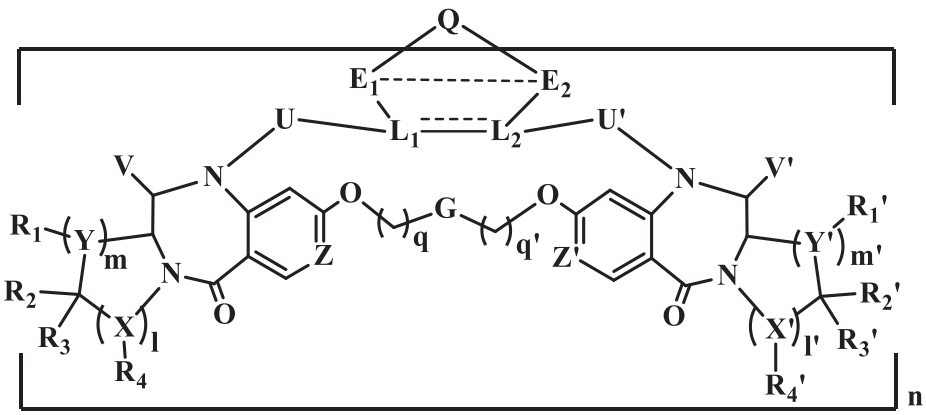
CLAIMS

What is claimed is:

1. A cross-linked PBD dimer derivative and its conjugate to a cell-binding molecule having the structure of Formula (I):



(I)

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:

----- represents an optional single bond or can be absent;

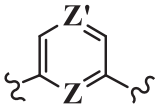
═══ represents an optional single bond or a double bond;

V and V', the same or different, are independently selected from the group consisting of H, OH, -NHOH; OR_5 (an ether); $OCOR_5$ (an ester); $OCOOR_5$ (a carbonate); NR_5R_5', NR_5COR_5', or $NR_5NR_5'NR_5''$ (an amine); $OCONR_5R_5$' (a carbamate); $NR_5(C{=}NH)NR_5'R_5''$ (a guanidinum); $NR_5CONR_5'R_5''$ (a urea); $OCSNHR_5$ (a thiocarbamate); -SH (a thiol); $-SR_5$ (a sulfide); SOR_5 a sulphoxide (a sulphoxide); $SOOR_5$ (a sulfone); SO_3, HSO_3, HSO_2, or a salt of HSO^{3-}, SO_3^{2-} or $-HSO_2^-$ (a sulphite); OSO_3 (a bisulphite); NR_5SOOR_5' (a sulfonamide); $H_2S_2O_5$ or a salt of $S_2O_5^{2-}$ (a metabisulfite); PO_3SH_3, $PO_2S_2H_2$, POS_3H_2, PS_4H_2 or a salt of PO_3S^{3-}, $PO_2S_2^{3-}$, POS_3^{3-}, PS_4^{3-} (mono-,di-, tri-, and tetra-thiophosphate); $(R_5O)_2POSR_5$' (a thiophosphate ester); HS_2O_3 or a salt of $S_2O_3^{2-}$ (a thiosulfate); HS_2O_4 or a salt of $S_2O_4^{2-}$ (a dithionite); $P(=S)(OR_5)(S)(OH)$ (a phosphorodithioate) or a salt thereof form with a cation; $-NR_5OR_5$' (a hydroxylamine derivative); $R_5C(=O)NOH$ (a hydroxamic acid) or a salt formed with a cation; $HOCH_2SO_2^-$, or its salts (a formaldehyde sulfoxylate); $NR_5COR_{5'}$ (an amide); O-glycoside; N_3 (an azido); CN (a cyano); X (a halo: F, Cl, Br, or I); $C(R_5)(R_{5'})(R_{5''})$ (a trialkyl), $OP(O)(OR_5)(NHR_{5'})$ or $OP(O)(NHR_5)(NHR_{5'})$ (a phosphoramidate (phosphoramidic acid), or $P(R_5)(R_{5'})(R_{5''})$ triarylphosphonium; Aa (an amino acid), or $NR_5CO(Aa)_t$ (a peptide), wherein Aa is an amino acid or a polypeptide containing between t =1~ 100 amino acid units; an aminoacid-derived group: an α-, β-, γ-, or ω-aminoacid, or an unnatural aminoacid; wherein R_5, R_5' and R_5'' are described below;

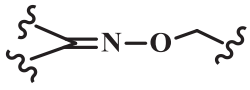
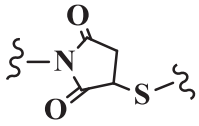
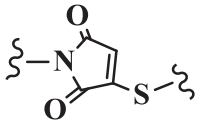
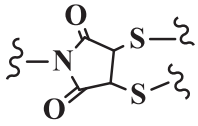
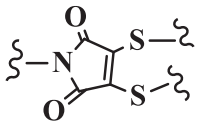
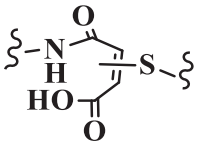
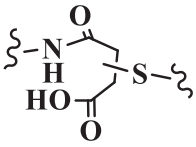
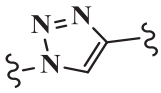
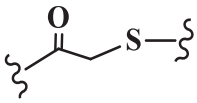
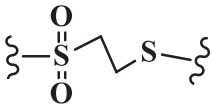
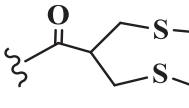
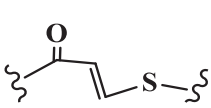
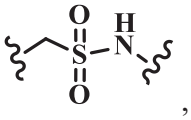
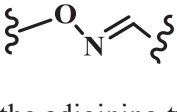
l, m, q, l', m' and q' are independently a number of 0, 1, 2, 3, 4, or 5; n is 1~30;

X, X', Y and Y' the same or different, independently, represent N, O, S, an alkyl, such as CH_2 or CHR_5, an alkene, such as =CH- or $=CR_5$-, an ether, such as $–C(OR_5)H$-;

Z and Z' the same or different, independently, represent N, CH, CR_5, COH, CNH_2, $CNHR_5$, or COR_5, or Z and Z' link together with $–COR_5OC$-; wherein R_5 is independently selected from C_1~C_8 alkyl and aryl;

G is $-CH_2$-, O, $-N(R_5)$-, S, $-P(O)(OR_5)$-, $-P(O)(N\ R_5R_{5'})$-,  wherein Z and Z' are defined above;

U and U' are independently C(O), C(O)O, C(O)NH, $C(O)N(R_5)$, C(=NH), C(=NH)O, C(=NH)NH, $C(=NH)N(R_5)$, -C=N-, C(=S), C(O)S, C(S)NH, $C(S)N(R_5)$, S(O), S(O)O, S(O)NH, $S(O)(OR_5)$, $S(O)(N(R_5))$, $S(O_2)$, $S(O_2)O$, $P(O)(OR_5)$, $P(O)(OR_5)O$, $P(O)(NH_2)$, $P(O)(NR_5R_{5'})$, $P(O)(OR_5)NH$-, $P(O)(OR_5)NR_{5'}$-, P(O) $(N(R_5R_{5'})$ $(N(R_5)$, $P(S)(OR_5)$, $P(S)(OR_5)O$, $P(S)(NH_2)$, $P(S)(NR_5R_{5'})$, $P(S)(OR_5)NH$-, $P(S)(OR_5)NR_{5'}$-, $P(S)(N(R_5R_{5'})N(R_5)$, R_5, R_5O;

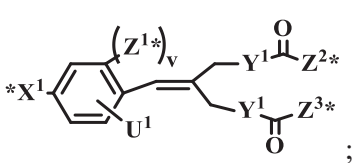
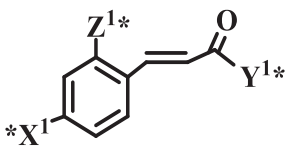
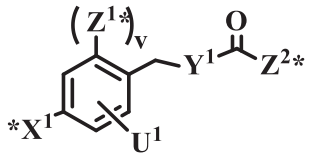
E_1 and E_2 are independently S, R_5S, C(O)S, C(O)NH, C(O)O, $C(O)R_5S$, C(=NH)NH, $C(=NH)N(R_5)$, C(=NH)S, -C=N-, C(=S)S, C(O)S, C(=S)NH, $C(=S)N(R_5)$, Ar-S, $NC(O)CH_2S$, $ArC(O)CH_2S$, S-S,  ,  ,  ,  ,  ,  ,  ,  ,  ,  ,  ,  ,  ,  ; wherein the chemical bond in the middle of two atoms means it can link either of the adjoining two atoms; wavery line is a connecting site;

L_1, and L_2 have independently the formula of: —Ww—(Aa)r—Tt—; or —Ww—(Aa)r—Tt—Q; or Q—Ww—(Aa)r—Tt—; wherein: -W- is a Stretcher unit; w is 0 or 1; -Aa- is independently an Amino Acid unit; r is independently an integer ranging from 1 to 100; -T- is a Spacer unit which is a linear alkyl or branched alkyl, or polyethylene glycol spacer; and t is 0, or 1~100; The Stretcher unit W independently contains a self-immolative spacer, peptidyl units, a hydrazone bond, a disulfide, an ester, or a thioether bond; w is 1 or 2 or 3; The Stretcher unit (--W--), when present, links a targeted binding molecular unit (CBA) to an amino acid unit (--Aa--), or

links T when an Aa is not present $(Aa)_r$, r =1-12(one to 12 amino acid units), which is composed from natural or unnatural amino acids, or the same or different sequences of dipeptide, tripeptide, tetrapeptide, pentapeptide, hexapeptide, heptapeptide, octapeptide, nonapeptide, decapeptide, undecapeptide or dodecapeptide unit; or

L_1 or L_2 independently contain a self-immolative or a non-self-imolative component, peptidic units, a hydrazone bond, a disulfide, an ester, an oxime, an amide, or a thioether bond;

wherein the self-immolative spacer is an aromatic compound that is electronically similar to the para-aminobenzylcarbamoyl (PAB) groups such as 2-aminoimidazol-5-methanol derivatives, heterocyclic PAB analogs, beta-glucuronide, and ortho or para-aminobenzylacetals or has one of the following structures:


; 
; 
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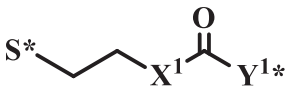
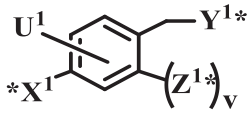
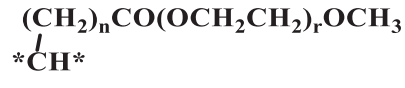

; or 

wherein the (*) atom is the point of attachment of additional spacer or releasable linker units, or the cytotoxic agent, and/or the binding molecule (CBA); X^1, Y^1, Z^2 and Z^3 are independently NH, O, or S; Z^1 is H, OH, 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 selected from 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;

wherein the non-self-immolative component contains one of the following structures: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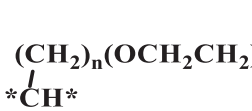
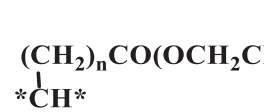
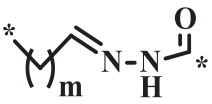

; 
; 
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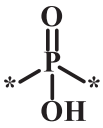
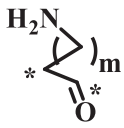
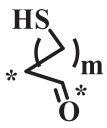
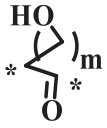
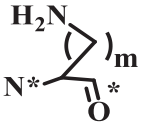
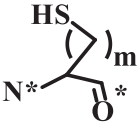
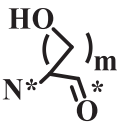
; 
; 
; 
; 
; 
; 
; 
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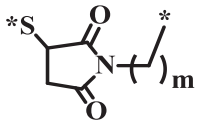
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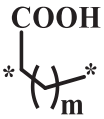
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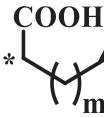
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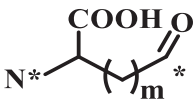
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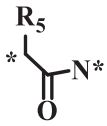
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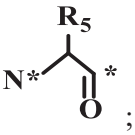
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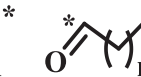
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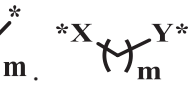
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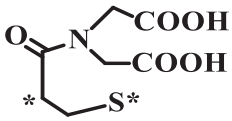
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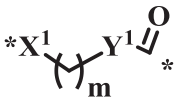
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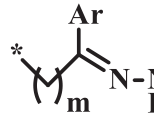
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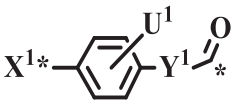
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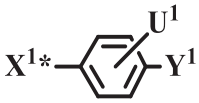
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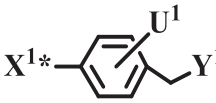
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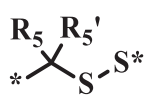
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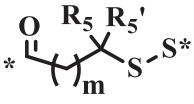
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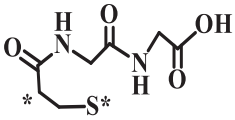
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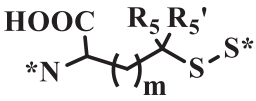
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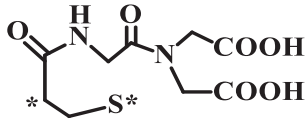
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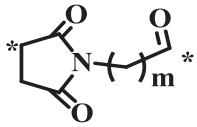
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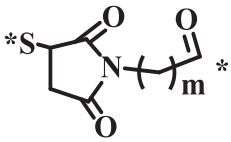
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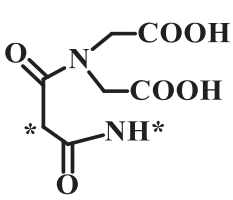
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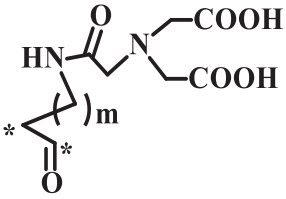
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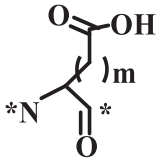
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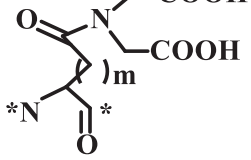
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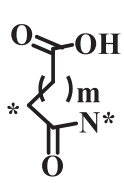
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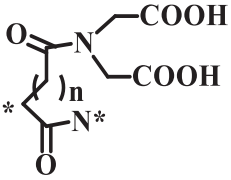
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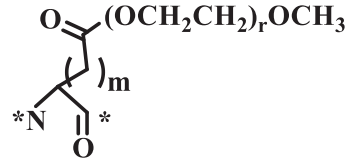
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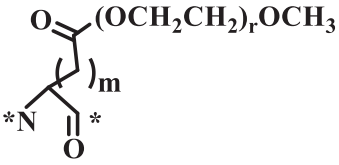
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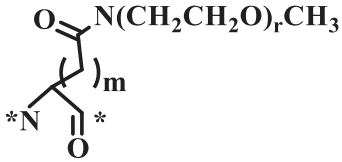
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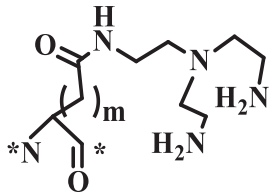
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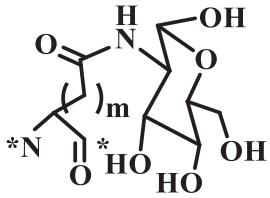
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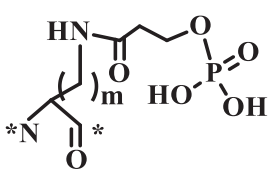
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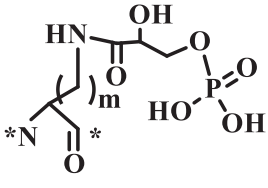
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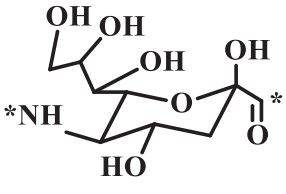
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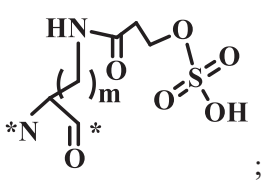
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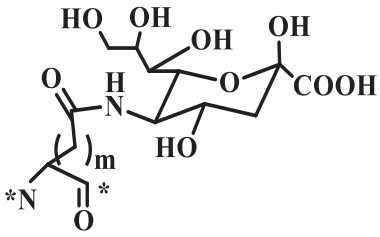
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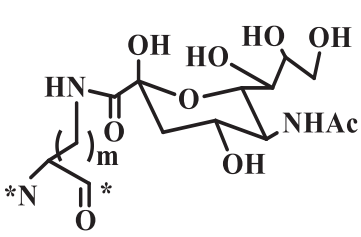
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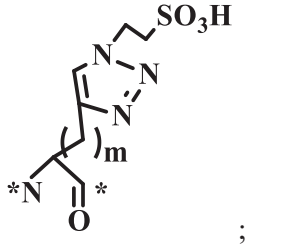
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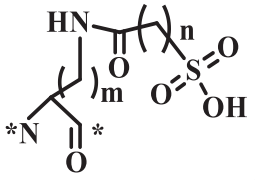
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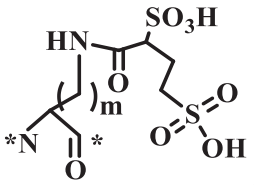
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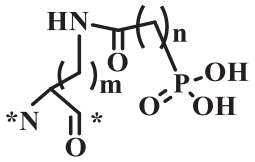

;

wherein the (*) atom is the site of attachment; 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;

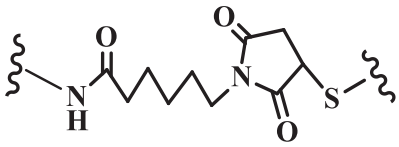
R_1, R_2, R_3, R_4, R_1', R_2', R_3', and R_4' are the same or different and independently chosen from -H, substituted linear, branched or cyclic alkyl, alkenyl or alkynyl having from 1 to 10 carbon atoms, $-(OCH_2CH_2)_tR_5$ (a polyethylene glycol unit), halogen, $NH(C{=}NH)NH_2$ (a guanidinium), $-OR_5$, $-NR_5R_5'$, $-NO_2$, -NCO, $-NR_5COR_5'$, $-SR_5$, $-SOR_5$ (a sulfoxide), $-SO_2R_5$ (a sulfone), $--SO_3^-M^+$ or $-SO_3H$ (a sulfonate), $-OSO_3^-M^+$ or OSO_3H (a sulfate), $-SO_2NR_5R_5'$ (a sulfonamide), CN (a cyano), N_3 (an azido), $--COR_5$, $--OCOR_5$, $-OCONR_5R_5'$, CF_3, OR_5, Aryl, heterocycle, or $P(O)R_5R_5'R_5''$;

R_5, R_5' and R_5'' are independently selected from H, C_1~C_8 of alkyl, alkenyl, alkinyl, heteroalkyl, aryl, arylalkyl, carbonyl, or pharmaceutical salts;

In addition, R_1 and R_2 join together, or R_1' and R_2' join together form a =O (ketone), =S, =NR, -C(=O)R, or a double bond containing group $=CR_5R_5'$; and R_1 and R_2 join together, or R_1' and R_2' join together, or R_3 and R_4 join together, or R_3' and R_4' join together to form a C_3-C_{12} aromatic, heterocyclic, carbocyclic, or heteroaryl ring;

Q is a cell binding molecule (CBA), or a functional group that enables reaction with a cell-binding agent, or a functional group capable of reacting with a linker attached on a cell binding agent; The function group is chosen from a thiol, an amine, a hydrazine, an alkoxylamino, a disulfide substituent, a maleimido, a haloacetyl group, an *N*-hydroxy succinimide ester, a keton, an ester, an aldehyde, an alkynyl, an alkenyl, or protected thiol or disulfide group, SAc, SSR_1 or SSAr, wherein Ar is aromatic group or hetero aromatic group; The cell-binding agent/ molecule is selected from the group consisting of 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, a domain antibody fragment that binds to the target cell, an adnectin that mimics antibody, DARPins, a lymphokine, a hormone, a vitamin, a growth factor, a colony stimulating factor, a nutrient-transport molecule (a transferrin), and a binding peptide, protein, or small molecule attached on albumin, a polymer, a dendrimer, a liposome, a nanoparticle, a vesicle, or a (viral) capsid;

In addition, U, U', L_1, L_2, L', E_1 or E_2 may independently be composed of one or more following components as shown below: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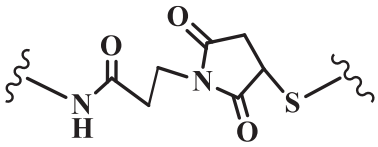
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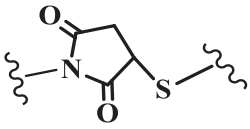
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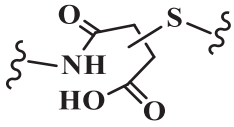
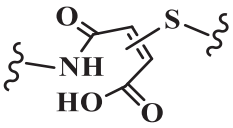

thio-amino-oxobutanoic acid,

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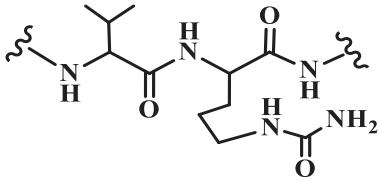
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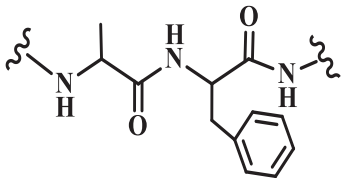
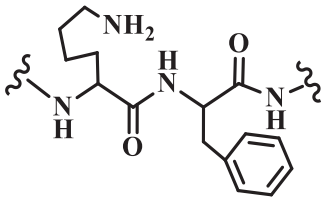

alanine-phenylalanine (ala-phe),

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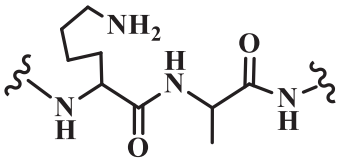
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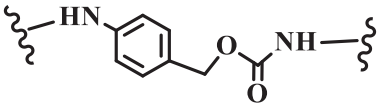
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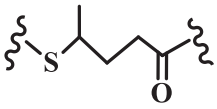
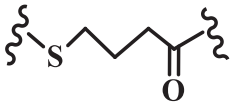

4-thio-pentanoate (SPP),

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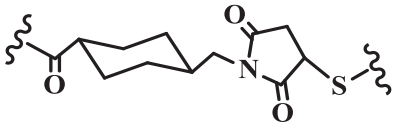
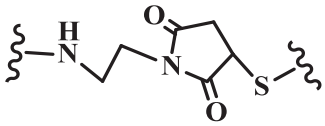
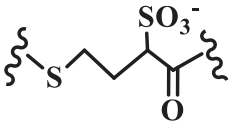
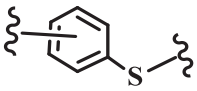

4-(N-maleimidomethyl)cyclo-hexane-1-carboxylate (MCC),

maleimidoethyl (ME),

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

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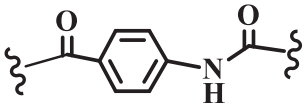
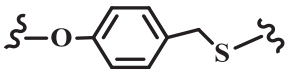
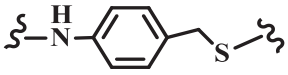
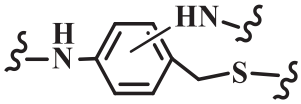
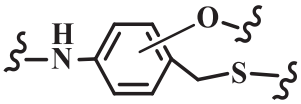
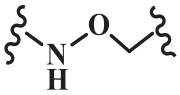
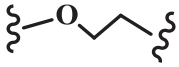
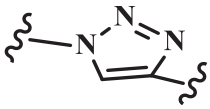
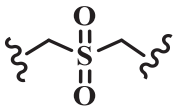
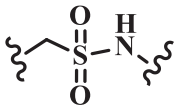
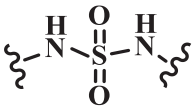
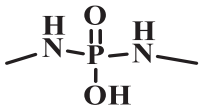
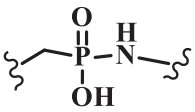
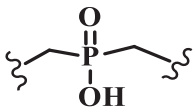
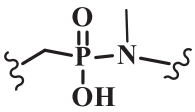
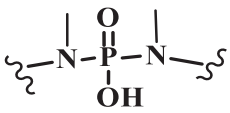
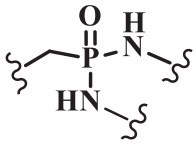
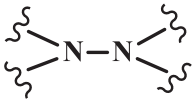
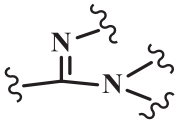
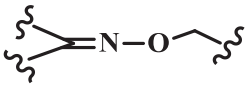
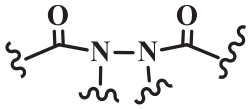
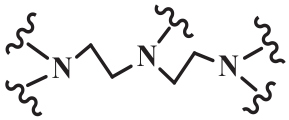
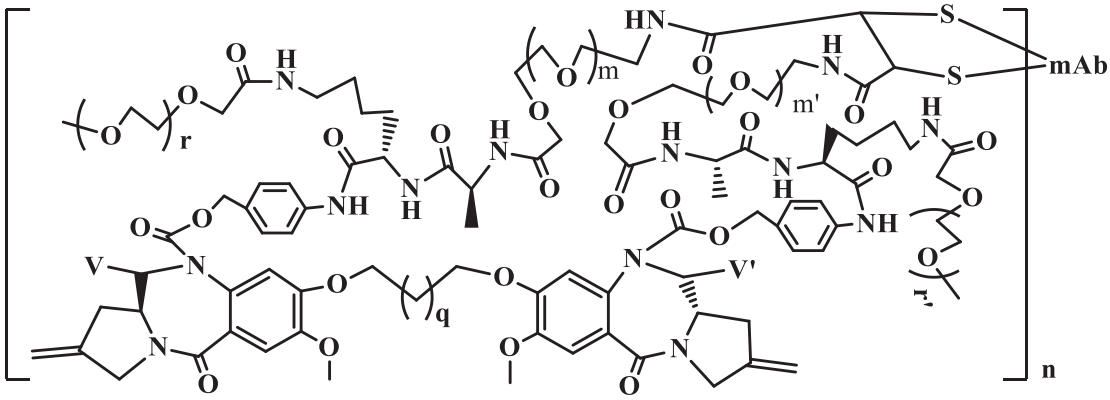
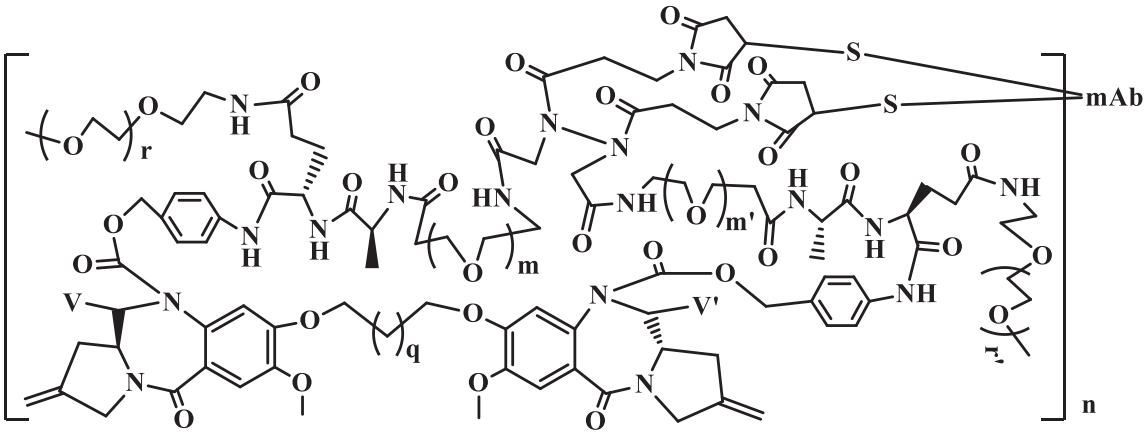

(4-acetyl)aminobenzoate (SIAB),

, oxylbenzylthio,


aminobenzylthio, dioxylbenzylthio,  diamino-benzylthio,  amino-oxylbenzylthio,  alkoxy amino (AOA),  ethyleneoxy (EO), 4-methyl-4-dithio-pentanoic (MPDP),  triazole, dithio,  alkylsulfonyl,  alkylsulfonamide,  sulfon-bisamide,  Phosphondi-amide,  alkylphosphonamide,  phosphinic acid,  N-methylphosphonamidic acid,  N,N'-dimethylphosphon-amidic acid,  N,N'-dimethylphosphondiamide,  hydrazine,  acetimidamide;  oxime,  acetylacetohydrazide, aminoethyl-amine,  aminoethyl-aminoethyl-amine, and L- or D-, natural or unnatural peptides containing 1-20 of the same or different amino acids; wherein a connecting bond in the middle of atoms means that it can connect either neighbor carbon atom bonds; wavery line is the site wherein another bond can be connected to;or

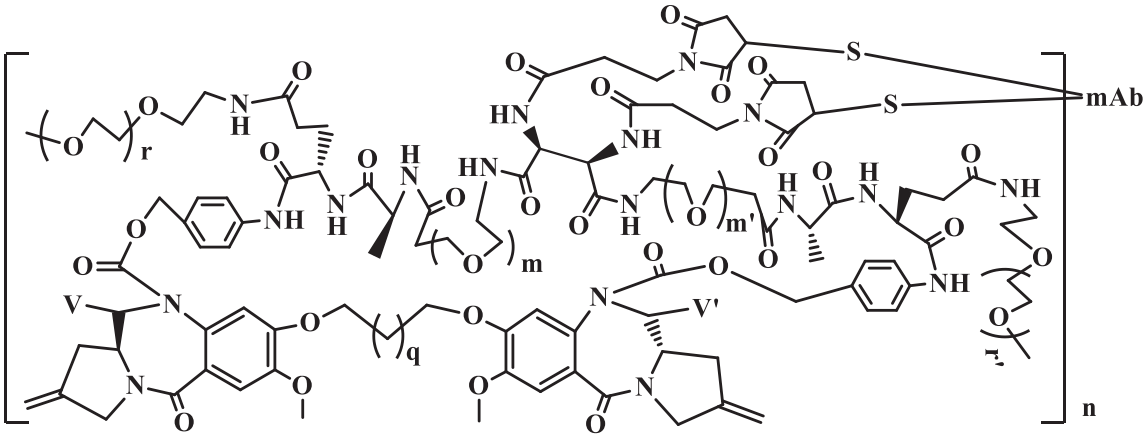
wherein the cross-linked PBD dimer derivative and its conjugate is



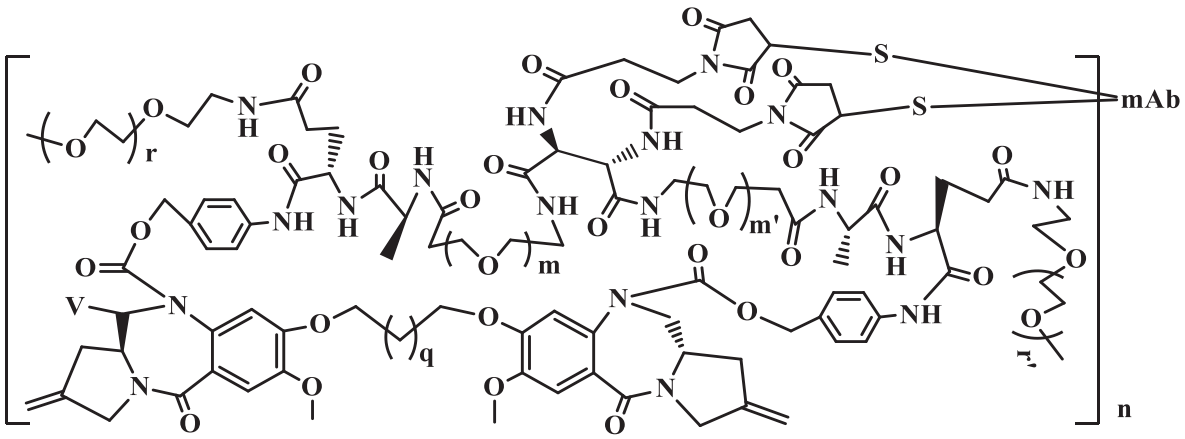
(I-05),



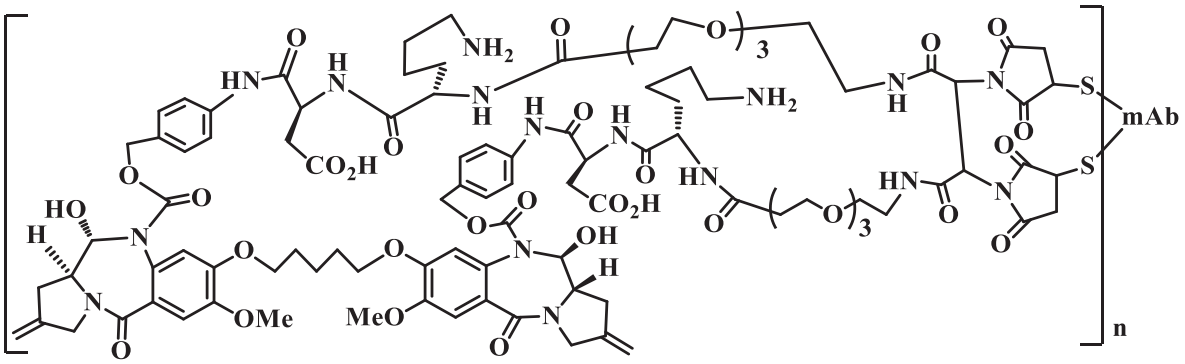
(I-15),



(I-16),



(I-17),



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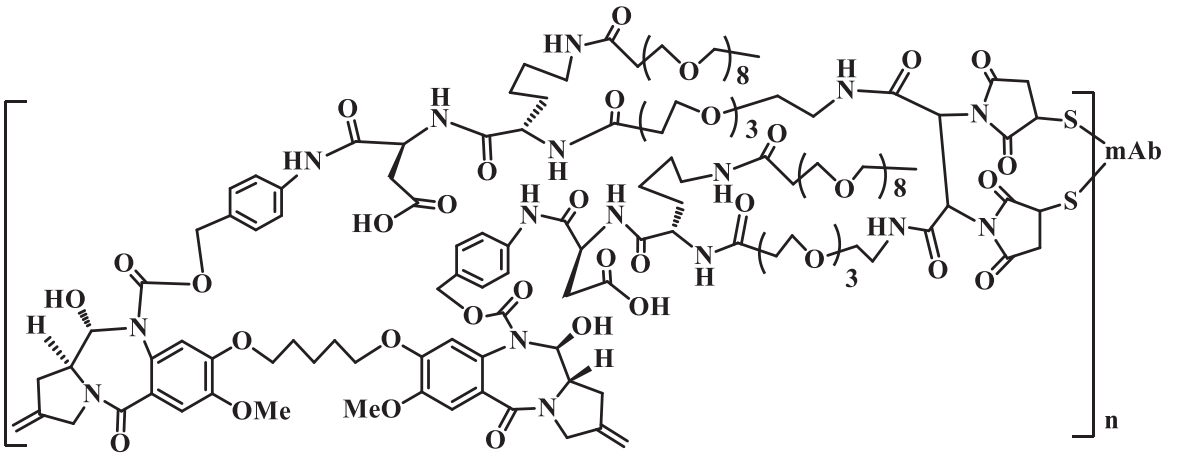

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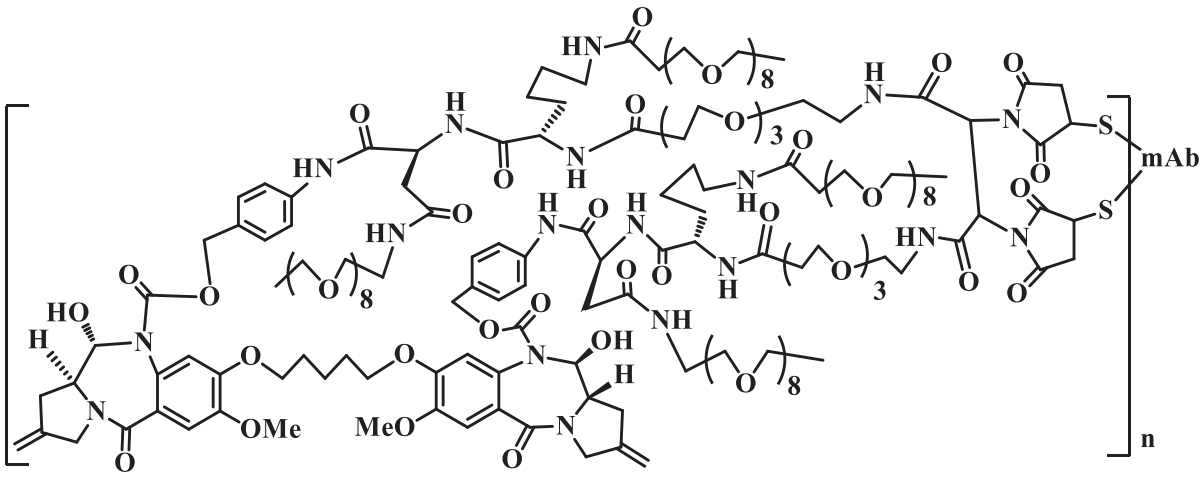

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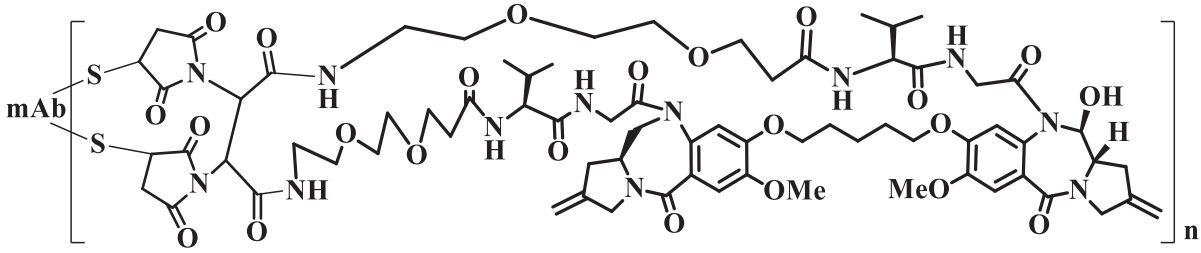

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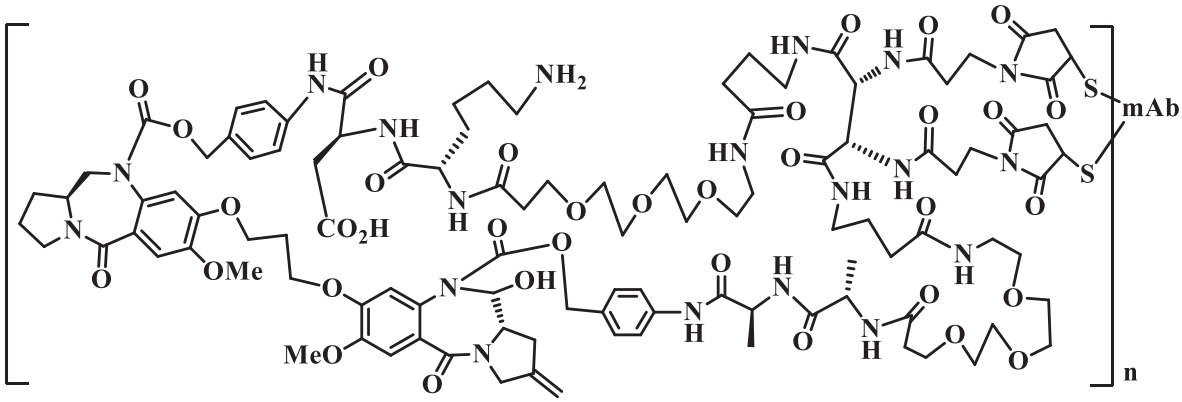

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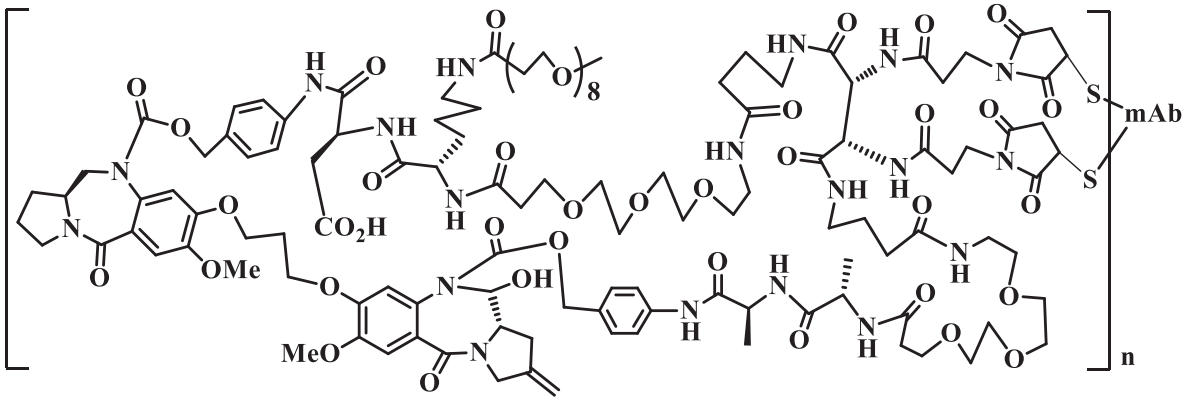

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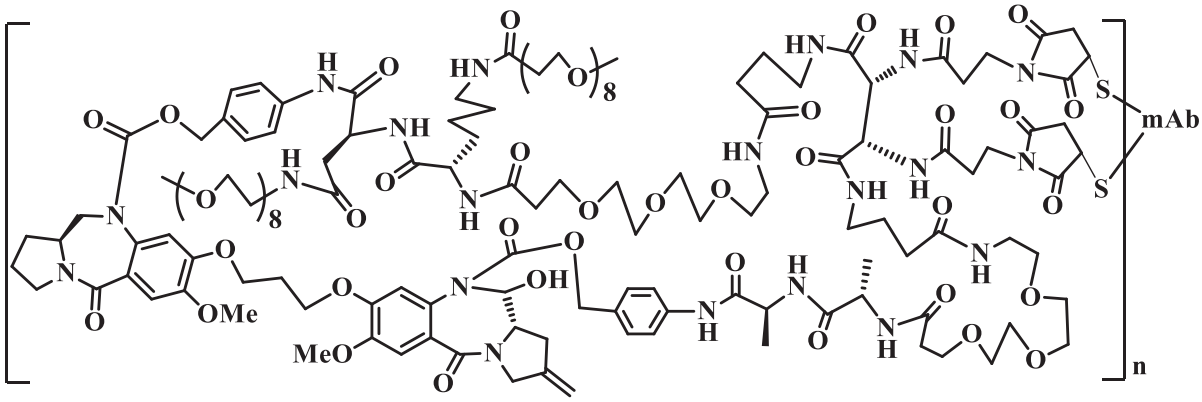

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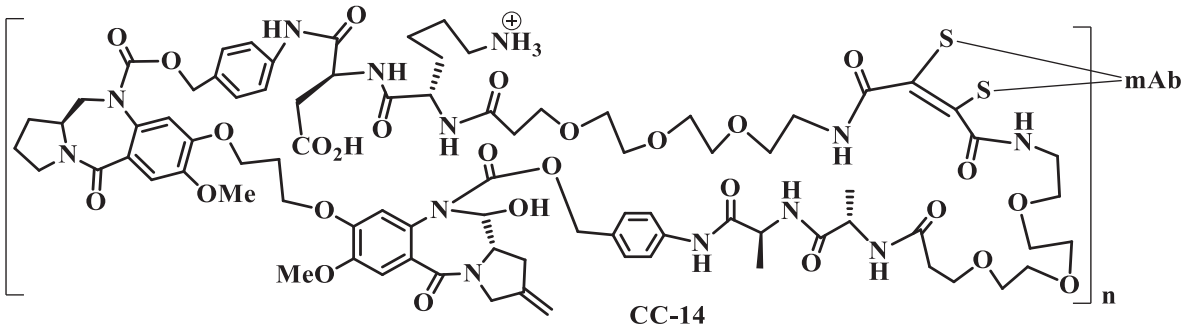

CC-14

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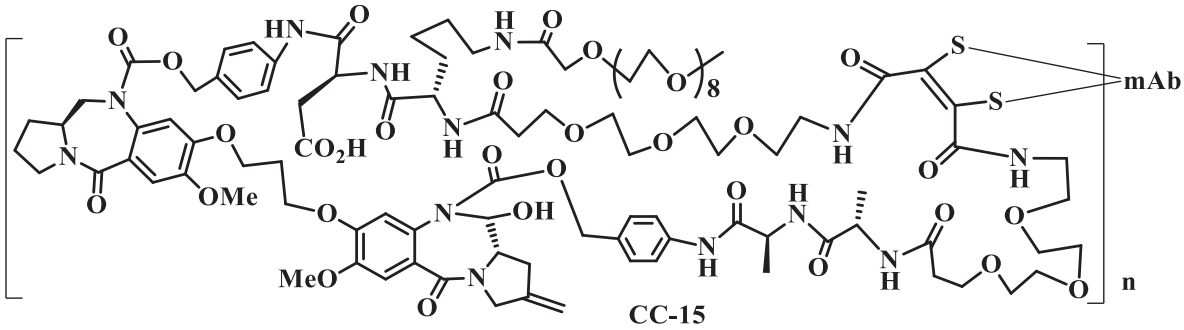

CC-15

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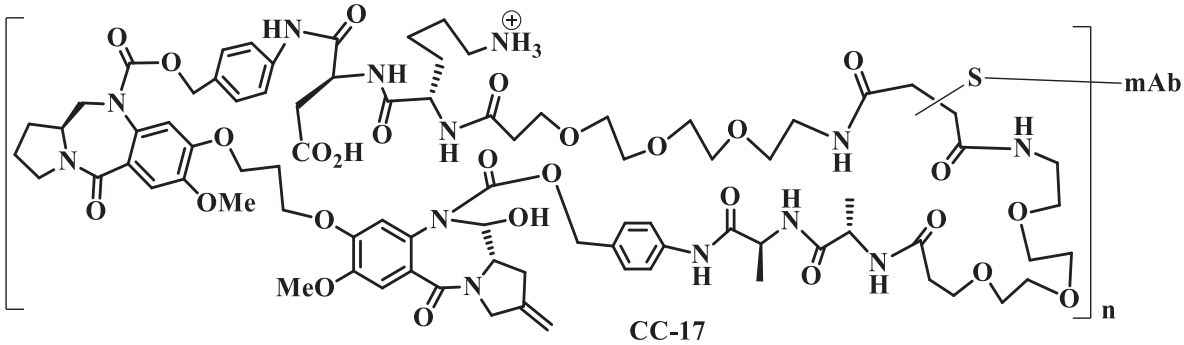

CC-17

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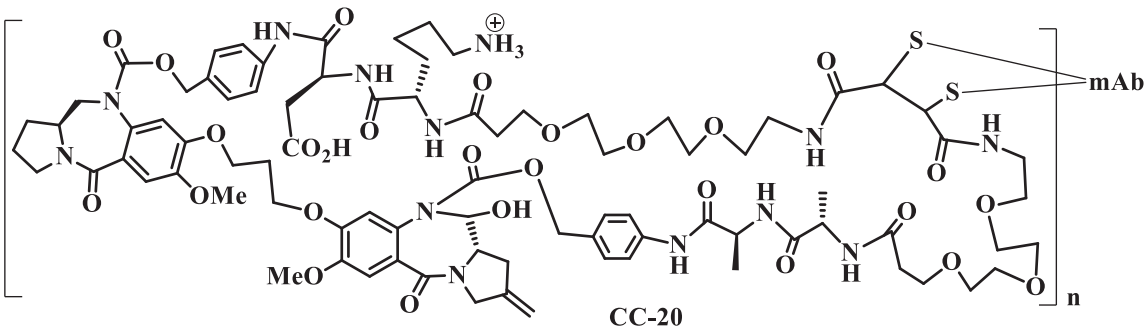

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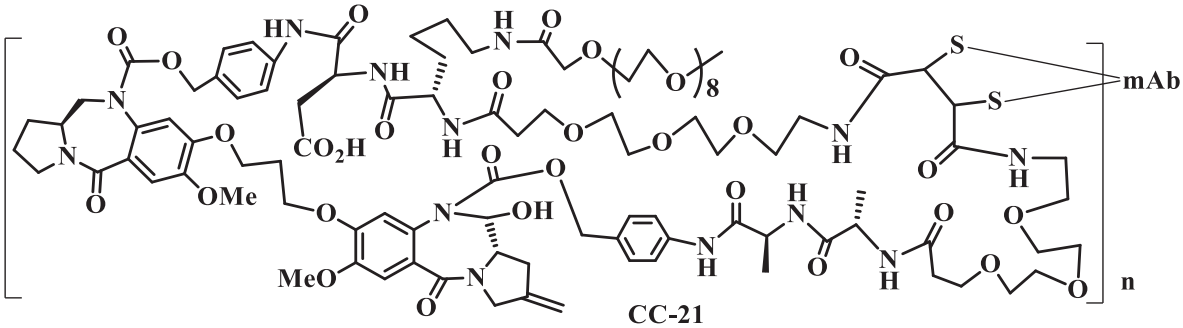
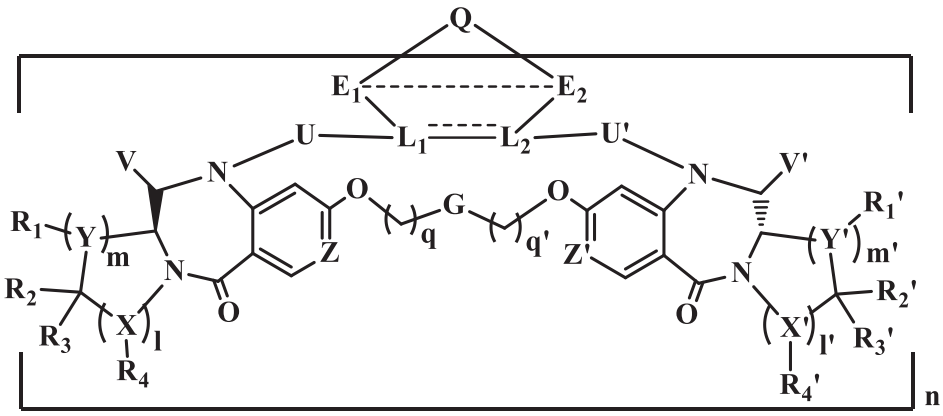


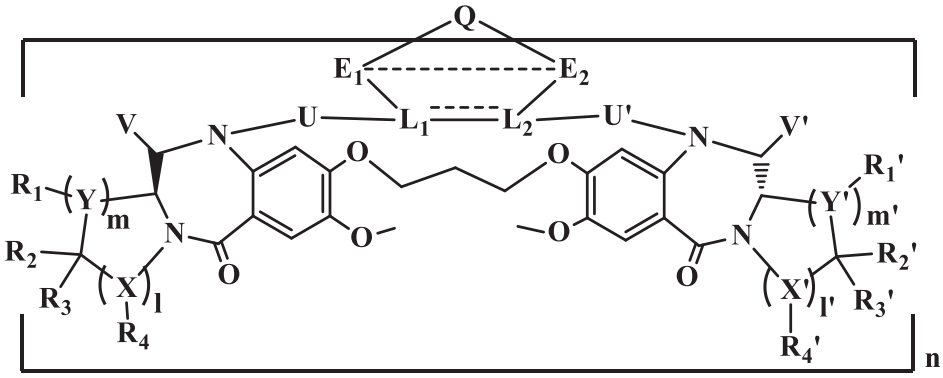
CC-21 ,

.

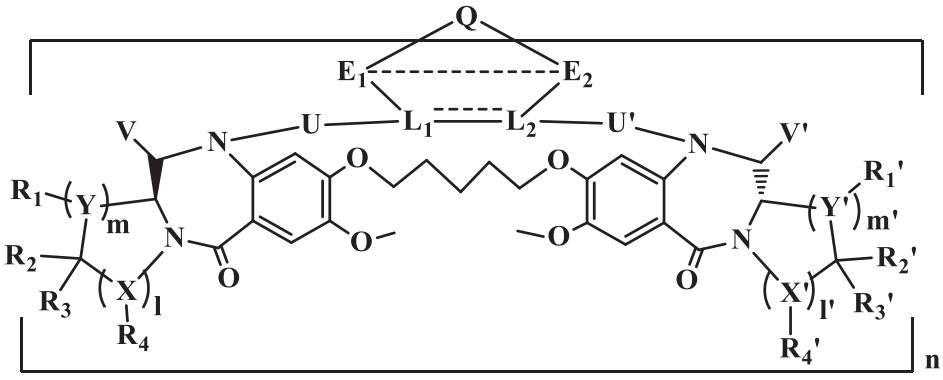
2. A cross-linked PBD dimer derivative and its conjugate according to Claim 1 having the Formula (Ia), (Ib), (Ic), and (Ie):



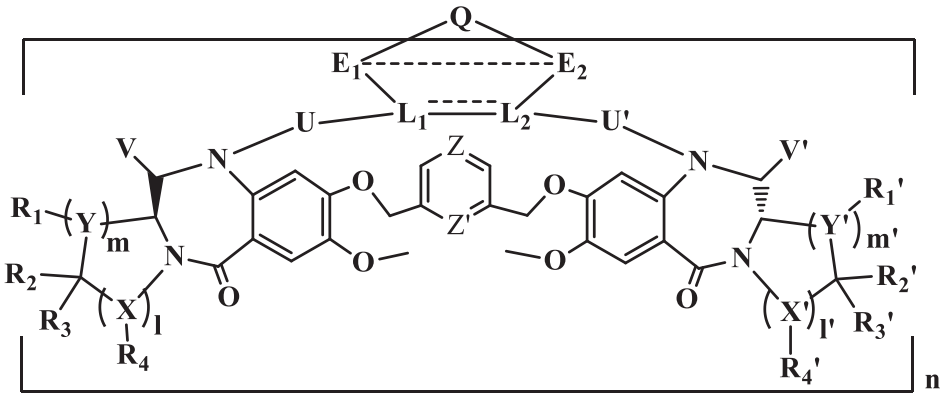
(Ia) ,



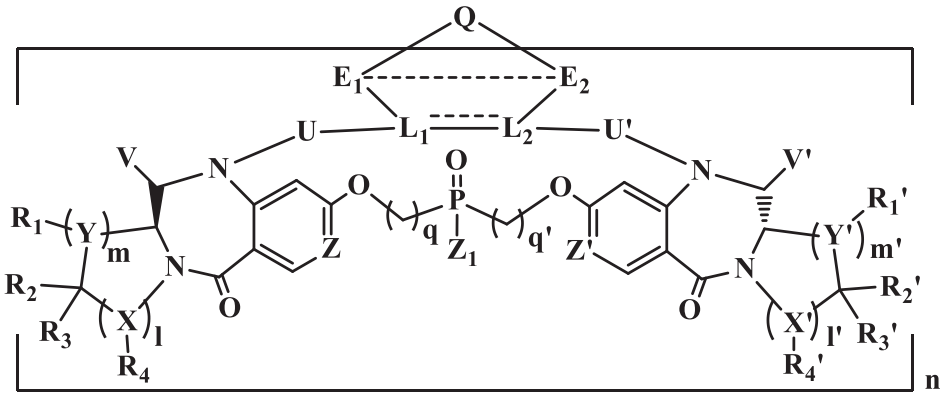
(Ib),



(Ic),



(Id),

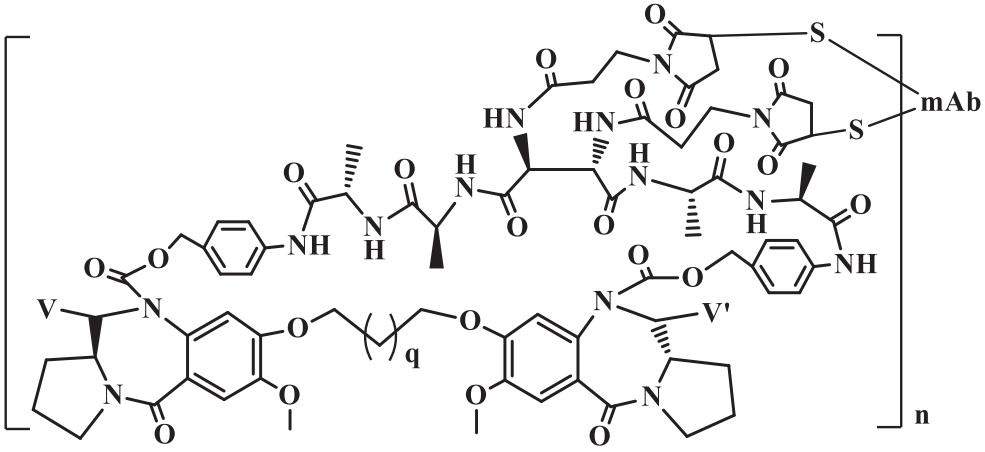


(Ie),

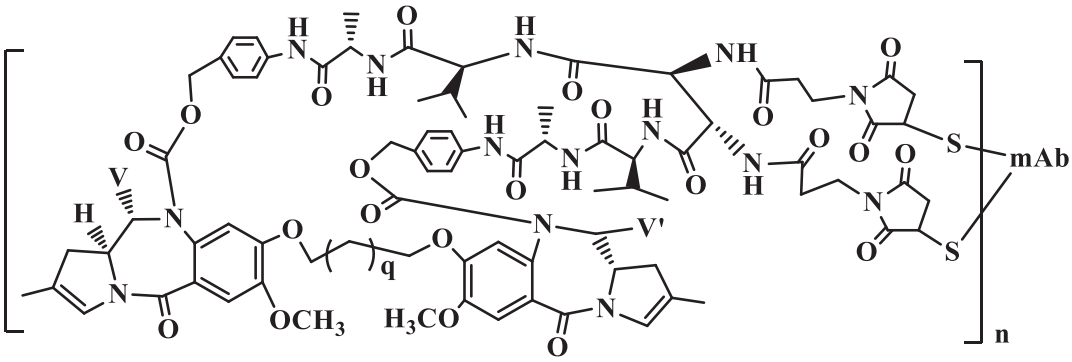
or their pharmaceutically acceptable salts, hydrates, or hydrated salts, or the polymorphic crystalline structures of these compounds or their optical isomers, racemates, diastereomers or enantiomers;

wherein Z_1 is OH, NH_2, OR_1, NHR_1, NR_1R_2, SR_1, $NHR_1COX_1R_1$, $OR_1COX_1R_1$, or $N(R_2)R_1COX_1R_1$; ═══, -----, X, X', Y, Y', Z, Z', l, l', m, m', n, q, q', R_1, R_1', R_2, R_2', R_3, R_3', R_4, R_4', V, V', U, U' L_1, L_2, E_1, E_2 and Q are defined the same as in Claim 1.

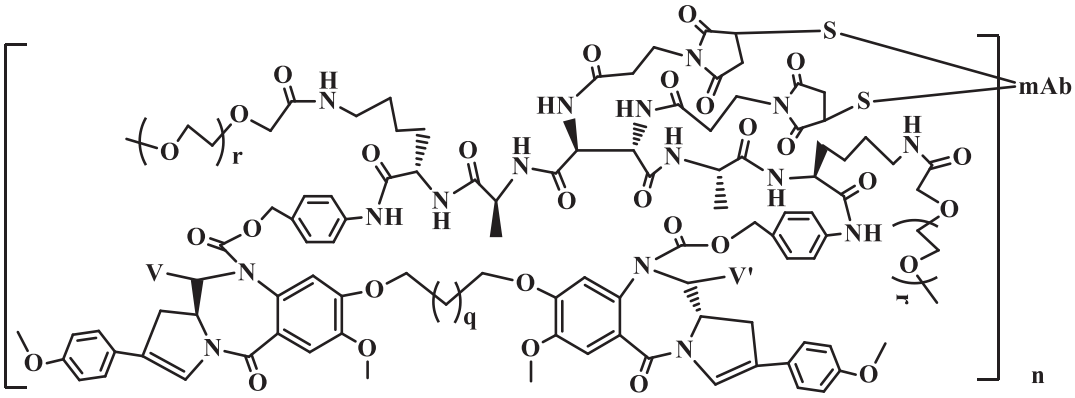
3. A conjugate of a cross-linked PBD dimer derivative to a cell-binding molecule according to Claim 1 having the Formula (I-01) ~ (I-19) below:



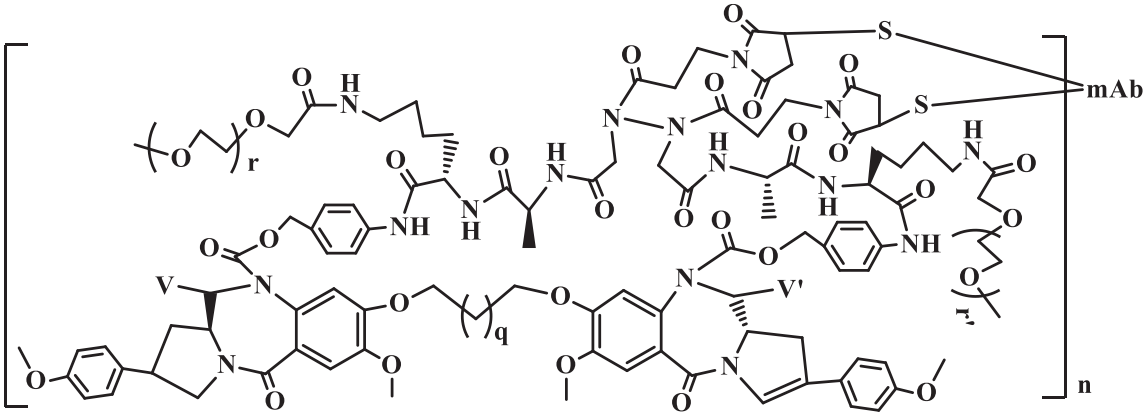
(I-01),



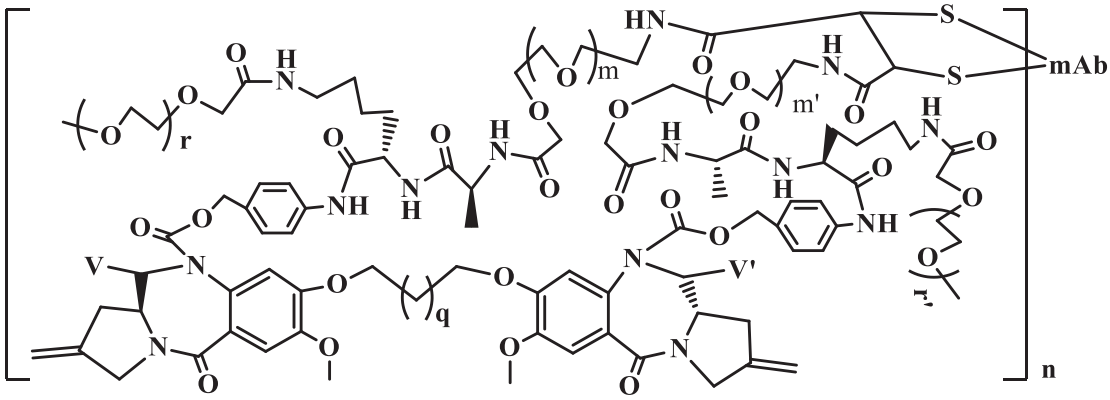
(I-02),



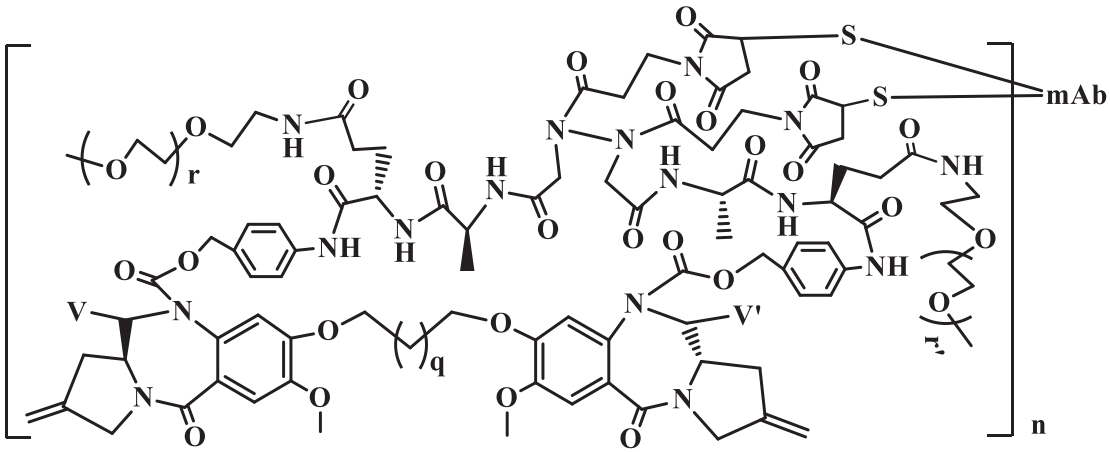
(I-03),



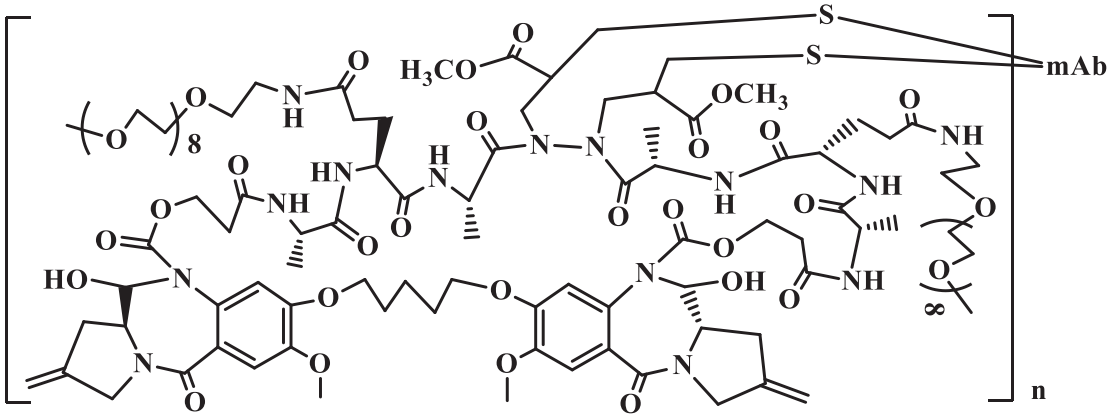
(I-04),



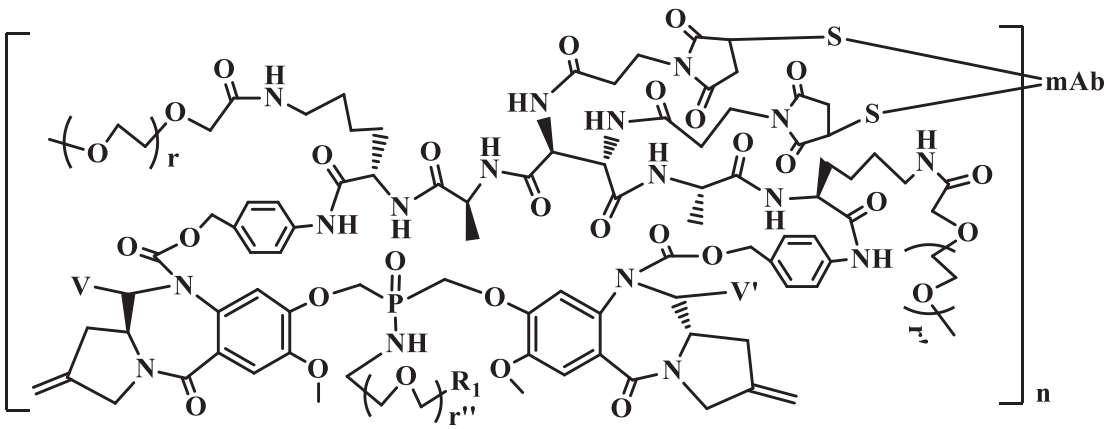
(I-05),



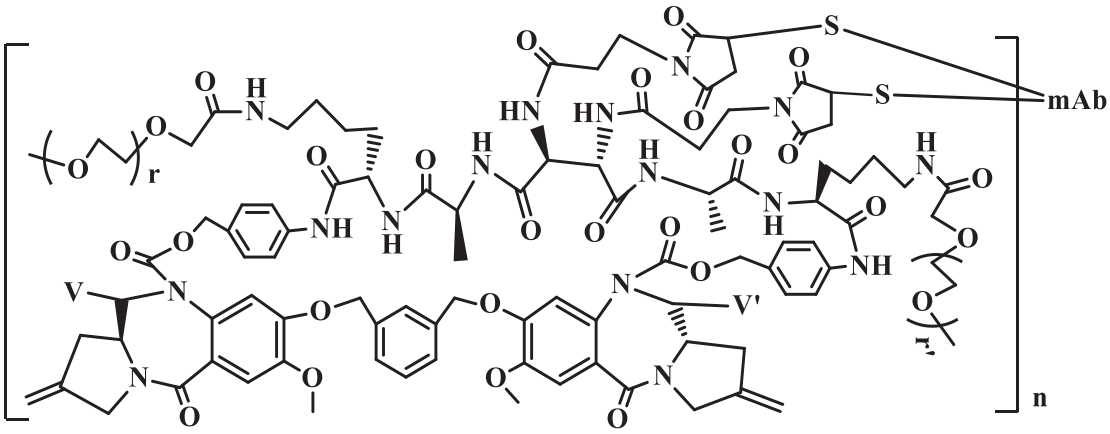
(I-06),



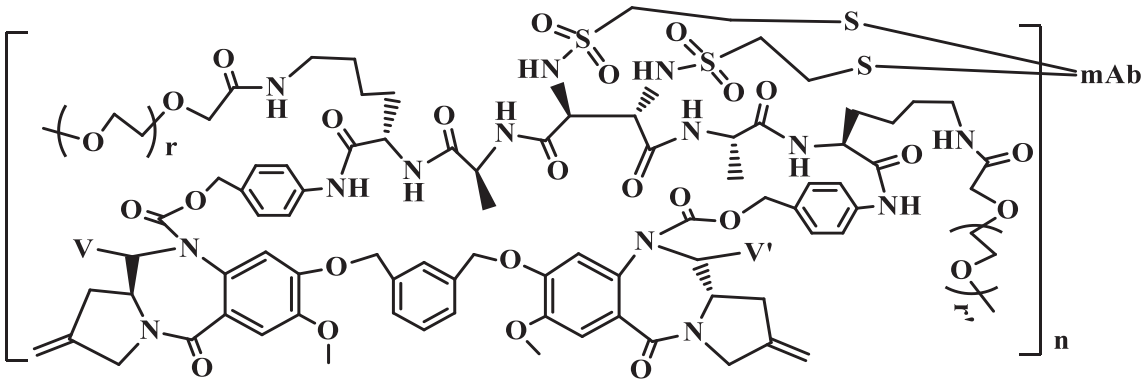
(I-07),



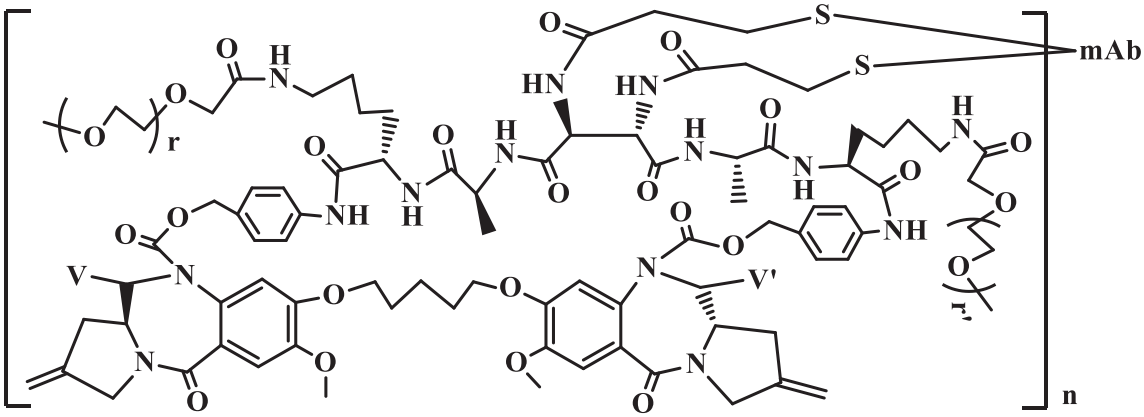
(I-08),



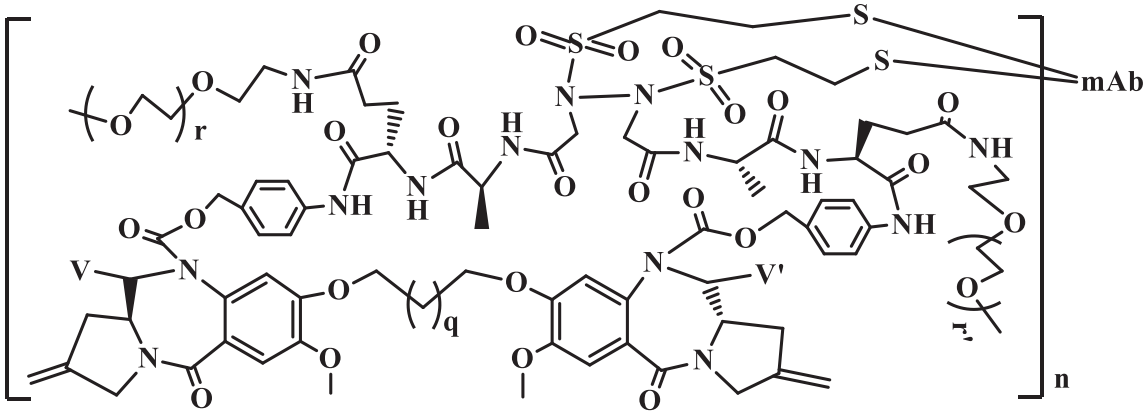
(I-09),



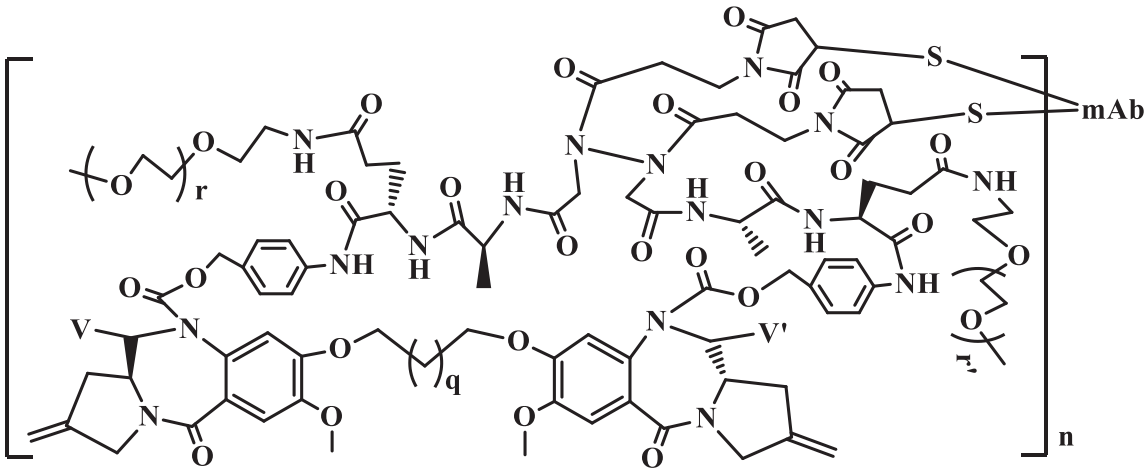
(I-10),



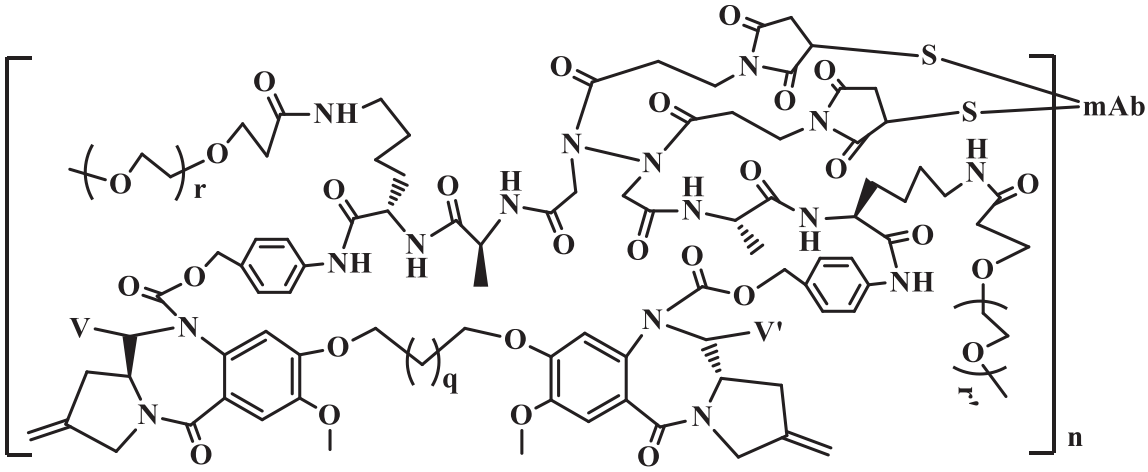
(I-11),



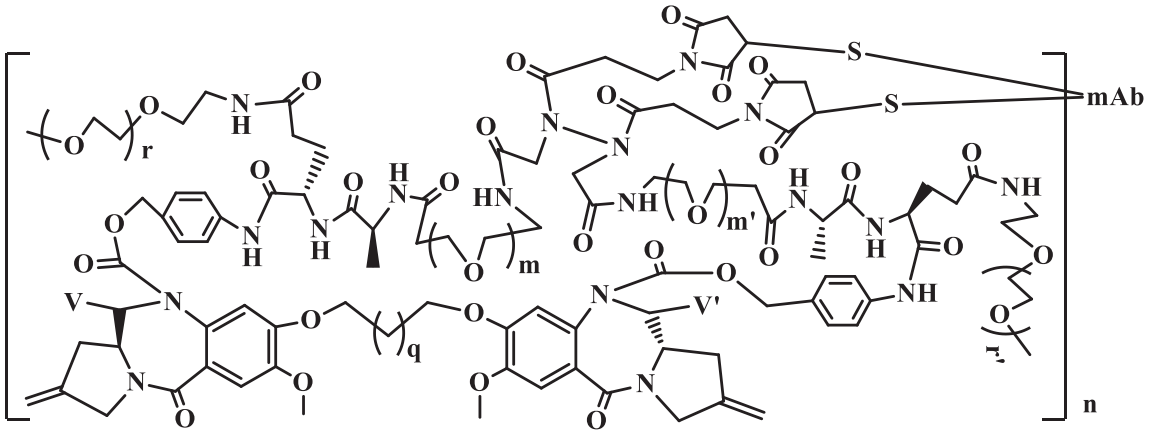
(I-12),



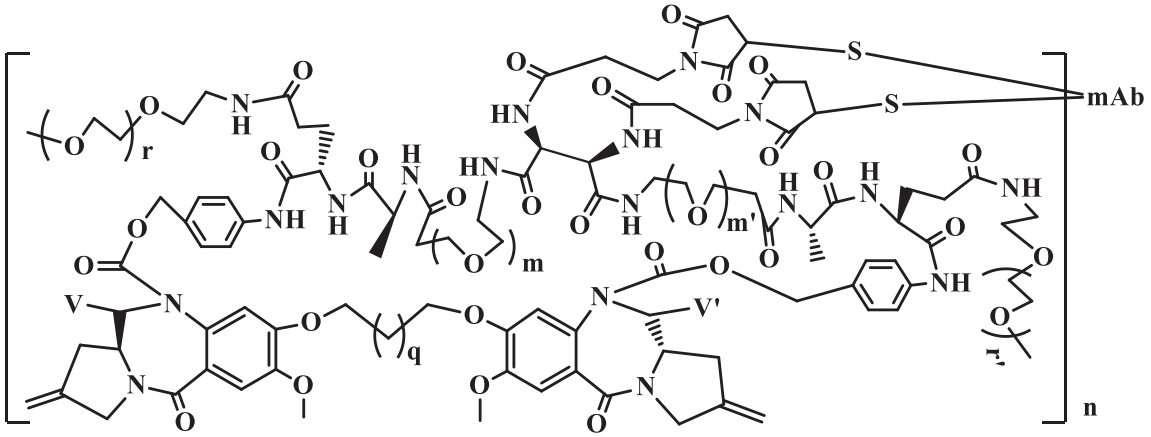
(I-13),



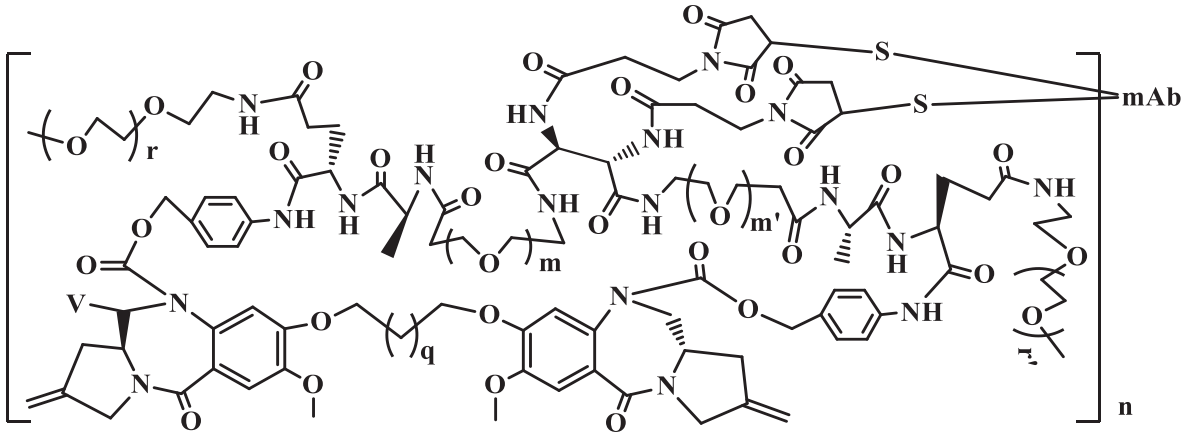
(I-14),



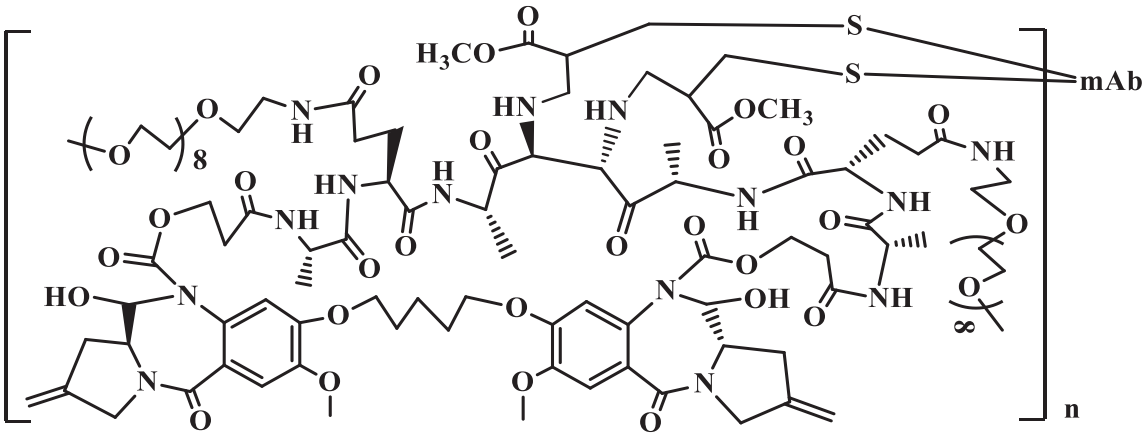
(I-15),



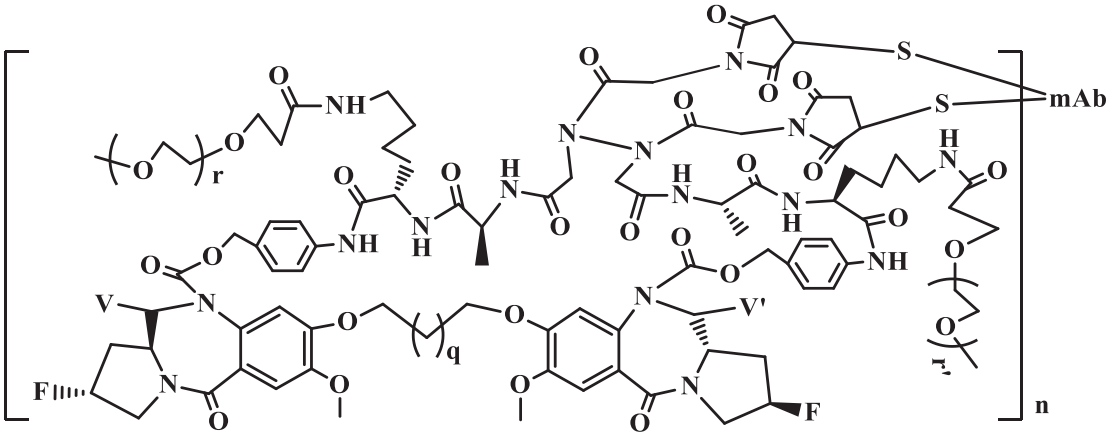
(I-16),



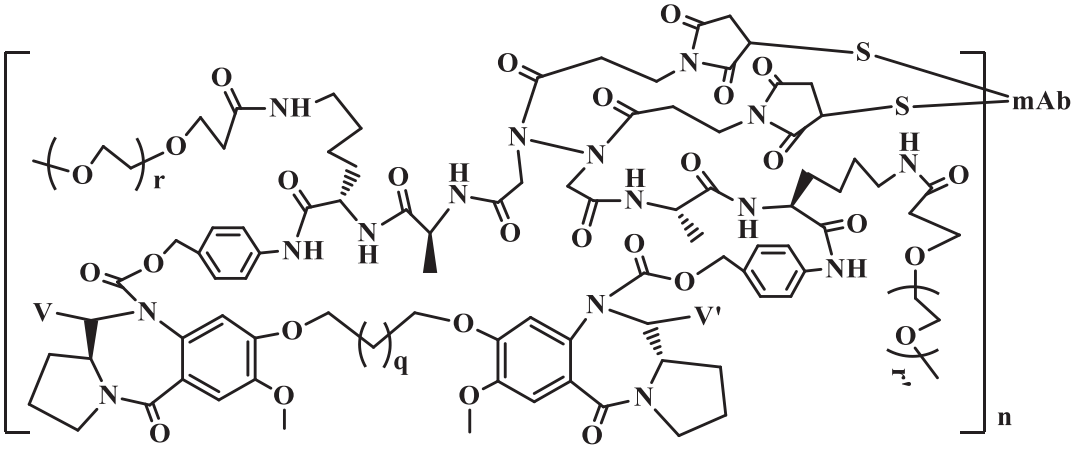
(I-17),



(I-18),



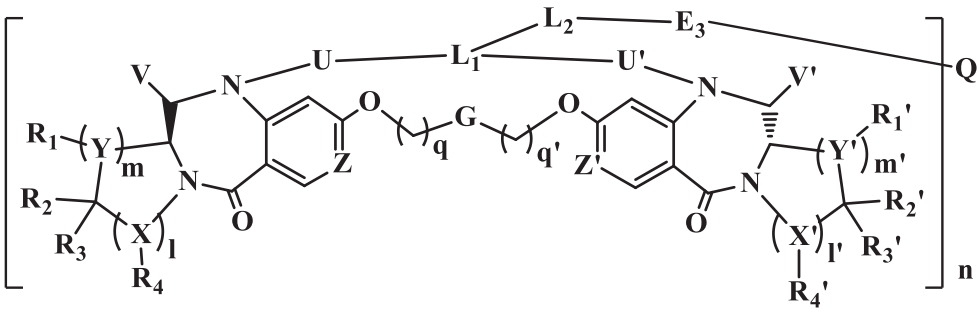
(I-19),



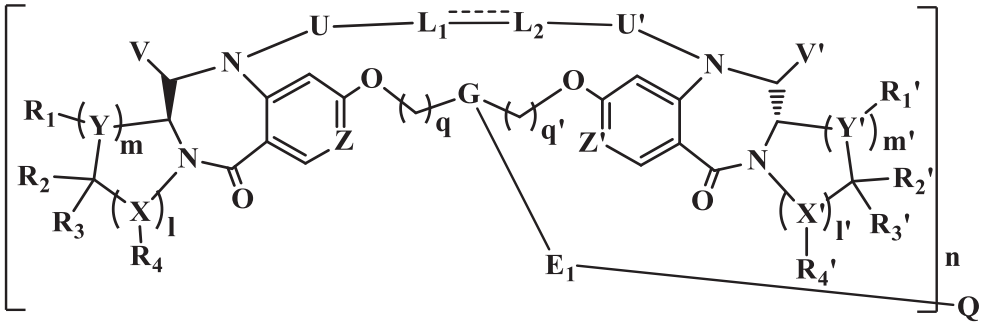
(I-20),

wherein V, V', n and q are defined the same in Claim 1; mAb is a cell-binding molecule; r, r' and r'' are independently 0-200.

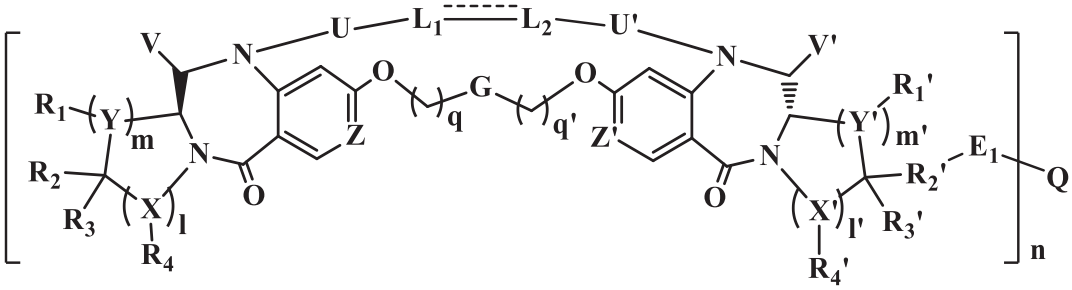
4. A cross-linked PBD dimer derivative and its conjugate to a cell-binding molecule having the structure of Formula (II), (III) and (IV):



(II),



(III),



(IV),

wherein:

----- represents an optional single bond or can be absent;

═══ represents an optional single bond or a double bond;

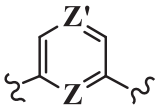
V and V', the same or different, are independently selected from the group consisting of H, OH, -NHOH; OR_5 (an ether); $OCOR_5$ (an ester); $OCOOR_5$ (a carbonate); NR_5R_5', NR_5COR_5', or $NR_5NR_5'NR_5''$ (an amine); $OCONR_5R_5'$ (a carbamate); $NR_5(C{=}NH)NR_5'R_5''$ (a guanidinum); $NR_5CONR_5'R_5''$ (a urea); $OCSNHR_5$ (a thiocarbamate); -SH (a thiol); $-SR_5$ (a sulfide); SOR_5 a sulphoxide (a sulphoxide); $SOOR_5$ (a sulfone); SO_3, HSO_3, HSO_2, or a salt of HSO^{3-}, SO_3^{2-} or $-HSO_2^-$ (a sulphite); OSO_3 (a bisulphite); NR_5SOOR_5' (a sulfonamide); $H_2S_2O_5$ or a salt of $S_2O_5^{2-}$ (a metabisulfite); PO_3SH_3, $PO_2S_2H_2$, POS_3H_2, PS_4H_2 or a salt of PO_3S^{3-}, $PO_2S_2^{3-}$, POS_3^{3-}, PS_4^{3-} (mono-,di-, tri-, and tetra-thiophosphate); $(R_5O)_2POSR_5'$ (a thiophosphate ester); HS_2O_3 or a salt of $S_2O_3^{2-}$ (a thiosulfate); HS_2O_4 or a salt of $S_2O_4^{2-}$ (a dithionite); $P(=S)(OR_5)(S)(OH)$ (a phosphorodithioate) or a salt thereof form with a cation; $-NR_5OR_5'$ (a hydroxylamine derivative); $R_5C(=O)NOH$ (a hydroxamic acid) or a salt formed with a cation; $HOCH_2SO_2^-$, or its salts (a formaldehyde sulfoxylate); $NR_5COR_{5'}$ (an amide); O-glycoside; N_3 (an azido); CN (a cyano); X (a halo: F, Cl, Br, or I); $C(R_5)(R_{5'})(R_{5''})$ (a trialkyl), $OP(O)(OR_5)(NHR_{5'})$ or $OP(O)(NHR_5)(NHR_{5'})$ (a phosphoramidate (phosphoramidic acid),

or $P(R_5)(R_{5'})(R_{5''})$ triarylphosphonium; Aa (an amino acid), or $NR_5CO(Aa)_t$ (a peptide), wherein Aa is an amino acid or a polypeptide containing between t =1~ 100 amino acid units; an aminoacid-derived group: an α-, β-, γ-, or ω-aminoacid, or an unnatural aminoacid; wherein R_5, R_5' and R_5'' are described below;

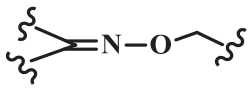
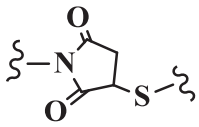
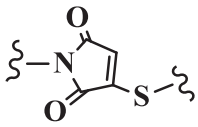
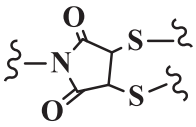
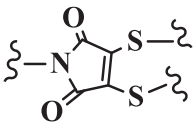
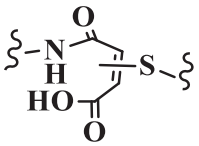
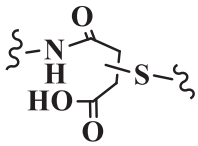
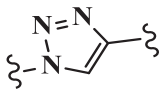
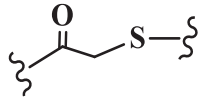
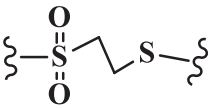
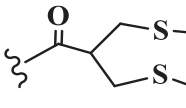
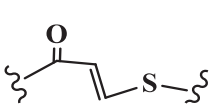
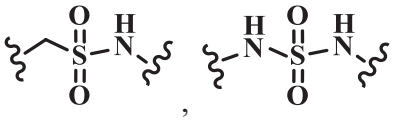
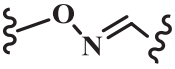
l, m, q, l', m' and q' are independently a number of 0, 1, 2, 3, 4, or 5; n is 1~30;

X, X', Y and Y' the same or different, independently, represent N, O, S, an alkyl, such as CH_2 or CHR_5, an alkene, such as =CH- or $=CR_5$-, an ether, such as $–C(OR_5)H$-;

Z and Z' the same or different, independently, represent N, CH, CR_5, COH, CNH_2, $CNHR_5$, or COR_5, or Z and Z' link together with $–COR_5OC$-; wherein R_5 is independently selected from C_1~C_8 alkyl and aryl;

G is $-CH_2$-, O, $-N(R_5)$-, S, $-P(O)(OR_5)$-, $-P(O)(N R_5R_{5'})$-,  wherein Z and Z' are defined above;

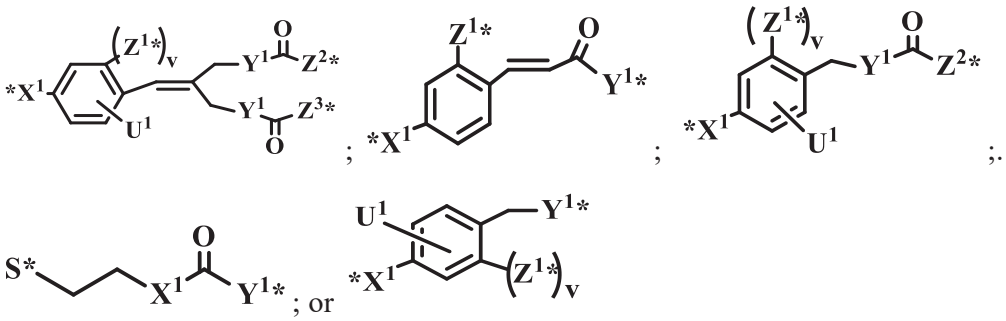
U and U' are independently C(O), C(O)O, C(O)NH, $C(O)N(R_5)$, C(=NH), C(=NH)O, C(=NH)NH, $C(=NH)N(R_5)$, -C=N-, C(=S), C(O)S, C(S)NH, $C(S)N(R_5)$, S(O), S(O)O, S(O)NH, $S(O)(OR_5)$, $S(O)(N(R_5))$, $S(O_2)$, $S(O_2)O$, $P(O)(OR_5)$, $P(O)(OR_5)O$, $P(O)(NH_2)$, $P(O)(NR_5R_{5'})$, $P(O)(OR_5)NH$-, $P(O)(OR_5)NR_{5'}$-, P(O) $(N(R_5R_{5'})$ $(N(R_5)$, $P(S)(OR_5)$, $P(S)(OR_5)O$, $P(S)(NH_2)$, $P(S)(NR_5R_{5'})$, $P(S)(OR_5)NH$-, $P(S)(OR_5)NR_{5'}$-, $P(S)(N(R_5R_{5'})N(R_5)$, R_5, R_5O;

E_1 and E_2 are independently S, R_5S, C(O)S, C(O)NH, C(O)O, $C(O)R_5S$, C(=NH)NH, $C(=NH)N(R_5)$, C(=NH)S, -C=N-, C(=S)S, C(O)S, C(=S)NH, $C(=S)N(R_5)$, Ar-S, $NC(O)CH_2S$, $ArC(O)CH_2S$, S-S,  ,  ,  ,  ,  ,  ,  ,  ,  ,  ,  ,  ,  ,  ; wherein the chemical bond in the middle of two atoms means it can link either of the adjoining two atoms; wavery line is a connecting site;

L_1, and L_2 have independently the formula of: —Ww—(Aa)r—Tt—; or —Ww—(Aa)r—Tt—Q; or Q—Ww—(Aa)r—Tt—; wherein: -W- is a Stretcher unit; w is 0 or 1; -Aa- is independently an Amino Acid unit; r is independently an integer ranging from 1 to 100; -T- is a

Spacer unit which is a linear alkyl or branched alkyl, or polyethylene glycol spacer; and t is 0, or 1~100; The Stretcher unit W independently contains a self-immolative spacer, peptidyl units, a hydrazone bond, a disulfide, an ester, or a thioether bond; w is 1 or 2 or 3; The Stretcher unit (--W--), when present, links a targeted binding molecular unit (CBA) to an amino acid unit (--Aa--); or L_1, and L_2 are independently selected from O, NH, N, S, P, NNH, NHNH, $N(R_3)$, $N(R_3)N(R_{3'})$, CH, CO, C(O)NH, C(O)O, NHC(O)NH, NHC(O)O, C_1-C_8 alkyl, amide, amines, imines, hydrazines, hydrazones; C_2-C_8 heteroalkyl, alkylcycloalkyl, ethers, esters, hydrazones, ureas, semicarbazides, carbazides, alkoxyamines, alkoxylamines, urethanes, amino acids, peptides, acyloxylamines, hydroxamic acids, or heterocycloalkyl; C_3-C_8 aryl, Ar-alkyl, heterocyclic, carbocyclic, cycloalkyl, heteroalkylcycloalkyl, alkylcarbonyl, or heteroaryl; polyethyleneoxy unit of formula $(OCH_2CH_2)_pOR_3$, or $(OCH_2CH(CH_3))_pOR_3$, or $NH(CH_2CH_2O)_pR_3$, or $NH(CH_2CH(CH_3)O)_pR_3$, or $N[(CH_2CH_2O)_pR_3][(CH_2CH_2O)_{p'}R_3']$, or $(OCH_2CH_2)_pCOOR_3$, or $CH_2CH_2(OCH_2CH_2)_pCOOR_3$, wherein p and p' are independently an integer selected from 0 to 5000 (optionally 0 to 1000), or combination thereof; wherein R_3 and R_3' are independently H; C_1-C_8 alkyl; C_2-C_8 heteroalkyl, alkylcycloalkyl, or heterocycloalkyl; C_3-C_8 aryl, Ar-alkyl, heterocyclic, carbocyclic, cycloalkyl, heteroalkylcycloalkyl, alkylcarbonyl, or heteroaryl; or C_2-C_8 esters, ether, or amide; or 1~8 amino acids; or polyethyleneoxy having formula $(OCH_2CH_2)_p$ or $(OCH_2CH(CH_3))_p$, wherein p is an integer from 0 to 5000, or combination above thereof; or $(Aa)_r$, r =1-12(one to 12 amino acid units), which is composed from natural or unnatural amino acids, or the same or different sequences of dipeptide, tripeptide, tetrapeptide, pentapeptide, hexapeptide, heptapeptide, octapeptide, nonapeptide, decapeptide, undecapeptide or dodecapeptide unit;

wherein the self-immolative spacer has one of the following structures:



wherein the (*) atom is the point of attachment of additional spacer or releasable linker units, or the cytotoxic agent, and/or the binding molecule (CBA); X^1, Y^1, Z^2 and Z^3 are independently NH, O, or S; Z^1 is H, OH, 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 selected from 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;

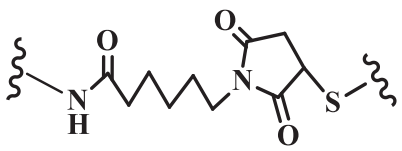
R_1, R_2, R_3, R_4, R_1', R_2', R_3', and R_4' are the same or different and independently chosen from -H, substituted linear, branched or cyclic alkyl, alkenyl or alkynyl having from 1 to 10 carbon atoms, $-(OCH_2CH_2)_tR_5$ (a polyethylene glycol unit), halogen, $NH(C{=}NH)NH_2$ (a guanidinium), $-OR_5$, $-NR_5R_5'$, $-NO_2$, -NCO, $-NR_5COR_5'$, $-SR_5$, $-SOR_5$ (a sulfoxide), $-SO_2R_5$ (a sulfone), $--SO_3^-M^+$ or $-SO_3H$ (a sulfonate), $-OSO_3^-M^+$ or OSO_3H (a sulfate), $-SO_2NR_5R_5$' (a sulfonamide), CN (a cyano), N_3 (an azido), $--COR_5$, $--OCOR_5$, $-OCONR_5R_5'$, CF_3, OR_5, Aryl, heterocycle, or $P(O)R_5R_5'R_5''$;

R_5, R_5' and R_5'' are independently selected from H, C_1~C_8 of alkyl, alkenyl, alkinyl, heteroalkyl, aryl, arylalkyl, carbonyl, or pharmaceutical salts;

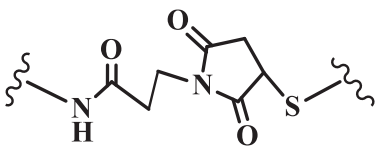
In addition, R_1 and R_2 join together, or R_1' and R_2' join together form a =O (ketone), =S, =NR, -C(=O)R, or a double bond containing group $=CR_5R_5'$; and R_1 and R_2 join together, or R_1' and R_2' join together, or R_3 and R_4 join together, or R_3' and R_4' join together to form a C_3-C_{12} aromatic, heterocyclic, carbocyclic, or heteroaryl ring;

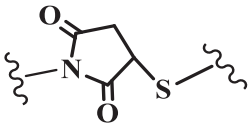
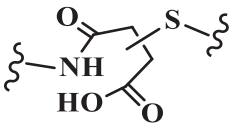
Q is a cell binding molecule (CBA), or a functional group that enables reaction with a cell-binding agent, or a functional group capable of reacting with a linker attached on a cell binding agent; The function group is chosen from a thiol, an amine, a hydrazine, an alkoxylamino, a disulfide substituent, a maleimido, a haloacetyl group, an *N*-hydroxy succinimide ester, a keton, an ester, an aldehyde, an alkynyl, an alkenyl, or protected thiol or disulfide group, SAc, SSR_1 or SSAr, wherein Ar is aromatic group or hetero aromatic group; The cell-binding agent/ molecule is selected from the group consisting of 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, a domain antibody fragment that binds to the target cell, an adnectin that mimics antibody, DARPins, a lymphokine, a hormone, a vitamin, a growth factor, a colony stimulating factor, a nutrient-transport molecule (a transferrin), and a binding peptide, protein, or small molecule attached on albumin, a polymer, a dendrimer, a liposome, a nanoparticle, a vesicle, or a (viral) capsid;

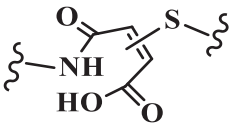
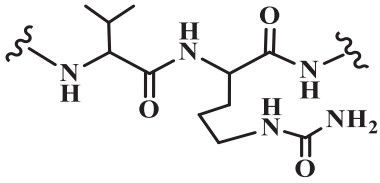
In addition, U, U', L_1, L_2, L', E_1 or E_2 may independently be composed of one or more following components as shown below:

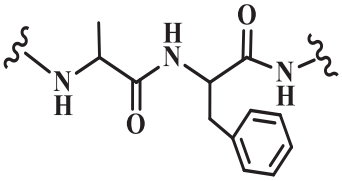


6-maleimidocaproyl (MC),

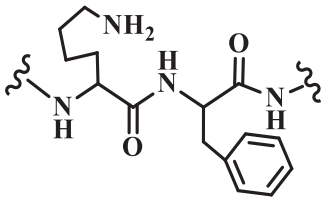
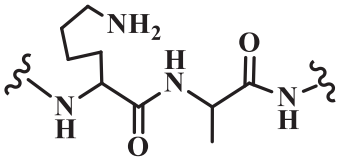


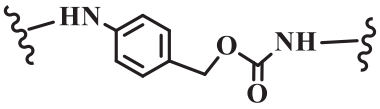
maleimido propanoyl (MP),  thio-maleido,  thio-amino-ox-

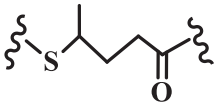
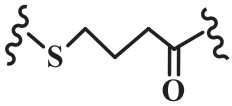
obutanoic acid,  thio-amino-oxobutenoic acid, 

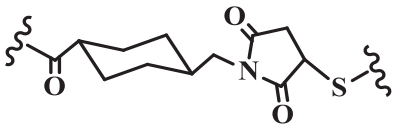


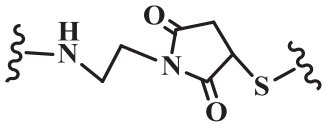
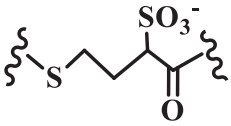
valine-citrulline (val-cit), alanine-phenylalanine (ala-phe),

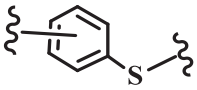
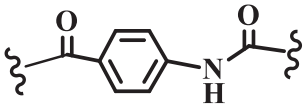
 lysine-phenylalanine (lys-phe),  lysine-

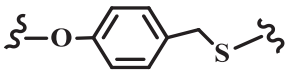
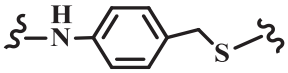
alanine (lys-ala),  p-aminobenzyloxycarbonyl (PAB),

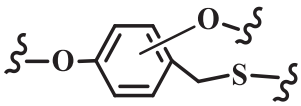
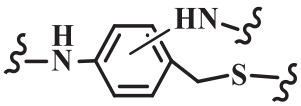
 4-thio-pentanoate (SPP),  4-thio-butyrate (SPDB),

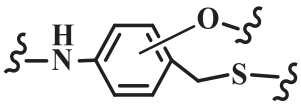
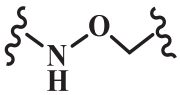
 4-(N-maleimidomethyl)cyclo-hexane-1-carboxylate (MCC),

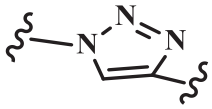
 maleimidoethyl (ME),  4-thio-2-hydroxysulfonyl-

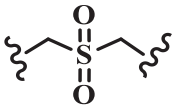
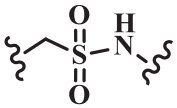
butyrate (2-Sulfo-SPDB),  aryl-thiol (PySS),  (4-ace-

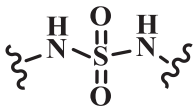
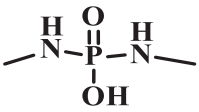
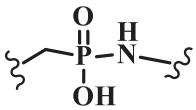
tyl)aminobenzoate (SIAB),  , oxylbenzylthio,  ami-

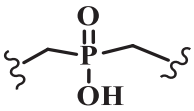
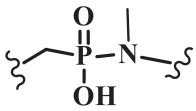
nobenzylthio,  dioxylbenzylthio,  diaminoben-

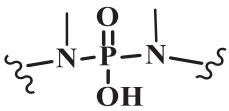
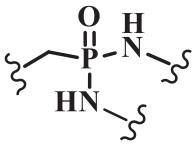
zylthio,  amino-oxylbenzylthio,  alkoxy amino (AOA),

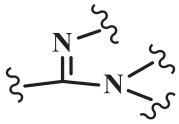
ethyleneoxy (EO), 4-methyl-4-dithio-pentanoic (MPDP), 

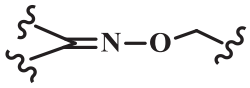
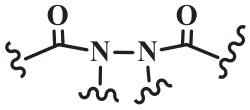
triazole, dithio,  alkylsulfonyl,  alkylsulfonamide,

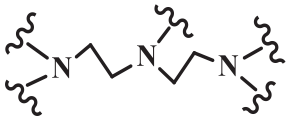
 sulfon-bisamide,  Phosphondiamide,  al-

kylphosphonamide,  phosphinic acid,  N-methylphosphonamidic

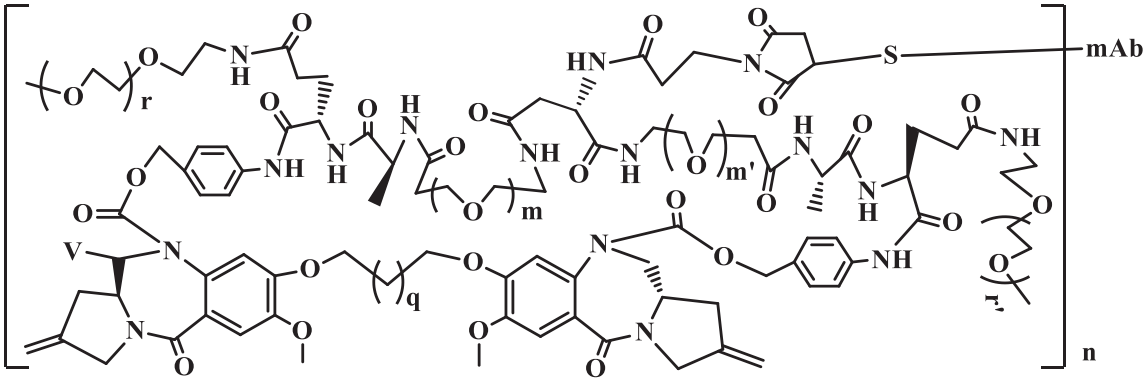
acid,  N,N'-dimethylphosphon-amidic acid,  N,N'-dime-

thylphosphondiamide, hydrazine,  acetimidamide;

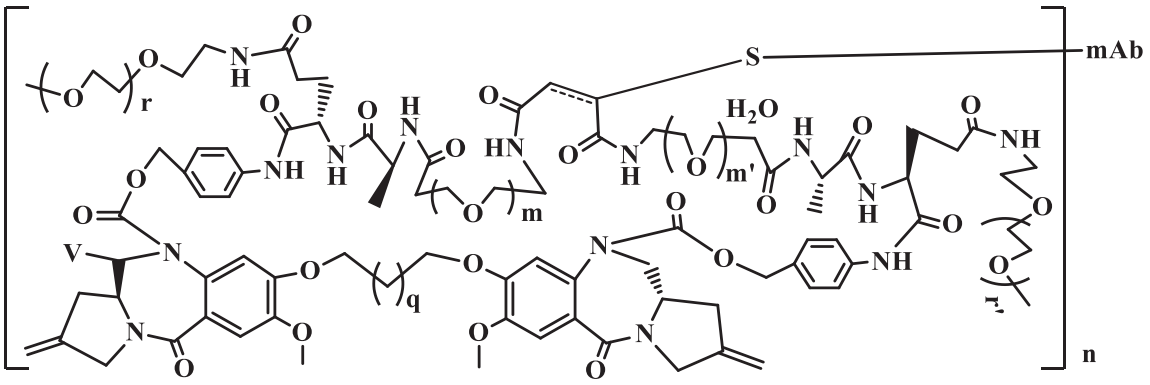
 oxime,  acetylacetohydrazide, ami-

noethyl-amine,  aminoethyl-aminoethyl-amine, and L- or D-, natural or un-natural peptides containing 1-20 of the same or different amino acids; wherein a connecting bond in the middle of atoms means that it can connect either neighbor carbon atom bonds; wavery line is the site wherein another bond can be connected to.

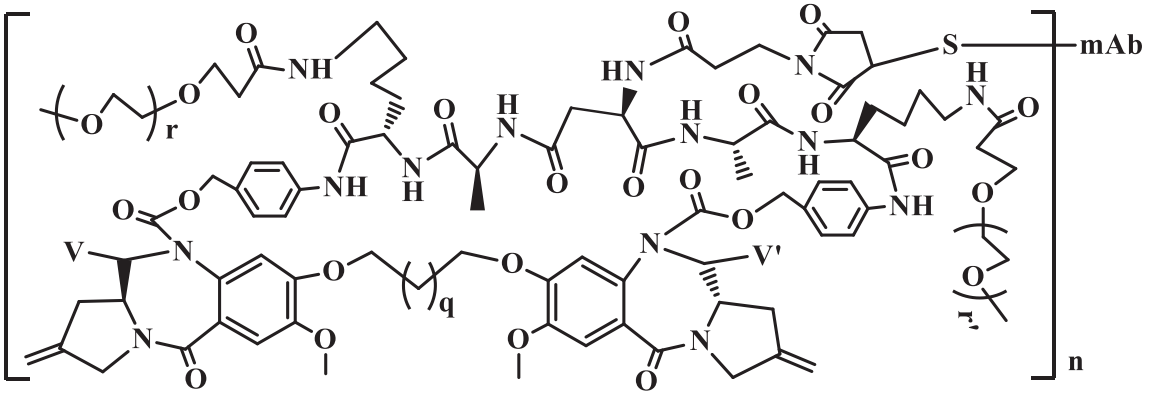
5. A conjugate of a cross-linked PBD dimer derivative to a cell-binding molecule according to Claim 4 having the Formula (II-01) ~ (II-08), (III-01)~ (III-05) and (IV-01)~(IV-11) below:



(II-01),



(II-02),



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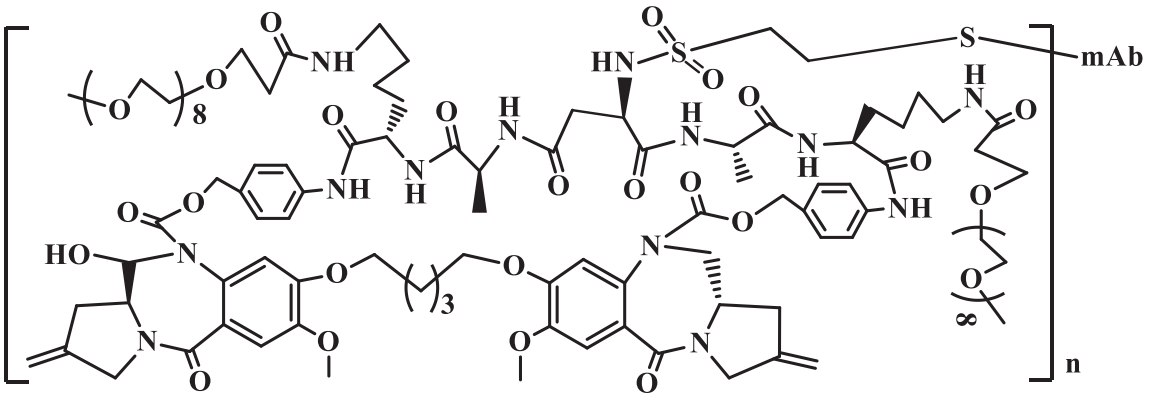

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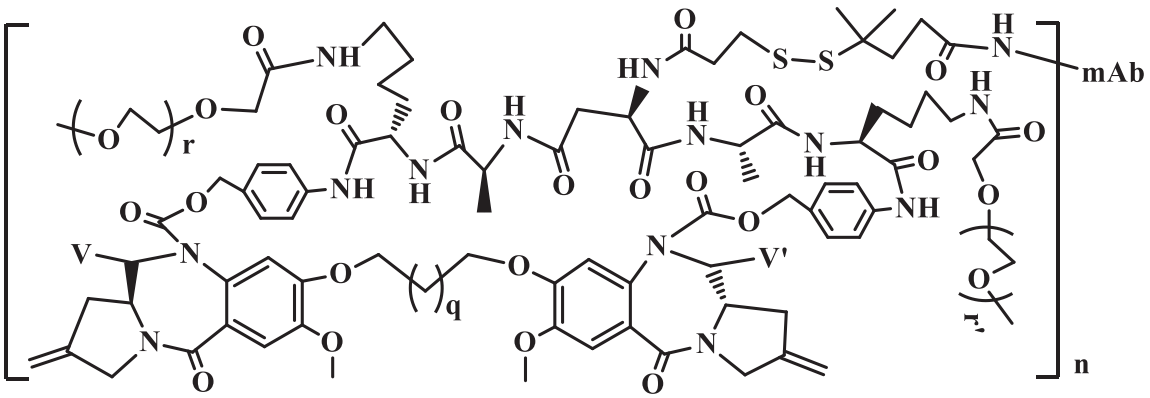

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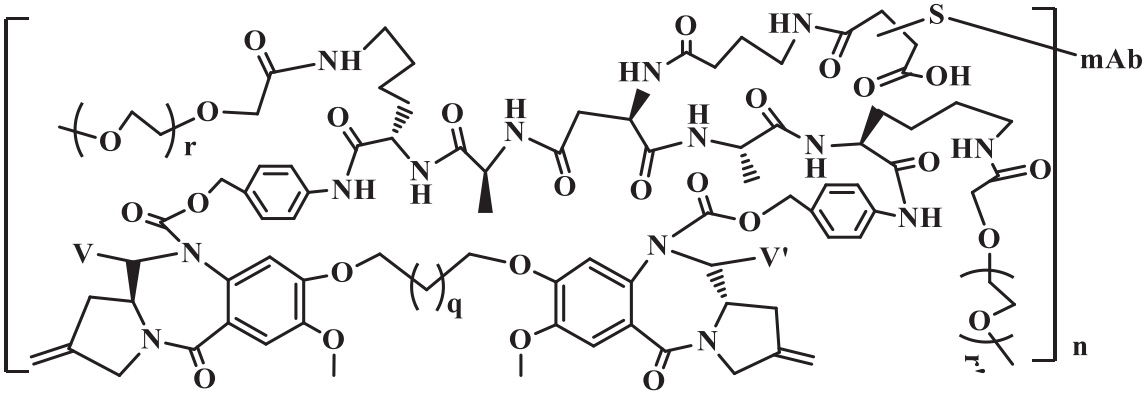

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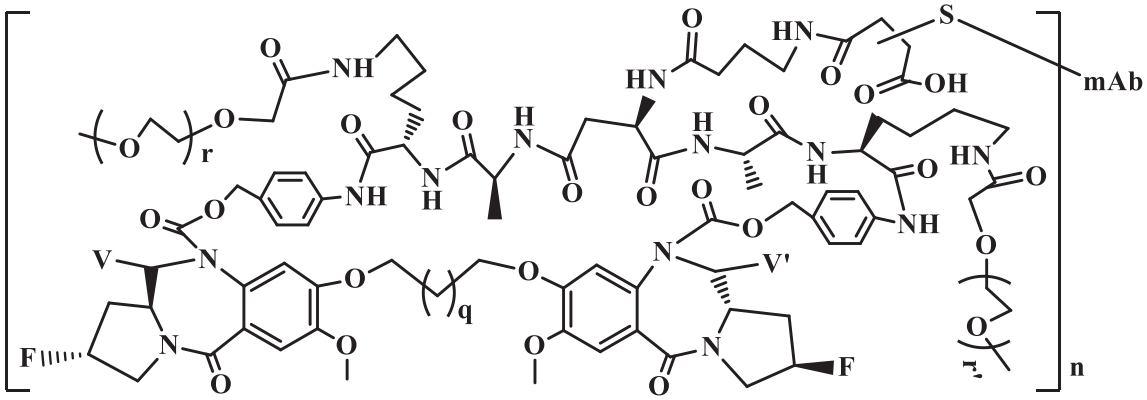

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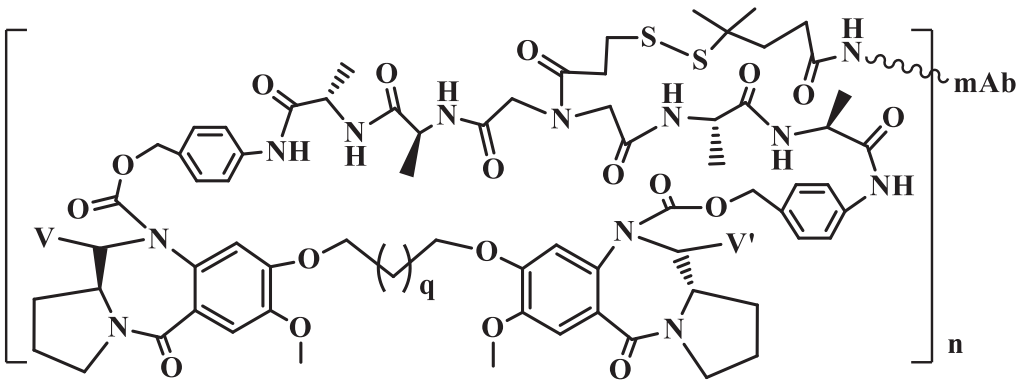

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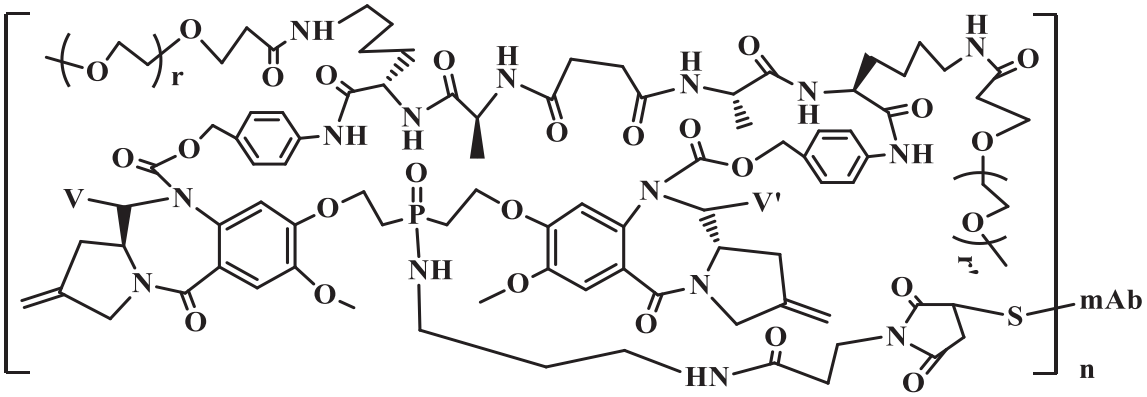

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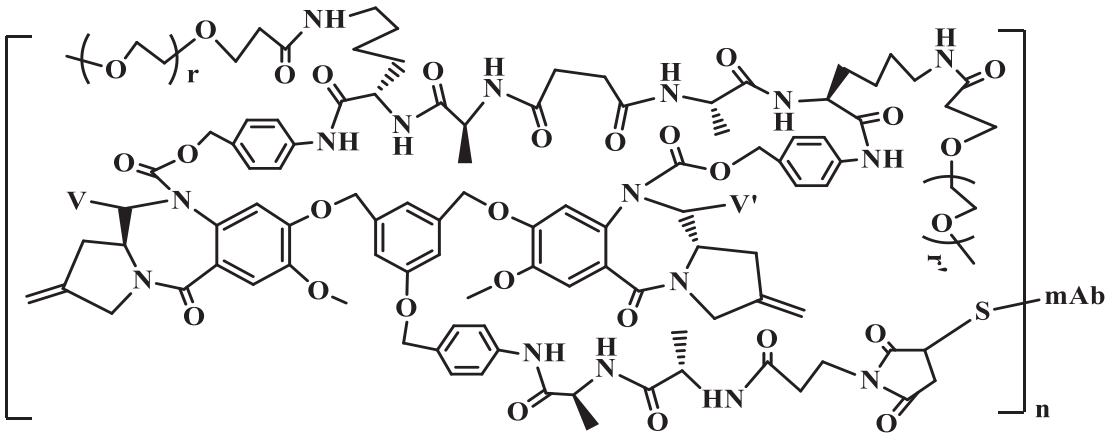

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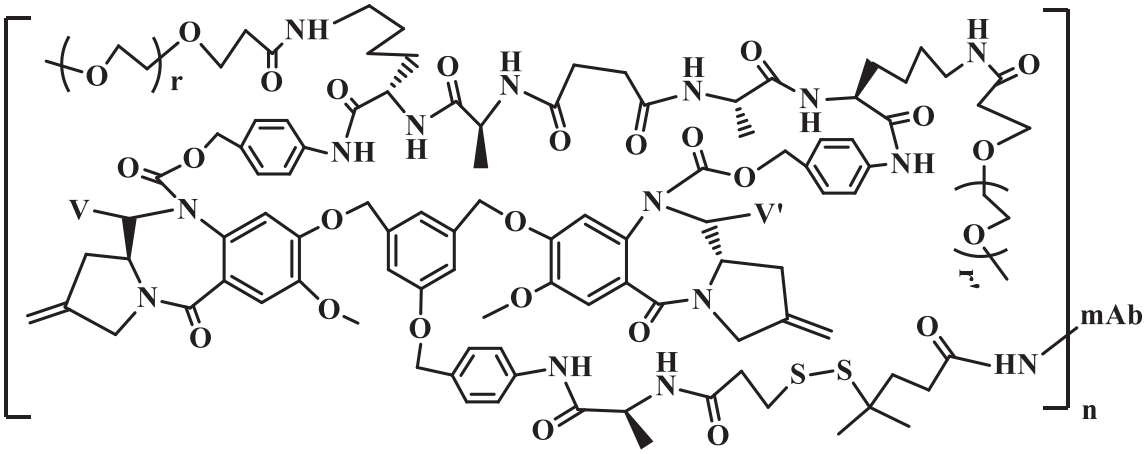
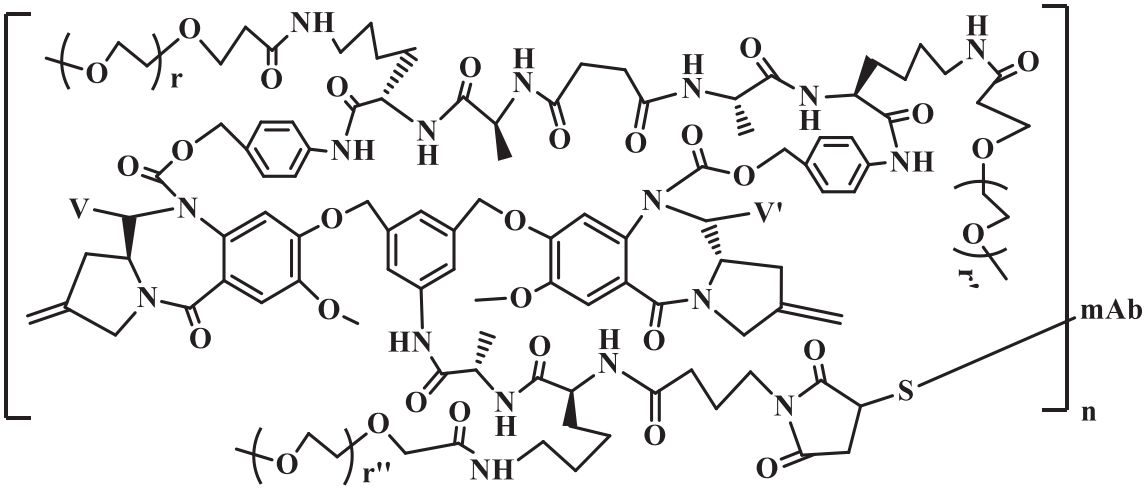


(III-03),



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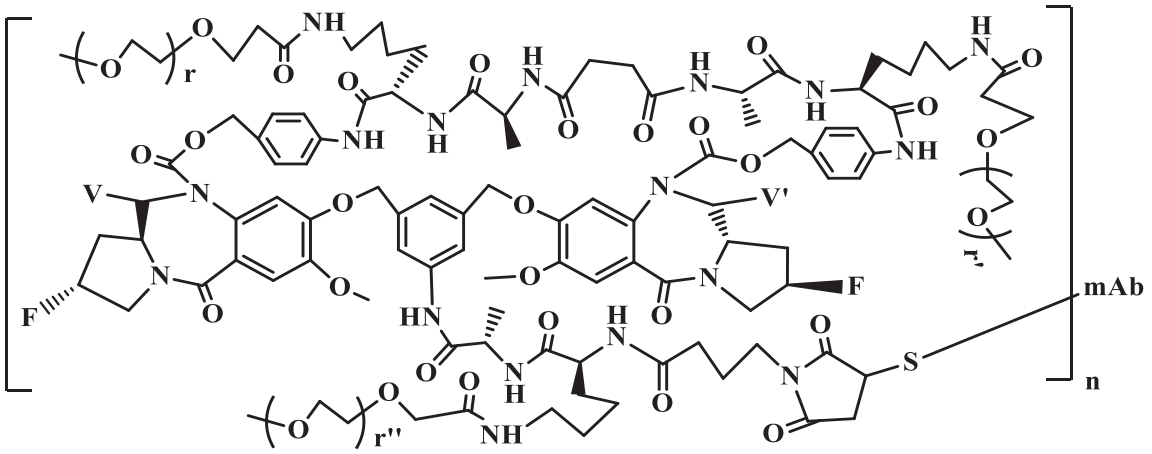
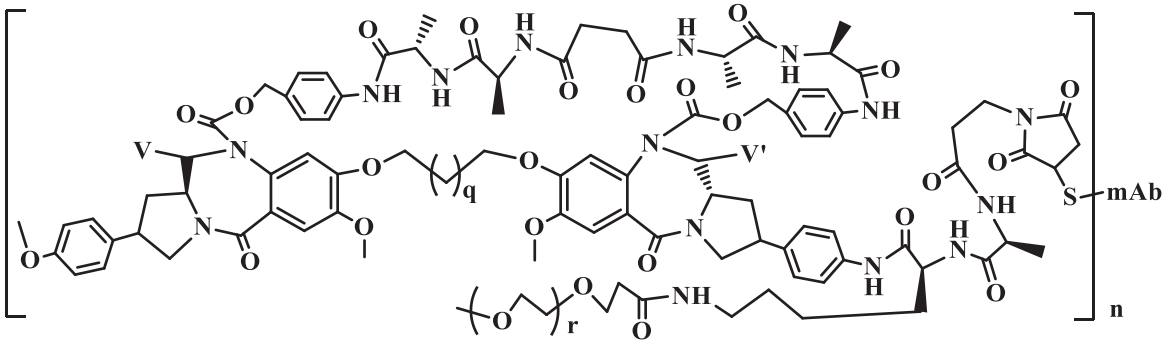
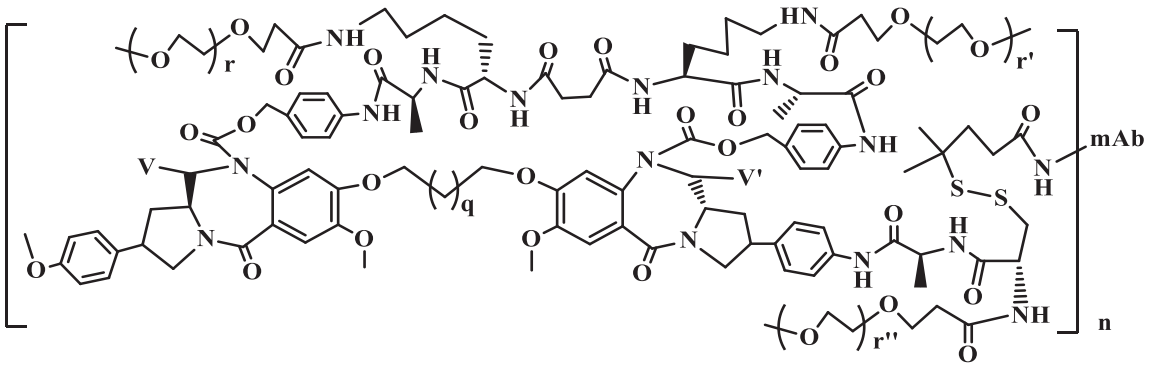


(III-05),



(IV-01),



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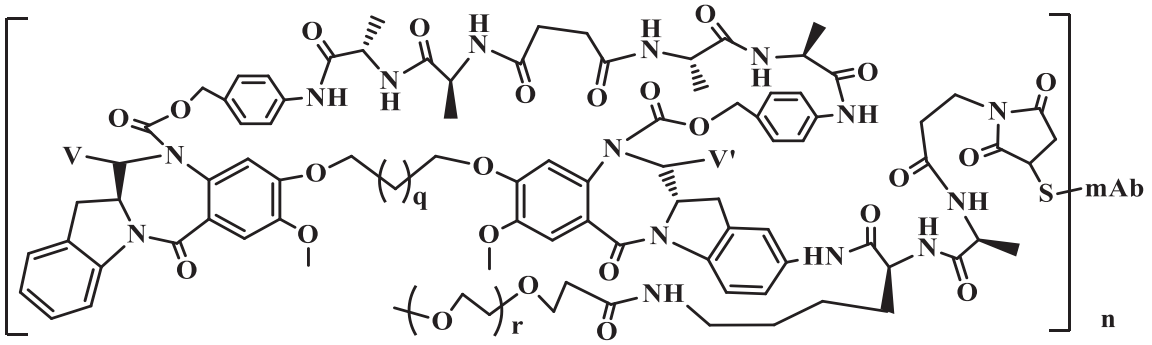
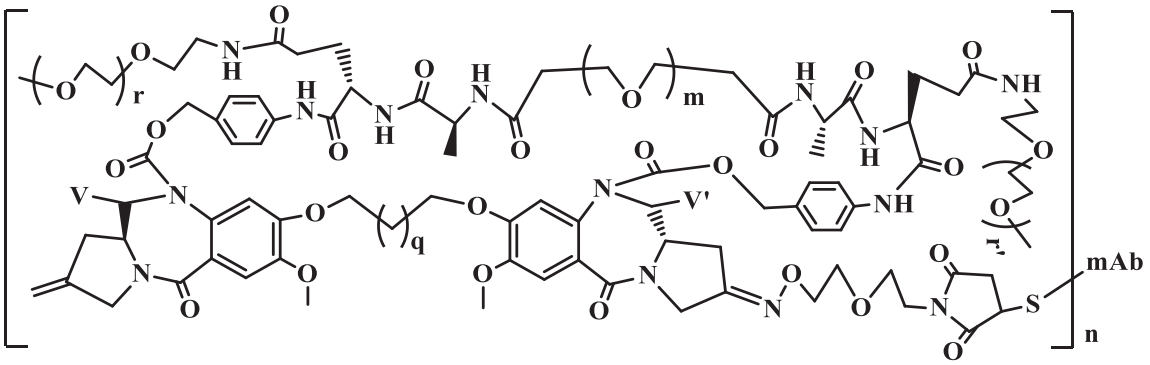


(IV-03),



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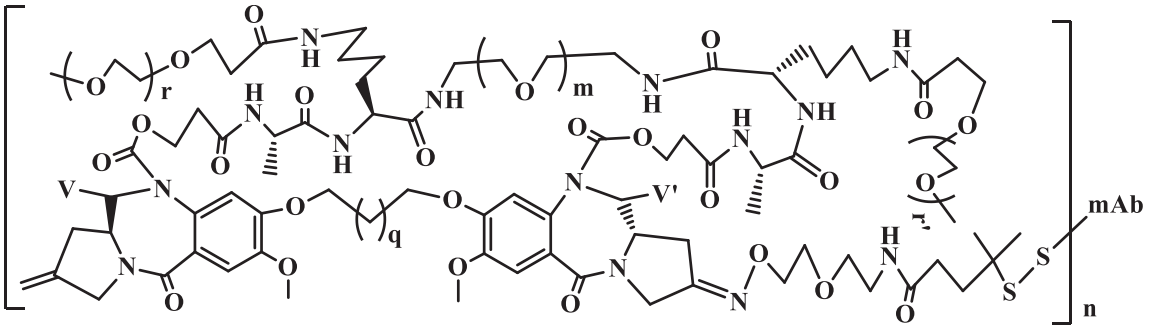

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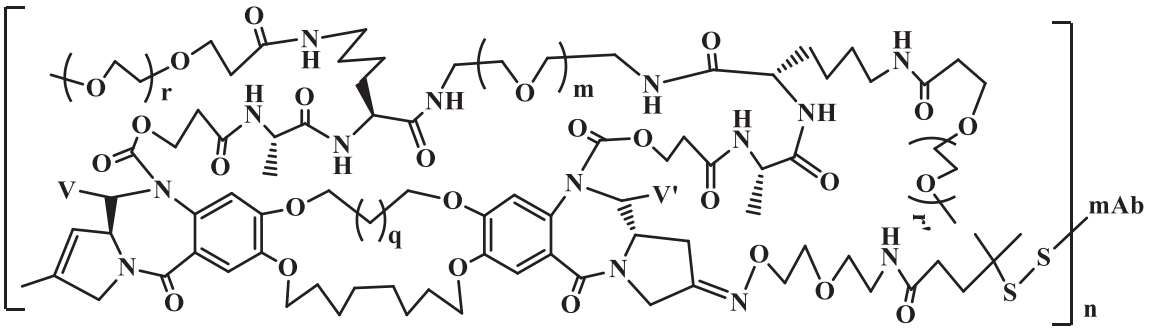
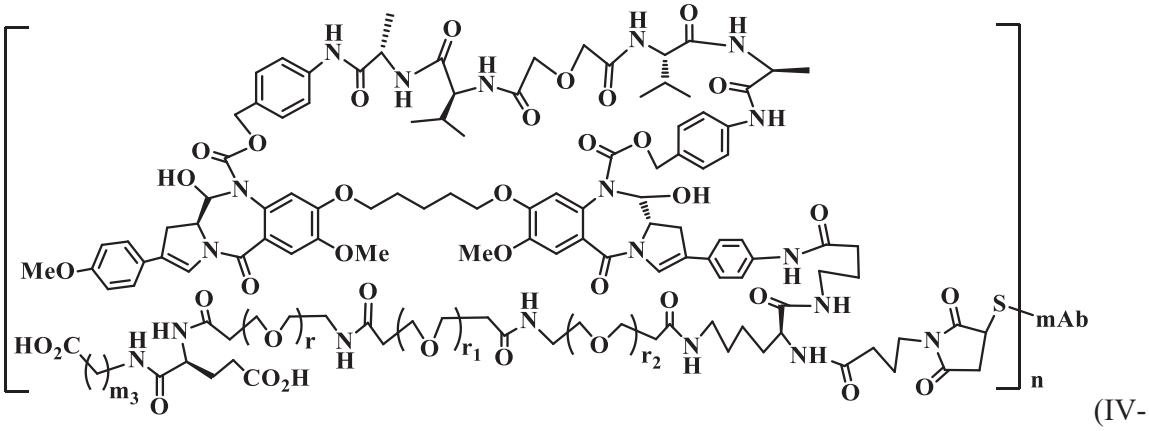
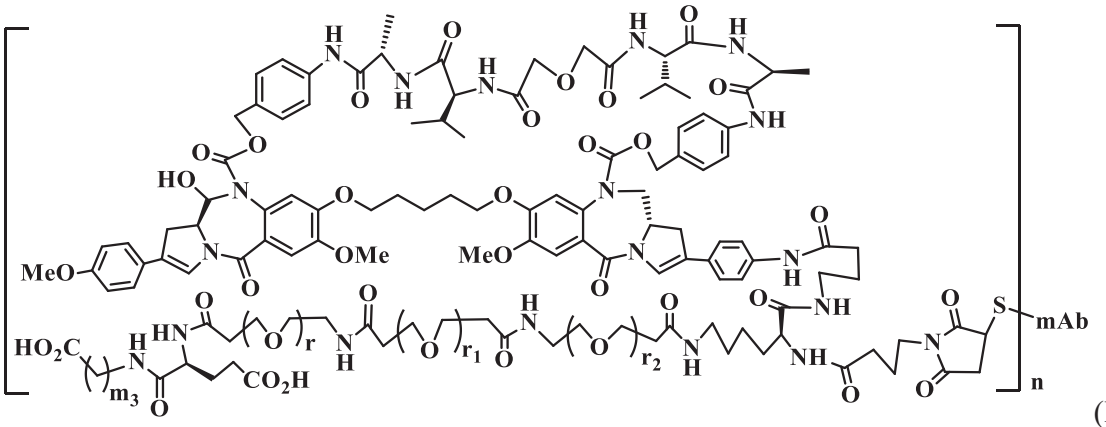


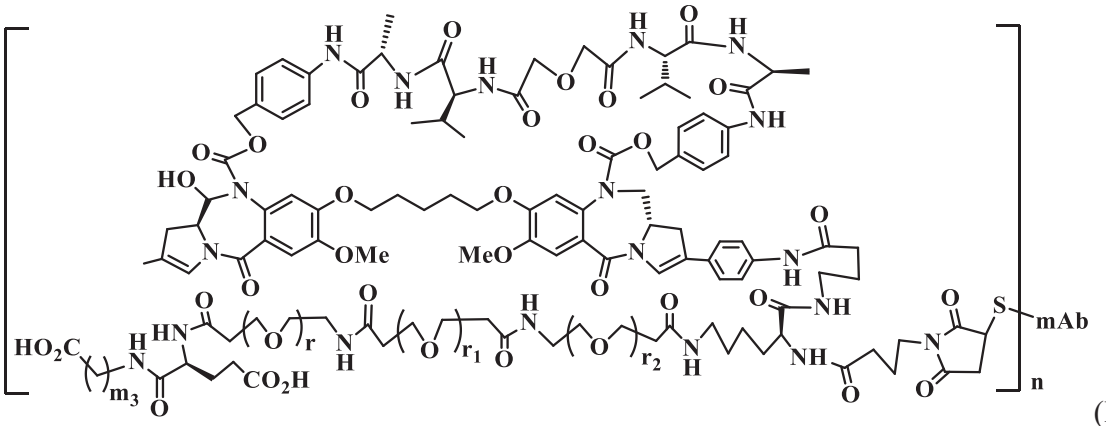
(IV-06),



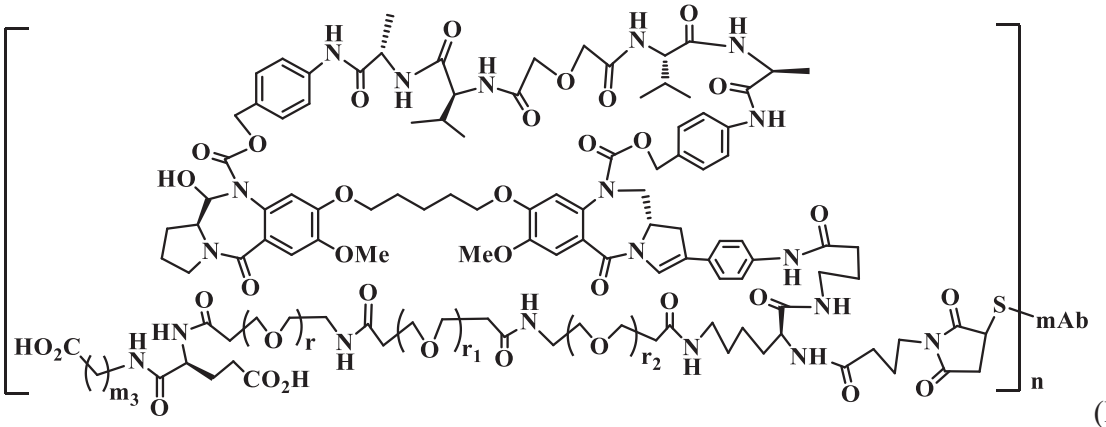
(IV-07),



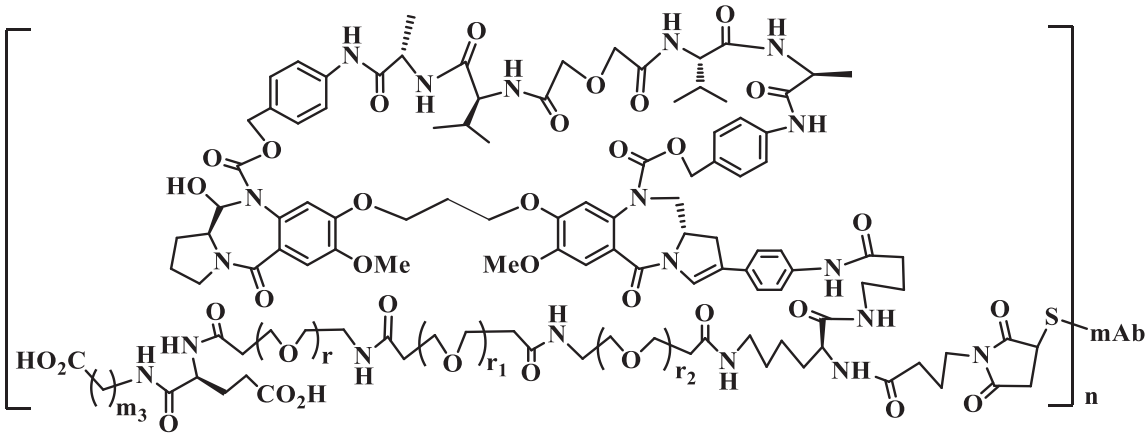
(IV-08),



(IV-09),



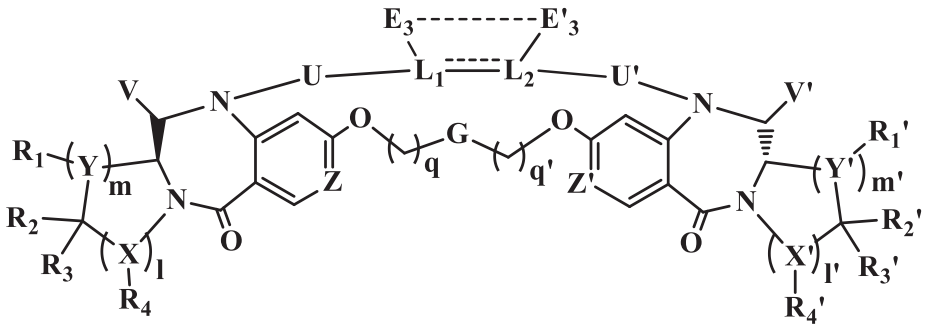
(IV-10),



(IV-11),

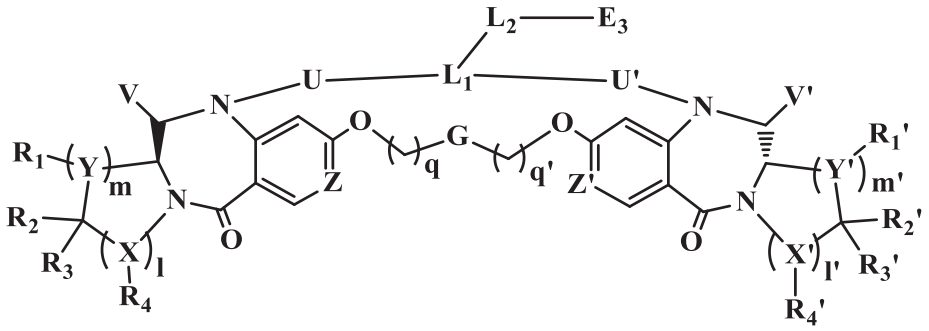
wherein ═══, ----- , m, m', n, q, and q' are the same defined as in Claim 1; r, r', and r'' are independently 0 – 200, m_3 is 0-30.

6. A cross-linked PBD dimer derivative having the Formula (V) (VI), (VII), and (VIII):

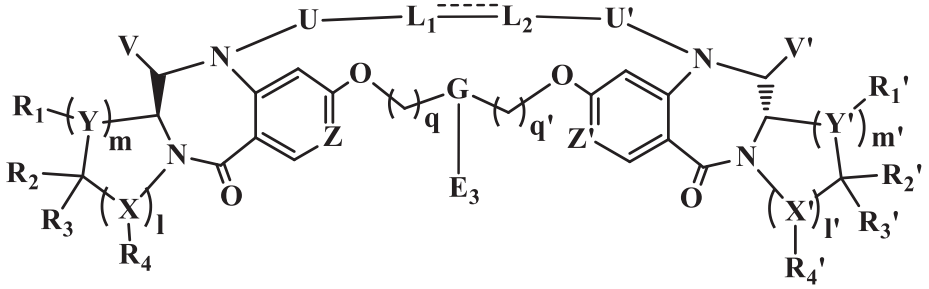


(V),

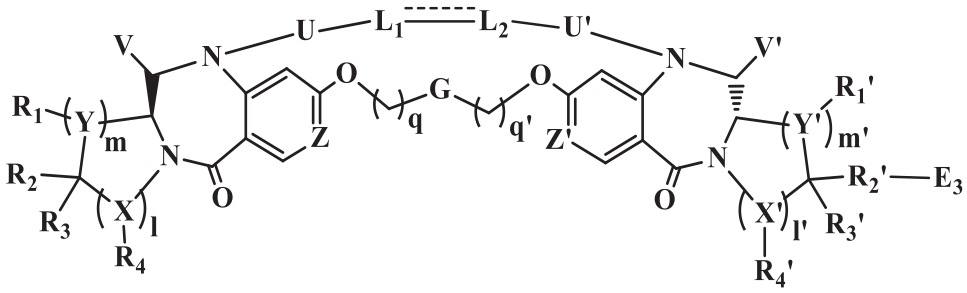
wherein ═══, ----- , X, X', Y, Y', Z, Z', l, l', m, m', n, q, q', R_1, R_1', R_2, R_2', R_3, R_3', R_4, R_4', V, V', U, U' L_1, L_2, E_1, and E_2 are the same defined as in Claim 1; or



(VI),



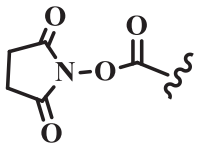
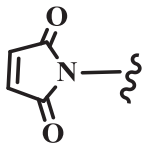
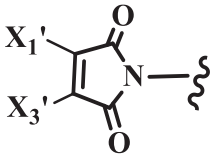
(VII),

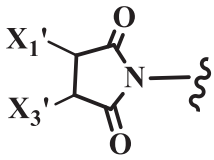
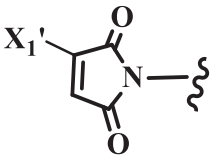
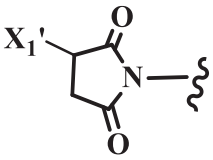
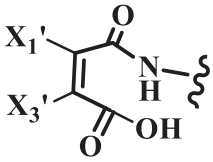
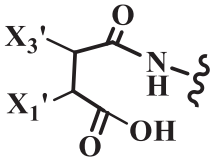


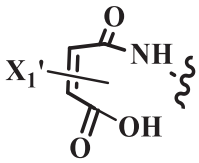
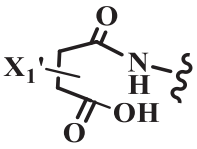
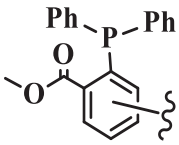
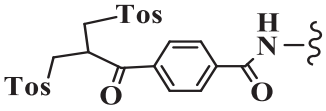
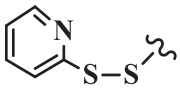
(VIII),

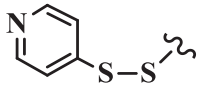
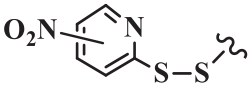
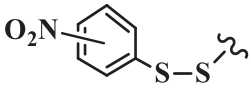
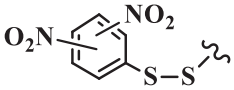
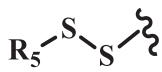
wherein ⎓, -----, X, X', Y, Y', Z, Z', l, l', m, m', n, q, q', R_1, R_1', R_2, R_2', R_3, R_3', R_4, R_4', V, V', U, U' L_1, L_2, E_1, and E_2 are the same defined as in Claim 4;

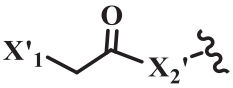
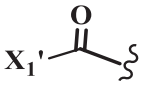
wherein E_3 and E'_3 are independently selected from:

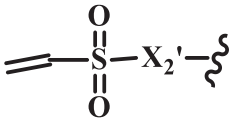
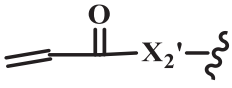
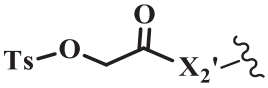
 *N*-hydroxysuccinimide ester;  maleimide;  ,

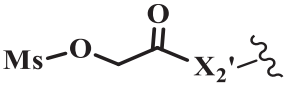
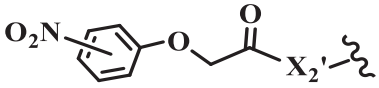
 ,  ,  ,  ,  ,

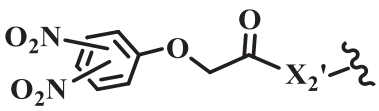
 ,  ,  ,  ,  ,

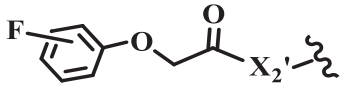
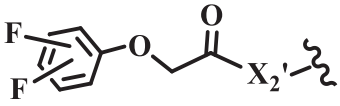
 ,  ,  ,  , 

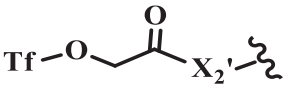
disulfide;  haloacetyl;  acyl halide (acid halide),

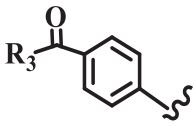
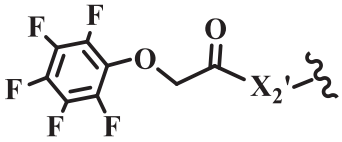
 ethenesulfonyl;  acryl (acryloyl); 

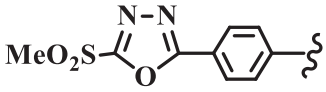
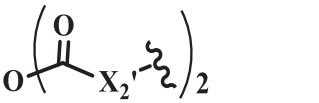
2-(tosyloxy)acetyl;  2-(mesyloxy)acetyl; 

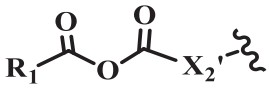
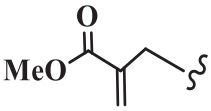
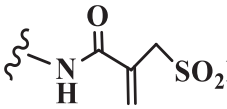
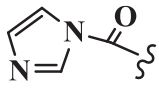
2-(nitrophenoxy)acetyl;  2-(dinitrophenoxy)acetyl;

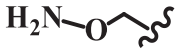
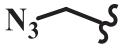
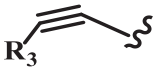
 2-(fluorophenoxy)-acetyl;  2-

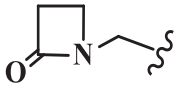
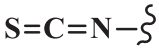
(difluorophenoxy)-acetyl;  2-(((trifluoromethyl)-sulfonyl)oxy)acetyl;

 ketone, or aldehyde,  2-(pentafluorophenoxy)acetyl;

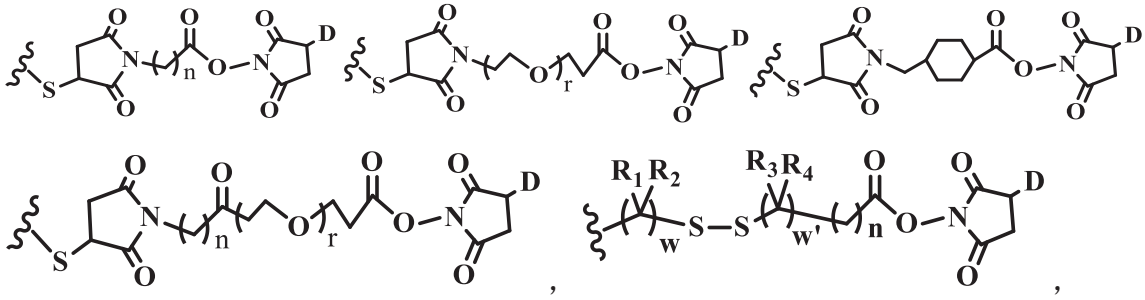
 , methylsulfone phenyloxadiazole (ODA);  ,

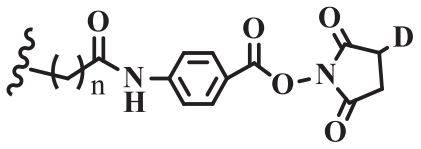
 acid anhydride,  ,  , 

carbonylimidazole,  alkyloxyamino;  azido,  alkynyl,

 β-lactam, or hydrazide,  isothiocyanato; wherein X_1' and X_3' are independently F, Cl, Br, I or Lv_3; X_2' is O, NH, N(R_1), or CH_2; R_3 and R_5 are independently H, R_1, 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 selected from methanesulfonyl (mesyl), toluenesulfonyl (tosyl), trifluoromethyl-sulfonyl (triflate), trifluoromethylsulfonate, nitrophenoxyl, phenylthio, pyridinylthio, N-succinimidyloxyl (NHS), phenoxyl; dinitrophenoxyl; pentafluorophenoxyl, tetrafluorophenoxyl, trifluorophenoxyl, difluorophenoxyl, monofluoro-phenoxyl, pentachlorophenoxyl, 1H-imidazole-1-yl, chlorophenoxyl, dichlorophenoxyl, trichlorophenoxyl, tetrachlorophenoxyl, N-(benzotriazol-yl)oxyl, 2-ethyl-5-phenylisoxazolium-yl, phenyloxadiazol-yl (ODA), oxadiazol-yl, or an intermediate molecule generated with a condensation reagent for Mitsunobu reactions, wherein R_1 and R_2 are defined above;

Additionally, E_3 and E'_3 are independently selected from -SH, -S-SCH_3, -S-SAc, -S-S-pyridine, -S-S-Ar(-NO_2), -S-cell-binding agent, or any one of the following formulas:

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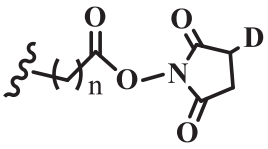
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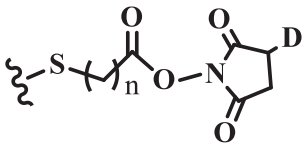
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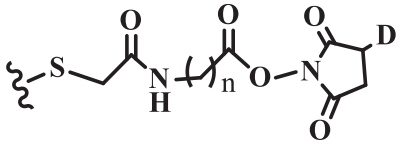
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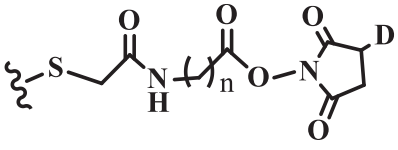
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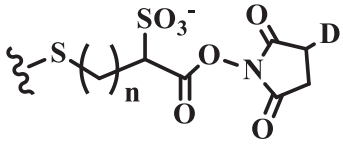
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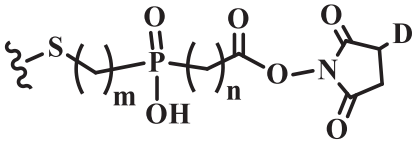
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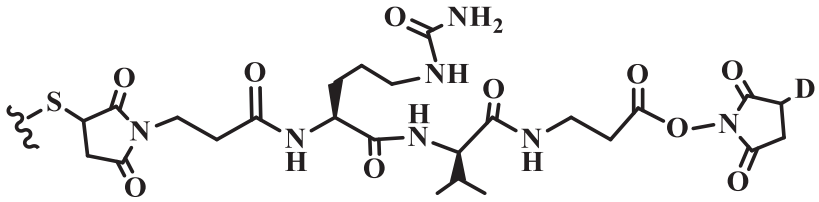
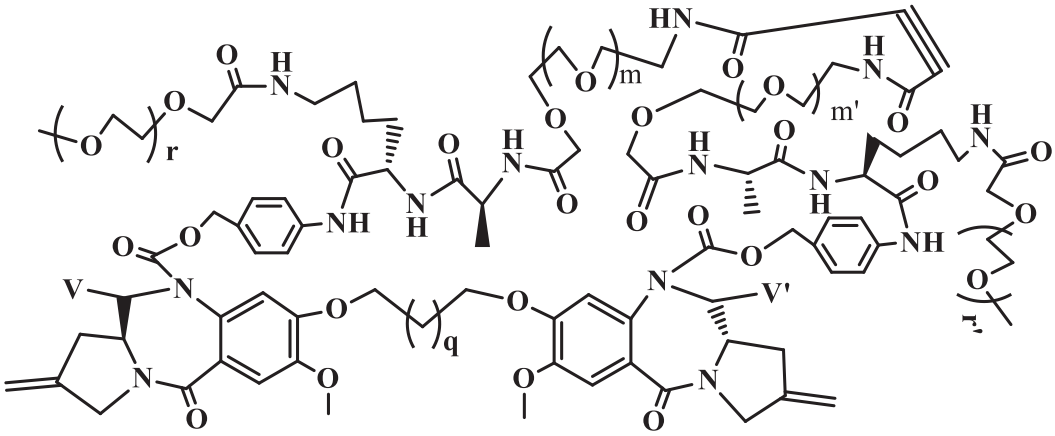


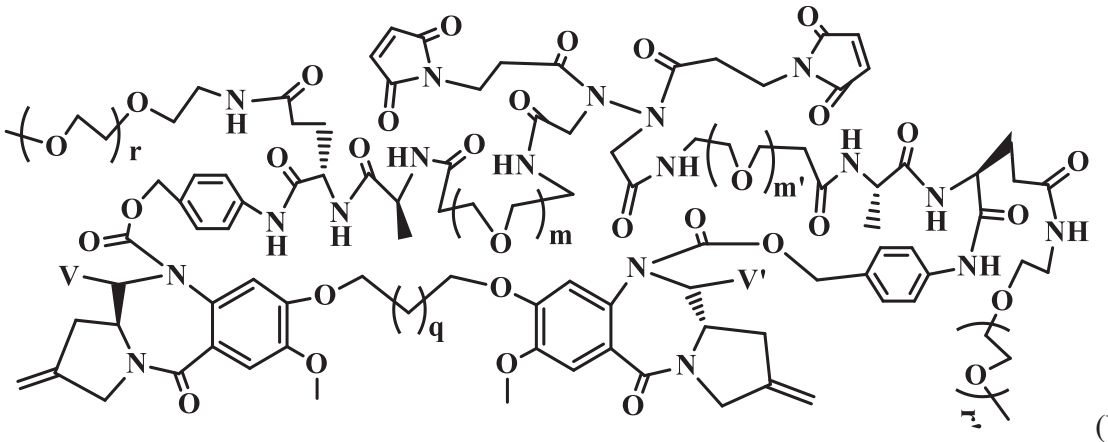
wherein D is H, $-NO_2$, SO^3H, or F; wherein R_1, R_2, R_3, R_4, r, m and n are defined above; w and w' are independently 0, 1 or 2;

wherein R_5 and R_5' are independently selected from C_1~C_6 alkyl, aryl, cyclic, cyclohetero, H, or M, wherein M is Na, K, Ca, ammonium or the other pharmaceutically acceptable salt;

or wherein the PBD dimer derivative is



(V-05),



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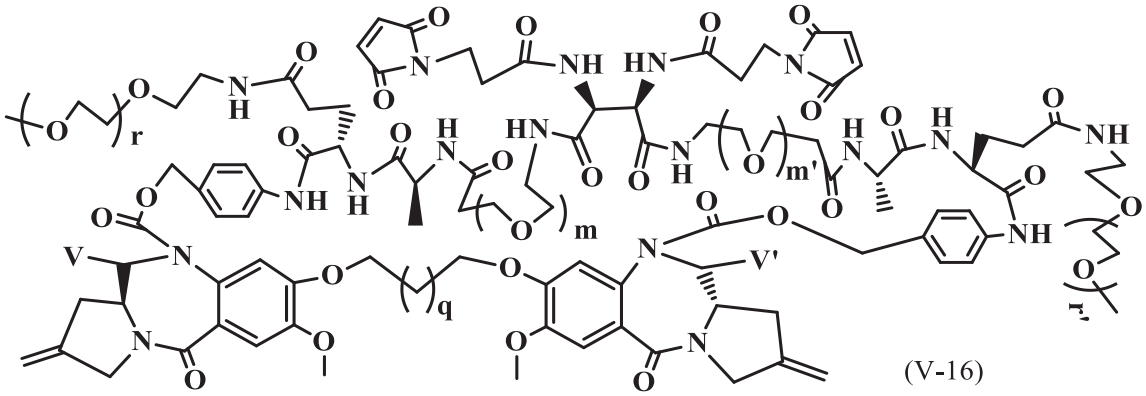

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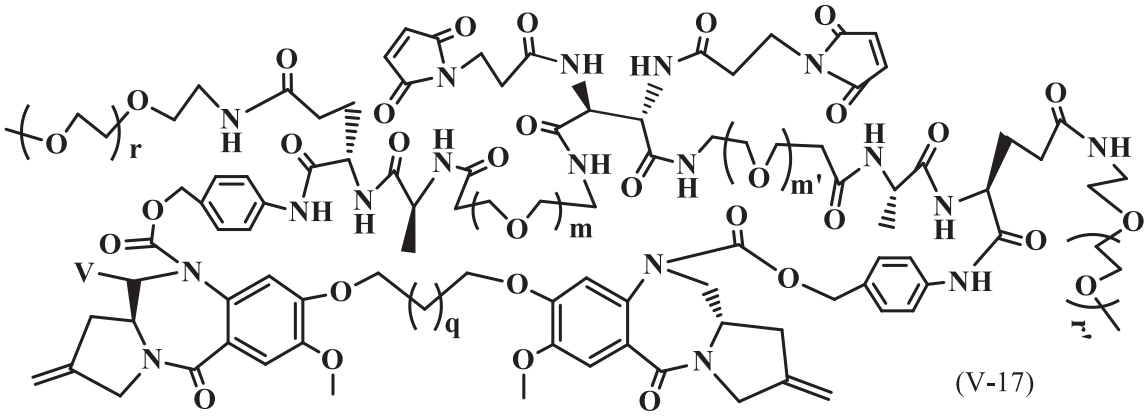

(V-17)

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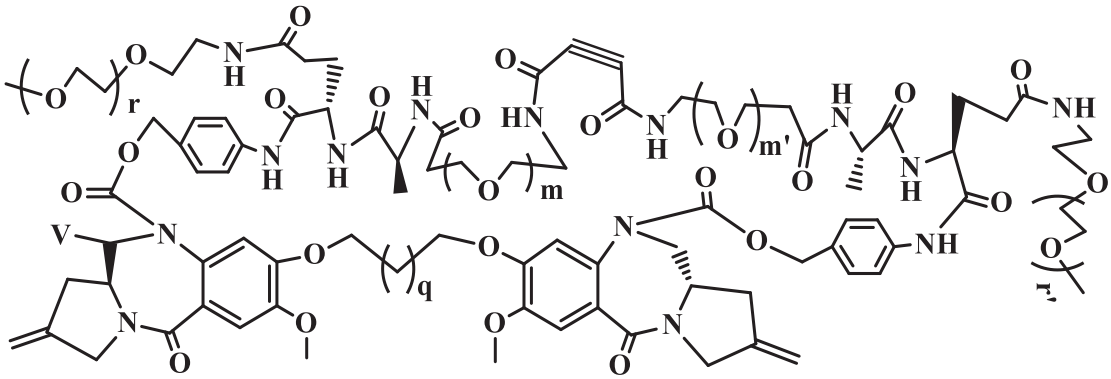

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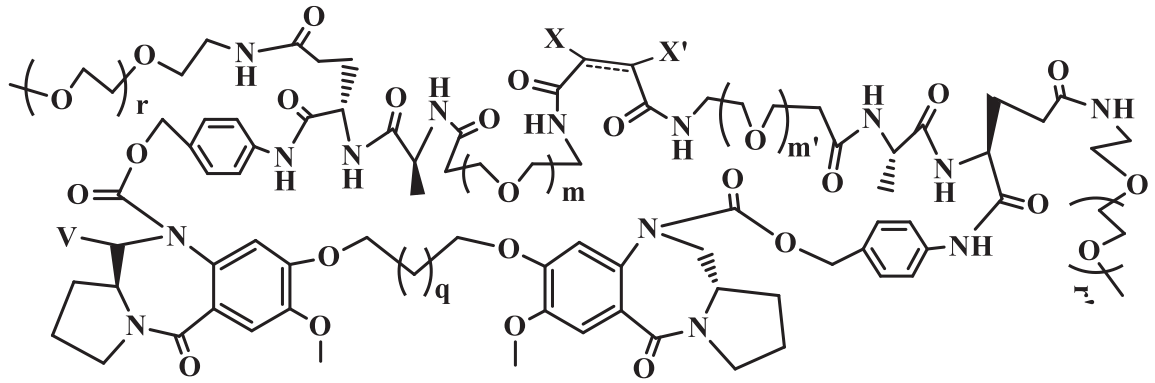

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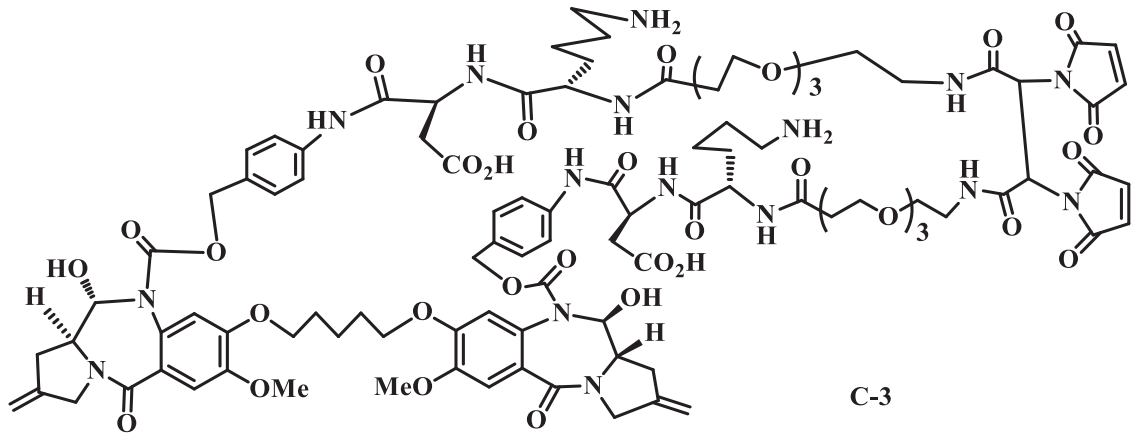

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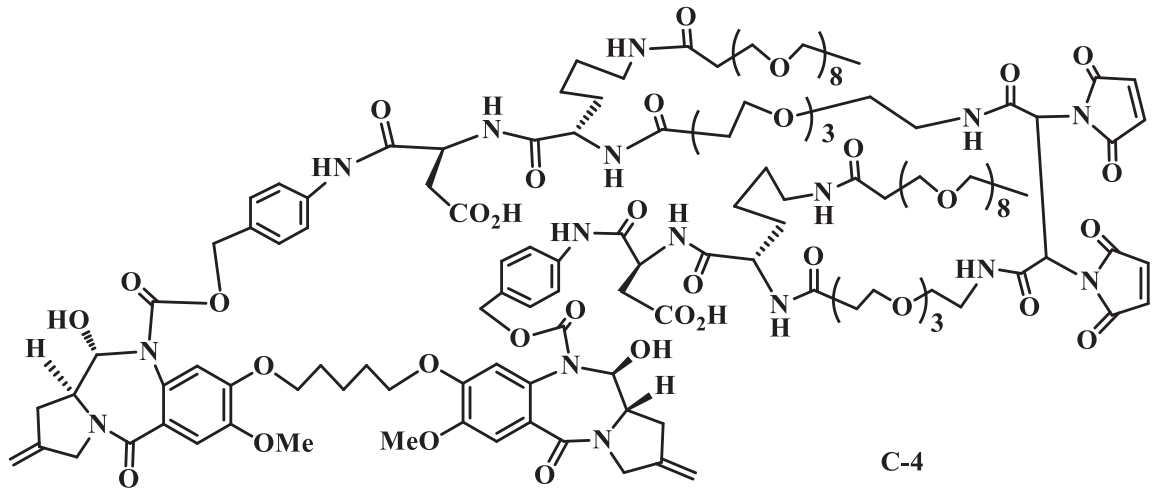

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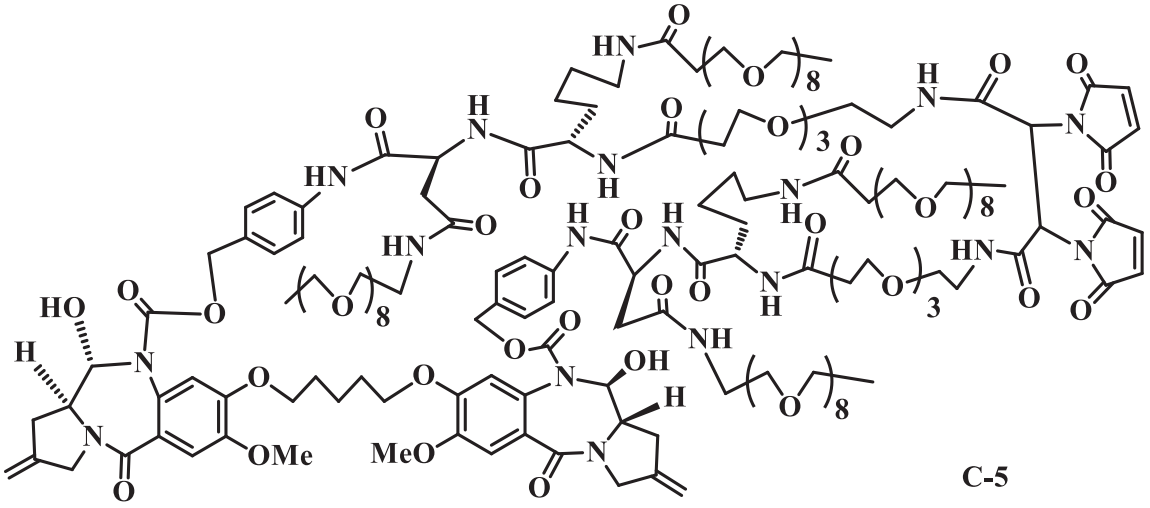

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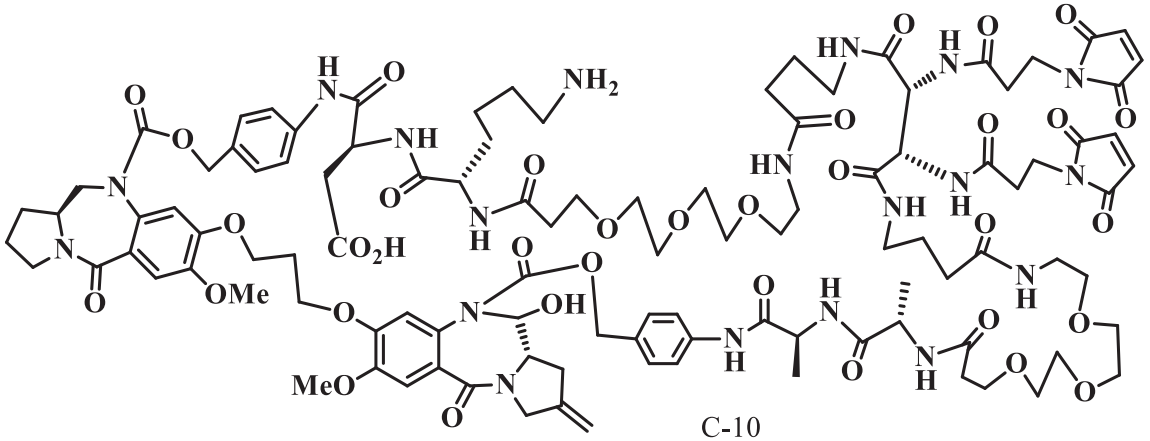

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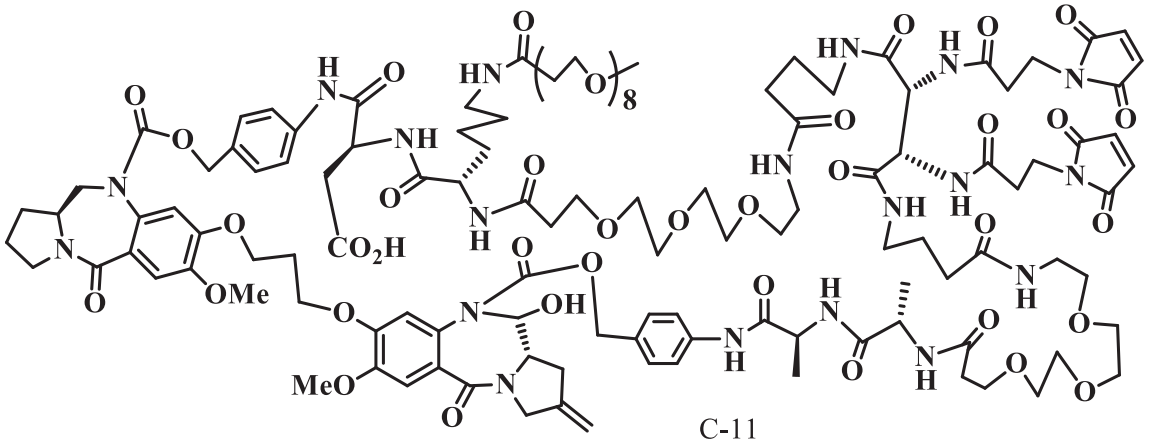

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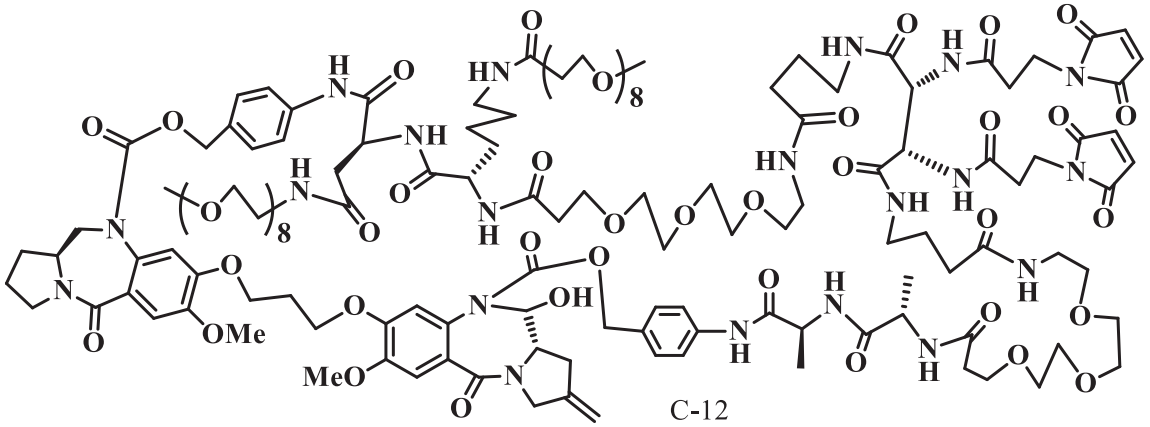

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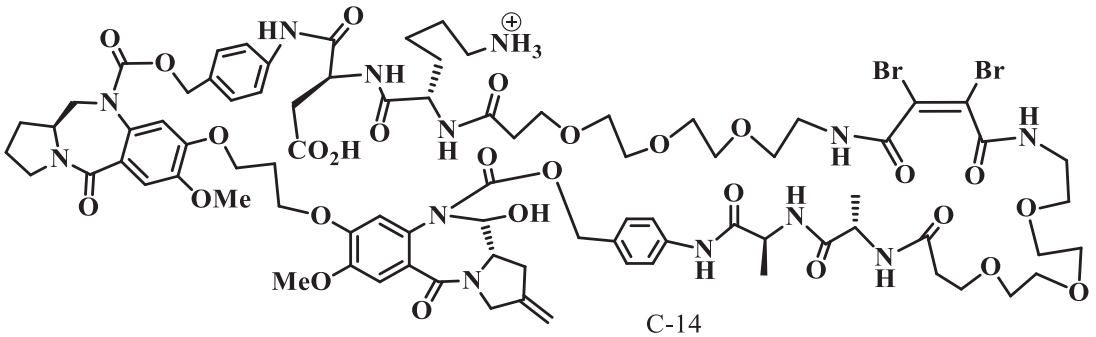

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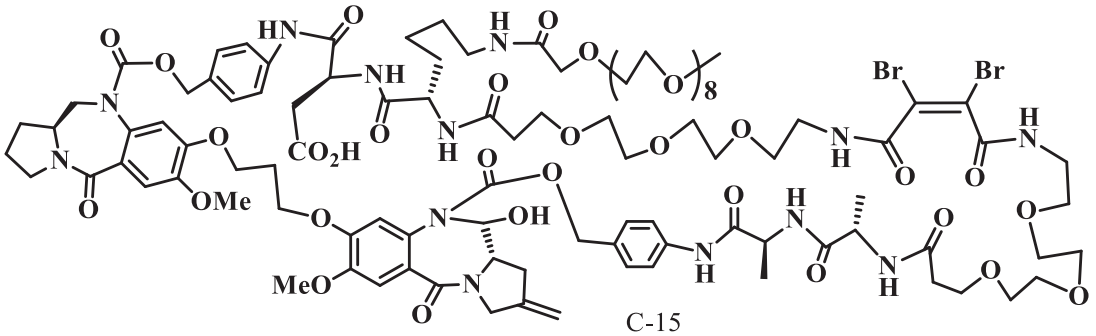

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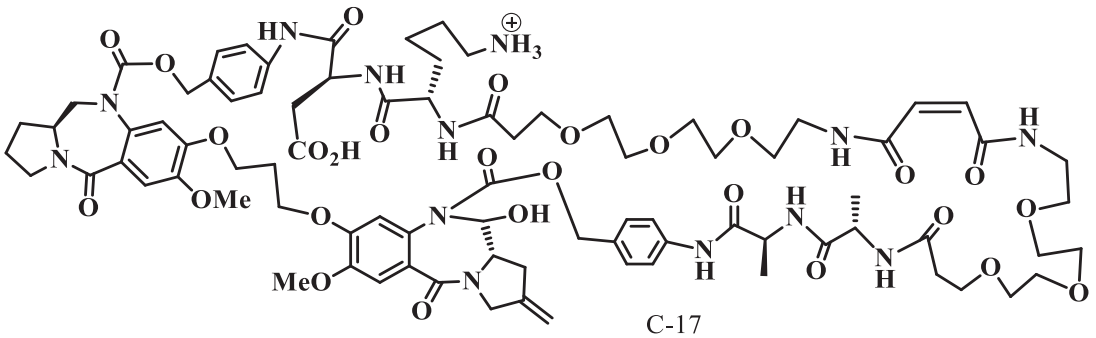

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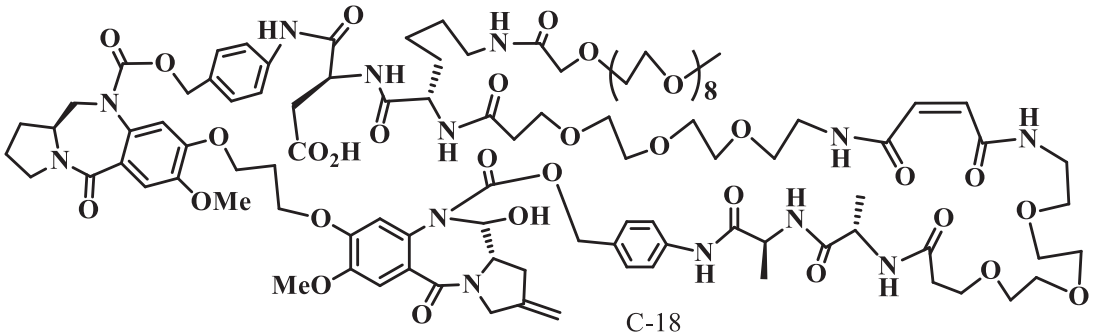

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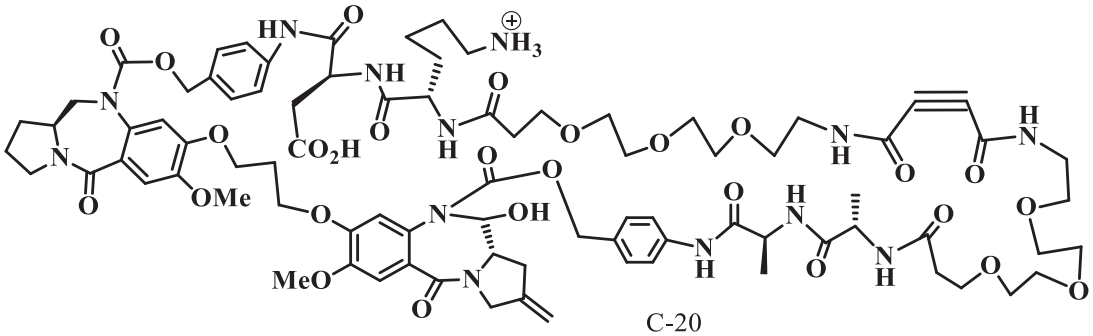

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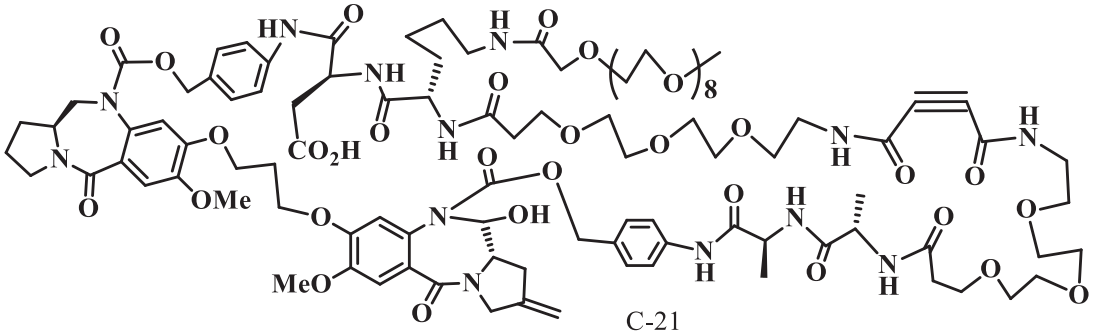

C-21 ,

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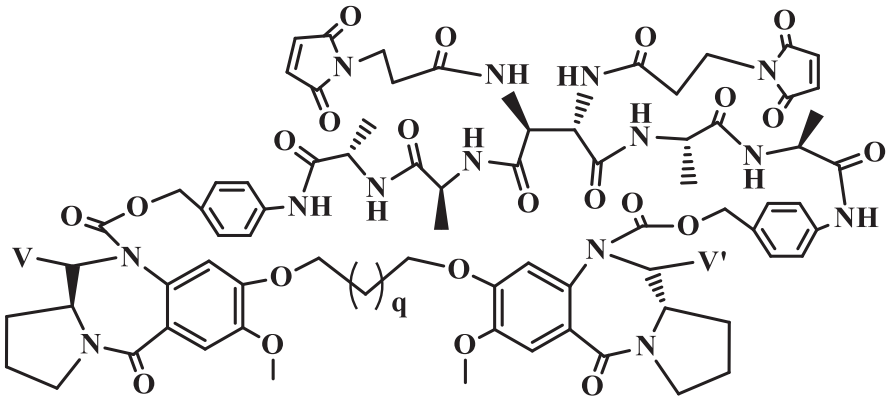
7. A PBD dimer derivative according to Claim 6 having Formulas (V-01)~(V-20), (VI-01) ~ (VI-12), (VII-01)~ (VII-06), (VIII-01) ~(VIII-06) below:



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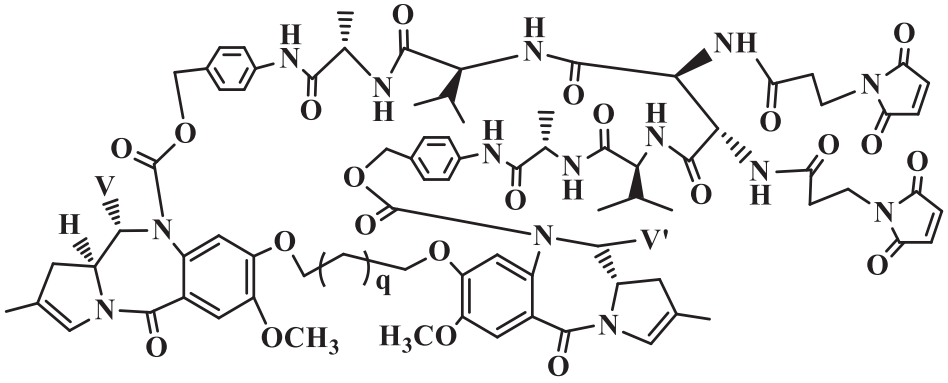
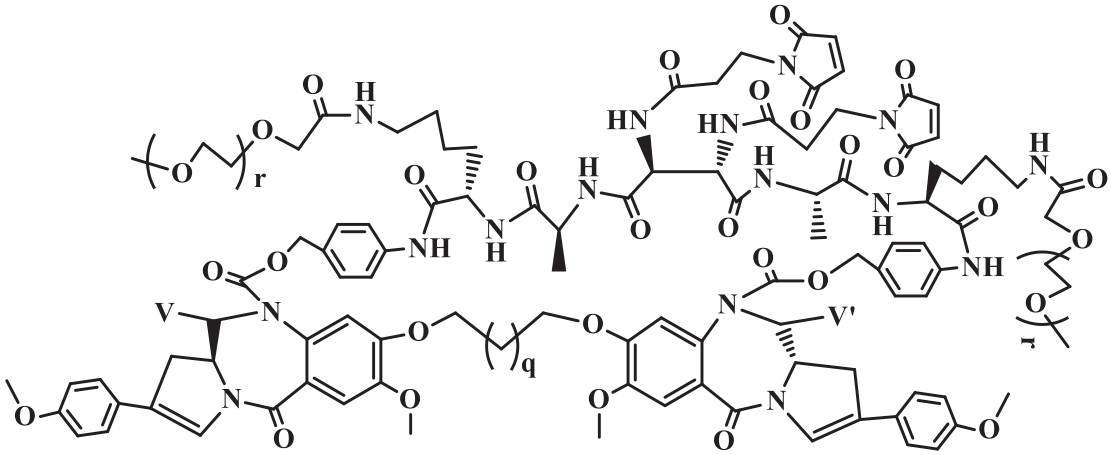


(V-02),



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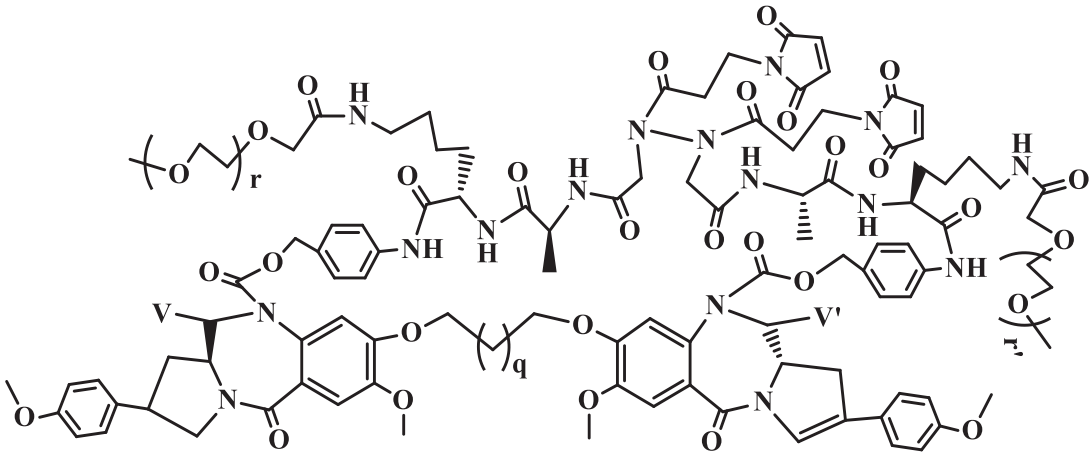

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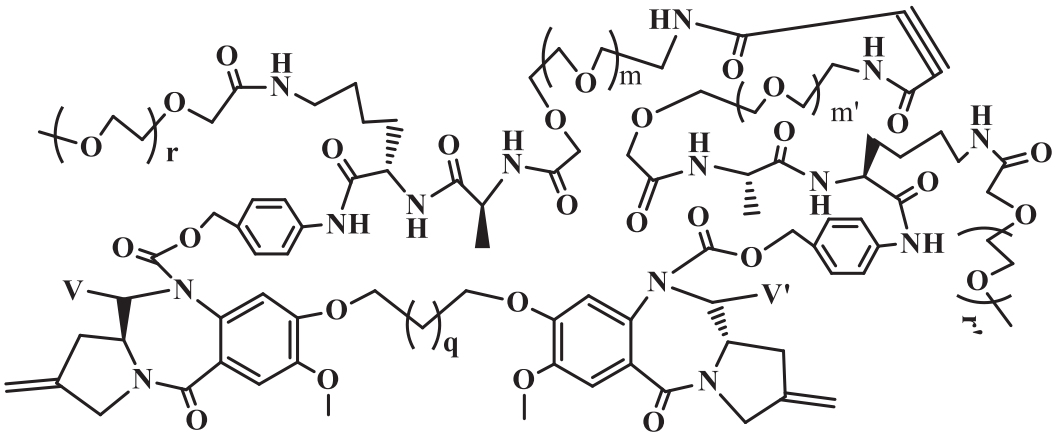

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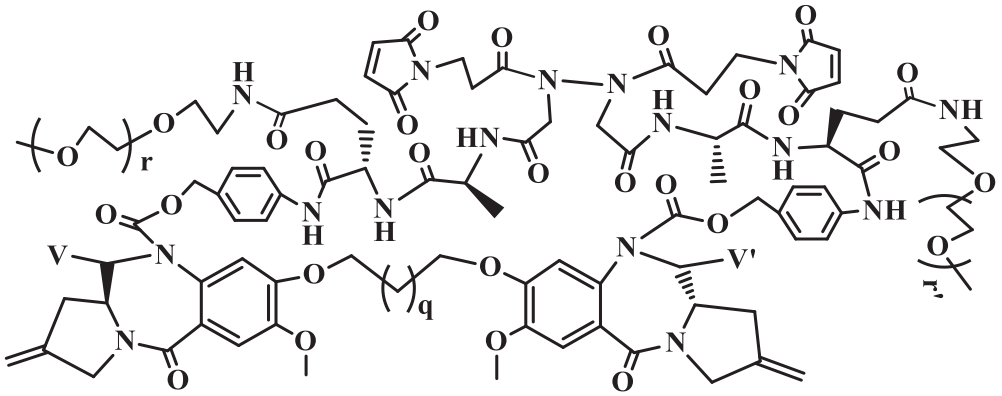

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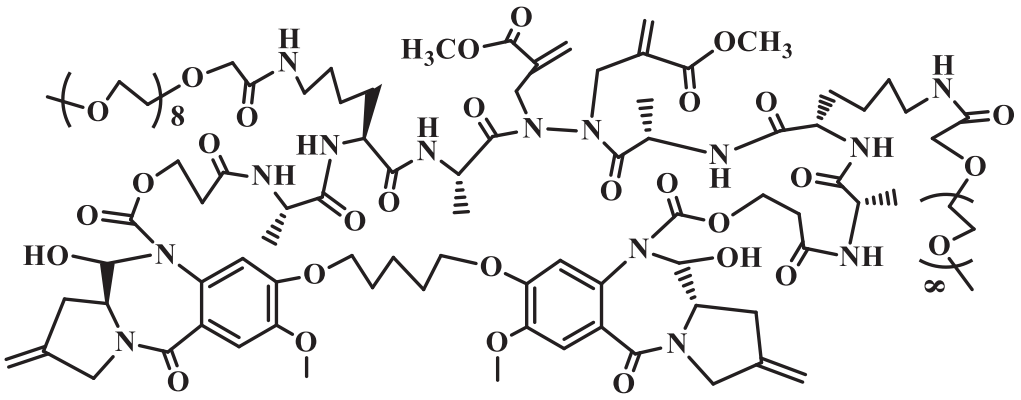

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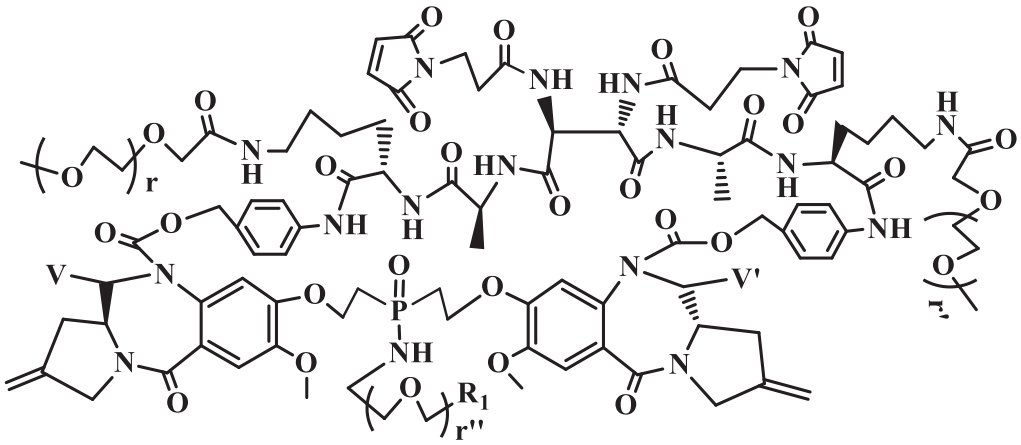

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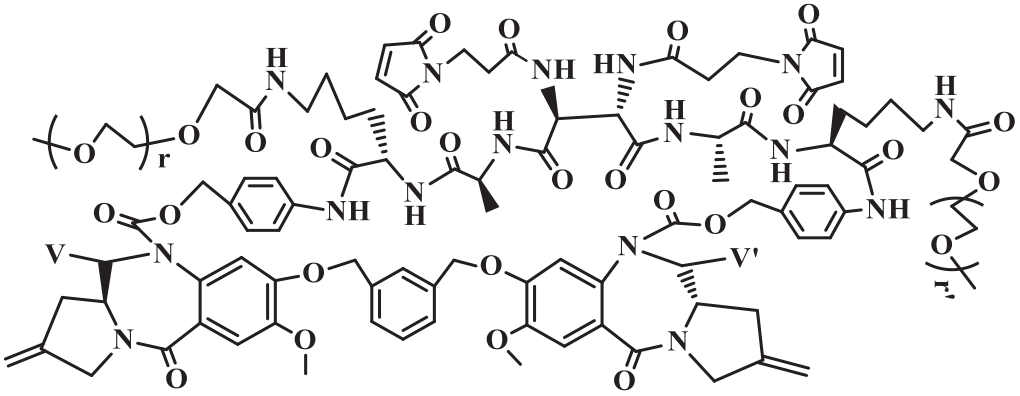

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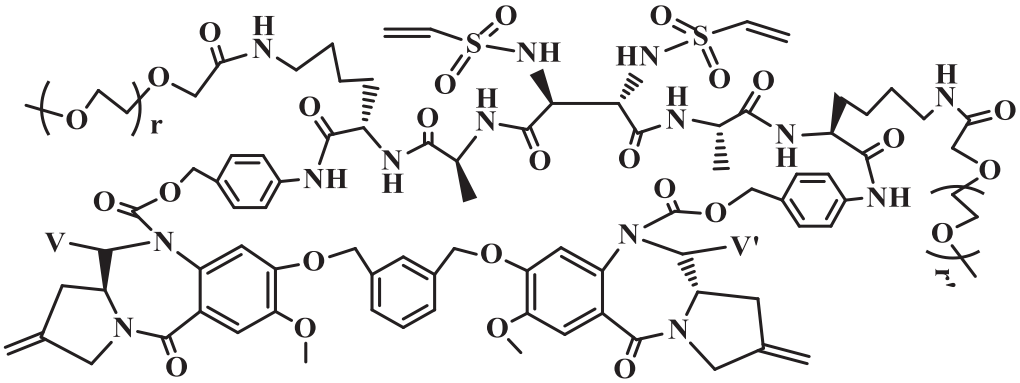

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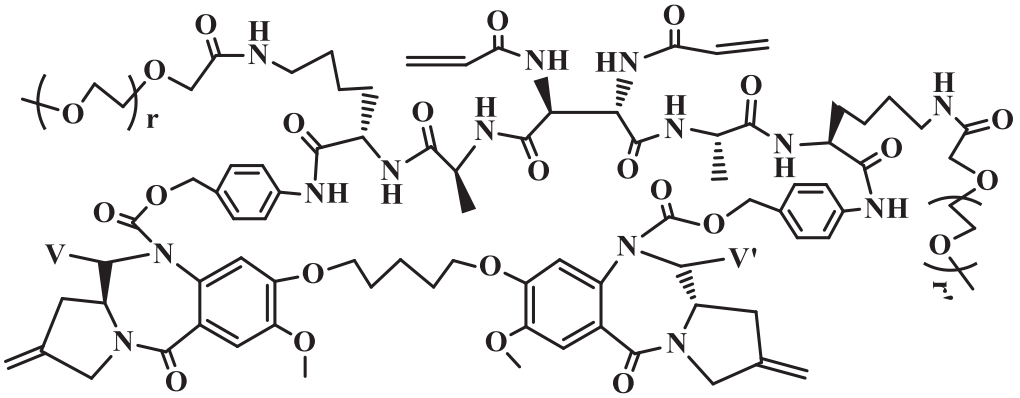

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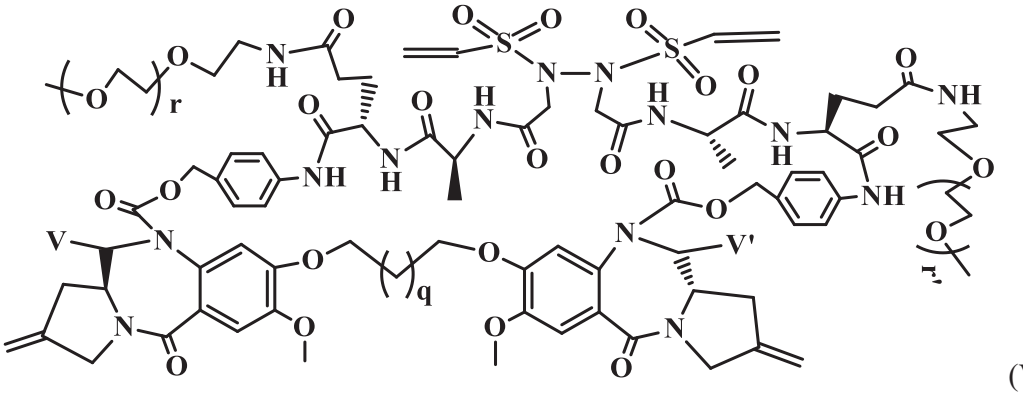

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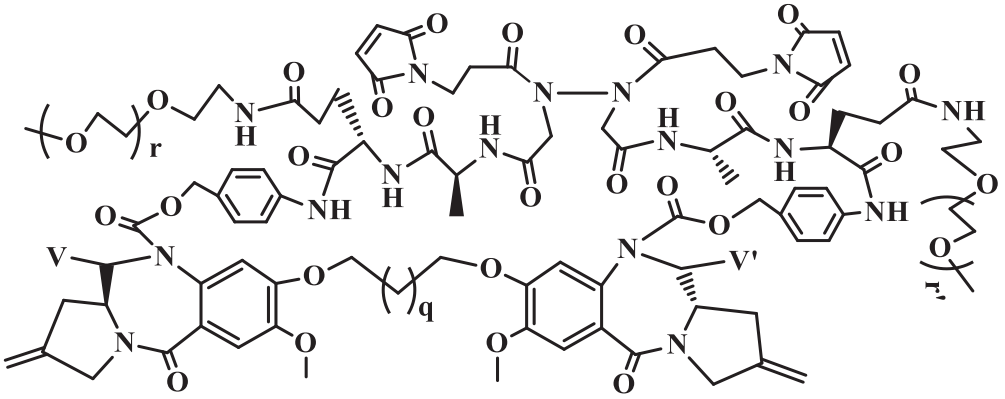

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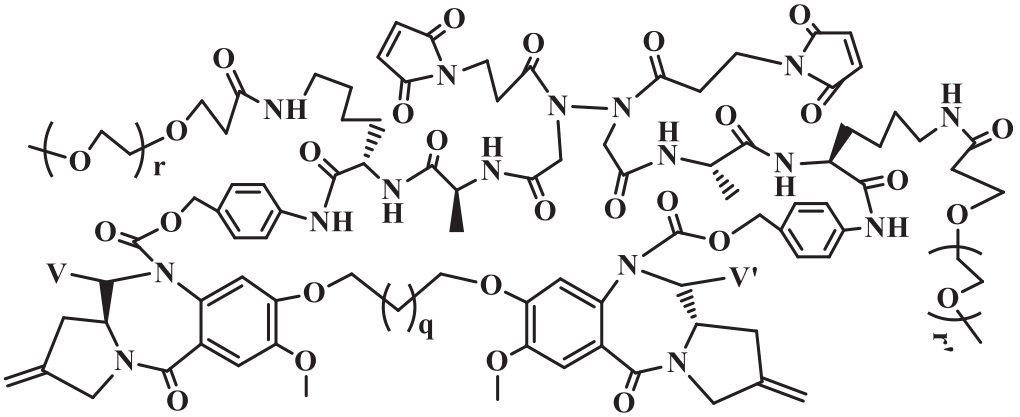

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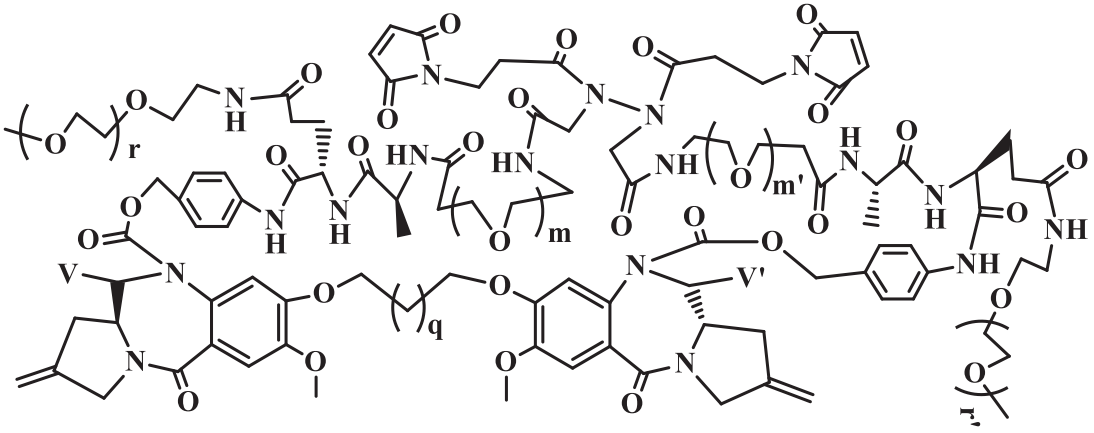

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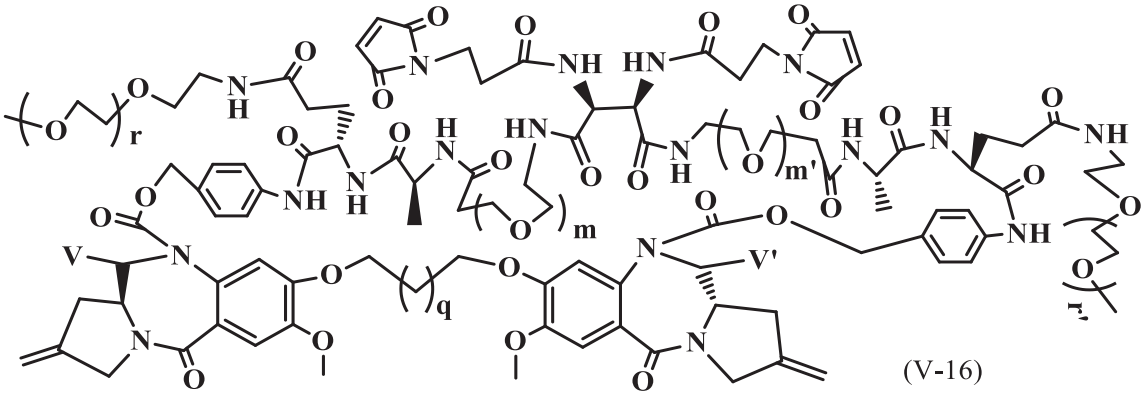

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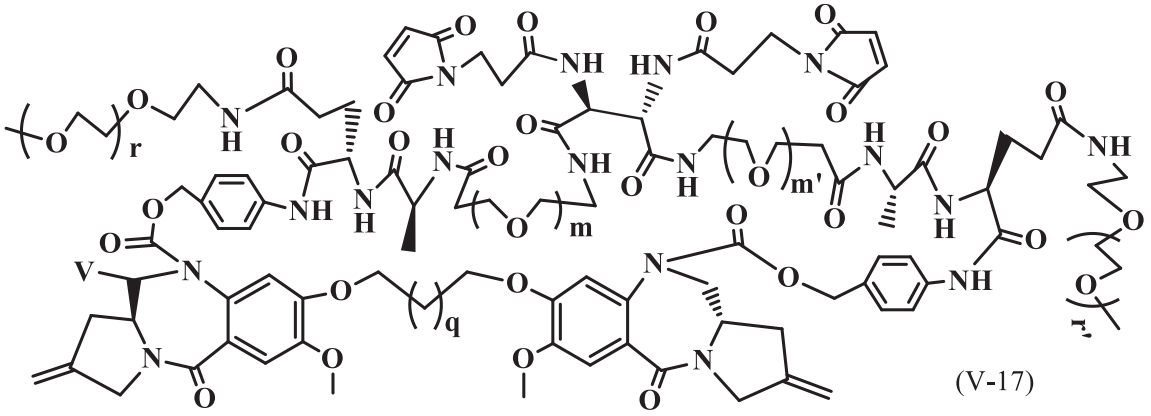

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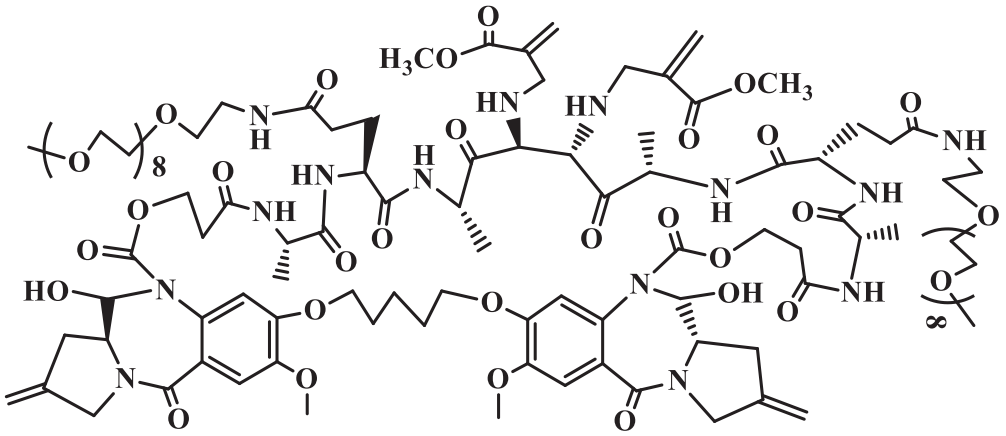

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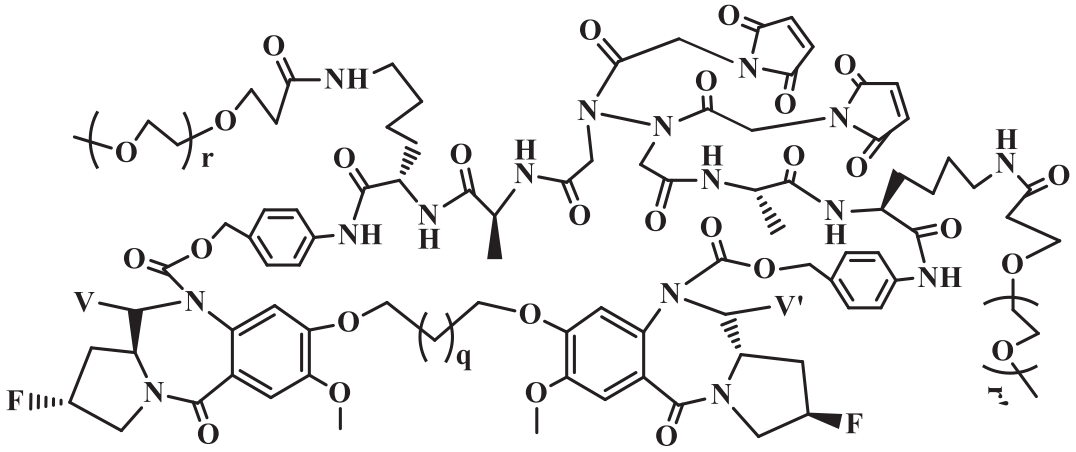

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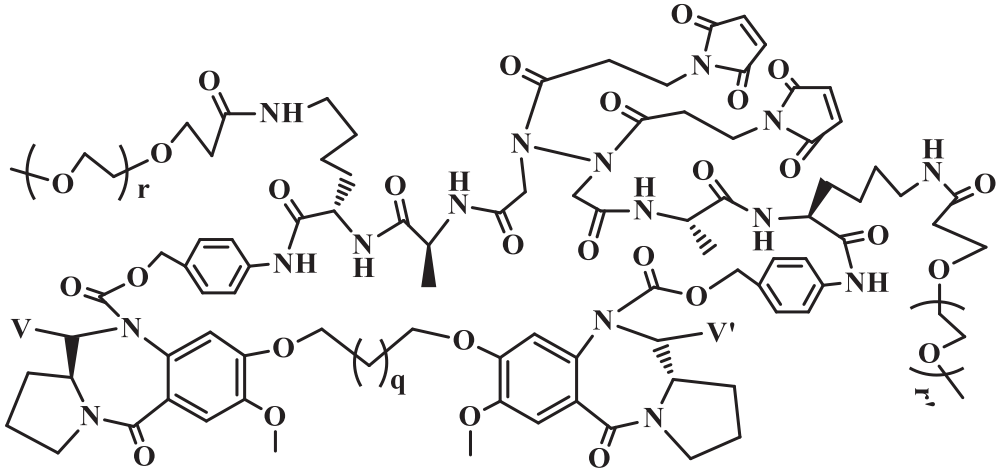

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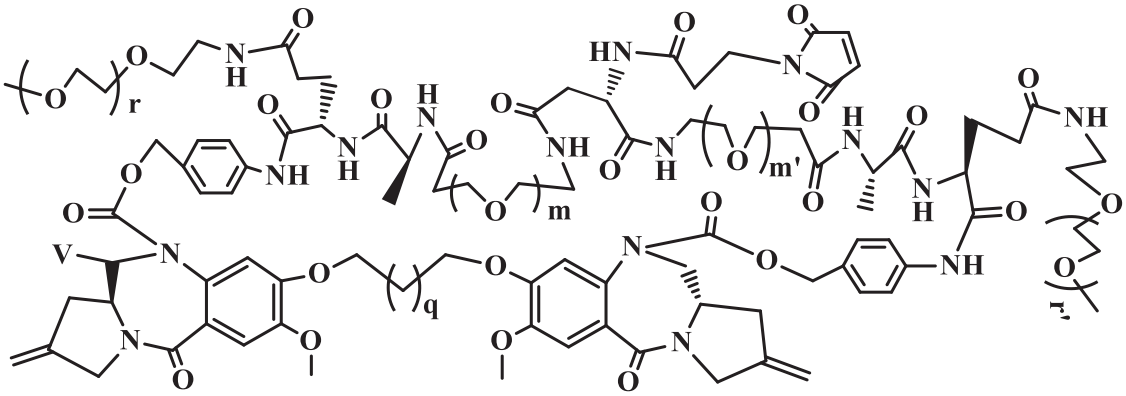

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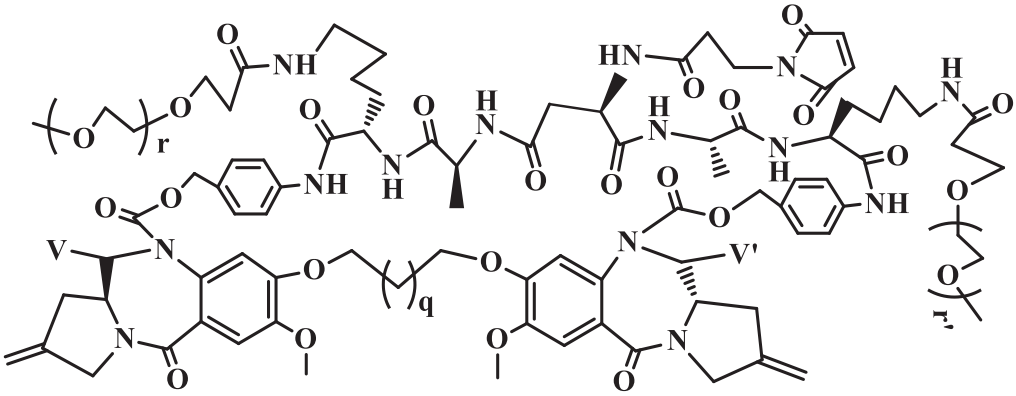

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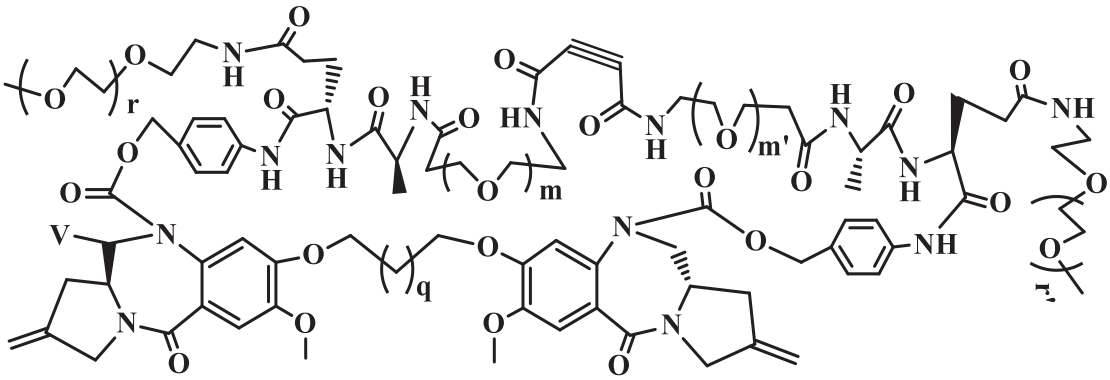

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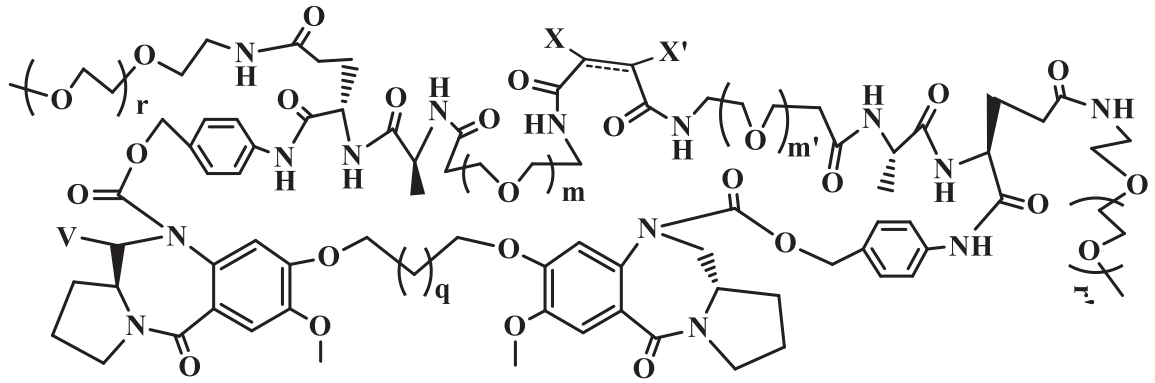

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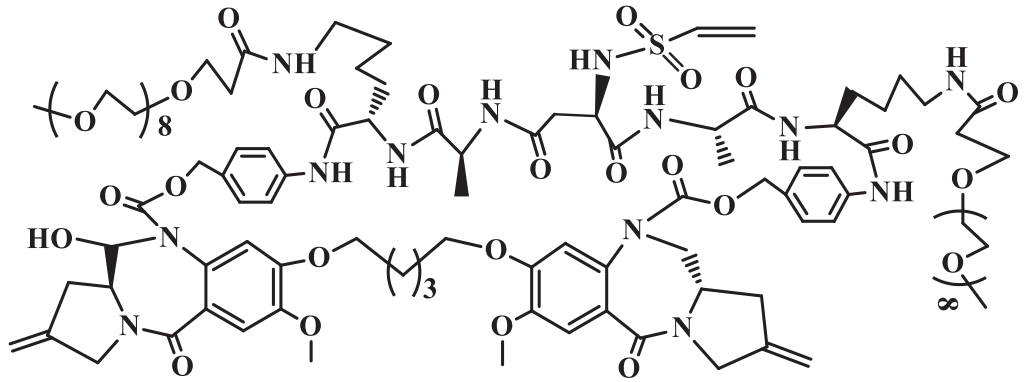

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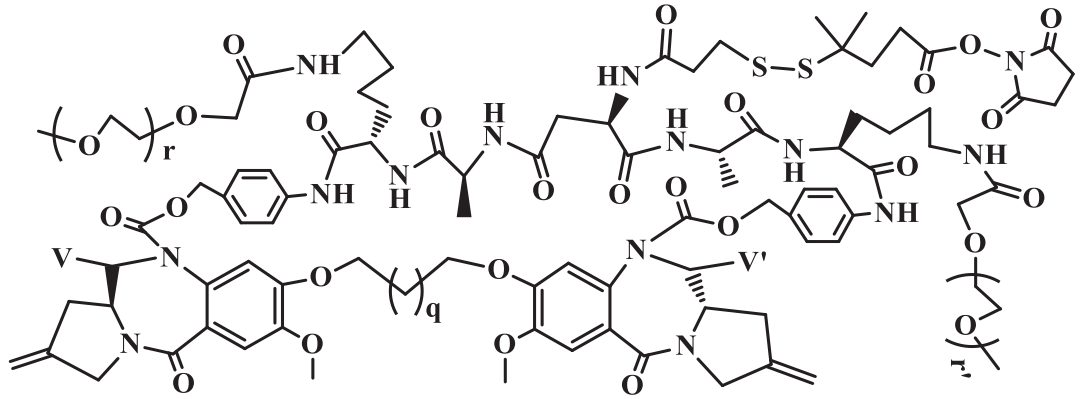

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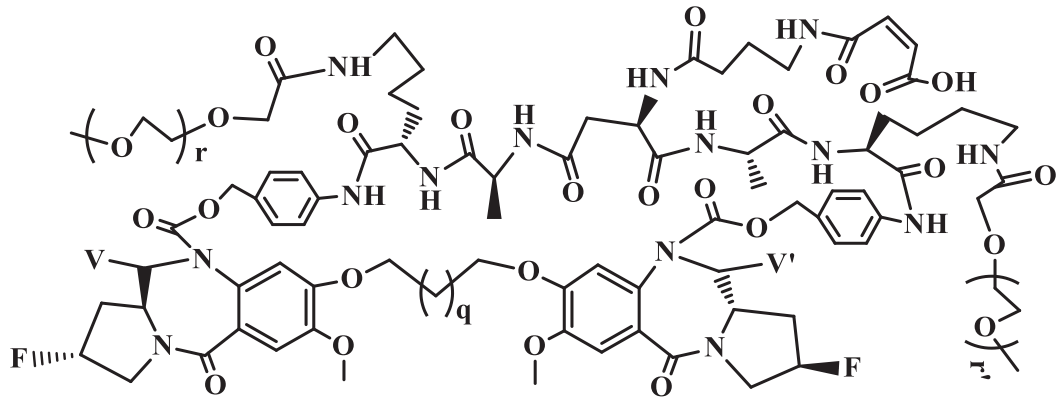

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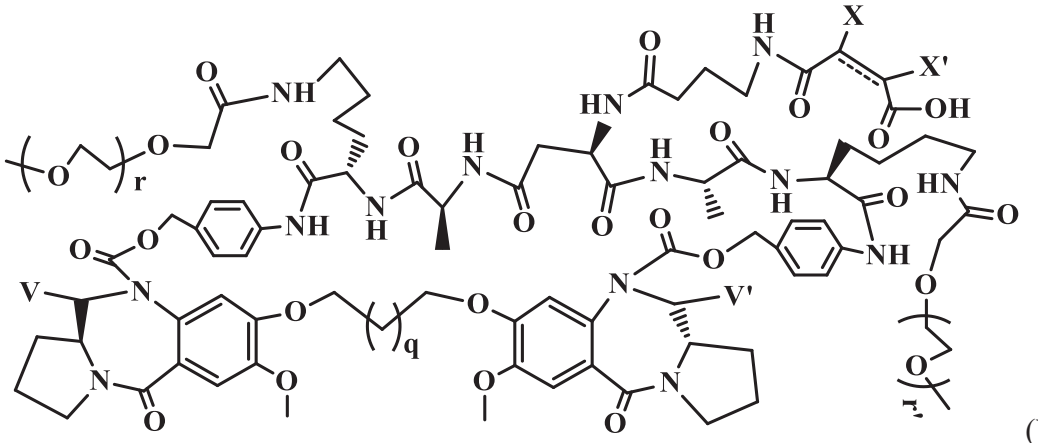

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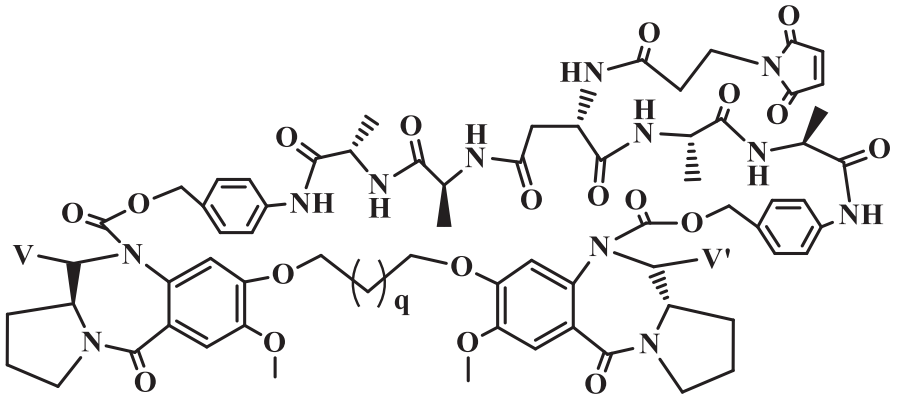

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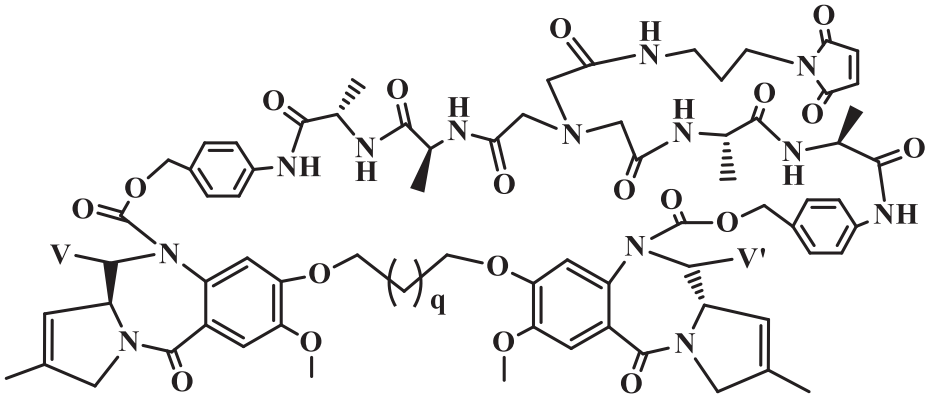

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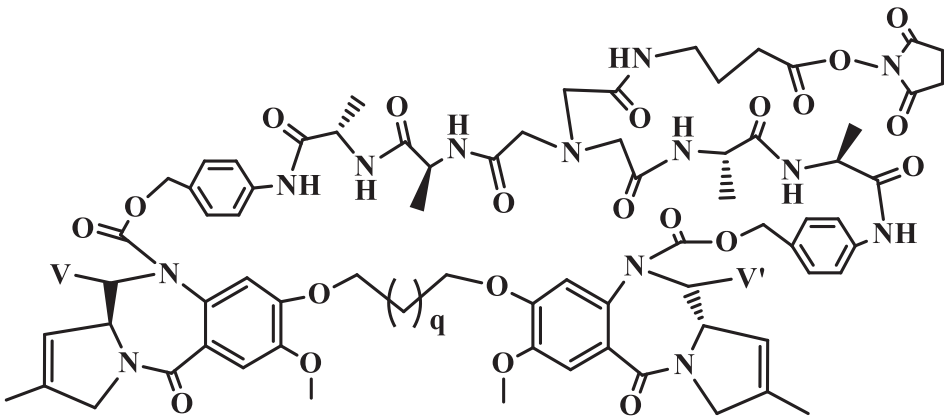

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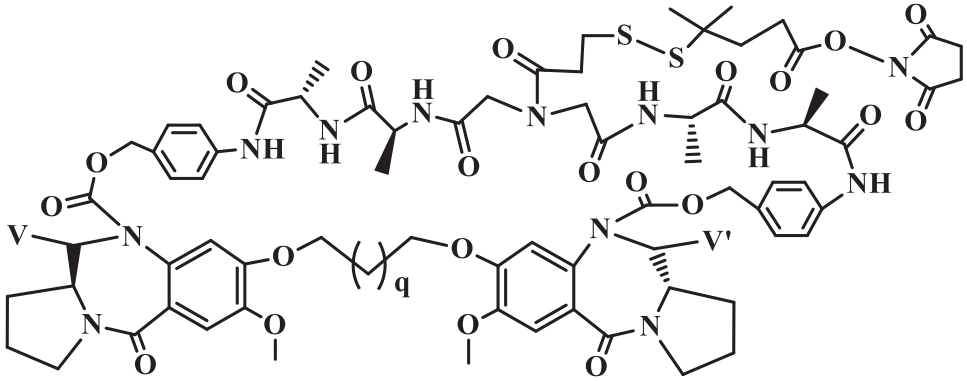

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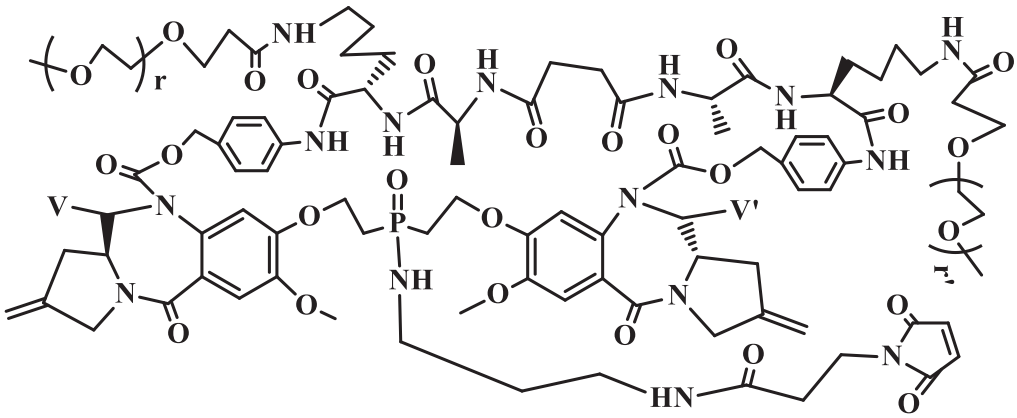

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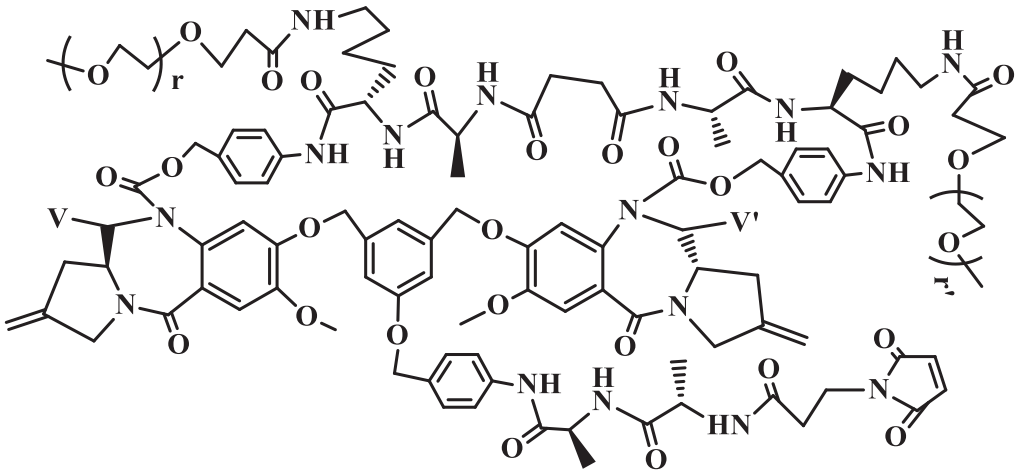

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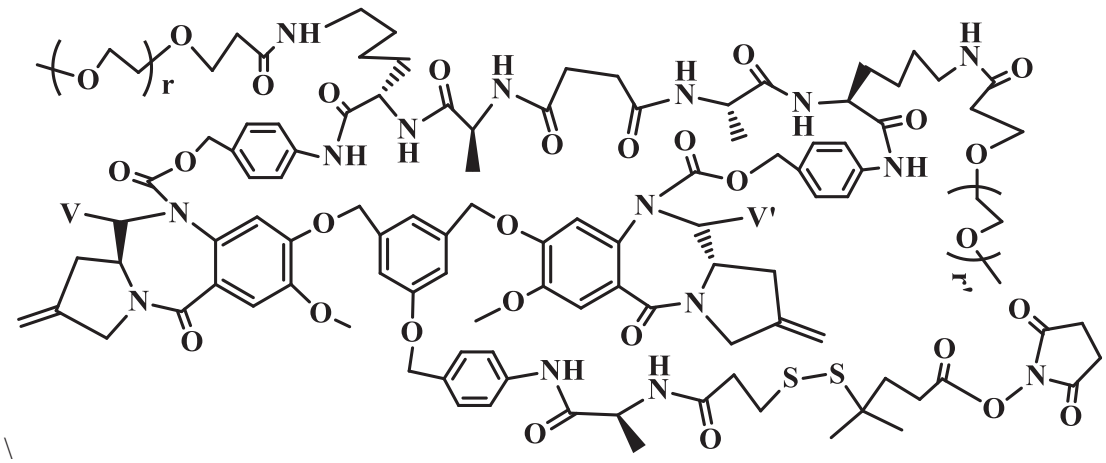

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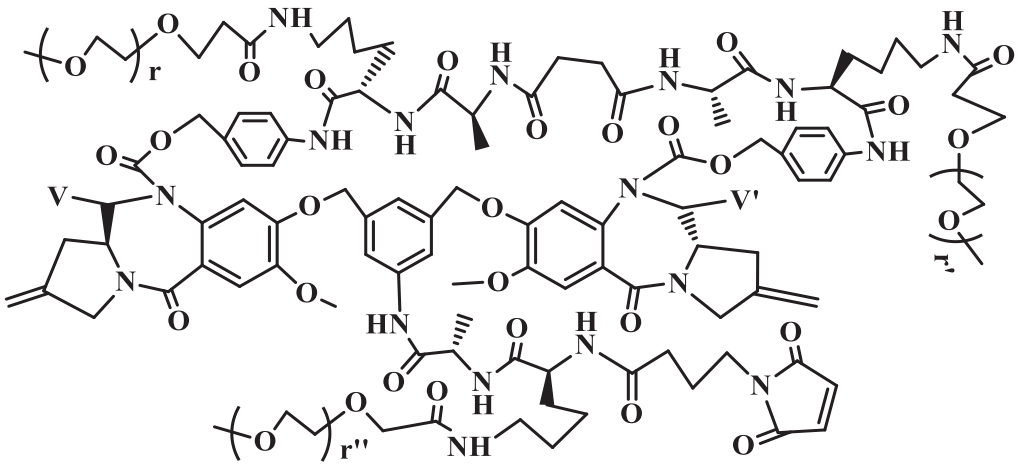

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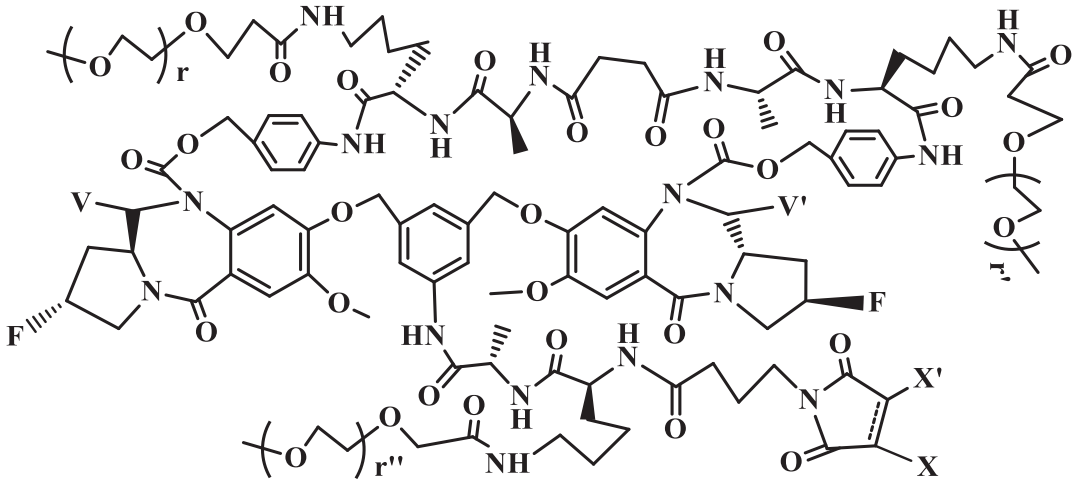

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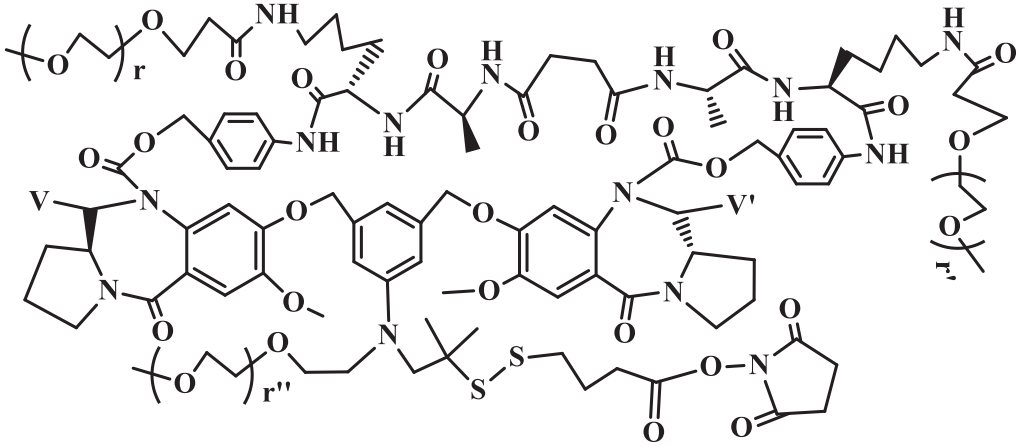

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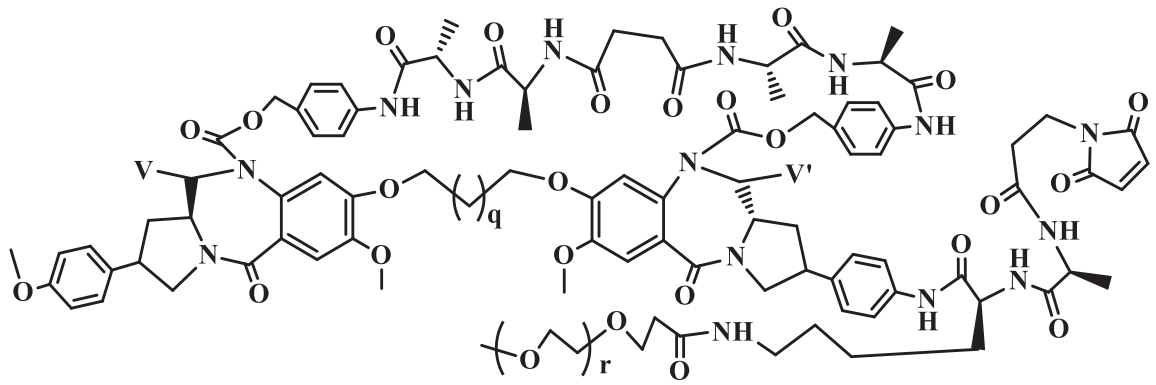

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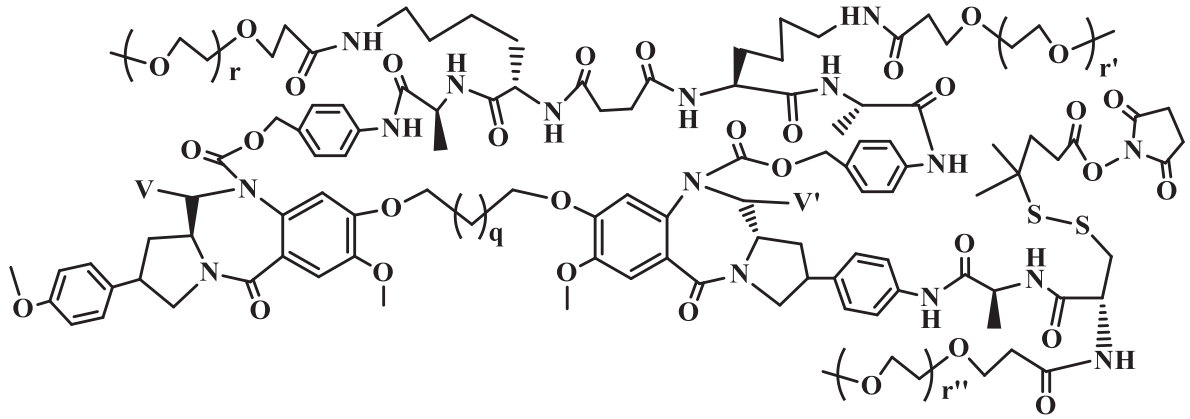

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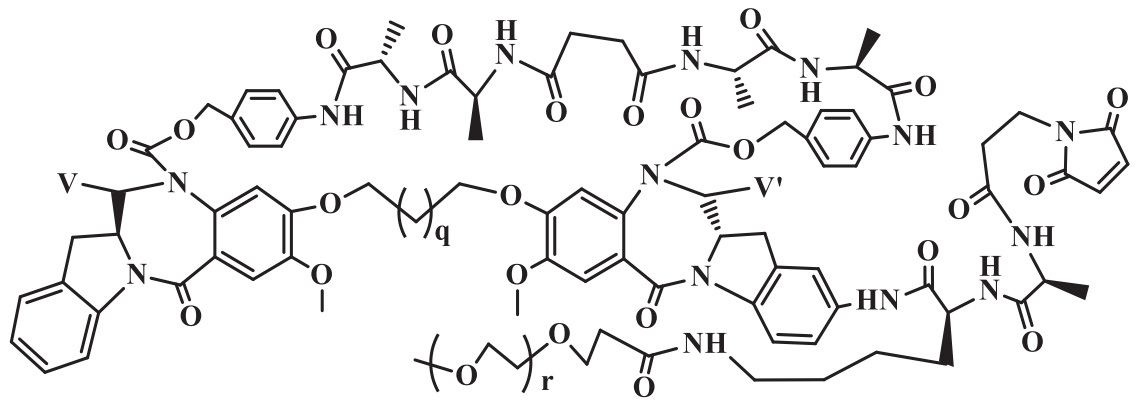

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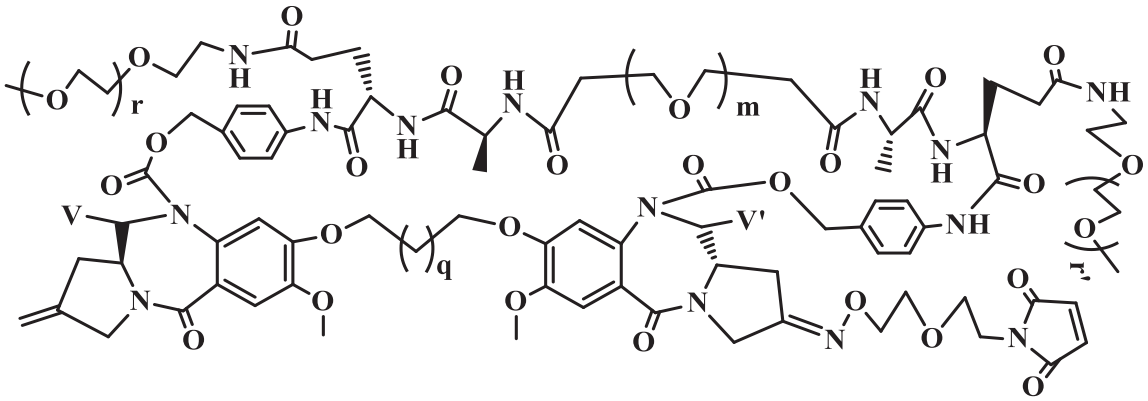

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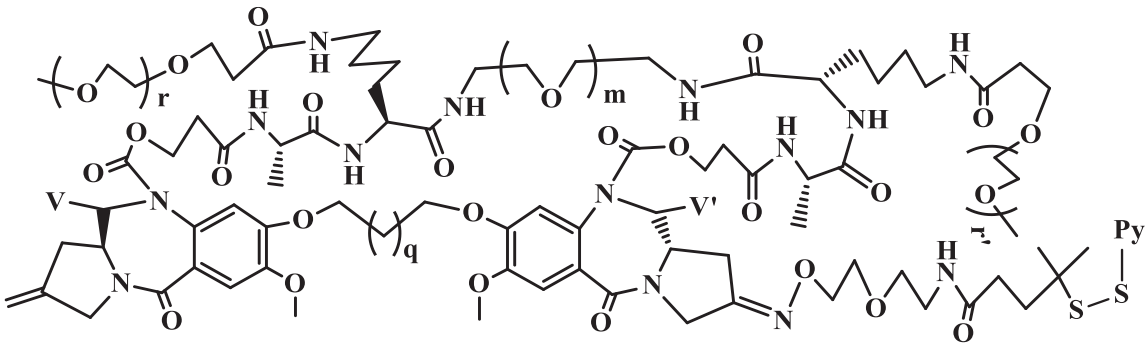

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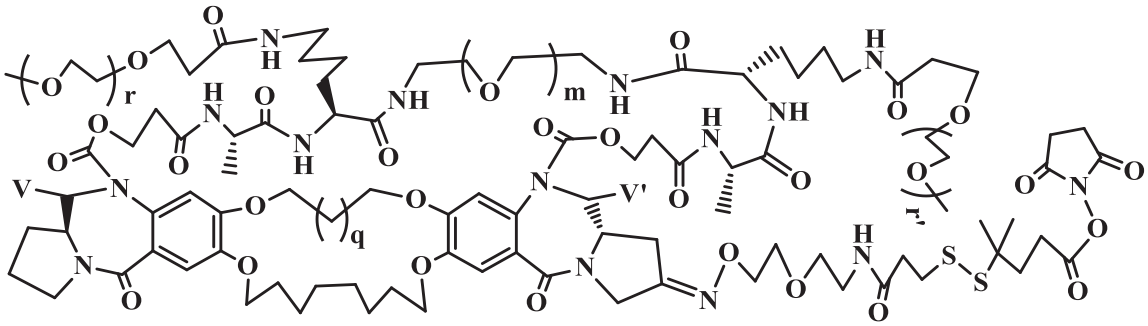
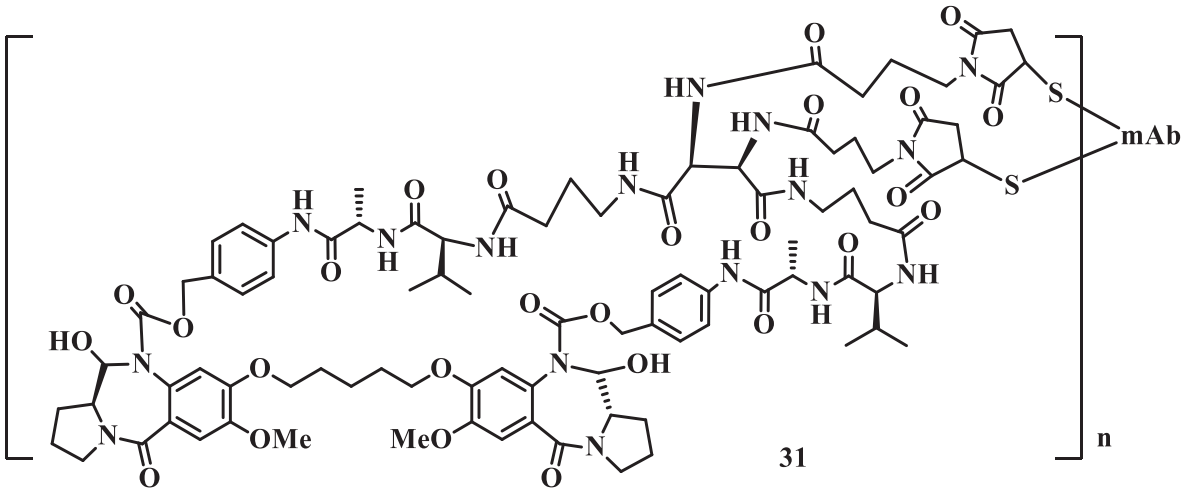


(VIII-06)

wherein U, U', V, V', n, n', X, X' and L are defined the same as in Claim 1; R_6 and R_6' are independently selected from C_1~C_6 alkyl, aryl, cyclic, cyclohetero, halogen, haloalkyl, alkoxy, haloalkoxy alkylamino, -NO_2, -CN or H; r, r_1, r_2 and r' are independently 0~200.

8. A conjugate of a cross-linked PBD dimer derivative to a cell-binding molecule according to Claim 1 or 4 having the Formula 31, 45, 57, 59, 61, 67, 90, 96, 148, 162, 176, 178, 184, 188, 209, 214, 224, 232, 255, 268, 271, CC-3, CC-4, CC-5, CC-6, CC-7, CC-8, CC-10, CC-11, CC-12, CC-14, CC-15, CC-17, CC-18, CC-20, CC-21, CC-27, CC-29, shown below:



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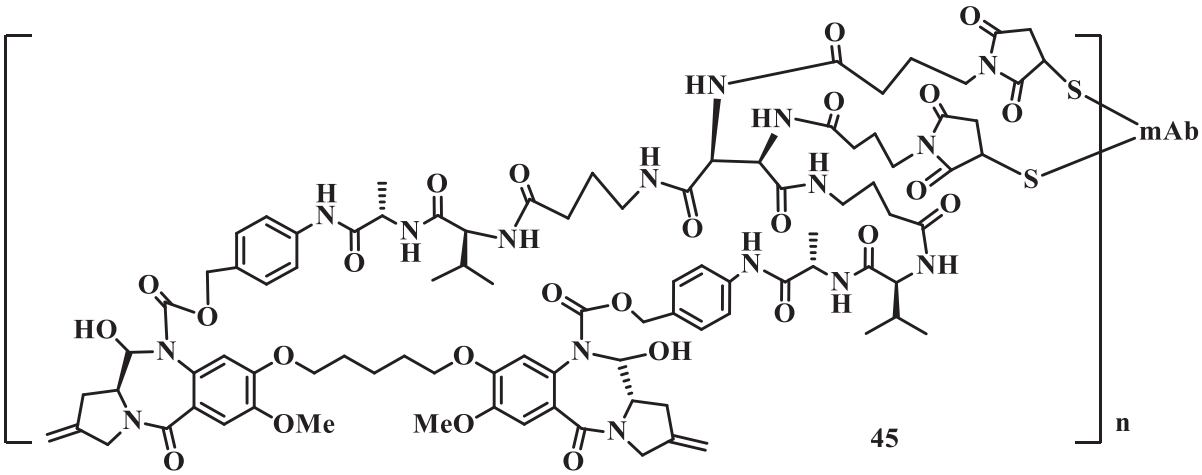

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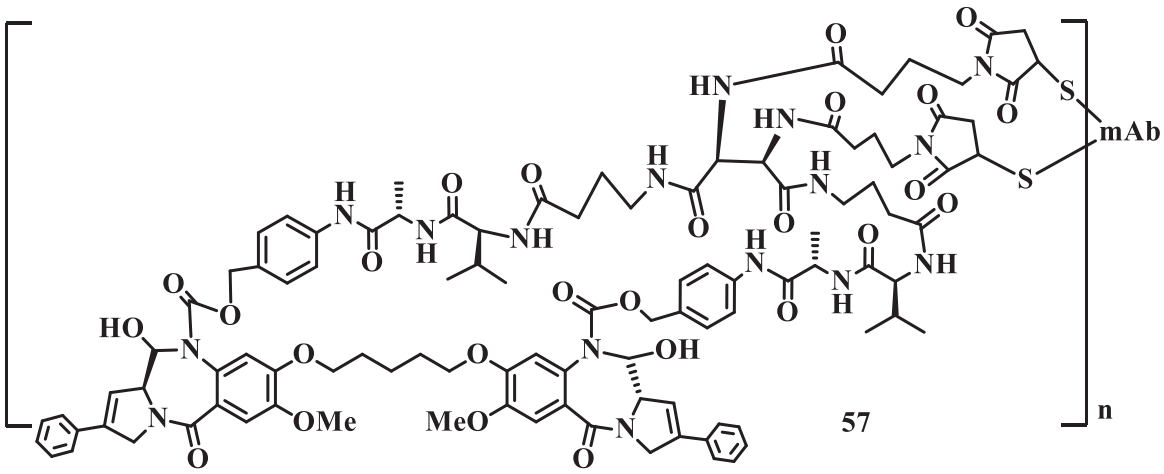

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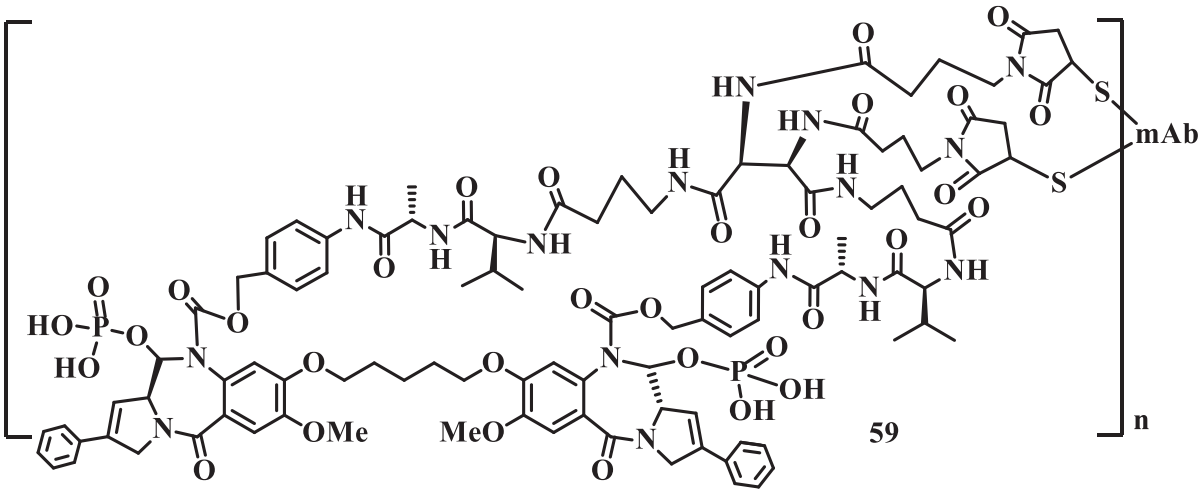

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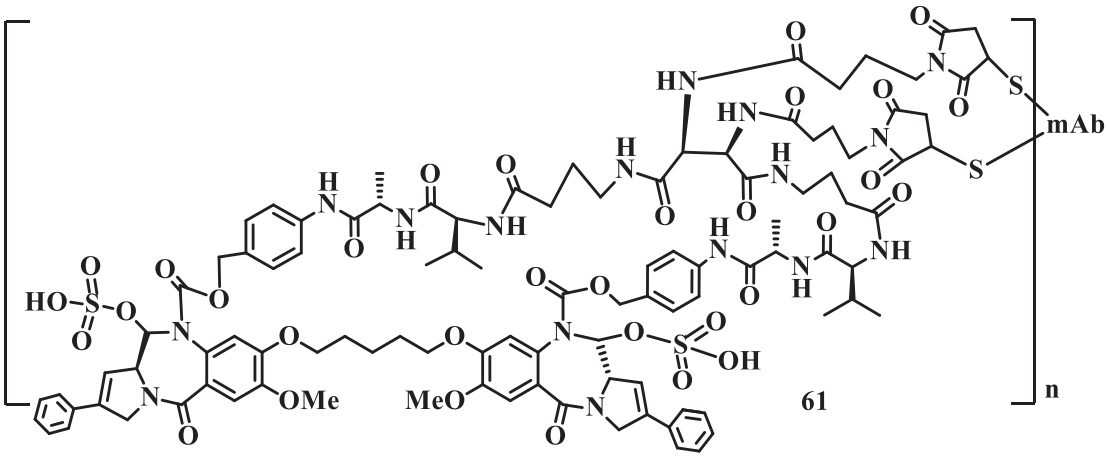

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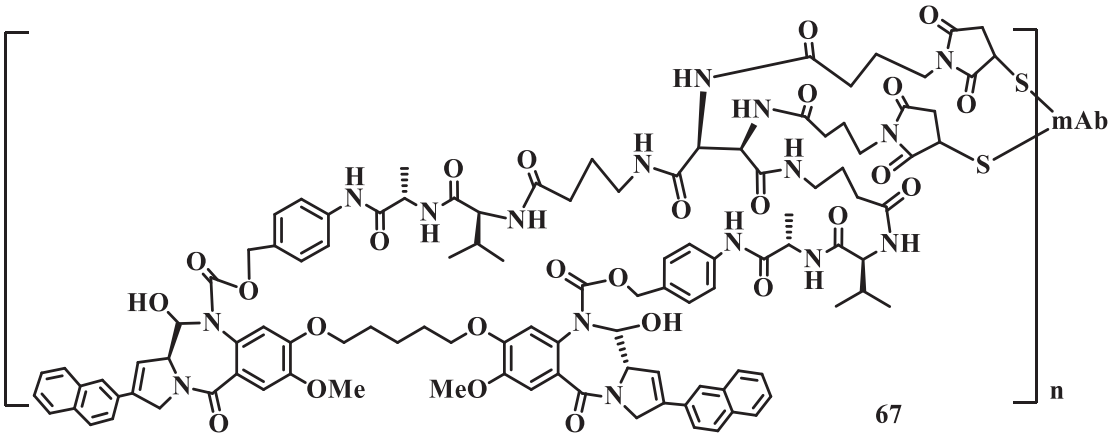

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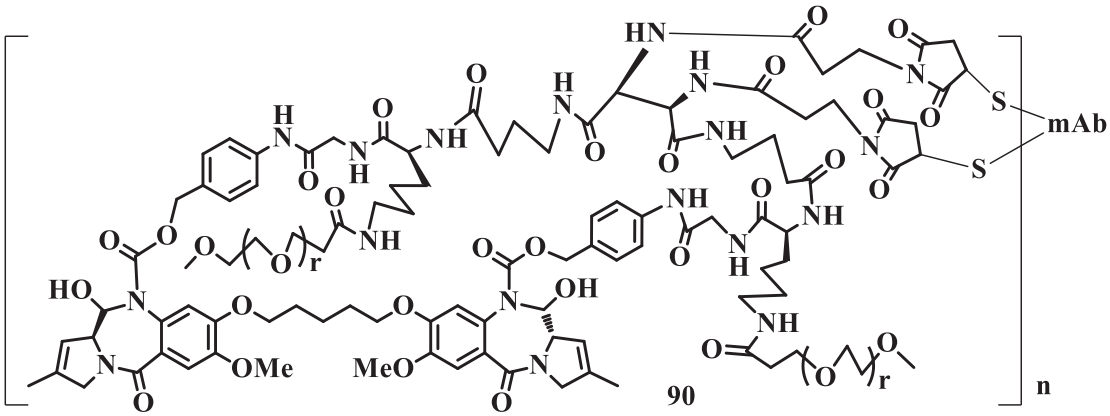

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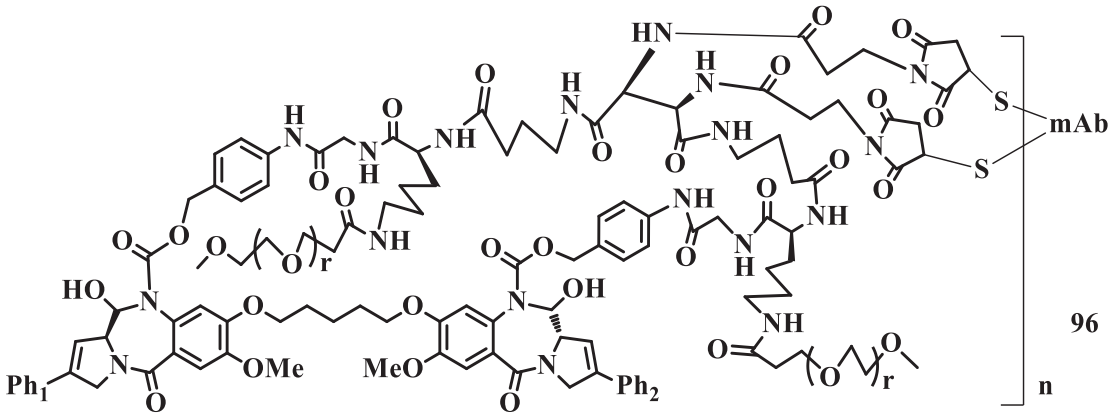

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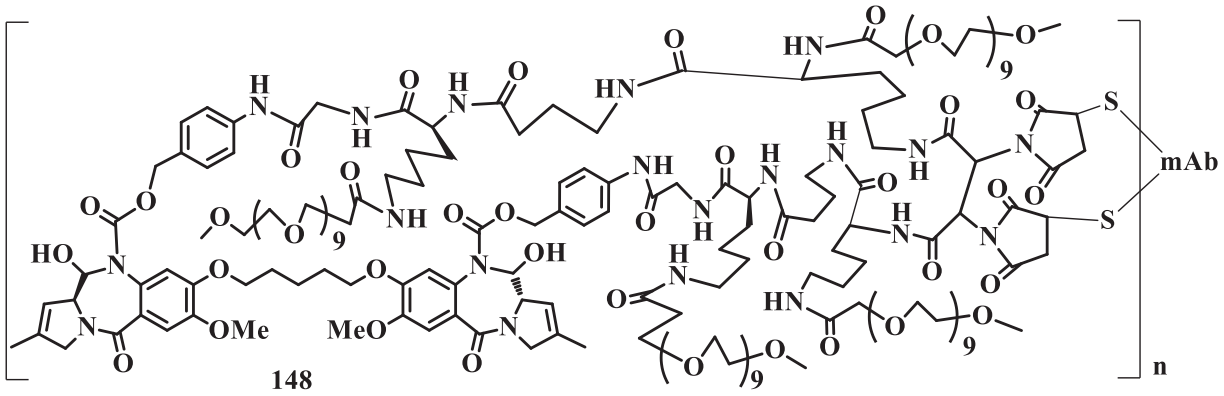

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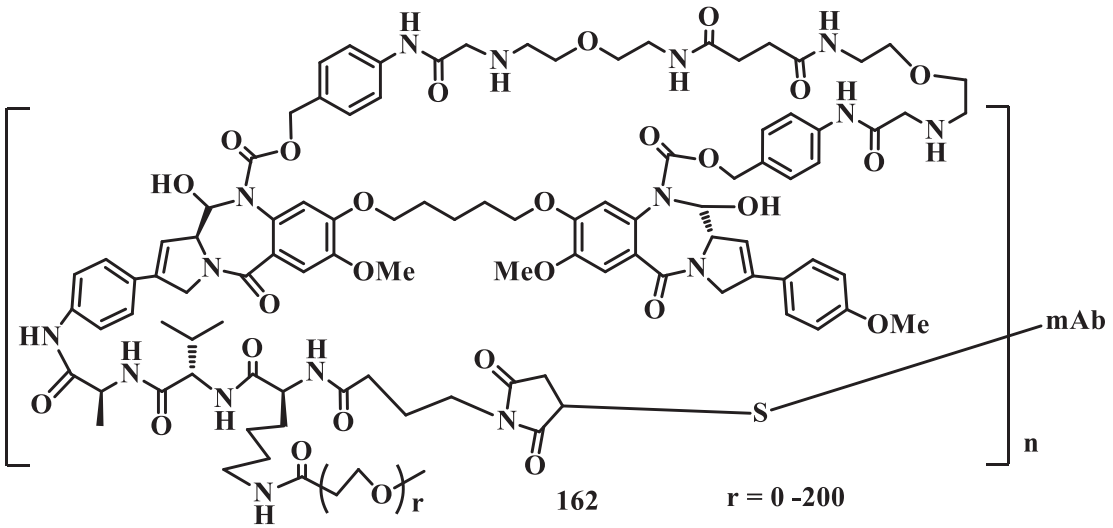

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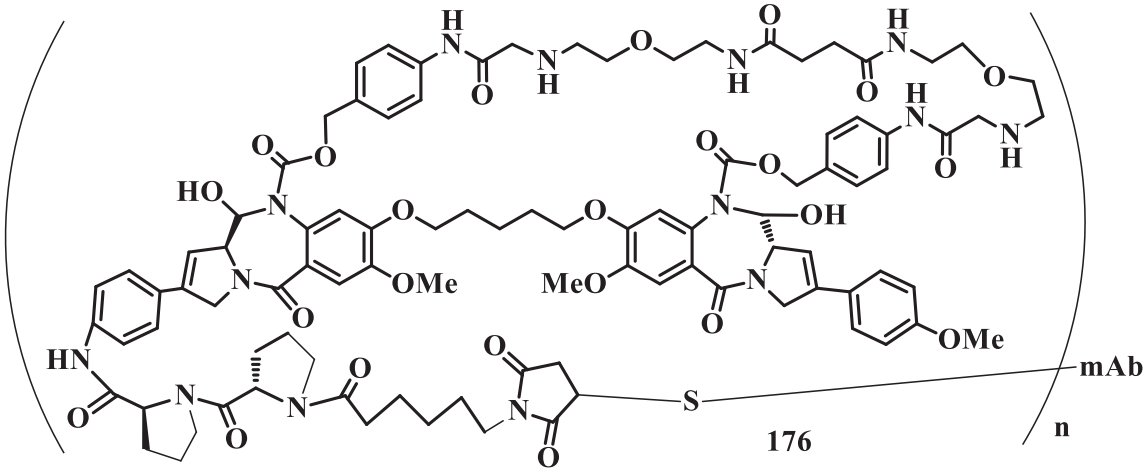

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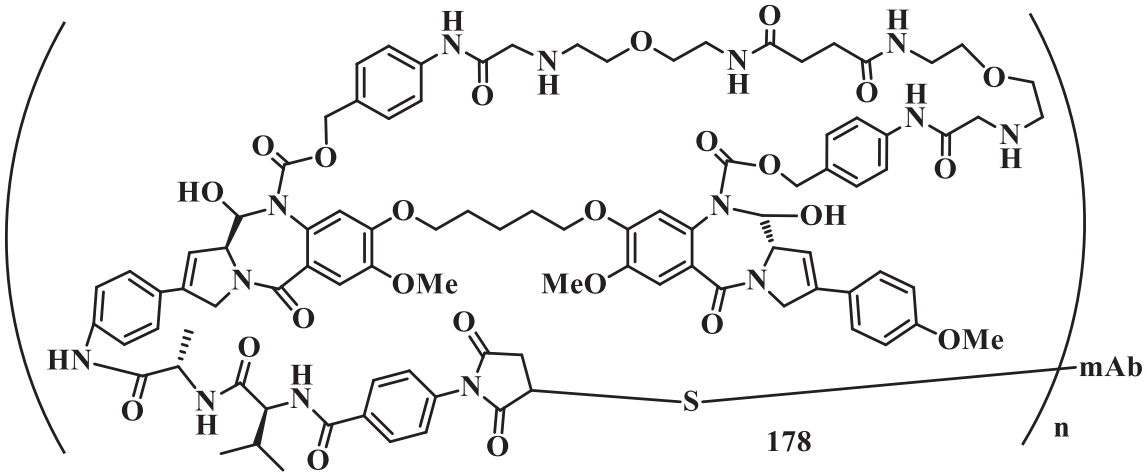

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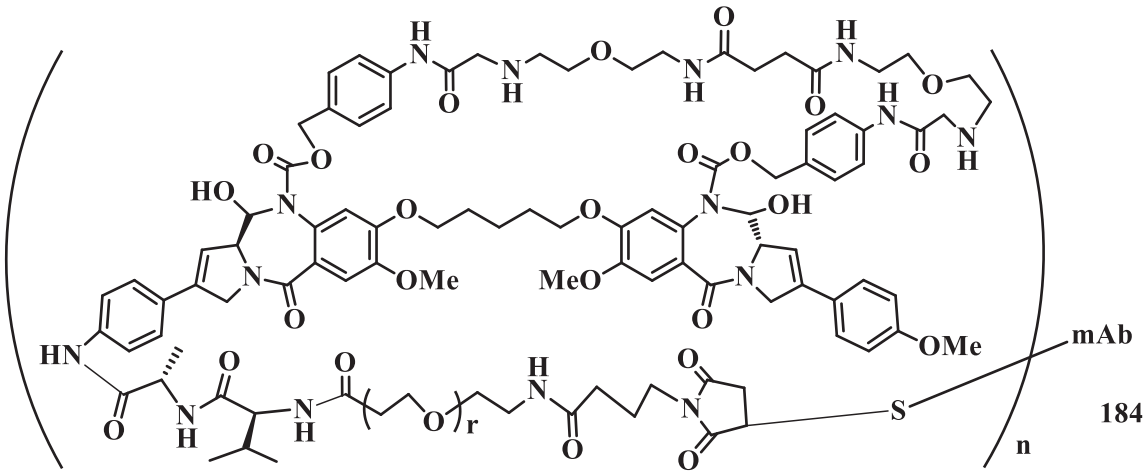

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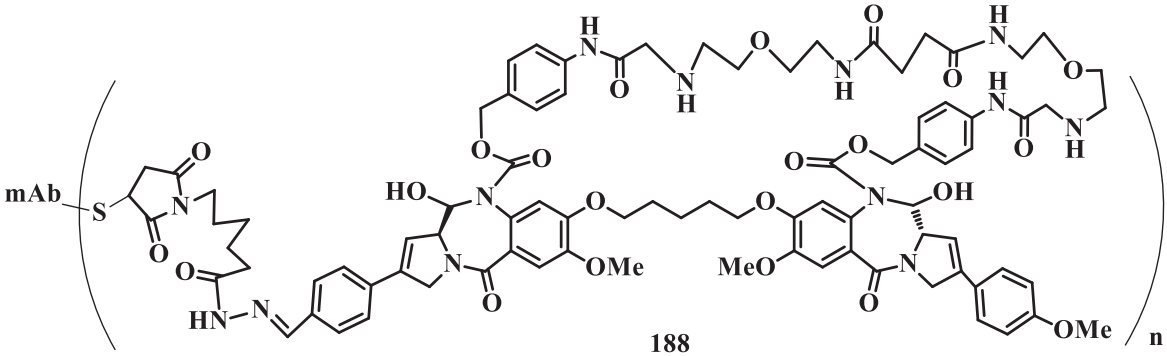

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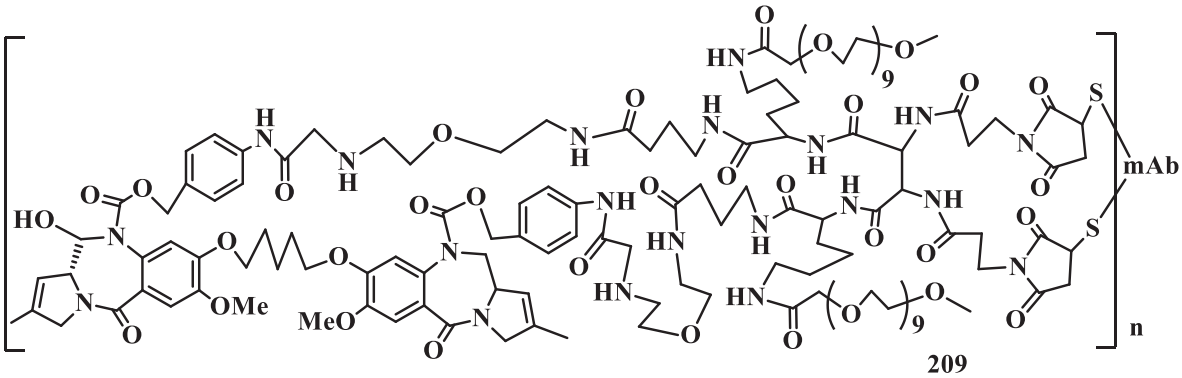

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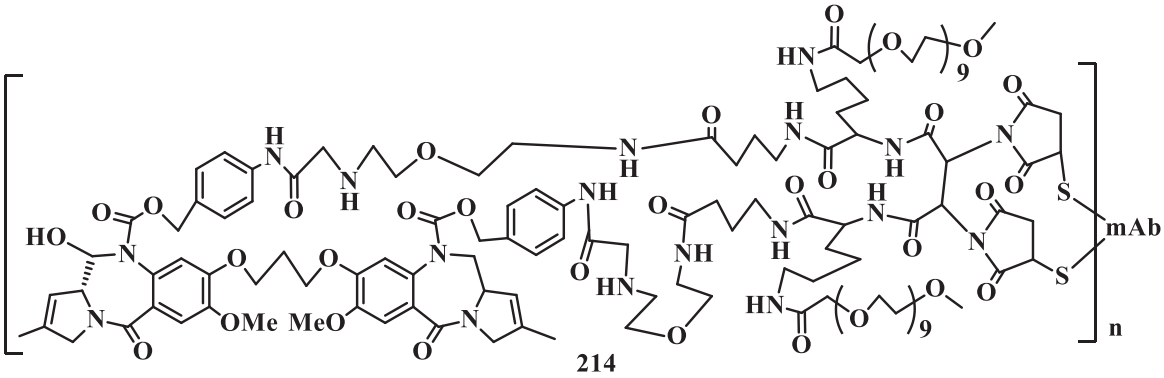

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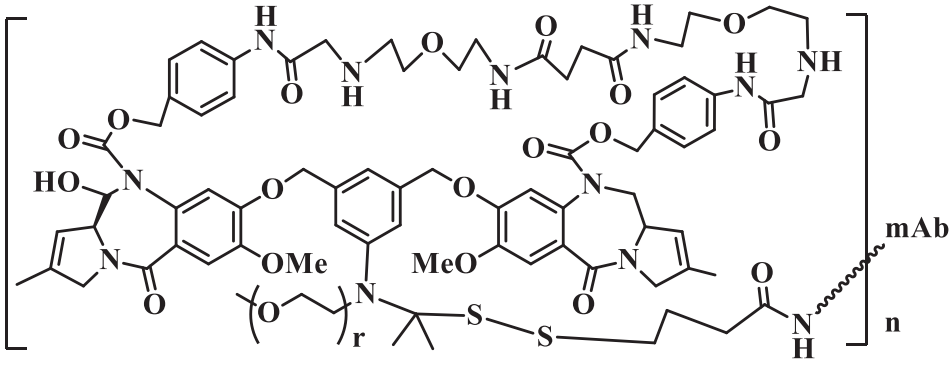

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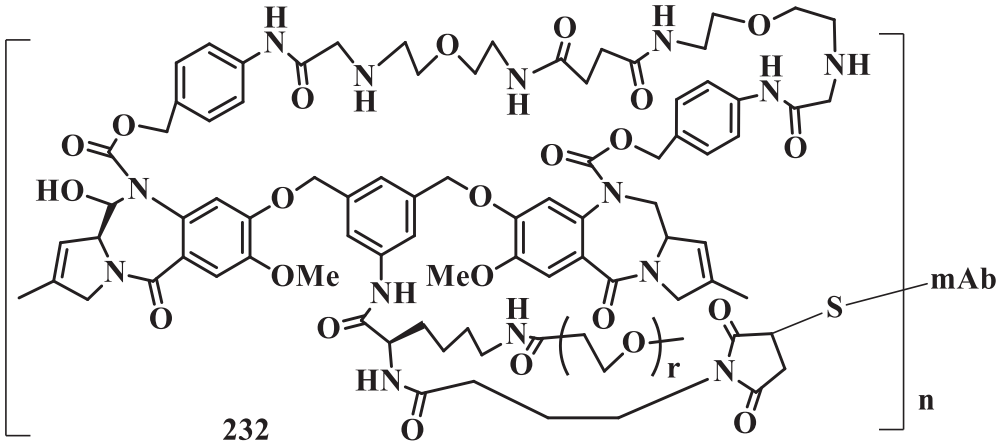

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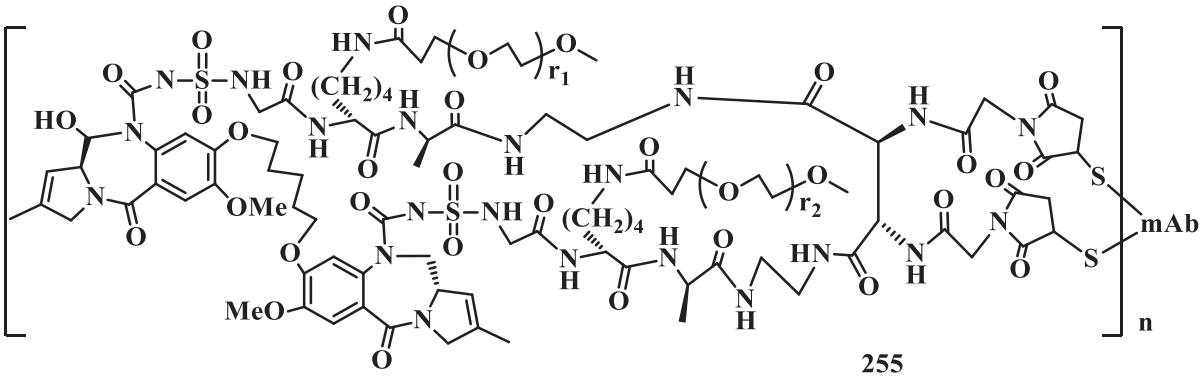

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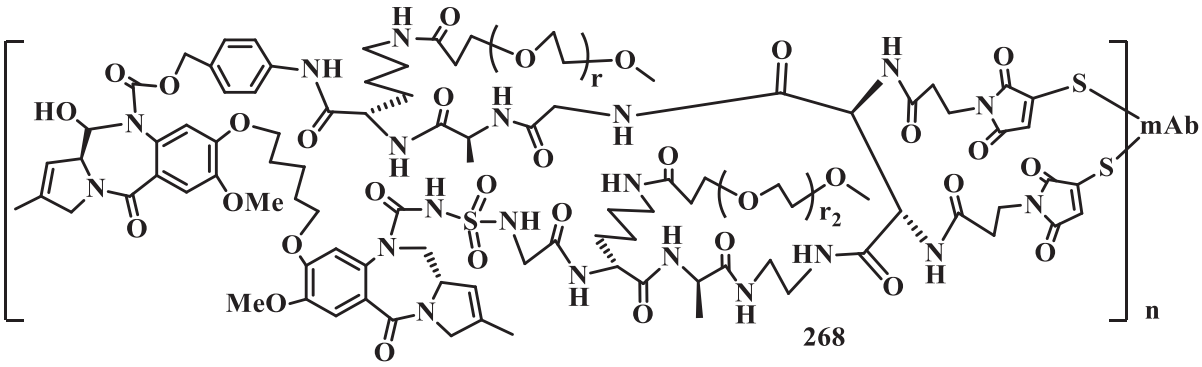

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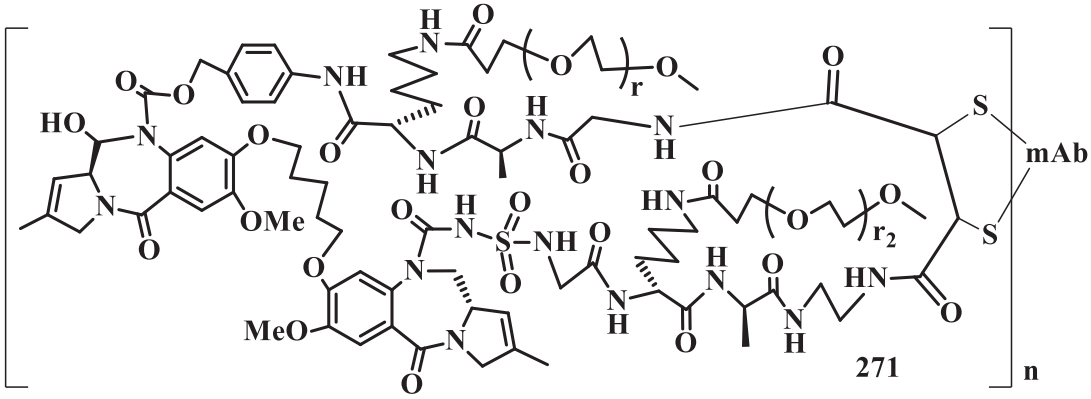

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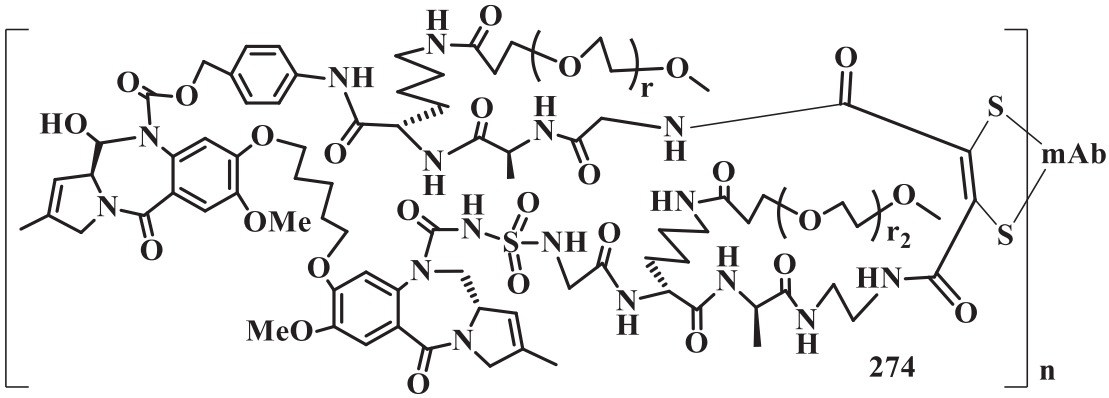

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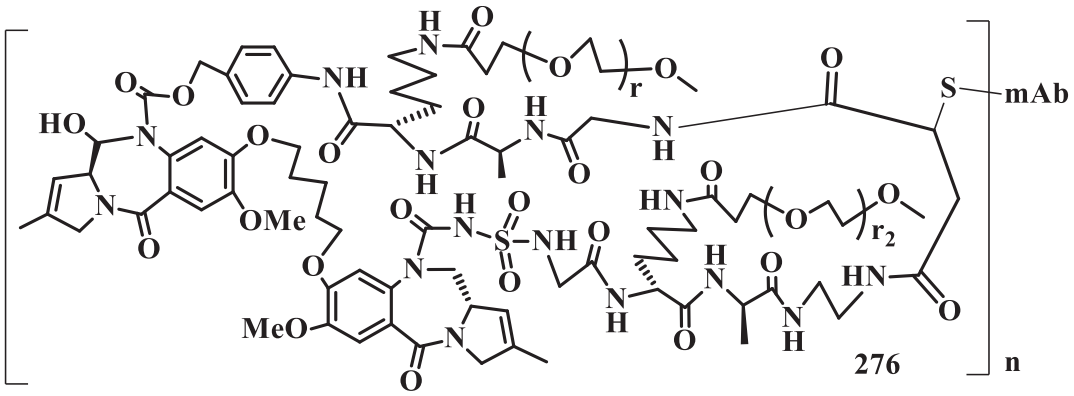

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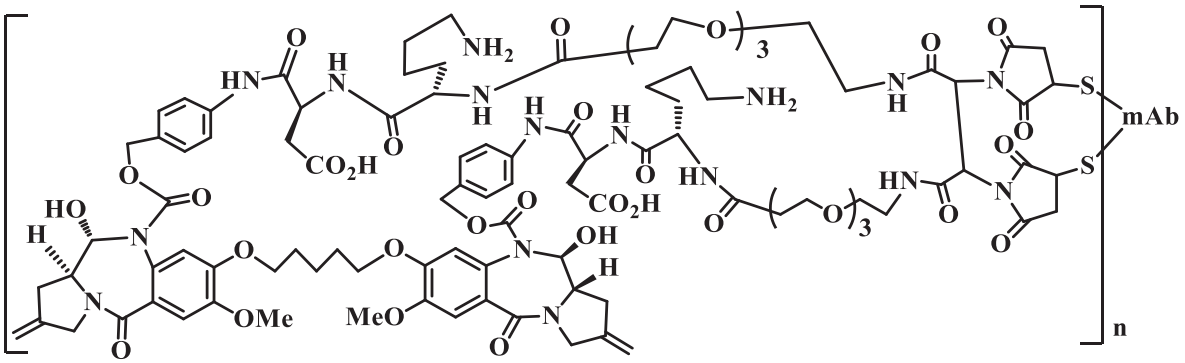

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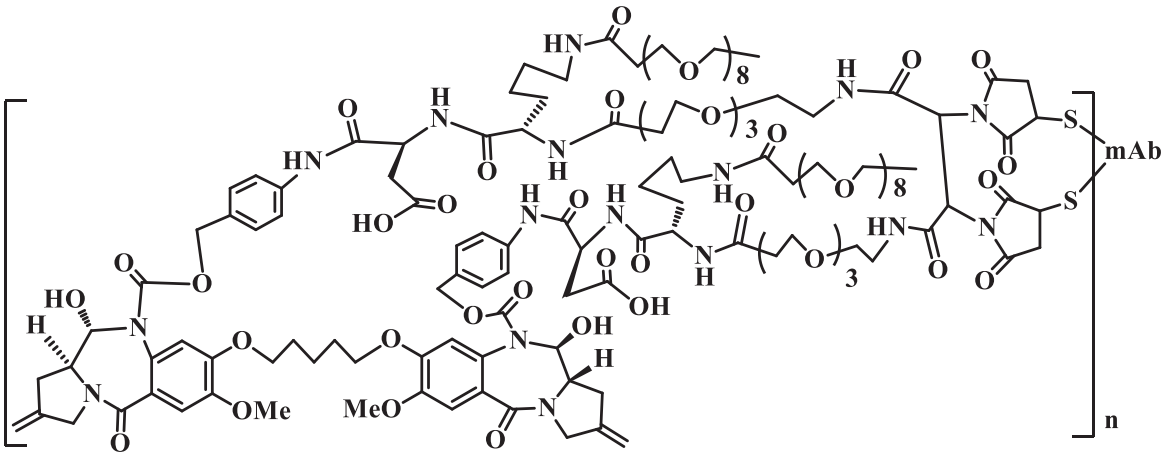

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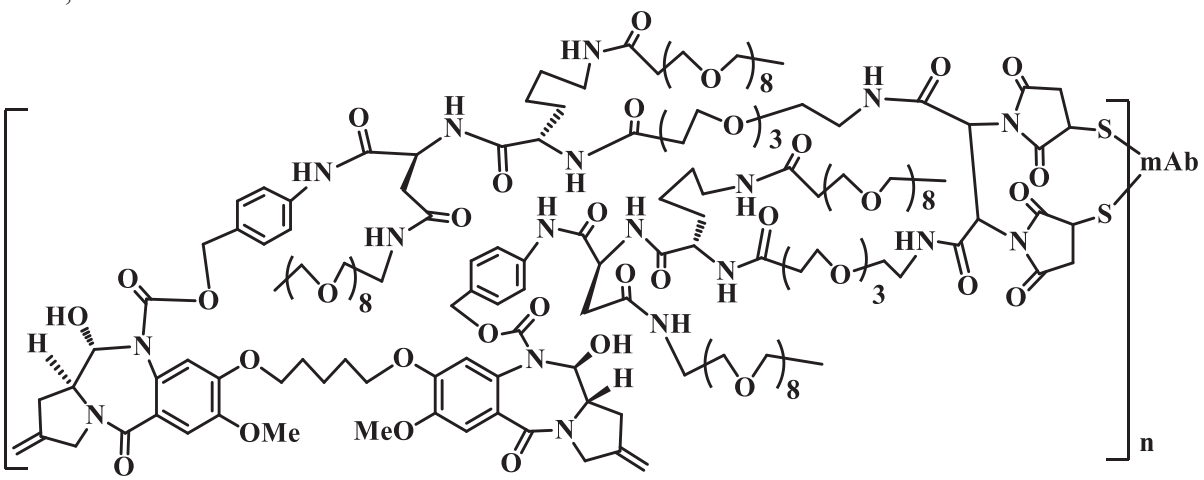

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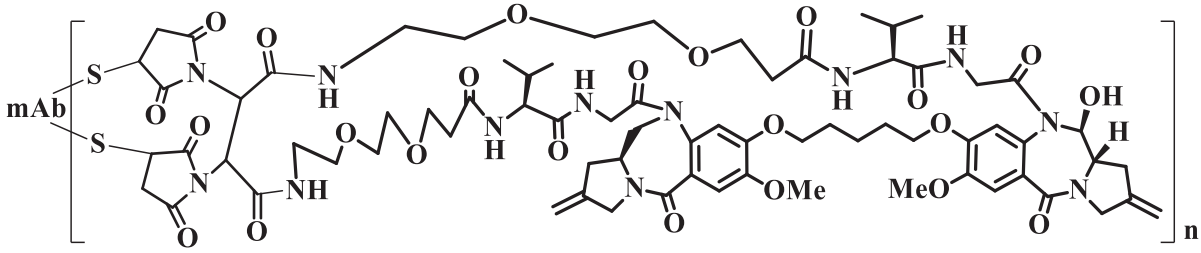

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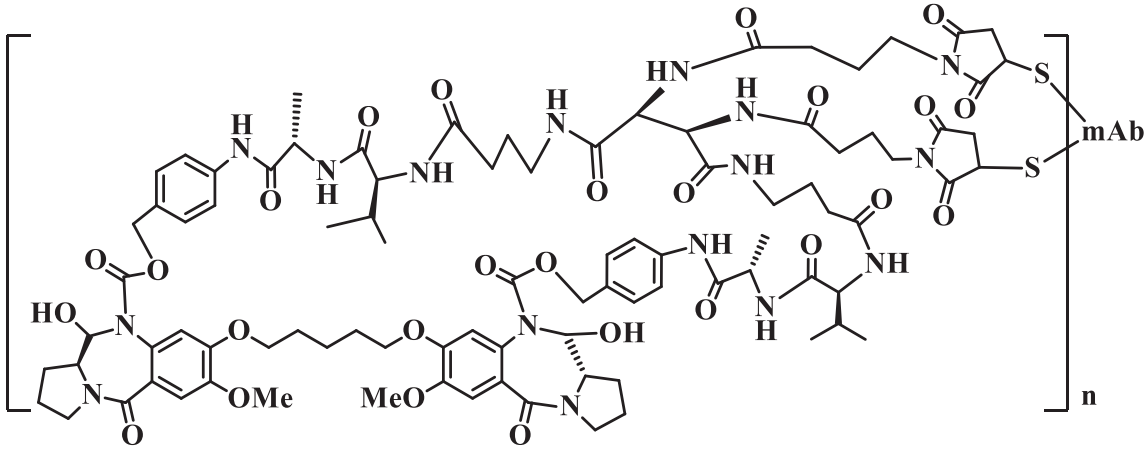

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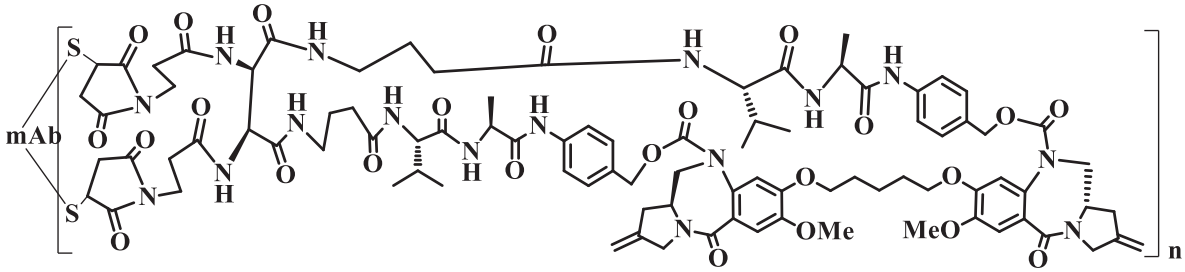

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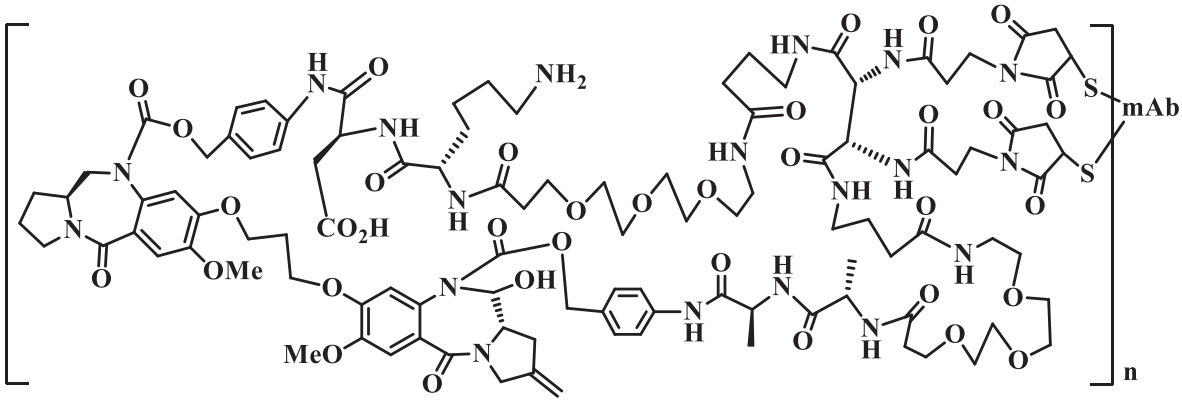

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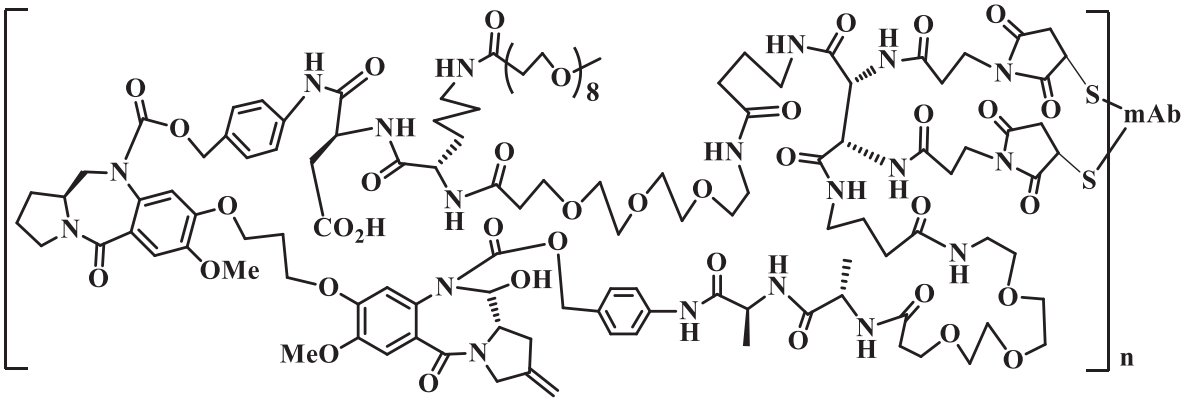

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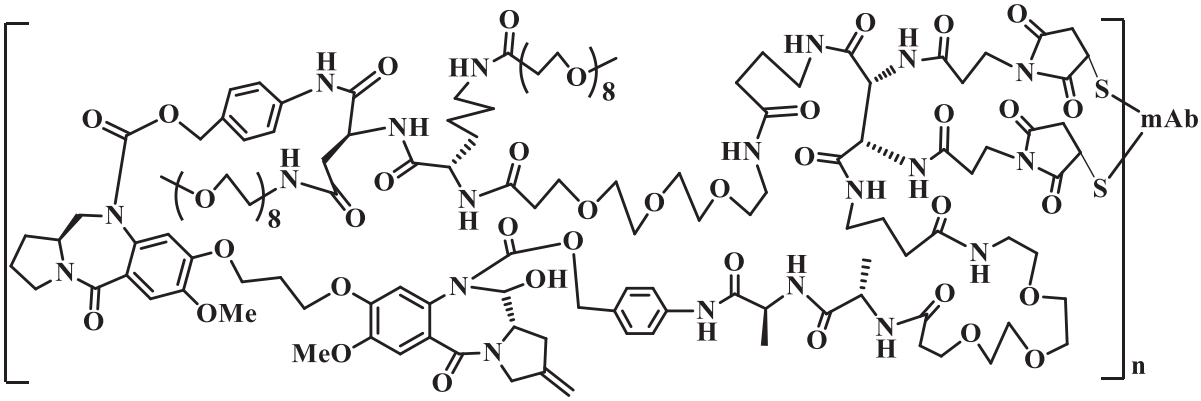

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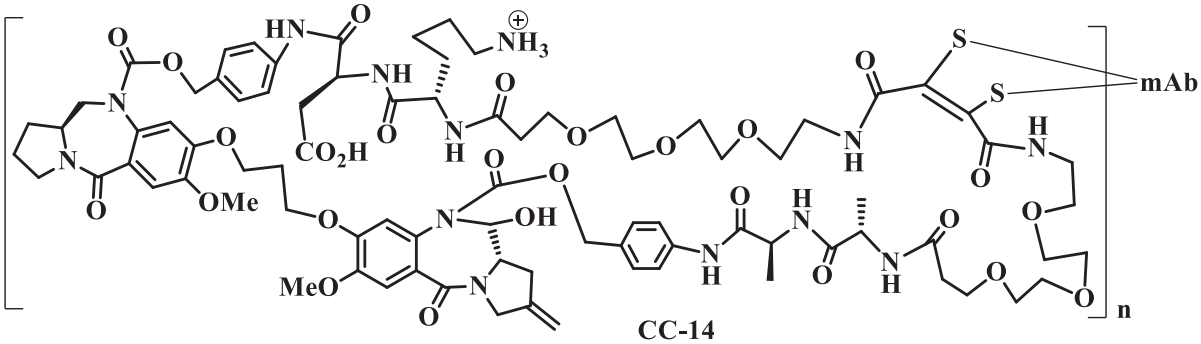

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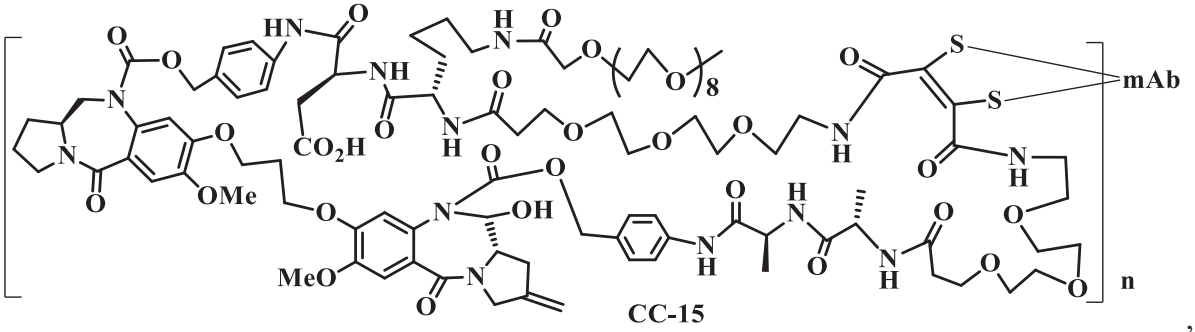

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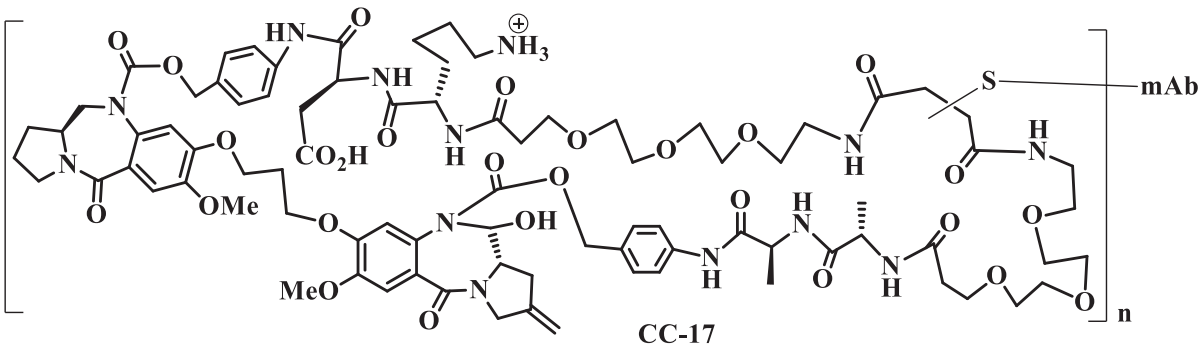
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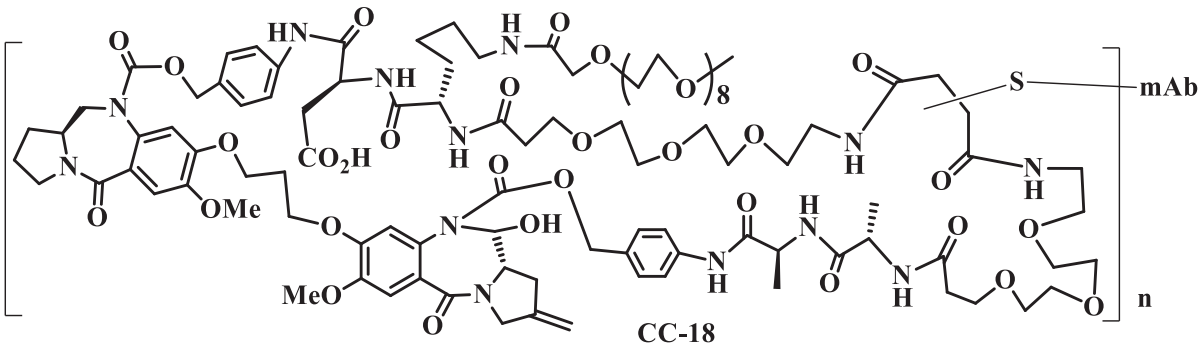
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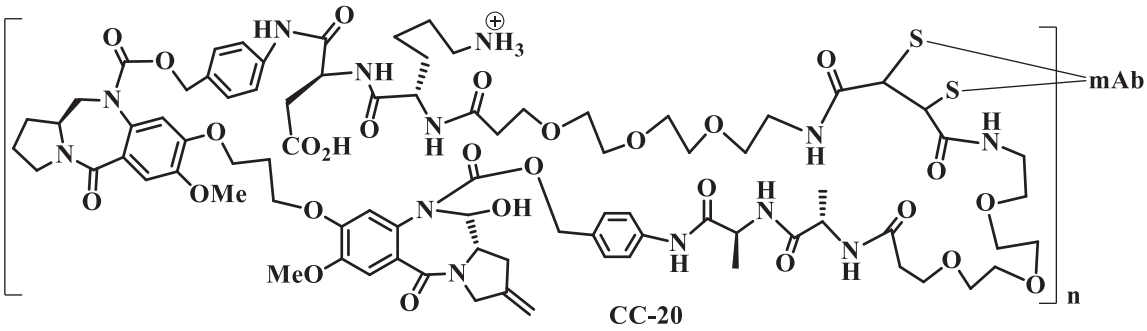
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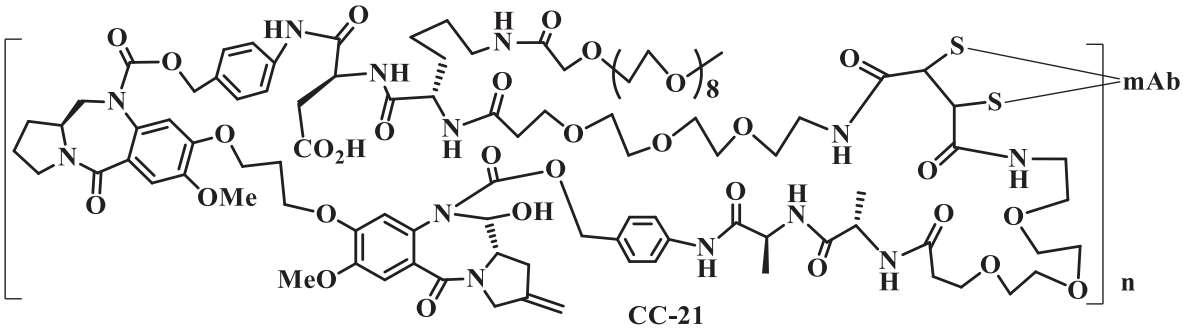
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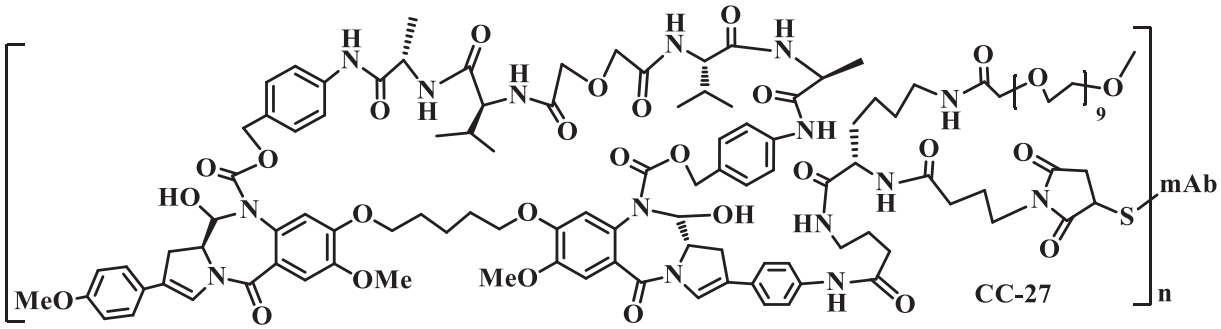

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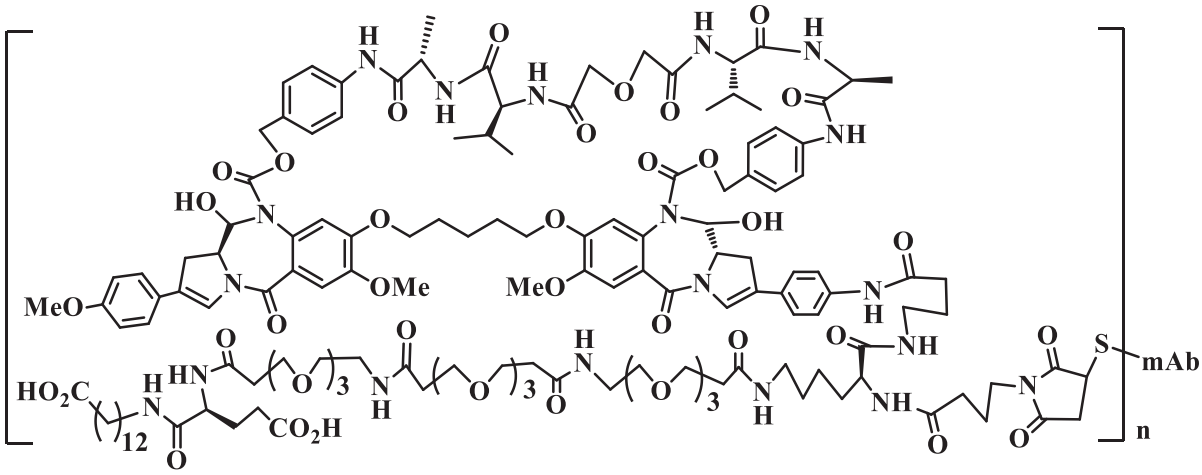
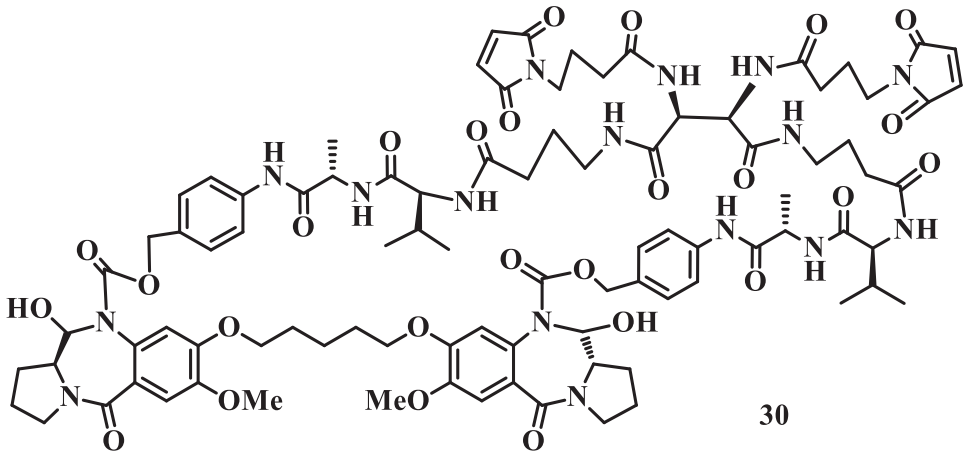


CC-29,

wherein r, r_1, r_2 and r' are independently 0~200; n is 1~30.

9. A PBD dimer derivative according to Claim 6 having Formulas 30, 44, 56, 58, 60, 66, 89, 95, 147, 161, 175, 177, 183, 187, 208, 213, 223, 231, 254, 267, 270, 273, 275, 277, C-3, C-4, C-5, C-6, C-7, C-8, C-10, C-11, C-12, C-14, C-15, C-17, C-18, C-20, C-21, C-27, C-29 below:



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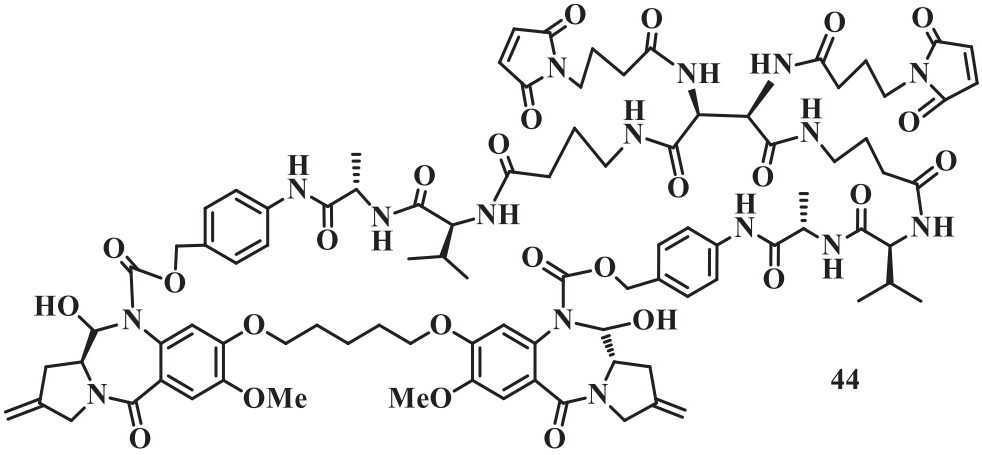

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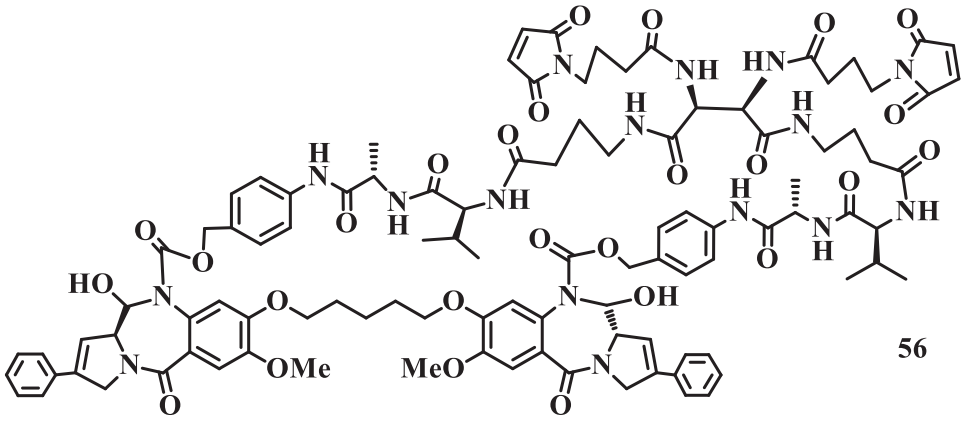

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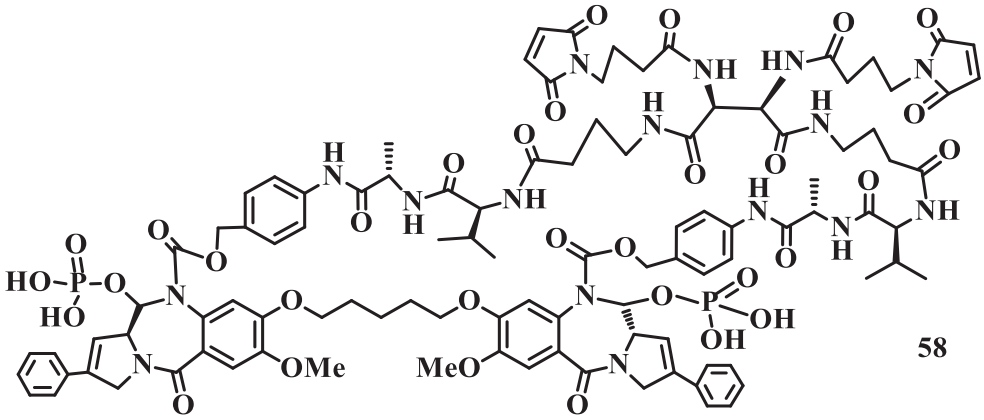

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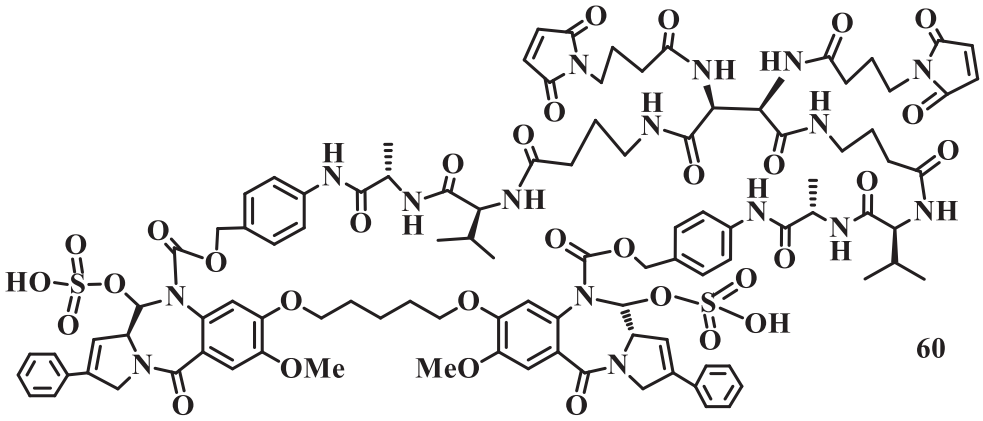

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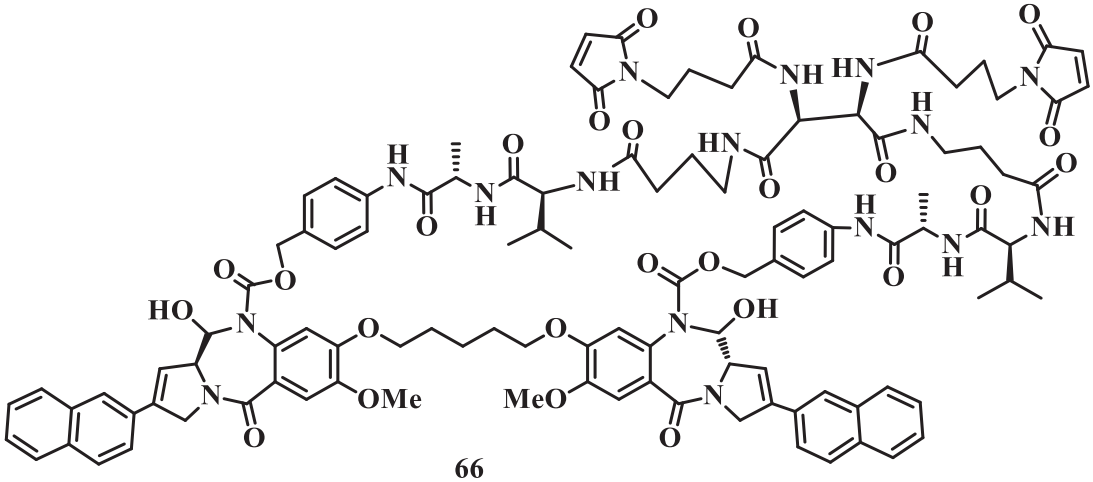

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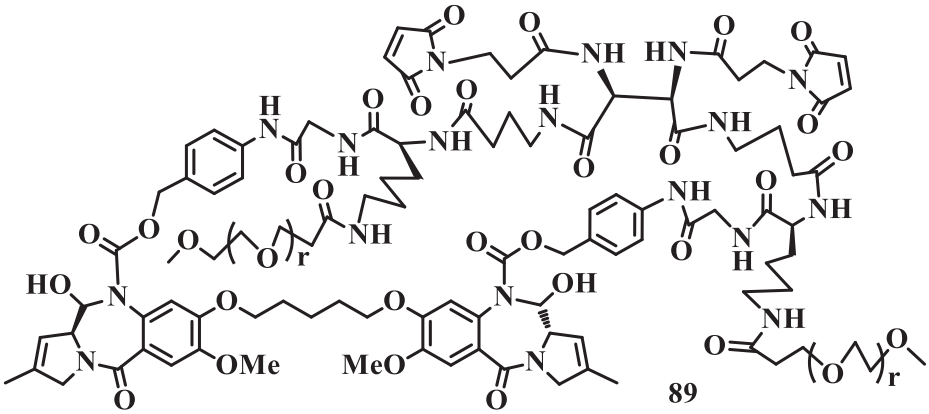

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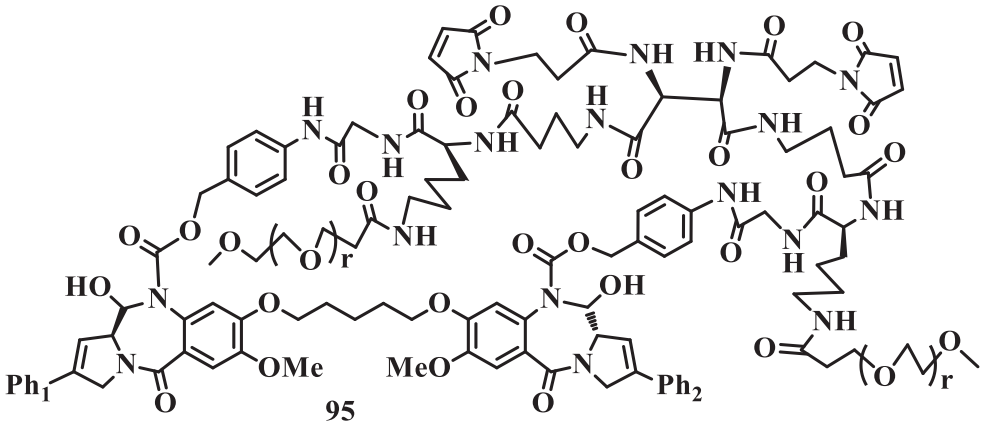

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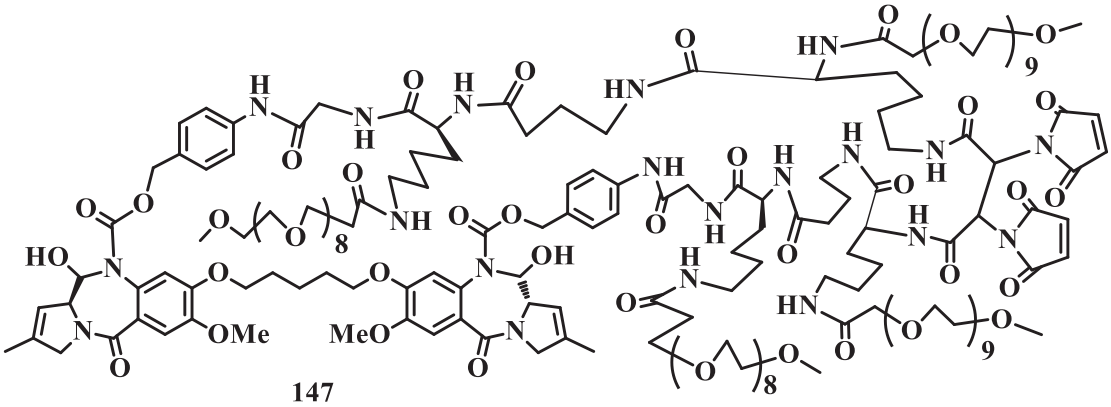

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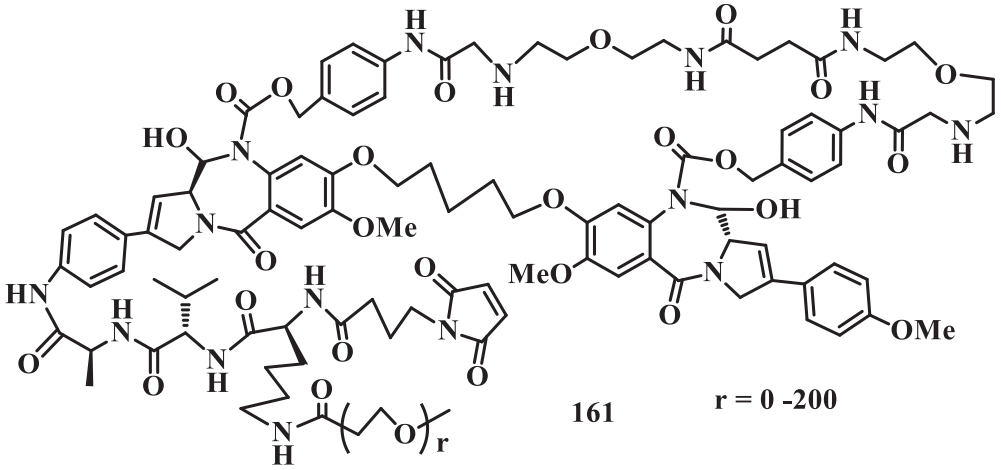

161 r = 0 -200

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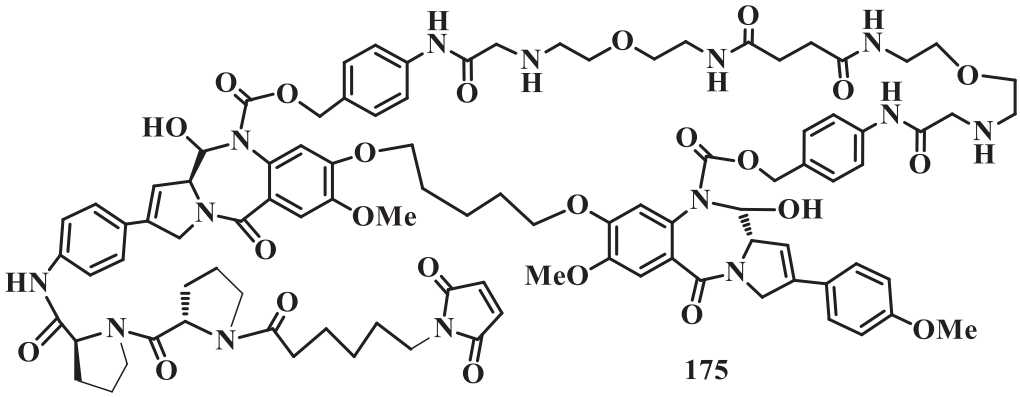

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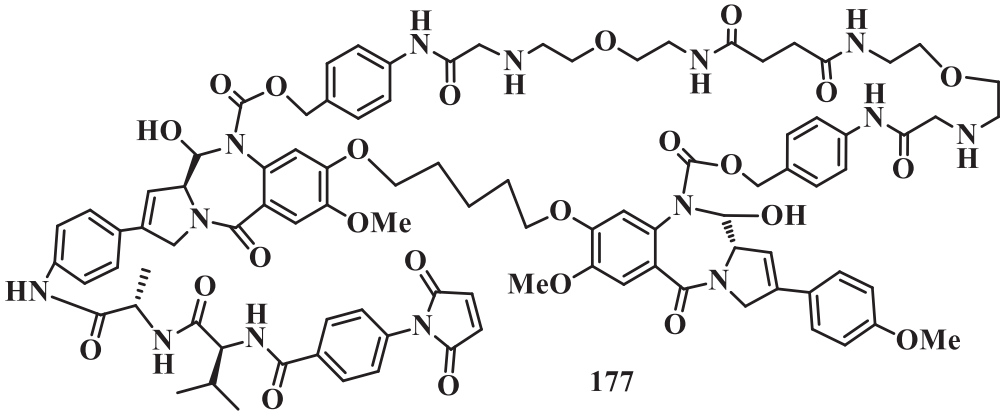

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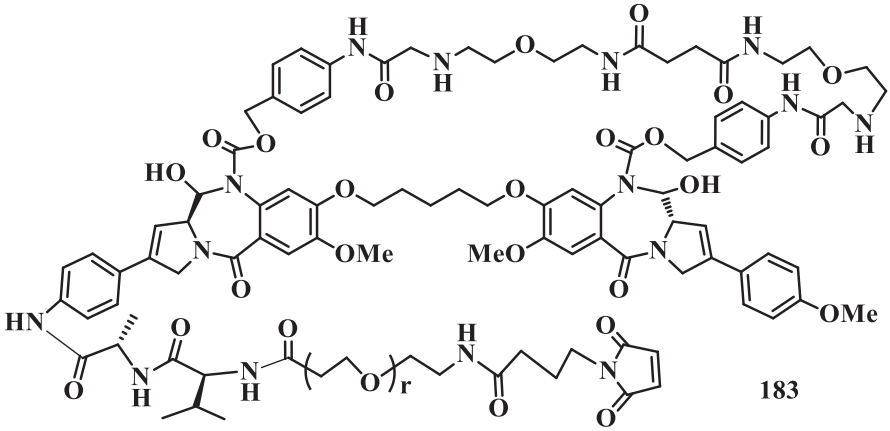

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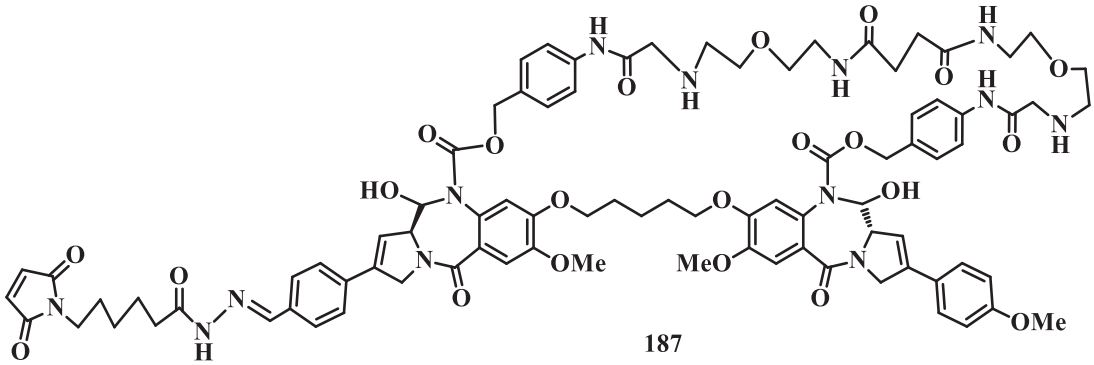

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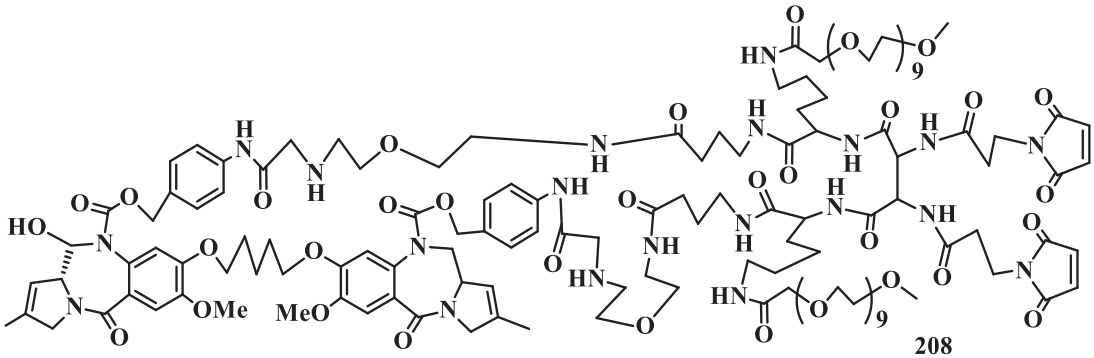

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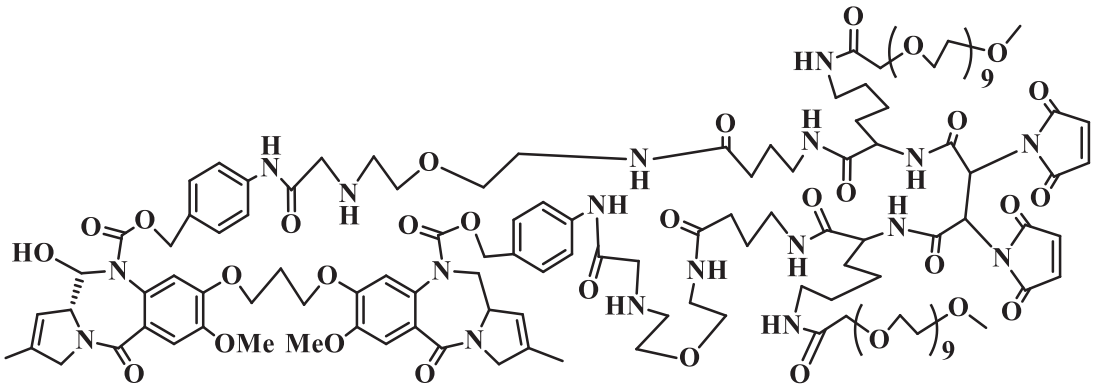

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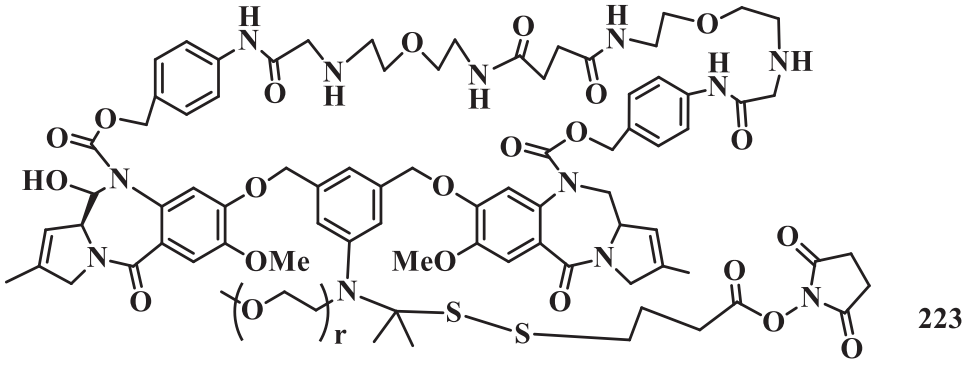

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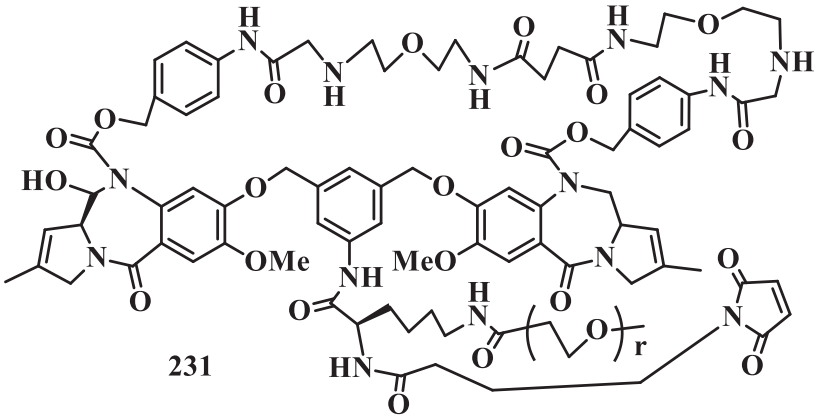

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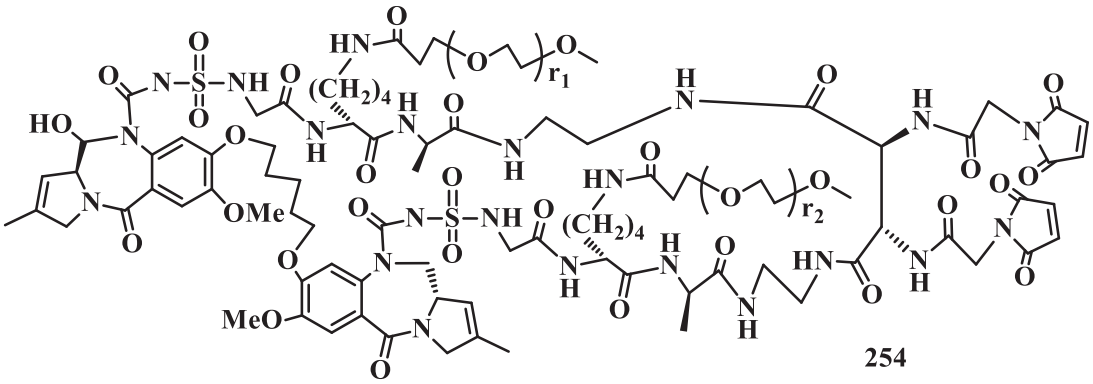

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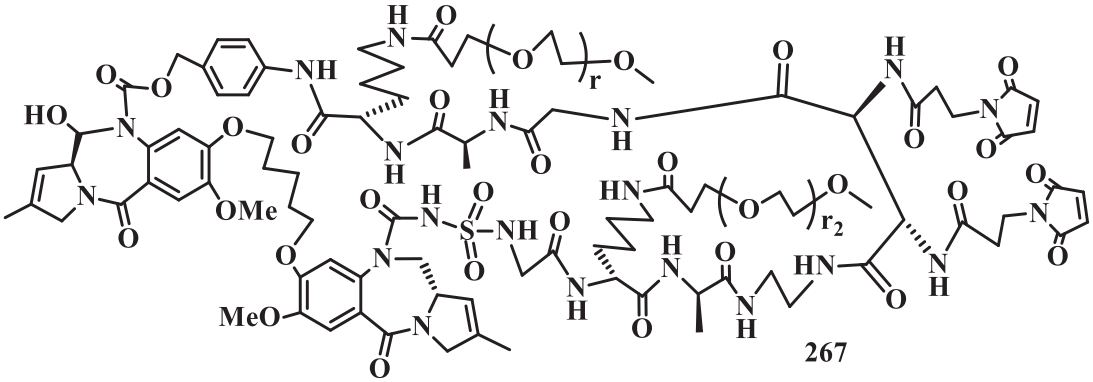

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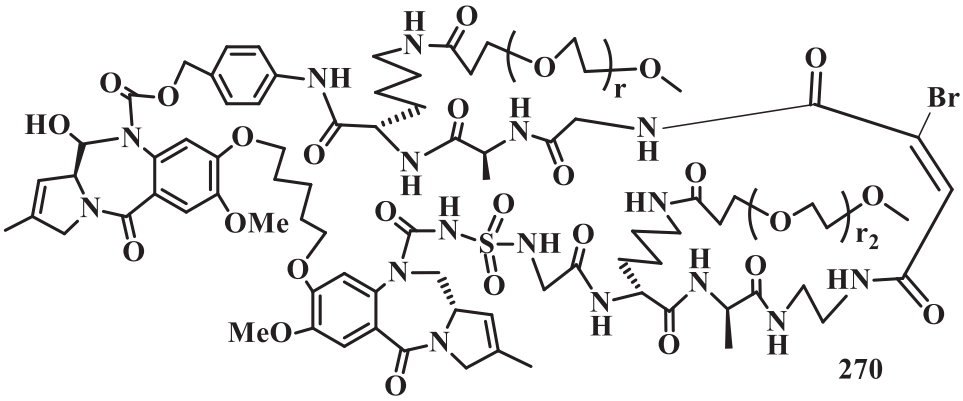

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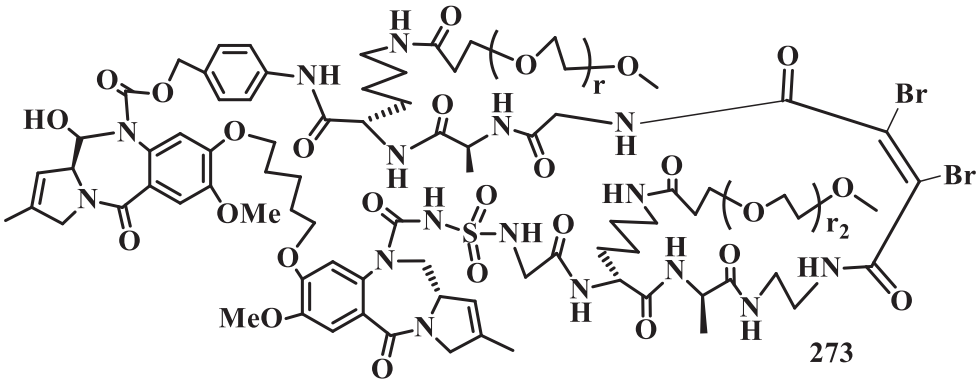

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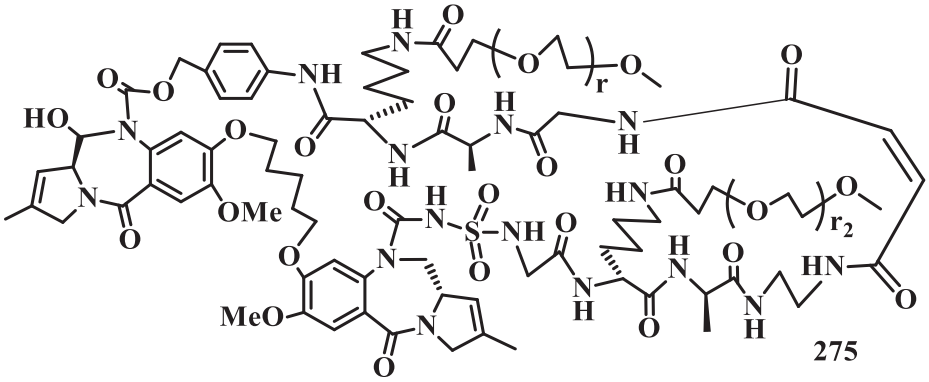

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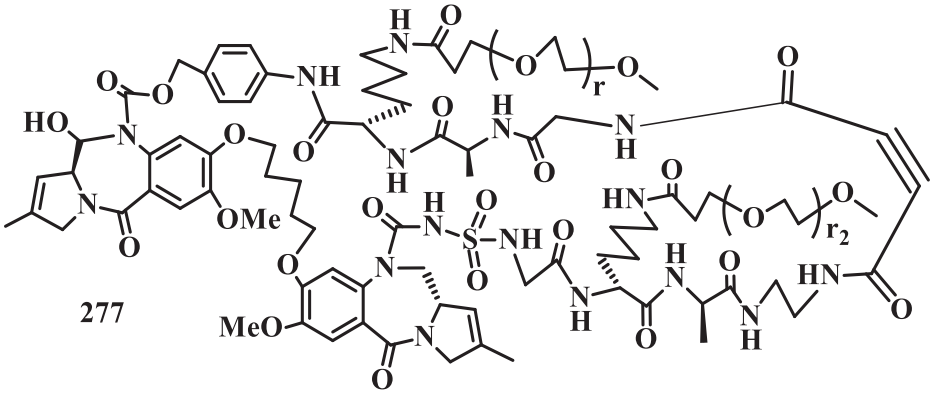

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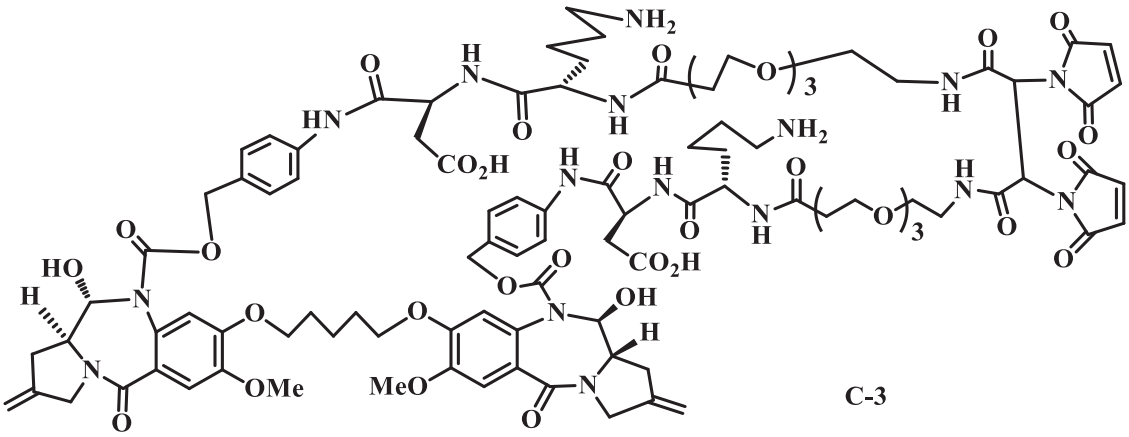

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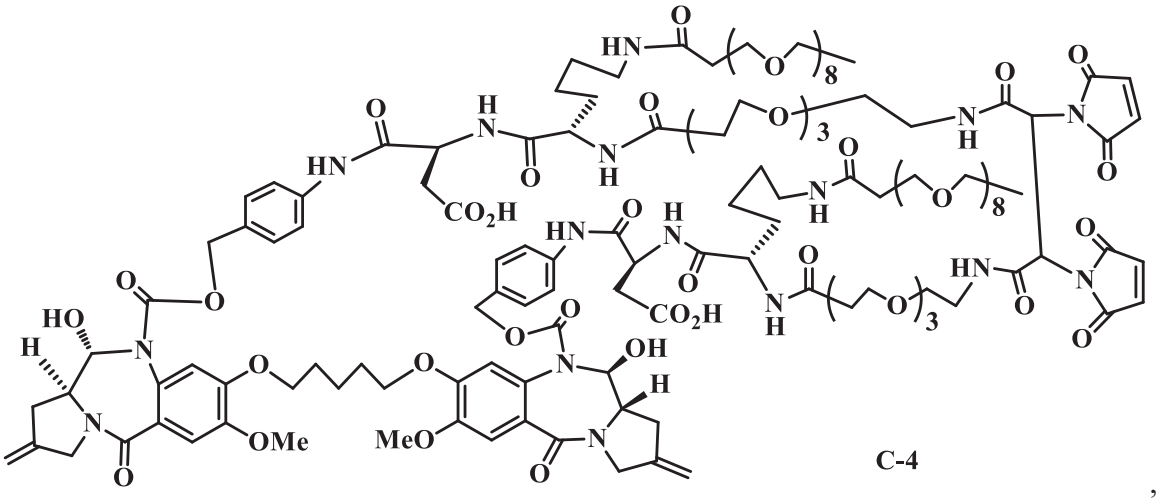

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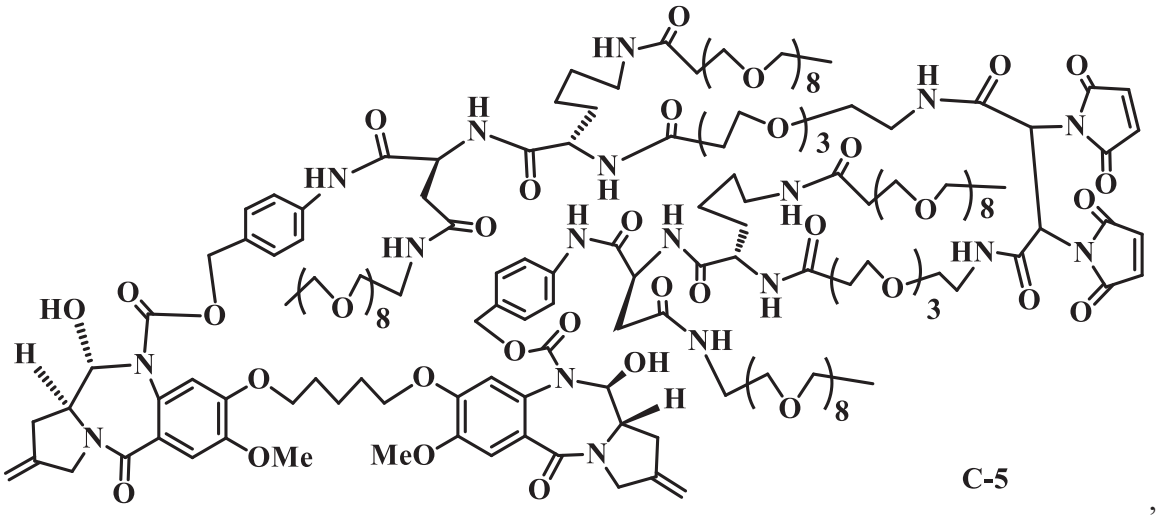

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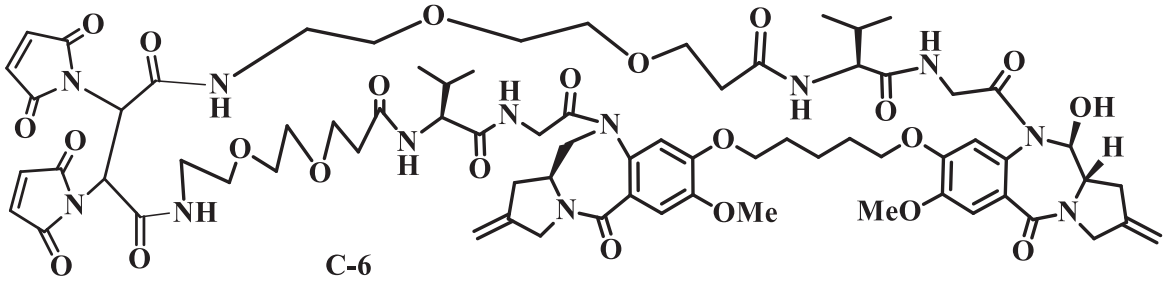

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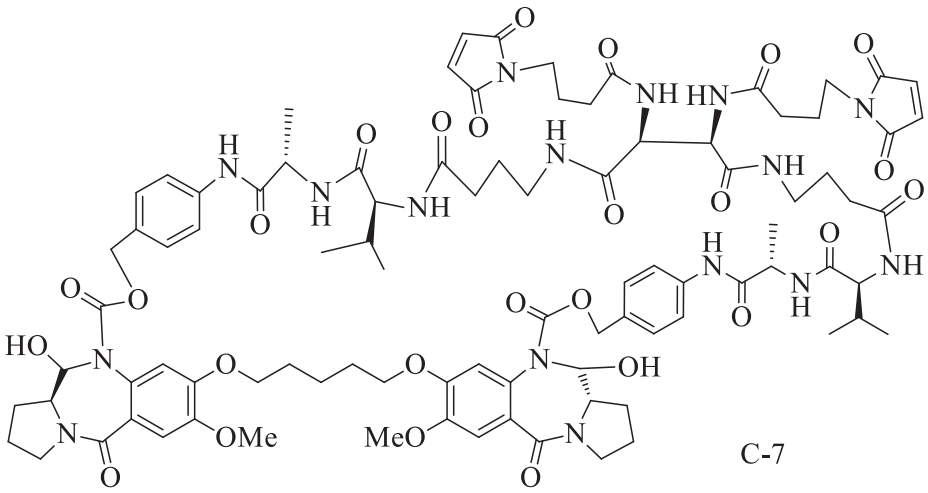

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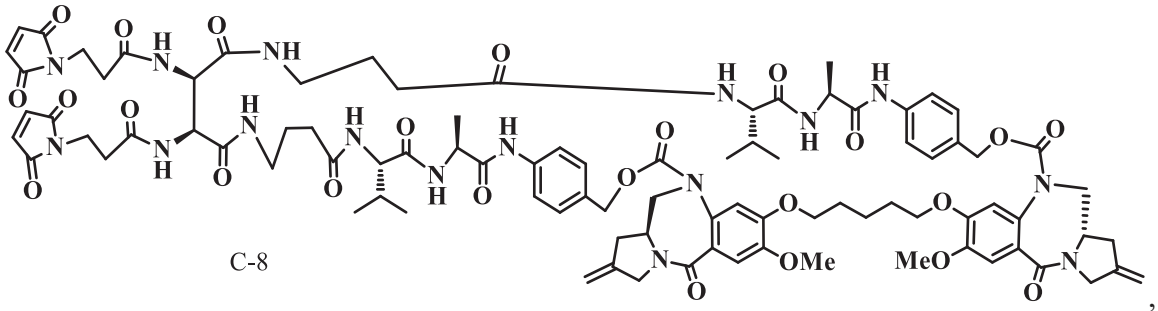

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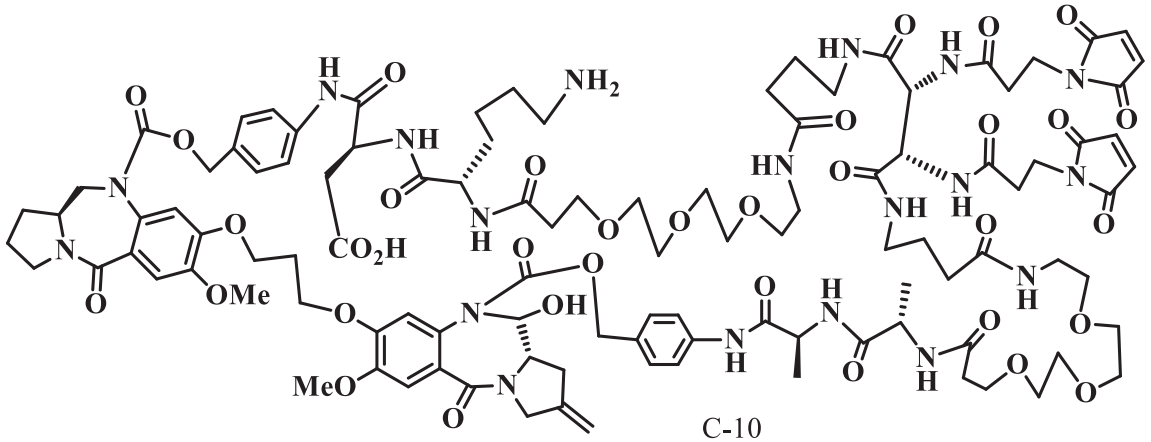

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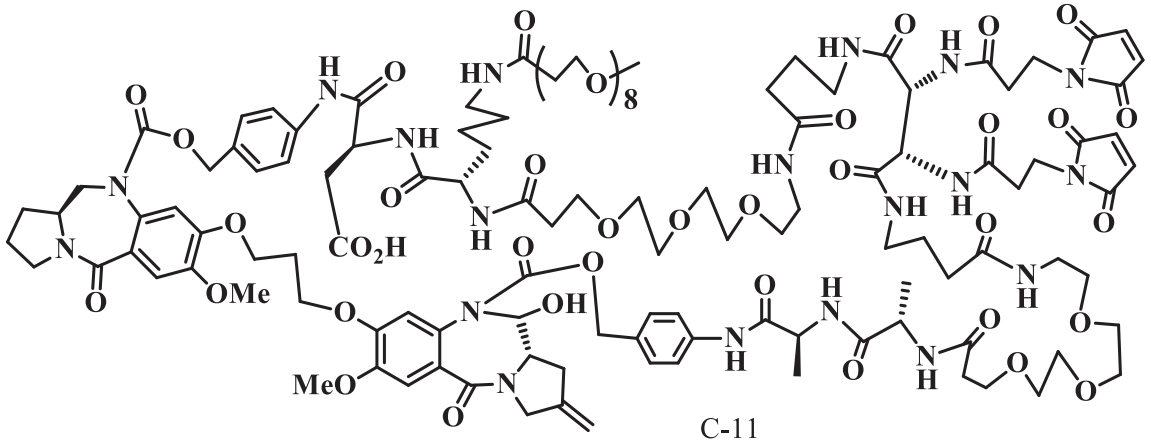

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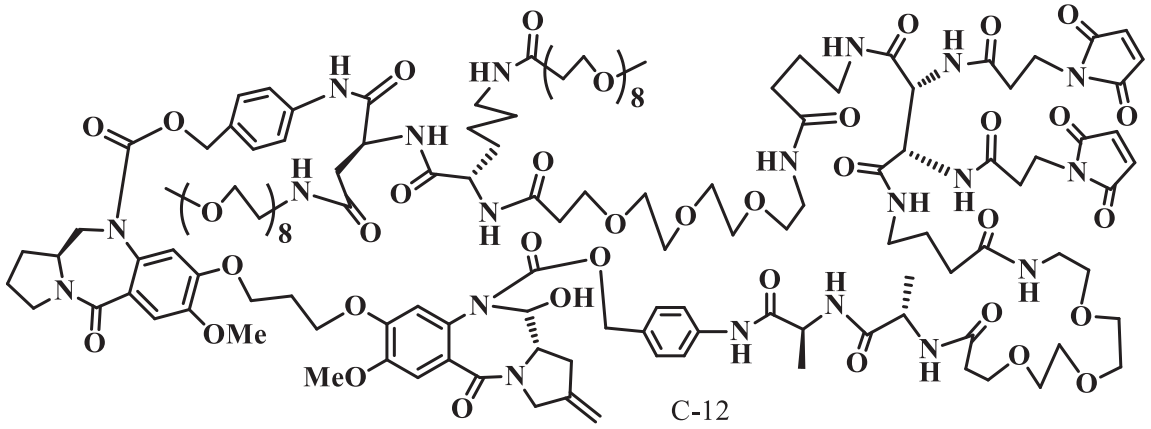

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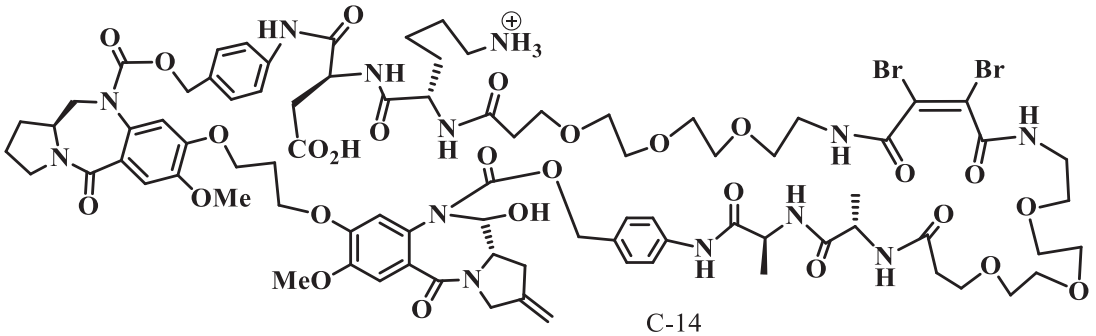

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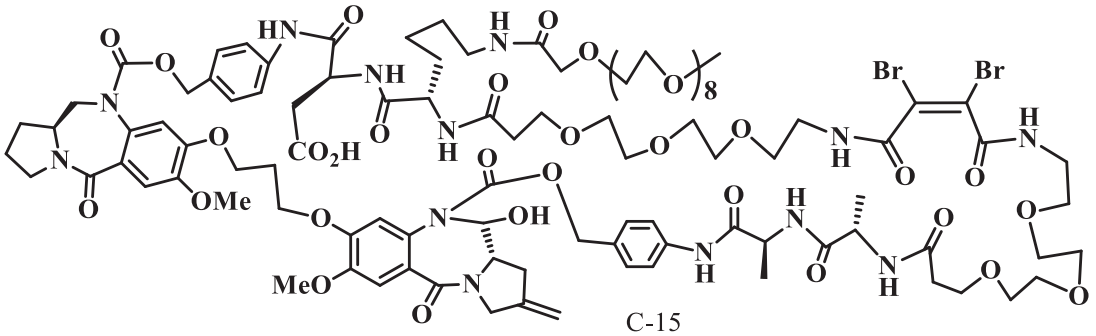

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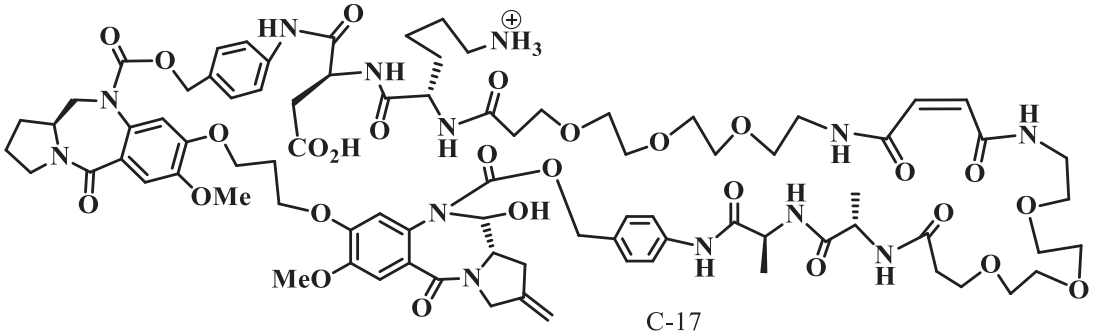

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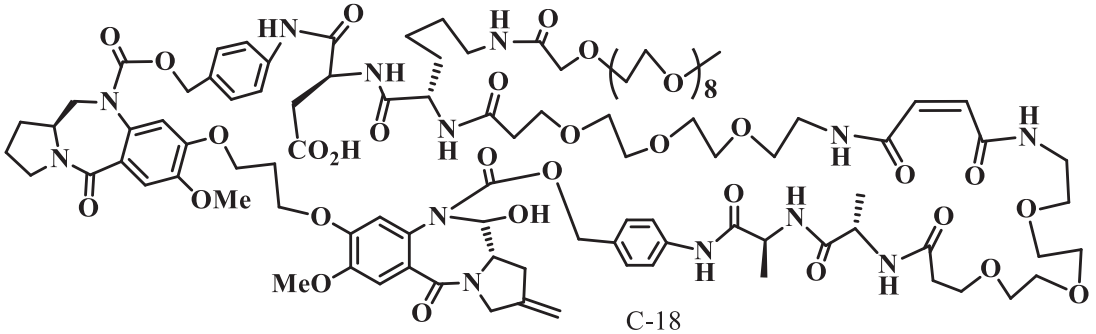

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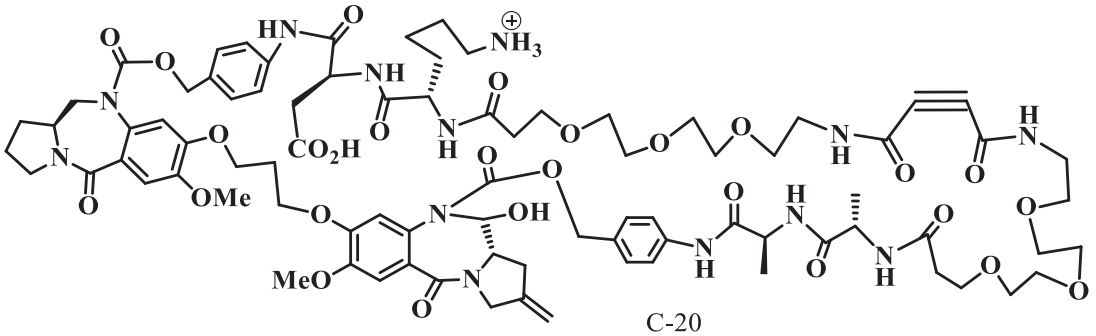

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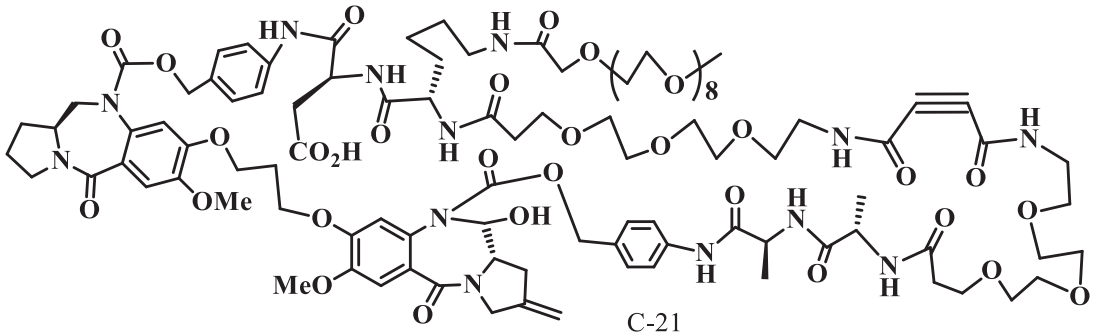

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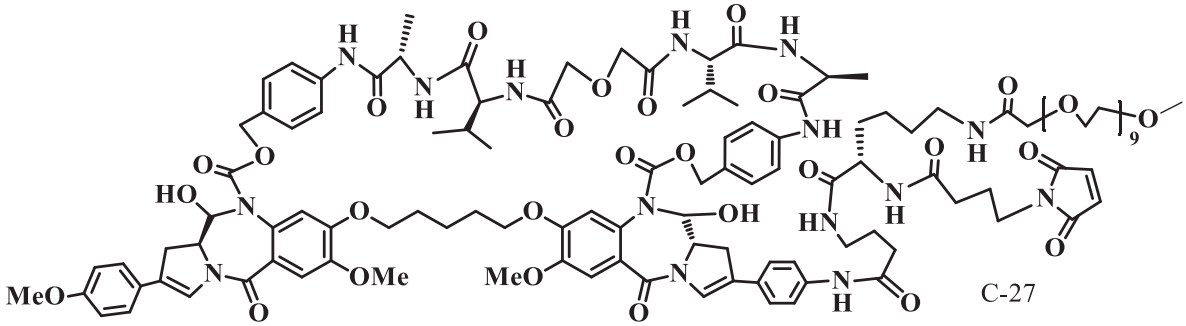

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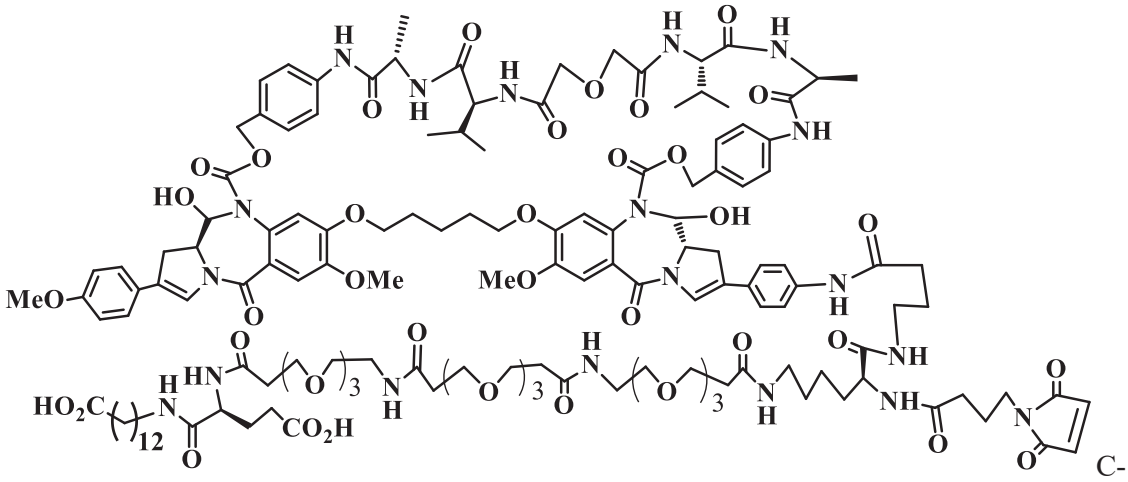


C-29,

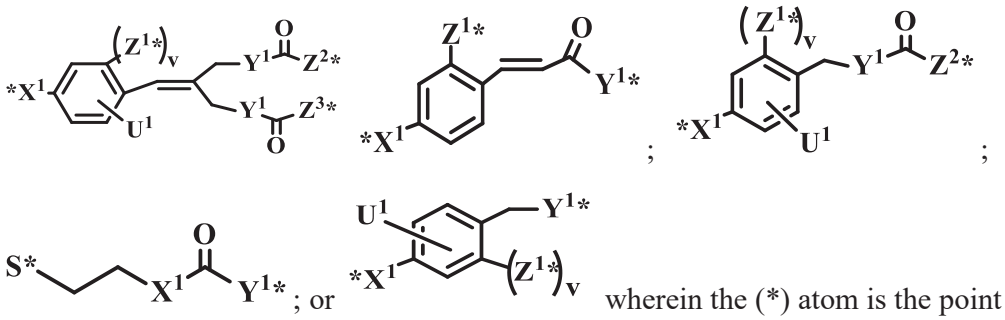
wherein r, r_1, r_2 and r' are independently 0~200; n is 1~30.

10. A cross-linked PBD dimer derivative and its conjugate to a cell-binding molecule according to Claim **4,** or a cross-linked PBD dimer derivative according to claim **6**, wherein $L_1$and L_2 are independently composed of:

(A): one or more components of 6-maleimidocaproyl ("MC"), maleimidopropanoyl ("MP"), valine-citrulline ("val-cit" or "vc"), alanine-phenylalanine ("ala-phe" or "af"), p-aminobenzyloxycarbonyl ("PAB"), 4-thiopentanoate ("SPP"), 4-(N-maleimidomethyl)-cyclohexane-1 carboxylate ("MCC"), (4-acetyl)amino-benzoate ("SIAB"), ethyleneoxy (--CH_2CH_2O--) as one or more repeating units ("EO" or "PEO"), 4-thio-butyrate (SPDB), 4-thio-2-

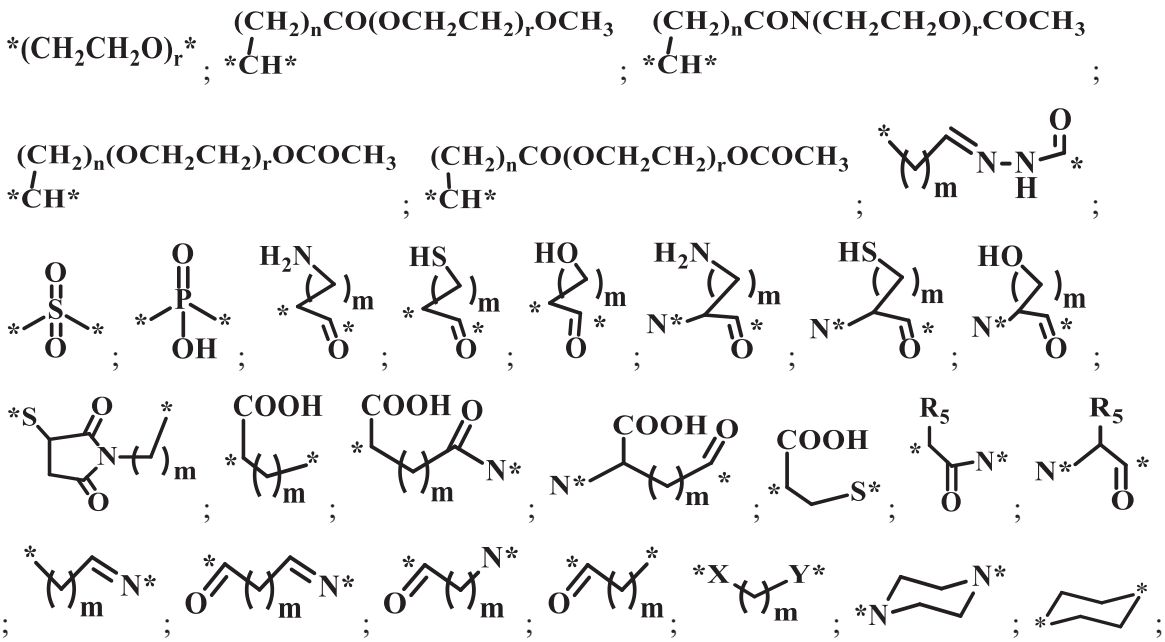
hydroxysulfonyl-butyrate (2-Sulfo-SPDB), or natural or unnatural peptides having 1~12 the same or different sequences of natural or unnatural amino acid unites;

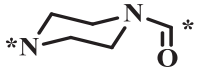
(B): one or more of a self-immolative component, a peptidic unit, a hydrazone bond, a disulfide, an ester, an oxime, an amide, or a thioether bond; The self-immolative unit includes aromatic compounds that are electronically similar to the para-aminobenzyl-carbamoyl (PAB) groups, 2-aminoimidazol-5-methanol derivatives, heterocyclic PAB analogs, beta-glucuronides, 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 selected from 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;

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

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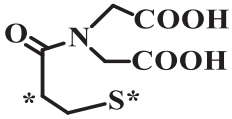
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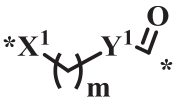
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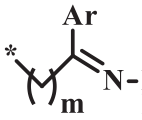
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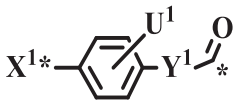
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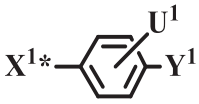
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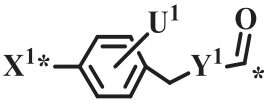
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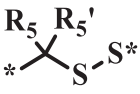
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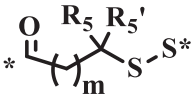
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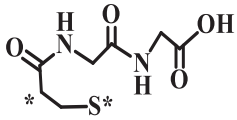
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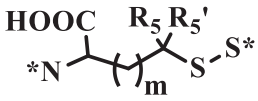
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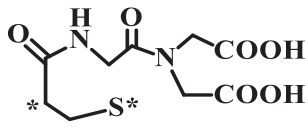
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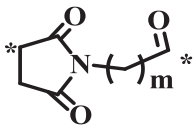
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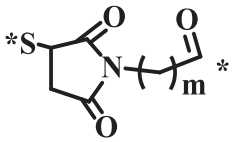
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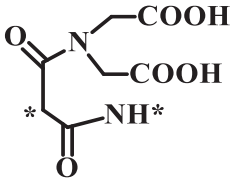
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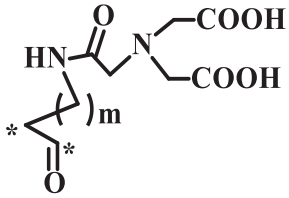
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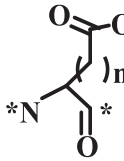
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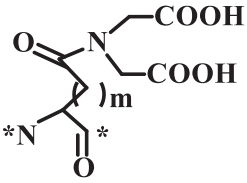
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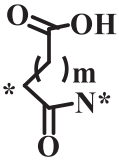
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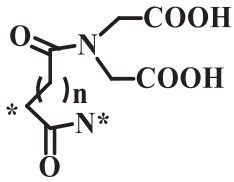
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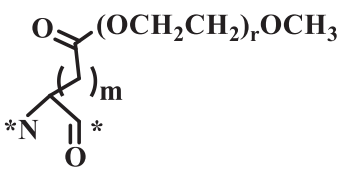
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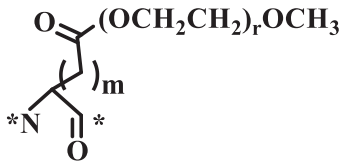
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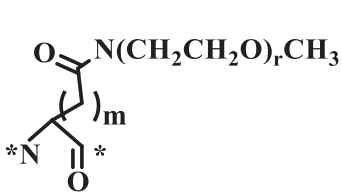
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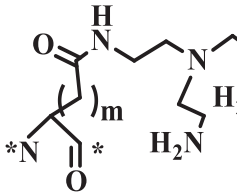
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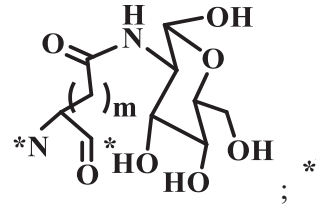
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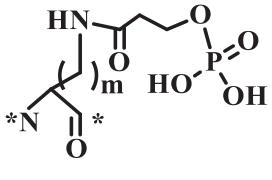
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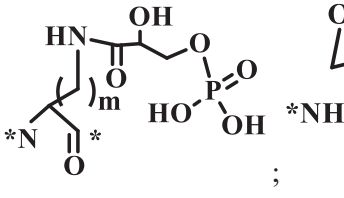
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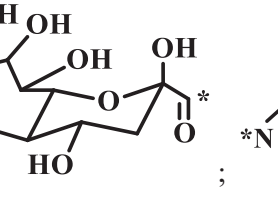
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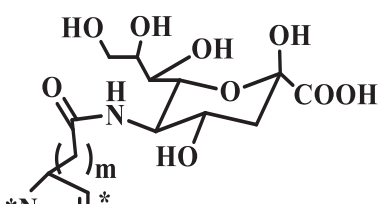
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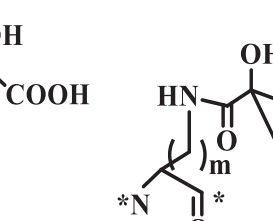
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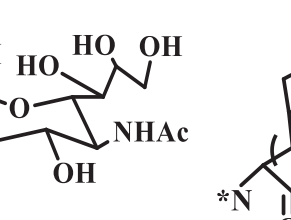
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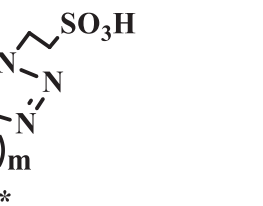
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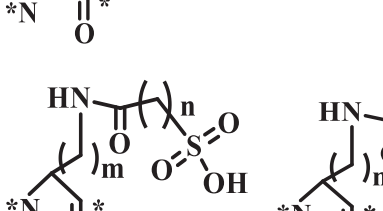
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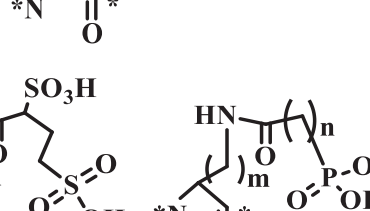
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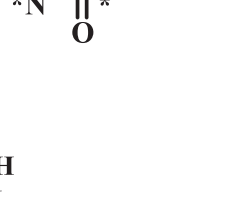
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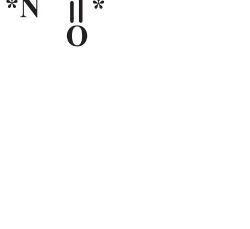
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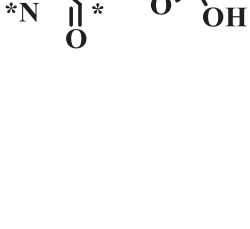
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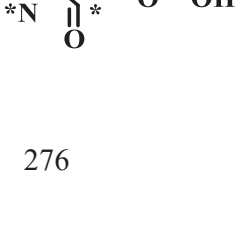
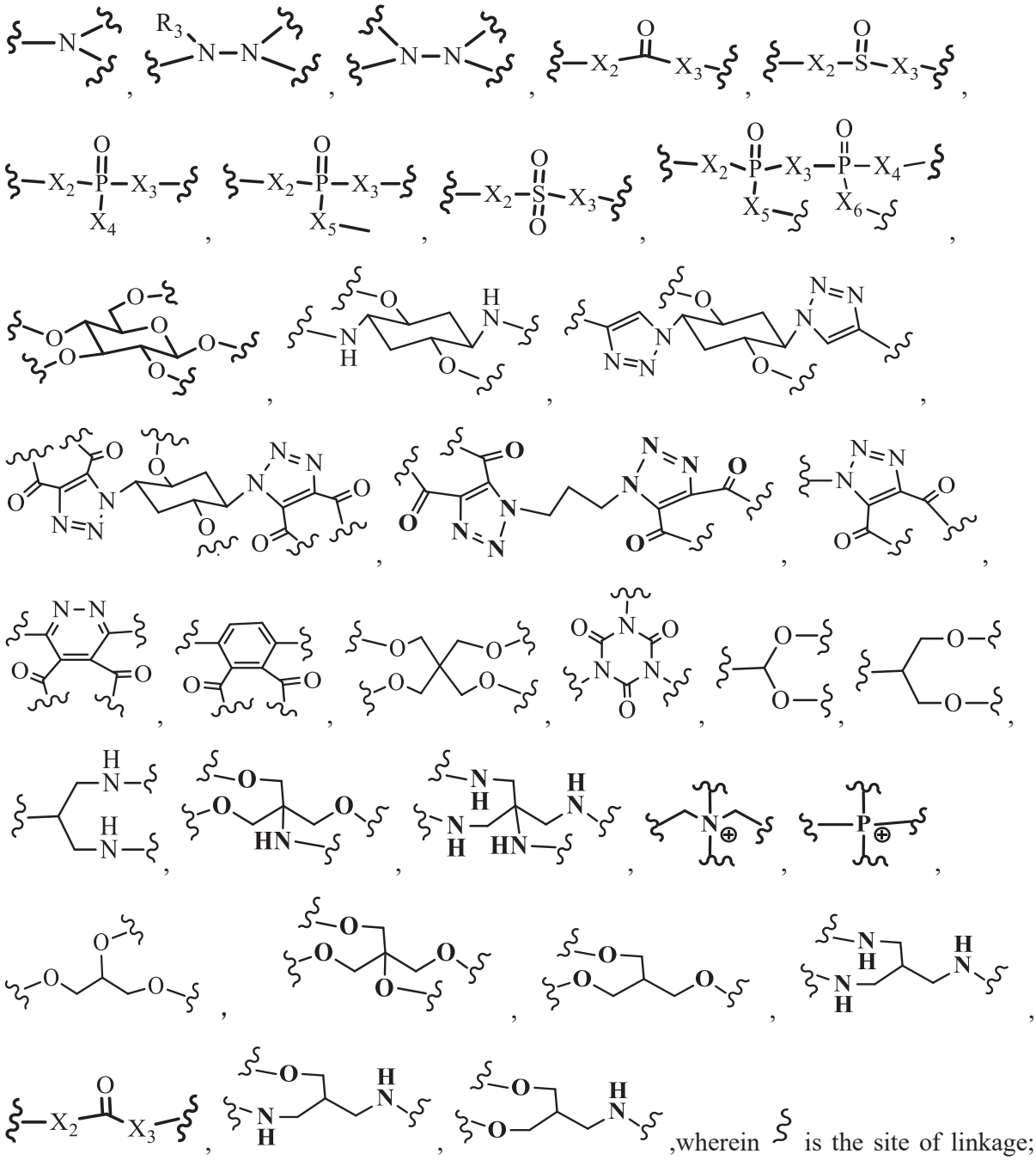

;

wherein the (*) atom is the site of attachment; 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;

(D): one or more of a releasable component that at least one bond can be broken under physiological conditions: a pH-labile, acid-labile, base-labile, oxidatively labile, metabolically labile, biochemically labile or enzyme-labile bond, which having one of the following structures: -$(CR_5R_6)_m$(Aa)r$(CR_7R_8)_n(OCH_2CH_2)_t$-, -$(CR_5R_6)_m(CR_7R_8)_n$(Aa)$_r(OCH_2CH_2)_t$-, -(Aa)$_r$-$(CR_5R_6)_m(CR_7R_8)_n(OCH_2CH_2)_t$-, -$(CR_5R_6)_m(CR_7R_8)_n(OCH_2CH_2)_r(Aa)_t$-, -$(CR_5R_6)_m$-$(CR_7{=}CR_8)(CR_9R_{10})_n$(Aa) $_t(OCH_2CH_2)_r$-, -$(CR_5R_6)_m(NR_{11}CO)$(Aa)$_t(CR_9R_{10})_n$-$(OCH_2CH_2)_r$-, -$(CR_5R_6)_m$(Aa)$_t(NR_{11}CO)(CR_9R_{10})_n(OCH_2CH_2)_r$-,-$(CR_5R_6)_m$(OCO)(Aa)$_t(CR_9R_{10})_n$-$(OCH_2CH_2)_r$-, -$(CR_5R_6)_m(OCNR_7)(Aa)_t(CR_9R_{10})_n(OCH_2CH_2)_r$-, -$(CR_5R_6)_m$(CO)(Aa)$_t$-$(CR_9R_{10})_n(OCH_2CH_2)_r$-, -$(CR_5R_6)_m(NR_{11}CO)(Aa)_t(CR_9R_{10})_n(OCH_2CH_2)_r$-, -$(CR_5R_6)_m$-(OCO)(Aa)$_t(CR_9R_{10})_n$-$(OCH_2CH_2)_r$-, -$(CR_5R_6)_m(OCNR_7)(Aa)_t(CR_9R_{10})_n(OCH_2CH_2)_r$-, -$(CR_5R_6)_m$(CO)(Aa)$_t(CR_9R_{10})_n$-$(OCH_2CH_2)_r$-, -$(CR_5R_6)_m$-phenyl-CO(Aa)$_t(CR_7R_8)_n$-, -$(CR_5R_6)_m$-furyl-CO(Aa)$_t(CR_7R_8)_n$-, -$(CR_5R_6)_m$-oxazolyl-CO(Aa)$_t(CR_7R_8)_n$-, -$(CR_5R_6)_m$-thiazolyl-CO(Aa)$_t(CCR_7R_8)_n$-, -$(CR_5R_6)_t$-thienyl-CO$(CR_7R_8)_n$-, -$(CR_5R_6)_t$-imidazolyl-CO-$(CR_7R_8)_n$-, -$(CR_5R_6)_t$-morpholino-CO(Aa)$_t$-$(CR_7R_8)_n$-, -$(CR_5R_6)_t$piperazino-CO(Aa)$_t$-$(CR_7R_8)_n$-, -$(CR_5R_6)_t$-N-methylpiperazin-CO(Aa)$_t$-$(CR_7R_8)_n$-, -$(CR_5R)_m$-(Aa)$_t$phenyl-, -$(CR_5R_6)_m$-(Aa)$_t$furyl-, -$(CR_5R_6)_m$-oxazolyl(Aa)$_t$-, -$(CR_5R_6)_m$-thiazolyl(Aa)$_t$-, -$(CR_5R_6)_m$-thienyl-(Aa)$_t$-, -$(CR_5R_6)_m$-imidazolyl(Aa)$_t$-, -(C $R_5R_6)_m$-morpholino-(Aa)$_t$-, -$(CR_5R_6)_m$-piperazino-(Aa)$_t$-, -$(CR_5R_6)_m$-N-methylpiperazino-(Aa)$_t$-, -K$(CR_5R_6)_m$(Aa)r$(CR_7R_8)_n(OCH_2CH_2)_t$-, -K$(CR_5R_6)_m$-$(CR_7R_8)_n$-(Aa)$_r(OCH_2CH_2)_t$-, -K(Aa)$_r$-$(CR_5R_6)_m(CR_7R_8)_n(OCH_2CH_2)_t$-, -K$(CR_5R_6)_m(CR_7R_8)_n$-$(OCH_2$-$CH_2)_r(Aa)_t$-, -K$(CR_5R_6)_m(CR_7{=}CR_8)(CR_9R_{10})_n(Aa)_t(OCH_2CH_2)_r$-, -K$(CR_5R_6)_m$-$(NR_{11}CO)(Aa)_t(CR_9R_{10})_n(OCH_2CH_2)_r$, -K$(CR_5R_6)_m(Aa)_t(NR_{11}CO)$-$(CR_9R_{10})_n(OCH_2CH_2)_r$-, -K$(CR_5R_6)_m$(OCO)(Aa)$_t(CR_9R_{10})_n$-$(OCH_2CH_2)_r$-, -K$(CR_5R_6)_m(OCNR_7)(Aa)_t(CR_9R_{10})_n$-$(OCH_2CH_2)_r$-, -K$(CR_5R_6)_m$(CO)(Aa)$_t$-$(CR_9R_{10})_n(OCH_2CH_2)_r$-, -K$(CR_5R_6)_m(NR_{11}CO)(Aa)_t$-$(CR_9R_{10})_n(OCH_2CH_2)_r$-, -K$(CR_5R_6)_m$-(OCO)(Aa)$_t(CR_9R_{10})_n(OCH_2CH_2)_r$-, -K$(CR_5R_6)_m$-$(OCNR_7)(Aa)_t(CR_9R_{10})_n(OCH_2CH_2)_r$-, -K-$(CR_5R_6)_m$(CO)(Aa)$_t(CR_9R_{10})_n(OCH_2CH_2)_r$-, -K$(CR_5R_6)_m$-phenyl-CO(Aa)$_t(CR_7R_8)_n$-, -K-$(CR_5R_6)_m$-furyl-CO(Aa)$_t$-$(CR_7R_8)_n$-, -K$(CR_5R_6)_m$-oxazolyl-CO(Aa)$_t(CR_7R_8)_n$-, -K$(CR_5R_6)_m$-thiazolyl-CO(Aa)$_t$-$(CR_7R_8)_n$-, -K$(CR_5R_6)_t$-thienyl-CO$(CR_7R_8)_n$-, -K$(CR_5R_6)_t$imidazolyl-CO-$(CR_7R_8)_n$-, -K$(CR_5R_6)_t$morpholinoCO-(Aa)$_t(CR_7R_8)_n$-, -K$(CR_5R_6)_t$piperazino-CO(Aa)$_t$-$(CR_7R_8)_n$-, -K$(CR_5R_6)_t$-N-methylpiperazin-CO(Aa)$_t(CR_7R_8)_n$-, -K$(CR_5R)_m$(Aa)$_t$phenyl, -K-$(CR_5R_6)_m$-(Aa)$_t$furyl-, -K$(CR_5R_6)_m$-oxazolyl(Aa)$_t$-, -K$(CR_5R_6)_m$-thiazolyl(Aa)$_t$-, -K$(CR_5R_6)_m$-thienyl-(Aa)$_t$-, -K$(CR_5R_6)_m$-imidazolyl(Aa)$_t$-, -K$(CR_5R_6)_m$-morpholino(Aa)$_t$-, -K$(CR_5R_6)_m$-piperazino-(Aa)$_t$G, -K$(CR_5R_6)_m$-N-methylpiperazino(Aa)$_t$-; wherein m, Aa, m, and n are described above; t and r are 0 – 100

independently; R_3, R_4, R_5, R_6, R_7, and R_8 are independently chosen from H; halide; C_1~C_8 alkyl; C_2~C_8 aryl, alkenyl, alkynyl, ether, ester, amine or amide, which optionally substituted by one or more halide, CN, NR_1R_2, CF_3, OR_1, Aryl, heterocycle, $S(O)R_1$, SO_2R_1, $-CO_2H$, $-SO_3H$, $-OR_1$, $-CO_2R_1$, $-CONR_1$, $-PO_2R_1R_2$, $-PO_3H$ or $P(O)R_1R_2R_3$; K is NR_1, -SS-, -C(=O)-, -C(=O)NH-, -C(=O)O-, -C=NH-O-, -C=N-NH-, -C(=O)NH-NH-, O, S, Se, B, Het (heterocyclic or heteroaromatic ring having C_3-C_8), or peptides containing 1- 20 amino acids;

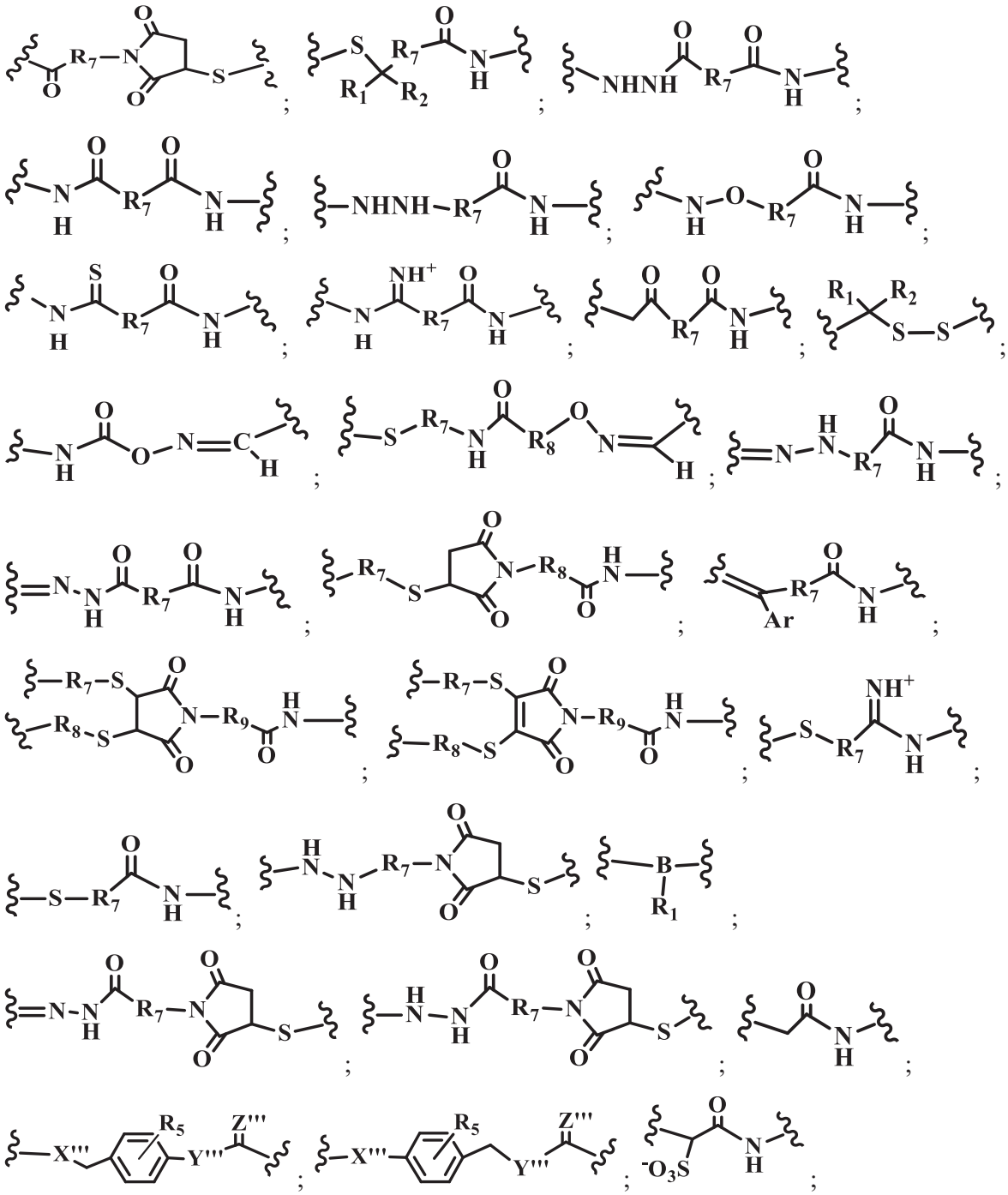
(E): one or more of a hydrophilic structure of following:

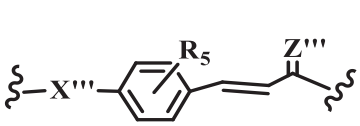
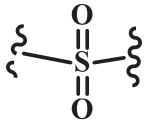
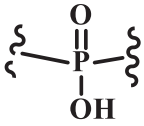
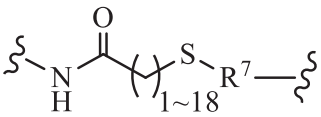
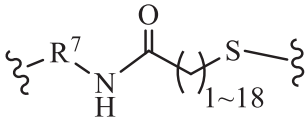
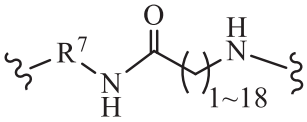
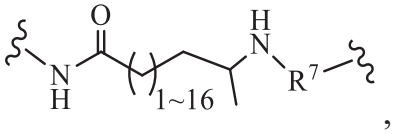
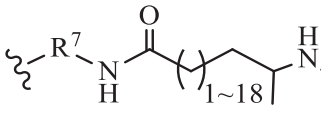
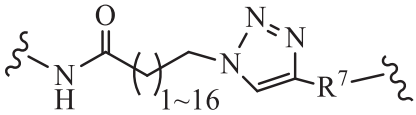
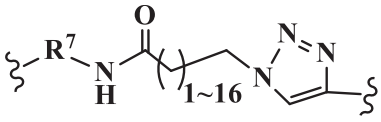
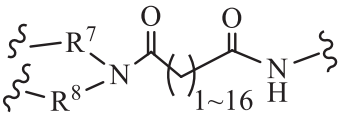
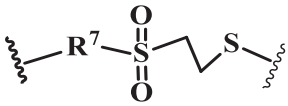
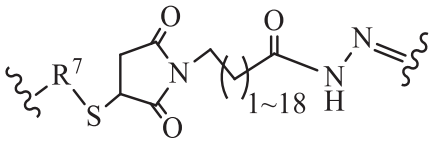
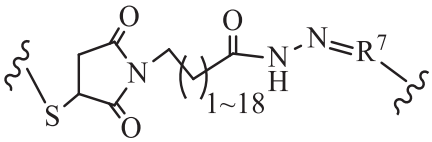
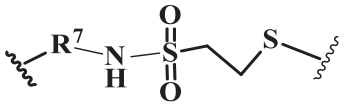
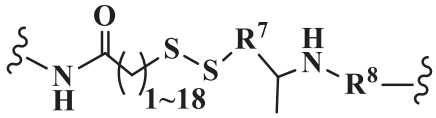
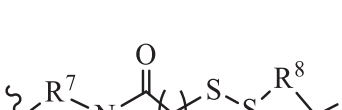


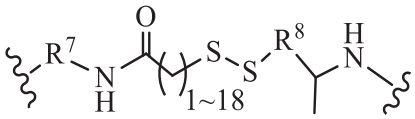
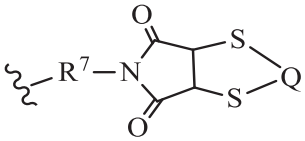
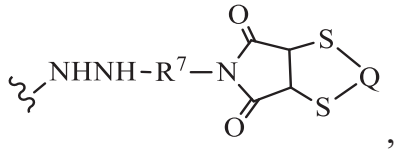
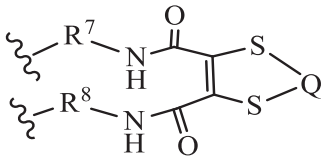
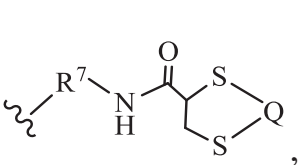
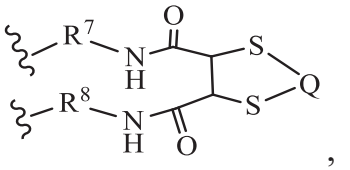
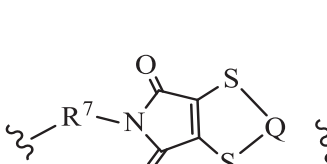
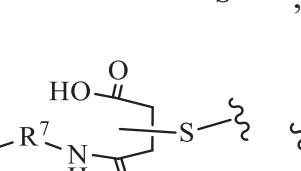
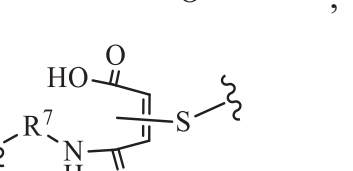
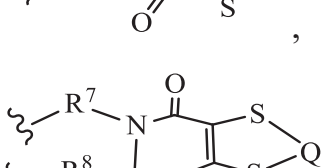
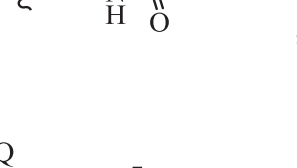
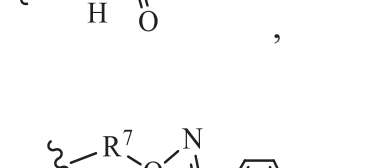
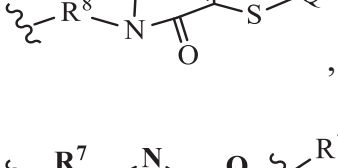
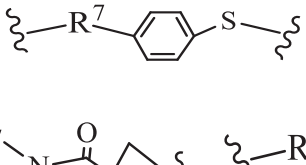
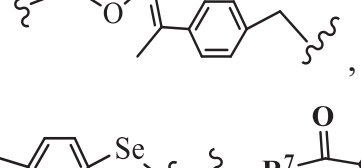
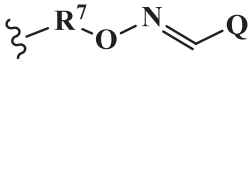
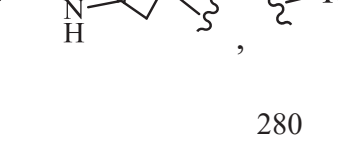
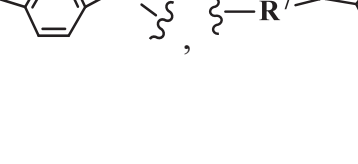
,wherein ∿ is the site of linkage; X_2, X_3, X_4, X_5, or X_6, are independently selected from NH; NHNH; $N(R_3)$; $N(R_3)N(R_{3'})$; O; S; C_1-C_6 alkyl; C_2-C_6 heteroalkyl, alkylcycloalkyl, or heterocycloalkyl; C_3-C_8 aryl, Ar-alkyl, heterocyclic,

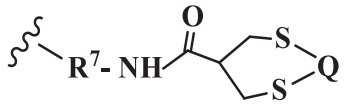
carbocyclic, cycloalkyl, heteroalkylcycloalkyl, alkylcarbonyl, or heteroaryl; or 1~8 of the same or different amino acids; wherein R_3 and $R_{3'}$ are independently H;C_1-C_8 alkyl; C_2-C_8 hetero-alkyl, alkylcycloalkyl, or heterocycloalkyl; C_3-C_8 aryl, Ar-alkyl, heterocyclic, carbocyclic, cycloalkyl, heteroalkylcycloalkyl, alkylcarbonyl, or heteroaryl; or C_2-C_8 esters, ether, or amide; or polyethyleneoxy unit having formula $(OCH_2CH_2)_p$ or $(OCH_2CH(CH_3))_p$, wherein p is an integer from 0 to 5000, or combination above thereof;

(F) one or more following components linking to E_1 and/or E_2, of Formula (I), (Ia), (Ib), (Ic), (Ie): (III), (II), (III) or (IV); or when Q directly linking to L_1 and/or L_2 of Formula (I), (Ia), (Ib), (Ic), (Ie): (III), (II), (III) or (IV), wherein V_1, and/or V_2, are independently absent:

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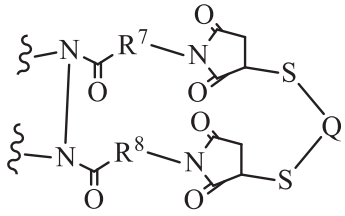
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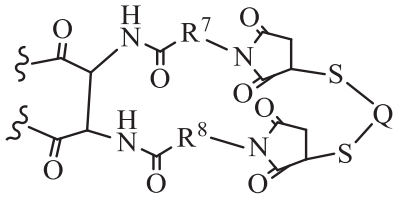
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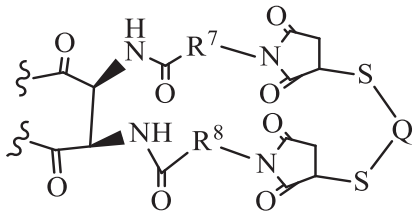
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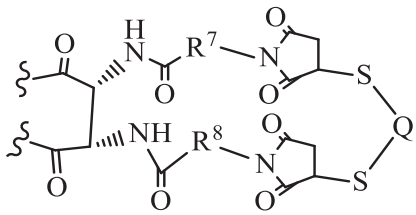
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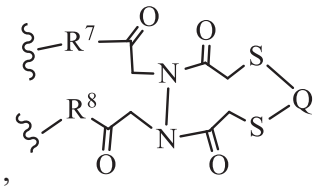
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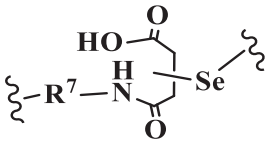
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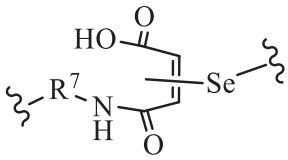
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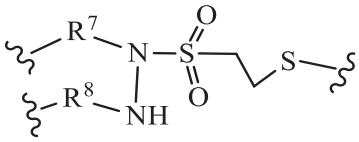
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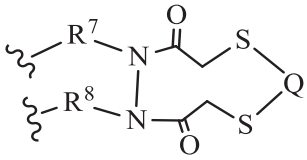
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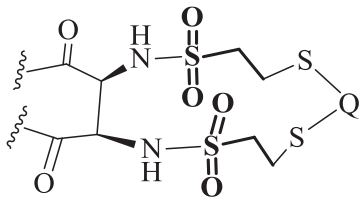
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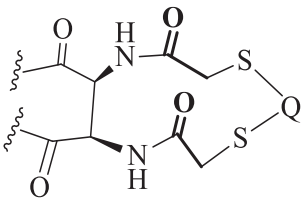

wherein R_7, R_8 and R_9 are independently selected from –C_1~C_8 alkylene-, -- C_1~C_7 carbocyclo-, -O-(C_1~C_8 alkyl)-, -arylene-, -- C_1~C_8 alkylene-arylene-, -arylene, -C_1~C_8 alkylene-, -C_1~C_8 alkylene-(C_1~C_8 carbocyclo)-, -(C_3~C_7 carbocyclo)- C_1~C_8 alkylene-, -C_3~C_8 heterocyclo-, -C_1~C_8 alkylene-(C_3~C_8 heterocyclo)-, -(C_3~C_8 heterocyclo)- C_1~C_9 alkylene-, -$(CH_2CH_2O)_k$-, -$(CH(CH_3)CH_2O)_k$-, and -($CH_2CH_2O)_k$-CH_2-; k is an integer ranging from 1-30; X’’’, Y’’’ and Z’’’ are independently selected from NH, O or S; Q, R_1 and R_2 are described above.

11. The cross-linked PBD dimer derivative and its conjugate according to claim **1, 2, 3, 4, 5,** or **8,** wherein the cell binding agent/molecule is selected from:

(A): the group consisting of an antibody, a protein, probody, nanobody, a vitamin (including folate), peptides, a polymeric micelle, a liposome, a lipoprotein-based drug carrier, a nanoparticle 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;

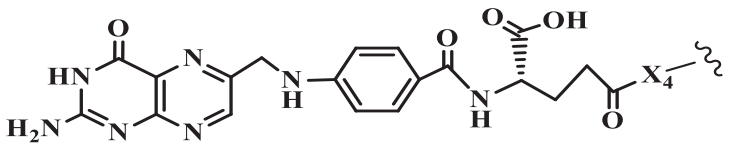
(B): an antibody-like protein, a full-length antibody (polyclonal antibody, monoclonal antibody, antibody dimer, antibody multimer), multispecific antibody (selected from, bispecific antibody, trispecific antibody, or tetraspecific antibody); a single chain antibody, an antibody fragment that binds to 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, CDR's, diabody, triabody, tetrabody, miniantibody, a probody, a probody fragment, small immune proteins (SIP), a lymphokine, a hormone, a vitamin, a growth factor, a colony stimulating factor, a nutrient-transport molecule, large molecular weight proteins, fusion proteins, kinase inhibitors, gene-targeting agents, nanoparticles or polymers modified with antibodies or large molecular weight proteins;

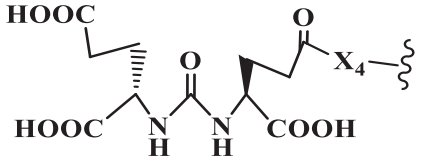
(C): a cell-binding molecule or receptor agonist selected from: Somatostatin and its analogs (selected from the group consisting of octreotide (Sandostatin) and lanreotide (Somatuline)); Aromatic sulfonamides; Pituitary adenylate cyclase activating peptides (PACAP) (PAC1); Vasoactive intestinal peptides (VIP/PACAP) (VPAC1, VPAC2); Melanocyte-stimulating hormones (α-MSH); Cholecystokinins (CCK) /gastrin receptor agonists; Bombesins (selected from the group consisting ofPyr-Gln-Arg-Leu-Gly-Asn-Gln-Trp-Ala-Val-Gly-His-Leu-Met-NH_2)/gastrin-releasing peptide (GRP); Neurotensin receptor ligands (NTR1, NTR2, NTR3); Substance P (NK1 receptor) ligands; Neuropeptide Y (Y1–Y6); Homing Peptides include RGD (Arg-Gly-Asp), NGR (Asn-Gly-Arg), the dimeric and multimeric cyclic RGD peptides (selected from cRGDfV), TAASGVRSMH and LTLRWVGLMS (Chondroitin sulfate proteoglycan NG2 receptor ligands) and F3 peptides; Cell Penetrating Peptides (CPPs); Peptide Hormones, selected from the group consisting of luteinizing hormone-releasing hormone (LHRH) agonists and antagonists, and gonadotropin-releasing hormone (GnRH) agonist, acts by targeting follicle stimulating hormone (FSH) and luteinizing hormone (LH), as well as testosterone production, selected from the group consisting of 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); Pattern Recognition Receptor (PRRs), selected from the group consisting of Toll-like receptors' (TLRs) ligands, C-type lectins and Nodlike Receptors' (NLRs) ligands; Calcitonin receptor agonists; integrin

receptors' and their receptor subtypes' (selected from the group consisting of$\alpha_V\beta_1$, $\alpha_V\beta_3$, $\alpha_V\beta_5$, $\alpha_V\beta_6$, $\alpha_6\beta_4$, $\alpha_7\beta_1$, $\alpha_L\beta_2$, $\alpha_{IIb}\beta_3$) agonists (selected from the group consisting of GRGDSPK, cyclo(RGDfV) (L1) and its derives [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-)(Cilengitide)]; Nanobody (a derivative of VHH (camelid Ig)); Domain antibodies (dAb, a derivative of VH or VL domain); Bispecific T cell Engager (BiTE, a bispecific diabody); Dual Affinity ReTargeting (DART, a bispecific diabody); Tetravalent tandem antibodies (TandAb, a dimerized bispecific diabody); Anticalin (a derivative of Lipocalins); Adnectins (10th FN3 (Fibronectin)); Designed Ankyrin Repeat Proteins (DARPins); Avimers; EGF receptors, or VEGF receptors' agonists;

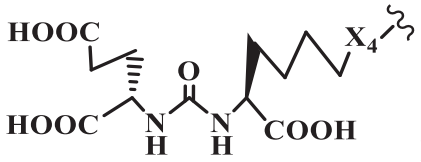
(D): A small molecule of cell-binding molecule/ligand or a cell receptor agonist selected from the following: LB01 (Folate), LB02 (PMSA ligand), LB03 (PMSA ligand), LB04 (PMSA ligand), LB05 (Somatostatin), LB06 (Somatostatin), LB07 (Octreotide, a Somatostatin analog), LB08 (Lanreotide, a Somatostatin analog), LB09 (Vapreotide (Sanvar) , a Somatostatin analog), 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 (cobalamin, vitamin B12 analog), LB17 (cobalamin, vitamin B12 analog), 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 (Rifabutin analog), LB26 (Rifabutin analog), LB27 (Rifabutin analog), LB28 (Fludrocortisone), LB29 (Dexamethasone), LB30 (fluticasone propionate), LB31 (Beclometasone dipropionate), LB32 (Triamcinolone acetonide), LB33 (Prednisone), LB34 (Prednisolone), LB35 (Methylprednisolone), LB36 (Betamethasone), LB37 (Irinotecan analog), LB38 (Crizotinib analog**),** LB39 (Bortezomib analog), LB40 (Carfilzomib analog), LB41 (Carfilzomib analog), LB42 (Leuprolide analog), LB43 (Triptorelin analog), LB44 (Clindamycin), LB45 (Liraglutide analog), LB46 (Semaglutide analog), LB47 (Retapamulin analog), LB48 (Indibulin analog), LB49 (Vinblastine analog), LB50 (Lixisenatide analog), LB51 (Osimertinib analog), LB52 (a nucleoside analog), LB53 (Erlotinib analog) or LB54 (Lapatinib analog) which are shown in the following structures:



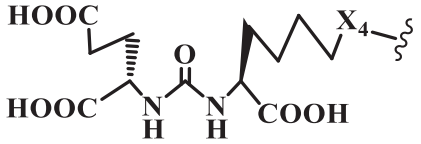
LB01 (Folate conjugate),



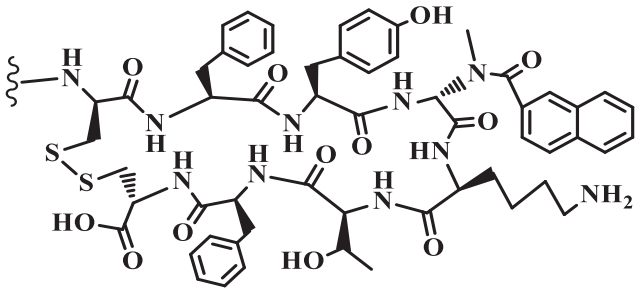
LB02 (PMSA ligand conjugate),



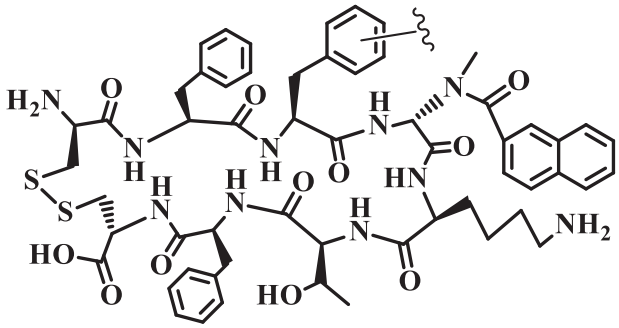
LB03 (PMSA ligand conjugate),



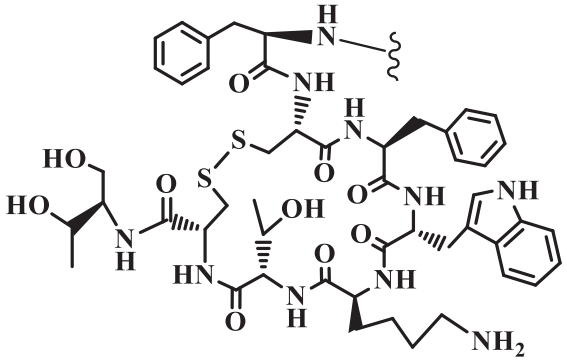
LB04 (PMSA ligand),



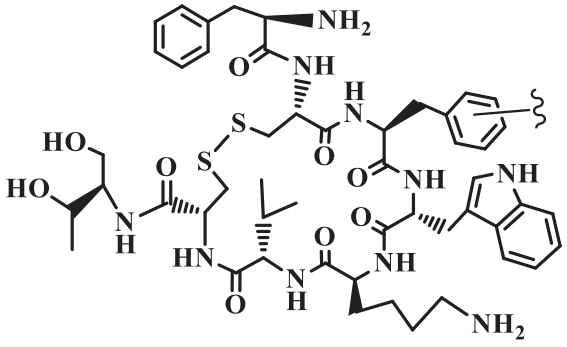
LB05 (Somatostatin),



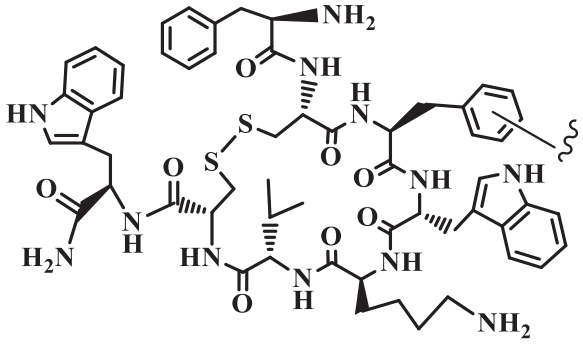
LB06 (Somatostatin),



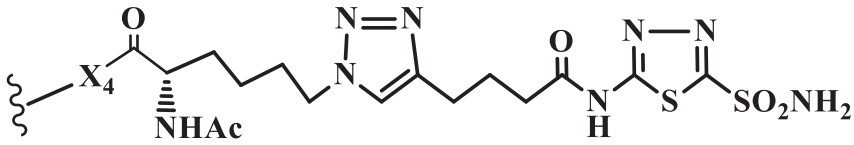
LB07 (Octreotide, a Somatostatin analog),



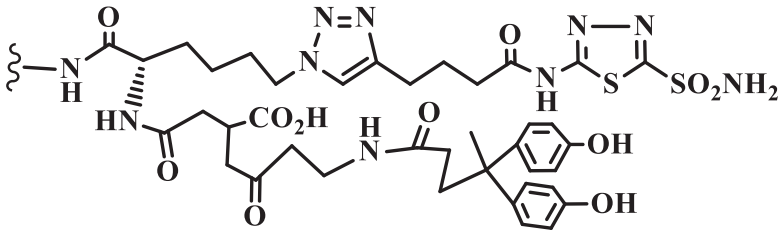
LB08 (Lanreotide, a Somatostatin analog),



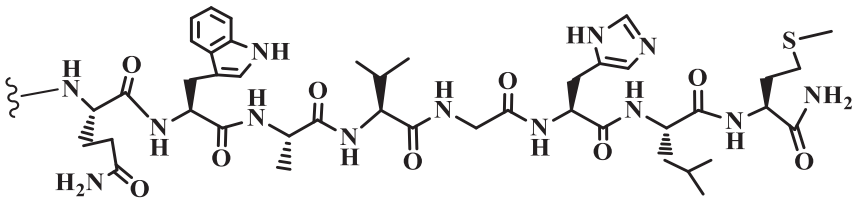
LB09 (Vapreotide (Sanvar), a Somatostatin analog),



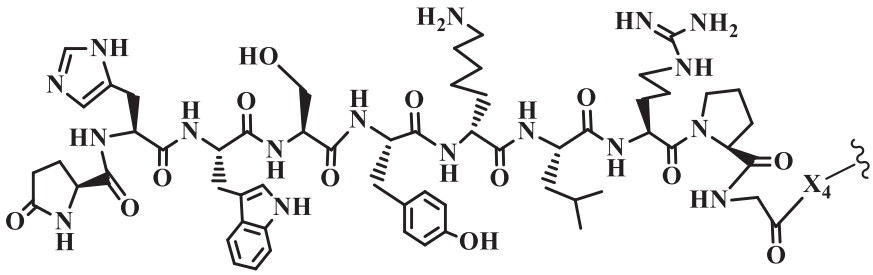
LB10 (CAIX ligand),



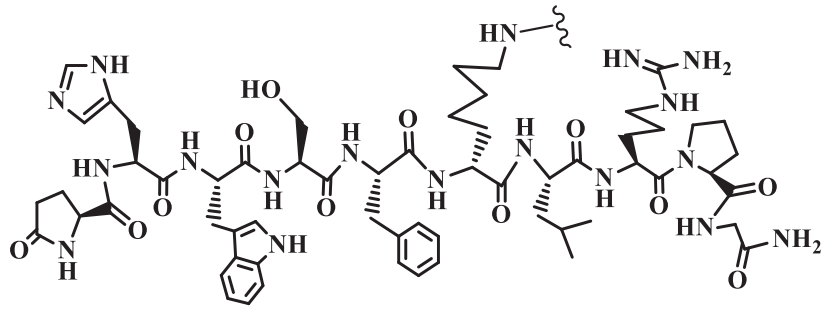
LB11 (CAIX ligand),



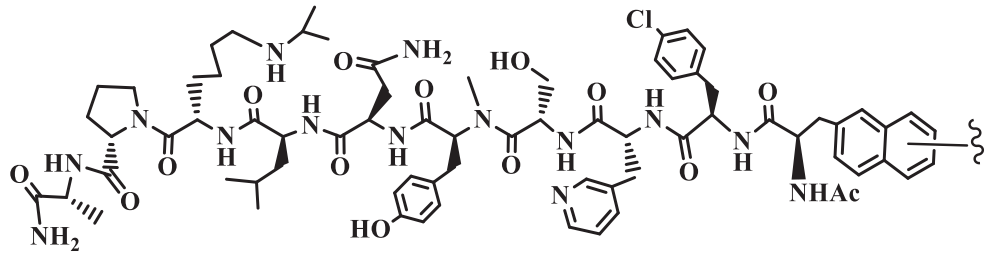
LB12 (Gastrin releasing peptide receptor (GRPr), MBA),



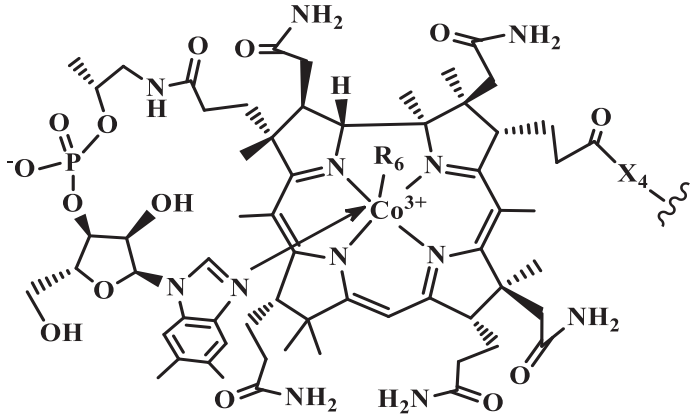
LB13 (luteinizing hormone-releasing hormone (LH-RH) ligand and GnRH),



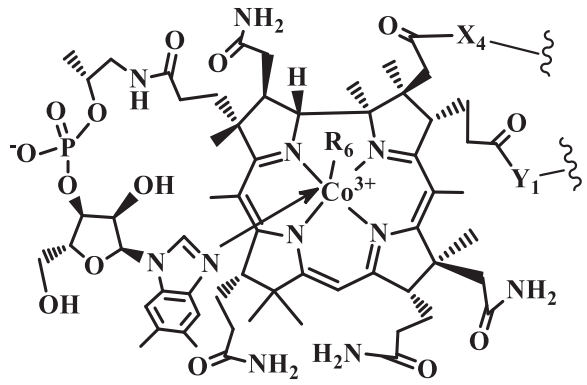
LB14 (luteinizing hormone-releasing hormone (LH-RH) and GnRH ligand),



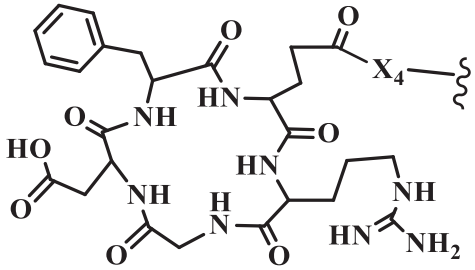
LB15 (GnRH antagonist, Abarelix),



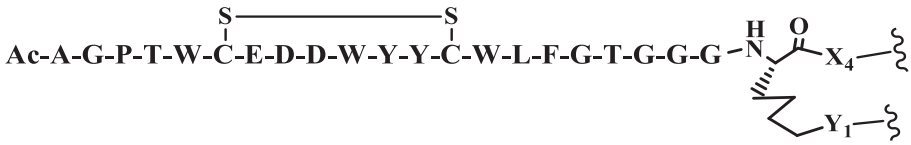
LB16 (cobalamin, vitamin B12 analog),



LB17 (cobalamin, vitamin B12 analog),



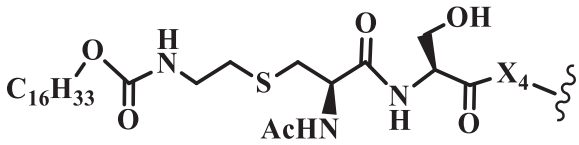
LB18 (for $\alpha_v\beta_3$ integrin receptor, cyclic RGD pentapeptide),



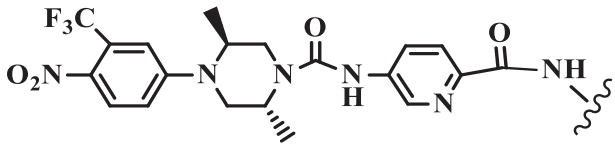
LB19 (hetero-bivalent peptide ligand conjugate for VEGF receptor),

LB20 (Neuromedin B),

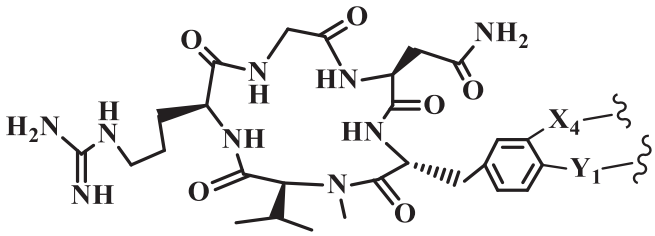
LB21 (bombesin conjugate for a G-protein coupled receptor),



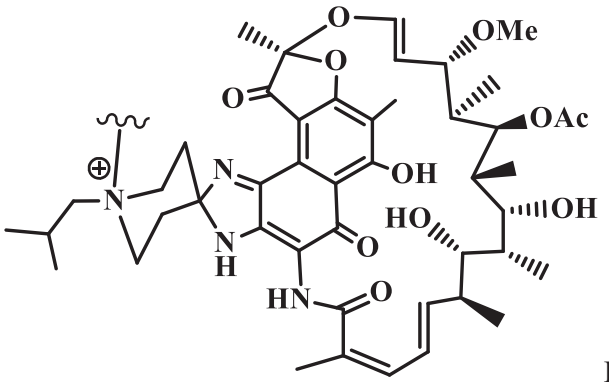
LB22 (TLR_2 conjugate for a Toll-like receptor),



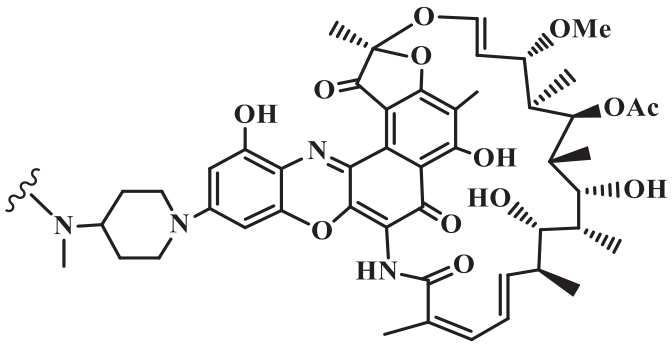
LB23 (an androgen receptor),



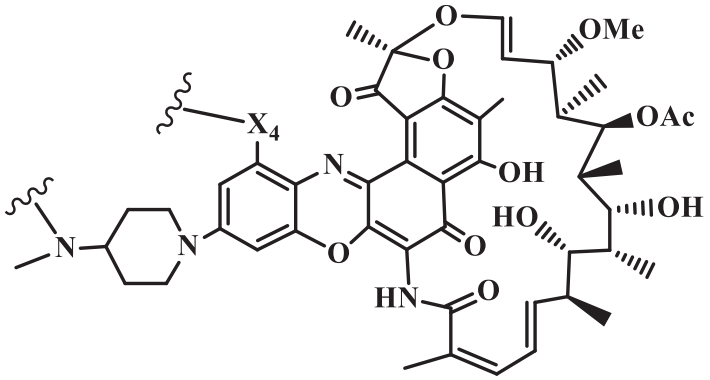
LB24 (Cilengitide/cyclo(-RGDfV-) conjugate for an α_v integrin receptor),



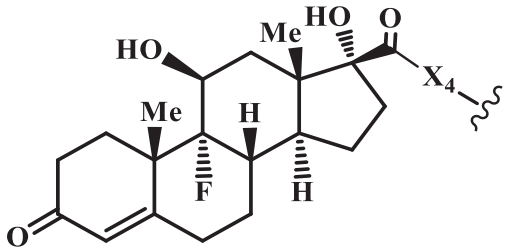
LB25 (Rifabutin analog),



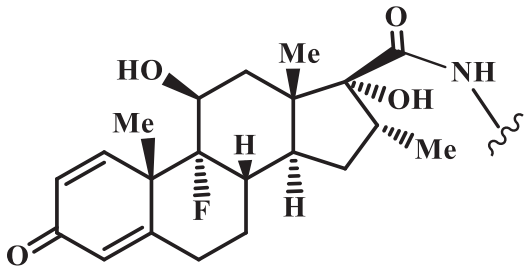
LB26 (Rifabutin analog),



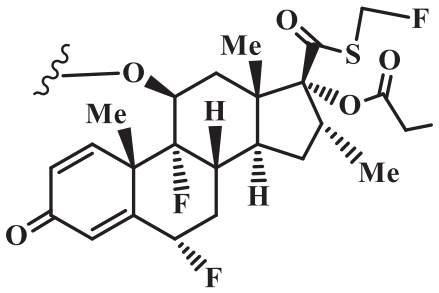
LB27 (Rifabutin analog),



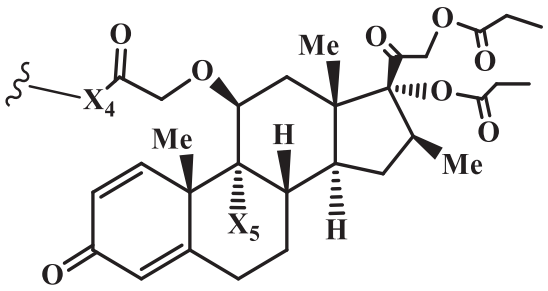
LB28 (Fludrocortisone),



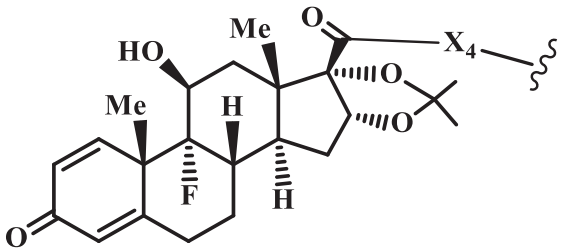
LB29 (Dexamethasone),



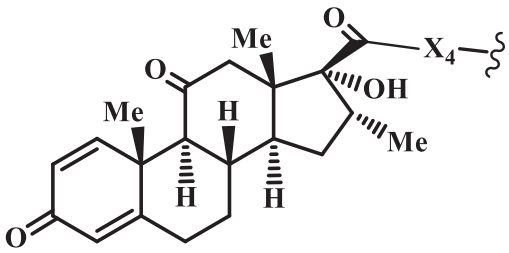
LB30 (fluticasone propionate),



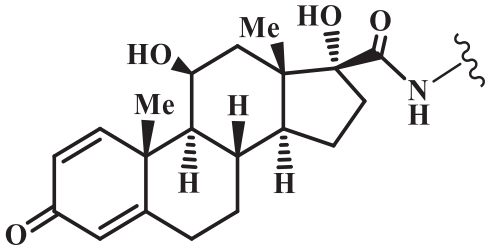
LB31 (Beclometasone dipropionate),



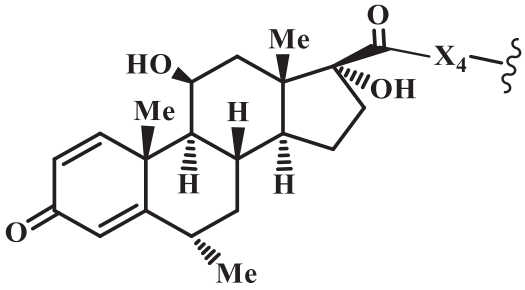
LB32 (Triamcinolone acetonide),



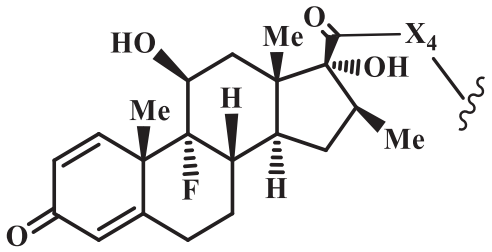
LB33 (Prednisone),



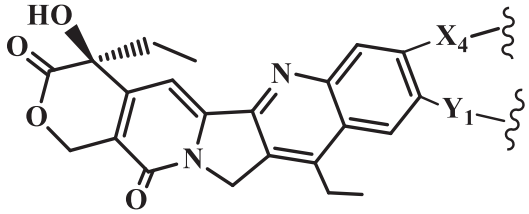
LB34 (Prednisolone),



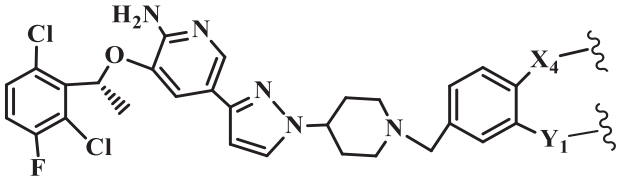
LB35 (Methylprednisolone),



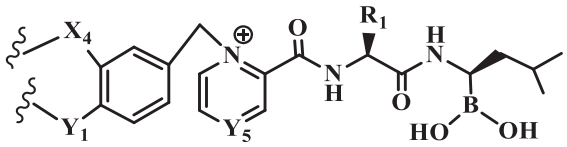
LB36 (Betamethasone),



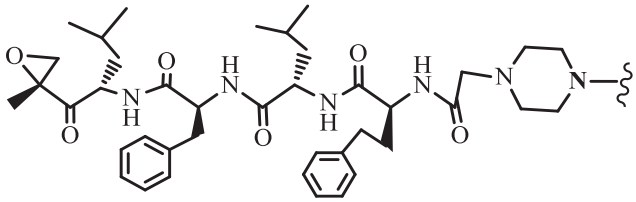
LB37 (Irinotecan analog),



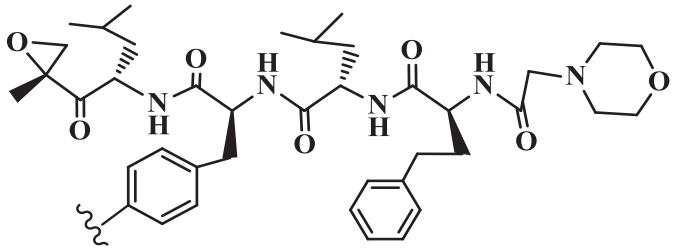
LB38 (Crizotinib analog**),**



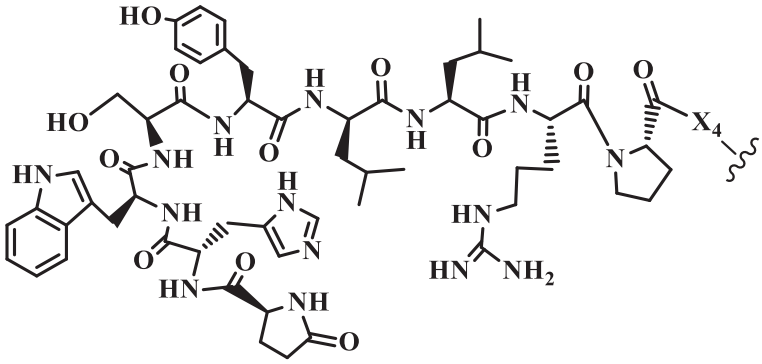
LB39 (Bortezomib analog), wherein Y_5, is N, CH, C(Cl), $C(CH_3)$, or $C(COOR_1)$; R_1 is H, C_1-C_6 Alkyl, C_3-C_8 Ar;



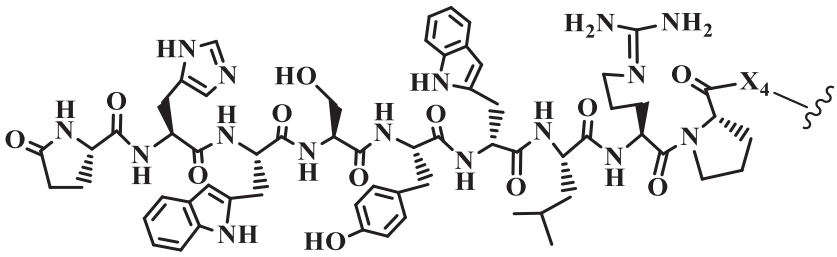
LB40 (Carfilzomib analog),



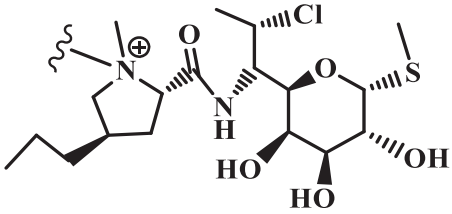
LB41 (Carfilzomib analog),



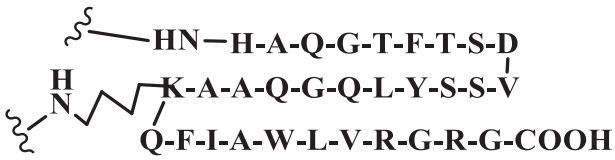
LB42 (Leuprolide analog),



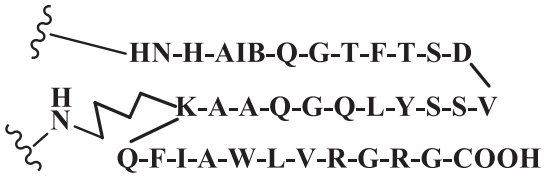
LB43 (Triptorelin analog),



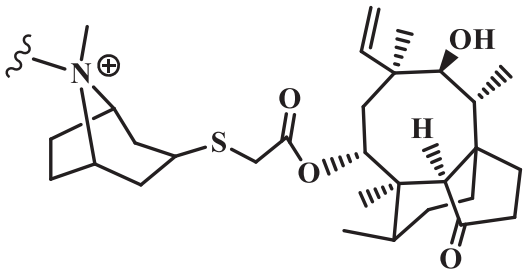
LB44 (Clindamycin),



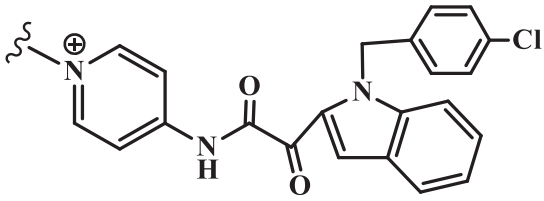
LB45 (Liraglutide analog),



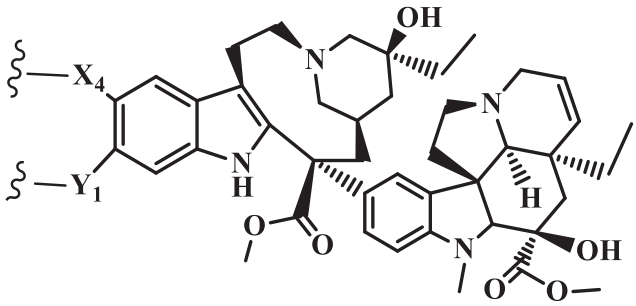
LB46 (Semaglutide analog),



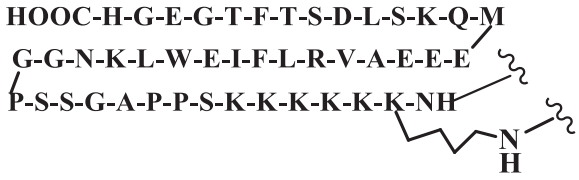
LB47 (Retapamulin analog),



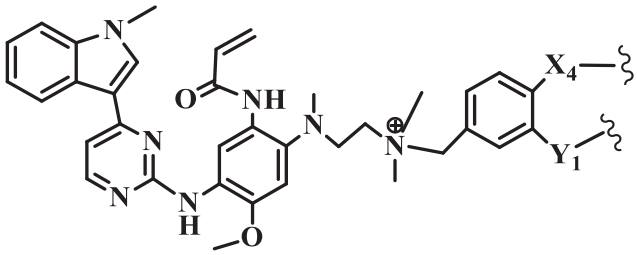
LB48 (Indibulin analog),



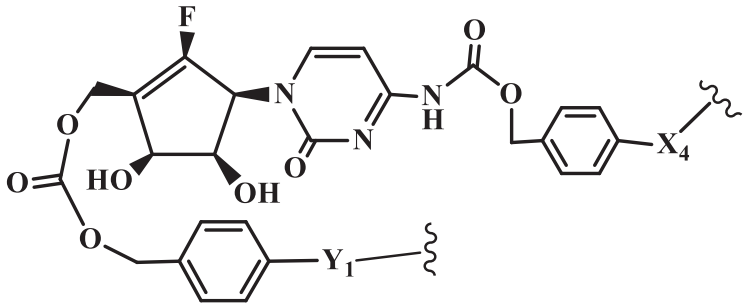
LB49 (Vinblastine analog),



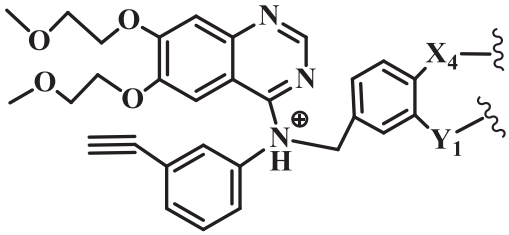
LB50 (Lixisenatide analog),



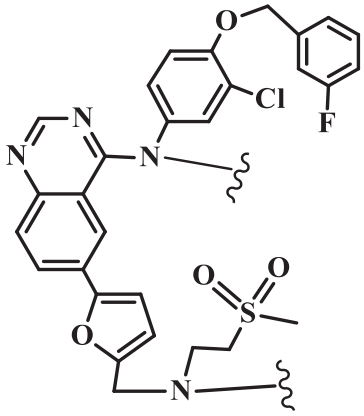
LB51 (Osimertinib analog),



LB52 (a nucleoside analog),



LB53 (Erlotinib analog),



LB54 (Lapatinib analog),

wherein "∿∿" is the site to link the PBD dimer derivative through the linker L_1 or/and L_2; 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) and 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($R_1R_2R_3$ R_4); R_1, R_2, R_3 and R_4 are defined in Claim 1.

12. The cross-linked PBD dimer derivative and its conjugate according to claim **1, 2, 3, 4, 5, 8,** or **10,** wherein the cell binding agent/molecule is capable of targeting against a tumor cell, a virus infected cell, a microorganism infected cell, a parasite infected cell, an autoimmune 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, CD202（a，b），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 familiaris 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, Cytomegalovirus, 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, EGFRvIII, 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 (a cell surface antigen glyvolipid), GD3 idiotype, GloboH, Glypican 3, N-glycolylneuraminic acid, GM3, GMCSF receptor α-chain, Growth differentiation factor 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 complex, 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 (Lymphocyte 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 factor (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, Myostatin, NA17, NARP-1, NCA-90 (granulocyte antigen), Nectin-4 (ASG-22ME), NGF, Neural apoptosis-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), Prostatic 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 glycoprotein), TRAIL-R1 (Tumor necrosis apoptosis Inducing ligand Receptor 1), TRAILR2 (Death receptor 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.

13. The cross-linked PBD dimer derivative and its conjugate according to claim **12**, wherein the tumor cell is selected from the group consisting of lymphoma cells, myeloma cells, renal cells, breast cancer cells, prostate cancer cells, ovarian cancer cells, colorectal cancer cells, gastric cancer cells, squamous cancer cells, small-cell lung cancer cells, none small-cell lung cancer cells, testicular cancer cells, malignant cells, or any cells that grow and divide at an unregulated, quickened pace to cause cancers.

14. A pharmaceutical composition comprising a therapeutically effective amount of the conjugate compounds of any one of claim **1, 2, 3, 4, 5,** or **8,** and a pharmaceutically acceptable salt,

carrier, diluent, or excipient therefore, or a combination of the conjugates thereof, for use in the treatment or prevention of a cancer, or an autoimmune disease, or an infectious disease.

15. The pharmaceutical composition either in in the liquid formula or in the formulated lyophilized solid for use according to Claim **14**, comprising by weight of: 0.01%-99% of one or more conjugates of any one of claim **1, 2, 3, 4, 5,** or **8**; 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 amino 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 8.5; and 0.0% -30.0% of one or more of isotonic agent for adjusting osmotic pressure bewteen 250 to 350 mOsm when reconstituted for administration to a patient;

wherein the polyol is selected from 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 and its metallic salts);

wherein the surfactant is selected from polysorbate 20, polysorbate 40, polysorbate 65, polysorbate 80, polysorbate 81, or polysorbate 85, poloxamer, poly(ethylene oxide)-poly(propylene oxide), polyethylene-polypropylene, Triton; 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-, cocamidopropyl-, 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 ethylimidonium ethosulfate; polyethyl glycol, polypropyl glycol, and copolymers of ethylene and propylene glycol;

wherein the preservative is selected from benzyl alcohol, octadecyldimethylbenzyl ammonium chloride, hexamethonium chloride, benzalkonium chloride, benzethonium chloride, phenol, butyl and benzyl alcohol, alkyl parabens, methyl or propyl paraben, catechol, resorcinol, cyclohexanol, 3-pentanol, or m-cresol;

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

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

wherein the chelating agent is selected from EDTA or EGTA;

wherein the buffer salt is selected from 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 selected from mannitol, sorbitol, sodium acetate, potassium chloride, sodium phosphate, potassium phosphate, trisodium citrate, or sodium chloride.

16. The pharmaceutical composition for use according to Claim **14** or **15,** is packed in a vial, bottle, pre-filled syringe, or pre-filled auto-injector syringe, in a form of a liquid or lyophilized powder/solid.

17. The conjugate of Claim **1, 2, 3, 4, 5,** or **8,** or in the form of the pharmaceutical composition of Claim **14** or **15,** having in vitro, in vivo or ex vivo cell killing activity.

18. A pharmaceutical composition for use according to Claim **14** or **15,** administered concurrently with a chemotherapeutic agent, a radiation therapy, an immunotherapy agent, an autoimmune disorder agent, an anti-infectious agents or the other conjugates for synergistically treatment or prevention of a cancer, or an autoimmune disease, or an infectious disease.

19. The pharmaceutical composition for use according to Claim **18,** wherein the chemotherapeutic agent is selected from:

(1) a) an alkylating agent: selected from 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 and its synthetic analogues, KW-2189, CBI-TMI, or CBI dimers; benzodiazepine dimers or pyrrolobenzodiazepine (PBD) dimers, tomaymycin dimers, indolinobenzodiazepine dimers, imidazobenzothiadiazepine dimers, or oxazolidinobenzodiazepine dimers; Nitrosoureas: comprising carmustine, lomustine, chlorozotocin, fotemustine, nimustine, 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 methylamelamines including altretamine, triethylenemelamine, trietylenephosphoramide, triethylenethiophosphoramide and trimethylolomelamine];

b) A plant alkaloid: selected from the group consisting of 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, cephalostatins; pancratistatin; a sarcodictyin; spongistatin;

c) A DNA Topoisomerase Inhibitor: selected from the groups of Epipodophyllins: comprising 9-aminocamptothecin, camptothecin, crisnatol, daunomycin, etoposide, etoposide phosphate, irinotecan, mitoxantrone, novantrone, retinoic acids (or retinols), teniposide, topotecan, 9-nitrocamptothecin or RFS 2000; and mitomycins;

d) An antimetabolite: selected from the group consisting of {[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 analogs: Uracil analogs: (including ancitabine, azacitidine, 6-azauridine, capecitabine, carmofur, cytarabine, dideoxyuridine, doxifluridine, enocitabine, 5-Fluorouracil, floxuridine, ratitrexed); Cytosine analogs: (including cytarabine, cytosine arabinoside, fludarabine); Purine analogs: (including azathioprine, fludarabine, mercaptopurine, thiamiprine, thioguanine)]; folic acid replenisher, frolinic acid};

e) A hormonal therapy: selected from 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 and other androgens inhibitors)]; Retinoids/Deltoids: [Vitamin D3 analogs: (including CB 1093, EB 1089 KH 1060, cholecalciferol, ergocalciferol); Photodynamic therapies: (including verteporfin, phthalocyanine, photosensitizer Pc4, demethoxyhypocrellin A); Cytokines: (comprising Interferon-alpha, Interferon-gamma, tumor necrosis factor (TNFs), human proteins containing a TNF domain)]};

f) A kinase inhibitor, selected from the group consisting of BIBW 2992 (anti-EGFR/Erb2), imatinib, gefitinib, pegaptanib, sorafenib, dasatinib, sunitinib, erlotinib, nilotinib, lapatinib, axitinib, pazopanib. vandetanib, E7080 (anti-VEGFR2), mubritinib, ponatinib, bafetinib, bosutinib, cabozantinib, vismodegib, iniparib, ruxolitinib, CYT387, axitinib, tivozanib, sorafenib, bevacizumab, cetuximab, Trastuzumab, Ranibizumab, Panitumumab, ispinesib;

g) A poly (ADP-ribose) polymerase (PARP) inhibitors selected from the group of olaparib, niraparib, iniparib, talazoparib, veliparib, CEP 9722 (Cephalon's), E7016 (Eisai's), BGB-290 (BeiGene's), or 3-aminobenzamide;

h) An antibiotic, selected from the group consisting of an enediyne antibiotic (selected from the group of calicheamicin, calicheamicin γ1, δ1, α1 or β1; dynemicin, including dynemicin A and deoxydynemicin; esperamicin, kedarcidin, C-1027, maduropeptin, or neocarzinostatin chromophore and related chromoprotein enediyne antibiotic chromomophores), aclacinomycins,

actinomycin, authramycin, 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, epirubicin, eribulin, esorubicin, idarubicin, marcellomycin, nitomycins, mycophenolic acid, nogalamycin, olivomycins, peplomycin, potfiromycin, puromycin, quelamycin, rodorubicin, streptonigrin, streptozocin, tubercidin, ubenimex, zinostatin, zorubicin;

i) A polyketide (acetogenin), bullatacin and bullatacinone; gemcitabine, epoxomicins andcarfilzomib, bortezomib, thalidomide, lenalidomide, pomalidomide, tosedostat, zybrestat, PLX4032, STA-9090, Stimuvax, allovectin-7, Xegeva, Provenge, Yervoy, Isoprenylation inhibitors and Lovastatin, Dopaminergic neurotoxins and1-methyl-4-phenylpyridinium ion, Cell cycle inhibitors (including staurosporine), Actinomycins (including Actinomycin D, dactinomycin), amanitins, Bleomycins (including 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, Romidepsin, 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, selected from the group of aminoglutethimide, mitotane, trilostane; aceglatone; aldophosphamide glycoside; aminolevulinic acid; amsacrine; arabinoside, bestrabucil; bisantrene; edatraxate; defofamine; demecolcine; 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, antisense drugs;

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

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

c) Ansamycins: geldanamycin, herbimycin;

d) Carbapenems: biapenem, doripenem, ertapenem, imipenem, cilastatin, meropenem, 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, cefoxitin, 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, cefuzonam, cephamycin (including cefoxitin, cefotetan, cefmetazole), oxacephem (flomoxef, latamoxef);

f) Glycopeptides: bleomycin, vancomycin (including oritavancin, telavancin), teicoplanin (dalbavancin), ramoplanin;

g) Glycylcyclines: tigecycline;

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

i) Lincosamides: clindamycin, lincomycin;

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

k) Macrolides: azithromycin, cethromycin, clarithromycin, dirithromycin, erythromycin, flurithromycin, josamycin, ketolide (telithromycin, cethromycin), midecamycin, miocamycin, oleandomycin, rifamycins (rifampicin, rifampin, rifabutin, rifapentine), rokitamycin, roxithromycin, spectinomycin, spiramycin, tacrolimus (FK506), troleandomycin, telithromycin;

l) Monobactams: aztreonam, tigemonam;

m) Oxazolidinones: linezolid;

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

o) Polypeptides: bacitracin, colistin, polymyxin B;

p) Quinolones: alatrofloxacin, balofloxacin, ciprofloxacin, clinafloxacin, danofloxacin, difloxacin, enoxacin, enrofloxacin, floxin, garenoxacin, gatifloxacin, gemifloxacin, grepafloxacin, kano trovafloxacin, levofloxacin, lomefloxacin, marbofloxacin, moxifloxacin, nadifloxacin, norfloxacin, orbifloxacin, ofloxacin, pefloxacin, trovafloxacin, grepafloxacin, sitafloxacin, sparfloxacin, temafloxacin, tosufloxacin, trovafloxacin;

q) Streptogramins: pristinamycin, quinupristin/dalfopristin;

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

s) Steroid antibacterials: selected from fusidic acid;

t) Tetracyclines: doxycycline, chlortetracycline, clomocycline, demeclocycline, lymecycline, meclocycline, metacycline, minocycline, oxytetracycline, penimepicycline, rolitetracycline, tetracycline, glycylcyclines (including tigecycline);

u) Other antibiotics: selected from the group consisting of annonacin, arsphenamine, bactoprenol inhibitors (Bacitracin), DADAL/AR inhibitors (cycloserine), dictyostatin, discodermolide, eleutherobin, 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, uvaricin;

(4) Anti-viral drugs comprising:

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

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

c) Maturation inhibitors: bevirimat, vivecon;

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

e) Nucleosides & nucleotides: abacavir, aciclovir, adefovir, amdoxovir, apricitabine, brivudine, cidofovir, clevudine, dexelvucitabine, didanosine (ddI), elvucitabine, emtricitabine (FTC), entecavir, famciclovir, fluorouracil (5-FU), 3'-fluoro-substituted 2', 3'-dideoxynucleoside analogues (including the group consisting of3'-fluoro-2',3'-dideoxythymidine (FLT) and 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), zidovudine (AZT);

f) Non-nucleosides: amantadine, ateviridine, capravirine, diarylpyrimidines (etravirine, rilpivirine)**,** delavirdine, docosanol, emivirine, efavirenz, foscarnet (phosphonoformic acid),

imiquimod, interferon alfa, loviride, lodenosine, methisazone, nevirapine, NOV-205, peginterferon alfa, podophyllotoxin, rifampicin, rimantadine, resiquimod (R-848), tromantadine;

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

h) Other types of 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, seliciclib;

(5) The 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.

20. The pharmaceutical composition for use according to claim **18** or **19**, wherein the synergistic agents are selected from one or several of the following drugs: Abatacept, abemaciclib, Abiraterone acetate, Abraxane, Acetaminophen/hydrocodone, Acalabrutinib, aducanumab, Adalimumab, ADXS31-142, ADXS-HER2, afatinib dimaleate, aldesleukin, alectinib, alemtuzumab, Alitretinoin, ado-trastuzumab emtansine, Amphetamine/ dextroamphetamine, anastrozole, Aripiprazole, anthracyclines, Aripiprazole, Atazanavir, Atezolizumab, Atorvastatin, Avelumab, Axicabtagene ciloleucel, axitinib, belinostat, BCG Live, Bevacizumab, bexarotene, blinatumomab, Bortezomib, bosutinib, brentuximab vedotin, brigatinib, Budesonide, Budesonide/ formoterol, Buprenorphine, 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, daclizumab, dacomotinib, daptomycin, Daratumumab, Darbepoetin alfa, Darunavir, dasatinib, denileukin diftitox, Denosumab, Depakote, Dexlansoprazole, Dexmethylphenidate, Dexamethasone, DigniCap Cooling System, Dinutuximab, Doxycycline, Duloxetine, Duvelisib, durvalumab, elotuzumab, Emtricibine/Rilpivirine/Tenofovir, disoproxil fumarate, Emtricitbine/tenofovir/efavirenz, Enoxaparin, ensartinib, 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, Interferon beta 1a, Interferon beta 1b, Interferon gamma-1a, lapatinib, Ipilimumab, Ipratropium bromide/ salbutamol, Ixazomib, Kanuma, Lanreotide acetate, lenalidomide, lenaliomide, lenvatinib mesylate, letrozole, 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, ofatumumab, 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, Salbutamol, 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, Temozolomide, temsirolimus, Tenofovir/ emtricitabine, tenofovir disoproxil fumarate, Testosterone gel, Thalidomide, TICE BCG, Tiotropium bromide, Tisagenlecleucel, toremifene, trametinib, Trastuzumab, Trabectedin (ecteinascidin 743), trametinib, tremelimumab, Trifluridine/tipiracil, Tretinoin, Uro-BCG, Ustekinumab, Valsartan, veliparib, vandetanib, vemurafenib, venetoclax, vorinostat, ziv-aflibercept, Zostavax, and theirpharmaceutically acceptable salts, carriers, diluents, or excipients thereof, or a combination above thereof.