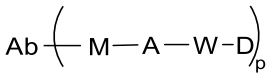
CLAIMS

1. A ligand-drug conjugate as shown in general formula I or a pharmaceutically acceptable salt or solvate thereof,



I

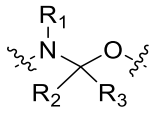
wherein:

Ab is a ligand unit selected from an antibody, an antibody fragment, a targeting protein or an Fc fusion protein;

M is a linker unit connected to Ab;

A is a peptide residue consisting of 2 to 7 amino acids, wherein, optionally, each amino acids is independently substituted by one or more substituents selected from: deuterium, halogens, hydroxyl group, cyano group, amino group, nitro group, alkyl group, substituted alkyl group, alkoxy group, cycloalkyl group, and substituted cycloalkyl group;

W represents an amino methylene oxide structural unit as shown in formula (i):



(i)

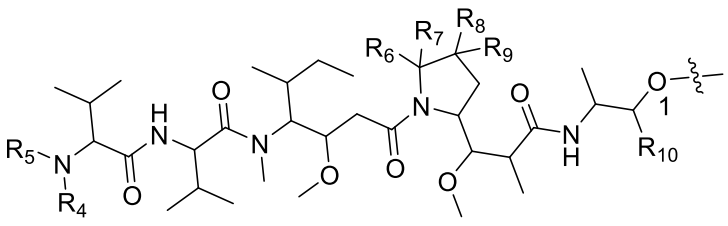
wherein:

the wavy line on the left represents the connection site between the nitrogen atom and A in formula (i), and the wavy line on the right represents the connection site between the oxygen atom in formula (i) and drug D, and the oxygen atom is a common group between D and W;

R_1, R_2 and R_3 are each independently selected from hydrogen, deuterium, alkyl and substituted alkyl;

p is an integer or decimal from 1 to 20; and

D is auristatin having a structure shown in formula D, or isomer, mesomorph, racemate, enantiomer or mixture thereof, or pharmaceutically acceptable salt thereof,



D

wherein:

R_4, R_5 are each independently selected from hydrogen, deuterium, alkyl, and deuterated alkyl,

or R_4, R_5 are linked to form the following structure: $-(CR_{11}R_{12})_n-B-(CR_{13}R_{14})_m-$, wherein

R_{11}, R_{12}, R_{13}, and R_{14} are selected from hydrogen, deuterium, alkyl and deuterated alkyl; B is selected from O, NR_{15}, and $CR_{16}R_{17}$, wherein R_{15}, R_{16}, and R_{17} are selected from hydrogen, deuterium, and alkyl; n and m are each independently an integer from 0-8; the nitrogen atom bonded with R_4 and R_5 forms a ring with $-(CR_{11}R_{12})_n-B-(CR_{(13)}R_{14)m}-$;

R_6, R_7, R_8, R_9 are each independently hydrogen, deuterium, halogen, an azide group, alkyl, or $NR_{18}R_{19}$, or any two of R_6, R_7, R_8, R_9 form a cycloalkyl group together with the atoms to which they are bonded, and the remaining two group are each independently hydrogen, halogen, an azide group, alkyl, and $NR_{18}R_{19}$, wherein R_{18}, R_{19} are each hydrogen or alkyl;

R_{10} is aryl, or heteroaryl, said aryl or heteroaryl being optionally substituted with one or more substituents, said substituents being selected from: hydrogen, a halogen, alkyl, an alkoxy group, an amino group, a nitro group;

the wavy line in formula D represents the connection site between the oxygen atom at position 1 in the structure of D and W, and the oxygen atom is a common group between D and W.

2. The ligand-drug conjugate according to Claim 1 or a pharmaceutically acceptable salt or solvate thereof, wherein Ab is an antibody, an antibody fragment or a protein, wherein the antibody is a murine antibody, a rabbit antibody, a phage display antibody, a yeast display antibody, a chimeric antibody, a humanized antibody, a fully human antibody, an antibody fragment, a bispecific antibody or a multispecific antibody.

3. The ligand-drug conjugate according to Claim 1 or 2, or a pharmaceutically acceptable salt or solvate thereof, wherein the antibody is a monoclonal antibody comprising anti-EGFRvIII antibody, anti-PD-1 antibody, anti-PD-L1 antibody, anti-DLL-3 antibody, anti-PSMA antibody, anti-CD70 antibody, anti-MUC16 antibody, anti-ENPP3 antibody, anti-TDGF1 antibody, anti-ETBR antibody, anti-MSLN antibody, anti-TIM-1 antibody, anti-LRRC15 antibody, anti-LIV-1 antibody, anti-CanAg/AFP antibody, anti-claudin 18.2 antibody, anti-Mesothelin antibody, anti-HER2 (ErbB2) antibody, anti-EGFR antibody, anti-c MET antibody, anti-SLITRK6 antibody, anti-KIT/CD117 antibody, anti-STEAP1 antibody, anti-SLAMF7/CS1 antibody, anti-NaPi2B/SLC34A2 antibody, anti-GPNMB antibody, anti-HER3 (ErbB3) antibody, anti-MUC1/CD227 antibody, anti-AXL antibody, anti-CD166 antibody, anti-B7-H3 (CD276) antibody, anti-PTK7/CCK4 antibody, anti-PRLR antibody, anti-EFNA4 antibody, anti-5T4 antibody, anti-NOTCH3 antibody, anti-Nectin 4 antibody, anti-Trop2 antibody, anti-CD142 antibody, anti-CA6 antibody, anti-GPR20 antibody, anti-CD174 antibody, anti-CD71 antibody, anti-EphA2 antibody, anti-LYPD3 antibody, anti-FGFR2 antibody, anti-FGFR3 antibody, anti-FRα antibody, anti-CEACAMs antibody, anti-GCC antibody, anti-Integrin Av antibody, anti-CAIX antibody, anti-P-cadherin antibody, anti-GD3 antibody, anti-Cadherin 6 antibody, anti-LAMP1 antibody, anti-FLT3 antibody, anti-BCMA antibody, anti-CD79b antibody, anti-CD19 antibody, anti-CD33 antibody, anti-CD56 antibody, anti-CD74 antibody, anti-CD22 antibody, anti-CD30 antibody, anti-CD37 antibody, anti-CD47 antibody, anti-CD138 antibody, anti-CD352 antibody, anti-CD25 antibody, or anti-CD123 antibody.

4. The ligand-drug conjugate or a pharmaceutically acceptable salt or solvate thereof

according to any one of Claims 1 to 3, wherein,

R_4 and R_5 are each independently selected from hydrogen, a C_1-C_4 alkyl group,

or R_4 and R_5 are connected to form the following structure: -$(CH_2)_2$-B-$(CH_2)_2$-, B is selected from O, NH, and the nitrogen atom bonded to R_4 and R_5 forms a ring with -$(CH_2)_2$-B-$(CH_2)_2$-.

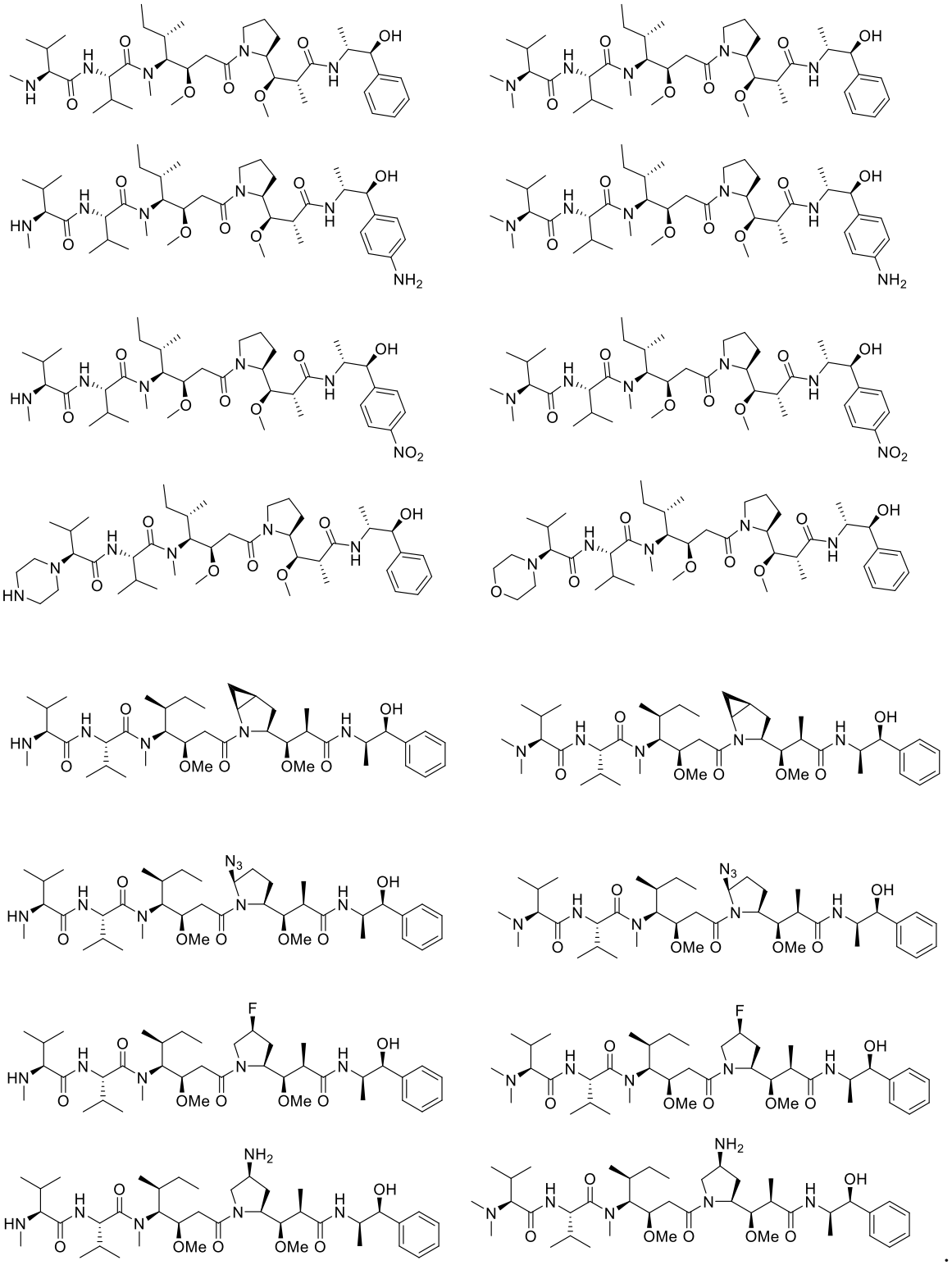
5. The ligand-drug conjugate or a pharmaceutically acceptable salt or solvate thereof according to any one of Claims 1 to 4,

wherein R_6, R_7, R_8, R_9 in formula D are each hydrogen; or, one of R_6, R_7, R_8, R_9 in formula D is selected from halogen, azido, and amino, and the remaining three are each hydrogen; or, any two group among R_6, R_7, R_8, R_9 in formula D together with the atoms to which they are bonded form a cyclopropyl group, and the remaining two group are each independently hydrogen.

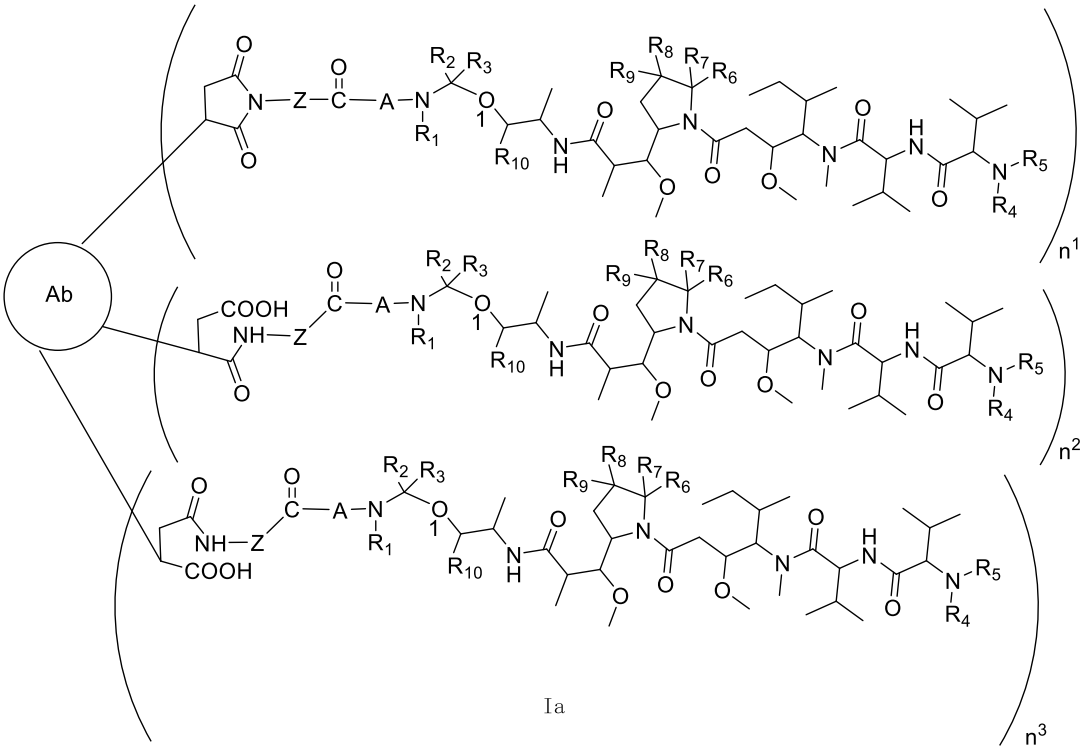
6. The ligand-drug conjugate or a pharmaceutically acceptable salt or solvate thereof according to any one of Claims 1 to 5,

wherein R_{10} in formula D is a phenyl group, and optionally, the phenyl group is substituted by one or more of the substituents; preferably, the substituents are selected from amino and nitro;

preferably, the drug unit D is selected from the following compounds or the isomers, mesomers, racemates, enantiomers or mixtures thereof, or pharmaceutically acceptable salts thereof:



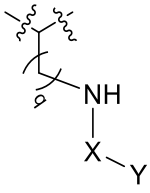
7. The ligand-drug conjugate according to any one of Claims 1 to 6 or a pharmaceutically acceptable salt or solvate thereof, wherein the ligand-drug conjugate has a structure shown in formula Ia



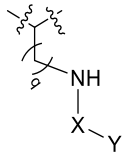
Ia

wherein:

Z is selected from -C_1-C10 alkylene-, -C_3-C8 carbocyclic-, -arylidene-, -C_1-C10 alkylene-arylidene-, -arylidene-C_1-C_{10}-alkylene-, -C_1-C_{10} alkylene-(C_3-C_8 carbocycle)-, -(C_3-C_8 carbocycle)-C_1-C_{10} alkylene-, -3-8 membered heterocycle-, -C_1-C_{10} alkylene-(3-8 membered heterocycle)-, -(3-8 membered heterocycle)-C_1-C_{10} alkylene-, -$(CH_2CH_2O)_r$-, -$(CH_2CH_2O)_r$-CH_2-



or , wherein X is selected from -C_1-C_{10} alkylene-, -C_3-C_8 carbocyclic-, -arylidene-, -C_1-C_{10} alkylene-arylidene-, , -arylidene-C_1-C_{10}-alkylene--C_1-C_{10} alkylene-(C_3-C_8 carbocyclylidene)-, -(C_3-C_8 carbocycle)-C_1-C_{10}-alkylene-, -3-8 meta-heterocyclic-, -C_1-C_{10} alkylene-(3-8 meta-heterocyclic)-, -(3-8 meta-heterocyclic)-C_1-C_{10} alkylene-, -$(CH_2CH_2O)_r$-, -$(CH_2CH_2O)_r$-CH_2; Y is a hydrophilic structure selected from carboxyl, phosphoric acid, polyphosphoric acid, phosphorous acid, sulfonic acid, sulfinic acid or polyethylene glycol (PEG); the heterocycles each independently contain 1 to 3 atoms selected from N, O and S; the -C_1-C_{10} alkylene-, -C_3-C_8 carbocycle- and heterocycles are each independently substituted by one or more substituents selected from deuterium, halogens, hydroxyl group, cyano group, nitro group, amino group, alkyl group, heteroalkyl group, substituted alkyl group, alkoxy group,



carboxyl group or cycloalkyl group; the left wavy line represents the connection site to N on maleimide, and the right wavy line represents the connection site to the carbonyl group; r is an integer from 1 to 10; q is an integer from 1 to 8;

n^1, n^2, and n^3 are independently selected from integers or decimals between 0 and 20, n^1, n^2,

and n^3 are not simultaneously 0, and $n^1 + n^2 + n^3 \leq 20$.

8. The ligand-drug conjugate of any one of Claims 1-7 or a pharmaceutically acceptable salt or solvate thereof,

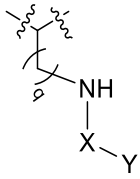
wherein A is a polypeptide residue formed by 2 to 7 amino acids selected from phenylalanine (F), glycine (G), valine (V), lysine (K), alanine (A), citrulline, serine (S), glutamic acid (E), and aspartic acid (D);

preferably, A is a peptide residue formed by 2 to 4 amino acids selected from phenylalanine and glycine;

preferably, A is a tetrapeptide residue consisting of glycine-glycine-phenylalanine-glycine.

9. The ligand-drug conjugate of Claim 7 or 8 or a pharmaceutically acceptable salt or solvate thereof,

Z is selected from -C_1-C_{10} alkylene-, such as -C_4-C_6 alkylene-, such as -C_5 alkylene-;

preferably, Z is , wherein q is selected from an integer between 1 and 8.

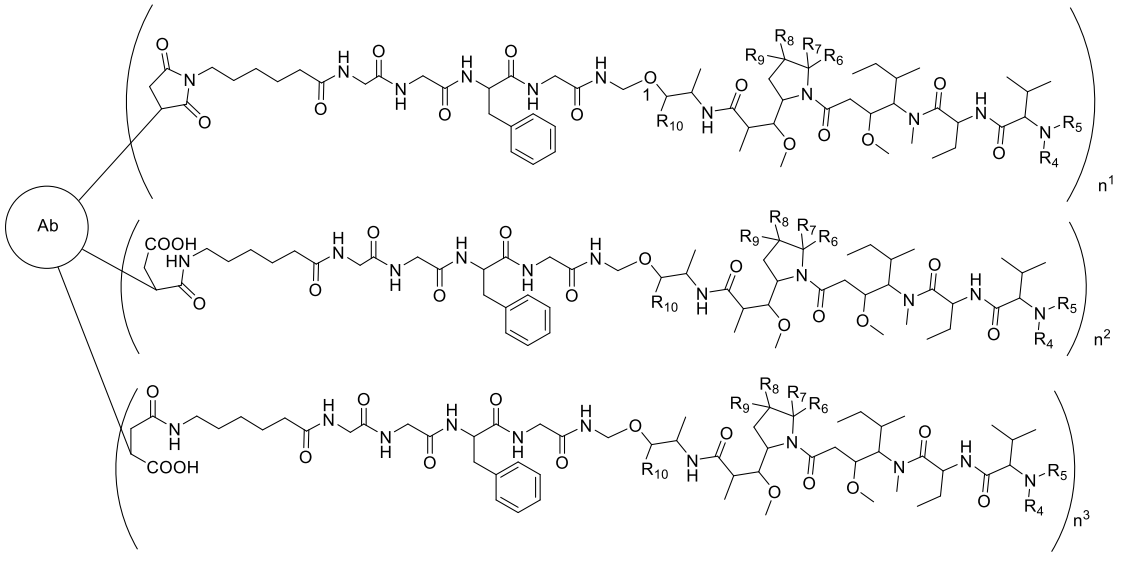
10. The ligand-drug conjugate of any one of Claims 7-9 or a pharmaceutically acceptable salt or solvate thereof,

R_1, R_2 and R_3 are each independently selected from hydrogen, deuterium, alkyl, a haloalkyl group, deuteroalkyl and a hydroxyalkyl group;

preferably, R_1, R_2 and R_3 are both hydrogen atoms or deuterium;

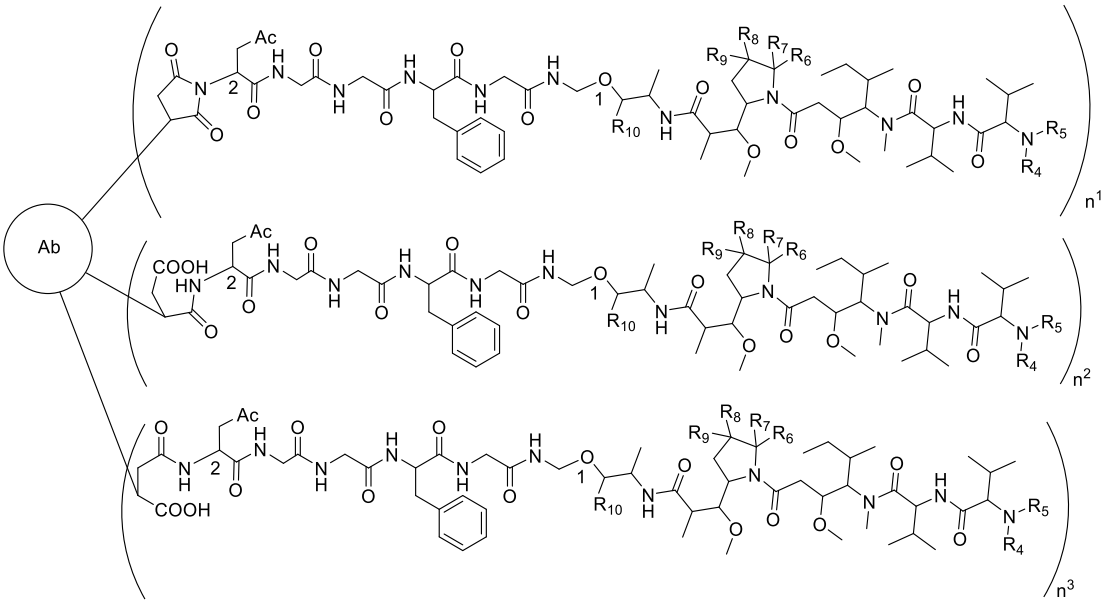
preferably, R_1, R_2 and R_3 are simultaneously hydrogen atoms.

11. The ligand-drug conjugate of any one of Claims 1-10 or a pharmaceutically acceptable salt or solvate thereof, said ligand-drug conjugate having a structure as shown in formula Ib:



Ib

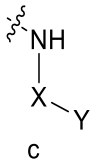
12. The ligand-drug conjugate of any one of Claims 1-10 or a pharmaceutically acceptable salt or solvate thereof, said ligand-drug conjugate having a structure as shown in Formula Ic



Ic

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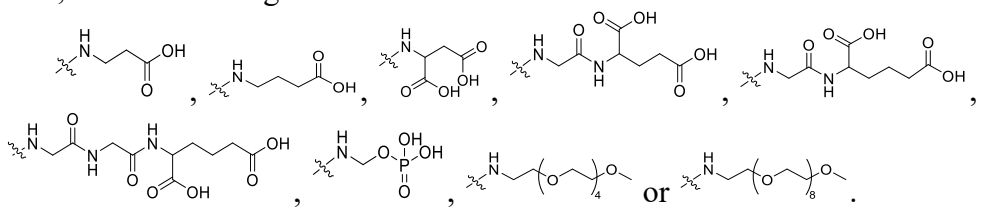
wherein Ac is a hydrophilic structural unit having the structure as shown in formula c:



c

Ac is linked, via an amino group, to 2-position methylene carbon as labeled in formula Ie; X, Y are as defined in Claim 7;

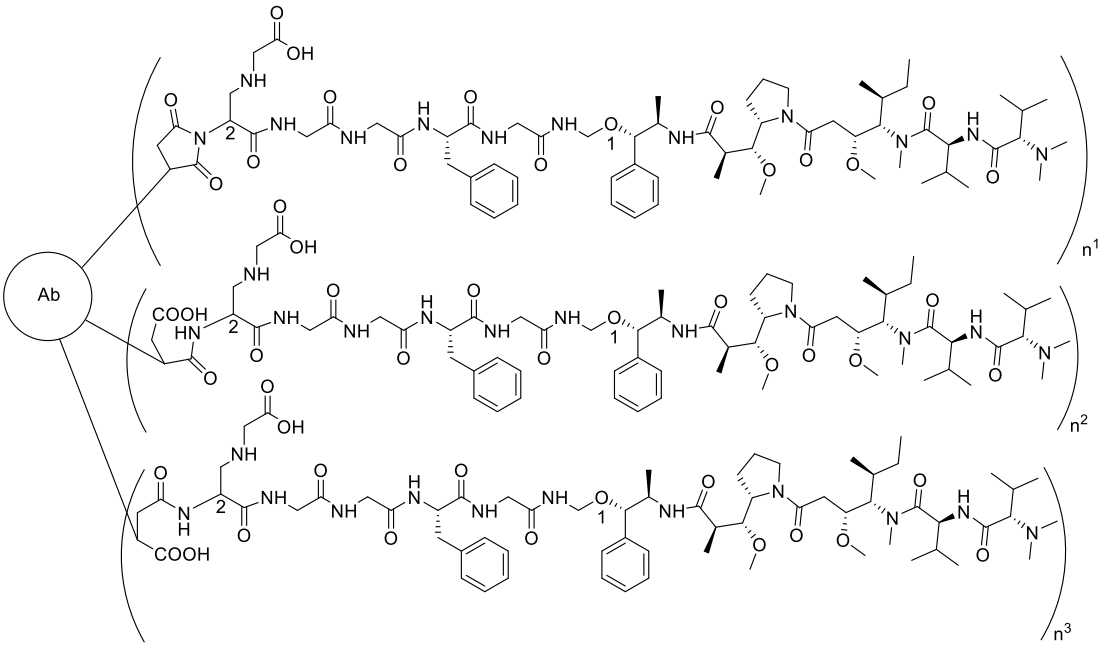
preferably, said Ac is selected from glycine, (D/L) alanine, (D/L) leucine, (D/L) isoleucine, (D/L) valine, (D/L) phenylalanine, (D/L) proline, (D/L) tryptophan, (D/L) serine, (D/L)) tyrosine, (D/Lcysteine, (D/L) cystine, (D/L) arginine, (D/L) histidine, (D/L) (D/L) methionine,asparagine, (D/L) glutamine, (D/L) threonine, (D/L) aspartic acid, or (D/L) glutamic acid, or the following structures:



or

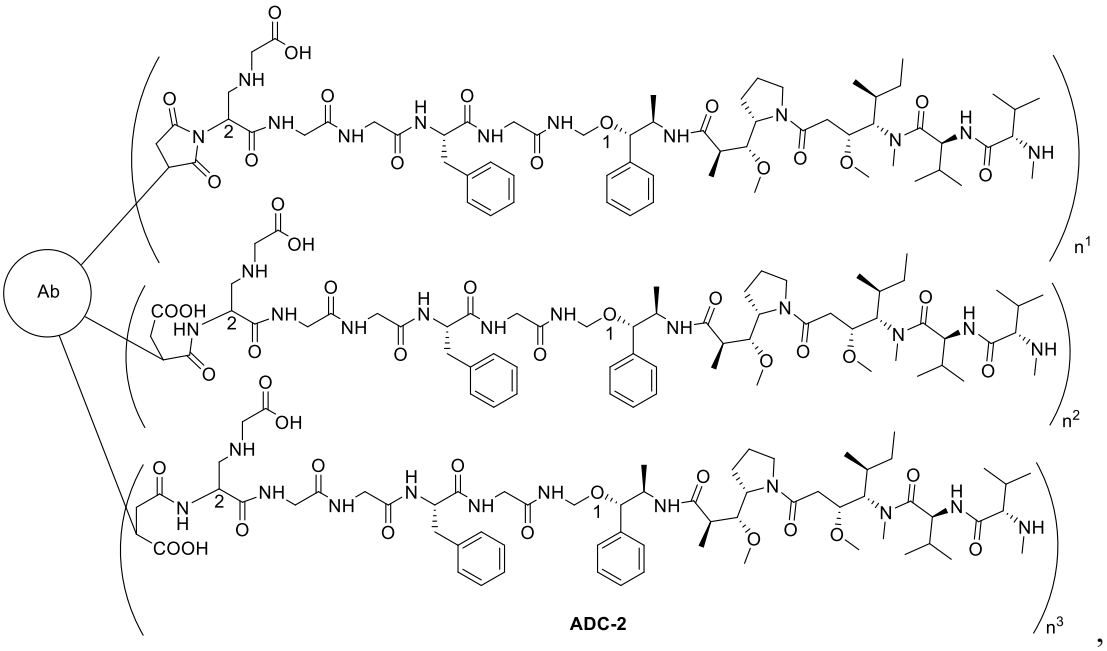
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13. The ligand-drug conjugate of any one of Claims 1-12 or a pharmaceutically acceptable salt or solvate thereof, said ligand-drug conjugate compound being selected from the following structures:



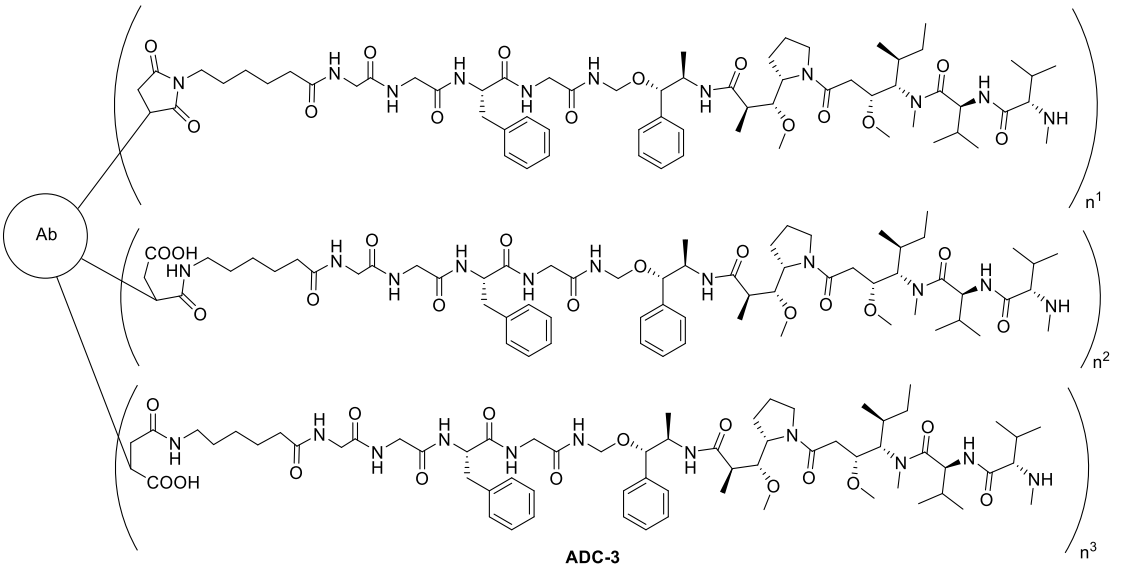
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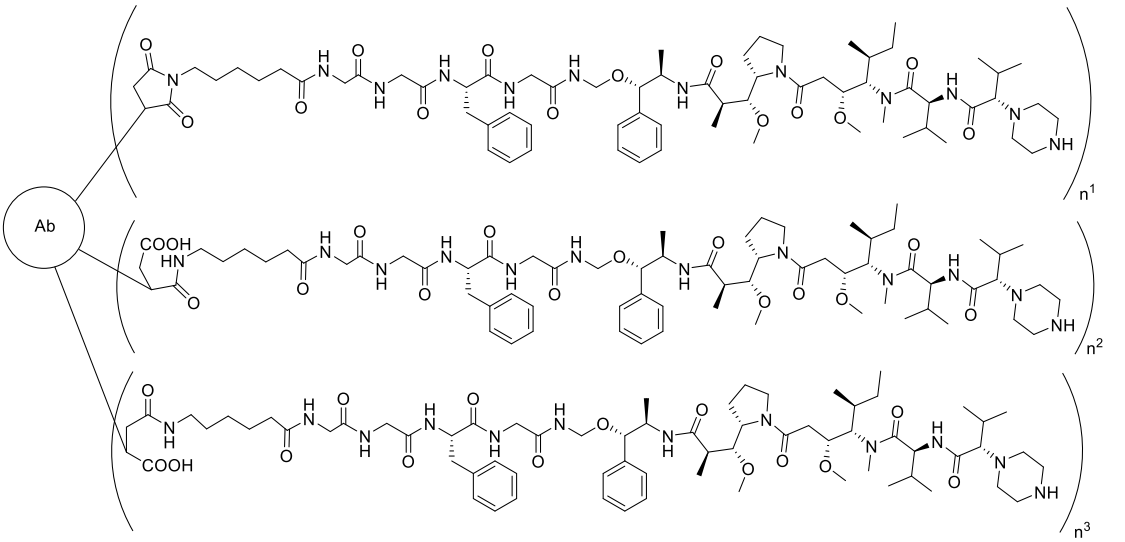


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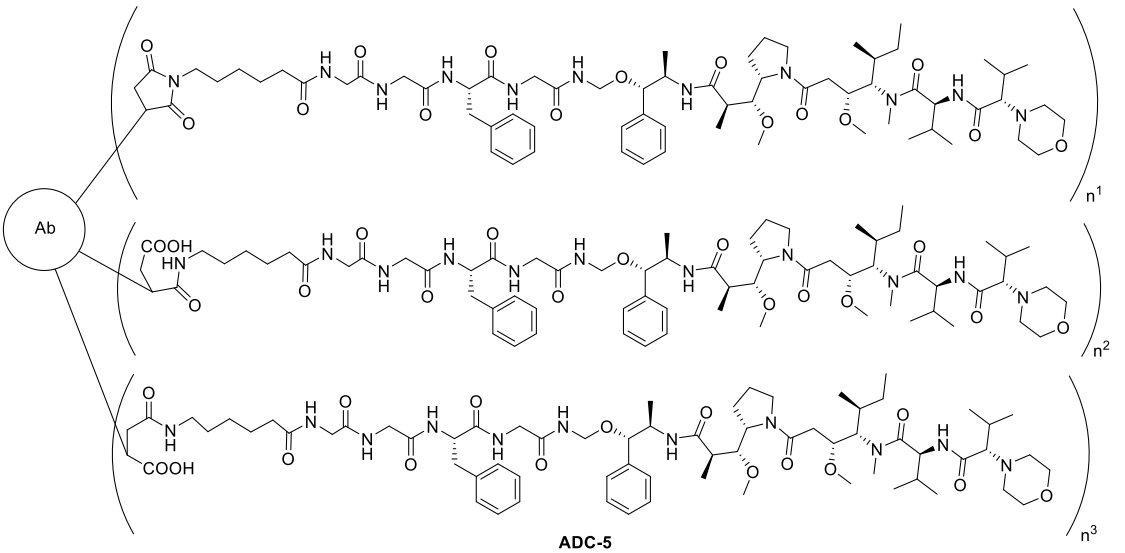
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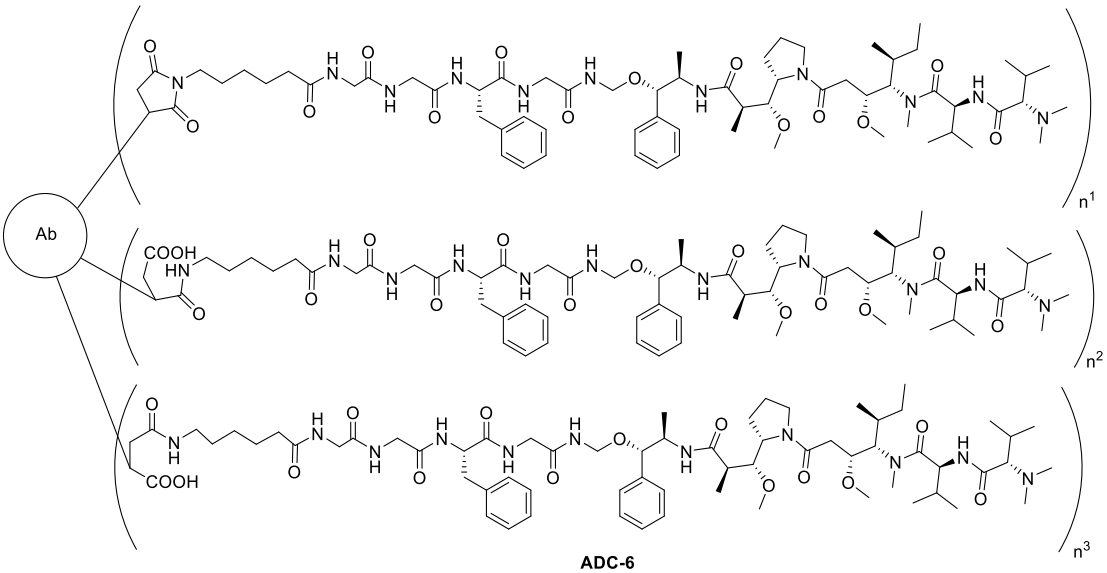
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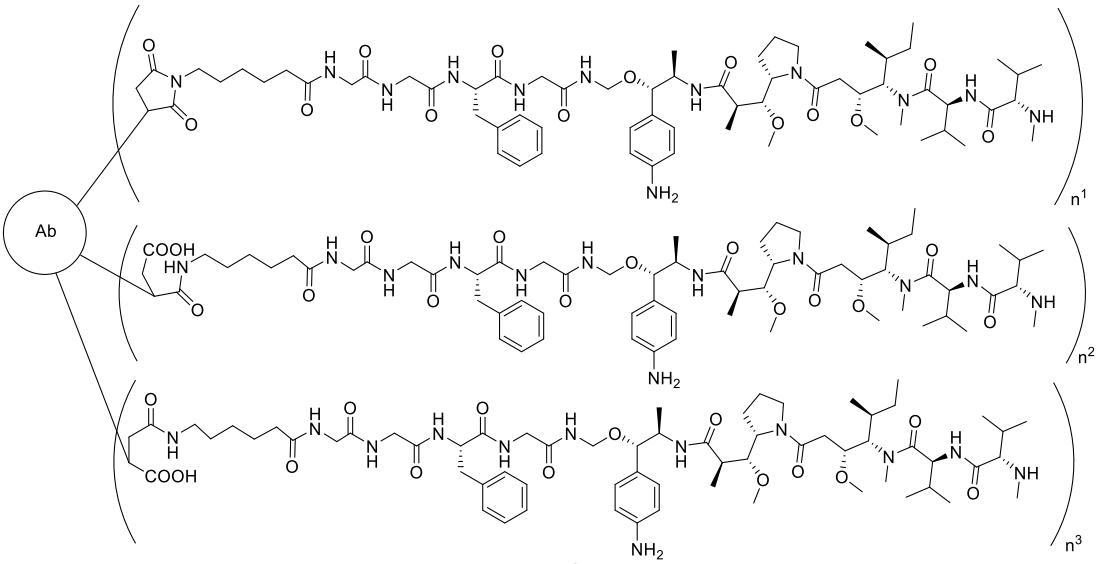


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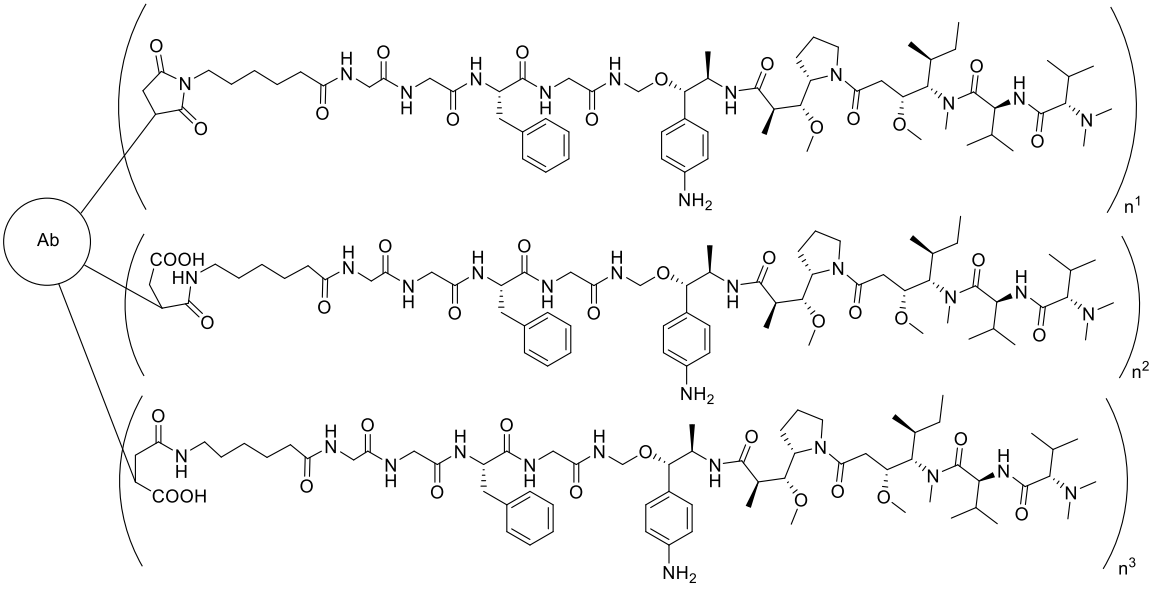
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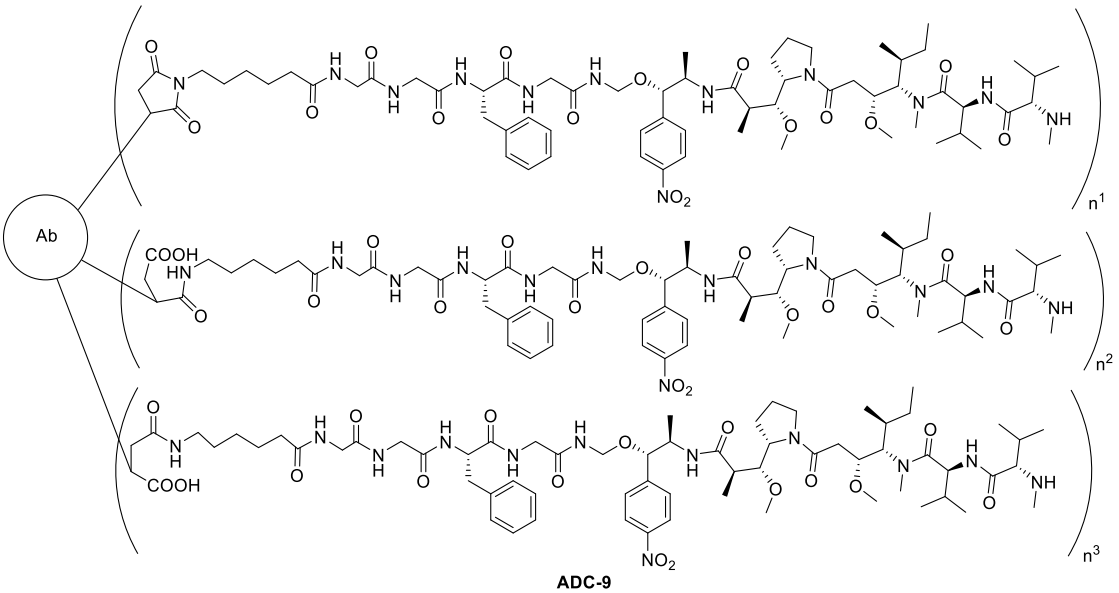
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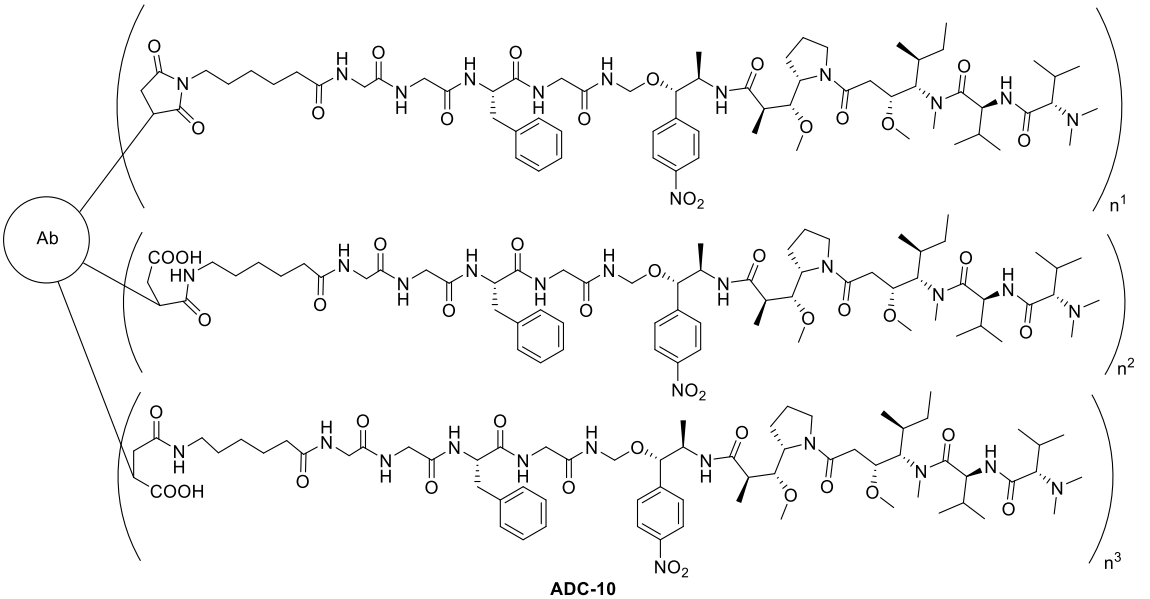
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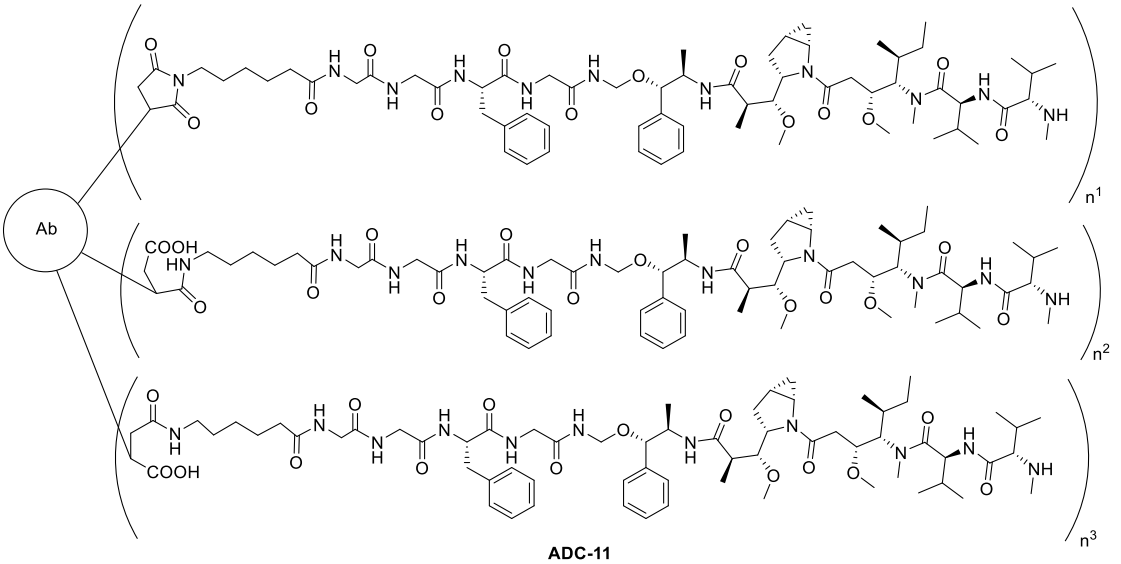
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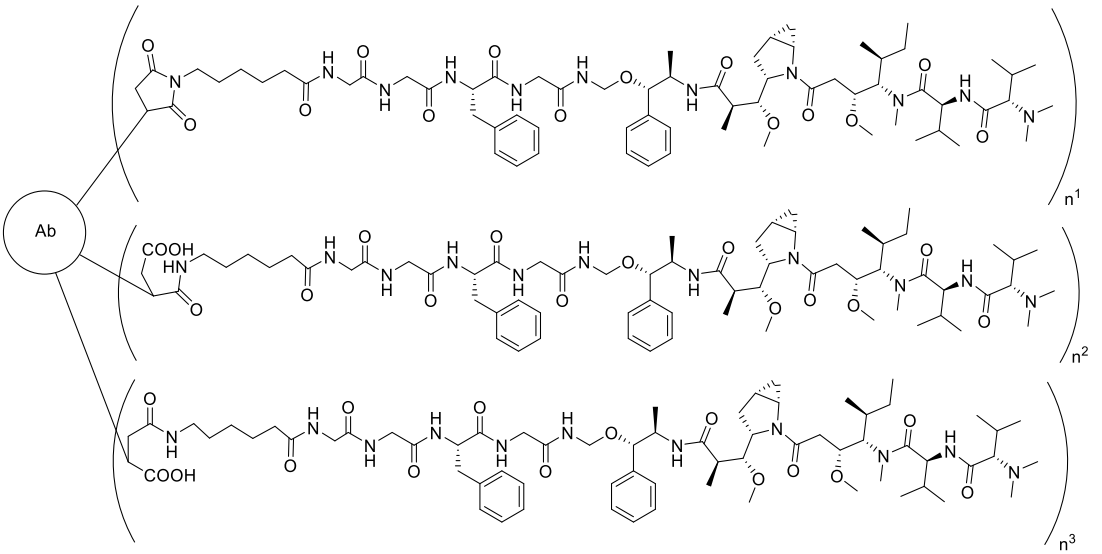
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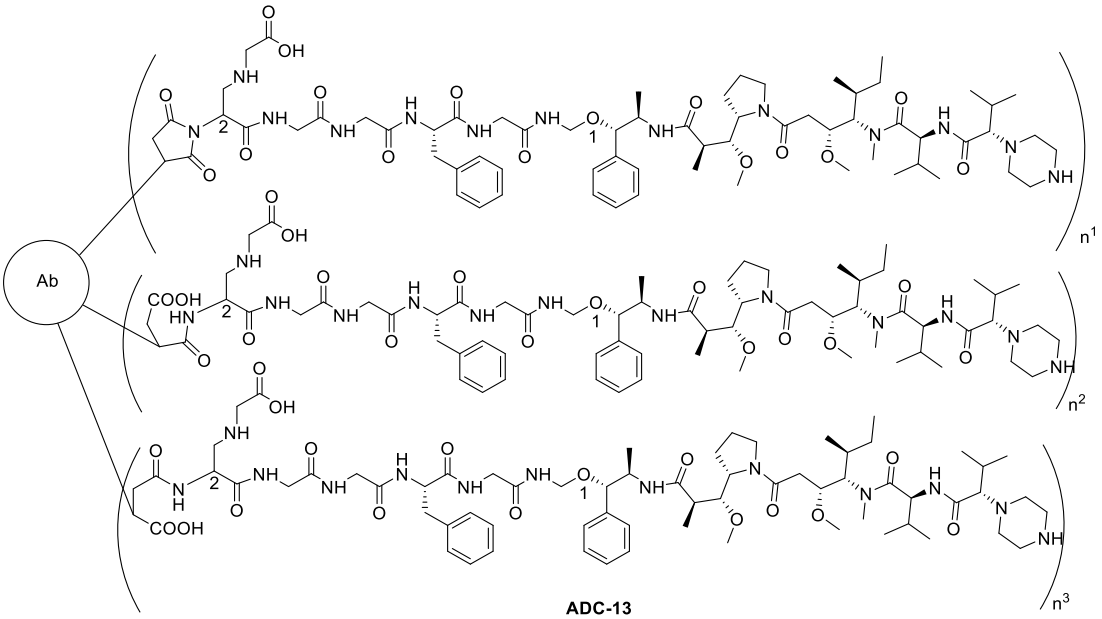


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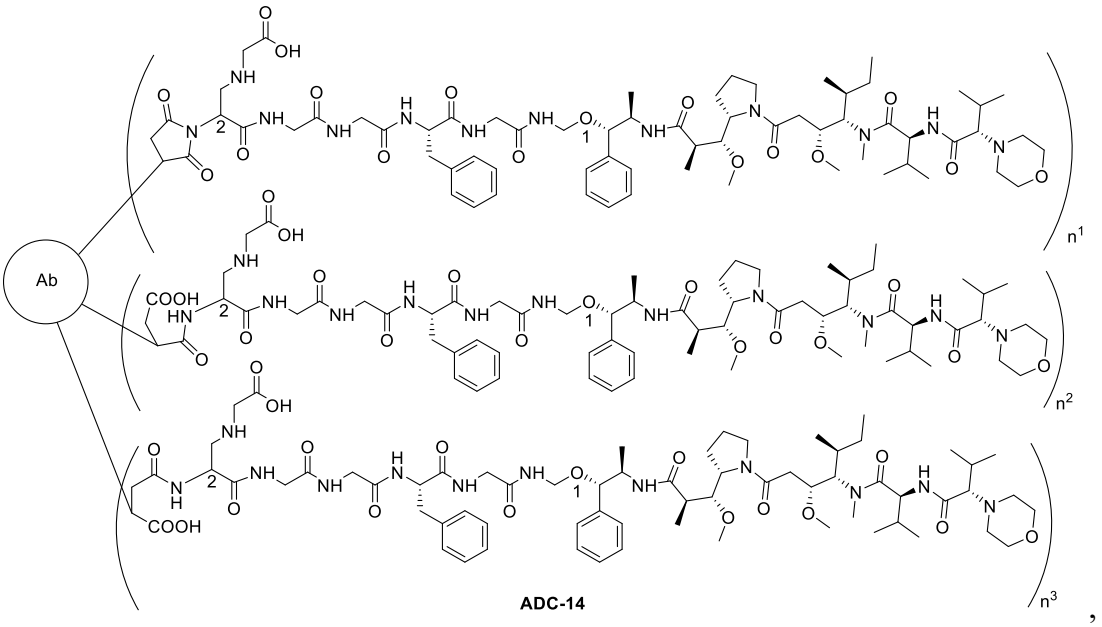
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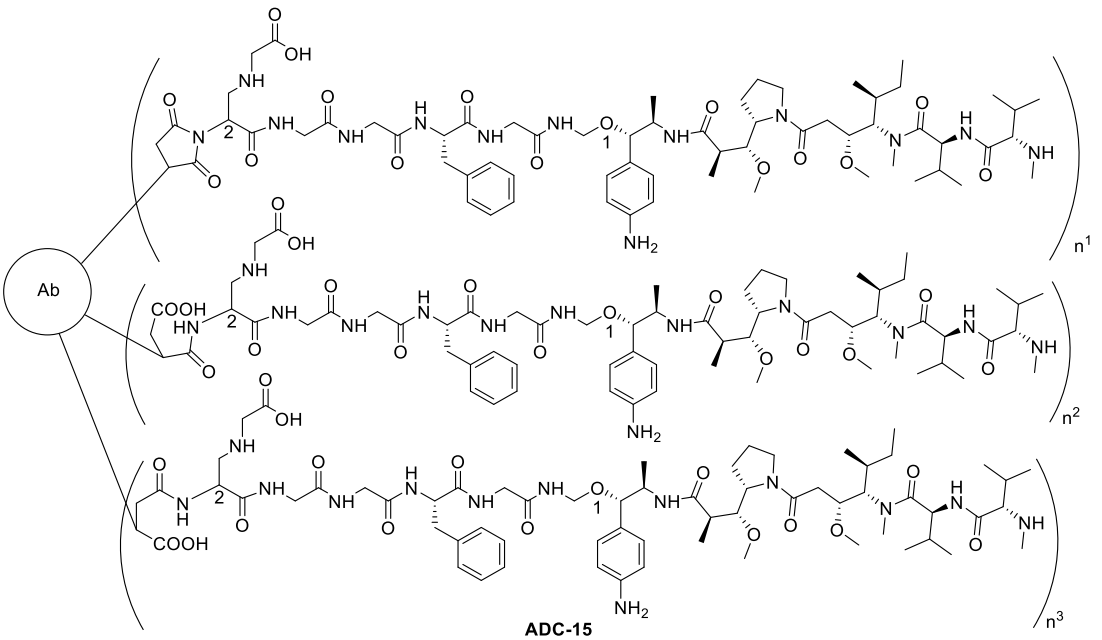
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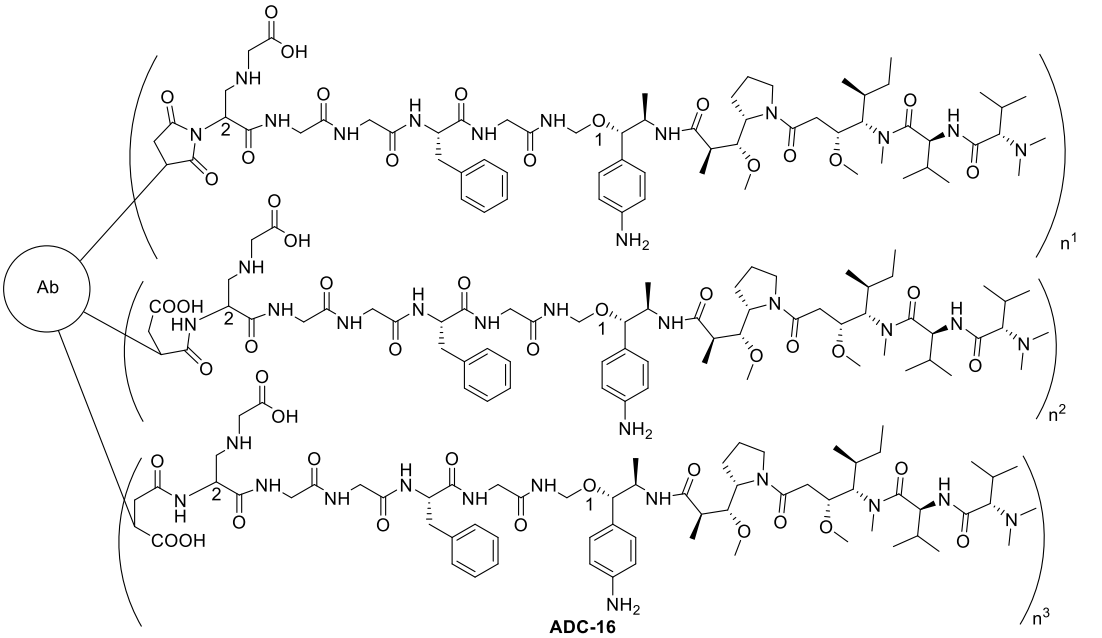
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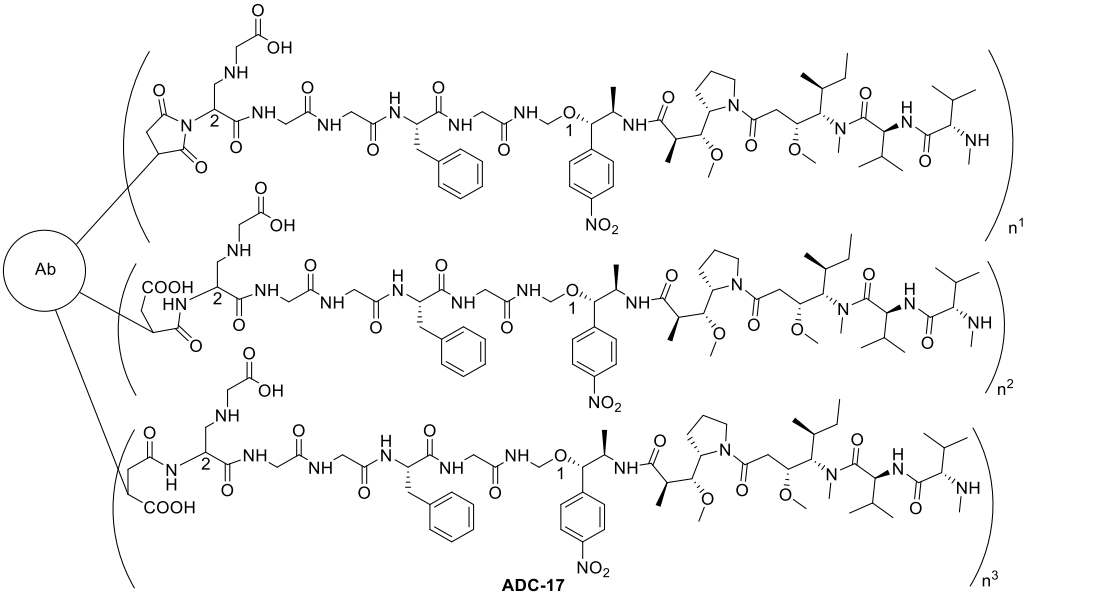
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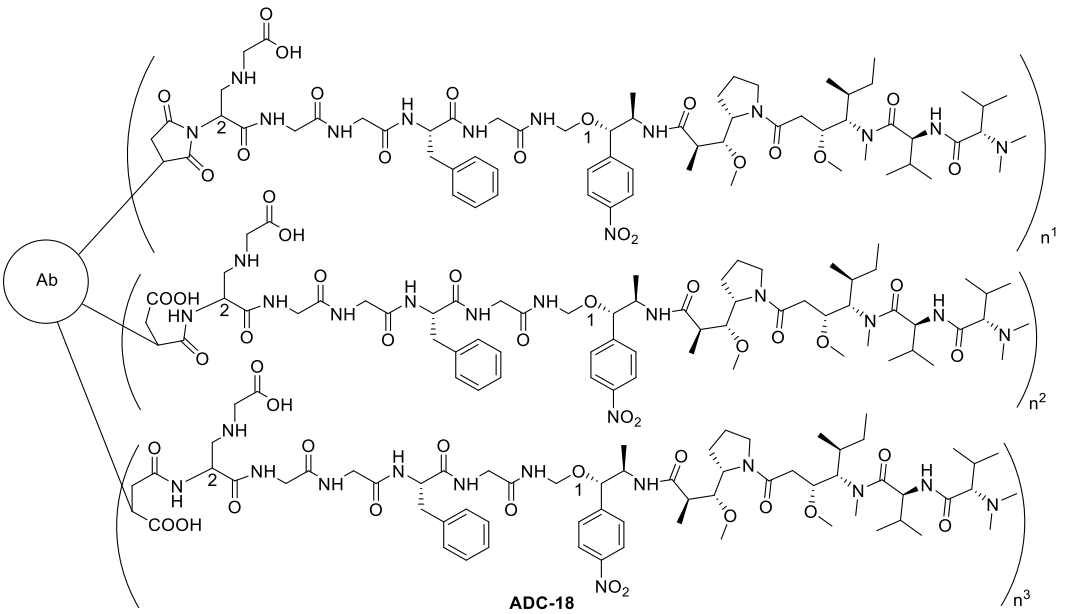
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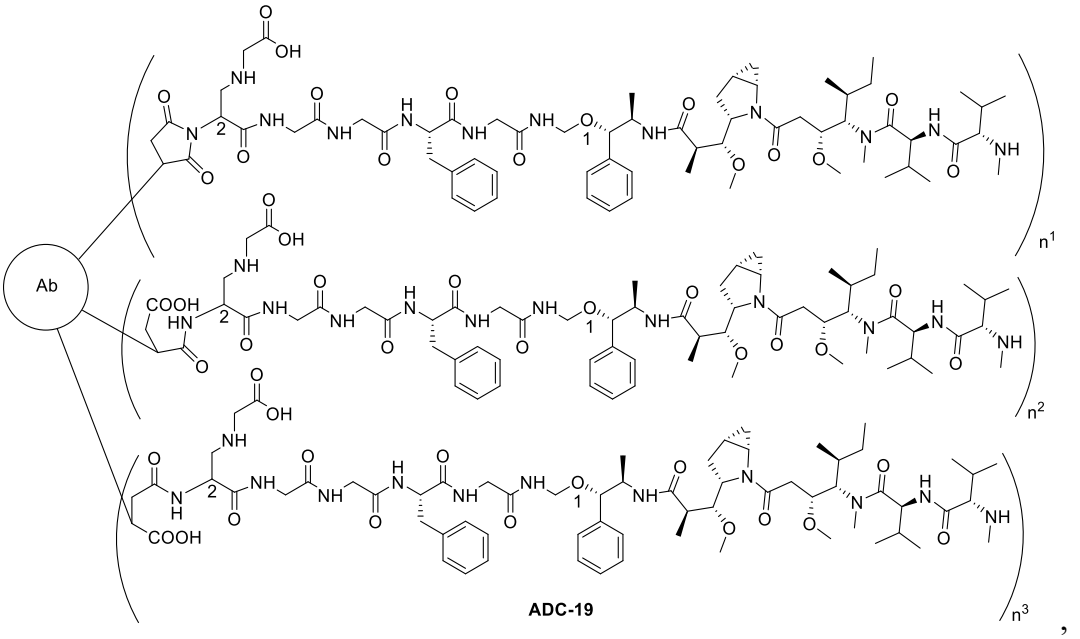
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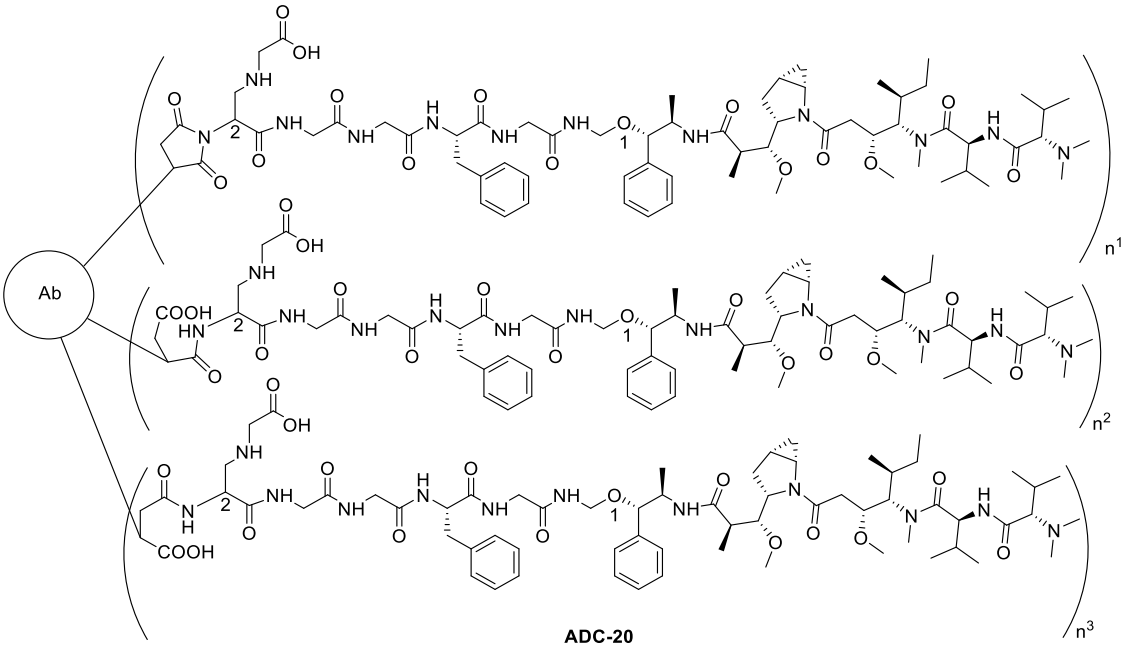
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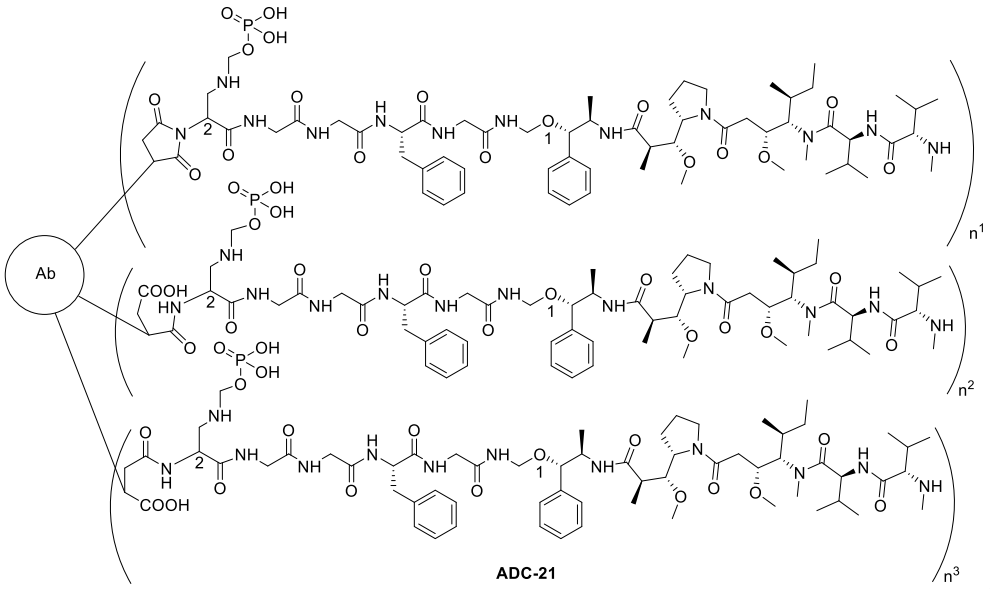
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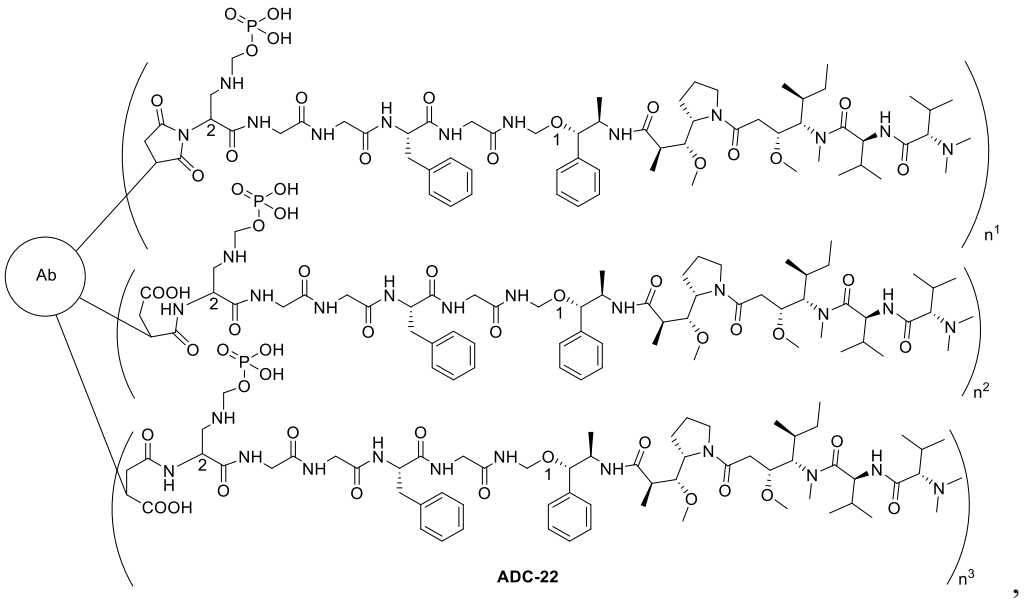
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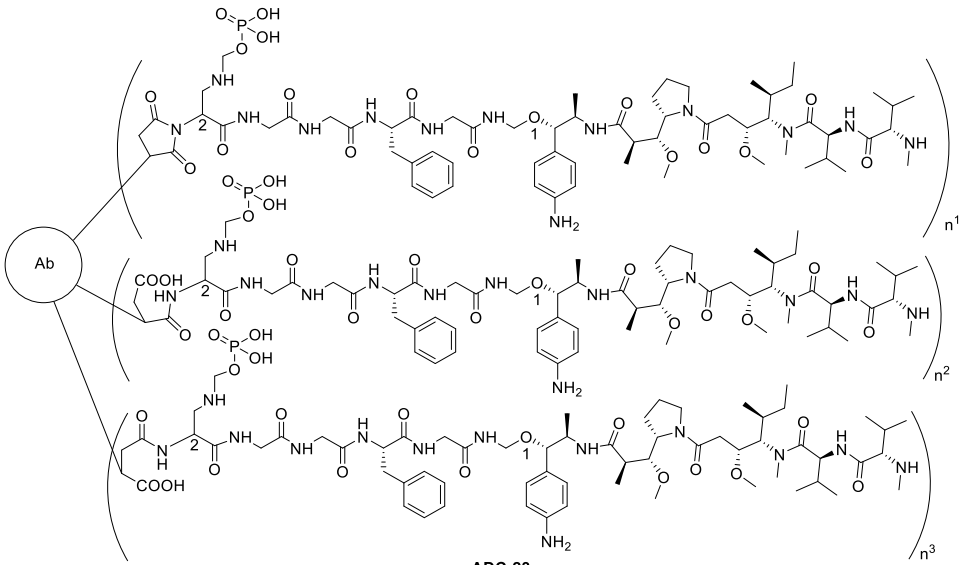
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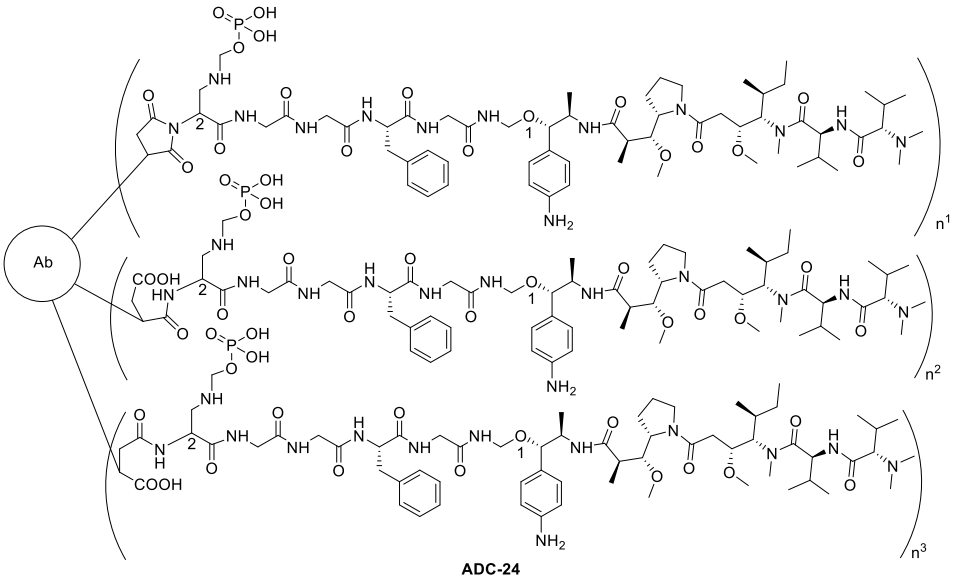
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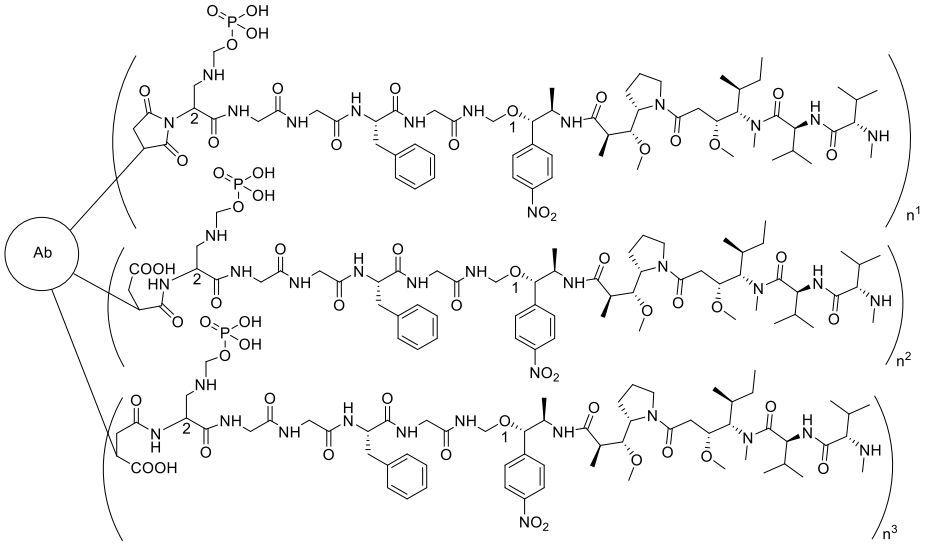
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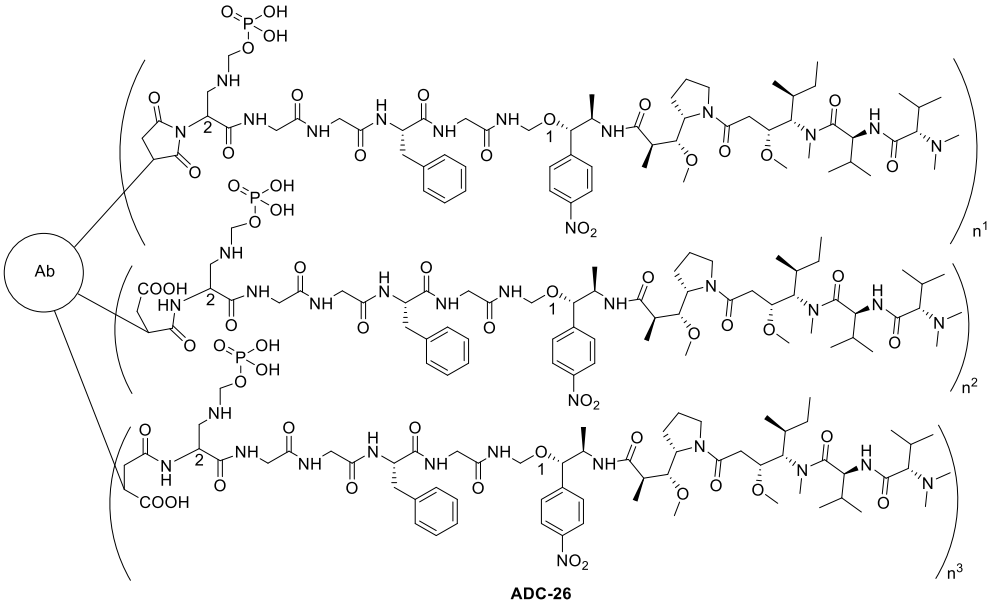
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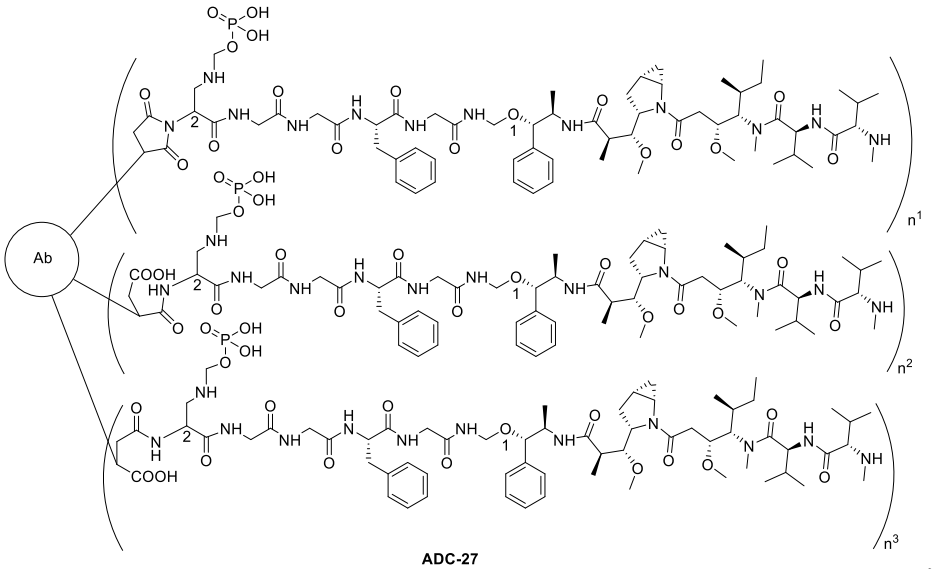
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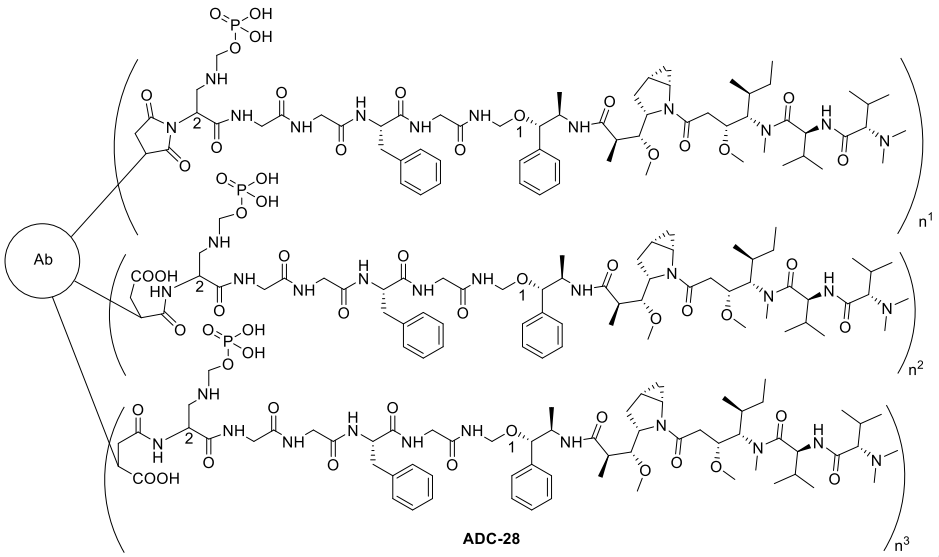
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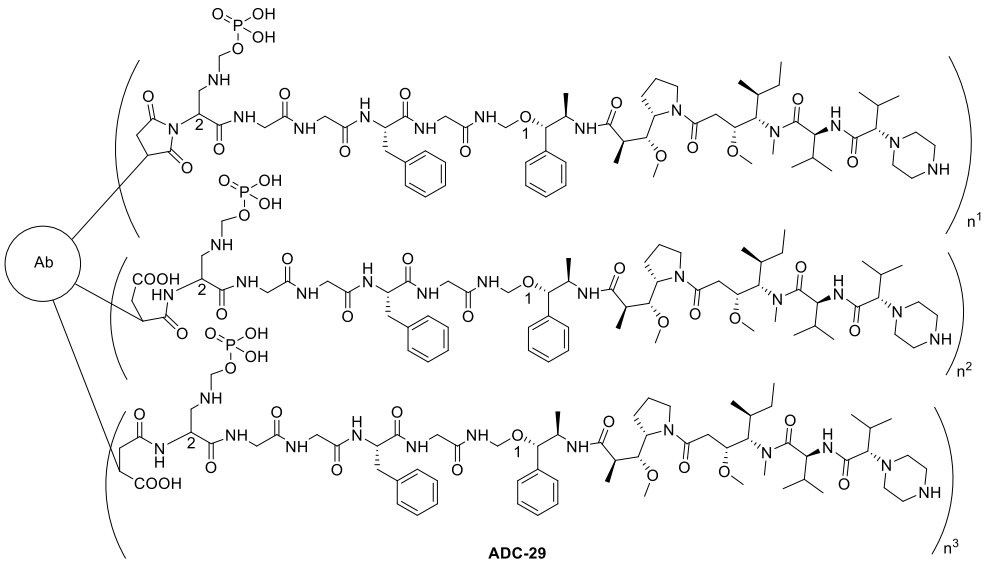
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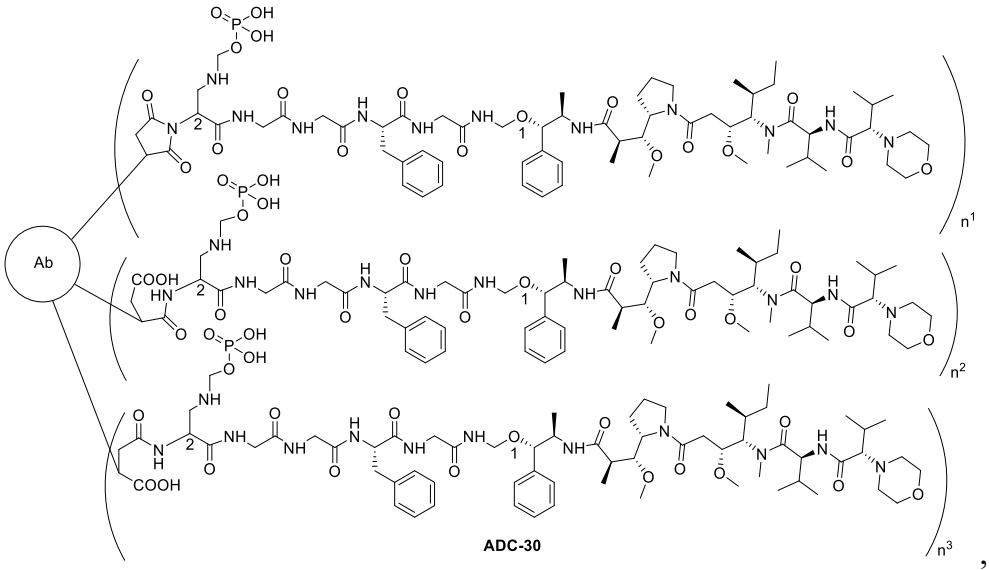
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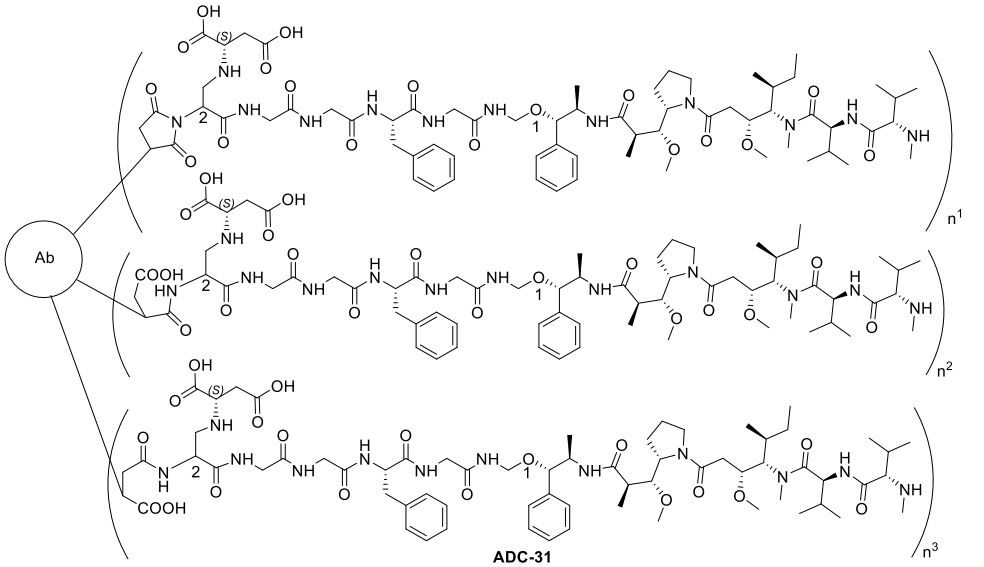
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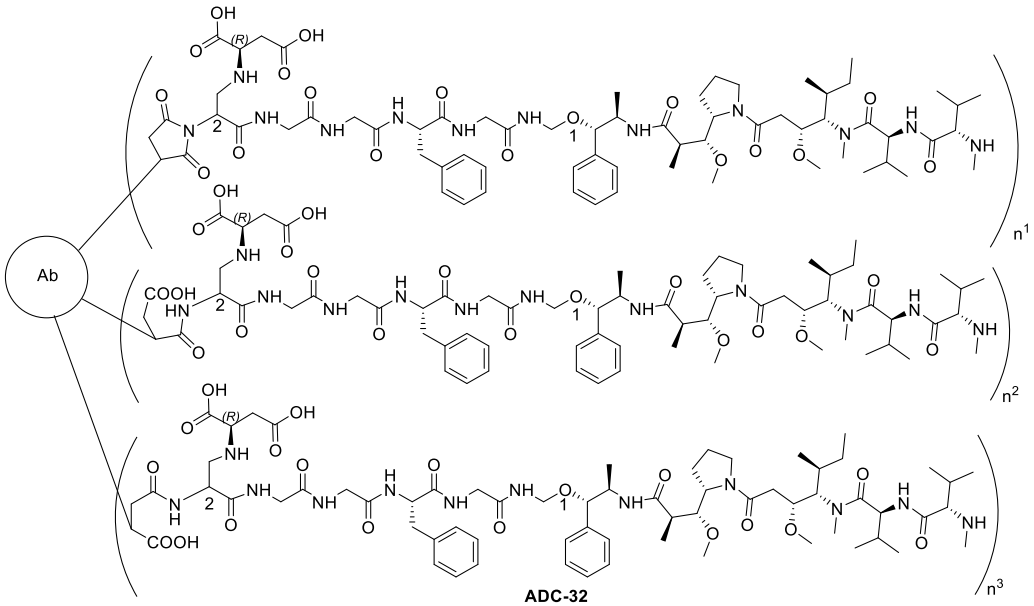
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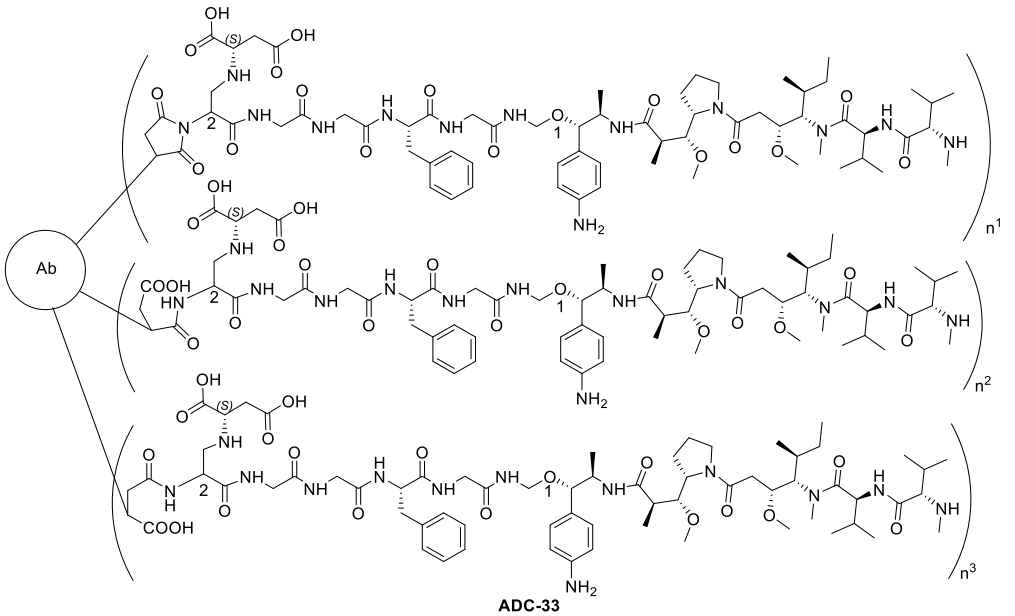
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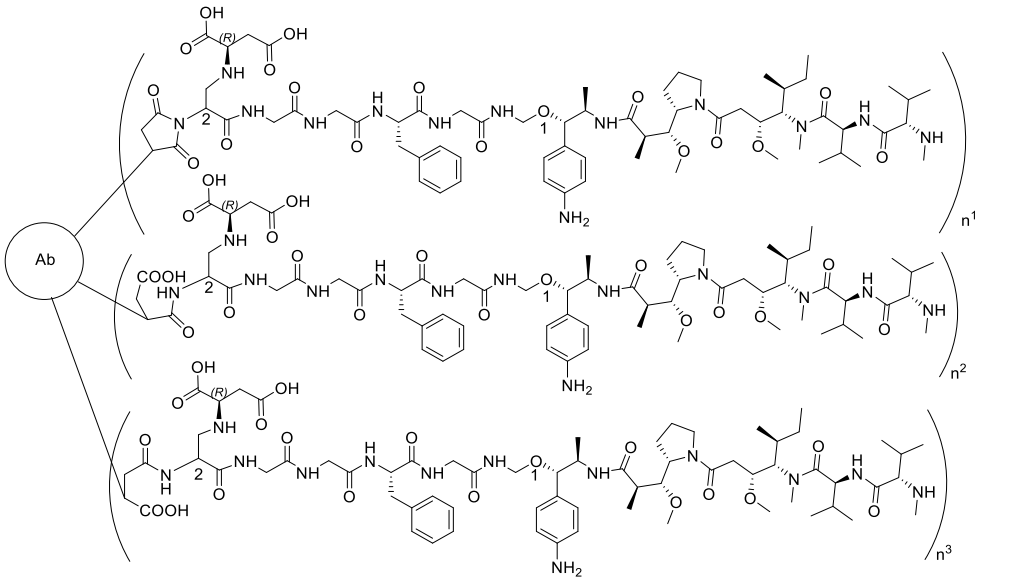


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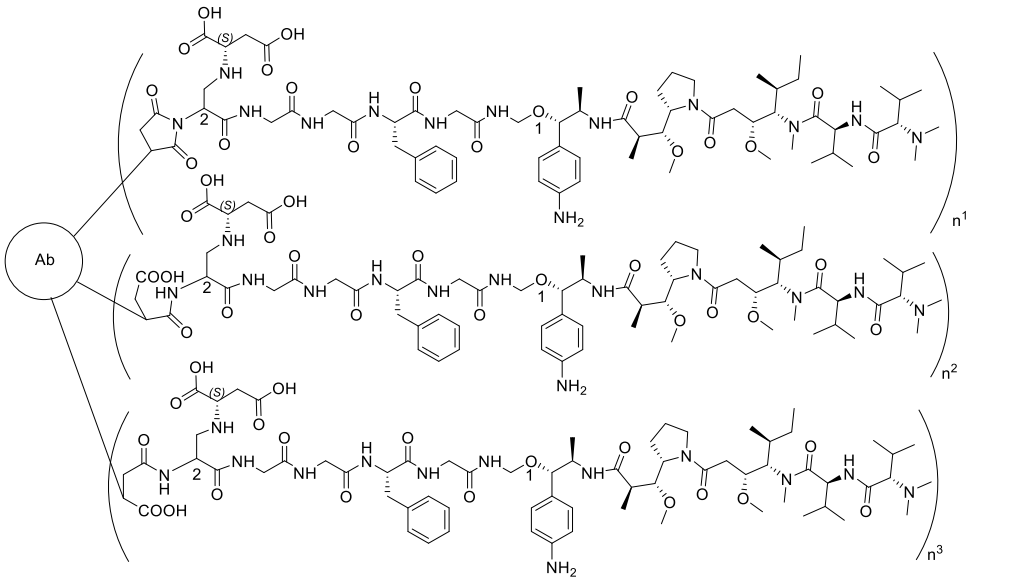
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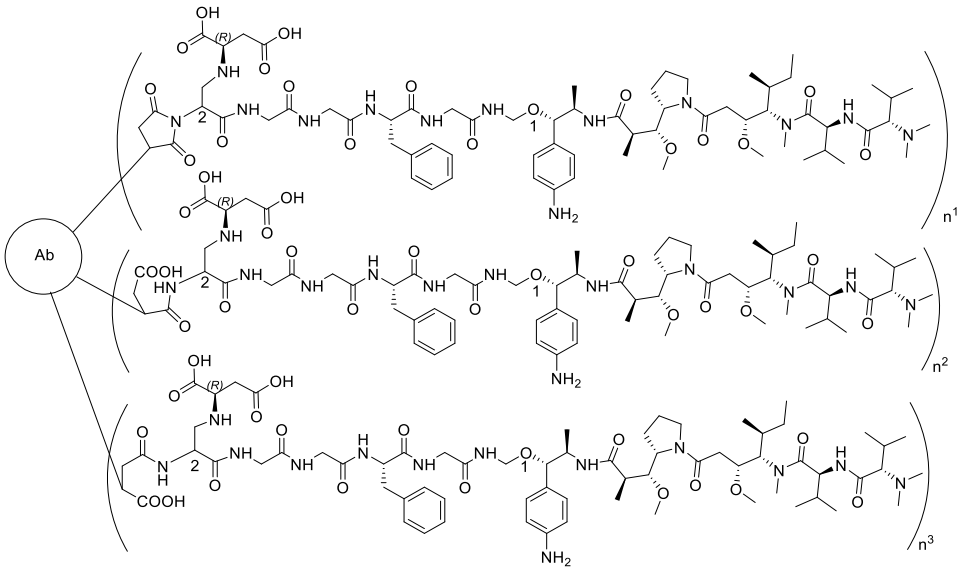
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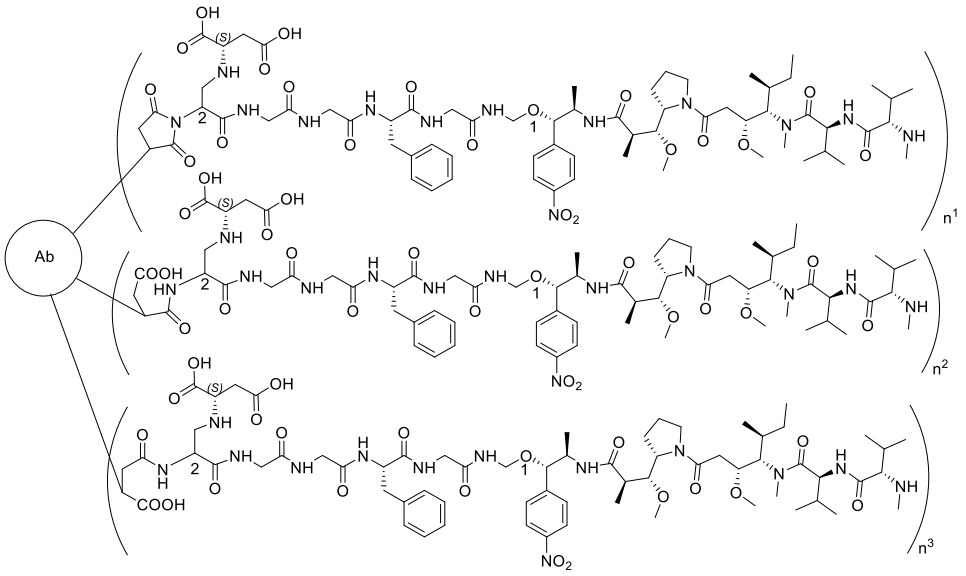
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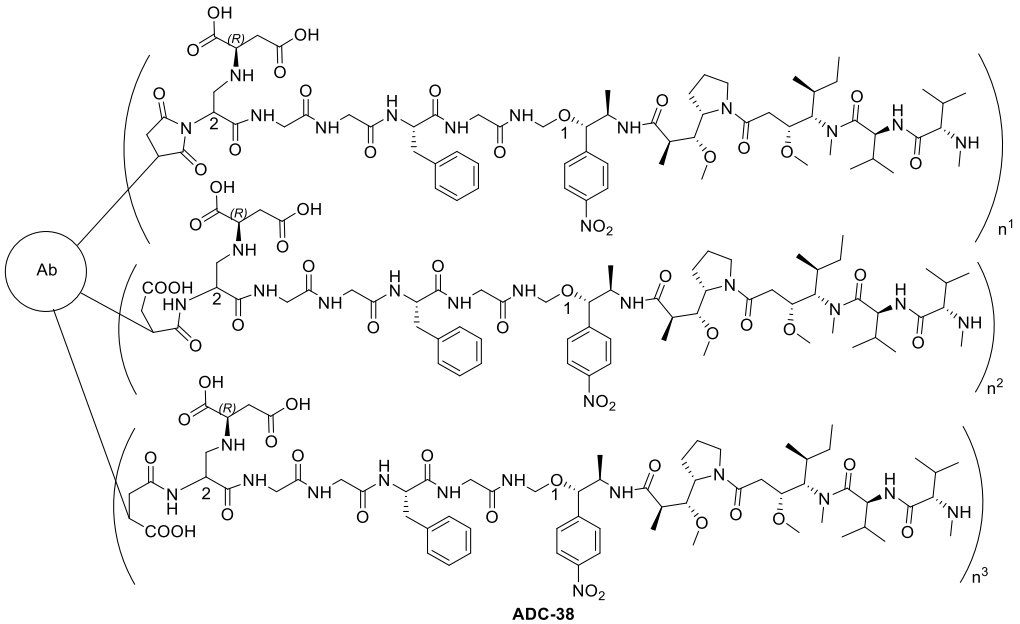
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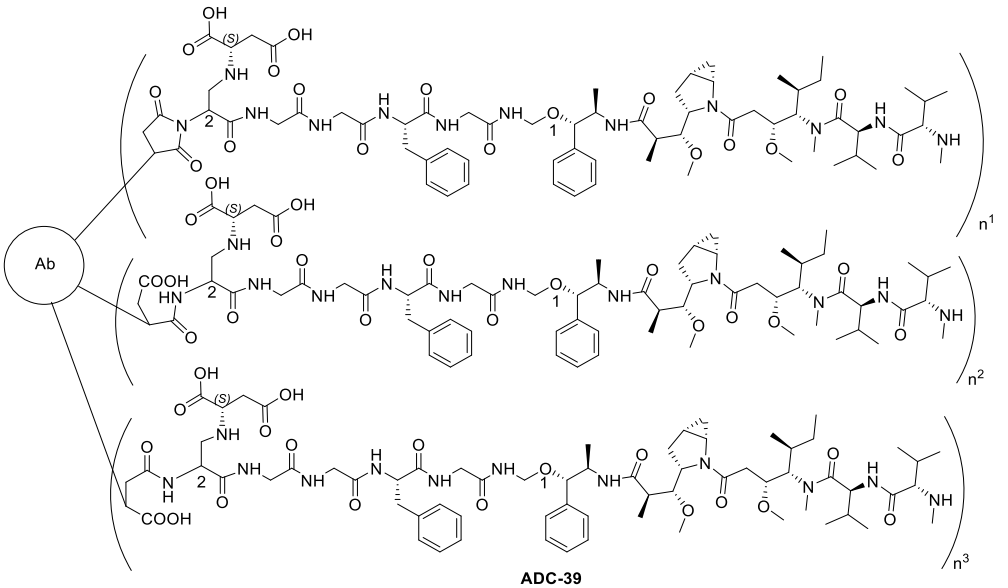
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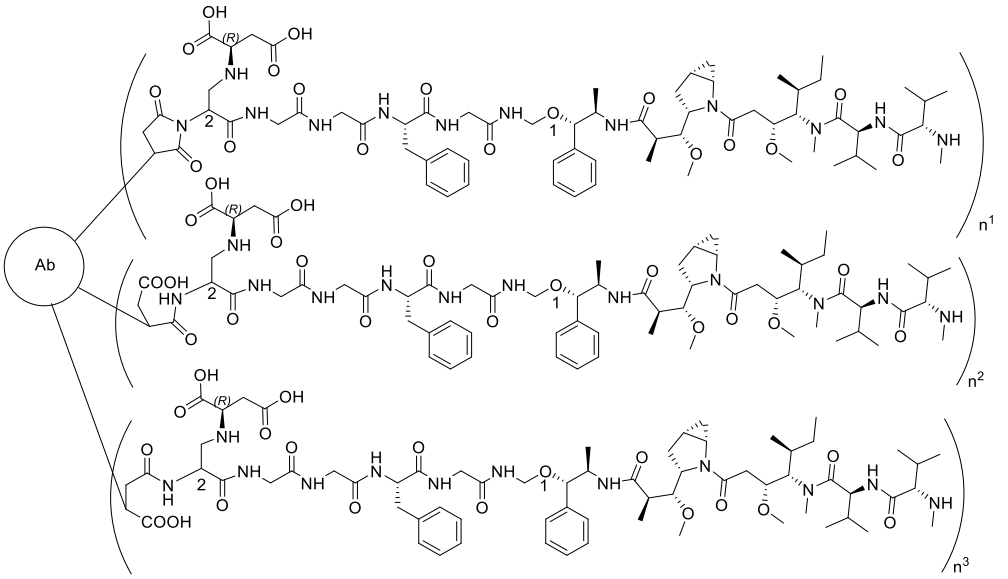
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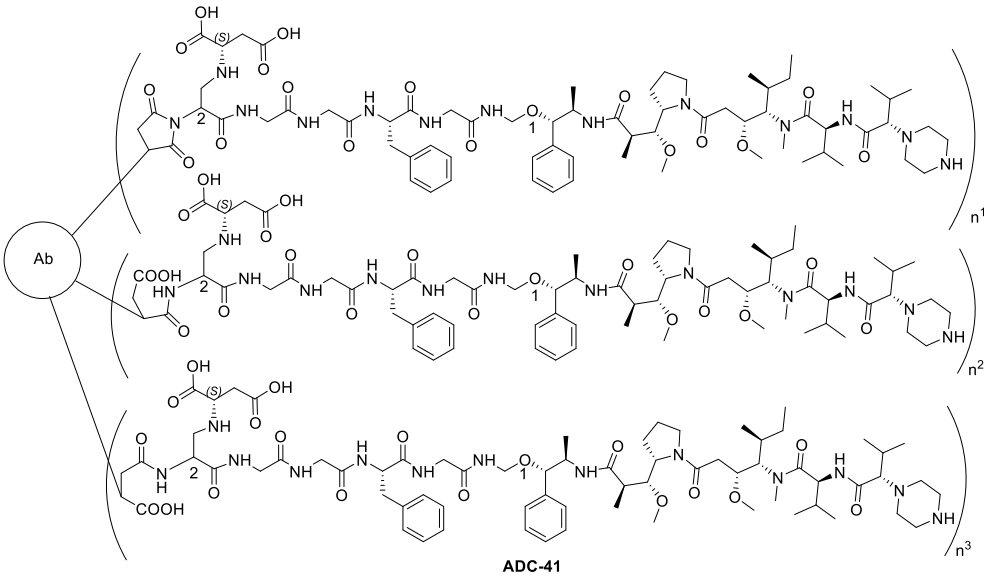
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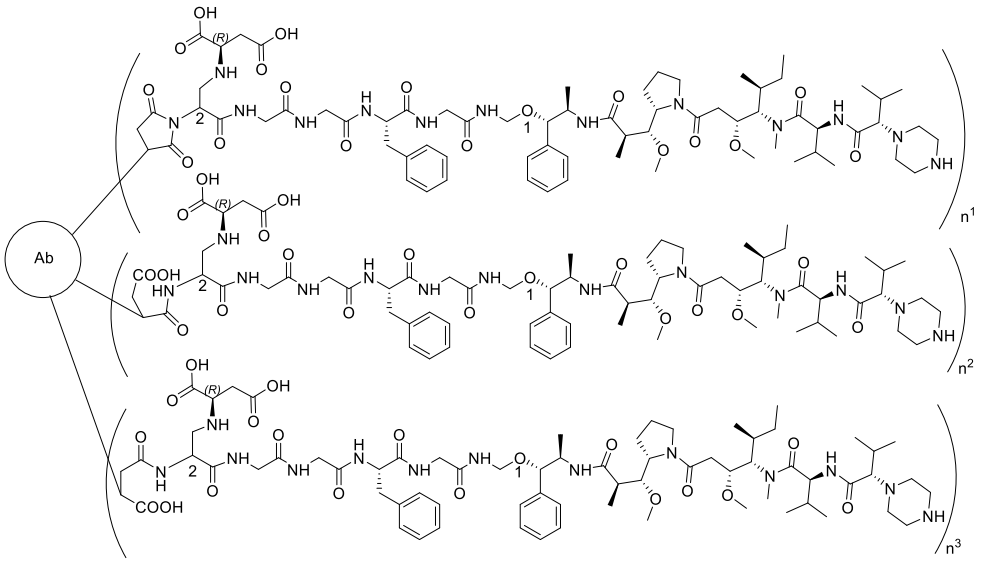
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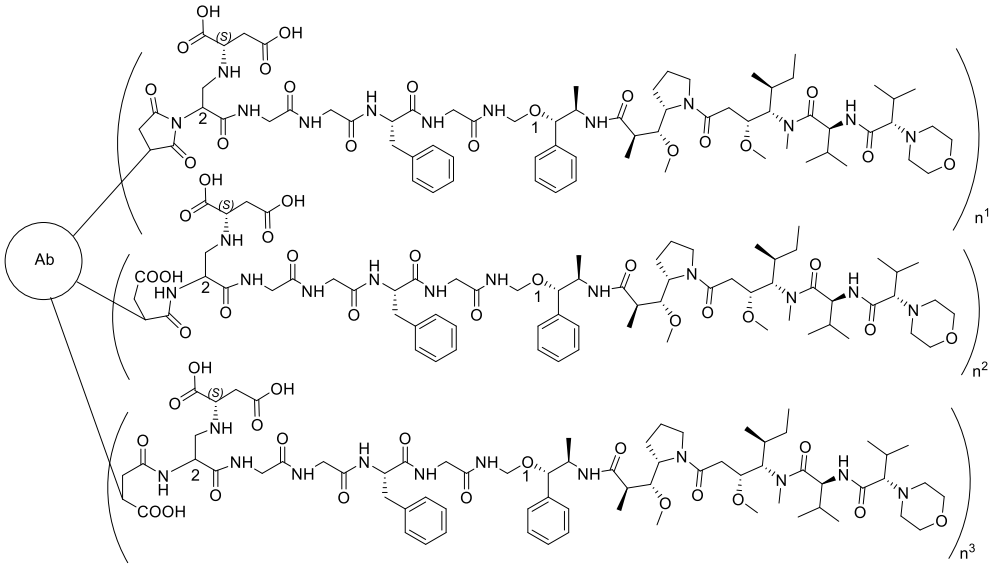


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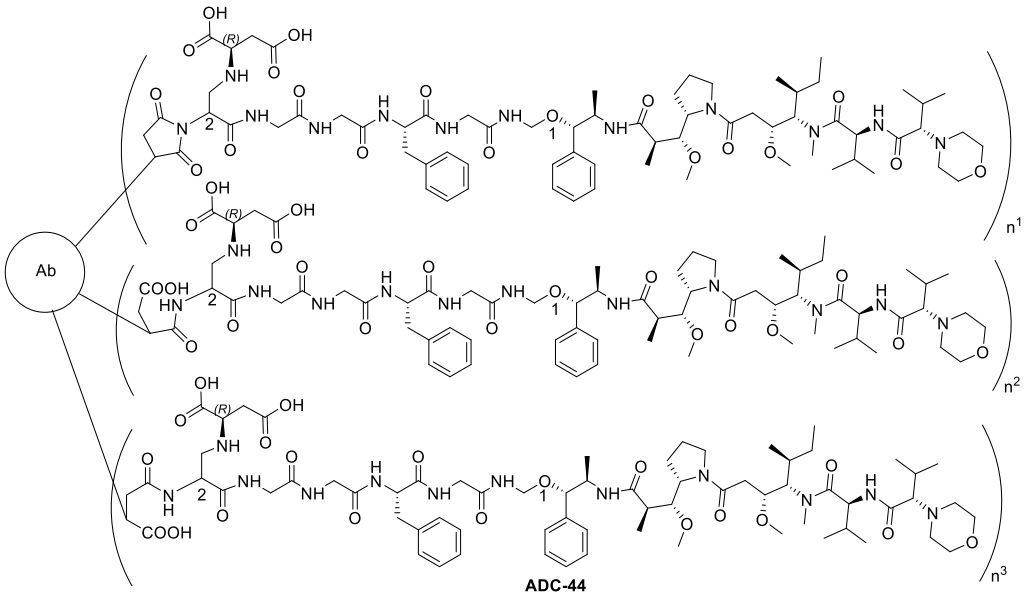
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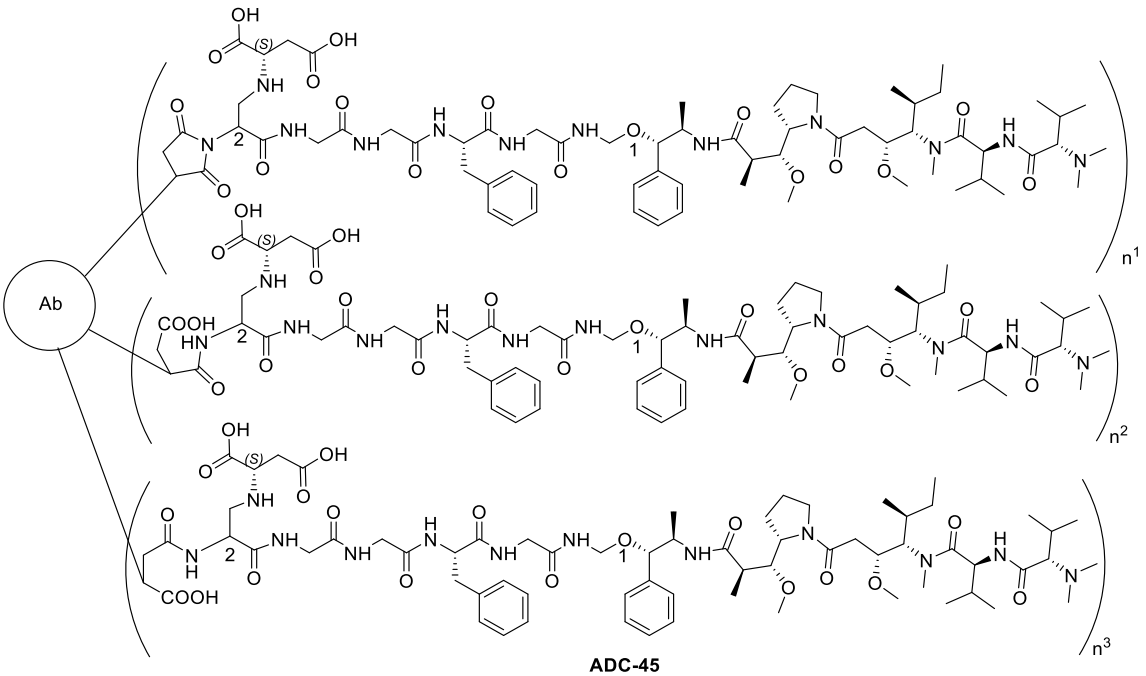
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ADC-43 ,

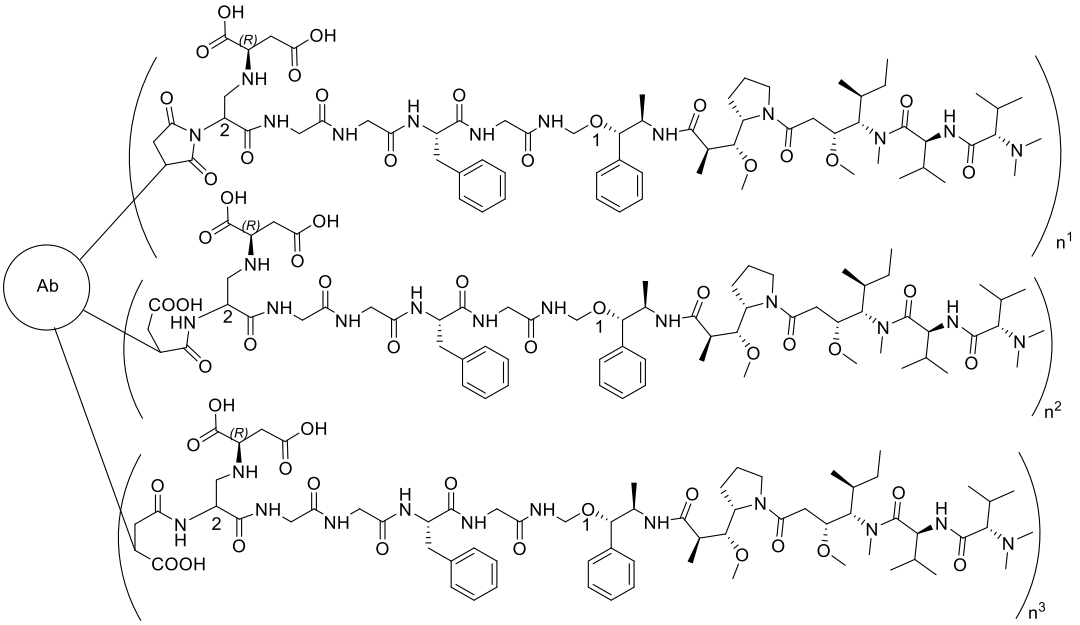


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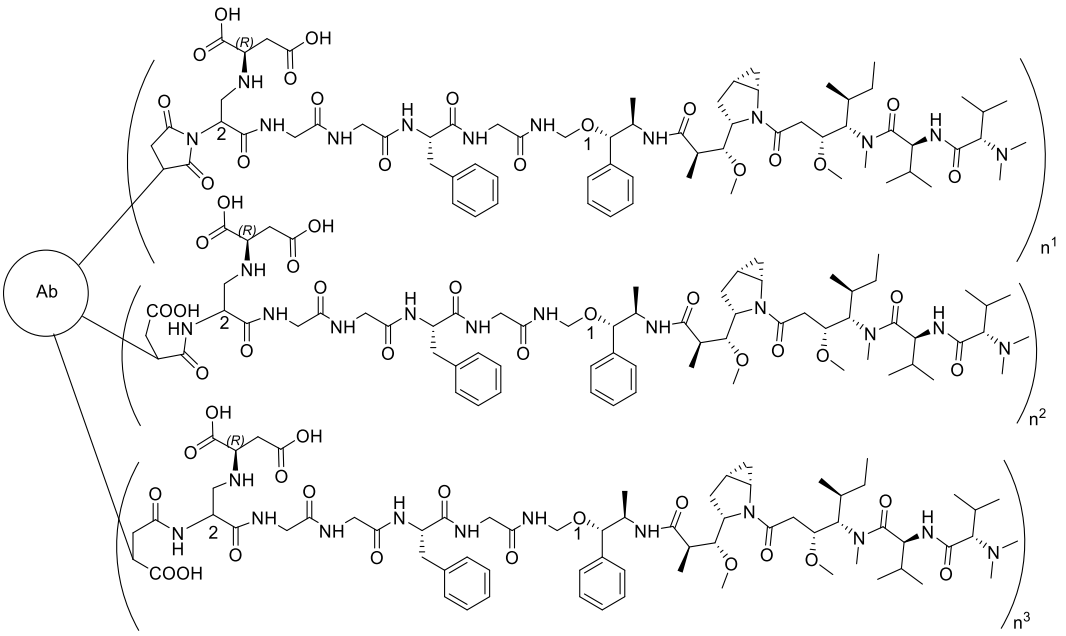
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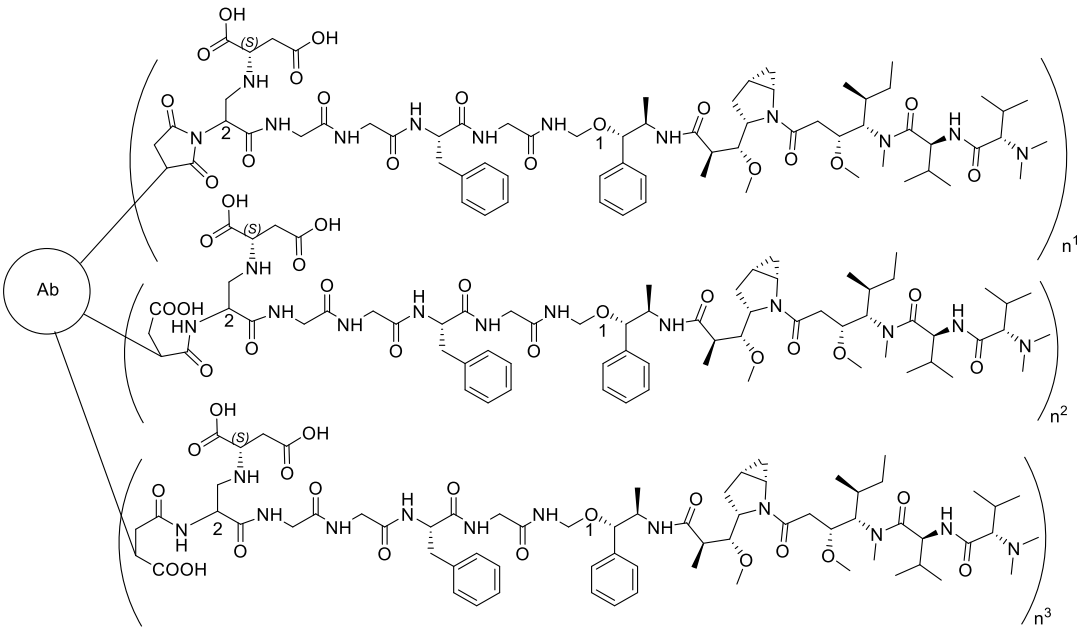
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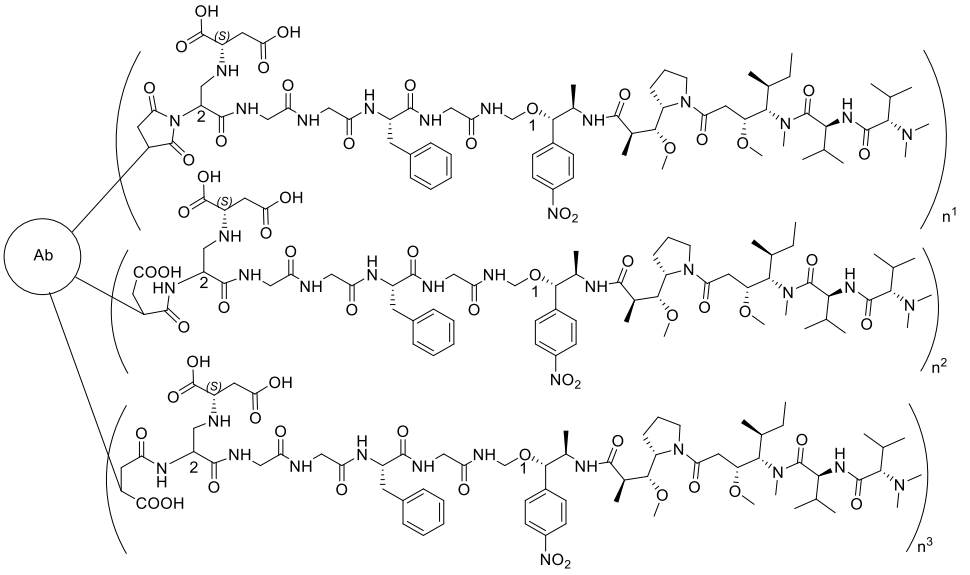
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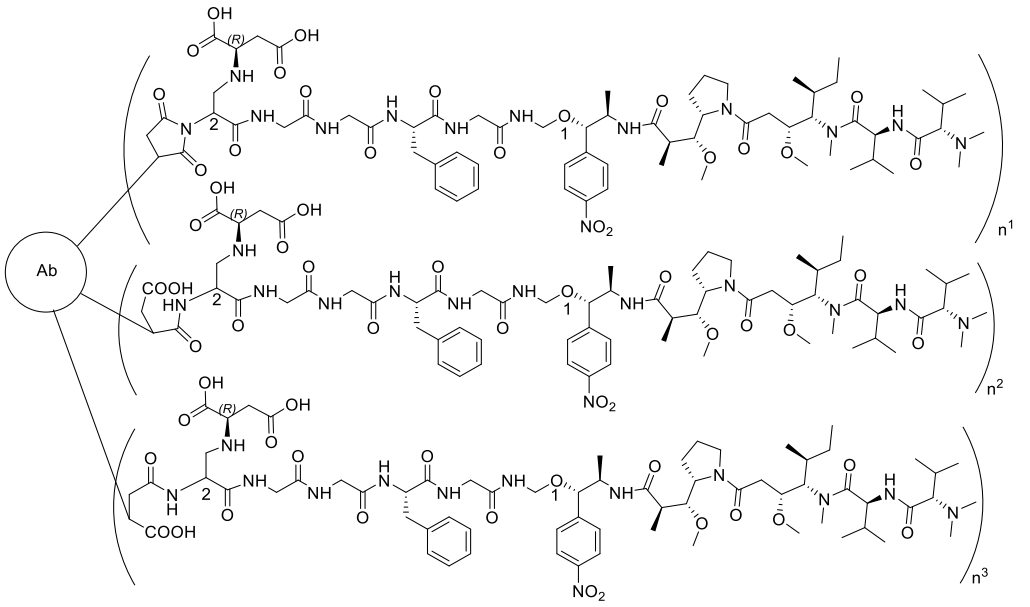
ADC-48

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ADC-49

or



ADC-50 ;

wherein the configuration of the chiral carbon at the 2-position is R- or S-.

14. The ligand-drug conjugate of any one of Claims 1-13 or a pharmaceutically acceptable salt or solvent compound thereof, said antibody being an anti-Trop2 antibody;

preferably, said antibody comprises a light chain and a heavy chain, said light chain comprising CDR-L1, CDR-L2 and CDR-L3 each having an amino acid sequence of SEQ ID NO: 1, SEQ ID NO: 2, SEQ ID NO: 3, respectively;

preferably, said heavy chain comprises CDR-H1, CDR-H2, CDR-H3 each having an amino acid sequence of SEQ ID NO: 4, SEQ ID NO: 5, SEQ ID NO: 6, respectively.

15. The ligand-drug conjugate of Claim 14 or a pharmaceutically acceptable salt or solvate thereof, wherein said light chain comprises a light chain variable region having an amino acid sequence of SEQ ID NO: 7;

preferably, said light chain further comprises a light chain constant region having an amino acid sequence of SEQ ID NO: 8

preferably, the amino acid sequence of said light chain is SEQ ID NO: 9.

16. The ligand-drug conjugate of Claim 14 or a pharmaceutically acceptable salt or solvate thereof, said light chain comprising a light chain variable region having an amino acid sequence of SEQ ID NO: 10;

preferably, said light chain further comprises a light chain constant region having an amino acid sequence of SEQ ID NO: 11

preferably, the amino acid sequence of said light chain is SEQ ID NO: 12.

17. The ligand-drug conjugate of Claim 15 or 16 or a pharmaceutically acceptable salt or solvate thereof, said heavy chain comprising a heavy chain variable region having an amino acid sequence of SEQ ID NO: 13;

preferably, said heavy chain further comprises a heavy chain constant region having an amino acid sequence of SEQ ID NO: 14

preferably, the amino acid sequence of said heavy chain is SEQ ID NO: 15.

18. The ligand-drug conjugate of any one of Claims 1-13 or a pharmaceutically acceptable salt or solvent compound thereof, said antibody being an anti-Trop2 antibody; said antibody comprising a light chain and a heavy chain, said light chain comprising CDR-L1, CDR-L2, and CDR-L3 each having an amino acid sequence as shown in SEQ ID NO: 31, SEQ ID NO: 32, , SEQ ID NO: 33, respectively;

preferably, said heavy chain comprises CDR-H1, CDR-H2, CDR-H3 each having an amino acid sequences as shown in SEQ ID NO:34, SEQ ID NO:35, , SEQ ID NO:36, respectively;

preferably, said light chain comprises a light chain variable region having amino acid sequence of SEQ ID NO: 37;

preferably, said light chain further comprises a light chain constant region amino acid sequence of SEQ ID NO: 38;

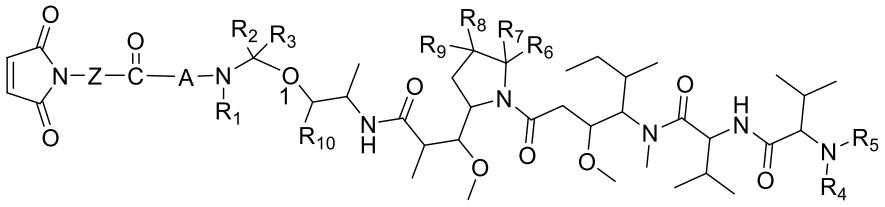
preferably, said light chain comprises an amino acid sequence of SEQ ID NO: 39;

preferably, said heavy chain comprises a heavy chain variable region having amino acid sequence of SEQ ID NO: 40;

preferably, said heavy chain further comprises a heavy chain constant region having amino acid sequence of SEQ ID NO: 41;

preferably, said heavy chain comprises an amino acid sequence of SEQ ID NO: 42.

19. A linker-payload as shown formula II, or isomers, mesomers, racemates, enantiomers or mixtures thereof, or pharmaceutically acceptable salts or solvates thereof,



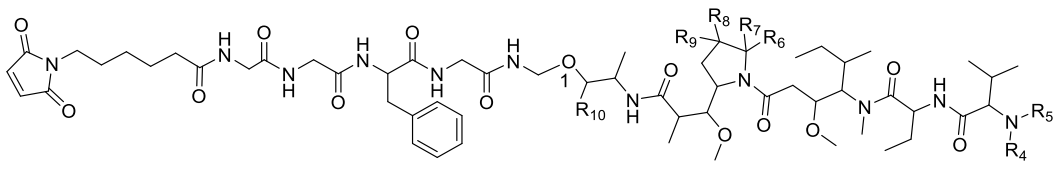
II

wherein:

Z, A, R_1, R_2, R_3, R_4, R_5, R_{11}, R_{12}, R_{13}, R_{14}, B, R_{15}, R_{16}, R_{17}, n, m, R_6, R_7, R_8, R_9, R_{18}, R_{19}, and R_{10} are as defined in any one of Claims 1-10.

20. The linker-payload of Claim 19, or isomers, mesomers, racemates, enantiomers or mixtures thereof, or pharmaceutically acceptable salts or solvates thereof,

said linker-payload having the structure shown in formula IIa

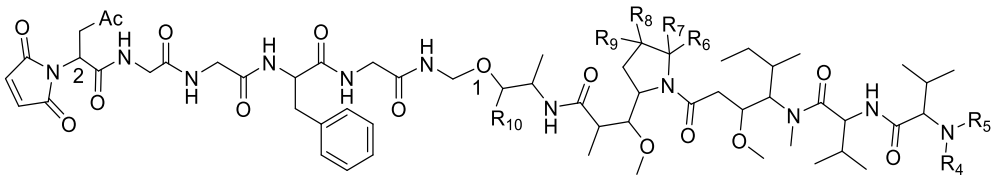


IIa

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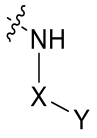
21. The linker-payload of Claim 20, or isomers, mesomers, racemates, enantiomers or mixtures thereof, or pharmaceutically acceptable salts or solvates thereof,

said linker-payload having the structure shown in formula IIb:



IIb

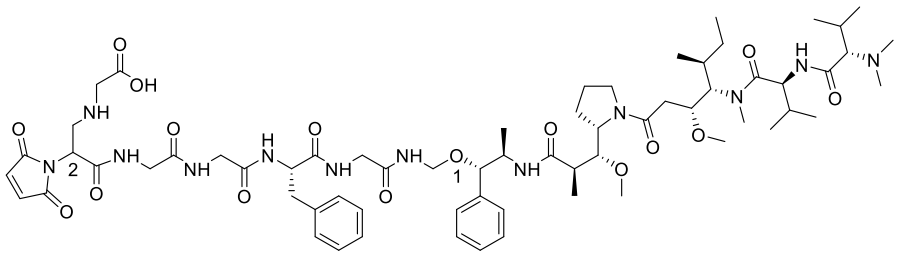
wherein Ac is a hydrophilic structural unit having the structure shown in formula c:



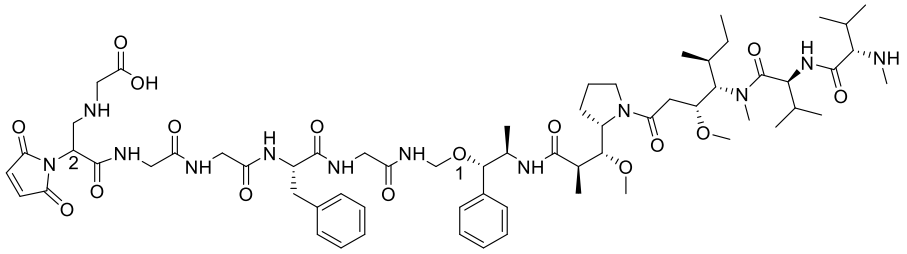
c

wherein X, Y are as defined in Claim 7, and Ac is linked, via -NH-, to 2-position methylene carbon as labeled in formula IIb.

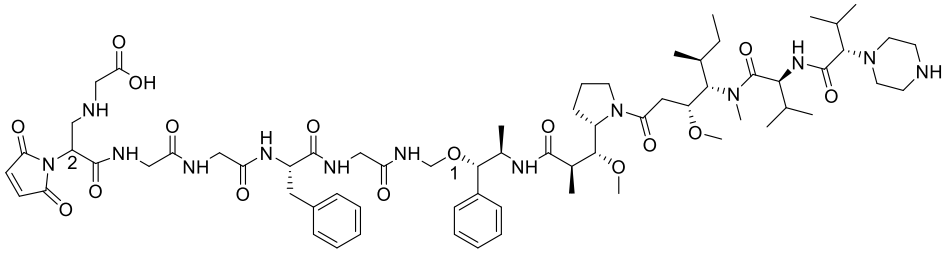
22. The linker-payload of any one of Claims 19-21, or isomers, mesomers, racemates, enantiomers or mixtures thereof, or pharmaceutically acceptable salts or solvates thereof, said linker-payload being selected from the following structures:



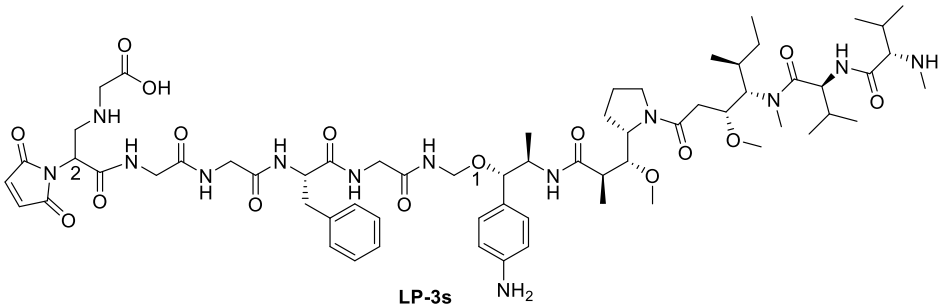
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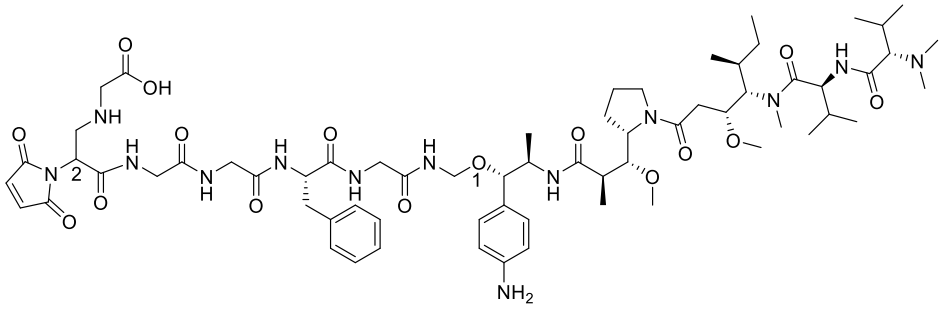
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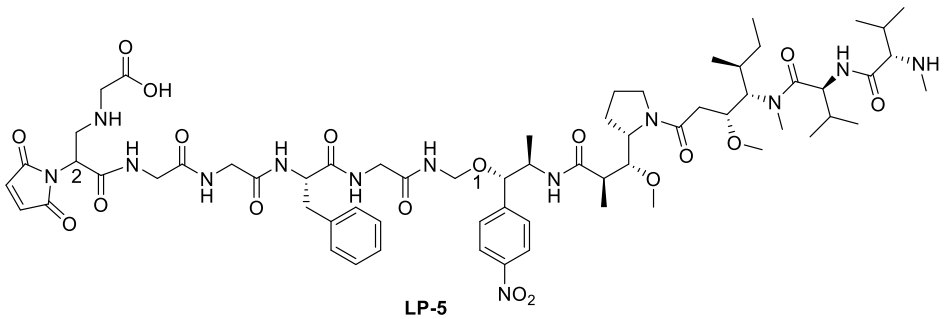
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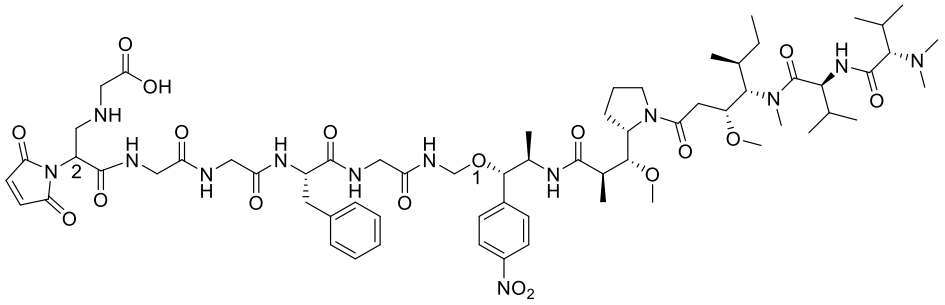
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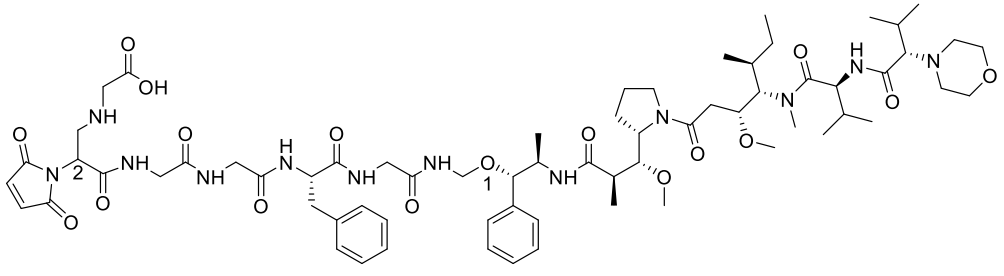
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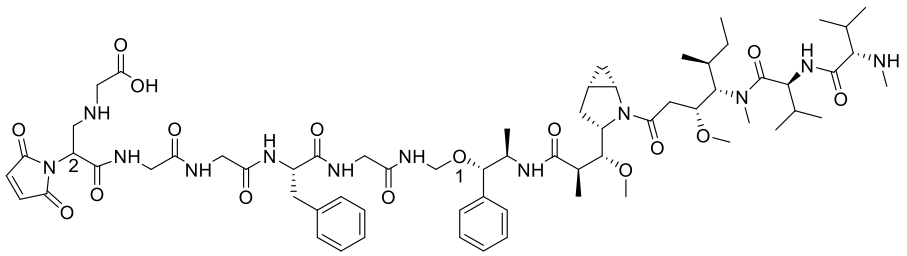
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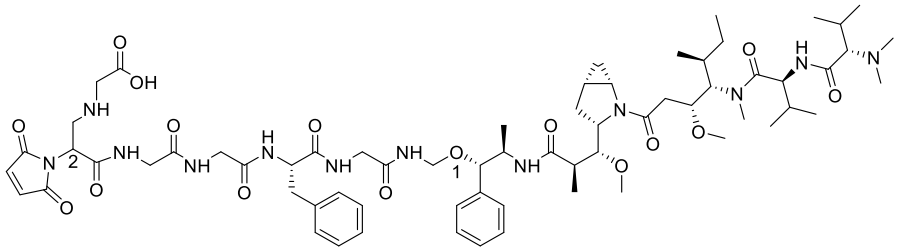
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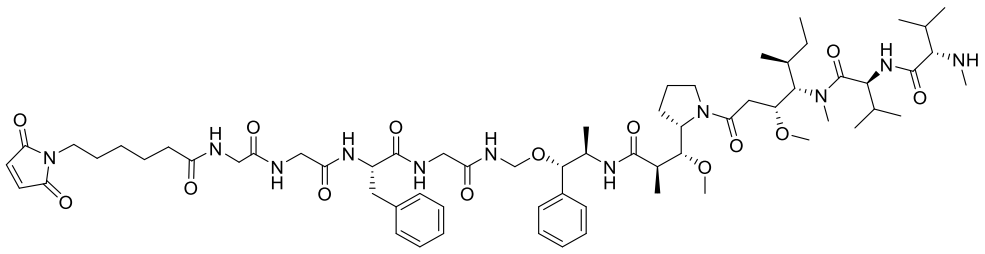
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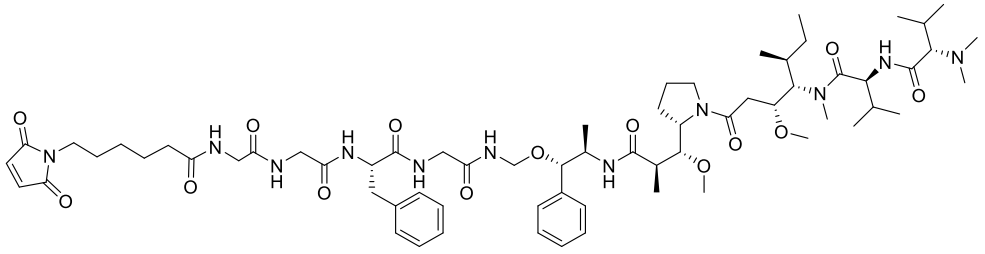
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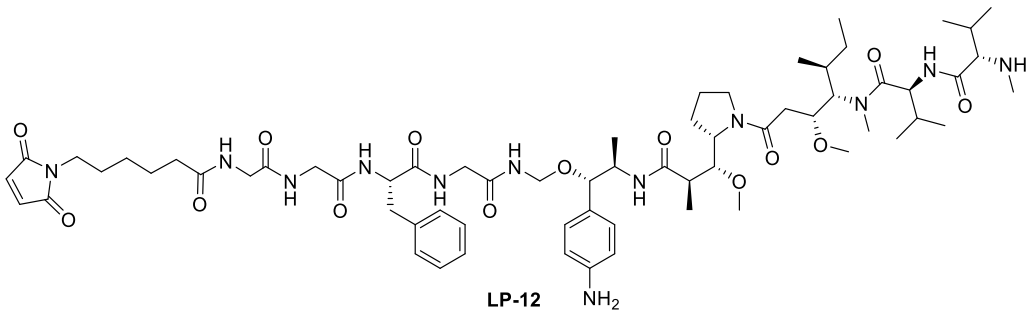
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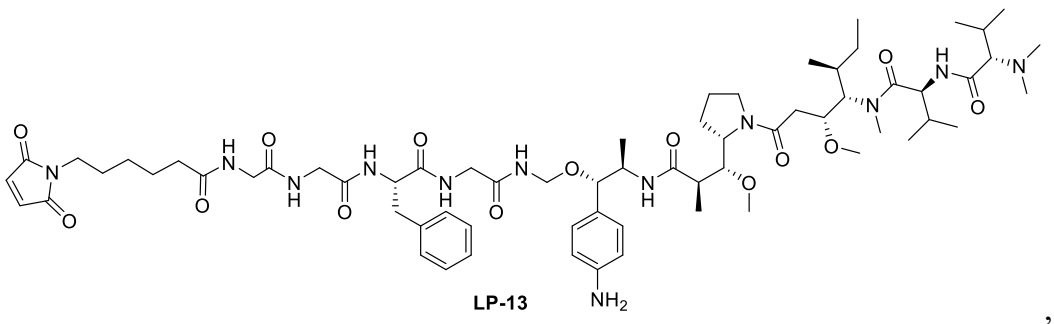
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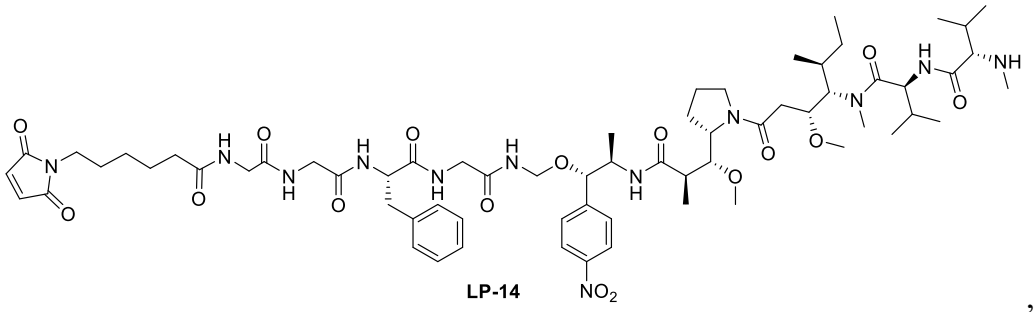
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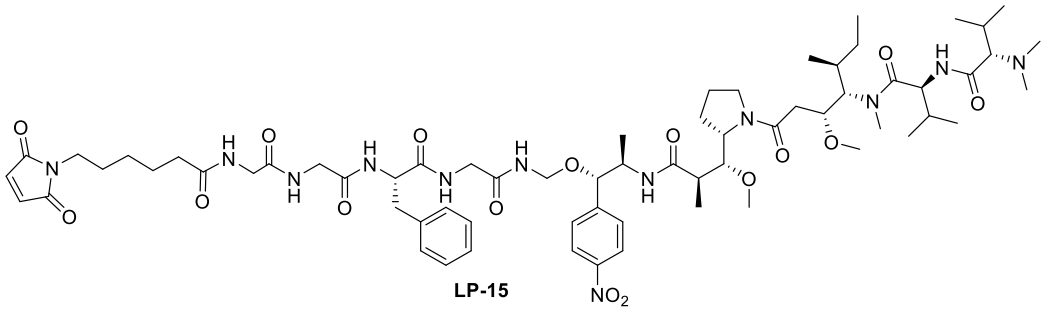
LP-12 NH_2 ,



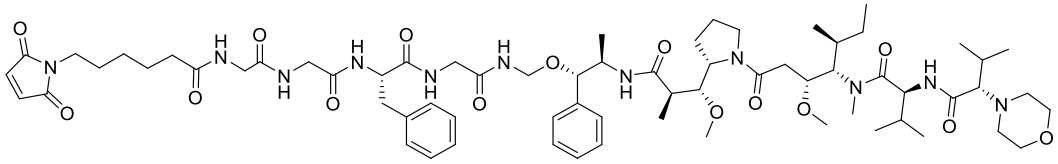
LP-13 NH_2 ,



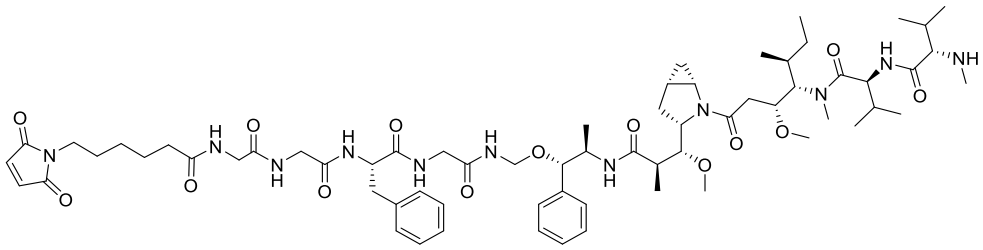
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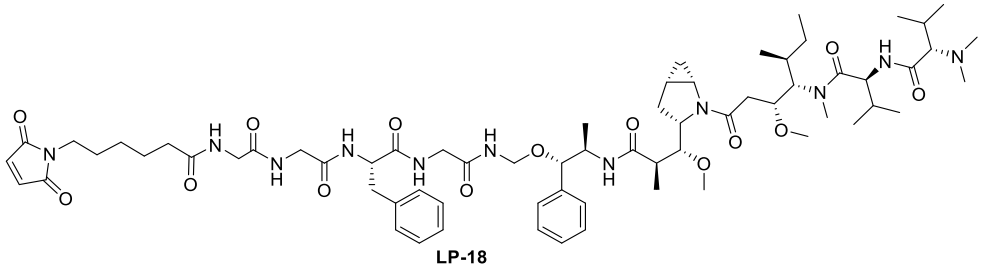
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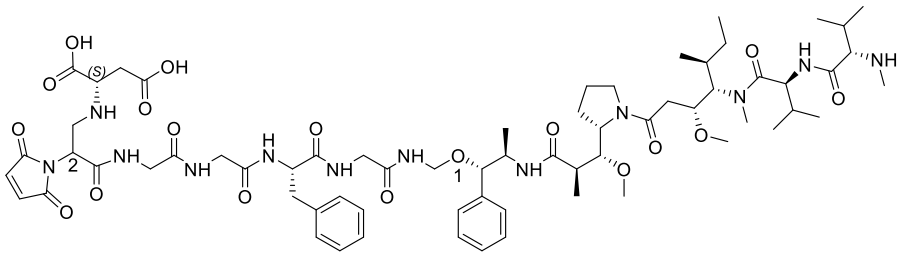
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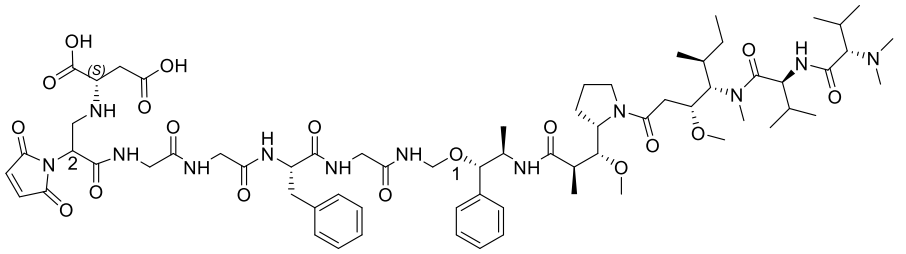
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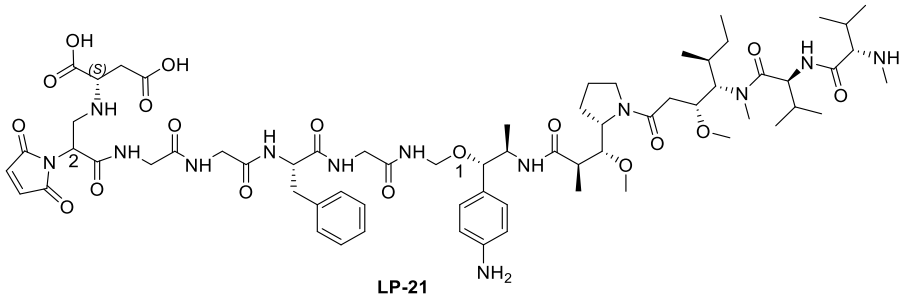
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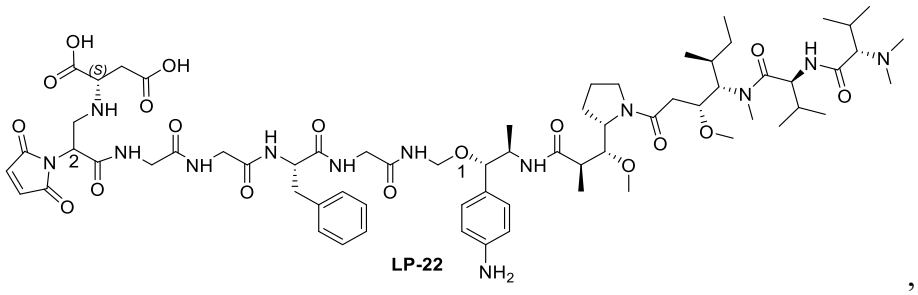
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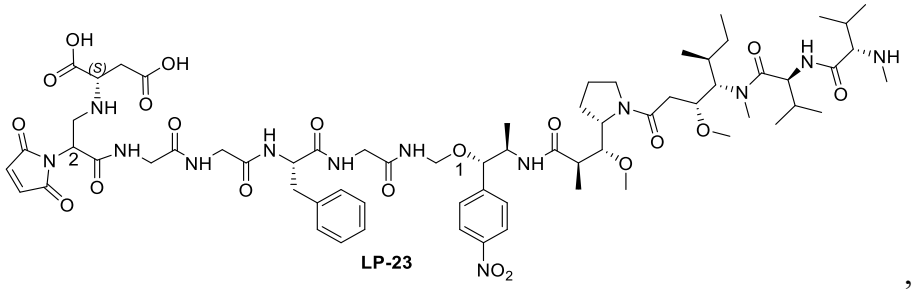
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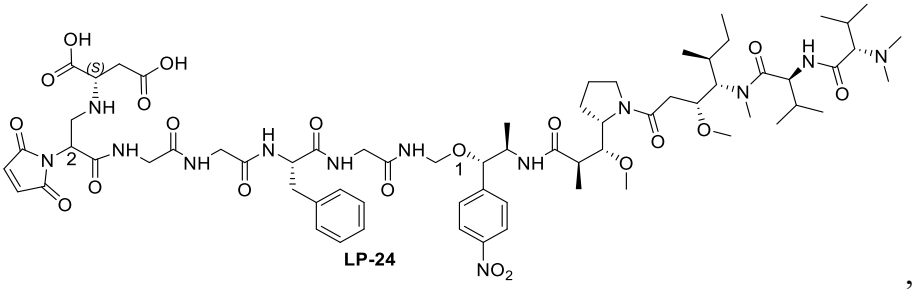
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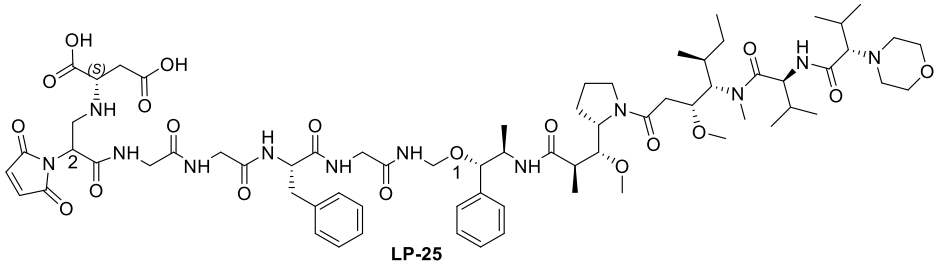
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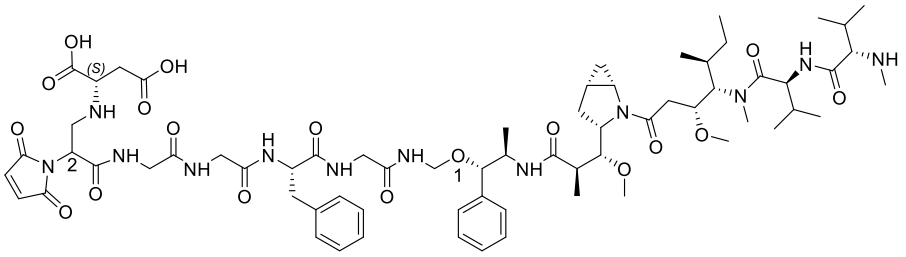
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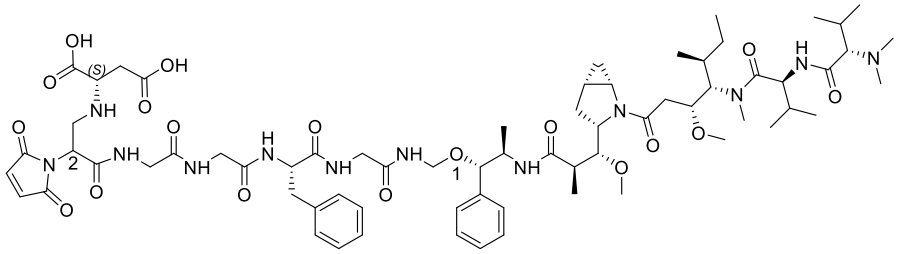
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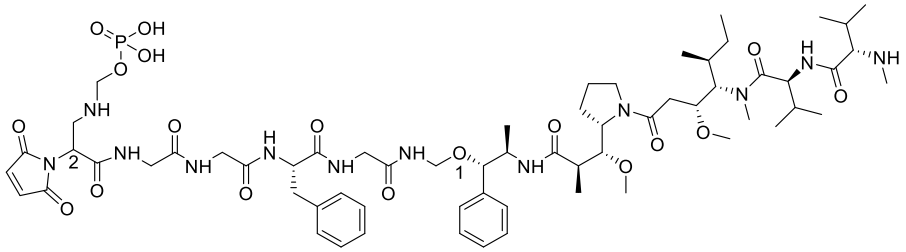
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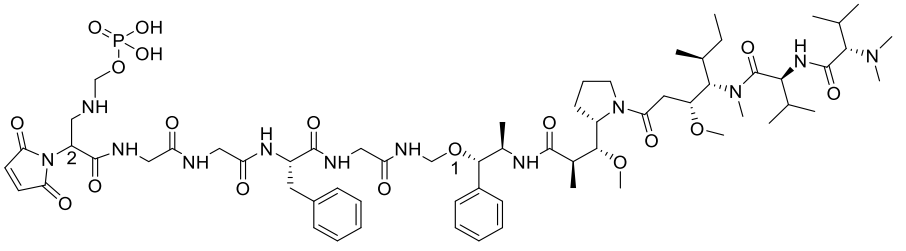
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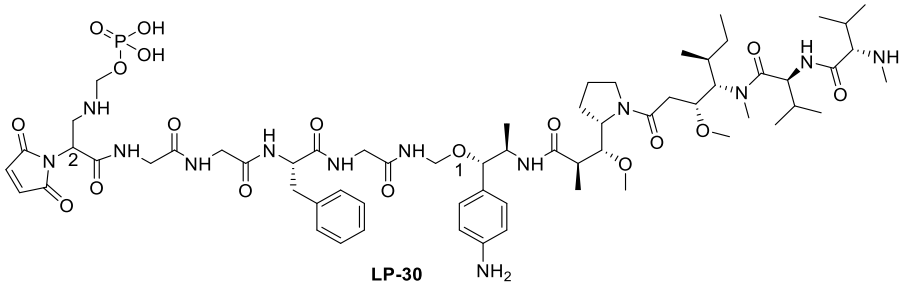
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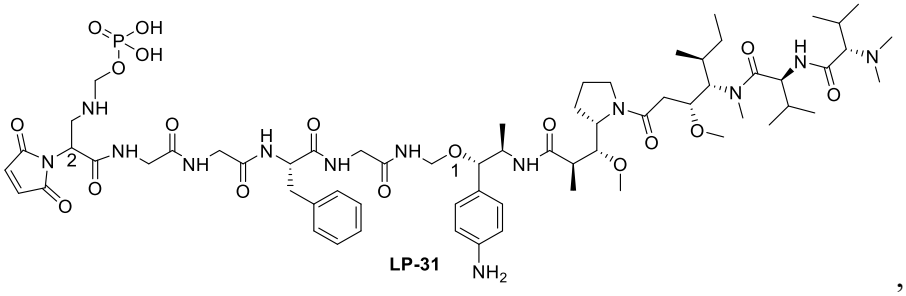
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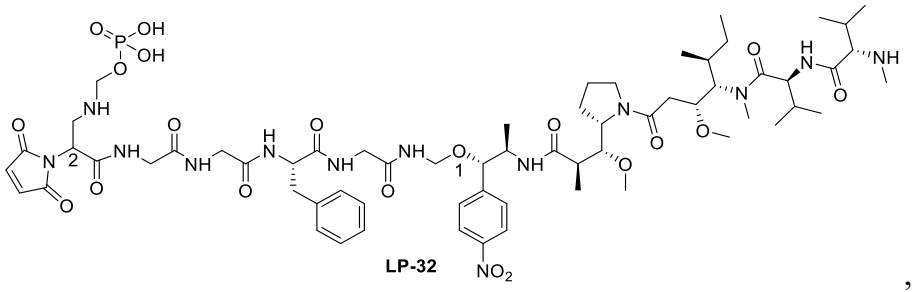
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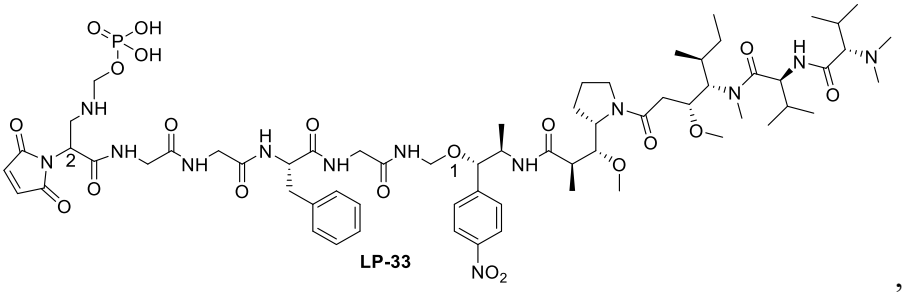
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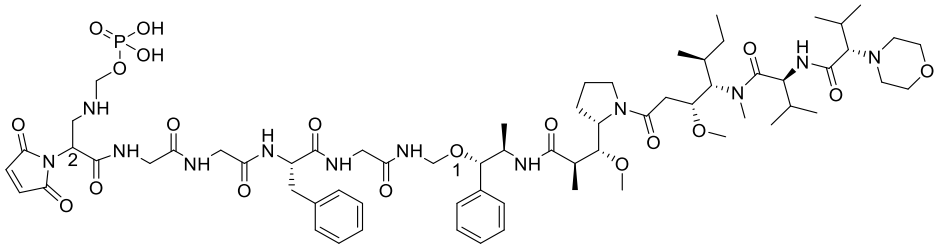
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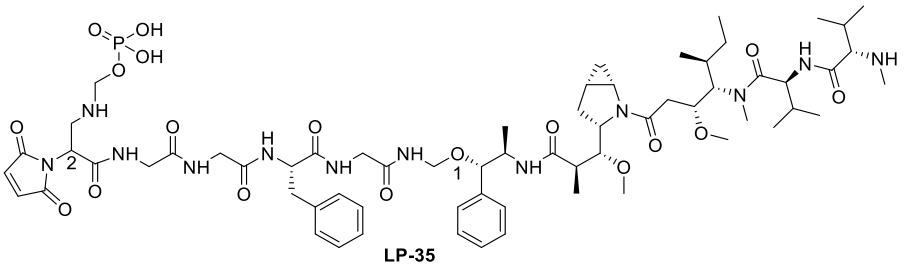
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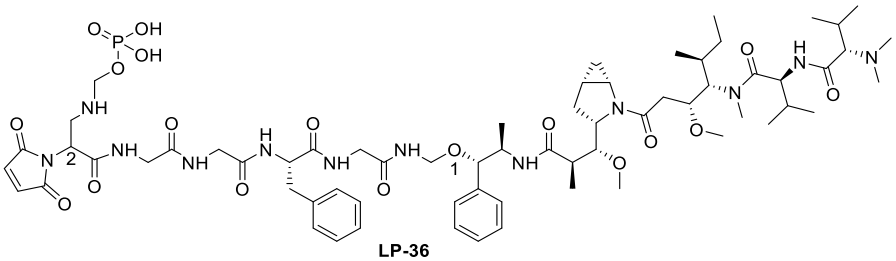
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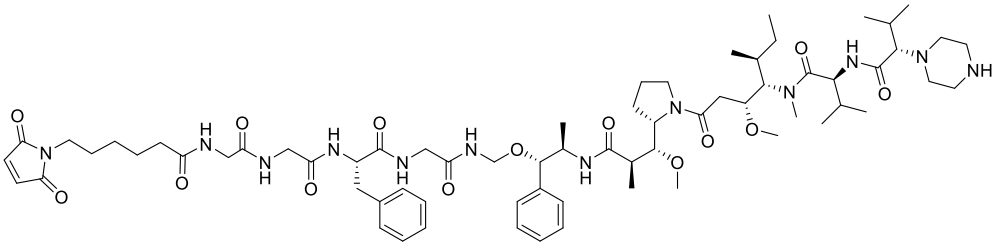
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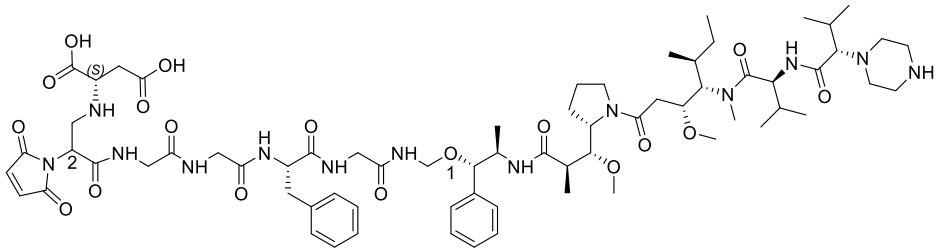
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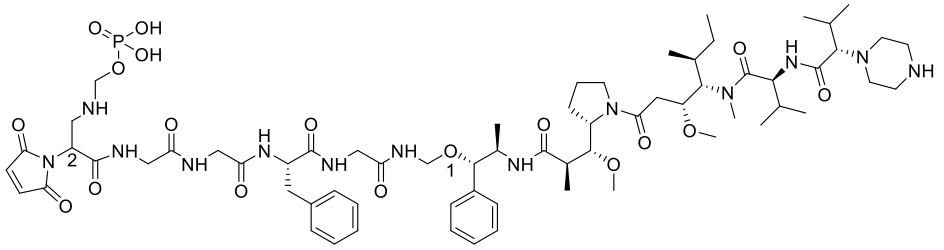
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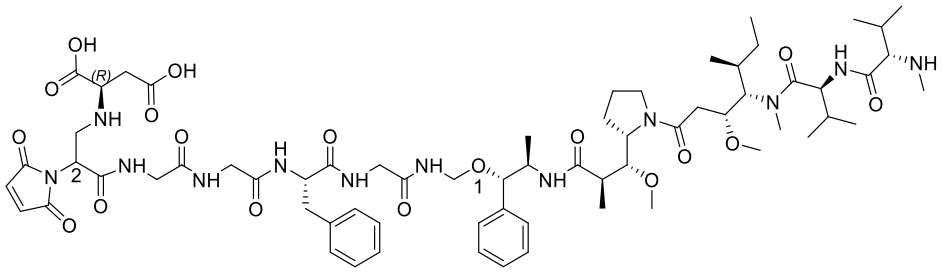
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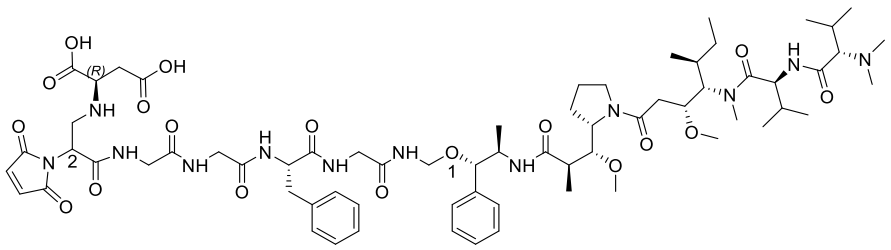
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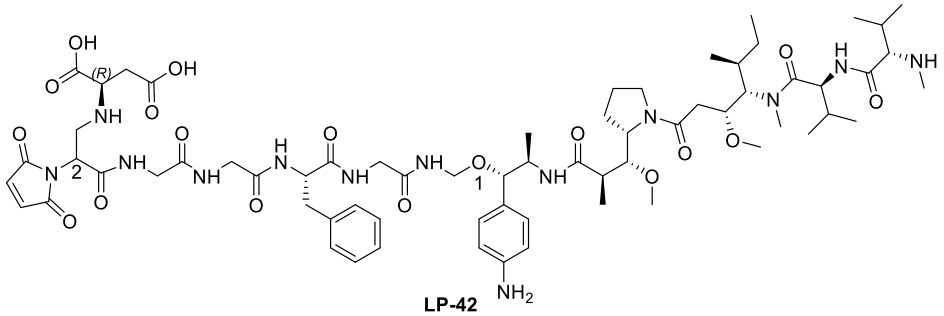
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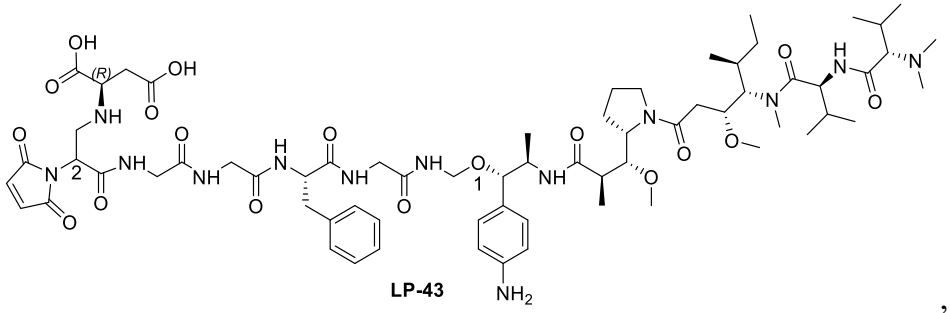
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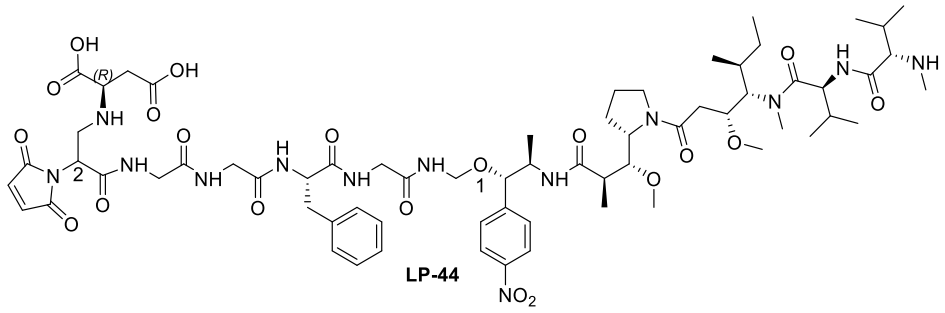
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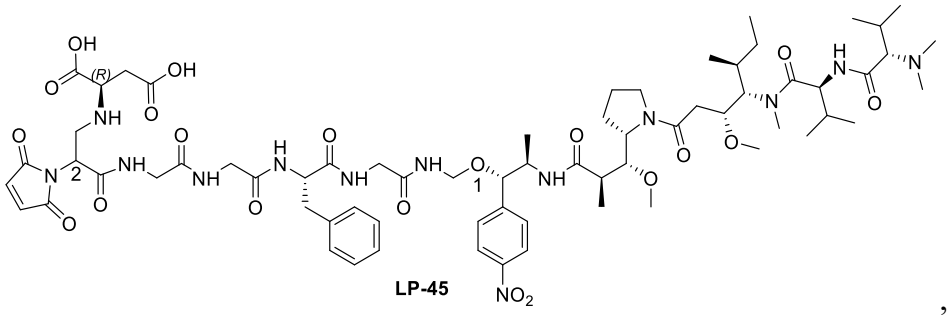
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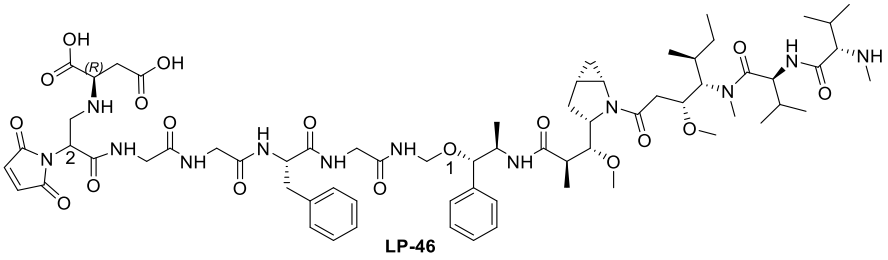
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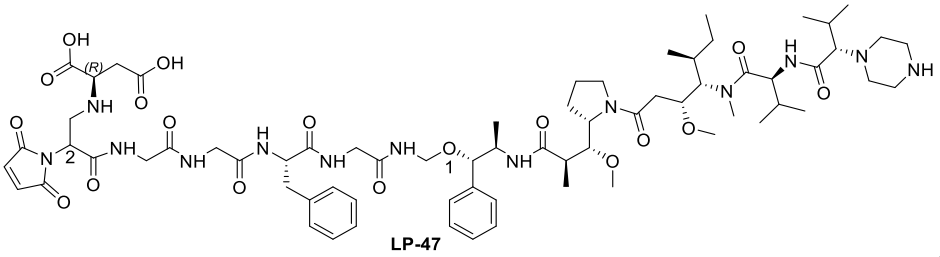
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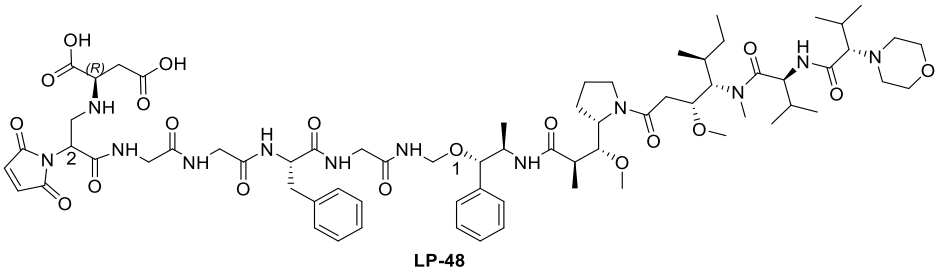
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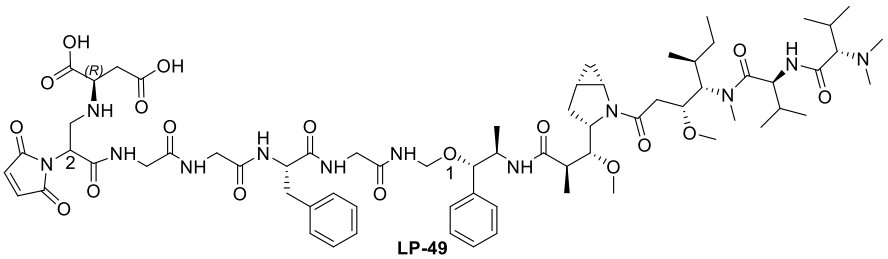
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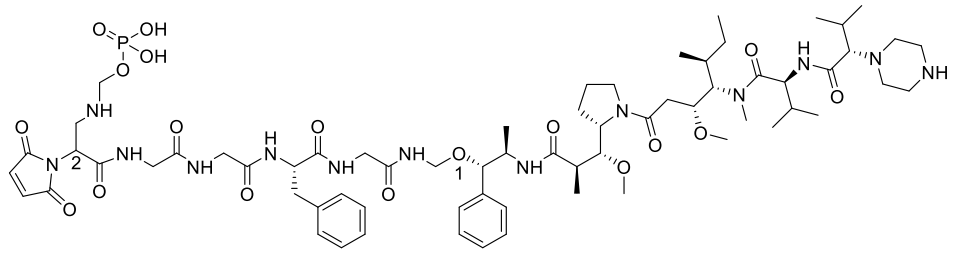
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wherein the configuration of the chiral carbon at the 2-position is R- or S-.

23. Use of the ligand-drug conjugate or pharmaceutically acceptable salts or solvates thereof of any one of Claims 1-18, or the linker-payload or isomers, mesomers, racemates, enantiomers or mixtures thereof, or pharmaceutically acceptable salts or solvates thereof of any one of Claims 19-22, for the preparation of a drug, said drug is used for the treatment or prevention of tumors;

preferably, said tumors are selected from solid or non-solid tumors, such as breast cancer, ovarian cancer, cervical cancer, uterine cancer, prostate cancer, renal cancer, urothelial cancer, bladder cancer, hepatocellular carcinoma, gastric cancer, endometrial cancer, salivary gland cancer, esophageal cancer, lung cancer, colon cancer, rectal cancer, colorectal cancer, bone cancer, skin cancer, thyroid cancer, pancreatic cancer, melanoma, glioma, neuroblastoma, glioblastoma multiforme cell tumors, sarcomas, lymphomas, and leukemias.

24. A pharmaceutical composition comprising an effective amount of the ligand-drug conjugate or a pharmaceutically acceptable salt or solvate thereof of any one of Claims 1-18, or the linker-payload or isomers, mesomers, racemates, enantiomers or mixtures thereof, or pharmaceutically acceptable salts or solvates thereof of any one of Claims 19-22, and pharmaceutically acceptable carriers, diluents or excipients.

25. Use of the linker-payload or isomers, mesomers, racemates, enantiomers or mixtures thereof, or pharmaceutically acceptable salts or solvates thereof of Claims 19-22, for the preparation of a ligand-drug conjugate or pharmaceutically acceptable salts or solvates thereof,

preferably, said ligand-drug conjugate is selected from the ligand-drug conjugate of any one of Claims 1-18.