S*)-3-{[(1*S*)-1-{[(1*S*)-1-[(4-{[(4*S*,6*S*,7*R*,8*S*)-11-amino-8-[(carbamoyloxy)methyl]-7-methoxy-12-methyl-10,13-dioxo-2,5-diazatetracyclo[7.4.0.0^{2},^{7}.0^{4},^{6}]trideca-1(9),11-diene-5-carbonyloxy]methyl}-3-{[2-(dimethylamino)ethyl]carbamoyl}phenyl)carbamoyl]-4-(carbamoylamino)butyl]carbamoyl}-2-methylpropyl]carbamoyl}-1-[(2,5,8,11,14,17,20,23-octaoxapentacosan-25-yl)carbamoyl]propyl]carbamoyl}butanamido)methyl]cyclohexyl]formamido}propanamido]pentyl]carbamoyl}amino)pentanedioic acid
60.	1.60	 (2*S*)-2-({[(1*S*)-1-carboxy-5-[(2*S*)-3-(naphthalen-2-yl)-2-{[(1*R*,4*R*)-4-[(4-{[(1*S*)-3-{[(1*S*)-1-{[(1*S*)-1-[(3-{[3-(dimethylamino)propyl]carbamoyl}-4-[({[(4-{6-fluoro-9-oxo-3,10-diazatricyclo[6.4.1.0^{4,13}]trideca-1,4,6,8(13)-tetraen-2-yl}phenyl)methyl](methyl)carbamoyl}oxy)methyl]phenyl)carbamoyl]ethyl]carbamoyl}-2-methylpropyl]carbamoyl}-1-[(2,5,8,11,14,17,20,23-octaoxapentacosan-25-yl)carbamoyl]propyl]carbamoyl}butanamido)methyl]cyclohexyl]formamido}propanamido]pentyl]carbamoyl}amino)pentanedioic acid

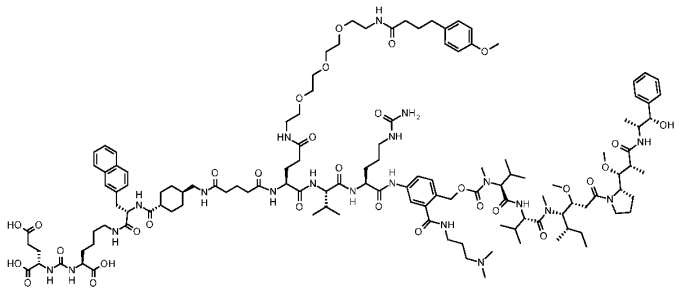
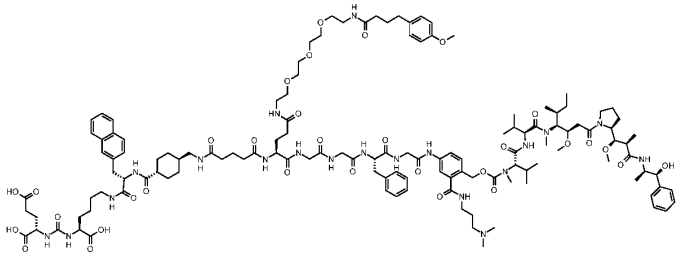
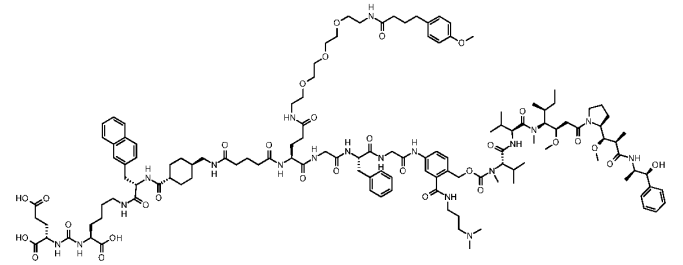
61.	1.61	 (2*S*)-2-({[(1*S*)-1-carboxy-5-[(2*S*)-3-(naphthalen-2-yl)-2-{[(1*R*,4*R*)-4-[(4-{[(1*S*)-1-{[(1*S*)-1-{[(1*S*)-4-(carbamoylamino)-1-({4-[({[(10*S*,23*S*)-10-ethyl-18-fluoro-10-hydroxy-19-methyl-5,9-dioxo-8-oxa-4,15-diazahexacyclo[14.7.1.0^{2},^{14}.0^{4},^{13}.0^{6},^{11}.0^{20},^{24}]tetracosa-1,6(11),12,14,16,18,20(24)-heptaen-23-yl]carbamoyl}oxy)methyl]phenyl}carbamoyl)butyl]carbamoyl}-2-methylpropyl]carbamoyl}-3-[(2,5,8,11,14,17,20,23-octaoxapentacosan-25-yl)carbamoyl]propyl]carbamoyl}butanamido)methyl]cyclohexyl]formamido}propanamido]pentyl]carbamoyl}amino)pentanedioic acid
62.	1.62	 (2S)-2-({[(1S)-1-carboxy-5-[(2S)-3-(naphthalen-2-yl)-2-{[(1r,4r)-4-[(4-{[(1S)-1-{[(1S)-1-{[(1S)-4-(carbamoylamino)-1-[(3-{[2-(dimethylamino)ethyl]carbamoyl}-4-[({[(1S)-1-{[(1S)-1-{[(3R,4S,5S)-1-[(2S)-2-[(1R,2R)-2-{[(1S,2R)-1-hydroxy-1-phenylpropan-2-yl]carbamoyl}-1-methoxy-2-methylethyl]pyrrolidin-1-yl]-3-methoxy-5-methyl-1-oxoheptan-4-yl](methyl)carbamoyl}-2-methylpropyl]carbamoyl}-2-methylpropyl](methyl)carbamoyl}oxy)methyl]phenyl)carbamoyl]butyl]carbamoyl}-2-methylpropyl]carbamoyl}-3-[(2,5,8,11,14,17,20,23-octaoxapentacosan-25-yl)carbamoyl]propyl]carbamoyl}butanamido)methyl]cyclohexyl]formamido}propanamido]pentyl]carbamoyl}amino)pentanedioic acid
63.	1.63	 (2S)-2-({[(1S)-1-carboxy-5-[(2S)-3-(naphthalen-2-yl)-2-{[(1r,4r)-4-{[4-({{[(1S)-1-({[(3-{[2-(dimethylamino)ethyl]carbamoyl}-4-[({[(1S)-1-{[(1S)-1-{[(3R,4S,5S)-1-[(2S)-2-[(1R,2R)-2-{[(1S,2R)-1-hydroxy-1-phenylpropan-2-yl]carbamoyl}-1-methoxy-2-methylethyl]pyrrolidin-1-yl]-3-methoxy-5-methyl-1-oxoheptan-4-yl](methyl)carbamoyl}-2-methylpropyl]carbamoyl}-2-methyl propyl](methyl)carbamoyl}oxy)methyl]phenyl)carbamoyl]methyl}carbamoyl)-2-phenylethyl]carbamoyl}methyl)carbamoyl]methyl}carbamoyl)butanamido]methyl}cyclohexyl]formamido}propanamido]pentyl]carbamoyl}amino)pentanedioic acid

64.	1.64	 (2S)-2-({[(1S)-1-carboxy-5-[(2S)-3-(naphthalen-2-yl)-2-{[(1r,4r)-4-{[4-({[({[(1S)-1-({[(3-{[2-(dimethylamino)ethyl]carbamoyl}-4-[({[(10S,23S)-10-ethyl-18-fluoro-10-hydroxy-19-methyl-5,9-dioxo-8-oxa-4,15-diazahexacyclo [14.7.1.$0^{2,14}$.$0^{4,13}$.$0^{6,11}$.$0^{20,24}$]tetracosa-1,6(11),12,14,16,18,20(24)-heptaen-23-yl]carbamoyl}oxy)methyl]phenyl)carbamoyl]methyl}carbamoyl)-2-phenylethyl] carbamoyl}methyl)carbamoyl]methyl}carbamoyl)butanamido]methyl}cyclohexyl]formamido}propanamido]pentyl]carbamoyl}amino)pentanedioic acid
65.	1.65	 (2S)-2-({[(1S)-1-carboxy-5-[(2S)-3-(naphthalen-2-yl)-2-{[(1r,4r)-4-[(4-{[(1S)-1-{[(1S)-4-(carbamoylamino)-1-[(3-{[2-(dimethylamino)ethyl]carbamoyl}-4-[({[(1S)-1-{[(1S)-1-{[(3R,4S,5S)-1-[(2S)-2-[(1R,2R)-2-{[(1S,2R)-1-hydroxy-1-phenylpropan-2-yl]carbamoyl}-1-methoxy-2-methylethyl]pyrrolidin-1-yl]-3-methoxy-5-methyl-1-oxoheptan-4-yl](methyl)carbamoyl}-2-methylpropyl] carbamoyl}-2-methylpropyl](methyl)carbamoyl}oxy)methyl]phenyl)carbamoyl] butyl]carbamoyl}-2-methylpropyl]carbamoyl}-3-[4-(4-methoxyphenyl) butanamido]butanamido)methyl]cyclohexyl]formamido}propanamido]pentyl]carbamoyl}amino)pentanedioic acid
66.	1.66	 (2S)-2-({[(1S)-1-carboxy-5-[(2S)-3-(naphthalen-2-yl)-2-{[(1r,4r)-4-[(4-{[(1S)-1-{[(1S)-4-(carbamoylamino)-1-[(3-{[(5S)-5-carboxy-5-({[(1S)-1,3-dicarboxy propyl]carbamoyl}amino)pentyl]carbamoyl}-4-[({[(4-{6-fluoro-9-oxo-3,10-diazatricyclo[6.4.1.$0^{4,13}$]trideca-1,4,6,8(13)-tetraen-2-yl}phenyl)methyl](methyl) carbamoyl}oxy)methyl]phenyl)carbamoyl]butyl]carbamoyl}-2-methylpropyl] carbamoyl}butanamido)methyl]cyclohexyl]formamido}propanamido]pentyl]carbamoyl}amino)pentanedioic acid

67.	1.67	 (2S)-2-({[(1S)-1-carboxy-5-[(2S)-3-(naphthalen-2-yl)-2-{[(1r,4r)-4-{[4-({[({[(1S)-1-({[(3-{[2-(dimethylamino)ethyl]carbamoyl}-4-[({[(4-{6-fluoro-9-oxo-3,10-diazatricyclo[6.4.1.0^{4,13}]trideca-1,4,6,8(13)-tetraen-2-yl}phenyl)methyl](methyl)carbamoyl}oxy)methyl]phenyl)carbamoyl]methyl}carbamoyl)-2-phenylethyl]carbamoyl}methyl)carbamoyl]methyl}carbamoyl)butanamido]methyl}cyclohexyl]formamido}propanamido]pentyl]carbamoyl}amino)pentanedioic acid
68.	1.68	 (2S)-2-({[(1S)-1-carboxy-5-[(2R)-3-(naphthalen-2-yl)-2-{[(1r,4r)-4-[(4-{[(1S)-1-{[(1S)-4-(carbamoylamino)-1-[(3-{[2-(dimethylamino)ethyl]carbamoyl}-4-[({[(1S)-1-{[(1S)-1-{[(3R,4S,5S)-1-[(2S)-2-[(1R,2R)-2-{[(1S,2R)-1-hydroxy-1-phenylpropan-2-yl]carbamoyl}-1-methoxy-2-methylethyl]pyrrolidin-1-yl]-3-methoxy-5-methyl-1-oxoheptan-4-yl](methyl)carbamoyl}-2-methylpropyl]carbamoyl}-2-methylpropyl](methyl)carbamoyl}oxy)methyl]phenyl)carbamoyl]butyl]carbamoyl}-2-methylpropyl]carbamoyl}butanamido)methyl]cyclohexyl]formamido}propanamido]pentyl]carbamoyl}amino)pentanedioic acid
69.	1.69	 (2S)-2-({[(1S)-1-carboxy-5-[(2S)-3-(naphthalen-2-yl)-2-{[(1r,4r)-4-[(4-{[(1S)-1-{[(1S)-4-(carbamoylamino)-1-[(3-{[2-(dimethylamino)ethyl]carbamoyl}-4-[({[(10S,23S)-10-ethyl-18-fluoro-10-hydroxy-19-methyl-5,9-dioxo-8-oxa-4,15-diazahexacyclo[14.7.1.0^{2,14}.0^{4,13}.0^{6,11}.0^{20,24}]tetracosa-1,6(11),12,14,16,18,20(24)-heptaen-23-yl]carbamoyl}oxy)methyl]phenyl)carbamoyl]butyl]carbamoyl}-2-methylpropyl]carbamoyl}butanamido)methyl]cyclohexyl]formamido}propanamido]pentyl]carbamoyl}amino)pentanedioic acid
70.	1.70	

		(2S)-2-({[(1S)-1-carboxy-5-[(2S)-3-(naphthalen-2-yl)-2-{[(1r,4r)-4-[(4-{[(1S)-1-{[(1S)-1-[(4-{[(3S)-3-[4-(7-carbamoyl-2H-indazol-2-yl)phenyl]piperidine-1-carbonyloxy]methyl}-3-{[2-(dimethylamino)ethyl]carbamoyl}phenyl) carbamoyl]-4-(carbamoylamino)butyl]carbamoyl}-2-methylpropyl]carbamoyl} butanamido)methyl]cyclohexyl]formamido}propanamido]pentyl]carbamoyl}amino)pentanedioic acid
71.	1.71	 (2S)-2-({[(1S)-1-carboxy-5-[(2S)-3-(1H-indol-3-yl)-2-{[(1r,4r)-4-[(4-{[(1S)-1-{[(1S)-4-(carbamoylamino)-1-[(3-{[2-(dimethylamino)ethyl]carbamoyl}-4-[({[(1S)-1-{[(1S)-1-{[(3R,4S,5S)-1-[(2S)-2-[(1R,2R)-2-{[(1S,2R)-1-hydroxy-1-phenylpropan-2-yl]carbamoyl}-1-methoxy-2-methylethyl]pyrrolidin-1-yl]-3-methoxy-5-methyl-1-oxoheptan-4-yl](methyl)carbamoyl}-2-methylpropyl] carbamoyl}-2-methylpropyl](methyl)carbamoyl}oxy)methyl]phenyl)carbamoyl] butyl]carbamoyl}-2-methylpropyl]carbamoyl}butanamido)methyl]cyclohexyl] formamido}propanamido]pentyl]carbamoyl}amino)pentanedioic acid
72.	1.72	 (2S)-2-({[(1S)-1-carboxy-5-[(2S)-3-(naphthalen-2-yl)-2-{[(1r,4r)-4-{[1-({[({[(1S)-1-({[(3-{[2-(dimethylamino)ethyl]carbamoyl}-4-[({[(4-{6-fluoro-9-oxo-3,10-diazatricyclo[6.4.1.0^{4,13}]trideca-1,4,6,8(13)-tetraen-2-yl}phenyl)methyl](methyl)carbamoyl}oxy)methyl]phenyl)carbamoyl]methyl}carbamoyl)-2-phenylethyl]carbamoyl}methyl)carbamoyl]methyl}carbamoyl)-2,5,8,11,14,17,20,23,26-nonaoxaoctacosan-28-amido]methyl}cyclohexyl] formamido}propanamido]pentyl]carbamoyl}amino)pentanedioic acid
73.	1.73	 (2S)-2-({[(1S)-1-carboxy-5-[(2S)-3-(naphthalen-2-yl)-2-{[(1r,4r)-4-[(1-{[(1S)-1-{[(1S)-4-(carbamoylamino)-1-[(3-{[2-(dimethylamino)ethyl]carbamoyl}-4-[({[(1S)-1-{[(1S)-1-{[(3R,4S,5S)-1-[(2S)-2-[(1R,2R)-2-{[(1S,2R)-1-hydroxy-1-phenylpropan-2-yl]carbamoyl}-1-methoxy-2-methylethyl]pyrrolidin-1-yl]-3-methoxy-5-methyl-1-oxoheptan-4-yl](methyl)carbamoyl}-2-methylpropyl] carbamoyl}-2-methylpropyl](methyl)carbamoyl}oxy)methyl]phenyl)carbamoyl] butyl]carbamoyl}-2-methylpropyl]carbamoyl}-2,5,8,11,14,17,20,23,26-nonaoxaoctacosan-28-amido)methyl]cyclohexyl]formamido}propanamido] pentyl]carbamoyl}amino)pentanedioic acid
74.	1.74	

		(2S)-2-({[(1S)-1-carboxy-5-[(2S)-3-(naphthalen-2-yl)-2-{[(1r,4r)-4-[(4-{[(1S)-1-{[(1S)-4-(carbamoylamino)-1-[(3-{[2-(dimethylamino)ethyl]carbamoyl}-4-[({[(1S)-1-{[(1S)-1-{[(3R,4S,5S)-1-[(2S)-2-[(1R,2R)-2-{[(1S,2R)-1-hydroxy-1-phenylpropan-2-yl]carbamoyl}-1-methoxy-2-methylethyl]pyrrolidin-1-yl]-3-methoxy-5-methyl-1-oxoheptan-4-yl](methyl)carbamoyl}-2-methylpropyl] carbamoyl}-2-methylpropyl](methyl)carbamoyl}oxy)methyl]phenyl)carbamoyl] butyl]carbamoyl}-2-methylpropyl]carbamoyl}-3-{1-[4-(4-methoxyphenyl) butanamido]-3,6,9,12-tetraoxapentadecan-15-amido}butanamido)methyl] cyclohexyl]formamido}propanamido]pentyl]carbamoyl}amino)pentanedioic acid
75.	1.75	 (2S)-2-({[(1S)-1-carboxy-5-[(2S)-3-(naphthalen-2-yl)-2-{[(1r,4r)-4-[(4-{[(1S)-1-{[(1S)-1-{[(1S)-4-(carbamoylamino)-1-[(3-{[2-(dimethylamino)ethyl] carbamoyl}-4-[({[(1S)-1-{[(1S)-1-{[(3R,4S,5S)-1-[(2S)-2-[(1R,2R)-2-{[(1S,2R)-1-hydroxy-1-phenylpropan-2-yl]carbamoyl}-1-methoxy-2-methylethyl] pyrrolidin-1-yl]-3-methoxy-5-methyl-1-oxoheptan-4-yl](methyl)carbamoyl}-2-methylpropyl]carbamoyl}-2-methylpropyl](methyl)carbamoyl}oxy)methyl] phenyl)carbamoyl]butyl]carbamoyl}-2-methylpropyl]carbamoyl}-3-({2-[2-(2-{2-[4-(4-methoxyphenyl)butanamido]ethoxy}ethoxy)ethoxy]ethyl}carbamoyl) propyl]carbamoyl}butanamido)methyl]cyclohexyl]formamido}propanamido]pentyl]carbamoyl}amino)pentanedioic acid
76.	1.76	 (2S)-2-({[(1S)-1-carboxy-5-[(2S)-3-(naphthalen-2-yl)-2-{[(1r,4r)-4-{[4-({[({[(1S)-1-({[(3-{[3-(dimethylamino)propyl]carbamoyl}-4-[({[(1S)-1-{[(1S)-1-{[(3R,4S,5S)-1-[(2S)-2-[(1R,2R)-2-{[(1S,2R)-1-hydroxy-1-phenylpropan-2-yl]carbamoyl}-1-methoxy-2-methylethyl]pyrrolidin-1-yl]-3-methoxy-5-methyl-1-oxoheptan-4-yl](methyl)carbamoyl}-2-methylpropyl]carbamoyl}-2-methyl propyl](methyl)carbamoyl}oxy)methyl]phenyl)carbamoyl]methyl}carbamoyl)-2-phenylethyl]carbamoyl}methyl)carbamoyl]methyl}carbamoyl)butanamido]methyl}cyclohexyl]formamido}propanamido]pentyl]carbamoyl}amino)pentanedioic acid
77.	1.77	 (2S)-2-({[(1S)-1-carboxy-5-[(2S)-3-(naphthalen-2-yl)-2-{[(1r,4r)-4-[(4-{[(1S)-1-{[(1S)-1-{[(1S)-4-(carbamoylamino)-1-[(3-{[2-(dimethylamino)ethyl]carbamoyl} -4-[({[(1S)-1-{[(1S)-1-{[(3R,4S,5S)-1-[(2S)-2-[(1R,2R)-2-{[(1S,2R)-1-hydroxy-1-phenylpropan-2-yl]carbamoyl}-1-methoxy-2-methylethyl]pyrrolidin-1-yl]-3-methoxy-5-methyl-1-oxoheptan-4-yl](methyl)carbamoyl}-2-methylpropyl] carbamoyl}-2-

		methylpropyl](methyl)carbamoyl}oxy)methyl]phenyl)carbamoyl] butyl]carbamoyl}-2-methylpropyl]carbamoyl}-5-[4-(4-methoxyphenyl) butanamido]pentyl]carbamoyl}butanamido)methyl]cyclohexyl]formamido}propanamido]pentyl]carbamoyl}amino)pentanedioic acid
78.	1.78	 (2S)-2-({[(1S)-1-carboxy-5-[(2S)-3-(naphthalen-2-yl)-2-{[(1r,4r)-4-[(4-{[(1S)-1-{[(1S)-1-{[(1S)-4-(carbamoylamino)-1-[(3-{[3-(dimethylamino)propyl] carbamoyl}-4-[({[(1S)-1-{[(1S)-1-{[(3R,4S,5S)-1-[(2S)-2-[(1R,2R)-2-{[(1S,2R)-1-hydroxy-1-phenylpropan-2-yl]carbamoyl}-1-methoxy-2-methylethyl]pyrrolidin -1-yl]-3-methoxy-5-methyl-1-oxoheptan-4-yl](methyl)carbamoyl}-2-methyl propyl]carbamoyl}-2-methylpropyl](methyl)carbamoyl}oxy)methyl]phenyl) carbamoyl]butyl]carbamoyl}-2-methylpropyl]carbamoyl}-3-({2-[2-(2-{2-[4-(4-methoxyphenyl)butanamido]ethoxy}ethoxy)ethoxy]ethyl}carbamoyl)propyl]carbamoyl}butanamido)methyl]cyclohexyl]formamido}propanamido]pentyl]carbamoyl}amino)pentanedioic acid
79.	1.79	 (2S)-2-({[(1S)-1-carboxy-5-[(2S)-3-(naphthalen-2-yl)-2-{[(1r,4r)-4-[(4-{[(1S)-1-({[({[(1S)-1-({[(3-{[3-(dimethylamino)propyl]carbamoyl}-4-[({[(1S)-1-{[(1S)-1-{[(3R,4S,5S)-1-[(2S)-2-[(1R,2R)-2-{[(1S,2R)-1-hydroxy-1-phenylpropan-2-yl]carbamoyl}-1-methoxy-2-methylethyl]pyrrolidin-1-yl]-3-methoxy-5-methyl-1-oxoheptan-4-yl](methyl)carbamoyl}-2-methylpropyl]carbamoyl}-2-methyl propyl](methyl)carbamoyl}oxy)methyl]phenyl)carbamoyl]methyl}carbamoyl)-2-phenylethyl]carbamoyl}methyl)carbamoyl]methyl}carbamoyl)-3-({2-[2-(2-{2-[4-(4-methoxyphenyl)butanamido]ethoxy}ethoxy)ethoxy]ethyl}carbamoyl)propyl] carbamoyl}butanamido)methyl]cyclohexyl]formamido}propanamido]pentyl]carbamoyl}amino)pentanedioic acid
80.	1.80	 (2S)-2-({[(1S)-1-carboxy-5-[(2S)-3-(naphthalen-2-yl)-2-{[(1r,4r)-4-[(4-{[(1S)-1-[({[(1S)-1-({[(3-{[3-(dimethylamino)propyl]carbamoyl}-4-[({[(1S)-1-{[(1S)-1-{[(3R,4S,5S)-1-[(2S)-2-[(1R,2R)-2-{[(1S,2R)-1-hydroxy-1-phenylpropan-2-yl]carbamoyl}-1-methoxy-2-methylethyl]pyrrolidin-1-yl]-3-methoxy-5-methyl-1-oxoheptan-4-yl](methyl)carbamoyl}-2-methylpropyl]carbamoyl}-2-

		methylpropyl](methyl)carbamoyl}oxy)methyl]phenyl)carbamoyl]methyl}carbamoyl)-2-phenylethyl]carbamoyl}methyl)carbamoyl]-3-({2-[2-(2-{2-[4-(4-methoxyphenyl)butanamido]ethoxy}ethoxy)ethoxy]ethyl}carbamoyl)propyl]carbamoyl}butanamido)methyl]cyclohexyl]formamido}propanamido]pentyl]carbamoyl}amino)pentanedioic acid

Method of Treatment

The compounds of the present invention were found to have affinity towards PSMA expressing cells. The capacity of the compounds of present invention to selectively inhibit PSMA expressing cells was studied in PSMA-expressing human prostate cancer (PC3) - PIP as against PSMA-negative PC3 flu cells *in vitro*. The table below (Table 2) shows inhibitory concentration (IC_{50}) that was required to show half-maximal response to inhibit PSMA-expressing PC3 PIP cells and PSMA-negative PC3 flu cells by the compounds of present invention.

Table 2: IC_{50} for cytotoxicity of the compounds against PC3-PIP and PC3 flu cells

Compound No	IC_{50} PC3-PIP cells (nM)	IC_{50} PC3 flu cells (nM)
1.2	70	110
1.4	0.1	69
1.5	0.14	1242
1.7	0.19	30.14
1.8	0.49	73.45
1.10	0.12	35.57
1.14	0.09	90.76
1.15	0.95	176.9
1.16	0.05	16.28
1.18	1.32	81.81
1.19	0.49	108.9
1.20	0.99	108.2

As can be seen from Table 2, the inhibitory concentrations (IC_{50}) of the compounds of present invention against PC3 PIP cells were considerably lower than that against PC3 flu cells. For almost all of the compounds the IC_{50} for PC3 PIP was more than 100 times lower than that for PC3 flu. For some of the compounds, the IC_{50} for PC3 PIP was more than 200 times lower than that for the PC3 flu cells. For Compound no 1.10 and 1.16, the IC_{50} for PC3 PIP was 300 times lower than that for PC3 flu cells. For Compound no 1.4, the IC_{50} for PC3 PIP was 690 times lower than that for PC3 flu. For Compound no 1.5, the IC_{50} for PC3 PIP was 8935 times lower than that for PC3 flu. This indicated that the compounds of the present invention were highly selective towards inhibition of PSMA-expressing cells as compared to that against PSMA-negative cells. Further, the considerably lower values of the IC_{50} for PC3 PIP cells indicate that

the compounds show high cytotoxicity at a very low concentration. Especially Compound no 1.16 showed IC_{50} value of 0.054 nM, indicating very high efficacy. Similarly Compound nos 1.5, 1.7, 1.10 also showed the IC_{50} values less than 0.2 nM indicating potent cytotoxicity against PC3 PIP cells. These studies indicate that the compounds of the present invention are highly selective and effective in the cytotoxicity of the cells expressing PSMA. As such, it is believed that the compounds of the present invention provide an option for the treatment of a disease that is associated with the cells expressing PSMA.

Cell viability assay to evaluate the anti-proliferative effect of NCEs on the growth of LNCaPWT and LNCaP-PSMA-/- cells:

Cell lines were cultured in RPMI-1640 (HiMedia) containing 10% FBS (Gibco) and 100U/ml Penicillin, 0.1mg/ml Streptomycin and 0.25µg/ml Amphoterecin B. The cells were maintained in a humidified environment at 37°C and 5% CO_2.

Cells were seeded at an optimal density in 96-or 384-well plate in RPMI-1640 medium supplemented with 10% FBS. After 24h, the cells were treated with varying concentrations of the compounds or vehicle. The final DMSO concentration was maintained at 0.5%. The treated cells were incubated for 96h post which cell viability was measured using Cell Titer Glo luminescence assay (Promega, USA). Briefly, the plates were equilibrated at room temperature for 30min.75µl/well of Cell Titer Glo was added and the plates were mixed on an orbital shaker for 4 min to induce cell lysis followed by incubation at room temperature for 10 min. The luminescence values were recorded and the cell viability was measured as percentage growth inhibition relative to the vehicle control (0.5% DMSO). IC_{50} for the compounds was calculated using statistical analysis Log (inhibitor) vs % growth inhibition – variable slope (four parameters) using GraphPad Prism software.

Compound No	IC_{50} (µM) LNCap WT cells	IC_{50} (µM) LNCaP-PSMA$^{-/-}$ cells
1.14	0.015	0.37
1.19	0.022	0.49
1.49	0.24	0.59
1.50	1.1	0.97
1.61	0.01	0.11
1.58	0.41	0.76
1.59	0.82	4.7
1.62	0.025	0.52
1.63	0.007	0.42
1.64	0.016	0.39
1.65	0.007	0.32
1.66	>30	>30
1.69	0.054	0.99

1.72	>30	>30
1.78	0.015	0.72
1.75	0.007	0.52
1.76	0.001	0.20

In an aspect of the present invention, there is provided a method of treatment of a disease. According to another aspect, the present invention provides a method of treatment of a disease that is associated with the expression of PSMA. According to a particular aspect, the present invention provides a method of treatment of cancer. According to another particular aspect, the present invention provides a method of treatment of cancer that is associated with the expression of PSMA.

PSMA is a membrane antigen that is expressed in all types of prostate tissues. In prostate cancer tissues the expression is considerably enhanced as compared to the normal tissue. Apart from prostate tissue, PSMA is expressed in other cancer cells such as conventional renal cell, transitional cell of the bladder, testicular-embryonal, neuroendocrine, colon, and breast cancer cells. Specifically PSMA is expressed in the neovasculature of solid tumours. In an embodiment, the present invention provides a method of treatment of all such solid tumours or cancers that are associated with PSMA expressing cells. Non-limiting examples of such cancers include prostate cancer, lung cancer, renal cell cancer, glioblastoma, pancreatic cancer, bladder cancer, breast cancer, colon cancer, oesophageal cancer, stomach cancer head cancer, neck cancer, head and neck cancer, colorectal cancer, leukemia/lymphoma, uterine cancer, skin cancer, endocrine cancer, urinary cancer, gastrointestinal cancer, ovarian cancer, and cervical cancer.

In an embodiment, the present invention also provides a method of treating certain benign lesions occurring in the PSMA expressing tissue cells such as conventional renal cell, transitional cell of the bladder, testicular-embryonal, neuroendocrine, colon, and breast cells.

According to an aspect of the present invention, there is provided a method of treatment of a disease, wherein the method comprises administering to the subject in need thereof a compound of the present invention. In an embodiment, the method comprises administering to the subject a compound of Formula I or pharmaceutically acceptable salt, stereoisomer or isotope thereof. In an embodiment, the method comprises administering to the subject a compound of Formula II or pharmaceutically acceptable salt, stereoisomer or isotope thereof. In an embodiment, the method comprises administering to the subject a compound of Formula III or pharmaceutically acceptable salt, stereoisomer or isotope thereof. In an embodiment, the method comprises administering to the subject a compound of Formula IV or pharmaceutically acceptable salt,

stereoisomer or isotope thereof. In an embodiment, the method comprises administering to the subject a compound of Formula V or pharmaceutically acceptable salt, stereoisomer or isotope thereof. In an embodiment, the method comprises administering to the subject a compound of Formula VI or pharmaceutically acceptable salt, stereoisomer or isotope thereof. In an embodiment, the method comprises administering to the subject a compound of Formula VII or pharmaceutically acceptable salt, stereoisomer or isotope thereof.

It would be appreciated by the skilled person that the method comprises administration of the compound of present invention in a therapeutically effective amount. The therapeutically effective amount would depend on several factors including but not limited to the type and stage of the disease; the gender and age of the subject, the way the compound is administered (e.g. oral, parenteral, subcutaneous), and the composition of the compound.

According to an aspect of the present invention, there is provided a method of treatment of a disease, wherein the method comprises administering to a subject in need thereof a therapeutically effective amount a compound selected from the group consisting of a compound of Formula I, a compound of Formula II, a compound of Formula III, a compound of Formula IV, a compound of Formula V, a compound of Formula VI, a compound of Formula VII or their pharmaceutically acceptable salts, stereoisomers or isotopes.

Pharmaceutical Compositions

Any of the compounds disclosed herein may be formulated into a composition that additionally comprises one or more suitable pharmaceutically acceptable excipients, including carrier and other compounds that facilitate administration of the compound to a subject. The pharmaceutical compositions may be formulated in a conventional manner using one or more pharmaceutically acceptable excipients. Such pharmaceutical compositions and the processes for preparing the same are described, for example, in Remington: The Science and Practice of Pharmacy, the contents of which are incorporated herein by reference in their entirety.

Thus, in one embodiment, the present invention provides a pharmaceutical composition comprising a compound of Formula I, or a pharmaceutically acceptable salt or stereoisomer or isotope thereof, and a pharmaceutically excipient. In one embodiment, the present invention provides a pharmaceutical composition comprising a compound of Formula II, or a pharmaceutically acceptable salt or stereoisomer or isotope thereof, and a pharmaceutically excipient. In one embodiment, the present invention provides a pharmaceutical composition comprising a compound of Formula III, or a pharmaceutically acceptable salt or stereoisomer or isotope thereof, and a pharmaceutically excipient. In one embodiment, the present invention provides a pharmaceutical composition comprising a compound of Formula IV, or a

pharmaceutically acceptable salt or stereoisomer or isotope thereof, and a pharmaceutically excipient. In one embodiment, the present invention provides a pharmaceutical composition comprising a compound of Formula V, or a pharmaceutically acceptable salt or stereoisomer or isotope thereof, and a pharmaceutically excipient. In one embodiment, the present invention provides a pharmaceutical composition comprising a compound of Formula VI, or a pharmaceutically acceptable salt or stereoisomer or isotope thereof, and a pharmaceutically excipient. In one embodiment, the present invention provides a pharmaceutical composition comprising a compound of Formula VII, or a pharmaceutically acceptable salt or stereoisomer or isotope thereof, and a pharmaceutically excipient.

Suitable doses of the compounds for use in treating any of the diseases, disorders and/or conditions described herein can be determined by those skilled in the relevant art. Doses must be sufficient to result in a desired therapeutic benefit without causing unwanted side effects. The mode of administration, dosage forms, and suitable pharmaceutical excipients can also be understood and is within the knowledge of those skilled in the art.

In an embodiment, the present invention provides a method of treatment of cancer that is positive for expression of the PSMA comprising administering a pharmaceutical composition comprising a compound of Formula I, or a pharmaceutically acceptable salt or stereoisomer or isotope thereof, and a pharmaceutically excipient. In an embodiment, the present invention provides a method of treatment of cancer that is positive for expression of the PSMA comprising administering a pharmaceutical composition comprising a compound of Formula II, or a pharmaceutically acceptable salt or stereoisomer or isotope thereof, and a pharmaceutically excipient. In an embodiment, the present invention provides a method of treatment of cancer that is positive for expression of the PSMA comprising administering a pharmaceutical composition comprising a compound of Formula III, or a pharmaceutically acceptable salt or stereoisomer or isotope thereof, and a pharmaceutically excipient. In an embodiment, the present invention provides a method of treatment of cancer that is positive for expression of the PSMA comprising administering a pharmaceutical composition comprising a compound of Formula IV, or a pharmaceutically acceptable salt or stereoisomer or isotope thereof, and a pharmaceutically excipient. In an embodiment, the present invention provides a method of treatment of cancer that is positive for expression of the PSMA comprising administering a pharmaceutical composition comprising a compound of Formula V, or a pharmaceutically acceptable salt or stereoisomer or isotope thereof, and a pharmaceutically excipient. In an embodiment, the present invention provides a method of treatment of cancer that is positive for expression of the PSMA comprising administering a pharmaceutical

composition comprising a compound of Formula VI, or a pharmaceutically acceptable salt or stereoisomer or isotope thereof, and a pharmaceutically excipient. In an embodiment, the present invention provides a method of treatment of cancer that is positive for expression of the PSMA comprising administering a pharmaceutical composition comprising a compound of Formula VII, or a pharmaceutically acceptable salt or stereoisomer or isotope thereof, and a pharmaceutically excipient.

Pharmaceutical composition of the present invention, may be formulated as, for example a tablet, capsule, liquid, gel, syrup, suspension or slurry. The excipients may be selected from those known in the art.

Administration according to the present invention may be performed by the routes known to the skilled person. Non-limiting examples of routes of administration are oral administration, intravenous, intramuscular, intraperitoneal, intrathecal, or subcutaneous injection; intra-rectal administration; intranasal administration, ocular administration, or topical administration.

In an embodiment, there is provided the use of the compounds of present invention for the treatment of cancer that is positive for expression of the PSMA. In another embodiment there is provided the use of compounds of present invention in the preparation of a medicament for use in the treatment of a cancer that is positive for expression of PSMA.

General Method of Preparation

The compounds of the present invention can be prepared by the methods that involve several steps including coupling reactions, protections and de-protections, oxidations, reductions, additions, eliminations and such other reactions, which the skilled person is well aware of. Further these steps may be performed by using known methods, for example as documented in the Richard C. Larock, Comprehensive Organic Transformations; Peter G. M. Wuts, Greene's Protective Groups In Organic Synthesis; George R. Petit. Synthetic peptides; M. Bodanszky, Principles of Peptide Synthesis; James Ralph Hanson, Protecting Groups in Organic Synthesis; Michael B. Smith, March's Advanced Organic Chemistry (2019); E Gross, The Peptides: Analysis, Synthesis, Biology; J. F. W. McOmie, Protective Groups in Organic Chemistry; N. Leo Benoiton, Chemistry of Peptide Synthesis.

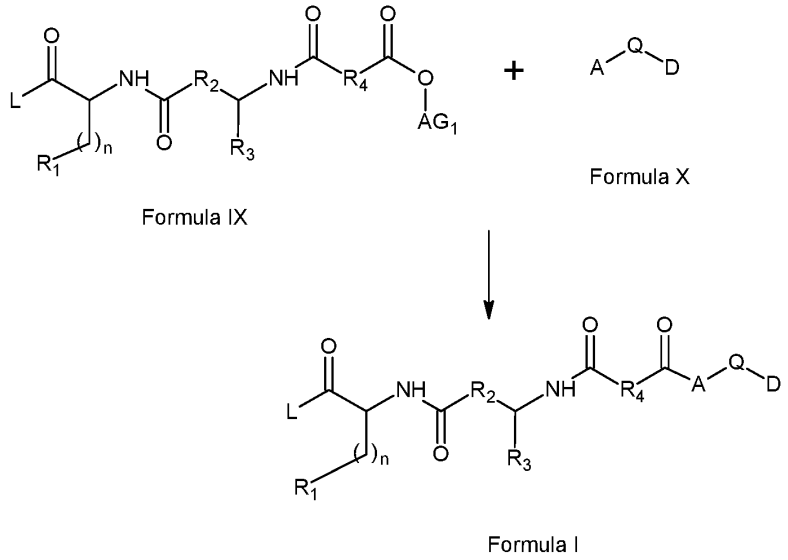
Any variation from the methods reported in above literature would be within the knowledge of the skilled person.

The compounds of the present invention and their intermediates can be separated from the reaction mixture and purified using the methods known in the art. Some of the non-limiting examples of separation methods are filtration, distillation of solvents, liquid-liquid extraction and phase separation or centrifugation and/or decantation. Some of the separation methods may

involve purification steps such as treatment with acids and/or bases or with charcoal. The chiral compounds and their chiral intermediates can be optionally separated by known methods, for example, as described in N. L. Allinger in Topics in Stereochemistry; Ganapathy Subramanian, Chiral Separation Techniques: A Practical Approach, as their enantiomers and/or diastereomers. One possible method of enantiomeric separation is the use of chromatography. The methods of purification of the compounds of the present invention and their intermediates may include acid-base or base-acid treatments, distillation, filtration and solvent treatment, chromatographic purification methods such as column chromatography, preparative chromatography etc. The methods of separation and purification listed above are exemplary and vary depending on the nature of the product to be separated. Such variations are well within the understanding of the skilled person.

One of the methods of preparation of the compounds of present invention is described below. However the modification and diversions from the given methods are well within the knowledge of the skilled person, who can envision that the compounds may be prepared by several other methods with different starting materials, reagents and conditions.

The compound of Formula I can be prepared as per Scheme 1, wherein L, m, R_1, R_2, R_3, R_4, A, Q and D is as defined above.



Scheme 1

AG_1 is an activating group. An "activating group" is a group when reacted with the functional moiety of interest, results in a group that is selectively reactive in certain conditions and stable in other conditions. For example, in Formula IX in Scheme 1, AG_1 is an activating group that

reacts with a –COOH functional moiety and results in an ester like compound. In certain other conditions this ester might remain stable, while when reacting it with the compound of Formula X, it readily forms an amide bond with A. The skilled person is well aware of various activating groups, their selection criteria and their use in the process of preparation of a particular product.

For example, to make a carboxylic group (-COOH) active towards certain reagents, it may be converted into an ester or acid chloride. To prepare such compounds, a carboxylic group is reacted with the pre-cursor of the activating group, wherein the skilled person has knowledge about the selection of the pre-cursors of activating group and the reaction conditions under which such pre-cursors of activating group are converted to activated carboxylic groups. Non-limiting examples of pre-cursor of activating group are N-hydroxysuccinimide, pentafluorophenol or those listed in Vincent Gembus *et al.*, Maciej Adamczyk *et al.* or Yoon-Sik Lee *et al.*

It will be appreciated by the person skilled in the art that under certain conditions the activating group may also act as a protecting group, wherein the functional moiety to which it is attached may not react while the same functional moiety without this particular activating or protecting group might react and get transformed into another functional moiety. The difference between an activating group and protecting group, factors involved in the selection of any one of these groups and the conditions under which such groups are used in the reactions is within the knowledge of the skilled person.

"Protecting group" as the name suggests is a group that is used to mask a functional group, wherein said functional group is at a risk of getting reacted in a particular medium or getting converted to some other form in the series of reactions. The protecting group when removed (de-protection of the functional group) results in the functional moiety or group that was present before protection.

According an embodiment, the present invention relates to compounds that are formed by protection and de-protection of their precursors. In another embodiment the present invention relates to compounds formed by protection and de-protection of the intermediates involved in the preparation of the compounds of the present invention. Such compounds include amino protected intermediates, and carboxyl protected intermediates.

In the present invention, the functional groups that are particularly protected are carboxylic groups and amino groups (both primary and secondary). The suitable protecting groups for different functional moieties can be selected, for example, as given in Peter G. M. Wuts, Greene's Protective Groups in organic synthesis (Fifth edition, 2014), Pathalk *et al.*, Yong-qian Wu *et al*, James Ralph Hanson, Protecting Groups in Organic Synthesis, E Gross, The

Peptides: Analysis, Synthesis, Biology, J. F. W. McOmie, Protective Groups in Organic Chemistry, and N. Leo Benoiton, Chemistry of peptide synthesis.

Examples of protecting groups for hydroxyl groups or carboxylic groups include, but are not limited to, benzyl, *p*-methoxybenzyl (PMB), *tert*-butyl (*t*-Bu), methoxymethyl (MOM), methoxyethoxymethyl (MEM), methylthiomethyl (MTM), tetrahydropyranyl (THP), tetrahydrofuranyl (THF), benzyloxymethyl (BOM), trimethylsilyl (TMS), triethylsilyl (TES), *tert*-butyldimethylsilyl (TBDMS), and triphenylmethyl (trityl, Tr). Similarly, specific examples of protecting groups for amino groups include, but are not limited to, *tert*-butylcarbonyloxy (Boc), fluorenylmethyocycarbonyl (Fmoc), benzyloxycarbonyl (Cbz), allyoxycarbonyl (Alloc), benzyl, p-methoxybenzyl (PMB), triphenylmethyl (trityl, Tr), trifluoroaceatmide, acetyl (Ac), and benzylidene.

As per Scheme 1, a compound of Formula IX and Formula X can be condensed to form a compound of Formula I. The condensation can be carried out by combining both the compounds of Formula IX and Formula X in the presence or absence of, preferably in the presence, of a base, including an organic base, for example, triethyl amine, *N, N*-diisopropylethylamine, *N*-methyl morpholine, and 4-(dimethylamino)piperidine (DMAP) and inorganic bases for example sodium hydrogen carbonate or potassium carbonate. A solvent may be optionally used in the condensation of the compound of Formula IX and Formula X. Non-limiting examples of such solvents are *N,N*-dimethylformamide (DMF), tetrahydrofuran (THF) 1,4-dioxane, dimehyl sulfoxide, acetonitrile, *N,N*-dimethylacetamide. Further, the reaction conditions such as temperature, pressure or time are variable factors that would depend on and would vary with the different definitions of L, m, R_1, R_2, R_3, R_4, AG_1, A, Q and D. The final product can be separated and purified by the methods given above.

According to an embodiment of the present invention, the compound of Formula I is prepared using corresponding precursors of Formula IX and Formula X by reacting them together in the presence of a base selected from *N,N*-diisopropylethylamine or trimethylamine, triethylamine (TEA) and *N,N*-dimethylformamide (DMF).

The compounds of the present invention including the intermediates thereof that may have one or more chiral centres. All the possible chiral isomers (or optical isomers or stereoisomers) formed due to the presence of chiral centre/s in the compounds and their intermediates are well within the scope of the present invention. Such compounds may be prepared as optically active or racemic compounds. The process to prepare either of the two forms (optically active or racemic) is well known in the art. A skilled person can predict all the optical isomers of each compound and can prepare each optical isomer using the known processes. For example, an

optical isomer of compound of Formula I can be prepared by resolution from chiral mixtures, by asymmetric synthesis, or by synthesis from optically active starting materials. Resolution of the racemates can be accomplished, for example, by conventional methods such as crystallization in the presence of a resolving agent, or chromatography using, for example, a chiral HPLC column.

Further, the compounds of the present invention may exhibit geometric isomerism in the presence of olefins, C=N double bonds, and the like. According to an embodiment, the present invention relates to all such isomers, including but not limited to *cis* and *trans* geometric isomers, *E* and *Z* isomers or mixtures of isomers or in the form of zwitter ions. These isomers can be prepared and separated by the methods well known in the art.

The pharmaceutically acceptable salts of the present invention can be synthesized from a parent compound that contains a basic or acidic moiety by conventional chemical methods. Generally, such salts can be prepared by reacting free acid forms of these compounds with a stoichiometric amount of the appropriate base or by reacting free base forms of these compounds with a stoichiometric amount of the appropriate acid. Such reactions are typically carried out in solvents such as water, ether, ethyl acetate, ethanol, isopropanol, acetonitrile, *N,N*-dimethylformamide, dimethyl sulfoxide or in a mixture of one or more of such solvents.

It is within the knowledge of the skilled person to arrive at the intermediates of Formula IX and Formula X. Further, the skilled person will also have understanding about how to arrive at these intermediates with different variables of L, m, R_1, R_2, R_3, R_4, AG_1, A, Q and D. A retrosynthesis of the compound of Formula IX would lead to more than one possible method of preparing it. As can be seen from Figure 1 below, there are several fragments which can be used in different combinations to prepare the compound of IX.

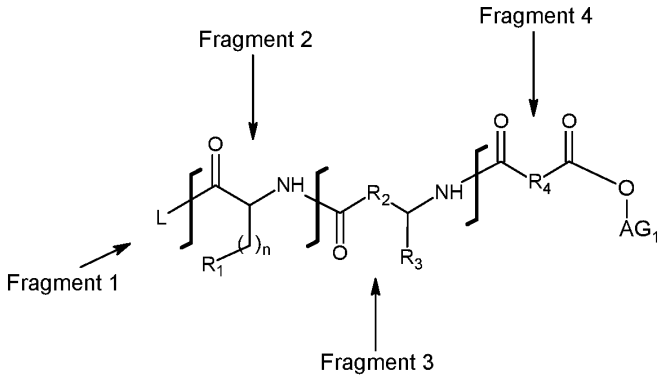
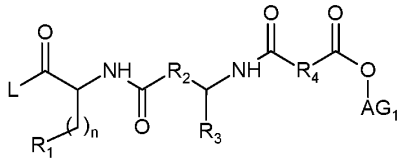


Figure 1

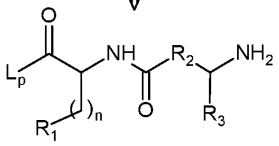
The bond on which the symbol "⌠" is shown indicates it can be formed by condensing or coupling the fragment on its right with the fragment on its left.

It is within the knowledge of the skilled person to select preferred fragments, prepare intermediates and sequentially arrive at the compound of Formula IX.

For example, according to one method the compound of Formula IX can be prepared from the compound of Formula XI (Scheme 2) wherein R_1, R_2 and R_3 are as defined above. L_p is protected L, wherein one or more or sometimes all –COOH in L may be protected as esters.



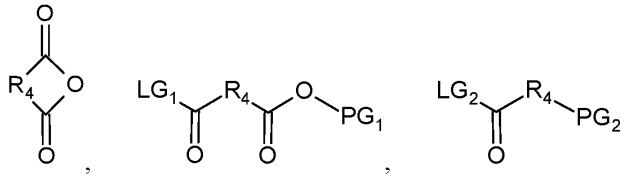
Formula IX



Formula XI

Scheme 2

The compound of Formula IX can be prepared by reacting the compound of Formula XI with the precursor of R_4. For example, the compound of Formula XI can be coupled with a compound selected from:

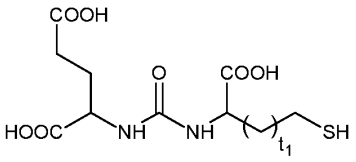


Wherein LG_1 and LG_2 is –OH or a leaving group. It is within the knowledge of the skilled person to appropriately select a leaving group according to the purpose it is required. For example a leaving can be a halogen selected from F, Cl or Br or it can be a group such as *N*-hydroxy succinimide, 1-hydroxybenztriazole (HOBt) or pentafluorophenol.

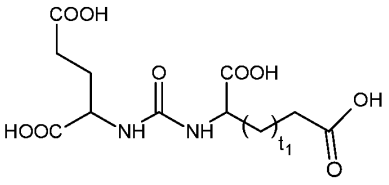
PG_1 and PG_2 are the same or different protecting groups. The skilled person has knowledge and understanding about the conversion of the intermediates formed by reaction between Formula XI and the precursors of R_4 to the compound of Formula IX. This may involve de-

protection by removal of protecting groups and then reacting with an appropriate reagent comprising an activating group. In another method, the protecting groups PG_1 and PG_2 may be directly replaced with AG_1. The de-protection of L_p can be carried out simultaneously or sequentially along with de-protection of PG_1 or PG_2, which would depend on how the skilled person seems it feasible.

The compound of Formula XI can be prepared by the coupling reaction between L_p, Fragment 1 and Fragment 2. Fragment 1 and Fragment 2, prior to coupling together, can be seen as unconventional amino acids and therefore synthesis of compound of Formula XI may be carried out by methods known for peptide synthesis such as those disclosed by N. Leo Benoiton in "Chemistry of Peptide Synthesis" and M. Bodanszky, Principles of peptide synthesis. It will be appreciated by the skilled person that the combination of L_p, Fragment 1 and Fragment 2 may be sequential or may be carried out randomly, wherein Fragment 1 and Fragment 2 can be coupled first and the resulting peptide can be coupled with L_p. Fragment 1 and Fragment 2 can be commercially procured or prepared as per methods known in the art. L_p can be prepared by protection of a compound of Formula L_1, which can be commercially procured or may be prepared as per methods known in the art or that disclosed in Sung-Hyun Moon *et al.* or in Michael Felber *et al.* The compound of Formula L_1, wherein Z is of the Formula Z_1 or Z_2 can be prepared by reacting a compound of Formula L_2 or L_3 with a substituted maleimide or a diamine compounds, respectively.



Formula L_2

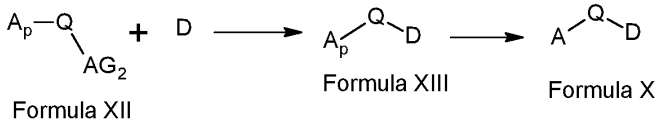


Formula L_3

The choice of the compound of Formula L_2 or L_3 and the maleimide or diamine compounds would depend on the target compound of Formula L_1 which is within the understanding of the skilled person.

The compound of Formula X include A, Q and D. Each A, Q and D is a different moiety that may require independent preparation before combining them together. In some methods, the compound of Formula X may be prepared sequentially from A to D. In some other methods, A or it's precursor may be combined to form an amide with Fragment 4 in Figure 1 and then the compound of Formula I may be built stepwise.

For example, in one method, the compound of Formula X can be prepared as given below (Scheme 3):



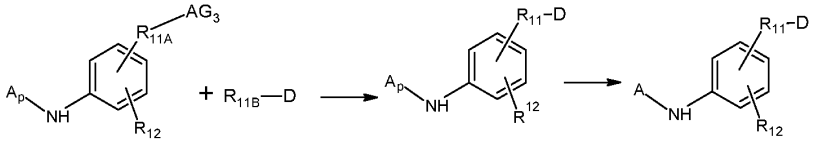
Scheme 3

wherein A_p is protected A and AG_2 is an activating group. The free N terminal of A can be protected as *N*-alkyl or as amide or as carbamates and activating the group with Q may form a carbonate. Reaction between the compounds of Formula XII and D can be carried out for example in the presence of a catalyst such as 1-hydroxybenzotirazole (HOBt) or those given in Yanming Wang *et al.* and Stephen J. Walsh *et al.*, and a base such as *N, N*-disiopropylethyl amine, triethyl amine, or pyridine. The compound of Formula XIII prepared as an intermediate may be de-protected in an acidic or basic medium, preferably in the presence of a catalyst to arrive at the compound of Formula X.

A and Q can be procured commercially or can be prepared as per known methods. Where A is a peptide, it may be prepared by the methods as known in the art or as disclosed by M Bodanszky in "Principles of Peptide Synthesis", N. Leo Benoiton in "Chemistry of Peptide Synthesis" or Deboprosad Mondal *et al.*

For peptides such as of Formula P_1 to P_{12}, the NH_2 may be reacted with the appropriate polyethylene glycol derivative, while protecting other reactive sites. NH_2 may be activated using an activating group prior to such reaction.

In another method, the compound of Formula X can be prepared as per Scheme 4 below:



Scheme 4

where, AG_3 is an activating group which may be same or different from AG_2. R_{11A} is —C_{1-3} alkyl-O-C(O)- and R_{11B} is:

$HN(R_{19})$-C_{1-5} alkyl-$N(R_{19})$-C(O)—*, $HN[C_{1-5}$ alkyl-$N(R_{20}R_{21})]$-C_{1-3} alkyl—*, and Het_2-C_{1-3} alkyl-$N(R_{19})$-C(O)—*, wherein R_{19}, R_{20}, R_{21} and Het_2 is as defined above.

The compounds of the present invention can also include all isotopes of atoms occurring in the intermediates or final compounds. Isotopes include those atoms having the same atomic

number but different mass numbers. For example, isotopes of hydrogen include tritium and deuterium.

Such compounds can be synthesized by means well known in the art, for example by employing starting materials in which one or more hydrogen atoms have been replaced with deuterium. Deuterated analogs may have improved drug metabolism and pharmacokinetics properties, *See*, for example, Allan B. Foster *et al*.

All of the above listed methods are for illustrative purposes. For a more detailed description of the preparation of the compounds of the present invention with detail individual reaction steps, see the Examples section set forth below. Although specific starting materials and reagents are depicted in the Example section, other starting materials and reagents can be easily substituted to provide a variety of derivatives and/or reaction conditions. In addition, many of the compounds prepared by the methods described below can be further modified in light of this disclosure using methods known to those skilled in the art. The examples given below are for illustrative purpose. These examples are non-binding and do not limit or restrict the scope of the invention in any manner.

EXAMPLE

The final products of the present invention were identified using Mass spectroscopy (Make – Waters, Model: Quattro premier, Software: Masslynx V 4.1, SCN80). Preparative HPLC (Make: Shimadzu, Model: Prominence) was used in some examples.

Abbreviations:

EDAC – 1-ethyl-3-(3-dimethylaminopropyl)carbodiimide hydrochloride

EEDQ – *N*-Ethoxycarbonyl-2-ethoxy-1,2-dihydroquinoline

MDC/DCM – Dichromethane

DIPEA – *N,N*-diisopropylethylamine

DMF – *N,N*-dimethylformamide

DMAP – 4-dimethylaminopyridine

HATU – 1-[*bis*(dimethylamino)methylene]-1*H*-1,2,3-triazolo[4,5-b]pyridinium 3-oxide hexafluoro phosphate

HCl – Hydrochloric acid

HOBt – 1-Hydroxybenzotriazole

HPLC – High Performance Liquid Chromatography

NaCl – Sodium chloride

NHS – *N*-Hydroxysuccinimide

RT – Room temperature

TBTU – *O*-(Benzotriazol-1-yl)-*N,N,N',N'*-tetramethyluronium tetrafluoroborate

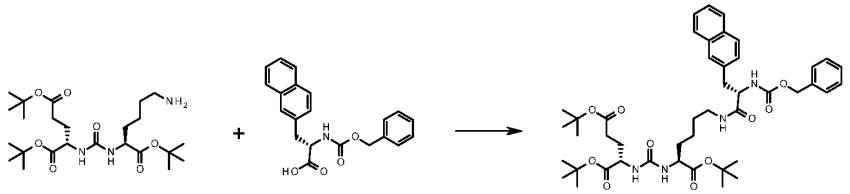
THF – Tetrahydrofuran

TFA – Trifluoroacetic acid

hr/h/hrs – hours

Example 1: Preparation of Compound No 1.4

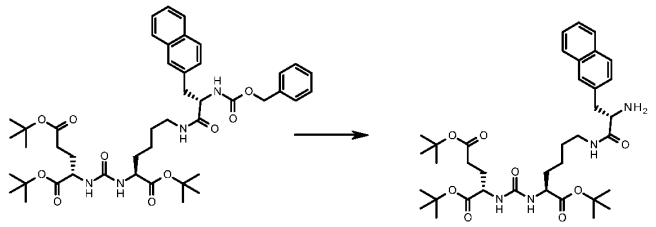
Step I: Preparation of *di-tert*-butyl (2*S*)-2-[[(1*S*)-5-[[(2*S*)-2-(benzyloxycarbonylamino)-3-(2-naphthyl)propanoyl]amino]-1-*tert*-butoxycarbonyl-pentyl]carbamoylamino] pentanedioate (Formula 1c).



Formula 1a Formula 1b Formula 1c

TBTU (1.98 g, 6.2 mmol) and DIPEA (2.2 mL, 12.9 mmol) were added to a stirred solution of the compound of Formula 1a (2.76 g, 5.7 mmol) and the compound of Formula 1b (1.8 g, 5.2 mmol) in DMF (25 mL) at RT and stirred overnight. The reaction mixture was concentrated under reduced pressure at 50°C, the crude product obtained was purified by column chromatography (silica gel 230-400 mesh, DCM:methanol, 97:3) to get the compound of Formula 1c.

Step II: Preparation of *di-tert*-butyl (2*S*)-2-[[(1*S*)-5-[[(2*S*)-2-amino-3-(2-naphthyl) propanoyl]amino]-1-*tert*-butoxycarbonyl-pentyl]carbamoylamino]pentanedioate (Formula 1d).

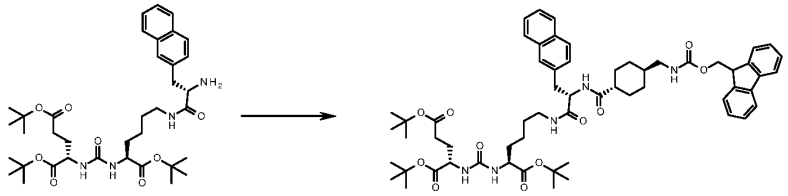


Formula 1c Formula 1d

To a stirred solution of the compound of Formula 1c (4.7 g, 5.7 mmol) in methanol (50 mL) was added 10% Palladium on charcoal (50% wet) (0.5 g). The mixture was stirred under hydrogen pressure at RT for 6 hours. The reaction mixture was filtered through Celite® bed and washed with methanol (2x50 mL). The combined filtrate was concentrated under reduced

pressure to get the compound of Formula 1d, which was used for the next step without purification.

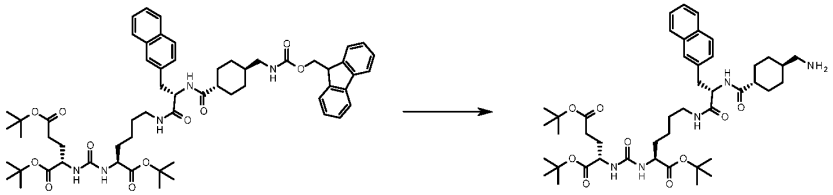
Step III: Preparation of *di-tert*-butyl (2*S*)-2-[[(1*S*)-1-*tert*-butoxycarbonyl-5-[[(2*S*)-2-[[4-[(9*H*-fluoren-9-ylmethoxycarbonylamino)methyl]cyclohexanecarbonyl] amino]-3-(2-naphthyl)propanoyl]amino]pentyl]carbamoylamino]pentanedioate (Formula 1e).



Formula 1d Formula 1e

TBTU (2.16 g, 6.7 mmol) and DIPEA (2.3 mL, 12.9 mmol) were added to a stirred solution of the compound of Formula 1d (3.55 g, 5.2 mmol) and 4-[(9*H*-fluoren-9-ylmethoxycarbonylamino)methyl]cyclohexanecarboxylic acid (2.55 g, 6.7 mmol) in DMF (35 mL) at RT and stirred overnight. The reaction mixture was concentrated under reduced pressure at 50°C. Water (150 mL) was added to the residue and the resulting mixture was stirred at 55°C for 1 hr. The product obtained was filtered, washed with water and dried. Dissolved the dried product in a mixture of MDC & methanol, concentrated and dried under reduced pressure at 50°C to get the compound of Formula 1e.

Step IV: Preparation of *di-tert*-butyl (2*S*)-2-[[(1*S*)-5-[[(2*S*)-2-[[4-(aminomethyl) cyclohexanecarbonyl]amino]-3-(2-naphthyl)propanoyl]amino]-1-*tert*-butoxycarbonyl-pentyl]carbamoylamino]pentanedioate (Formula 1f).

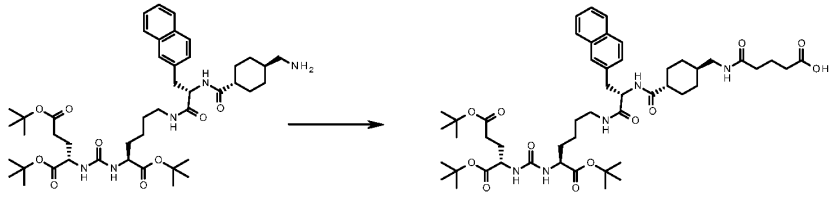


Formula 1e Formula 1f

Piperidine (2.5 mL, 43.0 mmol) was added to a stirred solution of the compound of Formula 1e (9.0 g, 8.6 mmol) in DMF (90 mL) and stirred at RT for 1 hr. The reaction mixture was concentrated under reduced pressure at 50°C. Diethyl ether (10 mL) was added to the residue and stirred at RT for 30 min. The product obtained was filtered, washed with diethyl ether (2x10 mL) and dried under vacuum to get crude product which was purified by column

chromatography (silica gel 230-400 mesh; DCM:methanol:aqueous ammonia, 83:15:2) to get the compound of Formula 1f.

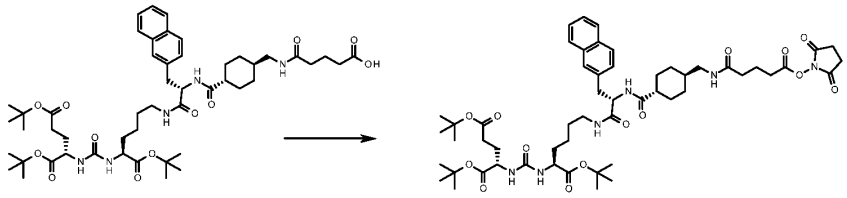
Step V: Preparation of 5-[[4-[[(1*S*)-2-[[(5*S*)-6-*tert*-butoxy-5-[[(1*S*)-4-*tert*-butoxy-1-*tert*-butoxycarbonyl-4-oxo-butyl]carbamoylamino]-6-oxo-hexyl]amino]-1-(2-naphthyl methyl)-2-oxo-ethyl]carbamoyl]cyclohexyl]methylamino]-5-oxo-pentanoic acid (Formula 1g).



Formula 1f Formula 1g

DIPEA (0.32 mL, 1.8 mmol) was added to a stirred solution of the compound of Formula 1f (1.0 g, 1.2 mmol) and glutaric anhydride (0.17 g, 1.5 mmol) in acetonitrile (10 mL) under nitrogen atmosphere and then stirred overnight at RT. The reaction mixture was concentrated under reduced pressure at 40°C. Water (10 mL) was added to the residue and the resulting mixture was acidified with an aqueous citric acid solution (20% solution). The mixture was then extracted with ethyl acetate (3x30 mL). Combined organic layers were washed with brine solution and dried over anhydrous sodium sulphate. Removal of ethyl acetate under reduced pressure gave the compound of Formula 1g which was used for the next step without purification.

Step VI: Preparation of *di-tert*-butyl (2*S*)-2-[[(1*S*)-1-*tert*-butoxycarbonyl-5-[[(2*S*)-2-[[4-[[[5-(2,5-dioxopyrrolidin-1-yl)oxy-5-oxo-pentanoyl]amino]methyl] cyclohexanecarbonyl] amino]-3-(2-naphthyl)propanoyl]amino]pentyl]carbamoyl-amino]pentanedioate (Formula 1h).

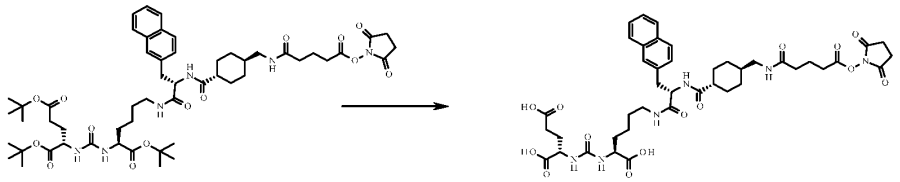


Formula 1g Formula 1h

NHS (0.23 g, 1.8 mmol) and EDAC (0.38 g, 1.8 mmol) were added sequentially to a stirred solution of the compound of Formula 1g (1.0 g, 1.1 mmol) in DMF (10 mL) at RT and stirred overnight. The reaction mixture was quenched in water (10 mL) and extracted with ethyl acetate (3x20 mL). The combined organic layers were washed with a brine, dried over

anhydrous sodium sulphate and concentrated under reduced pressure at 40°C to get the compound of Formula 1h.

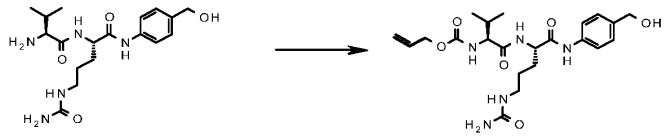
Step VII : Preparation of (2*S*)-2-[[(1*S*)-1-carboxy-5-[[(2*S*)-2-[[4-[[[5-(2,5-dioxopyrrolidin-1-yl)oxy-5-oxo-pentanoyl]amino]methyl]cyclohexanecarbonyl] amino]-3-(2-naphthyl) propanoyl]amino]pentyl]carbamoylamino]pentanedioic acid (Formula 1i).



Formula 1h Formula 1i

TFA (5.5 mL) was added to a stirred solution of the compound of Formula 1h (0.55 g, 0.53 mmol) in DCM (5.5 mL) at 0-5°C. The reaction mixture was then stirred at RT for 6 hrs. After this time, the reaction mixture was concentrated and degassed under reduced pressure at 30°C. The crude product was leached with diethyl ether (2x2 ml). The diethyl ether layer was decanted off and dried to get the compound of Formula 1i.

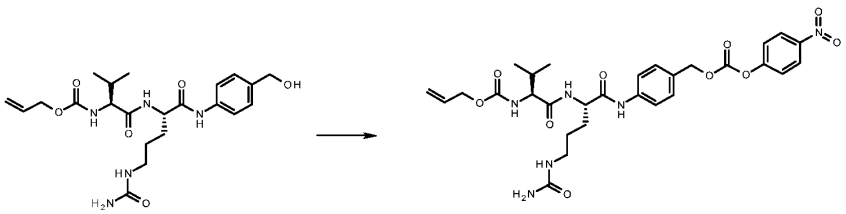
Step VIII: Preparation of {(*S*)-1-[(*S*)-1-(4-hydroxymethyl phenylcarbamoyl)-4-ureido butylcarbamoyl]-2-methyl propyl}carbamic acid allyl ester (Formula 1k).



Formula 1j Formula 1k

DIPEA (1.43 mL, 11 mmol) was added to a stirred solution of the compound of Formula 1j (2.1 g, 5 mmol) in mixture of THF (21 mL) and DMF (5 mL). The reaction mixture was cooled to 0-5°C and allyl chloroformate (0.62 mL, 5.8 mmol) was added dropwise, and the resulting mixture was stirred at 0-5°C for 1 hr. The mixture was concentrated under reduced pressure at 40°C, water (20 mL) was added to the residue and extracted with ethyl acetate (3x50mL). The combined extracts were washed with water (1x30 mL), followed by a brine, dried over anhydrous sodium sulphate and concentrated under reduced pressure at 50°C to get the crude product, which was purified by column chromatography (silica gel 230-400 mesh; DCM:methanol, 93:7) to get the compound of Formula 1k.

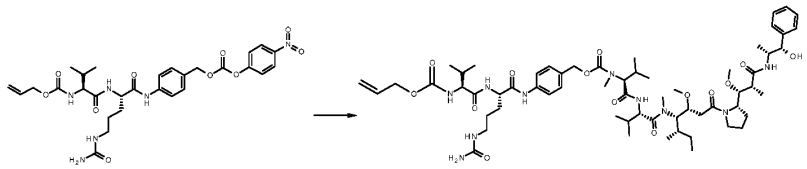
Step IX: Preparation of carbonic acid 4-[(*S*)-2-((*S*)-2-allyloxycarbonylamino-3-methyl butyrylamino)-5-ureido-pentanoylamino]benzyl 4-nitro phenyl ester (Formula 1l).



Formula 1k Formula 1l

DIPEA (0.45 mL, 2.5 mmol) was added to a stirred solution of the compound of Formula 1k (0.6 g, 1.2 mmol) in DMF (6 mL) at RT. *Bis*(4-nitrophenyl)carbonate (0.6 g, 1.9 mmol) was added to the reaction mixture, and the resulting mixture was stirred for 3 hrs. The reaction mixture was concentrated under reduced pressure at 55°C. Diethyl ether (5 mL) was added to the residue and leached and dried to get the crude product, which was purified by column chromatography (silica gel 230-400 mesh, DCM:methanol, 93:7) to get the compound of Formula 1l (0.6 g).

Step X : Preparation of [4-[[(2*S*)-2-[[(2*S*)-2-(allyloxycarbonylamino)-3-methyl-butanoyl]amino]-5-ureido-pentanoyl]amino]phenyl]methyl *N*-[(1*S*)-1-[[(1*S*)-1-[[(1*S*,2*R*)-4-[(2*S*)-2-[(1*R*,2*R*)-3-[[(1*R*,2*S*)-2-hydroxy-1-methyl-2-phenyl-ethyl]amino]-1-methoxy-2-methyl-3-oxo-propyl]pyrrolidin-1-yl]-2-methoxy-1-[(1*S*)-1-methylpropyl]-4-oxo-butyl]-methyl-carbamoyl]-2-methyl-propyl]carbamoyl]-2-methyl-propyl]-*N*-methyl-carbamate (Formula 1m)

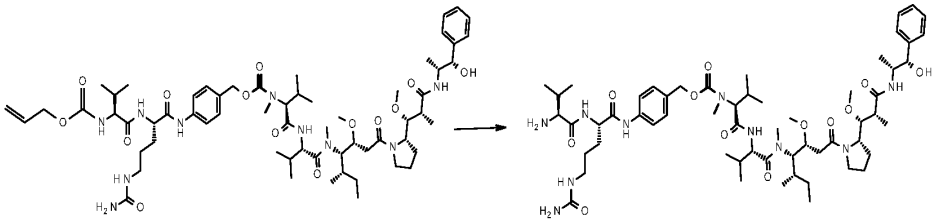


Formula 1l Formula 1m

HOBt (57 mg, catalytic amount) and DIPEA (0.28 mL, 1.5 mmol) were sequentially added to a stirred solution of the compound of Formula 1l (0.5 g, 0.8 mmol) and monomethyl auristatin E (0.57 g, 0.8 mmol) in DMF (5 mL) at RT and stirred for 30 hrs. The mixture was concentrated under reduced pressure at 55°C. The crude material obtained was purified by column chromatography (silica gel 230-400 mesh; DCM:methanol, 90:10) to get the compound of Formula 1m.

Step XI : Preparation of [4-[[(2*S*)-2-[[(2*S*)-2-amino-3-methyl-butanoyl]amino]-5-ureido-pentanoyl]amino]phenyl]methyl *N*-[(1*S*)-1-[[(1*S*)-1-[[(1*S*,2*R*)-4-[(2*S*)-2-[(1*R*,2*R*)-3-[[(1*R*,2*S*)-2-hydroxy-1-methyl-2-phenyl-ethyl]amino]-1-methoxy-2-methyl-3-oxo-propyl]pyrrolidin-1-

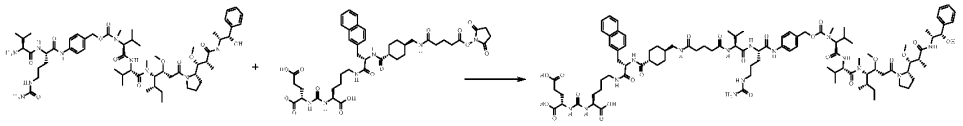
yl]-2-methoxy-1-[(1*S*)-1-methylpropyl]-4-oxo-butyl]-methyl-carbamoyl]-2-methyl-propyl]carbamoyl]-2-methyl-propyl]-*N*-methyl-carbamate (Formula 1n)



Formula 1m Formula 1n

Palladium tetrakis(triphenylphosphine) (0.065 g, 0.06 mmol) was added to a stirred solution of the compound of Formula 1m (0.9 g, 0.74 mmol) in mixture of DCM (6.3 mL) and methanol (2.7 mL) at RT. Morpholine (0.45 mL, 5.2 mmol) was added to the mixture, and the mixture was stirred for 1.5 hr. The reaction mixture was concentrated under reduced pressure at 35°C. The crude material obtained was purified by column chromatography (silica gel 230-400 mesh; DCM:methanol, 90:10) to get the compound of Formula 1n.

Step XII: Preparation of Compound No 1.4



Formula 1n Formula 1i Compound no 1.4 DIPEA (0.096 mL, 0.55 mmol) was added to a stirred solution of the compound of Formula 1n (0.076 g, 0.14 mmol) in DMF (1.25 mL), followed by compound of Formula 1i (0.125 g, 0.11 mmol), and stirred at RT for 24 hrs. The reaction mixture was concentrated and degassed under reduced pressure at 50°C. DCM (5 mL) was added to the resulting residue and stirred for 30 min. The solid obtained was filtered, washed with DCM (3x5 mL) and dried under vacuum. The crude product (0.135 g) obtained was purified by preparative HPLC to get Compound 1.4.

Table 3 set forth below provides mass spectral data for the compounds of the instant invention. The compounds for which data is provided below but for which a description of the synthesis is not explicitly provided above were made in an analogous manner to the synthetic procedures provided above in Example 1.

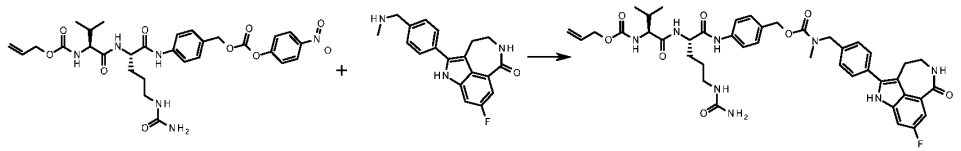
Table 3:

Compound No	Mass (m/z) $[M+H]^+$
1.4	1875.42
1.5	1788.82

1.7	1861.55
1.10	1864.76
1.11	1877.06
1.12	1825.56
1.14	1988.95
1.15	1933.17
1.17	1870.11
1.18	1977.34
1.19	2003.17
1.20	2077.14
1.35	2001.52
1.41	2030.23
1.66	913.81 $[M+2H]^{2+}$
1.68	995.48 $[M+2H]^{2+}$
1.69	1708.17 $[M+H]^{+}$
1.70	1592.0 $[M+H]^{+}$
1.71	1976.4 $[M+H]^{+}$

Example 2: Preparation of Compound No 1.6

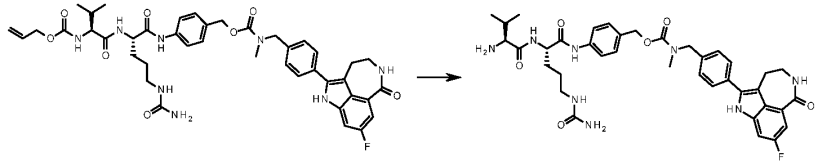
Step I: Preparation of {4-[(2*S*)-5-(carbamoylamino)-2-[(2*S*)-3-methyl-2-{[(prop-2-en-1-yloxy)carbonyl] amino}butanamido]pentanamido]phenyl}methyl *N*-[(4-{6-fluoro-9-oxo-3,10-diazatricyclo[6.4.1.0^{4,13}]trideca-1,4,6,8(13)-tetraen-2-yl}phenyl)methyl]-*N*-methyl carbamate (Formula 2a)



Formula 11 Formula 2a

DIPEA (0.22 mL, 1.3 mmol) was added to a stirred solution of the compound of Formula 11 (0.4 g, 0.64 mmol) and Rucaparib (0.21 g, 0.64 mmol) in DMF (5 mL) at RT, and the mixture was stirred for 2 hrs. The reaction mixture was concentrated under reduced pressure at 55°C. The crude material obtained was purified by column chromatography (silica gel 230-400 mesh; DCM:methanol, 90:10) to get the compound of Formula 2a.

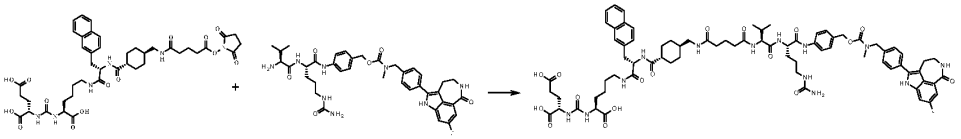
Step II: Preparation of {4-[(2*S*)-2-[(2*S*)-2-amino-3-methylbutanamido]-5-(carbamoylamino) pentanamido]phenyl}methyl *N*-[(4-{6-fluoro-9-oxo-3,10-diazatricyclo [6.4.1.0^{4,13}]trideca-1,4,6,8(13)-tetraen-2-yl}phenyl)methyl]-*N*-methylcarbamate (Formula 2b)



Formula 2a Formula 2b

Palladium tetrakis(triphenylphosphine) (0.04 g, 0.035 mmol) was added to a stirred solution of the compound of Formula 2a (0.38 g, 0.47 mmol) in a mixture of DCM (2.6 mL) and methanol (1.2 mL) at RT. Morpholine (0.3 mL, 3.5 mmol) was added to the reaction mixture, and the mixture was stirred for 4 hrs. The reaction mixture was then concentrated under reduced pressure at 35°C. The crude material obtained was purified by column chromatography (silica gel 230-400 mesh; DCM: methanol: aqueous ammonia, 83.5:15:1.5) to get the compound of Formula 2b (0.3 g).

Step III: Preparation of (Compound No 1.6).

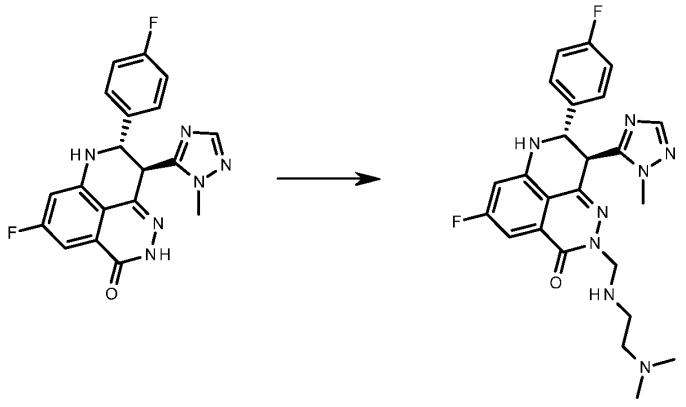


Formula 1i Formula 2b Compound No 1.6

The compound of Formula 2b (0.1 g, 0.11 mmol) was added to a stirred solution the compound of Formula 1i (0.08 g, 0.15 mmol) and triethylamine (0.16 mL, 1.13 mmol) in DMF (2 mL) at RT and the mixure was stirred for 4 hrs. Additionally the compound of Formula 1i (0.23 g, 0.27 mmol) was added to the reaction mixture, and the resulting mixture was stirred for 4 hrs more. The reaction mixture was concentrated and degassed under reduced pressure at 50°C. DCM (5 mL) was added to the residue and the mixture was stirred at RT for 30 min. The product obtained was filtered, washed with DCM (3x5 mL) and dried under vacuum. The crude product (0.15 g) obtained was purified by preparative HPLC to get Compound No 1.6 (0.025 g). Mass (m/z) 1481.02 $[M+H]^+$.

Example 3: Preparation of Compound No 1.13

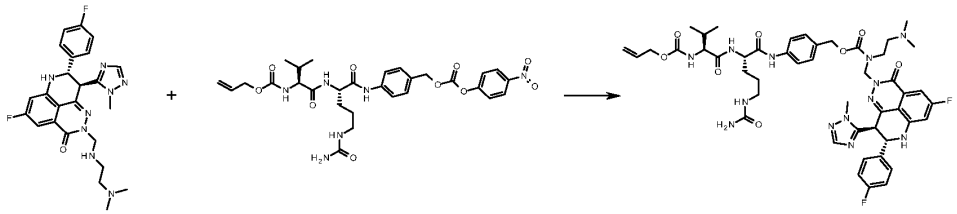
Step I : Preparation of (11*S*,12*R*)-3-({[2-(dimethylamino)ethyl]amino}methyl)-7-fluoro-11-(4-fluorophenyl)-12-(1-methyl-1*H*-1,2,4-triazol-5-yl)-2,3,10-triazatricyclo[7.3.1.$0^{5,13}$] trideca-1,5,7,9(13)-tetraen-4-one (Formula 3a).



Formula 3a

N,N-Dimethylethylenediamine (1.7 mL, 15.8 mmol) was added to a stirred solution of talazoparib (0.5 g, 1.3 mmol) and formaldehyde solution (37% aqueous solution, 0.75 mL, 10.5 mmol) in ethanol (5 mL) at RT, and the mixture was further stirred in a sealed tube. The mixture was then heated in the sealed tube at 80°C for 5 hrs. After 5 hrs the reaction mixture was concentrated and degassed under reduced pressure at 80°C. n-Hexane (10 mL) was added to the residue, and the resulting mixture was stirred at RT for 30 min. The product obtained was filtered, washed with n-hexane and dried to get the compound of Formula 3a (0.5 g), which was used for the next step without further purification.

Step II: Preparation of {4-[(2*S*)-5-(carbamoylamino)-2-[(2*S*)-3-methyl-2-{[(prop-2-en-1-yloxy)carbonyl] amino}butanamido]pentanamido]phenyl}methyl *N*-[2-(dimethylamino) ethyl]-*N*-{[(11*S*,12*R*)-7-fluoro-11-(4-fluorophenyl)-12-(1-methyl-1*H*-1,2,4-triazol-5-yl)-4-oxo-2,3,10-triazatricyclo[7.3.1.$0^{5,13}$]trideca-1,5,7,9(13)-tetraen-3-yl]methyl}carbamate (Formula 3b).

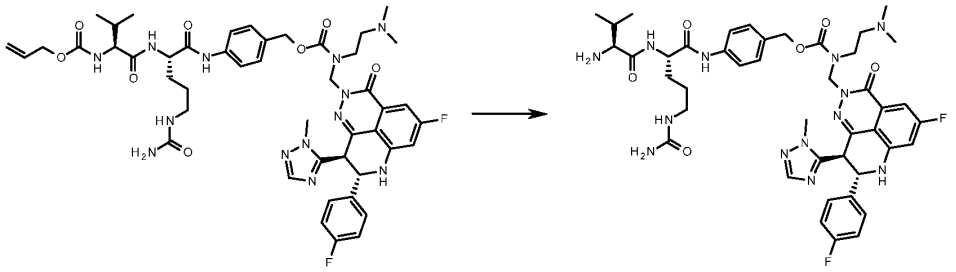


Formula 3a Formula 1l Formula 3b

HOBt (35 mg, catalytic amount) followed by DIPEA (0.25 mL, 1.7 mmol) was added to a stirred solution of the compound of Formula 1l (0.35 g, 0.56 mmol) and the compound of Formula 3a (0.35 g, 0.73 mmol) in DMF (5 mL) at RT. The mixture was stirred for 30 hrs and then concentrated under reduced pressure at 55°C. The crude material obtained was purified by

column chromatography (silica gel 230-400 mesh; DCM:methanol:aq ammonia, 87.4:12:0.6) to get the compound of Formula 3b (0.27 g).

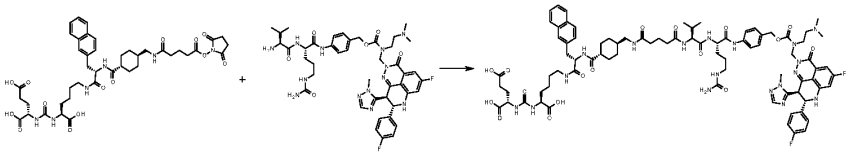
Step III : Preparation of {4-[(2*S*)-2-[(2*S*)-2-amino-3-methylbutanamido]-5-(carbamoylamino)pentanamido]phenyl}methyl *N*-[2-(dimethylamino)ethyl]-*N*-{[(11*S*,12*R*)-7-fluoro-11-(4-fluorophenyl)-12-(1-methyl-1*H*-1,2,4-triazol-5-yl)-4-oxo-2,3,10-triazatricyclo[7.3.1.0^{5},^{13}]trideca-1,5,7,9(13)-tetraen-3-yl]methyl}carbamate (Formula 3c)



Formula 3b Formula 3c

Palladium tetrakis(triphenylphosphine) (0.024 g, 0.021 mmol) was added to a stirred solution of the compound of Formula 3b (0.27 g, 0.28 mmol) in a mixture of DCM (1.9 mL) and methanol (0.8 mL) at RT. Morpholine (0.18 mL, 2.1 mmol) was added to the reaction mixture, and the mixture was stirred for 4 hrs. The reaction mixture was concentrated under reduced pressure at 35°C. The crude material obtained was purified by column chromatography (silica gel 230-400 mesh; DCM: methanol: aqueous ammonia, 84:15:1) to get the compound of Formula 3c.

Step IV : Preparation of (2*S*)-2-({[(1*S*)-1-carboxy-5-[(2*S*)-3-(naphthalen-2-yl)-2-{[(1*R*,4*R*)-4-[(4-{[(1*S*)-1-{[(1*S*)-4-(carbamoylamino)-1-({4-[({[2-(dimethyl amino)ethyl]({[(11*S*,12*R*)-7-fluoro-11-(4-fluorophenyl)-12-(1-methyl-1*H*-1,2,4-triazol-5-yl)-4-oxo-2,3,10-triazatricyclo[7.3.1.0^{5},^{13}]trideca-1,5,7,9(13)-tetraen-3-yl]methyl})carbamoyl}oxy)methyl]phenyl}carbamoyl)butyl] carbamoyl}-2-methylpropyl]carbamoyl}butanamido)methyl]cyclohexyl]formamido}propanamido]pentyl]carbamoyl}amino)pentanedioic acid.

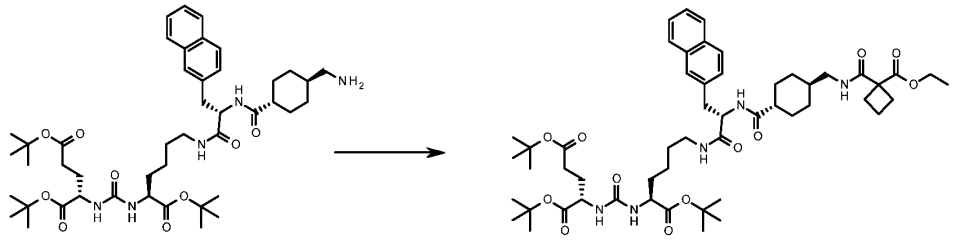


Formula 1i Formula 3c Compound No 1.13

The compound of Formula 3c (0.1 g, 0.11 mmol) was added to a stirred solution of the compound of Formula 1i (0.19 g, 0.22 mmol) and triethylamine (0.16 mL, 1.13 mmol) in DMF (2 mL) at RT, and the resulting mixture was stirred for 4 hrs. An additional amount of the compound of Formula 1i (0.04 g, 0.075 mmol) was added to the reaction mixture, and the mixture was stirred for further 4 hrs. The reaction mixture was then concentrated and degassed under reduced pressure at 50°C. DCM (5 mL) was added to the residue and the mixture was stirred at RT for 30 min. The solid obtained was filtered, washed with DCM (3x5 mL) and dried under vacuum. The crude product was purified by preparative HPLC to get Compound No 1.13. Mass (m/z) - 1637.3$[M+H]^+$.

Example 4: Preparation of Compound no 1.8

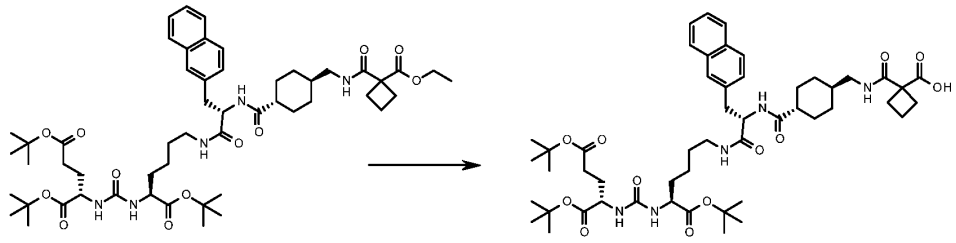
Step I: Preparation of *di-tert*-butyl (2*S*)-2-[[(1*S*)-1-*tert*-butoxycarbonyl-5-[[(2*S*)-2-[[4-[[(1-ethoxy carbonylcyclobutanecarbonyl)amino]methyl]cyclohexanecarbo-nyl]amino]-3-(2-naphthyl)propanoyl]amino]pentyl]carbamoylamino] pentanedioate (Formula 4a).



Formula 1f Formula 4a

EEDQ (0.18 g, 0.73 mmol) was added to a stirred solution of the compound of Formula 1f (0.4 g, 0.48 mmol) and 1-ethoxycarbonylcyclobutanecarboxylic acid (0.093 g, 0.53 mmol) in a mixture of DCM (4 mL) and methanol (2 mL). The mixture was stirred overnight at RT then concentrated at 40°C under reduced pressure. Diethyl ether (10 mL) was added to the crude product and the resulting mixture was stirred at RT for 30 min. The solid obtained was filtered, washed with diethyl ether and dried under reduced pressure to get the compound of Formula 4a.

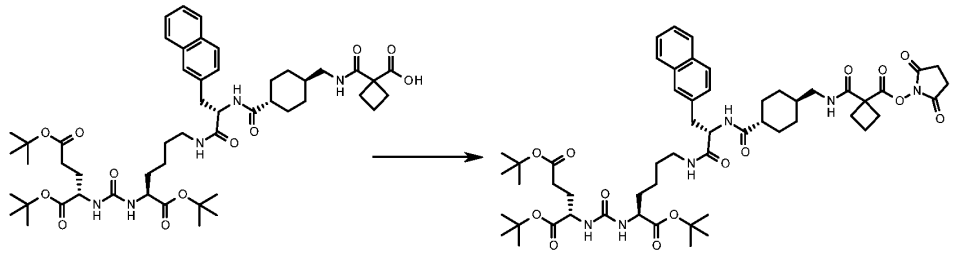
Step II: Preparation of 1-[[4-[[(1*S*)-2-[[(5*S*)-6-*tert*-butoxy-5-[[(1*S*)-4-*tert*-butoxy-1-*tert*-butoxycarbonyl-4-oxo-butyl]carbamoylamino]-6-oxo-hexyl]amino]-1-(2-naphthyl methyl)-2-oxo-ethyl]carbamoyl]cyclohexyl]methylcarbamoyl] cyclobutanecarboxylic acid (Formula 4b)



Formula 4a Formula 4b

A solution of lithium hydroxide (0.058 g, 1.39 mmol) in water (3 mL) was added to a stirred solution of the compound of Formula 4a (0.34 g, 0.34 mmol) in ethanol (7 mL) at RT. The reaction mixture was stirred for 3 hours and then concentrated under reduced pressure at 40°C. Water (5 mL) was added to the residue and the resulting mixture was acidified to pH~4 using saturated citric acid solution. The aqueous layer was extracted with ethyl acetate (3x20 mL). The combined organic layers were dried over anhydrous sodium sulphate and concentrated under reduced pressure at 40°C to get the compound of Formula 4b.

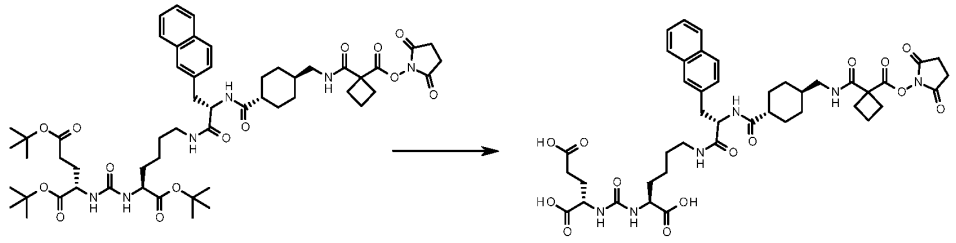
Step III : Preparation of *di-tert*-butyl (2*S*)-2-[[(1*S*)-1-*tert*-butoxycarbonyl-5-[[(2*S*)-2-[[4-[[[1-(2,5-dioxopyrrolidin-1-yl)oxycarbonylcyclobutanecarbonyl]amino] methyl]cyclohexanecarbonyl]amino]-3-(2-naphthyl)propanoyl]amino]pentyl] carbamoylamino] pentanedioate (Formula 4c).



Formula 4b Formula 4c

NHS (0.053 g, 0.46 mmol) followed by EEDQ (0.088 g, 0.46 mmol) was added to a stirred solution of the compound of Formula 4b (0.25 g, 0.26 mmol) in DMF (4 mL). The reaction mixture was stirred overnight at RT. After this time, the reaction mixture was diluted with DCM (30 mL). The organic layer was washed with water (2 x 15 mL) followed by brine, dried over anhydrous sodium sulphate and concentrated under reduced pressure at 50°C to get the compound of Formula 4c.

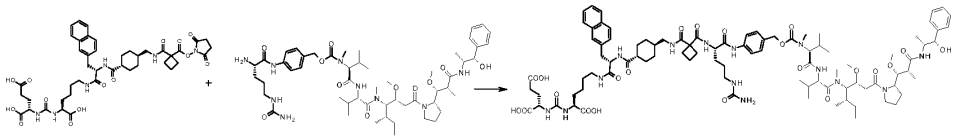
Step IV : Preparation of (2*S*)-2-[[(1*S*)-1-carboxy-5-[[(2*S*)-2-[[4-[[[1-(2,5-dioxopyrrolidin-1-yl) oxycarbonylcyclobutanecarbonyl]amino]methyl] cyclohexanecarbonyl]amino]-3-(2-naphthyl)propanoyl]amino]pentyl] carbamoylamino]pentanedioic acid (Formula 4d)



Formula 4c Formula 4d

TFA (1.5 mL) was added to a stirred solution of the compound of Formula 4c (0.3 g, 0.29 mmol) in DCM (3.0 mL) at RT. The reaction mixture was stirred for 6 hrs and then concentrated and degassed under reduced pressure at 40°C. The residual solid was triturated with diethyl ether (3 x 5 mL) and decanted. The solid obtained was dried at 40°C to get the compound of Formula 4d.

Step V : Preparation of Compound number 1.8



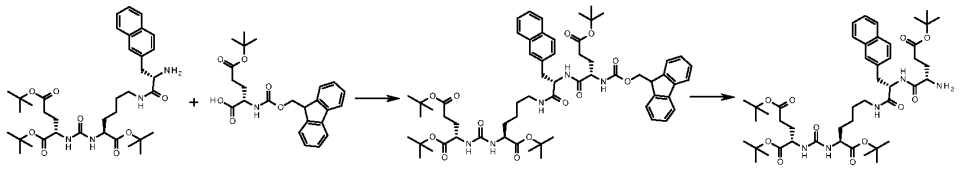
Formula 4d Formula 4e Compound number 1.8

Note: The compound of Formula 4e was prepared by a similar method as that for the compound of Formula 1n.

Triethylamine (0.2 mL, 1.46 mmol) was added to a stirred solution of the compound of Formula 4e (0.15 g, 0.14 mmol) in DMF (3 mL). The compound of Formula 4d (0.31 g, 0.35 mmol) was added to the mixture and the resulting mixture was stirred overnight at RT. The mixture was then concentrated at 50°C under reduced pressure. The residue obtained was dissolved in DCM (2 mL) to get clear solution. Diethyl ether (6 mL) was added to the solution, and the resulting mixture was stirred at RT for 3 hours. The product obtained was filtered, washed with diethyl ether and purified by preparative HPLC to get Compound number 1.8. Mass (m/z) 1788.78 $[M+H]^+$.

Example 5: Preparation of Compound No 1.3

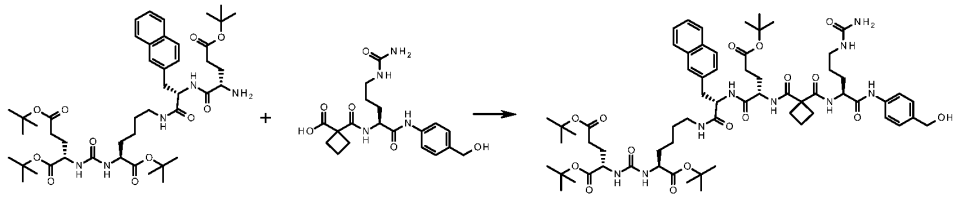
Step I: Preparation of *di-tert*-butyl (2*S*)-2-[[(1*S*)-5-[[(2*S*)-2-[[(2*S*)-2-amino-5-*tert*-butoxy-5-oxo-pentanoyl]amino]-3-(2-naphthyl)propanoyl]amino]-1-*tert*-butoxycarbonyl-pentyl]carbamoylamino]pentanedioate (Formula 5d).



Formula 5a Formula 5b Formula 5c Formula 5d

EEDQ (0.3 g, 1.5 mmol) was added to a stirred solution of the compound of Formula 5b (0.5 g, 1.2 mmol) and 1-hydroxy benzotriazole (0.21 g, 1.5 mmol) in DMF (5 mL), and the mixture was stirred at RT for 2 hrs. A solution of the compound of Formula 5a (0.8 g, 1.2 mmol) in DMF (5 mL) was added to the reaction mixture, and the mixture was stirred overnight. Piperidine (2 mL) was added to the reaction mixture and this mixture was stirred for 2 hrs at RT. The reaction mixture was concentrated at 50°C under reduced pressure. The crude product obtained was purified by column chromatography (silica gel 230-400 mesh; ethyl acetate : methanol, 95:5) to get the compound of Formula 5d.

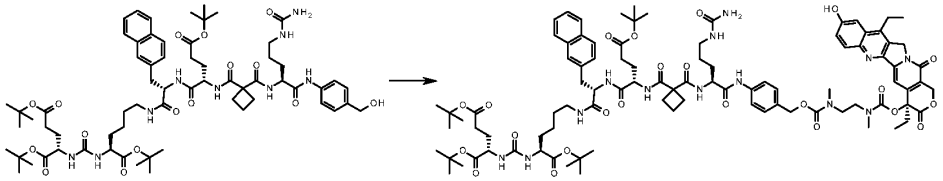
Step II : Preparation of *di-tert*-butyl (2*S*)-2-[[(1*S*)-1-*tert*-butoxycarbonyl-5-[[(2*S*)-2-[[(2*S*)-5-*tert*-butoxy-2-[[1-[[(1*S*)-1-[[4-(hydroxymethyl)phenyl]carbamoyl]-4-ureido-butyl] carbamoyl]cyclobutanecarbonyl]amino]-5-oxo-pentanoyl]amino]-3-(2-naphthyl) propanoyl]amino]pentyl]carbamoylamino]pentanedioate (Formula 5f) .



Formula 5d Formula 5e Formula 5f

EEDQ (0.28 g, 1.1 mmol) was added to a stirred solution of the compound of Formula 5d (0.5 g, 0.57 mmol) and the compound of Formula 5e (0.26 g, 0.63 mmol) in a mixture of DCM (5 mL) and methanol (2.5 mL). The reaction mixture was stirred overnight at RT and then concentrated at 40°C under reduced pressure. Diethyl ether (10 mL) was added to the crude product and the resulting mixture was stirred at RT for 30 min. The solid obtained was filtered, washed with diethyl ether and dried under reduced pressure. The crude product was purified by column chromatography (silica gel 230-400 mesh; DCM: methanol, 90:10) to get the compound of Formula 5f.

Step III : Preparation of 1,5-*di-tert*-butyl (2*S*)-2-({[(2*S*)-1-(*tert*-butoxy)-6-[(2*S*)-2-[(2*S*)-5-(*tert*-butoxy)-2-[(1-{[(1*S*)-4-(carbamoylamino)-1-[(4-{[({2-[({[(19*S*)-10,19-diethyl-7-hydroxy-14,18-dioxo-17-oxa-3,13-diazapentacyclo[11.8.0.0^{2},^{11}.0^{4},^{9}.0^{15},^{20}]henicosa-1(21),2(11),3,5,7,9,15(20)-heptaen-19-yl]oxy}carbonyl)(methyl)amino]ethyl}(methyl) carbamoyl)oxy]methyl}phenyl)carbamoyl]butyl]carbamoyl}cyclobutyl)formamido]-5-oxopentanamido]-3-(naphthalen-2-yl)propanamido]-1-oxohexan-2-yl]carbamoyl} amino)pentanedioate (Formula 5g).

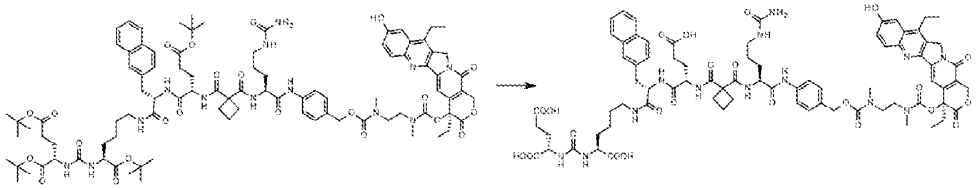


Formula 5f Formula 5g

DIPEA (0.1 mL, 0.43 mmol) followed by bis(4-nitrophenyl)carbonate (0.065 g, 0.21 mmol) was added to a stirred solution of the compound of Formula 5f (0.18 g, 0.14 mmol) in DMF (2 mL) under nitrogen atmosphere at RT. The reaction mixture was stirred for 5 hrs then concentrated under reduced pressure at 55°C. Triturated the residue with diethyl ether (5 mL), decanted and the resulting residue was dried under vacuum at 50°C to get *di-tert*-butyl (2*S*)-2-[[(1*S*)-1-*tert*-butoxycarbonyl-5-[[(2*S*)-2-[[(2*S*)-5-*tert*-butoxy-2-[[1-[[(1*S*)-1-[[4-[(4-nitrophenoxy)carbonyloxymethyl]phenyl] carbamo-yl]-4-ureido-butyl]carbamoyl]cyclobutanecarbonyl]amino]-5-oxo-pentanoyl] amino]-3-(2-naphthyl)propanoyl]amino]pentyl]carbamoylamino]pentanedioate (Formula 5f'), which was used for the next step without purification.

The compound of Formula 5f' and (19*S*)-10,19-diethyl-7-hydroxy-14,18-dioxo-17-oxa-3,13-diazapentacyclo[11.8.0.0^{2},^{11}.0^{4},^{9}.0^{15},^{20}]henicosa-1(21),2(11),3,5,7, 9,15(20)-heptaen-19-yl *N*-methyl-*N*-[2-(methylamino)ethyl]carbamate hydrochloride (0.12 g, 0.21 mmol) were dissolved in DMF (2 mL). DIPEA (0.1 mL, 0.43 mmol) was added to the reaction mixture, and the resulting mixture was stirred for 2 hrs. After 2 hrs, the reaction mixture was concentrated under reduced pressure at 50°C to obtain the crude product of the compound of Formula 5g, which was then purified by column chromatography (silica gel 230-400 mesh, DCM: methanol, 93:7).

Step IV: Preparation of Compound No 1.3:



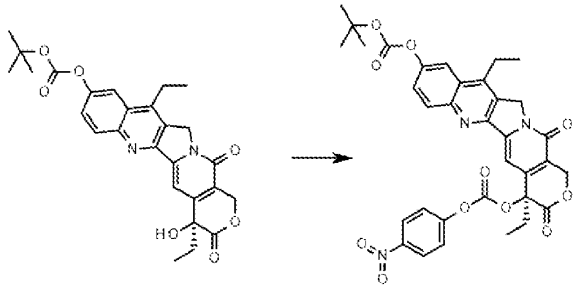
Formula 5g Compound No 1.3

TFA (0.9 mL) was added to a stirred solution of the compound of Formula 5g (0.19 g, 0.11 mmol) in hexafluoro propan-2-ol (3.8 mL) at RT. The reaction mixture was stirred for 4 hrs and then concentrated and degassed under reduced pressure at 40°C. The residual crude product was purified by preparative HPLC to get Compound No 1.3. Mass (m/z): 1567.27.

Compound No 1.1 was prepared by the similar method as given in Example 5. Mass (m/z) of Compound No 1.1 is 1514.31 $[M+H]^+$.

Example 6: Preparation of Compound no 1.2

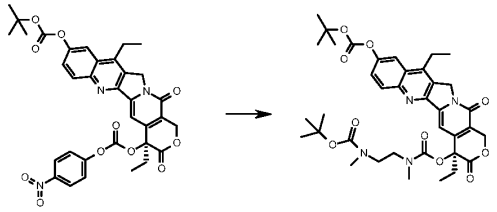
Step I: Preparation of (19*S*)-7-{[(*tert*-butoxy)carbonyl]oxy}-10,19-diethyl-14,18-dioxo-17-oxa-3,13-diazapentacyclo[11.8.0.0^{2,11}.0^{4,9}.0^{15,20}]henicosa-1(21),2(11),3,5,7,9,15(20)-heptaen-19-yl 4-nitrophenyl carbonate (Formula 6a).



Formula 6a

DMAP (3.97 g, 32.5 mmol) was added to a stirred solution of *tert*-butyl (19*S*)-10,19-diethyl-19-hydroxy-14,18-dioxo-17-oxa-3,13-diazapentacyclo [11.8.0.0^{2,11}.0^{4,9}.0^{15,20}]henicosa-1(21),2(11),3,5,7,9,15(20)-heptaen-7-yl carbonate (5.0 g, 10.1 mmol) and 4-nitrophenyl chloroformate (3.06 g, 15.2 mmol) in DCM (250 mL) at RT. The reaction mixture was stirred for 1 hr, diluted with DCM (500 mL), washed with aqueous 0.1 N HCl solution (3x50 mL) and dried over anhydrous sodium sulphate. Removal of DCM under reduced pressure at 40°C resulted in the crude product, which was purified by column chromatography (silica gel 230-400 mesh, ethyl acetate : DCM, 10:90) to get the compound of Formula 6a.

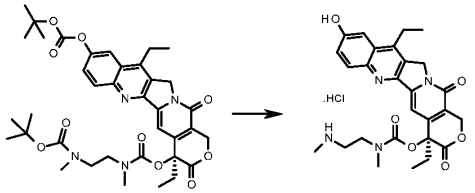
Step II: Preparation of (19*S*)-19-{[(2-{[(*tert*-butoxy)carbonyl](methyl)amino}ethyl)(methyl)carbamoyl]oxy}-10,19-diethyl-14,18-dioxo-17-oxa-3,13-diazapentacyclo[11.8.0.0^{2},^{11}.0^{4},^{9}.0^{15},^{20}]henicosa-1(21),2(11),3,5,7,9,15(20)-heptaen-7-yl *tert*-butyl carbonate (Formula 6b)



Formula 6a Formula 6b

A solution of the compound of Formula 6a (3.5 g, 5.3 mmol) in DMF (17.5 mL) was added to a stirred solution of *tert*-butyl *N*-methyl-*N*-[2-(methylamino)ethyl]carbamate (1.1 g, 5.85 mmol) and DIPEA (1.4 mL, 07.98 mmol) in acetonitrile (17.5 mL) at RT. The reaction mixture was stirred for 4 hrs and concentrated under reduced pressure at 35°C. The concentrated residue obtained was dissolved in ethyl acetate (175 mL) and this ethyl acetate layer was washed with water (1x35 mL) followed by a brine solution (1x35 mL) and then dried over anhydrous sodium sulphate. Concentration under reduced pressure gave the crude product, which was purified by column chromatography (silica gel 230-400 mesh, ethyl acetate : DCM, 30:70) to get the compound of Formula 6b.

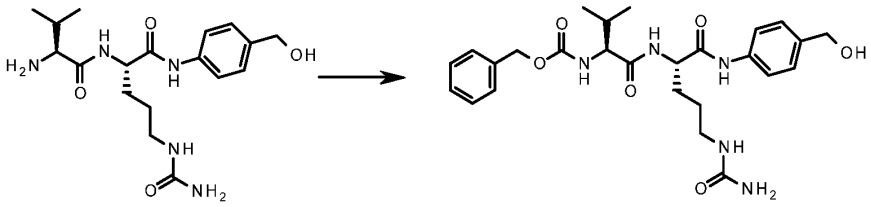
Step III: Preparation of (19*S*)-10,19-diethyl-7-hydroxy-14,18-dioxo-17-oxa-3,13-diazapentacyclo[11.8.0.0^{2},^{11}.0^{4},^{9}.0^{15},^{20}]henicosa-1(21),2(11),3,5,7,9,15(20)-heptaen-19-yl *N*-methyl-*N*-[2-(methylamino)ethyl]carbamate hydrochloride (Formula 6c).



Formula 6b Formula 6c

HCl (4M) in 1,4-dioxane (1.65 mL) was added to a stirred solution of the compound of Formula 6b (0.33 g, 0.47 mmol) in 1,4-dioxane (1.0 mL) at RT. The reaction mixture was stirred for 5 hrs and then was concentrated and degassed under reduced pressure at 35°C to get the compound of Formula 6c (0.25 g), which was used for the next step without purification.

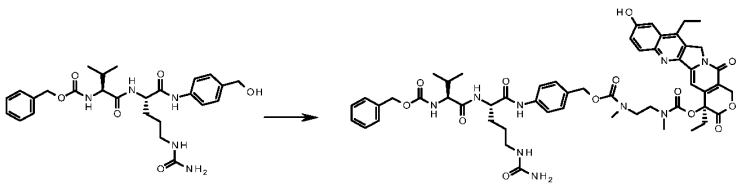
Step IV: Preparation of benzyl *N*-[(1*S*)-1-[[(1*S*)-1-[[4-(hydroxymethyl)phenyl] carbamoyl]-4-ureido butyl]carbamoyl]-2-methyl propyl]carbamate (Formula 6e).



Formula 6d Formula 6e

DIPEA (0.5 mL, 2.6 mmol) was added to a stirred solution of the compound of Formula 6d (1.0 g, 2.6 mmol) in a mixture of THF (5 mL) and DMF (5 mL). The reaction mixture was cooled to 0-5°C. Benzyl chloroformate (50% solution in toluene, 0.9 mL, 2.6 mmol) was added dropwise to the reaction mixture, and the resulting mixture was stirred at 0-5°C for 1 hr. The reaction mixture was then concentrated and degassed completely under reduced pressure at 45°C. DCM (10 mL) was added to the residue and the resulting solution was stirred at RT for 30 min. Product obtained was filtered, washed with DCM and dried to get the compound of Formula 6e (1.1 g).

Step V: Preparation of (19*S*)-10,19-diethyl-7-hydroxy-14,18-dioxo-17-oxa-3,13-diazapentacyclo[11.8.0.0^{2},^{11}.0^{4},^{9}.0^{15},^{20}]henicosa-1(21),2(11),3,5,7,9,15(20)-heptaen-19-yl *N*-(2-{[({4-[(2*S*)-2-[(2*S*)-2-{[(benzyloxy)carbonyl]amino}-3-methylbutanamido]-5-(carbamoylamino)pentanamido]phenyl}methoxy)carbonyl] (methyl)amino}ethyl)-N-methylcarbamate (Formula 6f).



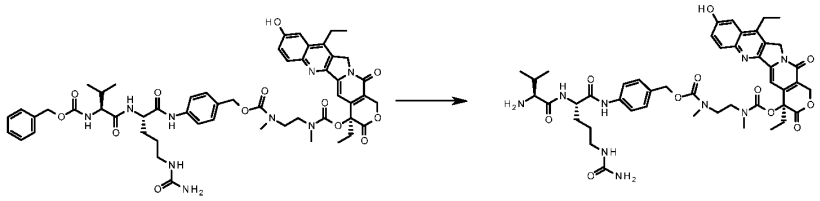
Formula 6e Formula 6f

DIPEA (1.2 mL, 7.0 mmol) followed by bis(4-nitrophenyl)carbonate (1.06 g, 3.5 mmol) was added to a stirred solution of the compound of Formula 6e (1.2 g, 2.3 mmol) in DMF (10 mL) under nitrogen atmosphere at RT. the resulting mixture was stirred for 5 hrs and then concentrated under reduced pressure at 55°C. Diethyl ether (10 mL) was added to the residue, the resulting mixture was leached and decanted to obtain another residue, which was dried under reduced pressure at 50°C to get the compound of Formula 6e', which was used for the next step without purification.

The compound of Formula 6e' and the compound of Formula 6c (1.52 g, 2.8 mmol) were dissolved in DMF (10 mL). DIPEA (1.2 mL, 7.0 mmol) was added to the mixture and the

resulting mixture was stirred for 2 hrs. The reaction mixture was concentrated under reduced pressure at 50°C to give the crude product which was purified by column chromatography (silica gel 230-400 mesh, DCM : methanol, 90:10) to get the compound of Formula 6f.

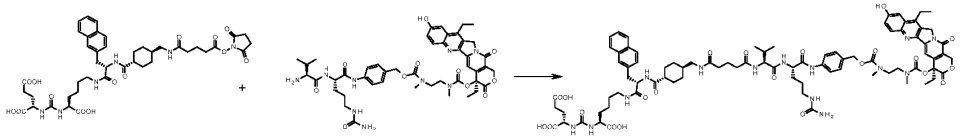
Step VI: Preparation of (19*S*)-10,19-diethyl-7-hydroxy-14,18-dioxo-17-oxa-3,13-diazapentacyclo [11.8.0.0^{2},^{11}.0^{4},^{9}.0^{15},^{20}]henicosa-1(21),2(11),3,5,7,9,15(20)-heptaen-19-yl *N*-(2-{[({4-[(2*S*)-2-[(2*S*)-2-amino-3-methylbutanamido]-5-(carbamoylamino) pentanamido]phenyl}methoxy)carbonyl](methyl)amino}ethyl)-*N*-methylcarbamate (Formula 6g).



Formula 6f Formula 6g

Palladium on carbon (10%, 50% wet, 0.1 g) was added to a stirred solution of the compound of Formula 6f (0.5 g, 0.48 mmol) in a mixture of THF (2.5 mL) and methanol (10 mL) at RT. Hydrogen gas was purged through the reaction mixture at RT, and the reaction mixture was stirred for 2 hrs. After 2 hrs the reaction mixture was filtered through Celite® bed and washed with an excess mixture of methanol and THF. The combined filtrate was concentrated under reduced pressure at 45°C to get the compound of Formula 6g (0.42 gm), which was used for the next step without further purification.

Step VII: Preparation of Compound no 1.2

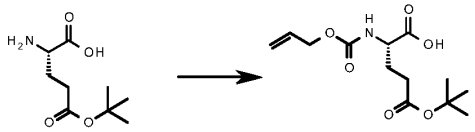


Formula 1i Formula 6g Compound no 1.2

DIPEA (0.12 mL, 0.69 mmol) was added to a stirred solution of the compound of Formula 6g (0.12 g, 0.12 mmol) in DMF (3 mL). The compound of Formula 1i (0.12 g, 0.14 mmol) was added to the mixture, and the resulting mixture was stirred at RT for 24 hrs. After 24 hrs the reaction mixture was concentrated and degassed under reduced pressure at 50°C. DCM (5 mL) was added to the residue and stirred at RT for 30 min. The product obtained was filtered, washed with DCM (3x5 mL) and dried under vacuum. The crude product (0.2 g) obtained was purified by preparative HPLC to get Compound no 1.2 (0.06 g). Mass (m/z): 1664.07

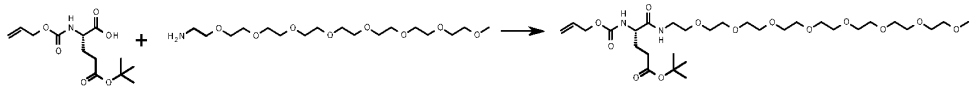
Example 7: Preparation of Compound no 1.56

Step I: Preparation of (*S*)-2-allyloxycarbonylaminopentanedioic acid 5-*tert*-butyl ester.



Allylchloroformate (1.1 mL, 10.3 mmol) was added dropwise to a stirred solution of (*S*)-2-amino-pentanedioic acid 5-*tert*-butyl ester (2.0 gm, 9.8 mmol) in a mixture of THF (40 ml), DMF (5.0 mL) and DIPEA (2.55 mL, 14.7 mmol) at 0°C. The mixture was stirred for 1h and then concentrated under reduced pressure at 50°C. Water (20 mL) was added to the residue obtained and the aqueous layer was extracted with ethyl acetate (3x50 mL). The combined organic layers were washed with a brine solution (1x25 mL), dried over anhydrous sodium sulphate and concentrated under reduced pressure at 45°C to get (*S*)-2-allyloxycarbonylaminopentanedioic acid 5-*tert*-butyl ester (2.25 gm), which was used for the next step without purification.

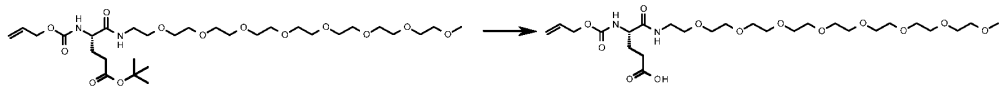
Step II: Preparation of (*S*)-4-allyloxycarbonylamino-4-[2-(2-{2-[2-(2-{2-[2-(2-methoxyethoxy)ethoxy]ethoxy}ethoxy)ethoxy]ethoxy}ethoxy)ethylcarbamoyl]butyric acid *tert*-butyl ester (Formula 7a).



Formula 7a

TBTU (0.704 gm, 2.2 mmol) was added to a stirred solution of (*S*)-2-allyloxycarbonylamino pentanedioic acid 5-*tert*-butyl ester (0.485 gm, 1.68 mmol), 2-(2-{2-[2-(2-{2-[2-(2-methoxyethoxy)ethoxy] ethoxy}ethoxy)ethoxy]ethoxy} ethoxy)ethylamine (0.64 gm, 1.68 mmol) and *N,N*-diisopropylethyl amine (0.73 mL, 4.2 mmol) in DMF (4.85 mL) at RT. The reaction mixture was stirred overnight and then was quenched in water (10 mL). The aqueous layer was extracted with ethyl acetate (3x30 mL). The combined organic layers were washed with brine, dried over anhydrous sodium sulphate and concentrated under reduced pressure at 35°C to get the compound of Formula 7a (1.04 gm), which was used for the next step without purification.

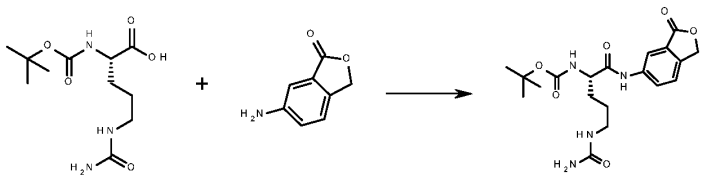
Step III: Preparation of (S)-4-allyloxycarbonylamino-4-[2-(2-{2-[2-(2-{2-[2-(2-methoxyethoxy)ethoxy]ethoxy}ethoxy)ethoxy]ethoxy}ethoxy)ethylcarbamoyl]butyric acid (Formula 7b).



Formula 7a Formula 7b

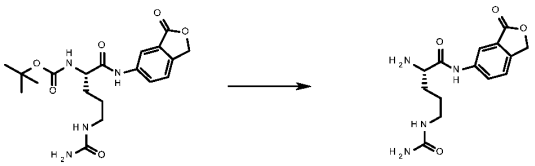
TFA (4 mL) was added dropwise to a stirred solution of the compound of Formula 7a (1.0 gm, 1.53 mmol) in DCM (14 mL) at 0°C, the mixture was stirred for 15 mins. The reaction mixture was then stirred at RT for 2 hours. Concentrated the mixture under reduced pressure at 50°C to get the crude product (0.9 gm), which was purified by column chromatography (silica gel 230-400 mesh; DCM: methanol, 95:5) to get the compound of Formula 7b

Step IV: Preparation of [(*S*)-1-(3-oxo-1, 3-dihydro-isobenzofuran-5-ylcarbamoyl)-4-ureido-butyl]carbamic acid *tert*-butyl ester.



EEDQ (6.8 gm, 27.27 mmol) was added to a stirred solution of (*S*)-2-*tert*-butoxycarbonylamino-5-ureido pentanoic acid (5.0 gm, 18.18 mmol) and 6-amino-3*H*-isobenzofuran-1-one (3.0 gm, 20.0 mmol) in a mixture of DCM (60 mL) and methanol (30 mL). The reaction mixture was stirred overnight at RT and then concentrated under reduced pressure at 45°C. Ethyl acetate (5 mL) was added to the residue, and the resulting mixture was stirred for 2 hrs. The solid obtained was filtered and dried to get [(*S*)-1-(3-oxo-1,3-dihydro-isobenzofuran-5-ylcarbamoyl)-4-ureido-butyl] carbamic acid *tert*-butyl ester.

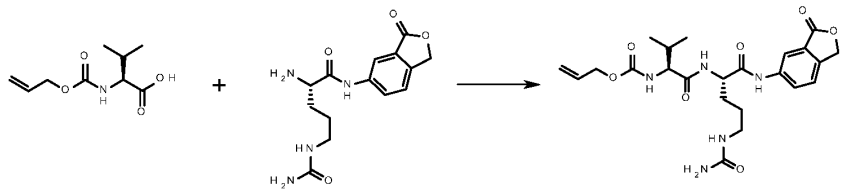
Step V: Preparation of (*S*)-2-amino-5-ureido-pentanoic acid(3-oxo-1,3-dihydro-isobenzofuran-5-yl)amide trifluoroacetate.



TFA (2.8 mL) was added to a stirred solution of [(*S*)-1-(3-oxo-1, 3-dihydro-isobenzofuran-5-ylcarbamoyl)-4-ureido butyl]carbamic acid *tert*-butyl ester (0.7 gm, 1.72 mmol) in DCM (7.0 mL) and continued stirring at RT for 3 hrs. diethylether (20 ml) was added to the reaction mixture, and the resulting mixture was stirred for 30 mins. The ether layer was decanted and

the product was dried to get (*S*)-2-amino-5-ureido-pentanoic acid(3-oxo-1,3-dihydro-isobenzofuran-5-yl)-amide trifluoroacetate.

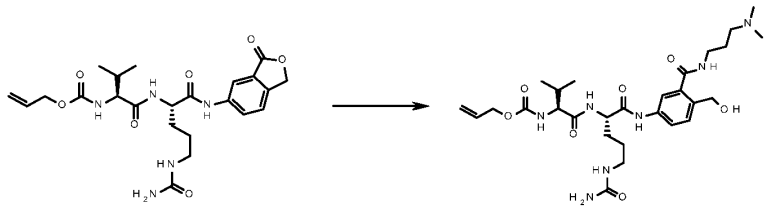
Step VI: Preparation of {(*S*)-2-methyl-1-[(*S*)-1-(3-oxo-1, 3-dihydro-isobenzofuran-5-ylcarbamoyl)-4-ureido-butylcarbamoyl]-propyl}-carbamic acid allyl ester (Formula 7c).



Formula 7c

HATU (5.6 gm, 14.7 mmol) was added to a stirred solution of (*S*)-2-amino-5-ureidopentanoic acid(3-oxo-1,3-dihydro-isobenzofuran-5-yl)amide trifluoroacetate salt (5.6 gm, 13.7 mmol), (*S*)-2-allyloxycarbonylamino-3-methyl butyric acid (2.52 gm, 12.5 mmol) and DIPEA (3.36 mL, 18.7 mmol) in DMF (56 mL), and the mixture was stirred overnight at RT. After completion of the reaction, the reaction mixture was quenched in water (50 mL) and the aqueous layer was extracted with ethyl acetate (3x100 mL). The combined organic layers were washed with a brine solution (1x50 mL) and was dried over anhydrous sodium sulphate and concentrated under reduced pressure at 50°C to get the crude product (5.8 gm), which was purified by column chromatography (silica gel 230-400 mesh; DCM: methanol, 95:05) to get the compound of Formula 7c.

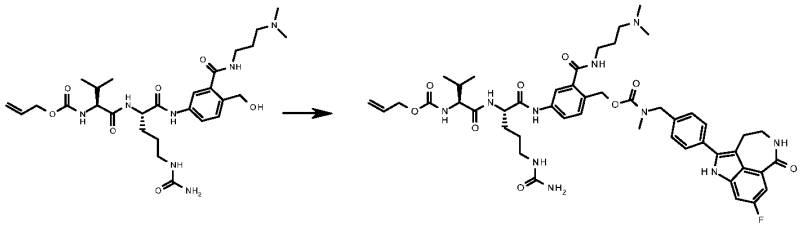
Step VII: Preparation of ((*S*)-1-{(*S*)-1-[3-(3-dimethylamino-propylcarbamoyl)-4-hydroxymethyl-phenylcarbamoyl]-4-ureido-butylcarbamoyl}-2-methyl-propyl)-carbamic acid allyl ester (Formula 7d).



Formula 7c Formula 7d

N′,*N*′-dimethylpropane-1,3-diamine (1.5 mL) was added to the compound of Formula 7c (0.5 gm, 0.84 mmol) at RT and this mixture was heated under stirring at 85°C for 2 hrs. After this time the reaction mixture was concentrated under reduced pressure at 50° C to get the crude product, which was purified by column chromatography (silica gel 230-400 mesh; DCM: methanol: ammonia, 85:13:2) to get the compound of Formula 7d.

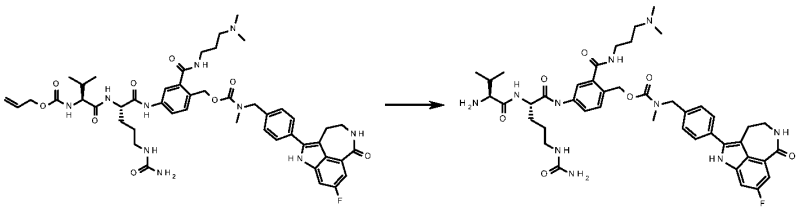
Step VIII: Preparation of ((*S*)-1-{(*S*)-1-[3-(3-dimethylaminopropylcarbamoyl)-4-({[4-(8-fluoro-6-oxo-3,4,5,6-tetrahydro-1*H*-azepino[5,4,3-cd]indol-2-yl)-benzyl]methylcarbamoyloxy}methyl)phenylcarbamoyl]-4-ureidobutylcarbamoyl}-2-methylpropyl) carbamic acid allyl ester (Formula 7e).



Formula 7d Formula 7e

DIPEA (0.36 mL, 2.0 mmol) was added to a stirred solution of the compound of Formula 7d (0.3 g, 0.5 mmol) in DMF (3 mL) at RT. *Bis*(4-nitrophenyl)carbonate (0.32 g, 1.0 mmol) was added to the reaction mixture and the resulting mixture was stirred for 2 hrs. After this time the reaction mixture was concentrated under reduced pressure at 55°C. The residue was triturated with diethyl ether (5 mL). Diethyl ether was decanted and the resulting residue was dried under reduced pressure to get the crude product. The crude is dissolved in DMF (3 mL) to which Rucaparib (0.185 gm, 5.7 mmol), HOBt (57 mg) and DIPEA (0.28 mL, 1.5 mmol) was added at RT. The reaction mixture was stirred for 30 hrs and then concentrated under reduced pressure at 55°C. The crude material obtained was purified by column chromatography (silica gel 230-400 mesh; DCM: methanol: ammonia, 86:12:2) to get the compound of Formula 7e.

Step IX: Preparation of [4-(8-fluoro-6-oxo-3,4,5,6-tetrahydro-1*H*-azepino[5,4,3-cd]indol-2-yl)benzyl]methylcarbamic acid 4-[(*S*)-2-((*S*)-2-amino-3-methylbutyrylamino)-5-ureidopentanoylamino]-2-(3-dimethylaminopropylcarbamoyl)benzyl ester (Formula 7f).

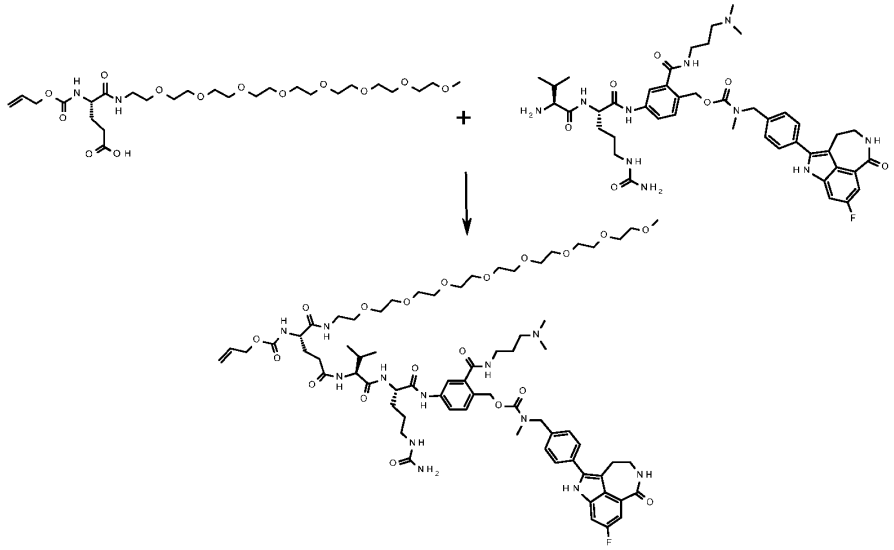


Formula 7e Formula 7f

Palladium tetrakis(triphenylphosphine) (0.021 g, 0.018 mmol) was added to a stirred solution of the compound of Formula 7e (0.22 g, 0.23 mmol) in a mixture of DCM (1.54 mL) and methanol (0.66 mL) at RT. Morpholine (0.16 mL, 1.84 mmol) was added to the reaction mixture and the mixture was stirred for 2.5 hr. After this time the reaction mixture was

concentrated under reduced pressure at 35°C. The crude material obtained was purified by column chromatography (silica gel 230-400 mesh; DCM: methanol: ammonia, 88:10:2) to get the compound of Formula 7f.

Step X: Preparation of {4-[(2*S*)-5-(carbamoylamino)-2-[(2*S*)-3-methyl-2-[(4*S*)-4-[(2,5,8,11,14,17,20,23-octaoxapentacosan-25-yl)carbamoyl]-4-{[(prop-2-en-1-yloxy) carbonyl]amino}butanamido]butanamido]pentanamido]-2-{[3-(dimethylamino)propyl] carbamoyl}phenyl}methyl *N*-[(4-{6-fluoro-9-oxo-3,10-diazatricyclo[6.4.1.04,13]trideca-1,4,6,8(13)-tetraen-2-yl}phenyl)methyl]-*N*-methylcarbamate (Formula 7g).

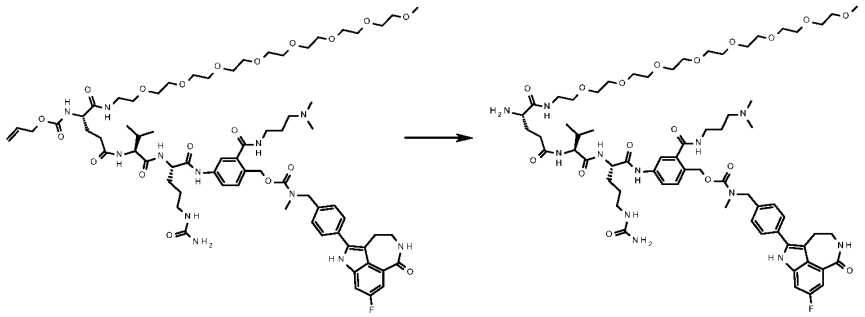


Formula 7g

TBTU (0.073 gm, 0.22 mmol) was added to a stirred solution of (*S*)-4-allyloxycarbonylamino-4-[2-(2-{2-[2-(2-{2-[2-(2-methoxyethoxy)ethoxy] ethoxy}ethoxy)ethoxy]ethoxy}ethoxy)ethyl carbamoyl]butyric acid (0.15 gm, 0.175 mmol), the compound of Formula 7f (0.64 gm, 1.68 mmol) and *N,N*-diisopropylethyl amine (0.73 ml, 0.45 mmol) in DMF (1.5 mL) at RT. The reaction mixture was stirred overnight and then concentrated under reduced pressure at 55°C. The crude material obtained was purified by column chromatography (silica gel 230-400 mesh; DCM: methanol: ammonia, 88:10:2) to get the compound of Formula 7g.

Step XI: Preparation of {4-[(2*S*)-2-[(2*S*)-2-[(4*S*)-4-amino-4-[(2,5,8,11,14,17,20,23-octaoxapentacosan-25-yl)carbamoyl]butanamido]-3-methylbutanamido]-5-(carbamoylamino)pentanamido]-2-{[3-(dimethylamino)propyl]carbamoyl} phenyl}methyl *N*-

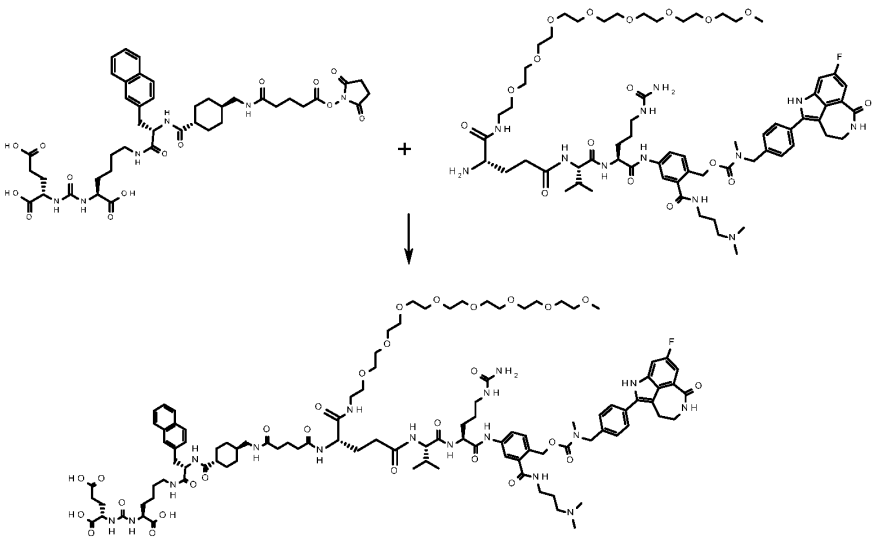
[(4-{6-fluoro-9-oxo-3,10-diazatricyclo[6.4.1.04,13]trideca-1,4,6,8(13)-tetraen-2-yl}phenyl) methyl]-*N*-methylcarbamate (Formula 7h).



Formula 7g Formula 7h

Palladium tetrakis(triphenylphosphine) (0.007 g, 0.006 mmol) was added to a stirred solution of the compound of Formula 7g (0.11 g, 0.076 mmol) in a mixture of DCM (0.77 mL) and methanol (0.33 mL) at RT. Morpholine (0.053 mL, 0.608 mmol) was added to the reaction mixture. and the mixture was stirred for 2.0 hr. Following this period, the reaction mixture was concentrated under reduced pressure at 35°C. The crude material obtained was purified by column chromatography (silica gel 230-400 mesh; DCM : methanol : ammonia, 84:14:2) to get the compound of Formula 7h.

Step XII: Preparation of the Compound no 1.56



Compound no 1.56

The compound of Formula 7h (0.09 gm, 0.066 mmol) was added to a stirred solution of the compound of Formula 1i (0.075 g, 0.086 mmol) in DMF (1.0 mL) and TEA (0.093 ml, 0.66 mmol) and continued stirring the mixture at RT for 14 hrs. The reaction mixture was then concentrated and degassed under reduced pressure at 50°C. DCM (5 mL) was added to the residue and the resulting mixture was stirred at RT for 30 min. The solid obtained was filtered, washed with DCM (3x 5 mL) and dried under vacuum. The crude product (0.2 g) obtained was purified by preparative HPLC to get the Compound no 1.56.

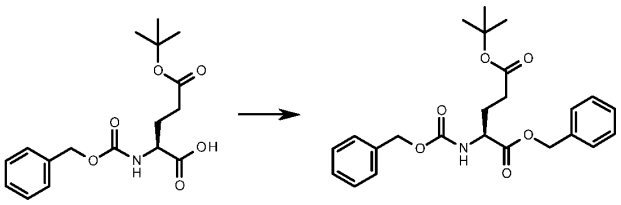
Table 4 below lists compounds prepared using similar methods as illustrated in Example 7.

Table 4:

Compound No	Mass (m/z) $[M+2H]^{2+}$
1.56	1052.9
1.57	1009.2
1.58	1100.8
1.59	1050.99

Example 8: Preparation of Compound no 1.51

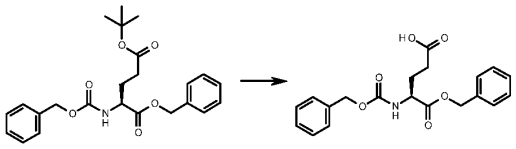
Step I: Preparation of *O*1-benzyl *O*5-*tert*-butyl (2*S*)-2-(benzyloxycarbonylamino) pentanedioate.



Potassium carbonate (3.6 g, 26.1 mmol) was added to a stirred solution of (2*S*)-2-(benzyloxycarbonylamino)-5-*tert*-butoxy-5-oxo-pentanoic acid (4.4 gm, 13.0 mmol) in acetonitrile (44 mL) at RT. The reaction mixture was stirred for 15 min and then benzyl bromide (1.7 mL, 14.3 mmol) was added dropwise to the reaction mixture at RT. The reaction mixture was stirred overnight. After this time the reaction mixture was filtered, washed with ethyl acetate (3x20 mL) and concentrated under reduced pressure at 45°C. Water (40 mL) was added to the residue and the aqueous layer was extracted with ethyl acetate (3x50 mL). The combined organic layers were washed with a 1N HCl solution (1x25 mL) followed by brine, dried over anhydrous sodium sulphate and concentrated under reduced pressure at 45°C to get the crude product. The crude product was purified by column chromatography (silica gel 230-

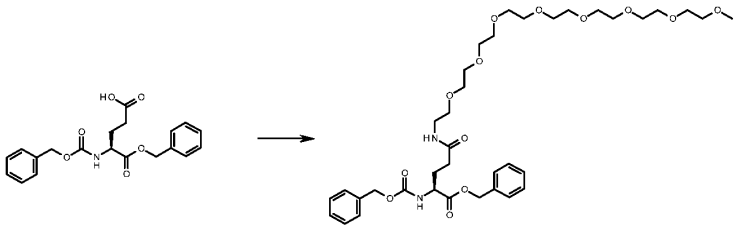
400 mesh; ethyl acetate: n-hexane, 50:50) to get *O*1-benzyl *O*5-tert-butyl (2*S*)-2-(benzyloxycarbonylamino) pentanedioate.

Step II: Preparation of (4*S*)-5-benzyloxy-4-(benzyloxycarbonylamino)-5-oxo-pentanoic acid.



TFA (11 mL) was added to a stirred solution of *O*1-benzyl *O*5-*tert*-butyl (2*S*)-2-(benzyloxycarbonylamino) pentanedioate (2.2 gm, 5.15 mmol) in DCM (33.0 mL). The reaction mixture was stirred at RT for 3 hrs and then concentrated and degassed completely under reduced pressure at 35°C to get the crude product (2.5 gm), which was purified by column chromatography (silica gel 230-400 mesh; ethyl acetate: n-hexane, 50:50) to get (4*S*)-5-benzyloxy-4-(benzyloxycarbonylamino)-5-oxo-pentanoic acid.

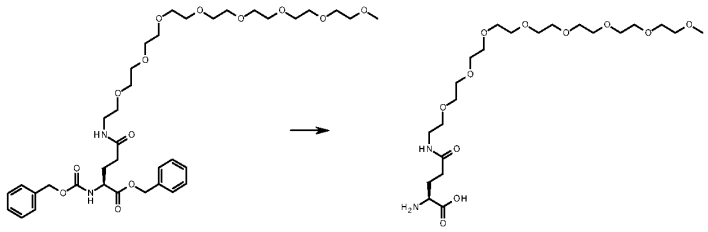
Step III: Preparation of benzyl (2*S*)-2-(benzyloxycarbonylamino)-5-[2-[2-[2-[2-[2-[2-[2-(2-methoxyethoxy)ethoxy]ethoxy]ethoxy]ethoxy]ethoxy]ethoxy]ethyl amino]-5-oxo-pentanoate (Formula 8a).



Formula 8a

TBTU (2.51 gm, 7.8 mmol) was added to a stirred solution of (4*S*)-5-benzyloxy-4-(benzyloxycarbonylamino)-5-oxo-pentanoic acid (1.94 gm, 5.2 mmol), 2-(2-{2-[2-(2-{2-[2-(2-Methoxyethoxy) ethoxy]ethoxy}ethoxy)ethoxy]ethoxy}ethoxy) ethylamine (2.0 gm, 5.2 mmol) and DIPEA (2.3 mL, 13.04 mmol) in DMF (20 mL) at RT. The reaction mixture was stirred overnight and then concentrated under reduced pressure at 55°C to get the crude product, which was purified by column chromatography (silica gel 230-400 mesh; DCM: methanol (95:5) to get the compound of Formula 8a.

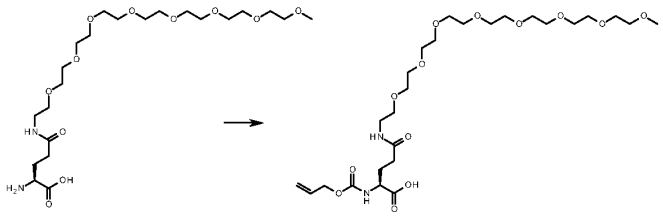
Step IV: Preparation of (2*S*)-2-amino-5-[2-[2-[2-[2-[2-[2-[2-(2-methoxyethoxy) ethoxy]ethoxy]ethoxy]ethoxy]ethoxy]ethoxy]ethylamino]-5-oxo-pentanoic acid (Formula 8b).



Formula 8a Formula 8b

Palladium on carbon (10%, 50% wet, 0.68 g) was added to a stirred solution of the compound of Formula 8a (3.4 g, 4.61 mmol) in methanol (34 mL) at RT. The reaction mixture was stirred at RT under hydrogen gas pressure for 2 hrs. After 2 hrs the reaction mixture was filtered through Celite® bed and washed with excess methanol. The combined filtrates were concentrated under reduced pressure at 45°C to get the compound of Formula 8b, which is used for the next step without further purification.

Step V: Preparation of (2*S*)-2-(allyloxycarbonylamino)-5-[2-[2-[2-[2-[2-[2-[2-(2-methoxyethoxy)ethoxy]ethoxy]ethoxy]ethoxy]ethoxy]ethoxy]ethylamino]-5-oxo-pentanoic acid (Formula 8c).

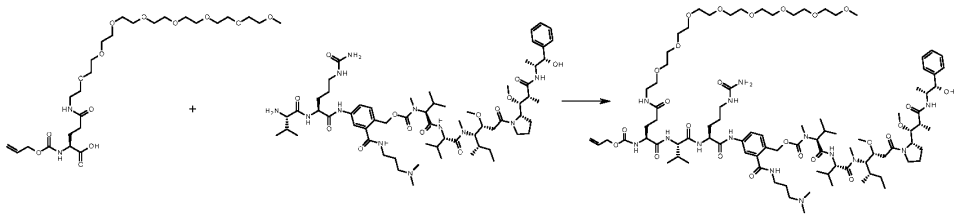


Formula 8b Formula 8c

Allyl chloroformate (0.43 mL, 4.1 mmol) was added dropwise to a stirred solution of the compound of Formula 8b (1.9 gm, 3.7 mmol) in a mixture of THF (30 ml), water (30 mL) and potassium carbonate (0.84 g, 5.56 mmol) at 0°C. The reaction mixture was stirred for 10 min and then allowed to attain RT where it was stirred overnight. After this time, concentrated the mixture under reduced pressure at 45°C. Water (20 mL) was added to the residue and the aqueous layer was acidified to pH~4 using a 2N HCl solution. The resulting mixture was extracted with ethyl acetate (3x50 mL). The combined organic layers were washed with a brine solution (1x25 mL), dried over anhydrous sodium sulphate and concentrated under reduced pressure at 45°C to get the crude product, which was purified by column chromatography (silica gel 230-400 mesh; DCM: methanol:acetic acid, 78:20:2) to get the compound of Formula 8c.

Step VI: Preparation of [4-[[(2*S*)-2-[[(2*S*)-2-[[(2*S*)-2-(allyloxycarbonylamino)-5-[2-[2-[2-[2-[2-[2-[2-(2-methoxyethoxy)ethoxy]ethoxy]ethoxy]ethoxy] ethoxy]ethylamino]-5-oxo-

pentanoyl]amino]-3-methyl-butanoyl]amino]-5-ureido-pentanoyl]amino]-2-[3-(dimethylamino)propylcarbamoyl]phenyl]methyl *N*-[(1*S*)-1-[[(1*S*)-1-[[(1*S*,2*R*)-4-[(2*S*)-2-[(1*R*,2*R*)-3-[[(1*R*,2*S*)-2-hydroxy-1-methyl-2-phenyl-ethyl]amino]-1-methoxy-2-methyl-3-oxo-propyl]pyrrolidin-1-yl]-2-methoxy-1-[(1*S*)-1-methylpropyl]-4-oxo-butyl]-methyl-carbamoyl]-2-methyl-propyl]carbamoyl]-2-methyl-propyl]-*N*-methyl-carbamate (Formula 8e).

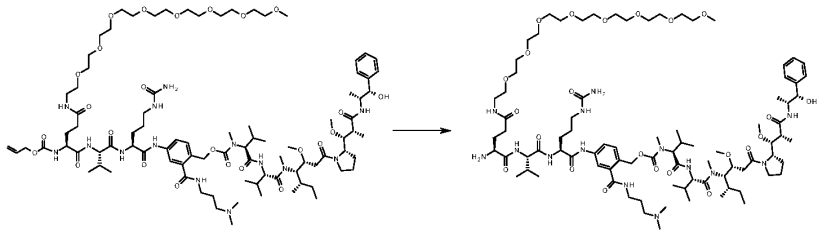


Formula 8c Formula 8d Formula 8e

The compound of Formula 8d was prepared by the similar process described for the compound of Formula 1n.

TBTU (0.046 gm, 0.15 mmol) was added to a stirred solution of the compound of Formula 8c (0.085 gm, 0.15 mmol), the compound of Formula 8d (0.14 gm, 0.11 mmol) and DIPEA (0.024 mL, 0.15 mmol) in DMF (2 mL) at RT. The reaction mixture was stirred overnight at RT and then concentrated under reduced pressure at 55°C to get the crude product, which was purified by column chromatography (silica gel 230-400 mesh; DCM: methanol: aqueous ammonia (89:10:1) to get the compound of Formula 8e.

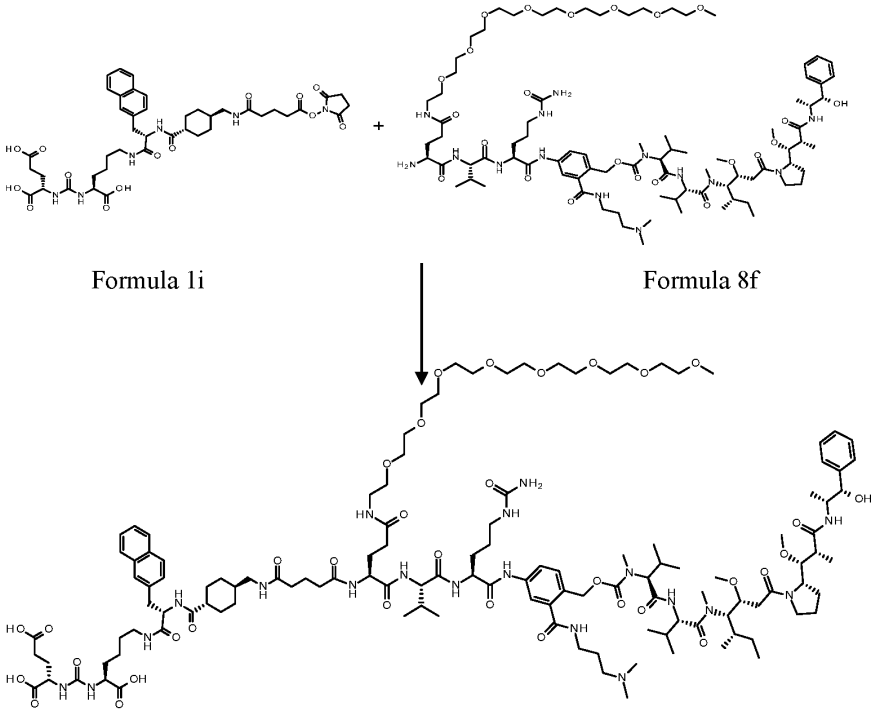
Step VII: Preparation of [4-[[(2*S*)-2-[[(2*S*)-2-[[(2*S*)-2-amino-5-[2-[2-[2-[2-[2-[2-[2-(2-methoxyethoxy)ethoxy]ethoxy]ethoxy]ethoxy]ethoxy]ethylamino]-5-oxo-pentanoyl]amino]-3-methyl-butanoyl]amino]-5-ureido-pentanoyl]amino]-2-[3-(dimethylamino)propylcarbamoyl]phenyl]methyl *N*-[(1*S*)-1-[[(1*S*)-1-[[(1*S*,2*R*)-4-[(2*S*)-2-[(1*R*,2*R*)-3-[[(1*R*,2*S*)-2-hydroxy-1-methyl-2-phenyl-ethyl]amino]-1-methoxy-2-methyl-3-oxo-propyl]pyrrolidin-1-yl]-2-methoxy-1-[(1*S*)-1-methylpropyl]-4-oxo-butyl]-methyl-carbamoyl]-2-methyl-propyl]carbamoyl]-2-methyl-propyl]-*N*-methyl-carbamate (Formula 8f).



Formula 8e Formula 8f

Palladium tetrakis(triphenylphosphine) (0.007 g, 0.09 mmol) was added to a stirred solution of the compound of Formula 8e (0.16 g, 0.09 mmol) in a mixture of DCM (1.12 mL) and methanol (0.48 mL) at RT. Morpholine (0.057 mL, 0.66 mmol) was added to the reaction mixture and the mixture was stirred for 2.5 hr. After this time the reaction mixture was concentrated under reduced pressure at 35°C. The crude material obtained was purified by column chromatography (silica gel 230-400 mesh; DCM:methanol:ammonia, 83:15:2) to get the compound of Formula 8f.

Step VIII: Preparation of Compound no 1.51



Formula 1i Formula 8f

Compound no 1.51

The compound of Formula 8f (0.05 gm, 0.029 mmol) was added to a stirred solution of the compound of Formula 1i (0.037 g, 0.043 mmol) in DMF (1.0 mL) and TEA (0.04 ml, 0.29 mmol). The reaction mixture was stirred at RT for 14 hrs and then concentrated and degassed under reduced pressure at 50°C. DCM (3 mL) and diethyl ether (3 mL) were added to the reaction mixture, and the resulting mixture was stirred at RT for 30 min. The product obtained was filtered, washed with DCM (3x 5 mL) and dried under vacuum. The crude product was purified by preparative HPLC to get Compound no 1.51.

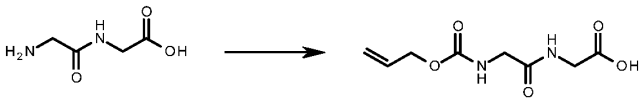
Table 5 below lists compounds prepared using similar methods illustrated in Example 8.

Table 5:

Compound No	Mass (m/z)
1.52	1050.72
1.50	1080.18
1.51	1249.87
1.60	1009.6
1.61	1044.49
1.62	1243.03 [M+2H]+2

Example 9: Preparation of Compound no 1.16

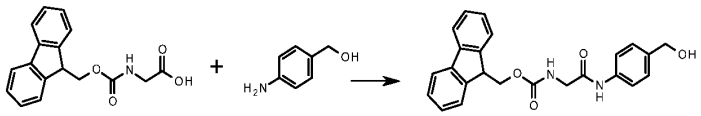
Step I: Preparation of 2-[[2-(allyloxycarbonylamino)acetyl]amino]acetic acid (Formula 9a).



Formula 9a

Potassium carbonate (7.85 gm, 56.8 mmol) was added to a stirred solution of glycylglycine (5.0 g, 37.8 mmol) in a mixture of THF (100 mL) and water (100 mL) at RT and the reaction mixture was stirred for 10 min. The reaction mixture was cooled to 0-5°C and allyl chloroformate (4.82 mL, 45.4 mmol) was added dropwise and continued stirring the reaction mixture for 15 min. The reaction mixture was stirred overnight at RT. Degassed under reduced pressure at 40°C and water (50 mL) was added to the resulting residue. Acidified to pH~4 using concentrated HCl after washing it with diethyl ether (2x100mL). The aqueous layer was further saturated with NaCl and then extracted with THF (3x100 mL). The combined THF layer were dried over anhydrous sodium sulphate and concentrated under reduced pressure at 50°C to get the compound of Formula 9a.

Step II: Preparation of 9*H*-fluoren-9-ylmethyl *N*-[2-[4-(hydroxymethyl)anilino]-2-oxo-ethyl]carbamate (Formula 9b).

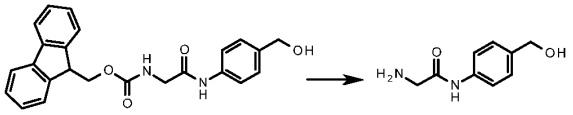


Formula 9b

EEDQ (24.95 g, 100.9 mmol) was added to a stirred solution of 2-(9*H*-fluoren-9-ylmethoxycarbonylamino)acetic acid (20.0 g, 67.2 mmol) and p-amino benzyl alcohol (9.11 g,

74.0 mmol) in a mixture of DCM (200 mL) and methanol (100 mL). The reaction mixture was stirred overnight at RT and then concentrated at 40°C under reduced pressure. Diethyl ether (200 mL) was added to the crude product and the resulting mixture was stirred at RT for 30 min. The product obtained was filtered, washed with diethyl ether and dried under reduced pressure to get the compound of Formula 9b, which was used for the next step without purification.

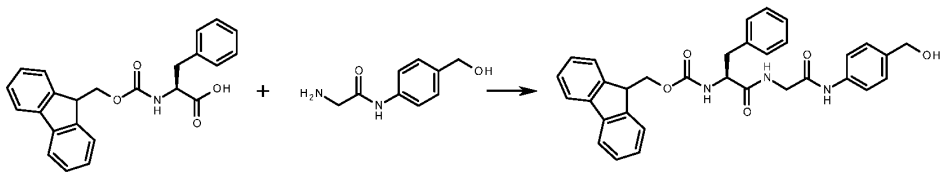
Step III: Preparation of 2-amino-*N*-[4-(hydroxymethyl)phenyl]acetamide (Formula 9c).



Formula 9b Formula 9c

Piperidine (7.4 mL, 74.5 mmol) was added to a stirred solution of the compound of Formula 9b (6.0 g, 14.9 mmol) in DMF (30 mL). The reaction mixture was stirred at room temperature for 1 hr and then concentrated under reduced pressure at 50°C. Diethyl ether (60 mL) was added to the residue, and the resulting mixture was stirred at room temperature for 30 min. The product obtained was filtered, washed with diethyl ether (2x10 mL) and dried under vacuum to get the compound of Formula 9c.

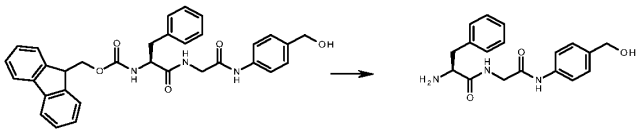
Step IV: Preparation of 9*H*-fluoren-9-ylmethyl *N*-[(1*S*)-1-benzyl-2-[[2-[4-(hydroxylmethyl)anilino]-2-oxo-ethyl]amino]-2-oxo-ethyl]carbamate (Formula 9d).



Formula 9c Formula 9d

EEDQ, 2.78 g, 11.2 mmol) was added to a stirred solution of (2*S*)-2-(9*H*-fluoren-9-ylmethoxycarbonylamino)-3-phenyl-propanoic acid (2.9 g, 7.49 mmol) and the compound of Formula 9c (1.4 g, 7.49 mmol) in a mixture of DCM (29 mL) and methanol (14.5 mL). The reaction mixture was stirred overnight at room and then concentrated at 40°C under reduced pressure. Diethyl ether (30 mL) was added to the crude product, and the resulting mixture was stirred at room temperature for 30 min. The solid obtained was filtered, washed with diethyl ether and dried under reduced pressure to get the compound of Formula 9d, which was used for next step as such.

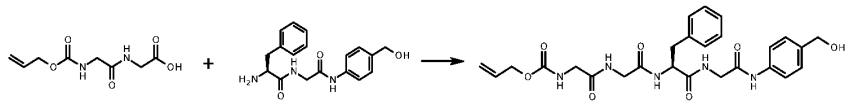
Step V: Preparation of (2*S*)-2-amino-*N*-[2-[4-(hydroxymethyl)anilino]-2-oxo-ethyl]-3-phenyl-propanamide (Formula 9e).



Formula 9d Formula 9e

Piperidine (0.87 mL, 8.8 mmol) was added to a stirred solution of the compound of Formula 9d (1.0 g, 1.76 mmol) in DMF (5 mL). The reaction mixture was stirred at RT for 1 hr and then concentrated under reduced pressure at 50°C. Diethyl ether (10 mL) was added to the residue, and the resulting mixture was stirred at RT for 30 min. The product obtained was filtered, washed with diethyl ether (2x10 mL) and dried under vacuum to get the compound of Formula 9e.

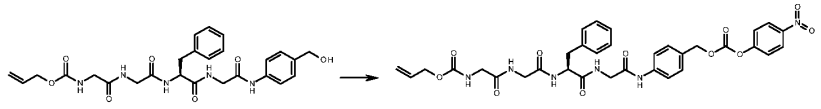
Step VI: Preparation of allyl *N*-[2-[[2-[[(1*S*)-1-benzyl-2-[[2-[4-(hydroxymethyl)anilino]-2-oxo-ethyl]amino]-2-oxo-ethyl]amino]-2-oxo-ethyl]amino]-2-oxo-ethyl]carbamate (Formula 9f).



Formula 9a Formula 9e Formula 9f

EEDQ (1.6 g, 4.6 mmol) was added to a stirred solution of the compound of Formula 9a (0.5 g, 2.3 mmol) and the compound of Formula 9e (0.75 g, 2.3 mmol) in a mixture of DCM (5 mL) and methanol (2.5 mL). The reaction mixture was stirred overnight at room temperature and then concentrated at 40°C under reduced pressure. Diethyl ether (10 mL) was added to the crude product, and the resulting mixture was stirred at RT for 30 min. The product obtained was filtered, washed with diethyl ether and dried under reduced pressure to get the compound of Formula 9f, which was used for the next step without purification.

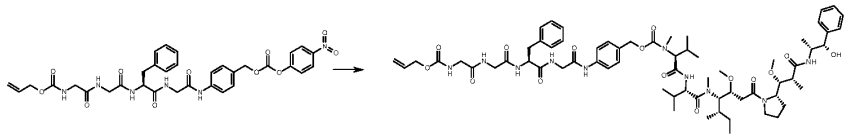
Step VII: Preparation of [4-[[2-[[(2*S*)-2-[[2-[[2-(allyloxycarbonylamino) acetyl]amino]acetyl]amino]-3-phenyl-propanoyl]amino]acetyl]amino]phenyl] methyl (4-nitrophenyl) carbonate (Formula 9g).



Formula 9f Formula 9g

DIPEA (0.6 mL, 3.4 mmol) was added to a stirred solution of the compound of Formula 9f (0.6 g, 1.14 mmol) in DMF (6 mL) at RT. *Bis*(4-nitrophenyl)carbonate (0.7 g, 2.3 mmol) was added to the reaction mixture. The reaction mixture was stirred for 2 hrs and then concentrated under reduced pressure at 55°C. The residue was trituriated with diethyl ether (10 mL), decanted and the resulting residue was dried to get the compound of Formula 9g, which is used for the next step without further purification.

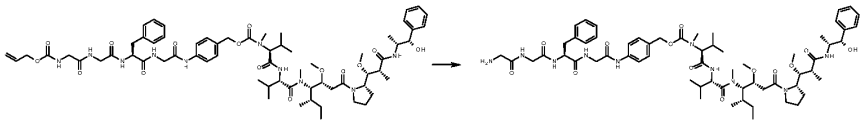
Step VIII : Preparation of [4-[[2-[[(2*S*)-2-[[2-[[2-(allyloxycarbonylamino) acetyl]amino] acetyl]amino]-3-phenyl-propanoyl]amino]acetyl]amino]phenyl] methyl *N*-[(1*S*)-1-[[(1*S*)-1-[[(1*S*,2*R*)-4-[(2*S*)-2-[(1*R*,2*R*)-3-[[(1*R*,2*S*)-2-hydroxy-1-methyl-2-phenyl-ethyl]amino]-1-methoxy-2-methyl-3-oxo-propyl]pyrrolidin-1-yl]-2-methoxy-1-[(1*S*)-1-methylpropyl]-4-oxo-butyl]-methyl-carbamoyl]-2-methyl-propyl]carbamoyl]-2-methyl-propyl]-*N*-methyl-carbamate (Formula 9h).



Formula 9g Formula 9h

HOBt (45 mg) and DIPEA (0.22 mL, 1.28 mmol) was added to a stirred solution of the compound of Formula 9g(0.44 g, 0.64 mmol) and monomethyl auristatin E (0.46 g, 0.64 mmol) in DMF (4.4 mL) at room temperature. The reaction mixture was stirred for 48 hrs and then concentrated under reduced pressure at 55°C. The crude material obtained was purified by column chromatography (silica gel 230-400 mesh; DCM : methanol : aqueous ammonia 88:10:2) to get the compound of Formula 9h.

Step IX: Preparation of [4-[[2-[[(2*S*)-2-[[2-[(2-aminoacetyl)amino]acetyl]amino]-3-phenyl-propanoyl]amino]acetyl]amino]phenyl]methyl *N*-[(1*S*)-1-[[(1*S*)-1-[[(1*S*, 2*R*)-4-[(2*S*)-2-[(1*R*,2*R*)-3-[[(1*R*,2*S*)-2-hydroxy-1-methyl-2-phenyl-ethyl]amino]-1-methoxy-2-methyl-3-oxo-propyl]pyrrolidin-1-yl]-2-methoxy-1-[(1*S*)-1-methyl propyl]-4-oxo-butyl]-methyl-carbamoyl]-2-methyl-propyl]carbamoyl]-2-methyl-propyl]-*N*-methyl-carbamate (Formula 9i).

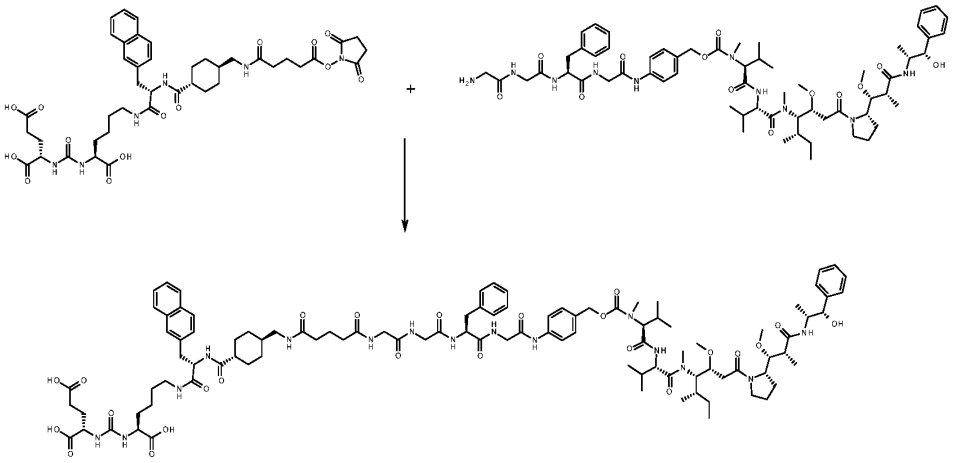


Formula 9h Formula 9i

Palladium tetrakis(triphenylphosphine) (0.034 g, 0.029 mmol) was added to a stirred solution of the compound of Formula 9h (0.5 g, 0.39 mmol) in a mixture of DCM (3.5 mL) and methanol

(1.5 mL) at RT. Morpholine (0.26 mL, 2.9 mmol) was added to the reaction mixture. The reaction mixture was stirred for 4 hrsand then concentrated under reduced pressure at 40°C. The crude material obtained was purified by column chromatography (silica gel 230-400 mesh; DCM : methanol : aqueous ammonia, 88:10:2) to get the compound of Formula 9i.

Step X: Preparation of Compound no 1.16



Compound no 1.16

DIPEA (0.11 mL, 0.82 mmol) was added to a stirred solution of the compound of Formula 9i (0.1 g, 0.082 mmol) in DMF (1 mL) and the reaction mixture was stirred for clear solution. The compound of Formula 1i (0.092 g, 0.11 mmol) was added and the reaction mixture was stirred at RT for 24 hrs. After this time, the reaction mixture was concentrated and degassed under reduced pressure at 50°C. DCM (10 mL) was added to the residue, and the resulting mixture was stirred at room temperature for 30 min. The solid obtained was filtered, washed with DCM (3x5 mL) and dried under vacuum. The crude product obtained was purified by preparative HPLC to get Compound no 1.16. Mass 1937.0 $[M+H]^+$.

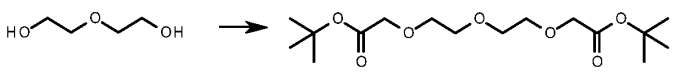
Table 6 set forth below provides mass spectral data for the compounds of the instant invention. The compounds for which data is provided below but for which a description of the synthesis is not explicitly provided above were made in an analogous manner to the synthetic procedures provided above in Example 9.

Table 6:

Compound No	Mass (m/z) $[M+H]^{2+}$
1.63	1026.0
1.64	883.19
1.67	829.21
1.76	1033.77

Example 10: Preparation of Compound no 1.9

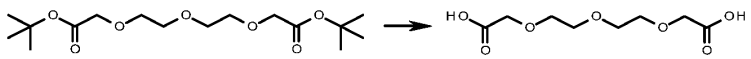
Step I: Preparation of *tert*-butyl 2-[2-[2-(2-*tert*-butoxy-2-oxo-ethoxy)ethoxy]ethoxy] acetate (Formula 10a).



Formula 10a

Sodium hydride (50% suspension in mineral oil, 4.5 g, 94.2 mmol) was added very slowly to a stirred solution of diethylene glycol (5.0 g, 47.1 mmol) in 1, 4-dioxane (50 mL) at RT. The reaction mixture was stirred for 30 min and then cooled to 0-5°C. *tert*-butyl bromo acetate (14.0 mL, 94.2 mmol) was added slowly and the reaction mixture was then stirred for 15 min. After this time, the reaction mixture was stirred overnight at RT and then cooled to 0-5°C. Once at the prescribed temperature, the reaction mixture was quenched slowly in saturated ammonium chloride solution (50 mL) and extracted with ethyl acetate (3x100 mL). The combined organic layers were washed with a brine solution (1x50 mL), dried over anhydrous sodium sulphate and concentrated under reduced pressure at 45°C to get crude product (8.0 gm), which was purified by column chromatography (silica gel 230-400 mesh; ethyl acetate : n-hexane, 30:70) to get the compound of Formula 10a.

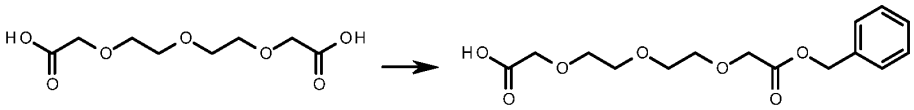
Step II: Preparation of 2-[2-[2-(carboxymethyloxy)ethoxy]ethoxy]acetic acid (Formula 10b).



Formula 10a Formula 10b

TFA (5 mL) was added dropwise to a stirred solution of the compound of Formula 10a (2.5 gm, 7.46 mmol) in DCM (15 mL) at RT. The reaction mixture was stirred for 2 hrs and then concentrated and degassed completely under reduced pressure at 40°C to get the compound of Formula 10b (2.0 gm), which was used as such for the next step.

Step III: Preparation of 2-[2-[2-(2-benzyloxy-2-oxo-ethoxy)ethoxy]ethoxy]acetic acid (Formula 10c).

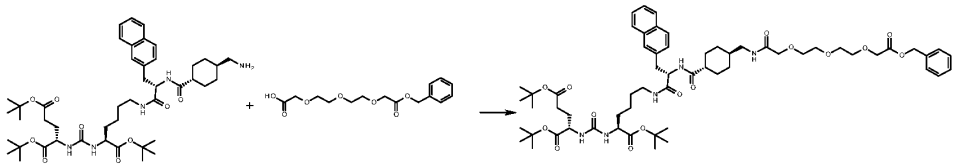


Formula 10b Formula 10c

TEA (3.25 mL, 23.4 mmol) was added to a stirred solution of the compound of Formula 10b (2.0 gm, 9.0 mmol) in acetone (14 mL) at RT. The reaction mixture was stirred for 15 min and then cooled to 0-5°C. Benzyl bromide (1.12 mL, 9.46 mmol) was added dropwise to the

reaction mixture at 0-5°C, and the reaction mixture was stirred for 15 min and then the overnight at RT. After the completion of reaction, the reaction mixture was filtered, washed with acetone (3x20 mL) and then the combined filtrates were concentrated under reduced pressure at 45°C. Water (20 mL) was added to the residue. The resulting mixture was acidified to pH~4 with a 2N HCl solution and then extracted with ethyl acetate (3x40 mL). The combined organic layers were washed with a brine solution (1x25 mL), dried over anhydrous sodium sulphate and concentrated under reduced pressure at 45°C to get the crude product, which was purified by column chromatography (silica gel 230-400 mesh; DCM: methanol, 95:5) to get the compound of Formula 10c.

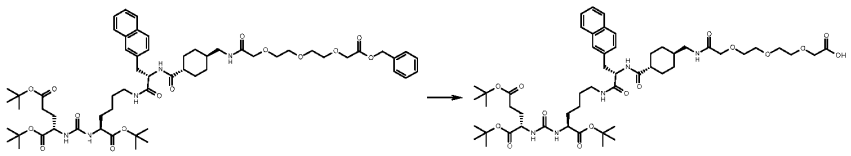
Step IV: Preparation of *di-tert*-butyl (2*S*)-2-[[(1*S*)-5-[[(2*S*)-2-[[4-[[[2-[2-[2-(2-benzyloxy-2-oxo-ethoxy)ethoxy]ethoxy]acetyl]amino]methyl]cyclohexane carbonyl]amino]-3-(2-naphthyl)propanoyl]amino]-1-*tert*-butoxycarbonyl-pentyl]carbamoylamino] pentanedioate (Formula 10d).



Formula 1f Formula 10c Formula 10d

TBTU (0.07 g, 0.21 mmol) and DIPEA (0.07 mL, 0.4 mmol) was added to a stirred solution containing the compound of Formula 1f (0.13 g, 0.16 mmol) and the compound of Formula 10c (0.05 g, 0.16 mmol) in DMF (2 mL) at RT. The reaction mixture was stirred overnight and then concentrated under reduced pressure at 50°C to give the crude product which was purified by column chromatography (silica gel 230-400 mesh, DCM:methanol, 95:5) to get the compound of Formula 10d.

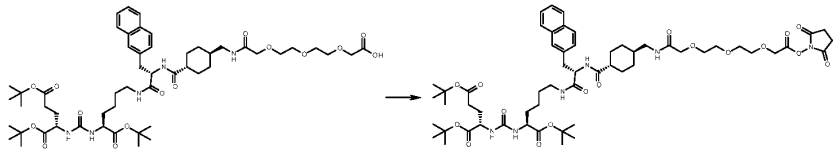
Step V : Preparation of 2-[2-[2-[2-[[4-[[(1*S*)-2-[[(5*S*)-6-*tert*-butoxy-5-[[(1*S*)-4-*tert*-butoxy-1-*tert*-butoxycarbonyl-4-oxo-butyl]carbamoylamino]-6-oxo-hexyl]amino] -1-(2-naphthylmethyl)-2-oxo-ethyl]carbamoyl]cyclohexyl]methylamino]-2-oxo-ethoxy]ethoxy]ethoxy] acetic acid Formula 10e.



Formula 10d Formula 10e

Palladium on carbon (10%, 50% wet, 0.03 g) was added to a stirred solution of the compound of Formula 10d (0.15 g, 0.134 mmol) in methanol (2.5 mL) at RT. Hydrogen gas was purged through the reaction mixture at RT and then the reaction mixture was stirred for 1 hr. After this time, the reaction mixture was filtered through Celite® bed and washed with excess methanol. The combined filtrates were concentrated under reduced pressure at 45°C to get the compound of Formula 10e (0.115 gm), which is used for the next step without further purification.

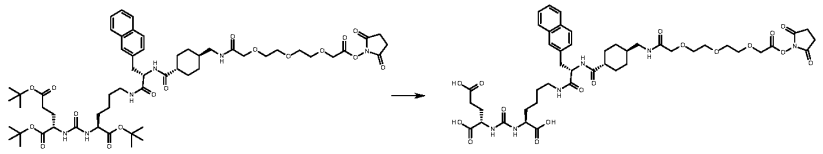
Step VI : Preparation of *di-tert*-butyl (2*S*)-2-[[(1*S*)-1-*tert*-butoxycarbonyl-5-[[(2*S*)-2-[[4-[[[2-[2-[2-[2-(2,5-dioxopyrrolidin-1-yl)oxy-2-oxo-ethoxy]ethoxy]ethoxy] acetyl]amino]methyl]cyclohexanecarbonyl]amino]-3-(2-naphthyl)propanoyl] amino]pentyl]carbamoyl amino]pentanedioate.



Formula 10e Formula 10f

NHS (0.02 g, 0.17 mmol) and EDAC (0.032 g, 0.17 mmol) was added to a stirred solution of the compound of Formula 10e (0.1 g, 0.097 mmol) in DMF (2 mL) at RT. the resulting mixture was stirred overnight. After this time, additional NHS (0.011 g, 0.097 mmol) and EDAC (0.019 g, 0.097 mmol) were added to the reaction mixture, and the reaction mixture was stirred at 55°C for 4 hrs. The reaction mixture was quenched in water (4 mL) and extracted with DCM (3x10 mL). The combined organic layers were washed by a brine solution (1x5 mL), dried over anhydrous sodium sulphate and concentrated under reduced pressure at 40°C to get the compound of Formula 10f (0.1 g), which was used for the next step without purification.

Step VII: Preparation of (2*S*)-2-[[(1*S*)-1-carboxy-5-[[(2*S*)-2-[[4-[[[2-[2-[2-[2-(2,5-dioxopyrrolidin-1-yl)oxy-2-oxo-ethoxy]ethoxy]ethoxy]acetyl]amino]methyl] cyclohexane carbonyl]amino]-3-(2-naphthyl)propanoyl]amino]pentyl]carbamoyl amino] pentanedioic acid Formula 10g.

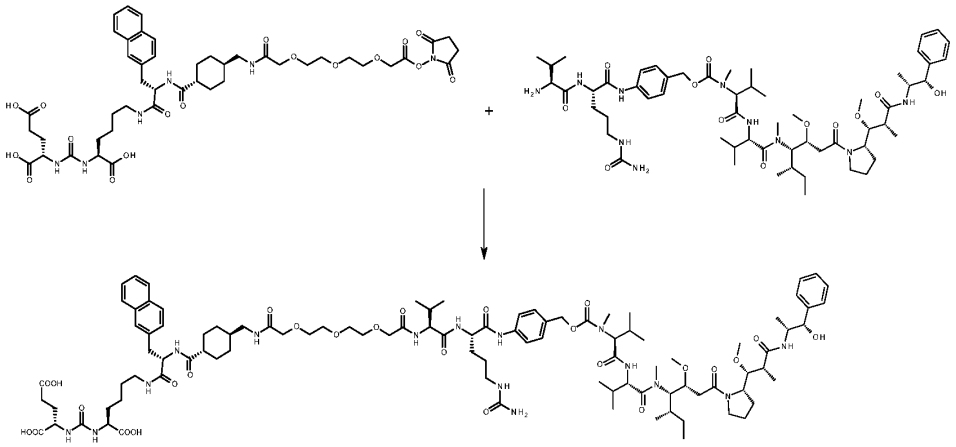


Formula 10f Formula 10g

TFA (0.5 mL) was added to a stirred solution of the compound of Formula 10f (0.1 g, 0.089 mmol) in DCM (2 mL) at 0-5°C. The reaction mixture was then stirred at RT for 6 hrs. After

completion of reaction the reaction mixture was concentrated and degassed under reduced pressure at 30°C. The crude product was leached with diethyl ether (2x2 ml). The diethyl ether layer was decanted and dried to get the compound of Formula 10g, which was used for next step as such.

Step VI : Preparation of Compound no 1.9



Compound no 1.9

TEA (0.06 mL, 0.45 mmol) was added to a stirred solution of the compound of Formula 1n (0.05 g, 0.045 mmol) in DMF (1 mL) and the resulting mixture was stirred for clear solution. The compound of Formula 10g (0.055 g, 0.057 mmol) was added to the reaction mixture, and the resulting mixture was stirred at RT for 24 hrs. . After this time, the reaction mixture was concentrated and degassed under reduced pressure at 50°C. DCM (5 mL) was added to the residue and the resulting mixture was stirred at RT for 30 min. The crude product obtained was filtered, washed with DCM (3x5 mL) and dried under vacuum. The crude product was purified using preparative HPLC to get Compound no 1.9, mass 1963.52$[M+H]^+$.

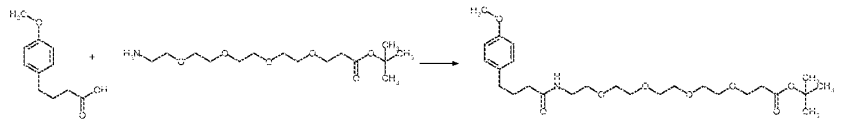
Table 7 set forth below provides mass spectral data for the compounds of the instant invention. The compounds for which data is provided below but for which a description of the synthesis is not explicitly provided above were made in an analogous manner to the synthetic procedures provided above in Example 10.

Table 7:

Compound No	Mass (m/z) $[M+H]^{2+}$
1.72	1006.66 $[M+2H]^{2+}$
1.73	1172.65 $[M+2H]^{2+}$

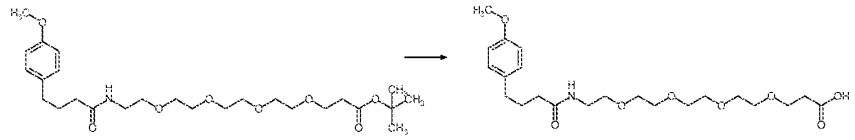
Example 11: Preparation of Compound no 1.74

Step I: Preparation of tert-butyl 3-[2-[2-[2-[2-[4-(4-methoxyphenyl)butanoylamino] ethoxy]ethoxy]ethoxy]ethoxy]propanoate.



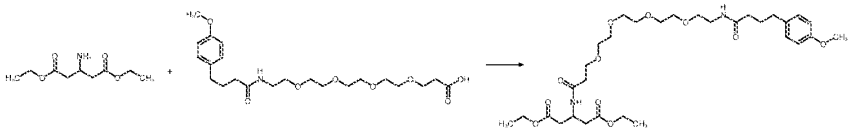
N, N-diisopropylethylamine (0.7 mL, 3.86 mmol) is added to stirred solution of 4-(4-methoxyphenyl)butanoic acid (0.3 gm, 1.54 mmol), tert-butyl 3-[2-[2-[2-(2-aminoethoxy)ethoxy]ethoxy]ethoxy]propanoate (0.5 gm, 1.54 mmol) and 1-[bis(dimethylamino)methylene]-1H-1,2,3-triazolo[4,5-b]pyridinium 3-oxide hexafluoro phosphate (HATU, 0.7 gm, 1.85 mmol) in N, N-dimethylformamide (10 mL) at room temperature and stirred overnight. Reaction mixture is quenched with D. M. water (1x20 mL) and extracted with ethyl acetate (3x30 mL). Combined organic layer is washed with 0.5 N HCl solution (1x20 mL) followed by saturated sodium bicarbonate solution (1x20 mL), D. M. water (1x20 mL) and brine solution (1x20 mL). Finally, it is dried over anhydrous sodium sulphate and concentrated under reduced pressure at 50^0 C to get tert-butyl 3-[2-[2-[2-[2-[4-(4-methoxyphenyl)butanoylamino]ethoxy]ethoxy]ethoxy]ethoxy]propanoate (0.75 gm), which is used for the next step without purification.

Step II: Preparation of 3-[2-[2-[2-[2-[4-(4-methoxyphenyl)butanoylamino]ethoxy] ethoxy]ethoxy]ethoxy]propanoic acid.



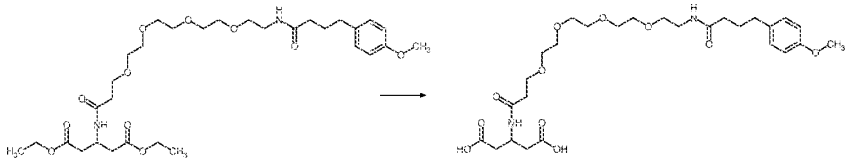
Trifluoroacetic acid (2.25 mL) is added to a stirred solution of tert-butyl 3-[2-[2-[2-[2-[4-(4-methoxyphenyl)butanoylamino]ethoxy]ethoxy]ethoxy]ethoxy]propanoate (0.75 gm, 1.51 mmol) in dichloromethane (7.5 mL) at $0\text{-}5^0$ C and stirred for 10 min. Reaction mixture is then allowed to attain room temperature and stirred for 3 hrs. Reaction mixture is concentrated under reduced pressure at 35^0 C. Diethyl ether (20 ml) is added to the residue and stirred for 30 min. Diethyl ether is then decant off. This process is repeated thrice to remove the traces of trifluoroacetic acid and then the residue is dried to get 3-[2-[2-[2-[2-[4-(4-methoxy phenyl)butanoylamino]ethoxy]ethoxy]ethoxy]ethoxy]propanoic acid (0.65 gm), whichisused for the next step without purification.

Step III: Preparation diethyl 3-[3-[2-[2-[2-[2-[4-(4-methoxyphenyl)butanoylamino] ethoxy]ethoxy]ethoxy]ethoxy]propanoylamino]pentanedioate.



N, N-diisopropylethylamine (0.63 mL, 3.68 mmol) is added to stirred solution of diethyl 3-aminopentanedioate (0.3 gm, 1.48 mmol), 3-[2-[2-[2-[2-[4-(4-methoxy phenyl)butanoylamino]ethoxy]ethoxy]ethoxy]ethoxy]propanoic acid (0.65 gm, 1.48 mmol) and 1-[bis(dimethylamino)methylene]-1H-1,2,3-triazolo[4,5-b]pyridinium 3-oxide hexafluoro phosphate (HATU, 0.67 gm, 1.77 mmol) in N, N-dimethylformamide (10 mL) at room temperature and stirred overnight. Reaction mixture is quenched with D. M. water (1x20 mL) and extracted with ethyl acetate (3x30 mL). Combined organic layer is washed with 0.5 N HCl solution (1x20 mL) followed by saturated sodium bicarbonate solution (1x20 mL), D. M. water (1x20 mL) and brine solution (1x20 mL). Finally, itisdried over anhydrous sodium sulphate and concentrated under reduced pressure at 50^0 C to get to crude product (0.8 gm), which is purified by column chromatography (silica gel 230-400 mesh; dichloromethane: methanol, 98:2) to get diethyl 3-[3-[2-[2-[2-[2-[4-(4-methoxyphenyl)butanoylamino]ethoxy]ethoxy] ethoxy]ethoxy]propanoylamino]pentanedioate (0.63 gm).

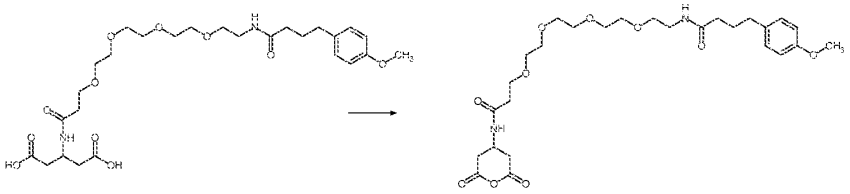
Step III: Preparation of 3-[3-[2-[2-[2-[2-[4-(4-methoxyphenyl)butanoylamino] ethoxy]ethoxy]ethoxy]ethoxy]propanoylamino]pentanedioic acid.



A solution of lithium hydroxide (0.093 g, 2.21 mmol) in D. M. water (1.9 mL) is added to a stirred solution of diethyl 3-[3-[2-[2-[2-[2-[4-(4-methoxyphenyl)butanoylamino]ethoxy]ethoxy]ethoxy]ethoxy]propanoylamino]pentanedioate (0.63 g, 1.0 mmol) in ethanol (4.4 mL) at room temperature and stirred for 2 hours. Reaction mixture is concentrated under reduced pressure at 35^0C. D. M. water (5 mL) is added to the residue and acidified using 0.5 N HCl solution upto pH~4. Aqueous layer is made saturated with solid NaCl and then extracted with ethyl acetate (3x20 mL). Combined organic layer is

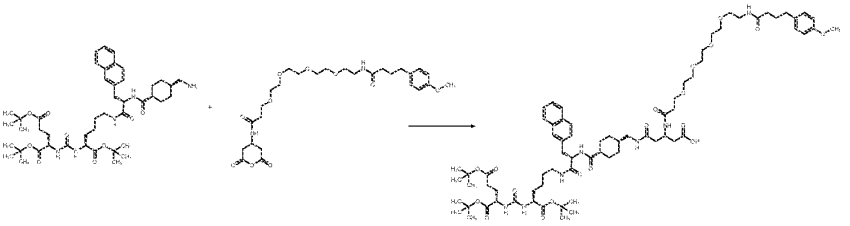
washed with brine solution (1x10 mL), dried over anhydrous sodium sulphate and concentrated under reduced pressure at 45^0 C to get 3-[3-[2-[2-[2-[2-[4-(4-methoxyphenyl)butanoylamino] ethoxy]ethoxy]ethoxy]ethoxy]propanoylamino]pentanedioic acid, (0.53 gm), which is used for the next step without purification.

Step IV: Preparation of N-[2-[2-[2-[2-[3-[(2, 6-dioxotetrahydropyran-4-yl)amino]-3-oxo-propoxy]ethoxy]ethoxy]ethoxy]ethyl]-4-(4-methoxyphenyl)butanamide.



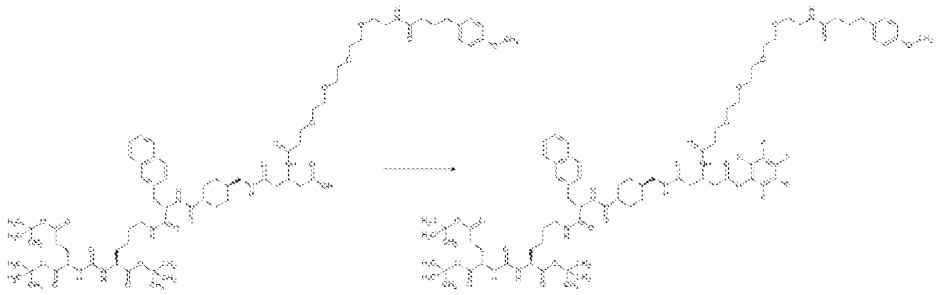
N, N′- Dicyclohexylcarbodiimide (DCC, 0.24 gm, 1.16 mmol) is added to a stirred solution of 3-[3-[2-[2-[2-[2-[4-(4-methoxyphenyl)butanoylamino]ethoxy]ethoxy]ethoxy]ethoxy] propanoylamino]pentanedioic acid (0.53 gm, 0.93 mmol) in tetrahydrofuran (10 mL) at room temperature and stirred overnight. Next day, again, N, N′-Dicyclohexylcarbodiimide (DCC, 0.24 gm, 1.16 mmol) followed by molecular sieves (4A^0, 0.5 gm) and tetrahydrofuran (10 mL) are added to the reaction mixture at room temperature and stirred for 8 hrs. Reaction mixture is filtered through celite bed and washed with tetrahydrofuran (3x10 mL). Combined filtrate is concentrated under vacuum at 45^0 C to get N-[2-[2-[2-[2-[3-[(2, 6-dioxotetrahydropyran-4-yl)amino]-3-oxo-propoxy]ethoxy]ethoxy]ethoxy]ethyl]-4-(4-methoxyphenyl)butanamide, which is used for the next step without purification by considering 100% yield (0.51 gm). Actual crude material is more around 0.8 g which contained DCU as side product. It is used as such for the next step without further purification.

Step V: Preparation of 5-[[4-[[(1S)-2-[[(5S)-6-tert-butoxy-5-[[(1S)-4-tert-butoxy-1-tert-butoxycarbonyl-4-oxo-butyl]carbamoylamino]-6-oxo-hexyl]amino]-1-(2-naphthyl methyl)-2-oxo-ethyl]carbamoyl]cyclohexyl]methylamino]-3-[3-[2-[2-[2-[2-[4-(4-methoxy phenyl)butanoylamino]ethoxy]ethoxy]ethoxy]ethoxy]propanoylamino]-5-oxo-pentanoic acid.



N, N - Diisopropylethylamine (0.3 mL, 1.82 mmol) is added to a stirred solution of di-tert-butyl (2S)-2-[[(1S)-5-[[(2S)-2-[[4-(aminomethyl)cyclohexanecarbonyl]amino]-3-(2-naphthyl) propanoyl]amino]-1-tert-butoxycarbonyl-pentyl]carbamoylamino]pentanedioate (0.6 g, 0.73 mmol) and N-[2-[2-[2-[2-[3-[(2, 6-dioxotetrahydropyran-4-yl)amino]-3-oxo-propoxy]ethoxy] ethoxy]ethoxy]ethyl]-4-(4-methoxyphenyl)butanamide (0.5 g, 0.87 mmol, by considering 100% yield) in a mixture of N, N-dimethyl formamide (6 mL) and acetonitrile (6 mL) under nitrogen atmosphere and then stirred overnight at room temperature. D. M. water (10 mL) is added to the reaction mixture and acidified it with aqueous citric acid solution (20% solution) up to pH~4. It is then extracted with ethyl acetate (3x30 mL). Combined organic layer is washed with brine solution (1x20 mL) and dried over anhydrous sodium sulphate. Organic layer is concentrated under reduced pressure to get to crude product, which is purified by column chromatography (silica gel 230-400 mesh; dichloromethane: methanol, 85:15) to get 5-[[4-[[(1S)-2-[[(5S)-6-tert-butoxy-5-[[(1S)-4-tert-butoxy-1-tert-butoxycarbonyl-4-oxo-butyl] carbamoylamino]-6-oxo-hexyl]amino]-1-(2-naphthylmethyl)-2-oxo-ethyl]carbamoyl] cyclohexyl]methylamino]-3-[3-[2-[2-[2-[2-[4-(4-methoxyphenyl)butanoylamino]ethoxy] ethoxy]ethoxy]ethoxy]propanoylamino]-5-oxo-pentanoic acid (0.66 gm).

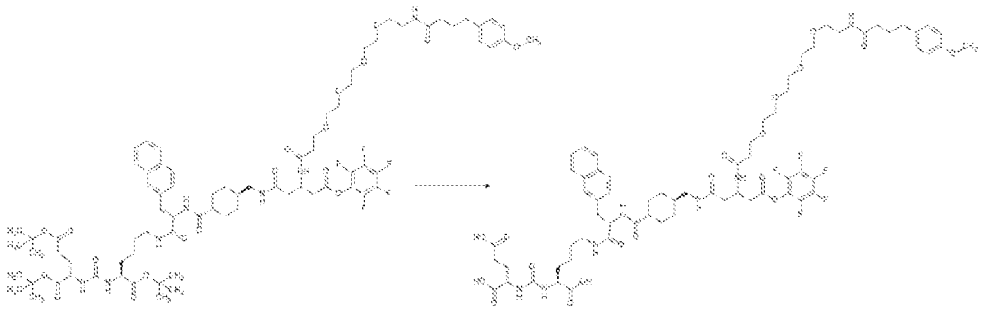
Step VI: Preparation of di-tert-butyl (2S)-2-[[(1S)-1-tert-butoxycarbonyl-5-[[(2S)-2-[[4-[[[3-[3-[2-[2-[2-[2-[4-(4-methoxyphenyl)butanoylamino]ethoxy]ethoxy]ethoxy]ethoxy] propanoylamino]-5-oxo-5-(2,3,4,5,6-pentafluorophenoxy)pentanoyl]amino]methyl] cyclohexanecarbonyl]amino]-3-(2-naphthyl)propanoyl]amino]pentyl]carbamoylamino] pentanedioate.



Pentafluorophenol (0.1 g, 0.57 mmol) followed by 1-ethyl-3-(3-dimethylaminopropyl)carbodiimide hydrochloride (0.11 g, 0.57 mmol) are added to a stirred solution of 5-[[4-[[(1S)-2-[[(5S)-6-tert-butoxy-5-[[(1S)-4-tert-butoxy-1-tert-butoxycarbonyl-4-oxo-butyl]carbamoylamino]-6-oxo-hexyl]amino]-1-(2-naphthylmethyl)-2-oxo-ethyl]

carbamoyl]cyclohexyl]methylamino]-3-[3-[2-[2-[2-[2-[4-(4-methoxyphenyl)butanoylamino] ethoxy]ethoxy]ethoxy]ethoxy]propanoylamino]-5-oxo-pentanoic acid (0.65 g, 0.47 mmol) in N, N-dimethyl formamide (6.5 mL) at room temperature and stirred overnight. Reaction mixture is quenched with D. M. water (10 mL) and extracted with dichloromethane (3x20 mL). Combined organic layer is washed by brine solution (1x20 mL), dried over anhydrous sodium sulphate and concentrated under reduced pressure at 40^0 C to get di-tert butyl (2S)-2-[[(1S)-1-tert-butoxycarbonyl-5-[[(2S)-2-[[4-[[[3-[3-[2-[2-[2-[2-[4-(4-methoxyphenyl) butanoylamino]ethoxy]ethoxy]ethoxy]ethoxy]propanoylamino]-5-oxo-5-(2,3,4,5,6-pentafluorophenoxy)pentanoyl]amino]methyl]cyclohexanecarbonyl]amino]-3-(2-naphthyl) propanoyl]amino]pentyl]carbamoylamino]pentanedioate (0.7 gm), which is used for the next step without purification.

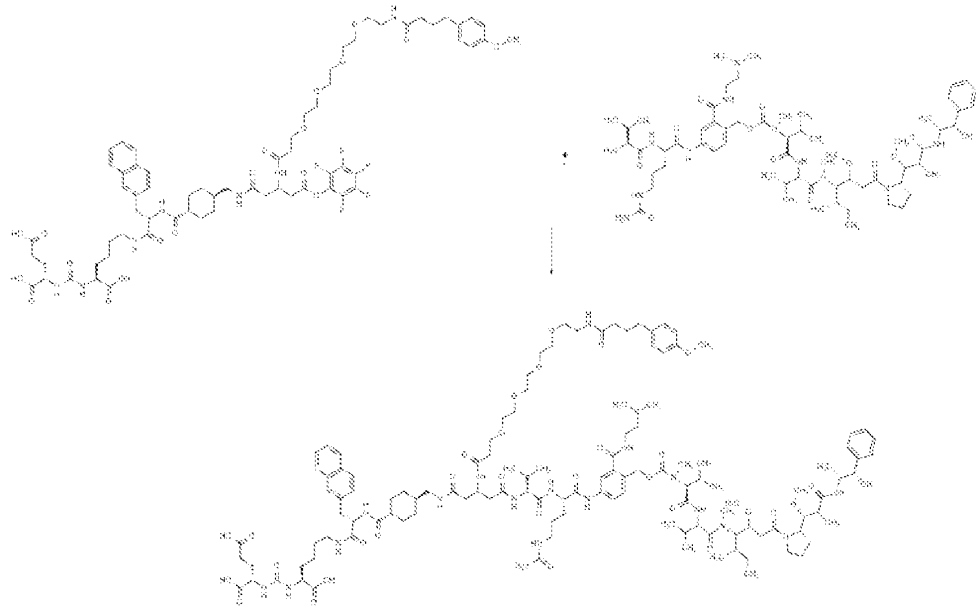
Step VII: Preparation of (2S)-2-[[(1S)-1-carboxy-5-[[(2S)-2-[[4-[[[3-[3-[2-[2-[2-[2-[4-(4-methoxyphenyl)butanoylamino]ethoxy]ethoxy]ethoxy]ethoxy]propanoylamino]-5-oxo-5-(2,3,4,5,6-pentafluorophenoxy)pentanoyl]amino]methyl]cyclohexanecarbonyl]amino]-3-(2-naphthyl)propanoyl]amino]pentyl]carbamoylamino]pentanedioic acid.



Trifluoroacetic acid (3.5 mL) is added to stirred solution of di-tert butyl (2S)-2-[[(1S)-1-tert butoxycarbonyl-5-[[(2S)-2-[[4-[[[3-[3-[2-[2-[2-[2-[4-(4-methoxyphenyl)butanoylamino] ethoxy]ethoxy]ethoxy]ethoxy]propanoylamino]-5-oxo-5-(2,3,4,5,6-pentafluorophenoxy) pentanoyl]amino]methyl]cyclohexanecarbonyl]amino]-3-(2-naphthyl)propanoyl]amino] pentyl]carbamoylamino]pentanedioate (0.7 g, 0.45 mmol) in dichloromethane (7 mL) at $0\text{-}5^0$ C. Reaction mixture is then allowed to stir at room temperature and stirred for 6 hrs. Reaction mixture is concentrated and degassed under reduced pressure at 30^0 C. Crude product is leached with diethyl ether (2x20 ml), decant off the diethyl ether layer and dried to get (2S)-2-[[(1S)-1-carboxy-5-[[(2S)-2-[[4-[[[3-[3-[2-[2-[2-[2-[4-(4-methoxyphenyl)butanoylamino] ethoxy]ethoxy]ethoxy]ethoxy]propanoylamino]-5-oxo-5-(2,3,4,5,6-pentafluorophenoxy)

pentanoyl]amino]methyl]cyclohexanecarbonyl]amino]-3-(2-naphthyl)propanoyl]amino] pentyl]carbamoylamino]pentanedioic acid (0.6 gm).

Step VIII: Preparation of (2S)-2-[[(1S)-1-carboxy-5-[[(2S)-2-[[4-[[[5-[[(1S)-1-[[(1S)-1-[[3-[2-(dimethylamino)ethylcarbamoyl]-4-[[[(1S)-1-[[(1S)-1-[[(1S,2R)-4-[(2S)-2-[(1R,2R)-3-[[(1R,2S)-2-hydroxy-1-methyl-2-phenyl-ethyl]amino]-1-methoxy-2-methyl-3-oxo-propyl]pyrrolidin-1-yl]-2-methoxy-1-[(1S)-1-methylpropyl]-4-oxo-butyl]-methyl-carbamoyl]-2-methyl-propyl]carbamoyl]-2-methyl-propyl]-methyl-carbamoyl] oxymethyl]phenyl]carbamoyl]-4-ureido-butyl]carbamoyl]-2-methyl-propyl]amino]-3-[3-[2-[2-[2-[2-[4-(4-methoxyphenyl)butanoylamino]ethoxy]ethoxy]ethoxy]ethoxy] propanoylamino]-5-oxo-pentanoyl]amino]methyl]cyclohexanecarbonyl]amino]-3-(2-naphthyl)propanoyl]amino]pentyl]carbamoylamino]pentanedioic acid.



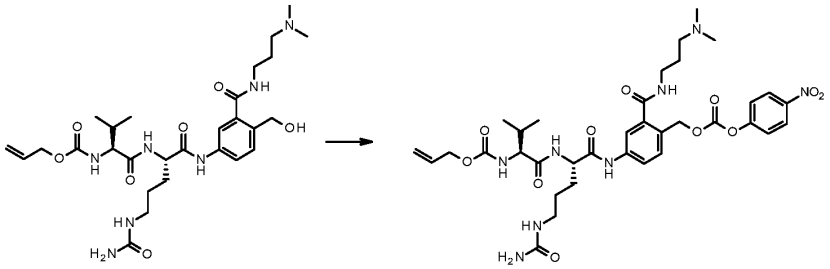
Triethylamine (0.09 mL, 0.61 mmol) is added to a stirred solution of [4-[[(2S)-2-[[(2S)-2-amino-3-methyl-butanoyl]amino]-5-ureido-pentanoyl]amino]-2-[2-(dimethylamino)ethyl carbamoyl]phenyl]methyl N-[(1S)-1-[[(1S)-1-[[(1S,2R)-4-[(2S)-2-[(1R,2R)-3-[[(1R,2S)-2-hydroxy-1-methyl-2-phenyl-ethyl]amino]-1-methoxy-2-methyl-3-oxo-propyl]pyrrolidin-1-yl]-2-methoxy-1-[(1S)-1-methylpropyl]-4-oxo-butyl]-methyl-carbamoyl]-2-methyl-propyl] carbamoyl]-2-methyl-propyl]-N-methyl-carbamate (0.075 g, 0.061 mmol) in DMF (1.5 mL). (2S)-2-[[(1S)-1-Carboxy-5-[[(2S)-2-[[4-[[[3-[3-[2-[2-[2-[2-[4-(4-methoxyphenyl)butanoyl amino]ethoxy]ethoxy]ethoxy]ethoxy]propanoylamino]-5-oxo-5-(2,3,4,5,6-pentafluoro

phenoxy)pentanoyl]amino]methyl]cyclohexanecarbonyl]amino]-3-(2-naphthyl)propanoyl] amino]pentyl]carbamoylamino]pentanedioic acid (0.1 g, 0.073 mmol) is added to the reaction mixture and stirred for 2 hrs at room temperature. Diethyl ether (6 mL) is added to the reaction mixture and stirred at room temperature for 1 hour. Solid thus obtained is filtered under nitrogen atmosphere, washed with diethyl ether and the crude is purified by preparative HPLC to get (2S)-2-[[(1S)-1-carboxy-5-[[(2S)-2-[[4-[[[1-[[(1S)-1-[[4-[[[(1S)-1-[[(1S)-1-[[(1S,2R)-4-[(2S)-2-[(1R,2R)-3-[[(1R,2S)-2-hydroxy-1-methyl-2-phenyl-ethyl]amino]-1-methoxy-2-methyl-3-oxo-propyl]pyrrolidin-1-yl]-2-methoxy-1-[(1S)-1-methyl propyl]-4-oxo-butyl]-methyl-carbamoyl]-2-methyl-propyl] carbamoyl]-2-methyl-propyl]-methyl-carbamoyl] oxymethyl]phenyl]carbamoyl]-4-ureido-butyl]carbamoyl]cyclobutane carbonyl]amino] methyl]cyclohexanecarbonyl]amino]-3-(2-naphthyl)propanoyl]amino]pentyl]carbamoyl amino]pentanedioic acid; mass (m/z) 1214.70 [M+2H]2+.

Compound no. 1.65 was made in an analogous manner as the synthetic procedures provided above in Example 11; 1.65: mass (m/z) 1090.86 [M+2H]2+

Example 12: Preparation of Compound no 1.78

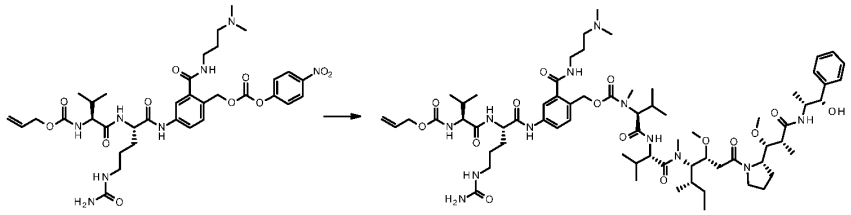
Step I: Preparation of [4-[[(2S)-2-[[(2S)-2-(allyloxycarbonylamino)-3-methyl-butanoyl] amino]-5-ureido-pentanoyl]amino]-2-[3-(dimethylamino)propylcarbamoyl] phenyl]methyl (4-nitrophenyl) carbonate.



N, N-Diisopropylethylamine (0.35 mL, 2.03 mmol) is added to stirred solution of allyl N-[(1S)-1-[[(1S)-1-[[3-[3-(dimethylamino)propylcarbamoyl]-4-(hydroxymethyl)phenyl]carbamoyl]-4-ureido-butyl]carbamoyl]-2-methyl-propyl]carbamate (0.4 g, 0.68 mmol) in tetrahydrofuran (4 mL) at room temperature. Bis(4-nitrophenyl)carbonate (0.35 g, 1.15 mmol) is added to the reaction mixture and stirred for 5 hrs. Reaction mixture is concentrated under reduced pressure at 40^0 C. Diethyl ether (20 mL) is added to the residue and stirred at room temperature for 45 min. Diethyl ether is decanted off. This process is repeated thrice and then the residue is dried to get [4-[[(2S)-2-[[(2S)-2-(allyloxycarbonylamino)-3-methyl-butanoyl]amino]-5-ureido-

pentanoyl]amino]-2-[3-(dimethylamino)propylcarbamoyl]phenyl]methyl (4-nitrophenyl) carbonate (0.75 g), which is used for the next step without further purification.

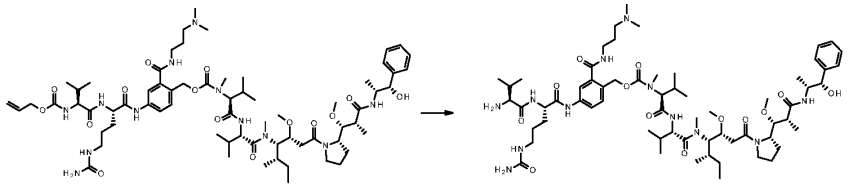
Step II : Preparation of [4-[[(2S)-2-[[(2S)-2-(allyloxycarbonylamino)-3-methyl-butanoyl] amino]-5-ureido-pentanoyl]amino]-2-[3-(dimethylamino)propylcarbamoyl]phenyl] methyl N-[(1S)-1-[[(1S)-1-[[(1S,2R)-4-[(2S)-2-[(1R,2R)-3-[[(1R,2S)-2-hydroxy-1-methyl-2-phenyl-ethyl]amino]-1-methoxy-2-methyl-3-oxo-propyl]pyrrolidin-1-yl]-2-methoxy-1-[(1S)-1-methylpropyl]-4-oxo-butyl]-methyl-carbamoyl]-2-methyl-propyl]carbamoyl]-2-methyl-propyl]-N-methyl-carbamate.



1-Hydroxybenzotriazole (40 mg, catalytic amount) followed by N, N-diisopropylethylamine (0.35 mL, 2.03 mmol) is added to a stirred solution of [4-[[(2S)-2-[[(2S)-2-(allyloxycarbonylamino)-3-methyl-butanoyl]amino]-5-ureido-pentanoyl]amino]-2-[3-(dimethylamino)propylcarbamoyl]phenyl]methyl (4-nitrophenyl) carbonate (0.5 g, 0.66 mmol) and Monomethyl auristatin E (0.48 g, 0.67 mmol) in N, N-dimethyl formamide (10 mL) at room temperature and stirred for 48 hrs. Reaction mixture is concentrated under reduced pressure at 55^0 C. Crude material thus obtained is purified by column chromatography (silica gel 230-400 mesh; dichloromethane : methanol : aqueous ammonia 83:15:2) to get [4-[[(2S)-2-[[(2S)-2-(allyloxycarbonylamino)-3-methyl-butanoyl]amino]-5-ureido-pentanoyl]amino]-2-[3-(dimethylamino)propylcarbamoyl]phenyl]methyl N-[(1S)-1-[[(1S)-1-[[(1S,2R)-4-[(2S)-2-[(1R,2R)-3-[[(1R,2S)-2-hydroxy-1-methyl-2-phenyl-ethyl]amino]-1-methoxy-2-methyl-3-oxo-propyl]pyrrolidin-1-yl]-2-methoxy-1-[(1S)-1-methylpropyl]-4-oxo-butyl]-methyl-carbamoyl]-2-methyl-propyl]carbamoyl]-2-methyl-propyl]-N-methyl-carbamate. (0.5 g).

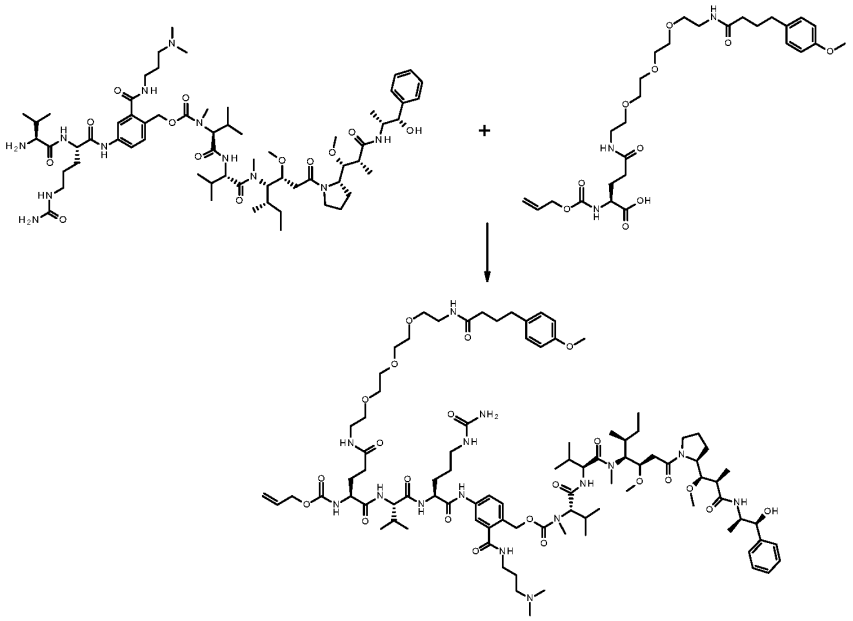
Step III: Preparation of [4-[[(2S)-2-[[(2S)-2-amino-3-methyl-butanoyl]amino]-5-ureido-pentanoyl]amino]-2-[3-(dimethylamino)propylcarbamoyl]phenyl]methyl N-[(1S)-1-[[(1S)-1-[[(1S,2R)-4-[(2S)-2-[(1R,2R)-3-[[(1R,2S)-2-hydroxy-1-methyl-2-phenyl-ethyl] amino]-1-methoxy-2-methyl-3-oxo-propyl]pyrrolidin-1-yl]-2-methoxy-1-[(1S)-1-methyl propyl]-4-

oxo-butyl]-methyl-carbamoyl]-2-methyl-propyl]carbamoyl]-2-methyl-propyl] -N-methyl-carbamate.



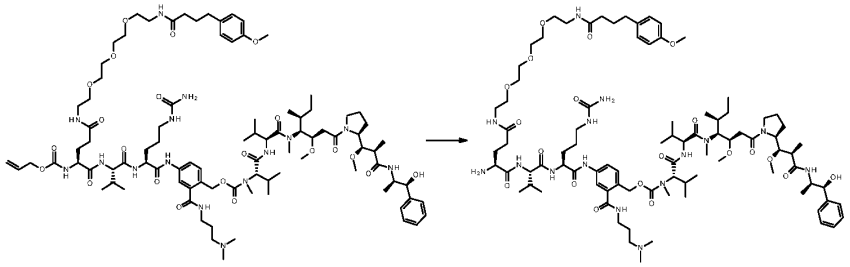
Palladium tetrakis(triphenylphosphine) (0.032 g, 0.028 mmol) is added to stirred solution of [4-[[(2S)-2-[[(2S)-2-(allyloxycarbonylamino)-3-methyl-butanoyl]amino]-5-ureido-pentanoyl] amino]-2-[3-(dimethylamino)propylcarbamoyl]phenyl]methyl N-[(1S)-1-[[(1S)-1-[[(1S,2R)-4-[(2S)-2-[(1R,2R)-3-[[(1R,2S)-2-hydroxy-1-methyl-2-phenyl-ethyl]amino]-1-methoxy-2-methyl-3-oxo-propyl]pyrrolidin-1-yl]-2-methoxy-1-[(1S)-1-methylpropyl]-4-oxo-butyl]-methyl-carbamoyl]-2-methyl-propyl]carbamoyl]-2-methyl-propyl]-N-methyl-carbamate (0.5 g, 0.37 mmol) in mixture of dichloromethane (3.5 mL) and methanol (1.5 mL) at room temperature. Morpholine (0.23 mL, 2.61 mmol) is added to the reaction mixture and stirred for 1 hr. Reaction mixture is concentrated under reduced pressure at 40^0 C. Diethyl ether (20 mL) is added to the residue and stirred at room temperature for 45 min. Diethyl ether is decanted off. This process is repeated thrice and then the residue is dried under reduced pressure at 40^0 C to get crude material, which is purified by column chromatography (silica gel 230-400 mesh; dichloromethane : methanol : aqueous ammonia, 84:14:2) to get [4-[[(2S)-2-[[(2S)-2-amino-3-methyl-butanoyl]amino]-5-ureido-pentanoyl]amino]-2-[3-(dimethylamino)propyl carbamoyl]phenyl]methyl N-[(1S)-1-[[(1S)-1-[[(1S,2R)-4-[(2S)-2-[(1R,2R)-3-[[(1R,2S)-2-hydroxy-1-methyl-2-phenyl-ethyl]amino]-1-methoxy-2-methyl-3-oxo-propyl]pyrrolidin-1-yl]-2-methoxy-1-[(1S)-1-methylpropyl]-4-oxo-butyl]-methyl-carbamoyl]-2-methyl-propyl]carbamoyl]-2-methyl-propyl]-N-methyl-carbamate. (0.26 g).

Step XI: Preparation of [4-[[(2S)-2-[[(2S)-2-[[(2S)-2-(allyloxycarbonylamino)-5-[2-[2-[2-[2-[4-(4-methoxyphenyl)butanoylamino]ethoxy]ethoxy]ethoxy]ethylamino]-5-oxo-pentanoyl]amino]-3-methyl-butanoyl]amino]-5-ureido-pentanoyl]amino]-2-[3-(dimethylamino)propylcarbamoyl]phenyl]methyl N-[(1S)-1-[[(1S)-1-[[(1S,2R)-4-[(2S)-2-[(1R,2R)-3-[[(1R,2S)-2-hydroxy-1-methyl-2-phenyl-ethyl]amino]-1-methoxy-2-methyl-3-oxo-propyl]pyrrolidin-1-yl]-2-methoxy-1-[(1S)-1-methylpropyl]-4-oxo-butyl]-methyl-carbamoyl]-2-methyl-propyl]carbamoyl]-2-methyl-propyl]-N-methyl-carbamate.



N, N-Diisopropylethylamine (0.1 mL, 0.49 mmol) is added to stirred solution of (2S)-2-(allyloxycarbonylamino)-5-[2-[2-[2-[2-[4-(4-methoxyphenyl)butanoylamino]ethoxy]ethoxy]ethoxy]ethylamino]-5-oxo-pentanoic acid (0.15 gm, 0.26 mmol), [4-[[(2S)-2-[[(2S)-2-amino-3-methyl-butanoyl]amino]-5-ureido-pentanoyl]amino]-2-[3-(dimethylamino)propyl carbamoyl]phenyl]methyl N-[(1S)-1-[[(1S)-1-[[(1S,2R)-4-[(2S)-2-[(1R,2R)-3-[[(1R,2S)-2-hydroxy-1-methyl-2-phenyl-ethyl]amino]-1-methoxy-2-methyl-3-oxo-propyl]pyrrolidin-1-yl]-2-methoxy-1-[(1S)-1-methylpropyl]-4-oxo-butyl]-methyl-carbamoyl]-2-methyl-propyl]carbamoyl]-2-methyl-propyl]-N-methyl-carbamate (0.25 gm, 0.2 mmol) and O-(benzotriazol-1-yl)-N,N,N',N'-tetramethyluronium tetrafluoroborate (TBTU, 0.09 gm, 0.26 mmol) in N, N-dimethylformamide (5 mL) at room temperature and stirred overnight. Reaction mixture is concentrated under reduced pressure at 55^0 C to get crude product, which is purified by column chromatography (silica gel 230-400 mesh; dichloromethane: methanol: aqueous ammonia (84:14:2) to get [4-[[(2S)-2-[[(2S)-2-[[(2S)-2-(allyloxycarbonylamino)-5-[2-[2-[2-[2-[4-(4-methoxyphenyl)butanoylamino]ethoxy]ethoxy]ethoxy]ethylamino]-5-oxo-pentanoyl]amino]-3-methyl-butanoyl]amino]-5-ureido-pentanoyl]amino]-2-[3-(dimethylamino)propylcarbamoyl]phenyl]methyl N-[(1S)-1-[[(1S)-1-[[(1S,2R)-4-[(2S)-2-[(1R,2R)-3-[[(1R,2S)-2-hydroxy-1-methyl-2-phenyl-ethyl]amino]-1-methoxy-2-methyl-3-oxo-propyl]pyrrolidin-1-yl]-2-methoxy-1-[(1S)-1-methylpropyl]-4-oxo-butyl]-methyl-carbamoyl]-2-methyl-propyl]carbamoyl]-2-methyl-propyl]-N-methyl-carbamate (0.26 g).

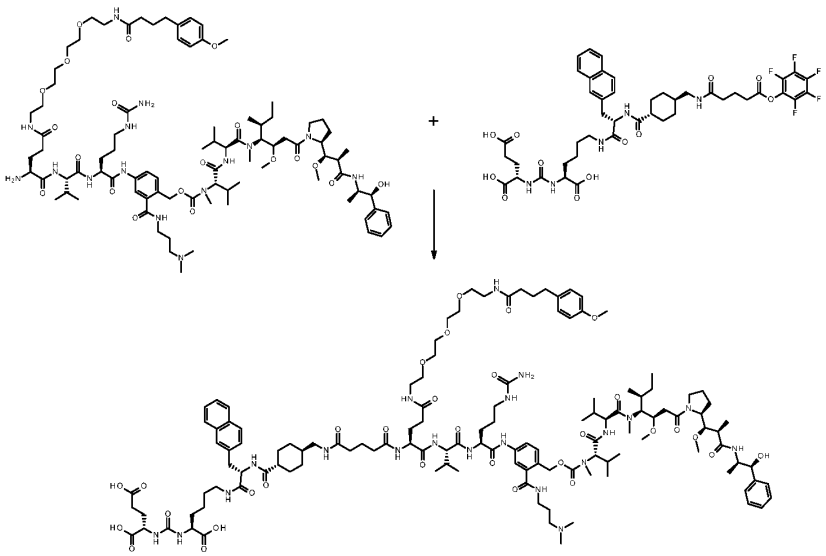
Step XII: Preparation of [4-[[(2S)-2-[[(2S)-2-[[(2S)-2-amino-5-[2-[2-[2-[2-[2-[4-(4-methoxyphenyl)butanoylamino]ethoxy]ethoxy]ethoxy]ethylamino]-5-oxo-pentanoyl] amino]-3-methyl-butanoyl]amino]-5-ureido-pentanoyl]amino]-2-[3-(dimethylamino) propylcarbamoyl]phenyl]methyl N-[(1S)-1-[[(1S)-1-[[(1S,2R)-4-[(2S)-2-[(1R,2R)-3-[[(1R,2S)-2-hydroxy-1-methyl-2-phenyl-ethyl]amino]-1-methoxy-2-methyl-3-oxo-propyl]pyrrolidin-1-yl]-2-methoxy-1-[(1S)-1-methylpropyl]-4-oxo-butyl]-methyl-carbamoyl]-2-methyl-propyl]carbamoyl]-2-methyl-propyl]-N-methyl-carbamate.



Palladium tetrakis(triphenylphosphine) (0.012 g, 0.01 mmol) is added to stirred solution of [4-[[(2S)-2-[[(2S)-2-[[(2S)-2-(allyloxycarbonylamino)-5-[2-[2-[2-[2-[4-(4-methoxyphenyl) butanoylamino]ethoxy]ethoxy]ethoxy]ethylamino]-5-oxo-pentanoyl]amino]-3-methyl-butanoyl]amino]-5-ureido-pentanoyl]amino]-2-[3-(dimethylamino)propylcarbamoyl]phenyl] methyl N-[(1S)-1-[[(1S)-1-[[(1S,2R)-4-[(2S)-2-[(1R,2R)-3-[[(1R,2S)-2-hydroxy-1-methyl-2-phenyl-ethyl]amino]-1-methoxy-2-methyl-3-oxo-propyl]pyrrolidin-1-yl]-2-methoxy-1-[(1S)-1-methylpropyl]-4-oxo-butyl]-methyl-carbamoyl]-2-methyl-propyl]carbamoyl]-2-methyl-propyl]-N-methyl-carbamate (0.25 g, 0.14 mmol) in mixture of dichloromethane (5 mL) and methanol (2.5 mL) at room temperature. Morpholine (0.09 mL, 0.96 mmol) is added to the reaction mixture and stirred for 1 hr. Reaction mixture is concentrated under reduced pressure at 35^0 C. Diethyl ether (15 mL) is added to the residue and stirred at room temperature for 45 min. Diethyl ether is decanted off. This process is repeated thrice and then the residue is dried under reduced pressure at 40^0 C to get crude material, which is purified by column chromatography (silica gel 230-400 mesh; dichloromethane : methanol : ammonia, 84:14:2) to get [4-[[(2S)-2-[[(2S)-2-[[(2S)-2-amino-5-[2-[2-[2-[2-[4-(4-methoxyphenyl)butanoylamino] ethoxy]ethoxy]ethoxy] ethylamino]-5-oxo-pentanoyl]amino]-3-methyl-butanoyl]amino]-5-ureido-pentanoyl]amino]-2-[3-(dimethylamino)propylcarbamoyl]phenyl]methyl N-[(1S)-1-[[(1S)-1-[[(1S,2R)-4-[(2S)-2-[(1R,2R)-3-[[(1R,2S)-2-hydroxy-1-methyl-2-phenyl-ethyl] amino]-1-methoxy-2-methyl-3-oxo-propyl]pyrrolidin-1-yl]-2-methoxy-1-[(1S)-1-methyl

propyl]-4-oxo-butyl]-methyl-carbamoyl]-2-methyl-propyl]carbamoyl]-2-methyl-propyl]-N-methyl-carbamate(0.22 gm).

Step XIII: Preparation of (2S)-2-[[(1S)-1-carboxy-5-[[(2S)-2-[[4-[[[5-[[(1S)-1-[[(1S)-1-[[(1S)-1-[[3-[3-(dimethylamino)propylcarbamoyl]-4-[[[(1S)-1-[[(1S)-1-[[(1S,2R)-4-[(2S)-2-[(1R,2R)-3-[[(1R,2S)-2-hydroxy-1-methyl-2-phenyl-ethyl]amino]-1-methoxy-2-methyl-3-oxo-propyl]pyrrolidin-1-yl]-2-methoxy-1-[(1S)-1-methylpropyl]-4-oxo-butyl]-methyl-carbamoyl]-2-methyl-propyl]carbamoyl]-2-methyl-propyl]-methyl-carbamoyl]oxymethyl]phenyl]carbamoyl]-4-ureido-butyl]carbamoyl]-2-methyl-propyl]carbamoyl]-4-[2-[2-[2-[2-[4-(4-methoxyphenyl)butanoylamino]ethoxy]ethoxy]ethoxy]ethylamino]-4-oxo-butyl]amino]-5-oxo-pentanoyl]amino]methyl]cyclohexanecarbonyl]amino]-3-(2-naphthyl)propanoyl]amino]pentyl]carbamoylamino]pentanedioic acid.



(2S)-2-[[(1S)-1-carboxy-5-[[(2S)-3-(2-naphthyl)-2-[[4-[[[5-oxo-5-(2,3,4,5,6-pentafluoro phenoxy)pentanoyl]amino]methyl]cyclohexanecarbonyl]amino]propanoyl]amino]pentyl]carb amoylamino]pentanedioic acid (0.07 gm, 0.075 mmol) is added to a stirred solution of [4-[[(2S)-2-[[(2S)-2-[[(2S)-2-amino-5-[2-[2-[2-[2-[4-(4-methoxyphenyl)butanoylamino]ethoxy] ethoxy]ethoxy]ethylamino]-5-oxo-pentanoyl]amino]-3-methyl-butanoyl]amino]-5-ureido-pentanoyl]amino]-2-[3-(dimethylamino)propylcarbamoyl]phenyl]methyl N-[(1S)-1-[[(1S)-1-[[(1S,2R)-4-[(2S)-2-[(1R,2R)-3-[[(1R,2S)-2-hydroxy-1-methyl-2-phenyl-ethyl]amino]-1-methoxy-2-methyl-3-oxo-propyl]pyrrolidin-1-yl]-2-methoxy-1-[(1S)-1-methylpropyl]-4-oxo-

butyl]-methyl-carbamoyl]-2-methyl-propyl]carbamoyl]-2-methyl-propyl]-N-methyl-carbamate (0.1 g, 0.058 mmol) and triethylamine (0.08 ml, 0.57 mmol) in N, N-dimethylformamide (2.0 mL) and stirred at room temperature for 4 hrs. Diethyl ether (15 mL) is added to the reaction mixture and stirred at room temperature for 1 hour. Diethyl ether is decanted-off. This process is repeated thrice. Residue is dried under reduced pressure at 40^0 C and purified by preparative HPLC to get (2S)-2-[[(1S)-1-carboxy-5-[[(2S)-2-[[4-[[[5-[[(1S)-1-[[(1S)-1-[[(1S)-1-[[3-[3-(dimethylamino)propylcarbamoyl]-4-[[[(1S)-1-[[(1S)-1-[[(1S,2R)-4-[(2S)-2-[(1R,2R)-3-[[(1R,2S)-2-hydroxy-1-methyl-2-phenyl-ethyl]amino]-1-methoxy-2-methyl-3-oxo-propyl]pyrrolidin-1-yl]-2-methoxy-1-[(1S)-1-methylpropyl]-4-oxo-butyl]-methyl-carbamoyl]-2-methyl-propyl]carbamoyl]-2-methyl-propyl]-methyl-carbamoyl] oxymethyl]phenyl]carbamoyl]-4-ureido-butyl]carbamoyl]-2-methyl-propyl]carbamoyl]-4-[2-[2-[2-[2-[4-(4-methoxyphenyl)butanoylamino]ethoxy]ethoxy]ethoxy]ethylamino]-4-oxo-butyl]amino]-5-oxo-pentanoyl]amino]methyl]cyclohexanecarbonyl]amino]-3-(2-naphthyl) propanoyl]amino]pentyl]carbamoylamino]pentanedioic acid (0.07 gm); mass (m/z) 1242.41 [M+2H]2+.

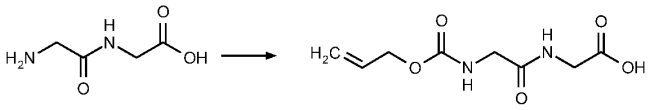
Compound no. 1.75 and 1.77 were made in an analogous manner as the synthetic procedures provided above in Example 12.

1.75: mass (m/z) 1235.61 [M+2H]2+

1.77: mass (m/z) 1146.82 [M+2H]2+

Example 13: Preparation of Compound no 1.75

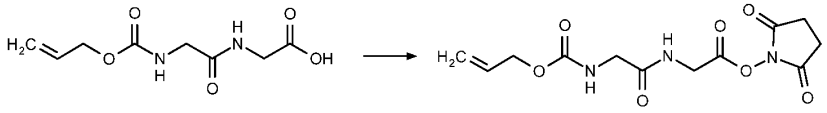
Step I: Preparation of 2-[[2-(allyloxycarbonylamino)acetyl]amino]acetic acid.



Potassium carbonate (7.85 gm, 56.8 mmol) is added to stirred solution of glycylglycine (5.0 g, 37.8 mmol) in mixture of tetrahydrofuran (100 mL) and D. M. water (100 mL) at room temperature and stirred for 10 min. Reaction mixture is cooled to $0\text{-}5^0$ C. Allyl chloroformate (4.82 mL, 45.4 mmol) is added dropwise to the reaction mixture and stirred at $0\text{-}5^0$ C for 15 min. Reaction mixture is allowed to attain room temperature and stirred overnight. Tetrahydrofuran is removed under reduced pressure at 40^0 C. D. M. water (50 mL) is added to the residue and back extracted with diethyl ether (2x100mL). Aqueous layer is acidified up to pH~4 using concentrated HCl, made saturated with solid sodium chloride and extracted with

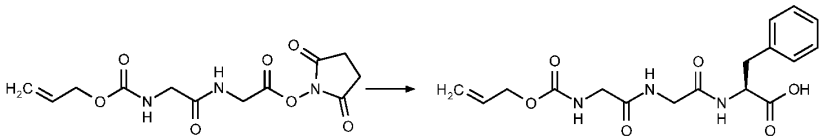
tetrahydrofuran (3x100 mL). Combined organic layer is dried over anhydrous sodium sulphate and concentrated under reduced pressure at 50^0 C to get 2-[[2-(allyloxycarbonylamino)acetyl]amino]acetic acid (7.8 g).

Step II: Preparation of (2, 5-dioxopyrrolidin-1-yl) 2-[[2-(allyloxycarbonylamino)acetyl] amino]acetate.



N-Hydroxysuccinimide (1.86 g, 16.2 mmol) followed by 1-ethyl-3-(3-dimethylamino propyl)carbodiimide hydrochloride (3.1 g, 16.2 mmol) is added to stirred solution of 2-[[2-(allyloxycarbonylamino)acetyl]amino]acetic acid (2.0 g, 9.26 mmol) in N, N-dimethyl formamide (20 mL) at room temperature and stirred overnight. Reaction mixture is diluted with dichloromethane (100 mL). Combined organic layer is washed with D. M. water (2x25 mL) followed by brine solution (1x25 mL), dried over anhydrous sodium sulphate and concentrated under reduced pressure at 40^0 C to get (2,5-dioxopyrrolidin-1-yl) 2-[[2-(allyloxycarbonylamino)acetyl]amino]acetate (2.7 gm), which is used for the next step without purification.

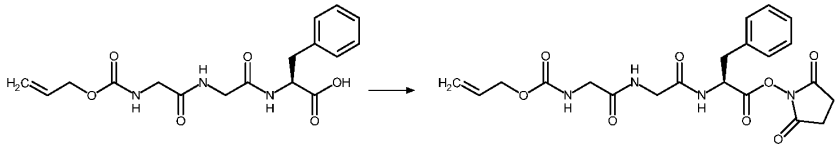
Step III: Preparation of (2S)-2-[[2-[[2-(allyloxycarbonylamino)acetyl]amino] acetyl] amino]-3-phenyl-propanoic acid.



(2, 5-Dioxopyrrolidin-1-yl) 2-[[2-(allyloxycarbonylamino)acetyl]amino]acetate (2.75 gm, 8.78 mmol) is dissolved in a mixture of N, N-dimethyl formamide (19.2 mL) and tetrahydrofuran (27.5 mL) at room temperature and stirred. Reaction mixture is cooled to $0\text{-}5^0$ C. A previously stirred clear solution of L-phenyl alanine (1.45 gm, 8.78 mmol) and triethylamine (1.1 mL, 7.9 mmol) in D. M. water (19.2 mL) is added dropwise to the reaction mixture at $0\text{-}5^0$ C and stirred for 15 min. Reaction mixture is then allowed to attain room temperature and stirred overnight. Reaction mixture is again cooled to $0\text{-}5^0$ C and acidified up to pH~4 using 2N HCl solution. It is then extracted with ethyl acetate (3x50 mL). Combined organic layer is washed with brine

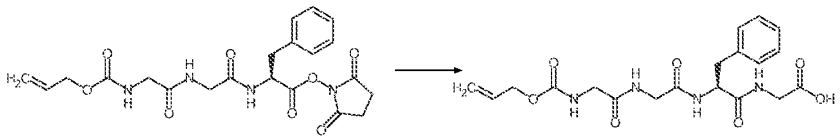
solution (1x50 mL), dried over anhydrous sodium sulphate and concentrated under reduced pressure at 50^0 C to get (2S)-2-[[2-[[2-(allyloxycarbonylamino)acetyl]amino]acetyl]amino]-3-phenyl-propanoic acid, (3.55 g), whichisused for the next step without purification.

Step IV: Preparation of (2,5-dioxopyrrolidin-1-yl) (2S)-2-[[2-[[2-(allyloxycarbonylamino) acetyl]amino]acetyl]amino]-3-phenyl-propanoate



N-Hydroxysuccinimide (1.96 g, 17.1 mmol) followed by 1-ethyl-3-(3-dimethylamino propyl)carbodiimide hydrochloride (3.26 g, 17.1 mmol) is added to stirred solution of (2S)-2-[[2-[[2-(allyloxycarbonylamino)acetyl]amino]acetyl]amino]-3-phenyl-propanoic acid (3.55 g, 9.76 mmol) in N, N-dimethyl formamide (35 mL) at room temperature and stirred overnight. Reaction mixture is diluted with dichloromethane (150 mL). Combined organic layer is washed with D. M. water (1x50 mL) followed by brine solution (1x50 mL), dried over anhydrous sodium sulphate and concentrated under reduced pressure at 40^0 C to get (2,5-dioxopyrrolidin-1-yl) (2S)-2-[[2-[[2-(allyloxycarbonylamino)acetyl]amino]acetyl]amino]-3-phenyl-propanoate (4.7 gm), whichisused for the next step without purification.

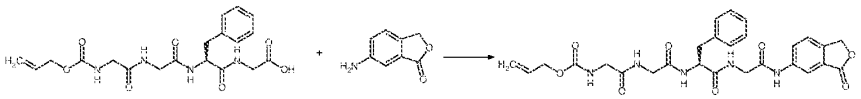
Step V: Preparation of 2-[[(2S)-2-[[2-[[2-(allyloxycarbonylamino)acetyl]amino]acetyl] amino]-3-phenyl-propanoyl]amino]acetic acid.



(2, 5-Dioxopyrrolidin-1-yl) (2S)-2-[[2-[[2-(allyloxycarbonylamino)acetyl]amino]acetyl] amino]-3-phenyl-propanoate (4.7 gm, 10.2 mmol) is dissolved in a mixture of N, N-dimethyl formamide (33.7 mL) and tetrahydrofuran (47 mL) at room temperature and stirred. Reaction mixture is cooled to $0\text{-}5^0$ C. A previously stirred clear solution of glycine (0.76 gm, 10.2 mmol) and triethylamine (1.42 mL, 10.2 mmol) in D. M. water (33.7 mL) is added dropwise to the reaction mixture at $0\text{-}5^0$ C and stirred for 15 min. Reaction mixture is then allowed to attain room temperature and stirred overnight. Reaction mixture is again cooled to $0\text{-}5^0$ C and acidified up to pH~4 using 2N HCl solution. It is then extracted with ethyl acetate (3x100 mL).

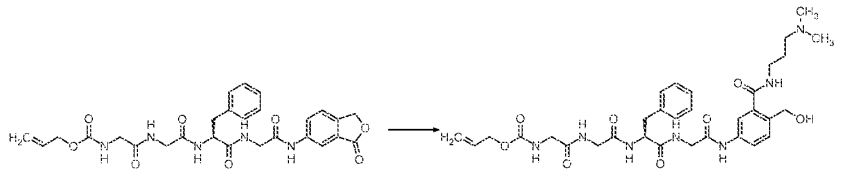
Combined organic layer is washed with brine solution (1x50 mL), dried over anhydrous sodium sulphate and concentrated under reduced pressure at 50^0 C to get 2-[[(2S)-2-[[2-[[2-(allyloxycarbonylamino)acetyl]amino]acetyl] amino]-3-phenyl-propanoyl]amino]acetic acid, (2.5 g), whichisused for the next step without purification.

Step VI: Preparation of allyl N-[2-[[2-[[(1S)-1-benzyl-2-oxo-2-[[2-oxo-2-[(3-oxo-1H-isobenzofuran-5-yl)amino]ethyl]amino]ethyl]amino]-2-oxo-ethyl]amino]-2-oxo-ethyl]carbamate.



N-Ethoxycarbonyl-2-ethoxy-1, 2-dihydroquinoline (EEDQ, 1.24 g, 5.03 mmol) is added to a stirred solution of 2-[[(2S)-2-[[2-[[2-(allyloxycarbonylamino)acetyl]amino]acetyl]amino]-3-phenyl-propanoyl]amino]acetic acid (1.55 g, 3.7 mmol) and 6-amino-3H-isobenzofuran-1-one (0.5 gm, 3.36 mmol) in a mixture of dichloromethane (16 mL) and methanol (8 mL) and stirred overnight at room temperature. Reaction mixture is concentrated at 40^0 C under reduced pressure. Diethyl ether (25 mL) is added to the crude product and stirred at room temperature for 30 min. Solid thus obtained is filtered, washed with diethyl ether. A mixture of ethyl acetate : n-hexane (75:25) is added to the solid residue and stirred at room temperature for 30 min. dried under reduced pressure to get allyl N-[2-[[2-[[(1S)-1-benzyl-2-oxo-2-[[2-oxo-2-[(3-oxo-1H-isobenzofuran-5-yl)amino]ethyl]amino]ethyl]amino]-2-oxo-ethyl]amino]-2-oxo-ethyl]carbamate, which is used for next step without purification.

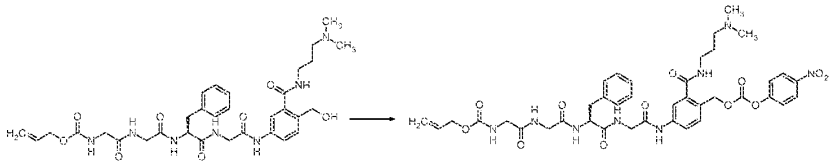
Step VII: Preparation of allyl N-[2-[[2-[[(1S)-1-benzyl-2-[[2-[3-[3-(dimethylamino) propylcarbamoyl]-4-(hydroxymethyl)anilino]-2-oxo-ethyl]amino]-2-oxo-ethyl]amino]-2-oxo-ethyl]amino]-2-oxo-ethyl]carbamate.



N', N'-Dimethylpropane-1,3-diamine (2.1 mL) is added to allyl N-[2-[[2-[[(1S)-1-benzyl-2-oxo-2-[[2-oxo-2-[(3-oxo-1H-isobenzofuran-5-yl)amino]ethyl]amino]ethyl]amino]-2-oxo-ethyl]amino]-2-oxo-ethyl]carbamate (0.7 gm, 1.81 mmol) at room temperature and then the reaction mixture is heated at 85^0C for 2 hours. Reaction mixture is concentrated under reduced

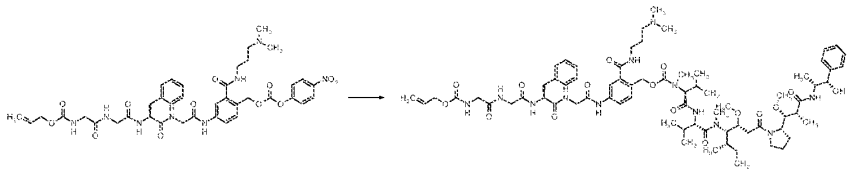
pressure at 50^0 C to get crude product, which is purified by column chromatography (silica gel 230-400 mesh; dichloromethane: methanol: ammonia, 83:15:2) to get allyl N-[2-[[2-[[(1S)-1-benzyl-2-[[2-[3-[3-(dimethylamino) propylcarbamoyl]-4-(hydroxymethyl)anilino]-2-oxo-ethyl]amino]-2-oxo-ethyl]amino]-2-oxo-ethyl]amino]-2-oxo-ethyl]carbamate (0.6 gm).

Step VIII: Preparation of [4-[[2-[[(2S)-2-[[2-[[2-(allyloxycarbonylamino)acetyl]amino] acetyl]amino]-3-phenyl-propanoyl]amino]acetyl]amino]-2-[3-(dimethylamino)propyl carbamoyl]phenyl]methyl (4-nitrophenyl) carbonate.



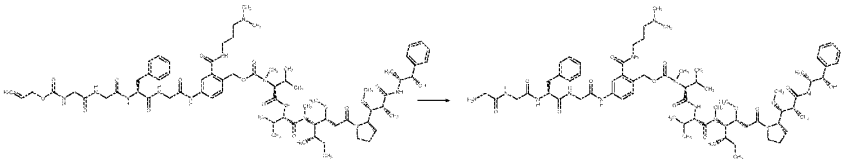
N, N-Diisopropylethylamine (0.48 mL, 2.75 mmol) is added to stirred solution of allyl N-[2-[[2-[[(1S)-1-benzyl-2-[[2-[3-[3-(dimethylamino)propylcarbamoyl]-4-(hydroxymethyl) anilino]-2-oxo-ethyl]amino]-2-oxo-ethyl]amino]-2-oxo-ethyl]amino]-2-oxo-ethyl]carbamate (0.6 g, 0.92 mmol) in tetrahydrofuran (6 mL) at room temperature. Bis(4-nitrophenyl)carbonate (0.5 g, 1.61 mmol) is added to the reaction mixture and stirred for 5 hrs. Reaction mixture is concentrated under reduced pressure at 40^0 C. Diethyl ether (20 mL) is added to the residue and stirred at room temperature for 45 min. Diethyl ether is decanted off. This process is repeated thrice and then the residue is dried to get [4-[[2-[[(2S)-2-[[2-[[2-(allyloxycarbonylamino)acetyl]amino]acetyl]amino]-3-phenyl-propanoyl]amino]acetyl] amino]-2-[3-(dimethylamino)propyl carbamoyl]phenyl]methyl (4-nitrophenyl) carbonate, which is used for the next step without further purification. (0.75 g).

Step IX : Preparation of [4-[[2-[[(2S)-2-[[2-[[2-(allyloxycarbonylamino)acetyl]amino] acetyl]amino]-3-phenyl-propanoyl]amino]acetyl]amino]-2-[3-(dimethylamino)propyl carbamoyl]phenyl]methyl N-[(1S)-1-[[(1S)-1-[[(1S,2R)-4-[(2S)-2-[(1R,2R)-3-[[(1R,2S)-2-hydroxy-1-methyl-2-phenyl-ethyl]amino]-1-methoxy-2-methyl-3-oxo-propyl]pyrrolidin-1-yl]-2-methoxy-1-[(1S)-1-methylpropyl]-4-oxo-butyl]-methyl-carbamoyl]-2-methyl-propyl]carbamoyl]-2-methyl-propyl]-N-methyl-carbamate.



1-Hydroxybenzotriazole (60 mg, catalytic amount) followed by N, N-diisopropylethylamine (0.48 mL, 2.75 mmol) is added to a stirred solution of [4-[[2-[[(2S)-2-[[2-[[2-(allyloxycarbonylamino)acetyl]amino]acetyl]amino]-3-phenyl-propanoyl]amino]acetyl] amino]-2-[3-(dimethylamino)propyl carbamoyl]phenyl]methyl (4-nitrophenyl) carbonate (0.75 g, 0.92 mmol) and Monomethyl auristatin E (0.6 g, 0.84 mmol) in N, N-dimethyl formamide (10 mL) at room temperature and stirred for 48 hrs. Reaction mixture is concentrated under reduced pressure at 55^0 C. Crude material thus obtained is purified by column chromatography (silica gel 230-400 mesh; dichloromethane : methanol : aqueous ammonia 84:15:1) to get [4-[[2-[[(2S)-2-[[2-[[2-(allyloxycarbonylamino)acetyl]amino] acetyl]amino]-3-phenyl-propanoyl]amino]acetyl]amino]-2-[3-(dimethylamino)propyl carbamoyl]phenyl]methyl N-[(1S)-1-[[(1S)-1-[[(1S,2R)-4-[(2S)-2-[(1R,2R)-3-[[(1R,2S)-2-hydroxy-1-methyl-2-phenyl-ethyl]amino]-1-methoxy-2-methyl-3-oxo-propyl]pyrrolidin-1-yl] -2-methoxy-1-[(1S)-1-methylpropyl]-4-oxo-butyl]-methyl-carbamoyl]-2-methyl-propyl] carbamoyl]-2-methyl-propyl]-N-methyl-carbamate. (0.6 g).

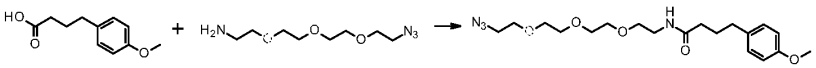
Step X: Preparation of [4-[[2-[[(2S)-2-[[2-[(2-aminoacetyl)amino]acetyl]amino]-3-phenyl-propanoyl]amino]acetyl]amino]-2-[3-(dimethylamino)propylcarbamoyl]phenyl] methyl N-[(1S)-1-[[(1S)-1-[[(1S,2R)-4-[(2S)-2-[(1R,2R)-3-[[(1R,2S)-2-hydroxy-1-methyl-2-phenyl-ethyl]amino]-1-methoxy-2-methyl-3-oxo-propyl]pyrrolidin-1-yl]-2-methoxy-1-[(1S)-1-methylpropyl]-4-oxo-butyl]-methyl-carbamoyl]-2-methyl-propyl]carbamoyl]-2-methyl-propyl]-N-methyl-carbamate.



Palladium tetrakis(triphenylphosphine) (0.037 g, 0.032 mmol) is added to stirred solution of [4-[[2-[[(2S)-2-[[2-[[2-(allyloxycarbonylamino)acetyl]amino] acetyl]amino]-3-phenyl-propanoyl]amino]acetyl]amino]-2-[3-(dimethylamino)propyl carbamoyl]phenyl]methyl N-[(1S)-1-[[(1S)-1-[[(1S,2R)-4-[(2S)-2-[(1R,2R)-3-[[(1R,2S)-2-hydroxy-1-methyl-2-phenyl-

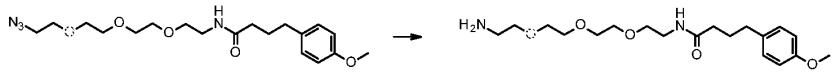
ethyl]amino]-1-methoxy-2-methyl-3-oxo-propyl]pyrrolidin-1-yl] -2-methoxy-1-[(1S)-1-methylpropyl]-4-oxo-butyl]-methyl-carbamoyl]-2-methyl-propyl] carbamoyl]-2-methyl-propyl]-N-methyl-carbamate (0.6 g, 0.43 mmol) in mixture of dichloromethane (4.2 mL) and methanol (1.8 mL) at room temperature. Morpholine (0.28 mL, 3.2 mmol) is added to the reaction mixture and stirred for 1.5 hrs. Reaction mixture is concentrated under reduced pressure at 40^0 C. Diethyl ether (20 mL) is added to the residue and stirred at room temperature for 45 min. Diethyl ether is decanted off. This process is repeated thrice and then the residue is dried under reduced pressure at 40^0 C to get crude material, which is purified by column chromatography (silica gel 230-400 mesh; dichloromethane : methanol : aqueous ammonia, 83.5:15:1.5) to get [4-[[2-[[(2S)-2-[[2-[(2-aminoacetyl)amino]acetyl]amino]-3-phenyl-propanoyl]amino]acetyl]amino]-2-[3-(dimethylamino)propylcarbamoyl]phenyl] methyl N-[(1S)-1-[[(1S)-1-[[(1S,2R)-4-[(2S)-2-[(1R,2R)-3-[[(1R,2S)-2-hydroxy-1-methyl-2-phenyl-ethyl]amino]-1-methoxy-2-methyl-3-oxo-propyl]pyrrolidin-1-yl]-2-methoxy-1-[(1S)-1-methylpropyl]-4-oxo-butyl]-methyl-carbamoyl]-2-methyl-propyl]carbamoyl]-2-methyl-propyl]-N-methyl-carbamate. (035 g).

Step XI: Preparation of N-[2-[2-[2-(2-azidoethoxy)ethoxy]ethoxy]ethyl]-4-(4-methoxy phenyl)butanamide.



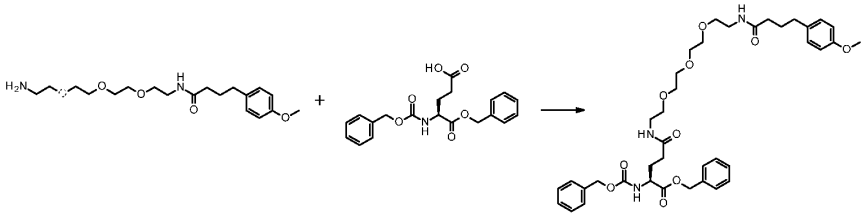
N, N-Diisopropylethylamine (1.8 mL, 10.3 mmol) is added to stirred solution of 4-(4-methoxyphenyl)butanoic acid (0.8 gm, 4.12 mmol), 2-[2-[2-(2-azidoethoxy)ethoxy]ethoxy] ethanamine (1.0 gm, 4.53 mmol) [Synthesis reference : Journal of Organic Chemistry, 1991, vol. 56, # 13, p. 4326 - 4329] and 1-[bis(dimethylamino)methylene]-1H-1,2,3-triazolo[4,5-b]pyridinium 3-oxide hexafluoro phosphate (HATU, 1.88 gm, 4.94 mmol) in N, N-dimethylformamide (10 mL) at room temperature and stirred overnight. Reaction mixture is quenched with D. M. water (1x20 mL) and extracted with ethyl acetate (3x30 mL). Combined organic layer is washed with 0.5 N HCl solution (1x20 mL) followed by saturated sodium bicarbonate solution (1x20 mL), D. M. water (1x20 mL) and brine solution (1x20 mL). Finally, it is dried over anhydrous sodium sulphate and concentrated under reduced pressure at 50^0 C to get crude product (2.1 gm), which is purified by column chromatography (silica gel 230-400 mesh; dichloromethane: methanol, 97:3) to get N-[2-[2-[2-(2-azidoethoxy)ethoxy] ethoxy]ethyl]-4-(4-methoxy phenyl) butanamide (1.3 gm).

Step XII: Preparation of N-[2-[2-[2-(2-aminoethoxy)ethoxy]ethoxy]ethyl]-4-(4-methoxy phenyl)butanamide.



Triphenyl phosphine (0.96 gm, 4.02 mmol) is added to a stirred solution of N-[2-[2-[2-(2-azidoethoxy)ethoxy]ethoxy]ethyl]-4-(4-methoxy phenyl) butanamide (1.32 gm, 3.35 mmol) in tetrahydrofuran (20 mL) at room temperature and stirred overnight. D. M. water (20 mL) is added to the reaction mixture and heated to reflux at 80^0 C for 1 hr. Tetrahydrofuran is removed under reduced pressure at 40^0 C. D. M. water (20 mL) is added to the residue and then extracted with dichloromethane (3x30 mL). Combined organic layer is washed with brine solution (1x20 mL) and dried over anhydrous sodium sulphate. Organic layer is concentrated under reduced pressure to get to crude product, which is purified by column chromatography (silica gel 230-400 mesh; dichloromethane: methanol:aqueous ammonia, 89:10:1) to get 3 N-[2-[2-[2-(2-aminoethoxy)ethoxy]ethoxy]ethyl]-4-(4-methoxy phenyl)butanamide.

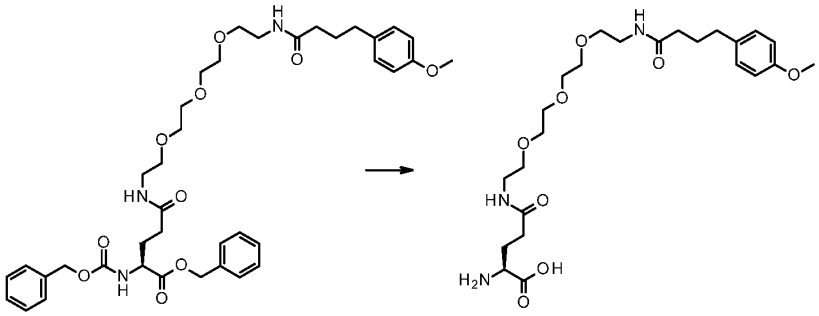
Step XIII: Preparation of benzyl (2S)-2-(benzyloxycarbonylamino)-5-[2-[2-[2-[2-[4-(4-methoxyphenyl)butanoylamino]ethoxy]ethoxy]ethoxy]ethylamino]-5-oxo-pentanoate.



N, N-Diisopropylethylamine (0.84 mL, 4.89 mmol) is added to stirred solution of N-[2-[2-[2-(2-aminoethoxy)ethoxy]ethoxy]ethyl]-4-(4-methoxyphenyl)butanamide (0.72 gm, 1.95 mmol), (4S)-5-benzyloxy-4-(benzyloxycarbonylamino)-5-oxo-pentanoic acid (0.8 gm, 2.15 mmol) and O-(benzotriazol-1-yl)-N,N,N',N'-tetramethyluronium tetrafluoroborate (TBTU, 0.94 gm, 2.93 mmol) in N, N-dimethylformamide (8 mL) at room temperature and stirred for 5 hrs. D. M. water (20 mL) is added to the residue and then extracted with ethyl acetate (3x30 mL). Combined organic layer is washed with D. M. water (1x20 mL) followed by brine solution (1x20 mL) and dried over anhydrous sodium sulphate. Organic layer is concentrated under reduced pressure to get to crude product (1.6 gm), which is purified by column chromatography (silica gel 230-400 mesh; dichloromethane: methanol, 95:5) to get benzyl

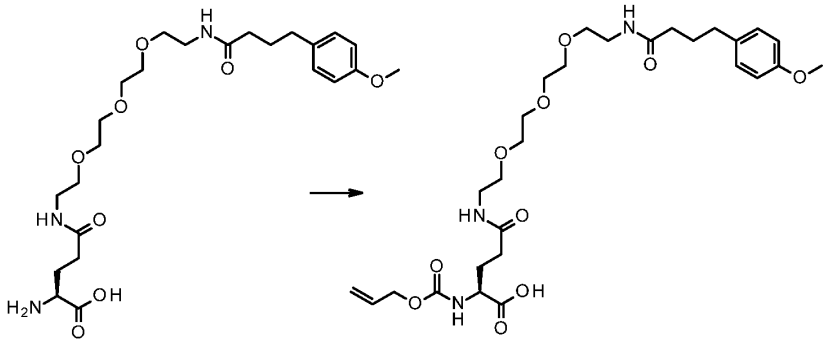
(2S)-2-(benzyloxycarbonylamino)-5-[2-[2-[2-[2-[4-(4-methoxyphenyl)butanoylamino] ethoxy]ethoxy]ethoxy]ethylamino]-5-oxo-pentanoate (1.3 g).

Step XIV: Preparation of (2S)-2-amino-5-[2-[2-[2-[2-[4-(4-methoxyphenyl)butanoylamino] ethoxy]ethoxy]ethoxy]ethylamino]-5-oxo-pentanoic acid



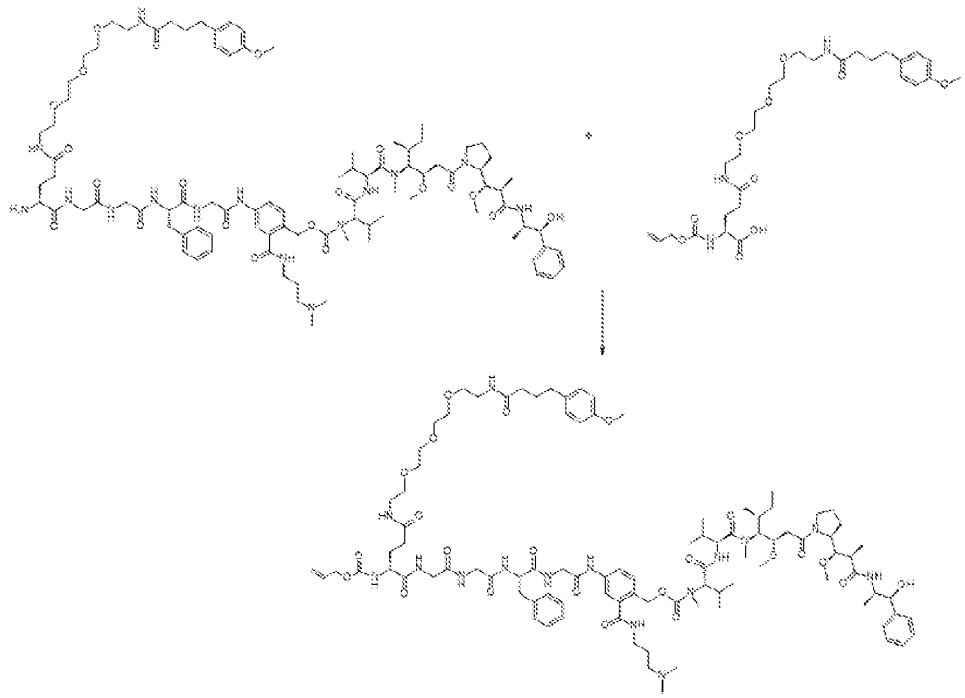
10% Palladium on charcoal (50% wet) (0.24 g) is added to a stirred solution of benzyl (2S)-2-(benzyloxycarbonylamino)-5-[2-[2-[2-[2-[4-(4-methoxyphenyl)butanoylamino]ethoxy] ethoxy]ethoxy]ethylamino]-5-oxo-pentanoate (1.2 g, 1.66 mmol) in methanol (10 mL). Reaction mixture is stirred under hydrogen pressure applied through a balloon filled with hydrogen gas at room temperature for 3 hrs. Reaction mixture is filtered through celite bed and washed with methanol (2x50 mL). Combined filtrate is concentrated under reduced pressure to get (2S)-2-amino-5-[2-[2-[2-[2-[4-(4-methoxyphenyl)butanoylamino]ethoxy]ethoxy]ethoxy] ethylamino]-5-oxo-pentanoic acid (0.72 gm), which is used for the next step without purification.

Step XV: Preparation of (2S)-2-(allyloxycarbonylamino)-5-[2-[2-[2-[2-[4-(4-methoxy phenyl)butanoylamino]ethoxy]ethoxy]ethoxy]ethylamino]-5-oxo-pentanoic acid.



Potassium carbonate (0.3 gm, 2.17 mmol) is added to stirred solution of (2S)-2-amino-5-[2-[2-[2-[2-[4-(4-methoxyphenyl)butanoylamino]ethoxy]ethoxy]ethoxy]ethylamino]-5-oxo-pentanoic acid (0.68 g, 1.41 mmol) in mixture of tetrahydrofuran (14 mL) and D. M. water (14 mL). Reaction mixture is cooled to 0-5^0 C. Allyl chloroformate (0.16 mL, 1.55 mmol) is added dropwise to the reaction mixture and stirred at 0-5^0 C for 1 hr. Tetrahydrofuran is removed under reduced pressure at 40^0 C. D. M. water (10 mL) is added to the residue, cooled to 0-5^0 C and acidified up to pH~4 using 2N HCl solution. It is made saturated with solid sodium chloride and then extracted with ethyl acetate (3x50mL). Combined organic layer is washed with brine solution (1x20 mL), dried over anhydrous sodium sulphate and concentrated under reduced pressure at 50^0 C to get crude product (0.8 gm), which is purified by column chromatography (silica gel 230-400 mesh; dichloromethane:methanol, 90:10) to get (2S)-2-(allyloxycarbonylamino)-5-[2-[2-[2-[2-[4-(4-methoxyphenyl)butanoylamino]ethoxy]ethoxy]ethoxy]ethylamino]-5-oxo-pentanoic acid (0.4 g).

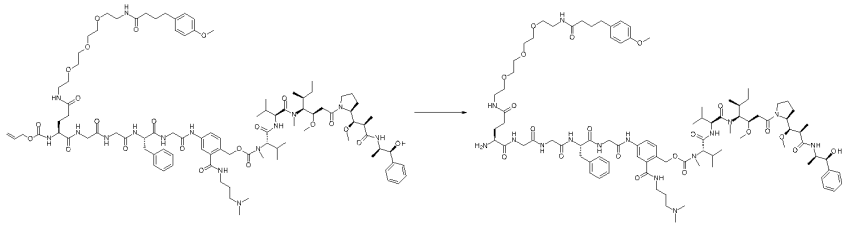
Step XVI: Preparation of [4-[[(2S)-2-[[(2S)-2-[[(2S)-2-(allyloxycarbonylamino)-5-[2-[2-[2-[2-[2-[2-[2-(2-methoxyethoxy)ethoxy]ethoxy]ethoxy]ethoxy]ethoxy]ethoxy]ethyl amino]-5-oxo-pentanoyl]amino]-3-methyl-butanoyl]amino]-5-ureido-pentanoyl]amino]-2-[3-(dimethylamino)propylcarbamoyl]phenyl]methyl N-[(1S)-1-[[(1S)-1-[[(1S,2R)-4-[(2S)-2-[(1R,2R)-3-[[(1R,2S)-2-hydroxy-1-methyl-2-phenyl-ethyl]amino]-1-methoxy-2-methyl-3-oxo-propyl]pyrrolidin-1-yl]-2-methoxy-1-[(1S)-1-methylpropyl]-4-oxo-butyl]-methyl-carbamoyl]-2-methyl-propyl]carbamoyl]-2-methyl-propyl]-N-methyl-carbamate.



N, N-Diisopropylethylamine (0.07 mL, 0.38 mmol) is added to stirred solution of (2S)-2-(allyloxycarbonylamino)-5-[2-[2-[2-[2-[4-(4-methoxyphenyl)butanoylamino]ethoxy]ethoxy] ethoxy]ethylamino]-5-oxo-pentanoic acid (0.115 gm, 0.198 mmol), [4-[[2-[[(2S)-2-[[2-[[2-[[(2S)-2-amino-5-[2-[2-[2-[2-[4-(4-methoxyphenyl)butanoylamino]ethoxy]ethoxy]ethoxy] ethylamino]-5-oxo-pentanoyl]amino]acetyl]amino]acetyl]amino]-3-phenyl-propanoyl]amino] acetyl]amino]-2-[3-(dimethylamino)propylcarbamoyl]phenyl]methyl N-[(1S)-1-[[(1S)-1-[[(1S,2R)-4-[(2S)-2-[(1R,2R)-3-[[(1R,2S)-2-hydroxy-1-methyl-2-phenyl-ethyl]amino]-1-methoxy-2-methyl-3-oxo-propyl]pyrrolidin-1-yl]-2-methoxy-1-[(1S)-1-methylpropyl]-4-oxo-butyl]-methyl-carbamoyl]-2-methyl-propyl]carbamoyl]-2-methyl-propyl]-N-methyl-carbamate (0.2 gm, 0.152 mmol) and O-(benzotriazol-1-yl)-N,N,N',N'-tetramethyluronium tetrafluoroborate (TBTU, 0.063 gm, 0.198 mmol) in N, N-dimethylformamide (2 mL) at room temperature and stirred overnight. Reaction mixture is concentrated under reduced pressure at 55^0 C to get crude product, which is purified by column chromatography (silica gel 230-400 mesh; dichloromethane: methanol: aqueous ammonia (87.5:12:0.5) to get [4-[[2-[[(2S)-2-[[2-[[2-[[(2S)-2-(allyloxycarbonylamino)-5-[2-[2-[2-[2-[4-(4-methoxyphenyl)butanoylamino] ethoxy]ethoxy]ethoxy]ethylamino]-5-oxo-pentanoyl]amino]acetyl]amino]acetyl]amino]-3-phenyl-propanoyl]amino]acetyl]amino]-2-[3-(dimethylamino)propylcarbamoyl]phenyl]

methyl N-[(1S)-1-[[(1S)-1-[[(1S,2R)-4-[(2S)-2-[(1R,2R)-3-[[(1R,2S)-2-hydroxy-1-methyl-2-phenyl-ethyl]amino]-1-methoxy-2-methyl-3-oxo-propyl]pyrrolidin-1-yl]-2-methoxy-1-[(1S)-1-methylpropyl]-4-oxo-butyl]-methyl-carbamoyl]-2-methyl-propyl]carbamoyl]-2-methyl-propyl]-N-methyl-carbamate (0.16 g).

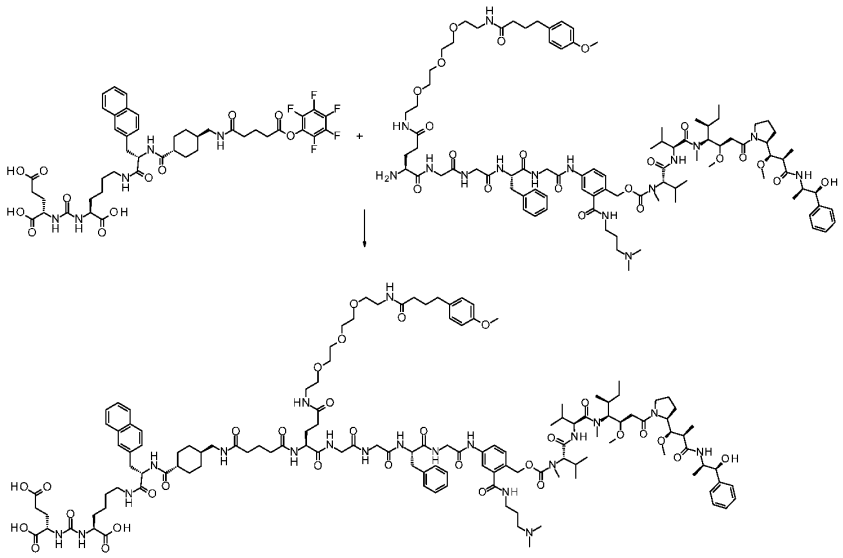
Step XVII: Preparation of [4-[[2-[[(2S)-2-[[2-[[2-[[(2S)-2-amino-5-[2-[2-[2-[2-[4-(4-methoxyphenyl)butanoylamino]ethoxy]ethoxy]ethoxy]ethylamino]-5-oxo-pentanoyl]amino]acetyl]amino]acetyl]amino]-3-phenyl-propanoyl]amino]acetyl]amino]-2-[3-(dimethylamino)propylcarbamoyl]phenyl]methyl N-[(1S)-1-[[(1S)-1-[[(1S,2R)-4-[(2S)-2-[(1R,2R)-3-[[(1R,2S)-2-hydroxy-1-methyl-2-phenyl-ethyl]amino]-1-methoxy-2-methyl-3-oxo-propyl]pyrrolidin-1-yl]-2-methoxy-1-[(1S)-1-methylpropyl]-4-oxo-butyl]-methyl-carbamoyl]-2-methyl-propyl]carbamoyl]-2-methyl-propyl]-N-methyl-carbamate.



Palladium tetrakis(triphenylphosphine) (0.008 g, 0.0064 mmol) is added to stirred solution of [4-[[2-[[(2S)-2-[[2-[[2-[[(2S)-2-(allyloxycarbonylamino)-5-[2-[2-[2-[2-[4-(4-methoxyphenyl)butanoylamino]ethoxy]ethoxy]ethoxy]ethylamino]-5-oxo-pentanoyl]amino]acetyl]amino]acetyl]amino]-3-phenyl-propanoyl]amino]acetyl]amino]-2-[3-(dimethylamino)propyl carbamoyl]phenyl]methyl N-[(1S)-1-[[(1S)-1-[[(1S,2R)-4-[(2S)-2-[(1R,2R)-3-[[(1R,2S)-2-hydroxy-1-methyl-2-phenyl-ethyl]amino]-1-methoxy-2-methyl-3-oxo-propyl]pyrrolidin-1-yl]-2-methoxy-1-[(1S)-1-methylpropyl]-4-oxo-butyl]-methyl-carbamoyl]-2-methyl-propyl] carbamoyl]-2-methyl-propyl]-N-methyl-carbamate (0.16 g, 0.085 mmol) in mixture of dichloromethane (1.2 mL) and methanol (0.5 mL) at room temperature. Morpholine (0.055 mL, 0.64 mmol) is added to the reaction mixture and stirred for 2 hr. Reaction mixture is concentrated under reduced pressure at 35^0 C. Crude material thus obtained is purified by column chromatography (silica gel 230-400 mesh; dichloromethane : methanol : ammonia, 84:15:1) to get [4-[[2-[[(2S)-2-[[2-[[2-[[(2S)-2-amino-5-[2-[2-[2-[2-[4-(4-methoxyphenyl)butanoylamino]ethoxy]ethoxy]ethoxy]ethylamino]-5-oxo-pentanoyl]amino]acetyl]amino]acetyl]amino]-3-phenyl-propanoyl]amino]acetyl]amino]-2-[3-(dimethylamino)propyl carbamoyl]phenyl]methyl N-[(1S)-1-[[(1S)-1-[[(1S,2R)-4-[(2S)-2-[(1R,2R)-3-[[(1R,2S)-2-

hydroxy-1-methyl-2-phenyl-ethyl]amino]-1-methoxy-2-methyl-3-oxo-propyl]pyrrolidin-1-yl]-2-methoxy-1-[(1S)-1-methylpropyl]-4-oxo-butyl]-methyl-carbamoyl]-2-methyl-propyl]carbamoyl]-2-methyl-propyl]-N-methyl-carbamate (0.1 gm).

Step XVIII: Preparation of (2S)-2-[[(1S)-5-[[(2S)-2-[[4-[[[5-[[(1S)-1-[[2-[[2-[[(1S)-1-benzyl-2-[[2-[3-[3-(dimethylamino)propylcarbamoyl]-4-[[[(1S)-1-[[(1S)-1-[[(1S,2R)-4-[(2S)-2-[(1R,2R)-3-[[(1R,2S)-2-hydroxy-1-methyl-2-phenyl-ethyl]amino]-1-methoxy-2-methyl-3-oxo-propyl]pyrrolidin-1-yl]-2-methoxy-1-[(1S)-1-methylpropyl]-4-oxo-butyl]-methyl-carbamoyl]-2-methyl-propyl]carbamoyl]-2-methyl-propyl]-methyl-carbamoyl]oxymethyl]anilino]-2-oxo-ethyl]amino]-2-oxo-ethyl]amino]-2-oxo-ethyl]amino]-2-oxo-ethyl]carbamoyl]-4-[2-[2-[2-[2-[4-(4-methoxyphenyl)butanoylamino]ethoxy]ethoxy]ethoxy]ethylamino]-4-oxo-butyl]amino]-5-oxo-pentanoyl]amino]methyl]cyclohexane carbonyl]amino]-3-(2-naphthyl)propanoyl]amino]-1-carboxy-pentyl]carbamoylamino]pentanedioic acid.



(2S)-2-[[(1S)-1-carboxy-5-[[(2S)-3-(2-naphthyl)-2-[[4-[[[5-oxo-5-(2,3,4,5,6-pentafluoro phenoxy)pentanoyl]amino]methyl]cyclohexanecarbonyl]amino]propanoyl]amino]pentyl]carb amoylamino]pentanedioic acid (0.075 gm, 0.073 mmol) is added to a stirred solution of [4-[[2-[[(2S)-2-[[2-[[2-[[(2S)-2-amino-5-[2-[2-[2-[2-[4-(4-methoxyphenyl)butanoylamino]ethoxy]ethoxy]ethoxy]ethylamino]-5-oxo-pentanoyl]amino]acetyl]amino] acetyl]amino]-3-phenyl-propanoyl]amino]acetyl]amino]-2-[3-(dimethylamino)propyl carbamoyl]phenyl]methyl N-[(1S)-1-[[(1S)-1-[[(1S,2R)-4-[(2S)-2-[(1R,2R)-3-[[(1R,2S)-2-hydroxy-1-methyl-2-phenyl-

ethyl]amino]-1-methoxy-2-methyl-3-oxo-propyl]pyrrolidin-1-yl]-2-methoxy-1-[(1S)-1-methylpropyl]-4-oxo-butyl]-methyl-carbamoyl]-2-methyl-propyl]carbamoyl]-2-methyl-propyl]-N-methyl-carbamate (0.1 g, 0.056 mmol) and triethylamine (0.08 ml, 0.56 mmol) in N, N-dimethylformamide (1.0 mL) and stirred at room temperature for 3 hrs. Diethyl ether (6 mL) is added to the reaction mixture and stirred at room temperature for 1 hour. Solid thus obtained is filtered, washed with diethyl ether and purified by preparative HPLC to get (2S)-2-[[(1S)-5-[[(2S)-2-[[4-[[[5-[[(1S)-1-[[2-[[2-[[(1S)-1-benzyl-2-[[2-[3-[3-(dimethylamino) propylcarbamoyl]-4-[[[(1S)-1-[[(1S)-1-[[(1S,2R)-4-[(2S)-2-[(1R,2R)-3-[[(1R,2S)-2-hydroxy-1-methyl-2-phenyl-ethyl]amino]-1-methoxy-2-methyl-3-oxo-propyl]pyrrolidin-1-yl]-2-methoxy-1-[(1S)-1-methylpropyl]-4-oxo-butyl]-methyl-carbamoyl]-2-methyl-propyl] carbamoyl]-2-methyl-propyl]-methyl-carbamoyl]oxymethyl]anilino]-2-oxo-ethyl]amino]-2-oxo-ethyl]amino]-2-oxo-ethyl]amino]-2-oxo-ethyl]carbamoyl]-4-[2-[2-[2-[2-[4-(4-methoxy phenyl)butanoylamino]ethoxy]ethoxy]ethoxy]ethylamino]-4-oxo-butyl]amino]-5-oxo-pentanoyl]amino]methyl]cyclohexane carbonyl]amino]-3-(2-naphthyl)propanoyl]amino]-1-carboxy-pentyl]carbamoylamino]pentanedioic acid (0.035 gm); mass (m/z) 1273.39 [M+2H]2+.

Compound no. 1.80 was made in an analogous manner as the synthetic procedures provided above in Example 13; 1.80: mass (m/z) 830.34 [M+3H]3+

Example 14: Biological Studies

PC3-PIP cell lines were a generous gift from the Pomper Lab at Johns Hopkins University (USA). Cells were selected by bleomycin and sorted by FACS. Cells were seeded at 1000 cells/well in 96-well plates, 24 hrs prior to the addiction of the compounds. All compounds were diluted three times from 10 μM into 7 concentrations that varied from 0.01 nM to 1000 nM. The concentration ranges were further optimized after first test data to cover the best concentration ranges. For high activity compounds, 10-fold or 20-fold dilution were applied to cover wider concentration ranges. The diluted compounds and DMSO as a control was then added into each cell well with 3 replicates. All cells (both PC3-PIP and PC3-flu) were transfected with Nuclight Red Lentivirus (Sartorius) and sorted for Nuclight Red positive population for Incucyte analysis. Incucyte scan was performed after every 8 hrs. For both the cells, kept scanning after every 8 hrs for 5 days. Analysis of cell counting based on Nuclight Red signals were run in Zoom software with optimized analytic model for each cell line. In brief, 4 representative whole well cell images of each cell line, at time points when cell grow up to roughly 10%, 30%, 60%, and 90% confluency were chosen into analysis groups. Parameters were adjusted for each cell line to best fit the cells at all confluency, and extinguish

each cell's or nuclei's edge and shape. All cell images were thus analyzed to get cell numbers, and picked the data set at the time point when cell numbers reach the peak. The drug response was plotted against concentrations using GraphPad Prism 9. IC_{50} values were determined at a concentration at which the number of cells were reduced by 50%.

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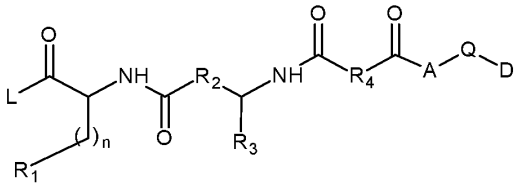
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We claim:

1. A compound of Formula I



Formula I

or pharmaceutically acceptable salt, stereoisomer or isotope thereof,

wherein: n is 0, 1, 2, 3 or 4;

L is a ligand;

R_1 is selected from a 6 to 14 membered aryl or a 5 to 13 membered heteroaryl containing one, two or three heteroatoms independently selected from nitrogen, oxygen or sulfur;

R_1 is unsubstituted or substituted with one or more R_5;

R_5, at each occurrence, is independently selected from halogen, —C(O)NH_2, —C(O)OR_6, —C_{1-3} alkyl, —OR_7, and a 6 to 10 membered aryl; wherein,

R_6 is hydrogen or C_{1-3} alkyl;

R_7 is hydrogen or C_{1-3} alkyl;

R_2 is absent or is selected from a 6 to 10 membered cycloalkyl or a 6 to 10 membered aryl;

R_3 is hydrogen or —C_1-C_5COOH;

R_4 is selected from a group consisting of —C_{1-10} alkyl-, —C_{2-6} alkenyl-, —C_{1-3} alkyl-O-C_{1-3} alkyl—, —C_{2-6} alkyl-N(R_8)—, —C_{2-6} alkyl(N(R_8)($R_{8'}$))—, —N(R_8)-C_{2-6} alkyl—, a 3 to 6 membered cycloalkyl and —C_{1-2} alkyl-(-OC_2H_4)$_{1-8}$-OC_{1-2} alkyl—; wherein,

R_8 and $R_{8'}$ are independently selected from hydrogen, C_{1-6} alkyl, -C(O)-C_{1-4}alkyl-aryl or -C(O)-(-C_2H_4O)$_{1-8}$-C_{1-2} alkyl-N(R)(R'), wherein said aryl is selected from 6 to 14 membered aryl and is optionally substituted by -C_{1-3}alkyl or -OC_{1-3}alkyl; wherein

R and R' are independently selected from hydrogen, -C_{1-6} alkyl or -C(O)-C_{1-4}alkyl-aryl, wherein said aryl is selected from 6 to 14 membered aryl and is optionally substituted by -C_{1-3}alkyl or -OC_{1-3}alkyl;

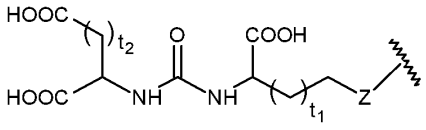
A is an amino acid or a peptide comprising 2-5 amino acids;

A is attached to Q through its C terminal;

Q is a self-immolative group; and

D is a cytotoxic agent or a therapeutic agent.

2. The compound as claimed in claim 1, wherein the ligand L is a ligand of Formula L_1:



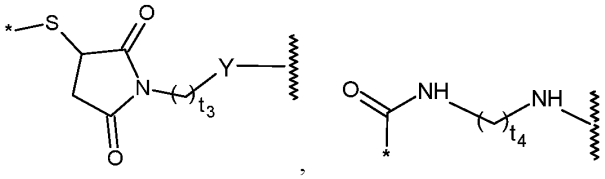
Formula L_1

wherein,

t_1 is 0, 1, 2, 3, or 4;

t_2 is 1, 2, 3 or 4;

Z is selected from the group consisting of $N(R_9)$, Formula Z_1 and Formula Z_2:



Formula Z_1 Formula Z_2

wherein:

t_3 is selected from 1, 2, 3, 4, 5 or 6;

t_4 is selected from 1, 2, 3, 4, 5 or 6;

Y is $-CH_2-$ or –NH- and

‘ wwwww ’ indicates attachment of Formula L_1 to the rest of the compound of Formula I;

R_9 is selected from the group consisting of hydrogen, C_{1-5} alkyl, a 6 to 10 membered aryl, a 5 to 10 membered heterocyclyl ring wherein the heterocyclyl ring contains one, two or three heteroatoms independently selected from nitrogen, oxygen or sulfur; and wherein R_9 is unsubstituted or substituted with halogen.

3. The compound as claimed in claim 2, wherein

t_1 is 3;

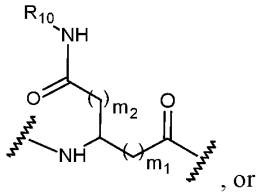
Z is $N(R_9)$; and

R_9 is hydrogen or phenyl, which is unsubstituted or substituted with halogen.

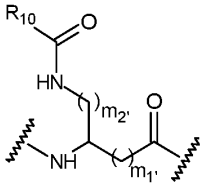
4. The compound as claimed in claim 2, wherein t_1 is 1 and Z is the compound of Formula Z_2.

5. The compound as claimed in claim 2, wherein t1 is 0; Z is the compound of Formula Z_1; and Y is –NH-.

6. The compound as claimed in claim 1, wherein the amino acid in A at each occurrence is independently selected from the group consisting of alanine (ala), arginine (arg), aspartic acid (asp), cysteine (cys), glutamic acid (glu), glycine (gly), lysine (lys), phenylalanine (phe), serine (ser), threonine (thr), tryptophan (trp), valine (val), ornithine (orn), citrulline (cit), homocitrulline (hct), lanthionine (lan), homocysteine (hcy) or an amino acid having Formula A1 or Formula A2



, or



Formula A_1 Formula A_2

wherein

m_1 and m_1' are 0, 1, 2 or 3;

m_2 and m_2' are is 0, 1, 2, 3 or 4;

R_{10} is selected from $(-C_2H_4O)_{1-24}CH_3$, $(-C_2H_4O)_{1-24}C_{1-2}$ alkyl($N(R_{10'})(R_{10''})$)—, C_{1-3} alkyl-aryl or —C_{1-3} alkyl-Het_1-$(-C_2H_4O)_{1-24}CH_3$, wherein Het_1 is a 5 to 10 membered heterocyclic ring containing one, two or three heteroatoms independently selected from nitrogen, oxygen or sulfur and wherein said aryl is selected from 6 to 14 membered aryl and is optionally substituted by -C_{1-3}alkyl or -OC_{1-3}alkyl; wherein

$R_{10'}$ and $R_{10''}$ are independently selected from hydrogen, C_{1-6} alkyl or -C(O)-C_{1-4}alkyl-aryl wherein said aryl is selected from 6 to 14 membered aryl and is optionally substituted by -C_{1-3}alkyl or -OC_{1-3}alkyl.

7. The compound as claimed in claim 6, wherein the amino acid in A at each occurrence is independently selected from alanine (ala), arginine (arg), aspartic acid (asp), cysteine (cys), glutamic acid (glu), glycine (gly), lysine (lys), phenylalanine (phe), serine (ser), threonine (thr), tryptophan (trp), valine (val), citrulline (cit), homocitrulline (hct), homocysteine (hcy), an amino acid having the Formula A_1 or Formula A_2; wherein,

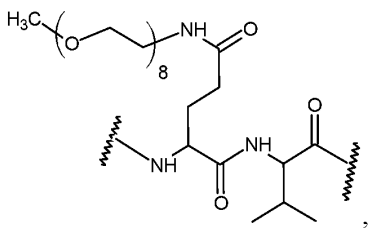
m_1 and m_1' are 0, 1 or 2;

m_2 is 2;

m_2' is 4;

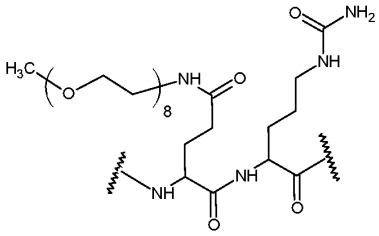
R_{10} is selected from $(-C_2H_4O)_{6-8}CH_3$, $(-C_2H_4O)_3C_2H_4(NH(C(O)C_3H_6\text{-aryl}))$—, C_3H_6-aryl or —CH_2-Het_1-$(-C_2H_4O)_8CH_3$, wherein Het_1 is triazolyl and aryl is 4-methyl phenyl or 4-methoxy phenyl.

8. The compound as claimed in claim 1, wherein A is a peptide selected from the group consisting of ala-ala, ala-ala-ala, ala-phe, val-ala, val-cit, ala-val-cit, ala(beta)-val-cit, glu-val-cit, glu-cit, glu-val, gly-gly, gly-gly-phe, gly-gly-phe-gly, asp-cit, asp-val-cit and asp-val; or the peptide is selected from a group of compounds having following formula:

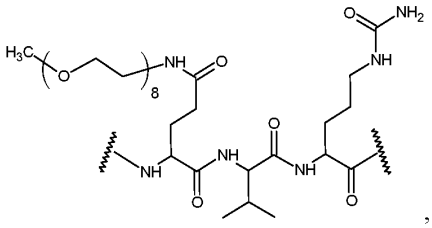


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Formula P_1

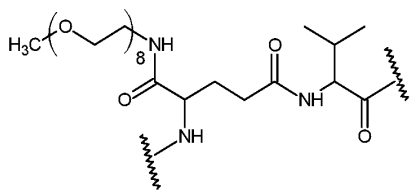


Formula P_2



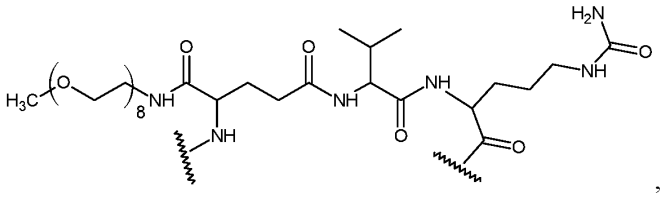
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Formula P_3



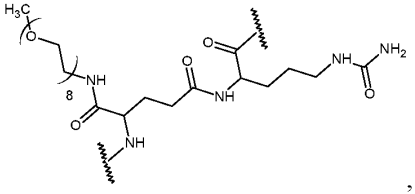
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Formula P_4



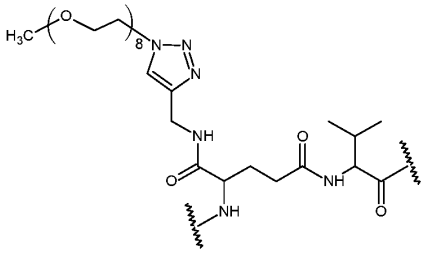
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Formula P_5

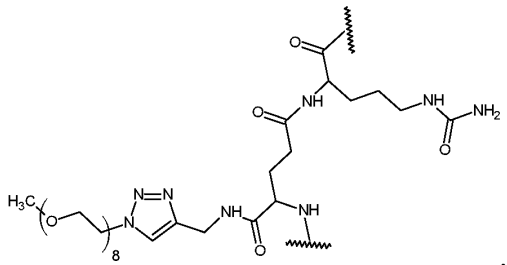


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Formula P_6

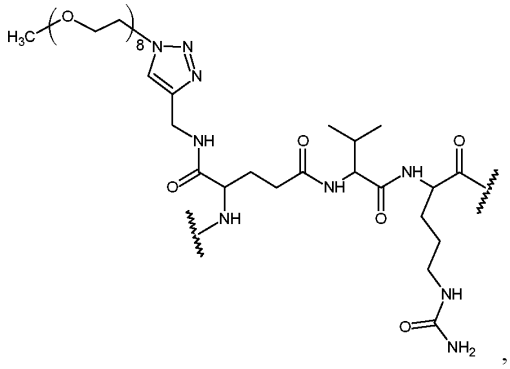


Formula P_7



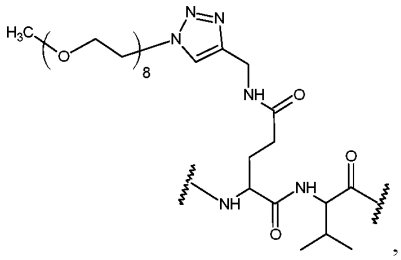
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Formula P_8

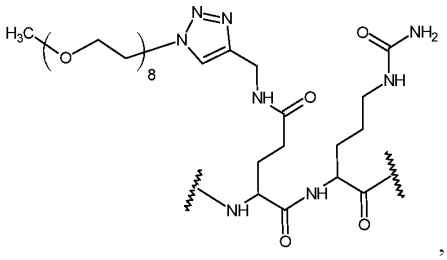


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Formula P_9

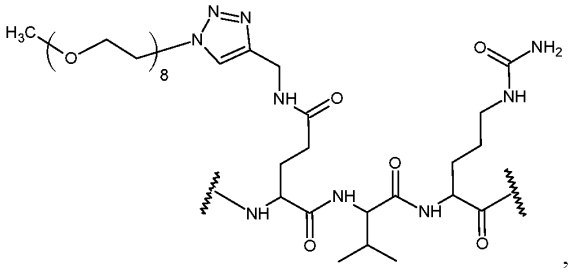


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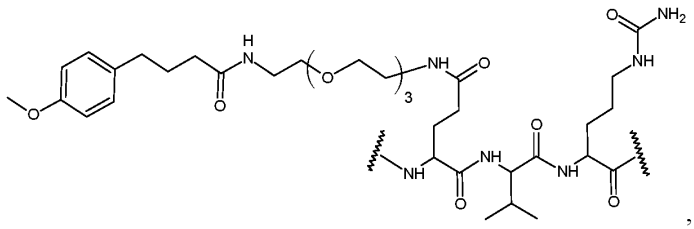
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Formula P_{10} Formula P_{11}



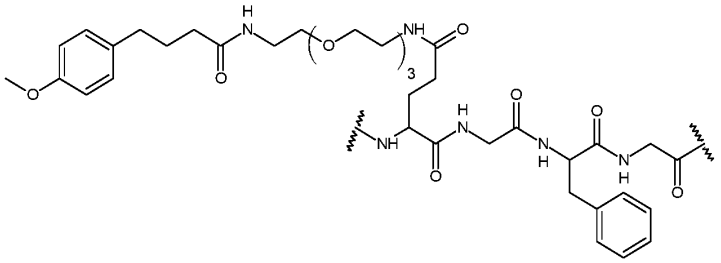
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Formula P_{12}



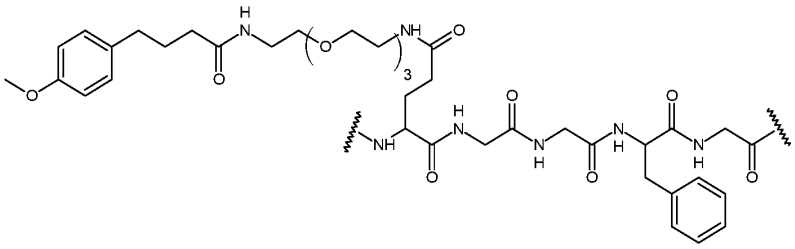
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Formula P_{13}



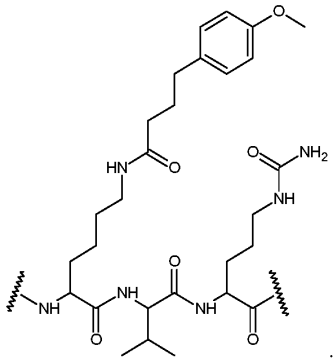
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Formula P_{14}



, and

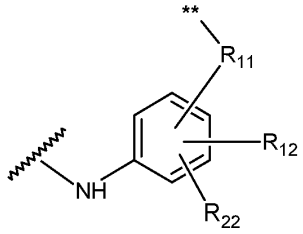
Formula P_{15}



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Formula P_{16}

9. The compound as claimed in claim 1, wherein the self-immolative group Q is of the Formula Q_1:



Formula Q_1

wherein,

R_{11} is selected from a group consisting of —C_{1-3} alkyl-OC(O)—**,

—C_{1-3} alkyl-O-C(O)-N(R_{19})-C_{1-5} alkyl-N(R_{19})-C(O)—**,

—C_{1-3} alkyl-O-C(O)-N[C_{1-5} alkyl-N($R_{20}R_{21}$)]-C_{1-3} alkyl—**, and

—C_{1-3} alkyl-O-C(O)-Het_2-C_{1-3} alkyl-N(R_{19})-C(O)—**,

wherein

R_{19} is selected from hydrogen, —C_{1-3} alkyl or —C_{1-3} alkyl-O-C_{1-3} alkyl-OH;

R_{20} is hydrogen or —C_{1-3} alkyl;

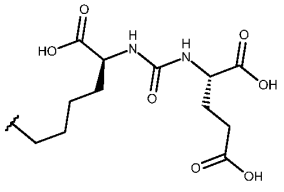
R_{21} is hydrogen or —C_{1-3} alkyl; and

Het_2 is a 5 to 10 membered heterocyclic ring containing one, two or three heteroatoms independently selected from nitrogen, oxygen or sulfur;

R_{12} is selected from hydrogen, —C(O)N(R_{13})(R_{14}) or —(-OC_2H_4)$_{1-10}$-CH_3

R_{13} is hydrogen;

R_{14} is selected from —C_{1-5} alkyl, —C_{2-5} alkenyl, —C_{2-5} alkynyl, —C_{1-5} alkyl-N(R_{15})(R_{16}), —C_{1-5} alkyl-O-C_{1-3} alkyl, —(-C_2H_4O)$_{1-10}C_2H_5$, —(-C_2H_4O)$_{1-10}$-C_2H_4-R_{17}, —C_{1-3} alkyl-Het_3-(-C_2H_4O)$_{1-10}$-C_2H_4-R_{18} or



; wherein:

R_{15} is hydrogen or C1 to C3 alkyl;

R_{16} is hydrogen or C1 to C3 alkyl; or

R_{15} and R_{16} along with the nitrogen atom to which they are attached form a 5 to 6 membered heterocyclic ring, wherein 1 or 2 carbon atoms in the heterocyclic ring are optionally replaced with additional heteroatoms independently selected from nitrogen,

oxygen and sulfur and wherein the 5 to 6 membered heterocyclic ring is unsubstituted or substituted with C_{1-3} alkyl, halogen or –OH;

R_{17} is selected from hydrogen or —C(O)NH-C_{2-5} alkyl-$N(CH_3)_2$;

R_{18} is selected from hydrogen or —C(O)NH-C_{2-5} alkyl-$N(CH_3)_2$;

Het_3 is a 5 to 10 membered heterocyclic ring containing one, two or three heteroatoms independently selected from nitrogen, oxygen and sulfur;

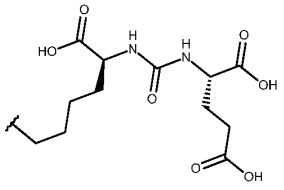
OR

R_{13} and R_{14} along with the nitrogen atom to which they are attached form a 4 to 6 membered heterocyclic ring, wherein 1 or 2 carbons in the heterocyclic ring are optionally replaced with additional heteroatoms independently selected from nitrogen, oxygen and sulfur, and wherein the 4 to 6 membered heterocyclic ring is unsubstituted or substituted with C_{1-3} alkyl, —$N(CH_3)_2$ or —$CH_2N(CH_3)_2$;

R_{22} is selected from hydrogen, —C(O)N(R_{23})(R_{24}) or —(-$OC_2H_4)_{1-10}$-CH_3

R_{23} is hydrogen;

R_{24} is selected from —C_{1-5} alkyl, —C_{2-5} alkenyl, —C_{2-5} alkynyl, —C_{1-5} alkyl-N(R_{25})(R_{26}), —C_{1-5} alkyl-O-C_{1-3} alkyl, —(-$C_2H_4O)_{1-10}C_2H_5$, —(-$C_2H_4O)_{1-10}$-C_2H_4-R_{27}, —C_{1-3} alkyl-Het_3-(-$C_2H_4O)_{1-10}$-C_2H_4-R_{28} or



; wherein:

R_{25} is hydrogen or C1 to C3 alkyl;

R_{26} is hydrogen or C1 to C3 alkyl; or

R_{25} and R_{26} along with the nitrogen atom to which they are attached form a 5 to 6 membered heterocyclic ring, wherein 1 or 2 carbon atoms in the heterocyclic ring are optionally replaced with additional heteroatoms independently selected from nitrogen, oxygen and sulfur and wherein the 5 to 6 membered heterocyclic ring is unsubstituted or substituted with C_{1-3} alkyl, halogen or –OH;

R_{27} is selected from hydrogen or —C(O)NH-C_{2-5} alkyl-$N(CH_3)_2$;

R_{28} is selected from hydrogen or —C(O)NH-C_{2-5} alkyl-$N(CH_3)_2$;

Het_3 is a 5 to 10 membered heterocyclic ring containing one, two or three heteroatoms independently selected from nitrogen, oxygen and sulfur;

OR

R_{23} and R_{24} along with the nitrogen atom to which they are attached form a 4 to 6 membered heterocyclic ring, wherein 1 or 2 carbons in the heterocyclic ring are optionally replaced with additional heteroatoms independently selected from nitrogen, oxygen and sulfur, and wherein the 4 to 6 membered heterocyclic ring is unsubstituted or substituted with C_{1-3} alkyl, —$N(CH_3)_2$ or —$CH_2N(CH_3)_2$; and

'wwwww' indicates the point of attachment of Q to C terminal of A and ** indicates point of attachment of Q to D.

10. The compound as claimed in claim 1, wherein

R_1 is selected from 6 to 10 membered aryl or 5 to 10 membered heteroaryl containing one, two or three heteroatoms independently selected from nitrogen, oxygen or sulfur; or R_1 is unsubstituted or substituted with one or more R_5;

R_5 at each occurrence is independently selected from halogen, —OH, —OCH_3, —OC_2H_5 or 6 to 10 membered aryl;

R_2 is selected from a group consisting of 5 to 6 membered cycloalkyl and 6 to 10 membered aryl;

R_3 is hydrogen;

R_4 is selected from a group consisting of —C_{1-10} alkyl-, —C_{2-6} alkenyl-, —C_{1-3} alkyl-O-C_{1-3} alkyl—, —C_{2-6} alkyl-N(R_8)—, —C_{2-6} alkyl(N(R_8)($R_{8'}$))—, —N(R_8)-C_{2-6} alkyl—, a 3 to 6 membered cycloalkyl and —C_{1-2} alkyl-(-OC_2H_4)$_{1-8}$-OC_{1-2} alkyl—; wherein,

R_8 and $R_{8'}$ are independently selected from hydrogen, C_{1-6} alkyl, -C(O)-C_{1-4}alkyl-aryl or -C(O)-(- C_2H_4O)$_{1-8}$-C_{1-2} alkyl-N(R)(R'), wherein said aryl is selected from 6 to 14 membered aryl and is optionally substituted by -C_{1-3}alkyl or -OC_{1-3}alkyl; wherein

R and R' are independently selected from hydrogen, -C_{1-6} alkyl or -C(O)-C_{1-4}alkyl-aryl, wherein said aryl is selected from 6 to 14 membered aryl and is optionally substituted by -C_{1-3}alkyl or -OC_{1-3}alkyl;

A is selected from the group consisting of cit, ala-ala, ala-ala-ala, ala-phe, val-ala, val-cit, ala-val-cit, ala(beta)-val-cit, glu-val-cit, glu-cit, glu-val, gly-gly, gly-gly-phe, gly-gly-phe-gly, Formula P_3, Formula P_5, Formula P_9, Formula P_{12}, Formula P_{13}, Formula P_{14}, Formula P_{15} and Formula P_{16}.

11. The compound as claimed in claim 1, wherein

n is 1

R^1 is naphthyl;

R^2 is cyclohexyl or phenyl;

R^3 is hydrogen;

R_4 is selected from a group consisting of —C_{1-10} alkyl-, —C_{2-6} alkenyl-, —C_{1-3} alkyl-O-C_{1-3} alkyl—, —C_{2-6} alkyl-N(R_8)—, —C_{2-6} alkyl(N(R_8)($R_{8'}$))—, —N(R_8)-C_{2-6} alkyl—, a 3 to 6 membered cycloalkyl and —C_{1-2} alkyl-(-OC_2H_4)$_{1-8}$-OC_{1-2} alkyl—; wherein,

R_8 and $R_{8'}$ are independently selected from hydrogen, C_{1-6} alkyl, -C(O)-C_{1-4}alkyl-aryl or -C(O)-(-C_2H_4O)$_{1-8}$-C_{1-2} alkyl-N(R)(R'), wherein said aryl is selected from 6 to 14 membered aryl and is optionally substituted by -C_{1-3}alkyl or -OC_{1-3}alkyl; wherein

R and R' are independently selected from hydrogen, -C_{1-6} alkyl or -C(O)-C_{1-4}alkyl-aryl, wherein said aryl is selected from 6 to 14 membered aryl and is optionally substituted by -C_{1-3}alkyl or -OC_{1-3}alkyl;

A is selected from the group consisting of cit, ala-ala, ala-ala-ala, ala-phe, val-ala, val-cit, ala-val-cit, ala(beta)-val-cit, glu-val-cit, glu-cit, glu-val, gly-gly, gly-gly-phe, gly-phe-gly, gly-gly-phe-gly, Formula P_3, Formula P_5, Formula P_9, Formula P_{12}, Formula P_{13}, Formula P_{14}, Formula P_{15} and Formula P_{16}.

12. The compound as claimed in claim 11, wherein

R^4 is selected from a group consisting of —C_{2-5} alkyl, —CH_2=CH_2—, —CH_2-O-CH_2—, —CH_2(-OC_2H_4)$_2$-OCH_2— and cyclobutyl; and

A is selected from the group consisting of cit, val-ala, val-cit, gly-gly-phe-gly, or the peptide selected from the group consisting of Formula P_3, Formula P_5, Formula P_9, Formula P_{12}, Formula P_{13}, Formula P_{14}, Formula P_{15} and Formula P_{16}.

13. The compound as claimed in claim 11, wherein

R_4 is selected from a group consisting of —C_{2-6} alkyl(N(R_8)($R_{8'}$))— and —C_{1-2} alkyl-(-OC_2H_4)$_{1-8}$-OC_{1-2} alkyl—; wherein,

R_8 and $R_{8'}$ are independently selected from hydrogen, -C(O)-C_{1-4}alkyl-aryl or -C(O)-(-C_2H_4O)$_{1-8}$-C_{1-2} alkyl-N(R)(R'), wherein said aryl is selected from 6 to 14 membered aryl and is optionally substituted by -C_{1-3}alkyl or -OC_{1-3}alkyl; wherein

R and R' are independently selected from hydrogen, -C_{1-6} alkyl or -C(O)-C_{1-4}alkyl-aryl, wherein said aryl is selected from 6 to 14 membered aryl and is optionally substituted by -C_{1-3}alkyl or -OC_{1-3}alkyl;

A is selected from the group consisting of val-cit, gly-gly-phe-gly.

14. The compound as claimed in claim 11, wherein

R^4 is selected from a group consisting of —$C_{2\text{-}5}$ alkyl and 3 to 6 membered cycloalkyl;

A is selected from the group consisting of cit, val-ala, val-cit, glu-val-cit, gly-gly-phe-gly.

15. The compound as claimed in claim 1, wherein

n is 0, 1 or 2;

R^1 is selected from the group consisting of phenyl, indolyl, thiophenyl, quinolinyl, and isoquinolinyl; or R^1 is unsubstituted or substituted with one or more R^5;

R^5 is selected from halogen, —OH, or 6 to 10 membered aryl ring;

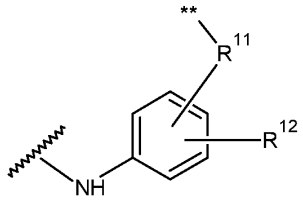
R^2 is cyclohexyl or phenyl;

R^3 is hydrogen;

R^4 is —$C_{1\text{-}10}$ alkyl;

A is val-cit; and

Q is a radical of Formula Q1,



Formula Q_1

wherein

R^{11} is —$CH_2OC(O)$—; and

R^{12} is hydrogen.

16. The compound as claimed in claim 1, wherein

R^1 is selected from 6 to 10 membered aryl;

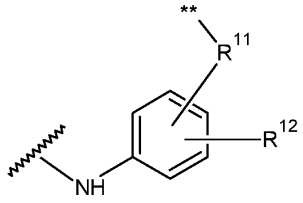
R^2 is absent;

R^3 is —CH_2COOH, —CH_2CH_2COOH;

R^4 is 3 to 6 membered cycloalkyl;

A is Cit;

Q is a radical of Formula Q1,



Formula Q_1

wherein

R^{11} is —CH_2-O-C(O)-N(CH_3)-C_2H_4-N(CH_3)-C(O)—; and

R^{12} is hydrogen.

17. The compound as claimed in claim 1, wherein

n is 0, 1 or 2;

R_1 is selected from a 6 to 10 membered aryl;

R_2 is cyclohexyl or phenyl;

R_3 is hydrogen;

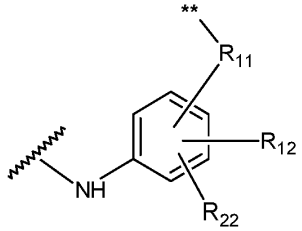
R_4 is selected from a group consisting of —C_{1-10} alkyl- and —C_{2-6} alkyl(N(R_8)($R_{8'}$))—; wherein,

R_8 and $R_{8'}$ are independently selected from hydrogen, C_{1-6} alkyl, -C(O)-C_{1-4}alkyl-aryl or -C(O)-(-C_2H_4O)$_{1-8}$-C_{1-2} alkyl-N(R)(R'), wherein said aryl is selected from 6 to 14 membered aryl and is optionally substituted by -C_{1-3}alkyl or -OC_{1-3}alkyl; wherein

R and R' are independently selected from hydrogen, -C_{1-6} alkyl or -C(O)-C_{1-4}alkyl-aryl, wherein said aryl is selected from 6 to 14 membered aryl and is optionally substituted by -C_{1-3}alkyl or -OC_{1-3}alkyl;

A is selected from the group consisting of val-cit, gly-gly-phe-gly, Formula P_2, Formula P_{13}, Formula P_{14}, Formula P_{15} and Formula P_{16};

Q is of Formula Q_1,

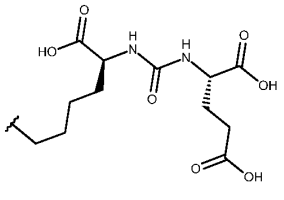


Formula Q_1

wherein:

R_{11} is —CH_2-O-C(O)—; and

R_{12} is selected from hydrogen or —C(O)N(R_{13})(R_{14}), wherein R_{13} is hydrogen and R_{14} is selected from —C_{1-5} alkyl-N(R_{15})(R_{16}) or

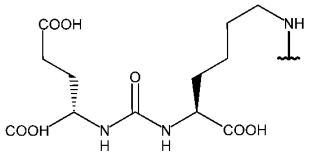


; and

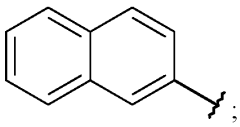
wherein at least one of R_{12} and R_{22} is hydrogen.

18. The compound as claimed in claim 1, wherein:

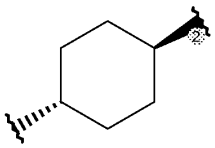
L is a ligand of formula:



;

R_1 is  ;

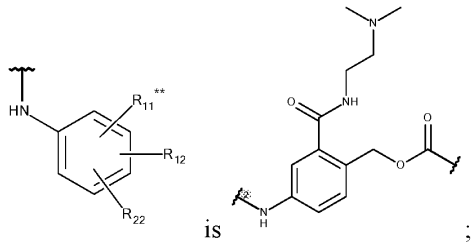
n is 1;

R_2 is  ;

R_3 is hydrogen;

R_4 is $-C_3H_6-$;

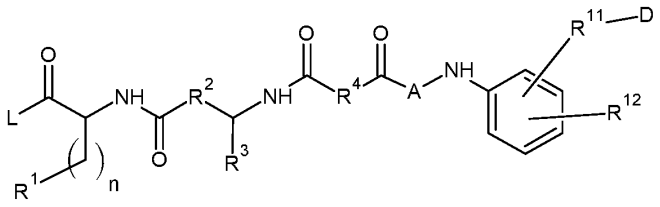
A is val-cit;



is ;

D is Monomethyl auristatin E (MMAE).

19. A compound of Formula II:



Formula II

or pharmaceutically acceptable salt, solvate, stereoisomer or isotope thereof; wherein,

n is 0, 1, 2, 3 or 4;

L is a Ligand;

R_1 is selected from a 6 to 14 membered aryl or a 5 to 13 membered heteroaryl containing one, two or three heteroatoms independently selected from nitrogen, oxygen or sulfur;

R_1 is unsubstituted or substituted with one or more R_5;

R_5, at each occurrence, is independently selected from halogen, —C(O)NH_2, —C(O)OR_6, —C_{1-3} alkyl, —OR_7, and a 6 to 10 membered aryl; wherein:

R_6 is hydrogen or C_{1-3} alkyl;

R_7 is hydrogen or C_{1-3} alkyl;

R_2 is absent or is selected from a 6 to 10 membered cycloalkyl or a 6 to 10 membered aryl;

R_3 is hydrogen, or —C_1-C_5COOH;

R_4 is selected from a group consisting of —C_{1-10} alkyl-, —C_{2-6} alkenyl-, —C_{1-3} alkyl-O-C_{1-3} alkyl—, —C_{2-6} alkyl-N(R_8)—, —C_{2-6} alkyl(N(R_8)($R_{8'}$))—, —N(R_8)-C_{2-6} alkyl—, a 3 to 6 membered cycloalkyl and —C_{1-2} alkyl-(-OC_2H_4)$_{1-8}$-OC_{1-2} alkyl—; wherein,

R_8 and $R_{8'}$ are independently selected from hydrogen, C_{1-6} alkyl, -C(O)-C_{1-4}alkyl-aryl or -C(O)-(-C_2H_4O)$_{1-8}$-C_{1-2} alkyl-N(R)(R'), wherein said aryl is selected from 6 to 14 membered aryl and is optionally substituted by -C_{1-3}alkyl or -OC_{1-3}alkyl; wherein

R and R' are independently selected from hydrogen, -C_{1-6} alkyl or -C(O)-C_{1-4}alkyl-aryl, wherein said aryl is selected from 6 to 14 membered aryl and is optionally substituted by -C_{1-3}alkyl or -OC_{1-3}alkyl;

A is an amino acid or a peptide comprising 2-5 amino acids;

A is attached to Q through its C terminal;

R_{11} is selected from —C_{1-3} alkyl-OC(O)—**,

—C_{1-3} alkyl-O-C(O)-N(R_{19})-C_{1-5} alkyl-N(R_{19})-C(O)—**,

—C_{1-3} alkyl-O-C(O)-N[C_{1-5} alkyl-N($R_{20}R_{21}$)]-C_{1-3} alkyl—**, or

—C_{1-3} alkyl-O-C(O)-Het_2-C_{1-3} alkyl-N(R_{19})-C(O)—**,

wherein ** indicates point of attachment to D;

R_{19} is selected from H, —C_{1-3} alkyl or —C_{1-3} alkyl-O-C_{1-3} alkyl-OH;

R_{20} is H or —C_{1-3} alkyl;

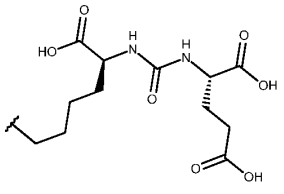
R_{21} is H or —C_1-C_3 alkyl; and

Het_2 is a 5 to 10 membered heterocyclic ring containing one, two or three heteroatoms independently selected from nitrogen, oxygen or sulfur;

R_{12} is selected from hydrogen, —C(O)N(R_{13})(R_{14}) or —$(-OC_2H_4)_{1-10}$-CH_3;

R_{13} is hydrogen;

R_{14} is selected from —C_{1-5} alkyl, —C_{2-5} alkenyl, —C_{2-5} alkynyl, —C_{1-5} alkyl-N(R_{15})(R_{16}), —C_{1-5} alkyl-O-C_{1-3} alkyl, —$(-C_2H_4O)_{1-10}C_2H_5$, —$(-C_2H_4O)_{1-10}$-C_2H_4-R_{17} or —C_{1-3} alkyl-Het_3-$(-C_2H_4O)_{1-10}$-C_2H_4-R_{18} or



; wherein:

R_{15} is hydrogen or C_{1-3} alkyl;

R_{16} is hydrogen or C_{1-3} alkyl; or

R_{15} and R_{16} along with the nitrogen atom to which they are attached form a 5 to 6 membered heterocyclic ring, wherein 1 or 2 carbon atoms in the heterocyclic ring are optionally replaced with additional heteroatoms independently selected from nitrogen, oxygen and sulfur and wherein the 5 to 6 membered heterocyclic ring is unsubstituted or substituted with C_{1-3} alkyl, halogen or –OH;

R_{17} is selected from hydrogen or —C(O)NH-C_{2-5} alkyl-$N(CH_3)_2$;

R_{18} is selected from hydrogen or —C(O)NH-C_{2-5} alkyl-$N(CH_3)_2$;

Het_3 is a 5 to 10 membered heterocyclic ring containing one, two or three heteroatoms independently selected from nitrogen, oxygen and sulfur;

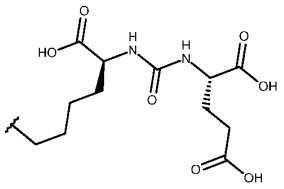
OR

R_{13} and R_{14} along with the nitrogen atom to which they are attached form a 4 to 6 membered heterocyclic ring, wherein 1 or 2 carbons in the heterocyclic ring are optionally replaced with additional heteroatoms independently selected from nitrogen, oxygen and sulfur, and wherein the 4 to 6 membered heterocyclic ring is unsubstituted or substituted with C_{1-3} alkyl, $—N(CH_3)_2$ or $—CH_2N(CH_3)_2$;

R_{22} is selected from hydrogen, $—C(O)N(R_{23})(R_{24})$ or $—(-OC_2H_4)_{1-10}-CH_3$, wherein:

R_{23} is hydrogen;

R_{24} is selected from $—C_{1-5}$ alkyl, $—C_{2-5}$ alkenyl, $—C_{2-5}$ alkynyl, $—C_{1-5}$ alkyl-$N(R_{25})(R_{26})$, $—C_{1-5}$ alkyl-O-C_{1-3} alkyl, $—(-C_2H_4O)_{1-10}C_2H_5$, $—(-C_2H_4O)_{1-10}-C_2H_4-R_{27}$ or $—C_{1-3}$ alkyl-Het_3-$(-C_2H_4O)_{1-10}-C_2H_4-R_{28}$ or



; wherein:

R_{25} is hydrogen or C1 to C3 alkyl;

R_{26} is hydrogen or C1 to C3 alkyl; or

R_{25} and R_{26} along with the nitrogen atom to which they are attached form a 5 to 6 membered heterocyclic ring, wherein 1 or 2 carbon atoms in the heterocyclic ring are optionally replaced with additional heteroatoms independently selected from nitrogen, oxygen and sulfur and wherein the 5 to 6 membered heterocyclic ring is unsubstituted or substituted with C_{1-3} alkyl, halogen or –OH;

R_{27} is selected from hydrogen or $—C(O)NH-C_{2-5}$ alkyl-$N(CH_3)_2$;

R_{28} is selected from hydrogen or $—C(O)NH-C_{2-5}$ alkyl-$N(CH_3)_2$;

Het_3 is a 5 to 10 membered heterocyclic ring containing one, two or three heteroatoms independently selected from nitrogen, oxygen and sulfur;

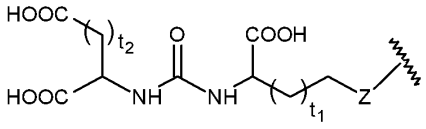
OR

R_{23} and R_{24} along with the nitrogen atom to which they are attached form a 4 to 6 membered heterocyclic ring, wherein 1 or 2 carbons in the heterocyclic ring are optionally replaced with additional heteroatoms independently selected from nitrogen, oxygen and

sulfur, and wherein the 4 to 6 membered heterocyclic ring is unsubstituted or substituted with C_{1-3} alkyl, —$N(CH_3)_2$ or —$CH_2N(CH_3)_2$; and

D is a cytotoxic agent or therapeutic agent.

20. The compound as claimed in claim 19, wherein the ligand L is a ligand of Formula L_1:



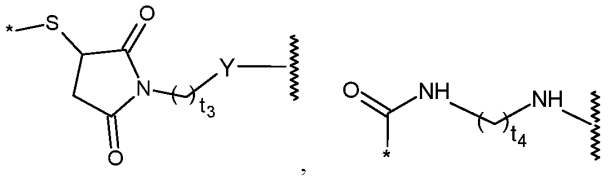
Formula L_1

wherein,

t_1 is 0, 1, 2, 3, or 4;

t_2 is 1, 2, 3 or 4;

Z is selected from the group consisting of $N(R_9)$, Formula Z_1 and Formula Z_2:



Formula Z_1 Formula Z_2

wherein:

t_3 is selected from 1, 2, 3, 4, 5 or 6;

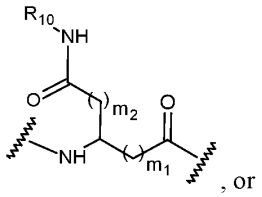
t_4 is selected from 1, 2, 3, 4, 5 or 6;

Y is $-CH_2-$ or –NH- and

‘ ’ indicates attachment of Formula L_1 to the rest of the compound of Formula I;

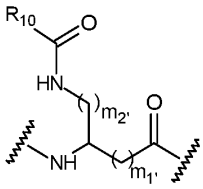
R_9 is selected from the group consisting of hydrogen, C_{1-5} alkyl, a 6 to 10 membered aryl, a 5 to 10 membered heterocyclyl ring wherein the heterocyclyl ring contains one, two or three heteroatoms independently selected from nitrogen, oxygen or sulfur; and wherein R_9 is unsubstituted or substituted with halogen.

21. The compound as claimed in claim 19, wherein the amino acid in A at each occurrence is independently selected from the group consisting of alanine (ala), arginine (arg), aspartic acid (asp), cysteine (cys), glutamic acid (glu), glycine (gly), lysine (lys), phenylalanine (phe), serine (ser), threonine (thr), tryptophan (trp), valine (val), ornithine (orn), citrulline (cit), homocitrulline (hct), lanthionine (lan), homocysteine (hcy) or an amino acid having Formula A_1 or Formula A_2



, or

Formula A_1



Formula A_2

wherein

m_1 and m_1' are 0, 1, 2 or 3;

m_2 and m_2' are is 0, 1, 2, 3 or 4;

R_{10} is selected from $(-C_2H_4O)_{1-24}CH_3$, $(-C_2H_4O)_{1-24}C_{1-2}$ alkyl$(N(R_{10'})(R_{10''}))$—, C_{1-3} alkyl-aryl or —C_{1-3} alkyl-Het_1-$(-C_2H_4O)_{1-24}CH_3$, wherein Het_1 is a 5 to 10 membered heterocyclic ring containing one, two or three heteroatoms independently selected from nitrogen, oxygen or sulfur and wherein said aryl is selected from 6 to 14 membered aryl and is optionally substituted by -C_{1-3}alkyl or -OC_{1-3}alkyl; wherein

$R_{10'}$ and $R_{10''}$ are independently selected from hydrogen, C_{1-6} alkyl or -C(O)-C_{1-4}alkyl-aryl wherein said aryl is selected from 6 to 14 membered aryl and is optionally substituted by -C_{1-3}alkyl or -OC_{1-3}alkyl.

22. The compound as claimed in claim 19, wherein R_2 is a 6 to 10 membered cycloalkyl; R_3 is hydrogen.

23. The compound as claimed in claim 19, wherein R_4 is selected from —C_{1-10} alkyl- or a 3 to 6 membered cycloalkyl.

24. The compound as claimed in claim 19, wherein R_1 is naphthyl.

25. The compound as claimed in claim 19, wherein

R_{12} is —C(O)N(R_{13})(R_{14}), wherein:

R_{13} is hydrogen; and

R_{14} is —C_{1-5} alkyl-N(R_{15})(R_{16}),

wherein:

R_{15} is C1 to C3 alkyl;

R_{16} is C1 to C3 alkyl; and

R_{22} is hydrogen.

26. The compound as claimed in claim 20, wherein

t_1 is 3;

Z is $N(R_9)$; and

R_9 is hydrogen or phenyl.

27. The compound as claimed in claim 20, wherein

t_1 is 1 and Z is the compound of Formula Z_2 wherein

t_3 is 1, 2, 3, 4, 5 or 6.

28. The compound as claimed in claim 20, wherein

t_1 is 0;

Z is the compound of Formula Z_1 wherein

t_2 is 1, 2, 3, 4, 5 or 6, and

Y is –NH-.

29. The compound as claimed in claim 19, wherein

R_1 is naphthyl;

R_2 is a 6 to 10 membered cycloalkyl;

R_3 is hydrogen;

R_4 is selected from —$C_{1\text{-}10}$ alkyl- or —$C_{2\text{-}6}$ alkyl($N(R_8)(R_{8'})$)—; wherein

R_8 and $R_{8'}$ are independently selected from hydrogen, -C(O)-$C_{1\text{-}4}$alkyl-aryl or -C(O)-(-$C_2H_4O)_{1\text{-}8}$-$C_{1\text{-}2}$ alkyl-N(R)(R'), wherein said aryl is selected from 6 to 14 membered aryl and is optionally substituted by -$C_{1\text{-}3}$alkyl or -O$C_{1\text{-}3}$alkyl, wherein both R_8 and $R_{8'}$ are not hydrogen; wherein

R and R' are independently selected from hydrogen or -C(O)-$C_{1\text{-}4}$alkyl-aryl, wherein said aryl is selected from 6 to 14 membered aryl and is optionally substituted by -$C_{1\text{-}3}$alkyl or -O$C_{1\text{-}3}$alkyl, wherein both R and R' are not hydrogen;

R_{11} is selected from —$C_{1\text{-}3}$ alkyl-OC(O)—**, wherein ** indicates point of attachment to D;

R_{12} is —C(O)$N(R_{13})(R_{14})$, wherein:

R_{13} is hydrogen; and

R_{14} is —$C_{1\text{-}5}$ alkyl-$N(R_{15})(R_{16})$,

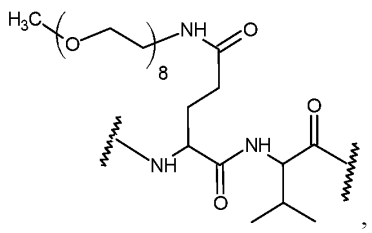
wherein:

R_{15} is C1 to C3 alkyl;

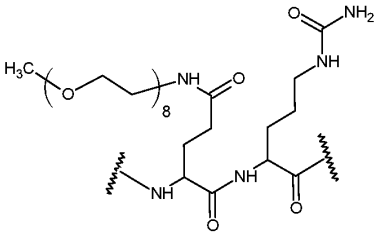
R_{16} is C1 to C3 alkyl; and

R_{22} is hydrogen.

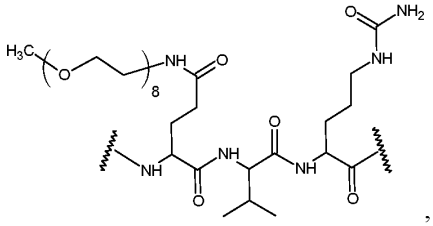
30. The compound as claimed in any of claims 19-29, wherein A is a peptide selected from the group consisting of ala-ala, ala-ala-ala, ala-phe, val-ala, val-cit, ala-val-cit, ala(beta)-val-cit, glu-val-cit, glu-cit, glu-val, gly-gly, gly-gly-phe, gly-phe-gly, gly-gly-phe-gly, asp-cit, asp-val-cit and asp-val; or the peptide is selected from a group of compounds having following formula:



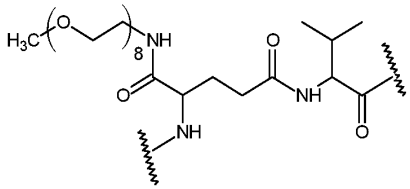
Formula P_1



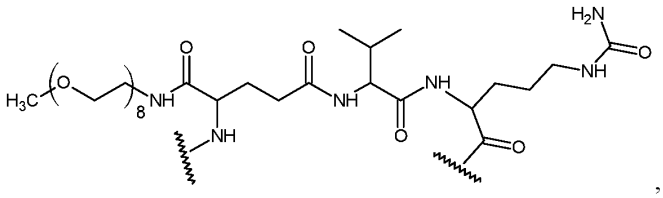
Formula P_2



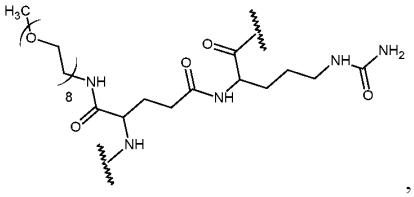
Formula P_3



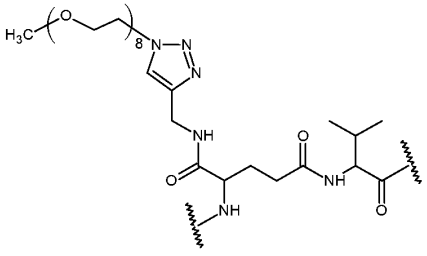
Formula P_4



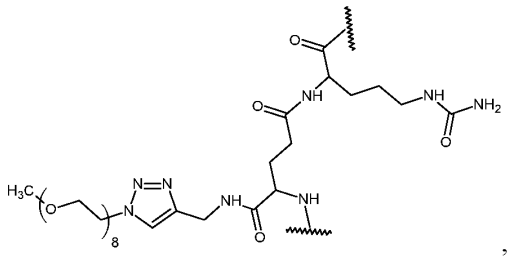
Formula P_5



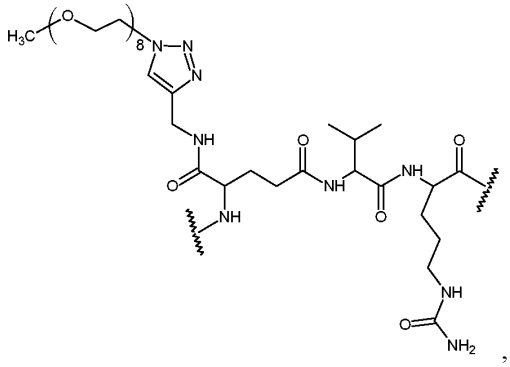
Formula P_6



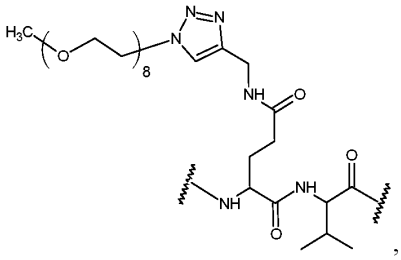
Formula P_7



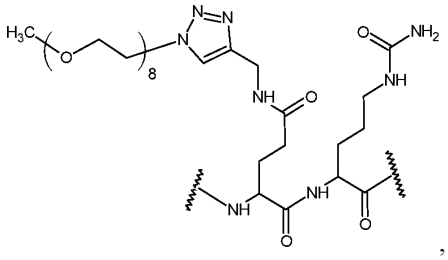
Formula P_8



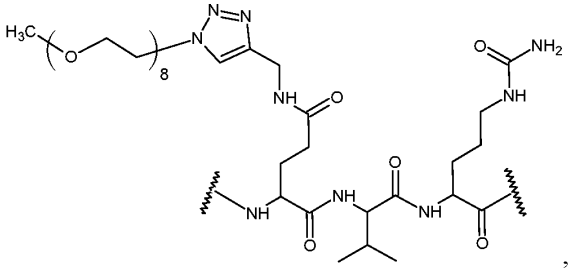
Formula P_9



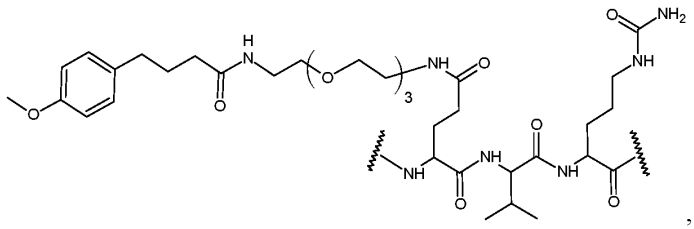
Formula P_{10}



Formula P_{11}

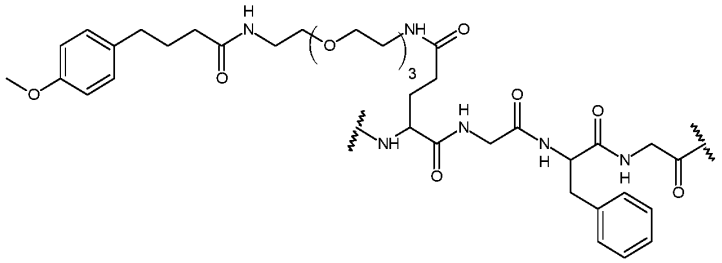


Formula P_{12}



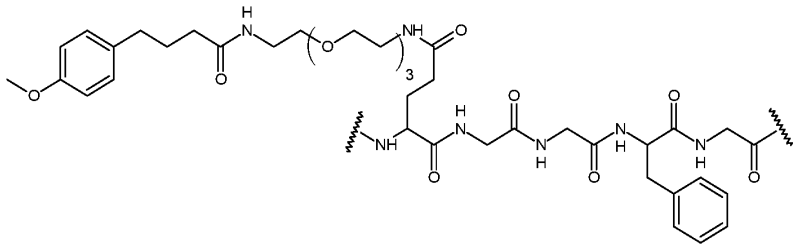
,

Formula P_{13}



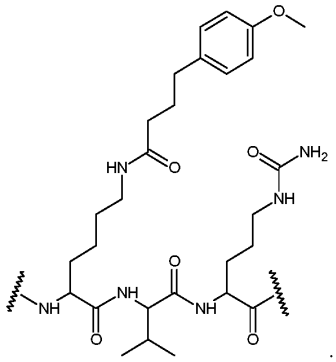
,

Formula P_{14}



, and

Formula P_{15}

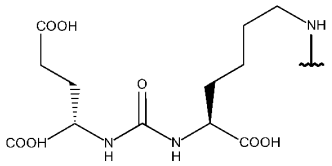


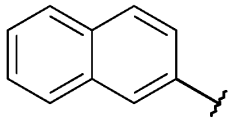
.

Formula P_{16}

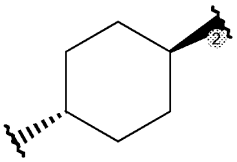
31. The compound as claimed in claim 19, wherein:

L is a ligand of formula:



; R_1 is  ;

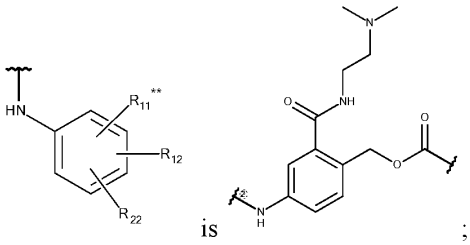
n is 1;

R_2 is  ;

R_3 is hydrogen;

R_4 is $-C_3H_6-$;

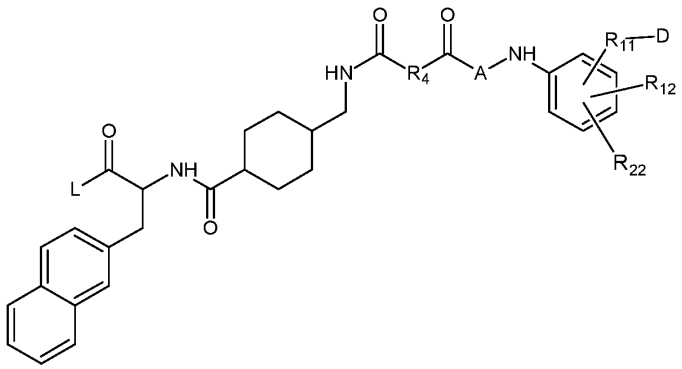
A is val-cit;



is ;

D is Monomethyl auristatin E (MMAE).

32. A compound of Formula III:



Formula III

or pharmaceutically acceptable salt, solvate, stereoisomer or isotope thereof; wherein,

L is a Ligand;

R_4 is selected from a group consisting of —C_{1-10} alkyl, —C_{2-6} alkenyl, —C_{1-3} alkyl-O-C_{1-3} alkyl—, —C_{2-6} alkyl-N(R_8)—, —C_{2-6} alkyl(N(R_8)($R_{8'}$))—, —N(R_8)-C_{2-6} alkyl—, a 3 to 6 membered cycloalkyl and —C_{1-2} alkyl $(-OC_2H_4)_{1-8}$-OC_{1-2} alkyl—; wherein:

R_8 and $R_{8'}$ are independently selected from hydrogen, C_{1-6} alkyl, -C(O)-C_{1-4}alkyl-aryl or -C(O)-$(-C_2H_4O)_{1-8}$-C_{1-2} alkyl-N(R)(R'), wherein said aryl is selected from 6 to 14 membered aryl and is optionally substituted by -C_{1-3}alkyl or -OC_{1-3}alkyl; wherein

R and R' are independently selected from hydrogen, -C_{1-6} alkyl or -C(O)-C_{1-4}alkyl-aryl, wherein said aryl is selected from 6 to 14 membered aryl and is optionally substituted by -C_{1-3}alkyl or -OC_{1-3}alkyl;

A is an amino acid or a peptide comprising 2-5 amino acids;

R_{11} is selected from —C_{1-3} alkyl-OC(O)—**,

—C_{1-3} alkyl-O-C(O)-N(R_{19})-C_{1-5} alkyl-N(R_{19})-C(O)—**,

—C_{1-3} alkyl-O-C(O)-N[C_{1-5} alkyl-N($R_{20}R_{21}$)]-C_{1-3} alkyl—**, or

—C_{1-3} alkyl-O-C(O)-Het_2-C_{1-3} alkyl-N(R_{19})-C(O)—**,

wherein ** indicates point of attachment to D;

R_{19} is selected from H, CH_3 or –C_2H_4-O-C_2H_4-OH;

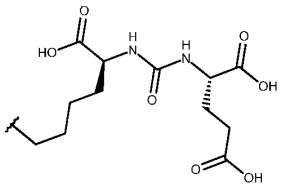
R_{20} is CH_3; R_{21} is CH_3; and

Het_2 is pyrrolidinyl.

R_{12} is selected from hydrogen, —C(O)N(R_{13})(R_{14}) or —$(-OC_2H_4)_{1-10}$-CH_3;

R_{13} is hydrogen;

R_{14} is —CH_3, —CH_2-C≡CH, —C_{1-3} alkyl-N(R_{15})(R_{16}), —$C_2H_4OCH_3$, —$(-C_2H_4O)_{3-8}$-C_2H_5, —$(-C_2H_4O)_{5-10}$-C_2H_4-R_{17}, —CH_2-triazole-$(-C_2H_4O)$4-C_2H_4-R_{18} or



;

R_{15} is —CH_3 or —C_2H_5; R_{16} is —CH_3 or —C_2H_5;

or

R_{15} and R_{16} along with the nitrogen atom to which they are attached form a 5 to 6 membered heterocyclic ring, wherein 1 or 2 carbon atoms in the heterocyclic ring are optionally replaced with additional heteroatoms independently selected from nitrogen,

oxygen and sulfur and wherein the 5 to 6 membered heterocyclic ring is unsubstituted or substituted with —CH_3;

R_{17} is —$C(O)NHC_2H_4N(CH_3)_2$;

R_{18} is —$C(O)NHC_2H_4N(CH_3)_2$;

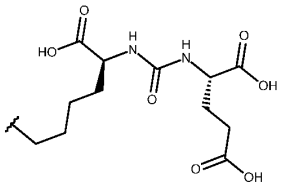
or

R_{13} and R_{14} along with the nitrogen atom to which they are attached form a 4 to 6 membered heterocyclic ring, wherein 1 or 2 carbons in the heterocyclic ring are optionally replaced with additional heteroatoms independently selected from nitrogen, oxygen and sulfur, and wherein the 4 to 6 membered heterocyclic ring is unsubstituted or substituted with C_{1-3} alkyl, —$N(CH_3)_2$ or —$CH_2N(CH_3)_2$;

R_{22} is selected from hydrogen, —$C(O)N(R_{23})(R_{24})$ or —$(-OC_2H_4)_{1-10}$-CH_3;

R_{23} is hydrogen;

R_{24} is selected from —CH_3, —CH_2-C≡CH, —C_{1-3} alkyl-$N(R_{25})(R_{26})$, —$C_2H_4OCH_3$, —$(-C_2H_4O)_{3-8}$-C_2H_5, —$(-C_2H_4O)_{5-10}$-C_2H_4-R_{27}, —CH_2-triazole-$(-C_2H_4O)_4$-C_2H_4-R_{28} or



; wherein:

R_{25} is —CH_3 or —C_2H_5;

R_{26} is —CH_3 or —C_2H_5; or

R_{25} and R_{26} along with the nitrogen atom to which they are attached form a 5 to 6 membered heterocyclic ring, wherein 1 or 2 carbon atoms in the heterocyclic ring are optionally replaced with additional heteroatoms independently selected from nitrogen, oxygen and sulfur and wherein the 5 to 6 membered heterocyclic ring is unsubstituted or substituted with —CH_3;

R_{27} is —$C(O)NH$-C_{2-5} alkyl-$N(CH_3)_2$;

R_{28} is —$C(O)NH$-C_{2-5} alkyl-$N(CH_3)_2$;

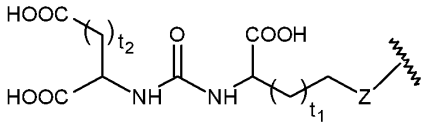
OR

R_{23} and R_{24} along with the nitrogen to which they are attached form a 4 to 6 membered heterocyclic ring, wherein 1 or 2 carbons in the heterocyclic ring are optionally replaced with additional heteroatoms independently selected from nitrogen, oxygen and sulfur, and wherein the 4 to 6 membered heterocyclic ring is unsubstituted or substituted with C_{1-3}

alkyl, —$N(CH_3)_2$ or —$CH_2N(CH_3)_2$; and D is a cytotoxic agent or therapeutic agent as defined above.

33. The compound as claimed in claim 32, wherein

the ligand L is of the Formula L_1:



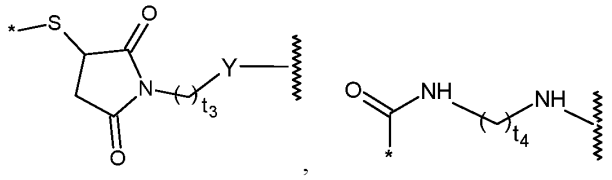
Formula L_1

wherein,

t_1 is 0, 1, 2, 3, or 4;

t_2 is 1, 2, 3 or 4;

Z is selected from the group consisting of $N(R_9)$, Formula Z_1 and Formula Z_2:



Formula Z_1 Formula Z_2

wherein:

t_3 is selected from 1, 2, 3, 4, 5 or 6;

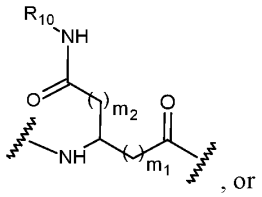
t_4 is selected from 1, 2, 3, 4, 5 or 6;

Y is $-CH_2-$ or –NH- and

‘ ’ indicates attachment of Formula L_1 to the rest of the compound of Formula I;

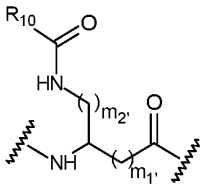
R_9 is selected from the group consisting of hydrogen, C_{1-5} alkyl, a 6 to 10 membered aryl, a 5 to 10 membered heterocyclyl ring wherein the heterocyclyl ring contains one, two or three heteroatoms independently selected from nitrogen, oxygen or sulfur; and wherein R_9 is unsubstituted or substituted with halogen.

34. The compound as claimed in claim 32, wherein the amino acid in A at each occurrence is independently selected from the group consisting of alanine (ala), arginine (arg), aspartic acid (asp), cysteine (cys), glutamic acid (glu), glycine (gly), lysine (lys), phenylalanine (phe), serine (ser), threonine (thr), tryptophan (trp), valine (val), ornithine (orn), citrulline (cit), homocitrulline (hct), lanthionine (lan), homocysteine (hcy) or an amino acid having Formula A_1 or Formula A_2



, or

Formula A_1



Formula A_2

wherein

m_1 and m_1' are 0, 1, 2 or 3;

m_2 and m_2' are is 0, 1, 2, 3 or 4;

R_{10} is selected from $(-C_2H_4O)_{1-24}CH_3$, $(-C_2H_4O)_{1-24}C_{1-2}$ alkyl$(N(R_{10'})(R_{10''}))$—, C_{1-3} alkyl-aryl or —C_{1-3} alkyl-Het_1-$(-C_2H_4O)_{1-24}CH_3$, wherein Het_1 is a 5 to 10 membered heterocyclic ring containing one, two or three heteroatoms independently selected from nitrogen, oxygen or sulfur and wherein said aryl is selected from 6 to 14 membered aryl and is optionally substituted by -C_{1-3}alkyl or -OC_{1-3}alkyl; wherein

$R_{10'}$ and $R_{10''}$ are independently selected from hydrogen, C_{1-6} alkyl or -C(O)-C_{1-4}alkyl-aryl wherein said aryl is selected from 6 to 14 membered aryl and is optionally substituted by -C_{1-3}alkyl or -OC_{1-3}alkyl.

35. The compound as claimed in claim 32, wherein

R_4 is selected from a group consisting of —C_{1-10} alkyl, —C_{2-6} alkenyl, —C_{1-3} alkyl-O-C_{1-3} alkyl—, —C_{2-6} alkyl-$N(R_8)$—, —C_{2-6} alkyl$(N(R_8)(R_{8'}))$—, —$N(R_8)$-C_{2-6} alkyl—, a 3 to 6 membered cycloalkyl and —C_{1-2} alkyl $(-OC_2H_4)_{1-8}$-OC_{1-2} alkyl—; wherein:

R_8 and $R_{8'}$ are independently selected from hydrogen, C_{1-6} alkyl, -C(O)-C_{1-4}alkyl-aryl or -C(O)-$(-C_2H_4O)_{1-8}$-C_{1-2} alkyl-N(R)(R'), wherein said aryl is selected from 6 to 14 membered aryl and is optionally substituted by -C_{1-3}alkyl or -OC_{1-3}alkyl; wherein

R and R' are independently selected from hydrogen, -C_{1-6} alkyl or -C(O)-C_{1-4}alkyl-aryl, wherein said aryl is selected from 6 to 14 membered aryl and is optionally substituted by -C_{1-3}alkyl or -OC_{1-3}alkyl;

36. The compound as claimed in claim 32, wherein

R_{11} is —C_{1-3} alkyl-OC(O)—**

wherein ** indicates point of attachment to D;

R_{12} is —C(O)$N(R_{13})(R_{14})$,

wherein:

R_{13} is hydrogen;

R_{14} is —C_{1-5} alkyl-N(R_{15})(R_{16}),

wherein:

R_{15} is C_{1-3} alkyl;

R_{16} is C_{1-3} alkyl; and

R_{22} is hydrogen.

37. The compound as claimed in claim 32, wherein

R_{11} is —C_{1-3} alkyl-OC(O)—**

wherein ** indicates point of attachment to D;

R_{12} is —C(O)N(R_{13})(R_{14}),

wherein:

R_{13} is hydrogen;

R_{14} is —C_{1-5} alkyl-N(R_{15})(R_{16}),

wherein:

R_{15} is C_{1-3} alkyl;

R_{16} is C_{1-3} alkyl; and

R_{22} is —C(O)N(R_{23})(R_{24}),

wherein:

R_{23} is hydrogen;

R_{24} is —C_{1-5} alkyl-N(R_{25})(R_{26}),

wherein:

R_{25} is C_{1-3} alkyl; and

R_{26} is C_{1-3} alkyl.

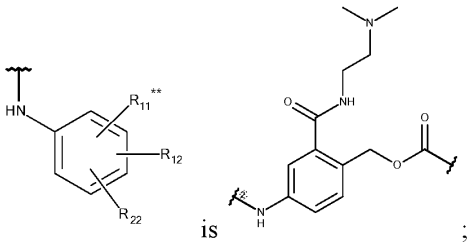
38. The compound as claimed in any of claims 32-37, wherein A is selected from cit, val-ala, val-cit, gly-gly-phe-gly, Formula P_3, Formula P_5, Formula P_9, Formula P_{12}, Formula P_{13} Formula P_{14} Formula P_{15} and Formula P_{16}.

39. The compound as claimed in claim 32, wherein:

wherein:

R_4 is -C_3H_6-;

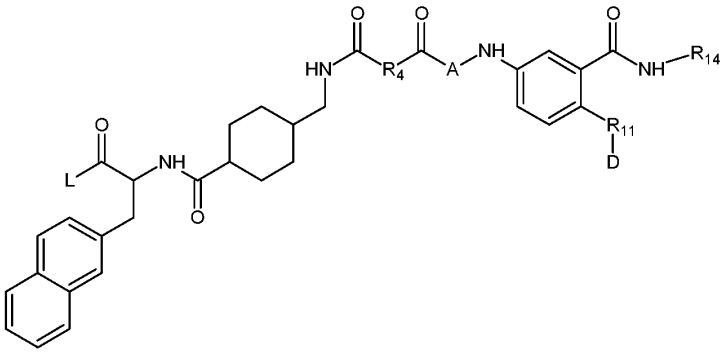
A is val-cit;



is ;

D is Monomethyl auristatin E (MMAE).

40. A compound of Formula IV,



Formula IV

or pharmaceutically acceptable salt, solvate, stereoisomer or isotope thereof; wherein,

L is a Ligand; D is a cytotoxic or therapeutic agent as defined above;

R_4 is selected from a group consisting of —C_{1-10} alkyl, —C_{2-6} alkenyl, —C_{1-3} alkyl-O-C_{1-3} alkyl—, —C_{2-6} alkyl-N(R_8)—, —C_{2-6} alkyl(N(R_8)($R_{8'}$))—, —N(R_8)-C_{2-6} alkyl—, 3 to 6 membered cycloalkyl and —C_{1-2} alkyl (-OC_2H_4)$_{1-8}$-OC_{1-2} alkyl—; wherein:

R_8 and $R_{8'}$ are independently selected from hydrogen, C_{1-6} alkyl, -C(O)-C_{1-4}alkyl-aryl or -C(O)-(-C_2H_4O)$_{1-8}$-C_{1-2} alkyl-N(R)(R'), wherein said aryl is selected from 6 to 14 membered aryl and is optionally substituted by -C_{1-3}alkyl or -OC_{1-3}alkyl; wherein

R and R' are independently selected from hydrogen, -C_{1-6} alkyl or -C(O)-C_{1-4}alkyl-aryl, wherein said aryl is selected from 6 to 14 membered aryl and is optionally substituted by -C_{1-3}alkyl or -OC_{1-3}alkyl;

A is an amino acid or a peptide comprising 2-5 amino acids;

R_{11} is selected from —C_{1-3} alkyl-OC(O)—**,

—C_{1-3} alkyl-O-C(O)-N(R_{19})-C_{1-5} alkyl-N(R_{19})-C(O)—**,

—C_{1-3} alkyl-O-C(O)-N[C_{1-5} alkyl-N($R_{20}R_{21}$)]-C_{1-3} alkyl—**, or

—C_{1-3} alkyl-O-C(O)-Het_2-C_{1-3} alkyl-N(R_{19})-C(O)—**,

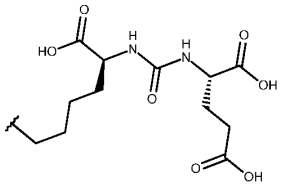
wherein ** indicates point of attachment to D and

R_{19} is selected from H, $-CH_3$ or $–C_2H_4-O-C_2H_4-OH$;

R_{20} is $-CH_3$; R_{21} is $-CH_3$;

Het_2 is pyrrolidine;

R_{14} is selected from —C_1-C_5 alkyl, —C_1 to C_5 alkyl-$N(R_{15})(R_{16})$, —C_1-C_5 alkyl-OCH_3, $(-C_2H_4O)_{1-10}CH_2-CH_3$, or



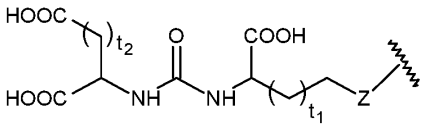
; wherein:

R_{15} is C_{1-3} alkyl; and

R_{16} is C_{1-3} alkyl.

41. The compound as claimed in claim 40, wherein

the ligand L is of the Formula L_1:



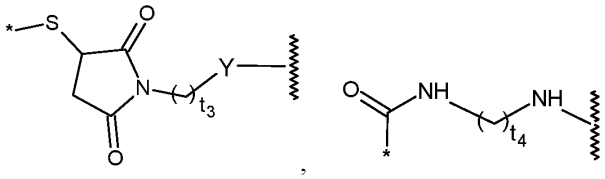
Formula L_1

wherein,

t_1 is 0, 1, 2, 3, or 4;

t_2 is 1, 2, 3 or 4;

Z is selected from the group consisting of $N(R_9)$, Formula Z_1 and Formula Z_2:



Formula Z_1 Formula Z_2

wherein:

t_3 is selected from 1, 2, 3, 4, 5 or 6;

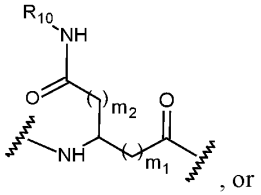
t_4 is selected from 1, 2, 3, 4, 5 or 6;

Y is $-CH_2-$ or –NH- and

‘ wwwww ’ indicates attachment of Formula L_1 to the rest of the compound of Formula I;

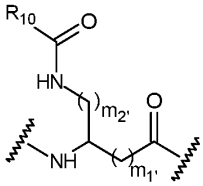
R_9 is selected from the group consisting of hydrogen, C_{1-5} alkyl, a 6 to 10 membered aryl, a 5 to 10 membered heterocyclyl ring wherein the heterocyclyl ring contains one, two or three heteroatoms independently selected from nitrogen, oxygen or sulfur; and wherein R_9 is unsubstituted or substituted with halogen.

42. The compound as claimed in claim 40, wherein the amino acid in A at each occurrence is independently selected from the group consisting of alanine (ala), arginine (arg), aspartic acid (asp), cysteine (cys), glutamic acid (glu), glycine (gly), lysine (lys), phenylalanine (phe), serine (ser), threonine (thr), tryptophan (trp), valine (val), ornithine (orn), citrulline (cit), homocitrulline (hct), lanthionine (lan), homocysteine (hcy) or an amino acid having Formula A_1 or Formula A_2



, or

Formula A_1



Formula A_2

wherein

m_1 and m_1' are 0, 1, 2 or 3;

m_2 and m_2' are is 0, 1, 2, 3 or 4;

R_{10} is selected from $(-C_2H_4O)_{1-24}CH_3$, $(-C_2H_4O)_{1-24}C_{1-2}$ alkyl$(N(R_{10'})(R_{10''}))$—, C_{1-3} alkyl-aryl or —C_{1-3} alkyl-Het_1-$(-C_2H_4O)_{1-24}CH_3$, wherein Het_1 is a 5 to 10 membered heterocyclic ring containing one, two or three heteroatoms independently selected from nitrogen, oxygen or sulfur and wherein said aryl is selected from 6 to 14 membered aryl and is optionally substituted by -C_{1-3}alkyl or -OC_{1-3}alkyl; wherein

$R_{10'}$ and $R_{10''}$ are independently selected from hydrogen, C_{1-6} alkyl or -C(O)-C_{1-4}alkyl-aryl wherein said aryl is selected from 6 to 14 membered aryl and is optionally substituted by -C_{1-3}alkyl or -OC_{1-3}alkyl.

43. The compound as claimed in claim 40, wherein

R_4 is selected from a group consisting of —C_{2-5} alkyl, —C_{2-5} alkyl$(N(R_8)(R_{8'}))$— and 3 to 6 membered cycloalkyl; wherein:

R_8 and $R_{8'}$ are independently selected from hydrogen, C_{1-6} alkyl, -C(O)-C_{1-4}alkyl-aryl or -C(O)-$(-C_2H_4O)_{1-8}$-C_{1-2} alkyl-N(R)(R'), wherein said aryl is selected from 6 to 14 membered aryl and is optionally substituted by -C_{1-3}alkyl or -OC_{1-3}alkyl; wherein

R and R' are independently selected from hydrogen, -C_{1-6} alkyl or -C(O)-C_{1-4}alkyl-aryl, wherein said aryl is selected from 6 to 14 membered aryl and is optionally substituted by -C_{1-3}alkyl or -OC_{1-3}alkyl.

44. The compound as claimed in claim 40, wherein

R_{11} is —C_{1-3} alkyl-OC(O)—**

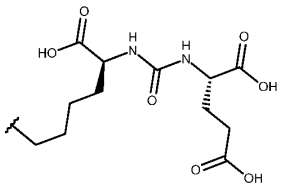
wherein ** indicates the point of attachment to D;

R_{12} is —C(O)N(R_{13})(R_{14}),

wherein:

R_{13} is hydrogen;

R_{14} is selected from —C_{1-5} alkyl-N(R_{15})(R_{16}) and



; wherein:

R_{15} is C_{1-3} alkyl; and

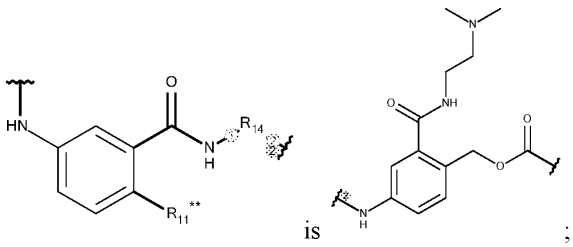
R_{16} is C_{1-3} alkyl.

45. The compound as claimed in claim 40, wherein A is a peptide selected from the group consisting of cit, val-ala, val-cit, glu-val-cit, gly-gly-phe-gly, Formula P_3, Formula P_5, Formula P_9, Formula P_{12}, Formula P_{13}, Formula P_{14}, Formula P_{15} and Formula P_{16}.

46. The compound as claimed in claim 40, wherein:

R_4 is -C_3H_6-;

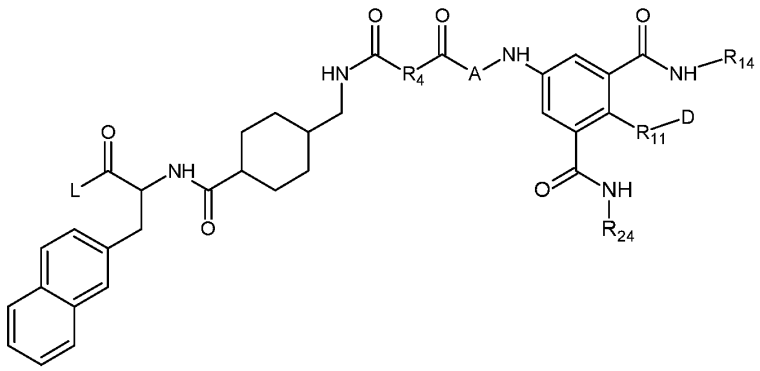
A is val-cit;



is ;

D is Monomethyl auristatin E (MMAE).

47. A compound of Formula V,



Formula V

wherein

or pharmaceutically acceptable salt, solvate, stereoisomer or isotope thereof; wherein,

L is a Ligand;

A is an amino acid or a peptide comprising 2-5 amino acids;

R_4 is selected from a group consisting of —C_{1-10} alkyl, —C_{2-6} alkenyl, —C_{1-3} alkyl-O-C_{1-3} alkyl—, —C_{2-6} alkyl-N(R_8)—, —N(R_8)-C_{2-6} alkyl—, a 3 to 6 membered cycloalkyl and —C_{1-2} alkyl $(-OC_2H_4)_{1-8}$-OC_{1-2} alkyl—; wherein:

R_8 is hydrogen or C_{1-6} alkyl;

R_{11} is selected from —C_{1-3} alkyl-OC(O)—**,

—C_{1-3} alkyl-O-C(O)-N(R_{19})-C_{1-5} alkyl-N(R_{19})-C(O)—**,

—C_{1-3} alkyl-O-C(O)-N[C_{1-5} alkyl-N($R_{20}R_{21}$)]-C_{1-3} alkyl—**, or

—C_{1-3} alkyl-O-C(O)-Het_2-C_{1-3} alkyl-N(R_{19})-C(O)—**,

wherein ** indicates point of attachment to D;

R_{19} is selected from H, -CH_3 or –C_2H_4-O-C_2H_4-OH;

R_{20} is -CH_3; R_{21} is -CH_3; and

Het_2 is pyrrolidinyl;

R_{14} is selected from —C_1-C_5 alkyl, —C_1 to C_5 alkyl-N(R_{15})(R_{16}), —C_1-C_5 alkyl-OCH_3, $(-C_2H_4O)_{1-10}$ CH_2-CH_3 wherein:

R_{15} is C_{1-3} alkyl;

R_{16} is C_{1-3} alkyl;

R_{24} is selected from —C_{1-5} alkyl, —C_{1-5} alkyl-N(R_{25})(R_{26}), —C_{1-5} alkyl-OCH_3, $(-C_2H_4O)_{1-10}CH_2$-CH_3 wherein:

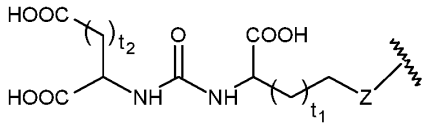
R_{25} is hydrogen or C_{1-3} alkyl; and

R_{26} is hydrogen or C_{1-3} alkyl

D is a cytotoxic agent or therapeutic agent.

48. The compound as claimed in claim 47, wherein

the ligand L is of the Formula L_1:



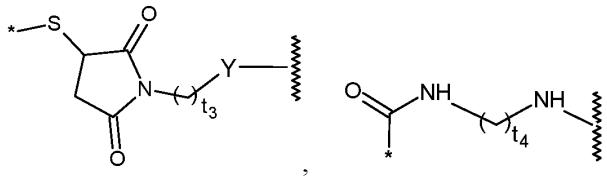
Formula L_1

wherein,

t_1 is 0, 1, 2, 3, or 4;

t_2 is 1, 2, 3 or 4;

Z is selected from the group consisting of $N(R_9)$, Formula Z_1 and Formula Z_2:



Formula Z_1 Formula Z_2

wherein:

t_3 is selected from 1, 2, 3, 4, 5 or 6;

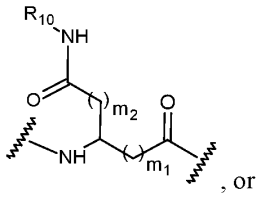
t_4 is selected from 1, 2, 3, 4, 5 or 6;

Y is $-CH_2-$ or –NH- and

‘ ’ indicates attachment of Formula L_1 to the rest of the compound of Formula I;

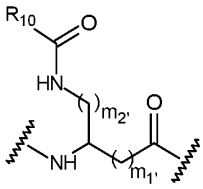
R_9 is selected from the group consisting of hydrogen, C_{1-5} alkyl, a 6 to 10 membered aryl, a 5 to 10 membered heterocyclyl ring wherein the heterocyclyl ring contains one, two or three heteroatoms independently selected from nitrogen, oxygen or sulfur; and wherein R_9 is unsubstituted or substituted with halogen.

49. The compound as claimed in claim 47, wherein the amino acid in A at each occurrence is independently selected from the group consisting of alanine (ala), arginine (arg), aspartic acid (asp), cysteine (cys), glutamic acid (glu), glycine (gly), lysine (lys), phenylalanine (phe), serine (ser), threonine (thr), tryptophan (trp), valine (val), ornithine (orn), citrulline (cit), homocitrulline (hct), lanthionine (lan), homocysteine (hcy) or an amino acid having Formula A_1 or Formula A_2



, or

Formula A_1



Formula A_2

wherein

m_1 and m_1' are 0, 1, 2 or 3;

m_2 and m_2' are is 0, 1, 2, 3 or 4;

R_{10} is selected from $(-C_2H_4O)_{1-24}CH_3$, $(-C_2H_4O)_{1-24}C_{1-2}$ alkyl$(N(R_{10'})(R_{10''}))$—, C_{1-3} alkyl-aryl or —C_{1-3} alkyl-Het_1-$(-C_2H_4O)_{1-24}CH_3$, wherein Het_1 is a 5 to 10 membered heterocyclic ring containing one, two or three heteroatoms independently selected from nitrogen, oxygen or sulfur and wherein said aryl is selected from 6 to 14 membered aryl and is optionally substituted by -C_{1-3}alkyl or -OC_{1-3}alkyl; wherein

$R_{10'}$ and $R_{10''}$ are independently selected from hydrogen, C_{1-6} alkyl or -C(O)-C_{1-4}alkyl-aryl wherein said aryl is selected from 6 to 14 membered aryl and is optionally substituted by -C_{1-3}alkyl or -OC_{1-3}alkyl.

50. The compound as claimed in claim 47, wherein

R_{11} is —C_{1-3} alkyl-OC(O)—**

wherein ** indicates point of attachment to D;

R_{12} is —C(O)N$(R_{13})(R_{14})$,

wherein:

R_{13} is hydrogen;

R_{14} is —C_{1-5} alkyl-N$(R_{15})(R_{16})$,

wherein:

R_{15} is C_{1-3} alkyl;

R_{16} is C_{1-3} alkyl; and

R_{22} is —C(O)N$(R_{23})R_{24}$,

wherein:

R_{23} is hydrogen;

R_{24} is —C_{1-5} alkyl-N$(R_{25})(R_{26})$,

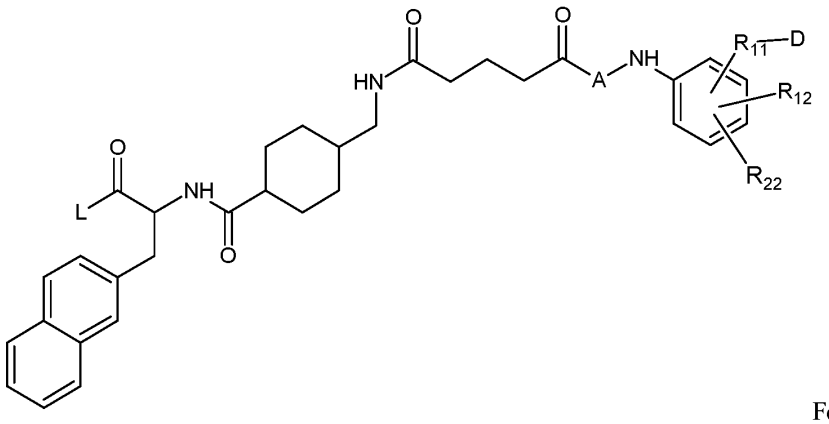
wherein:

R_{25} is C_{1-3} alkyl; and

R_{26} is C_{1-3} alkyl.

51. The compound as claimed in claim 47, wherein A is selected from cit, val-ala, val-cit, glu-val-cit, gly-gly-phe-gly, Formula P_3, Formula P_5, Formula P_9, Formula P_{12}, Formula P_{13}, Formula P_{14}, Formula P_{15} and Formula P_{16}.

52. A compound of Formula VI,



Formula VI

or pharmaceutically acceptable salt, stereoisomer or isotope thereof; wherein:

L is a Ligand;

A is an amino acid or a peptide comprising 2-5 amino acids;

R_{11} is selected from —C_{1-3} alkyl-OC(O)—**,

—C_{1-3} alkyl-O-C(O)-N(R_{19})-C_{1-5} alkyl-N(R_{19})-C(O)—**,

—C_{1-3} alkyl-O-C(O)-N[C_{1-5} alkyl-N($R_{20}R_{21}$)]-C_{1-3} alkyl—**, or

—C_{1-3} alkyl-O-C(O)-Het_2-C_{1-3} alkyl-N(R_{19})-C(O)—**,

wherein ** indicates point of attachment to D;

R_{19} is selected from H, CH_3 or –C_2H_4-O-C_2H_4-OH;

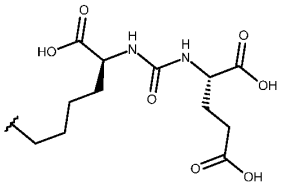
R_{20} is CH_3; R_{21} is CH_3; and

Het_2 is pyrrolidinyl;

R_{12} is selected from hydrogen, —C(O)N(R_{13})(R_{14}) or —(-OC_2H_4)$_{1-10}$-CH_3;

R_{13} is hydrogen;

R_{14} is —CH_3, —CH_2-C≡CH, —C_{1-3} alkyl-N(R_{15})(R_{16}), —$C_2H_4OCH_3$, —(-C_2H_4O)$_{3-8}$-C_2H_5, —(-C_2H_4O)$_{5-10}$-C_2H_4-R_{17}, —CH_2-triazole-(-C_2H_4O)4-C_2H_4-R_{18} or



; wherein:

R_{15} is —CH_3 or —C_2H_5;

R_{16} is —CH_3 or —C_2H_5; or

R_{15} and R_{16} along with the nitrogen atom to which they are attached form a 5 to 6 membered heterocyclic ring, wherein 1 or 2 carbon atoms in the heterocyclic ring are optionally replaced with additional heteroatoms independently selected from nitrogen, oxygen and sulfur and wherein the 5 to 6 membered heterocyclic ring is unsubstituted or substituted with —CH_3;

R_{17} is —$C(O)NHC_2H_4N(CH_3)_2$;

R_{18} is —$C(O)NHC_2H_4N(CH_3)_2$;

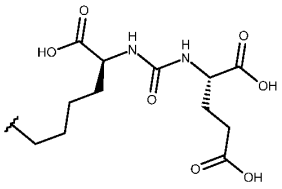
OR

R_{13} and R_{14} along with the nitrogen atom to which they are attached form a 4 to 6 membered heterocyclic ring, wherein 1 or 2 carbons in the heterocyclic ring are optionally replaced with additional heteroatoms independently selected from nitrogen, oxygen and sulfur, and wherein the 4 to 6 membered heterocyclic ring is unsubstituted or substituted with $C_{1\text{-}3}$ alkyl, —$N(CH_3)_2$ or —$CH_2N(CH_3)_2$;

R_{22} is selected from hydrogen, —$C(O)N(R_{23})(R_{24})$ or —$(\text{-}OC_2H_4)_{1\text{-}10}\text{-}CH_3$;

R_{23} is hydrogen;

R_{24} is —CH_3, —$CH_2\text{-}C{\equiv}CH$, —$C_{1\text{-}3}$ alkyl-$N(R_{25})(R_{26})$, —$C_2H_4OCH_3$, —$(\text{-}C_2H_4O)_{3\text{-}8}\text{-}C_2H_5$, —$(\text{-}C_2H_4O)_{5\text{-}10}\text{-}C_2H_4\text{-}R_{27}$, —$CH_2$-triazolyl-$(\text{-}C_2H_4O)4\text{-}C_2H_4\text{-}R_{28}$ or



; wherein:

R_{25} is —CH_3 or —C_2H_5;

R_{26} is —CH_3 or —C_2H_5; or

R_{25} and R_{26} along with the nitrogen atom to which they are attached form a 5 to 6 membered heterocyclic ring, wherein 1 or 2 carbon atoms in the heterocyclic ring are optionally replaced with additional heteroatoms independently selected from

nitrogen, oxygen and sulfur and wherein the 5 to 6 membered heterocyclic ring is unsubstituted or substituted with —CH_3;

R_{27} is —$C(O)NHC_2H_4N(CH_3)_2$;

R_{28} is —$C(O)NHC_2H_4N(CH_3)_2$;

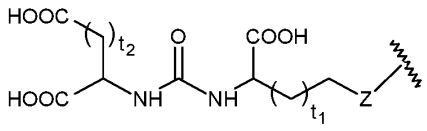
OR

R_{23} and R_{24} along with the nitrogen atom to which they are attached form a 4 to 6 membered heterocyclic ring, wherein 1 or 2 carbons in the heterocyclic ring are optionally replaced with additional heteroatoms independently selected from nitrogen, oxygen and sulfur, and wherein the 4 to 6 membered heterocyclic ring is unsubstituted or substituted with C_{1-3} alkyl, —$N(CH_3)_2$ or —$CH_2N(CH_3)_2$; and

D is a cytotoxic agent or therapeutic agent.

53. The compound as claimed in claim 52, wherein

the ligand L is of the Formula L_1:



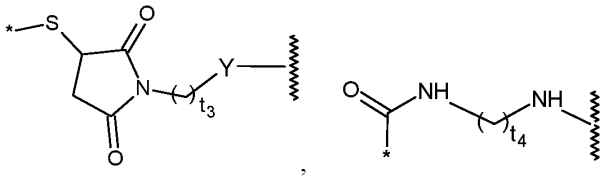
Formula L_1

wherein,

t_1 is 0, 1, 2, 3, or 4;

t_2 is 1, 2, 3 or 4;

Z is selected from the group consisting of $N(R_9)$, Formula Z_1 and Formula Z_2:



Formula Z_1 Formula Z_2

wherein:

t_3 is selected from 1, 2, 3, 4, 5 or 6;

t_4 is selected from 1, 2, 3, 4, 5 or 6;

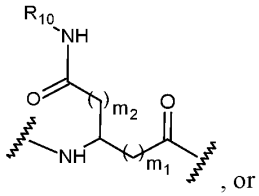
Y is -CH_2- or –NH- and

‘ wwwww ’ indicates attachment of Formula L_1 to the rest of the compound of Formula I;

R_9 is selected from the group consisting of hydrogen, C_{1-5} alkyl, a 6 to 10 membered aryl, a 5 to 10 membered heterocyclyl ring wherein the heterocyclyl ring contains one, two or

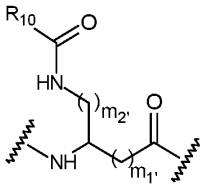
three heteroatoms independently selected from nitrogen, oxygen or sulfur; and wherein R_9 is unsubstituted or substituted with halogen.

54. The compound as claimed in claim 52, wherein the amino acid in A at each occurrence is independently selected from the group consisting of alanine (ala), arginine (arg), aspartic acid (asp), cysteine (cys), glutamic acid (glu), glycine (gly), lysine (lys), phenylalanine (phe), serine (ser), threonine (thr), tryptophan (trp), valine (val), ornithine (orn), citrulline (cit), homocitrulline (hct), lanthionine (lan), homocysteine (hcy) or an amino acid having Formula A_1 or Formula A_2



, or

Formula A_1



Formula A_2

wherein

m_1 and m_1' are 0, 1, 2 or 3;

m_2 and m_2' are is 0, 1, 2, 3 or 4;

R_{10} is selected from $(-C_2H_4O)_{1-24}CH_3$, $(-C_2H_4O)_{1-24}C_{1-2}$ alkyl$(N(R_{10'})(R_{10''}))$—, C_{1-3} alkyl-aryl or —C_{1-3} alkyl-Het_1-$(-C_2H_4O)_{1-24}CH_3$, wherein Het_1 is a 5 to 10 membered heterocyclic ring containing one, two or three heteroatoms independently selected from nitrogen, oxygen or sulfur and wherein said aryl is selected from 6 to 14 membered aryl and is optionally substituted by -C_{1-3}alkyl or -OC_{1-3}alkyl; wherein

$R_{10'}$ and $R_{10''}$ are independently selected from hydrogen, C_{1-6} alkyl or -C(O)-C_{1-4}alkyl-aryl wherein said aryl is selected from 6 to 14 membered aryl and is optionally substituted by -C_{1-3}alkyl or -OC_{1-3}alkyl.

55. The compound as claimed in claim 52, wherein

R_{11} is —C_{1-3} alkyl-OC(O)—**

wherein ** indicates the point of attachment to D;

R_{12} is —C(O)N(R_{13})(R_{14}),

wherein:

R_{13} is hydrogen;

R_{14} is —C_{1-5} alkyl-N(R_{15})(R_{16}),

wherein:

R_{15} is C_{1-3} alkyl;

R_{16} is C_{1-3} alkyl; and

R_{22} is hydrogen.

56. The compound as claimed in claim 52, wherein

R_{11} is —C_{1-3} alkyl-OC(O)—**

wherein ** indicates the point of attachment to D;

R_{12} is —C(O)N(R_{13})(R_{14}),

wherein:

R_{13} is hydrogen;

R_{14} is —C_{1-5} alkyl-N(R_{15})(R_{16}),

wherein:

R_{15} is C_{1-3} alkyl;

R_{16} is C_{1-3} alkyl; and

R_{22} is —C(O)N(R_{23})(R_{24}),

R_{23} is hydrogen;

R_{24} is —C_{1-5} alkyl-N(R_{25})(R_{26}),

wherein:

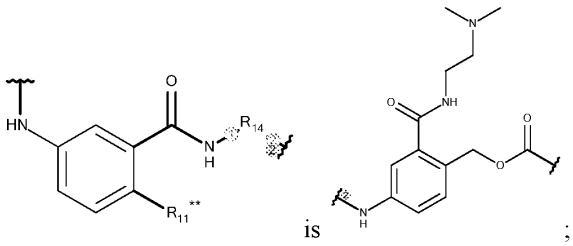
R_{25} is C_{1-3} alkyl; and

R_{26} is C_{1-3} alkyl.

57. The compound as claimed in claim 56, wherein:

R_4 is -C_3H_6-;

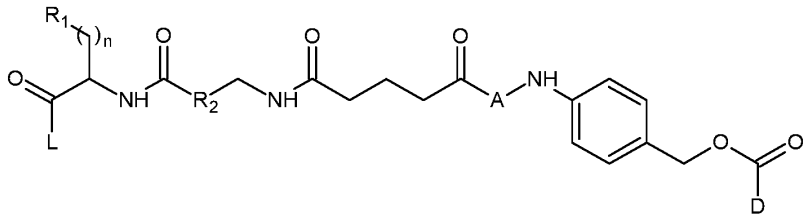
A is val-cit;



is ;

D is Monomethyl auristatin E (MMAE).

58. A compound of Formula VII



Formula VII

or pharmaceutically acceptable salt, stereoisomer or isotope thereof;

wherein:

L is a Ligand;

n is 0, 1, or 2;

R_1 is selected from the group consisting of phenyl, indolyl, thiophenyl, quinolinyl and isoquinolinyl;

R_1 is unsubstituted or substituted with one or more R_5;

R_5 is selected from halogen, —OH, or a 6 to 10 membered aryl ring;

R_2 is cyclohexyl or phenyl;

A is a peptide val-cit; and

D is a cytotoxic agent or therapeutic agent.

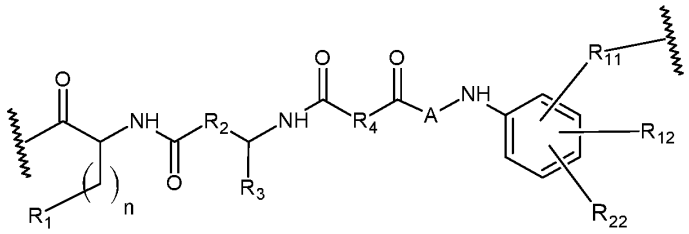
59. A method of treatment of cancer, wherein the method comprises, administering any of compound of Formula I-VII or a medicament comprising thereof.

60. A method of treatment of cancer that is positive for expression of PSMA comprising, administration of the compounds or medicament comprising the compounds as claimed in any of the preceding claims.

61. Use of compounds of Formula I-VII as claimed in any of the preceding claims for the preparation of medicament used in the treatment of cancer.

62. A pharmaceutical composition comprising compounds as claimed in any of the preceding claims, and a pharmaceutically acceptable carrier.

63. A ligand-drug conjugate, wherein the ligand L and the drug D is conjugated via linker of Formula VIII:



Formula VIII

wherein

n is 0, 1, 2, 3 or 4;

R_1 is selected from a 6 to 14 membered aryl or a 5 to 10 membered heteroaryl containing one, two or three heteroatoms independently selected from nitrogen, oxygen or sulfur;

R_1 is unsubstituted or substituted with one or more R_5;

R_5, at each occurrence, is independently selected from halogen, —$C(O)NH_2$, —$C(O)OR_6$, —C_{1-3} alkyl, —OR_7, and a 6 to 10 membered aryl; wherein:

R_6 is hydrogen or C_{1-3} alkyl;

R_7 is hydrogen or C_{1-3} alkyl;

R_2 is absent or is selected from a 6 to 10 membered cycloalkyl or a 6 to 10 membered aryl;

R_3 is hydrogen or —C_1-C_5COOH;

R_4 is selected from a group consisting of —C_{1-10} alkyl-, —C_{2-6} alkenyl-, —C_{1-3} alkyl-O-C_{1-3} alkyl—, —C_{2-6} alkyl-N(R_8)—, —C_{2-6} alkyl(N(R_8)($R_{8'}$))—, —N(R_8)-C_{2-6} alkyl—, a 3 to 6 membered cycloalkyl and —C_{1-2} alkyl-(-OC_2H_4)$_{1-8}$-OC_{1-2} alkyl—; wherein:

R_8 and $R_{8'}$ are independently selected from hydrogen, C_{1-6} alkyl, -C(O)-C_{1-4}alkyl-aryl or -C(O)-(-C_2H_4O)$_{1-8}$-C_{1-2} alkyl-N(R)(R'), wherein said aryl is selected from 6 to 14 membered aryl and is optionally substituted by -C_{1-3}alkyl or -OC_{1-3}alkyl; wherein

R and R' are independently selected from hydrogen, -C_{1-6} alkyl or -C(O)-C_{1-4}alkyl-aryl, wherein said aryl is selected from 6 to 14 membered aryl and is optionally substituted by -C_{1-3}alkyl or -OC_{1-3}alkyl;

A is an amino acid or a peptide comprising 2-5 amino acids;

A is attached to NH through its C terminal;

R_{11} is selected from a group consisting of —C_{1-3} alkyl-OC(O)—**,

—C_{1-3} alkyl-O-C(O)-N(R_{19})-C_{1-5} alkyl-N(R_{19})-C(O)—**,

—C_{1-3} alkyl-O-C(O)-N[C_{1-5} alkyl-N($R_{20}R_{21}$)]-C_{1-3} alkyl—**, and

—C_{1-3} alkyl-O-C(O)-Het_2-C_{1-3} alkyl-N(R_{19})-C(O)—**,

wherein:

R_{19} is selected from hydrogen, —C_{1-3} alkyl or —C_{1-3} alkyl-O-C_{1-3} alkyl-OH;

R_{20} is hydrogen or —C_{1-3} alkyl;

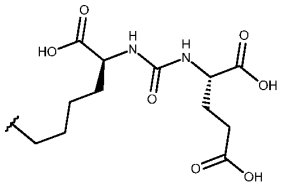
R_{21} is hydrogen or —C_{1-3} alkyl; and

Het_2 is a 5 to 10 membered heterocyclic ring containing one, two or three heteroatoms independently selected from nitrogen, oxygen or sulfur;

R_{12} is selected from hydrogen, —C(O)N(R_{13})(R_{14}) or —(-OC_2H_4)$_{1-10}$-CH_3;

R_{13} is hydrogen;

R_{14} is selected from —C_{1-5} alkyl, —C_{2-5} alkenyl, —C_{2-5} alkynyl, —C_{1-5} alkyl-N(R_{15})(R_{16}), —C_{1-5} alkyl-O-C_{1-3} alkyl, —(-C_2H_4O)$_{1-10}C_2H_5$, —(-C_2H_4O)$_{1-10}$-C_2H_4-R_{17} or —C_{1-3} alkyl-Het_3-(-C_2H_4O)$_{1-10}$-C_2H_4-R_{18} or



; wherein:

R_{15} is hydrogen or C1 to C3 alkyl;

R_{16} is hydrogen or C1 to C3 alkyl; or

R_{15} and R_{16} along with the nitrogen atom to which they are attached form a 5 to 6 membered heterocyclic ring, wherein 1 or 2 carbon atoms in the heterocyclic ring are optionally replaced with additional heteroatoms independently selected from nitrogen, oxygen and sulfur and wherein the 5 to 6 membered heterocyclic ring is unsubstituted or substituted with C_{1-3} alkyl, halogen or –OH;

R_{17} is selected from hydrogen or —C(O)NH-C_{2-5} alkyl-N(CH_3)$_2$;

R_{18} is selected from hydrogen or —C(O)NH-C_{2-5} alkyl-N(CH_3)$_2$;

Het_3 is a 5 to 10 membered heterocyclic ring containing one, two or three heteroatoms independently selected from nitrogen, oxygen and sulfur;

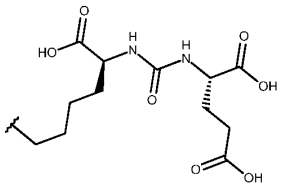
OR

R_{13} and R_{14} along with the nitrogen atom to which they are attached form a 4 to 6 membered heterocyclic ring, wherein 1 or 2 carbons in the heterocyclic ring are optionally replaced with additional heteroatoms independently selected from nitrogen, oxygen and sulfur, and wherein the 4 to 6 membered heterocyclic ring is unsubstituted or substituted with C_{1-3} alkyl, —N(CH_3)$_2$ or —CH_2N(CH_3)$_2$;

R_{22} is selected from hydrogen, —C(O)N(R_{23})(R_{24}) or —(-OC_2H_4)$_{1-10}$-CH_3;

R_{23} is hydrogen;

R_{24} is selected from —C_{1-5} alkyl, —C_{2-5} alkenyl, —C_{2-5} alkynyl, —C_{1-5} alkyl-$N(R_{25})(R_{26})$, —C_{1-5} alkyl-O-C_{1-3} alkyl, —$(-C_2H_4O)_{1-10}C_2H_5$, —$(-C_2H_4O)_{1-10}$-C_2H_4-R_{27} or —C_{1-3} alkyl-Het_3-$(-C_2H_4O)_{1-10}$-C_2H_4-R_{28} or



; wherein:

R_{25} is hydrogen or C1 to C3 alkyl;

R_{26} is hydrogen or C1 to C3 alkyl; or

R_{25} and R_{26} along with the nitrogen atom to which they are attached form a 5 to 6 membered heterocyclic ring, wherein 1 or 2 carbon atoms in the heterocyclic ring are optionally replaced with additional heteroatoms independently selected from nitrogen, oxygen and sulfur and wherein the 5 to 6 membered heterocyclic ring is unsubstituted or substituted with C_{1-3} alkyl, halogen or –OH;

R_{27} is selected from hydrogen or —C(O)NH-C_{2-5} alkyl-$N(CH_3)_2$;

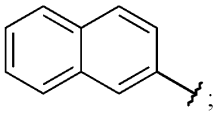
R_{28} is selected from hydrogen or —C(O)NH-C_{2-5} alkyl-$N(CH_3)_2$;

Het_3 is a 5 to 10 membered heterocyclic ring containing one, two or three heteroatoms independently selected from nitrogen, oxygen and sulfur;

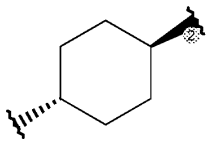
OR

R_{23} and R_{24} along with the nitrogen atom to which they are attached form a 4 to 6 membered heterocyclic ring, wherein 1 or 2 carbons in the heterocyclic ring are optionally replaced with additional heteroatoms independently selected from nitrogen, oxygen and sulfur, and wherein the 4 to 6 membered heterocyclic ring is unsubstituted or substituted with C_{1-3} alkyl, —$N(CH_3)_2$ or —$CH_2N(CH_3)_2$.

64. The compound as claimed in claim 63, wherein:

R_1 is  ;

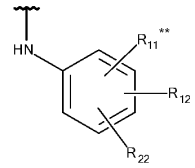
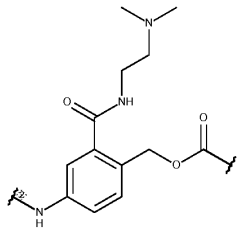
n is 1;

R_2 is  ;

R_3 is hydrogen;

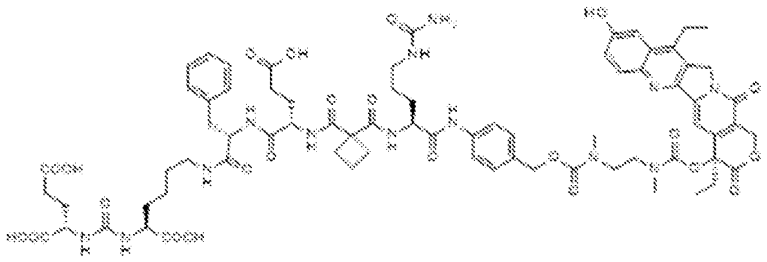
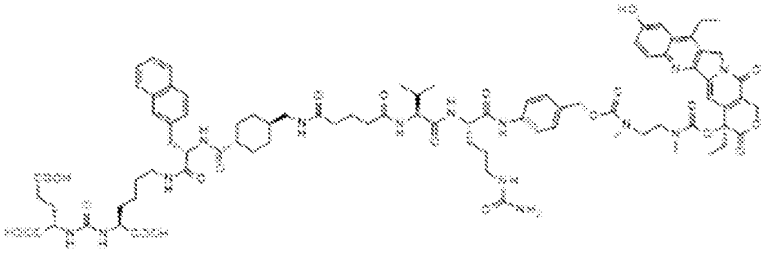
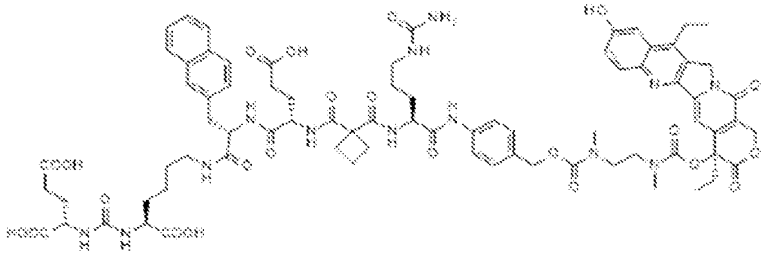
R_4 is $-C_3H_6-$;

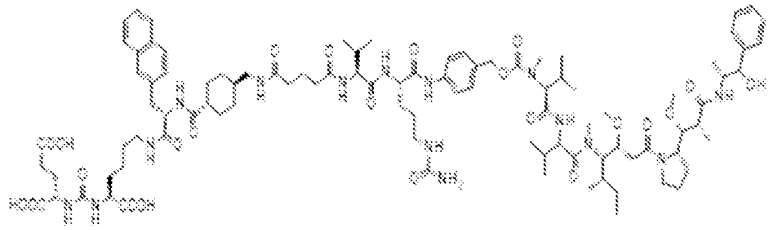
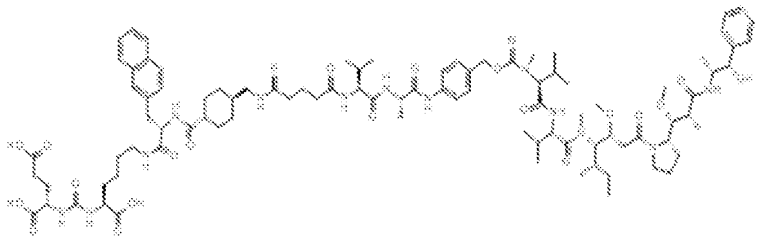
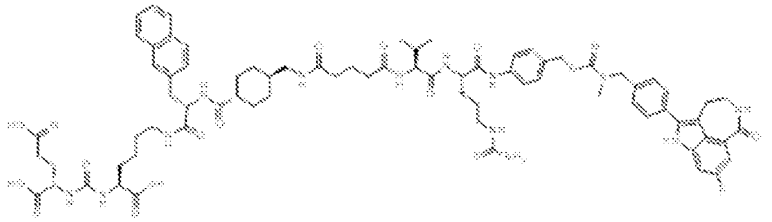
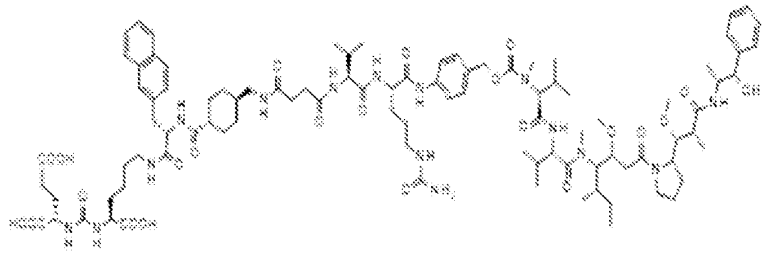
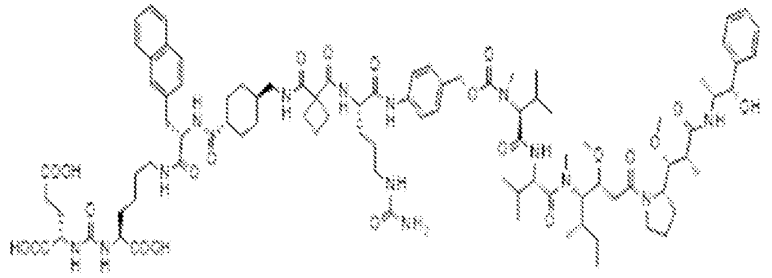
A is val-cit;

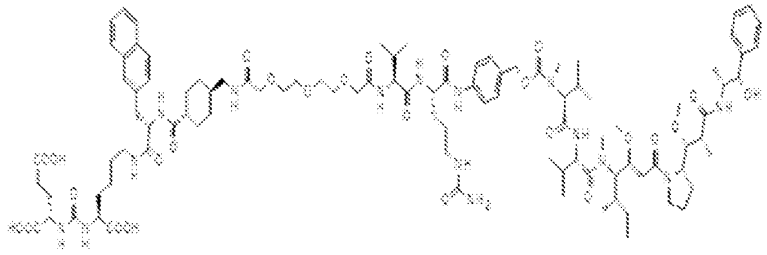
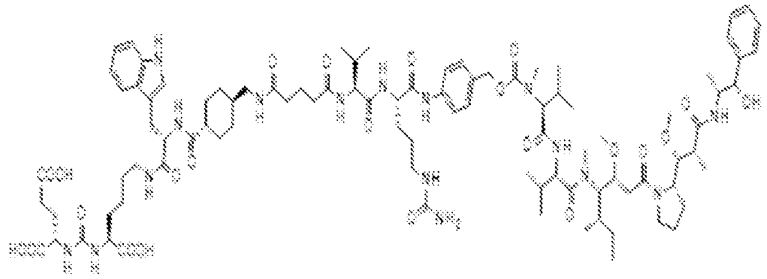
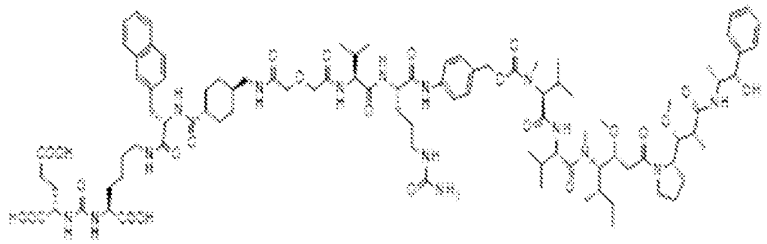
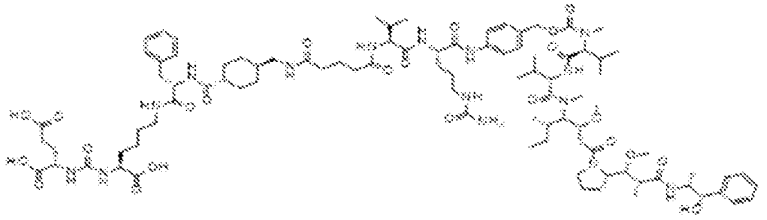
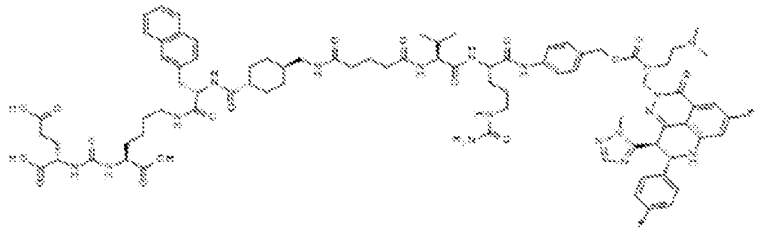



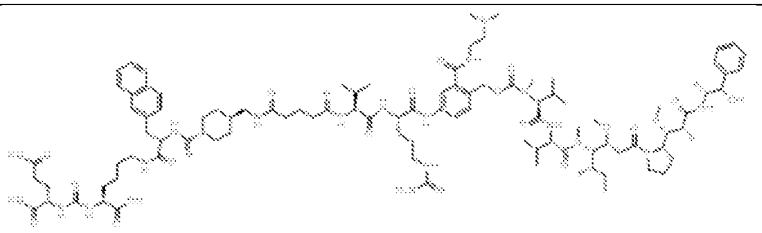
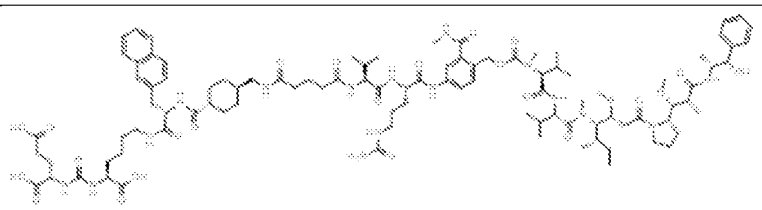
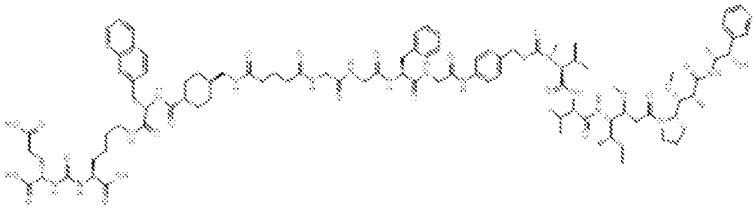
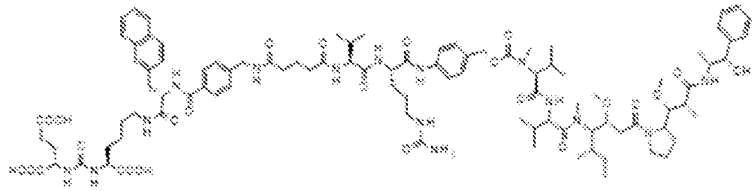
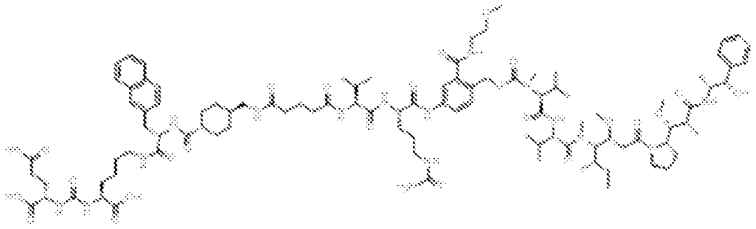
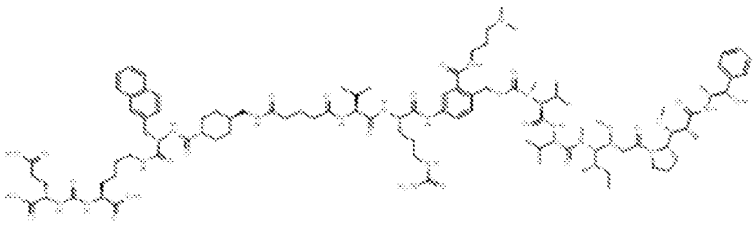
is .

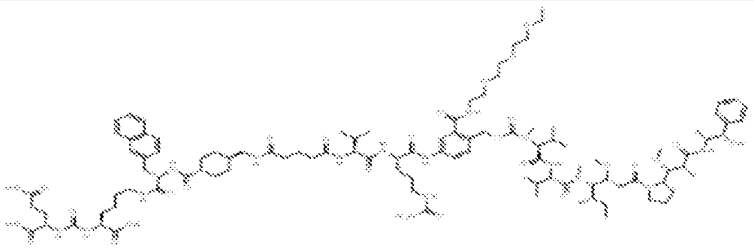
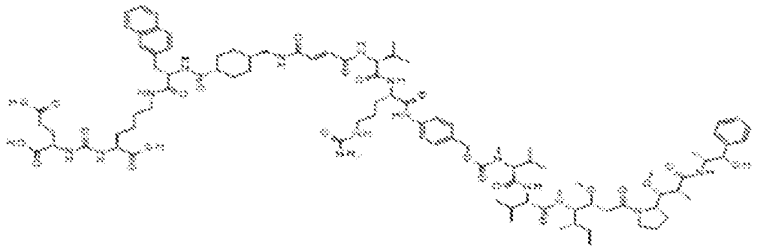
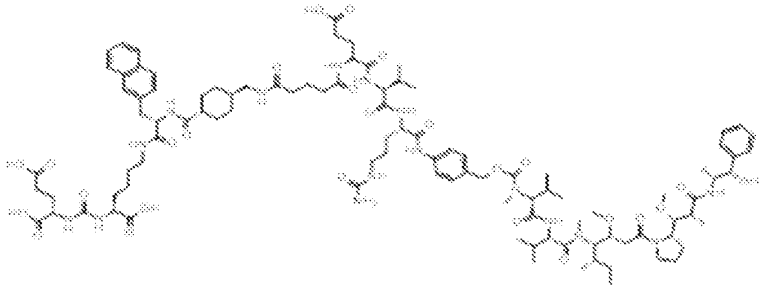
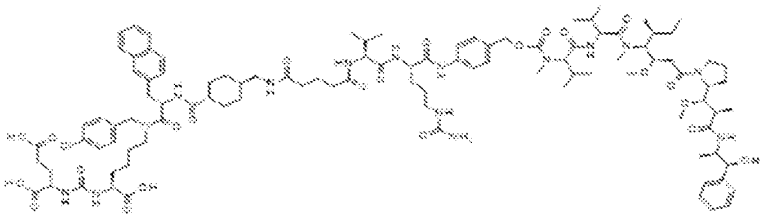
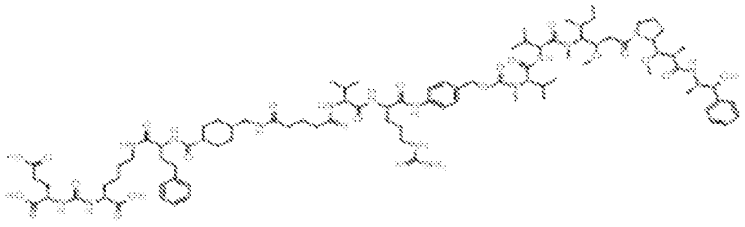
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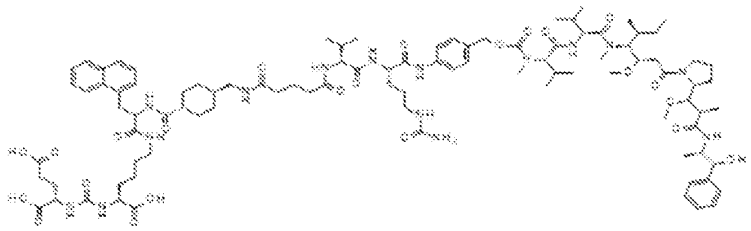
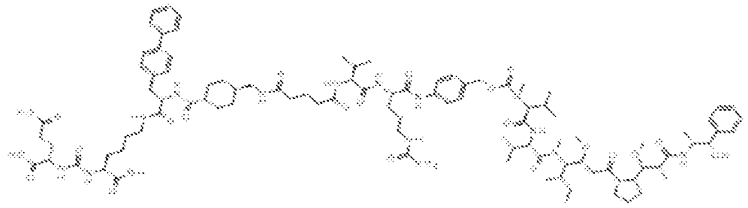
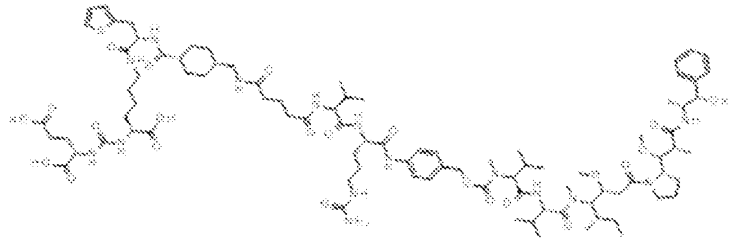
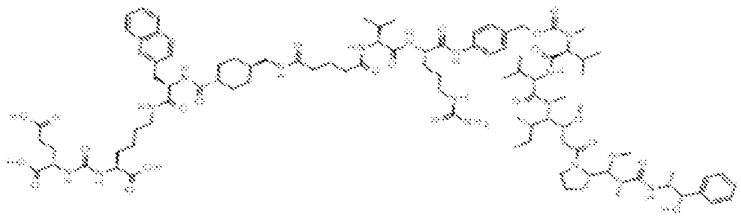
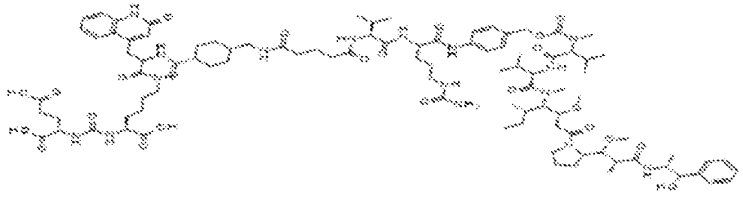
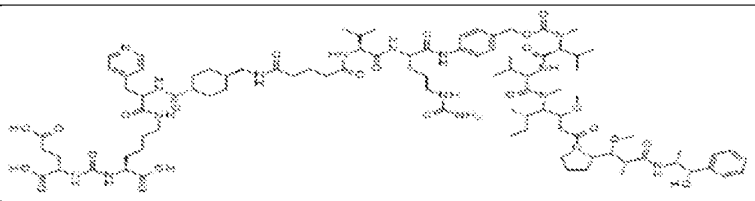
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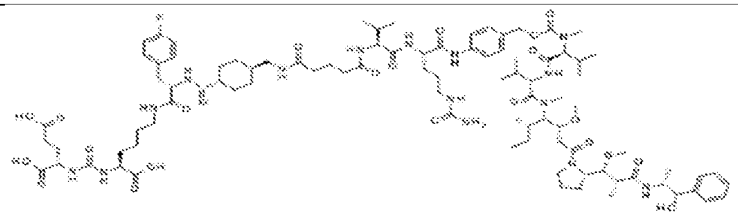
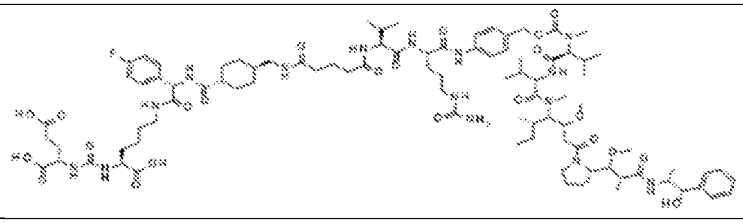
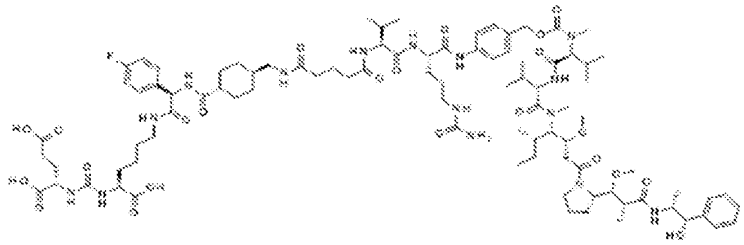
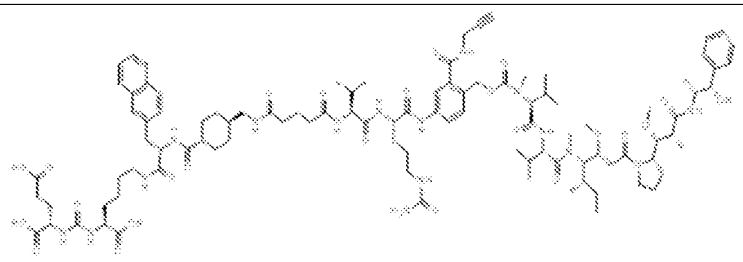
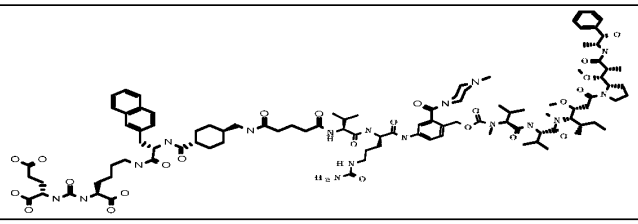
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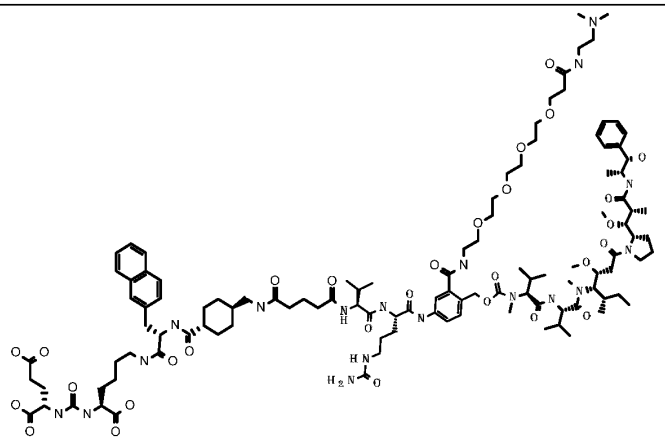
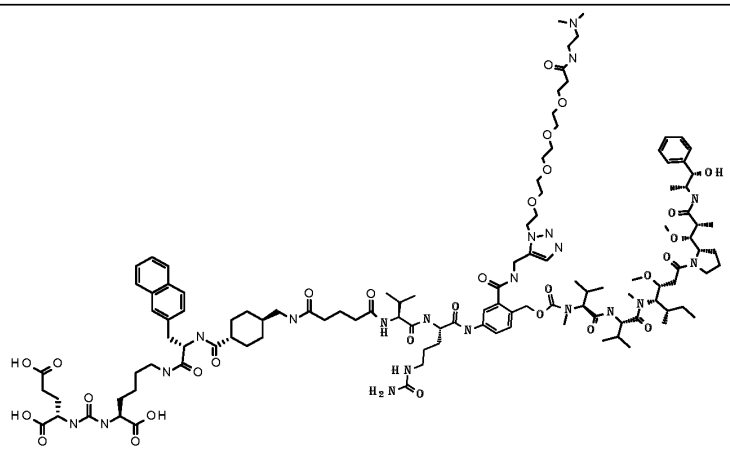
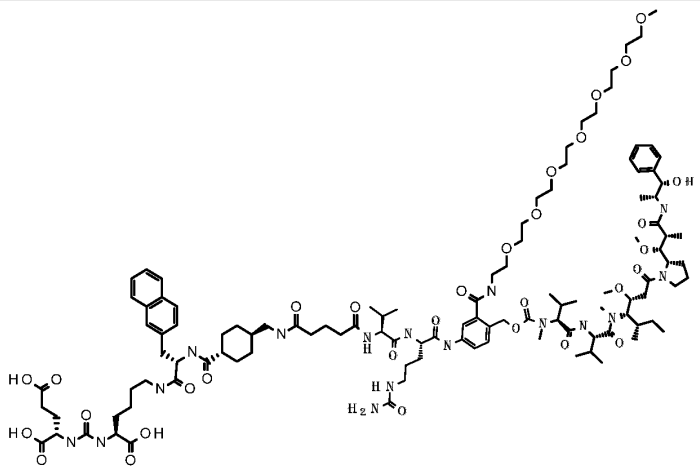
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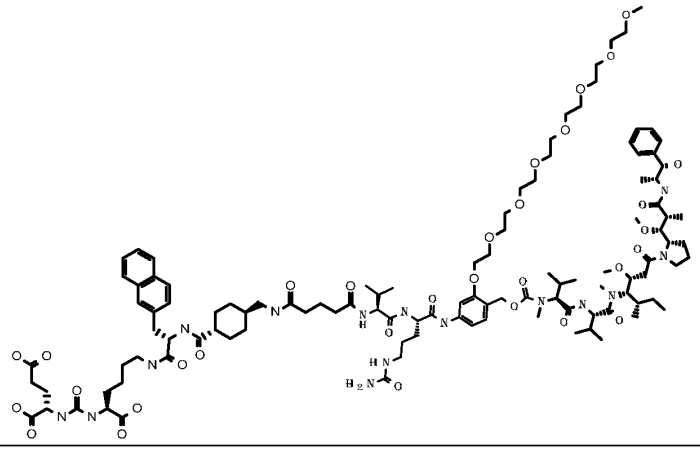
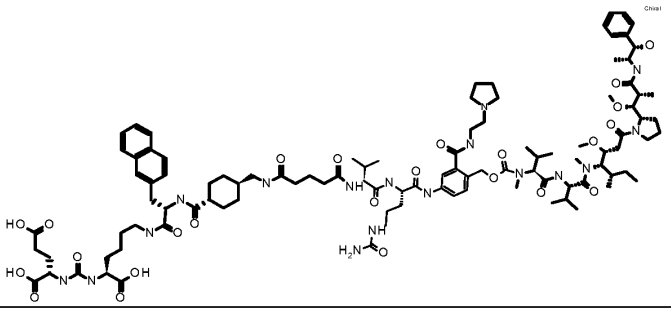
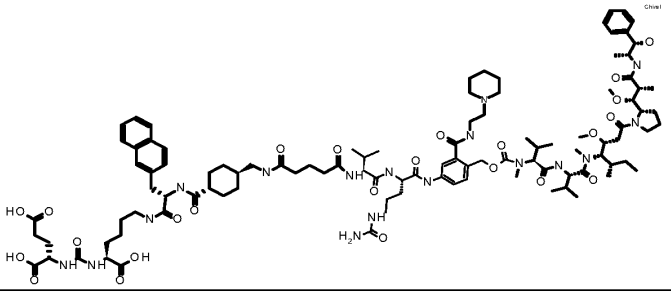
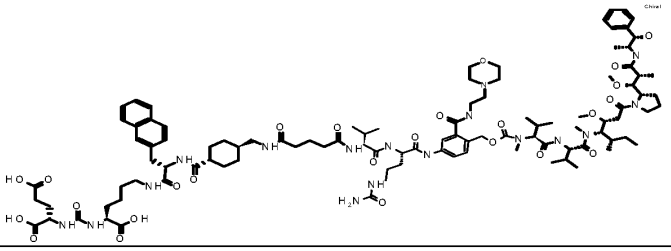
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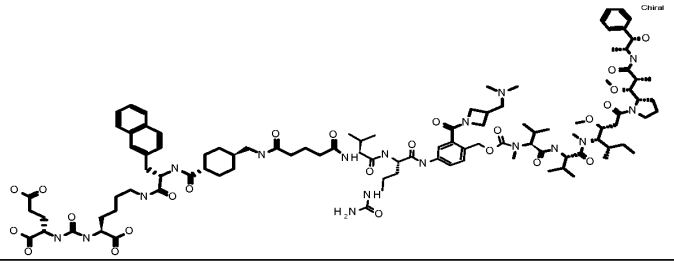
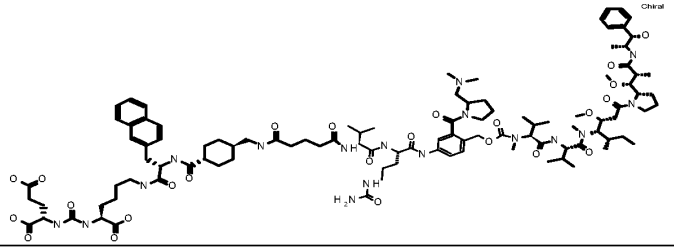
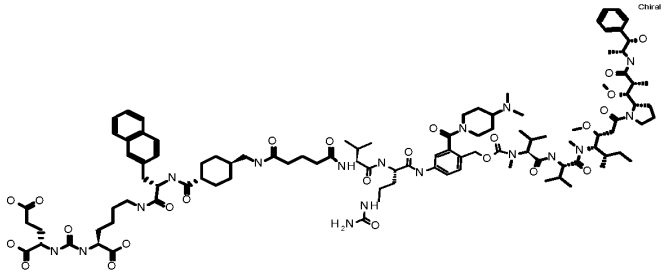
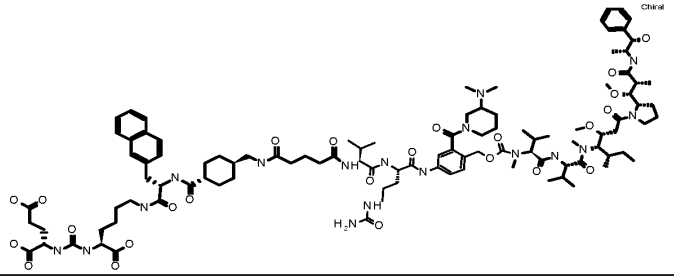
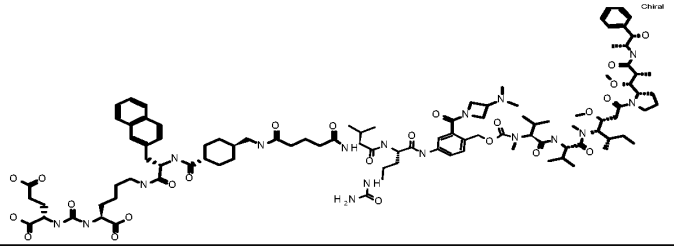
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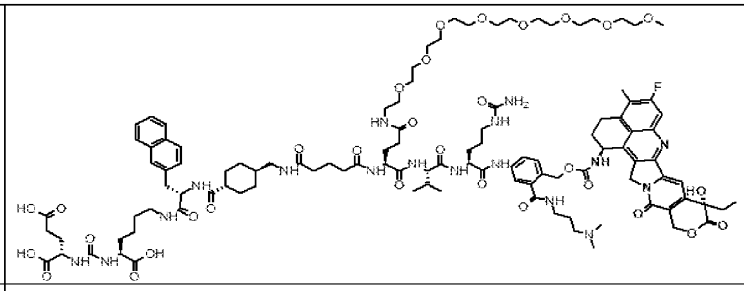
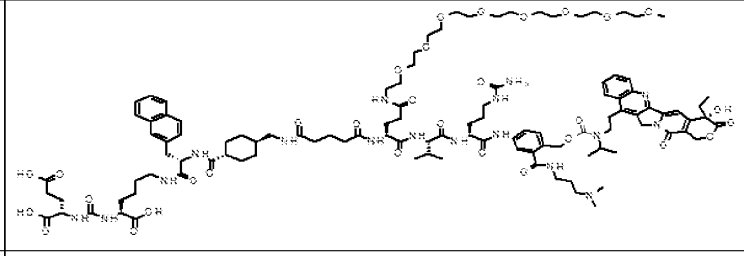
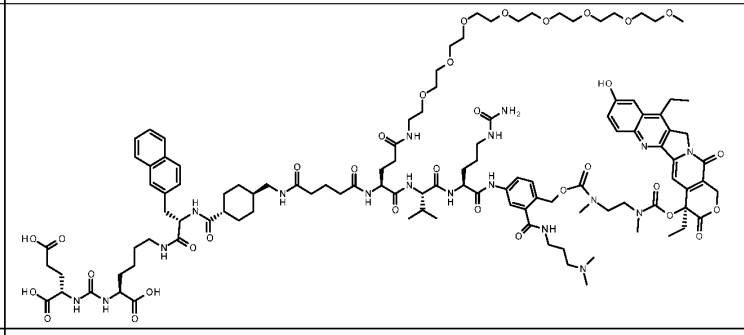
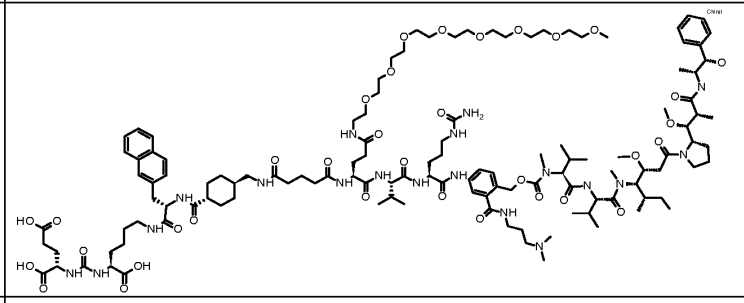
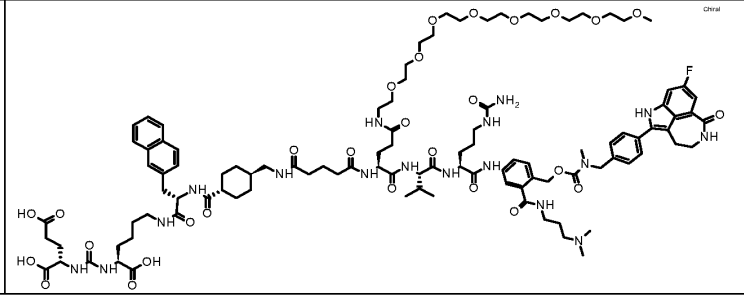
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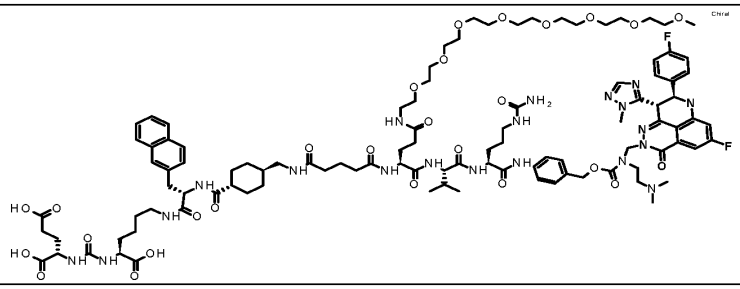
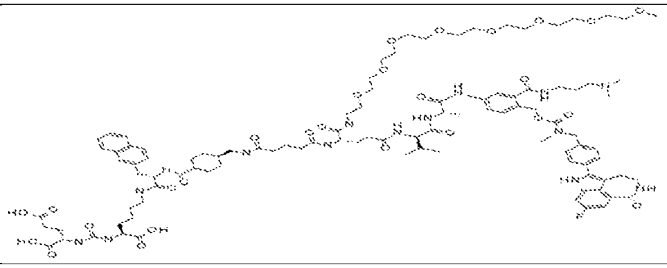
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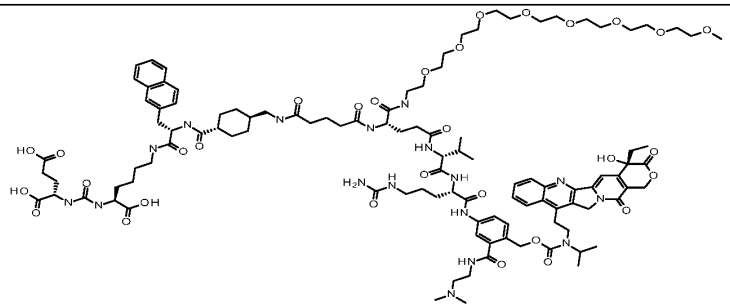
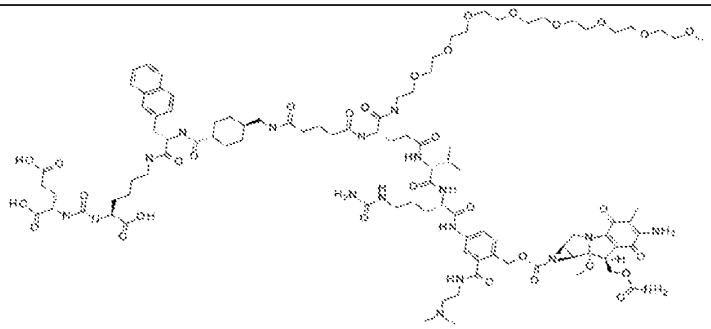
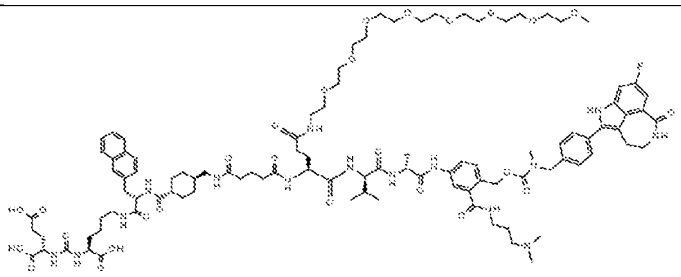
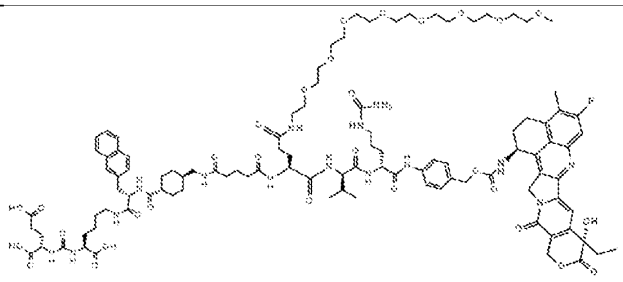
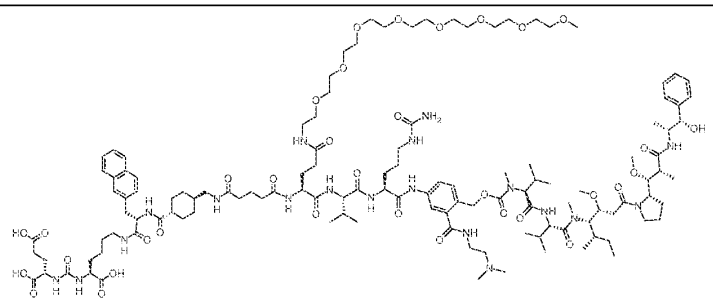
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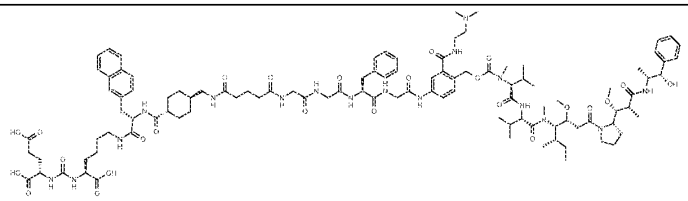
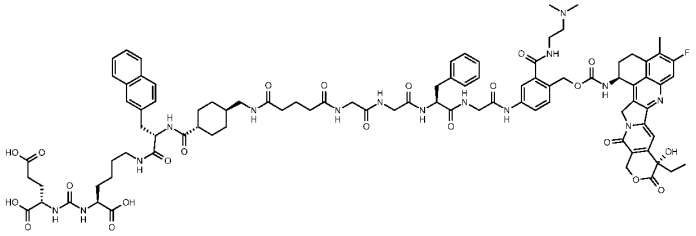
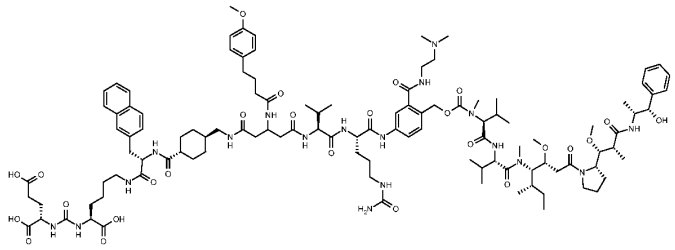
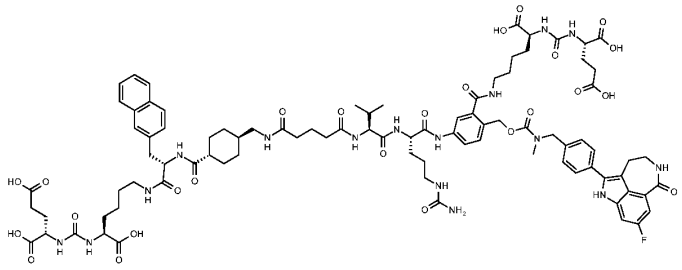
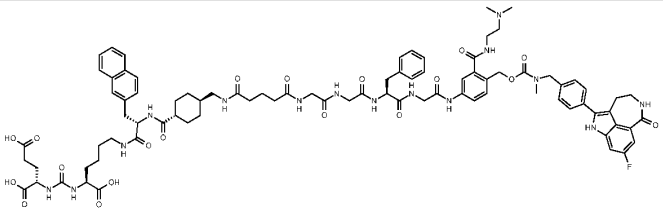
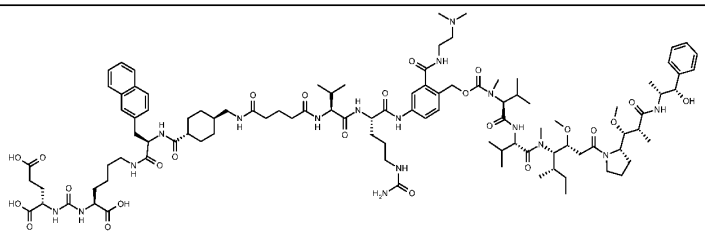
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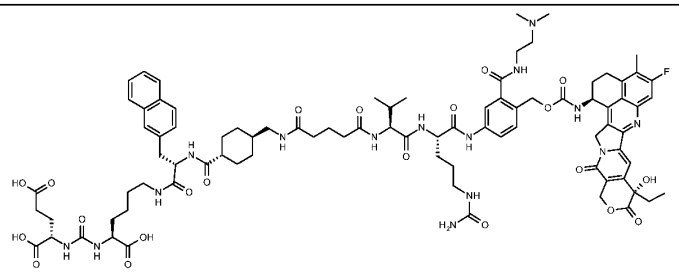
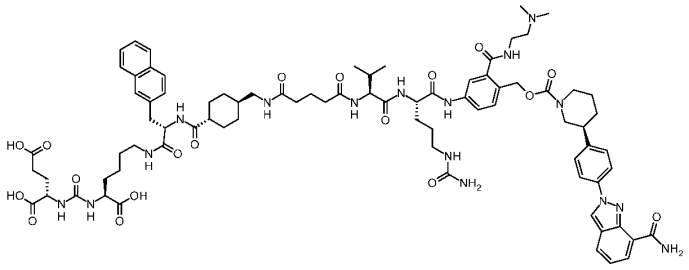
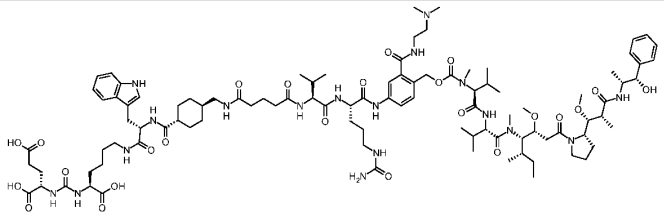
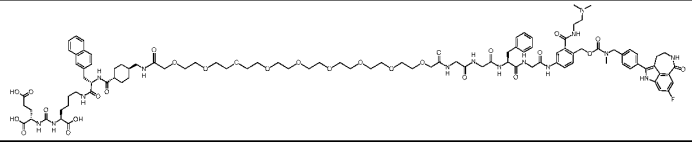
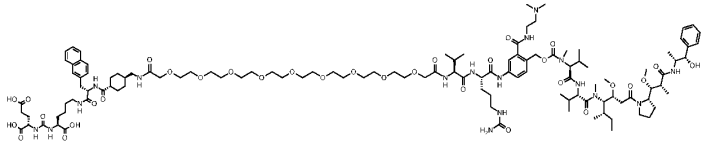
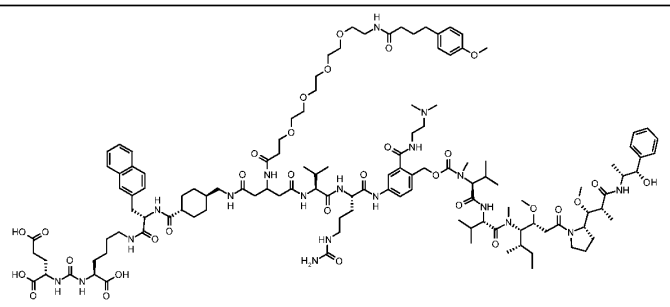
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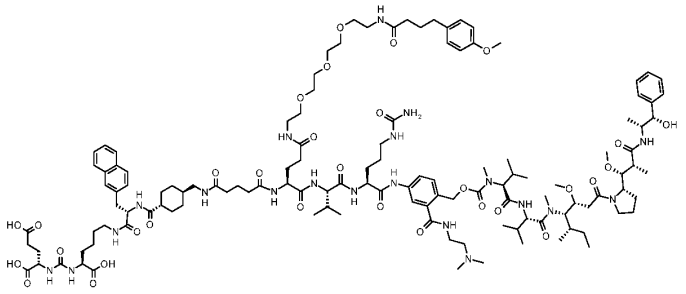
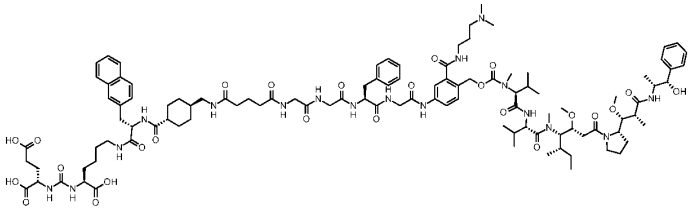
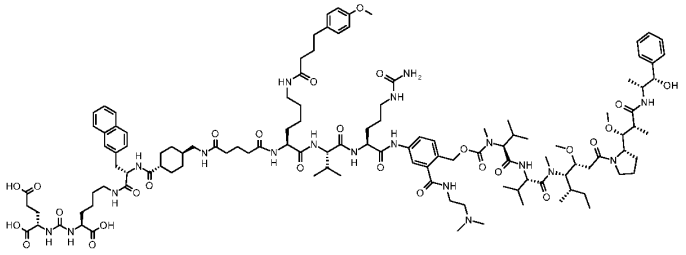
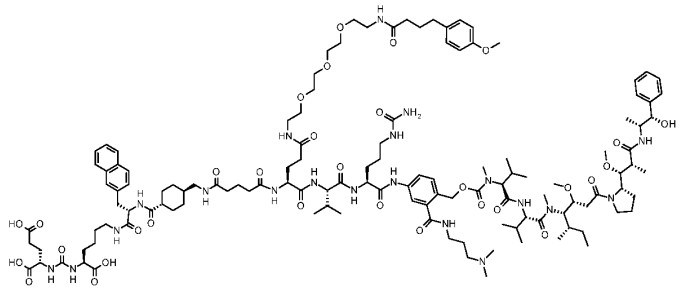
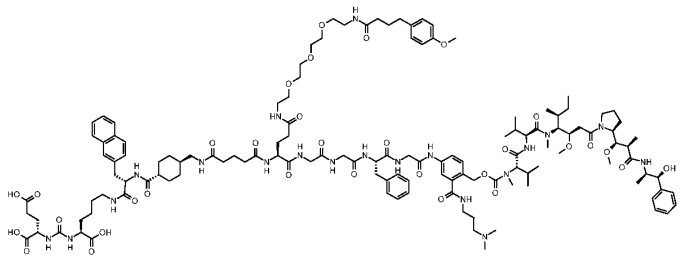
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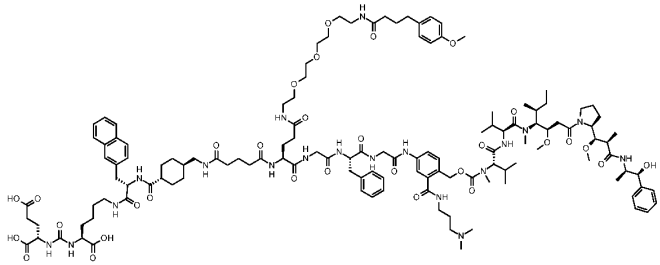
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