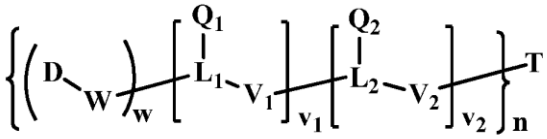
CLAIMS

What is claimed is:

1. A side chain-linkaged conjugate compound of the Formula (I):



(I)

wherein

"—"represents a single bond;

n is 1 to 30;

T is a cell-binding agent or molecule comprising an antibody, a single chain antibody, an antibody fragment that binds to a target cell, a monoclonal antibody, a single chain monoclonal antibody, a monoclonal antibody fragment that binds to the target cell, a chimeric antibody, a chimeric antibody fragment that binds to the target cell, a domain antibody fragment that binds to the target cell, protein, or an albumin-attached molecule;

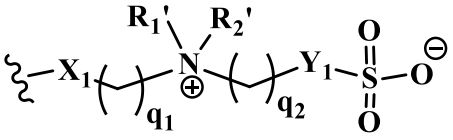
L_1 and L_2 are the same or different and are independently O, NH, N, S, P, NNH, NHNH, $N(R_{12})$, $N(R_{12})N(R_{12'})$, CH, CO, C(O)NH, C(O)O, NHC(O)NH, NHC(O)O, or $(Aa)_r$, wherein r=1 (one amino acid unit), which is a natural or unnatural amino acid;

W is a stretcher unit having C_1-C_8, comprising a peptidyl unit, a hydrazone, a disulfide, a thioether, an ester, or an amide bond;

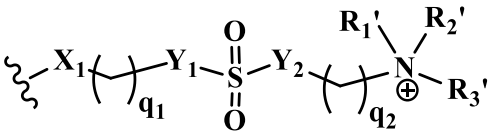
w is 1 or 2 or 3;

V_1 and V_2 are independently a spacer unit comprising O, NH, S, C_1-C_8 alkyl, C_2-C_8 heteroalkyl, C_3-C_8 aryl, heterocyclic, cycloalkyl, or alkylcarbonyl, or $(Aa)_r$, r=1-12 (one to 12 amino acid units), which is composed from a natural or unnatural amino acid, or the same or different sequences of dipeptide, tripeptide, tetrapeptide, pentapeptide, hexapeptide, heptapeptide, octapeptide, nonapeptide, decapeptide, undecapeptide or dodecapeptide unit; or $(CH_2CH_2O)_p$, p is 0-100; and v_1 and v_2 are independently 0, 1 or 2, but v_1 and v_2 are not 0 at the same time; when v_1 or v_2 is 0, it means one of the side chain Q_1 or Q_2 fragment is absent;

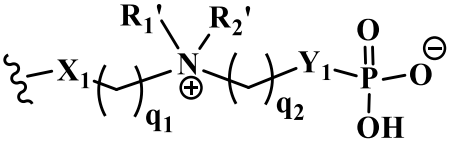
Q_1 and Q_2 are independently one of Iq-01 to Iq-35:



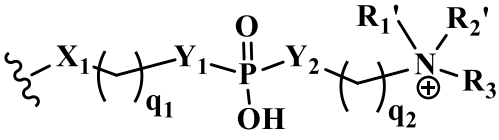
Iq-01,



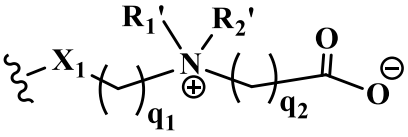
Iq-02,



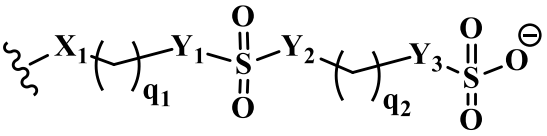
Iq-03,



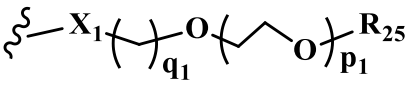
Iq-04,



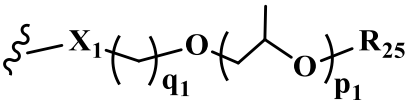
Iq-05,



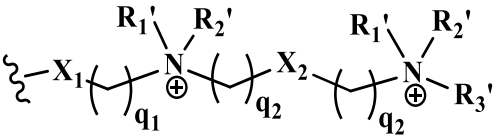
Iq-06,



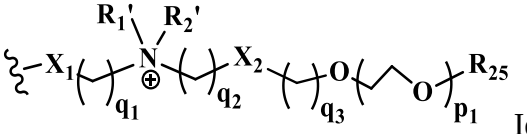
Iq-07,



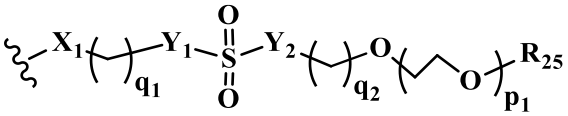
Iq-08,



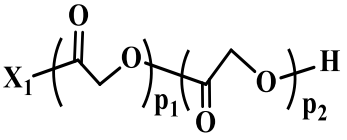
Iq-09,



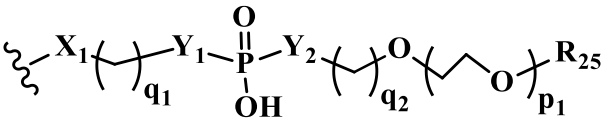
Iq-10,



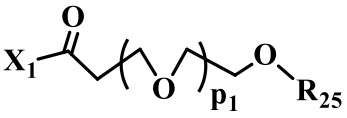
Iq-11,



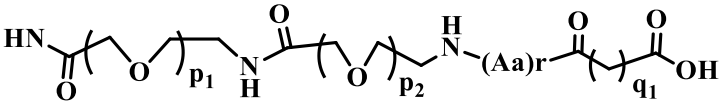
Iq-12,



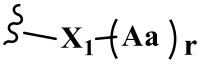
Iq-13,



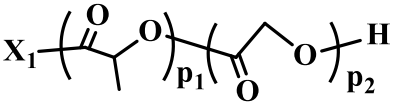
Iq-14,



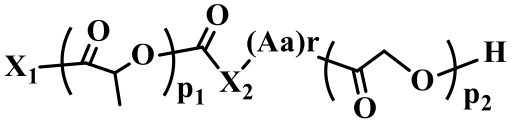
Iq-15,



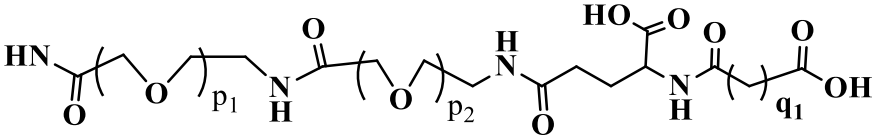
Iq-16,



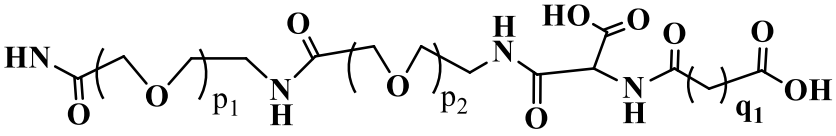
Iq-17,



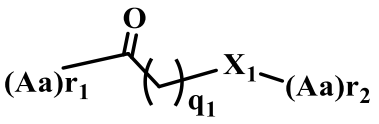
Iq-18,



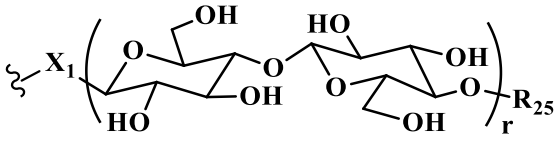
, Iq-19,



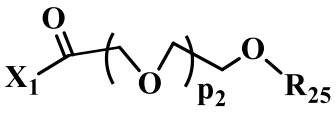
Iq-20,



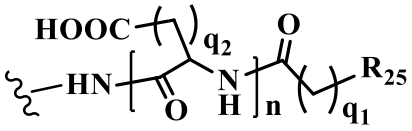
Iq-21,



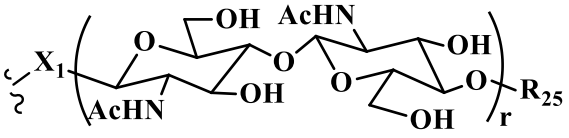
Iq-22,



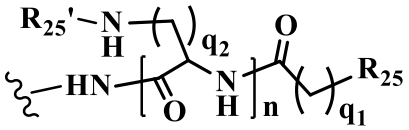
Iq-23,



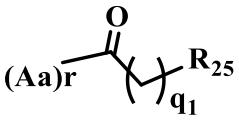
Iq-24,



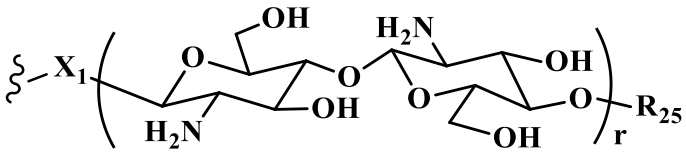
Iq-25,



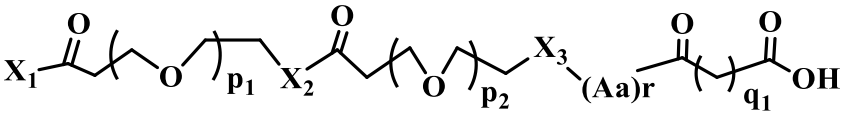
Iq-26,



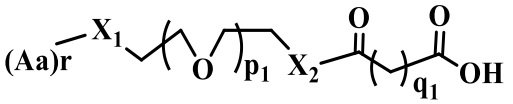
Iq-27,



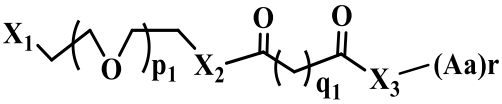
Iq-28,



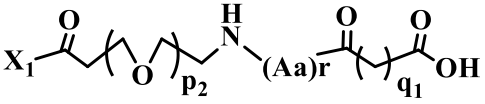
Iq-29,



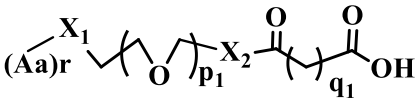
Iq-30,



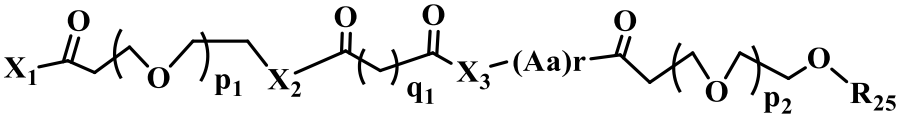
Iq-31,



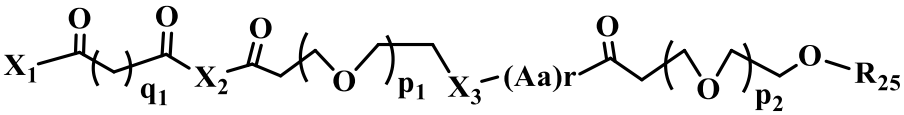
Iq-32,



Iq-33,



Iq-34



Iq-35

wherein R25 and R25’ are independently H; HC(O), CH3C(O), CH3C(NH), NH-(C1-C18)alkyl, C(O)NH-(C1-C18)alkyl, C(O)-(C1-C18)alkyl, C1-C18alkyl, C1-C18 alkyl, alkyl-Y1-SO3H, C1-C18alkyl-Y1-PO3H2, C1-C18alkyl-Y1-CO2H, C1-C18alkyl-Y1-N+R12R13R13’R14, C1-C18alkyl-Y1-CONH2, C2-C18alkylene, C2-C18 ester, C2-C18 ether, C2-C18 amine, C2-C18 alkyl carboxylamide, C3-C18 aryl, C3-C18 cyclic alkyl, C3-

C18 hyterocyclic, a peptide of 1～24 amino acids; C2-C18 lipid, a C2-C18 fatty acid or a C2-C18 fatty ammonium lipid; X1 and X2 are independently NH, N(R12'), O, CH2, S, C(O), S(O), S(O2), P(O)(OH), NHNH, CH=CH, Ar or (Aa)q1, q1 = 0-24 (0-24 amino acids, q1=0 means absent); X1, X2, X3, X4, Y1, Y2 and Y3 are independently NH, N(R12'), O, C(O), CH2, S, S(O), NHNH, C(O), OC(O), OC(O)O, OC(O)NH, NHC(O)NH, Ar or (Aa)q1, X1, X2, X3, X4, Y1, Y2 and Y3 can be independently absent; p1, p2 and p3 are independently 0 - 100 but are not 0 at the same time; q1, q2 and q3 are independently 0 -24; R12, R13, R13' and R14' are independently H or C1-C6 alkyl; Aa is natural or unnatural amino acid; Ar or (Aa)q1, is the same or different sequence of peptides; q1=0 means (Aa) q1 absent.

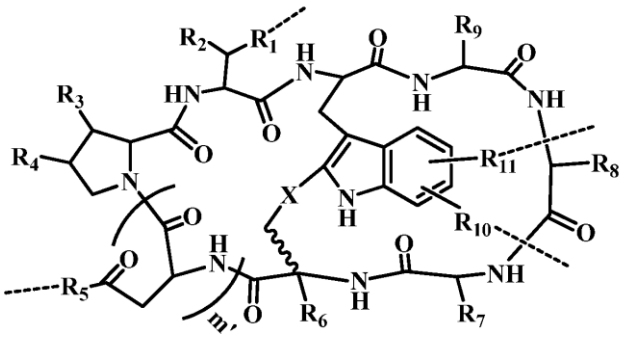
Y_2 is O, NH, NR_1, CH_2, S, NHNH, or Ar;

p_1, p_2 and p_3 are independently 0-100 but are not 0 at the same time;

q_1 and q_2 are independently 0-24;

alternatively, any one or more of W, Q_1, Q_2, L_1, L_2, V_1, or V_2, can be independently absent but Q_1, and Q_2 are not absent at the same time;

D is an amanita toxin having the following formula (II):



(II)

or an isotope of a chemical element, or a pharmaceutically acceptable salt, hydrates, or hydrated salt; or an optical isomer, racemate, diastereomer or enantiomer thereof,

wherein -----is a linkage site that links to W independently;

a single bond on aromatic ring means it links any one of carbon position of the aromatic ring;

〰 represents an optional single bond or an absent bond;

R_1 and R_2 are independently H, OH, CH_2OH, $CH(OH)CH_2OH$, $CH(CH_3)CH_2OH$, $CH(OH)CH_3$, C_1-C_8 alkyl,–OR_{12} (ether), C_2-C_8 alkenyl, alkynyl, heteroalkyl, –$OCOR_{12}$ (ester), –$OC(=O)OR_{12}$-(carbonate), –$OC(=O)NHR_{12}$ (carbamate); C_3-C_8 aryl, heterocyclic, carbocyclic, cycloalkyl, heterocycloalkyl, heteroaralkyl, or alkylcarbonyl;

R_3 and R_4 are independently H, OH, –OR_{12} (ether), –$OCOR_{12}$ (ester), –$OCOCH_3$ (acetate), –$OCOOR_{12}$ (carbonate), –$OC(=O)NHR_{12}$ (carbamate), -$OP(O)(OR_{12})(OR_{12}')$ (phosphate), $OP(O)(NHR_{12})(NHR_{12}')$ (phosphamide), O-SO_3^-, or O-glycoside;

R_5 is H, OH, NH_2, NHOH, $NHNH_2$, –OR_{12}, –NHR_{12}, $NHNHR_{12}$, –$NR_{12}R_{12}'$, or $N(H)(R_{12})R_{13}CO(Aa)_p$, (an amino acid or peptide, wherein Aa is an amino acid or a polypeptide, p represents 0-6);

R_6 is H, OH, CH_2OH, $CH(OH)CH_2OH$, $CH(CH_2OH)_2$, $CH(CH_3)OH$, CH_2CH_2OH, PrOH, BuOH, C_1～C_8 alkyl, –OR_{12} (ether), C_2～C_8 alkenyl, alkynyl, heteroalkyl, –$OCOR_{12}$ (ester); C_3～C_8 aryl, heterocyclic, or carbocyclic;

R_7, R_8 and R_9 are independently H, OH, CH_3, $CH(CH_3)_2$, $CH(CH_3)CH_2CH_3$, CH_2OH, $CH(OH)CH_2OH$, $CH_2CH(OH)$ CH_2OH, $CH(CH_2OH)_2$, $CH_2C(OH)(CH_2OH)_2$, $CH_2C(OH)(CH_3)(CH_2OH)$, $CH_2C(OH)(CH(CH_3)_2)(CH_2OH)$, CH_2CH_2OH, PrOH, BuOH, CH_2COOH, CH_2CH_2COOH, $CH(OH)COOH$, CH_2CONH_2, $CH_2CH_2CONH_2$, $CH_2CH_2CH_2CH_2NH_2$, $CH_2CH_2CH_2NHC(=NH)NH_2$, C_1～C_8 alkyl, CH_2Ar, CH_2SH, CH_2SR_{12}, CH_2SSR_{12}, CH_2SSAr, $CH_2CH_2SCH_3$, –OR_{12}(ether), C_2～C_8 alkenyl, alkynyl, heteroalkyl, –$OCOR_{12}$ (ester); C_3～C_8 aryl, het-erocyclic, or carbocyclic;

R_{10} and R_{11} are independently H, NH_2, OH, SH, NO_2, halogen, -NHOH, –N_3 (azido); -CN (cyano); C_1～C_8 alkyl; C_3～C_8 aryl, heterocyclic; –OR_{12} (ether), –$OCOR_{12}$ (ester), –$OCOCH_3$ (acetate), –$OC(O)OR_{12}$ (carbonate), -$OC(O)CH(R_{12})$ NHAa (Aa is an aminoacid group), -$NR_{12}R_{12}'$ (amine), -$NR_{12}COR_{12}'$ (amine), -$R_{12}NHCOR_{12}'$ (alkylamide), -$R_{12}NHR_{12}'$ (amine), -$NHR_{12}NHR_{12}'$ NHR_{12}'' (amine); –$R_{12}NCO$-NR_{12}'(urea), –$R_{12}NCOOR_{12}'$ (carbamate), -$OCONR_{12}R_{12}'$ (carbamate); –NR_{12} (C=NH) $NR_{12}'R_{12}''$ (guanidinum); –

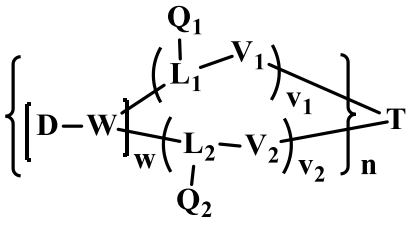
$R_{12}NHCO(Aa)_p$, $–R_{12}NHR_{12}'CO(Aa)_p$, $–NR_{12}CO(Aa)_p$, (an amino acid or peptide, wherein Aa is an amino acid or a polypeptide, p represents 0-6); $–N(R_{12})CONR_{12}'R_{12}''$ (urea); $–OCSNHR_{12}$ (thio-carbamate); $-R_{12}SH$ (thiol); $–R_{12}SR_{12}'$ (sulfide); $–R_{12}SSR_{12}'$ (disulfide); $–S(O)R_{12}$ (sulfoxide); $–S(O_2)R_{12}$ (sulfone); $–SO_3$, HSO_3, HSO_2, or a salt of HSO_3^-, SO_3^{2-} or $-HSO_2^-$ (sulphite); $–OSO_3^-$; $-N(R_{12})SOOR_{12}'$ (sulfonamide); $-N(R_{12})OR_{12}'$; $R_{12}C(=O)NOH$ or a salt formed with a cation (hydroxamic acid); ($HOCH_2SO_2^-$, or its salts (formaldehyde sulfoxylate); $–N(R_{12})COR_{12}'$ (amide); $R_{12}R_{12}'R_{12}''NPO_3H$ (trialkylphosphoramidate or phosphoramidic acid); $OP(O)(OM_1)(OM_2)$, $OCH_2OP(O)(OM_1)(OM_2)$, OSO_3M_1; O-glycoside (glucoside, galactoside, mannoside, glucuronoside, alloside, fructoside), NH-glycoside, S-glycoside or CH_2-glycoside; M_1 and M_2 are independently H, Na, K, Ca, Mg, NH_4, $NR_1'R_2'$ or R_3'; wherein R_1', R_2' and R_3' are independently H, C_1～$_8$ alkyl; Ar, Ar', and Ar" are C_3-C_8 aryl or heteroaromatic group;

wherein R_{12}, R_{12}', and R_{12}'' are independently H, C_1～C_8 alkyl; or 1-8 carbon atoms of esters, ether, or amide; or polyethyleneoxy unit of formula $(OCH_2CH_2)_p$ or $(OCH_2CH(CH_3))_p$, wherein p is an integer from 0 to 100;

X is S, O, NH, or CH_2;

m' is 0 or 1.

2. A side chain-linkaged conjugate compound of the Formula (III):

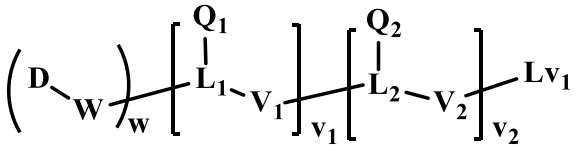


(III)

wherein D, W, w, L_1, L_2, Q_1, Q_2, V_1, V_2, v_1, v_2, n, and T are as defined in claim 1.

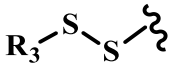
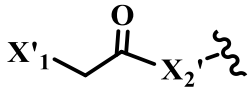
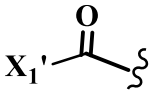
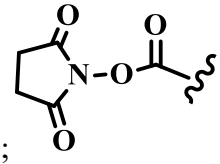
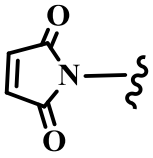
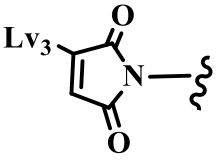
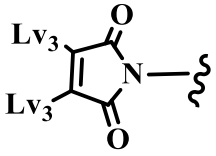
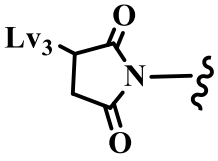
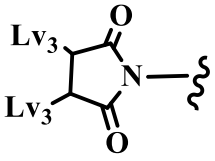
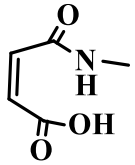
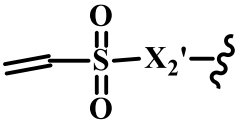
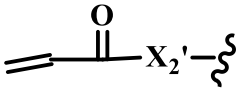
3. A side chain-linkage compound of Formula (IV), which can readily react to a cell-binding

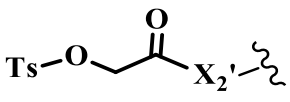
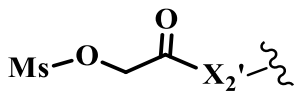
molecule T to form a conjugate of Formula (I) as defined in claim 1:

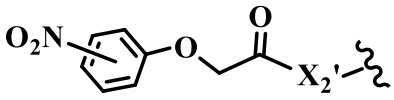
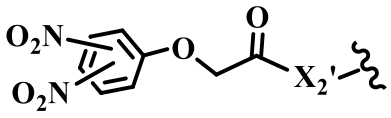
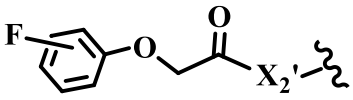


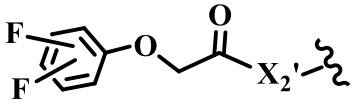
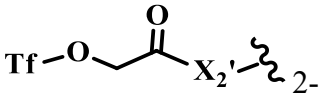
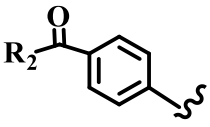
(IV)

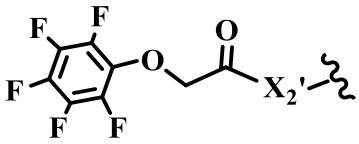
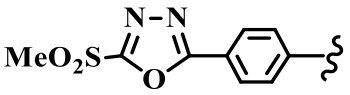
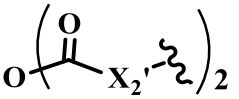
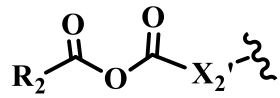
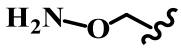
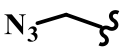
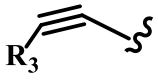
wherein D, W, w, L_1, L_2, Q_1, Q_2, V_1, V_2, v_1, v_2, and n are as defined in claim 1;

Lv_1 is a reacting group that can be reacted with a thiol, amine, carboxylic acid, selenol, phenol or hydroxyl group on a cell-binding molecule, wherein Lv_1 is OH; F; Cl; Br; I; nitrophenol; N-hydroxysuccinimide (NHS); phenol; dinitrophenol; pentafluorophenol; tetrafluorophenol; difluoro-phenol; mono-fluorophenol; pentachlorophenol; triflate; imidazole; dichlorophenol; tetrachlorophenol; 1-hydroxybenzotriazole;tosylate; mesylate; 2-ethyl-5-phenylisoxazolium-3′-sulfonate, anhydrides formed its self, or formed with acetyl anhydride or formyl anhydride;  disulfide;  haloacetyl;  acyl halide (acid halide);  *N*-hydroxysuccinimide ester;  maleimide;  monosubstituted maleimide;  disubstituted maleimide;  monosubstituted succinimide;  disubstituted succinimide;  substituted maleic acid; -CHO aldehyde;  ethenesulfonyl;  acryl (acryloyl);

 2-(tosyloxy)acetyl;  2-(mesyloxy)acetyl;

 2-(nitrophenoxy)acetyl;  2-(dinitrophenoxy)acetyl;  2-(fluorophenoxy)-acetyl;

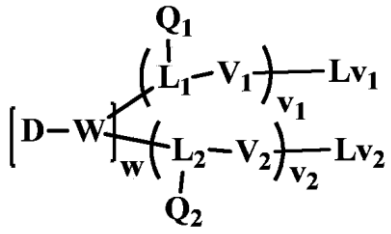
 2-(difluorophenoxy)-acetyl;  2-(((trifluoromethyl)-sulfonyl)oxy)acetyl;  ketone, or aldehyde,

 2-(pentafluorophenoxy)acetyl;  , methylsulfonephenyloxadiazole (ODA);  ,  acid anhydride,  alkyloxyamino;  azido,  alkynyl, or  hydrazide;

wherein X_1' is F, Cl, Br, I or Lv_3; X_2' is O, NH, N(R_1), or CH_2; R_3 is independently H, aromatic, heteroaromatic, or aromatic group wherein one or several H atoms are replaced independently by -R_1, -halogen, -OR_1, -SR_1, -NR_1R_2, -NO_2, -S(O)R_1, -$S(O)_2R_1$, or -$COOR_1$; Lv_3 is a leaving group comprising F, Cl, Br, I, nitrophenol; N-hydroxysuccinimide (NHS); phenol; dinitrophenol; pentafluorophenol; tetrafluorophenol; difluoro-phenol; monofluorophenol; pentachlorophenol; triflate; imidazole; dichlorophenol; tetrachlorophenol; 1-hydroxybenzotriazole; tosylate; mesylate; 2-ethyl-5-phenylisoxazolium-3′-sulfonate, anhydrides formed its self, or acetyl anhydride or formyl anhydride; or an intermediate molecule generated with a condensation reagent for peptide coupling reactions or for

Mitsunobu reactions.

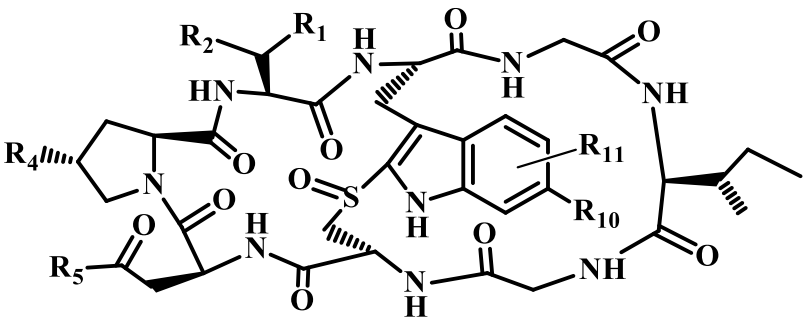
4. A side chain-linkage compound of Formula (V), which can readily react to a cell-binding molecule T to form a conjugate of Formula (III) as defined in claim 2:



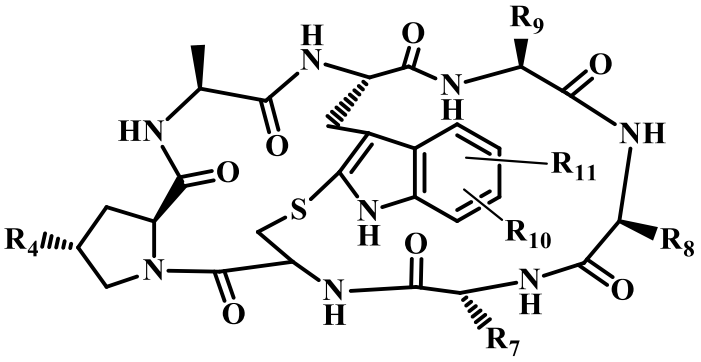
(V)

wherein D, W, w, L_1, L_2, Q_1, Q_2, V_1, V_2, v_1, v_2, and n, are as defined in claim 1; wherein Lv_1 and Lv_2 have independently the same definition of Lv_1 in Formula (IV) of claim 3 and both Lv_1 and Lv_2 can be the same or different in Formula (V).

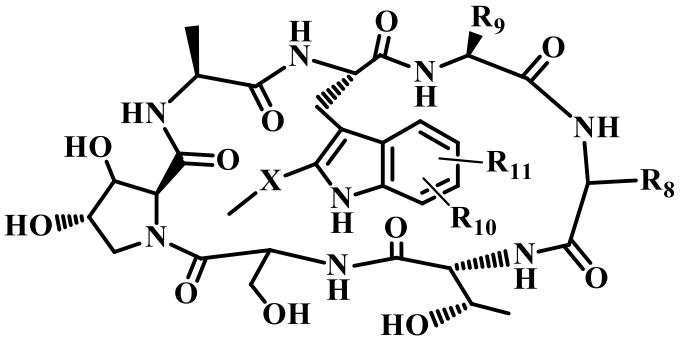
5. A side chain-linkage compound according to any one of claims 1 to 4, wherein D is IIa, IIb, IIc, II-01, II-02, II-03, II-04, II-05, II-06, II-07, II-08, II-09, II-10, II-11, II-12, II- 13, II-14, II-15, II-16, II-17, II-18, II-19, II-20, II-21, II-22, II-23, II-24, II-25, or II-26:



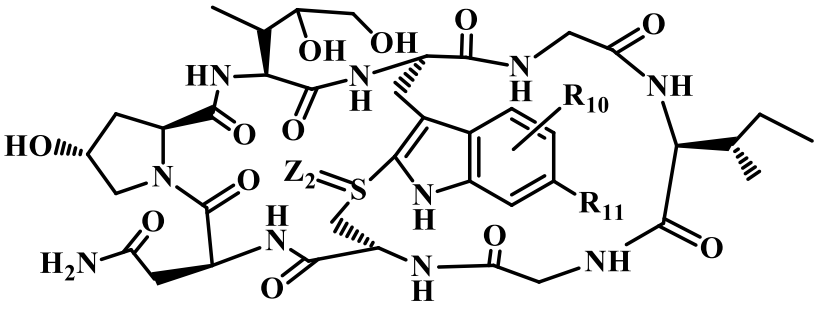
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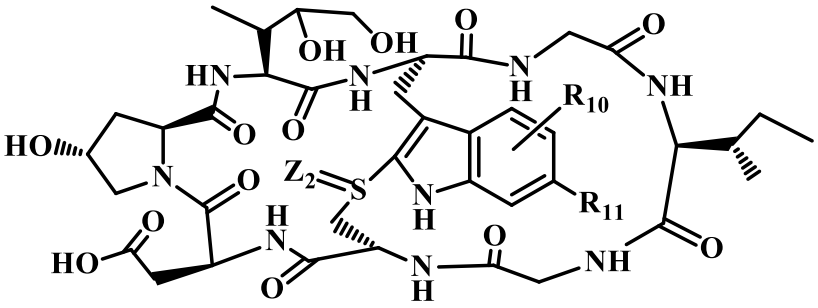
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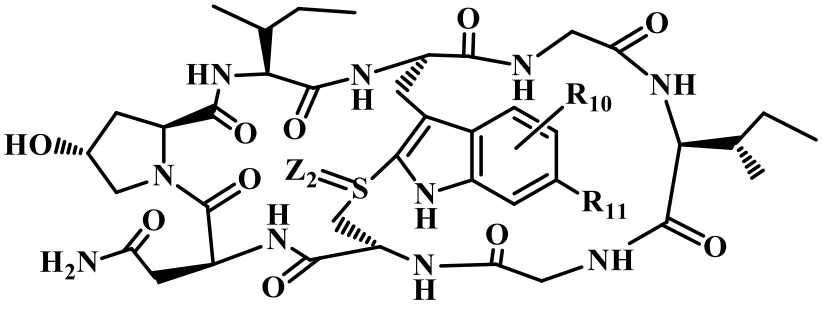
(IIc),



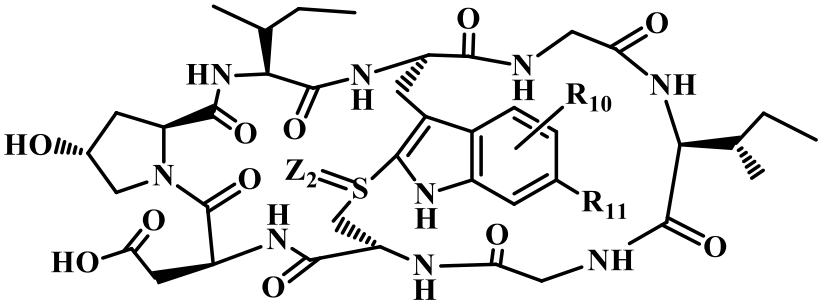
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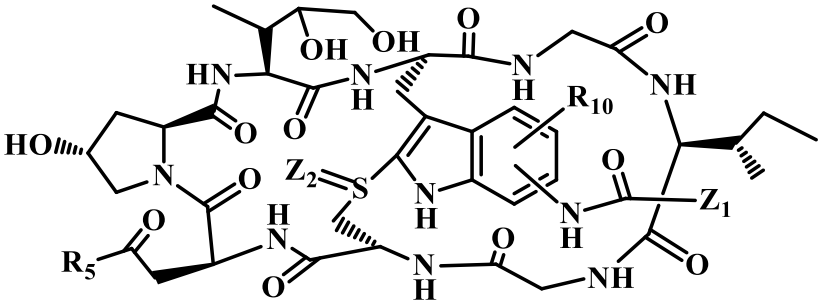
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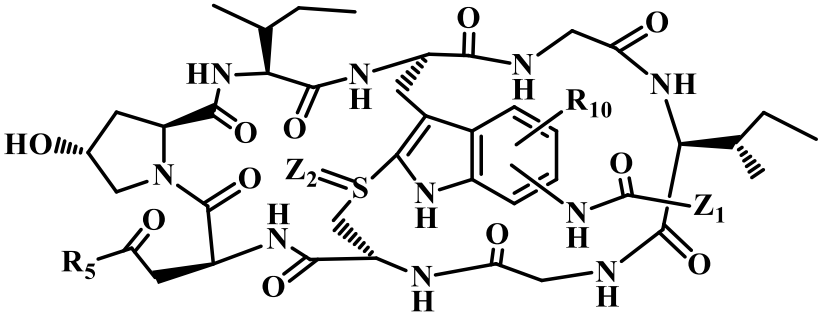
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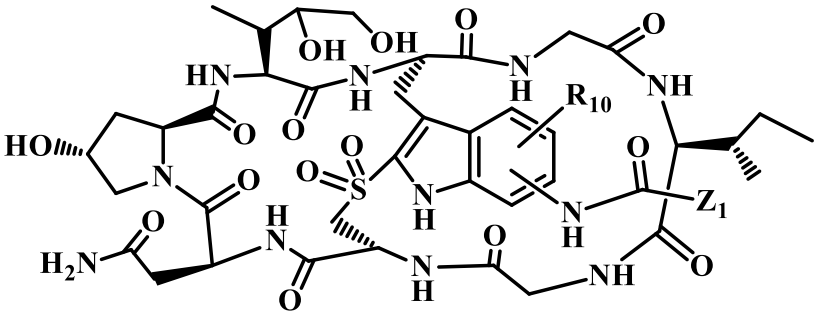
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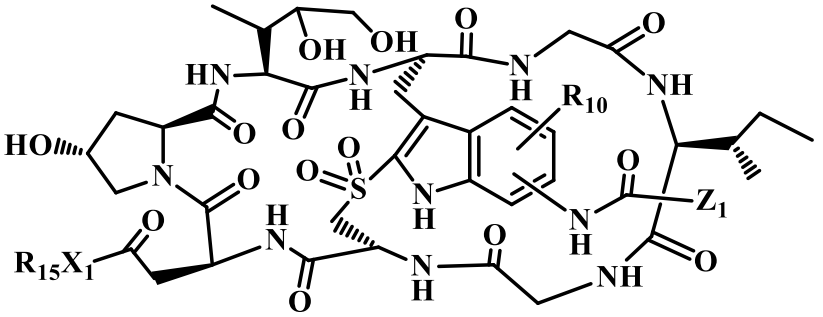
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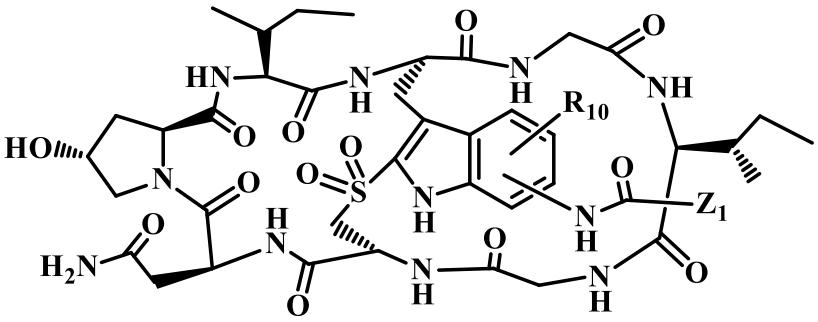
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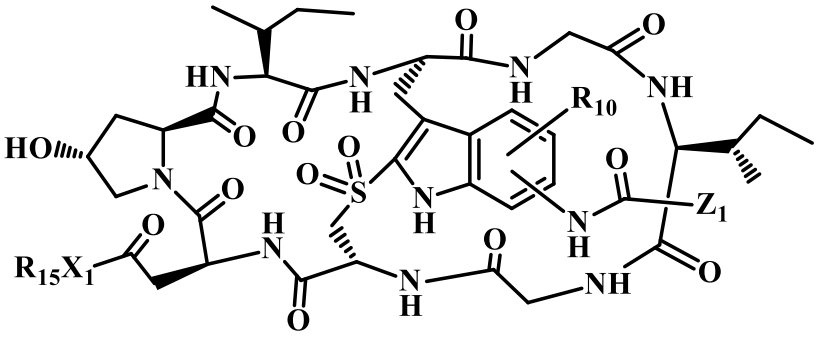
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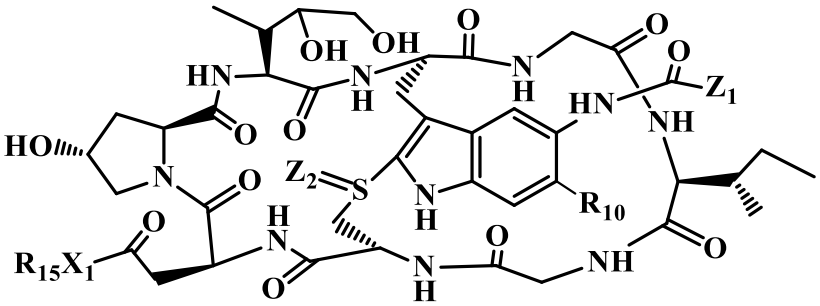
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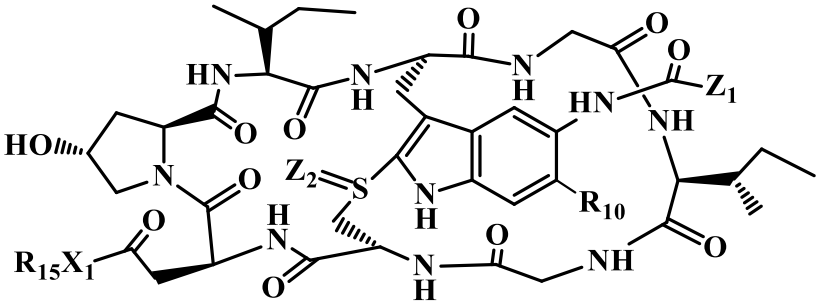
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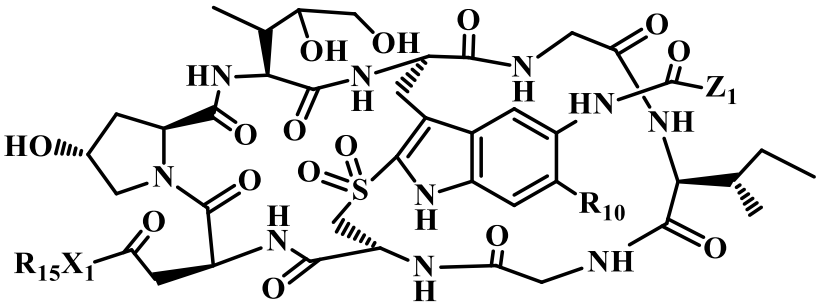
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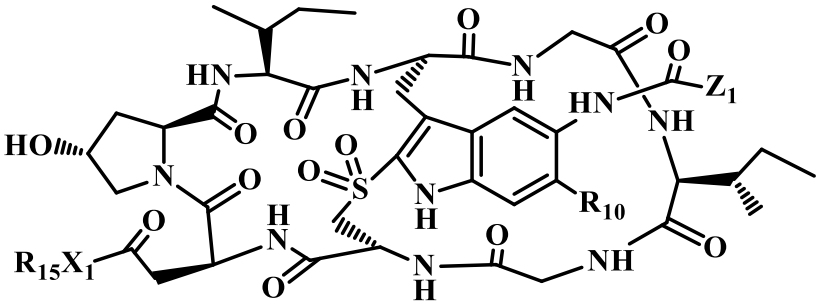
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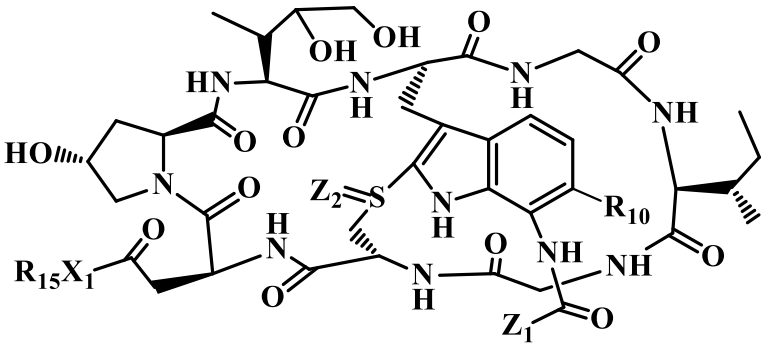
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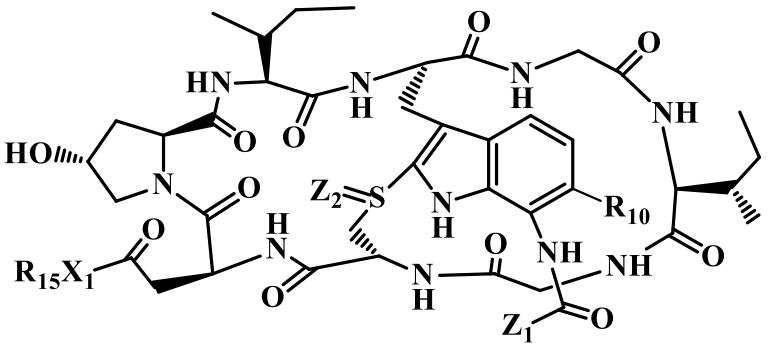
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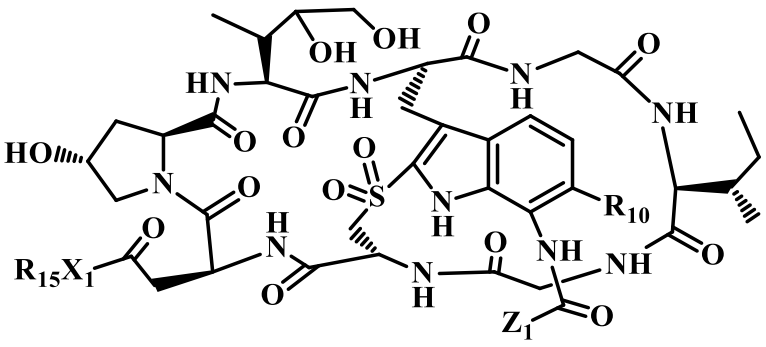
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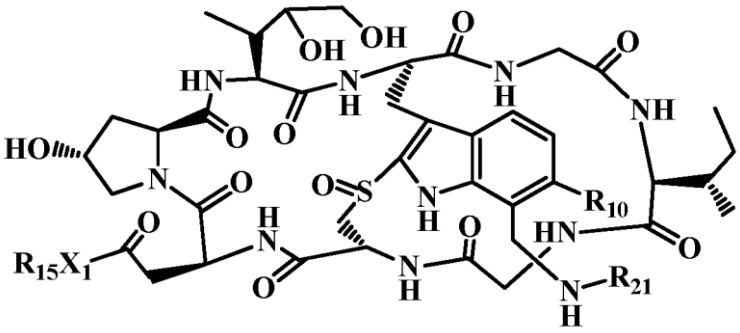
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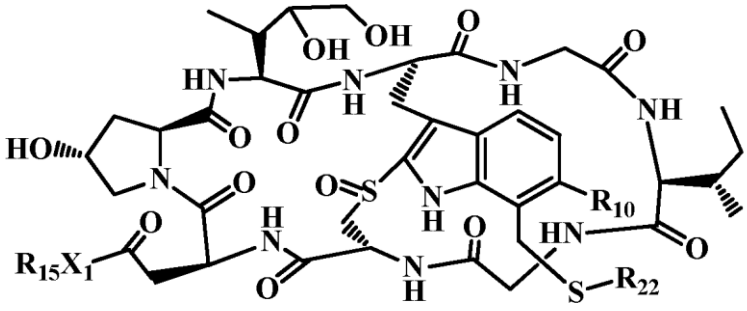
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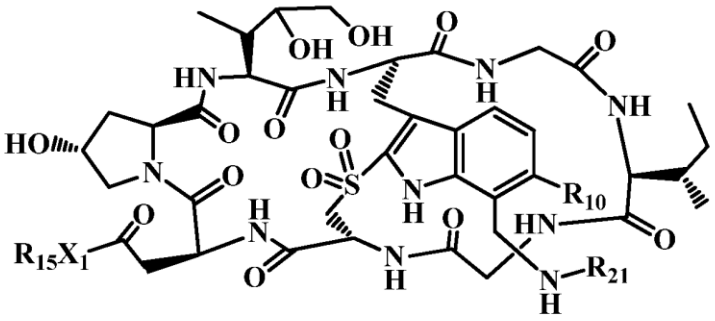
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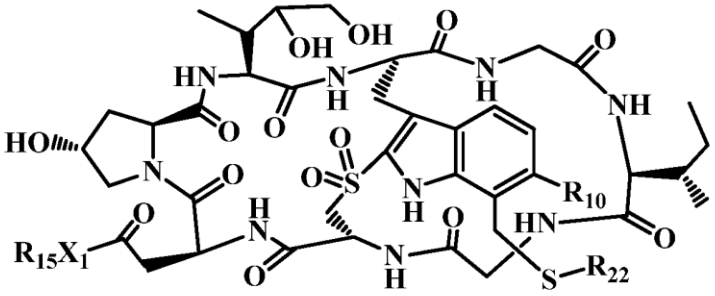
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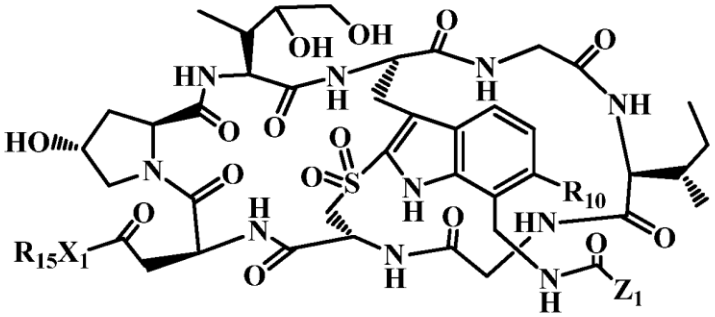
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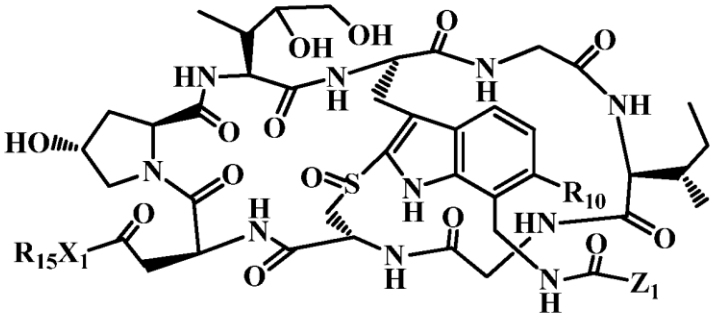
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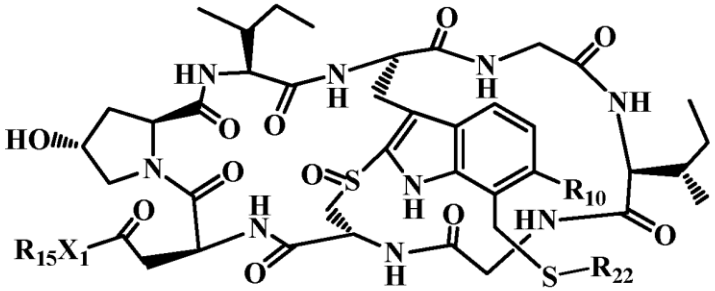
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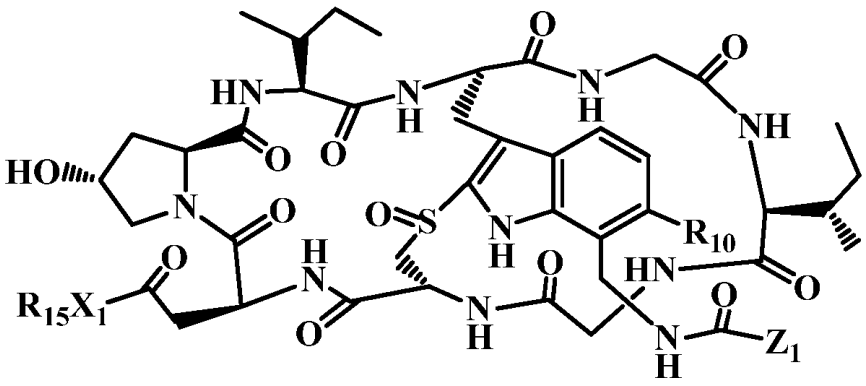
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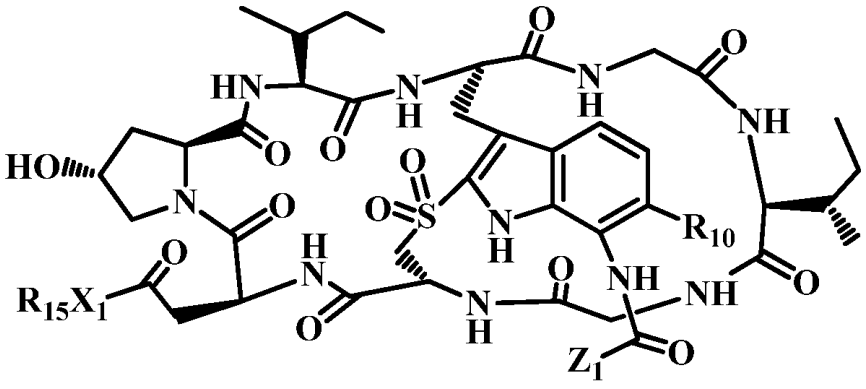
(II-23),



(II-24),



(II-25),

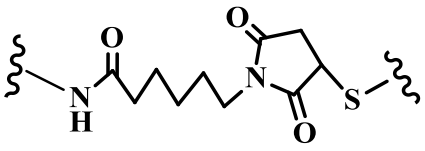


(II-26),

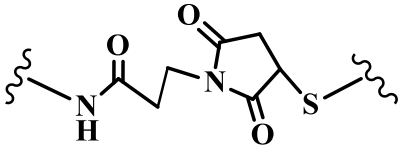
or an isotope of one or more chemical elements, or pharmaceutically acceptable salts, hydrates, or hydrated salts; or the polymorphic crystalline structures of these compounds; or the optical isomers, racemates, diastereomers or enantiomers; wherein Z_2: is an oxygen or lone pair of electrons; R_{15} is H; NHR_{12}, OR_{12}, C_1-C_8 linear or branched alkyl or heteroalkyl; C_2-C_8 linear or branched alkenyl, alkynyl, alkylcycloalkyl, heterocycloalkyl; C_3-C_8 linear or branched aryl, Ar-alkyl, heterocyclic, carbocyclic, cycloalkyl, heteroalkylcycloalkyl, alkylcarbonyl, heteroaryl; carbonate -$R_1C(O)OR_{12}$, carbamate -$R_{12}C(O)NR_{12'}R_{13}$; or C_1-C_8 carboxylate, esters, ether, or amide; or a peptide of 1～8 amino acids; or polyethyleneoxy unit of formula $(OCH_2CH_2)_p$ or $(OCH_2CH(CH_3))_p$, wherein p is an integer from 0 to 1000; Z_1 is H, O, S, NH, NHNH, R_{12}, or absent; R_{21} is COR_{12}, $NHCOR_{12}$, $COOR_{12}$, $CONHR_{12}$, R_{12}, $R_{12}NH$; R_{22} is R_{12}, SR_{12}, $SCH(CH_3)R_{12}$, $SC(CH_3)_2R_{12}$, X is O, S, NH, NHNH, or CH_2, R_1, R_2, R_3, R_4, R_5, R_6, R_7, R_8, R_9, R_{10}, R_{11}, R_{12}, $R_{12'}$, R_{13}, and X_1 are defined the same above.

6. A side chain-linkage compound according to any one of claims 1 to 4, wherein W, L_1, L_2, V_1, and V_2 independently comprise one or more linker components of the following

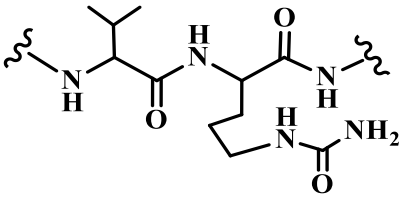
structures:



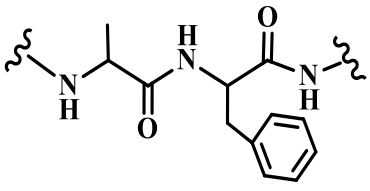
6-maleimidocaproyl (MC),



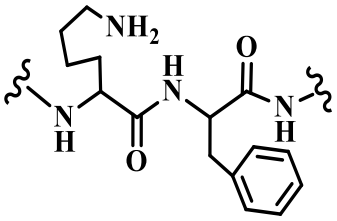
maleimido propanoyl (MP),



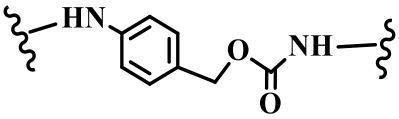
valine-citrulline (val-cit),



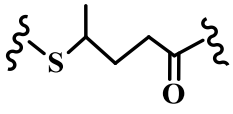
alanine-phenylalanine (ala-phe),



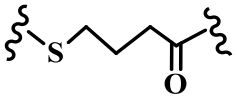
lysine-phenylalanine (lys-phe),



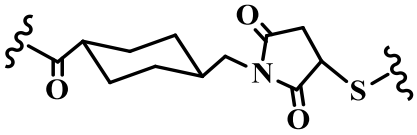
p-aminobenzyloxycarbonyl (PAB),



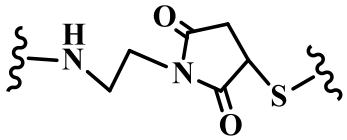
4-thio-pentanoate (SPP),



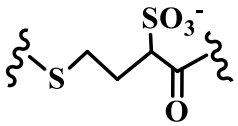
4-thio-butyrate (SPDB),



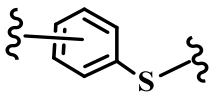
4-(N-maleimidomethyl)cyclo-hexane-1-carboxylate (MCC),



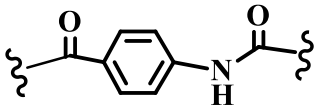
maleimidoethyl (ME),



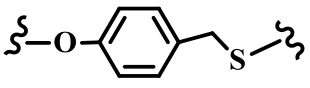
4-thio-2-hydroxysulfonyl-butyrate (2-Sulfo-SPDB),



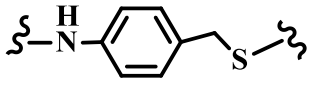
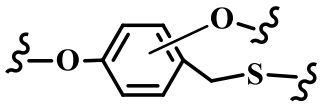
aryl-thiol (PySS),

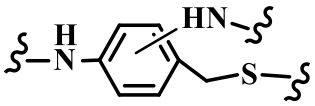
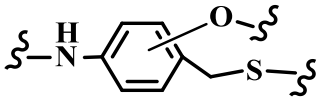


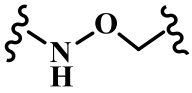
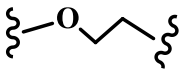
(4-acetyl)aminobenzoate (SIAB),

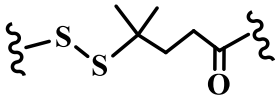
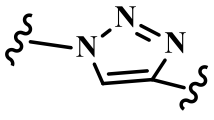


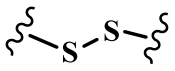
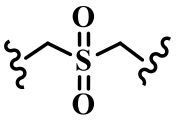
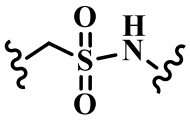
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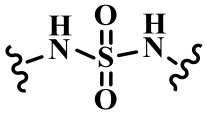
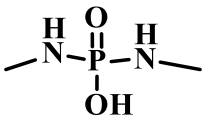
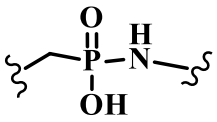
oxylbenzylthio,  aminobenzylthio, 

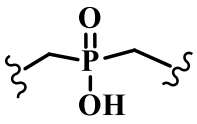
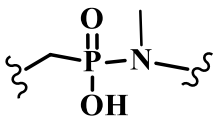
dioxylbenzylthio,  diaminobenzylthio, 

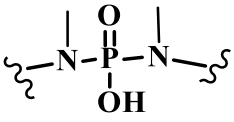
amino-oxylbenzylthio,  alkoxy amino (AOA),  ethyleneoxy

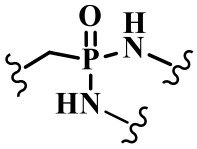
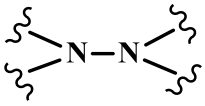
(EO),  4-methyl-4-dithio-pentanoic (MPDP),  triazole,

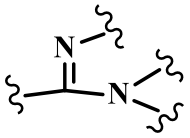
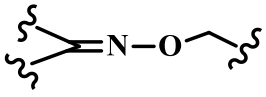
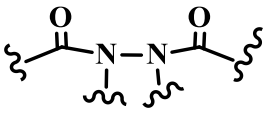
 dithio,  alkylsulfonyl,  alkylsulfonamide,

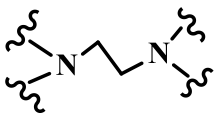
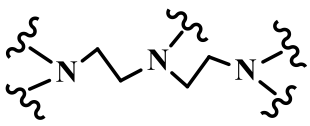
 sulfon-bisamide,  Phosphondiamide, 

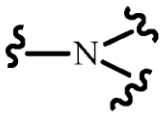
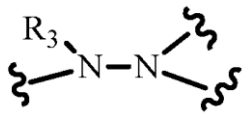
alkylphosphonamide,  phosphinic acid,  N-

methylphosphonamidic acid,  N,N’-dimethylphosphon-amidic acid,

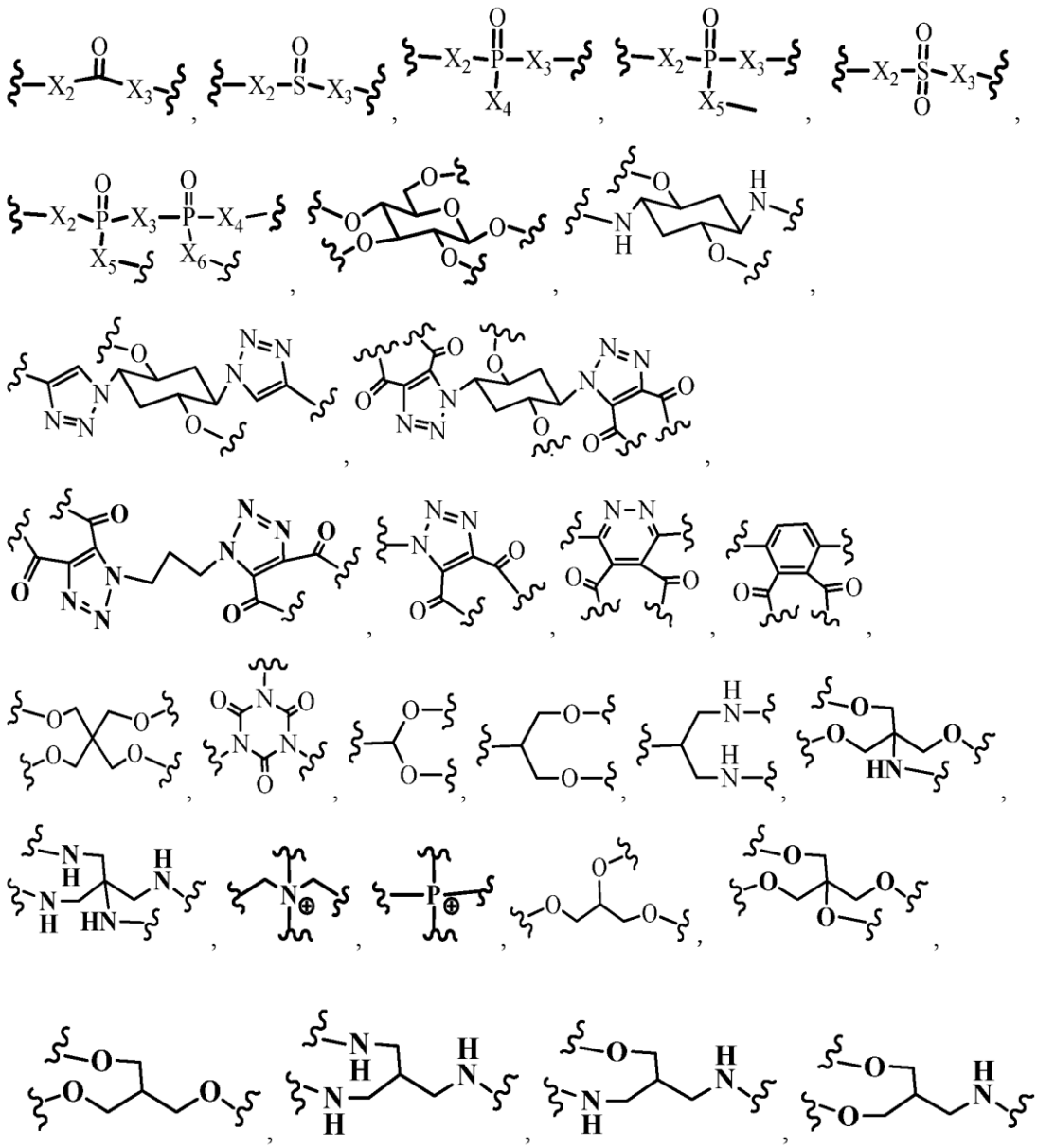
 N,N’-dimethylphosphondiamide,  hydrazine,

 acetimidamide;  oxime, 

acetylacetohydrazide,  aminoethyl-amine, 

 ,  ,

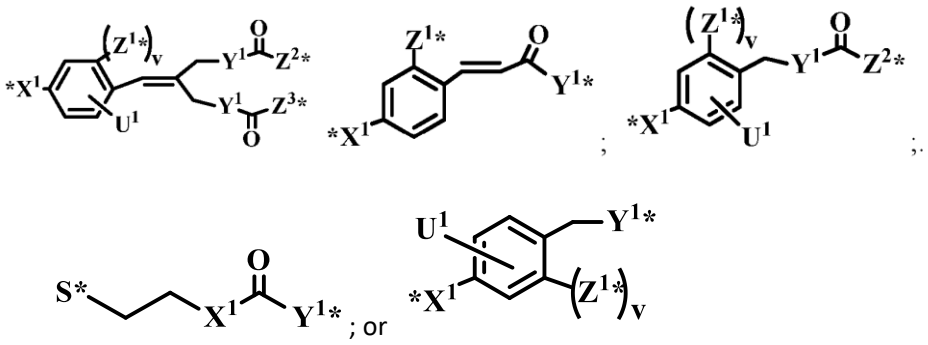
aminoethyl-aminoethyl-amine,



or L-or D-, natural or unnatural peptides containing 1-20 the same or different amino acids; wherein $\S$ is the site of linkage; X_2, X_3, X_4, X_5, or X_6, are independently NH; NHNH; $N(R_{12})$; $N(R_{12})N(R_{12'})$; O; S; C_1-C_6 alkyl; C_2-C_6 heteroalkyl, alkylcycloalkyl, heterocycloalkyl; C_3-C_8 aryl, Ar-alkyl, heterocyclic, carbocyclic, cycloalkyl, heteroalkylcycloalkyl, alkylcarbonyl, heteroaryl; CH_2OR_{12}, CH_2SR_{12}, CH_2NHR_{12}, or a peptide of 1～8 amino acids; wherein R_{12} and $R_{12'}$ are independently H; C_1-C_8 alkyl; C_2-C_8 hetero-alkyl, alkylcycloalkyl, heterocycloalkyl; C_3-C_8 aryl, Ar-alkyl, heterocyclic, carbo-cyclic, cycloalkyl, heteroalkylcycloalkyl, alkylcarbonyl, heteroaryl; or 1-8 carbon atoms of esters, ether, or

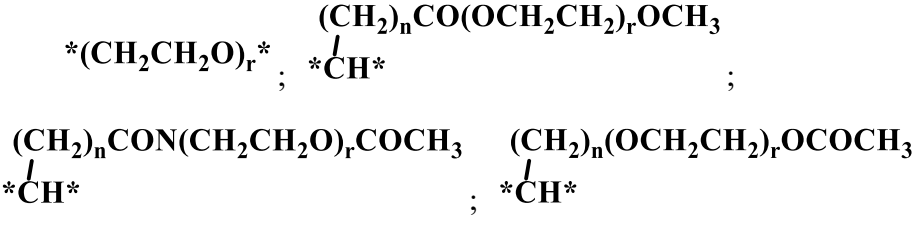
amide; or polyethyleneoxy unit of formula $(OCH_2CH_2)_p$ or $(OCH_2CH(CH_3))_p$, wherein p is an integer from 0 to 1000, or combination above thereof.

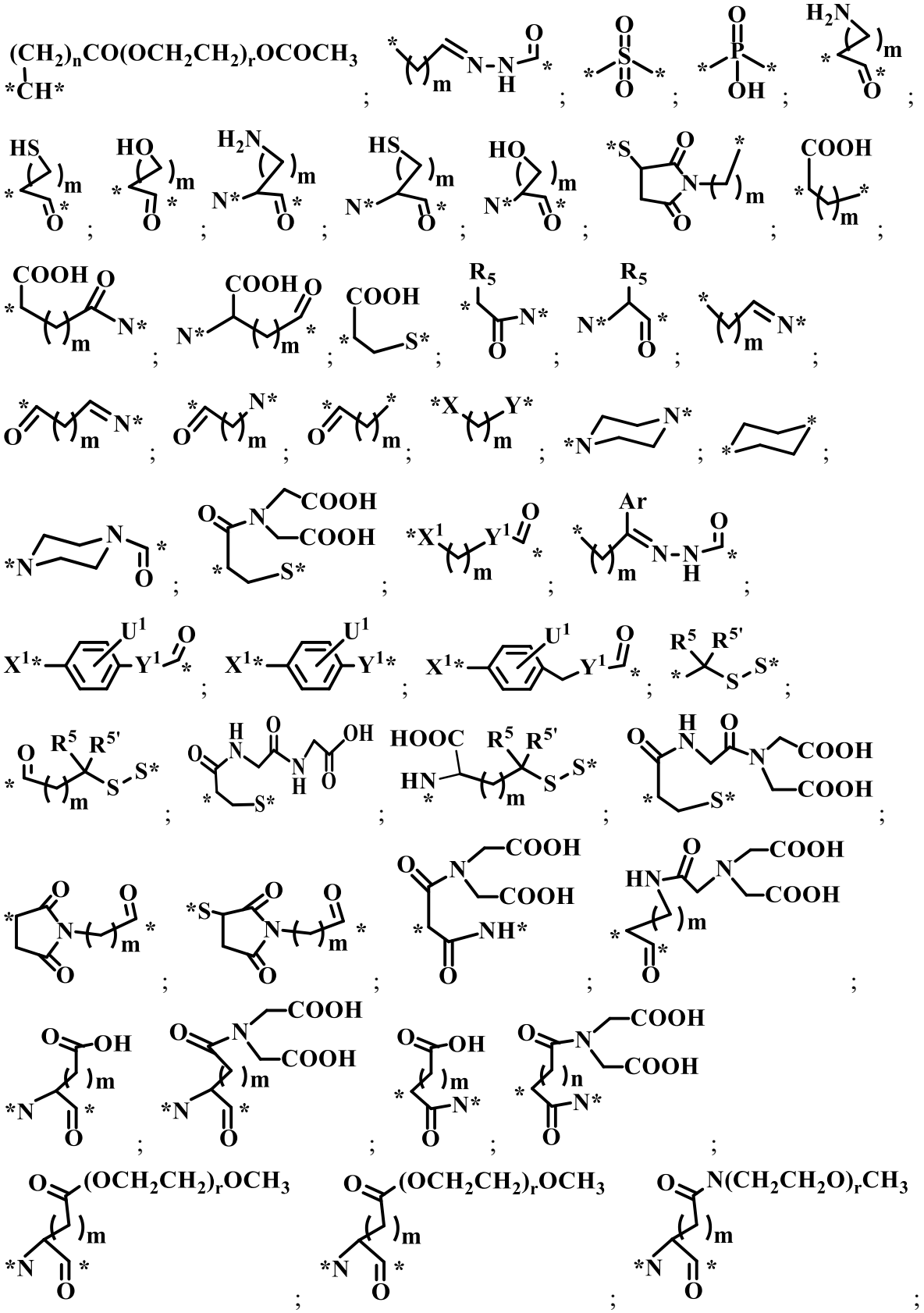
7. A side chain-linkage compound according to any one of claims 1 to 4, wherein W, L_1, L_2, V_1, and V_2 independently comprise: (A): a self-immolative component, peptidic units, a hydrazone bond, a disulfide, an ester, an ox-ime, an amide, or a thioether bond, the self-immolative unit comprises para-aminobenzyl-carbamoyl (PAB) groups, beta-glucuronide, and ortho or para-aminobenzylacetals; or one of the following structures:

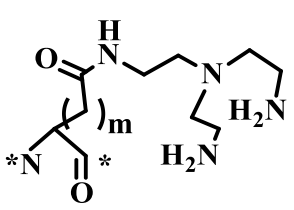
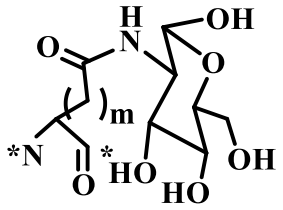


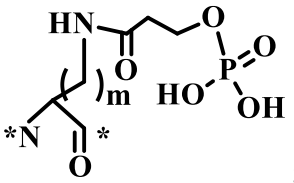
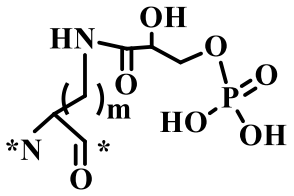
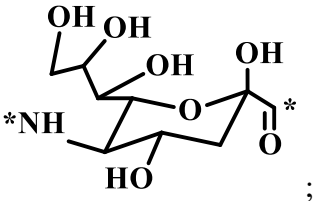
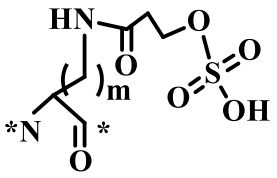
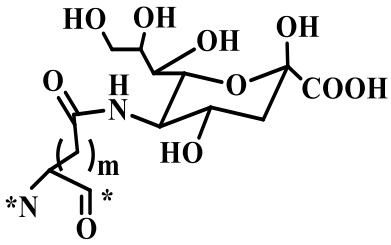
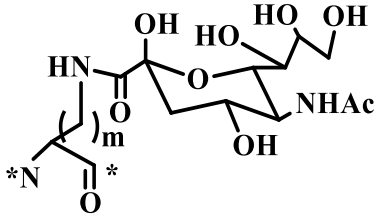
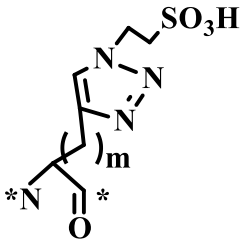
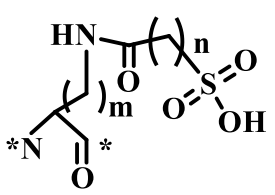
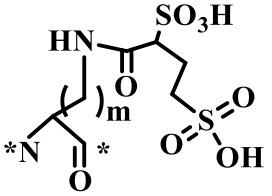
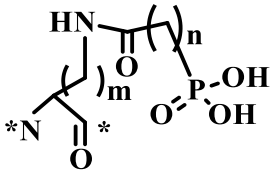
wherein the (*) atom is the point of attachment of another component; X^1, Y^1, Z^2 and Z^3 are independently NH, O, or S; Z^1 is independently H, NHR_1, OR_1, SR_1, COX_1R_1, wherein X_1 and R_1 are defined above; v is 0 or 1; U^1 is independently H, OH, C_1～C_6 alkyl, $(OCH_2CH_2)_n$, F, Cl, Br, I, OR_5, SR_5, NR_5R_5', N=NR_5, N=R_5, NR_5R_5', NO_2, SOR_5R_5', SO_2R_5, SO_3R_5, OSO_3R_5, PR_5R_5', POR_5R_5', $PO_2R_5R_5$', $OPO(OR_5)(OR_5')$, or $OCH_2PO(OR_5(OR_5')$, wherein R_5 and R_5' are independently H, C_1～C_8 alkyl; C_2～C_8 alkenyl, alkynyl, heteroalkyl, or amino acid; C_3～C_8 aryl, heterocyclic, carbocyclic, cycloalkyl, heterocycloalkyl, heteroaralkyl, alkylcarbonyl, or glycoside; or pharmaceutical cation salts;

(B): a non-self-immolative linker component containing one of the following structures:






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wherein the (*) atom is the point of attachment of additional spacer or releasable linkers, the cyto-toxic agents, and/or the binding molecules; X^1, Y^1, U^1, R^5, $R^{5'}$ are defined as above; r is 0～100; m and n are 0～20 independently;

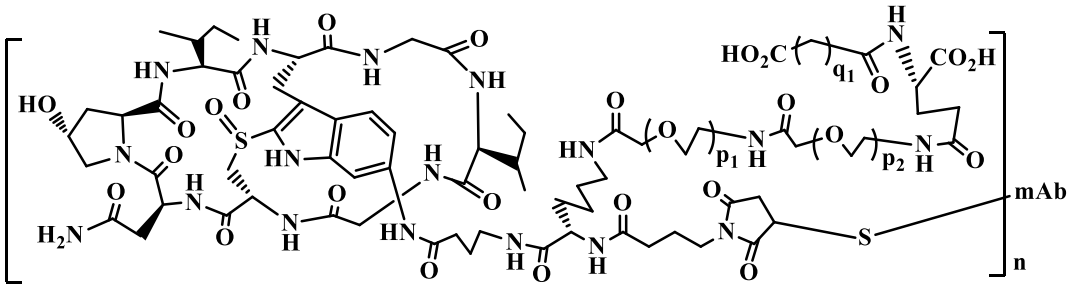
(C): a releasable component that at least one bond that can be broken under physiological conditions: a pH-labile, acid-labile, base-labile, oxidatively labile, metabolically labile, biochemi-cally labile or enzyme-labile bond, which having one of the following structures: -$(CR_{15}R_{16})_m(Aa)_r$ $(CR_{17}R_{18})_n(OCH_2CH_2)_t$-,- $(CR_{15}R_{16})_m(CR_{17}R_{18})_n(Aa)_r$ $(OCH_2CH_2)_t$-,-$(Aa)_r$-$(CR_{15}R_{16})_m$ $(CR_{17}R_{18})_n$ $(OCH_2CH_2)_t$-, -$(CR_{15}R_{16})_m(CR_{17}R_{18})_n(OCH_2CH_2)_r(Aa)_t$-, -$(CR_{15}R_{16})_m(CR_{17}=CR_{18})$ $(CR_{19}R_{20})_n(Aa)_t(OCH_2C_2)_r$-,-$(CR_{15}R_{16})_m(NR_{11}CO)(Aa)_t(CR_{19}R_{20})_n$- $(OCH_2CH_2)_r$-,-$(CR_{15}R_{16})_m(Aa)_t(NR_{21}CO)(CR_{19}R_{20})_n(OCH_2CH_2)_r$-, -$(CR_{15}R_6)_m(OCO)(Aa)_t$-$(CR_{19}R_{20})_n(OCH_2CH_2)_r$-,-$(CR_{15}R_{16})_m(OCNR_{17})(Aa)_t(CR_{19}R_{20})_n(OCH_2CH_2)_r$-,-$(CR_{15}R_{16})_m$-$(CO)(Aa)_t$- $(CR_{19}R_{20})_n(OCH_2CH_2)_r$-,-$(CR_{15}R_{16})_m(NR_{21}CO)(Aa)_t(CR_{19}R_{20})_n(OCH_2CH_2)_r$-,-

$(CR_{15}R_{16})_m$-(OCO)$(Aa)_t(CR_{19}R_{20})_n$-$(OCH_2CH_2)_r$-,

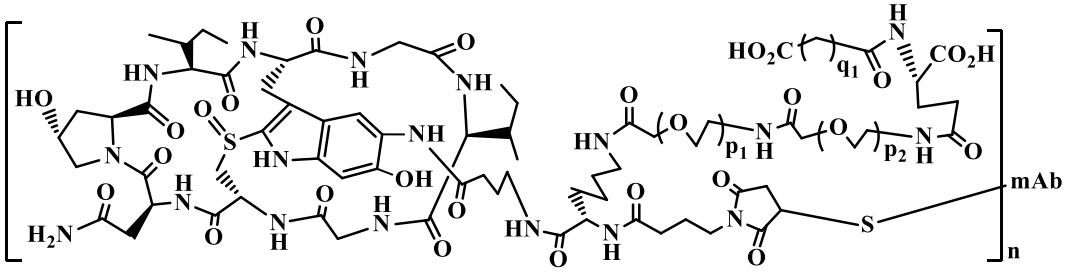
-$(CR_{15}R_{16})_m(OCNR_{17})(Aa)_t(CR_{19}R_{20})_n$-$(OCH_2CH_2)_r$-,-$(CR_{15}R_{16})_m(CO)(Aa)_t(CR_{19}R_{20})_n$-$(OCH_2CH_2)_r$-,-$(CR_{15}R_{16})_m$-phenyl-CO$(Aa)_t$-$(CR_{17}R_{18})_n$-,-$(CR_{15}R_{16})_m$-furyl-CO$(Aa)_t(CR_{17}R_{18})_n$-,-$(CR_{15}R_6)_m$-oxazolyl-CO$(Aa)_t(CR_{17}R_{18})_n$-,-$(CR_{15}R_{16})_m$-thiazolyl-CO$(Aa)_t(CCR_{17}R_{18})_n$-,-$(CR_{15}R_{16})_t$-thienyl-CO$(CR_{17}R_{18})_n$-,-$(CR_{15}R_{16})_t$-imidazolyl-CO-$(CR_{17}R_{18})_n$-,-$(CR_{15}R_{16})_t$-morpholino-CO$(Aa)_t$-$(CR_{17}R_{18})_n$-,-$(CR_{15}R_{16})_t$-piperazino-CO$(Aa)_t(CR_{17}R_{18})_n$- -$(CR_{15}R_{16})_t$-N-methylpiperazin-CO$(Aa)_t(CR_{17}R_{18})_n$-, -$(CR_{15}R_{16})_m$-$(Aa)_t$phenyl-, -$(CR_{15}R_{16})_m$-$(Aa)_t$furyl-, -$(CR_{15}R_{16})_m$-oxazolyl$(Aa)_t$-, -$(CR_{15}R_{16})_m$-thiazolyl$(Aa)_t$-,-$(CR_{15}R_{16})$ $_m$-thienyl-$(Aa)_t$-,-$(CR_{15}R_{16})_m$-imidazolyl$(Aa)_t$-,-$(CR_{15}R_{16})_m$-morpholino-$(Aa)_t$-,-$(CR_{15}R_{16})_m$-piperazino-$(Aa)_t$-,-$(CR_{15}R_{16})_m$-N-methylpiperazino-$(Aa)_t$-, -K$(CR_{15}R_{16})_m(Aa)_t(CR_{17}R_{18})_n(OCH_2CH_2)_t$-, -K$(CR_{15}R_{16})_m(CR_{17}R_{18})_n(Aa)_r(OCH_2CH_2)_t$-,-K$(Aa)_r$-$(CR_{15}R_{16})_m(CR_{17}R_{18})_n(OCH_2CH_2)_t$-,-K$(CR_{15}R_{16})_m(CR_{17}R_{18})_n(OCH_2CH_2)_r$ $(Aa)_t$-,-K$(CR_{15}R_{16})_m$-$(CR_{17}$=$CR_{18})(CR_{19}R_{20})_n(Aa)_t(OCH_2CH_2)_r$,-K$(CR_{15}R_{16})_m(NR_{11}CO)(Aa)_t$-$(CR_{19}R_{20})_n(OCH_2CH_2)_r$-,-K$(CR_5R_6)_m$ $(Aa)_t(NR_{21}CO)(CR_{19}R_{20})_n(OCH_2CH_2)_r$-,-K$(CR_{15}R_{16})_m(OCO)(Aa)_t(CR_{19}R_{20})_n$-$(OCH_2CH_2)_r$-,-K$(CR_{15}R_{16})_m(OCNR_{17})(Aa)_t(CR_{19}R_{20})_n(OCH_2CH_2)_r$-,-K$(CR_{15}R_{16})_m(CO)(Aa)_t$-$(CR_{19}R_{20})_n(OCH_2CH_2)_r$-,-K$(CR_{15}R_{16})_m(NR_{21}CO)(Aa)_t(CR_{19}R_{20})_n$-$(OCH_2CH_2)_r$-,-K$(CR_{15}R_{16})_m$-(OCO)$(Aa)_t(CR_{19}R_{20})_n(OCH_2CH_2)$ $_r$-,-K$(CR_{15}R_{16})_m(OCNR_{17})(Aa)_t$-$(CR_{19}R_{20})_n(OCH_2CH_2)_r$-,-K-$(CR_{15}R_{16})_m(CO)(Aa)_t(CR_{19}R_{20})_n(OCH_2CH_2)_r$-,-K$(CR_{15}R_{16})_m$-phenyl-CO$(Aa)_t(CR_{17}R_{18})_n$-,-K-$(CR_{15}R_{16})_m$-furyl-CO$(Aa)_t(CR_{17}R_{18})_n$-,-K$(CR_{15}R_{16})_m$-oxazolyl-CO$(Aa)_t(CR_{17}R_{18})_n$-, -K$(CR_{15}R_{16})_m$-thiazolyl-CO$(Aa)_t$-$(CR_{17}R_{18})_n$-, -K$(CR_{15}R_{16})_t$-thienyl-CO$(CR_{17}R_{18})_n$-,-K$(CR_{15}R_{16})_t$imidazolyl-CO-$(CR_{17}R_{18})_n$-, -K$(CR_5R_6)_t$morpholino-CO$(Aa)_t$-$(CR_{17}R_{18})_n$-, -K$(CR_{15}R_{16})_t$-piperazino-CO$(Aa)_t$-$(CR_{17}R_{18})_n$-, -K$(CR_{15}R_{16})_t$-N-methylpiperazin-CO$(Aa)_t(CR_{17}R_{18})_n$-, -K$(CR_{15}R_{16})_m$-$(Aa)_t$phenyl, -K-$(CR_{15}R_{16})_m$-$(Aa)_t$furyl-, -K$(CR_{15}R_{16})_m$-oxazolyl-(Aa) $_t$-, -K$(CR_{15}R_{16})_m$-thiazolyl$(Aa)_t$-, -K$(CR_{15}R_{16})_m$-thienyl-$(Aa)_t$-, -K$(CR_{15}R_{16})_m$-imidazolyl$(Aa)_t$-, -K$(CR_{15}R_{16})_m$-morpholino$(Aa)_t$-, -K$(CR_{15}R_{16})_m$-piperazino$(Aa)_t$G, -K$(CR_5R_6)_m$-N-methyl-piperazino$(Aa)_t$-; wherein m, Aa, m, n, R_{13}, R_{14}, and R_{15} are as defined

in claim 1; t and r here are 0–100 independently; R_{16}, R_{17}, R_{18}, R_{19}, and R_{20} are independently chosen from H; halide; C_1～C_8 alkyl or heteroalkkyl, C_2～C_8 aryl, alkenyl, alkynyl, ether, ester, amine or amide, C_3～C_8 aryl which is substituted by one or more halide, CN, $NR_{12}R_{12'}$, CF_3, OR_{12}, Aryl, heterocycle, $S(O)R_{12}$, SO_2R_{12}, $-CO_2H$, $-SO_3H$, $-OR_{12}$, $-CO_2R_{12}$, $-CONR_{12}$, $-PO_2R_{12}R_{13}$, $-PO_3H$ or $P(O)R_{12}R_{12'}R_{13}$; K is NR_{12}, -SS-, -C(=O)-, -C(=O)NH-, -C(=O)O-, -C=NH-O-, -C=N-NH-, -C(=O)NH-NH-, O, S, Se, B, heterocyclic or heteroaromatic ring having C_3-C_{12}; or peptides containing the same or different 2-20 amino acids.

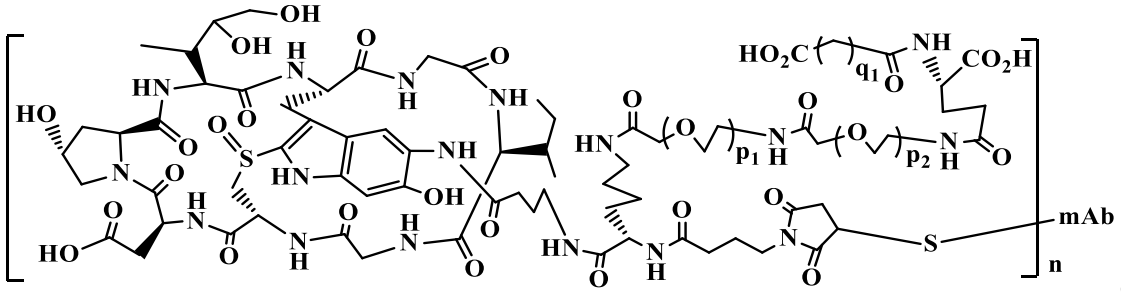
8. The conjugate compound of Formula (I) according to claim 1 having the following structures of a-01 to a-40, 78a-c, 91, 95, 97, 114, 117, 126, 132, 146, 154, 167, 179, 181, 197, 198, 206, 247, 250, 258, 260, 262 below:



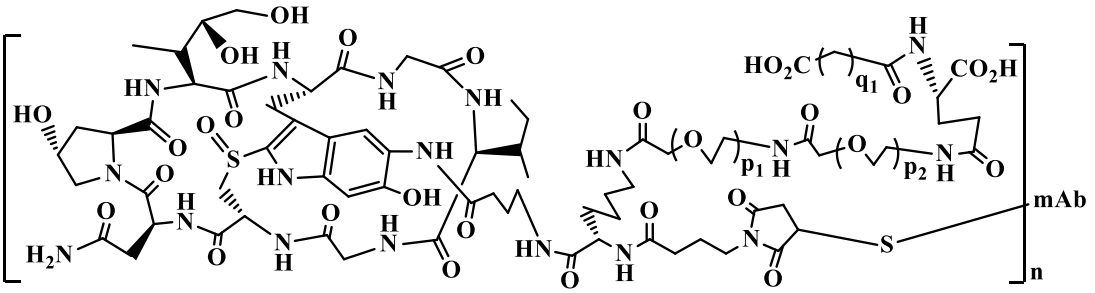
a-01,



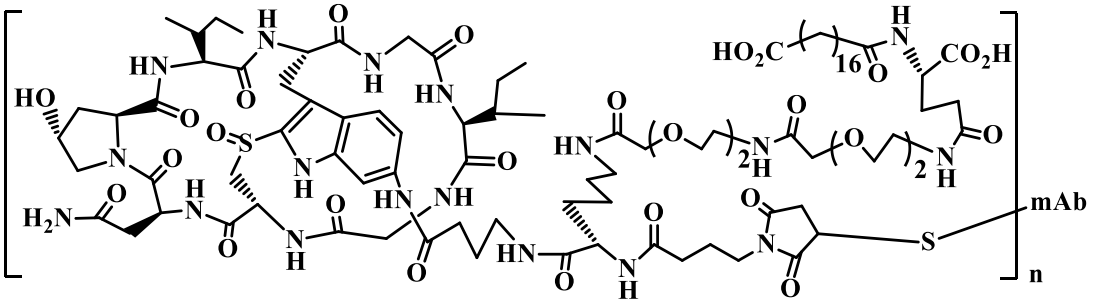
a-02,



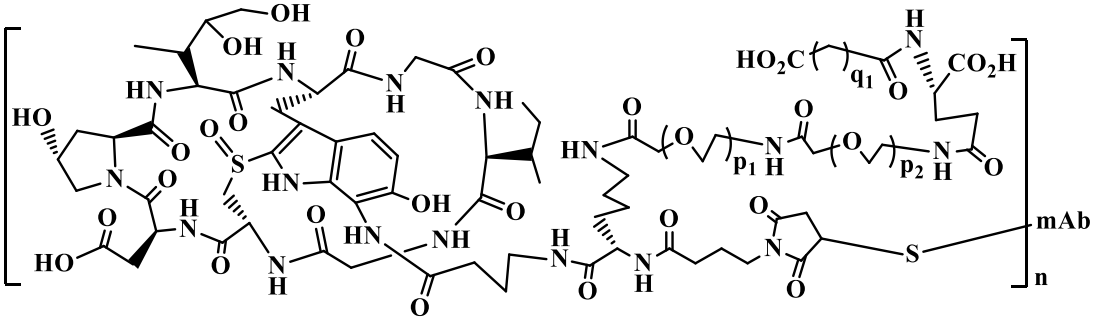
a-03,



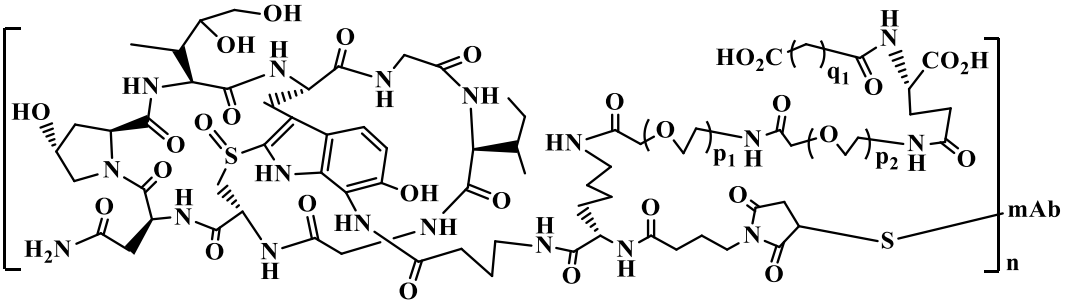
a-04,



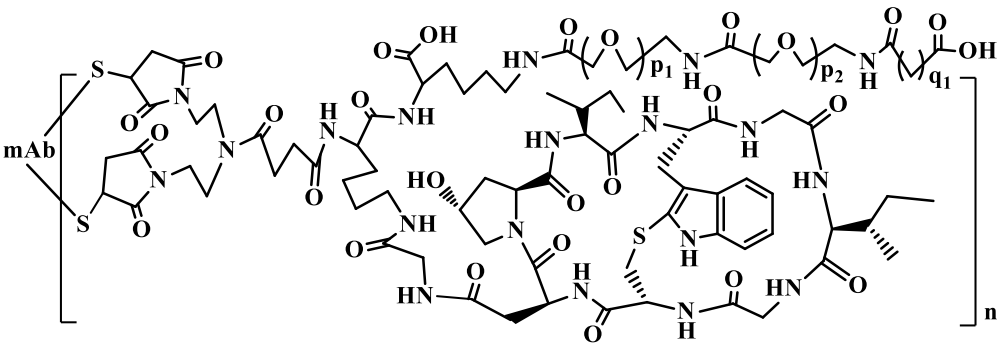
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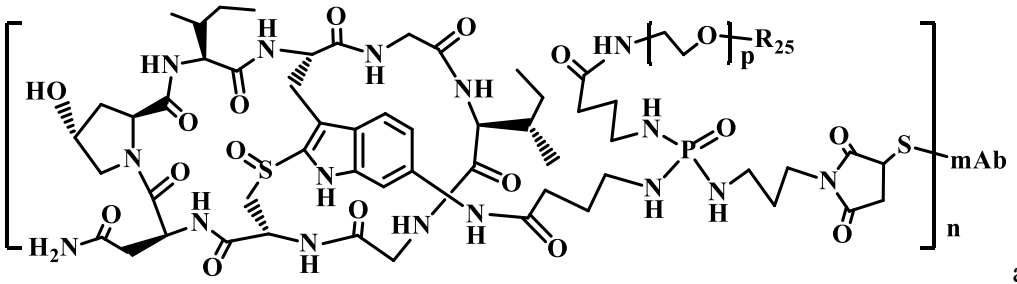
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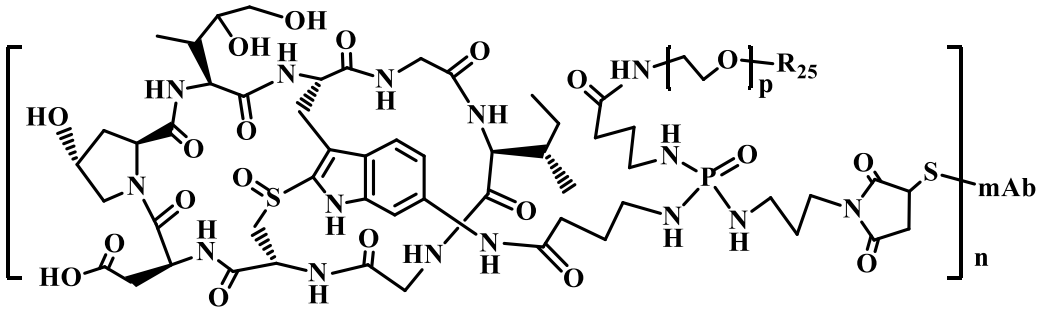
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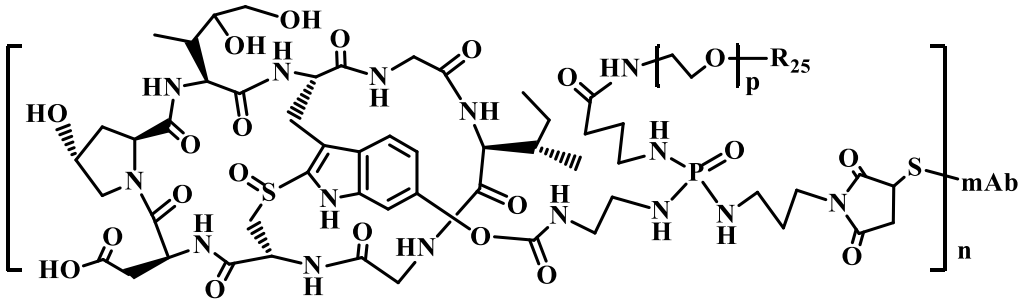
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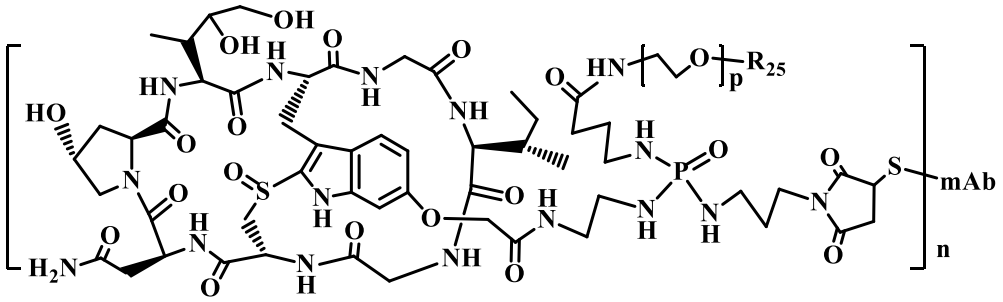
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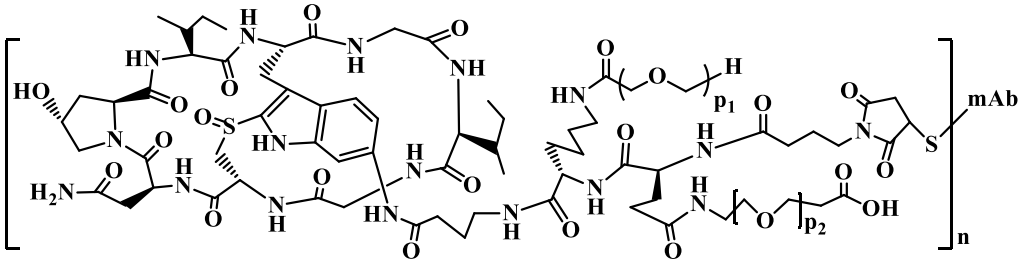
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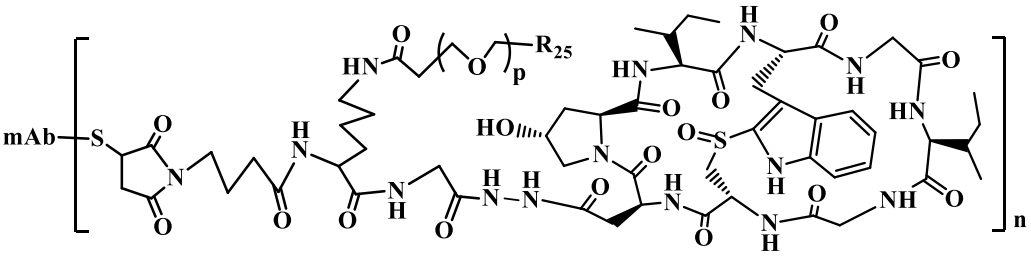
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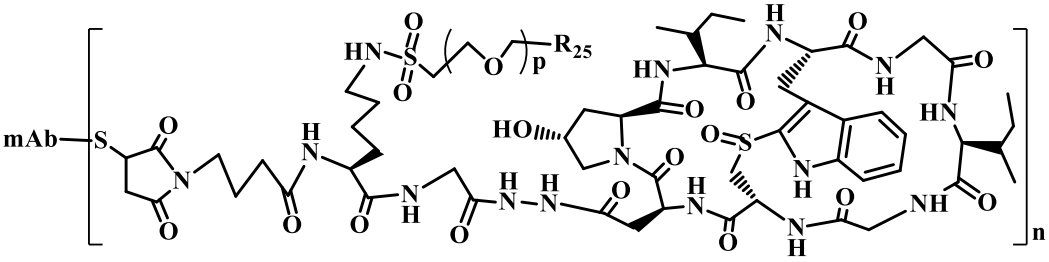
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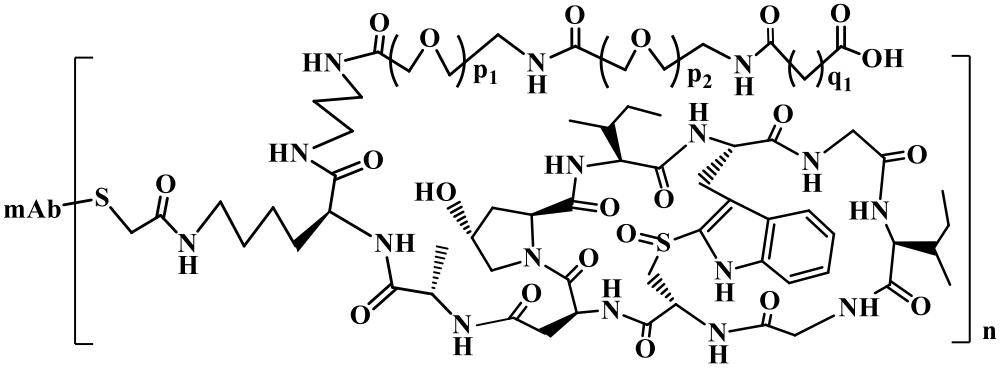
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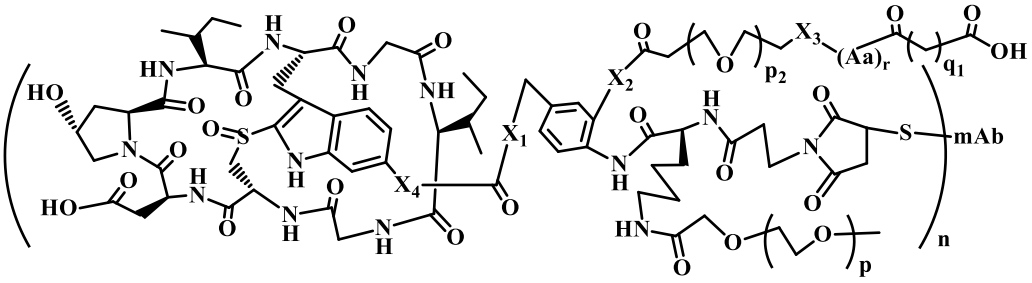
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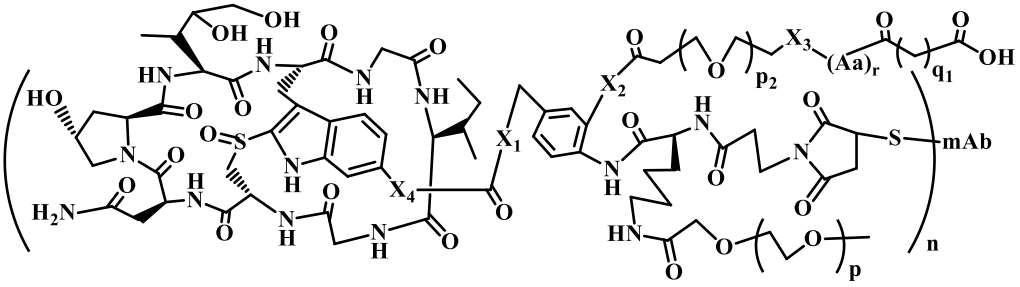
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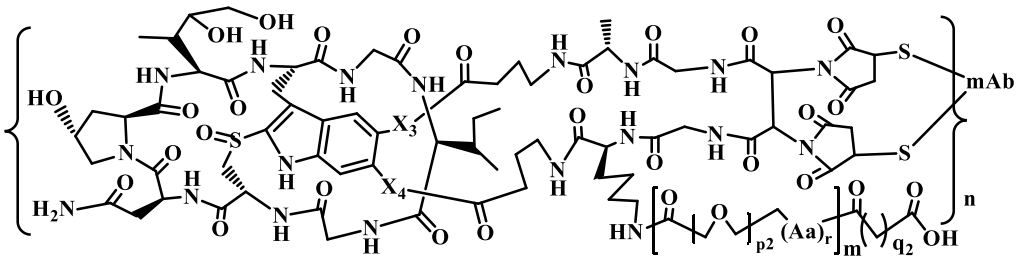
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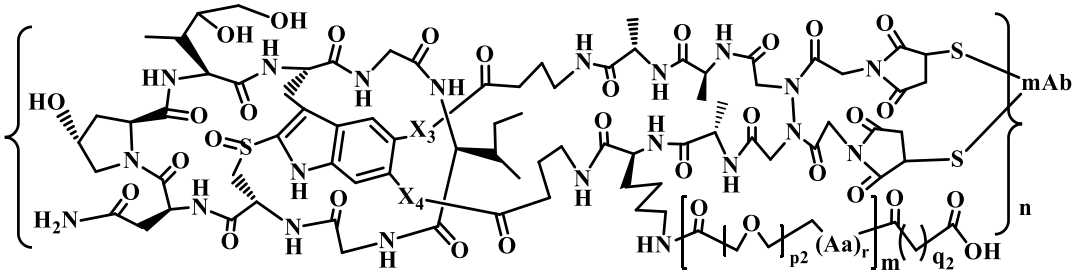
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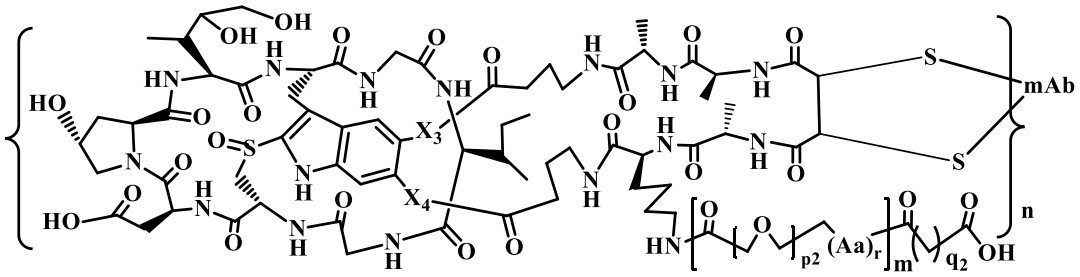
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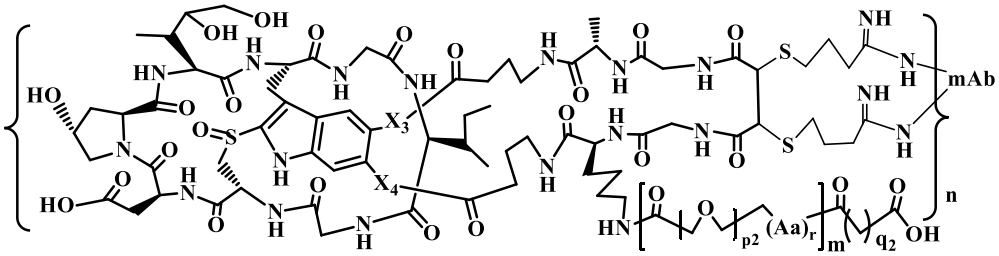
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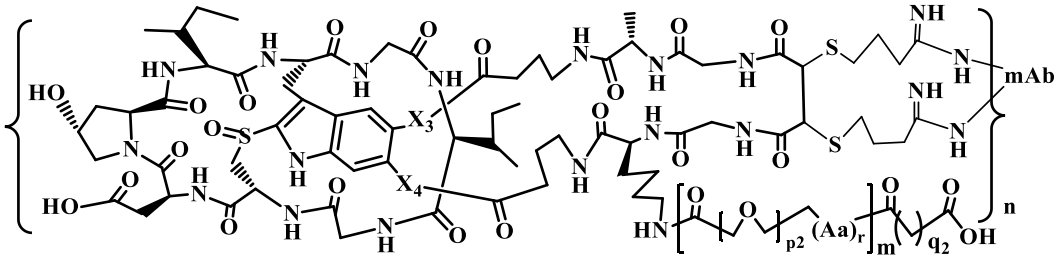
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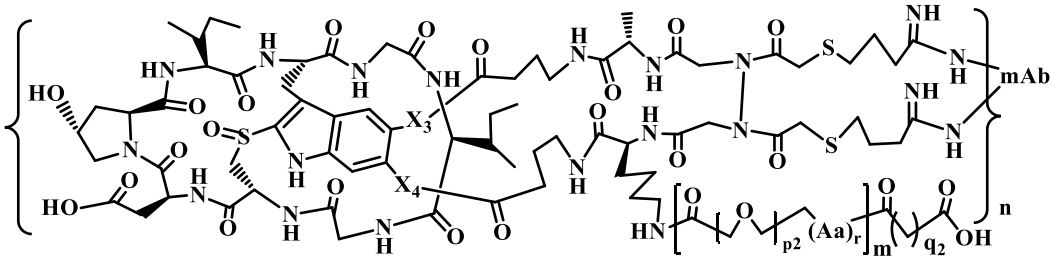
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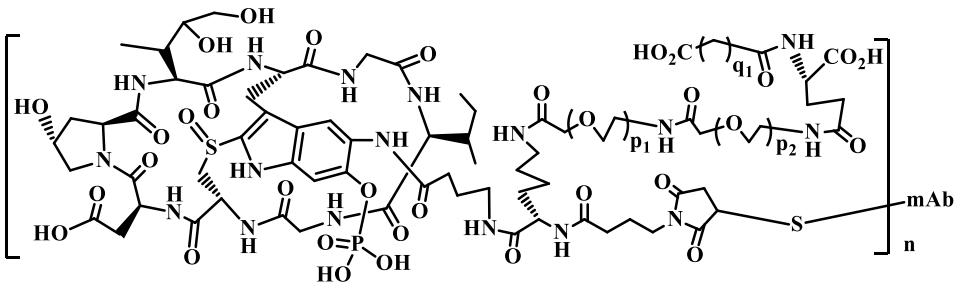
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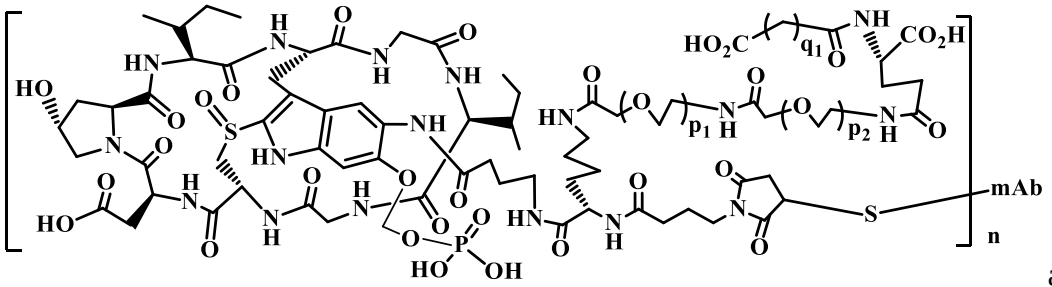
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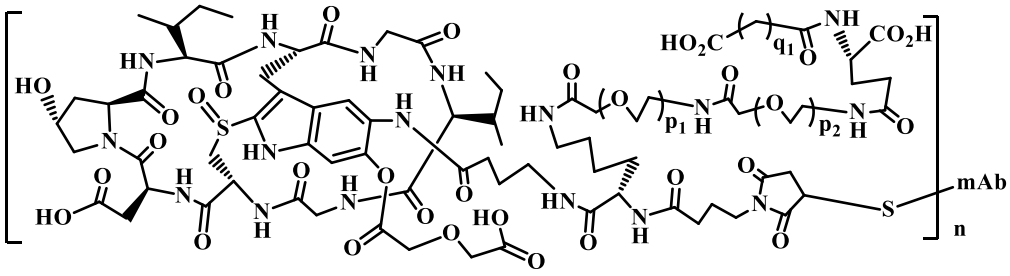
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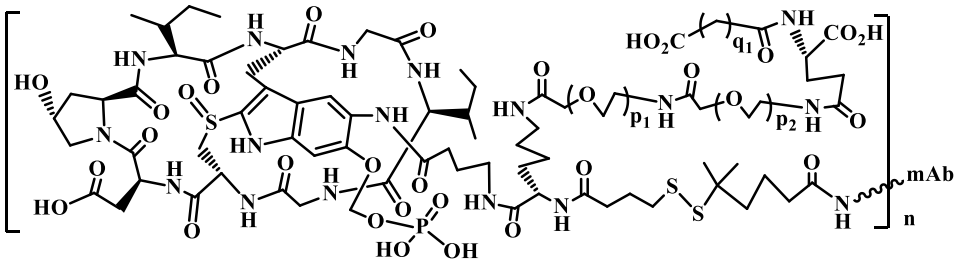
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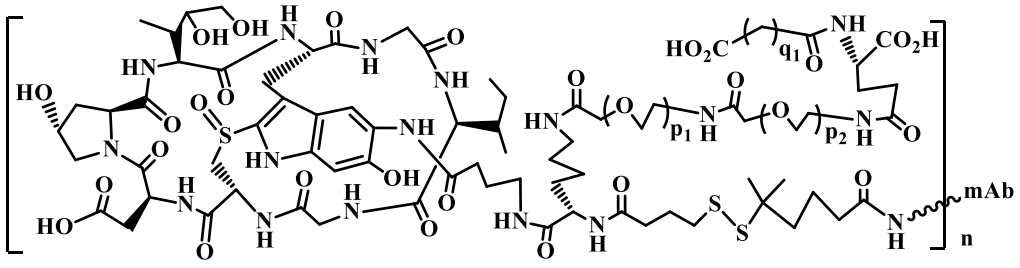
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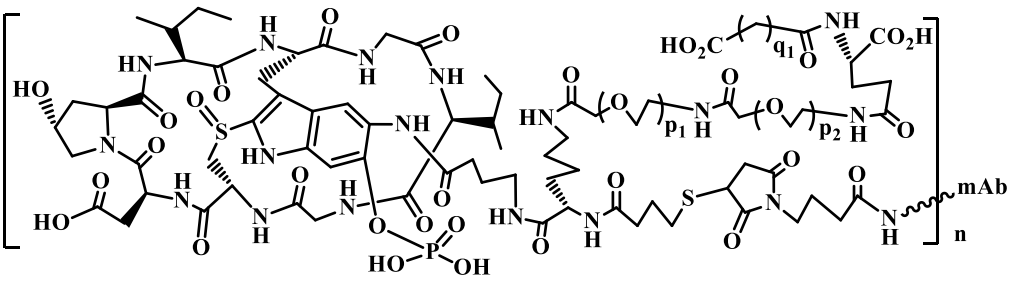
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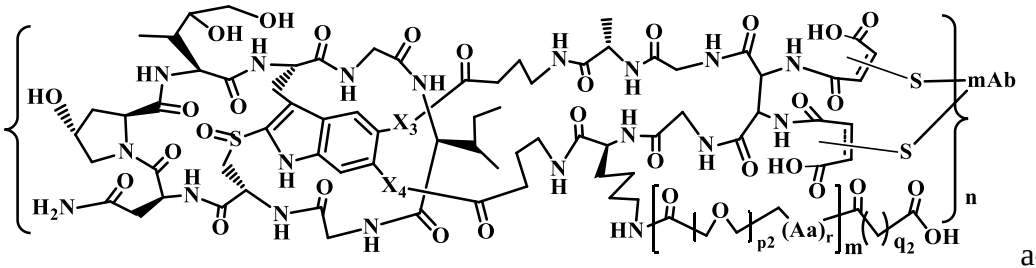
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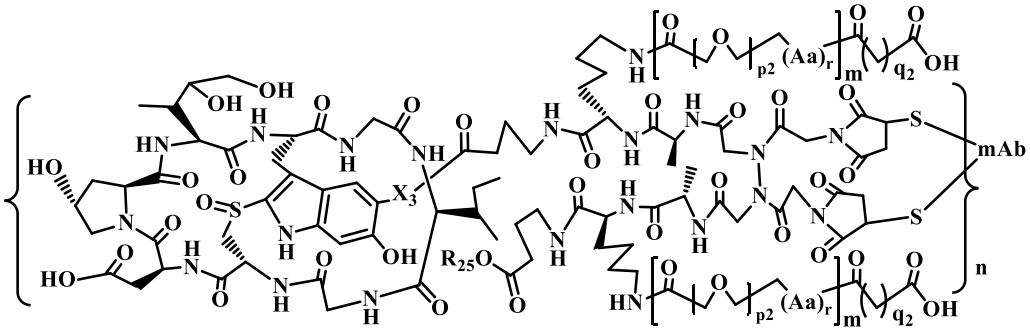
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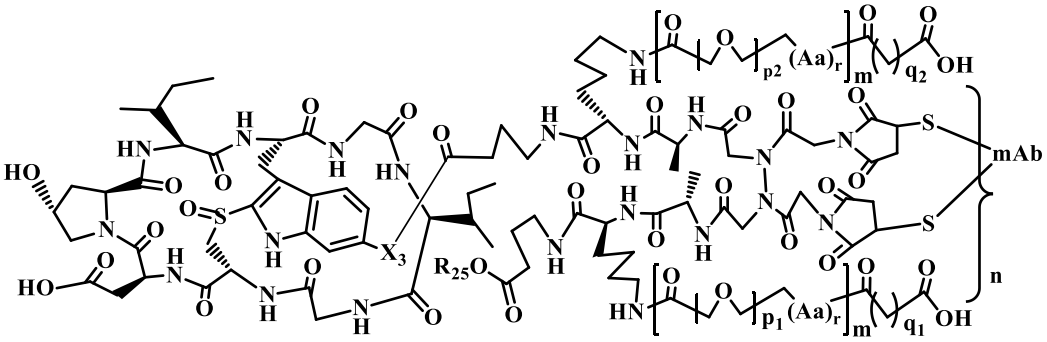
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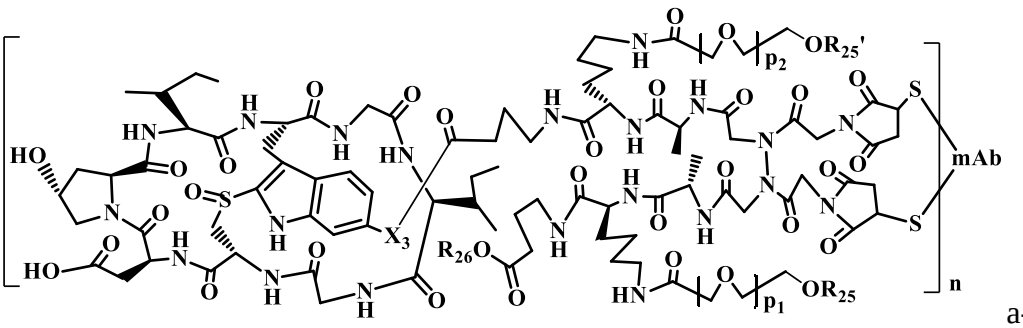
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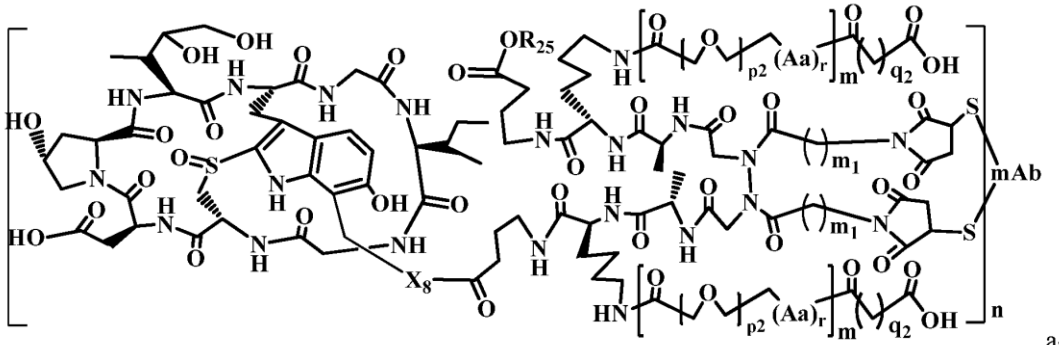
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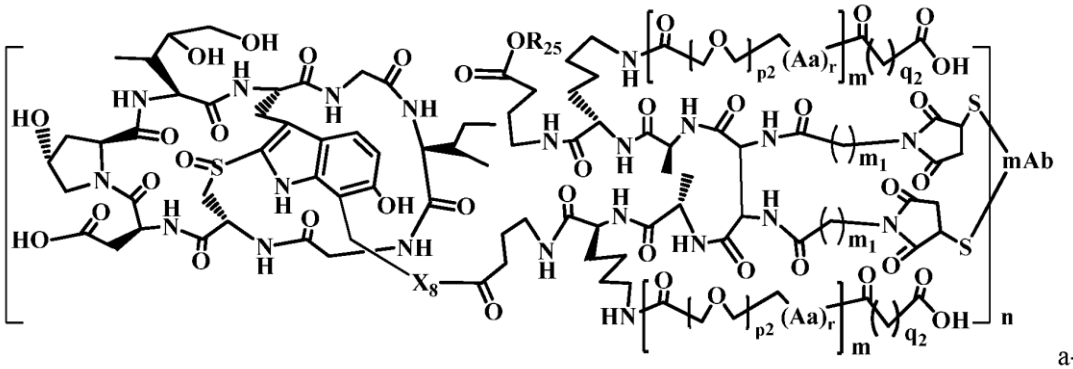
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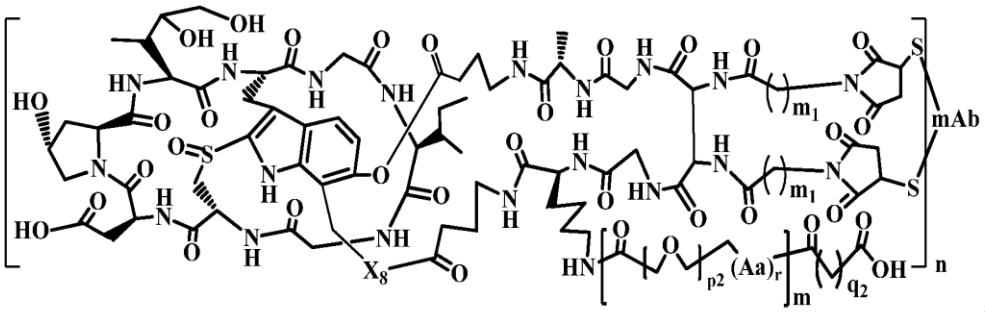
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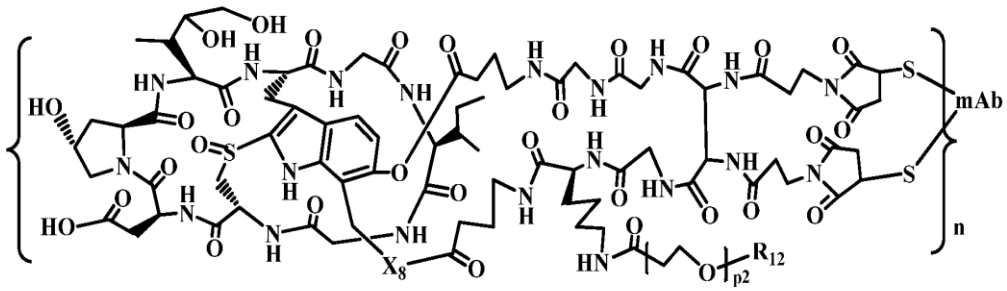
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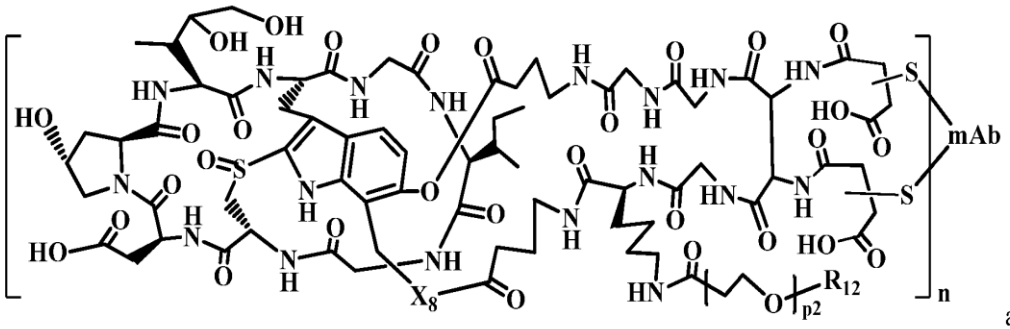
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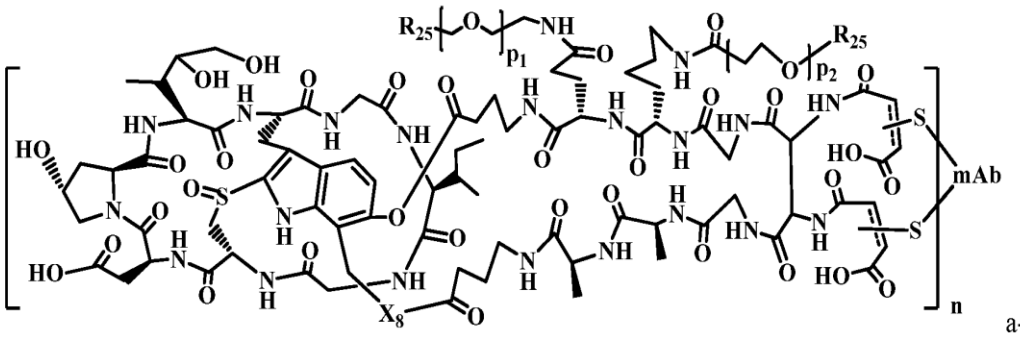
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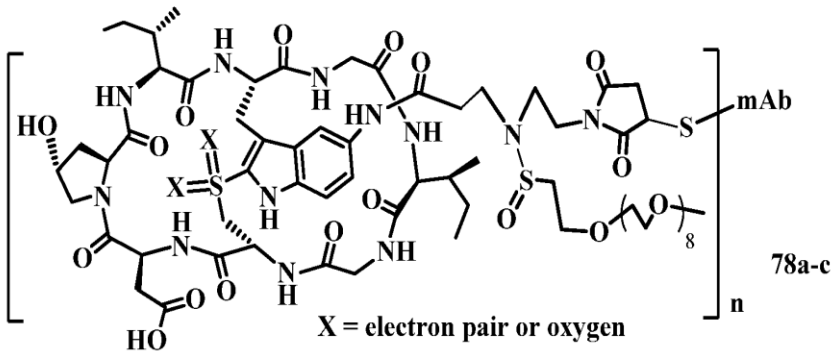
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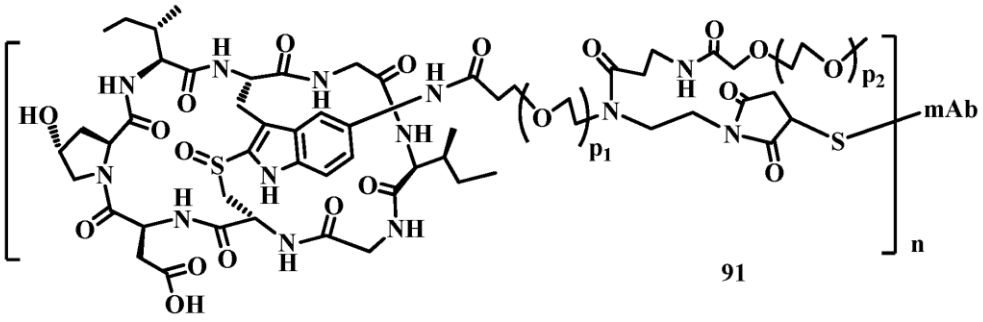


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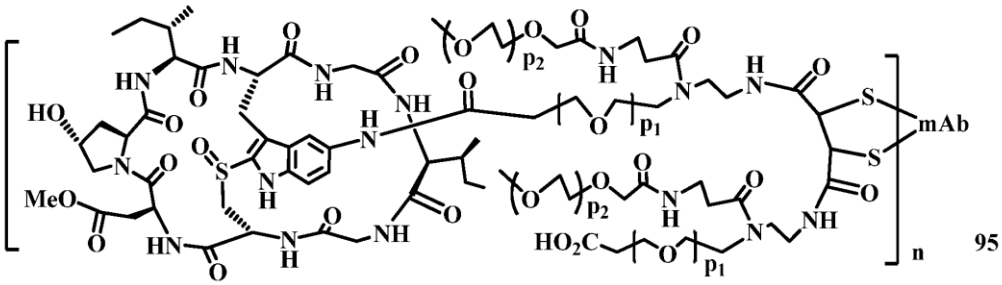


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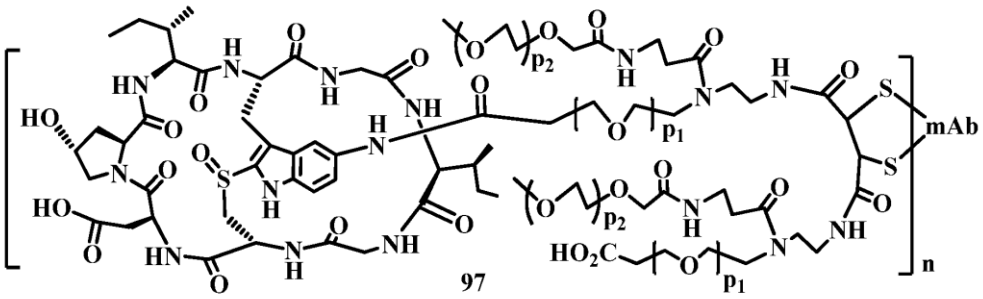
X = electron pair or oxygen



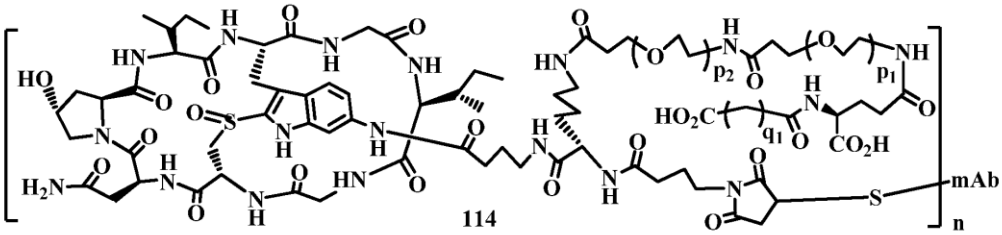
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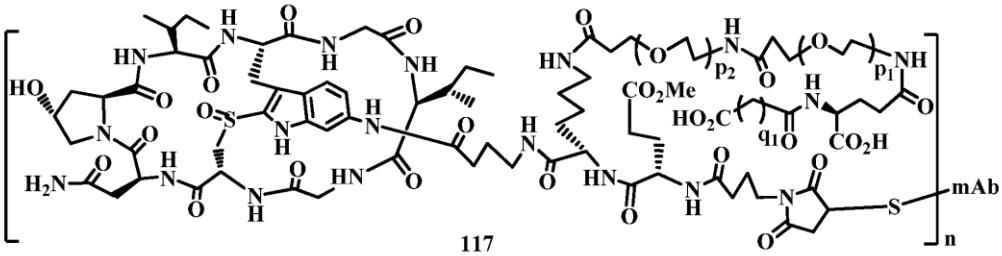
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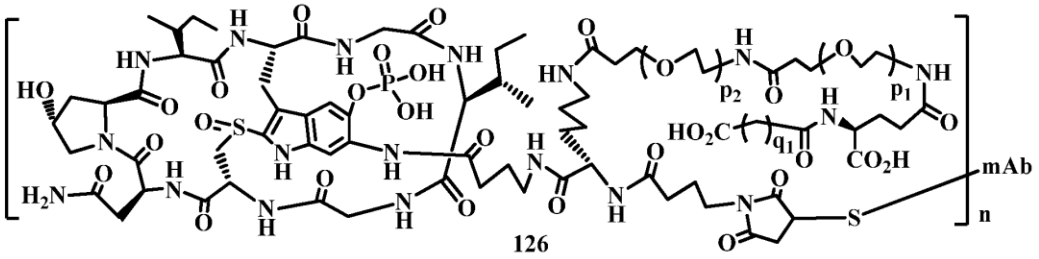
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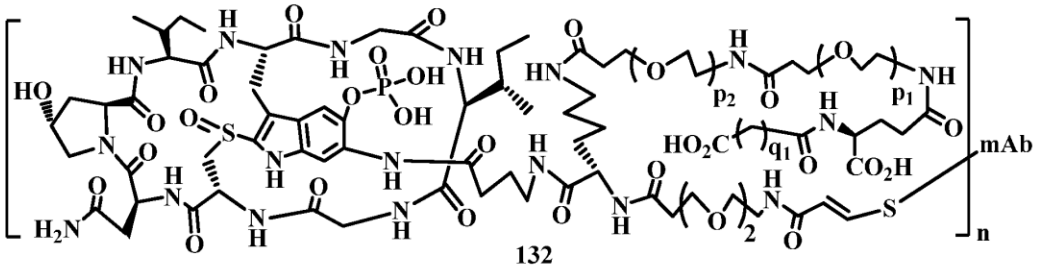
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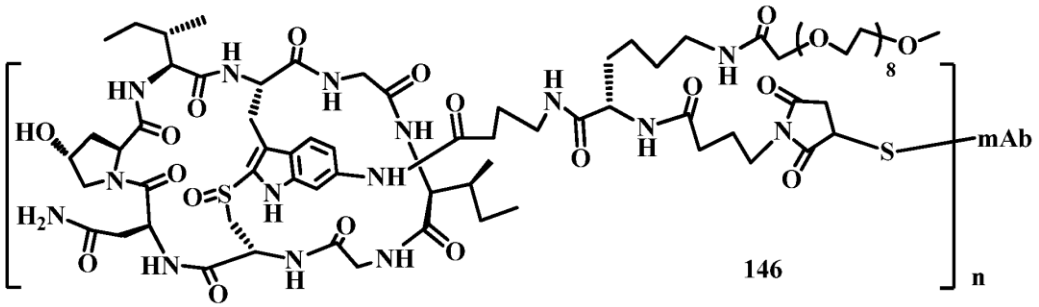
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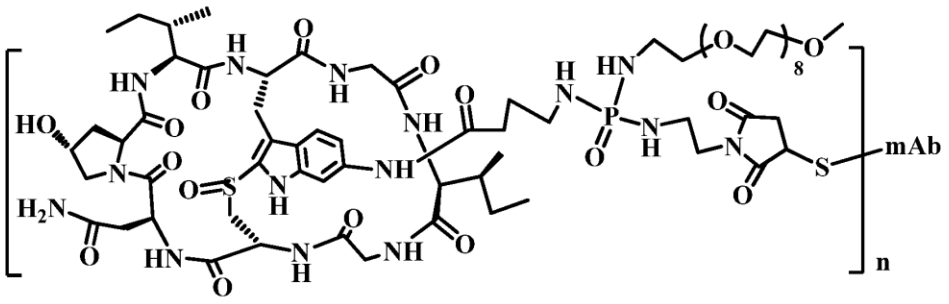
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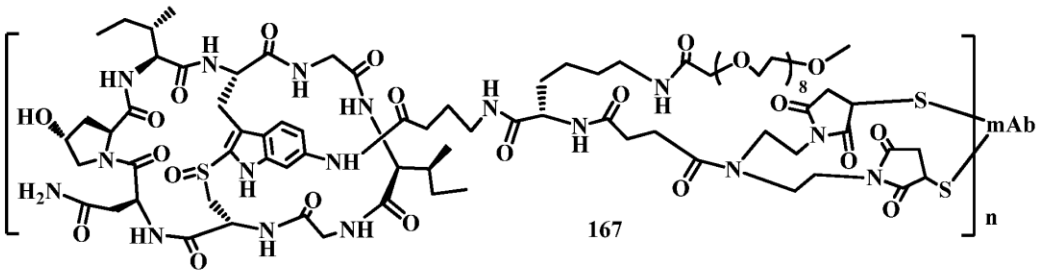
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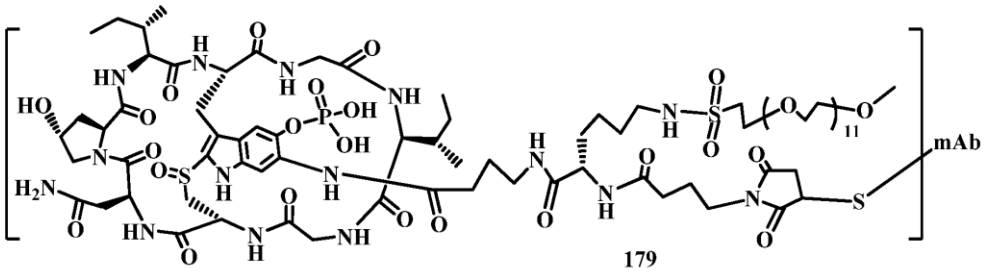
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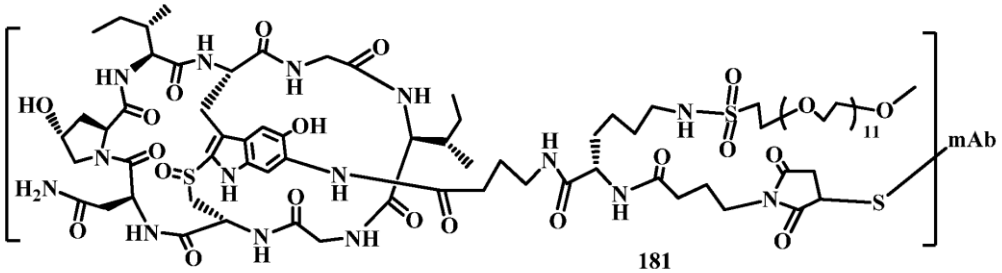
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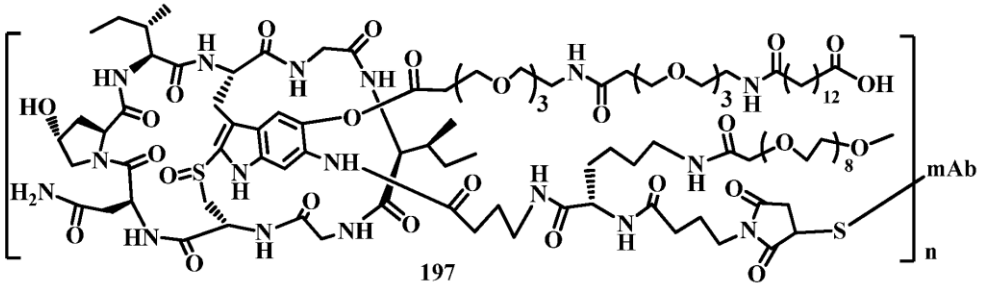
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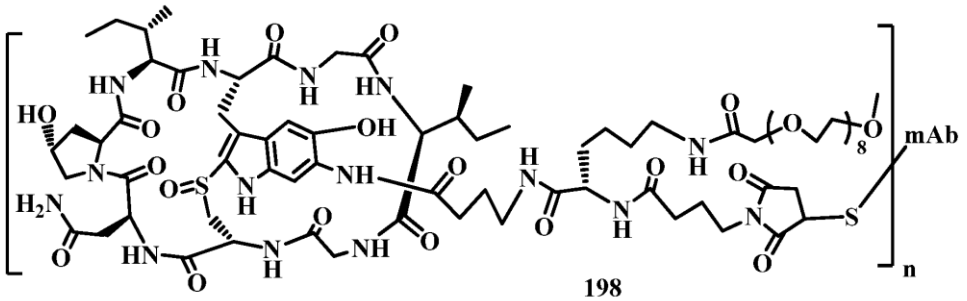
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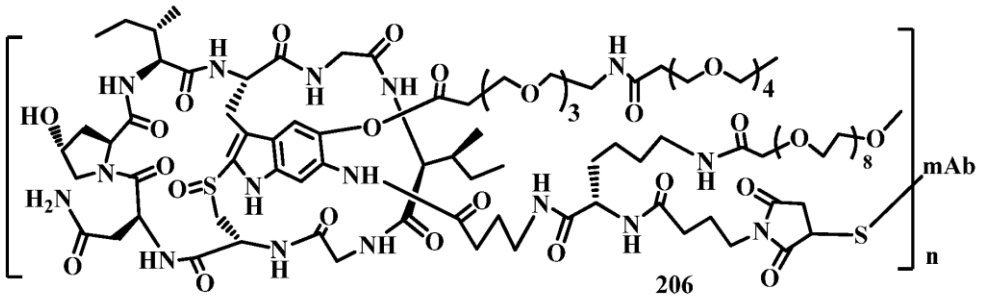
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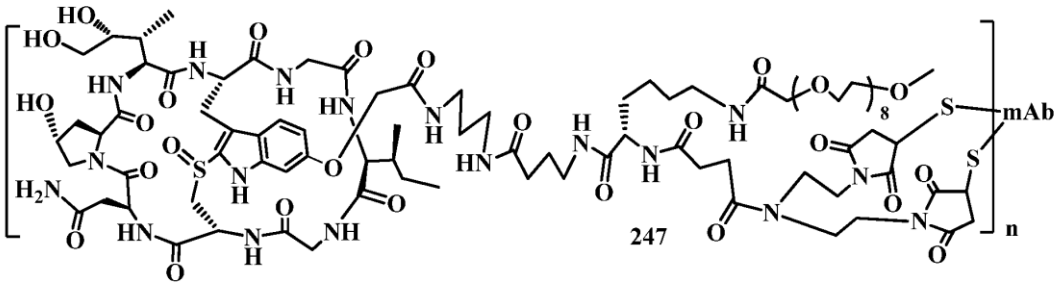
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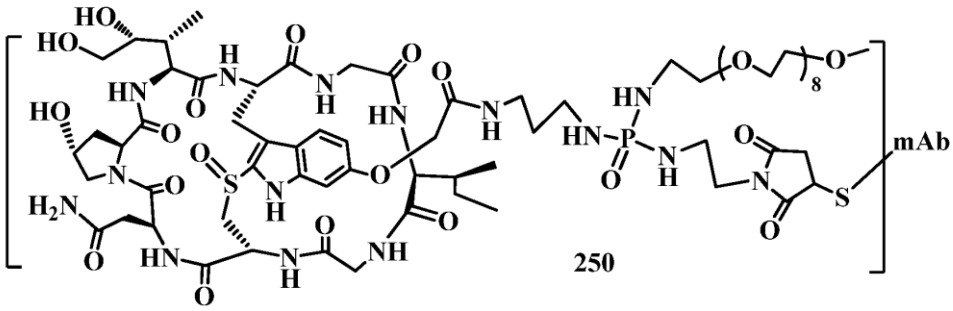
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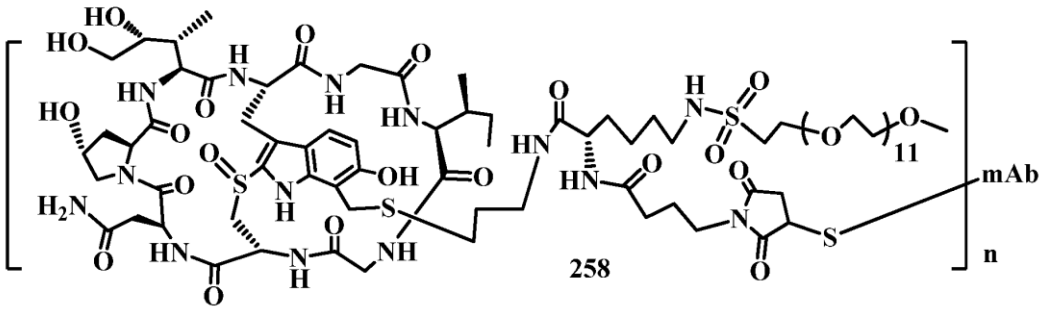
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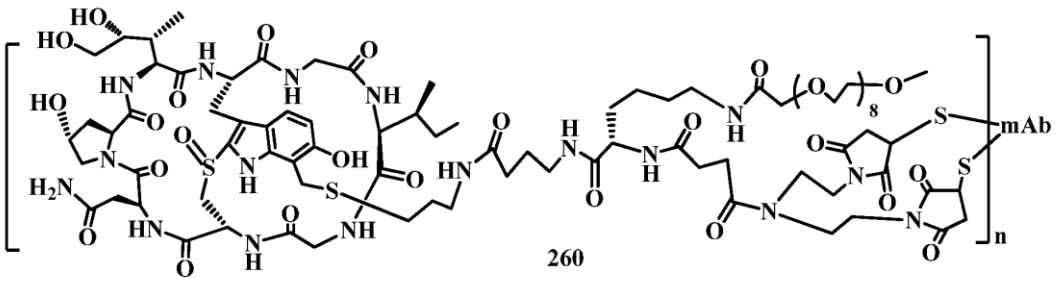
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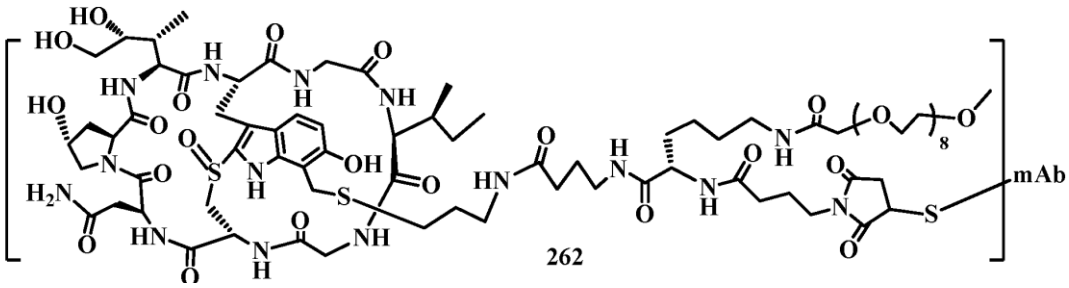
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260

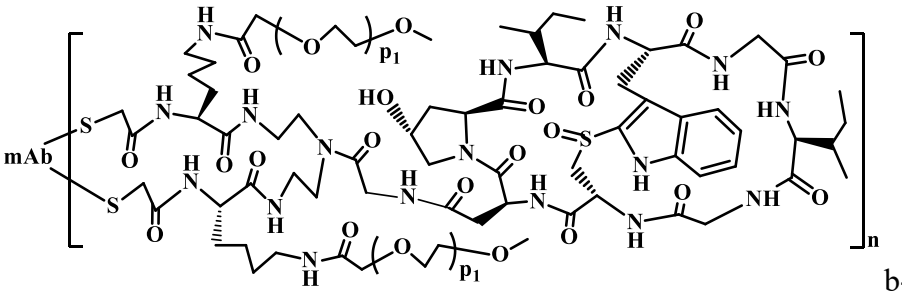


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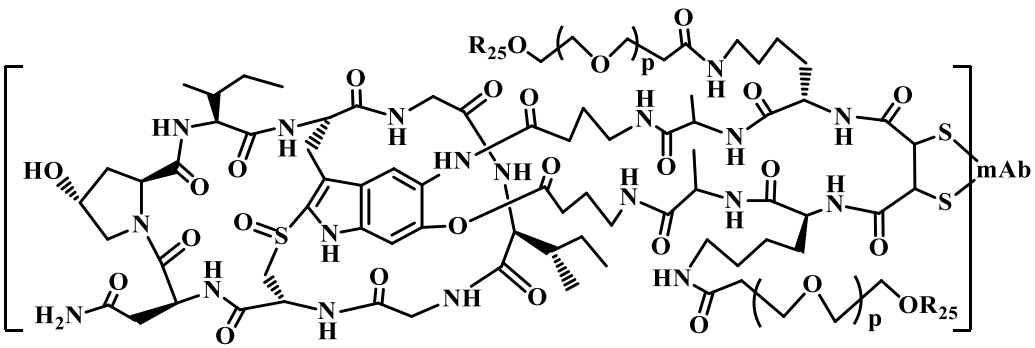
or one or more isotope of chemical elements, pharmaceutically acceptable salts, hydrates, or hydrated salts; or the polymorphic crystalline structures of these compounds; or the optical isomers, racemates, diastereomers or enantiomers; wherein X_8 is O, S, NH, NHNH, NHR_{12}, SR_{12}, SSR_{12}, $SSCH(CH_3)R_{12}$, $SSC(CH_3)_2R_{12}$, or $R_{12;}$ m_1 is 0-20; X_1, X_2, X_3, X_4, X_5, p_1, p_2, q_1,

q_2, m, n, R_{25}, $(Aa)_r$ and mAb are as defined in claim 1.

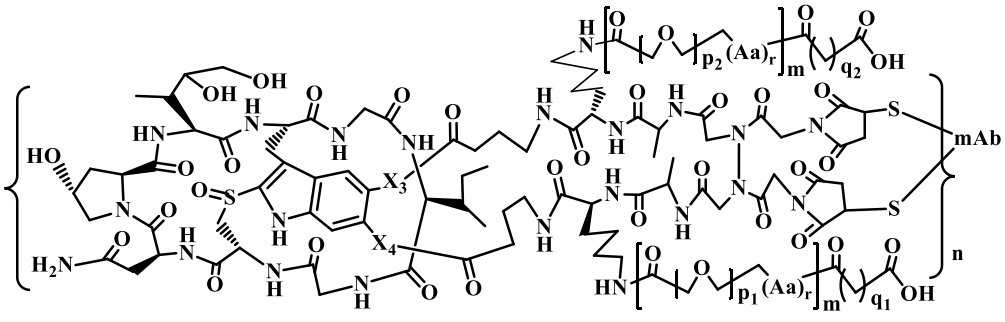
9. The conjugate compound of Formula (III) according to claim 2 having the following structures of b-01 to b-22, 216, 221, 240 below:



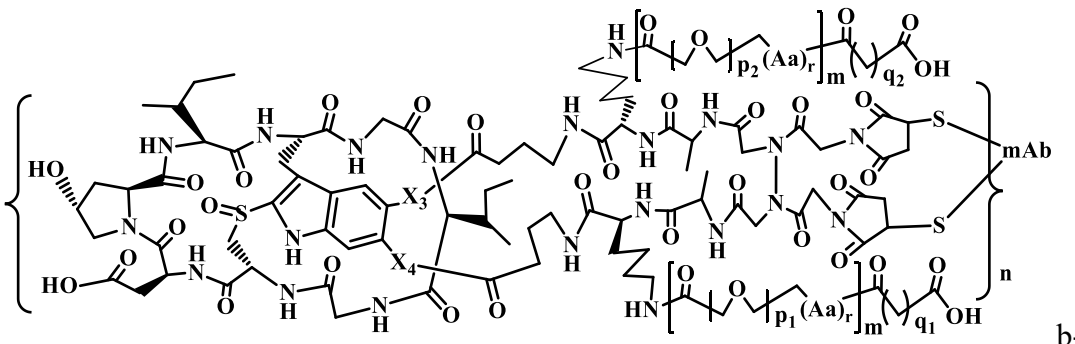
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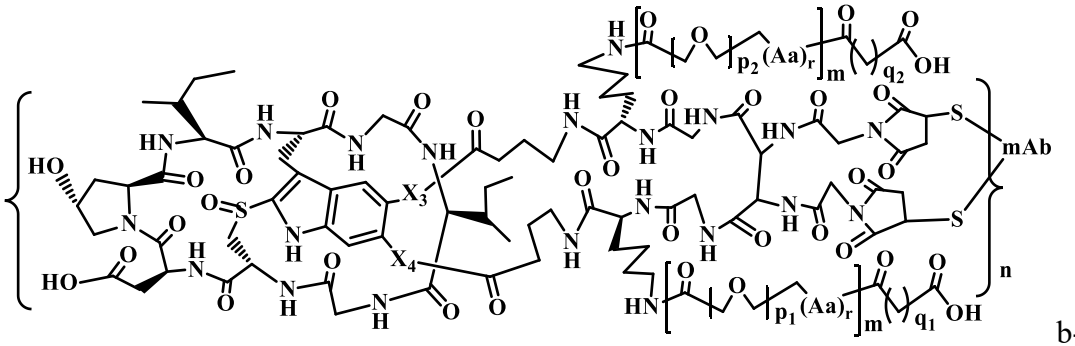
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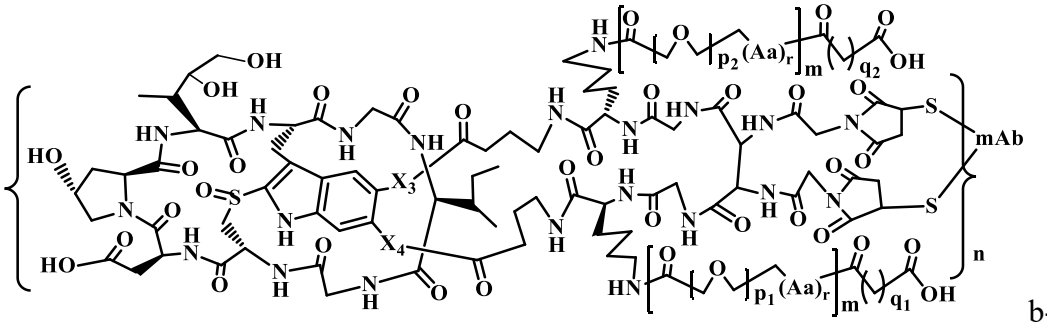
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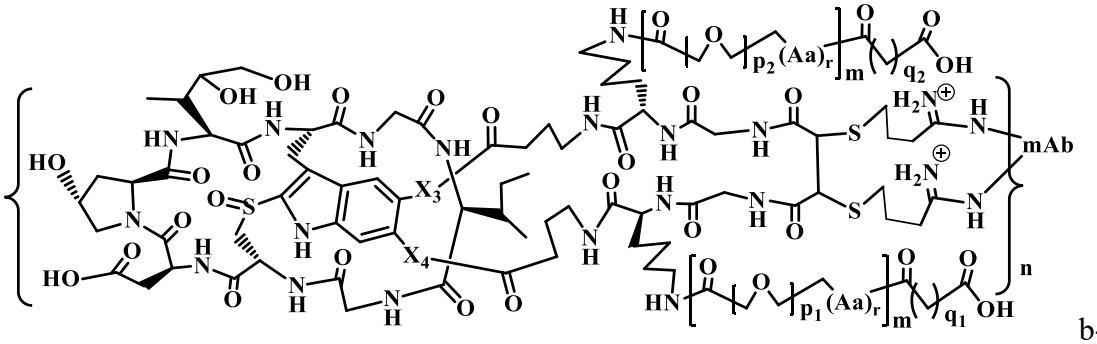
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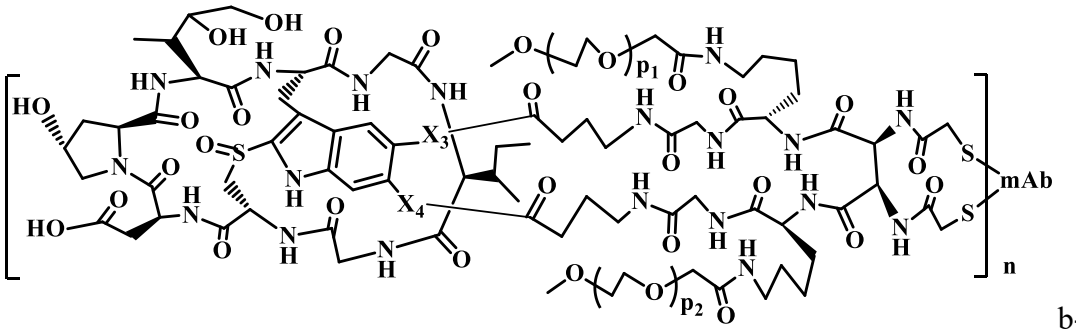
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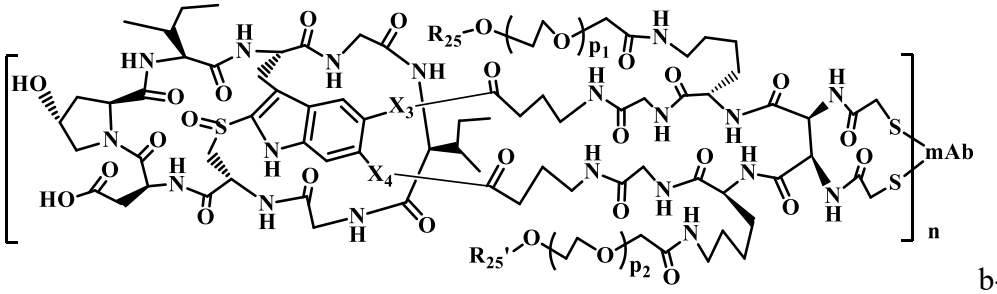
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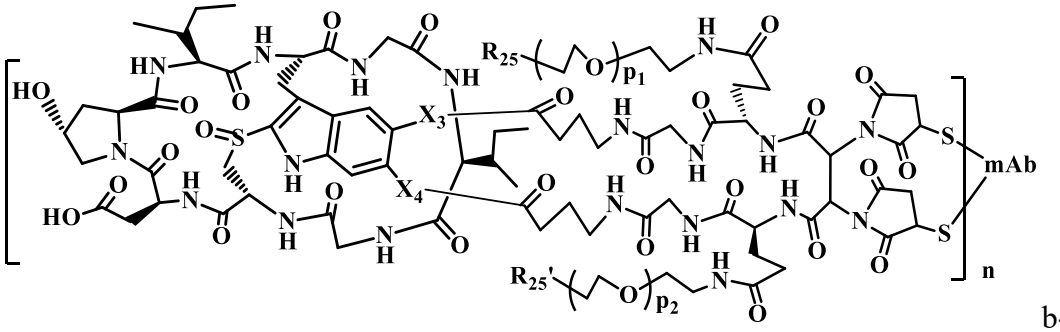
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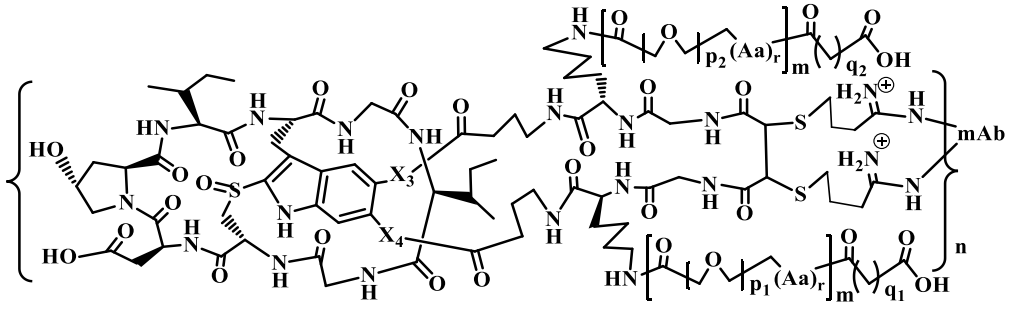
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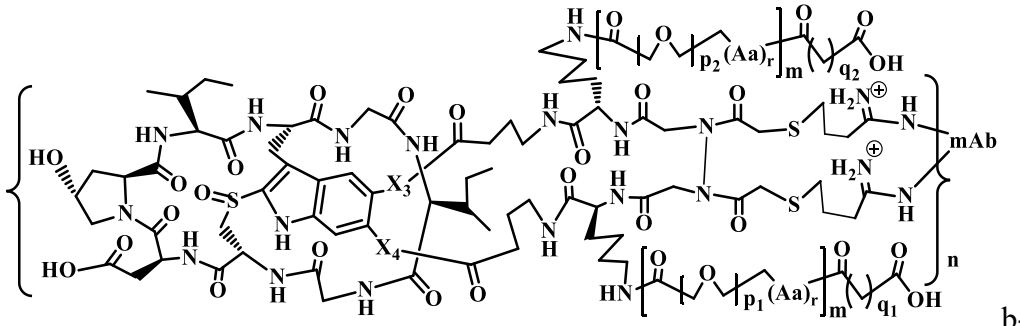
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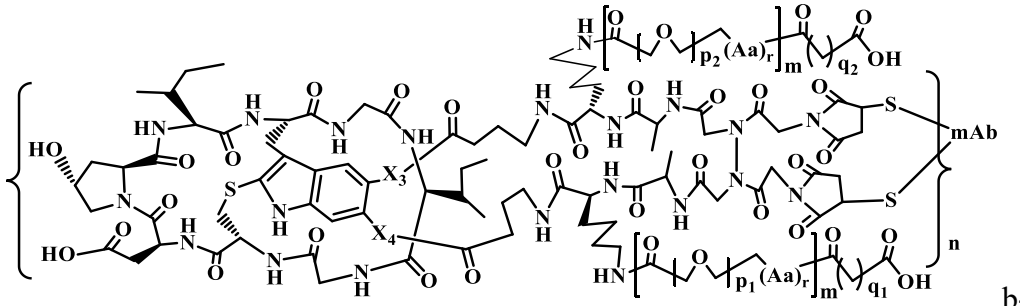
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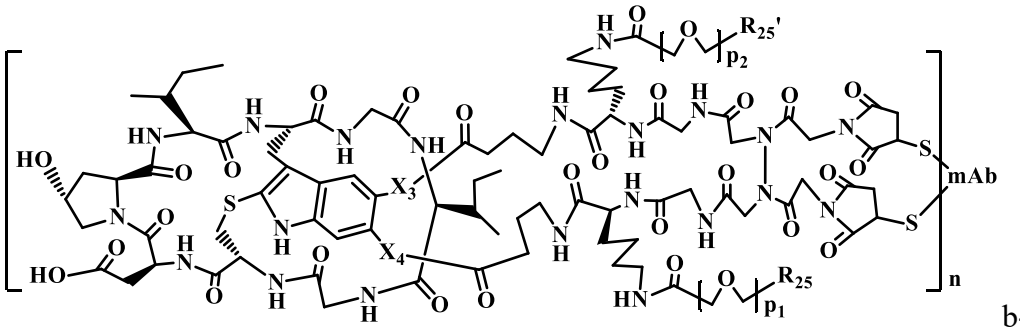
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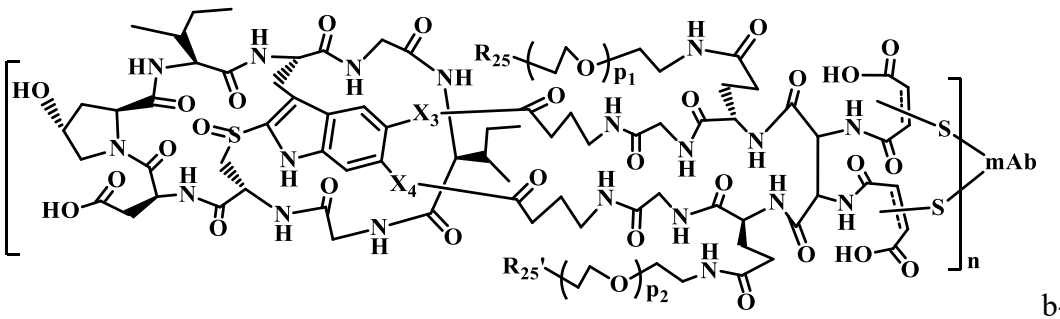
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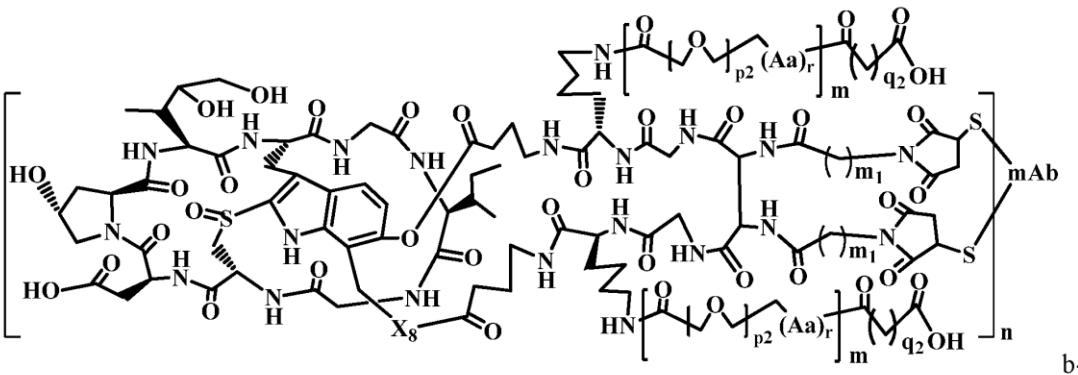
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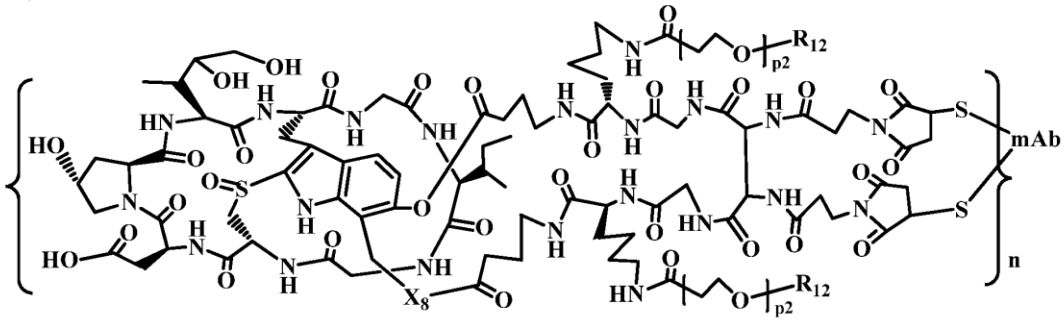
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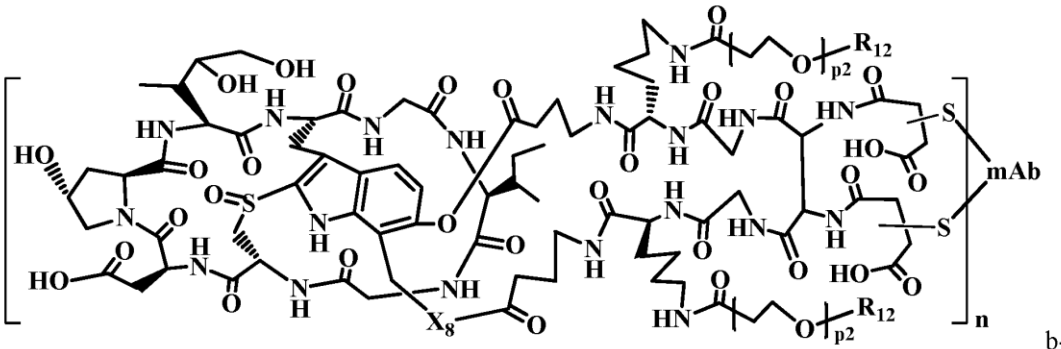
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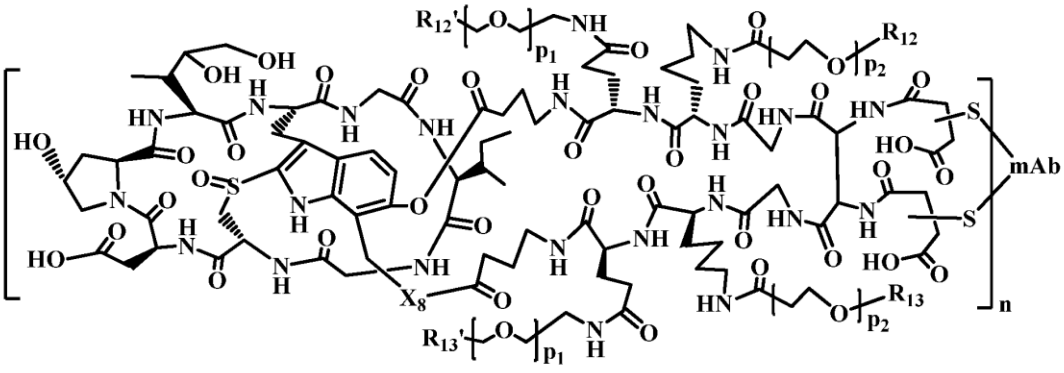
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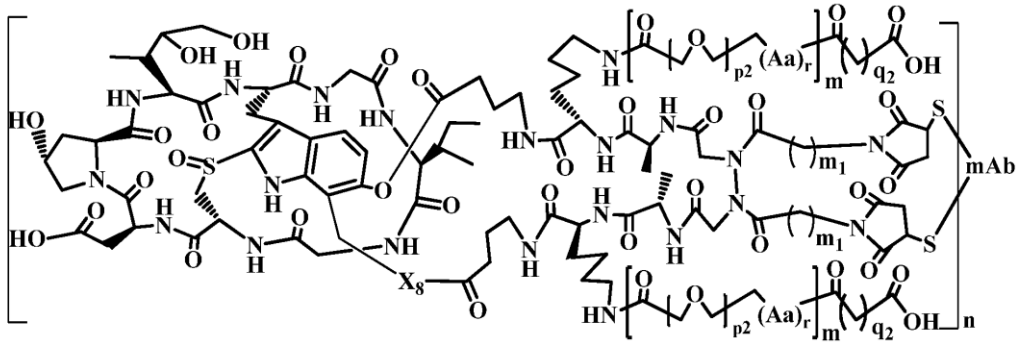
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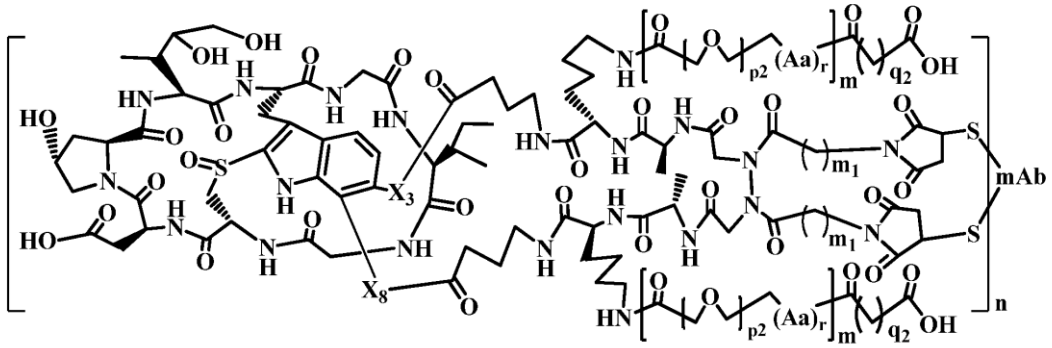
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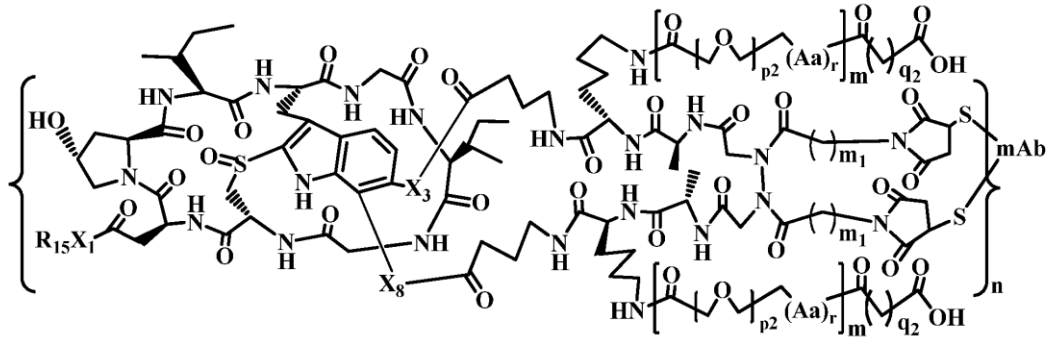
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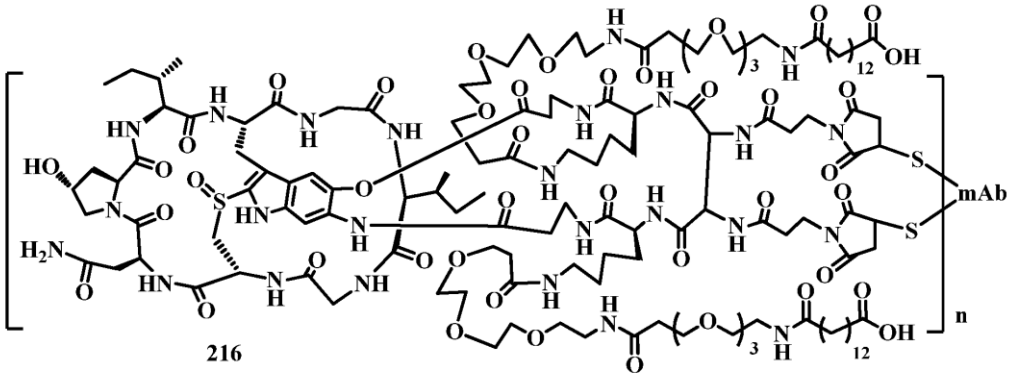
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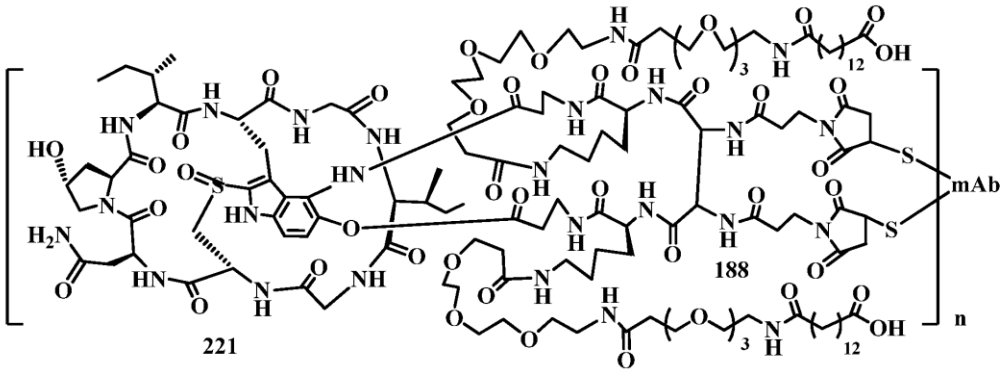
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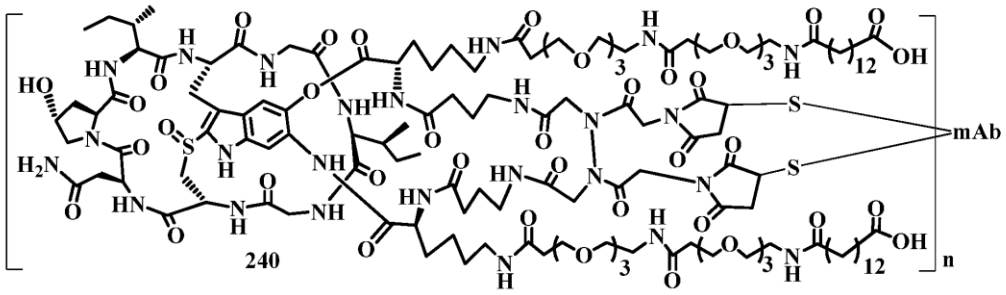


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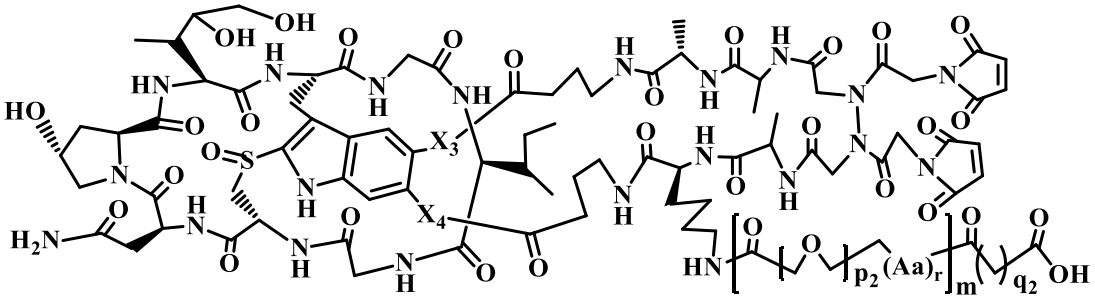
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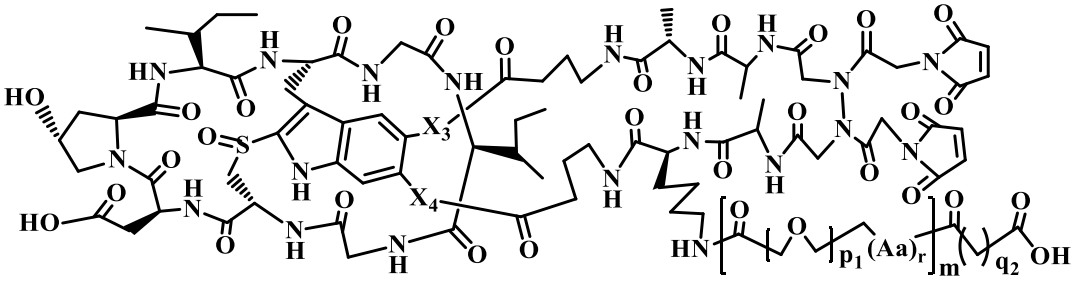


or one or more isotope of chemical elements, or their pharmaceutically acceptable salts, hydrates, or hydrated salts; or the polymorphic crystalline structures of these compounds; or their optical isomers, racemates, diastereomers or enantiomers; wherein X_8 is O, S, NH, NHNH, NHR_{12}, SR_{12}, SSR_{12}, $SSCH(CH_3)R_{12}$, $SSC(CH_3)_2R_{12}$, or R_{12}; X_1, X_2, X_3, X_4, X_5, R_{12}, $R_{12'}$, R_{13}, R_{13}', R_{25}, R_{25}', p_1, p_2, q_1, q_2, m, m_1, n, $(Aa)_r$ and mAb are as defined in claim 1.

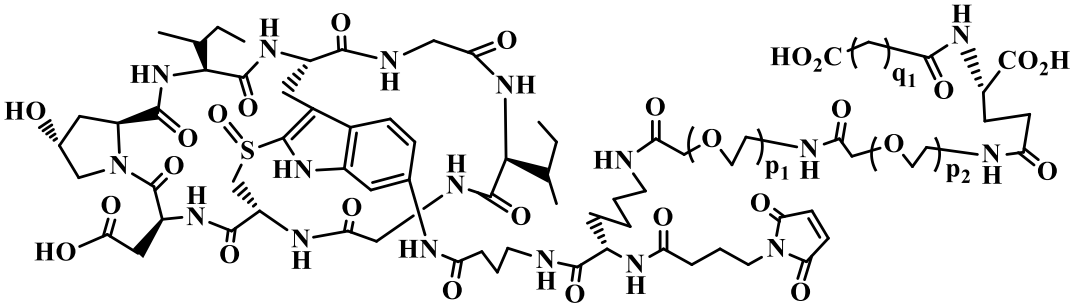
10. The compound of Formula (IV) according to claim 3 having the following structures c-01 to c-40, 71, 76, 77, 90, 94, 96, 113, 116, 126, 131, 145, 153, 166, 178, 180, 195, 196, 205, 246, 249, 257, 259, 261 below:



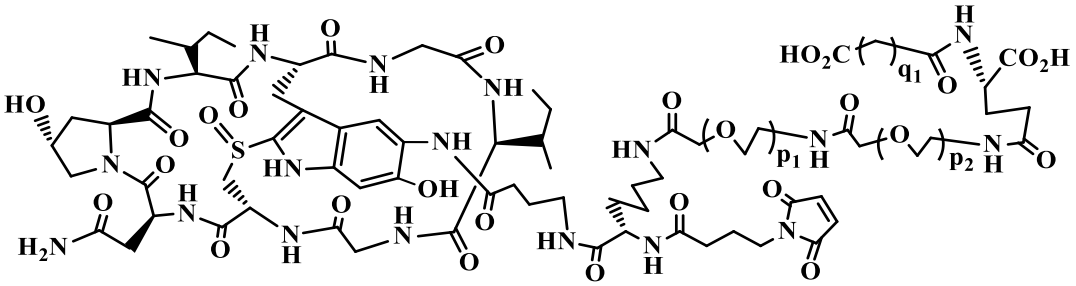
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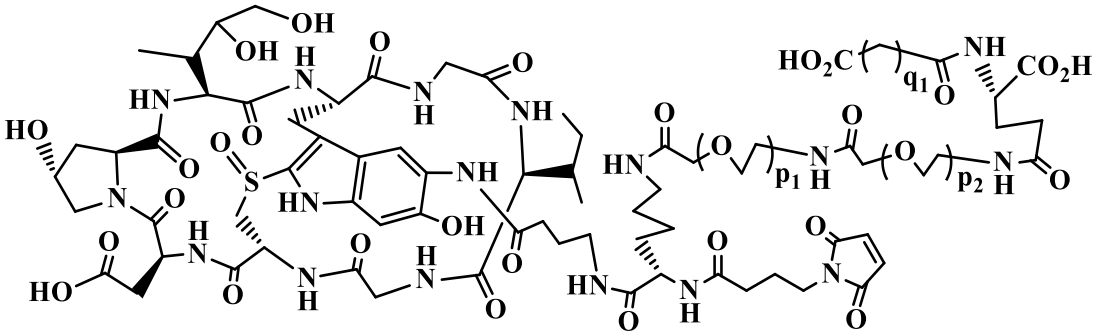
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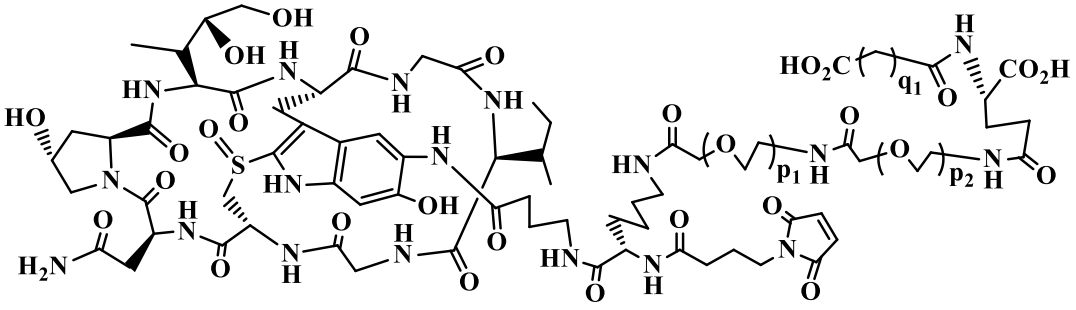
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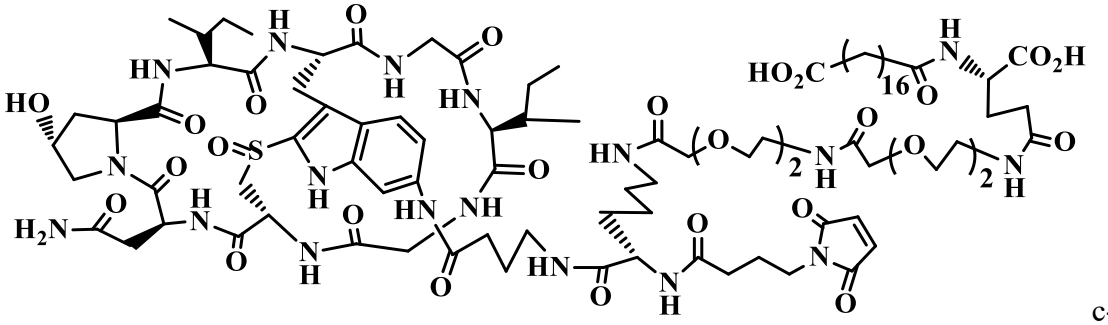
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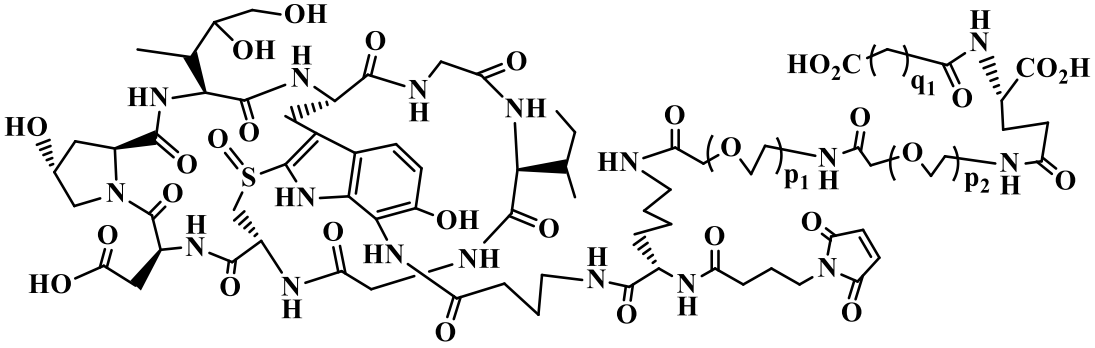
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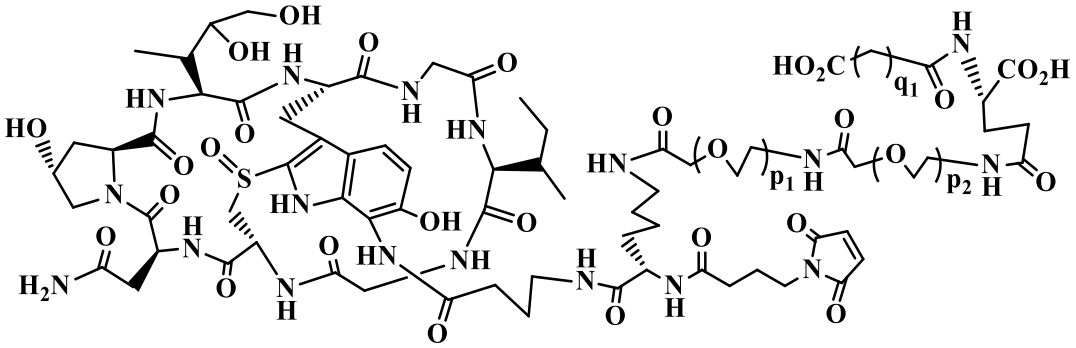
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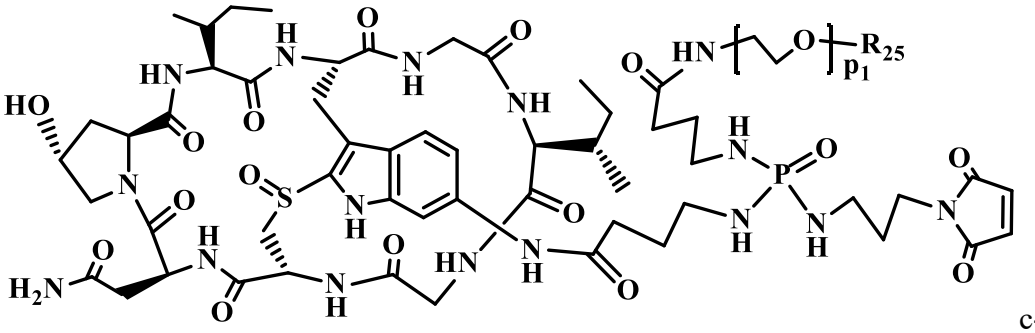
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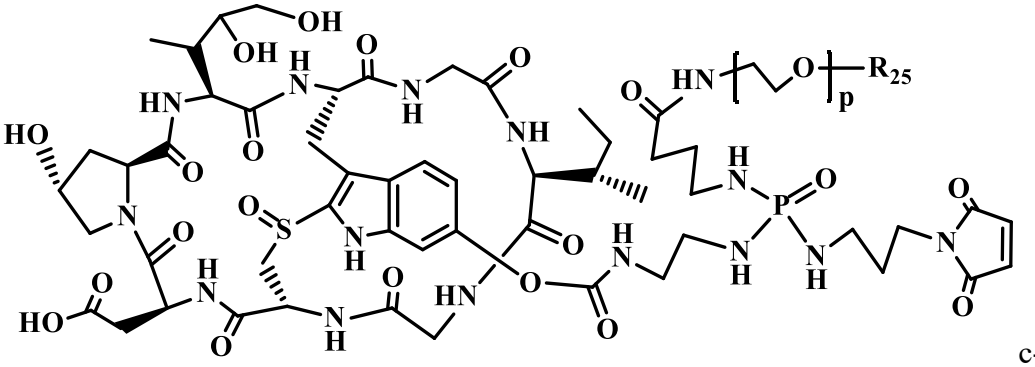
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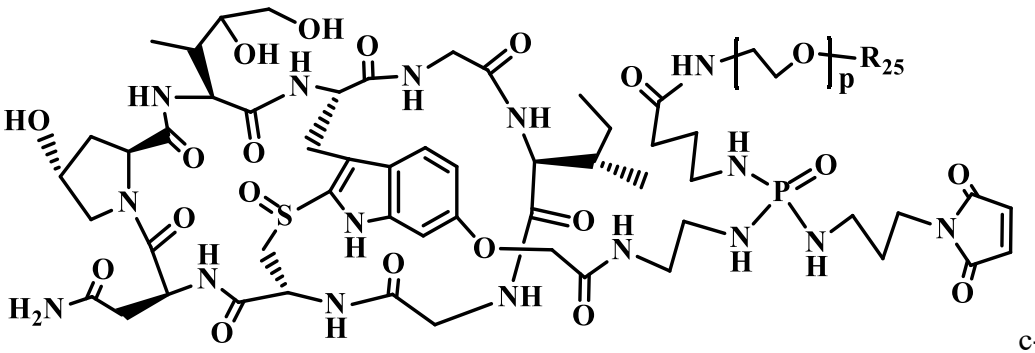
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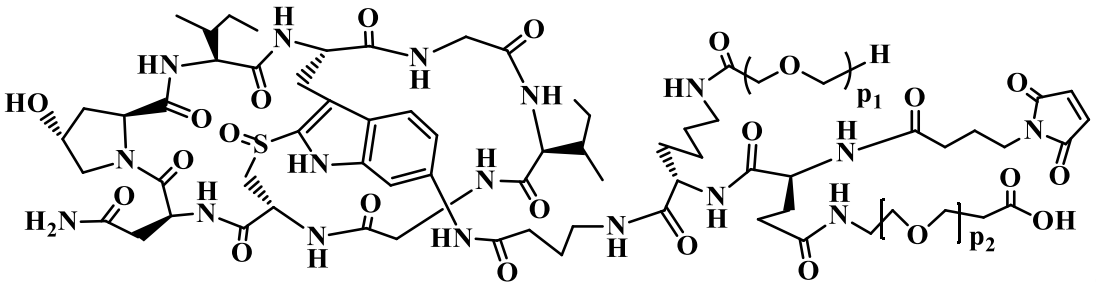
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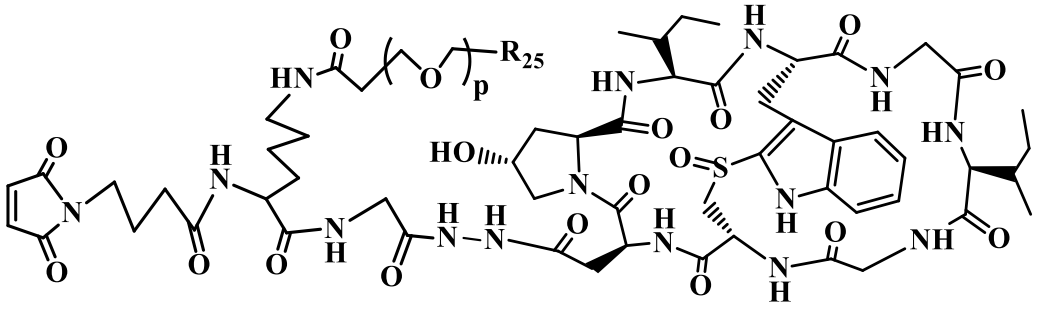
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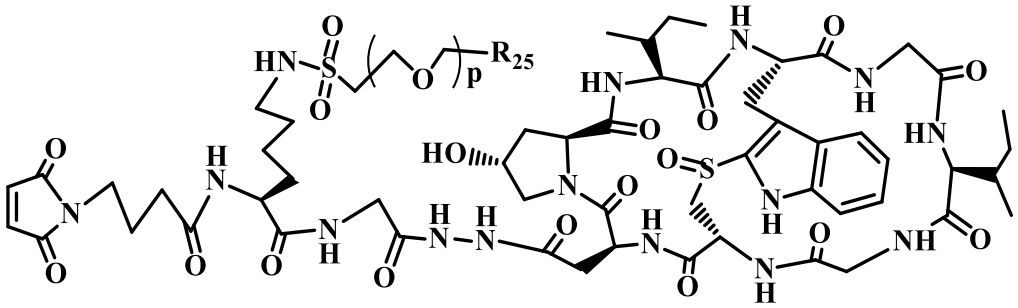
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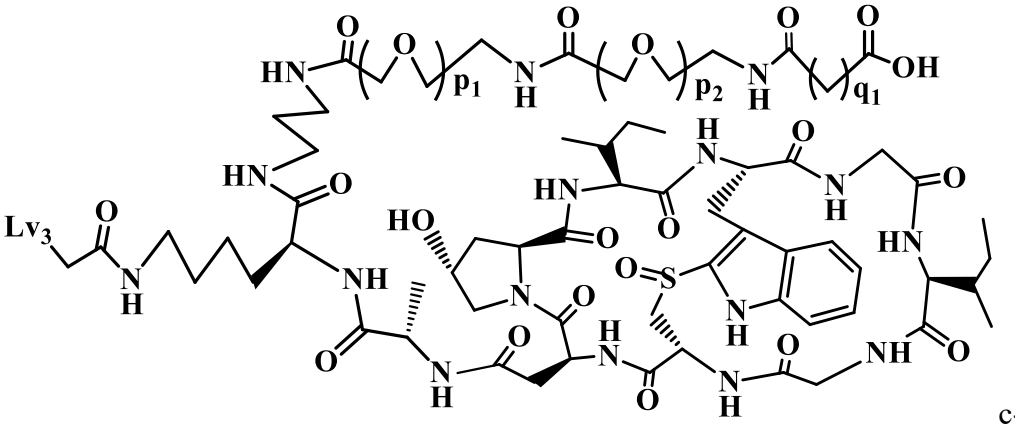
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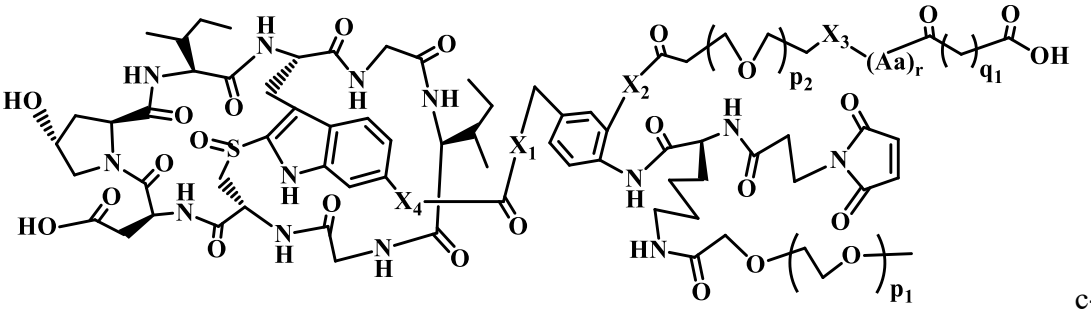
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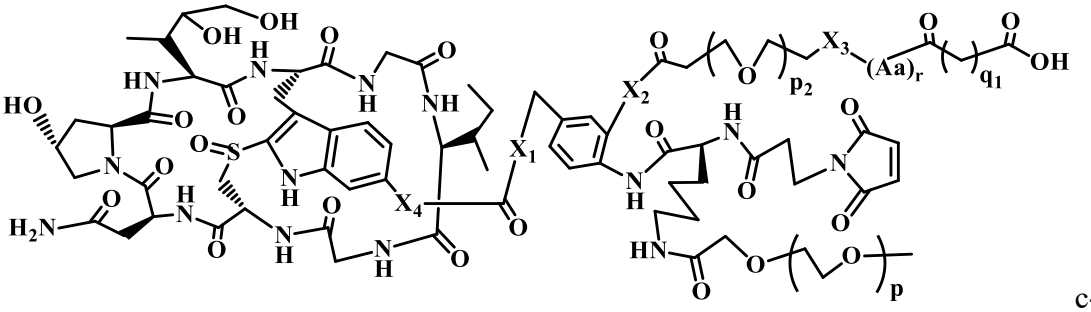
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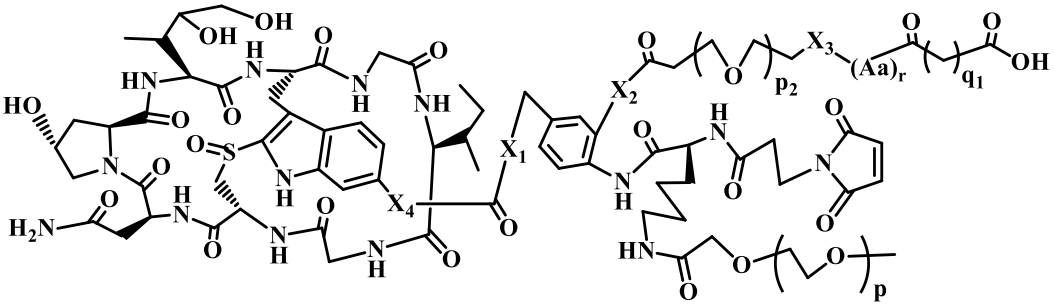
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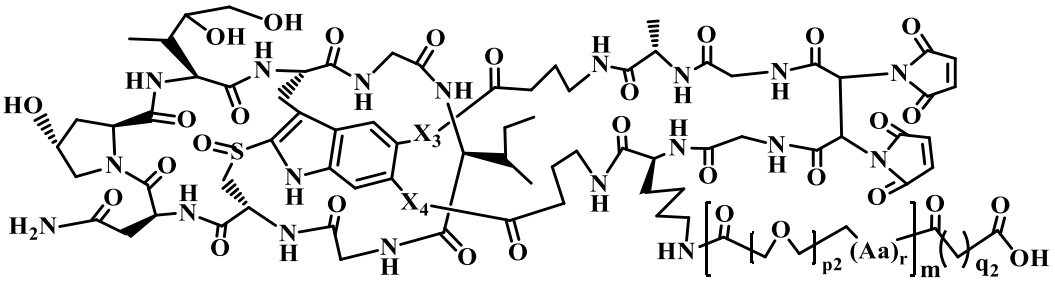
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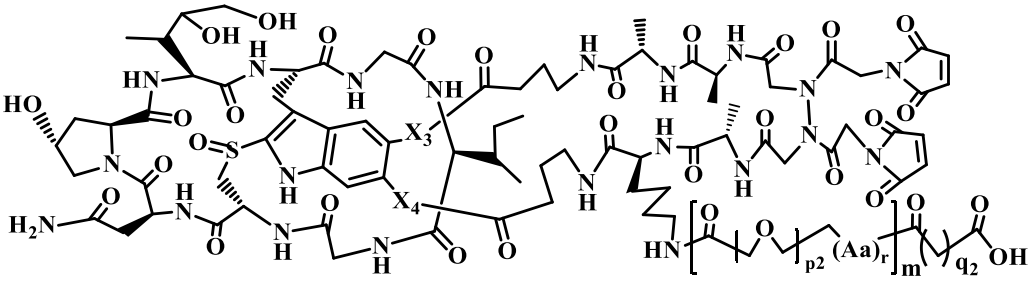
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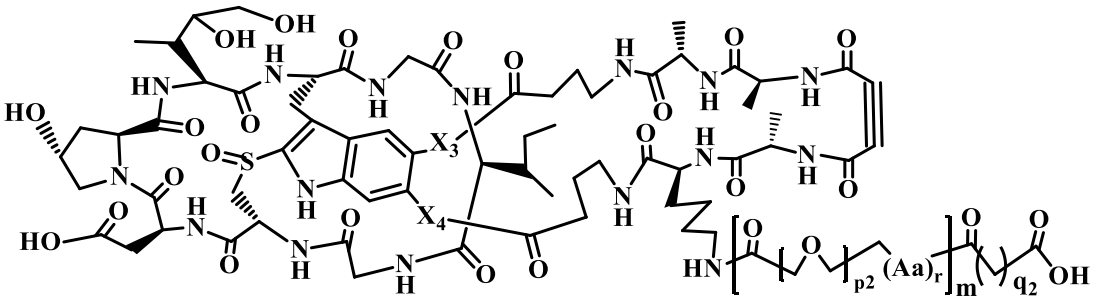
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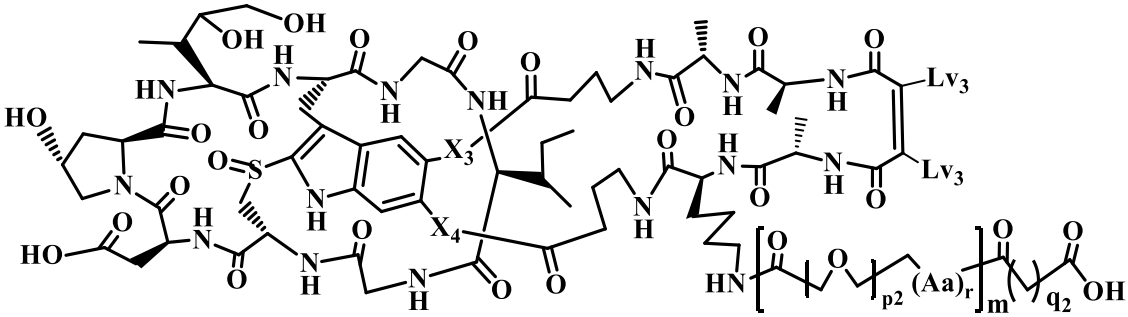
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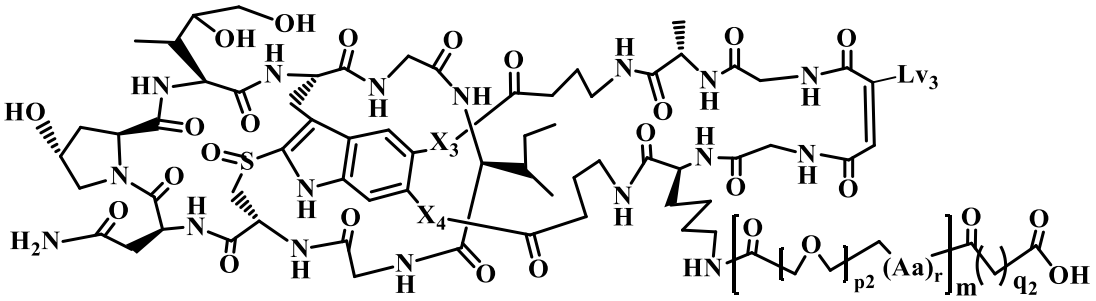
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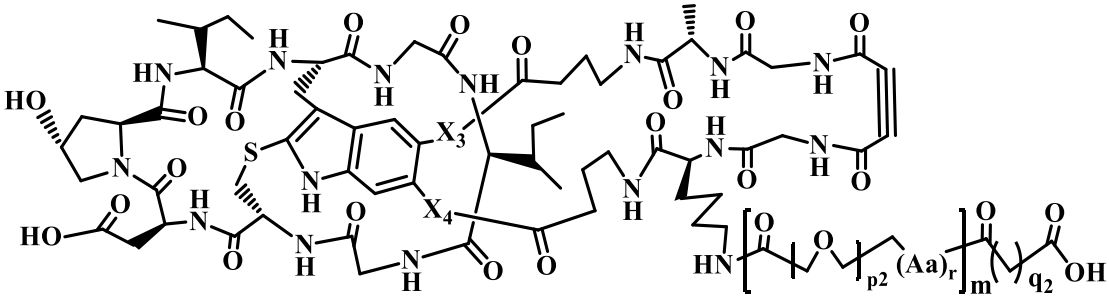
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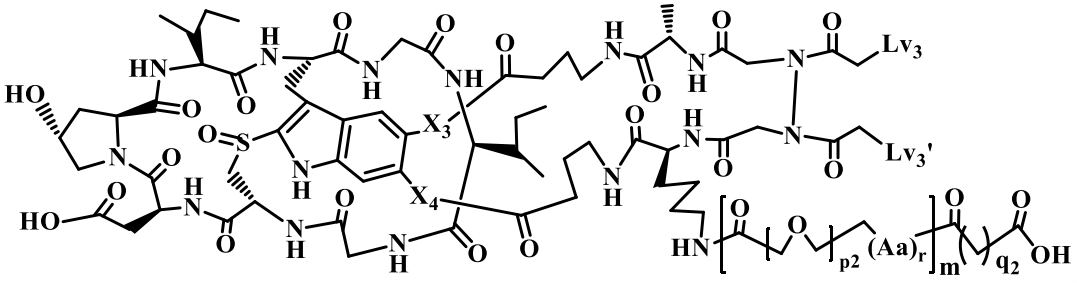
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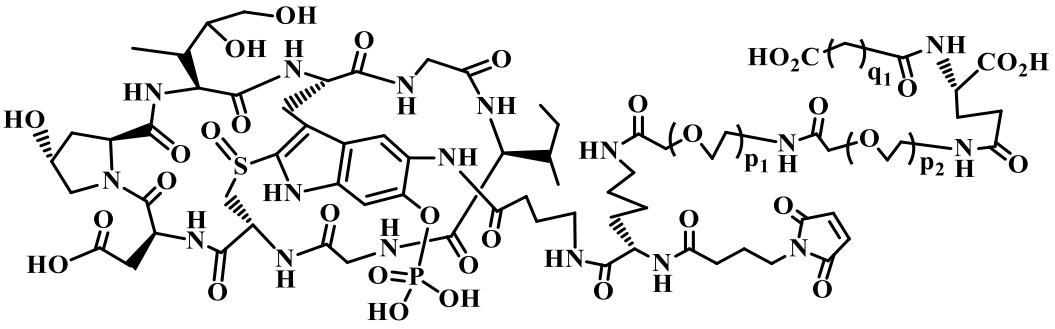
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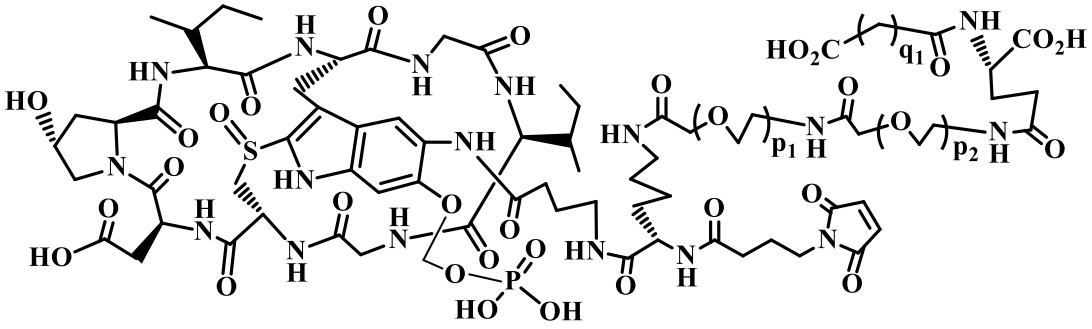
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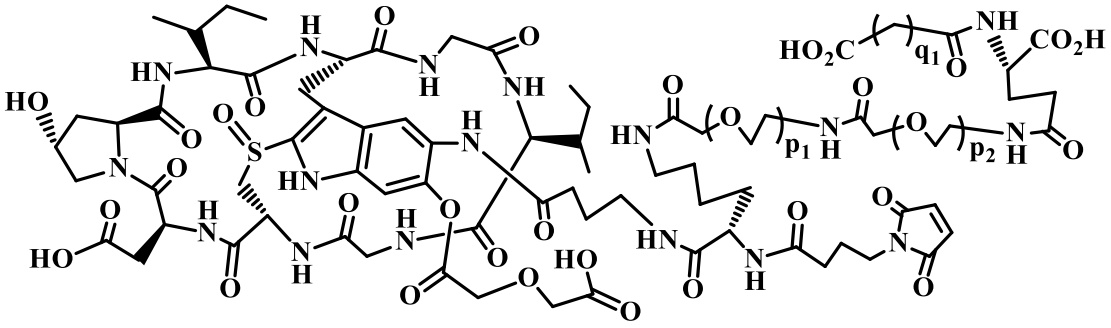
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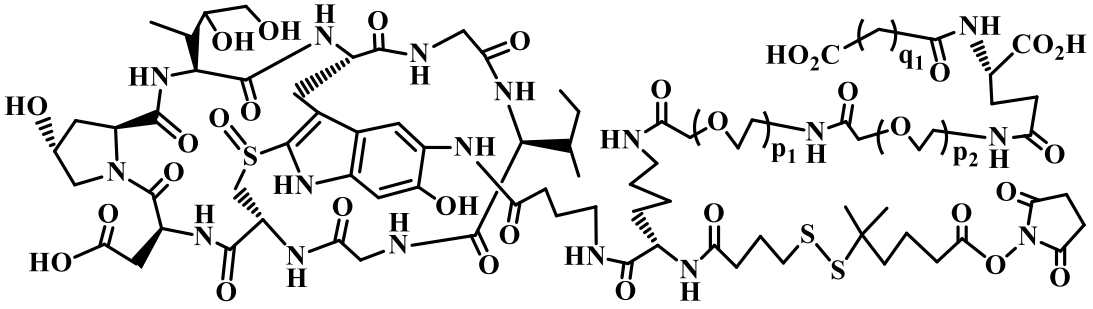
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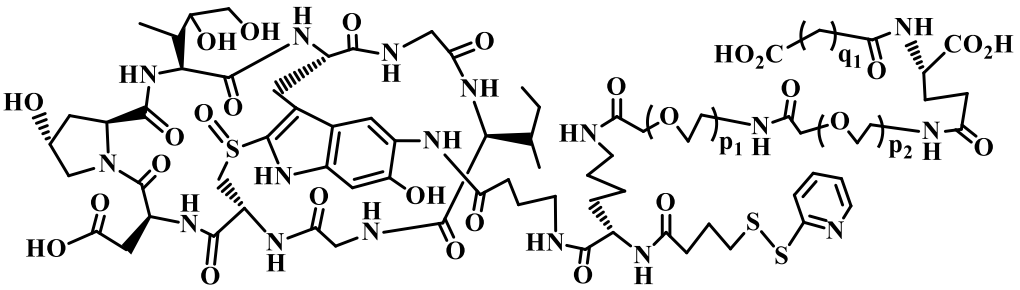
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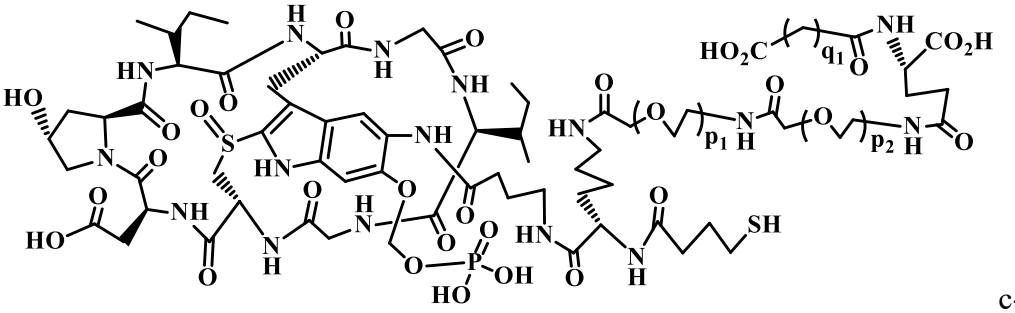
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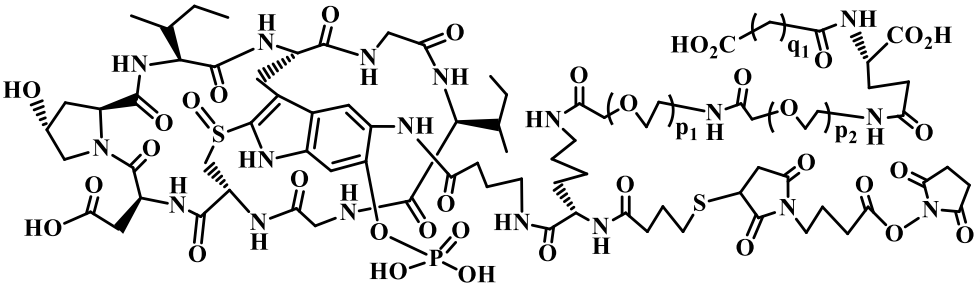
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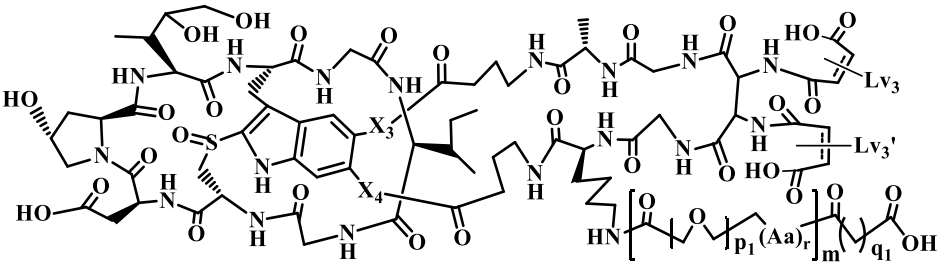
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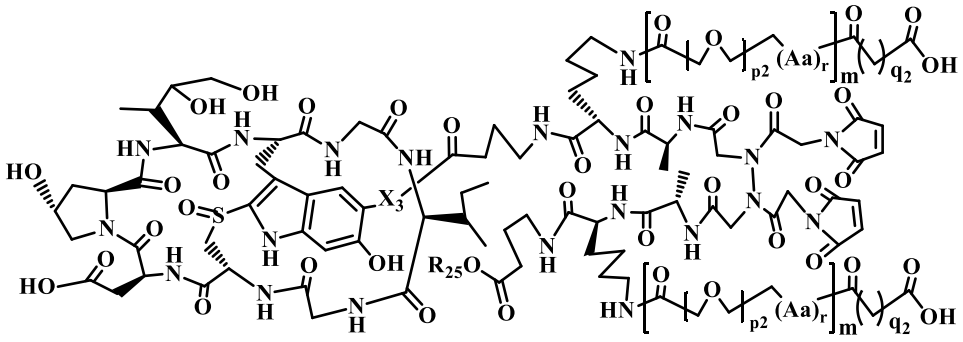
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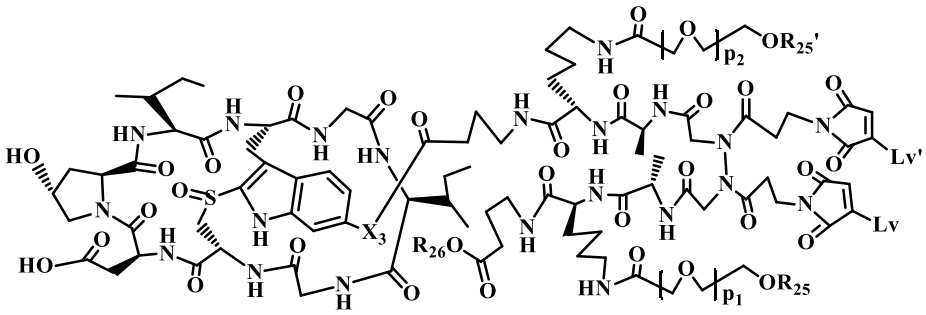
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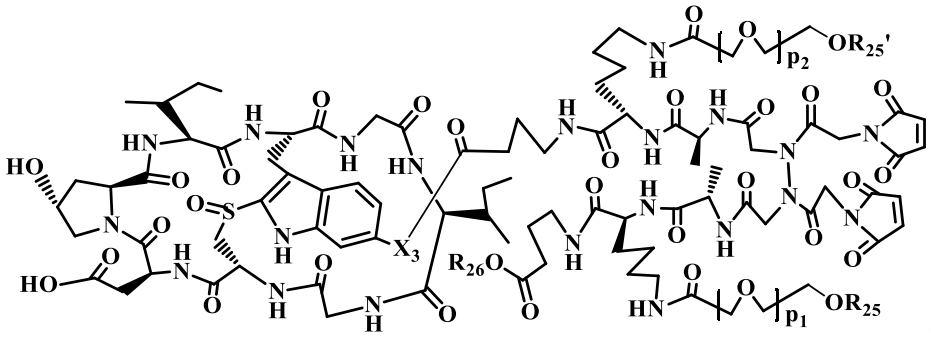
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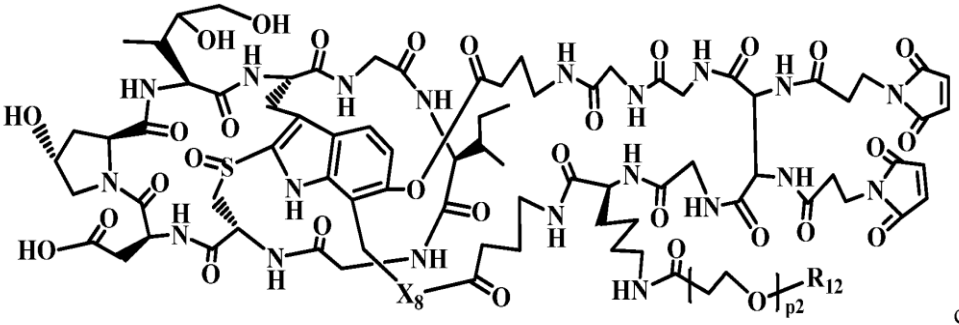
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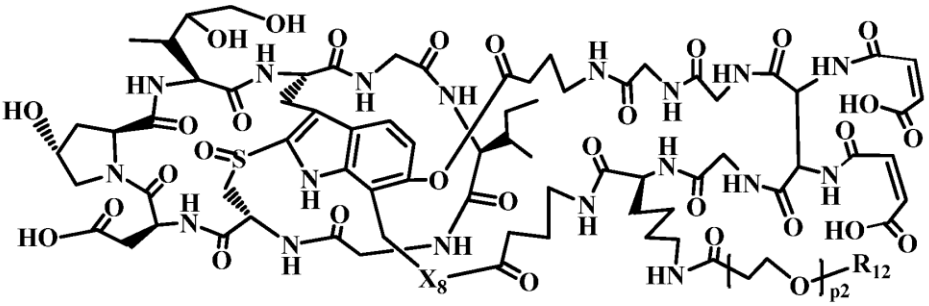
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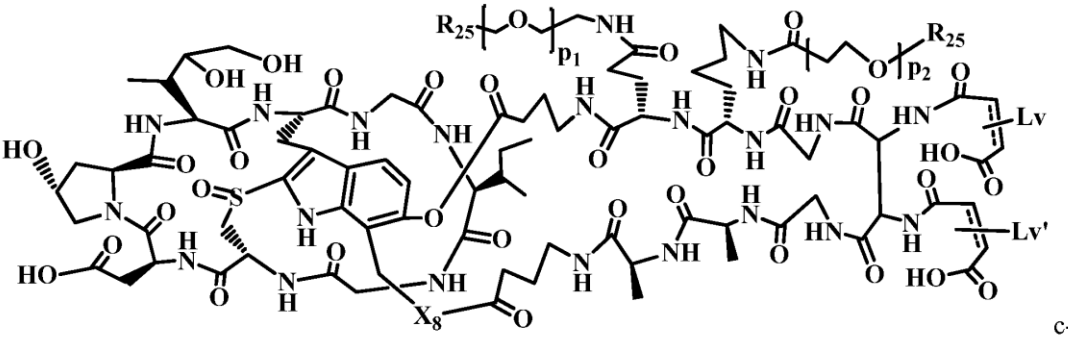
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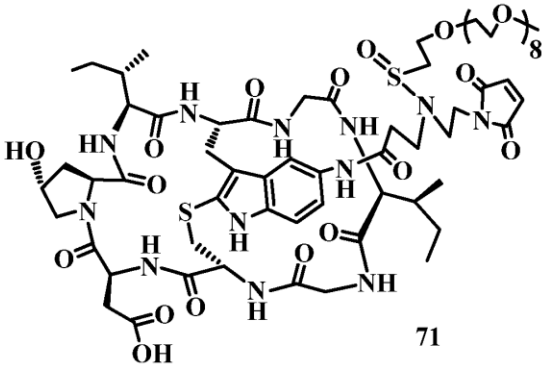
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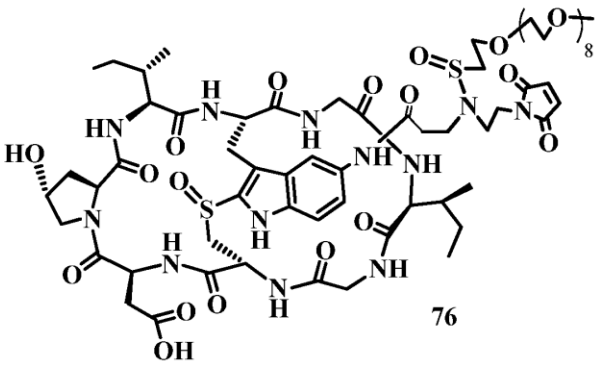
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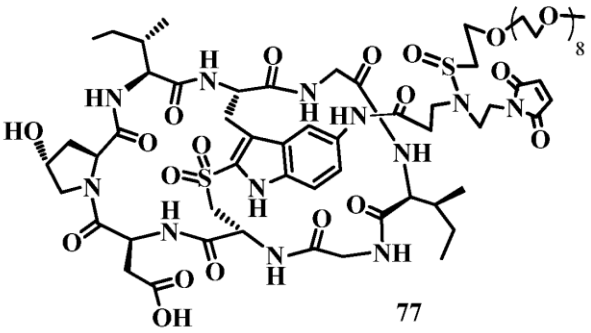
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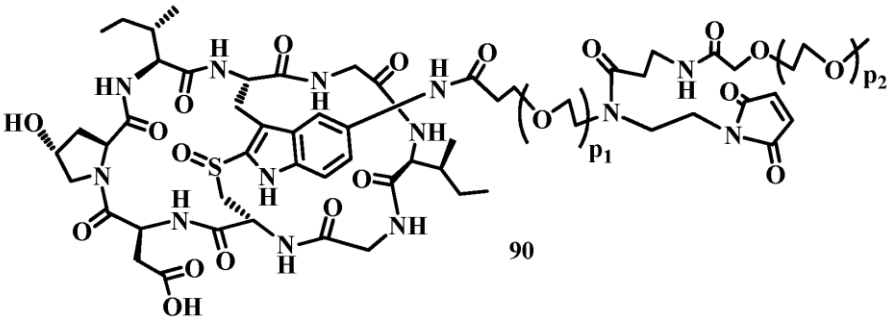
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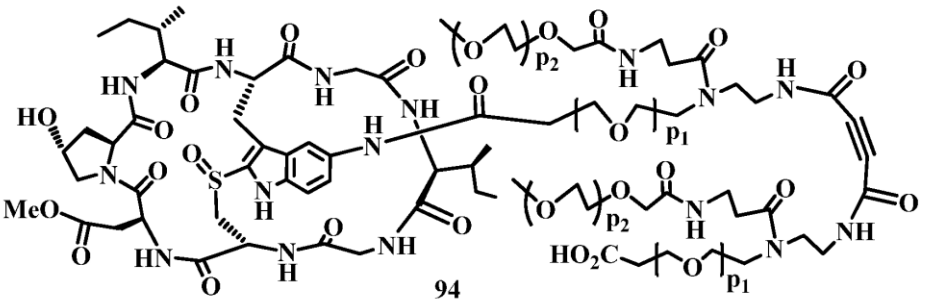
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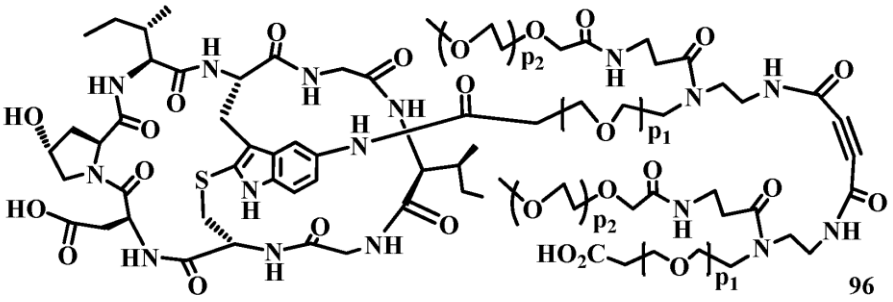
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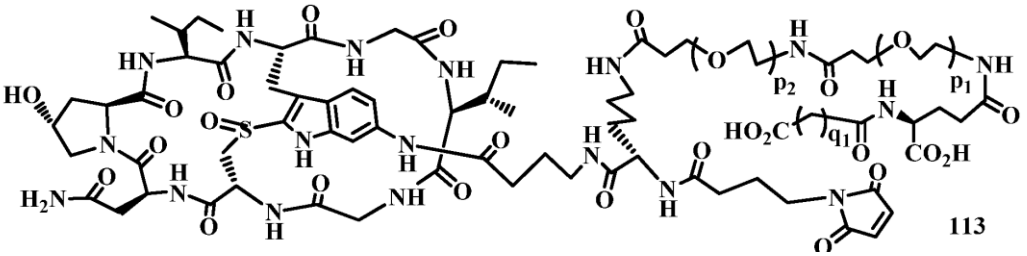
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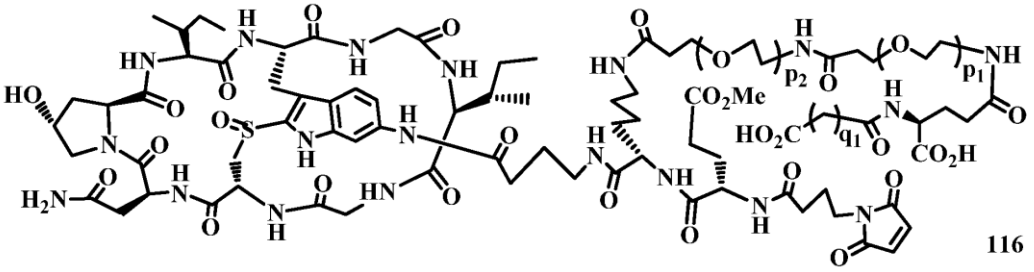
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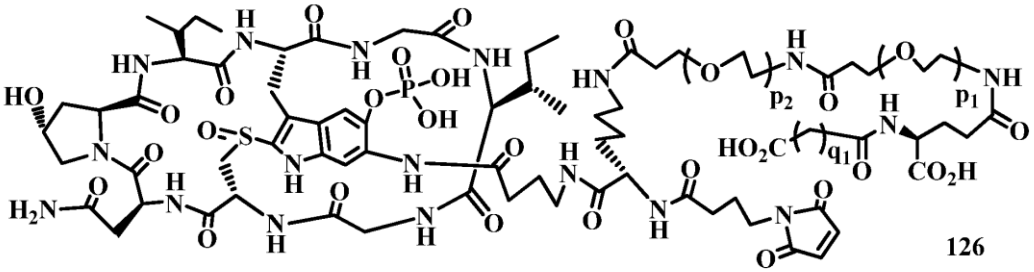
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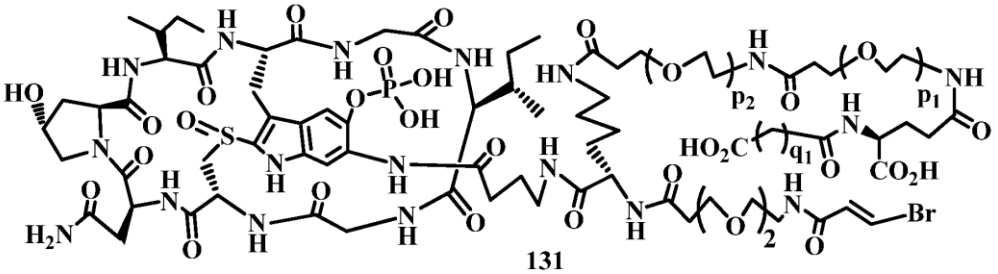
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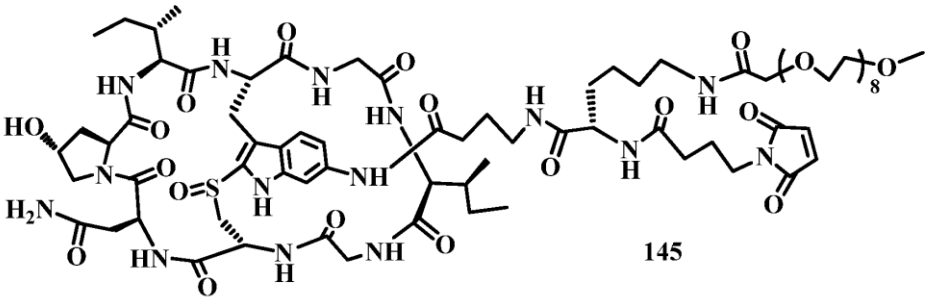
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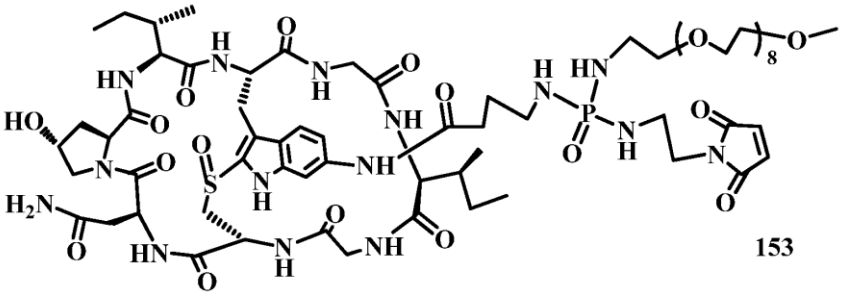
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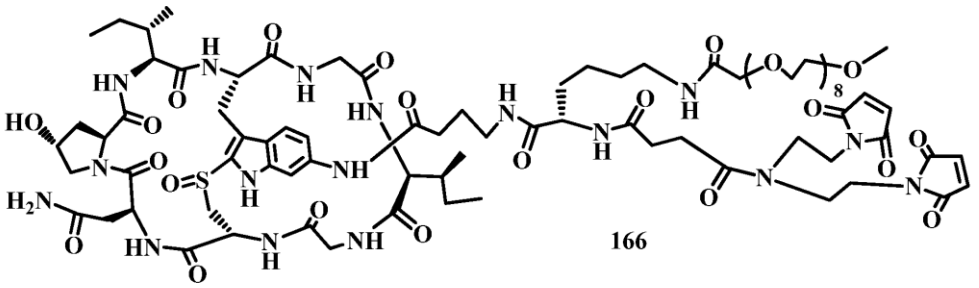
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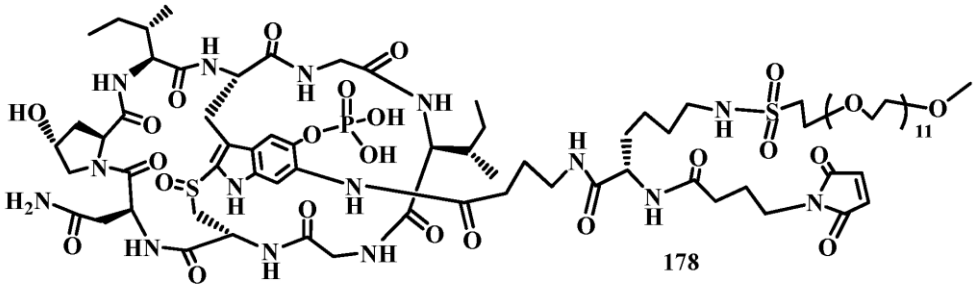
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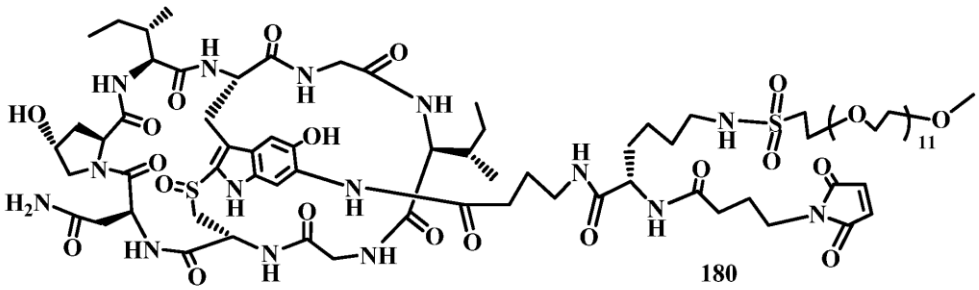
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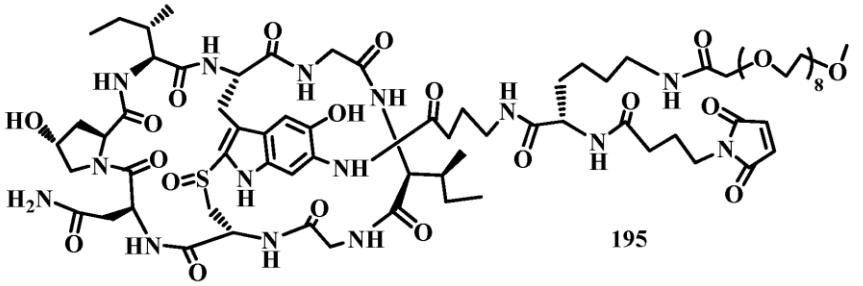
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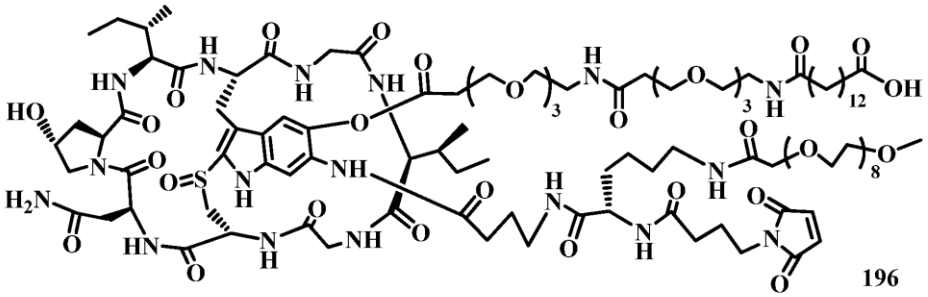
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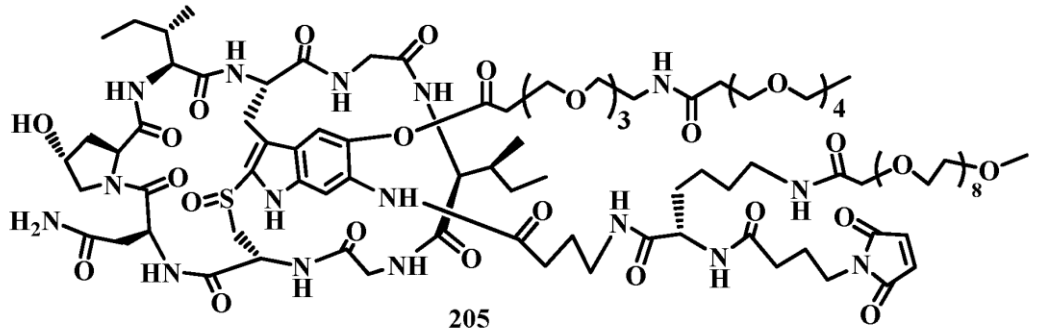
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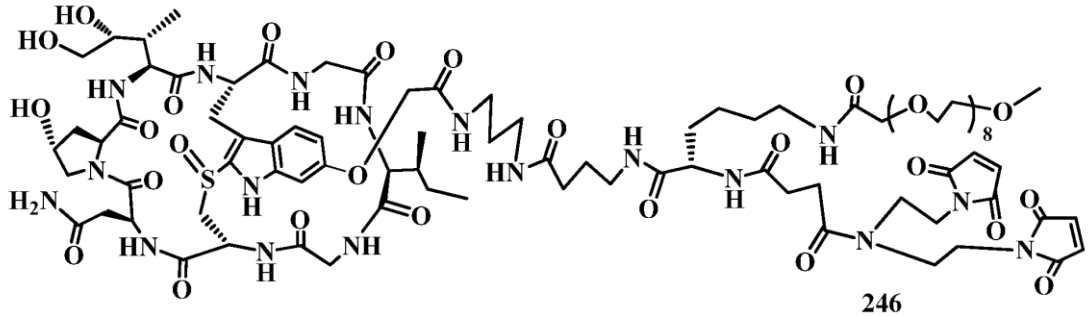
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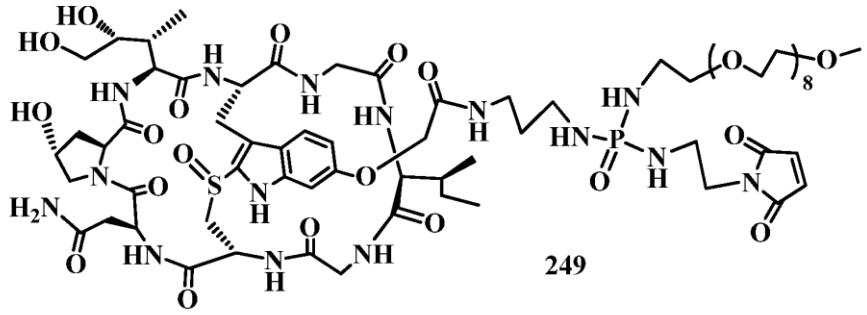
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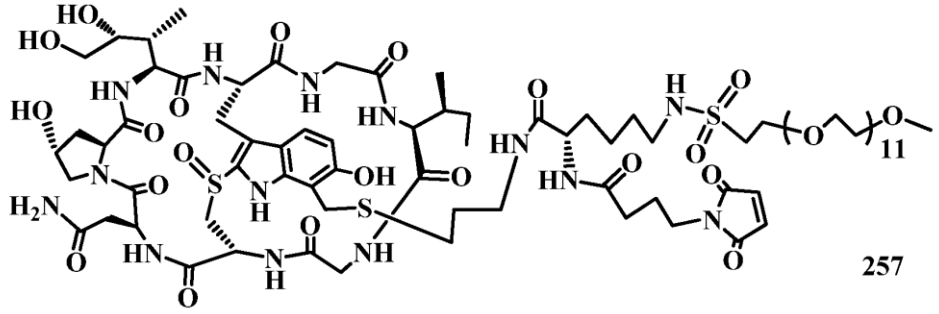
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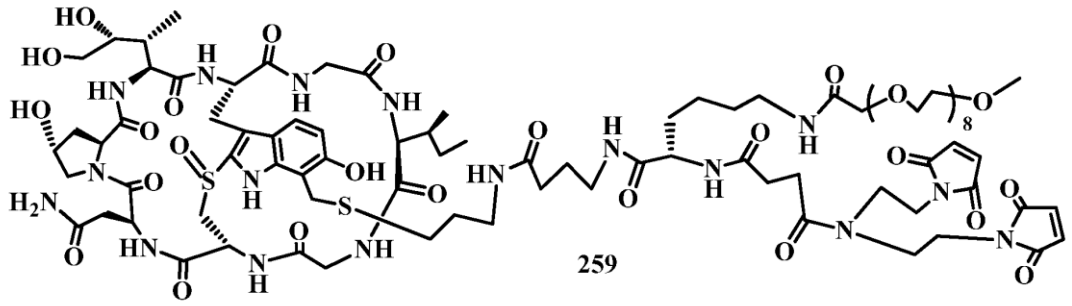
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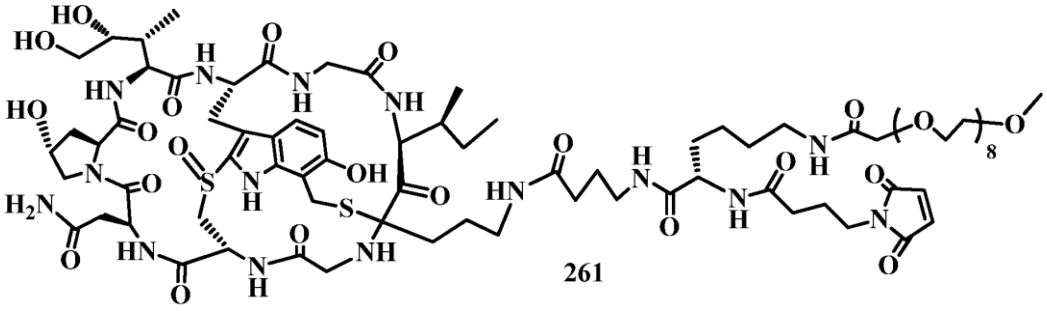
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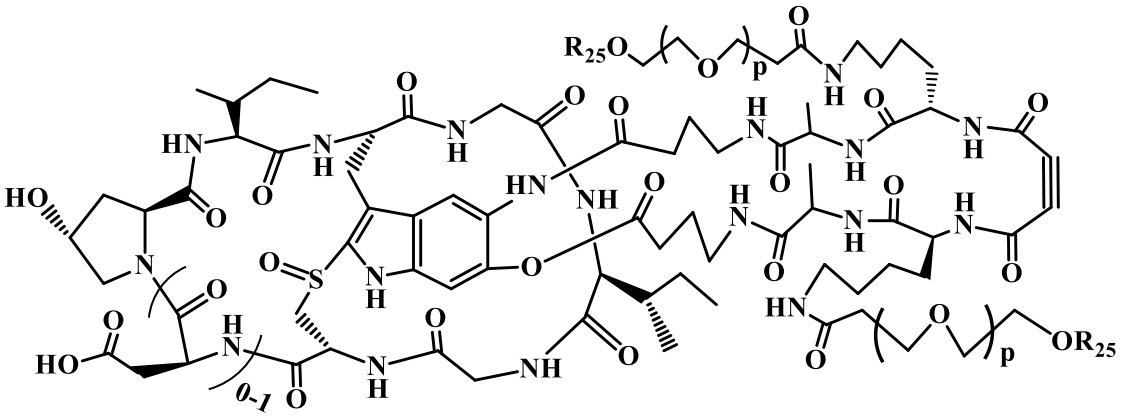
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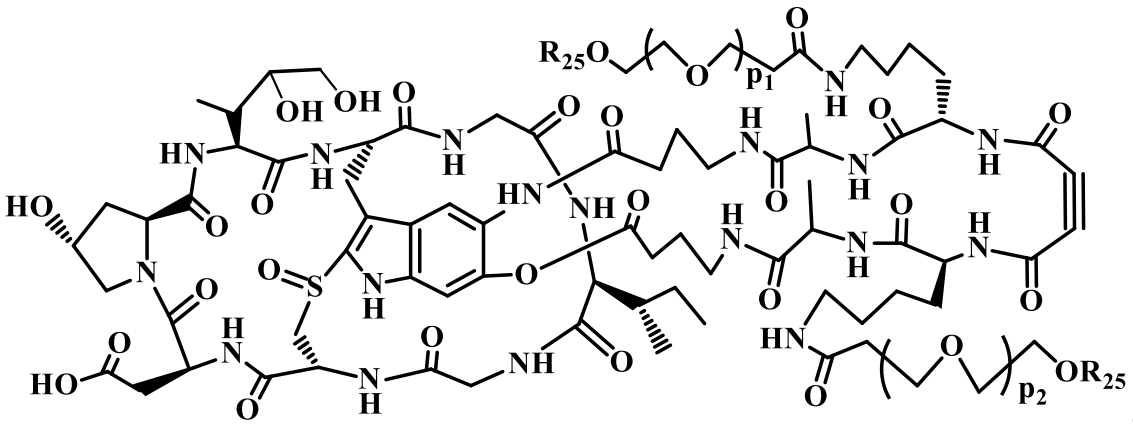
261

Or one or more isotope of chemical elements, pharmaceutically acceptable salts, hydrates, or hydrated salts; or the polymorphic crystalline structures of these compounds; or the optical isomers, racemates, diastereomers or enantiomers; wherein X_1, X_2, X_3, X_4, X_5, X_8, Z_2, Z_3, p, p_1, p_2, p_3, q_1, q_2, Lv_3, m, n, R_{12}, $R_{12'}$, R_{25}, $R_{25'}$, $(Aa)_r$ and mAb are as defined in claim 1.

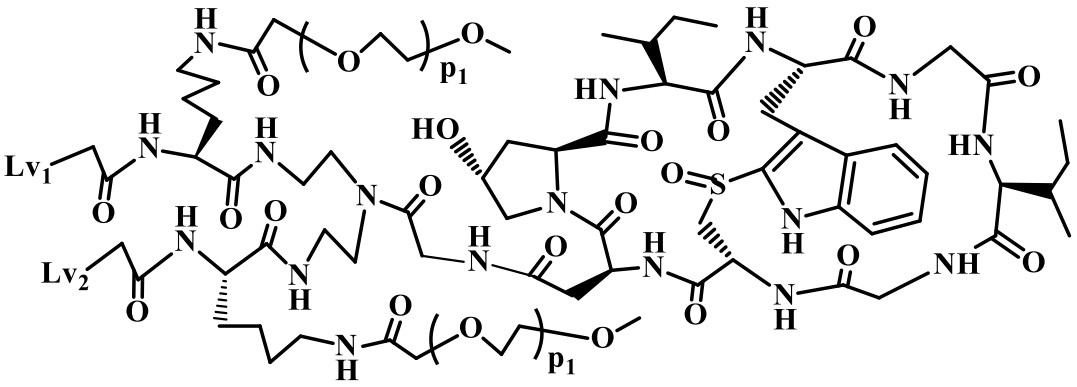
11. The compound of Formula (V) according to claim 4 having the following structures of d-01 to d-25, 215, 220, 239 below:



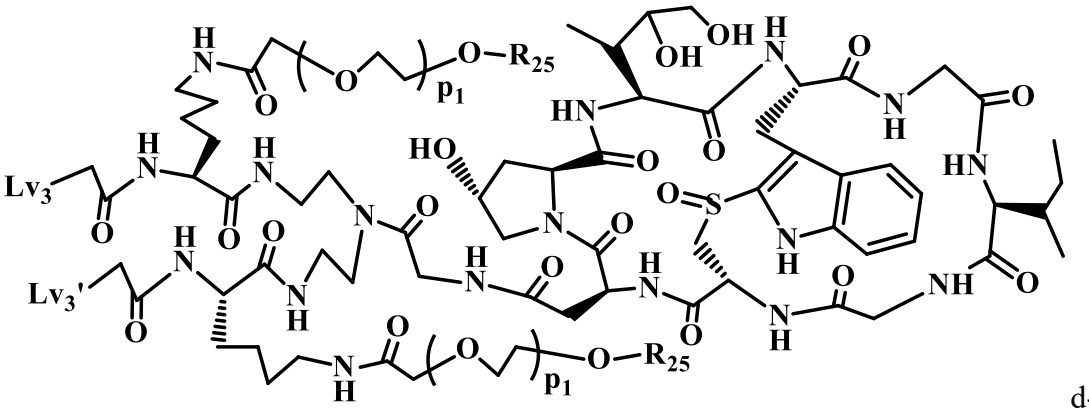
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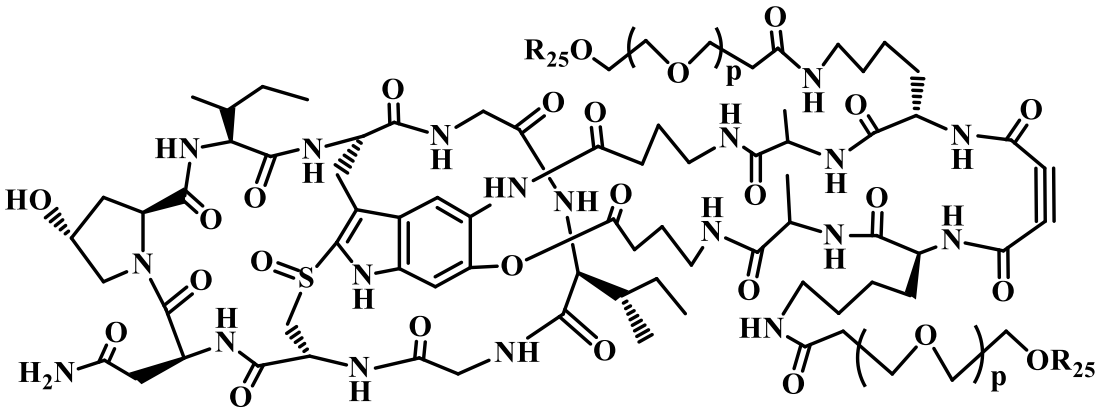
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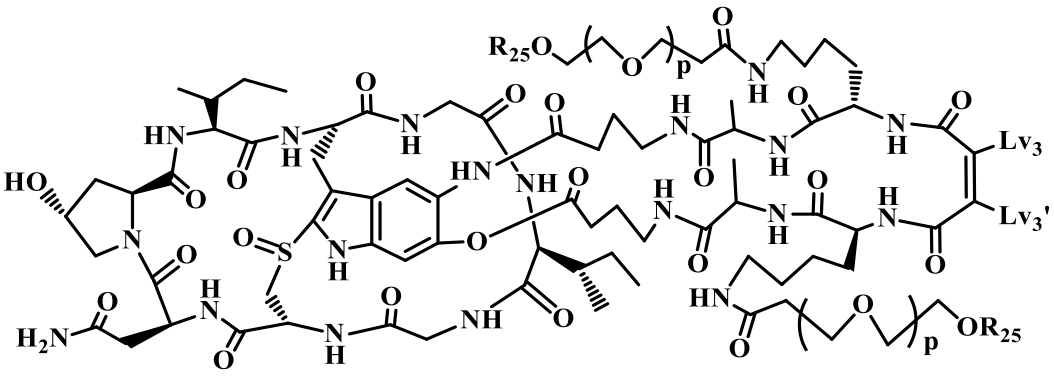
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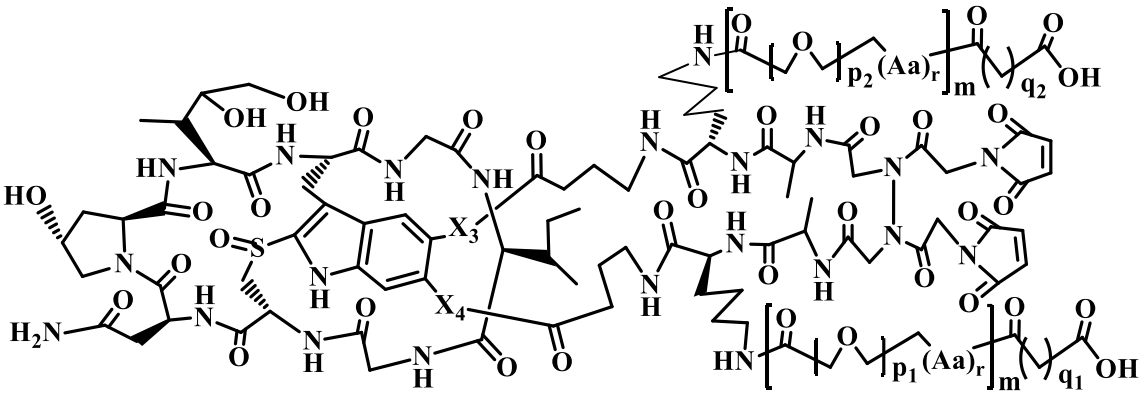
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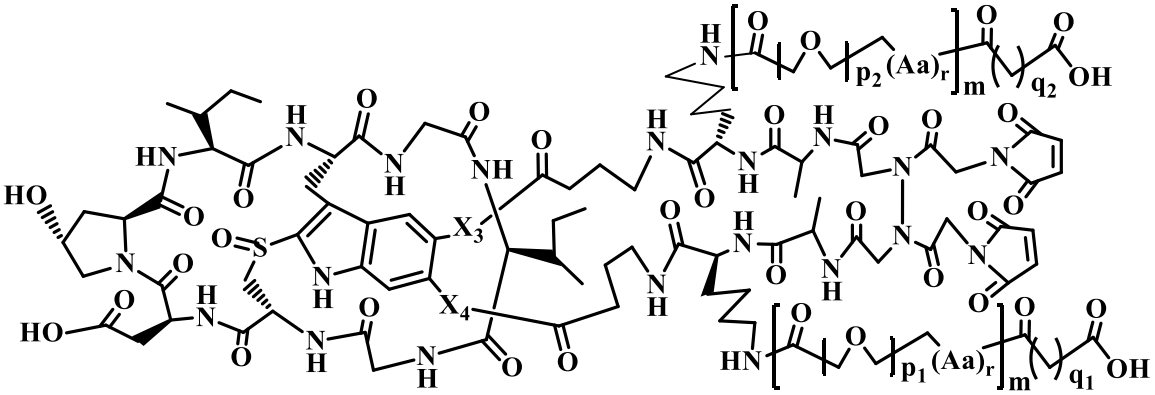
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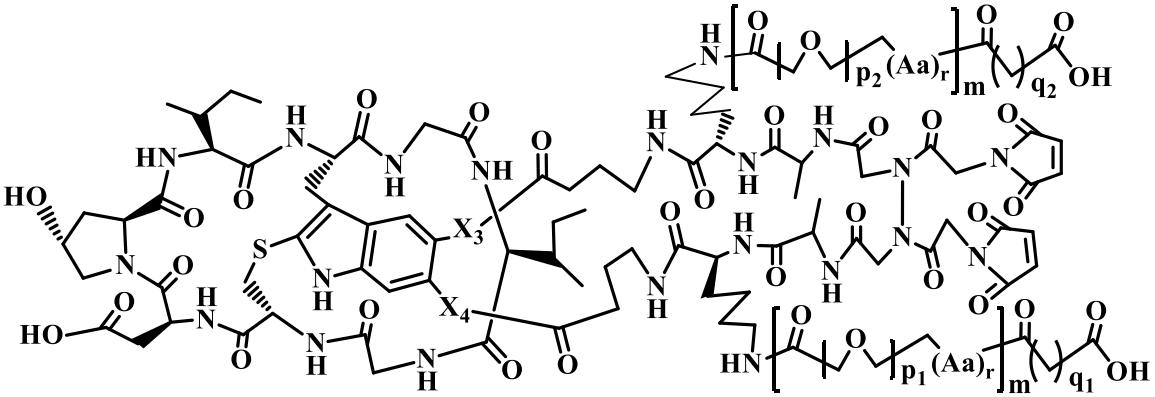
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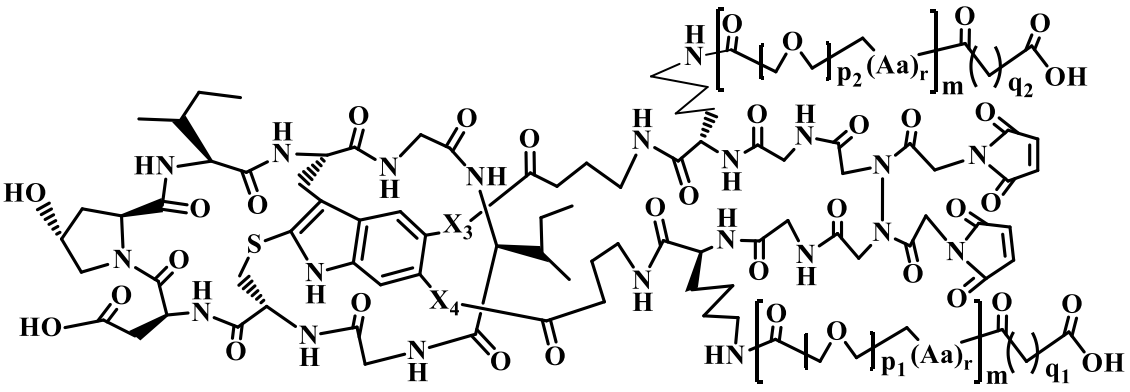
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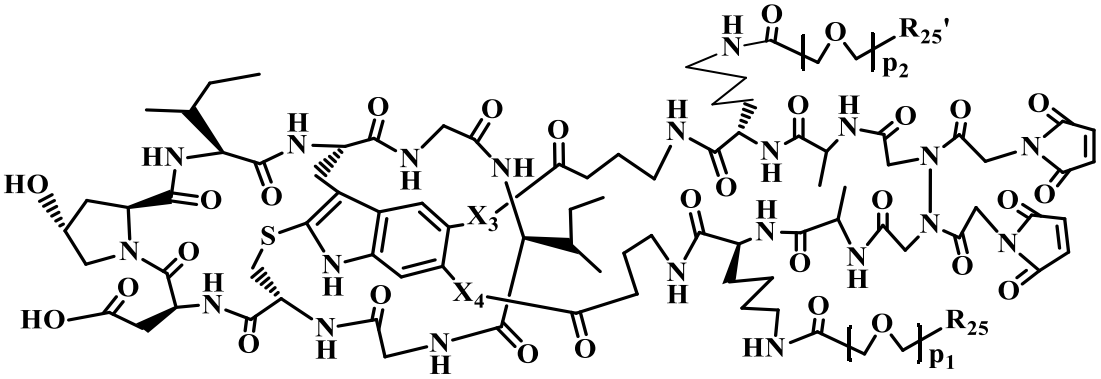
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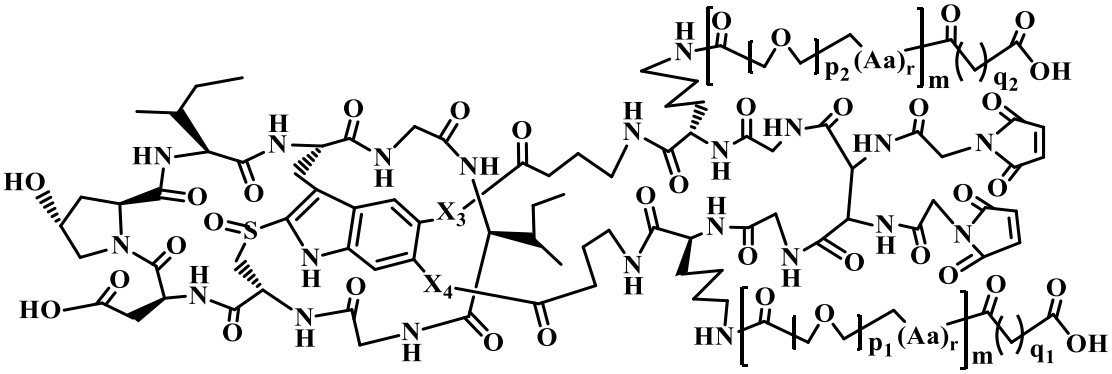
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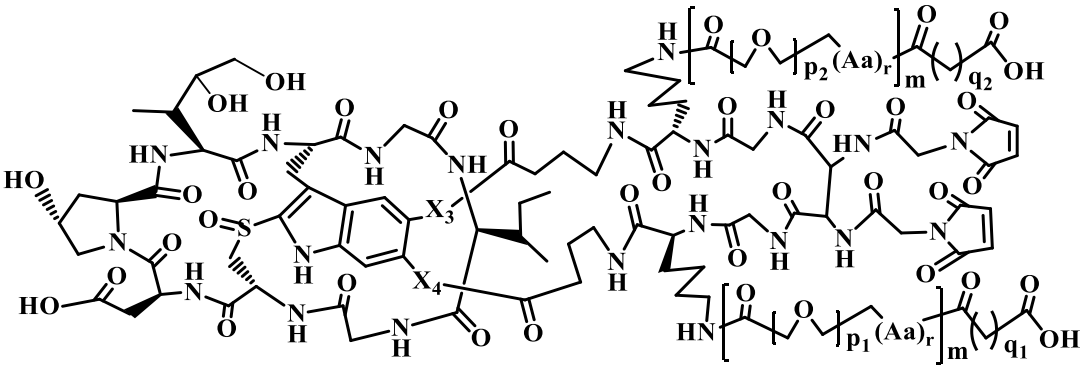
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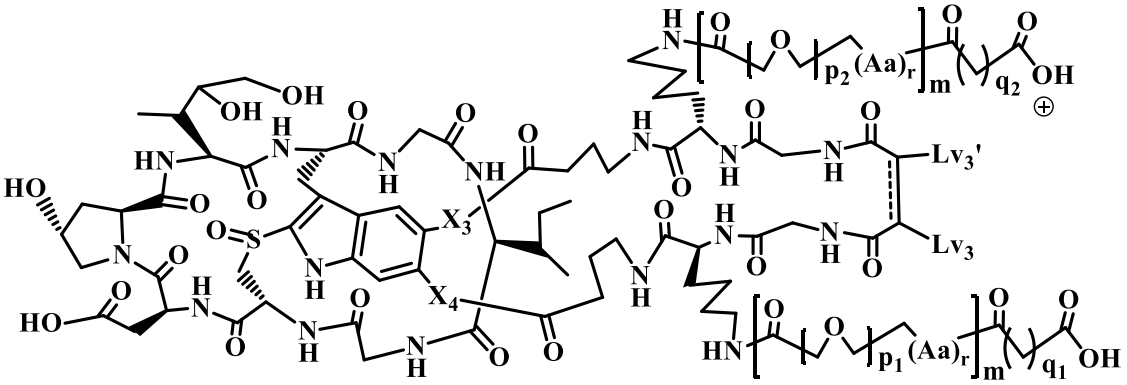
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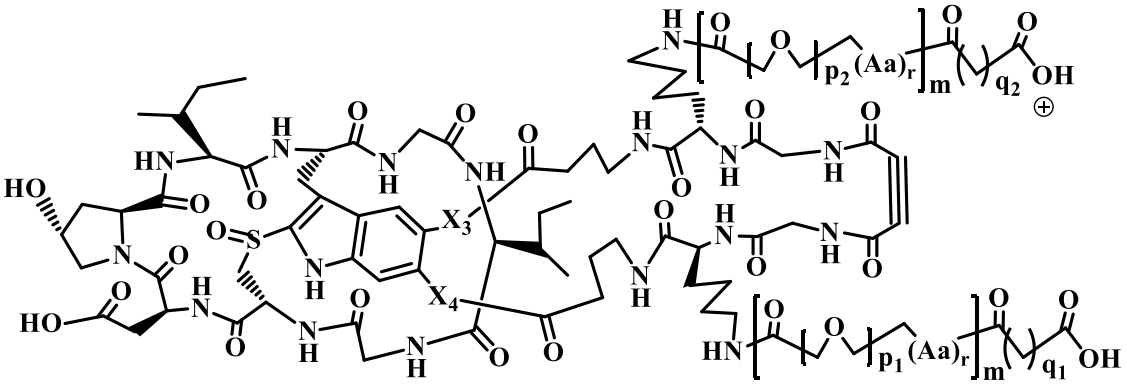
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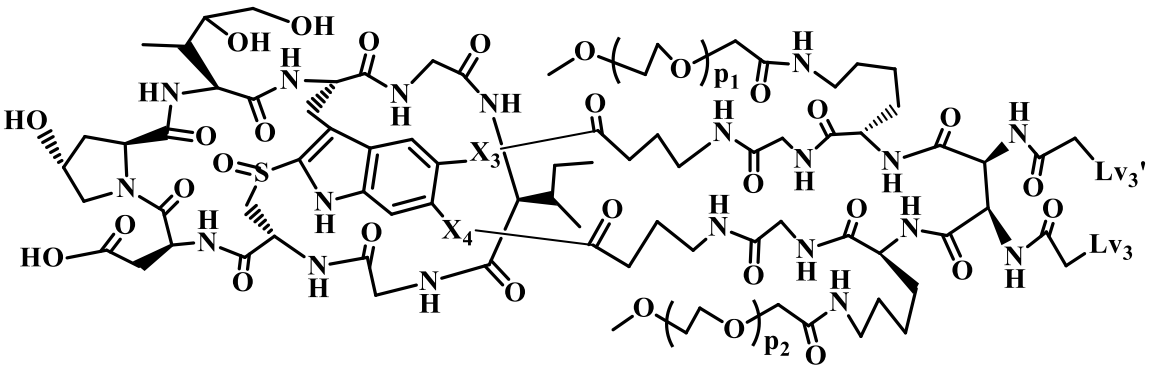
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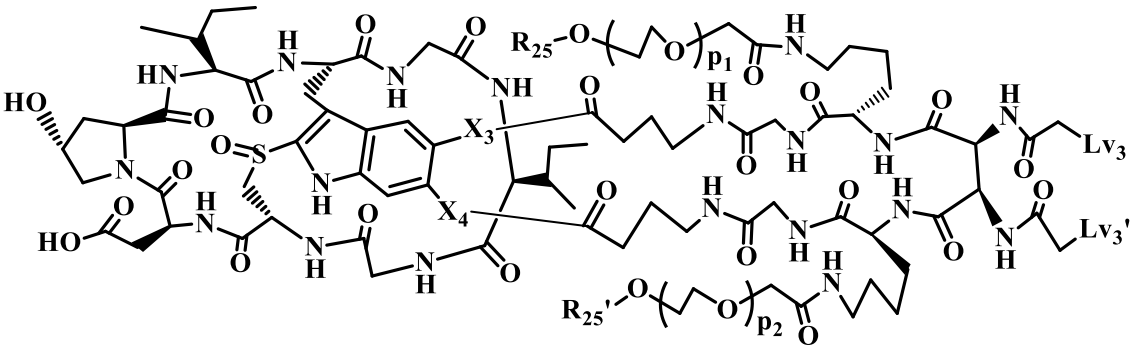
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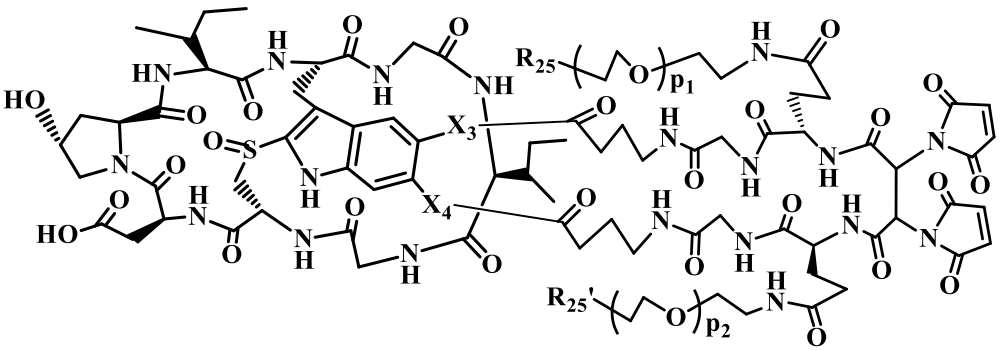
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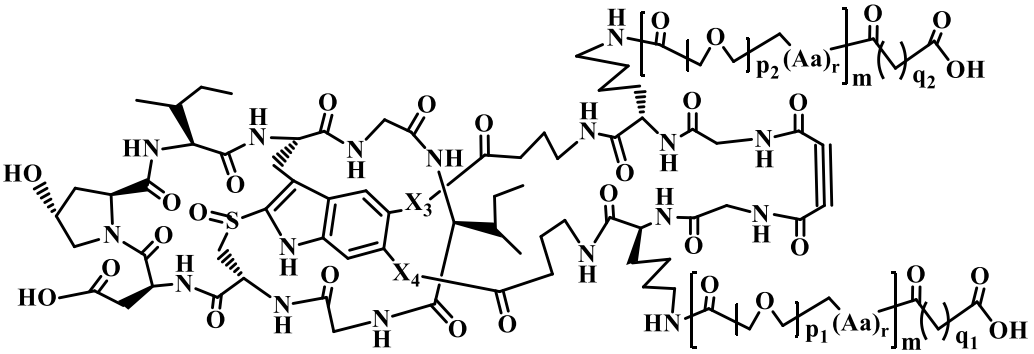
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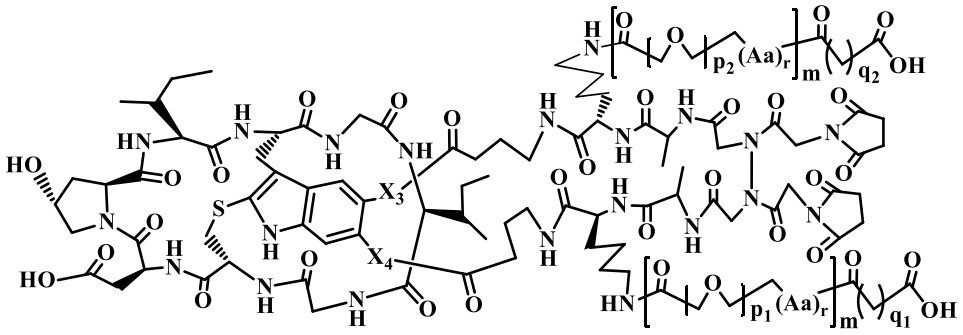
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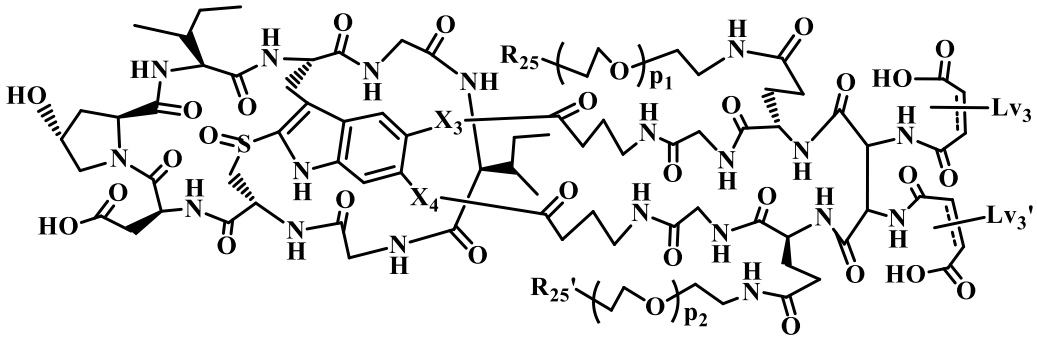
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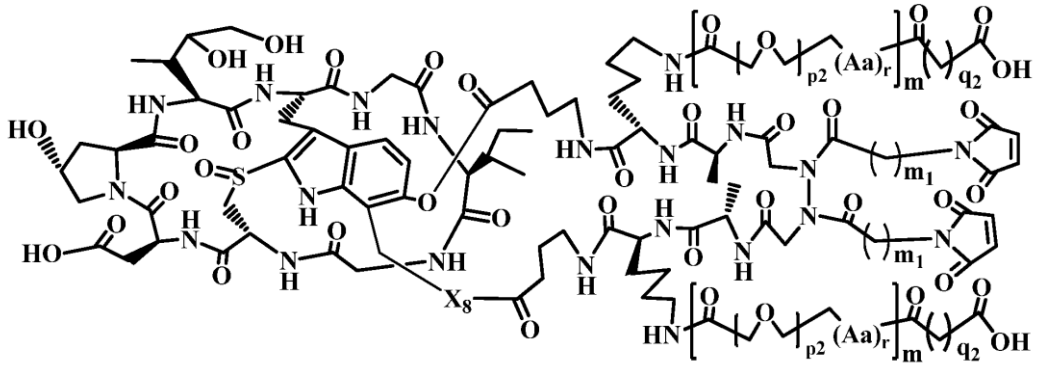
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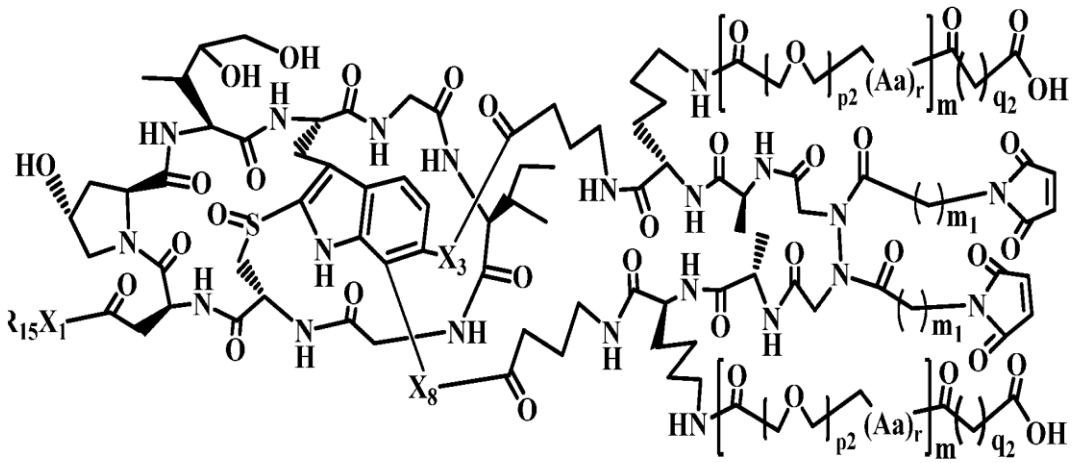
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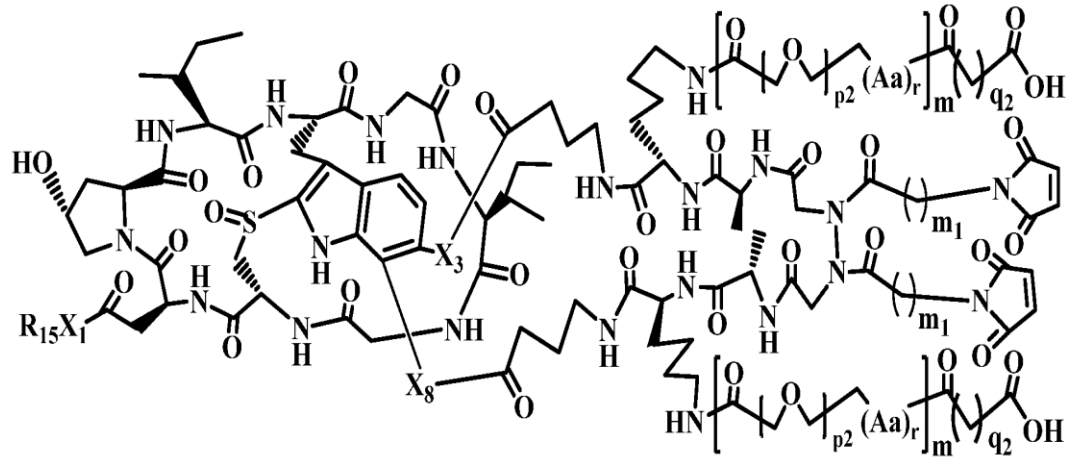
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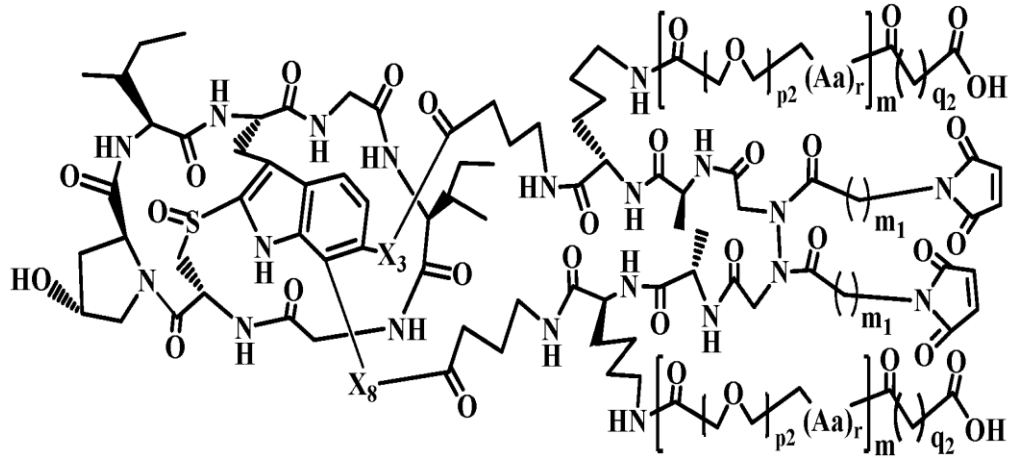
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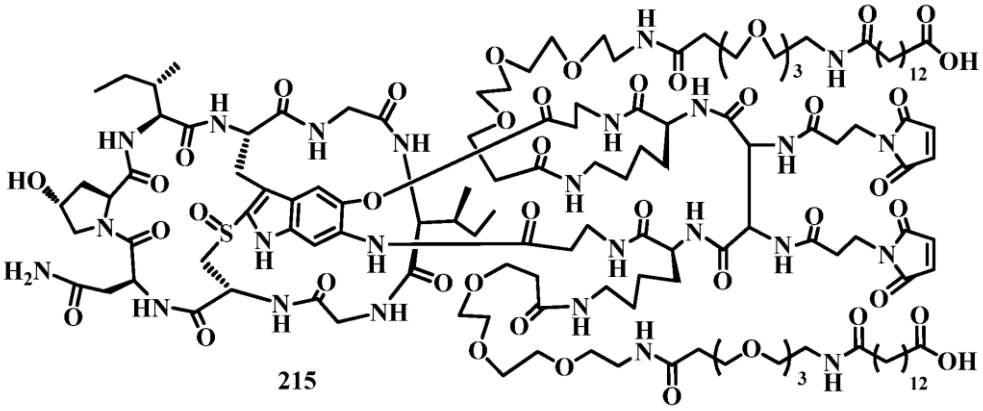
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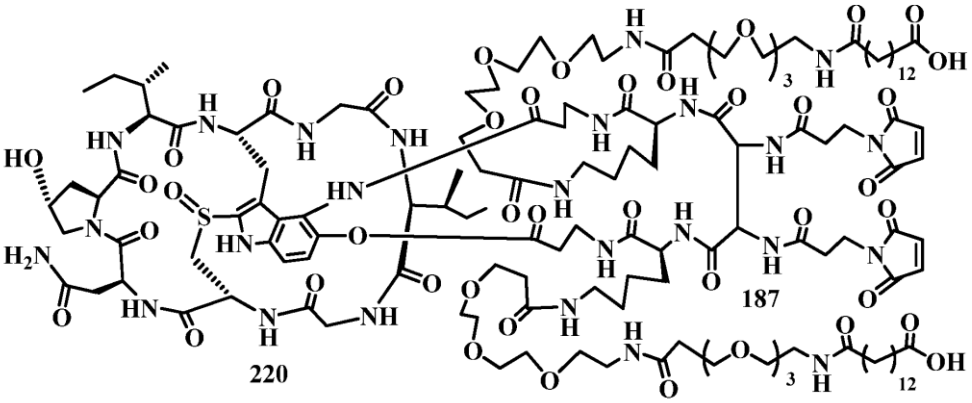
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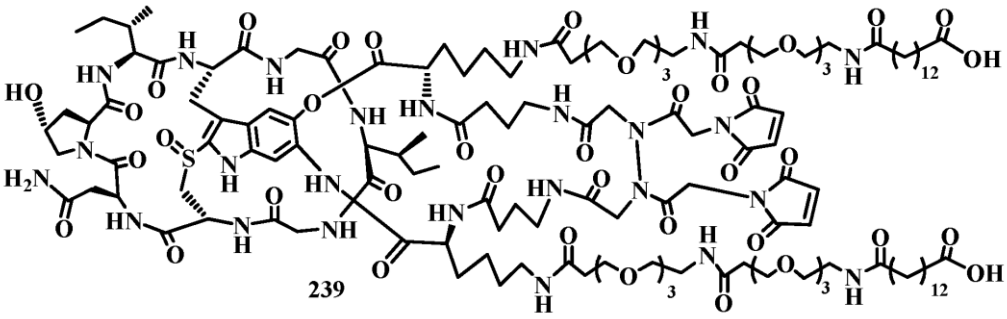
d-25,



215



220



239

or one or more isotope of chemical elements, pharmaceutically acceptable salts, hydrates, or hydrated salts; or the polymorphic crystalline structures of these compounds; or the optical isomers, racemates, diastereomers or enantiomers; wherein X_1, X_2, X_3, X_4, X_5, X_8, Z_2, Z_3, p, p_1, p_2, p_3, q_1, q_2, Lv_1, Lv_2, Lv_3, Lv_3', m, n, R_{12}, R_{12}', R_{15}, R_{25}, R_{25}', $(Aa)_r$ and mAb are as defined in claim 1.

12. The compound according to claim 1, 2, 8, or 9, wherein the cell binding agent or molecule according comprises:

(A) the group consisting of an antibody, a protein, probody, nanobody, a vitamin (including fo-late), a lipoprotein-based drug carrier, a nano-particle drug carrier, a dendrimer, and a molecule or a particle said above coating or linking with a cell-binding ligand, or a combination of said above thereof;

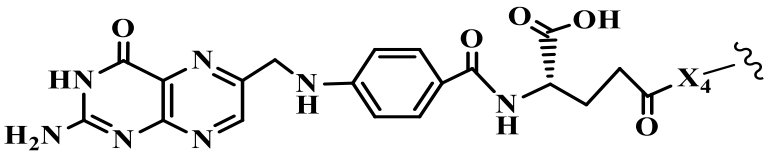
(B) an antibody-like protein, a full-length antibody, a polyclonal antibody, a monoclonal antibody, an antibody dimer, an antibody multimer, a multispecific antibody comprising a bispecific antibody, trispecific antibody, or tetraspecific antibody; a single chain antibody, an antibody fragment that binds to the target cell, a monoclonal antibody, a single chain monoclonal antibody, a monoclonal antibody fragment that binds the target cell, a chimeric antibody, a chimeric antibody fragment that binds to the target cell, a domain antibody, a domain antibody fragment that binds to the target cell, a resurfaced antibody, a resurfaced single chain antibody, or a resurfaced antibody fragment that binds to the target cell, a humanized antibody or a resurfaced antibody, a humanized single chain antibody, or a humanized antibody fragment that binds to the target cell, anti-idiotypic (anti-Id) antibodies, diabody, triabody, tetrabody, miniantibody, a probody, a probody fragment, small immune proteins (SIP);

(C) a cell-binding ligand or receptor agonist comprising folate; glutamic acid urea; somatostatin, octreotide (sandostatin), lanreotide (Somatuline); an aromatic sulfonamide; a pituitary adenylate cyclase activating peptide (PACAP) (PAC1); a vasoactive intestinal peptide (VIP) (VPAC1, VPAC2); a melanocyte-stimulating hormone (α-MSH); a cholecystokinin (CCK)/gastrin receptor agonist; a bombesin comprising Pyr-Gln-Arg-Leu-Gly-Asn-Gln-Trp-Ala-Val-Gly-His-Leu-Met-NH_2)/gastrin-releasing peptide (GRP); a neurotensin receptor ligand (NTR1, NTR2, NTR3); a substance P (NK1 receptor) ligand; a Neuropeptide Y (Y1–Y6); a homing peptide comprising RGD (Arg-Gly-Asp) or NGR (Asn-Gly-Arg), a dimeric and multimeric cyclic RGD peptide comprising cRGDfV, TAASGVRSMH or LTLRWVGLMS (Chondroitin sulfate proteoglycan NG2 receptor ligands) or F3 peptides; a cell penetrating peptide (CPPs); a peptide hormone comprising a

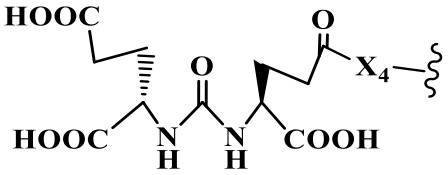
luteinizing hormone-releasing hormone (LHRH) agonist or antagonist, or a gonadotropin-releasing hormone (GnRH) agonist, acts by targeting follicle stimulating hormone (FSH) and luteinizing hormone (LH), as well as testosterone production, comprising buserelin (Pyr-His-Trp-Ser-Tyr-D-Ser(OtBu)-Leu-Arg-Pro-NHEt), Gonadorelin(Pyr-His-Trp-Ser-Tyr-Gly-Leu-Arg-Pro-Gly-NH_2), Goserelin (Pyr-His-Trp-Ser-Tyr-D-Ser(OtBu)-Leu-Arg-Pro-AzGly-NH_2), Histrelin (Pyr-His-Trp-Ser-Tyr-D-His(N-benzyl)-Leu-Arg-Pro-NHEt), leuprolide (Pyr-His-Trp-Ser-Tyr-D-Leu-Leu-Arg-Pro-NHEt), Nafarelin(Pyr-His-Trp-Ser-Tyr-2Nal-Leu-Arg-Pro-Gly-NH_2), Triptorelin(Pyr-His-Trp-Ser-Tyr-D-Trp-Leu-Arg-Pro-Gly-NH_2), Nafarelin, Deslorelin, Abarelix (Ac-D-2Nal-D-4-chloroPhe-D-3-(3-pyridyl)Ala-Ser-(N-Me)Tyr-D-Asn-Leu-isopropylLys-Pro-DAla-NH_2), Cetrorelix(Ac-D-2Nal-D-4-chloroPhe-D-3-(3-pyridyl) Ala-Ser-Tyr-D-Cit-Leu-Arg-Pro-D-Ala-NH_2), Degarelix (Ac-D-2Nal-D-4-chloroPhe-D-3-(3-pyridyl) Ala-Ser-4-aminoPhe(L-hydroorotyl) -D-4-aminoPhe (carba-moyl) -Leu-isopropylLys-Pro-D-Ala-NH_2), and Ganirelix (Ac-D-2Nal-D-4-chloroPhe-D-3- (3-pyridyl) Ala-Ser-Tyr-D- (N9, N10-diethyl) -homoArg-Leu- (N9, N10-diethyl) -homoArg-Pro-D-Ala-NH_2); a pattern recognition receptor (PRRs) comprising a Toll-like receptor (TLR) ligand, a C-type lectin or nodlike receptor (NLR) ligand; a calcitonin receptor agonist; an integrin receptor or their receptor subtype comprising $\alpha_V\beta_1$, $\alpha_V\beta_3$, $\alpha_V\beta_5$, $\alpha_V\beta_6$, $\alpha_6\beta_4$, $\alpha_7\beta_1$, $\alpha_L\beta_2$, $\alpha_{IIb}\beta_3$ agonist comprising GRGDSPK, cyclo (RGDfV) (L1), cyclo(-N(Me)R-GDfV), cyclo(R-Sar-DfV), cyclo(RG-N(Me)D-fV), cyclo(RGD-N(Me)f-V), cyclo(RGDf-N(Me)V-) or cilengitide; a nanobody (VHH (camelid Ig)); a domain antibody; a bispecific T cell engager (BiTE, a bispecific diabody); a Dual Affinity ReTargeting (DART, a bispecific diabody); Tetravalent tandem antibodies (TandAb, a dimerized bispecific diabody); Anticalin; Adnectins (10th FN3 (Fibron-ectin)); Designed Ankyrin Repeat Proteins (DARPins); Avimers; EGF receptors, or VEGF receptors' agonists;

(D) A molecule of cell-binding molecule or ligand or a cell receptor agonist comprising LB01 (Folate), LB02 (PMSA ligand), LB03 (PMSA ligand), LB04 (PMSA ligand), LB05 (Somatostatin), LB06 (Somatostatin), LB07 (Octreotide), LB08 (Lanreotide), LB09

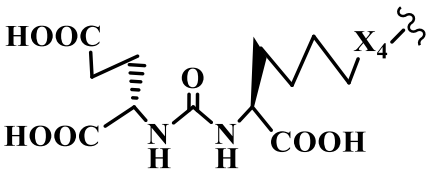
(Vapreotide (Sanvar)), LB10 (CAIX ligand), LB11 (CAIX ligand), LB12 (Gastrin releasing peptide receptor (GRPr), MBA), LB13 (luteinizing hormone-releasing hormone (LH-RH) ligand or GnRH), LB14 (luteinizing hormone-releasing hormone (LH-RH) and GnRH ligand), LB15 (GnRH antagonist, Abarelix), LB16, LB17 (cobalamin), LB18 (for $\alpha_v\beta_3$ integrin receptor, cyclic RGD pentapeptide), LB19 (hetero-bivalent peptide ligand for VEGF receptor), LB20 (Neuromedin B), LB21 (bombesin for a G-protein coupled receptor), LB22 (TLR $_2$ for a Toll-like receptor), LB23 (for an androgen receptor), LB24 (Cilengitide/cyclo (-RGDfV-) for an α_v integrin receptor, LB23 (Fludrocortisone), LB25, LB26, LB27, LB28 (Fludrocortisone), LB29 (Dexa-methasone), LB30 (fluticasone propionate), LB31 (Beclometasone dipropionate), LB32 (Triamcinolone acetonide), LB33 (Prednisone), LB34 (Prednisolone), LB35 (Methylprednisolone), LB36 (Betame-thasone), LB37, LB38, LB39, LB40, LB41, LB42, LB43, LB44 (Clindamycin), LB45, LB46, LB47, LB48, LB49, LB50, LB51, LB52, LB53 or LB54 which are shown in the following structures:



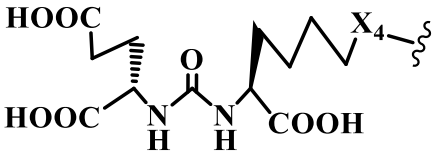
LB01 (Folate conjugate),



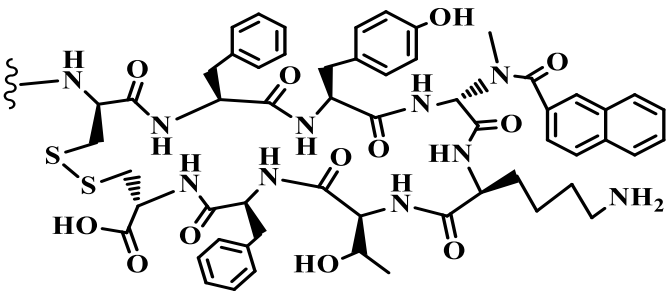
LB02 (PMSA ligand conjugate),



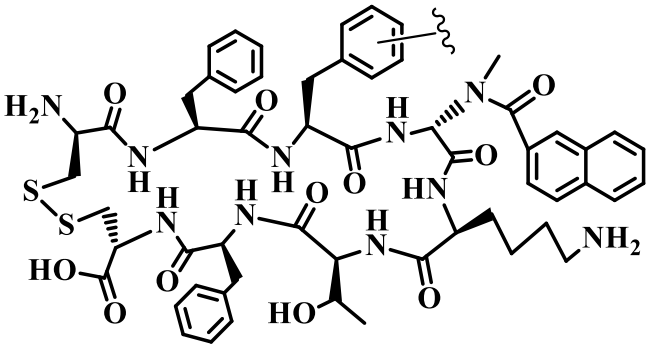
LB03 (PMSA ligand conjugate),



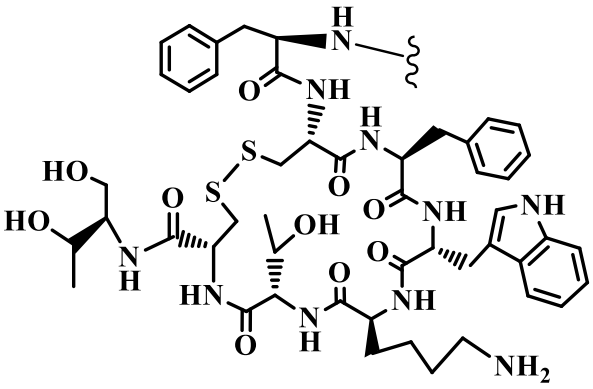
LB04 (PMSA ligand),



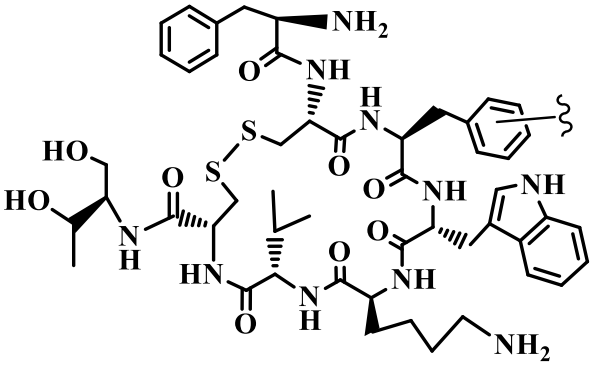
LB05 (Somatostatin),



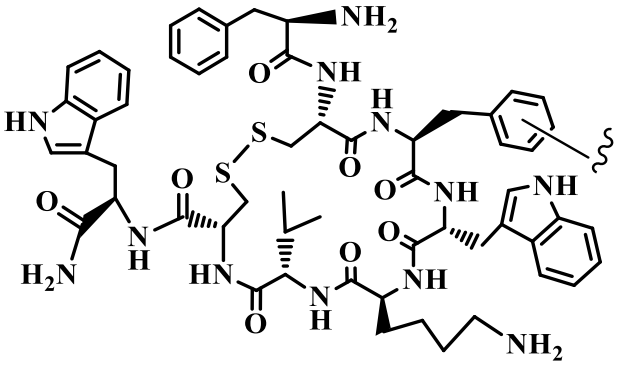
LB06 (Somatostatin),



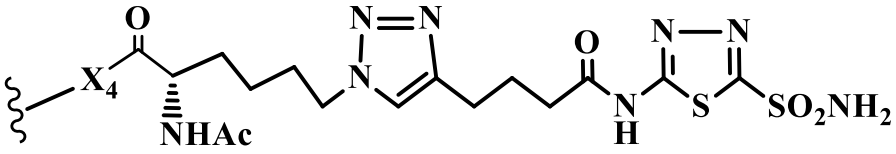
LB07 (Octreotide),



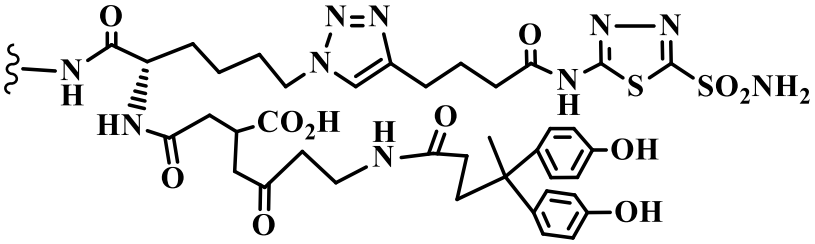
LB08 (Lanreotide),



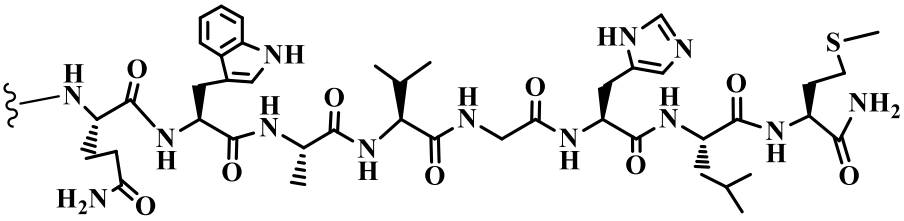
LB09 (Vapreotide (Sanvar)),



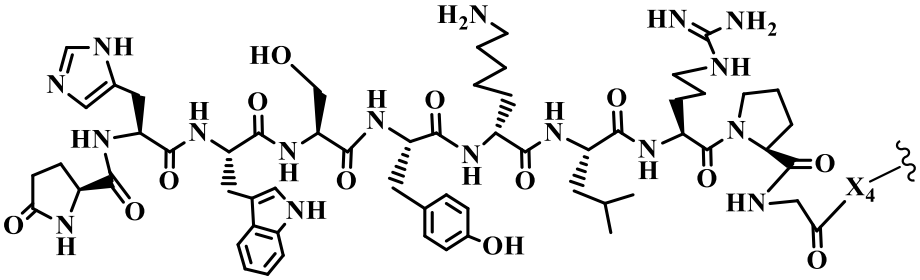
LB10 (CAIX ligand),



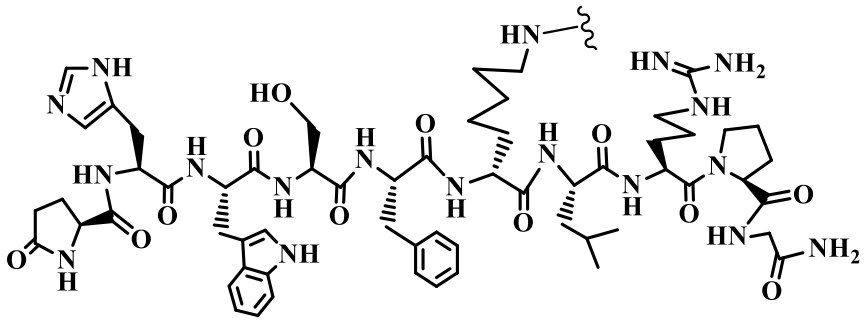
LB11 (CAIX ligand),



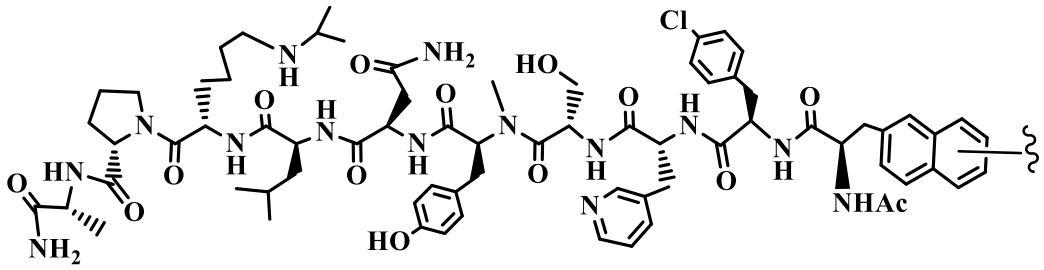
LB12 (Gastrin releasing peptide receptor (GRPr), MBA),



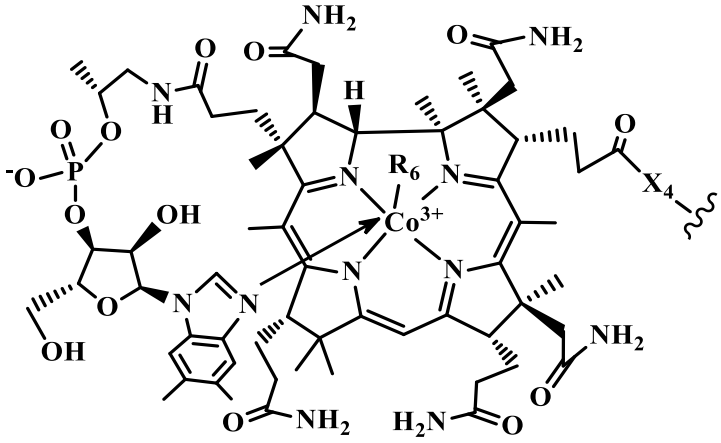
LB13 (luteinizing hormone-releasing hormone (LH-RH) ligand and GnRH),



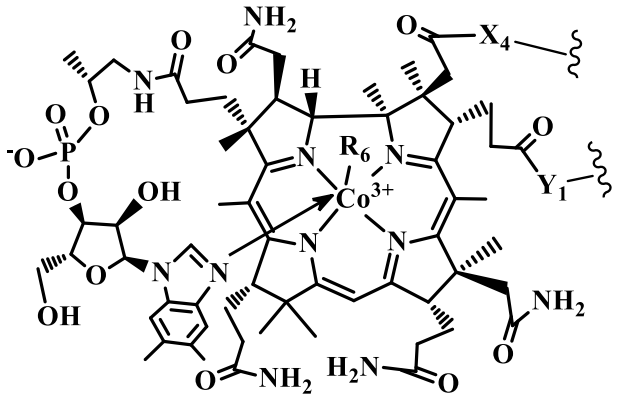
LB14 (luteinizing hormone-releasing hormone (LH-RH) and GnRH ligand),



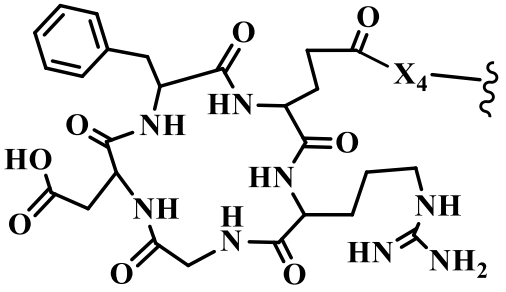
LB15 (GnRH antagonist, Abarelix),



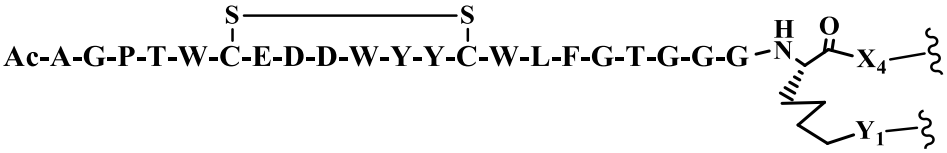
LB16,



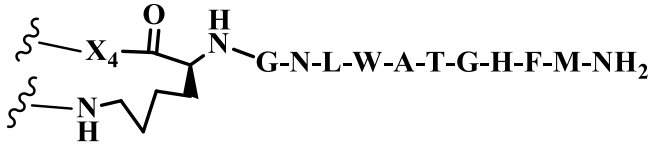
LB17,



LB18 (for $\alpha_v\beta_3$ integrin receptor, cyclic RGD pentapeptide),



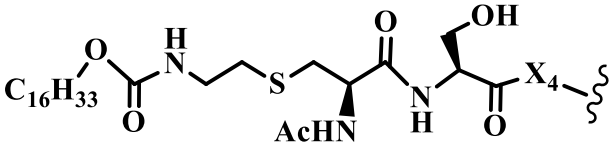
LB19 (hetero-bivalent peptide ligand conjugate for VEGF receptor),



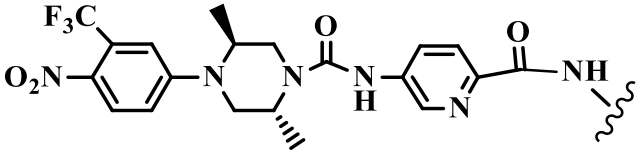
LB20 (Neuromedin B),



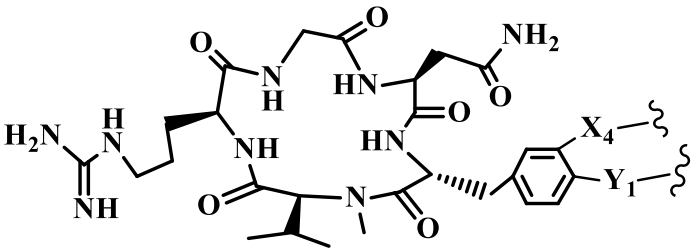
LB21 (bombesin conjugate for a G-protein coupled receptor),



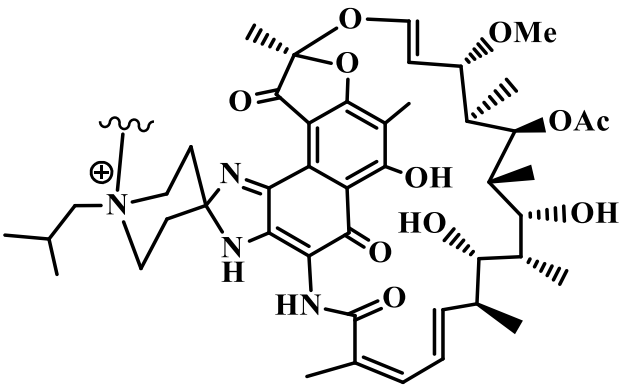
LB22 (TLR_2 conjugate for a Toll-like receptor),



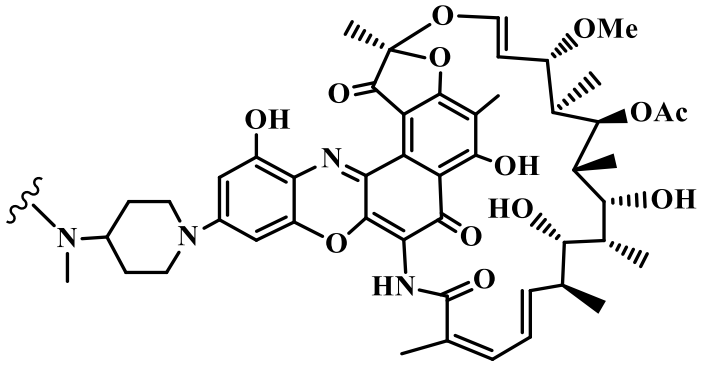
LB23 (an androgen receptor),



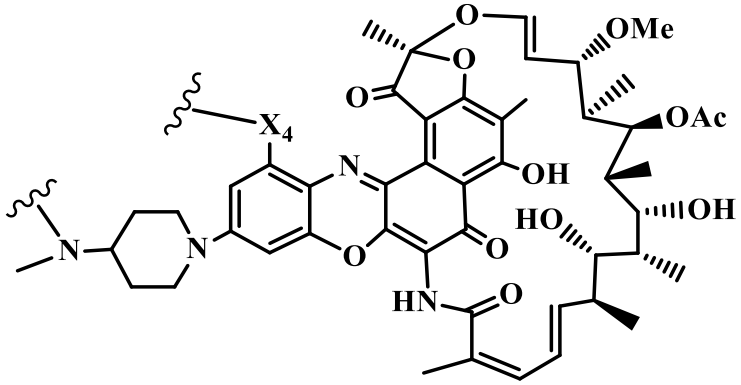
LB24 (Cilengitide/cyclo(-RGDfV-) conjugate for an α_v intergrin receptor)



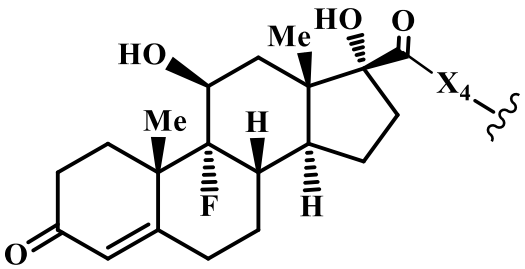
LB25,



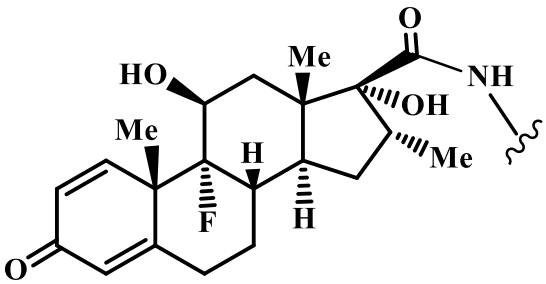
LB26,



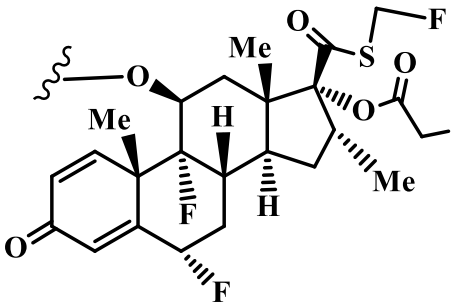
LB27,



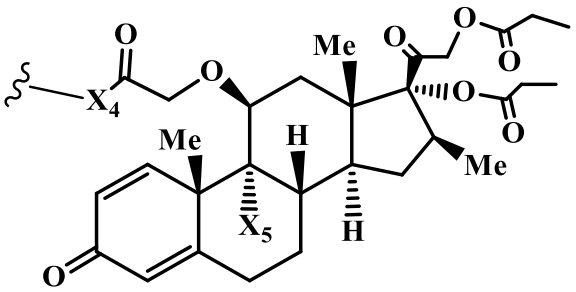
LB28 (Fludrocortisone),



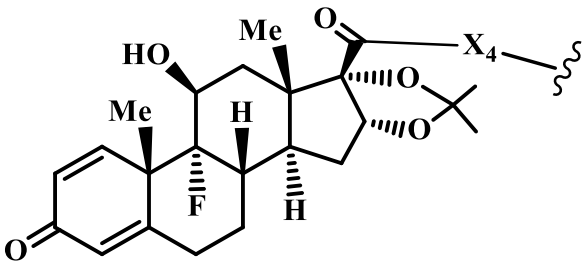
LB29 (Dexamethasone),



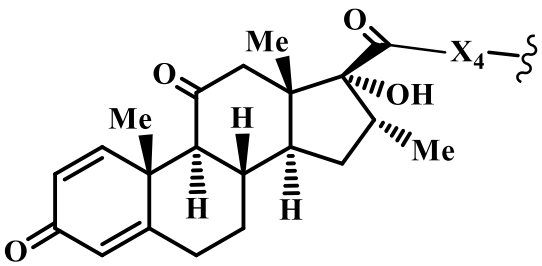
LB30 (fluticasone propionate),



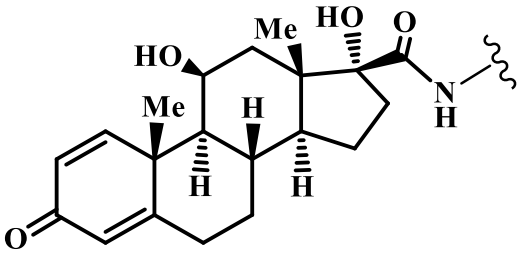
LB31 (Beclometasone dipropionate),



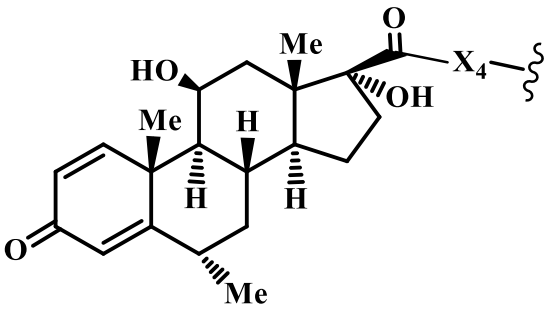
LB32 (Triamcinolone acetonide),



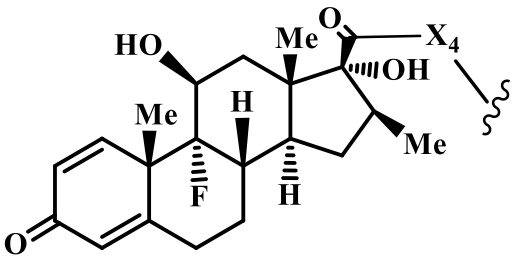
LB33 (Prednisone),



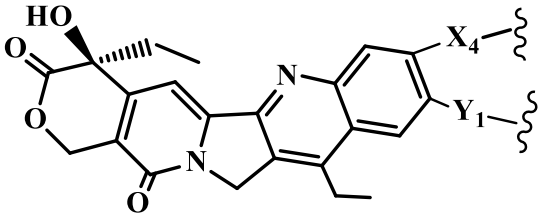
LB34 (Prednisolone),



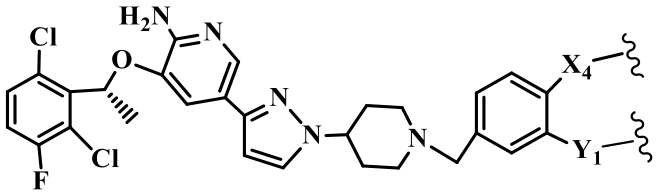
LB35 (Methylprednisolone),



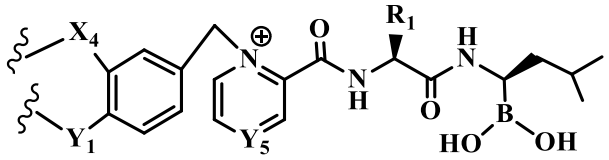
LB36 (Betamethasone),



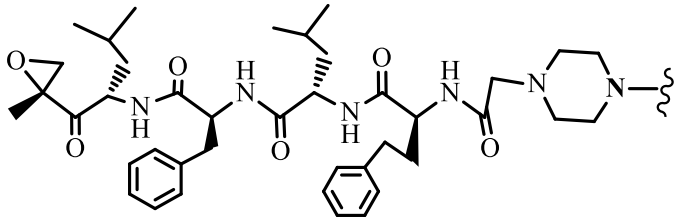
LB37,



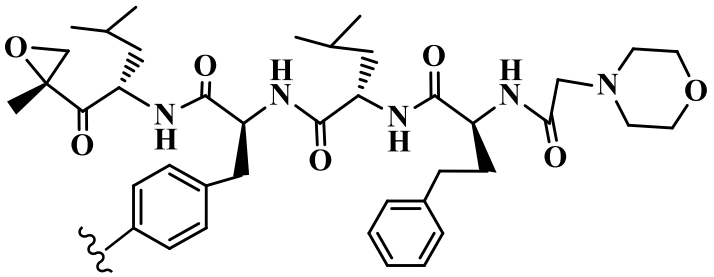
LB38,



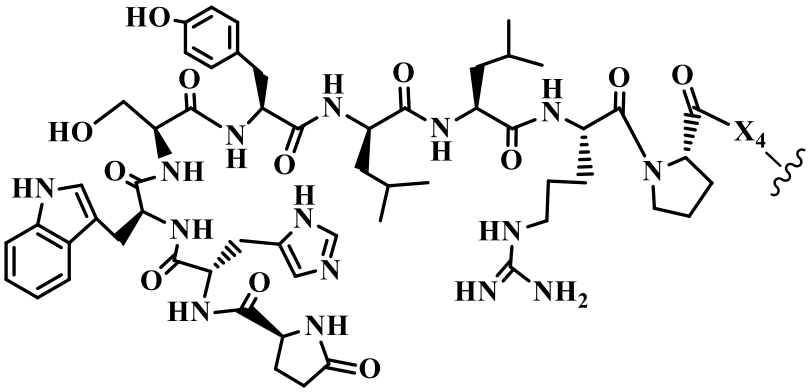
LB39, wherein Y_5, is N, CH, C(Cl), $C(CH_3)$, or $C(COOR_1)$; R_1 is H, C_1-C_6 Alkyl, C_3-C_8 Ar;



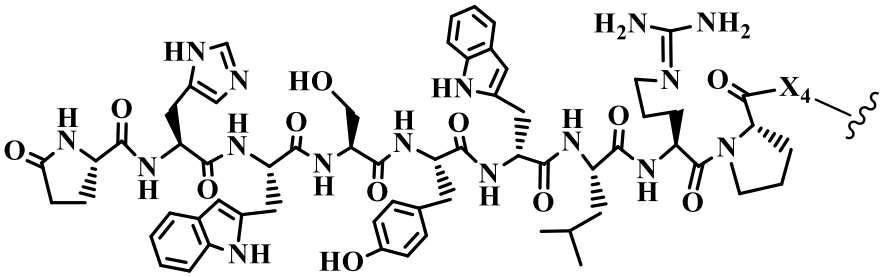
LB40,



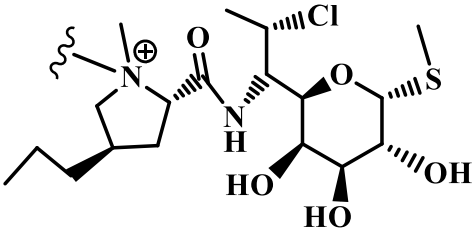
LB41,



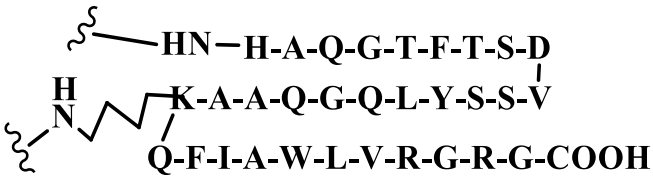
LB42,



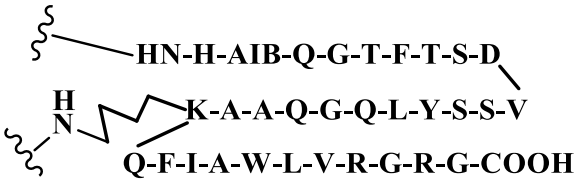
LB43,



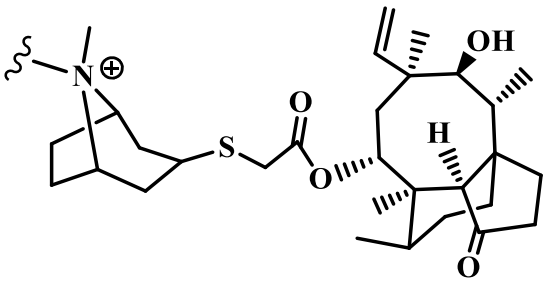
LB44 (Clindamycin),



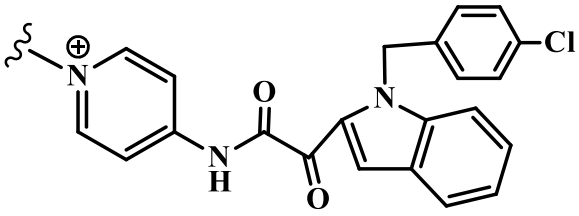
LB45,



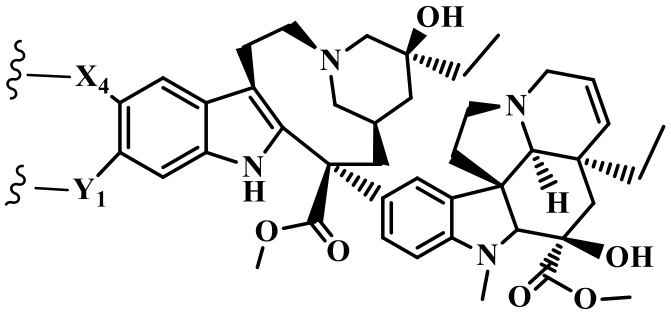
LB46,



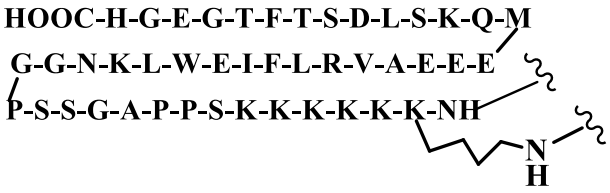
LB47,



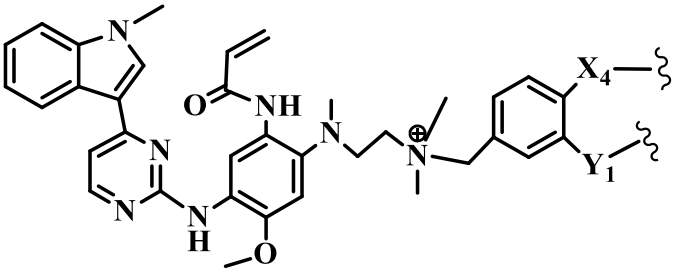
LB48,



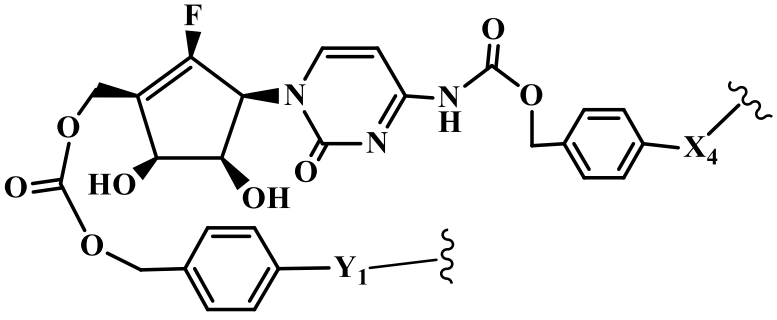
LB49,



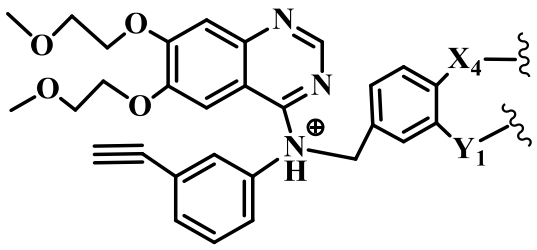
LB50,



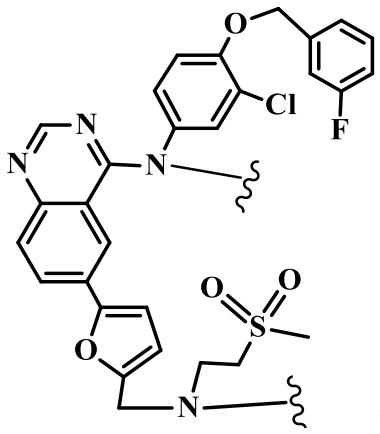
LB51,



LB52,



LB53,



LB54,

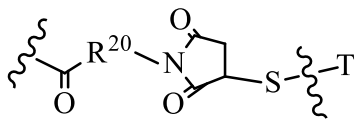
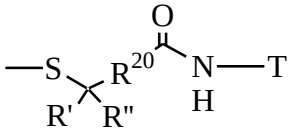
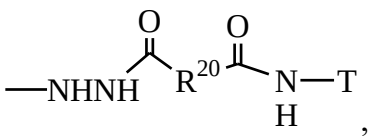
wherein "〰" is the site to link the side chain linker of the present patent;

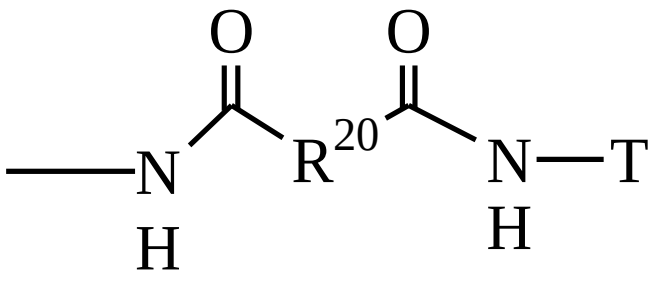
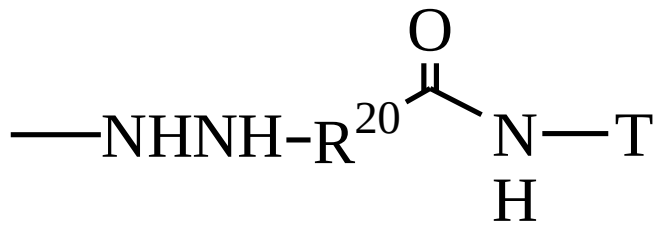
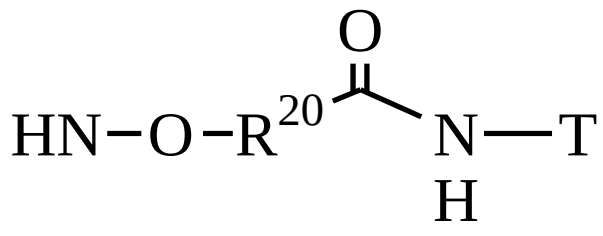
X_4, and Y_1 are independently O, NH, NHNH, NR_1, S, C(O)O, C(O)NH, OC(O)NH, OC(O)O, NHC(O)NH, NHC(O)S, $OC(O)N(R_1)$, $N(R_1)C(O)N(R_1)$, CH_2, C(O)NHNHC(O) or $C(O)NR_1$;

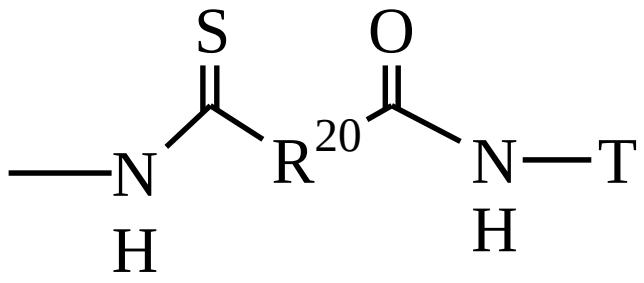
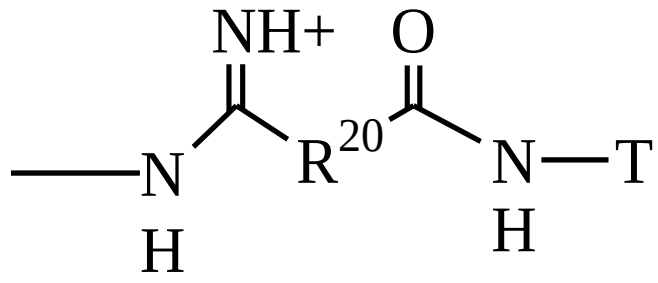
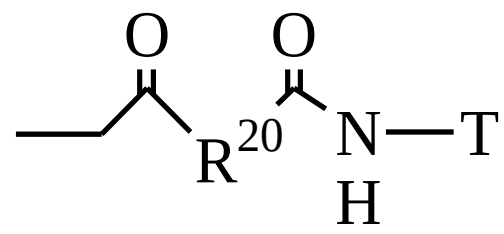
X_1 is H, CH_2, OH, O, C(O), C(O)NH, $C(O)N(R_1)$, R_1, NHR_1, NR_1, $C(O)R_1$ or C(O)O; X_5 is H, CH_3, F, or Cl;

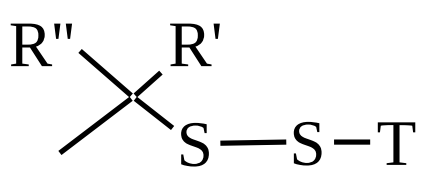
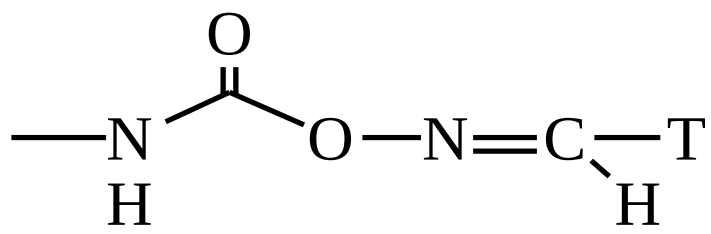
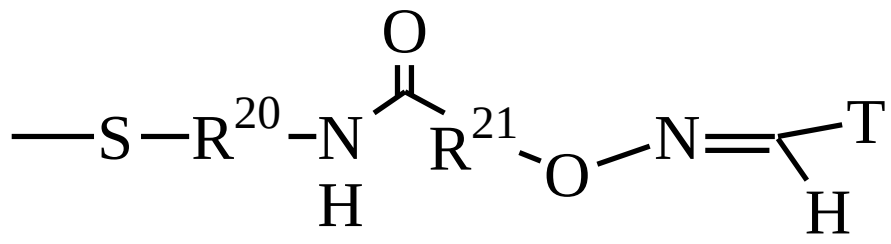
M_1 and M_2 are independently H, Na, K, Ca, Mg, NH_4, $N(R_{12}R_{12'}R_{13}R_{13'})$; R_{12}, $R_{12'}$, R_{13} and $R_{13'}$ are defined in claim 1.

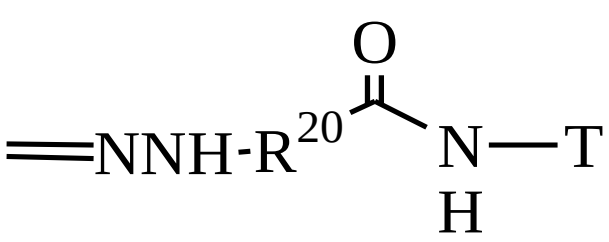
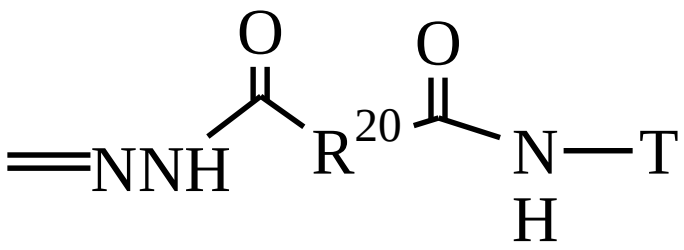
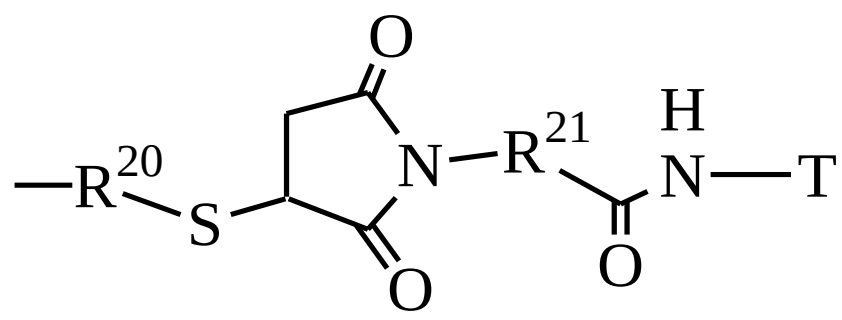
13. The compound according to claim 1, 2, or 12, wherein the cell-binding molecule, T, when linking to V_1 and/or V_2, of Formula (I) and (III), or when T directly linking to L_1 and/or L_2 of Formula (I) and (III), wherein V_1, and/or V_2, are absent, having one or more of the following the linkage structures:

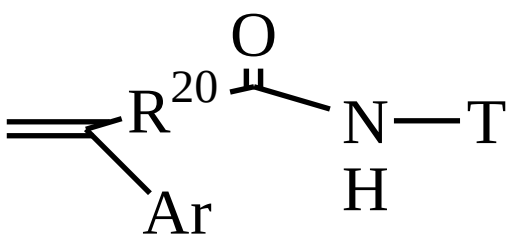
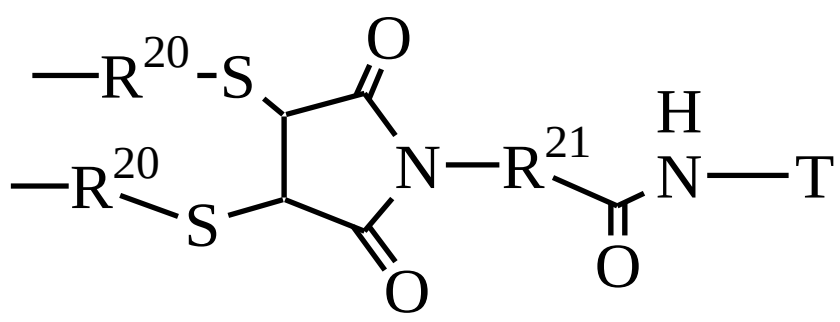
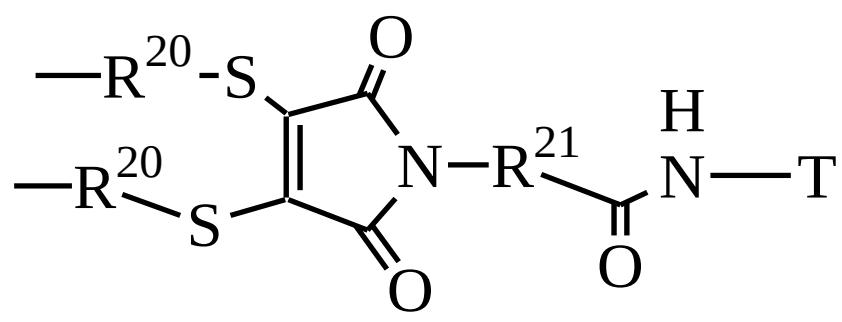

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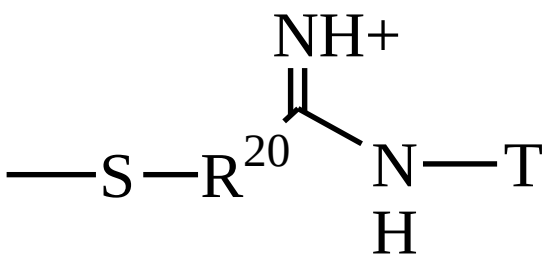
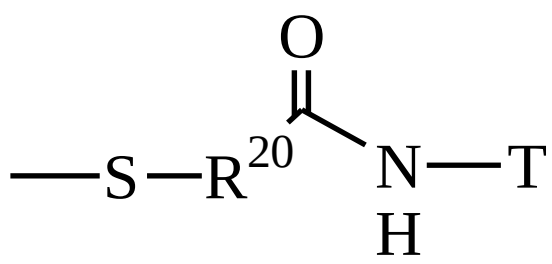
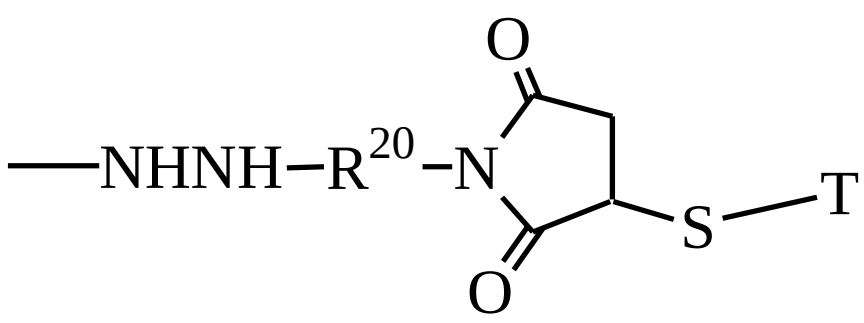
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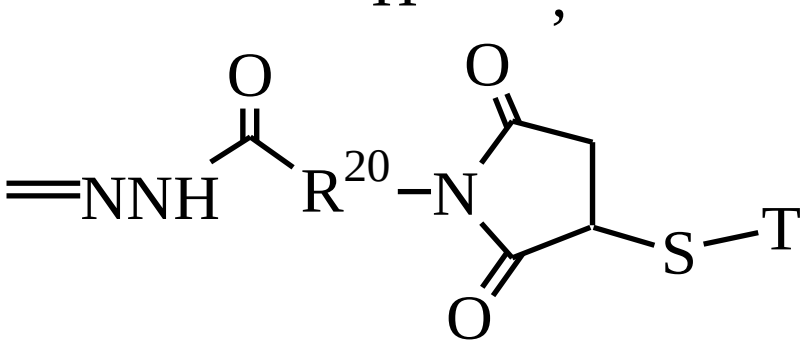
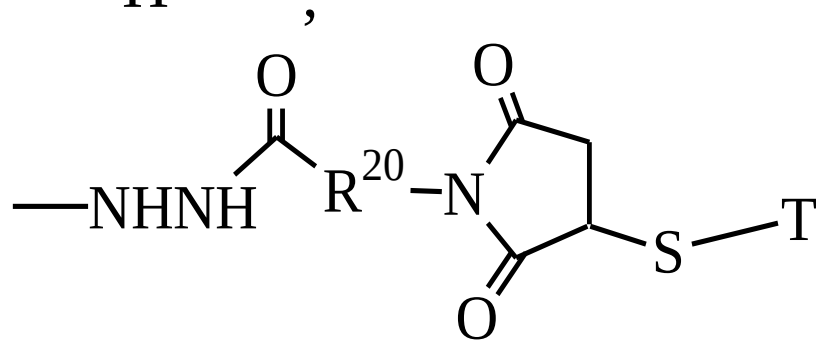
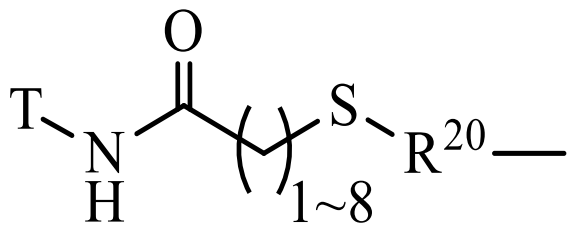
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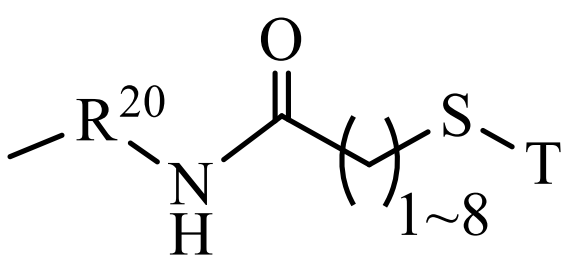
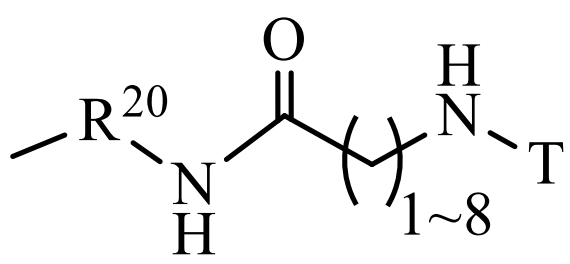
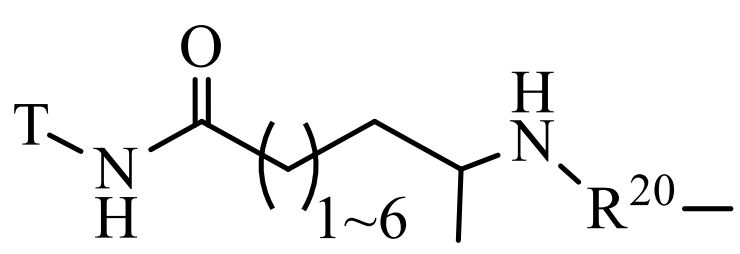
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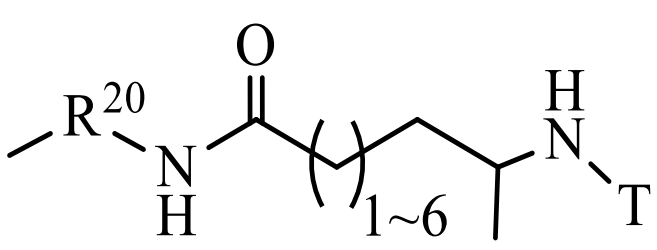
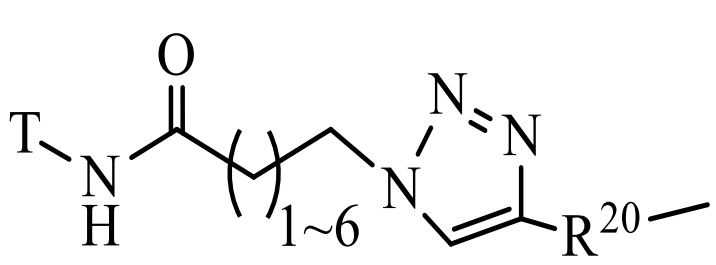
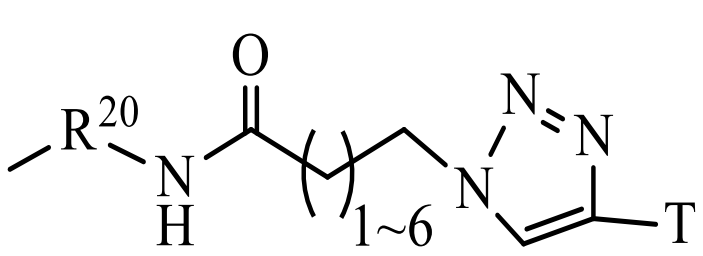
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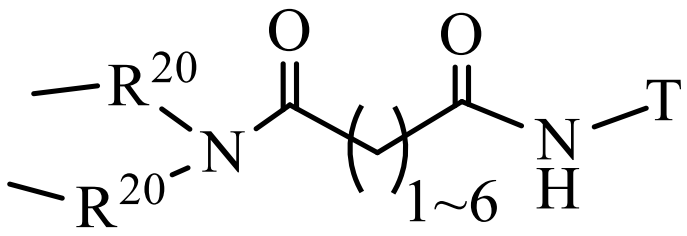
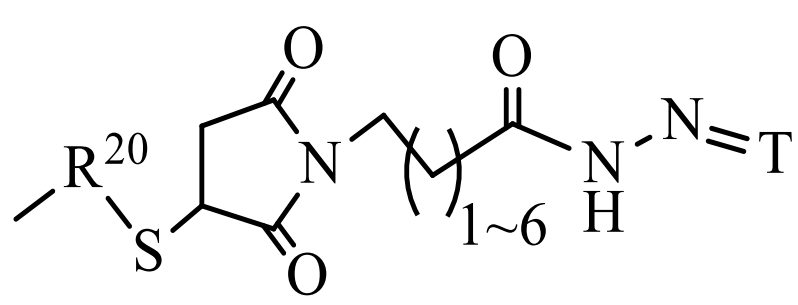
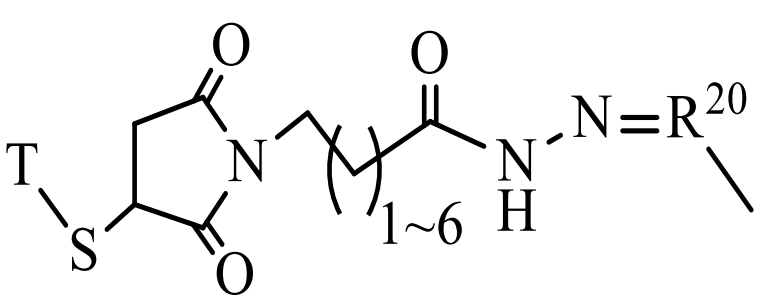
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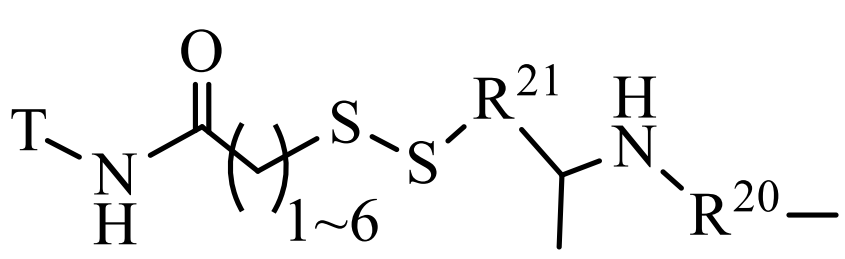
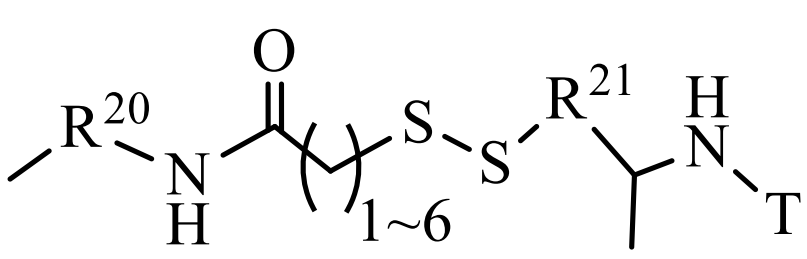
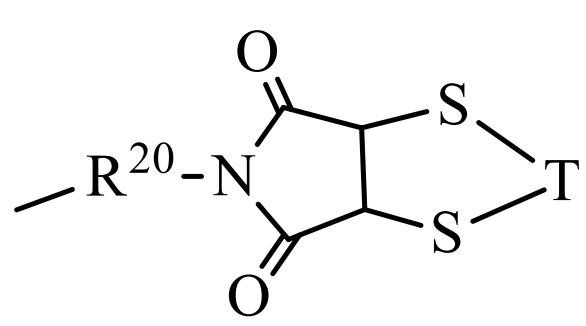
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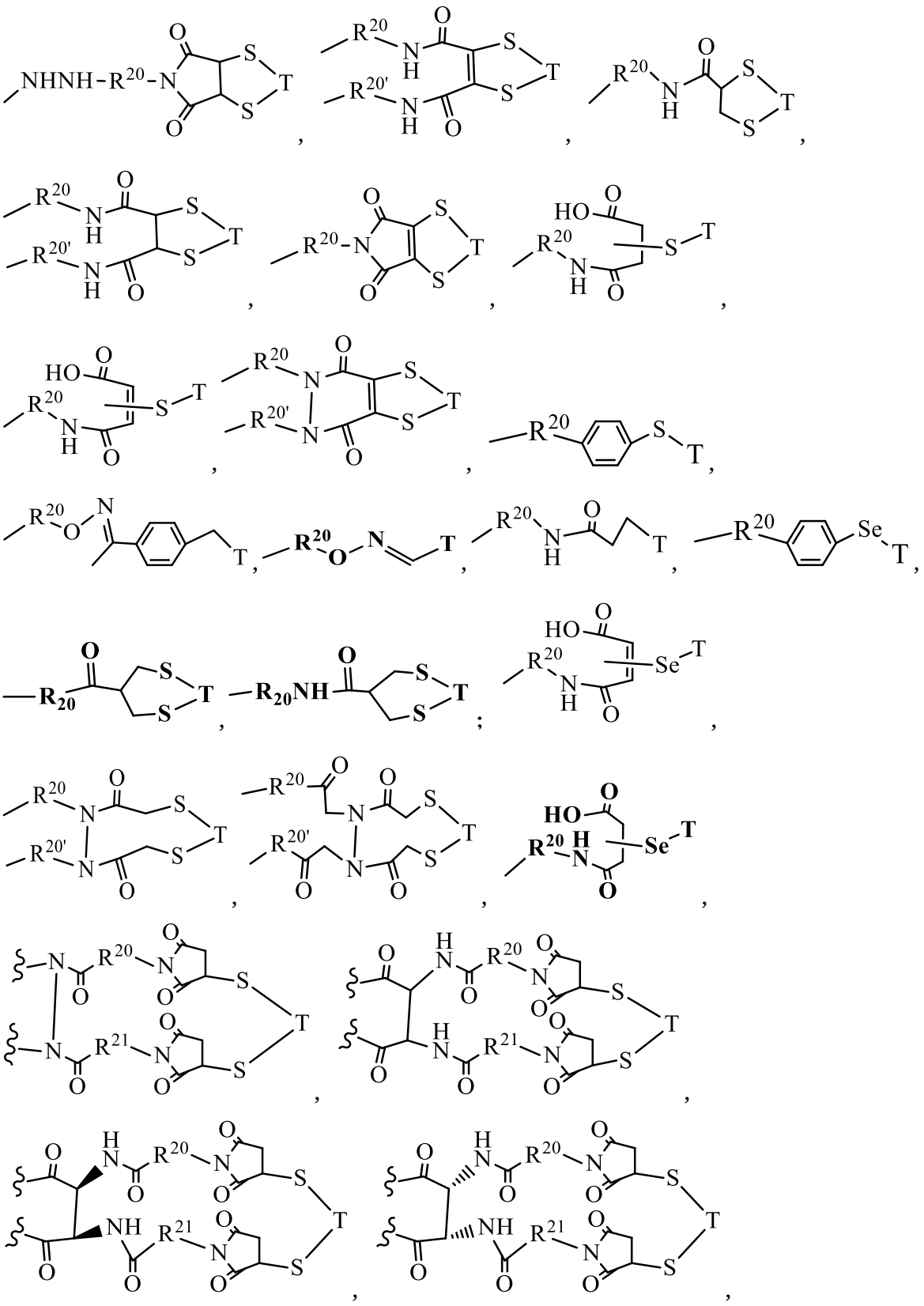
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wherein R^{20} and R^{21} are independently C_1～C_8 alkyl; C_2～C_8 heteroalkyl, or heterocyclic;

C_3～C_8 aryl, Ar-alkyl, cycloalkyl, alkylcycloalkyl, heterocycloalkyl, heteroalkylcycloal-kyl,

carbocyclic, or alkylcarbonyl; or C_2-C_{100} polyethylene glycol having formula of $(CH_2CH_2O)_p$ wherein p is 2-100.

14. The compound according to claim 1, 2, 8, or 9, wherein the cell binding agent or molecule is capable of targeting against a tumor cell, a virus infected cell, a microorganism infected cell, a parasite infected cell, an autoim-mune disease cell, an activated tumor cells, a myeloid cell, an activated T-cell, an affecting B cell, or a melanocyte, or any cells expressing any one of the following antigens or receptors: CD1, CD1a, CD1b, CD1c, CD1d, CD1e, CD2, CD3, CD3d, CD3e, CD3g, CD4, CD5, CD6, CD7, CD8, CD8a, CD8b, CD9, CD10, CD11a, CD11b, CD11c, CD11d, CD12w, CD14, CD15, CD16, CD16a, CD16b, CDw17, CD18, CD19, CD20, CD21, CD22, CD23, CD24, CD25, CD26, CD27, CD28, CD29, CD30, CD31, CD32, CD32a, CD32b, CD33, CD34, CD35, CD36, CD37, CD38, CD39, CD40, CD41, CD42, CD42a, CD42b, CD42c, CD42d, CD43, CD44, CD45, CD46, CD47, CD48, CD49b, CD49c, CD49c, CD49d, CD49f, CD50, CD51, CD52, CD53, CD54, CD55, CD56, CD57, CD58, CD59, CD60, CD60a, CD60b, CD60c, CD61, CD62E, CD62L, CD62P, CD63, CD64, CD65, CD65s, CD66, CD66a, CD66b, CD66c, CD66d, CD66e, CD66f, CD67, CD68, CD69, CD70, CD71, CD72, CD73, CD74, CD75, CD75s, CD76, CD77, CD78, CD79, CD79a, CD79b, CD80, CD81, CD82, CD83, CD84, CD85, CD85a, CD85b, CD85c, CD85d, CD85e, CD85f, CD85g, CD85g, CD85i, CD85j, CD85k, CD85m, CD86, CD87, CD88, CD89, CD90, CD91, CD92, CD93, CD94, CD95, CD96, CD97, CD98, CD99, CD100, CD101, CD102, CD103, CD104, CD105, CD106, CD107, CD107a, CD107b, CD108, CD109, CD110, CD111, CD112, CD113, CD114, CD115, CD116, CD117, CD118, CD119, CD120, CD120a, CD120b, CD121, CD121a, CD121b, CD122, CD123, CD123a, CD124, CD125, CD126, CD127, CD128, CD129, CD130, CD131, CD132, CD133, CD134, CD135, CD136, CD137, CD138, CD139, CD140, CD140a, CD140b, CD141, CD142, CD143, CD144, CD145, CDw145, CD146, CD147, CD148, CD149, CD150, CD151, CD152, CD153, CD154, CD155, CD156, CD156a, CD156b, CD156c, CD156d, CD157, CD158, CD158a, CD158b1,

CD158b2, CD158c, CD158d, CD158e1, CD158e2, CD158f2, CD158g, CD158h, CD158i, CD158j, CD158k, CD159, CD159a, CD159b, CD159c, CD160, CD161, CD162, CD163, CD164, CD165, CD166, CD167, CD167a, CD167b, CD168, CD169, CD170, CD171, CD172, CD172a, CD172b, CD172g, CD173, CD174, CD175, CD175s, CD176, CD177, CD178, CD179, CD179a, CD179b, CD180, CD181, CD182, CD183, CD184, CD185, CD186, CDw186, CD187, CD188, CD189, CD190, CD191, CD192, CD193, CD194, CD195, CD196, CD197, CD198, CD199, CDw198, CDw199, CD200, CD201, CD202, CD202a, CD202b, CD203, CD203c, CD204, CD205, CD206, CD207, CD208, CD209, CD210, CDw210a, CDw210b, CD211, CD212, CD213, CD213a1, CD213a2, CD214, CD215, CD216, CD217, CD218, CD218a, CD218, CD21b9, CD220, CD221, CD222, CD223, CD224, CD225, CD226, CD227, CD228, CD229, CD230, CD231, CD232, CD233, CD234, CD235, CD235a, CD235b, CD236, CD237, CD238, CD239, CD240, CD240ce, CD240d, CD241, CD242, CD243, CD244, CD245, CD246, CD247, CD248, CD249, CD250, CD251, CD252, CD253, CD254, CD255, CD256, CD257, CD258, CD259, CD260, CD261, CD262, CD263, CD264, CD265, CD266, CD267, CD268, CD269, CD270, CD271, CD272, CD273, CD274, CD275, CD276, CD277, CD278, CD279, CD281, CD282, CD283, CD284, CD285, CD286, CD287, CD288, CD289, CD290, CD291, CD292, CD293, CD294, CD295, CD296, CD297, CD298, CD299, CD300, CD300a, CD300b, CD300c, CD301, CD302, CD303, CD304, CD305, CD306, CD307, CD307a, CD307b, CD307c, CD307d, CD307e, CD307f, CD308, CD309, CD310, CD311, CD312, CD313, CD314, CD315, CD316, CD317, CD318, CD319, CD320, CD321, CD322, CD323, CD324, CD325, CD326, CD327, CD328, CD329, CD330, CD331, CD332, CD333, CD334, CD335, CD336, CD337, CD338, CD339, CD340, CD341, CD342, CD343, CD344, CD345, CD346, CD347, CD348, CD349, CD350, CD351, CD352, CD353, CD354, CD355, CD356, CD357, CD358, CD359, CD360, CD361, CD362, CD363, CD364, CD365, CD366, CD367, CD368, CD369, CD370, CD371, CD372, CD373, CD374, CD375, CD376, CD377, CD378, CD379, CD381, CD382, CD383, CD384, CD385, CD386, CD387, CD388, CD389, CRIPTO, CRIPTO, CR, CR1, CRGF, CRIPTO, CXCR5,

LY64, TDGF1, 4-1BB, APO2, ASLG659, BMPR1B, 4-1BB, 5AC, 5T4 Trophoblastic glycoprotein, TPBG, 5T4, Wnt-Activated Inhibitory Factor 1 or WAIF1, Adenocarcinoma antigen, AGS-5, AGS-22M6, Activin receptor-like kinase 1, AFP, AKAP-4, ALK, Alpha integrin, Alpha v beta6, Amino-peptidase N, Amyloid beta, Androgen receptor, Angiopoietin 2, Angiopoietin 3, Annexin A1, Anthrax toxin protective antigen, Anti-transferrin receptor, AOC3 (VAP-1), B7-H3, Bacillus anthracis anthrax, BAFF (B-cell activating factor), BCMA, B-lymphoma cell, bcr-abl, Bombesin, BORIS, C5, C242 antigen, CA125 (carbohydrate antigen 125, MUC16), CA-IX (or CAIX, carbonic anhydrase 9), CALLA, CanAg, Canis lupus famil-iaris IL31, Carbonic anhydrase IX, Cardiac myosin, CCL11 (C-C motif chemokine 11), CCR4 (C-C chemokine receptor type 4), CCR5, CD3E (epsilon), CEA (Carcinoembryonic antigen), CEACAM3, CEACAM5 (carcino-embryonic antigen), CFD (Factor D), Ch4D5, Cholecystokinin 2 (CCK2R), CLDN18 (Claudin-18), Clumping factor A, cMet, CRIPTO, FCSF1R (Colony stimulating factor 1 receptor), CSF2 (colony stimulating factor 2, Granulocyte-macrophage colony-stimulating factor (GM-CSF)), CSP4, CTLA4 (cytotoxic T-lymphocyte-associated protein 4), CTAA16.88 tumor antigen, CXCR4, C-X-C chemokine receptor type 4, cyclic ADP ribose hydrolase, Cyclin B1, CYP1B1, Cyto-megalovirus, Cytomegalovirus glycoprotein B, Dabigatran, DLL3 (delta-like-ligand 3), DLL4 (delta-like-ligand 4), DPP4 (Dipeptidyl-peptidase 4), DR5 (Death receptor 5), E. coli shiga toxin type-1, E. coli shiga toxin type-2, ED-B, EGFL7 (EGF-like domain-containing protein 7), EGFR, EGFRII, EG-FRvIII, Endoglin, Endothelin B receptor, Endotoxin, EpCAM (epithelial cell adhesion molecule), EphA2, Episialin, ERBB2 (Epidermal Growth Factor Receptor 2), ERBB3, ERG (TMPRSS2 ETS fusion gene), Escherichia coli, ETV6-AML, FAP (Fibroblast activation protein alpha), FCGR1, alpha-Fetoprotein, Fibrin II, beta chain, Fibronectin extra domain-B, FOLR (folate receptor), Folate receptor alpha, Folate hydrolase, Fos-related antigen 1F protein of respiratory syncytial virus, Frizzled receptor, Fucosyl GM1, GD2 ganglioside, G-28 (acell surface antigen glyvolipid), GD3 idiotype, GloboH, Glypican 3, N-glycolylneuraminic acid, GM3, GMCSF receptor α-chain, Growth differentiation fac-tor 8,

GP100, GPNMB (Trans-membrane glycoprotein NMB), GUCY2C (Guanylate cyclase 2C, guanylyl cyclase C (GC-C), intestinal Guanylate cyclase, Guanylate cyclase-C receptor, Heat-stable enterotoxin receptor (hSTAR)), Heat shock proteins, Hemagglutinin, Hepatitis B surface antigen, Hepatitis B virus, HER1 (human epidermal growth factor receptor 1), HER2, HER2/neu, HER3 (ERBB-3), IgG4, HGF/SF (Hepatocyte growth factor/scatter factor), HHGFR, HIV-1, Histone com-plex, HLA-DR (human leukocyte antigen), HLA-DR10, HLA-DRB, HMWMAA, Human chorionic gonadotropin, HNGF, Human scatter factor receptor kinase, HPV E6/E7, Hsp90, hTERT, ICAM-1 (Intercellular Adhesion Molecule 1), Idiotype, IGF1R (IGF-1, insulin-like growth factor 1 receptor), IGHE, IFN-γ, Influenza hemagglutinin, IgE, IgE Fc region, IGHE, interleukins (comprising IL-1, IL-2, IL-3, IL-4, IL-5, IL-6, IL-6R, IL-7, IL-8, IL-9, IL-10, IL-11, IL-12, IL-13, IL-15, IL-17, IL-17A, IL-18, IL-19, IL-20, IL-21, IL-22, IL-23, IL-27, or IL-28), IL31RA, ILGF2 (Insulin-like growth factor 2), Integrins (α4, $\alpha_{IIb}\beta_3$, αvβ3, $\alpha_4\beta_7$, α5β1, α6β4, α7β7, αllβ3, α5β5, αvβ5), Interferon gamma-induced protein, ITGA2, ITGB2, KIR2D, Kappa Ig, LCK, Le, Legumain, Lewis-Y antigen, LFA-1 (Lympho-cyte function-associated antigen 1, CD11a), LHRH, LINGO-1, Lipoteichoic acid, LIV1A, LMP2, LTA, MAD-CT-1, MAD-CT-2, MAGE-1, MAGE-2, MAGE-3, MAGE A1, MAGE A3, MAGE 4, MART1, MCP-1, MIF (Macrophage migration inhibitory factor, or glycosylation-inhibiting fac-tor (GIF)), MS4A1 (membrane-spanning 4-domains subfamily A member 1), MSLN (mesothelin), MUC1 (Mucin 1, cell surface associated (MUC1) or polymorphic epithelial mucin (PEM)), MUC1-KLH, MUC16 (CA125), MCP1 (monocyte chemotactic protein 1), MelanA/MART1, ML-IAP, MPG, MS4A1 (membrane-spanning 4-domains subfamily A), MYCN, Myelin-associated glycoprotein, My-ostatin, NA17, NARP-1, NCA-90 (granulocyte antigen), Nectin-4 (ASG-22ME), NGF, Neural apopto-sis-regulated proteinase 1, NOGO-A, Notch receptor, Nucleolin, Neu oncogene product, NY-BR-1, NY-ESO-1, OX-40, OxLDL (Oxidized low-density lipoprotein), OY-TES1, P21, p53 nonmutant, P97, Page4, PAP, Paratope of anti- (N-glycolylneuraminic acid), PAX3, PAX5, PCSK9, PDCD1 (PD-1, Programmed cell death protein 1), PDGF-Rα (Alpha-type platelet-derived

growth factor receptor), PDGFR-β, PDL-1, PLAC1, PLAP-like testicular alkaline phosphatase, Platelet-derived growth factor receptor beta, Phosphate-sodium co-transporter, PMEL 17, Polysialic acid, Proteinase3 (PR1), Prostat-ic carcinoma, PS (Phosphatidylserine), Prostatic carcinoma cells, Pseudomonas aeruginosa, PSMA, PSA, PSCA, Rabies virus glycoprotein, RHD (Rh polypeptide 1 (RhPI)), Rhesus factor, RANKL, RhoC, Ras mutant, RGS5, ROBO4, Respiratory syncytial virus, RON, ROR1, Sarcoma translocation breakpoints, SART3, Sclerostin, SLAMF7 (SLAM family member 7), Selectin P, SDC1 (Syndecan 1), sLe (a), Somatomedin C, SIP (Sphingosine-1-phosphate), Somatostatin, Sperm protein 17, SSX2, STEAP1 (six-transmembrane epithelial antigen of the prostate 1), STEAP2, STn, TAG-72 (tumor associated glycoprotein 72), Survivin, T-cell receptor, T cell transmembrane protein, TEM1 (Tumor endothelial marker 1), TENB2, Tenascin C (TN-C), TGF-α, TGF-β (Transforming growth factor beta), TGF-β1, TGF-β2 (Transforming growth factor-beta 2), Tie (CD202b), Tie2, TIM-1 (CDX-014), Tn, TNF, TNF-α, TNFRSF8, TNFRSF10B (tumor necrosis factor receptor superfamily member 10B), TNFRSF-13B (tumor necrosis factor receptor superfamily member 13B), TPBG (trophoblast glyco-protein), TRAIL-R1 (Tumor necrosis apoptosis Inducing ligand Receptor 1), TRAILR2 (Death recep-tor 5 (DR5)), tumor-associated calcium signal transducer 2, tumor specific glycosylation of MUC1, TWEAK receptor, TYRP1 (glycoprotein 75), TRP-2, Tyrosinase, VCAM-1, VEGF, VEGF-A, VEGF-2, VEGFR-1, VEGFR2, or vimentin, WT1, XAGE 1, or cells expressing any insulin growth factor receptors, or any epidermal growth factor receptors.

15. The compound according to claim 15, wherein the tumor cell is a lymphoma cell, myeloma cell, renal cell, breast cancer cell, prostate cancer cell, ovarian cancer cell, colorectal cancer cell, gastric cancer cell, squamous cancer cell, small-cell lung cancer cell, non-small-cell lung cancer cell, testicular cancer cell, or malignant cell.

16. A pharmaceutical composition comprising a therapeutically effective amount of the

conjugate compounds of claim 1, 2, 9, or 10, or a pharmaceutically acceptable salt thereof, or a combination of the conjugates thereof, together with a carrier, diluent, or excipient, for the treatment or prevention of a cancer, or an autoimmune disease, or an infectious disease.

17. The pharmaceutical composition either in the liquid formula or in the formulated lyophilized solid or powder according to claim 17, comprising by weight of: 0.01%-99% of one or more conjugates of claim 1, 2, 9, or 10; 0.0%-20.0% of one or more polyols; 0.0%-2.0% of one or more surfactants; 0.0%-5.0% of one or more preservatives; 0.0%-30% of one or more ami-no acids; 0.0%-5.0%of one or more antioxidants; 0.0%-0.3% of one or more metal chelating agents; 0.0%-30.0% of one or more buffer salts for adjusting pH of the formulation to pH 4.5 to 7.5; and 0.0%-30.0% of one or more of isotonic agent for adjusting osmotic pressure between 250 to 350 mOsm when reconstituted for administration to a patient;

wherein the polyol is fructose, mannose, maltose, lactose, arabinose, xylose, ribose, rhamnose, galactose, glucose, sucrose, trehalose, sorbose, melezitose, raffinose, mannitol, xylitol, erythritol, maltitol, lactitol, erythritol, threitol, sorbitol, glycerol, or L-gluconate or its metallic salts;

wherein the surfactant is polysorbate 20, polysorbate 40, polysorbate 65, poly-sorbate 80, polysorbate 81, or polysorbate 85, poloxamer, poly(ethylene oxide) -poly(propylene oxide), polyethylene-polypropylene, Triton^{TM}; sodium dodecyl sulfate (SDS), sodium laurel sulfate; sodium octyl glycoside; lauryl-, myristyl-, linoleyl-, or stearyl-sulfobetaine; lauryl-, myristyl-, linoleyl-or stearyl-sarcosine; linoleyl-, myristyl-, or cetyl-betaine; lauroamidopropyl-, cocami-dopropyl-, linoleamidopropyl-, myristamidopropyl-, palmidopropyl-, or isostearamidopropyl-betaine lauroamidopropyl; myristamidopropyl-, palmidopropyl-, or isostearamidopropyl-dimethylamine; sodium methyl cocoyl-, or disodium methyl oleyl-taurate; dodecyl betaine, dodecyl dimethylamine oxide, cocamidopropyl betaine and coco ampho glycinate; or isostearyl ethylimido-nium ethosulfate; polyethyl glycol,

polypropyl glycol, or a copolymer of ethylene and propylene glycol;

wherein the preservative is benzyl alcohol, octadecyldimethylbenzyl ammonium chloride, hexamethonium chloride, benzalkonium chloride, benzethonium chloride, phenol, butyl or benzyl alcohol, an alkyl paraben comprising methyl or propyl paraben, catechol, resorcinol, cyclo-hexanol, 3-pentanol, or m-cresol;

wherein the amino acid is arginine, cystine, glycine, lysine, histidine, ornithine, isoleucine, leucine, alanine, glycine glutamic acid or aspartic acid;

wherein the antioxidant is ascorbic acid, glutathione, cystine or methionine;

wherein the chelating agent is EDTA or EGTA;

wherein the buffer salt is sodium, potassium, ammonium, or trihydroxyethylamino salts of citric acid, ascorbic acid, gluconic acid, carbonic acid, tartaric acid, succinic acid, acetic acid or phthalic acid; Tris or tromethamine hydrochloride, phosphate or sulfate; arginine, glycine, glycylglycine, or histidine with anionic acetate, chloride, phosphate, sulfate, or succinate salts;

wherein the tonicity agent is mannitol, sorbitol, sodium acetate, potassium chloride, sodium phosphate, potassium phosphate, trisodium citrate, or sodium chloride.

18. A kit comprising the pharmaceutical composition according to claim 16 or 17 packed in a vial, bottle, pre-filled syringe, or pre-filled auto-injector syringe, wherein the pharmaceutical composition is in a form of a liquid or lyophilized solid.

19. The conjugate of claim 1, 2, 8, 9, or in the form of the pharmaceutical composition of claim 17 or 18, having in vitro, in vivo or ex vivo cell killing activity.

20. Use of the pharmaceutical composition according to claim 16 or 17, which is formulated for administration concurrently with a chemotherapeutic agent, a radiation therapy, an immunotherapy agent, an autoimmune disorder agent, an anti-infectious agent or a conjugate,

for synergistically treatment or prevention of a cancer, an autoimmune disease, or an infectious disease.

21. The use according to claim 20, further comprising use of:

(1) a) an alkylating agent comprising nitrogen mustards: chlorambucil, chlornaphazine, cyclophosphamide, dacarbazine, estramustine, ifosfamide, mechlorethamine, mechlorethamine oxide hydrochloride, mannomustine, mitobronitol, melphalan, mitolactol, pipobroman, novembichin, phenesterine, prednimustine, thiotepa, trofosfamide, uracil mustard; CC-1065 and adozelesin, carzelesin, bizelesin; duocarmycin, KW-2189, CBI-TMI, or CBI dimers; benzodiazepine dimers or pyrrolobenzodiazepine (PBD) dimers, tomaymy-cin dimers, indolinobenzodiazepine dimers, imidazobenzothiadiazepine dimers, or oxazolidinobenzo-diazepine dimers; Nitrosoureas: comprising carmustine, lomustine, chlorozotocin, fotemustine, ni- mustine, ranimustine; Alkylsulphonates: including busulfan, treosulfan, improsulfan and piposulfan; Triazenes or dacarbazine; Platinum containing compounds: comprising carboplatin, cisplatin, and oxaliplatin; aziridines, benzodopa, carboquone, meturedopa, or uredopa; ethylenimines and methyl-amelamines including altretamine, triethylenemelamine, trietylenephosphoramide, triethylenethio-phosphoramide or trimethylolomelamine;

b) A plant alkaloid comprising Vinca alkaloids: including vincristine, vinblastine, vindesine, vinorelbine, and navelbin; Taxoids: comprising paclitaxel, docetaxol, Maytansinoids including DM1, DM2, DM3, DM4, DM5, DM6, DM7, maytansine, ansamitocins, cryptophycins (including the group of cryptophycin 1 and cryptophycin 8); epothilones, eleutherobin, discodermolide, bryostatins, dolostatins, auristatins, tubulysins, cepha-lostatins; pancratistatin; a sarcodictyin; or spongistatin;

c) A DNA Topoisomerase Inhibitor comprising Epipodophyllins: comprising 9-aminocamptothecin, camptothecin, crisnatol, daunomycin, etoposide, etoposide phosphate, irinotecan, mitoxantrone, novantrone, retinoic acids, retinols, teniposide, topotecan, 9-

nitrocamptothecin or RFS 2000; or mitomycins;

d) an antimetabolite comprising { [Anti-folate: (DHFR inhibitors: comprising methotrexate, trimetrexate, denopterin, pteropterin, aminopterin (4-aminopteroic acid) or folic acid); IMP dehydrogenase inhibitors: (including mycophenolic acid, tiazofurin, ribavirin, EICAR); Ribonucleotide reductase Inhibitors: (including hydroxyurea, deferoxamine)]; pyrimidine: uracil, ancitabine, azacitidine, 6-azauridine, capecitabine, carmofur, cytarabine, dideoxyuridine, doxifluridine, enocitabine, 5-Fluorouracil, floxuridine, ratitrexed; cytosine, cytarabine, cytosine arabinoside, fludarabine; Purine, azathioprine, fludarabine, mercaptopurine, thiamiprine, thioguanine; folic acid replenisher, or frolinic acid};

e) a hormonal therapy comprising receptor antagonists: [Anti-estrogen: (including megestrol, raloxifene, tamoxifen); LHRH agonists: (including goscrclin, leuprolide acetate); Anti-androgens: (including bicalutamide, flutamide, calusterone, dromostanolone propionate, epitiostanol, goserelin, leuprolide, mepitiostane, nilutamide, testolactone, trilostane)]; Retinoids/Deltoids: [Vitamin D3, CB 1093, EB 1089 KH 1060, cholecalciferol, ergocal-ciferol; Photodynamic therapies: (including verteporfin, phthalocyanine, photosensitizer Pc4, demethoxyhypocrellin A); Cytokines: (comprising Interferon-alpha, Interferon-gamma, tumor necrosis factor (TNFs), or human proteins containing a TNF domain)] };

f) A kinase inhibitor comprising BIBW 2992 (anti-EGFR/Erb2), imatinib, gefitinib, pegaptanib, sorafenib, dasatinib, sunitinib, erlotinib, nilotinib, lapatinib, axitinib, pazopanib, vandetanib, E7080 (anti-VEGFR2), mubritinib, ponatinib, bafetinib, bosutinib, cabozantin- ib, vismodegib, iniparib, ruxolitinib, CYT387, axitinib, tivozanib, sorafenib, bevacizumab, cetuximab, Trastuzumab, Ranibizumab, Panitumumab, or ispinesib;

g) A poly(ADP-ribose) polymerase (PARP) inhibitors comprising olaparib, ni-raparib, iniparib, talazoparib, veliparib, CEP 9722 (Cephalon^{TM}'s), E7016 (Eisai^{TM}'s), BGB-290 (BeiGene^{TM}'s), or 3-aminobenzamide;

h) An antibiotic comprising an enediyne antibiotic comprising calicheamicin, calicheamicin γ1, δ1, α1 or β1; dynemicin, including dynemicin A and deox-ydynemicin;

esperamicin, kedarcidin, C-1027, maduropeptin, or neocarzinostatin chromophore and related chromoprotein enediyne antibiotic chromomophores), aclacinomycins, actinomycin, authramy-cin, azaserine, bleomycins, cactinomycin, carabicin, carminomycin, carzinophilin; chromomycins, dactinomycin, daunorubicin, detorubicin, 6-diazo-5-oxo-L-norleucine, doxorubicin, morpholino-doxorubicin, cyanomorpholino-doxorubicin, 2-pyrrolino-doxorubicin and deoxydoxorubicin, epirubi-cin, eribulin, esorubicin, idarubicin, marcellomycin, nitomycins, mycophenolic acid, nogalamycin, olivomycins, peplomycin, potfiromycin, puromycin, quelamycin, rodorubicin, streptonigrin, streptozo-cin, tubercidin, ubenimex, zinostatin, or zorubicin;

i) A polyketide (acetogenin), bullatacin and bullatacinone; gemcitabine, epoxomicins andcarfil-zomib, bortezomib, thalidomide, lenalidomide, pomalidomide, tosedostat, zybrestat, PLX4032, STA-9090, Stimuvax, allovectin-7, Xegeva, Provenge^{TM}, Yervoy^{TM}, Isoprenylation inhibitors and Lovastatin, Dopaminergic neurotoxins and1-methyl-4-phenylpyridinium ion, Cell cycle inhibitors (including stau-rosporine), Actinomycins (including Actinomycin D, dactinomycin), amanitins, Bleomycins (includ-ing bleomycin A2, bleomycin B2, peplomycin), Anthracyclines (including daunorubicin, doxorubicin (adriamycin), idarubicin, epirubicin, pirarubicin, zorubicin, mtoxantrone, MDR inhibitors or verapamil, Ca $^{2+}$ATPase inhibitors or thapsigargin, Histone deacetylase inhibitors ((including Vorinostat, Ro-midepsin, Panobinostat, Valproic acid, Mocetinostat (MGCD0103), Belinostat, PCI-24781, Entinostat, SB939, Resminostat, Givinostat, AR-42, CUDC-101, sulforaphane, Trichostatin A); Thapsigargin, Celecoxib, glitazones, epigallocatechin gallate, Disulfiram, Salinosporamide A.; Anti-adrenals comprising aminoglutethimide, mitotane, trilostane; aceglatone; aldophosphamide glycoside; aminolevulinic acid; amsacrine; arabinoside, bestrabucil; bisantrene; edatraxate; defofamine; demecol-cine; diaziquone; eflornithine (DFMO), elfomithine; elliptinium acetate, etoglucid; gallium nitrate; gacytosine, hydroxyurea; ibandronate, lentinan; lonidamine; mitoguazone; mitoxantrone; mopidamol; nitracrine; pentostatin; phenamet; pirarubicin; podophyllinic acid; 2-ethylhydrazide;

procarbazine; PSK®; razoxane; rhizoxin; sizofiran; spirogermanium; tenuazonic acid; triaziquone; 2,2',2″-trichlorotriethylamine; trichothecenes (including the group of T-2 toxin, verrucarin A, roridin A and anguidine); urethane, siRNA, or antisense drugs;

(2) An anti-autoimmune disease agent: cyclosporine, cyclosporine A, aminocaproic acid, azathio-prine, bromocriptine, chlorambucil, chloroquine, cyclophosphamide, corticosteroids (including the group consisting of amcinonide, betamethasone, budesonide, hydrocortisone, flunisolide, fluticasone propionate, fluocortolone danazol, dexamethasone, Triamcinolone acetonide, beclometasone dipropio-nate), DHEA, enanercept, hydroxychloroquine, infliximab, meloxicam, methotrexate, mofetil, myco-phenylate, prednisone, sirolimus, or tacrolimus;

(3) An anti-infectious disease agents comprising:

a) Aminoglycosides: amikacin, astromicin, gentamicin (netilmicin, sisomicin, isepamicin), hygromycin B, kanamycin (amikacin, arbekacin, bekanamycin, dibekacin, tobramycin), neomycin (framycetin, paromomycin, ribostamycin), netilmicin, spectinomycin, streptomycin, tobramycin, or verdamicin;

b) Amphenicols: azidamfenicol, chloramphenicol, florfenicol, or thiamphenicol;

c) Ansamycins: geldanamycin or herbimycin;

d) Carbapenems: biapenem, doripenem, ertapenem, imipenem, cilastatin, meropenem, or panipenem;

e) Cephems: carbacephem (loracarbef), cefacetrile, cefaclor, cefradine, cefadroxil, cefalonium, cefaloridine, cefalotin or cefalothin, cefalexin, cefaloglycin, cefamandole, cefapirin, cefatrizine, cefazaflur, cefazedone, cefazolin, cefbuperazone, cefcapene, cefdaloxime, cefepime, cefminox, cefox-itin, cefprozil, cefroxadine, ceftezole, cefuroxime, cefixime, cefdinir, cefditoren, cefepime, cefetamet, cefmenoxime, cefodizime, cefonicid, cefoperazone, ceforanide, cefotaxime, cefotiam, cefozopran, cephalexin, cefpimizole, cefpiramide, cefpirome, cefpodoxime, cefprozil, cefquinome, cefsulodin, ceftazidime, cefteram, ceftibuten, ceftiolene, ceftizoxime, ceftobiprole, ceftriaxone, cefuroxime, cefu-

zonam, cephamycin (including cefoxitin, cefotetan, cefmetazole), or oxacephem (flomoxef, latamoxef);

f) Glycopeptides: bleomycin, vancomycin (including oritavancin, telavancin), teicoplanin (dalba-vancin), or ramoplanin;

g) Glycylcyclines: tigecycline;

h) β-Lactamase inhibitors: penam (sulbactam, tazobactam) or clavam (clavulanic acid);

i) Lincosamides: clindamycin or lincomycin;

j) Lipopeptides: daptomycin, A54145, calcium-dependent antibiotics (CDA);

k) Macrolides: azithromycin, cethromycin, clarithromycin, dirithromycin, erythromycin, flurithromycin, josamycin, ketolide (telithromycin, cethromycin), midecamycin, miocamycin, olean-domycin, rifamycins (rifampicin, rifampin, rifabutin, rifapentine), rokitamycin, roxithromycin, spec-tinomycin, spiramycin, tacrolimus (FK506), troleandomycin, or telithromycin;

l) Monobactams: aztreonam or tigemonam;

m) Oxazolidinones: linezolid;

n) Penicillins: amoxicillin, ampicillin, pivampicillin, hetacillin, bacampicillin, metampicillin, talampicillin, azidocillin, azlocillin, benzylpenicillin, benzathine benzylpenicillin, benzathine phe-noxymethylpenicillin, clometocillin, procaine benzylpenicillin, carbenicillin (carindacillin), cloxacillin, dicloxacillin, epicillin, flucloxacillin, mecillinam (pivmecillinam), mezlocillin, meticillin, nafcillin, oxacillin, penamecillin, penicillin, pheneticillin, phenoxymethylpenicillin, piperacillin, propicillin, sulbenicillin, temocillin, or ticarcillin;

o) Polypeptides: bacitracin, colistin, or polymyxin B;

p) Quinolones: alatrofloxacin, balofloxacin, ciprofloxacin, clinafloxacin, danofloxacin, difloxacin, enoxacin, enrofloxacin, floxin, garenoxacin, gatifloxacin, gemifloxacin, grepafloxacin, kano trovaflox-acin, levofloxacin, lomefloxacin, marbofloxacin, moxifloxacin, nadifloxacin, norfloxacin, orbifloxacin, ofloxacin, pefloxacin, trovafloxacin, grepafloxacin,

sitafloxacin, sparfloxacin, temafloxacin, tosufloxacin, or trovafloxacin;

q) Streptogramins: pristinamycin, or quinupristin/dalfopristin;

r) Sulfonamides: mafenide, prontosil, sulfacetamide, sulfamethizole, sulfanilimide, sulfasalazine, sulfisoxazole, trimethoprim, or trimethoprim-sulfamethoxazole (co-trimoxazole);

s) Steroid antibacterials comprising fusidic acid;

t) Tetracyclines: doxycycline, chlortetracycline, clomocycline, demeclocycline, lymecycline, meclocycline, metacycline, minocycline, oxytetracycline, penimepicycline, rolitetracycline, tetracy-cline, glycylcyclines (including tigecycline); u) antibiotics comprising annonacin, arsphenamine, bactoprenol inhibitors (Bacitracin), DADAL/AR inhibitors (cycloserine), dictyostatin, discodermolide, eleuthero-bin, epothilone, ethambutol, etoposide, faropenem, fusidic acid, furazolidone, isoniazid, laulimalide, metronidazole, mupirocin, mycolactone, NAM synthesis inhibitors (fosfomycin), nitrofurantoin, paclitaxel, platensimycin, pyrazinamide, quinupristin/dalfopristin, rifampicin (rifampin), tazobactam tinidazole, or uvaricin;

(4) Anti-viral drugs comprising:

a) Entry/fusion inhibitors: aplaviroc, maraviroc, vicriviroc, gp41 (enfuvirtide), PRO 140, or CD4 (ibalizumab);

b) Integrase inhibitors: raltegravir, elvitegravir, or globoidnan A;

c) Maturation inhibitors: bevirimat or vivecon;

d) Neuraminidase inhibitors: oseltamivir, zanamivir, or peramivir;

e) Nucleosides or nucleotides: abacavir, aciclovir, adefovir, amdoxovir, apricitabine, brivudine, cidofovir, clevudine, dexelvucitabine, didanosine (ddI), elvucitabine, emtricitabine (FTC), entecavir, famciclovir, fluorouracil (5-FU), 3'-fluoro-2',3' -dideoxythymidine (FLT) or 3'-fluoro-2',3'-dideoxyguanosine (FLG), fomivirsen, ganciclovir, idoxuridine, lamivudine (3TC), l-nucleosides (including the group consisting of β-l-thymidine and β-l-2' -deoxycytidine), penciclovir, racivir, ribavirin, stampidine, stavudine (d4T), taribavirin

(viramidine), telbivudine, tenofovir, trifluridine valaciclovir, valganciclovir, zalcitabine (ddC), or zidovudine (AZT);

f) Non-nucleosides: amantadine, ateviridine, capravirine, diarylpyrimidines (etravirine, rilpi-virine), delavirdine, docosanol, emivirine, efavirenz, foscarnet (phosphonoformic acid), imiquimod, interferon alfa, loviride, lodenosine, methisazone, nevirapine, NOV-205, peginterferon alfa, podophyl-lotoxin, rifampicin, rimantadine, resiquimod (R-848), or tromantadine;

g) Protease inhibitors: amprenavir, atazanavir, boceprevir, darunavir, fosamprenavir, indinavir, lopinavir, nelfinavir, pleconaril, ritonavir, saquinavir, telaprevir (VX-950), or tipranavir;

h) anti-virus drugs: abzyme, arbidol, calanolide a, ceragenin, cyanovirin-n, diarylpyrimidines, epigallocatechin gallate (EGCG), foscarnet, griffithsin, taribavirin (viramidine), hydroxyurea, KP-1461, miltefosine, pleconaril, portmanteau inhibitors, ribavirin, or seliciclib;

(5) pharmaceutically acceptable salts, acids, hydrate or hydrated salt; or a crystalline structure; or an optical isomer, racemate, diastereomer or enantiomer of any of the above drugs.

22. The use according to claim 20, wherein the synergistic agents comprise Abatacept, abemaciclib, Abiraterone acetate, Abraxane, Acetaminophen/hydrocodone, Acalabru-tinib, aducanumab, Adalimumab, ADXS31-142, ADXS-HER2, afatinib dimaleate, aldesleukin, alec-tinib, alemtuzumab, Alitretinoin, ado-trastuzumab emtansine, Amphetamine/dextroamphetamine, anas-trozole, Aripiprazole, anthracyclines, Aripiprazole, Atazanavir, Atezolizumab, Atorvastatin, Avelumab, Axicabtagene ciloleucel, axitinib, belinostat, BCG Live, Bevacizumab, bexarotene, blinatumomab, Bortezomib, bosutinib, brentuximab vedotin, brigatinib, Budesonide, Budesonide/formoterol, Bupren-orphine, Cabazitaxel, Cabozantinib, capmatinib, Capecitabine, carfilzomib, chimeric antigen receptor-

engineered T (CAR-T) cells, Celecoxib, ceritinib, Cetuximab, Chidamide, Ciclosporin, Cinacalcet, crizotinib, Cobimetinib, Cosentyx, crizotinib, CTL019, Dabigatran, dabrafenib, dacarbazine, dacli-zumab, dacomotinib, daptomycin, Daratumumab, Darbepoetin alfa, Darunavir, dasatinib, denileukin diftitox, Denosumab, Depakote, Dexlansoprazole, Dexmethylphenidate, Dexamethasone, DigniCap Cooling System, Dinutuximab, Doxycycline, Duloxetine, Duvelisib, durvalumab, elotuzumab, Emtrici-bine/Rilpivirine/Tenofovir, disoproxil fumarate, Emtricitbine/tenofovir/efavirenz, Enoxaparin, en-sartinib, Enzalutamide, Epoetin alfa, erlotinib, Esomeprazole, Eszopiclone, Etanercept, Everolimus, exemestane, everolimus, exenatide ER, Ezetimibe, Ezetimibe/simvastatin, Fenofibrate, Filgrastim, fingolimod, Fluticasone propionate, Fluticasone/salmeterol, fulvestrant, gazyva, gefitinib, Glatiramer, Goserelin acetate, Icotinib, Imatinib, Ibritumomab tiuxetan, ibrutinib, idelalisib, ifosfamide, Infliximab, imiquimod, ImmuCyst, Immuno BCG, iniparib, Insulin aspart, Insulin detemir, Insulin glargine, Insulin lispro, Interferon alfa, Interferon alfa-1b, Interferon alfa-2a, Interferon alfa-2b, Interferon beta, Interfer on beta 1a, Interferon beta 1b, Interferon gamma-1a, lapatinib, Ipilimumab, Ipratropium bromide/sal-butamol, Ixazomib, Kanuma, Lanreotide acetate, lenalidomide, lenaliomide, lenvatinib mesylate, letro-zole, Levothyroxine, Levothyroxine, Lidocaine, Linezolid, Liraglutide, Lisdexamfetamine, LN-144, lorlatinib, Memantine, Methylphenidate, Metoprolol, Mekinist, mericitabine/Rilpivirine/Tenofovir, Modafinil, Mometasone, Mycidac-C, Necitumumab, neratinib, Nilotinib, niraparib, Nivolumab, ofatu-mumab, obinutuzumab, olaparib, Olmesartan, Olmesartan/hydrochlorothiazide, Omalizumab, Omega-3 fatty acid ethyl esters, Oncorine, Oseltamivir, Osimertinib, Oxycodone, palbociclib, Palivizumab, panitumumab, panobinostat, pazopanib, pembrolizumab, PD-1 antibody, PD-L1 antibody, Pemetrexed, pertuzumab, Pneumococcal conjugate vaccine, pomalidomide, Pregabalin, ProscaVax, Propranolol, Quetiapine, Rabeprazole, radium 223 chloride, Raloxifene, Raltegravir, ramucirumab, Ranibizumab, regorafenib, ribociclib, Rituximab, Rivaroxaban, romidepsin, Rosuvastatin, ruxolitinib phosphate, Sal-butamol, savolitinib, semaglutide, Sevelamer,

Sildenafil, siltuximab, Sipuleucel-T, Sitagliptin, Sitagliptin/metformin, Solifenacin, solanezumab, Sonidegib, Sorafenib, Sunitinib, tacrolimus, tacrimus, Tadalafil, tamoxifen, Tafinlar, Talimogene laherparepvec, talazoparib, Telaprevir, talazoparib, Te-mozolomide, temsirolimus, Tenofovir/emtricitabine, tenofovir disoproxil fumarate, Testosterone gel, Thalidomide, TICE BCG, Tiotropium bromide, Tisagenlecleucel, toremifene, trametinib, Trastuzumab, Trabectedin, trametinib, tremelimumab, Trifluridine/tipiracil, Tretinoin, Uro-BCG, Ustekinumab, Valsartan, veliparib, vandetanib, vemurafenib, venetoclax, vorinostat, ziv-aflibercept, Zostavax, or pharmaceutically acceptable salts thereof, or any combination thereof.