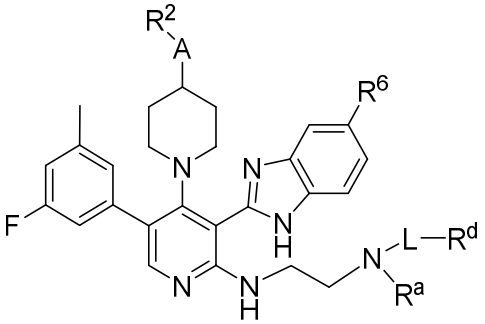
CLAIMS

WHAT IS CLAIMED IS:

1. A compound that has the structure of Formula (I), or a pharmaceutically acceptable salt thereof:



Formula (I)

wherein:

A is -N(H)- or -O-;

R^a is hydrogen or C_1-C_6alkyl;

R^2 is hydrogen or C_1-C_6alkyl;

R^6 is chloro or -C(=O)NH_2;

L is -L^1-L^2-;

L^1 is an optional spacer; and

L^2 is an optional linker;

wherein at least one of L^1 or L^2 is present; and

R^d is a payload moiety comprising a chemotherapeutic agent.

2. The compound of claim 1, or a pharmaceutically acceptable salt thereof, wherein A is -N(H)-.

3. The compound of any one of claims 1-2, or a pharmaceutically acceptable salt thereof, wherein R^2 is hydrogen.

4. The compound of any one of claims 1-3, or a pharmaceutically acceptable salt thereof, wherein R^a is hydrogen or methyl.

5. The compound of any one of claims 1-4, or a pharmaceutically acceptable salt thereof, wherein R^a is hydrogen.

6. The compound of any one of claims 1-5, or a pharmaceutically acceptable salt thereof, wherein R^6 is chloro.

7. The compound of any one of claims 1-6, or a pharmaceutically acceptable salt thereof, wherein L^2 is present, and is -$(L^{2a})_w$-L^{2b}- or -L^{2c}-;

each L^{2a} is independently selected from natural or unnatural amino acids, wherein any free amine of an amino acid is optionally independently substituted with $-CH_3$;

L^{2b} is absent or $-N(R^{10})$(unsubstituted or substituted benzyl)-OC(=O)-; wherein substituted benzyl is substituted with $-C(=O)NHR^{12}$ or a monosaccharide;

each R^{10} is independently selected from hydrogen, and C_1-C_6alkyl;

each R^{12} is independently selected from hydrogen, C_4-C_{20}polyethylene glycol, and unsubstituted or substituted C_1-C_6alkyl, wherein the substituted C_1-C_6alkyl is substituted with $-NHR^{13}$, $-C(=O)NHR^{13}$, or $-NHC(=O)R^{13}$;

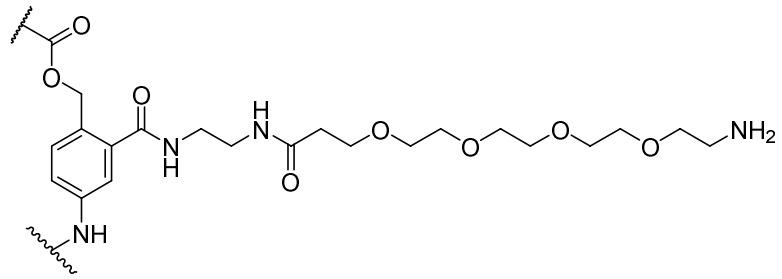
each R^{13} is independently selected from hydrogen, C_4-C_{20}polyethylene glycol, and C_4-C_{20}polyethylene glycol-NH_2;

or when R^{13} is present and at least one free carboxylic group of an amino acid of L^{2a} is present, then R^{13} and the free carboxylic group of the amino acid of L^{2a} are taken together to form a ring;

w is 1, 2, 3, 4, 5, or 6; and

each L^{2c} is N-maleimidomethyl-cyclohexane-1-carbonyl (MCC) or -S-.

8. The compound of claim 7, or a pharmaceutically acceptable salt thereof, wherein L^{2b} is selected from: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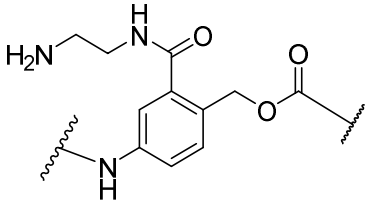
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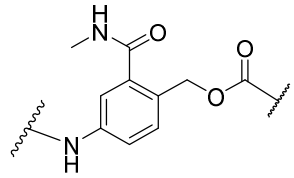
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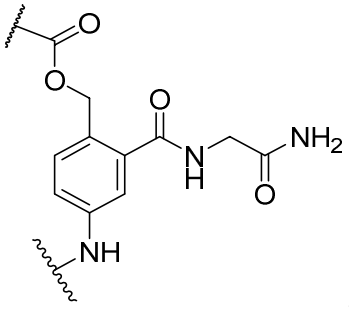
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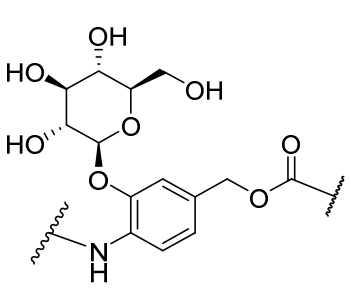
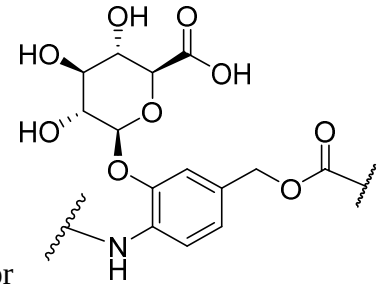


, or 

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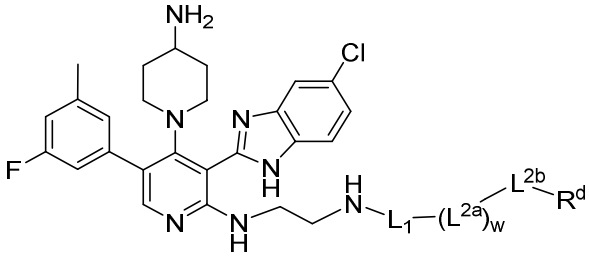
9. The compound of any one of claims 7-8, wherein the compound has the structure of Formula (Ia), or a pharmaceutically acceptable salt thereof:



Formula (Ia).

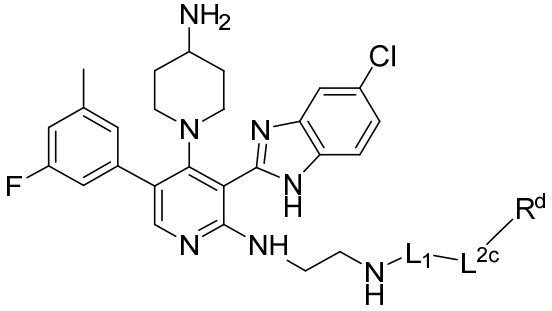
10. The compound of any one of claims 7-9, or a pharmaceutically acceptable salt thereof, wherein each L^{2a} is independently select from natural or unnatural amino acids, wherein any free amine of an amino acid is optionally independently substituted with -CH_3, wherein the natural or unnatural amino acids are selected from alanine (Ala), Ala(SO_3H), 3-(1-piperidinyl)alanine, cyclohexylalanine, arginine (Arg), asparagine (Asn), aspartate (Asp), cysteine (Cys), glutamine (Gln), glutamate (Glu), glycine (Gly), leucine (Leu), lysine(Lys), methionine (Met), phenylalanine (Phe), homophenylalanine, proline (Pro), serine (Ser), 3-homoserine, tyrosine (Tyr), Tyr(SO_3H), valine (Val), citrulline, β-alanine, β3-homoserine, β3-homolysine, and β3-homoglutamic acid.

11. The compound of any one of claims 7-10, or a pharmaceutically acceptable salt thereof, wherein each L^{2a} is independently select from natural or unnatural amino acids, wherein any free amine of an amino acid is optionally independently substituted with -CH_3, wherein the natural or unnatural amino acids are selected from alanine (Ala), Ala(SO_3H), arginine (Arg), asparagine (Asn), aspartate (Asp), cysteine (Cys), glutamine (Gln), glutamate (Glu), glycine (Gly), leucine (Leu), lysine(Lys), methionine (Met), phenylalanine (Phe), serine (Ser), valine (Val), and citrulline.

12. The compound of any one of claims 7-11, or a pharmaceutically acceptable salt thereof, wherein L^2 is -$(L^{2a})_w$-L^{2b}-; and -$(L^{2a})_w$- is valine-citrulline, valine-alanine, methionine-valine-lysine, glycine-phenylalanine-glycine-glycine, tyrosine-arginine-valine, arginine-

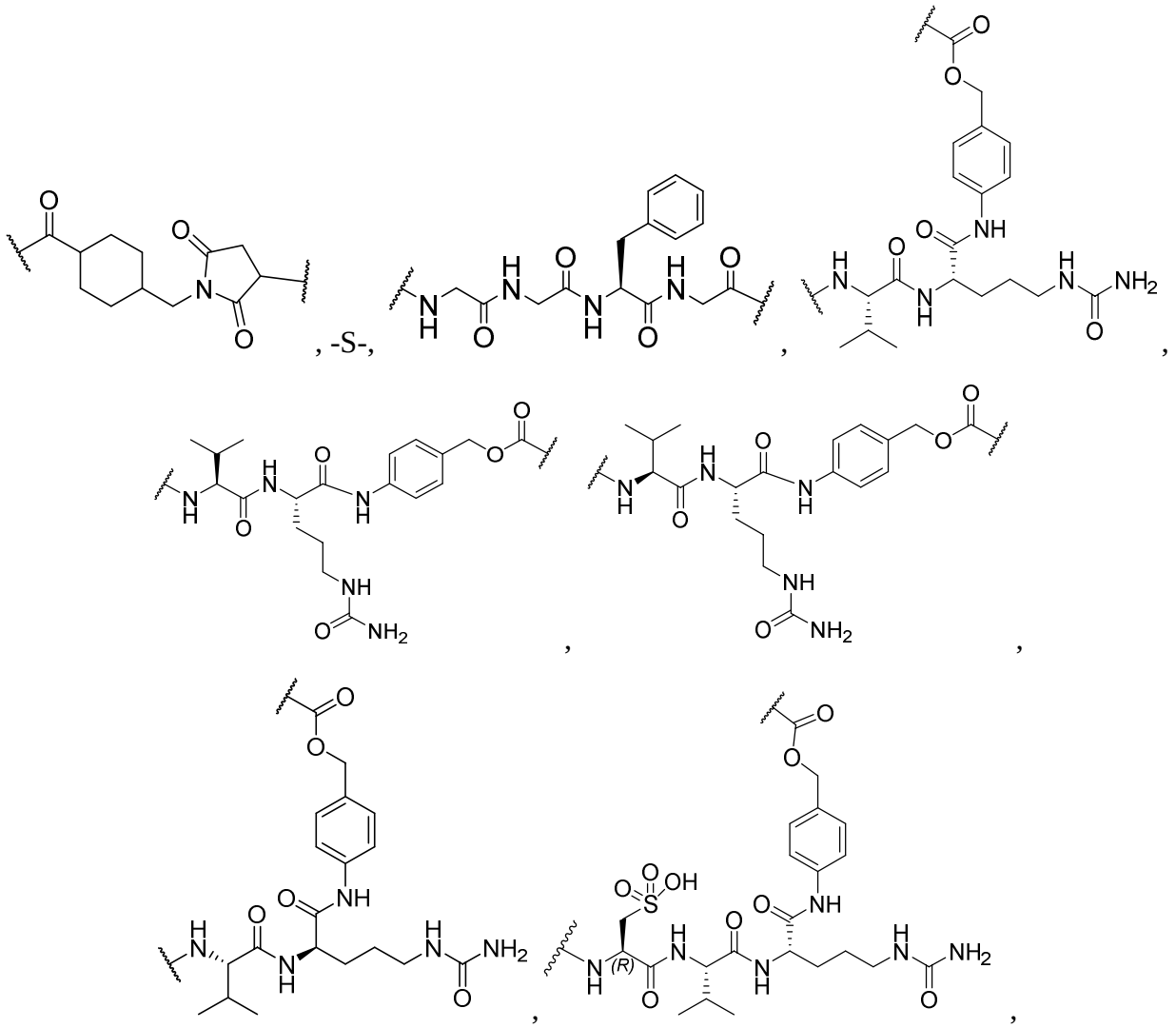
valine, and phenylalanine-lysine.

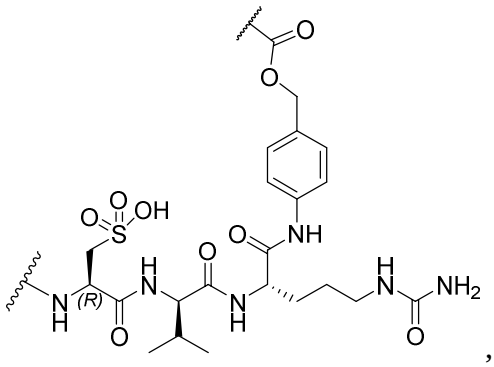
13. The compound of claim 7, wherein the compound has the structure of Formula (Ib), or a pharmaceutically acceptable salt thereof:



Formula (Ib).

14. The compound of claim 1, or a pharmaceutically acceptable salt thereof, wherein L^2 is absent or is:

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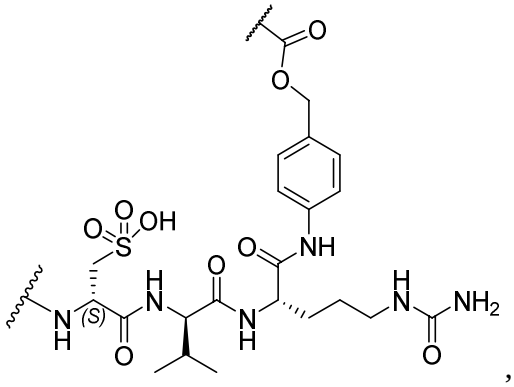
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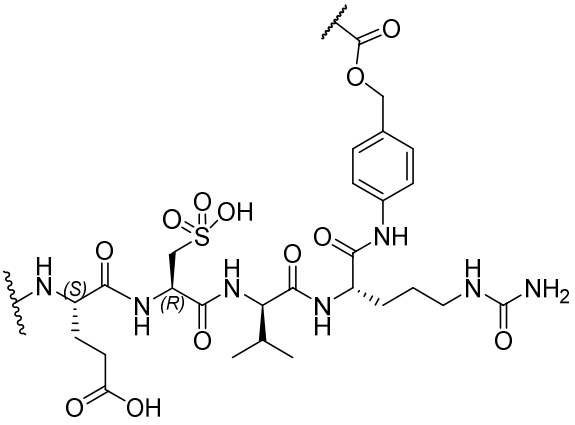
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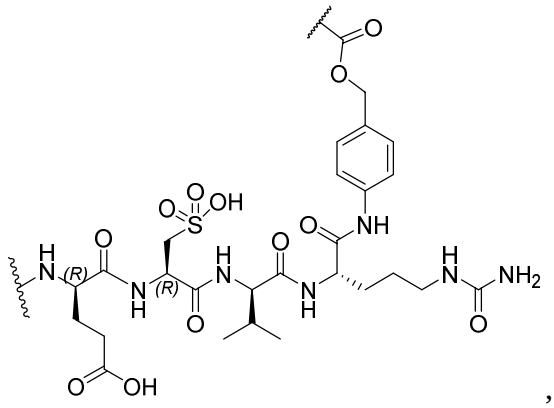
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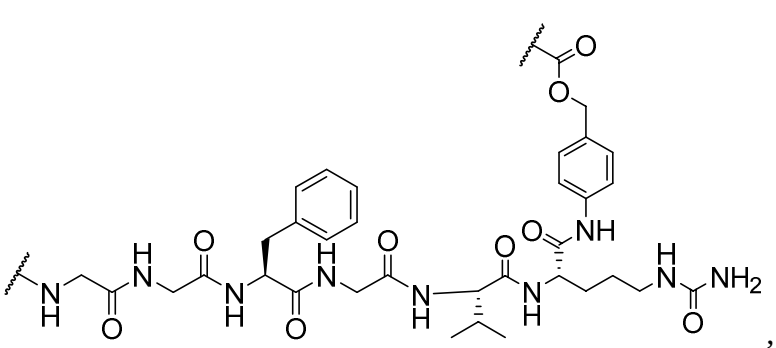
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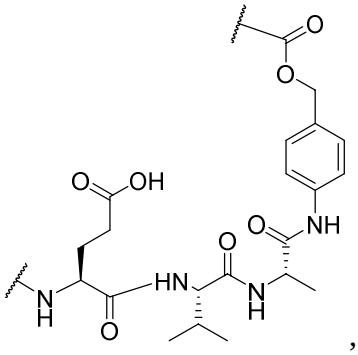
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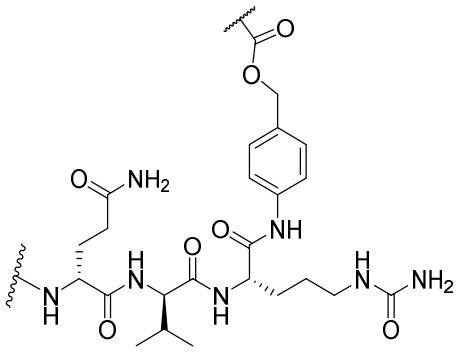
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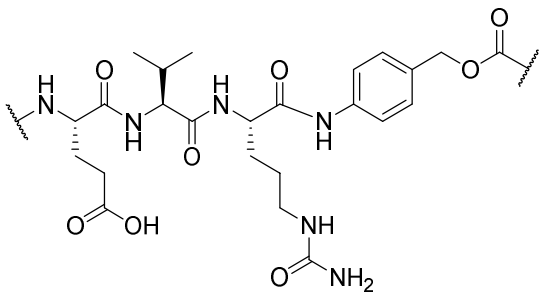
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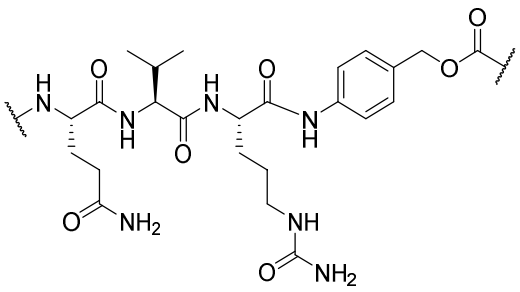
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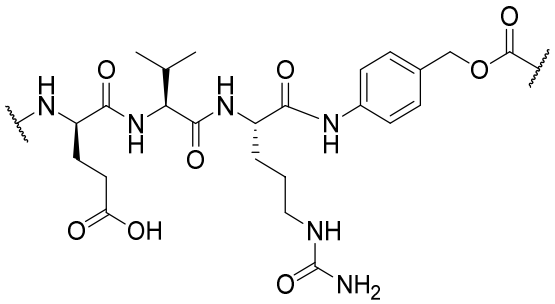
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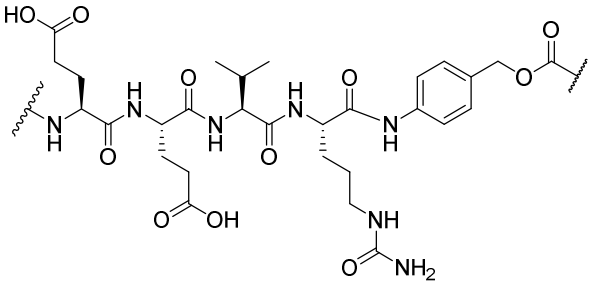
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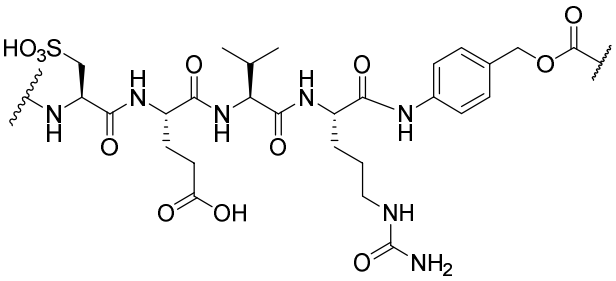
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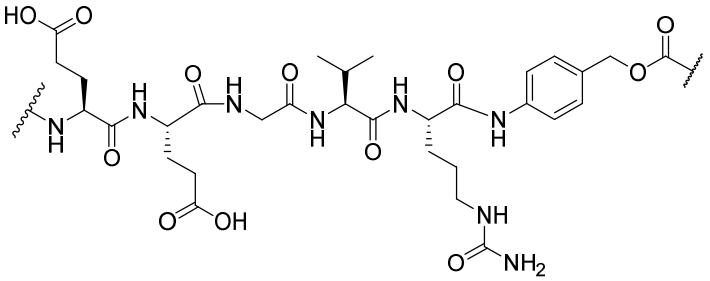
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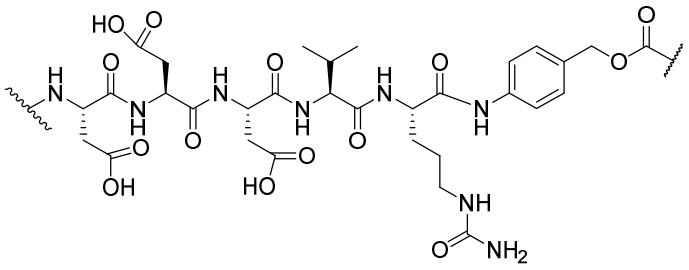
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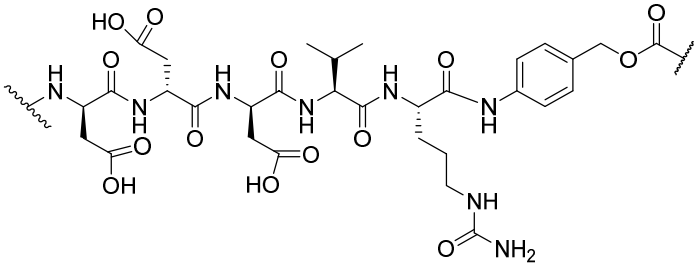
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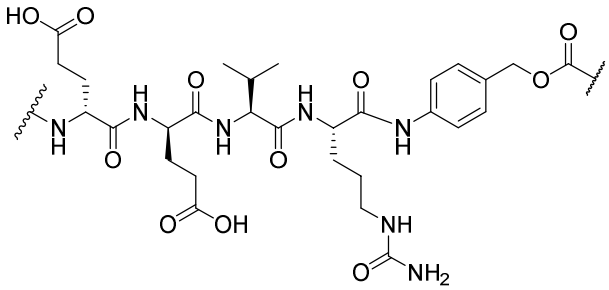
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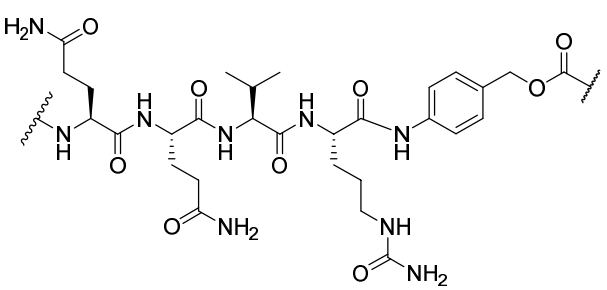
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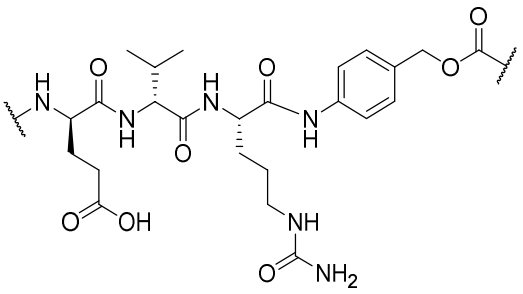
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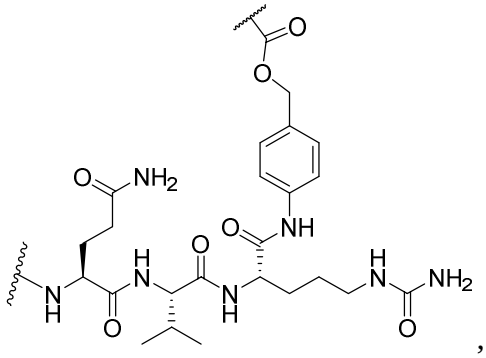
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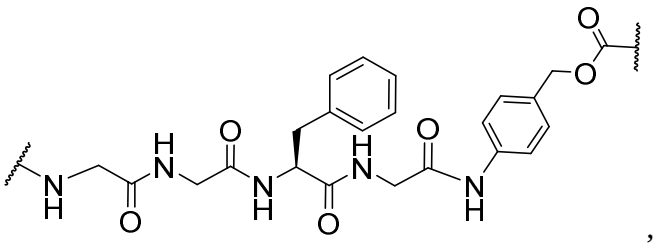
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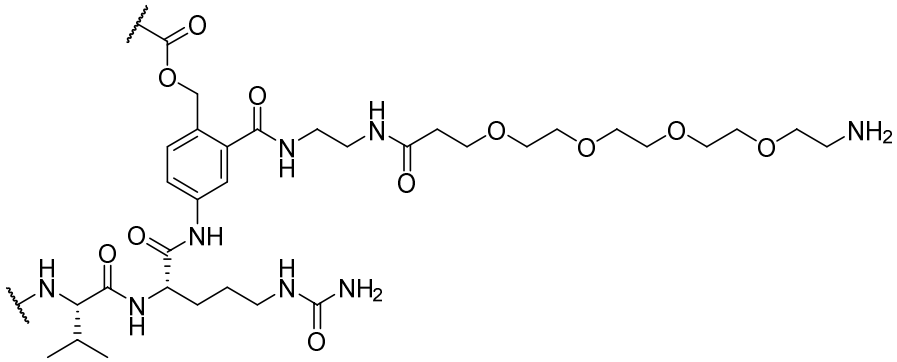
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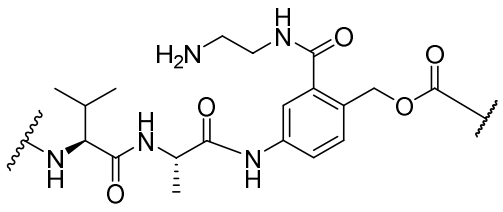
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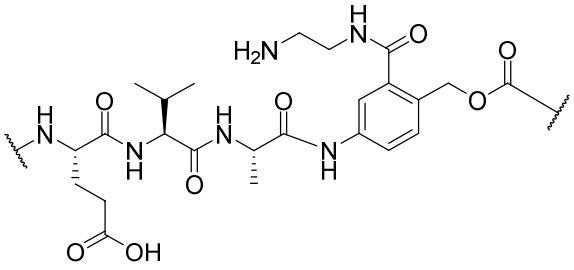
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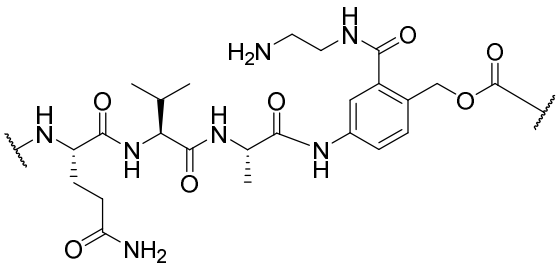
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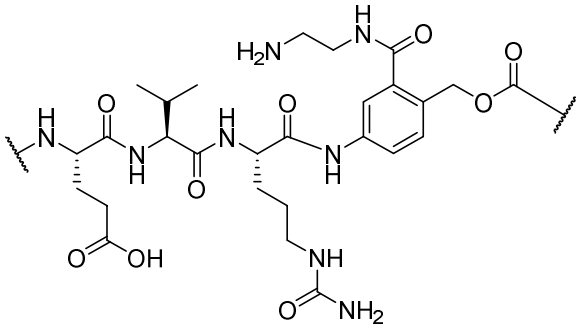
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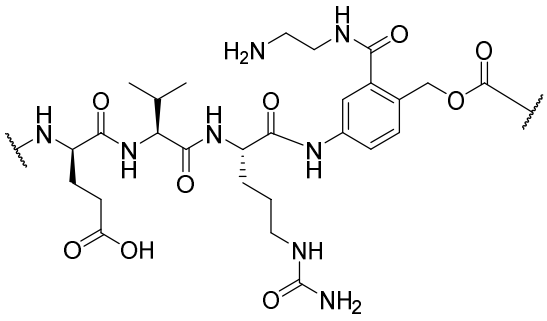
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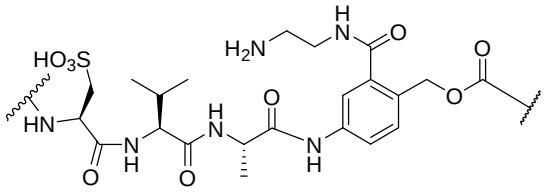
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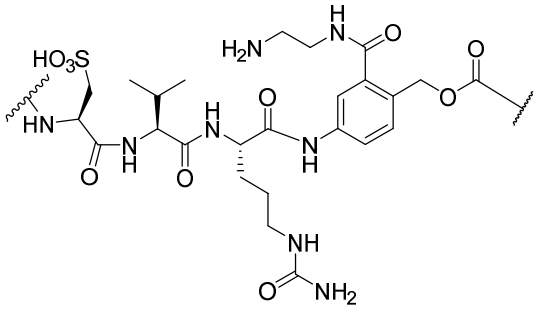
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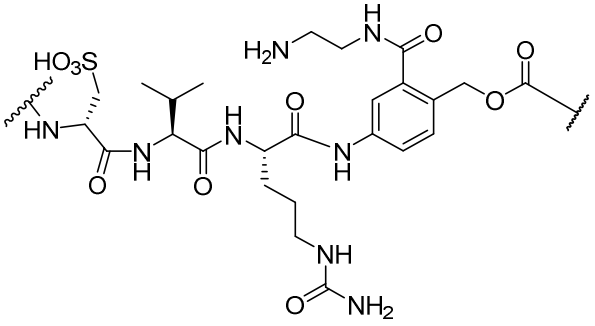
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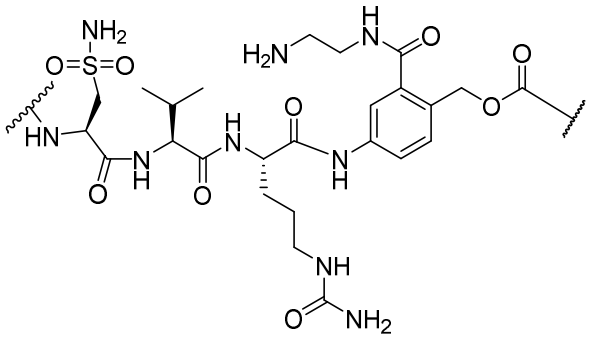
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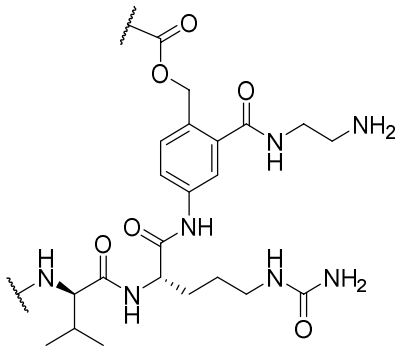
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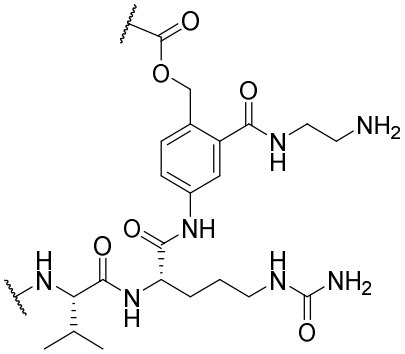
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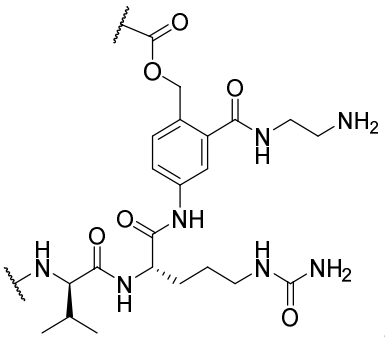
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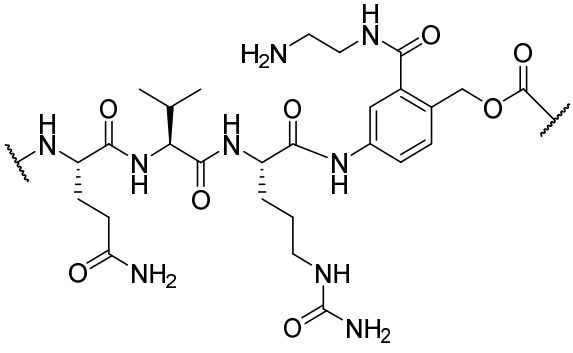
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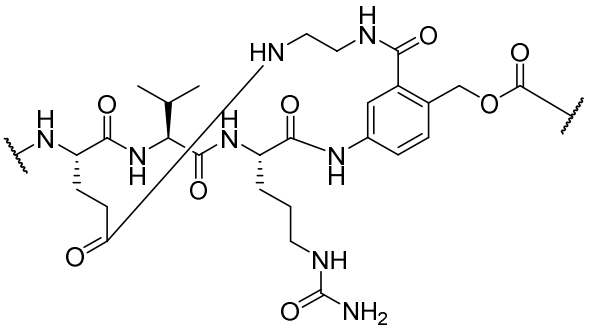
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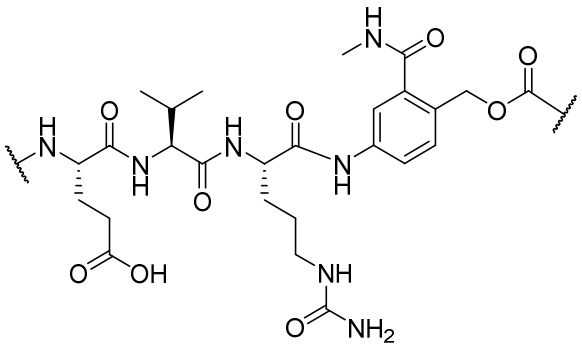
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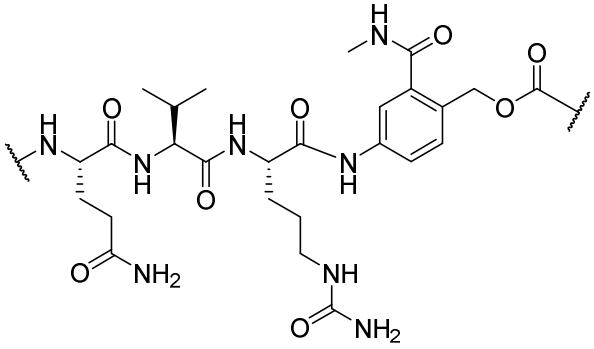
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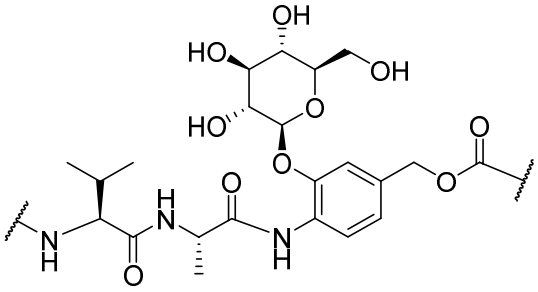
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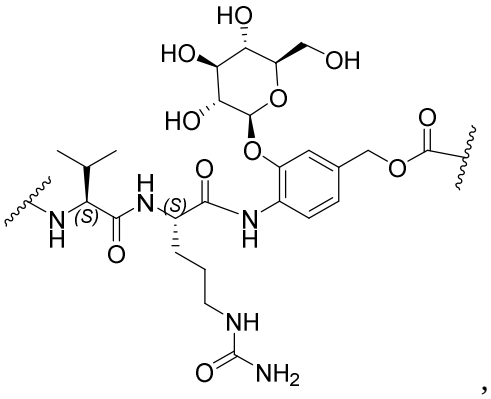
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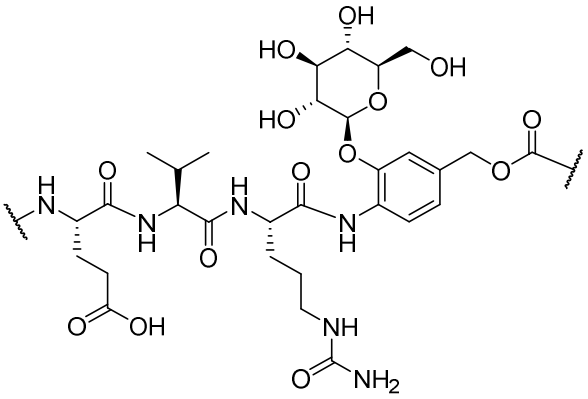
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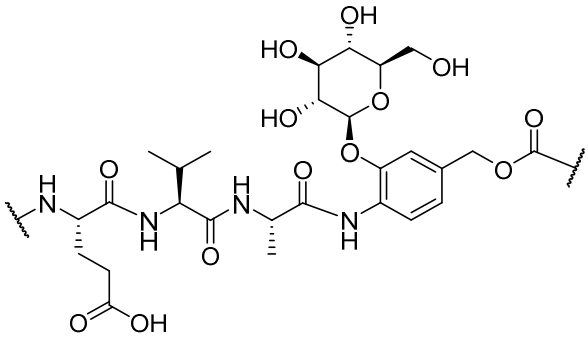
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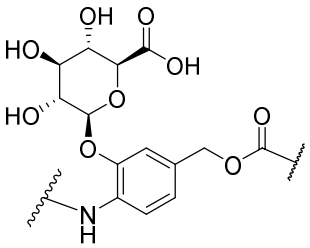
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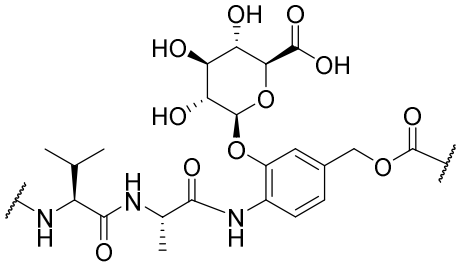
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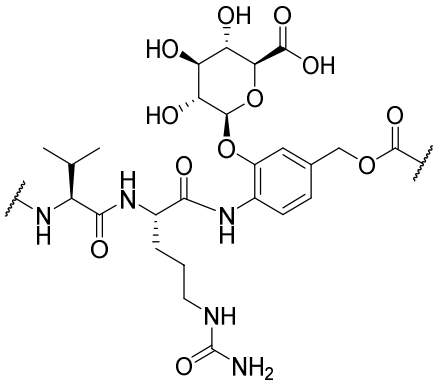
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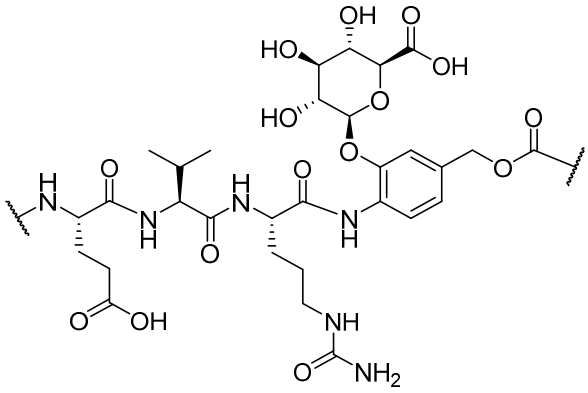
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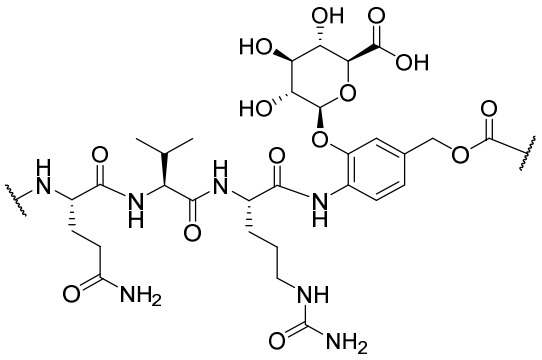
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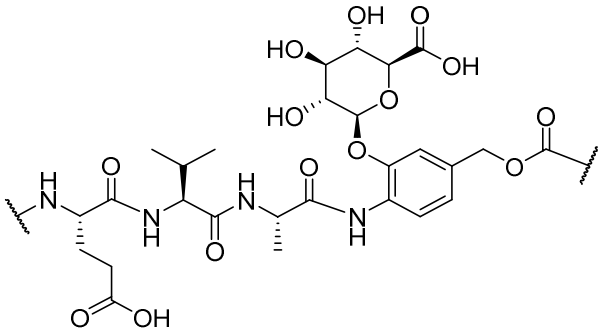
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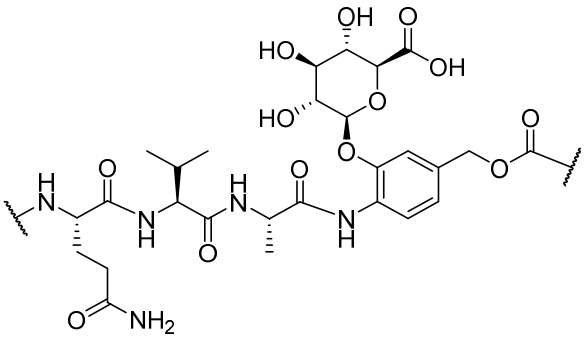
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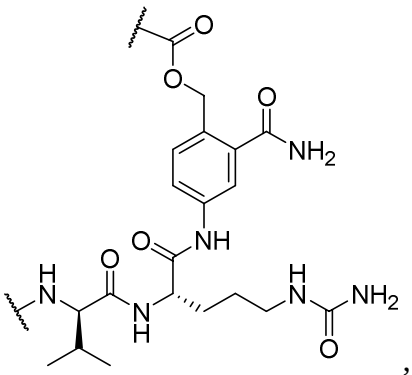
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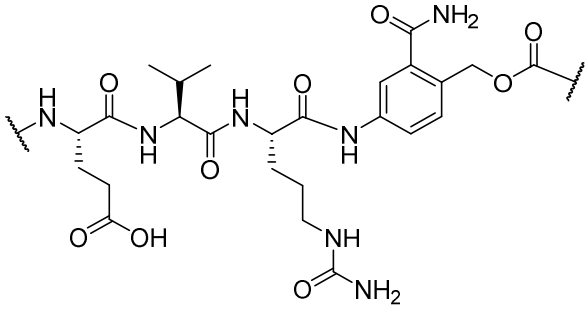
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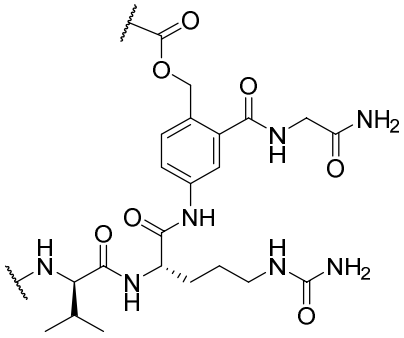
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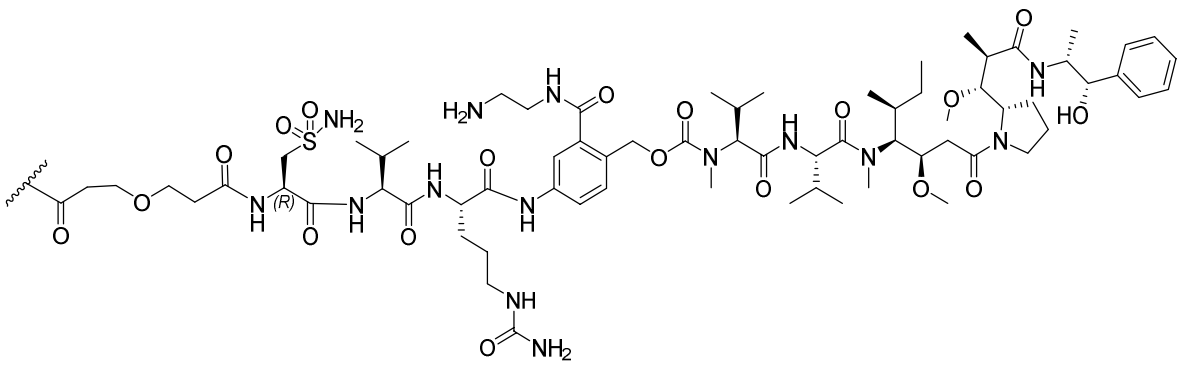
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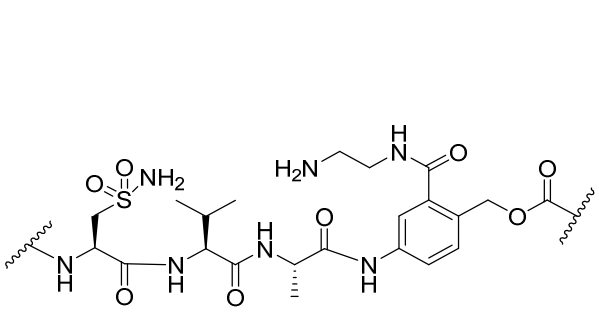
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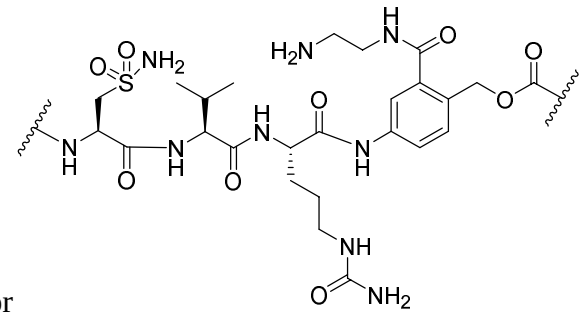
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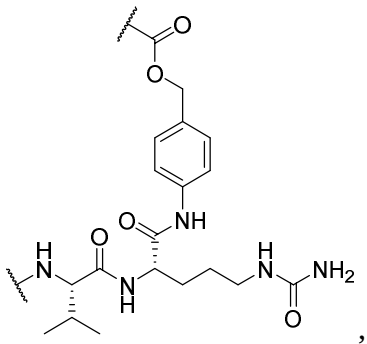
15. The compound of claim 1, or a pharmaceutically acceptable salt thereof, wherein L^2 is absent or is: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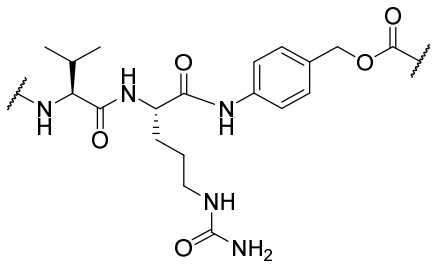
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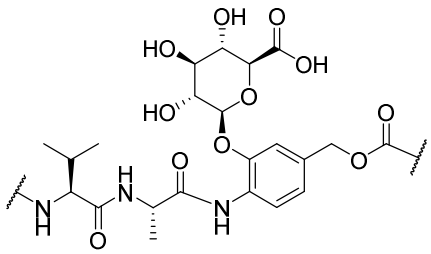
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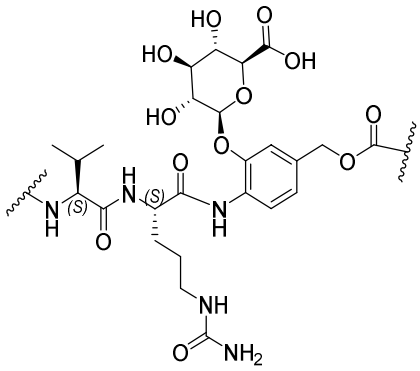
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16. The compound of any one of claims 1-10, or a pharmaceutically acceptable salt thereof, wherein L^1 is present and is $-X^2-L^3-L^4-$;

X^2 is $-C(=O)(CH_2)_p-$, $-(CH_2)_p-$, $-C(=O)CH(CH_2SO_3H)NHC(=O)-$, or $-(X^{2a})_p-$;

each X^{2a} is independently selected from natural or unnatural amino acids, wherein any free amine of an amino acid is optionally independently substituted with $-CH_3$;

p is 0, 1, 2, 3, 4, 5, or 6;

L^3 is absent, unsubstituted or substituted C_1-C_{10}alkylene, unsubstituted or substituted C_1-C_{10}heteroalkylene, C_4-C_{20}polyethylene glycol, or -$(X^3CH_2CH_2)_t$-;

each X^3 is independently selected from O and NR^{10};

each t is independently 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, or 12;

L^4 is absent, or -L^{4a}-$(CH_2)_u$-L^{4b}-$(CH_2)_u$-L^{4c}-;

L^{4a} is absent, -O-, -NR^{10}-, -$NR^{10}C(=O)$-, -$C(=O)NR^{10}$-, or -C(=O)-;

L^{4b} is absent, or unsubstituted or substituted *N*-containing 5 to 10 membered heterocycloalkylene; wherein any free amine of the *N*-containing 5 to 10 membered heterocycloalkylene is optionally independently substituted with -CH_2CO_2H;

L^{4c} is absent, -O-, -NR^{10}-, -$NR^{10}C(=O)$-, -$C(=O)NR^{10}$-, -$C(=O)NR^{10}(CH_2)_uO(CH_2)_uC(=O)$-, $CH(CH_2SO_3H)C(=O)NR^{10}(CH_2)_uO(CH_2)_uC(=O)$-, -C(=O)-, -CH(=N)-, -CH(=N-NH)-, -CCH_3(=N)-, -CCH_3(=N-NH)-, -C(=O)-(C_1-C_6alkylene)-, -$C(=O)NR^{10}$-(C_1-C_6alkylene)-, -$NR^{10}C(=O)$-(C_1-C_6alkylene)-, -NR^{10}-(C_1-C_6alkylene)- or C_1-C_6alkylene-;

each u is independently 0, 1, 2, 3, 4, 5, or 6; and

each R^{10} is independently selected from hydrogen, and C_1-C_6alkyl.

17. The compound of claim 11, or a pharmaceutically acceptable salt thereof, wherein:

X^2 is -$C(=O)(CH_2)_p$-; p is 0, 1, 2, 3 or 4;

L^3 is unsubstituted or substituted C_1-C_{10}heteroalkylene, C_4-C_{20}polyethylene glycol, or -$(X^3CH_2CH_2)_t$-;

each X^3 is independently selected from O and NR^{10}; and

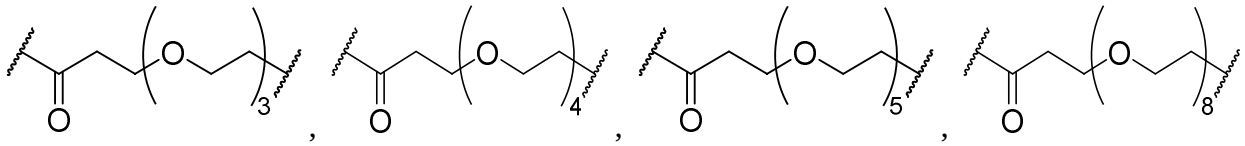
each t is independently 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, or 12.

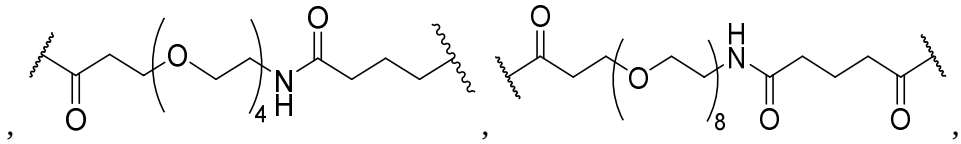
18. The compound of any one of claims 10-11, or a pharmaceutically acceptable salt thereof, wherein:

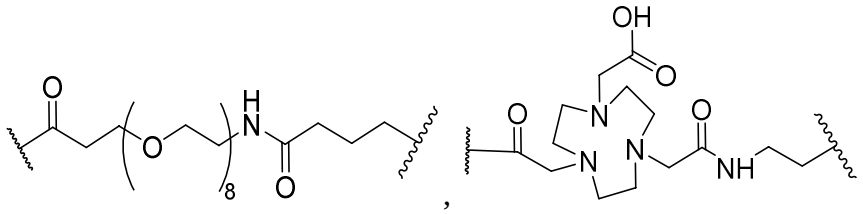
L^4 is absent or -L^{4a}-; and

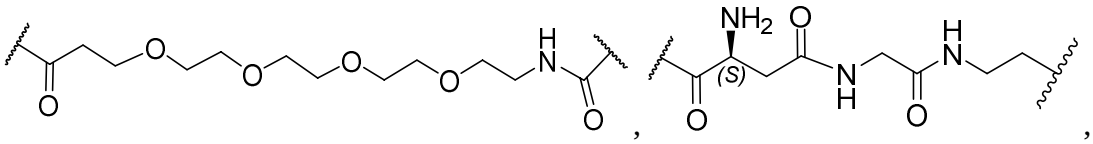
L^{4a} is -NR^{10}-, -$NR^{10}C(=O)$-, -$C(=O)NR^{10}$-, or -C(=O)-.

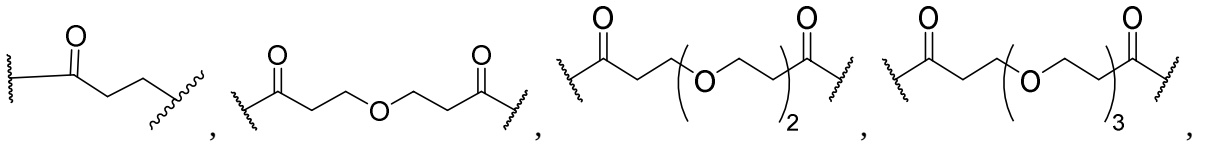
19. The compound of claim 10, or a pharmaceutically acceptable salt thereof, wherein L^1 is absent or is:

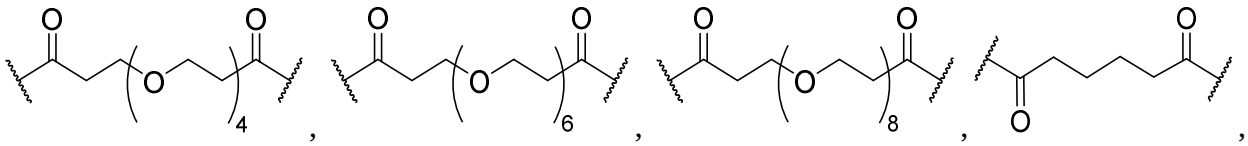


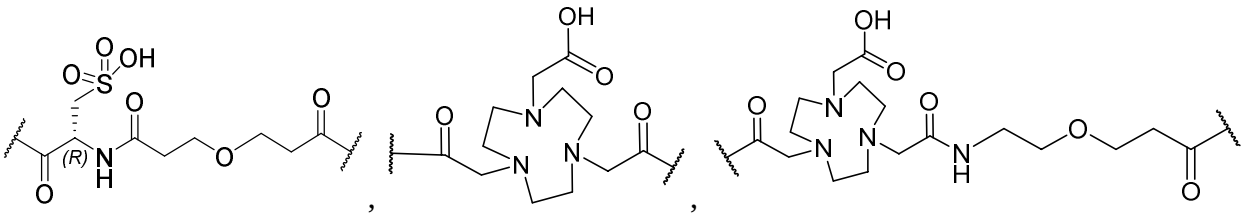


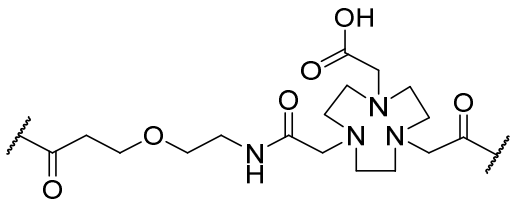


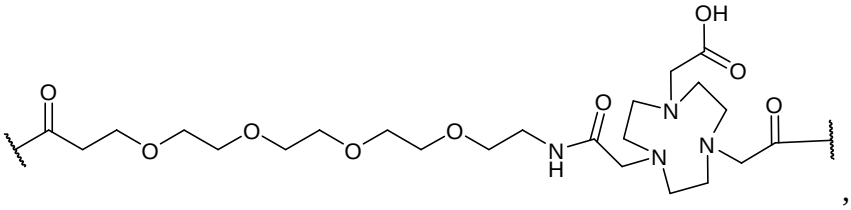


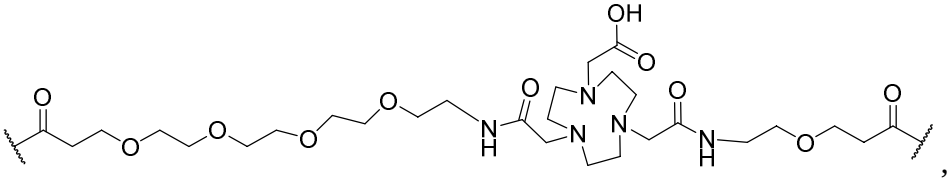












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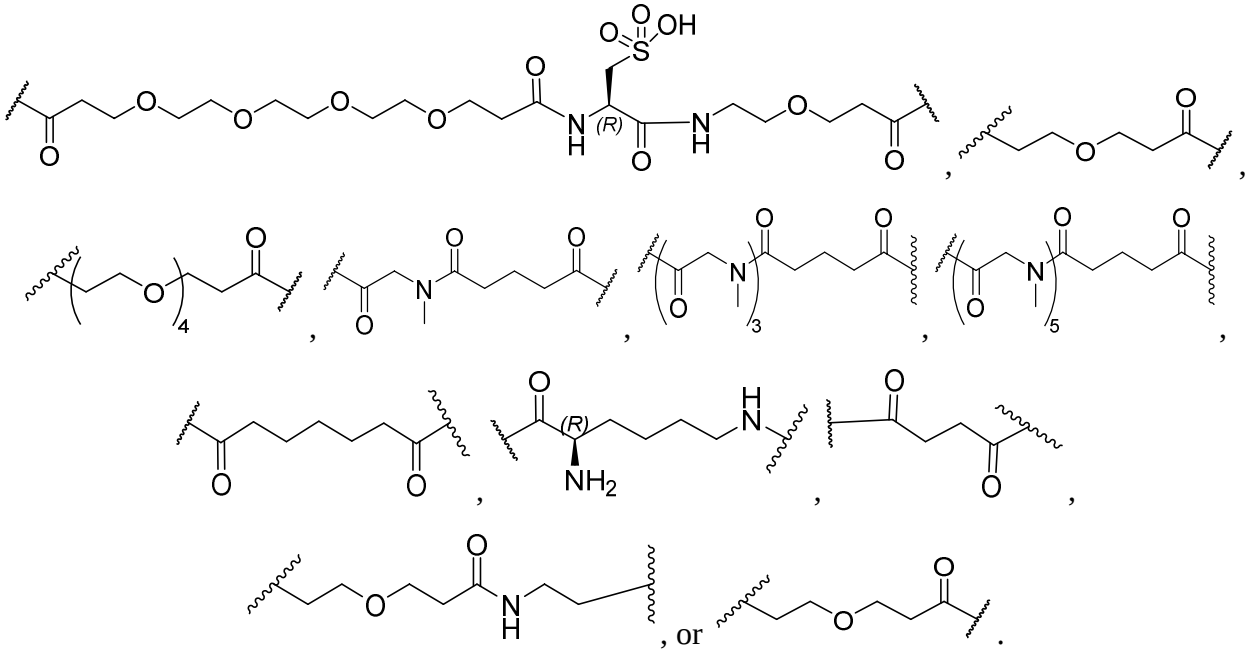
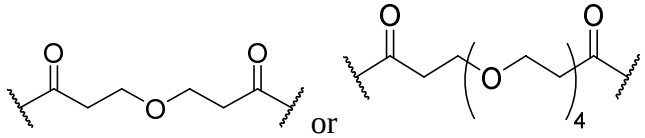
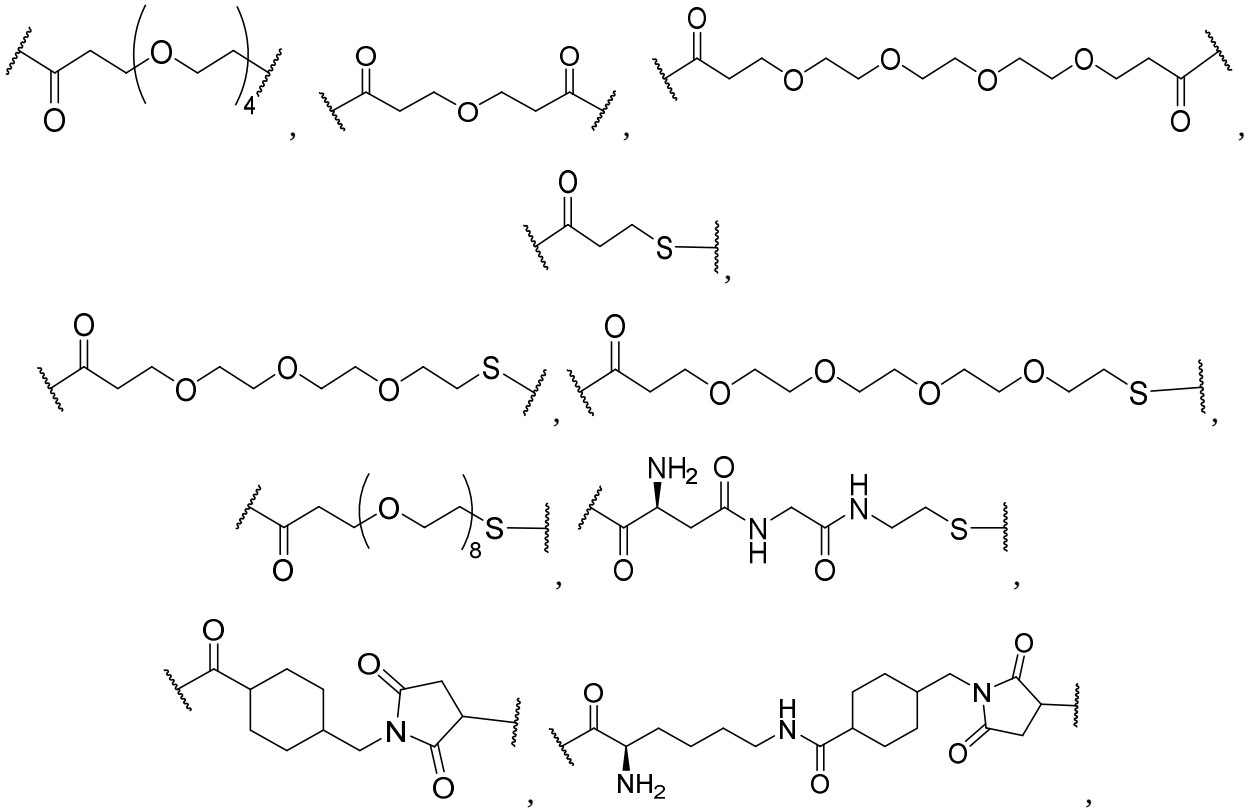
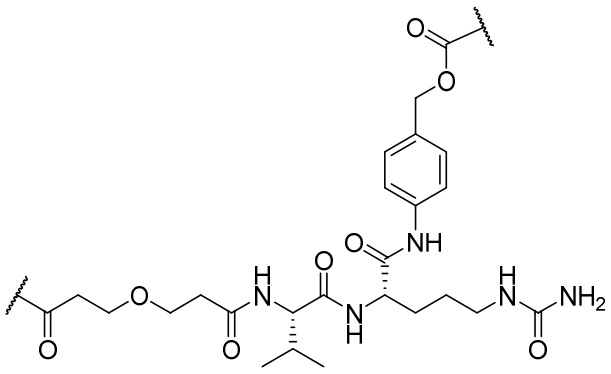


20. The compound of claim 10, or a pharmaceutically acceptable salt thereof, wherein L^1 is absent or is:



21. The compound of claim 1, or a pharmaceutically acceptable salt thereof, wherein L is:





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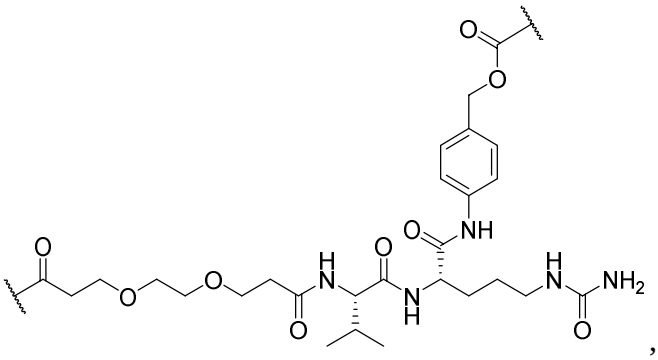

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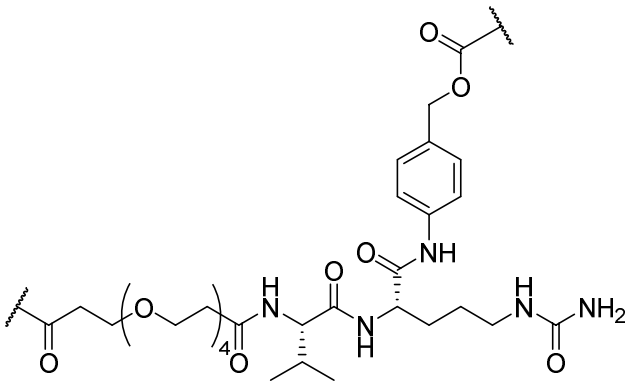

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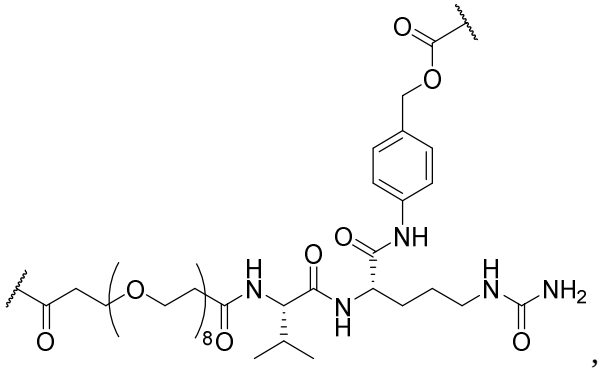

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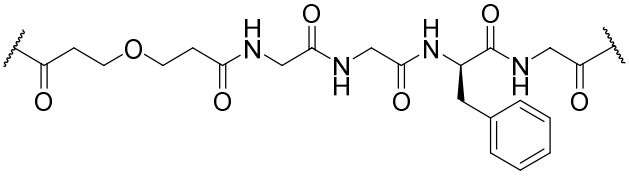

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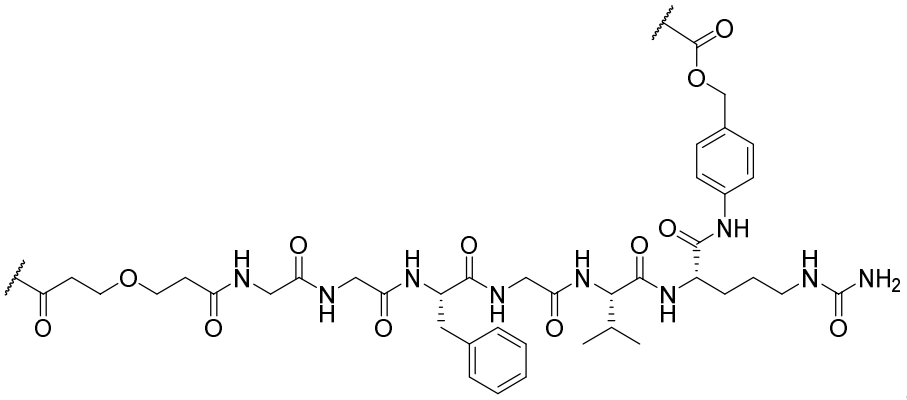

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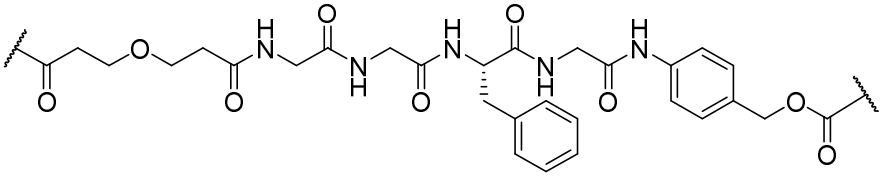

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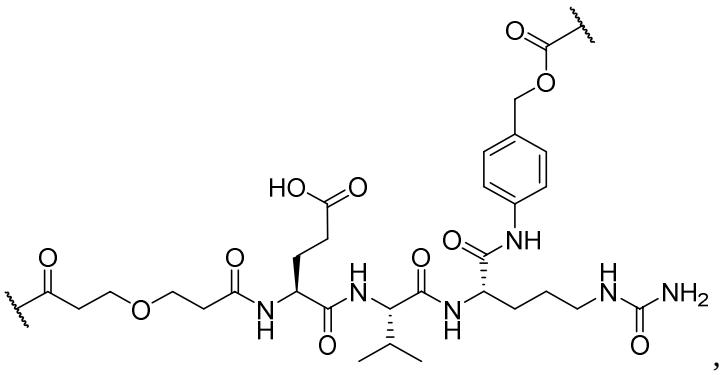

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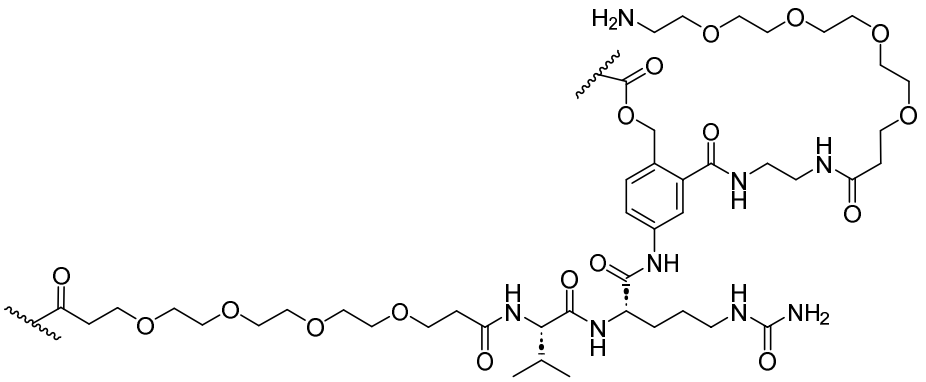

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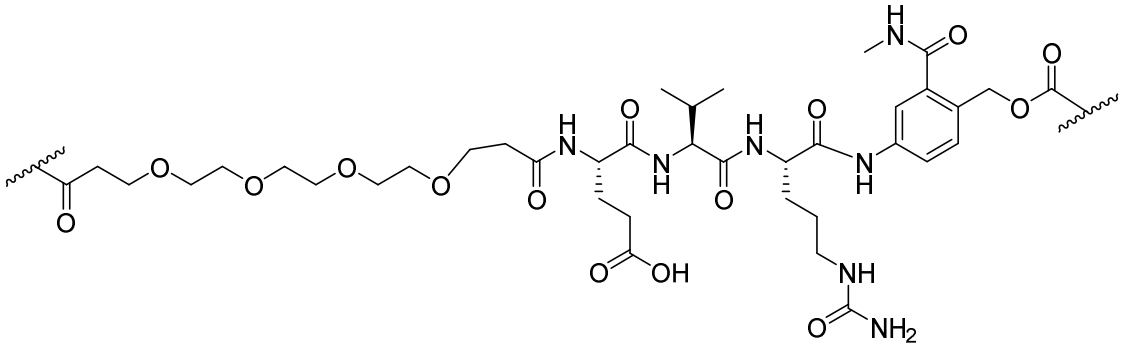

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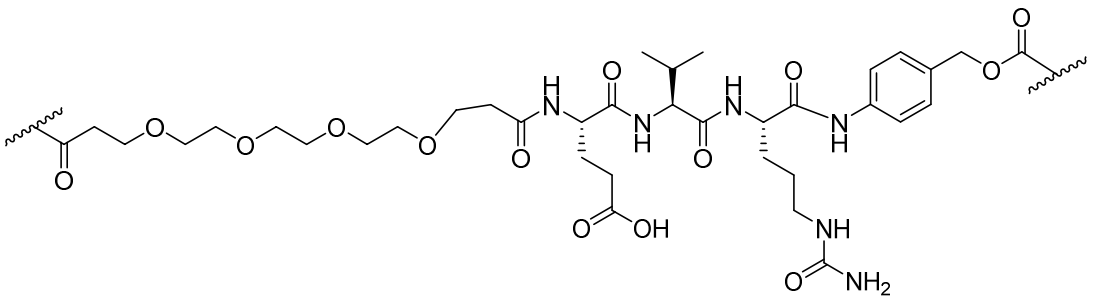

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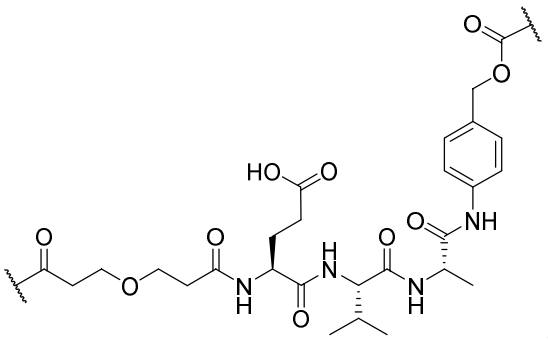

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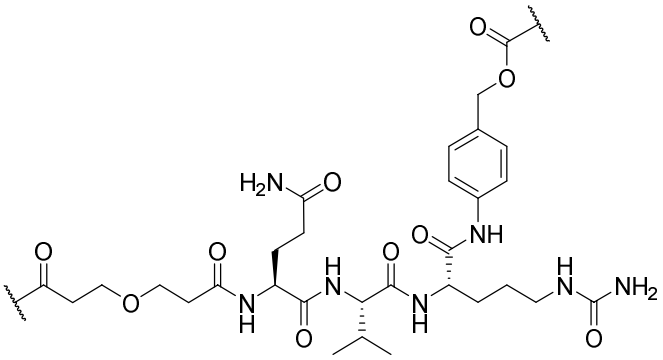

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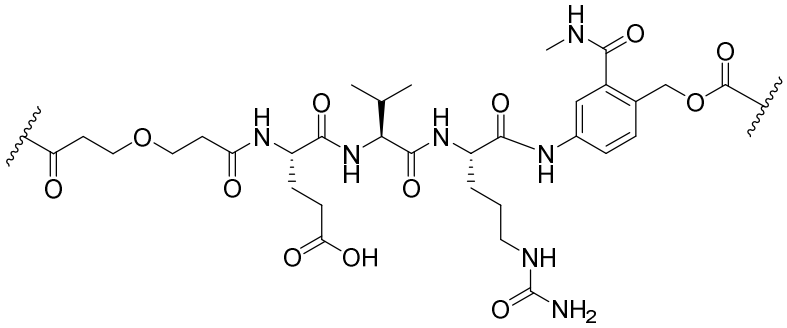

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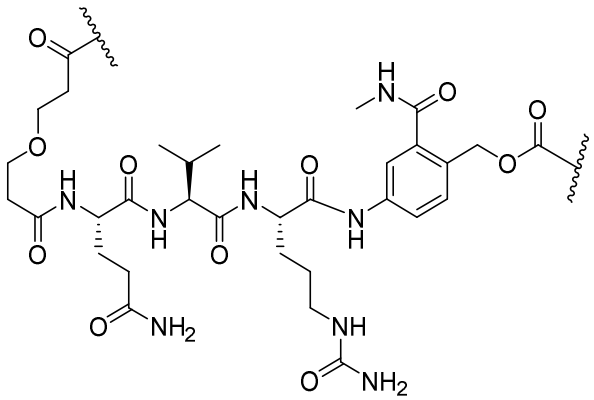

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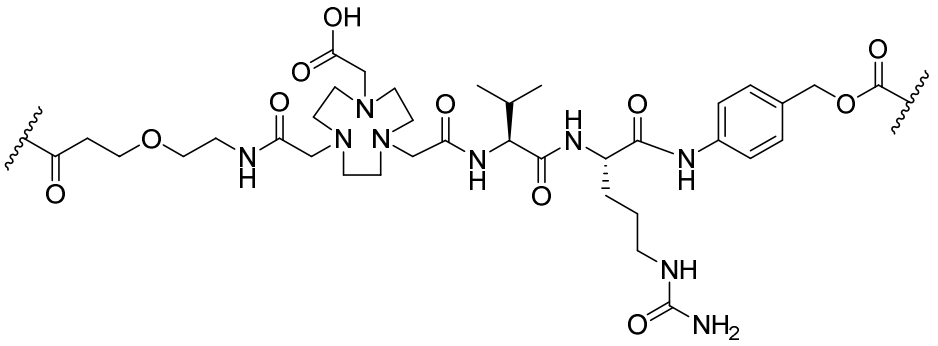

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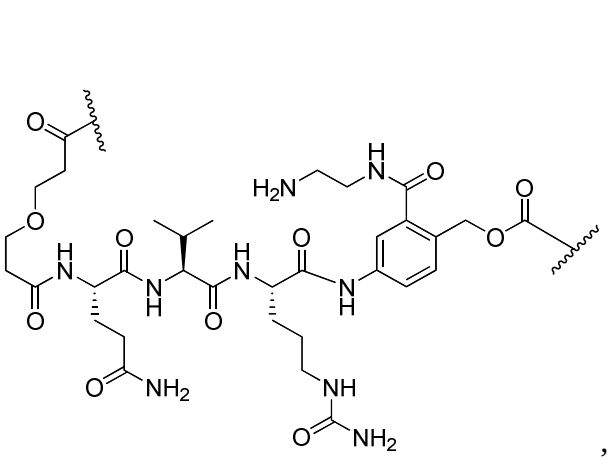

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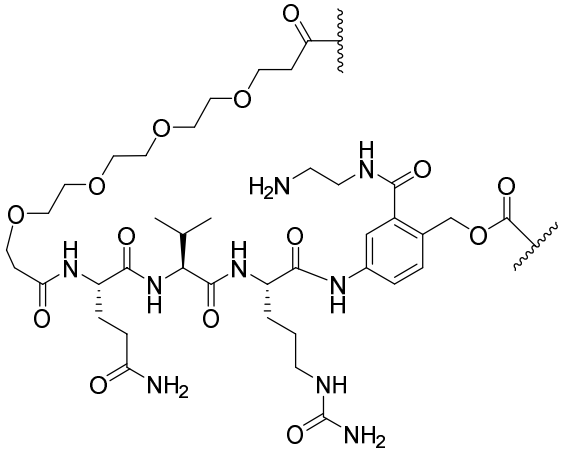

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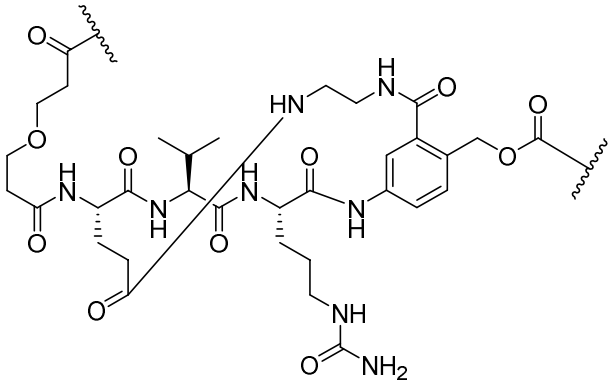

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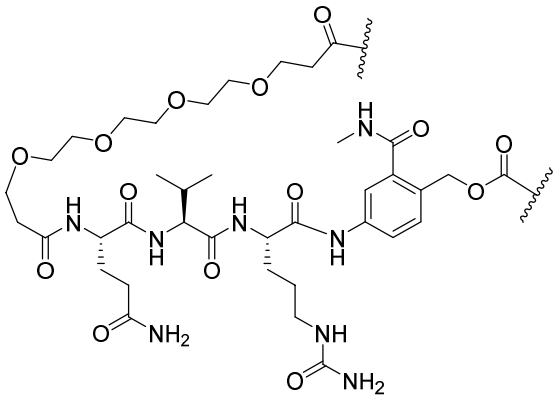

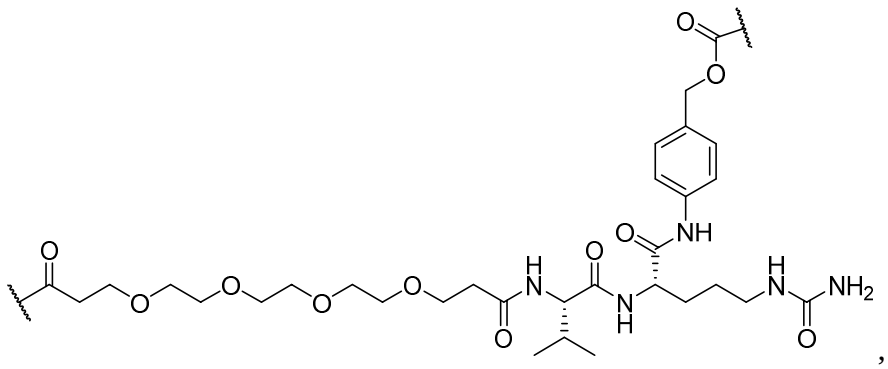

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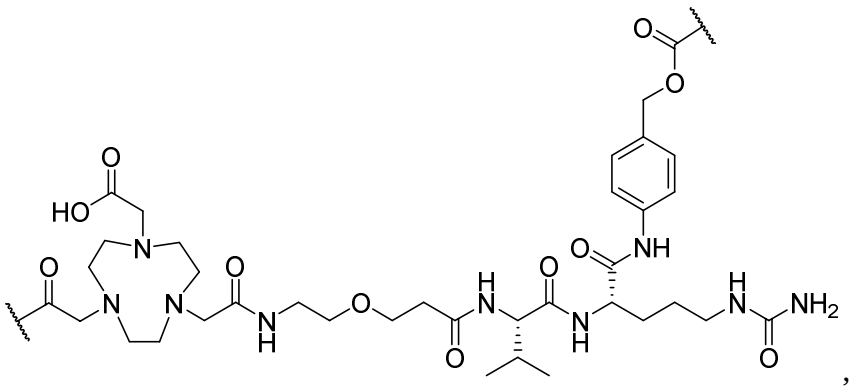

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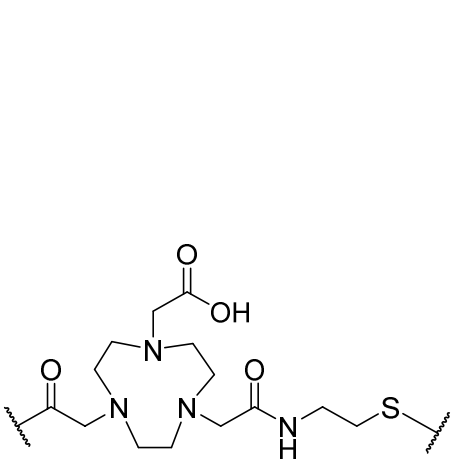

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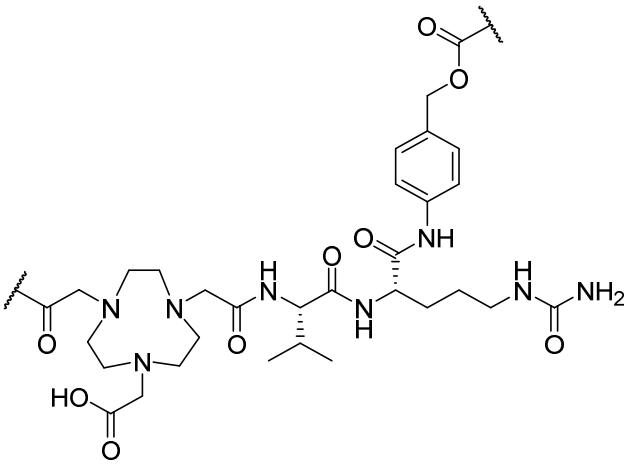

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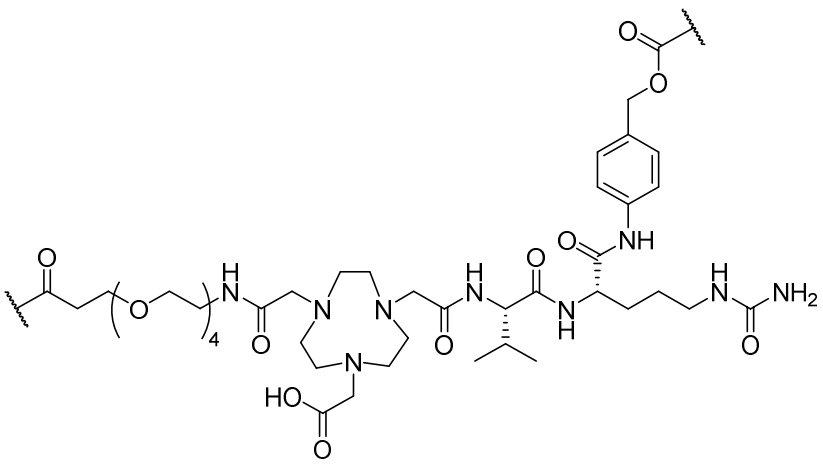

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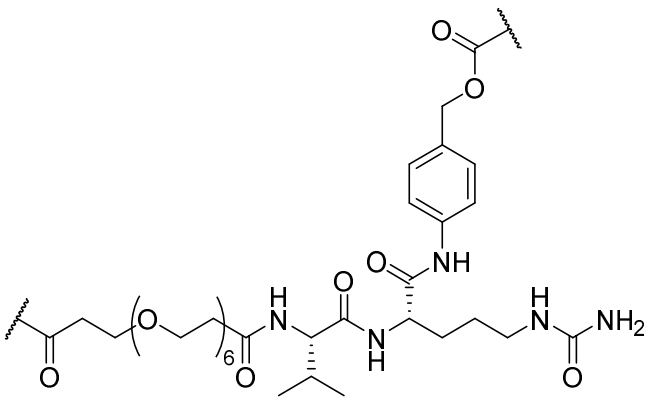

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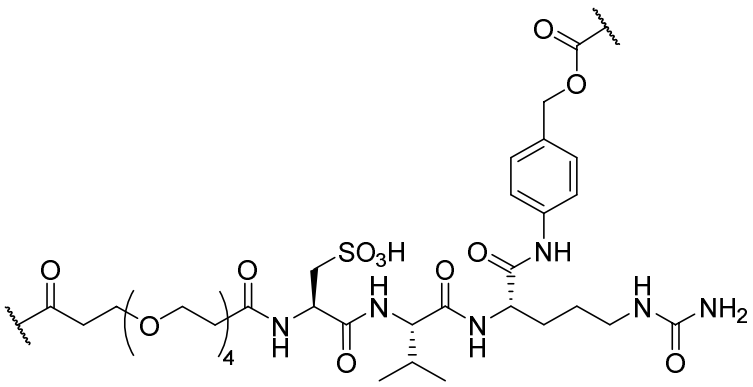

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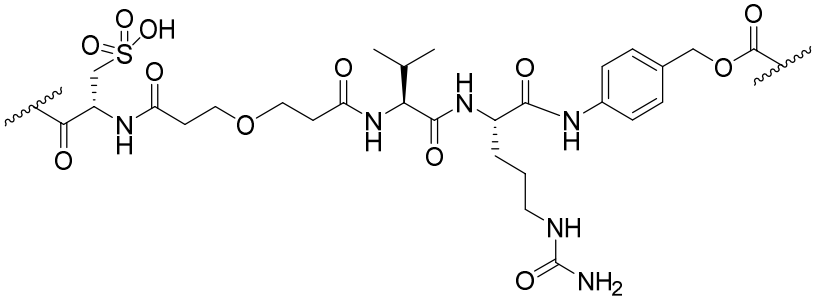

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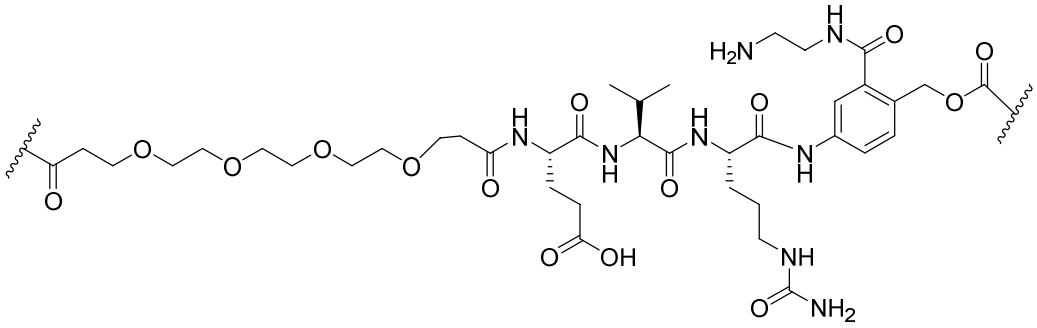

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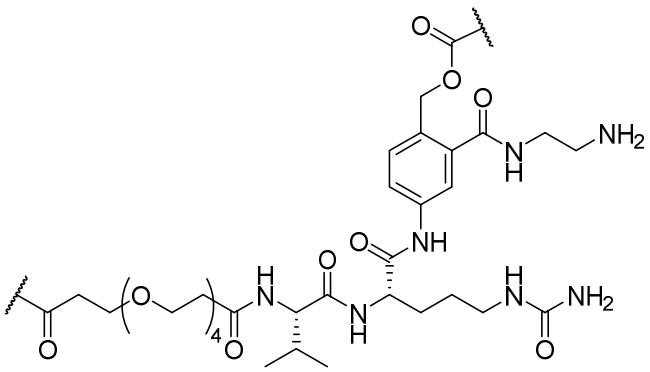

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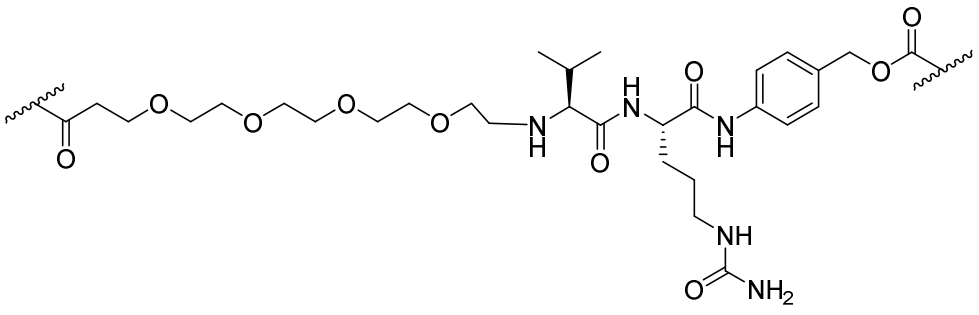

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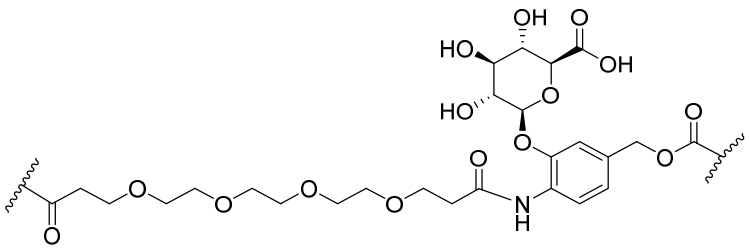

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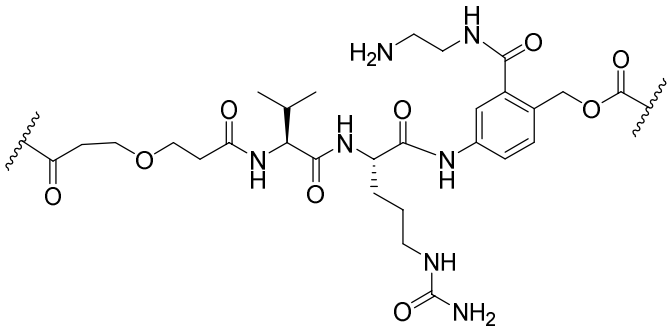

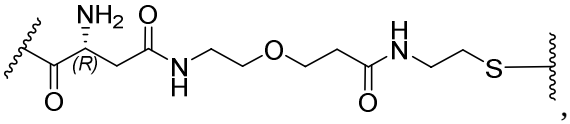

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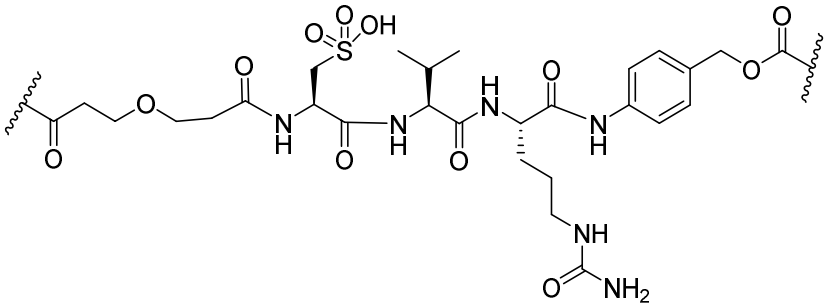

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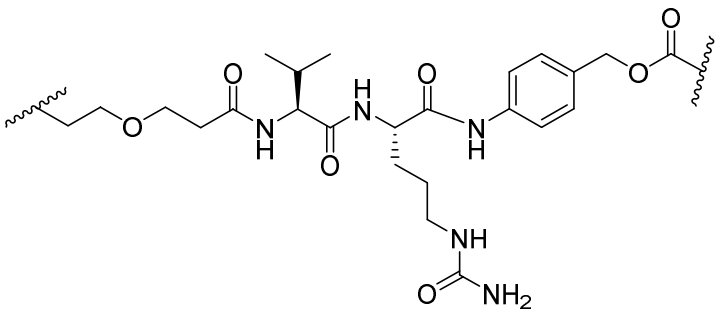

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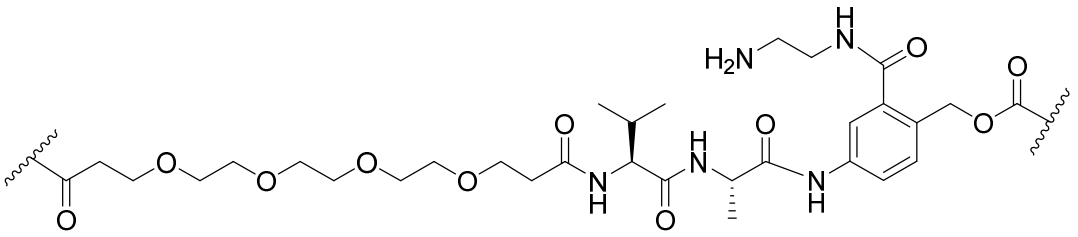

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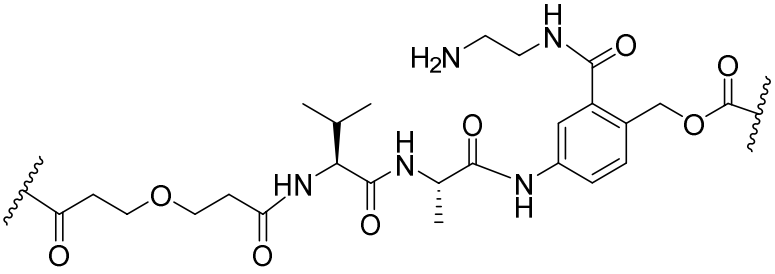

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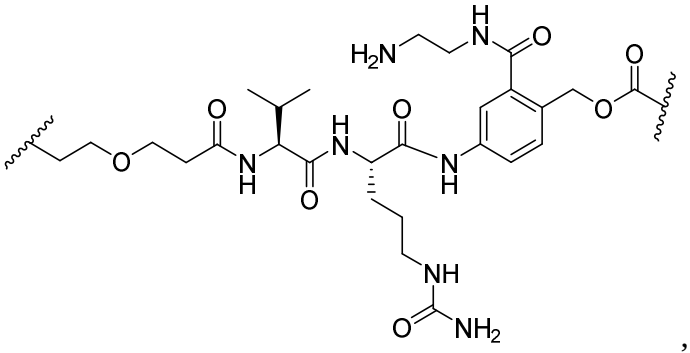

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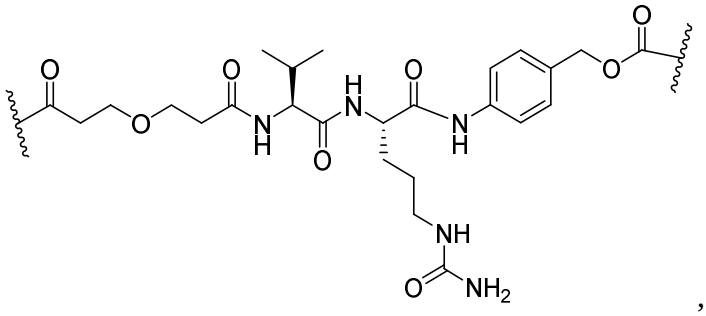

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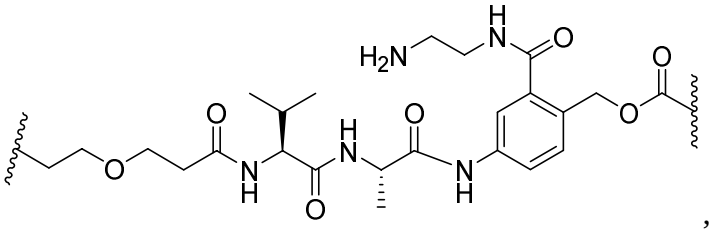

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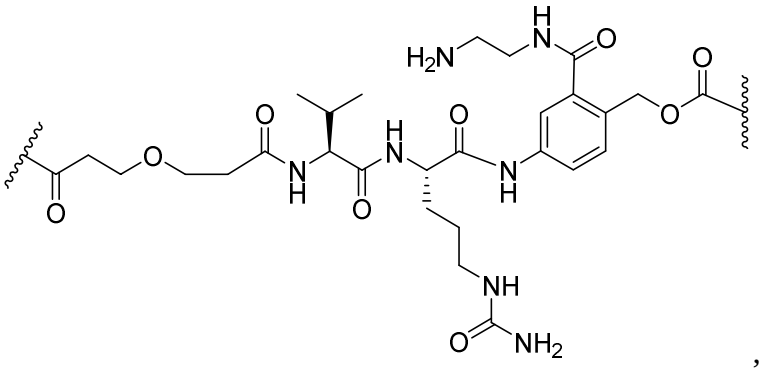

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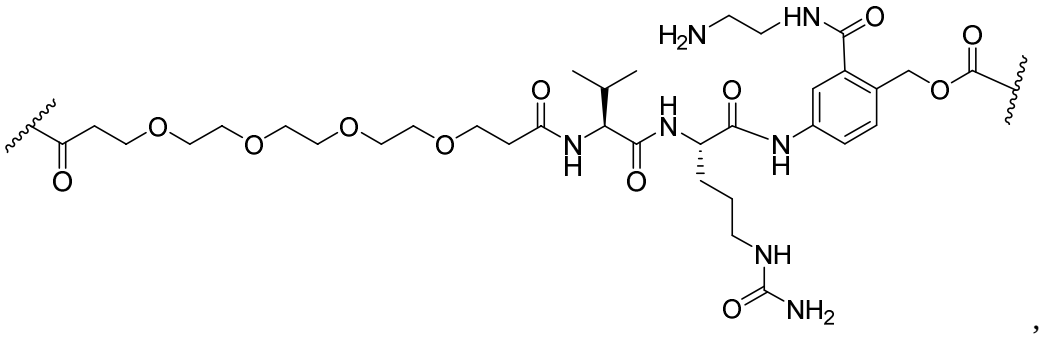

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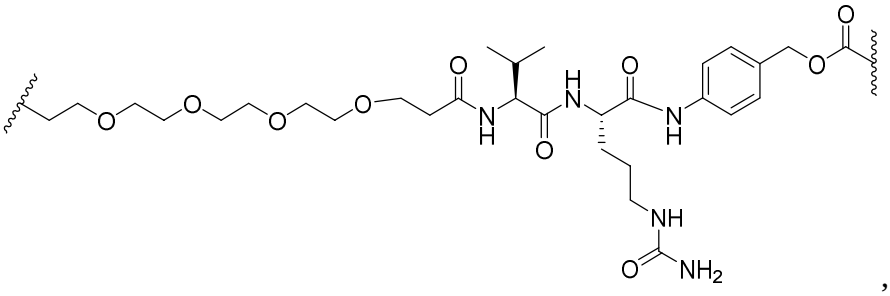

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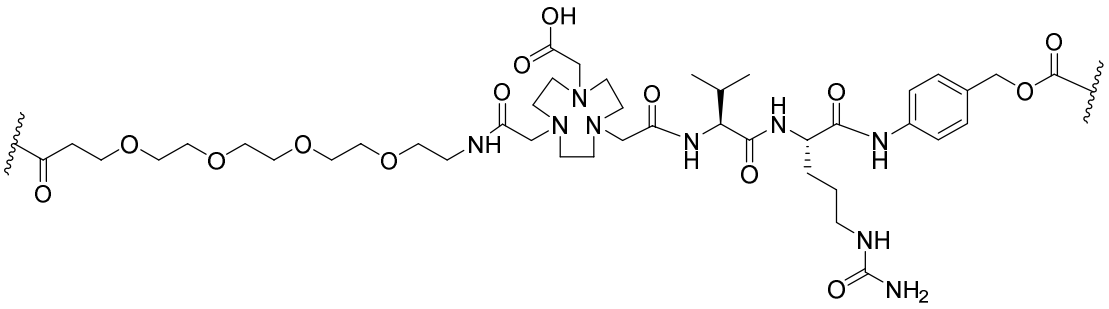

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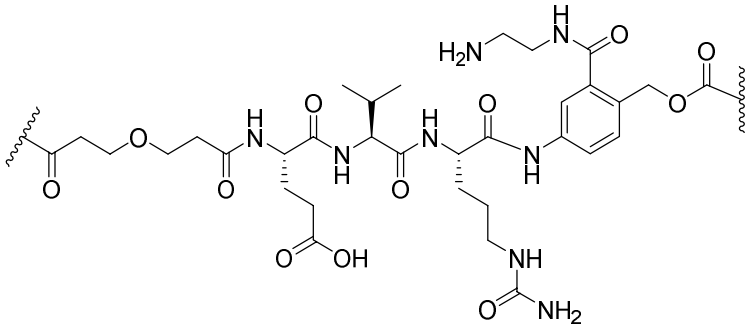

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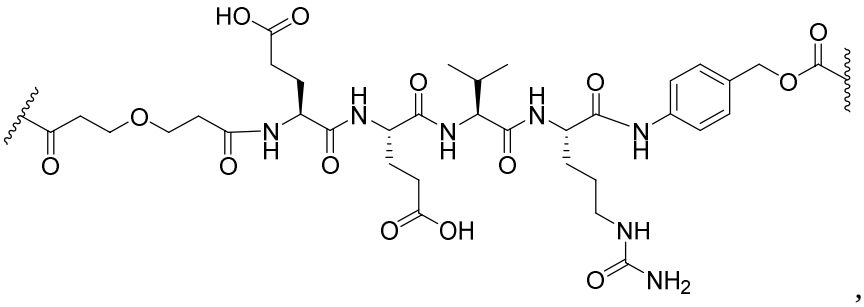

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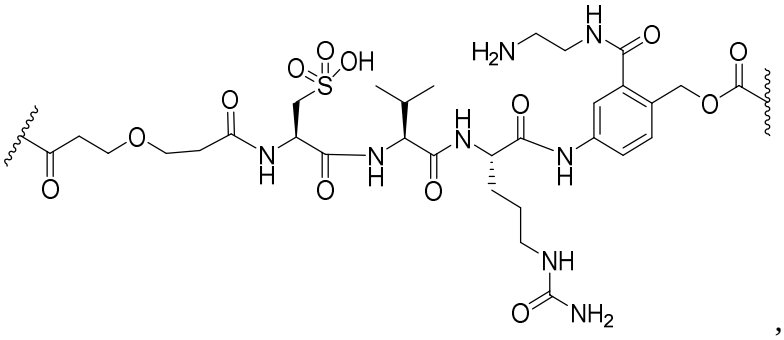

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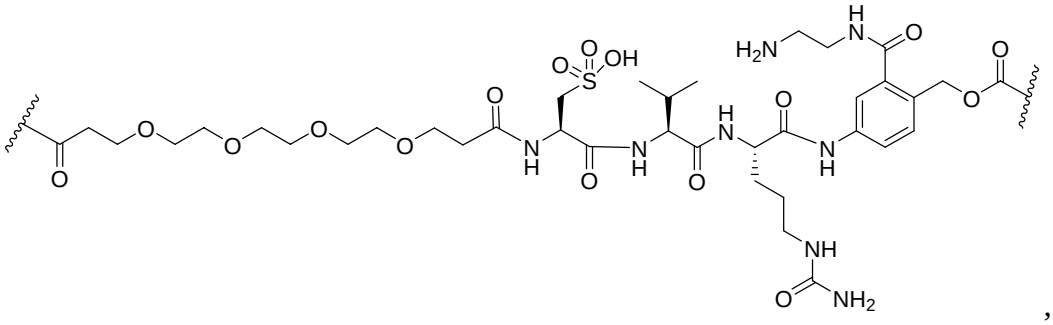

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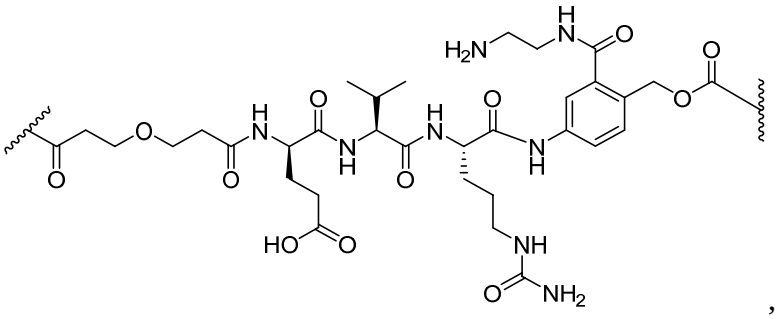

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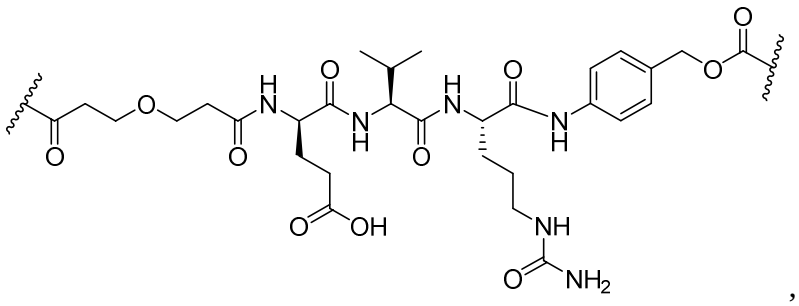

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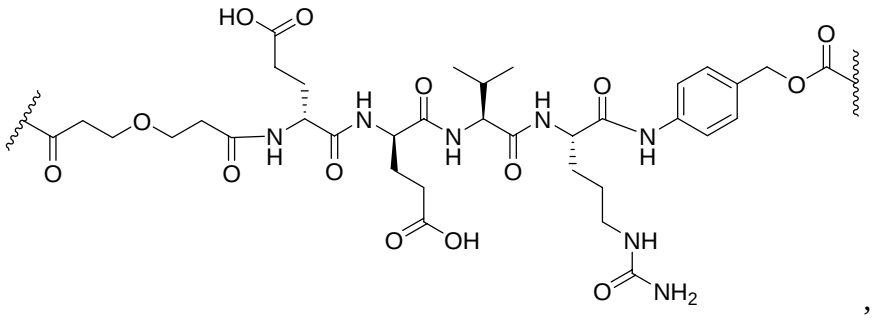

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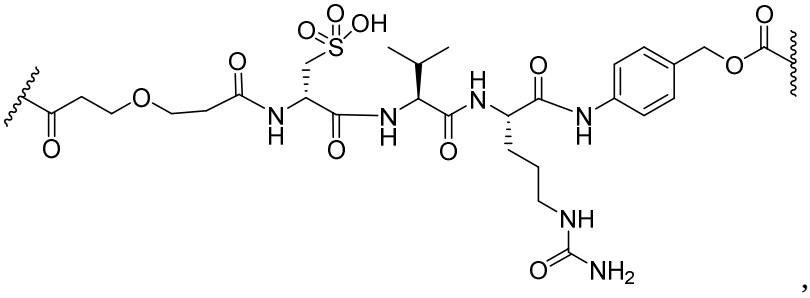

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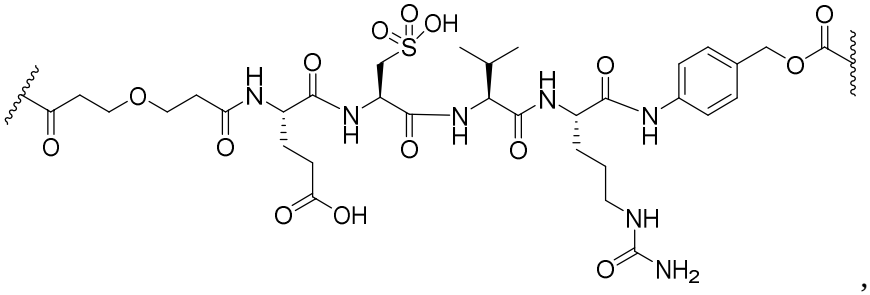

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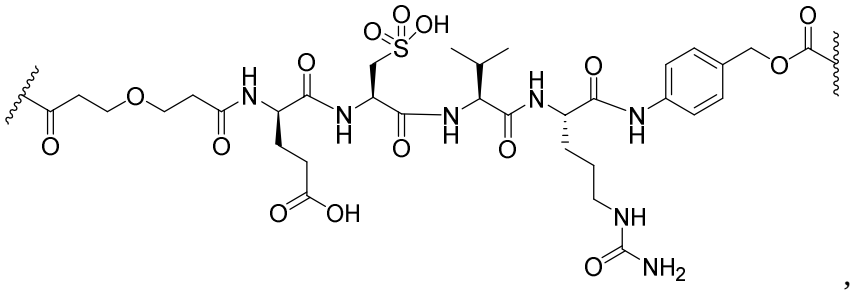

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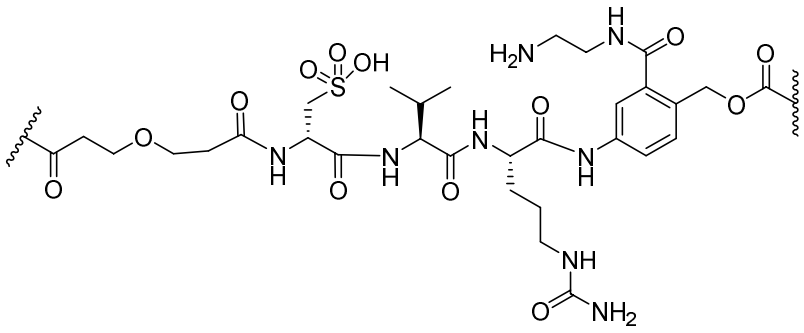

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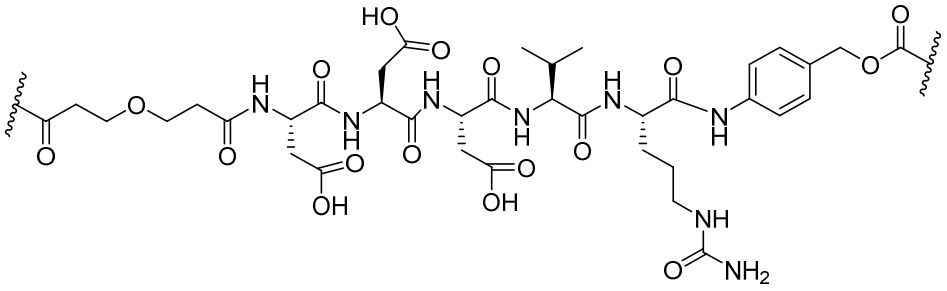

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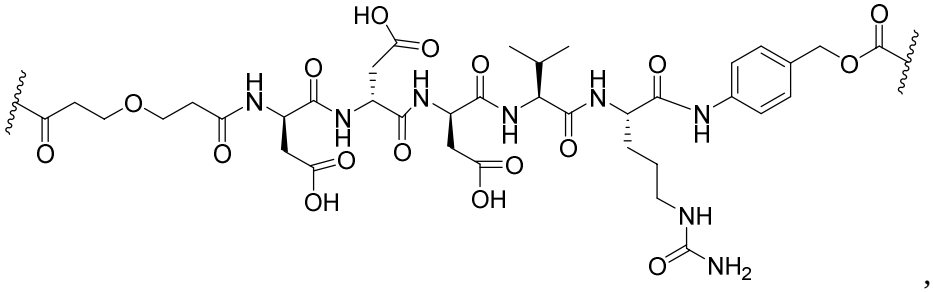

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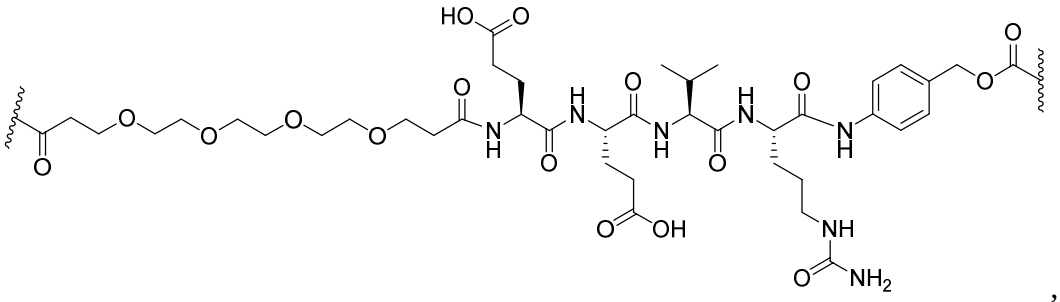

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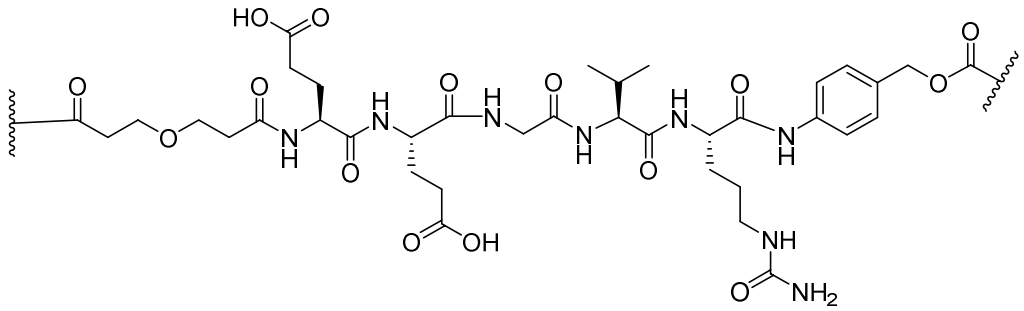

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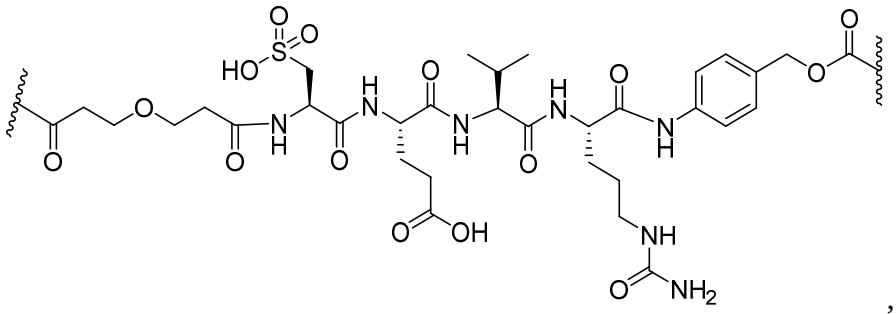

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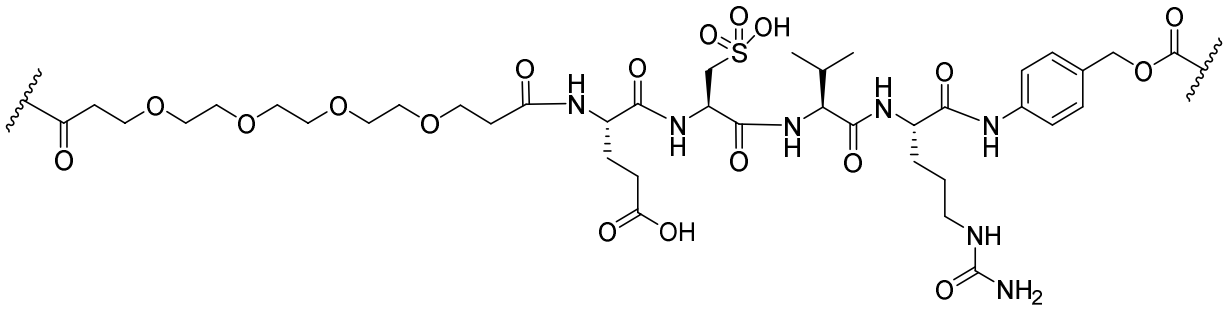

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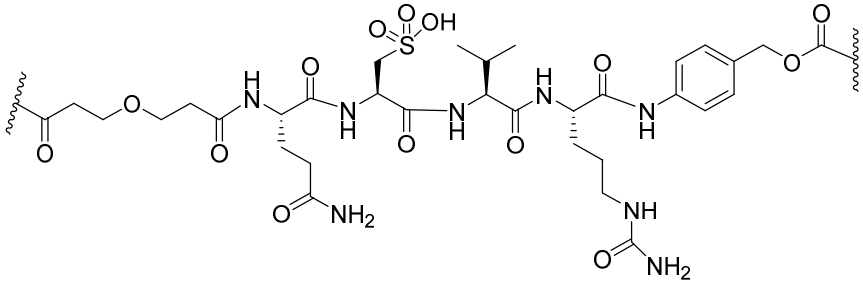

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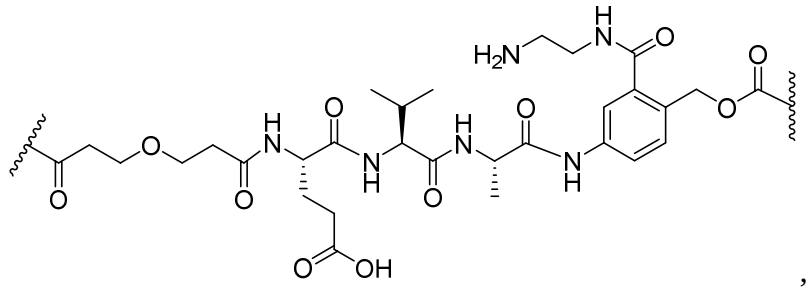

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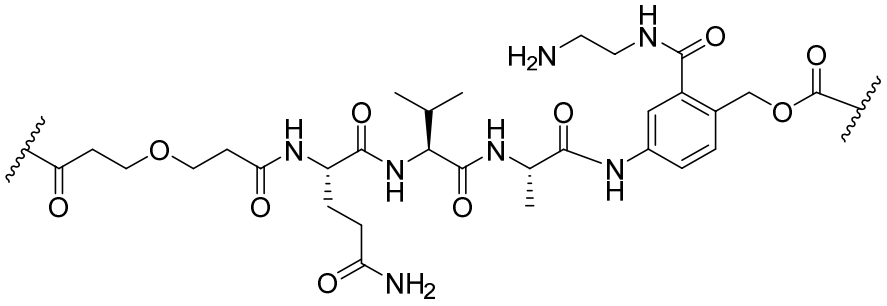

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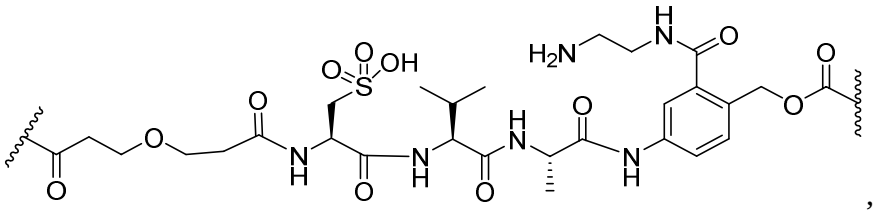

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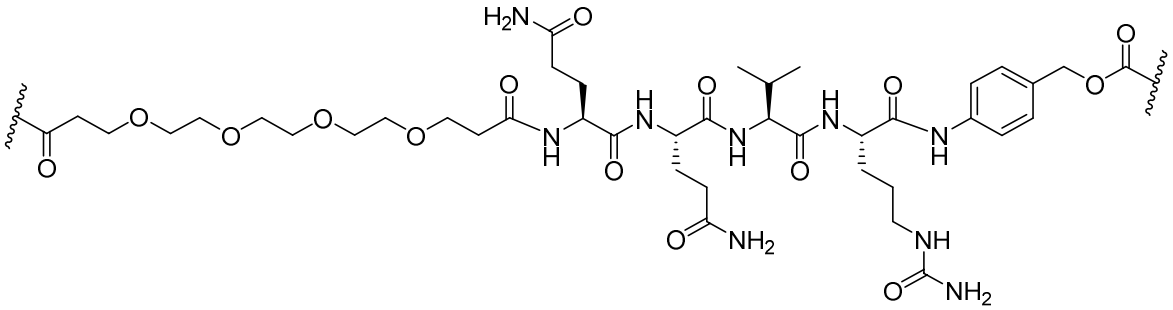

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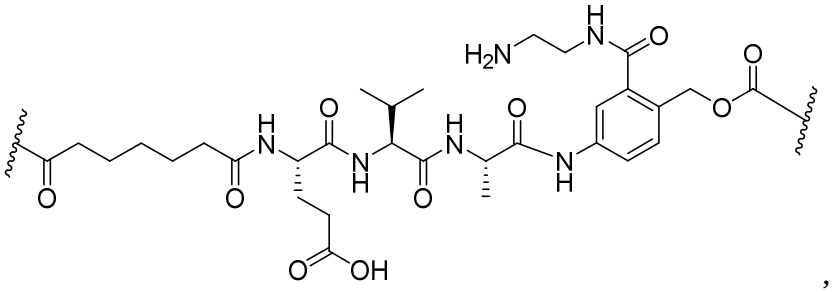

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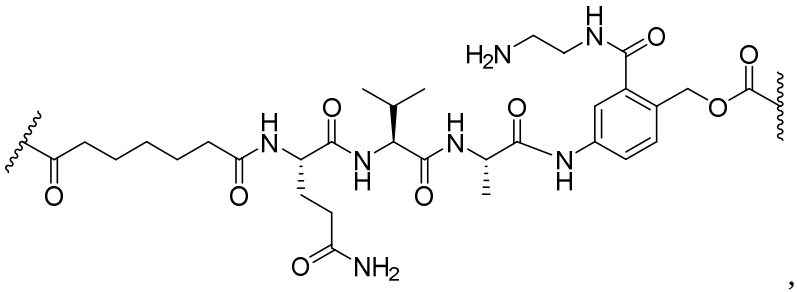

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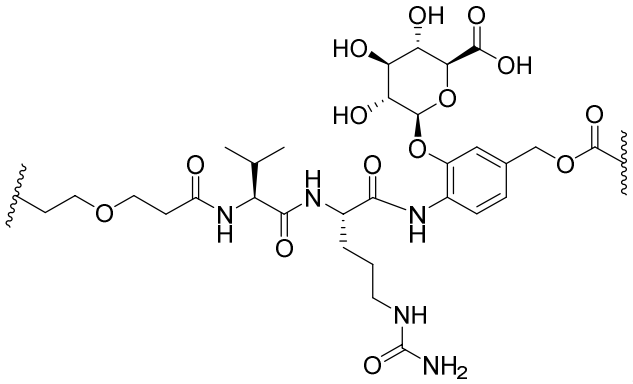

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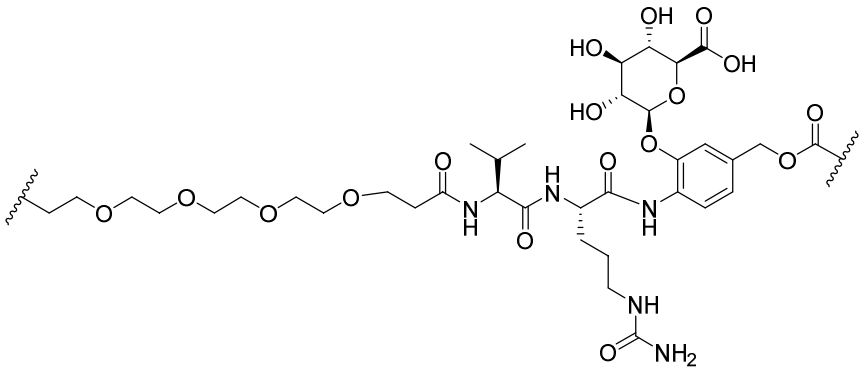

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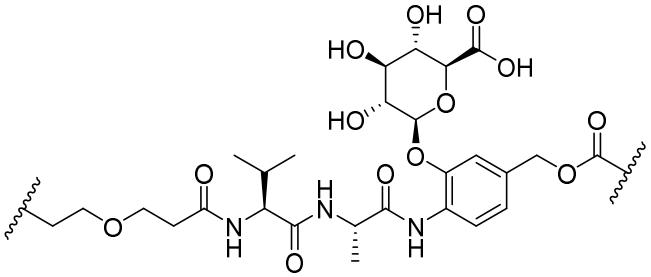

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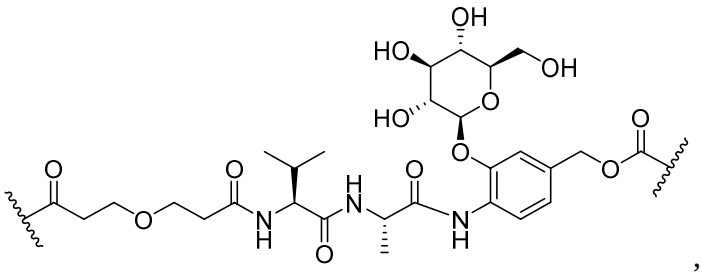

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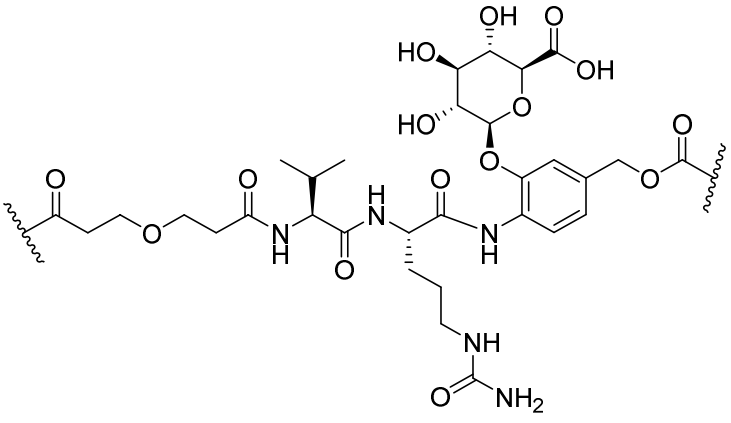

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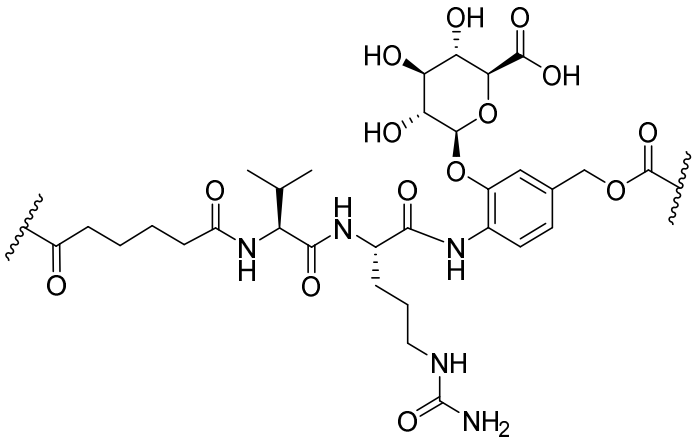
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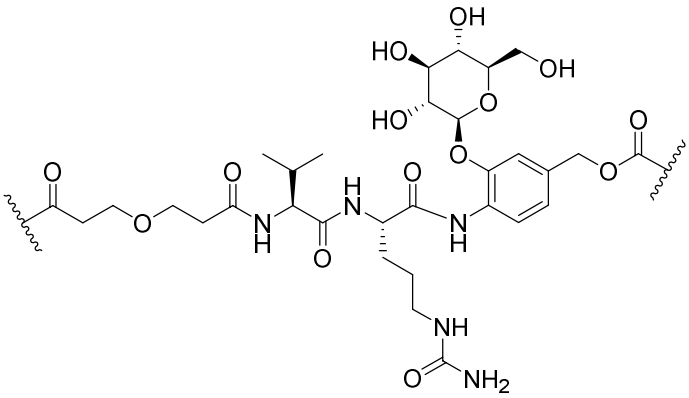
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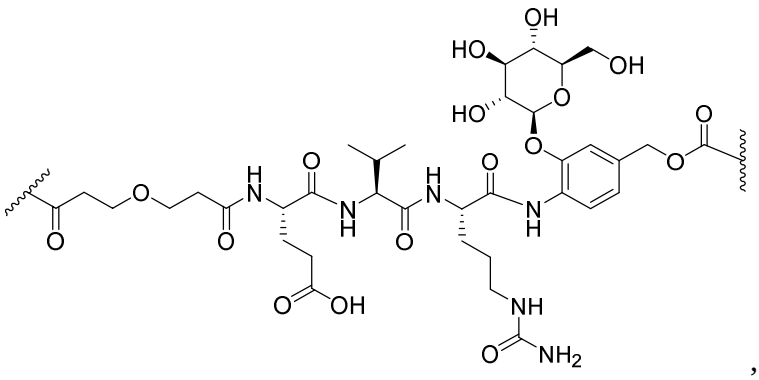
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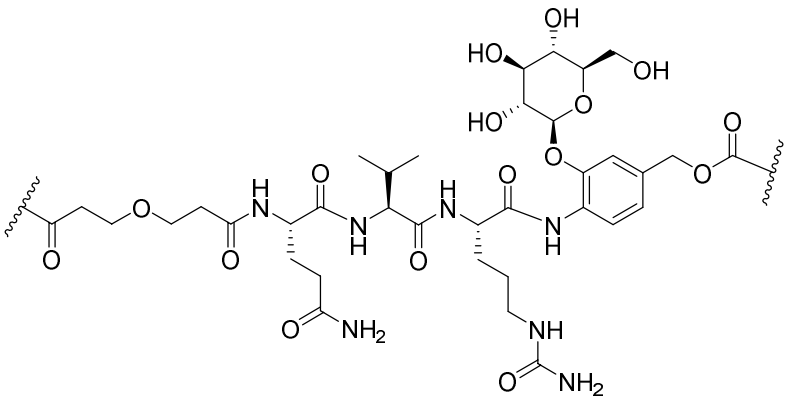
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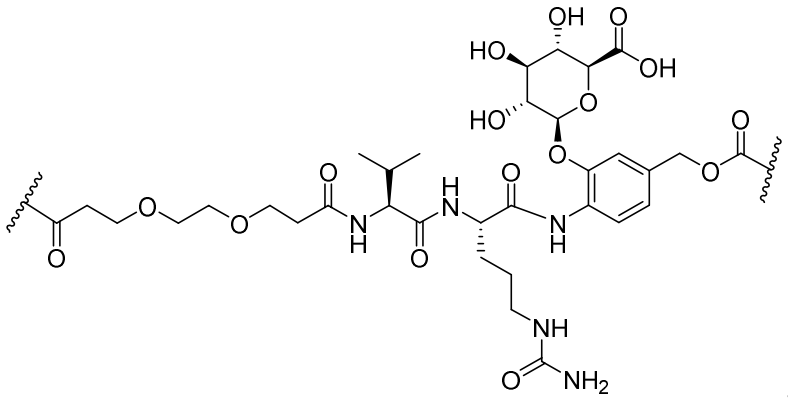

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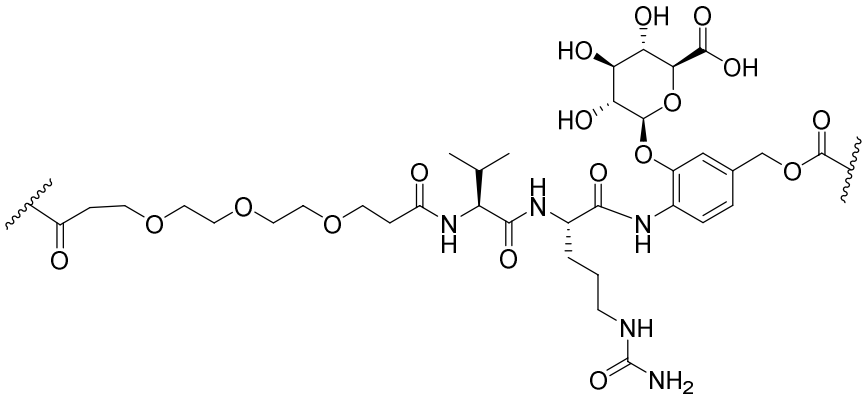

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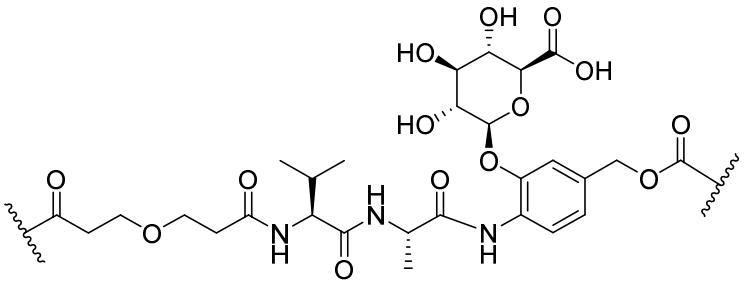

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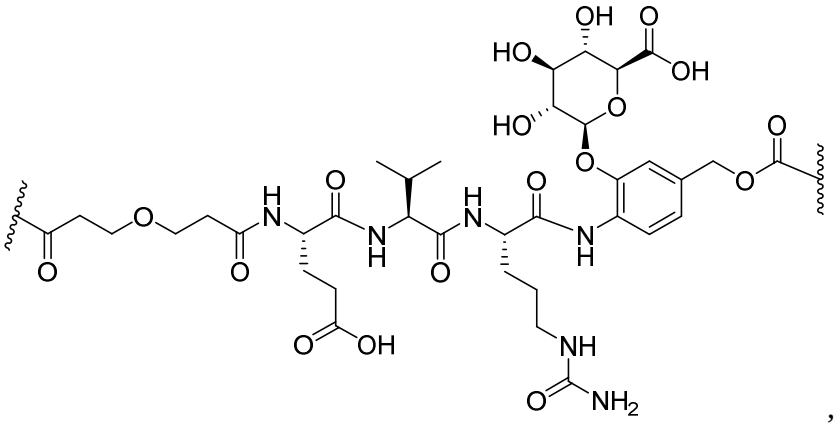

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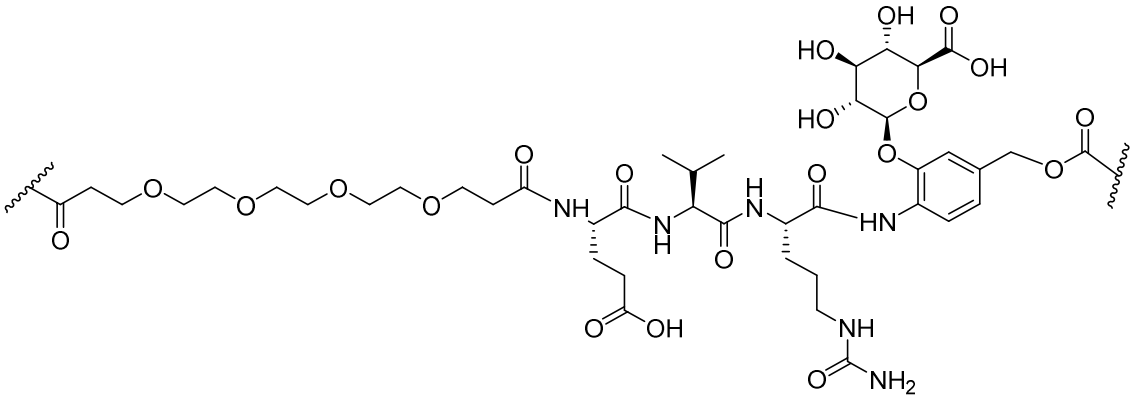

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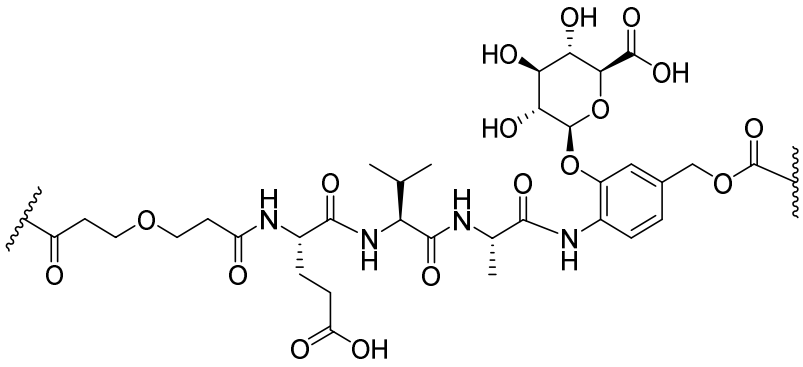

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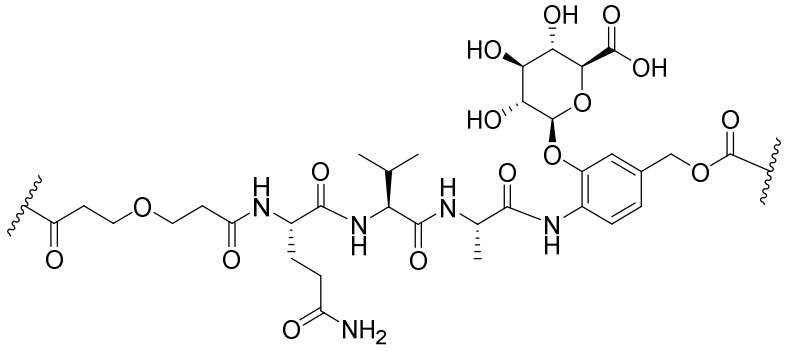

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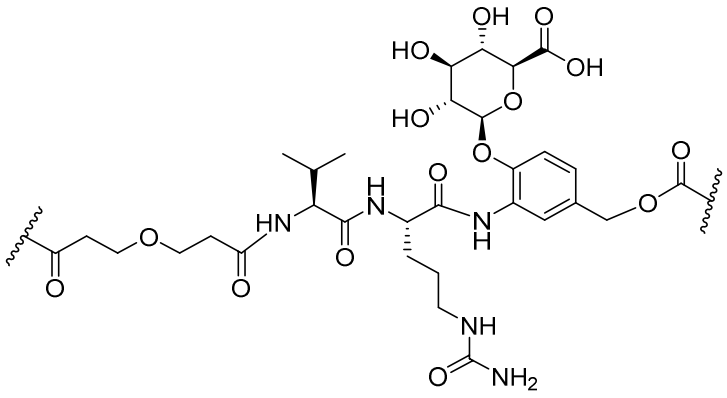

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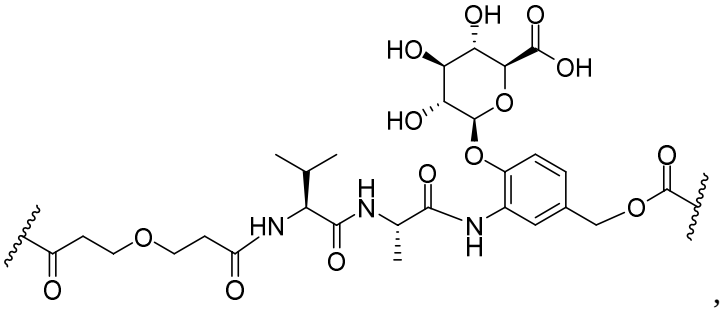

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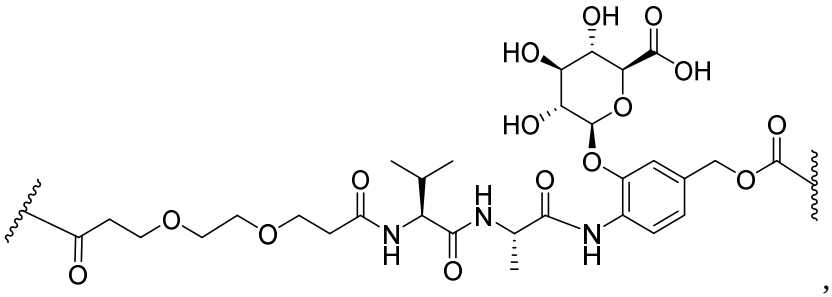

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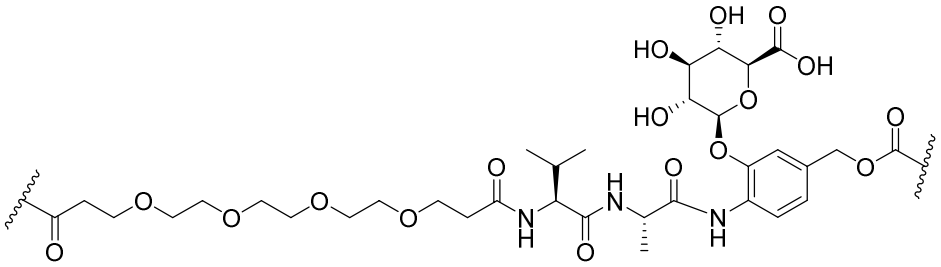

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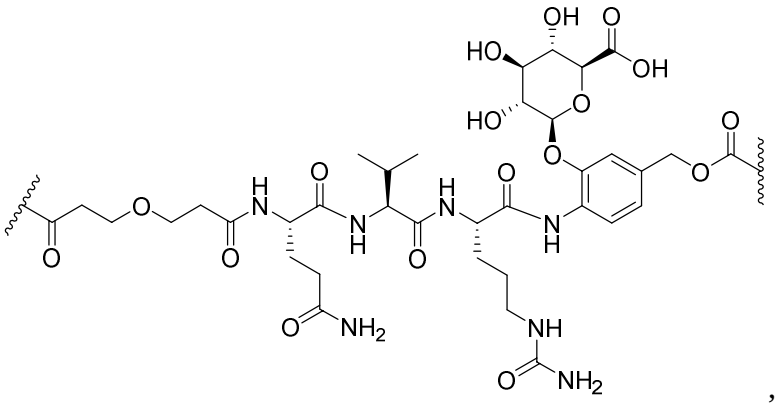

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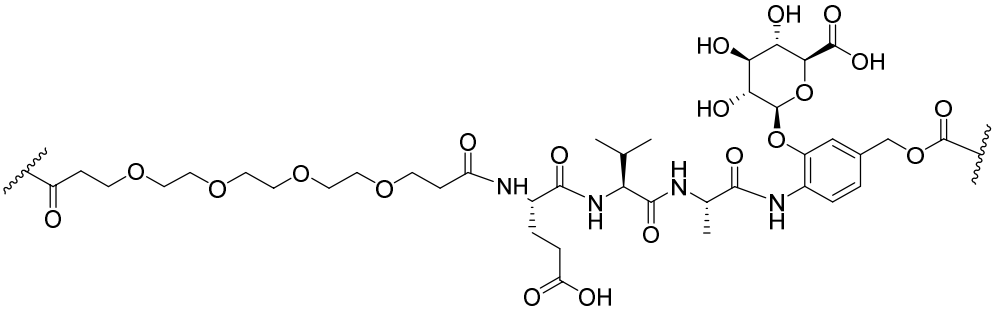

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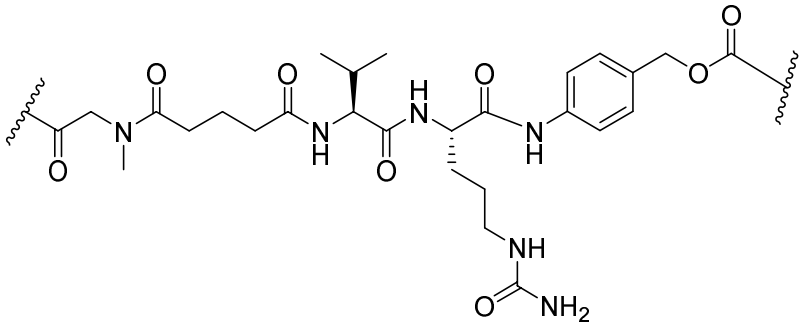

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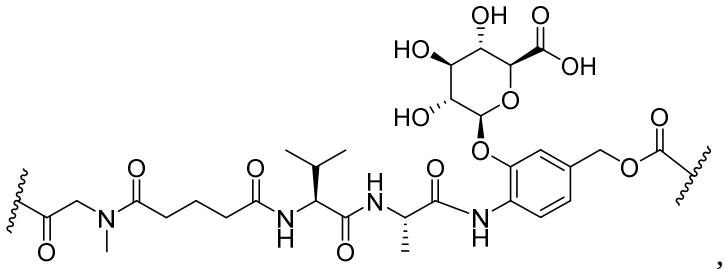

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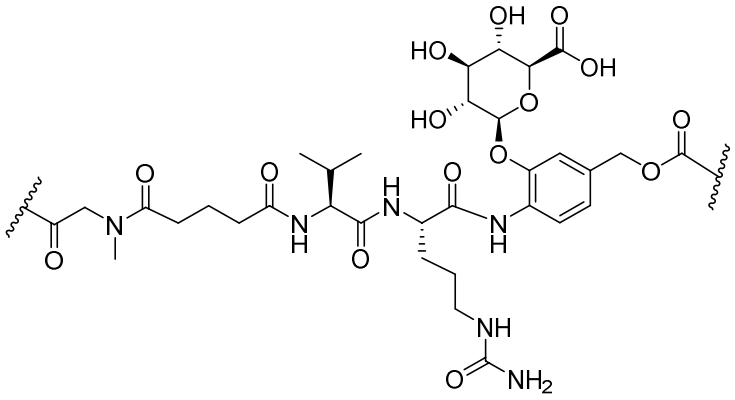

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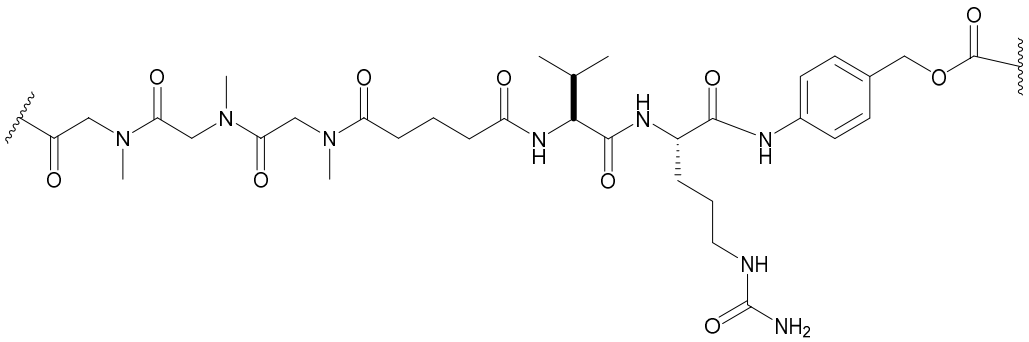

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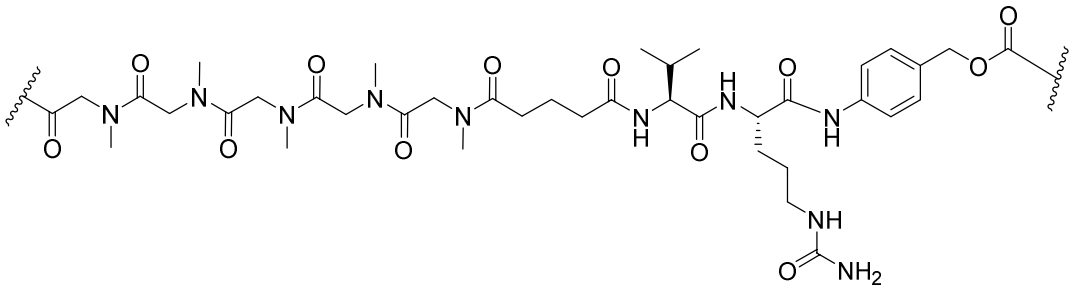

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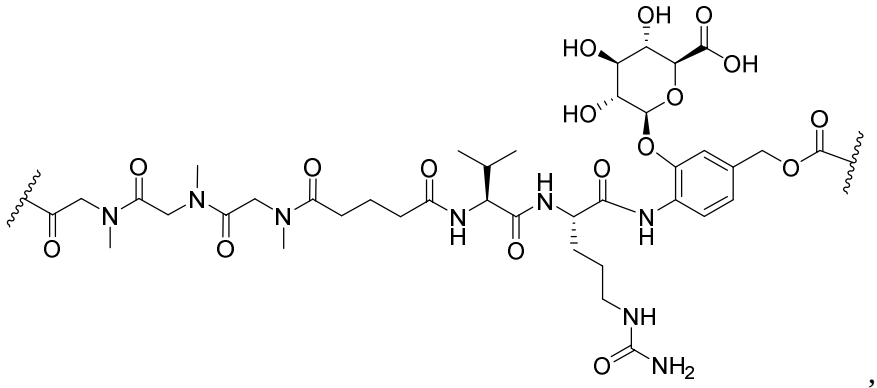

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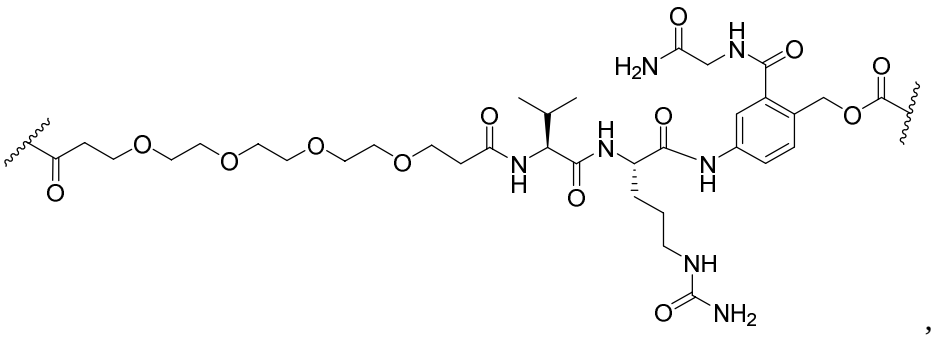

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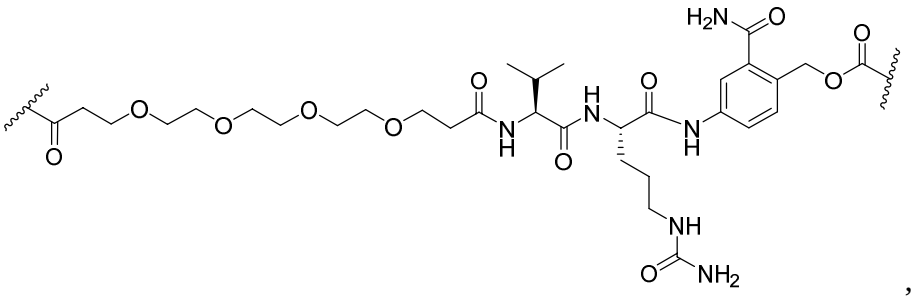

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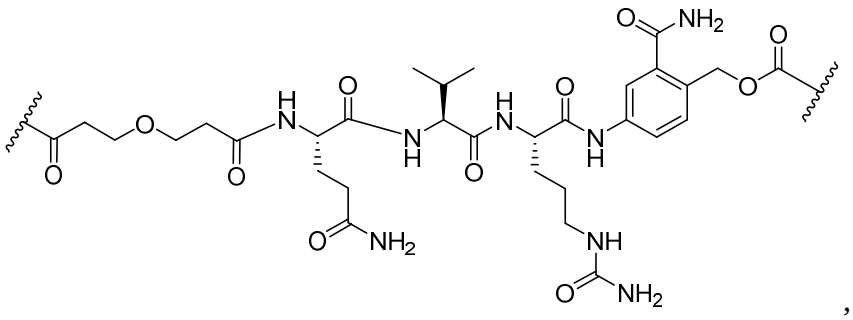

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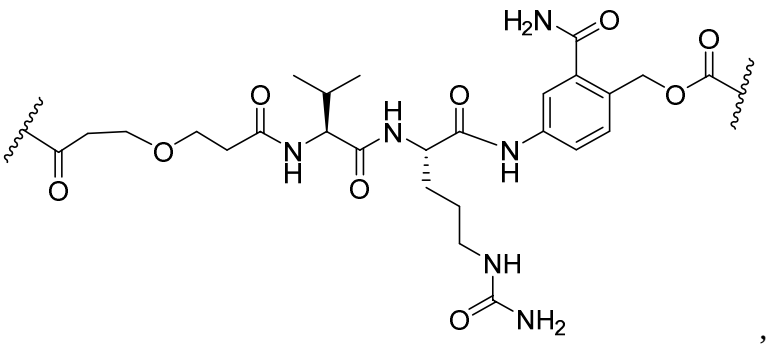

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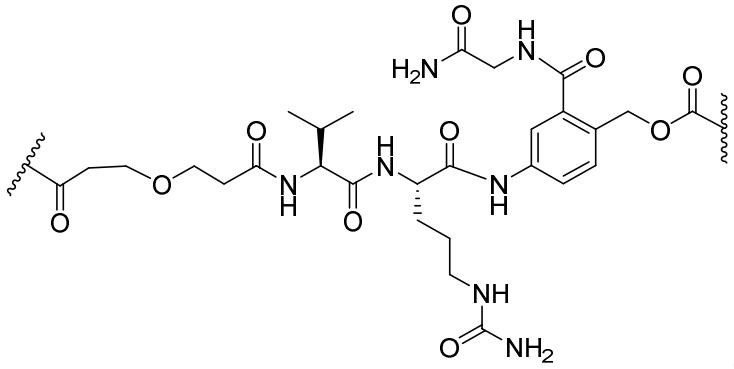

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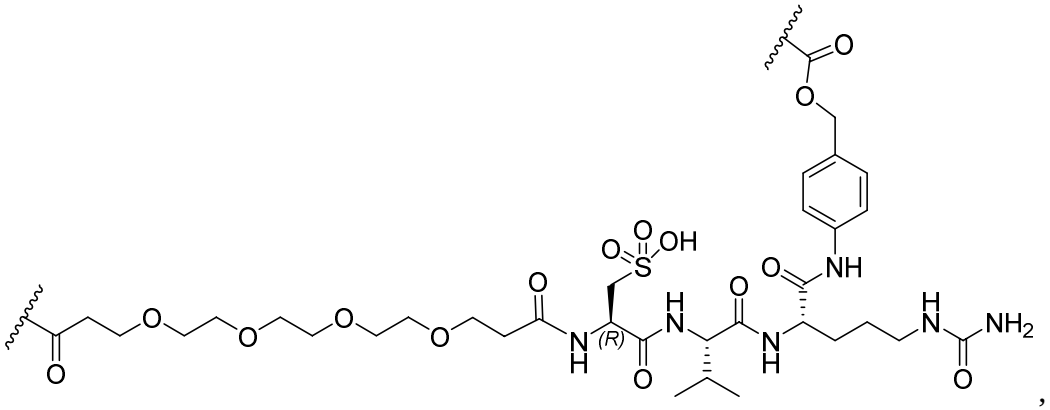

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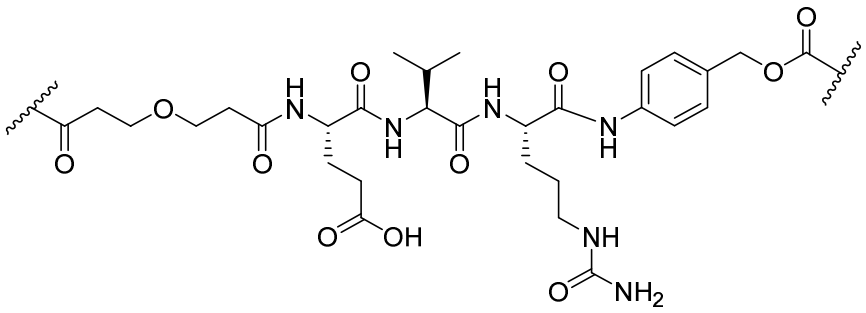

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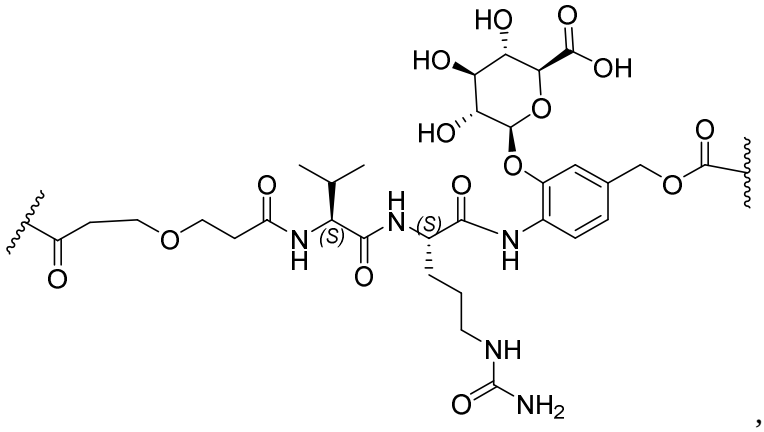

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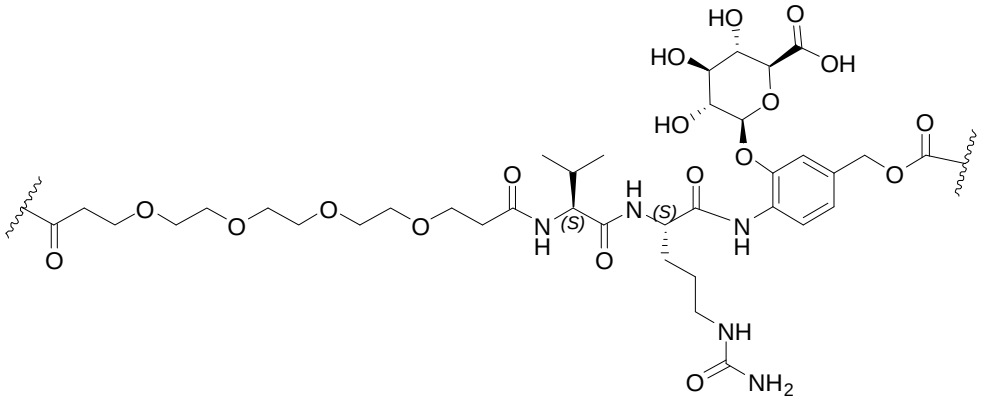

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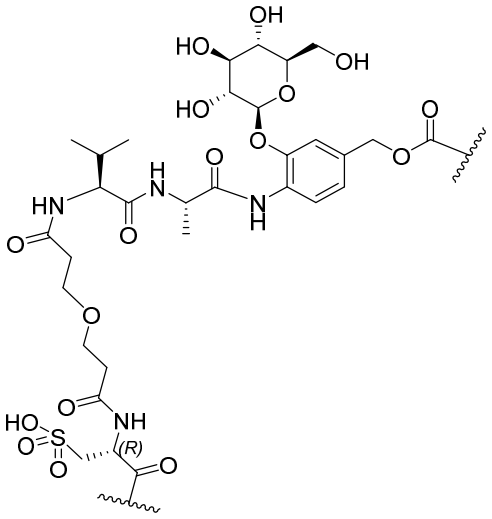

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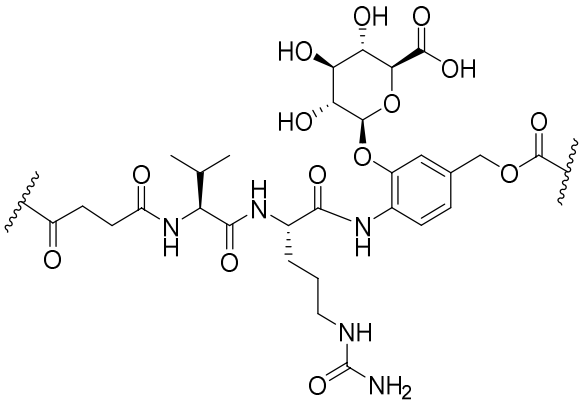

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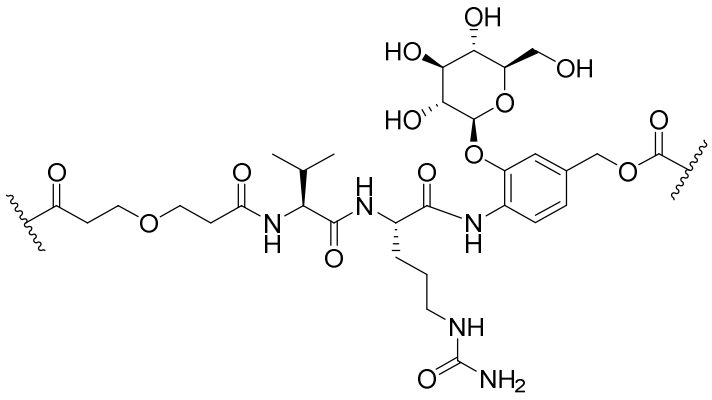

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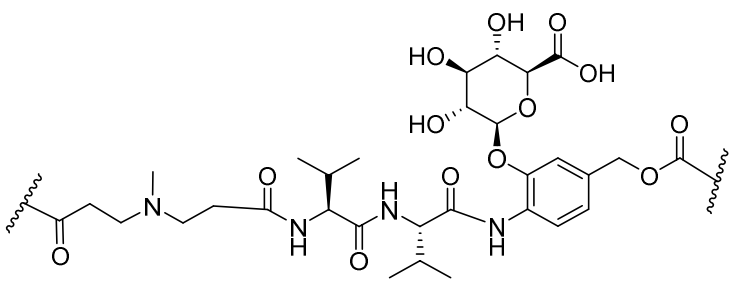

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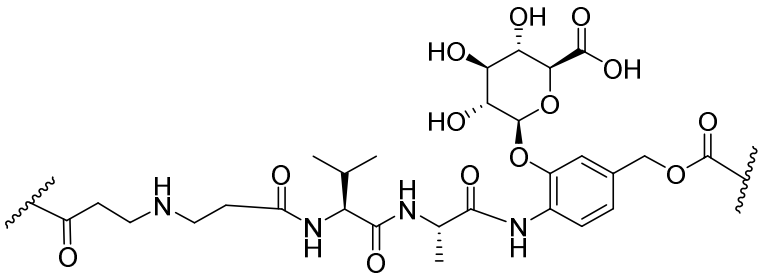

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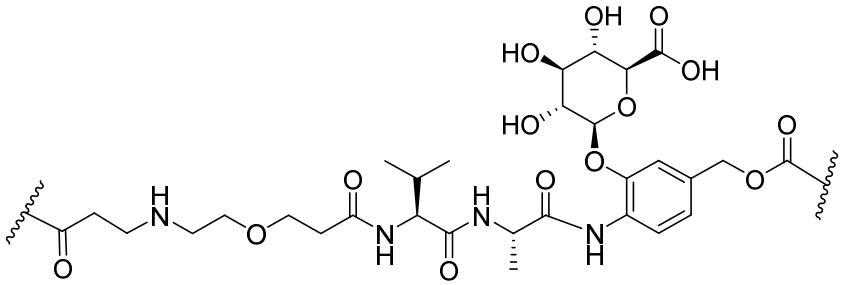

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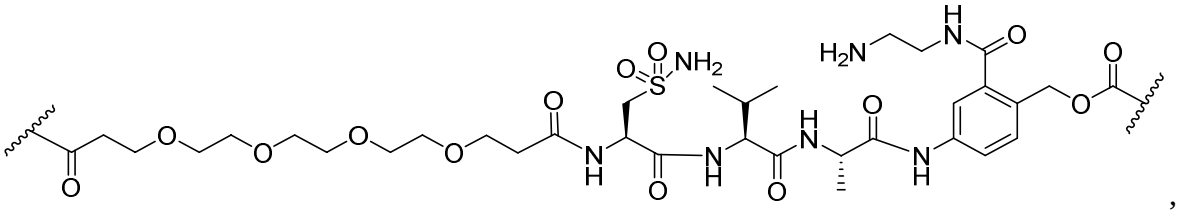

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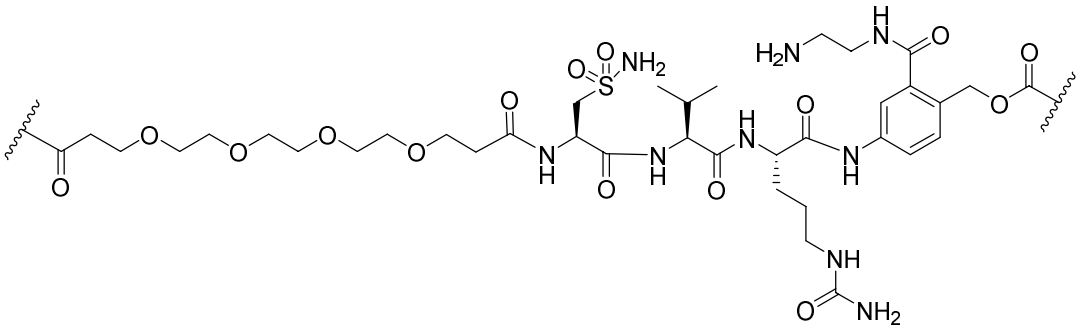

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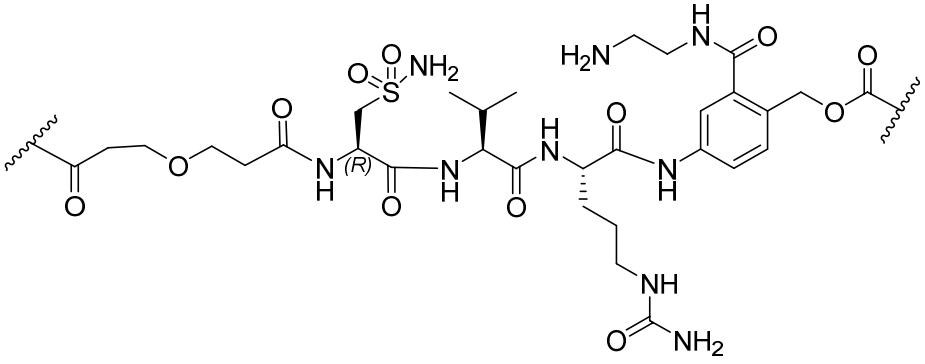

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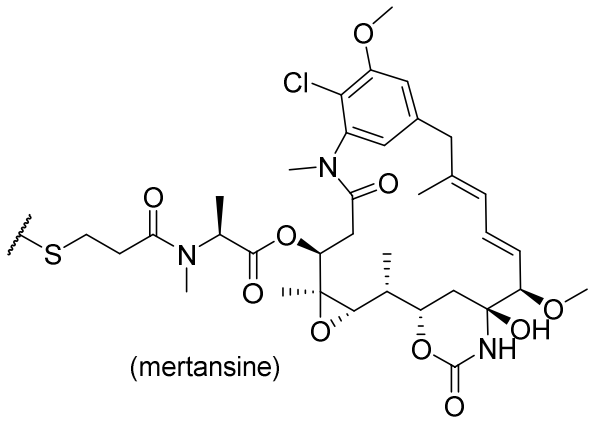
22. The compound of any one of claim 1-16, or a pharmaceutically acceptable salt thereof, wherein, R^d is:



(mertansine)

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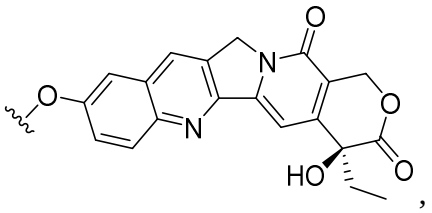

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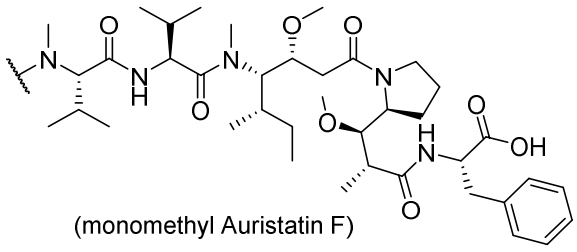

(monomethyl Auristatin F)

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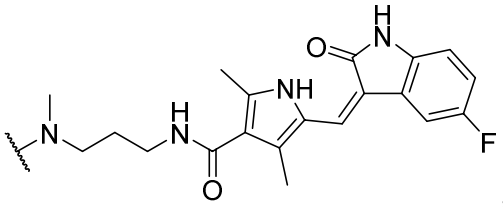

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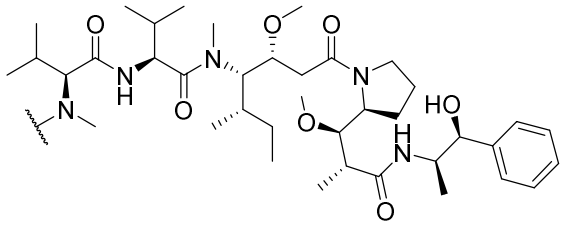
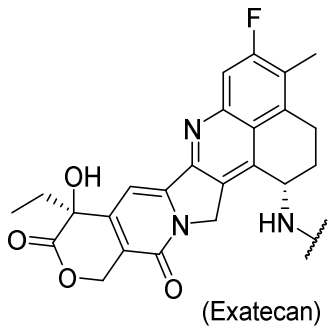


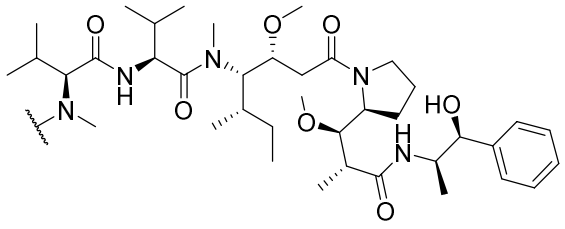
(monomethyl Auristatin E)

, or



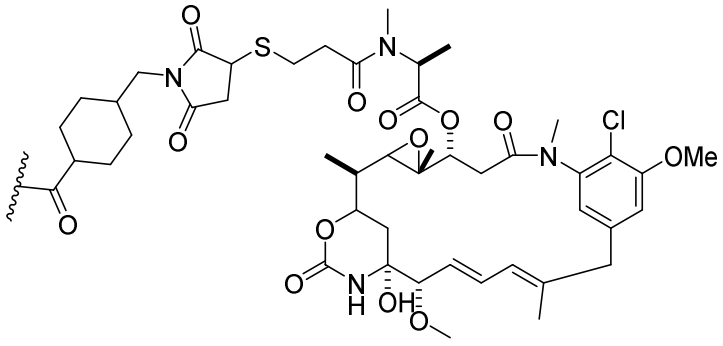
(Exatecan) .

23. The compound of any one of claim 1-17, or a pharmaceutically acceptable salt thereof, wherein, R^d is:



(monomethyl Auristatin E) .

24. The compound of any one of claim 1-15, or a pharmaceutically acceptable salt thereof, wherein, -L-R^d is:



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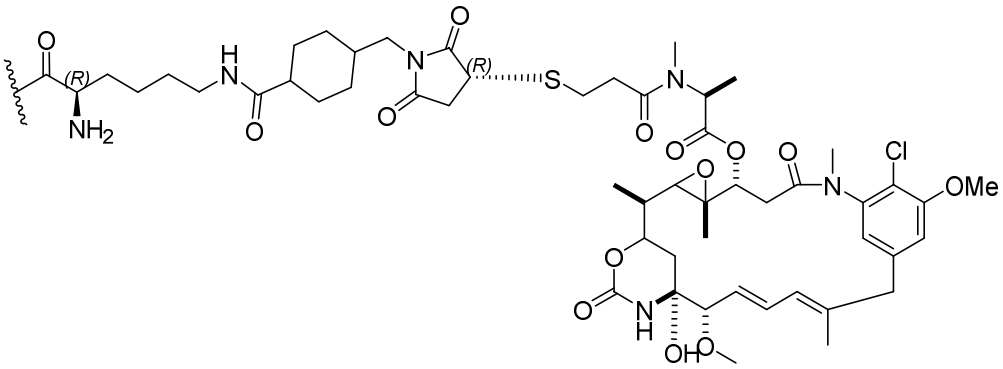

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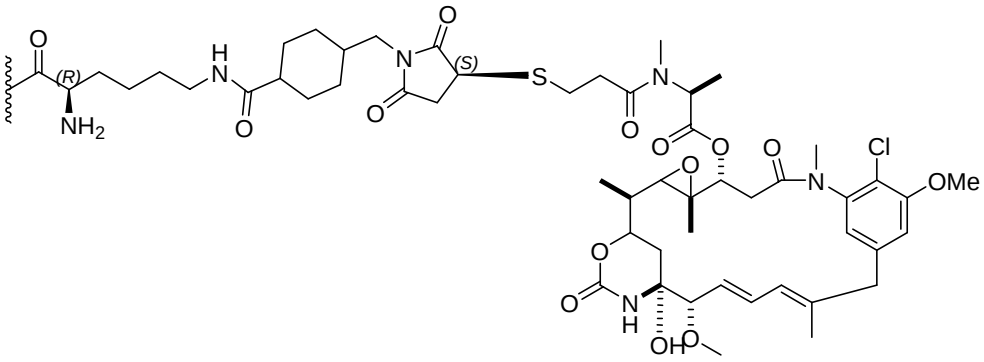

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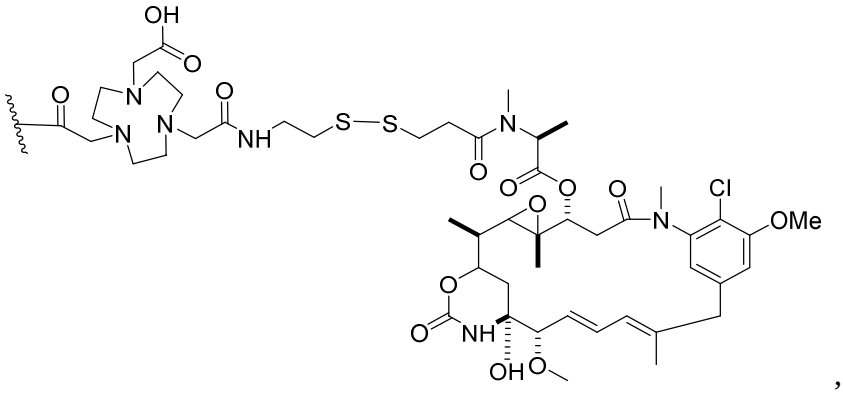

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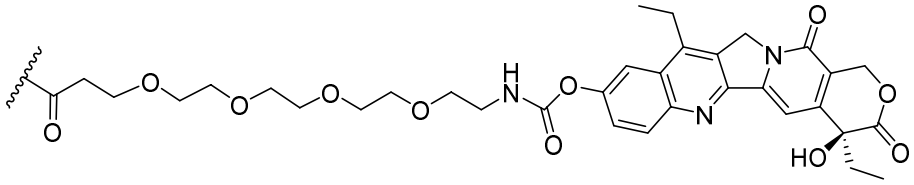

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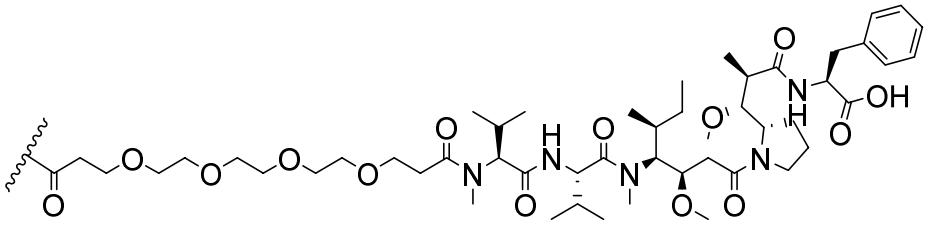

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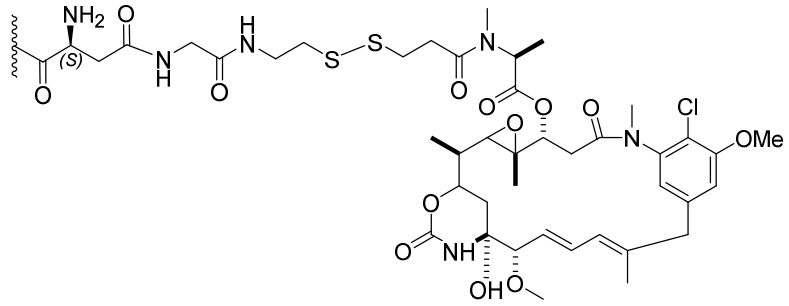

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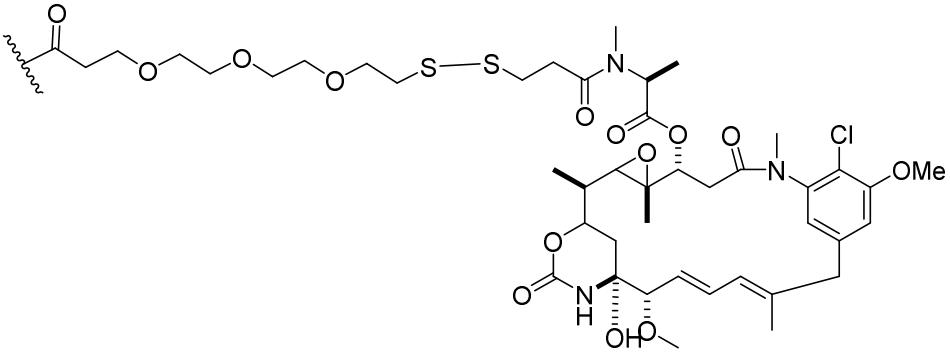

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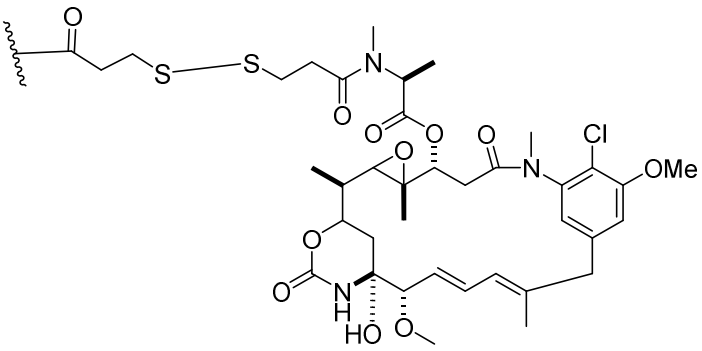

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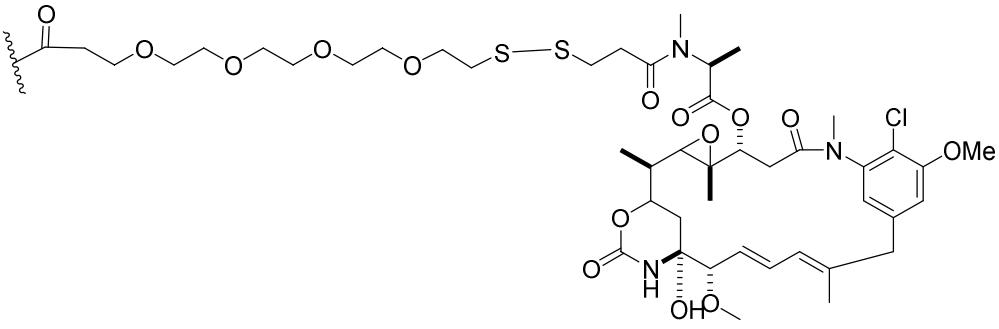

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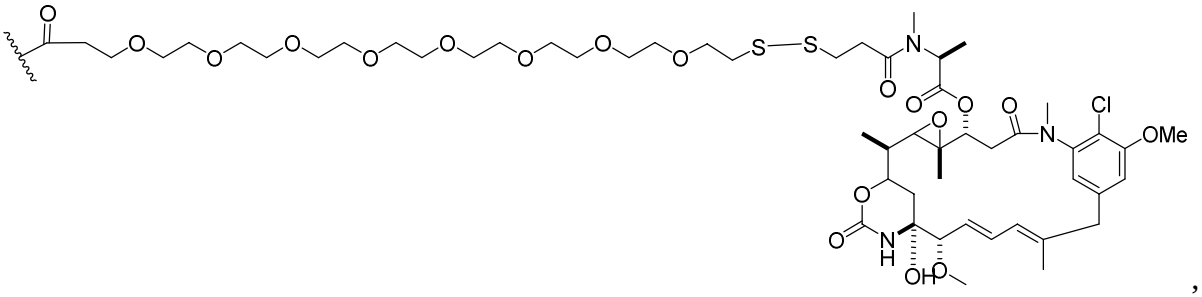

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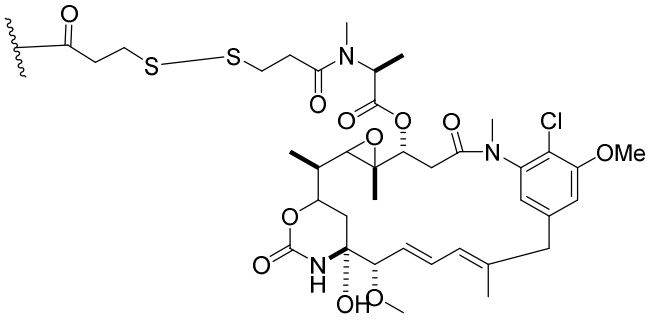

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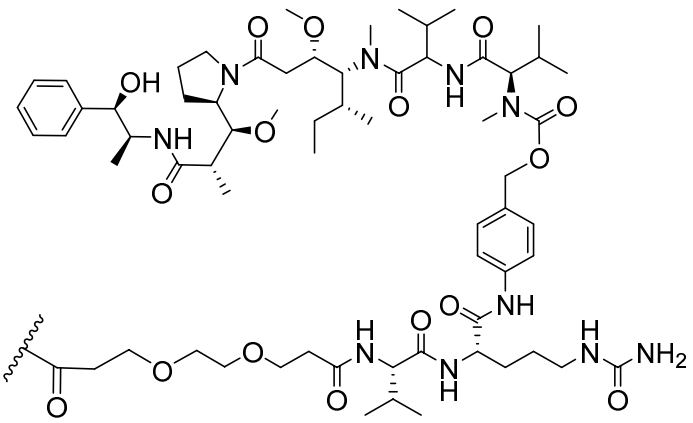

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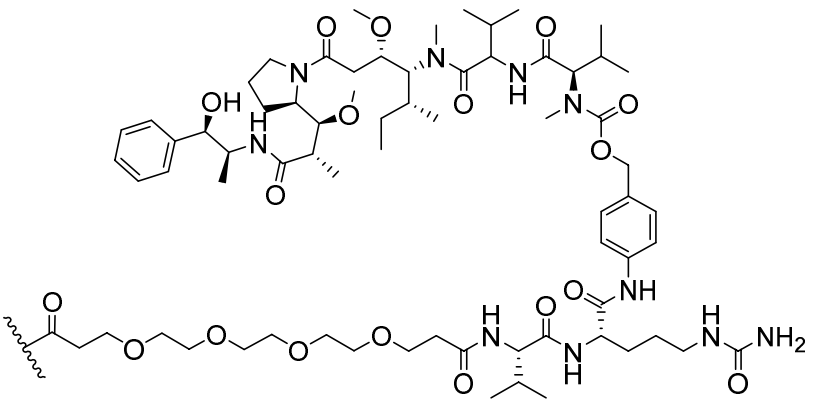

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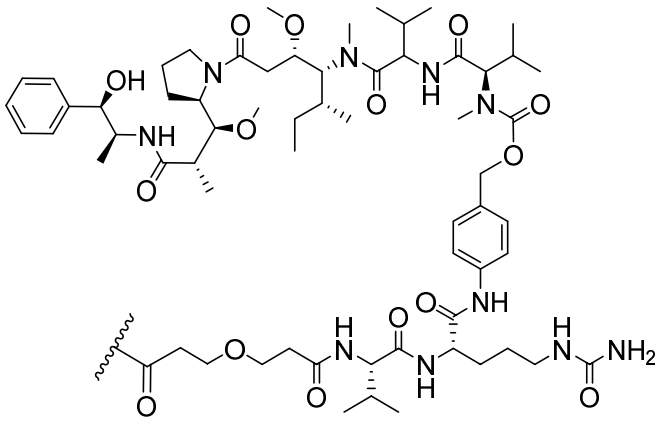
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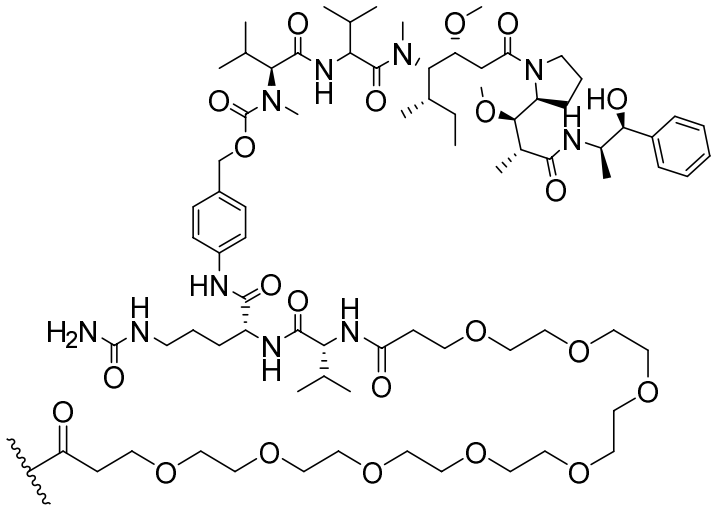
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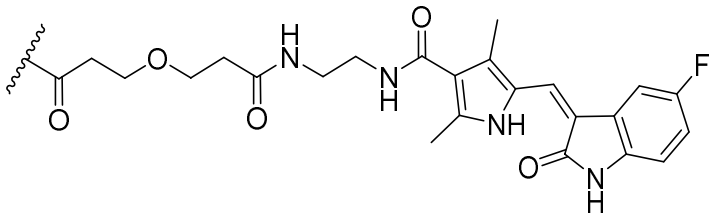
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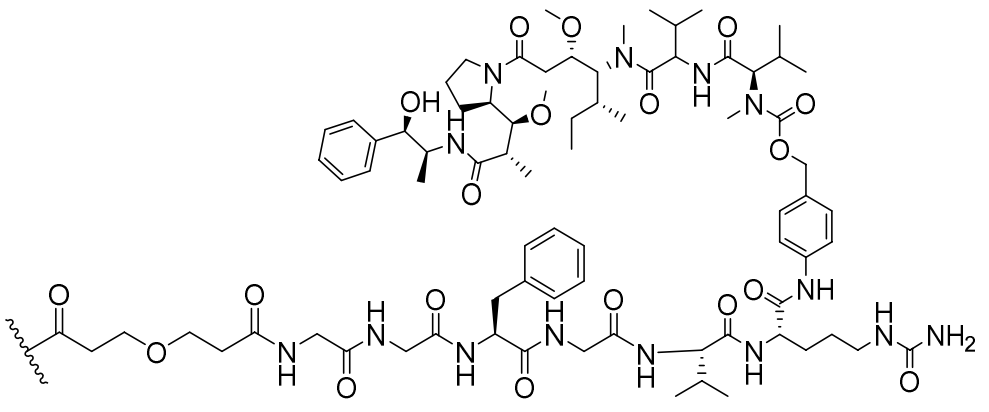
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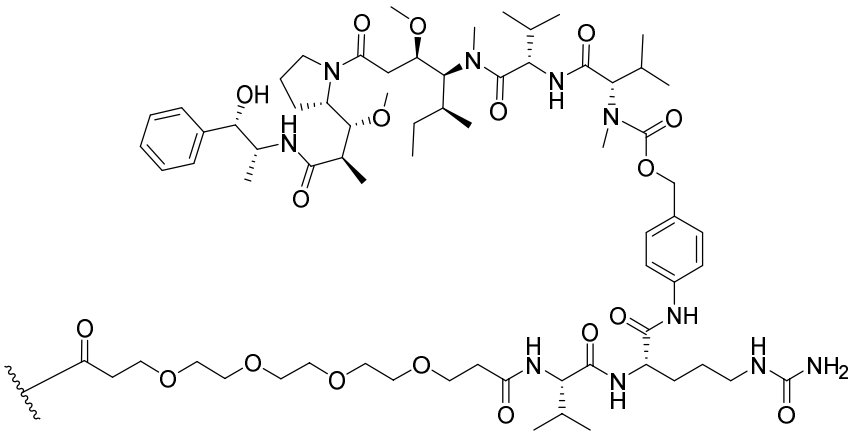

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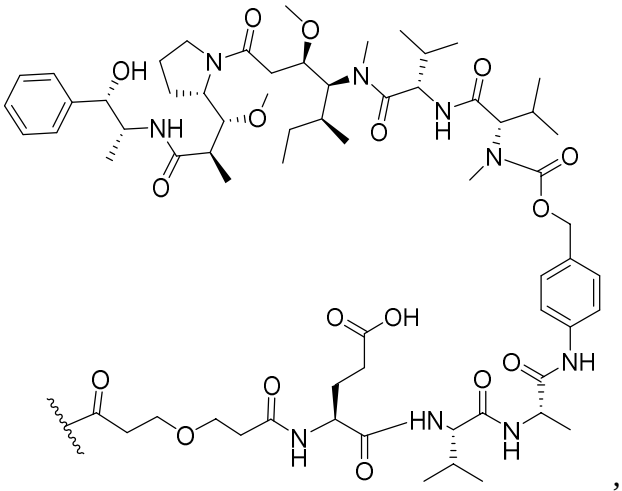

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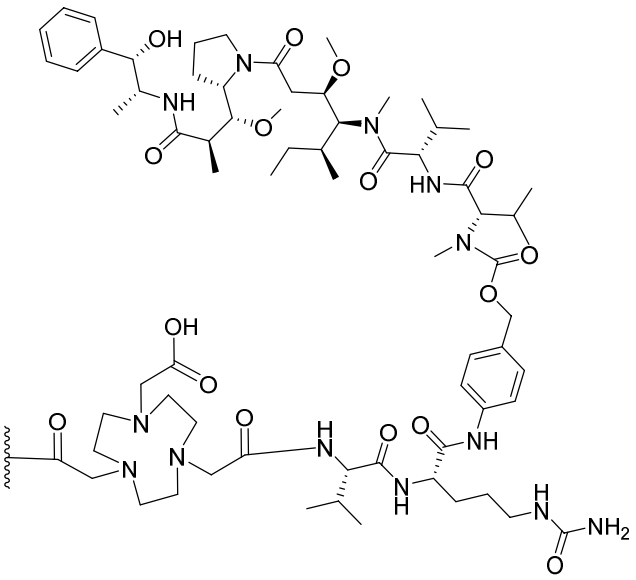

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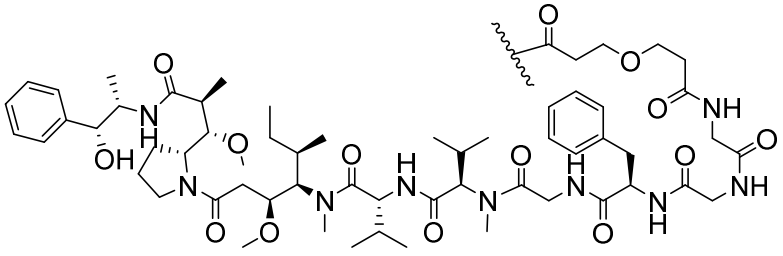

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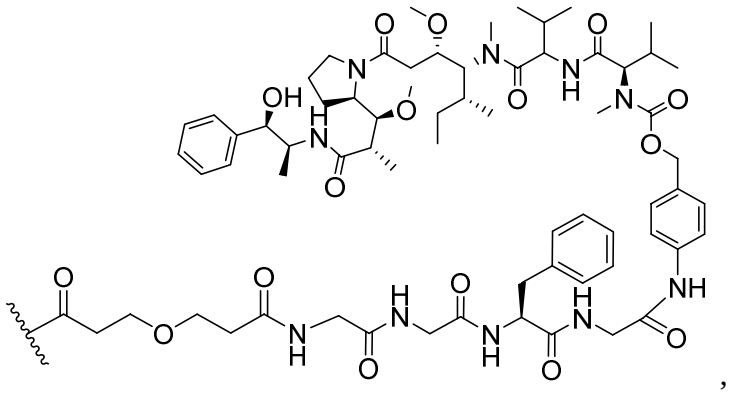

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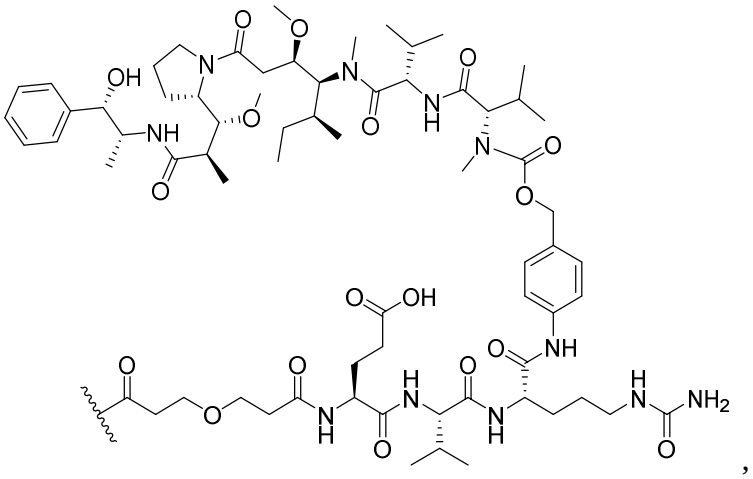

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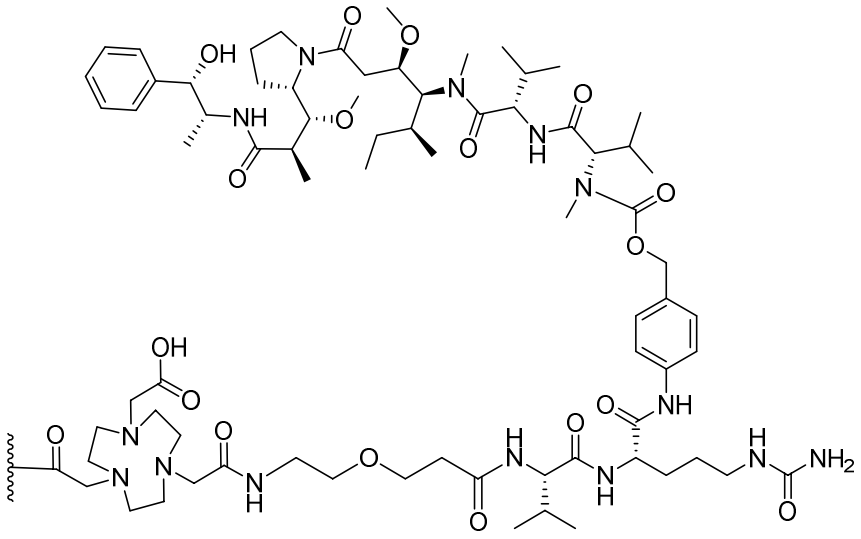

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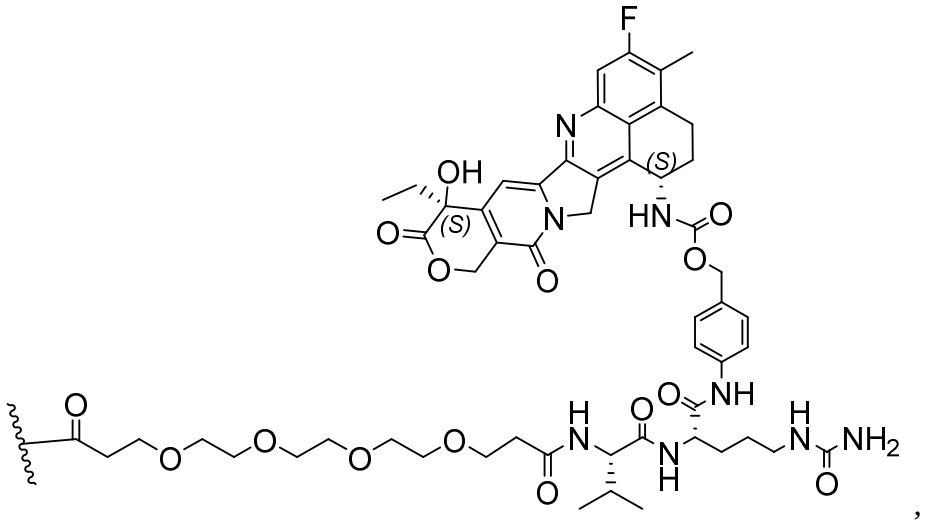

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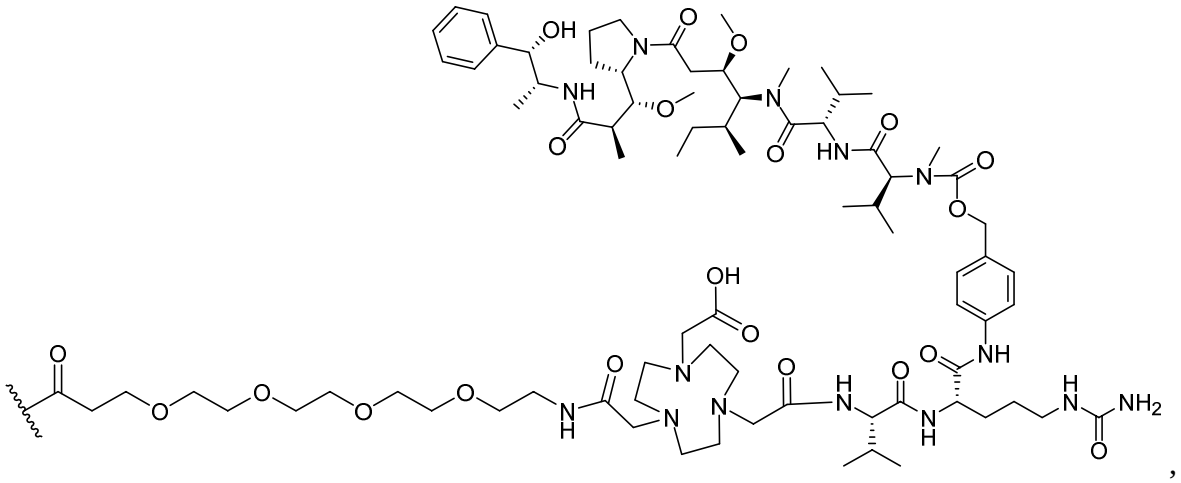

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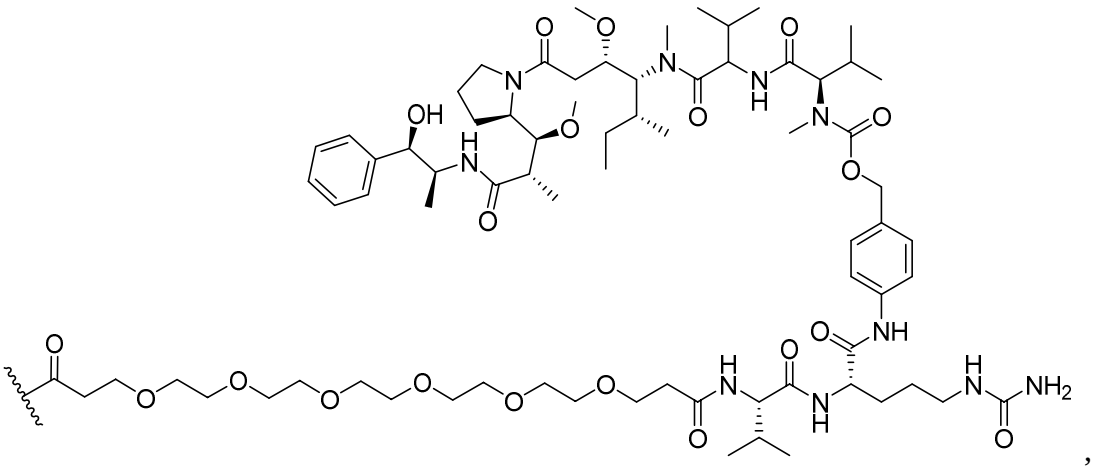

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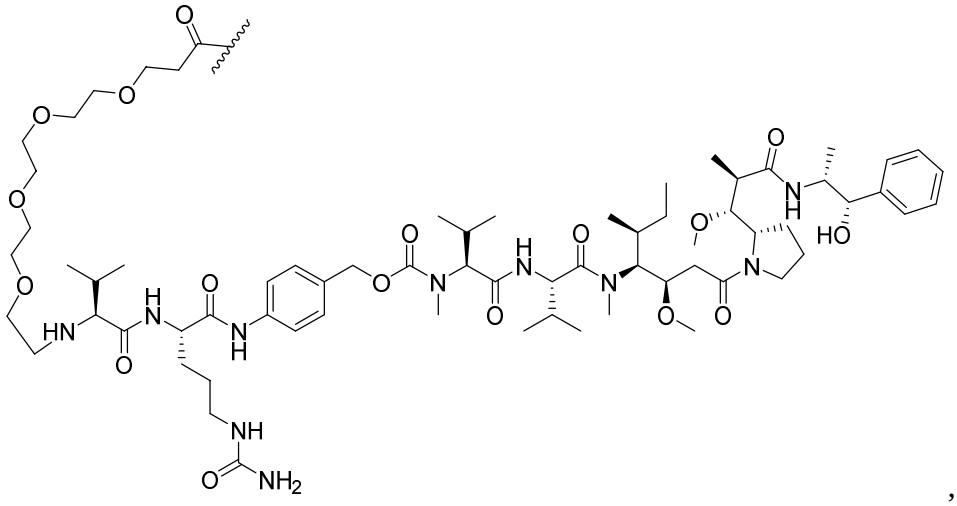

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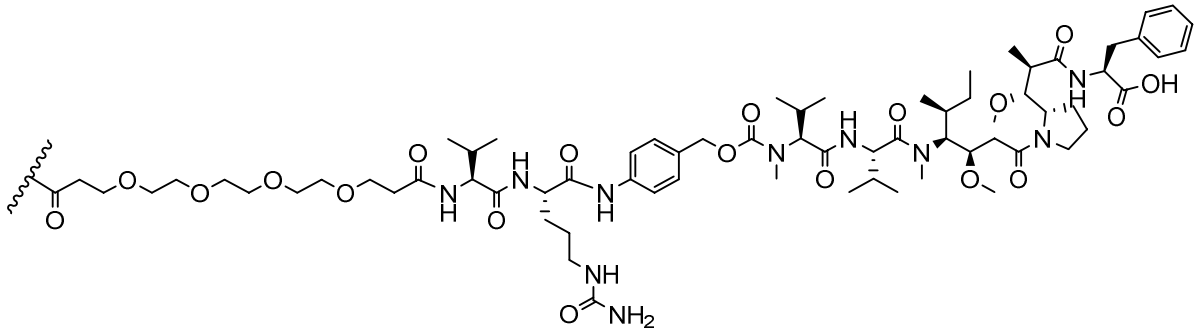

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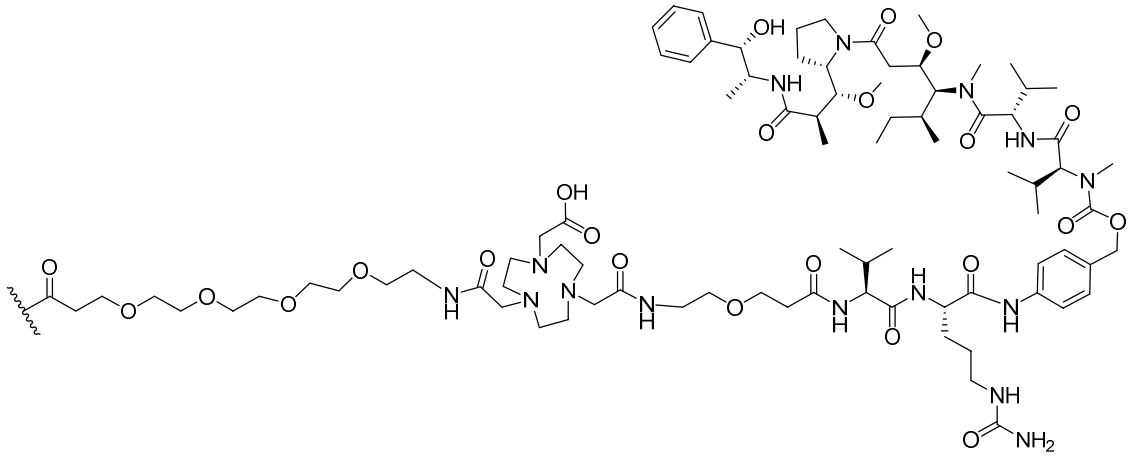

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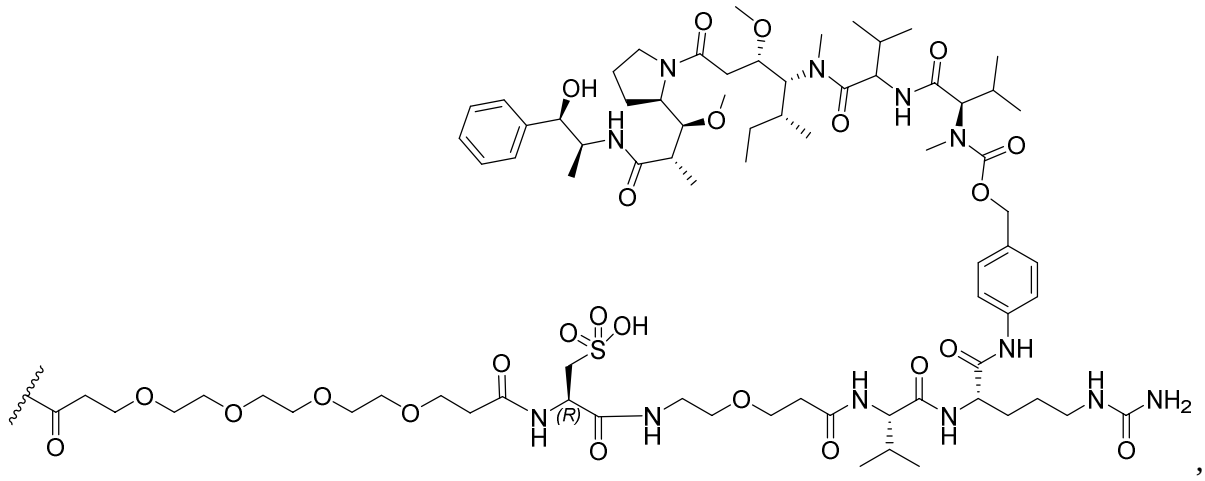

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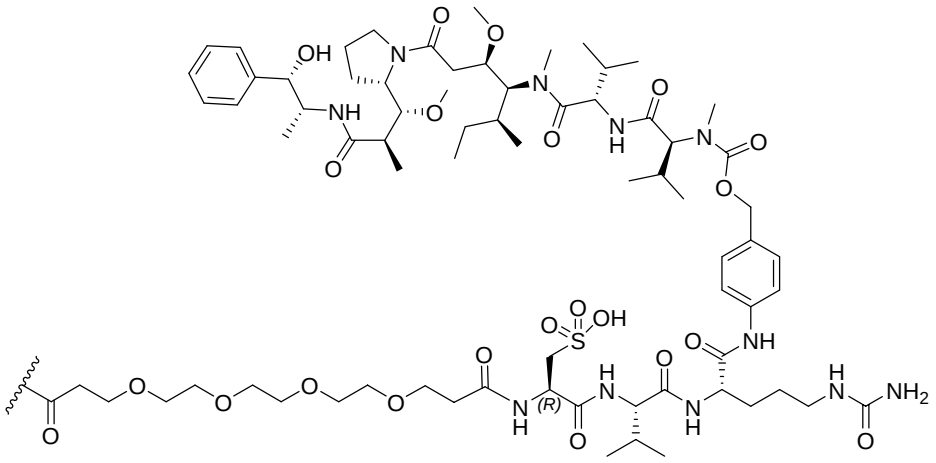

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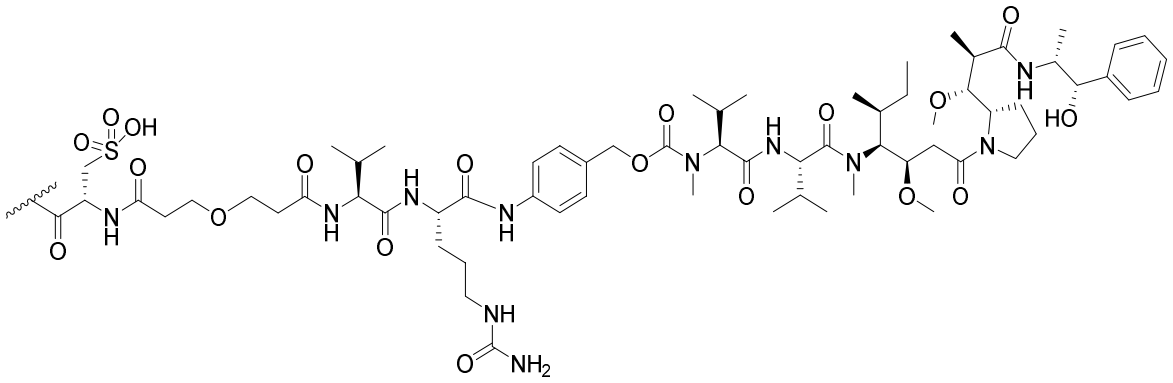

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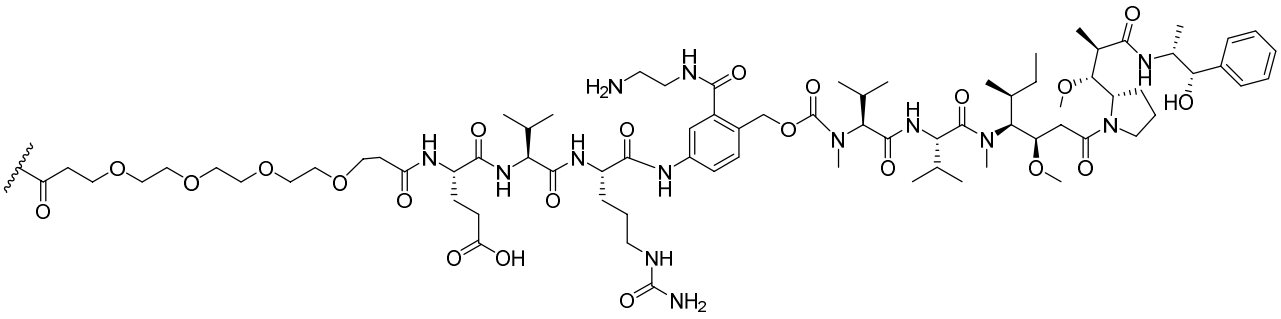

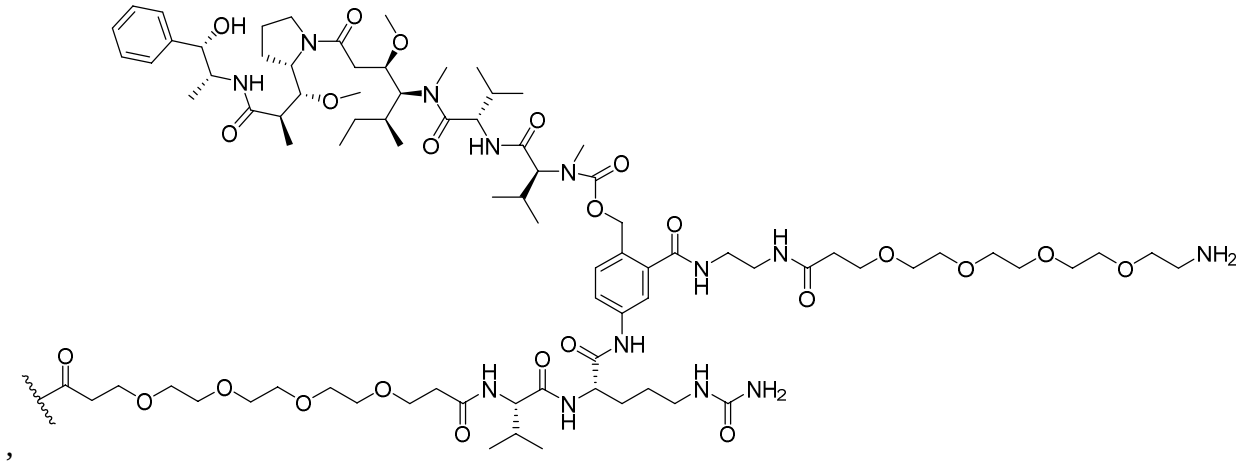

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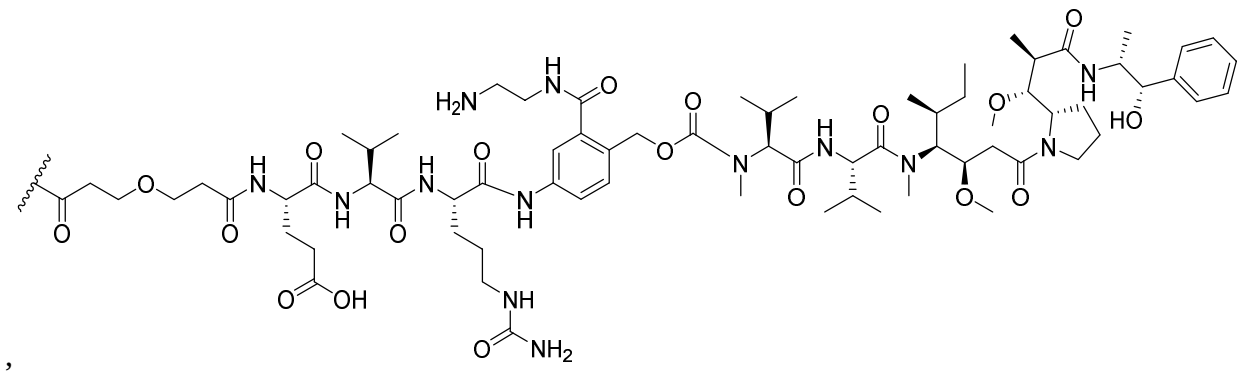

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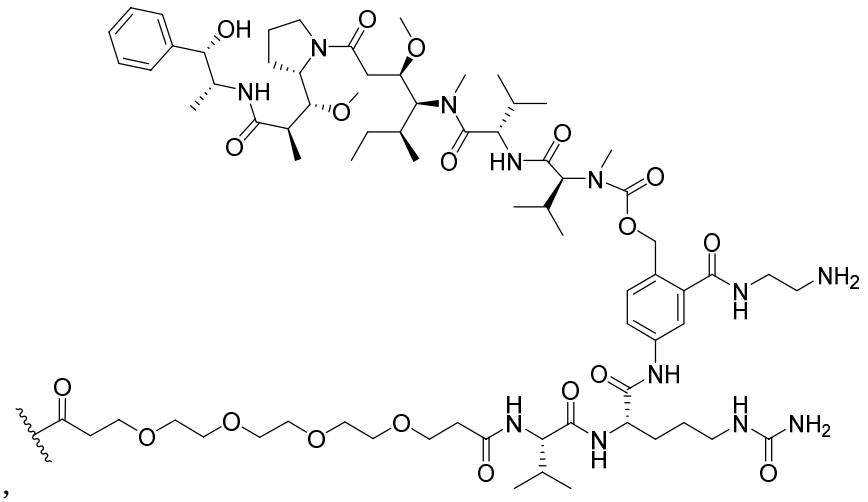

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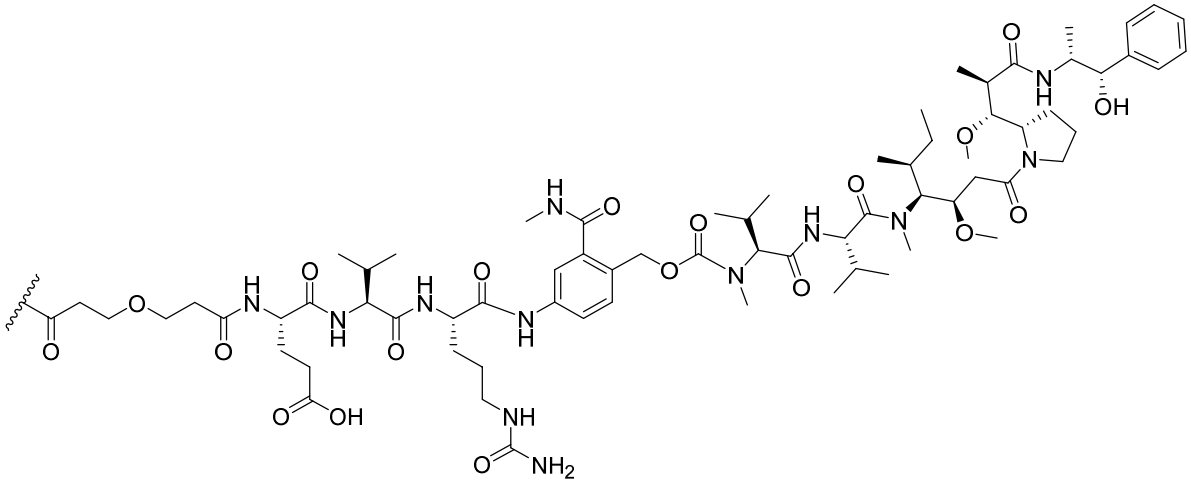

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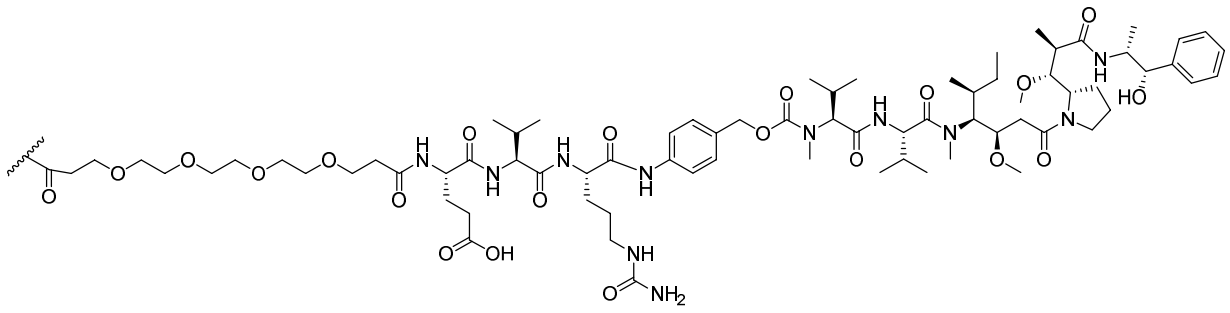

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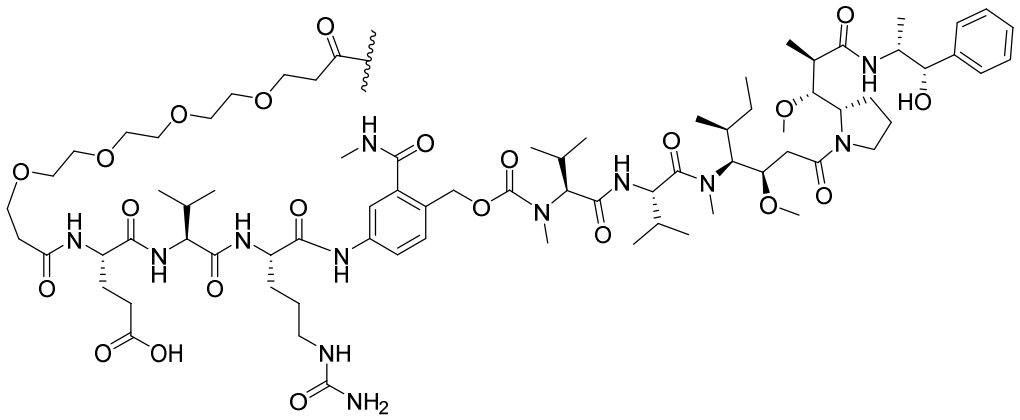

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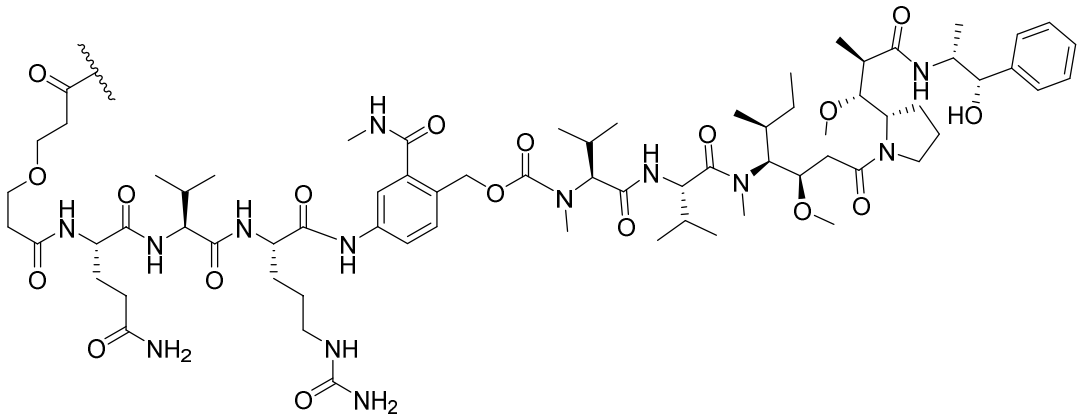

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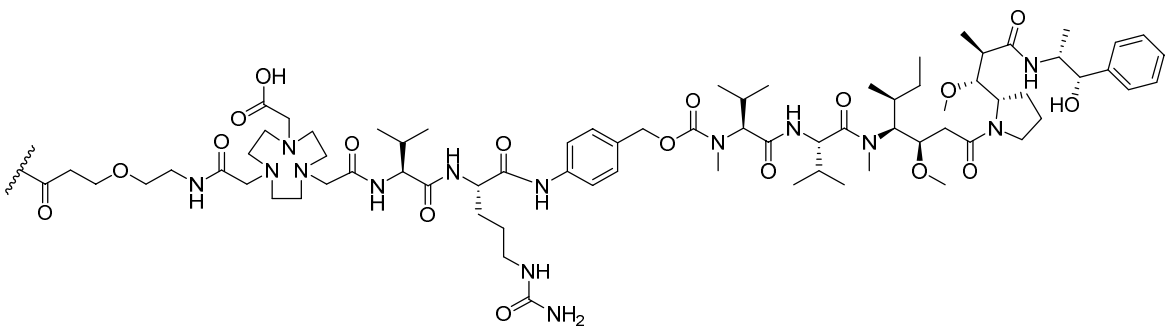

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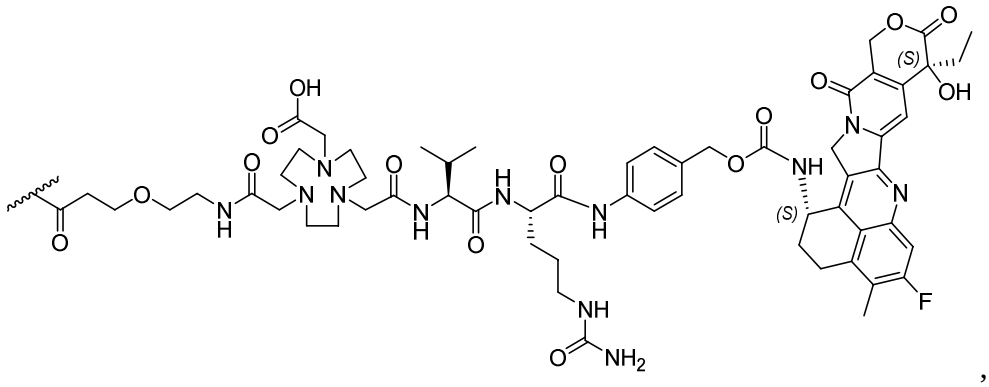

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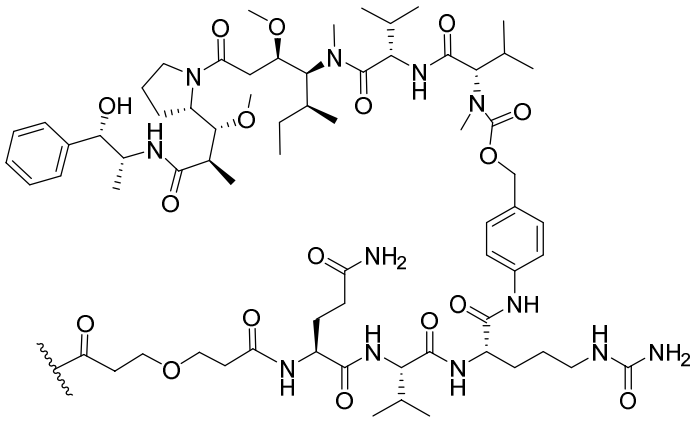

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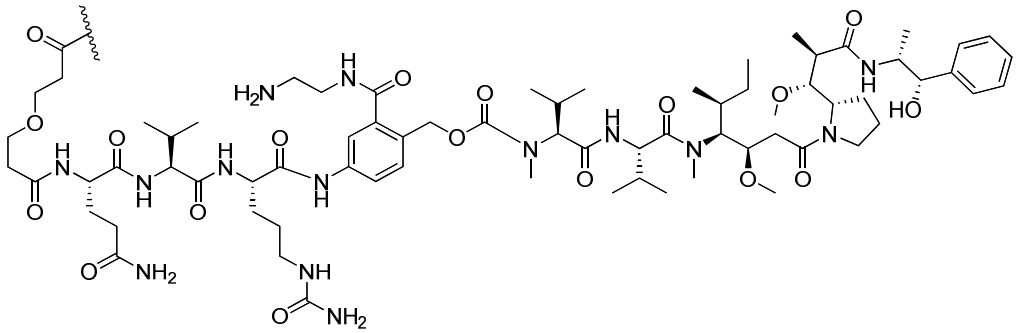

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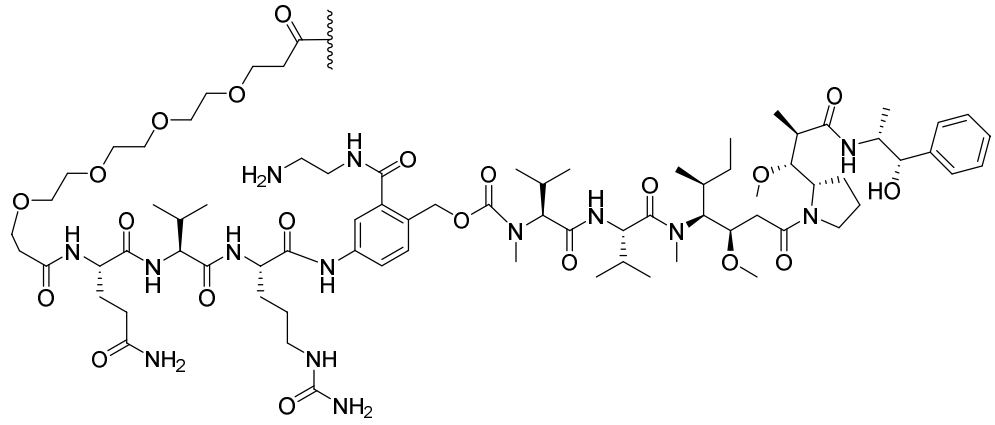

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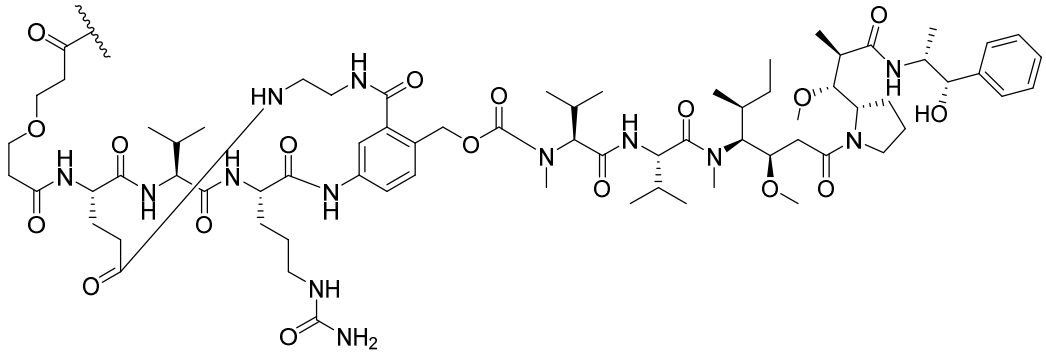

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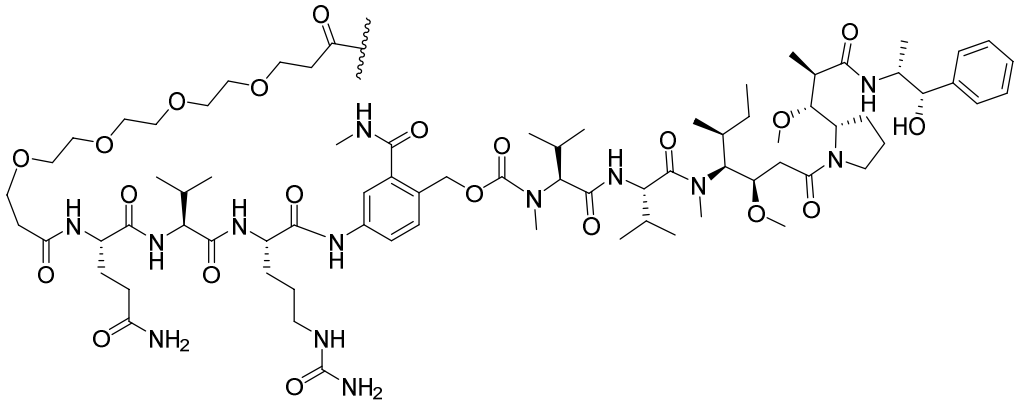

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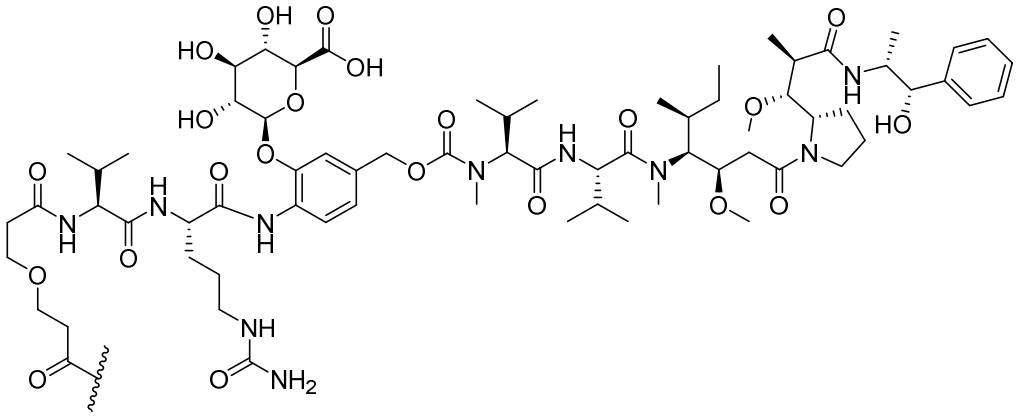

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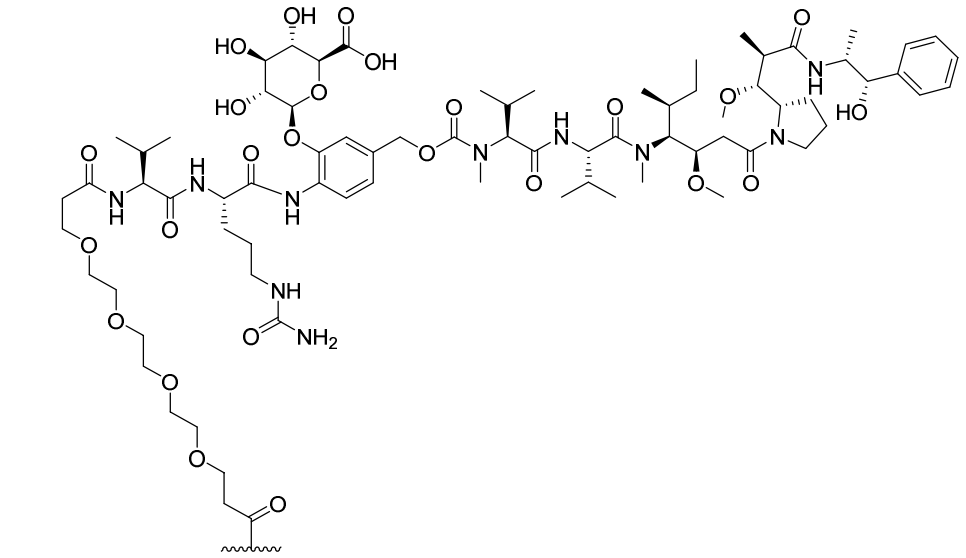

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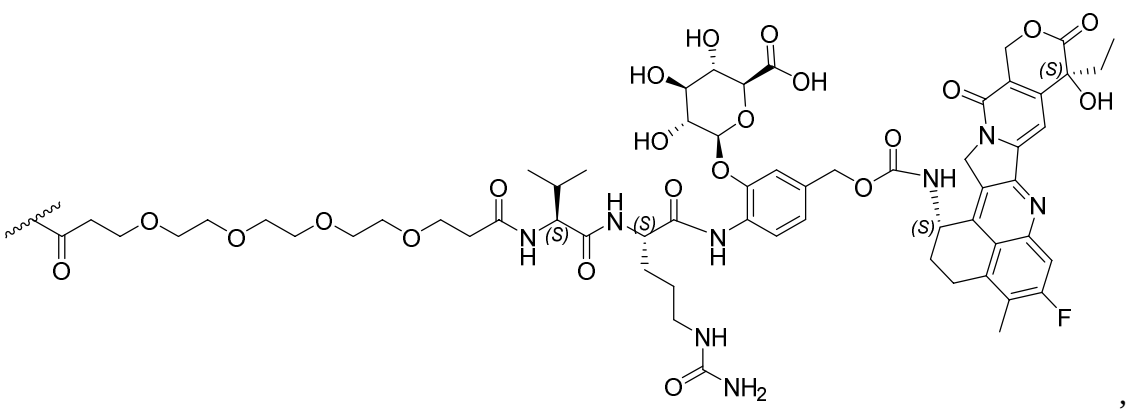

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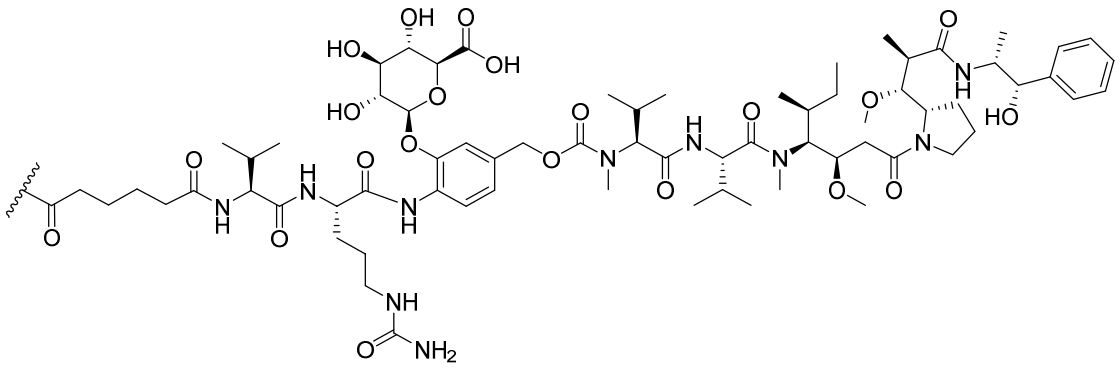

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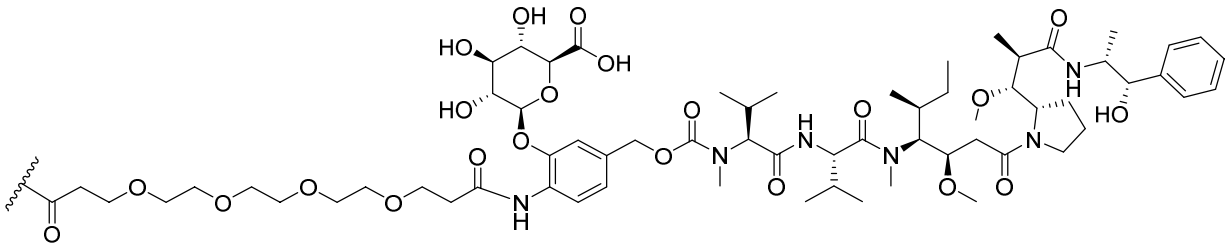

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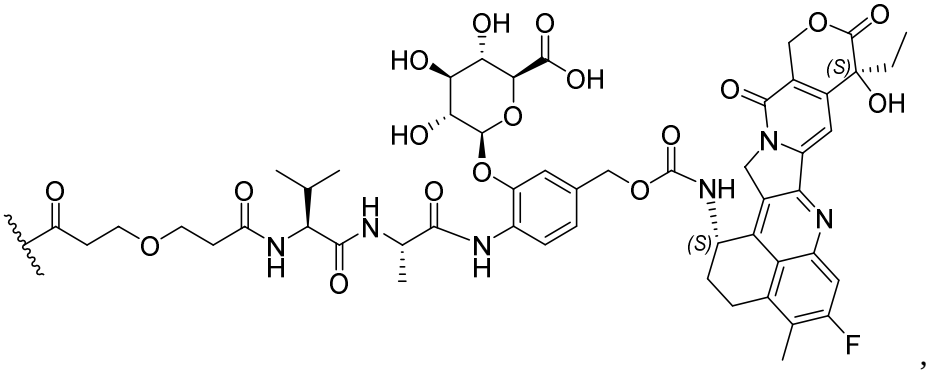

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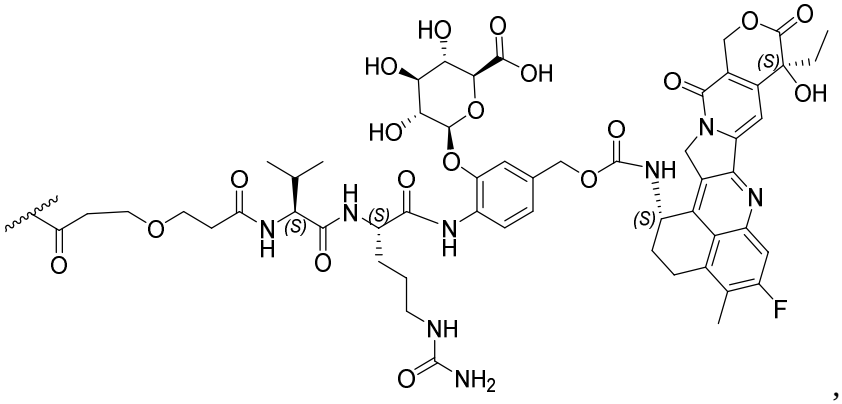

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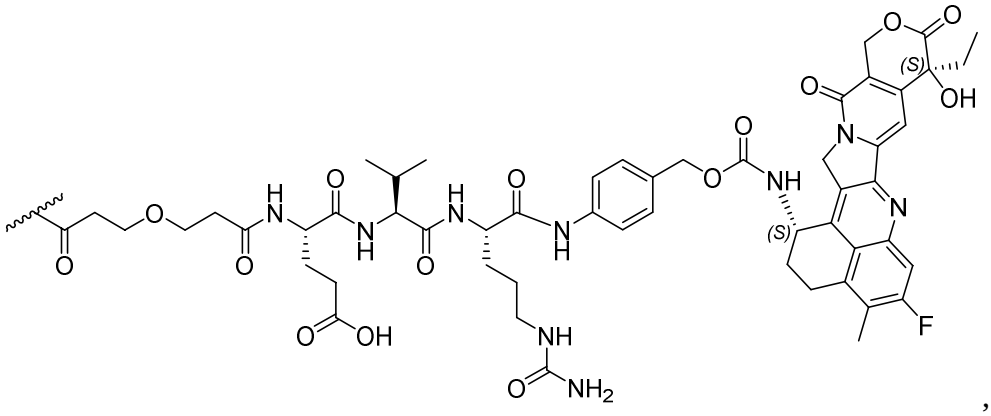

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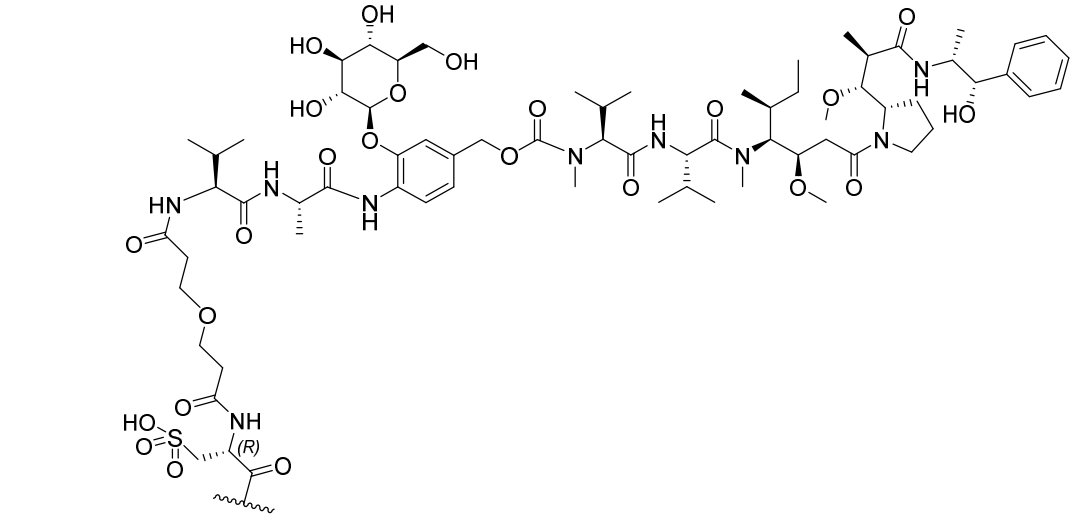

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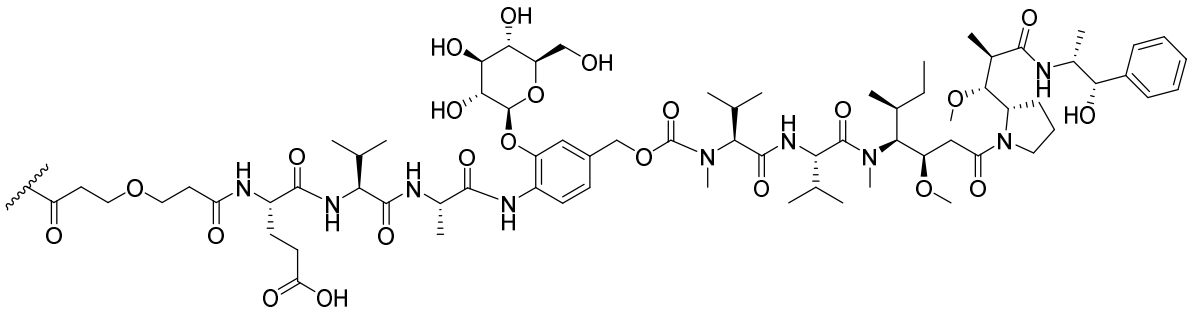

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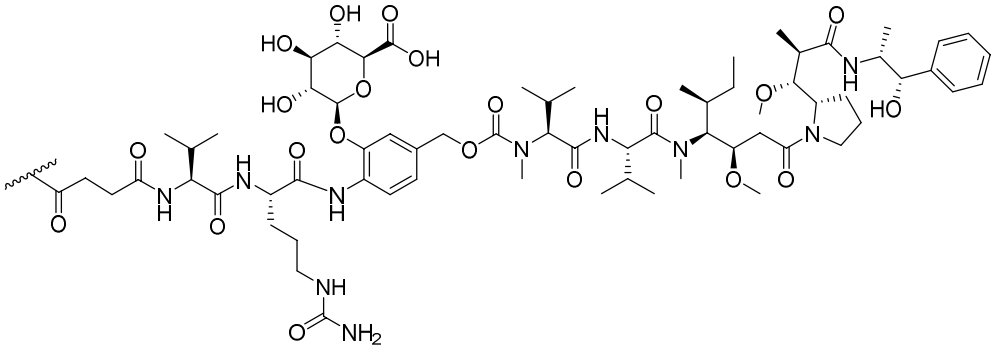

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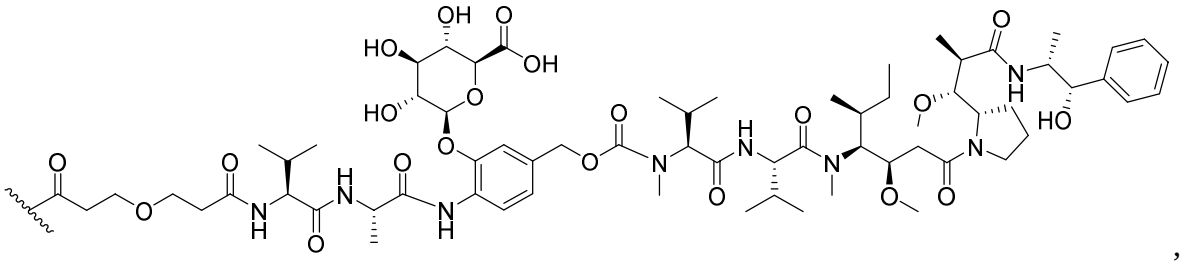

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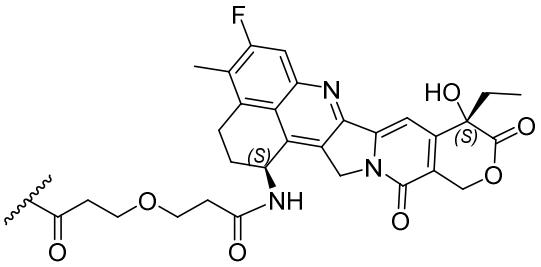

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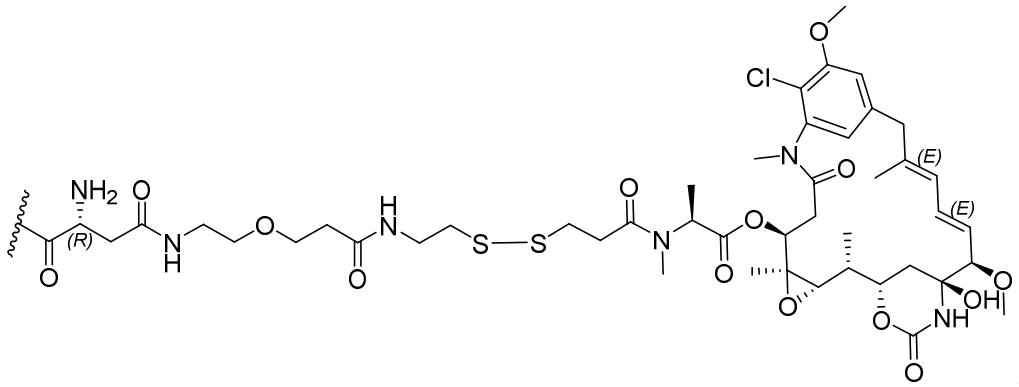

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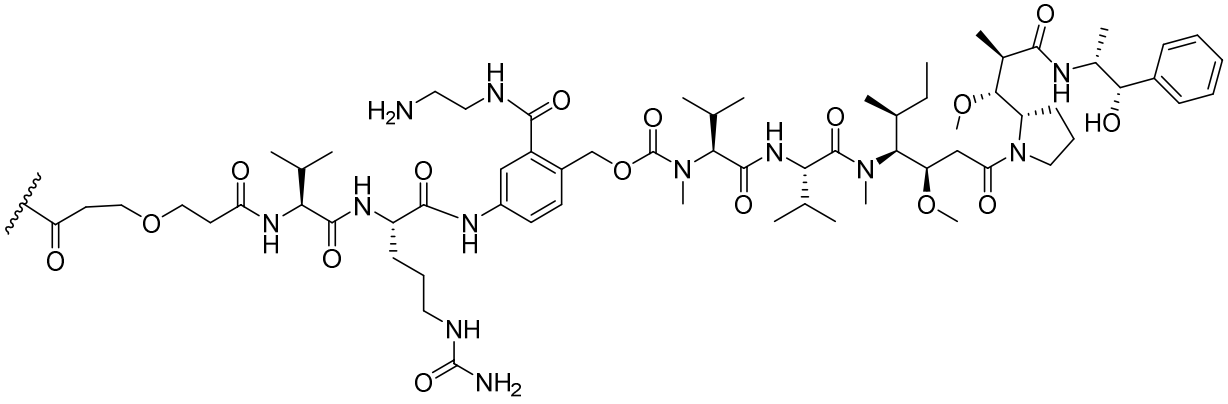

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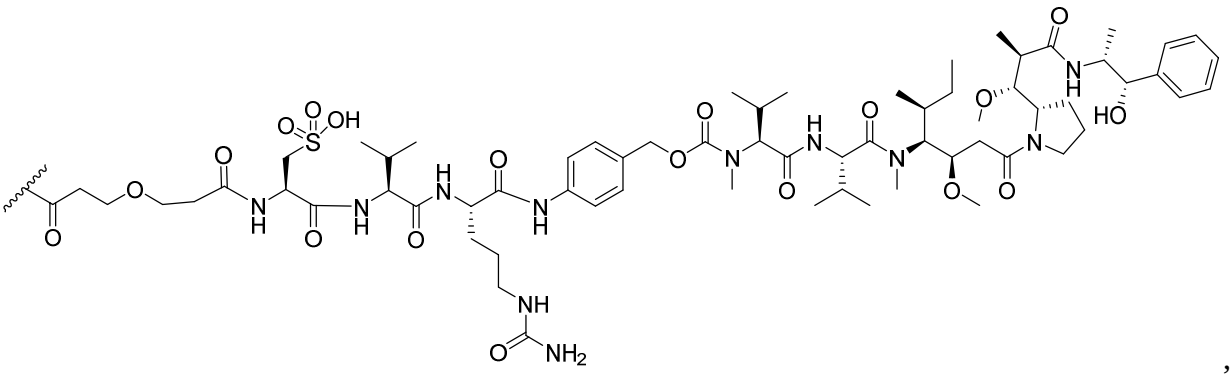

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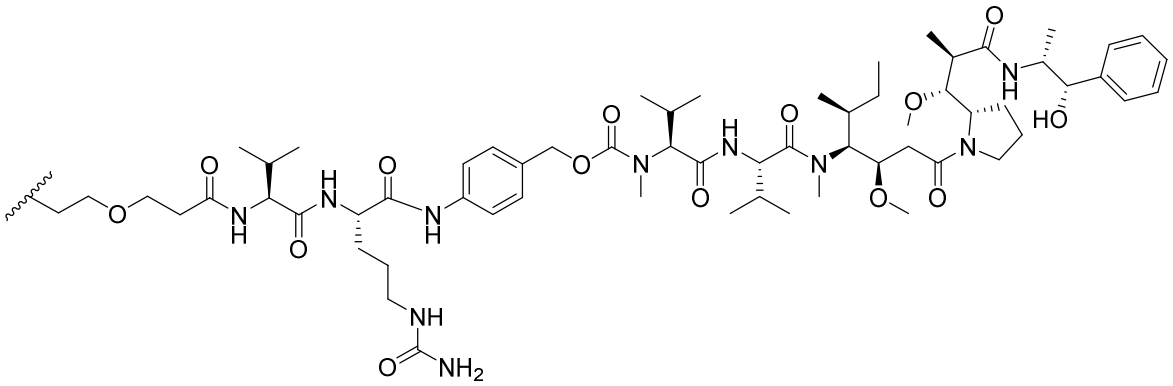

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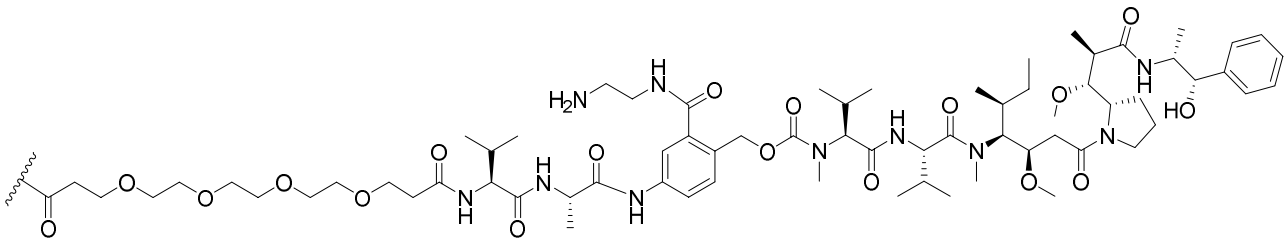

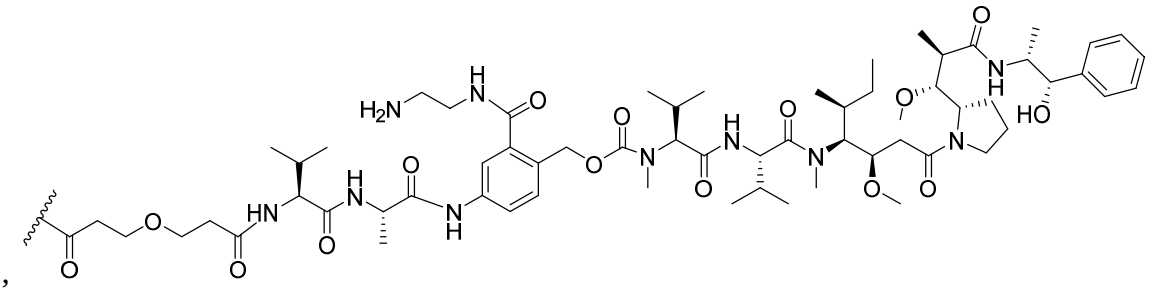

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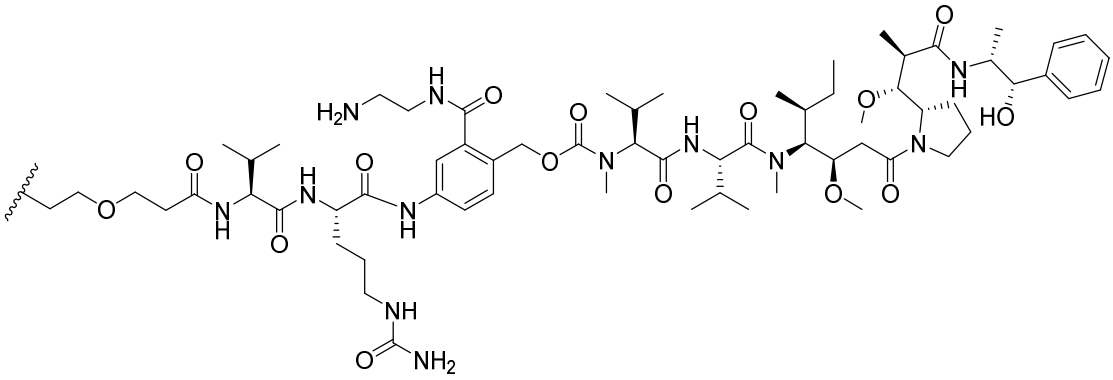

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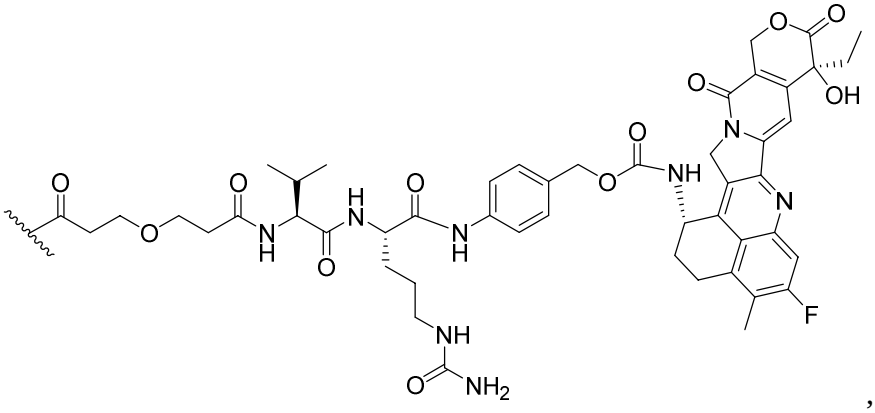

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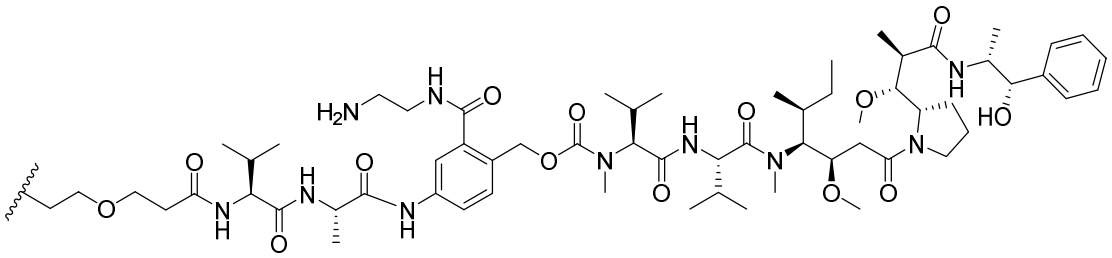

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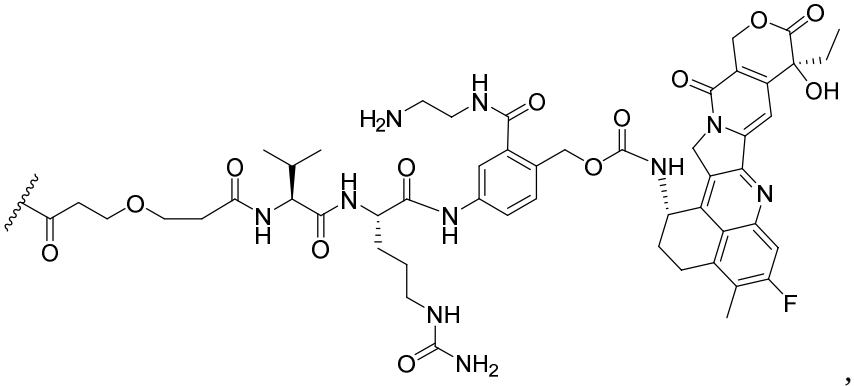

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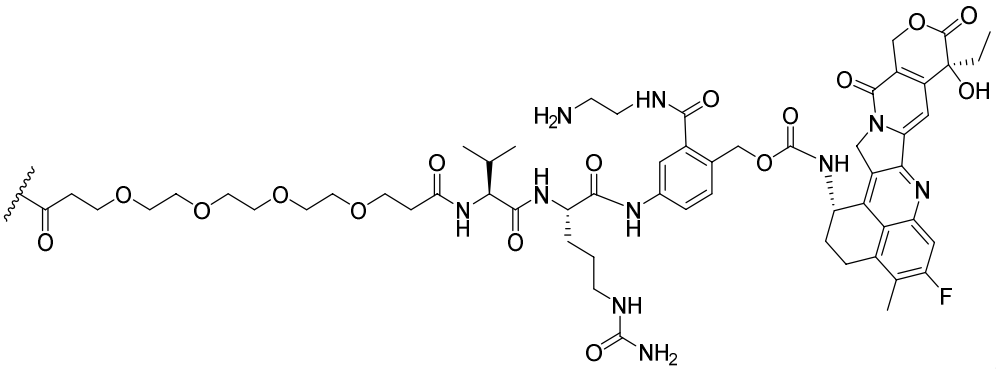

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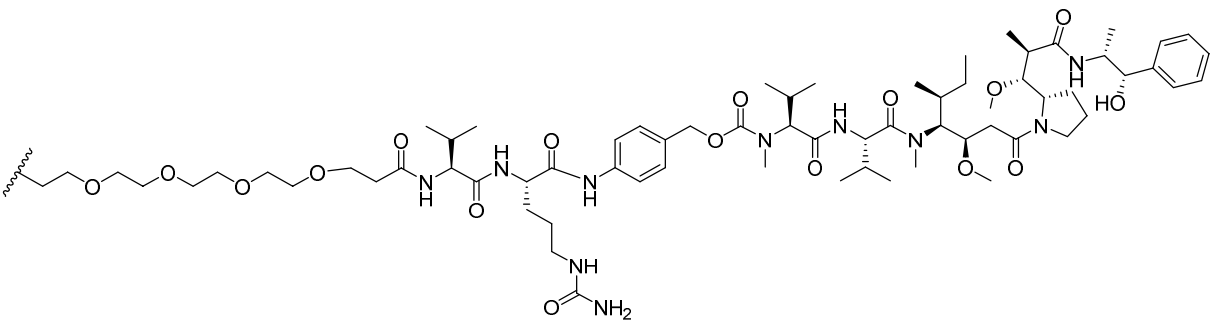

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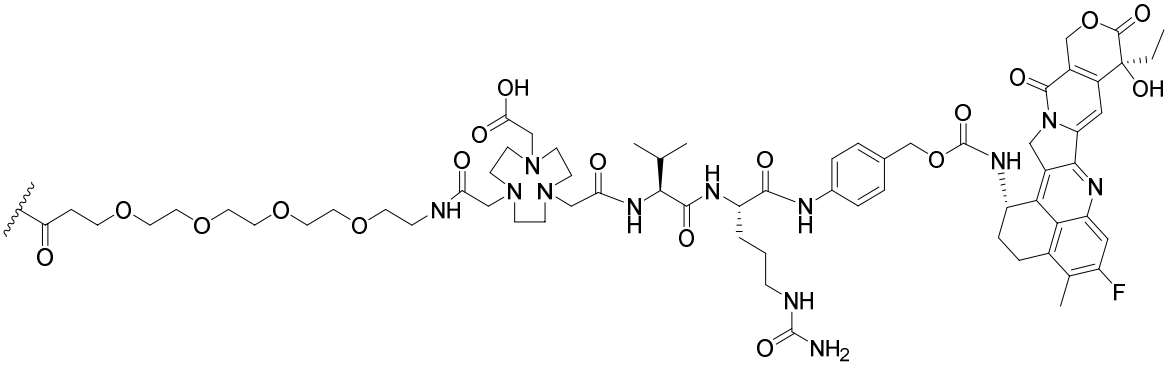

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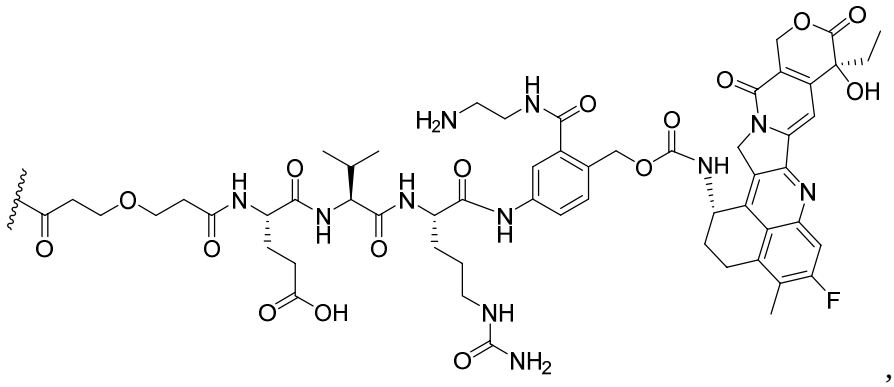

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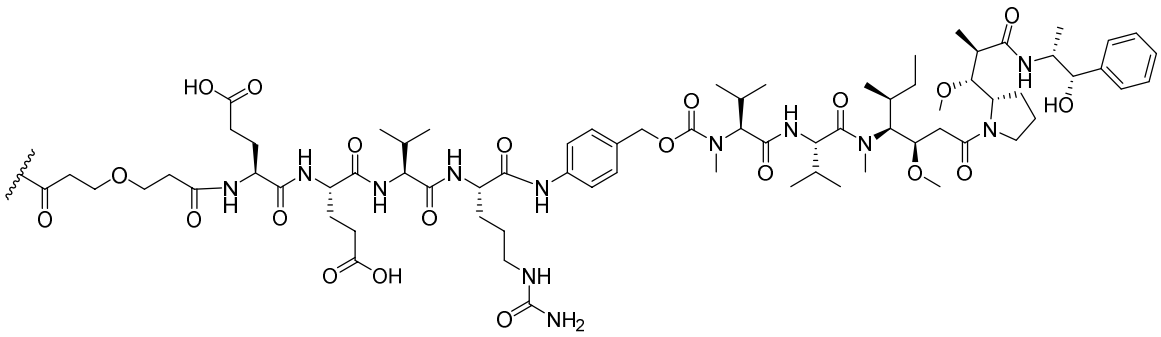

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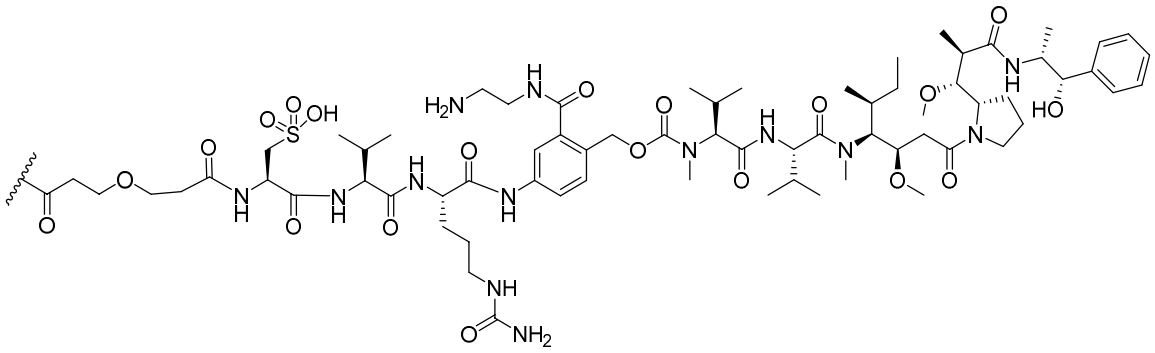

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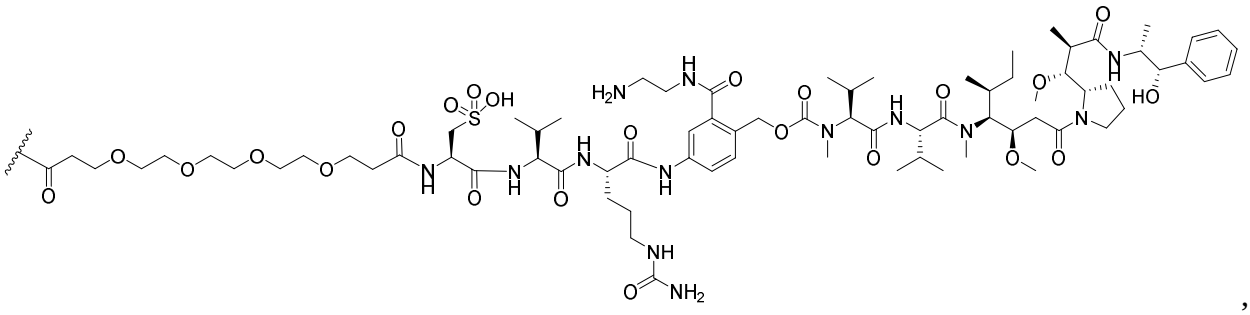

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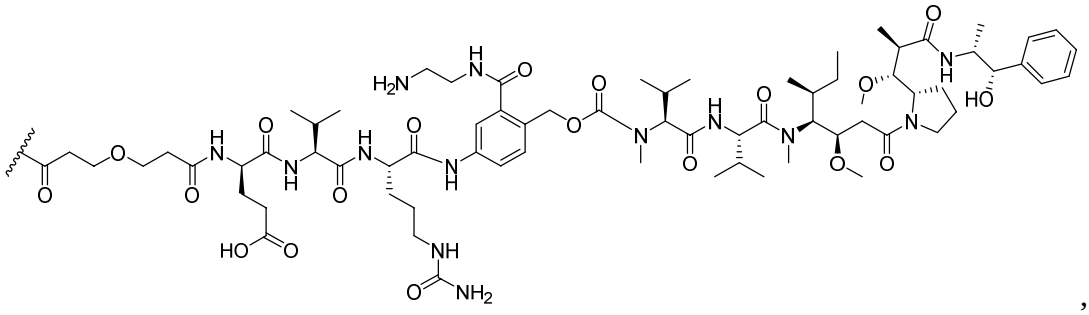

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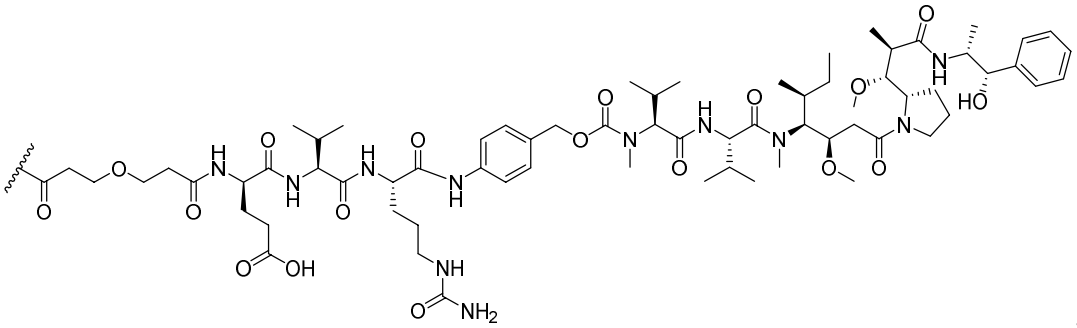

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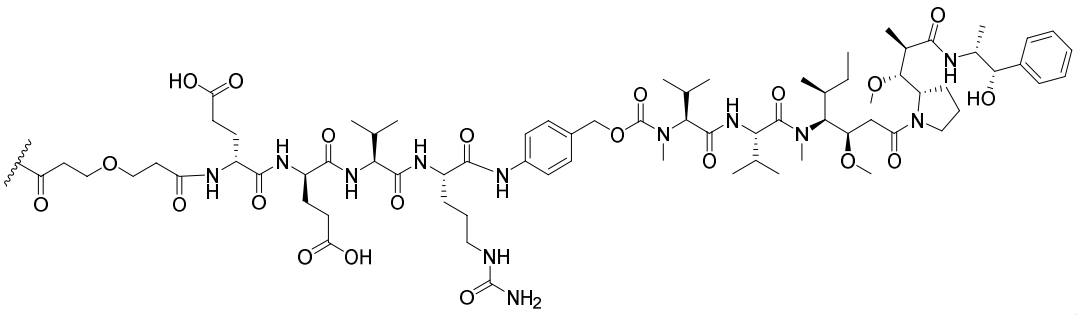

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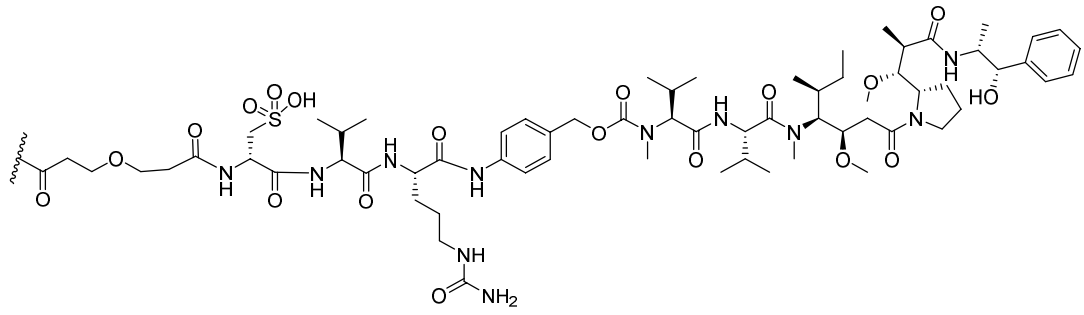

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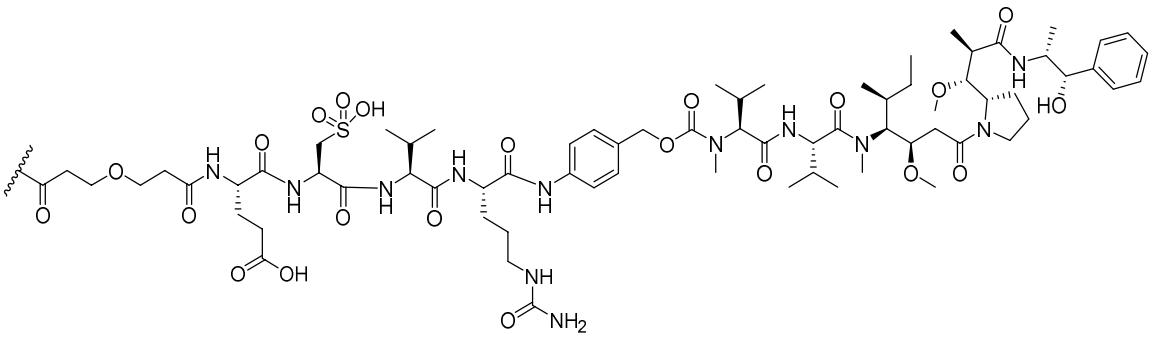

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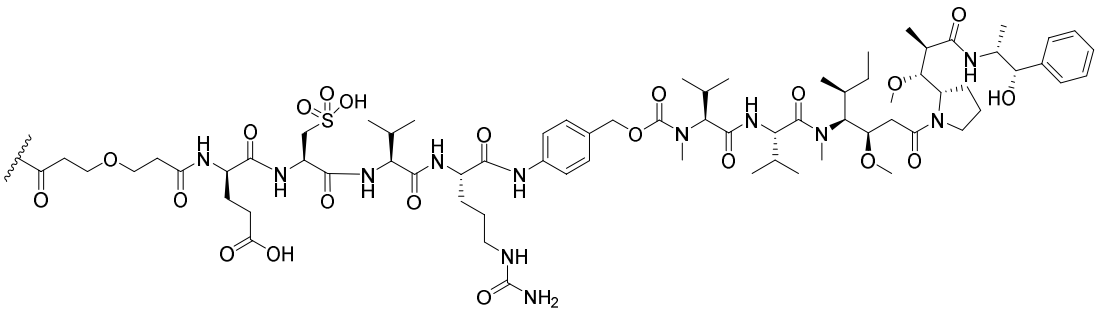

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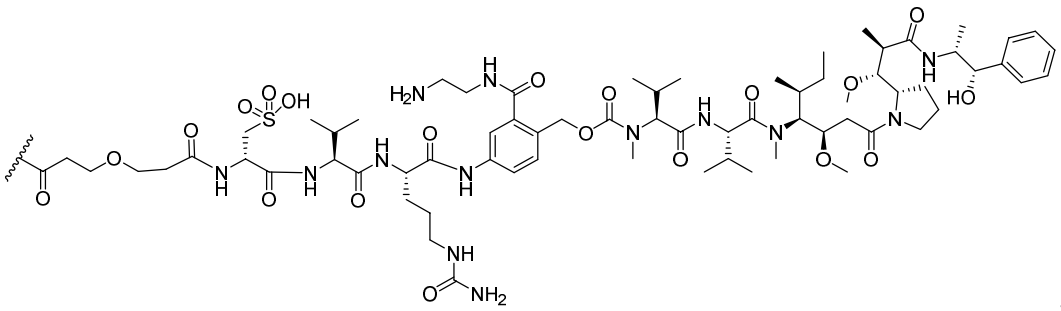

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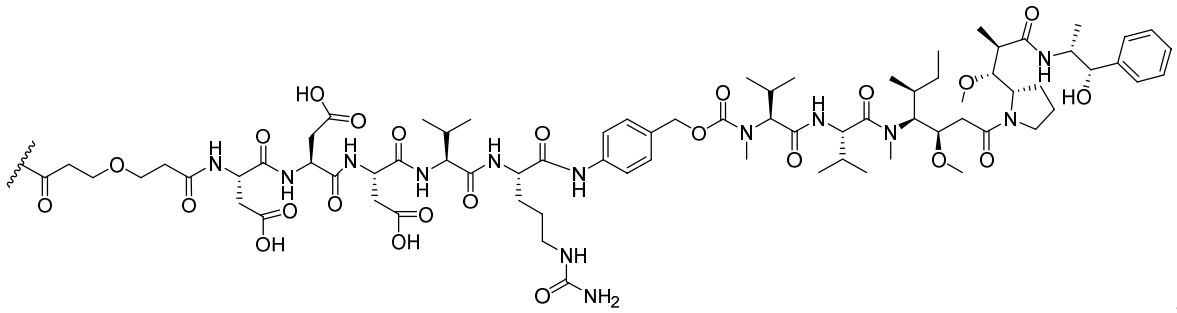

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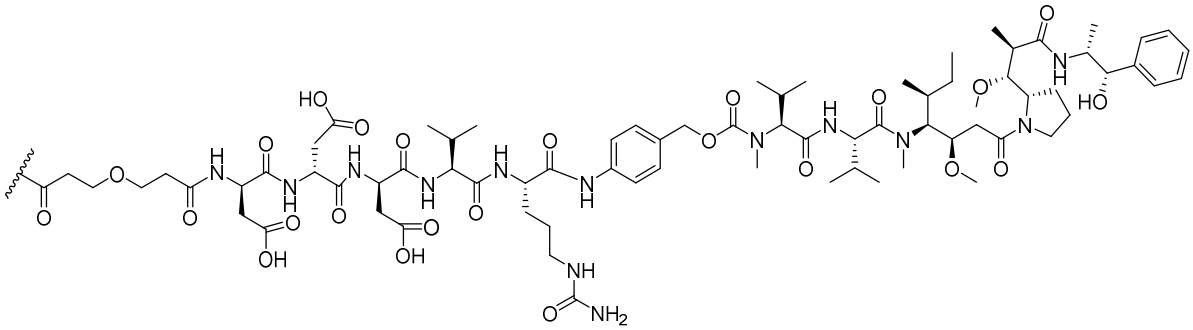

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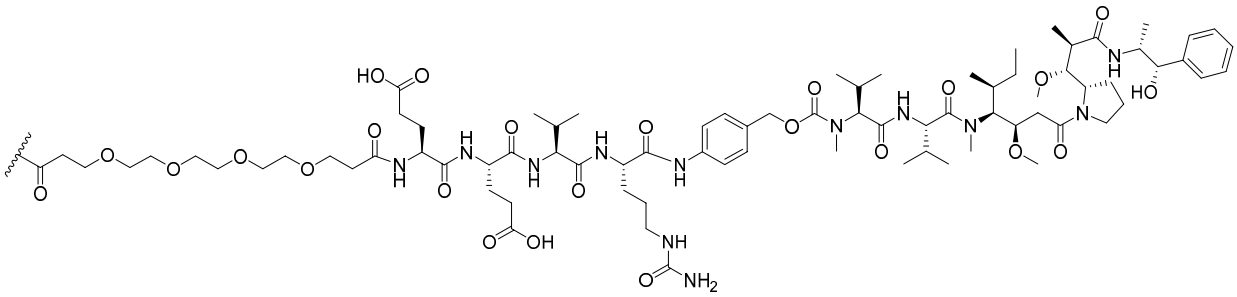

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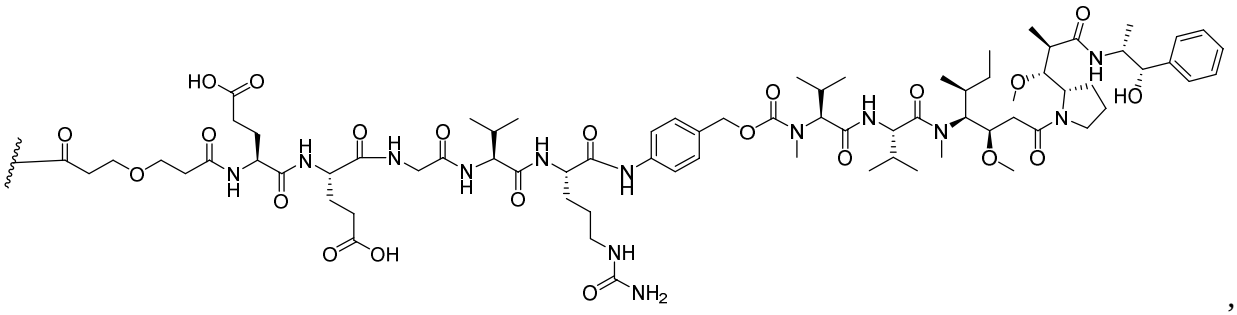

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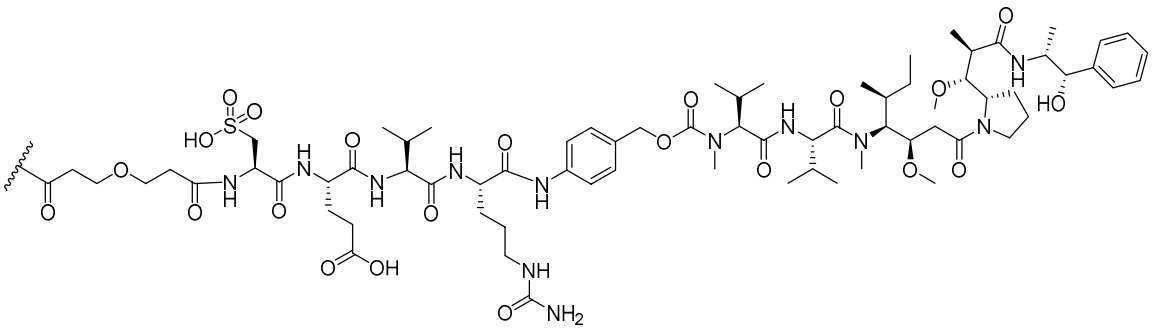

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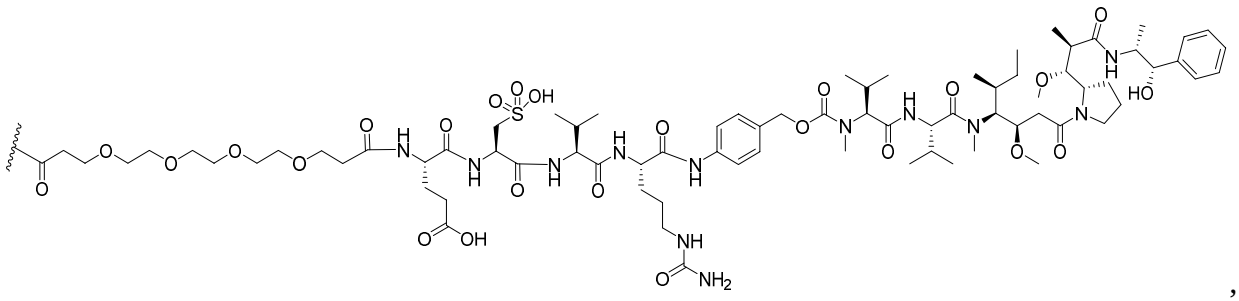

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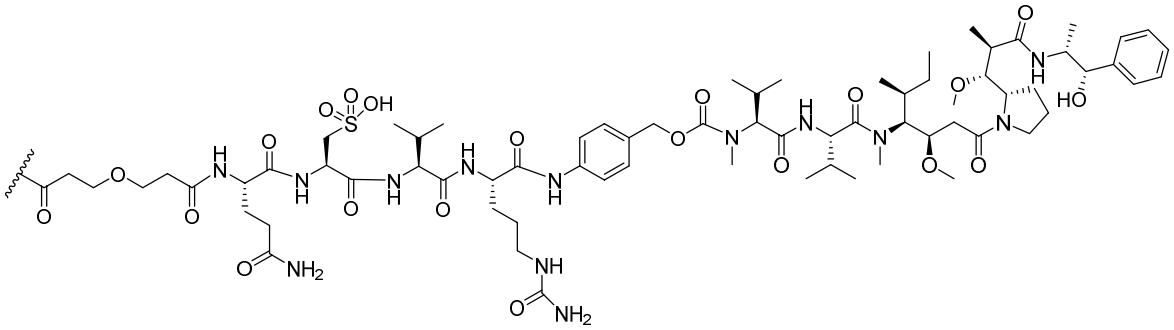

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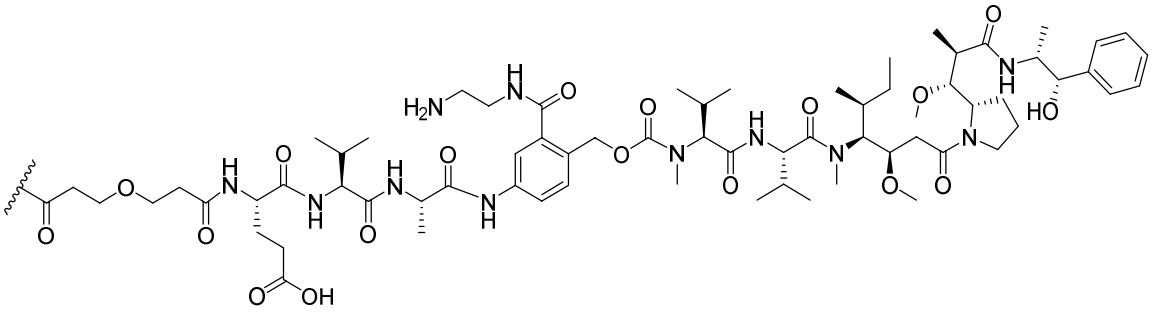

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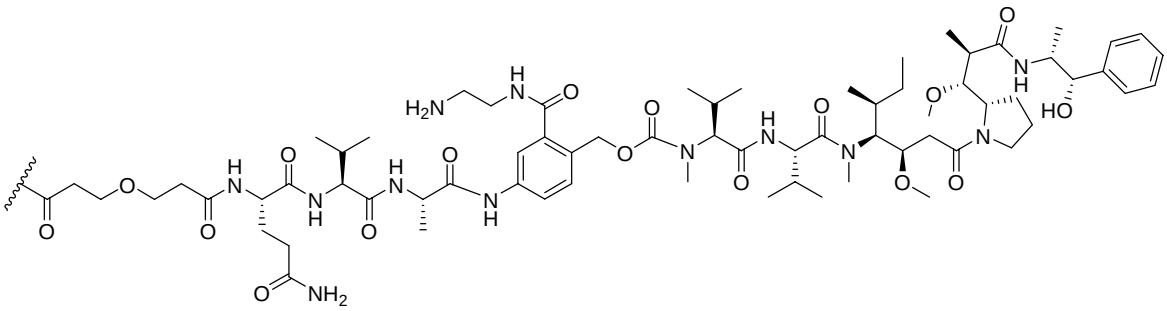

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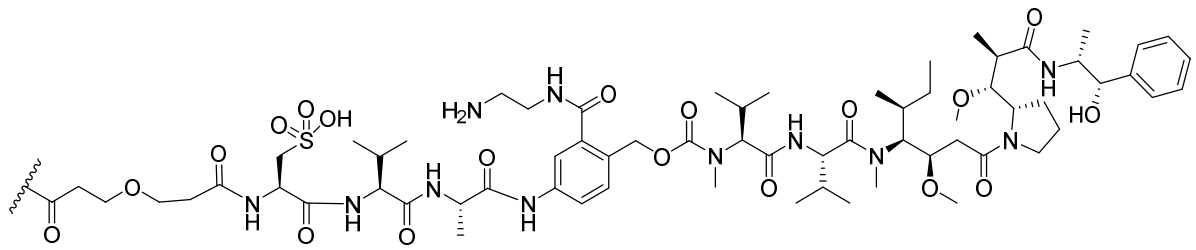

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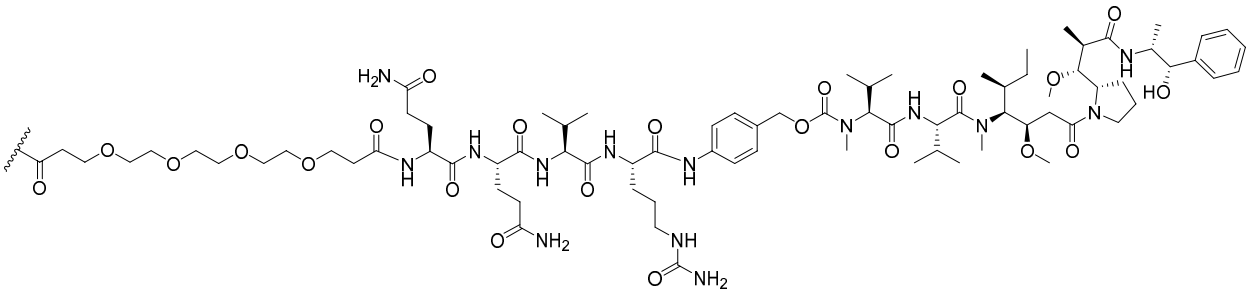

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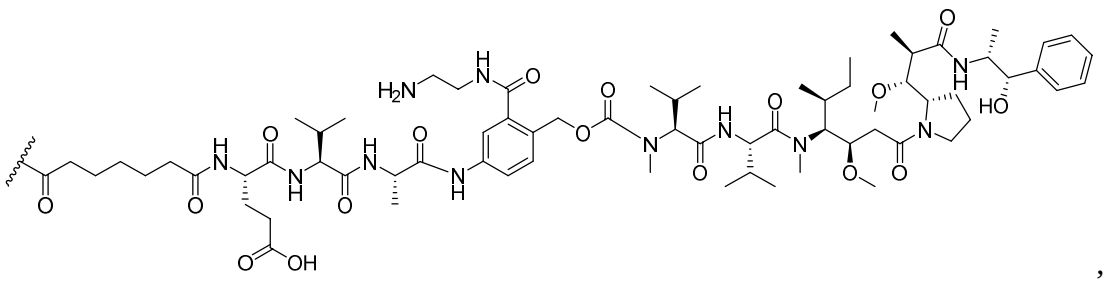

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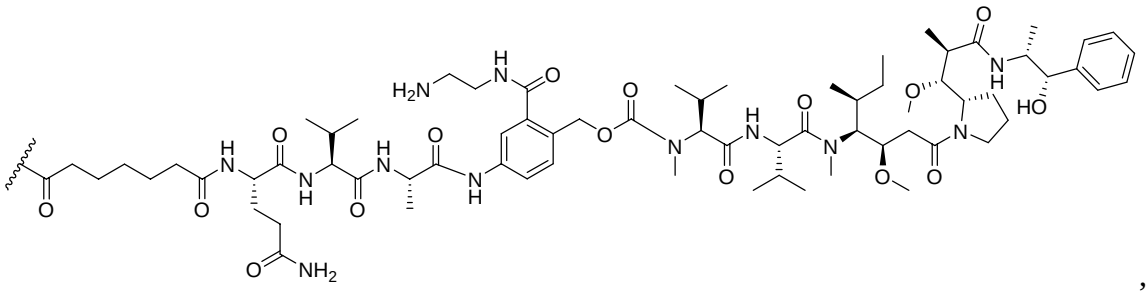

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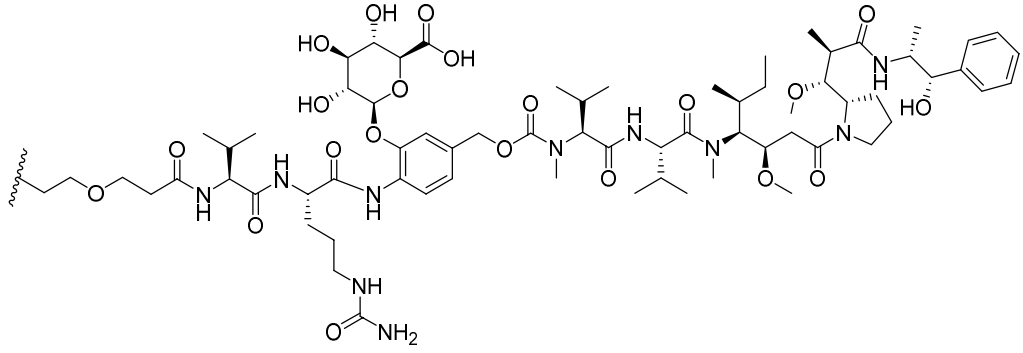

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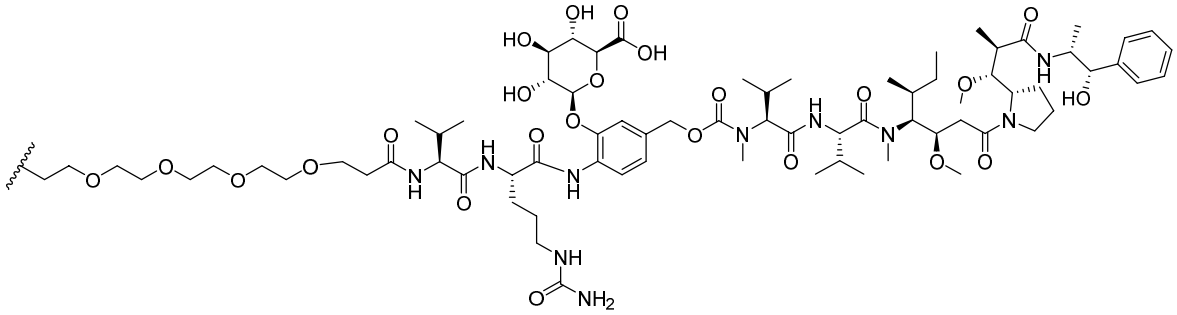

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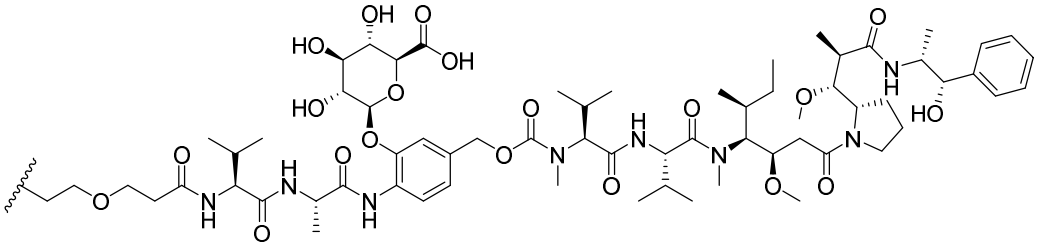

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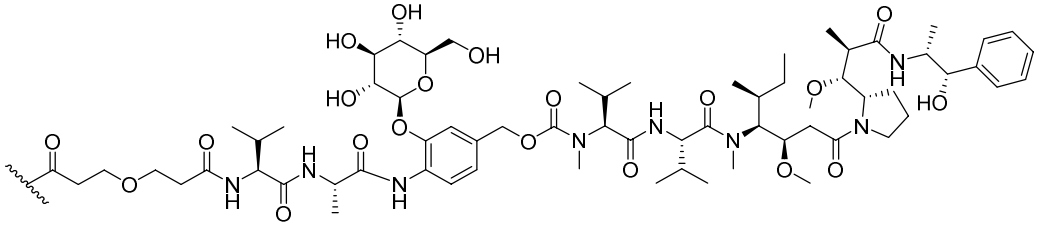

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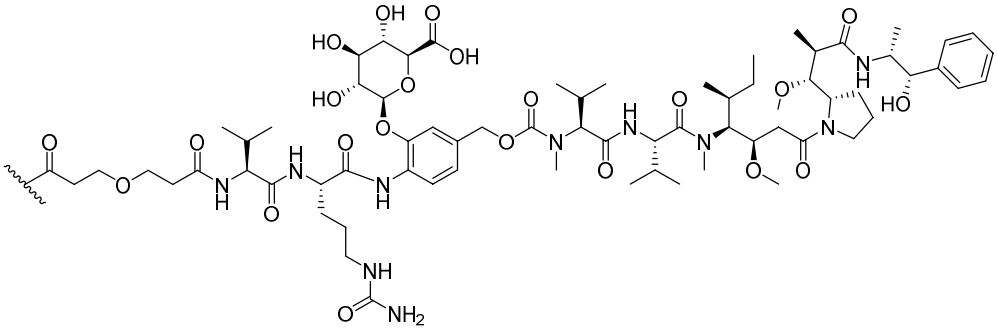

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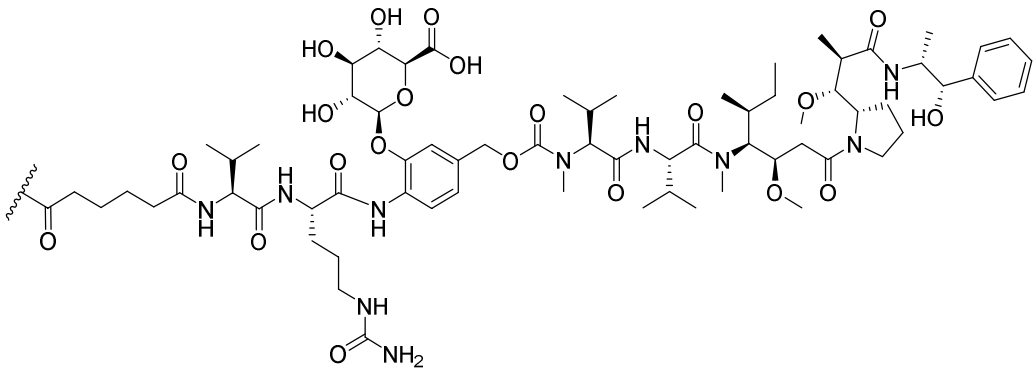

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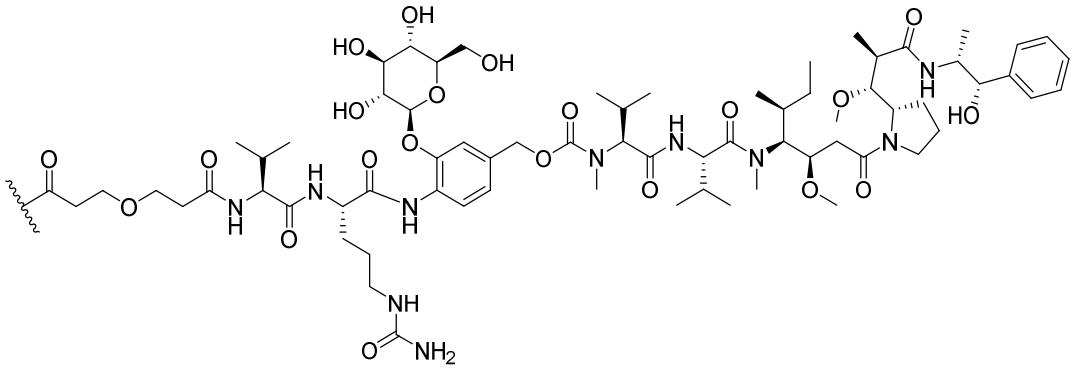

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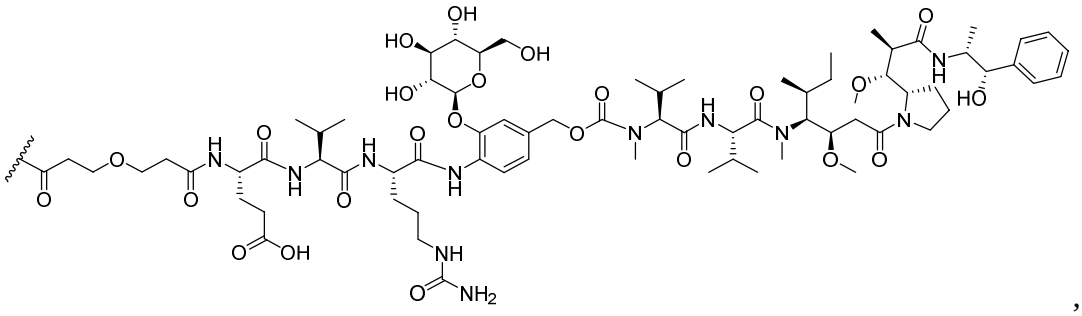

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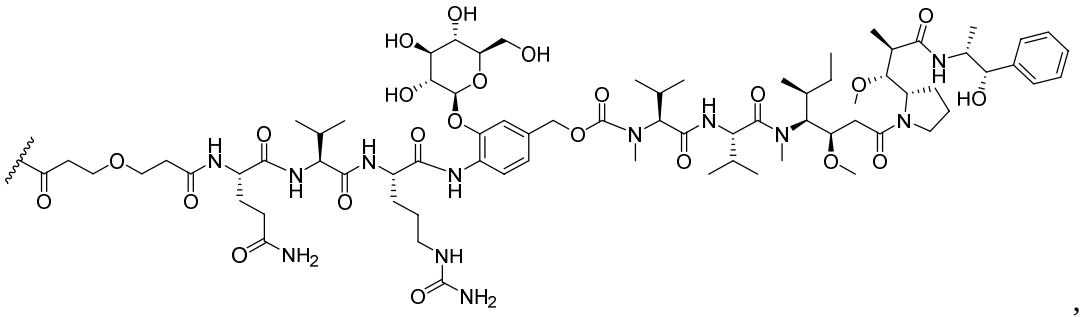

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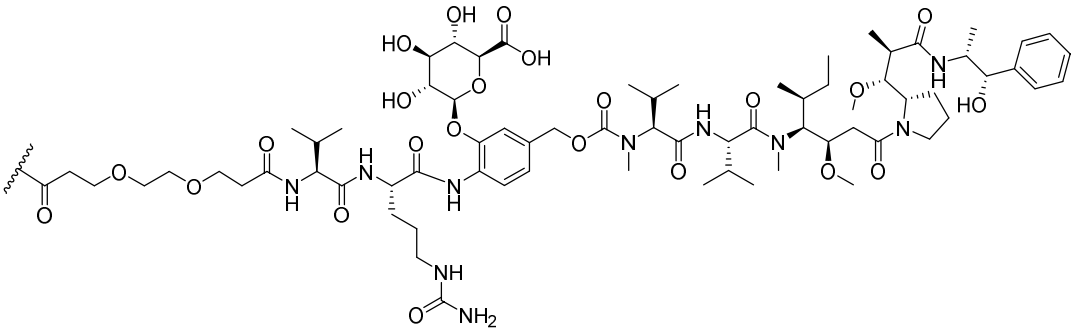

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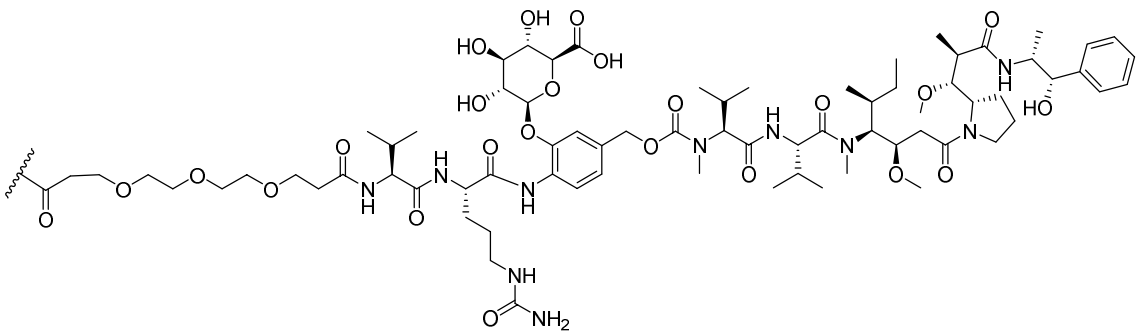

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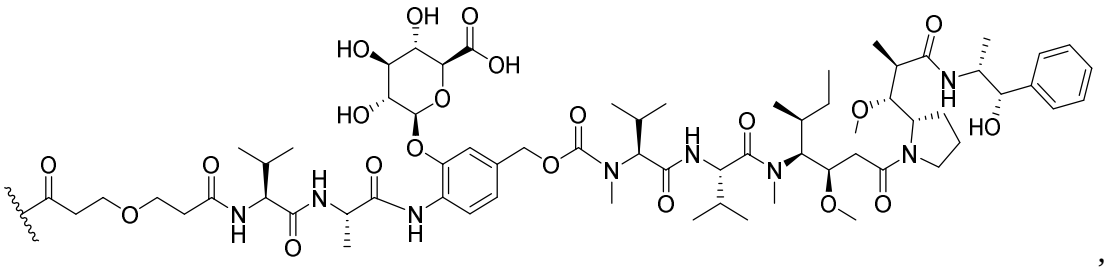

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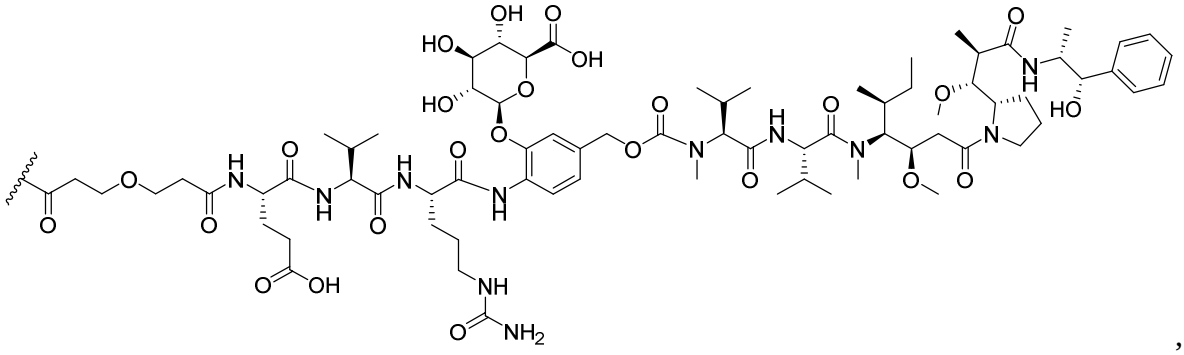

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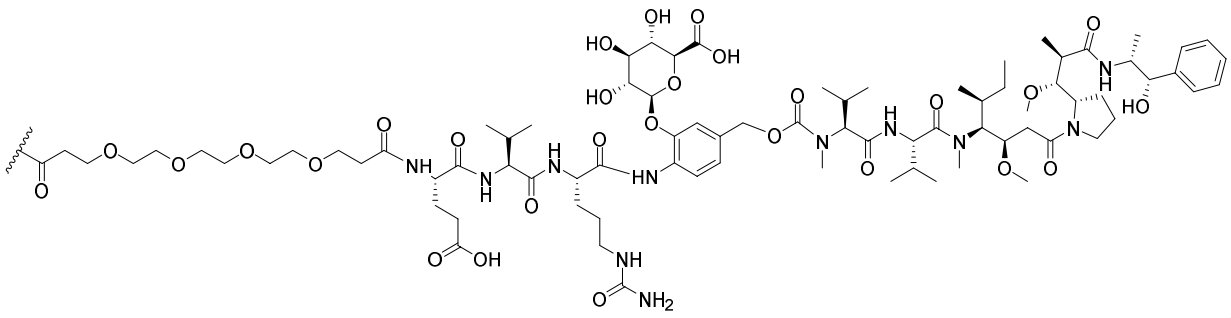

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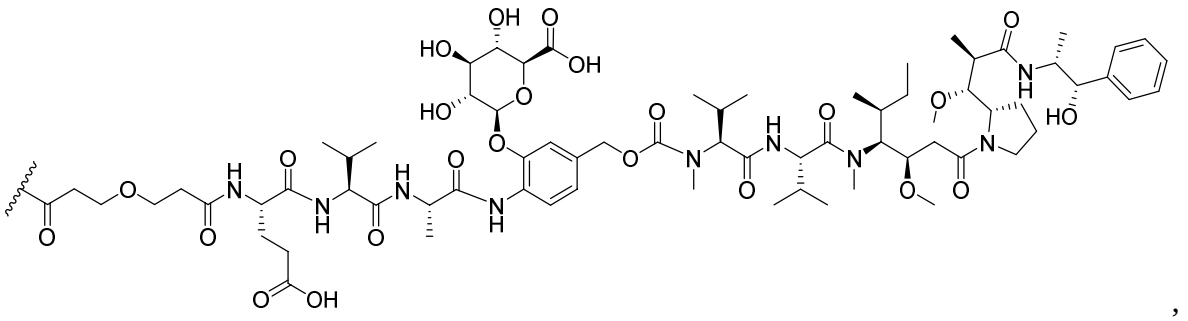

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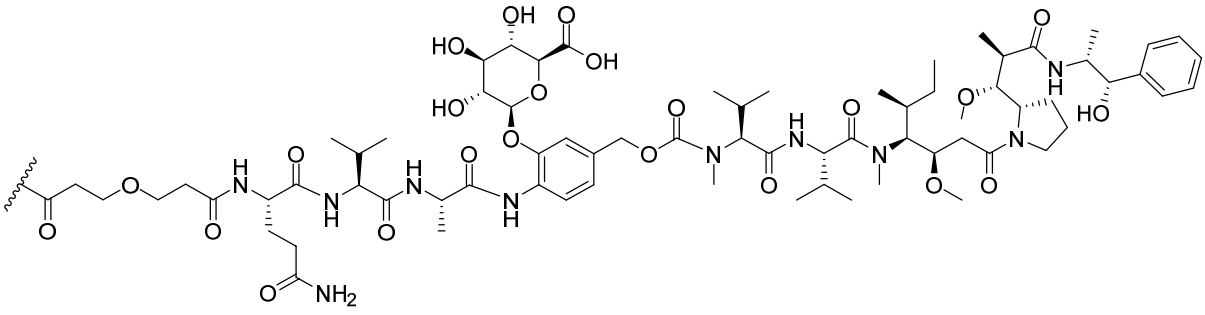

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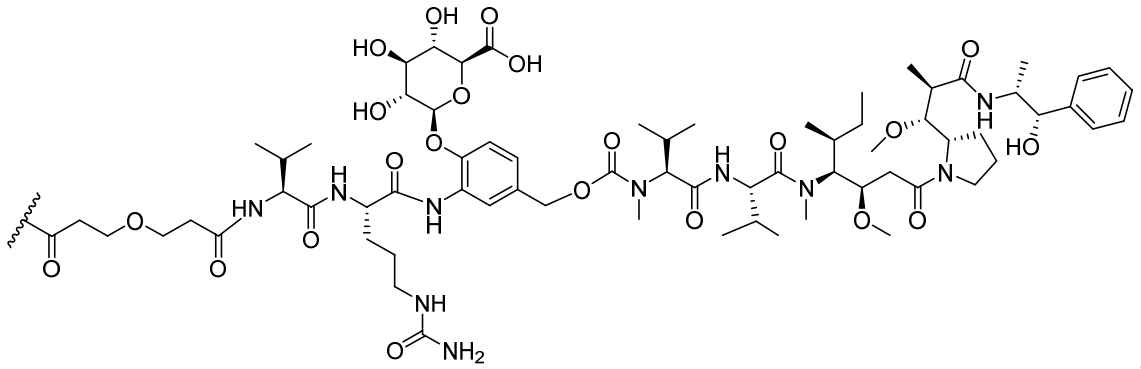

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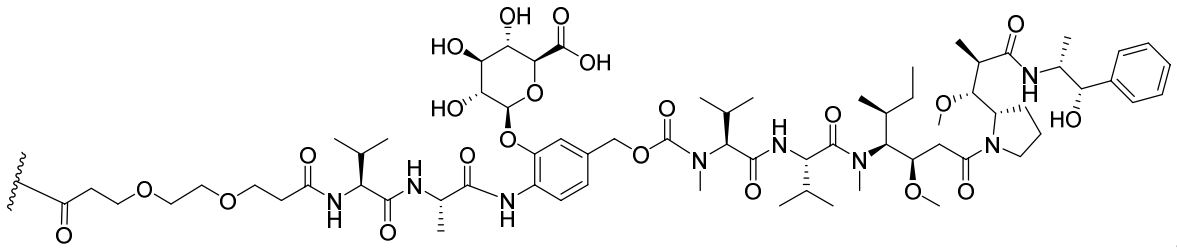

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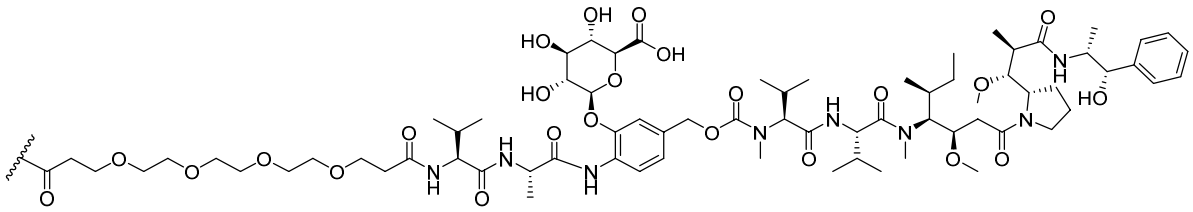

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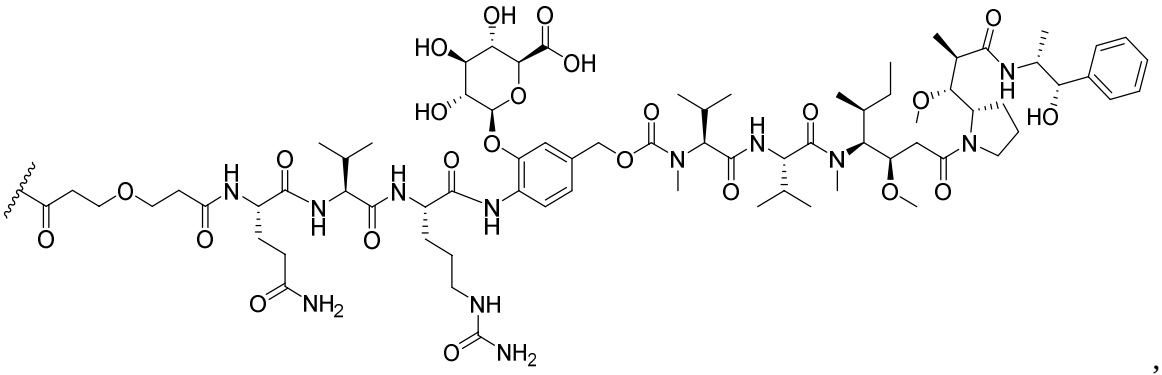

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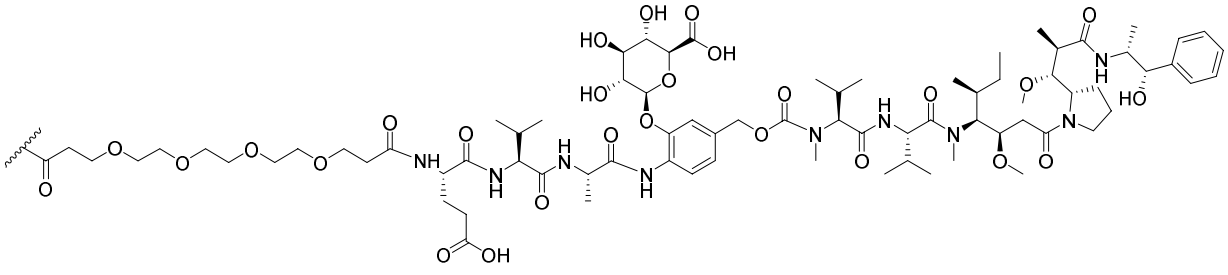

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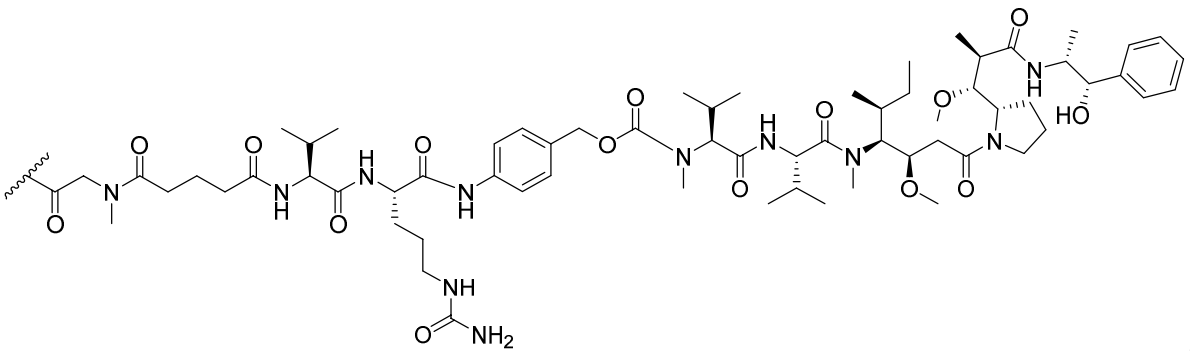

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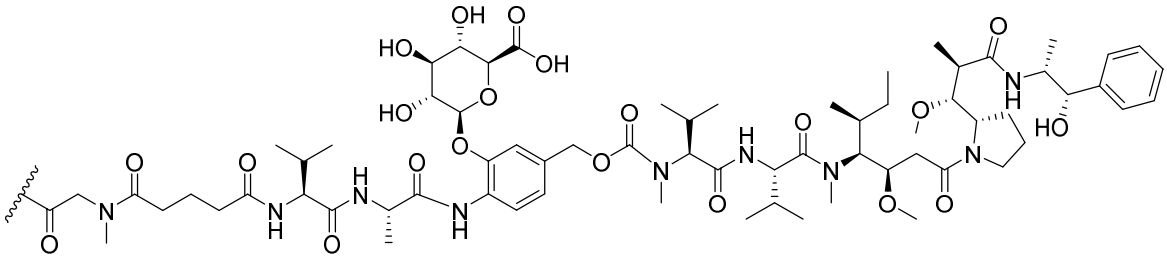

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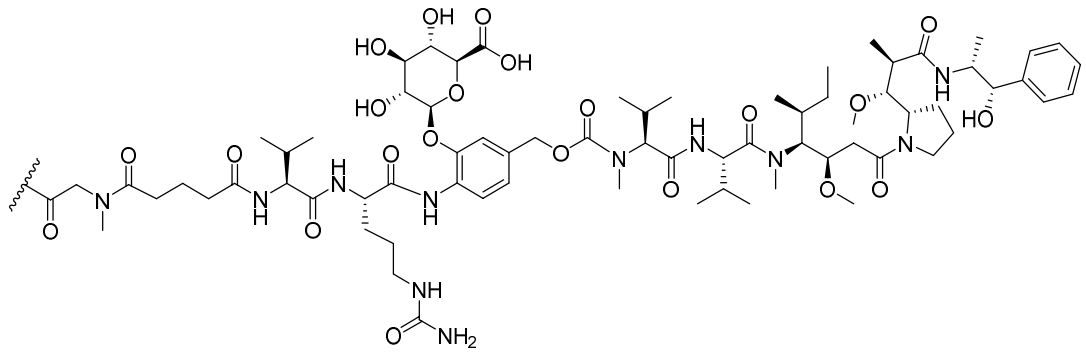

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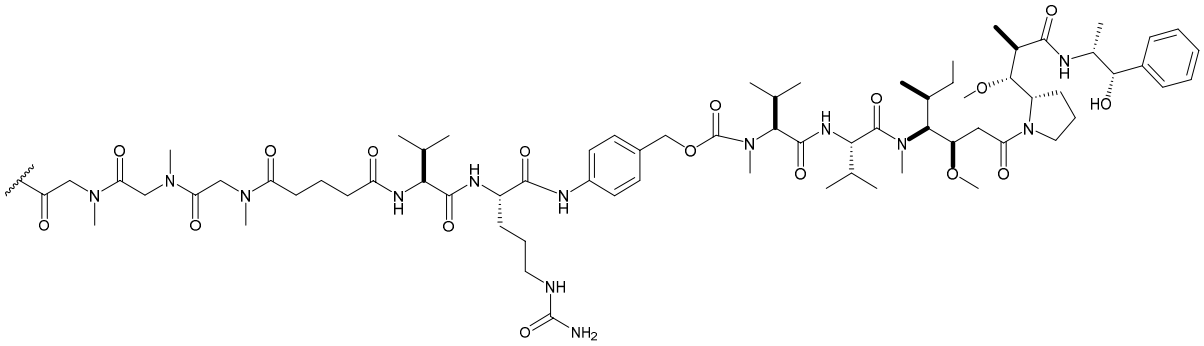

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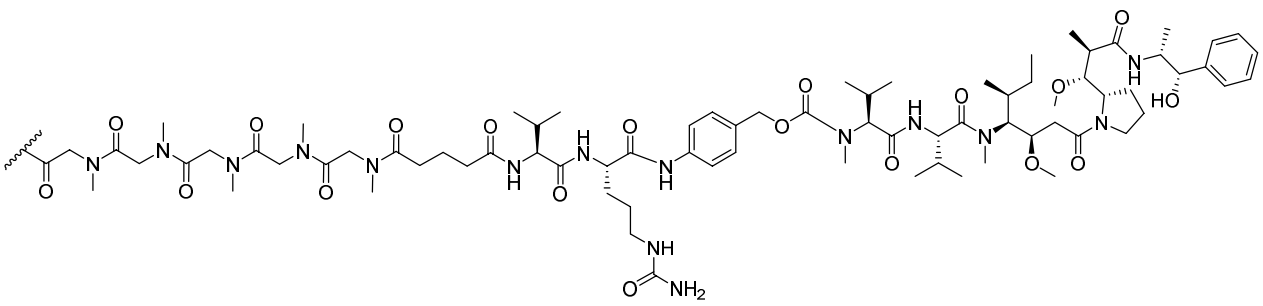

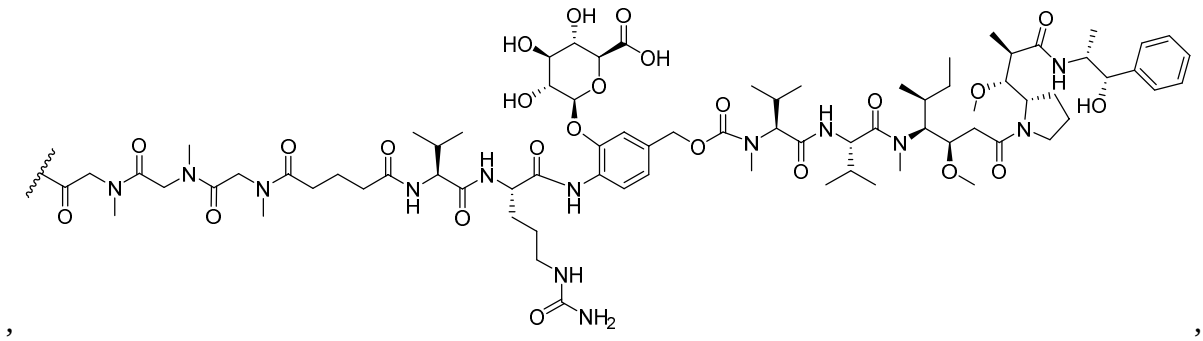

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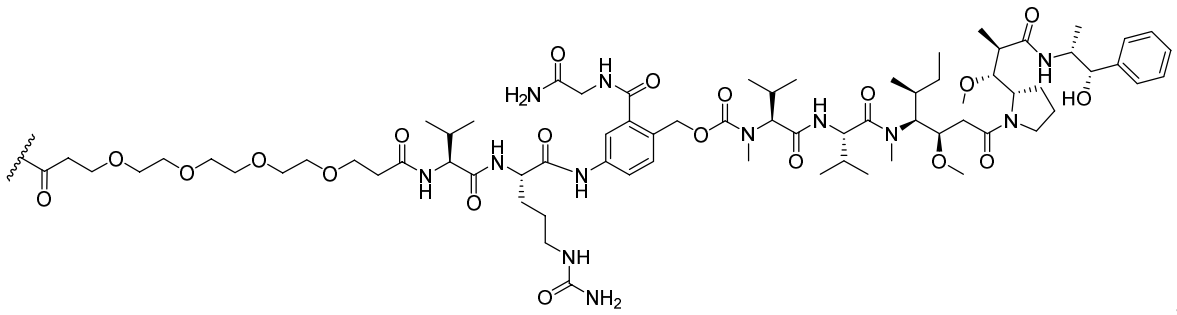

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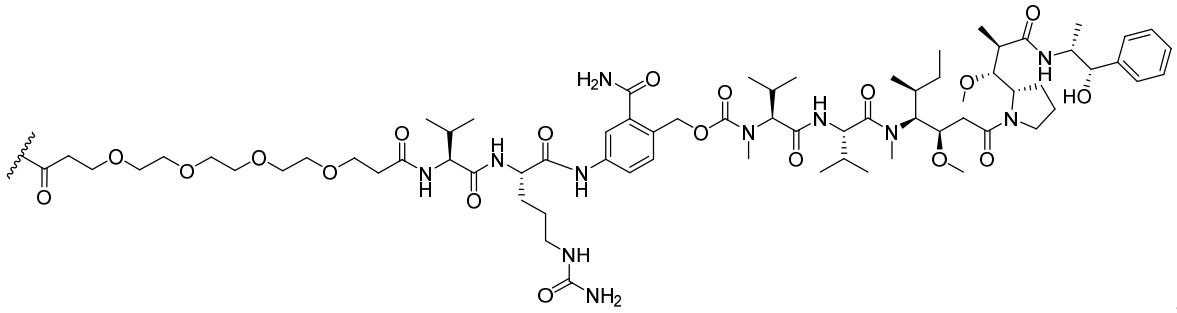

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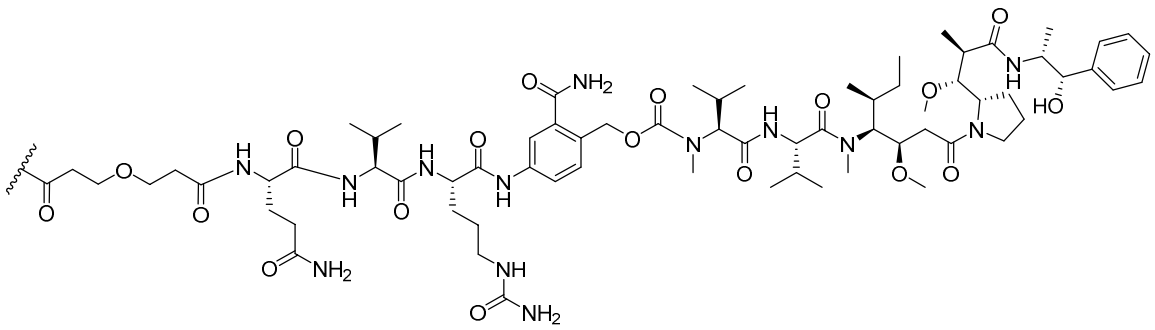

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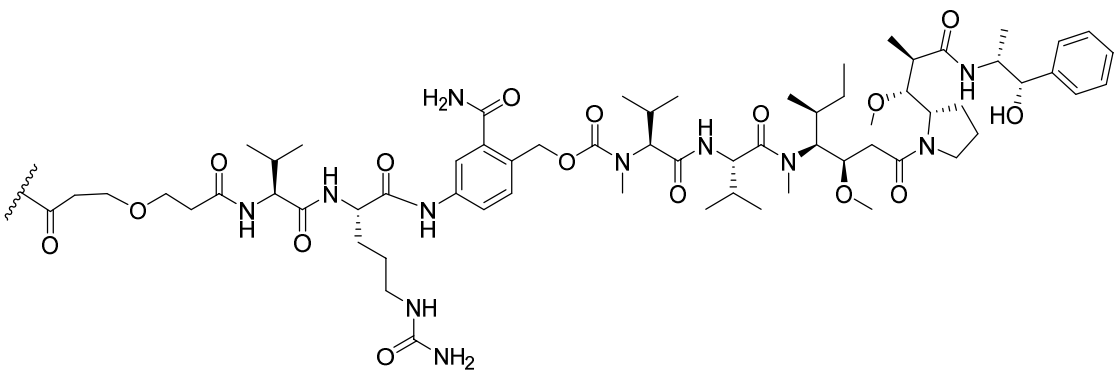

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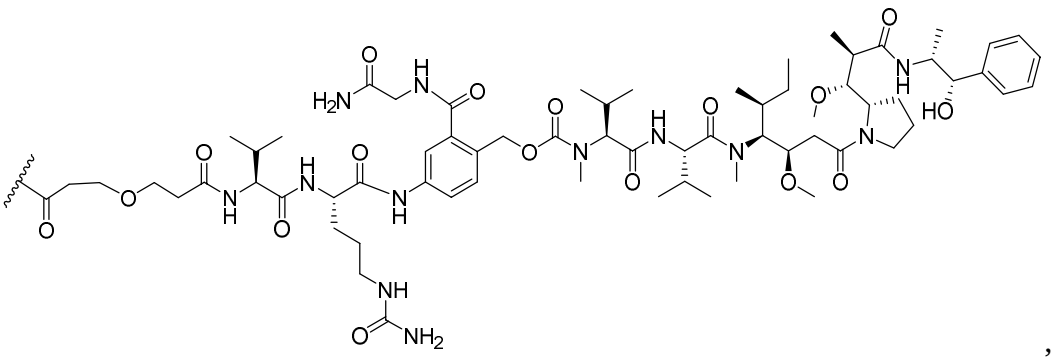

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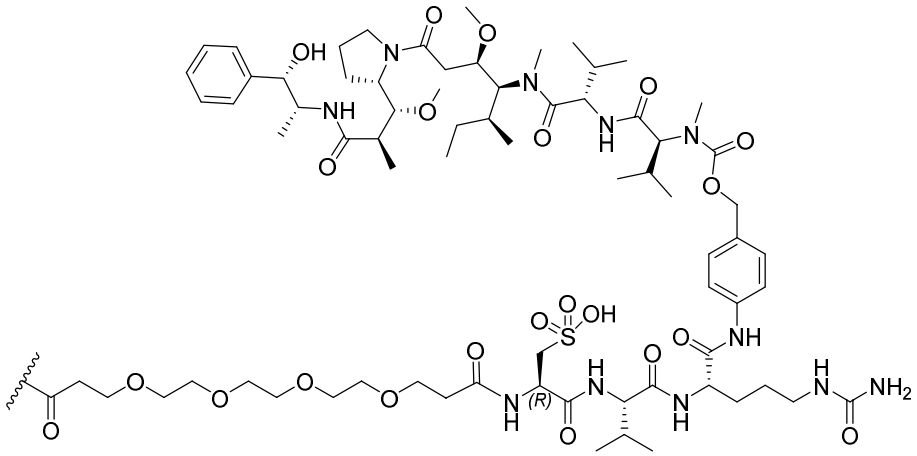

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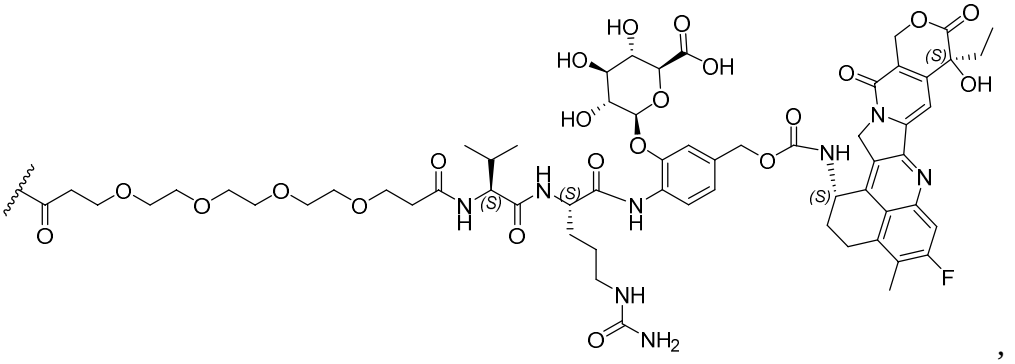

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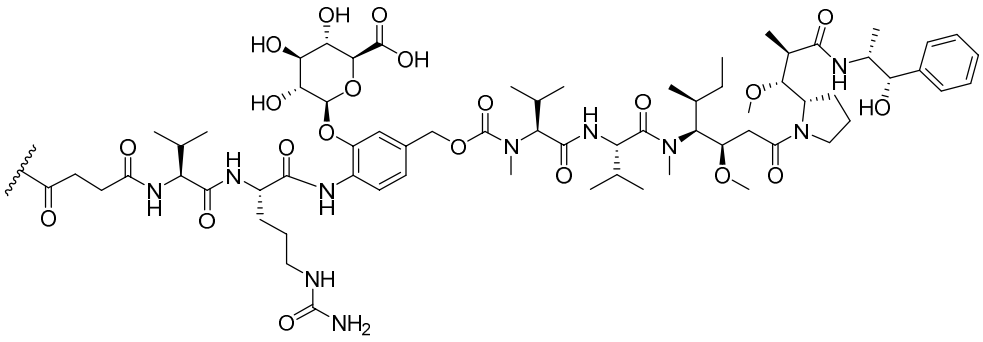

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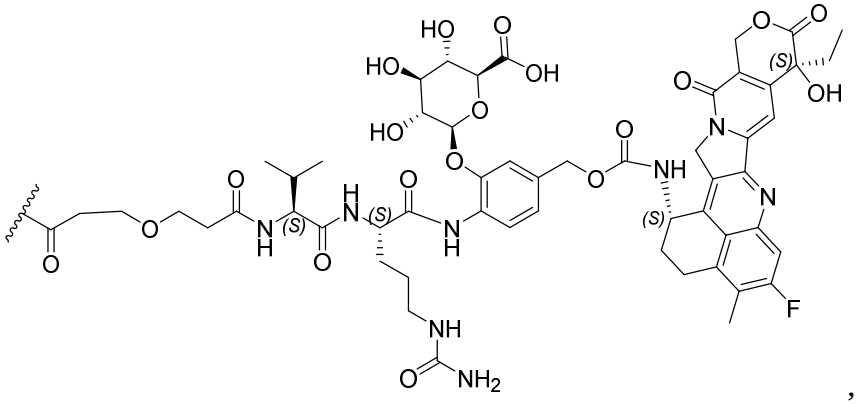

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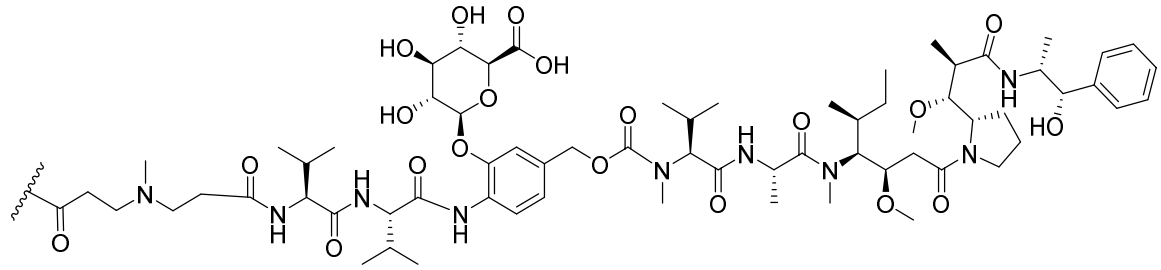

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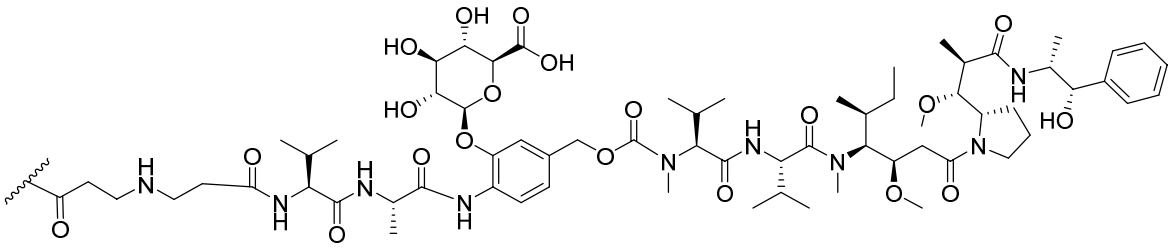

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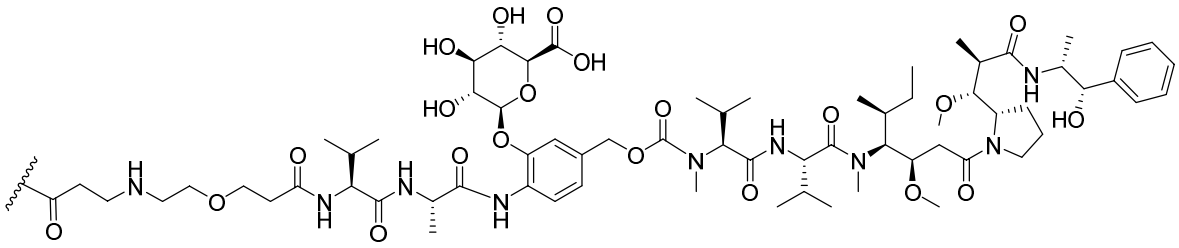

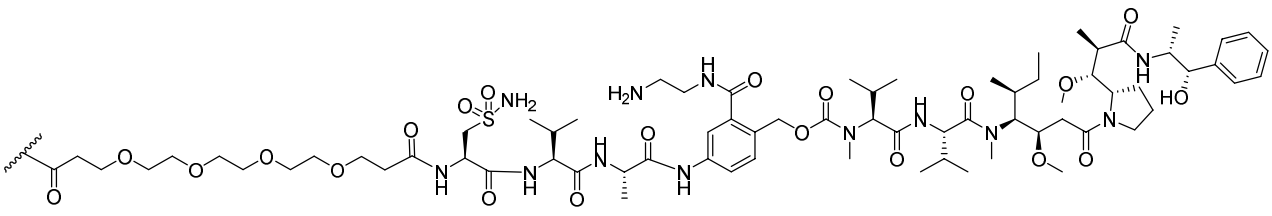

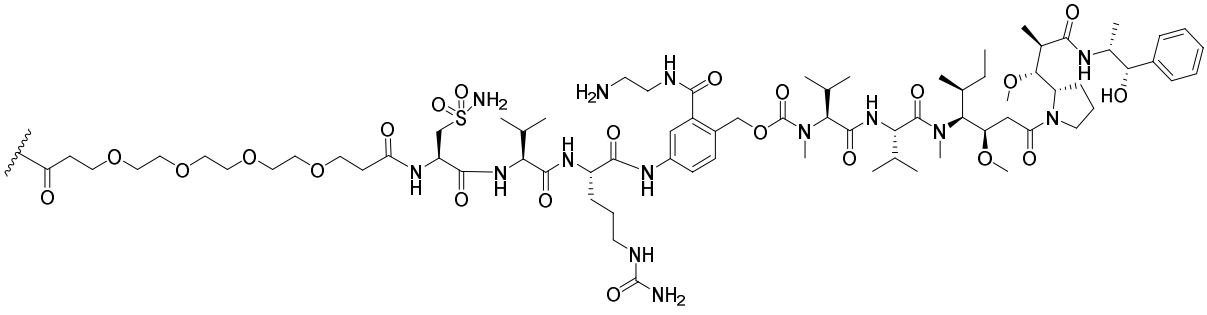

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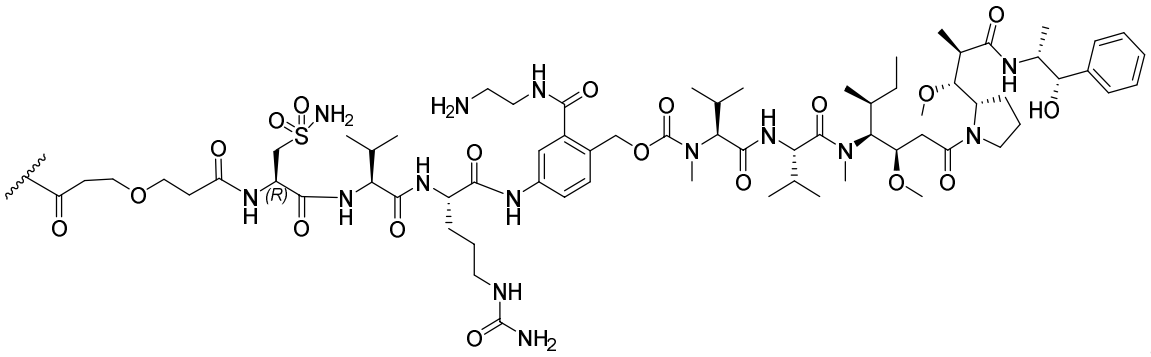

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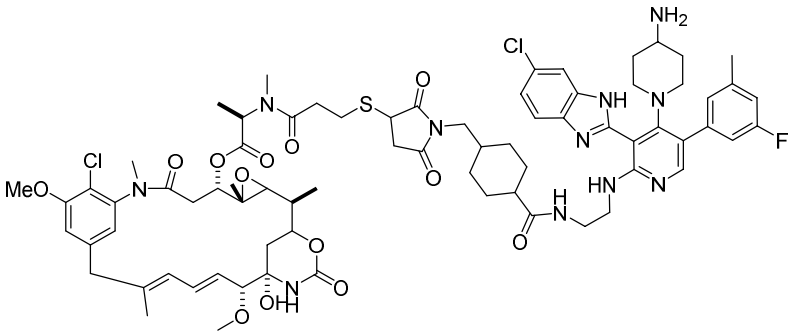
25. A compound, or pharmaceutically acceptable salt thereof, selected from the group consisting of:



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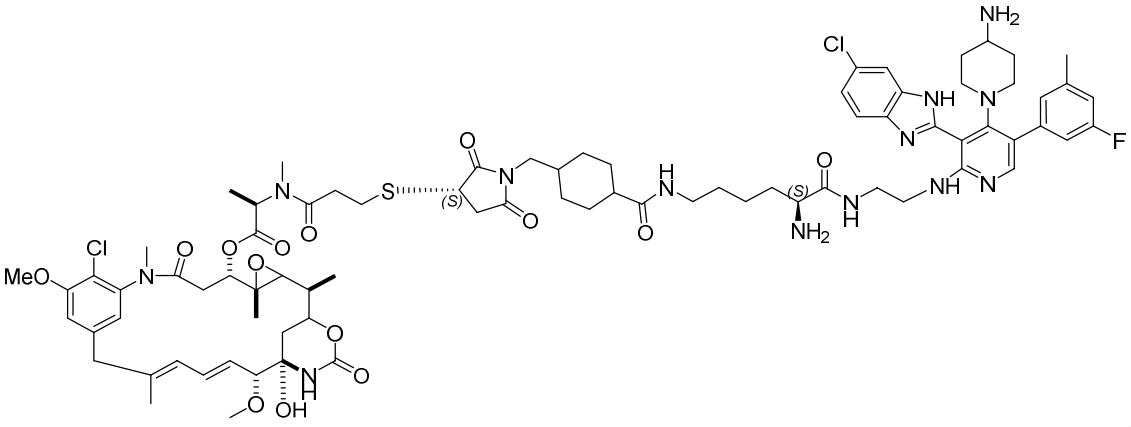

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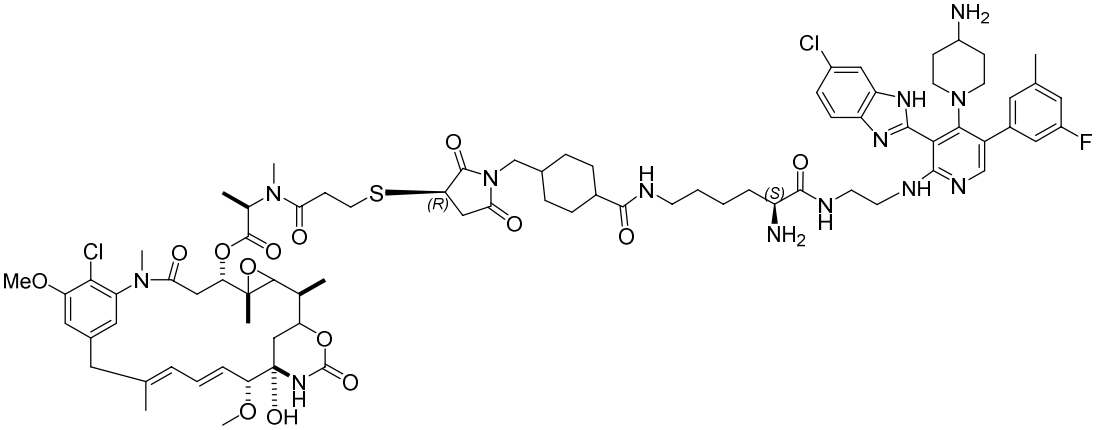

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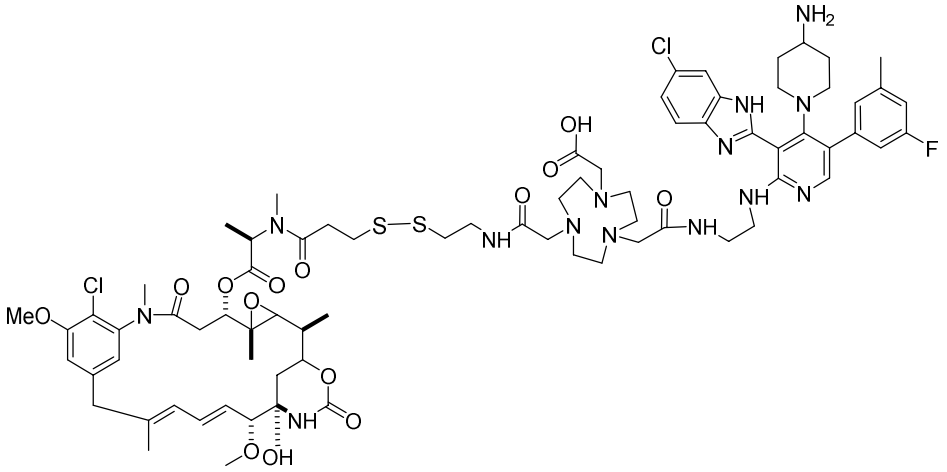

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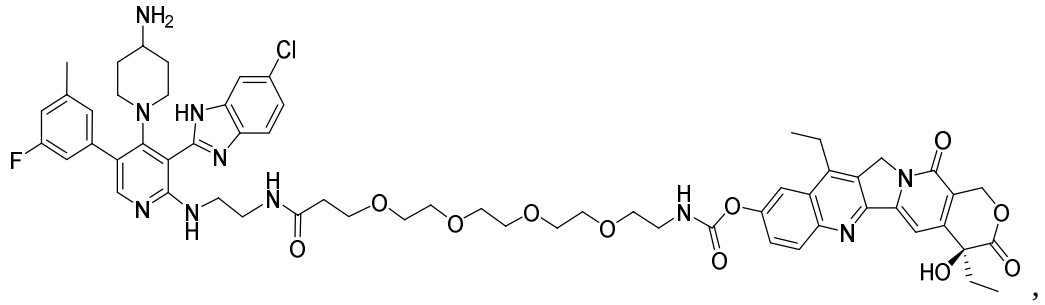

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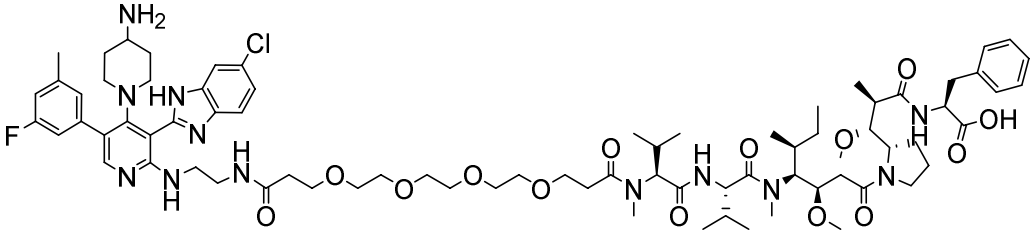

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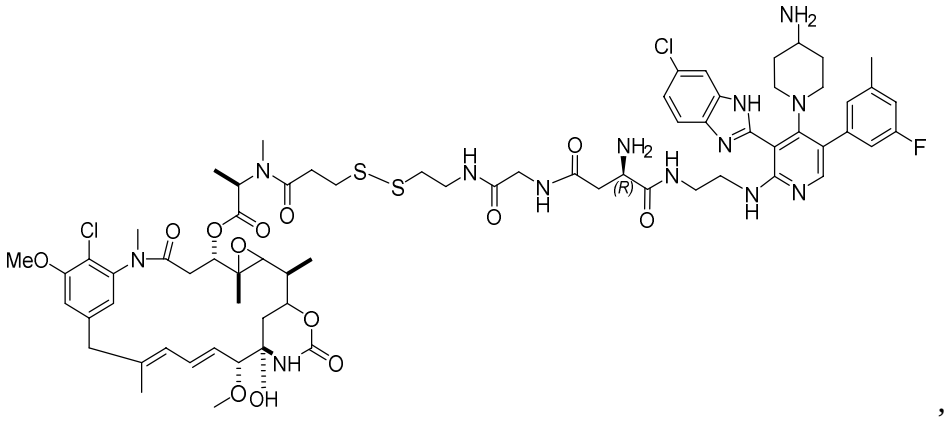

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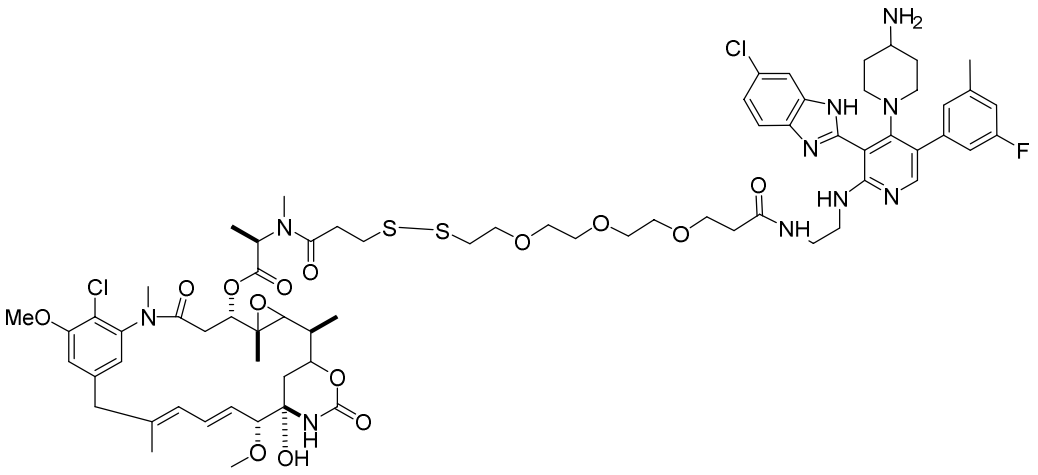

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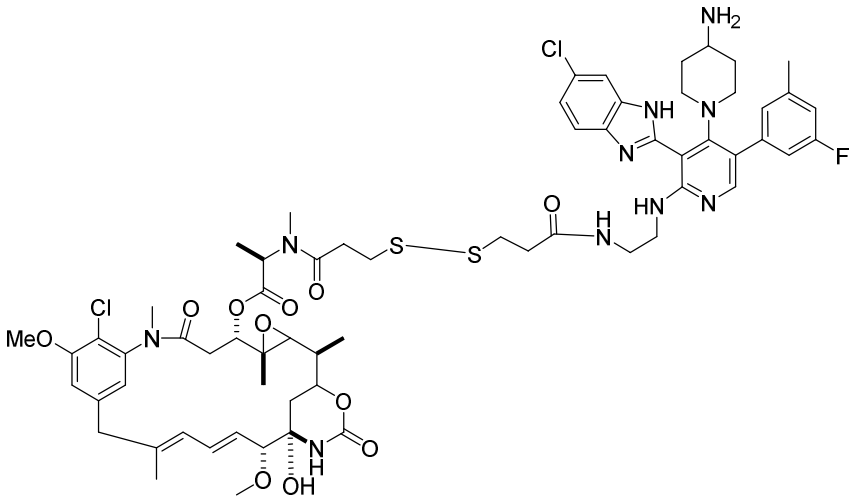

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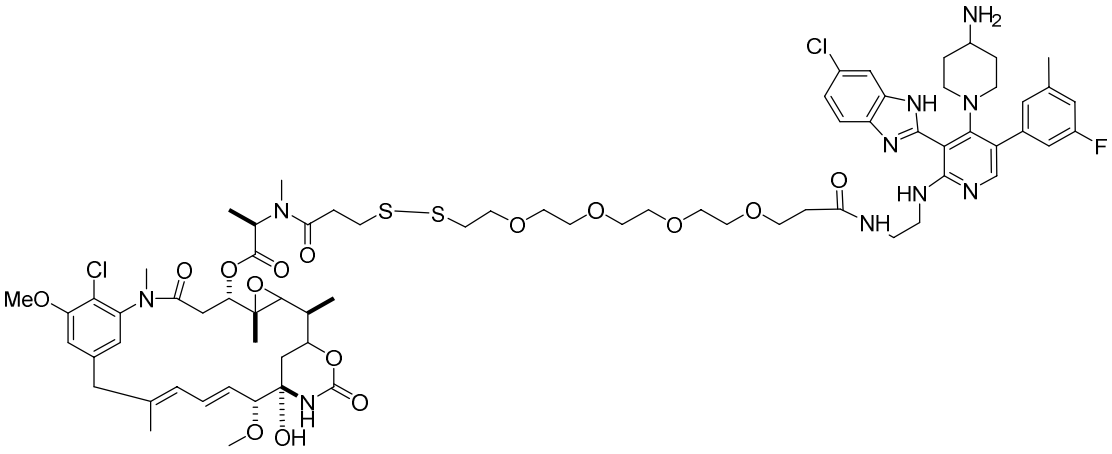

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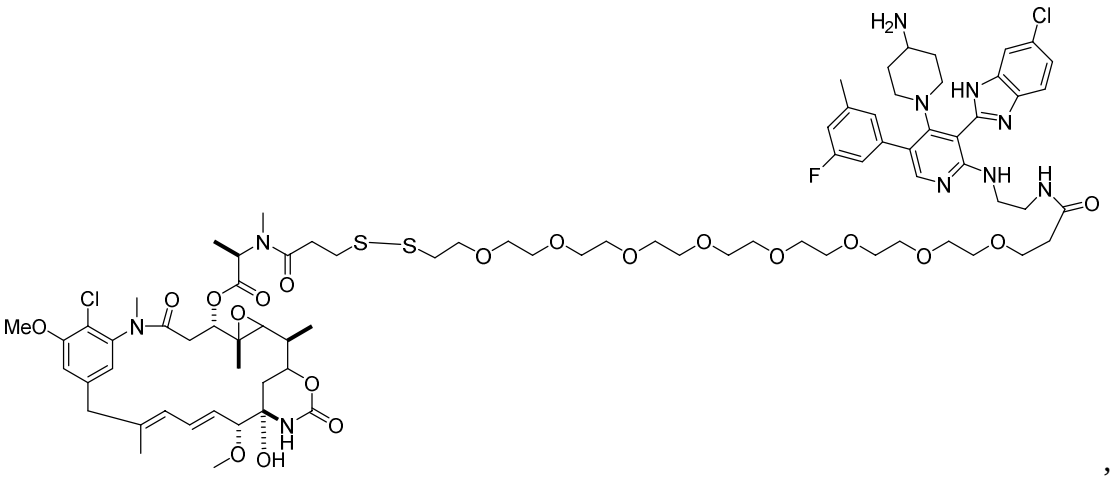

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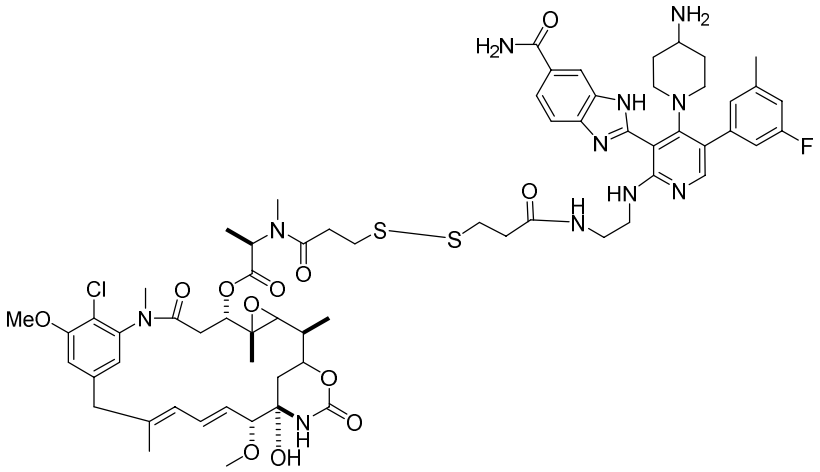

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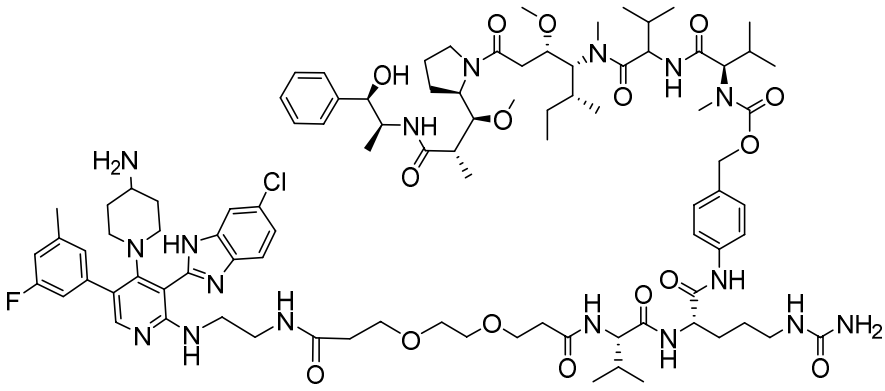

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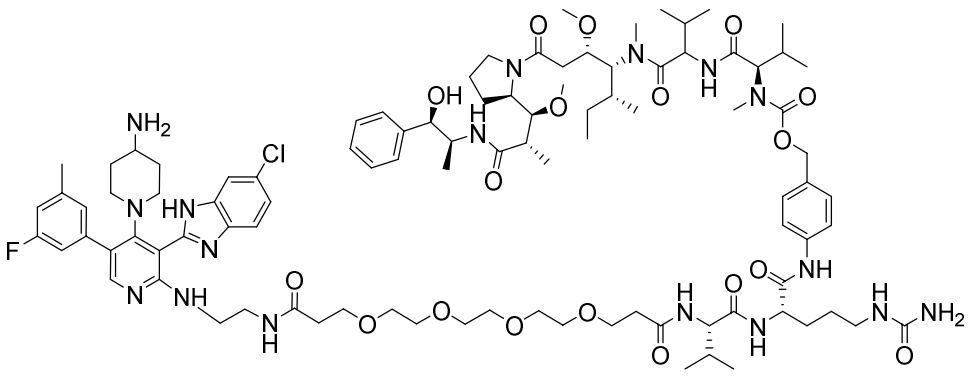

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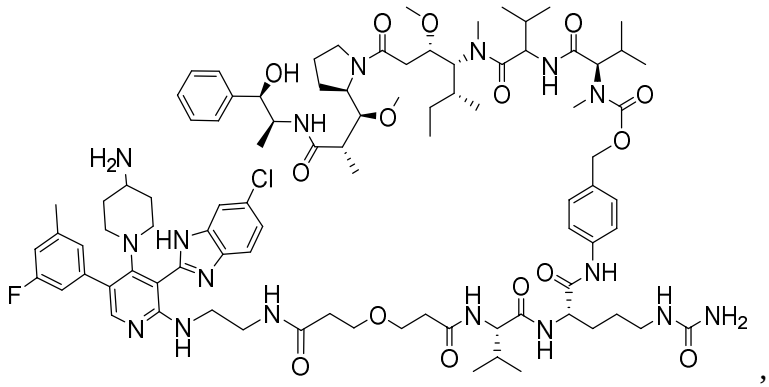

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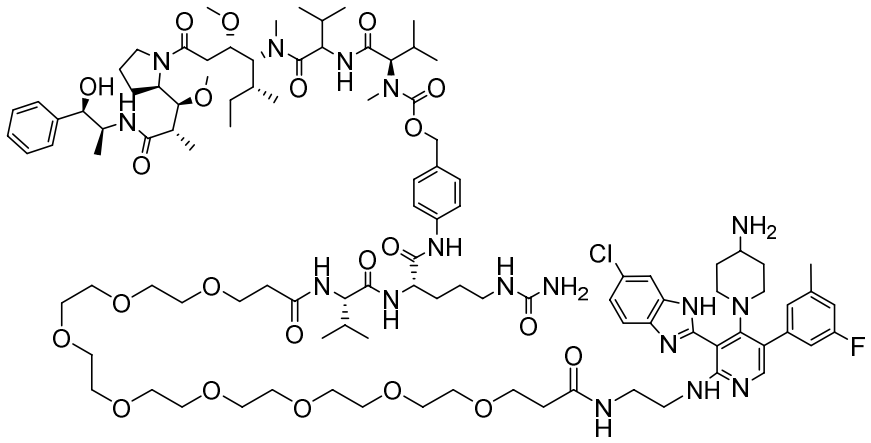

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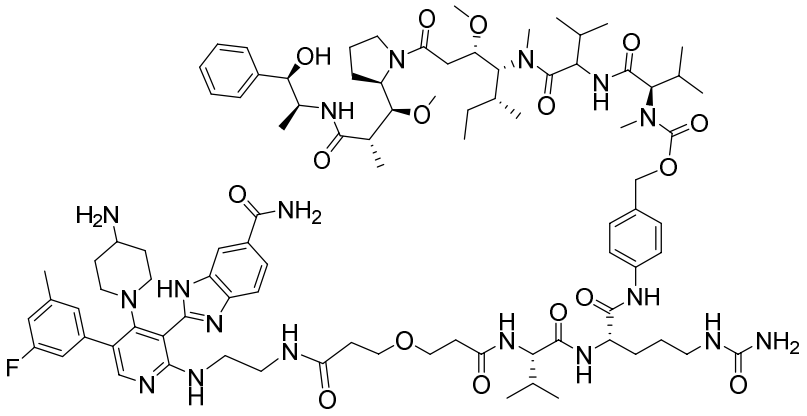

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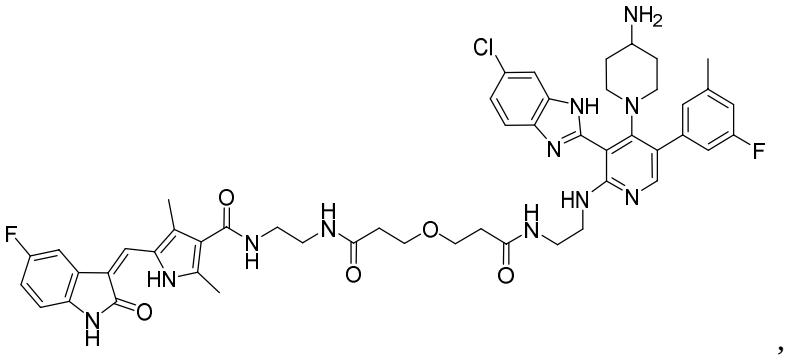

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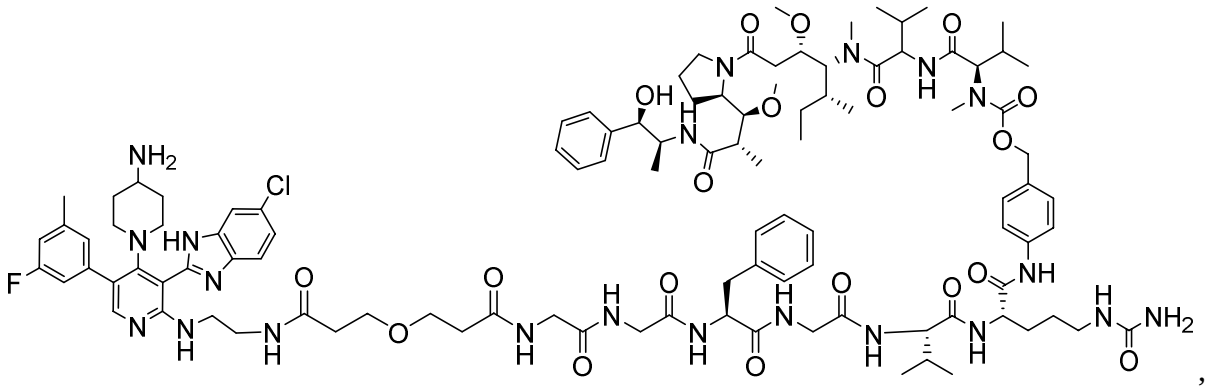

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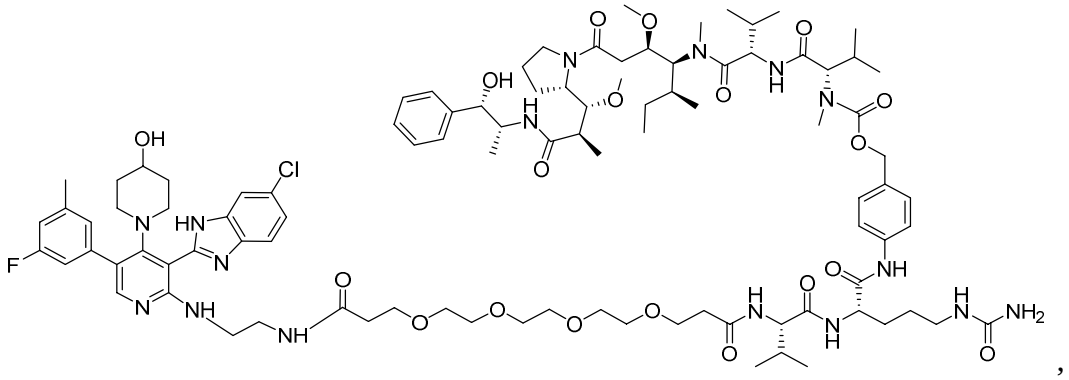

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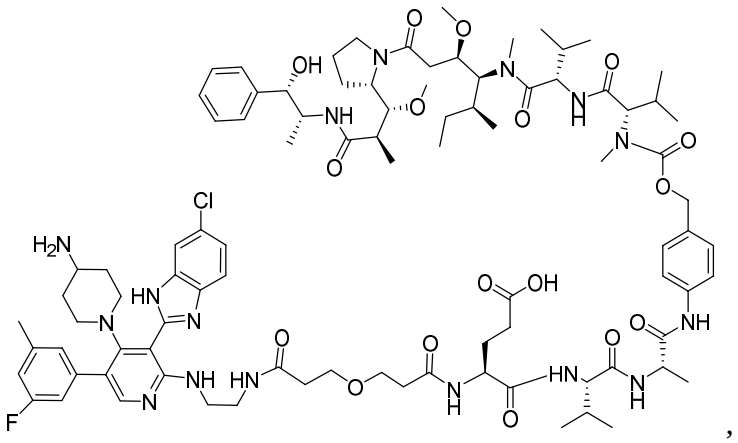

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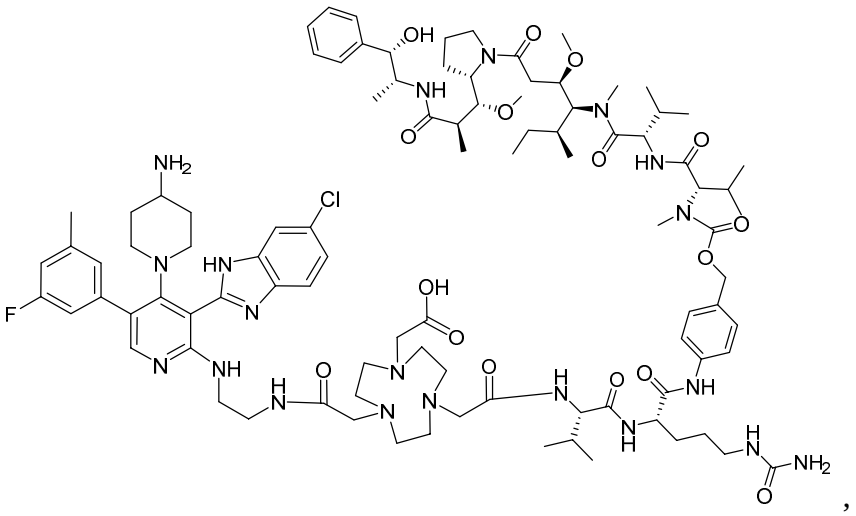

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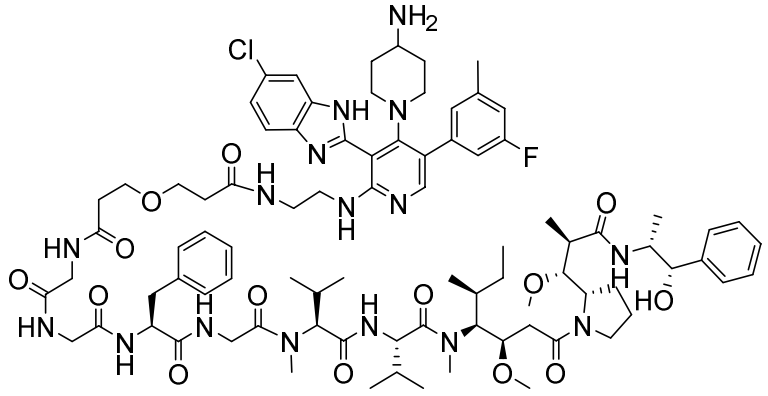

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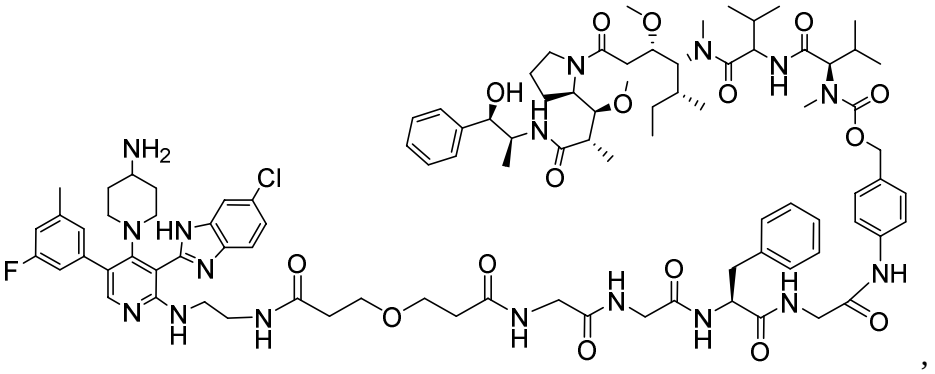

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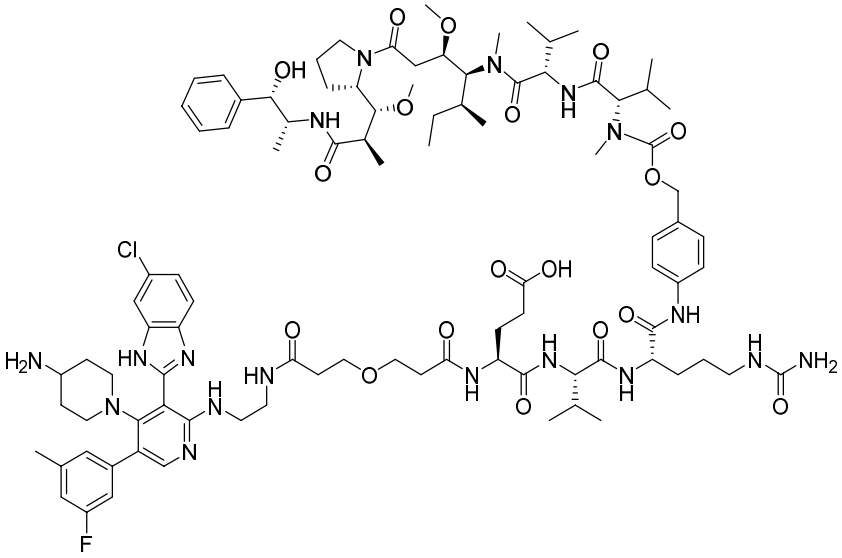

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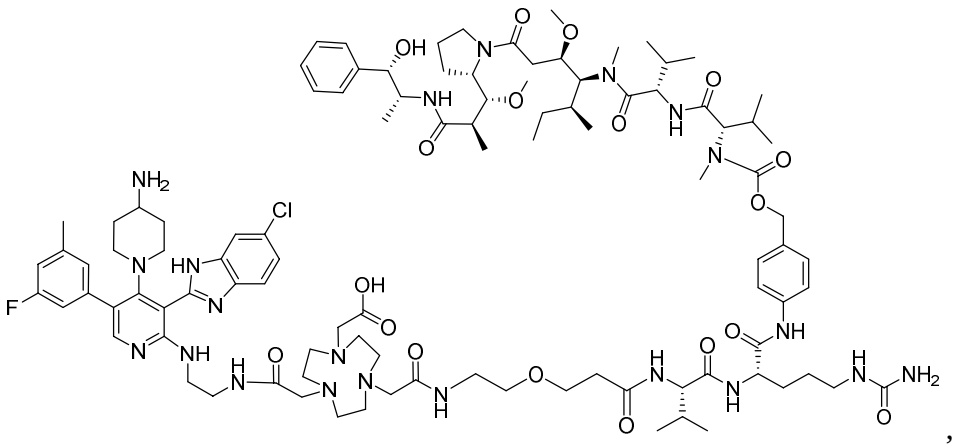

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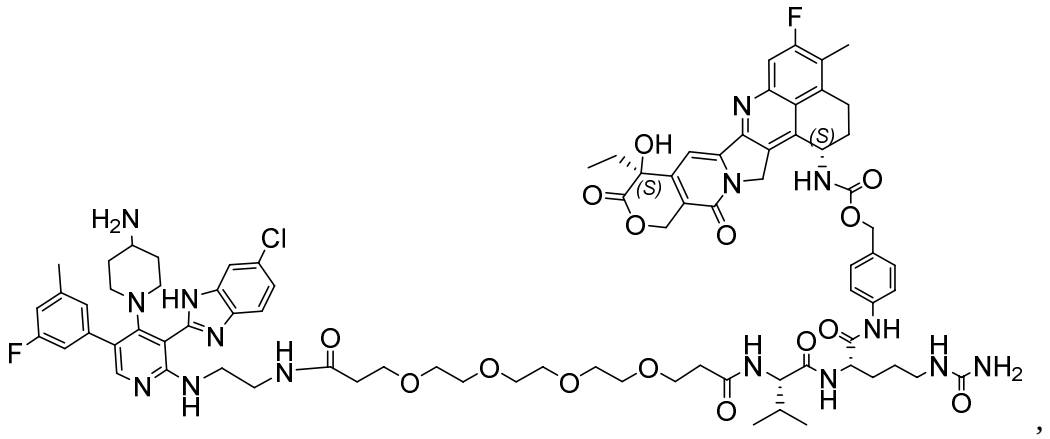

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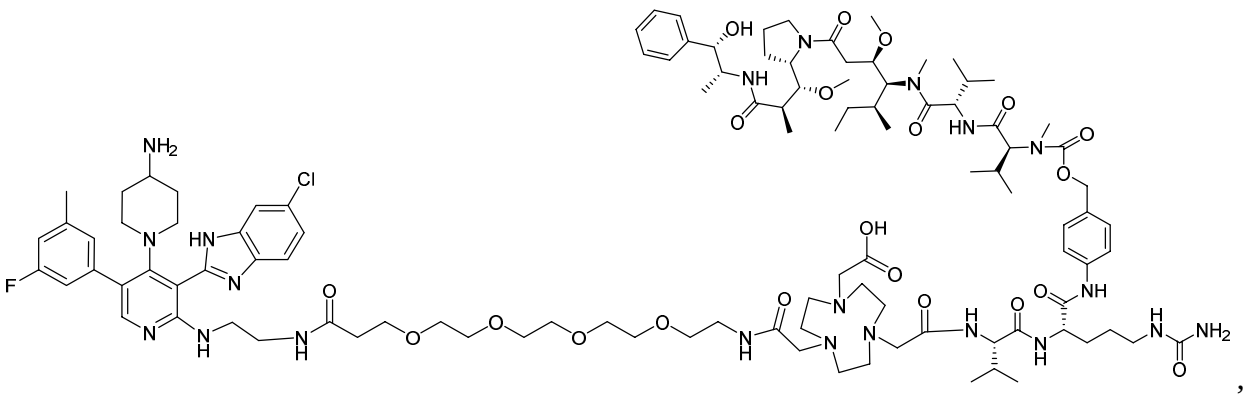

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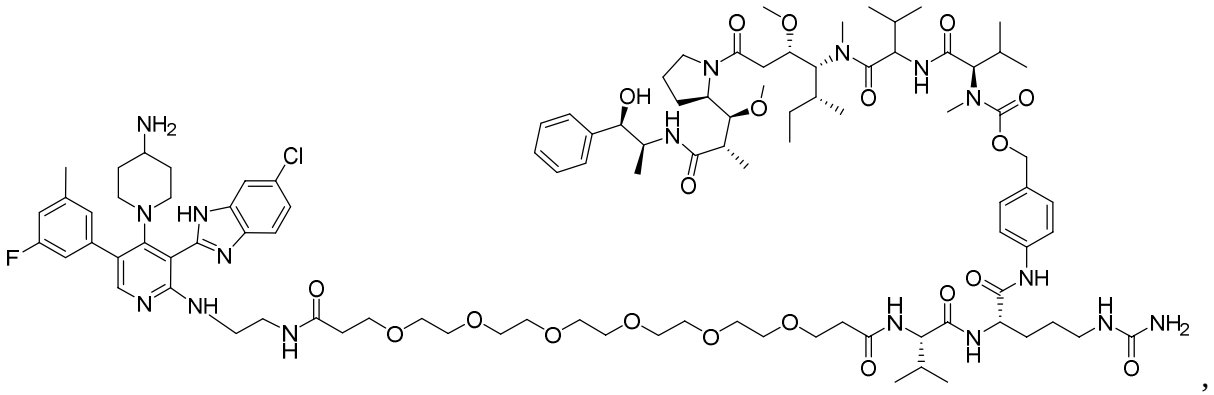

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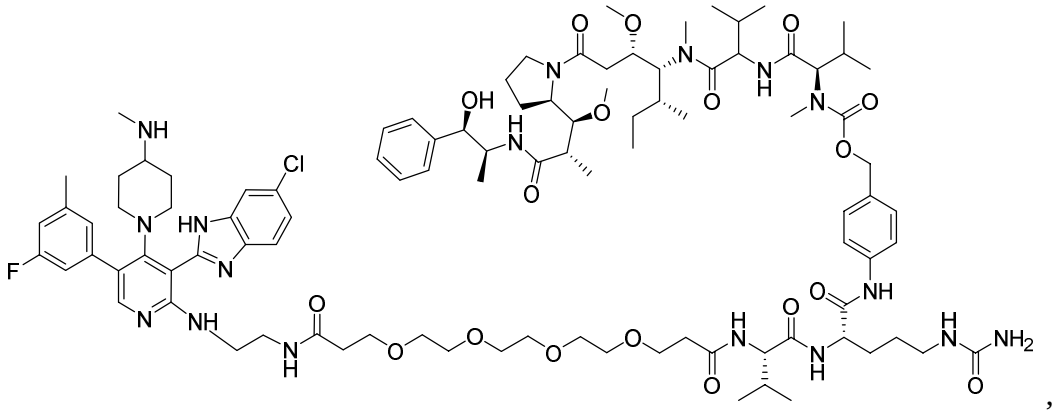

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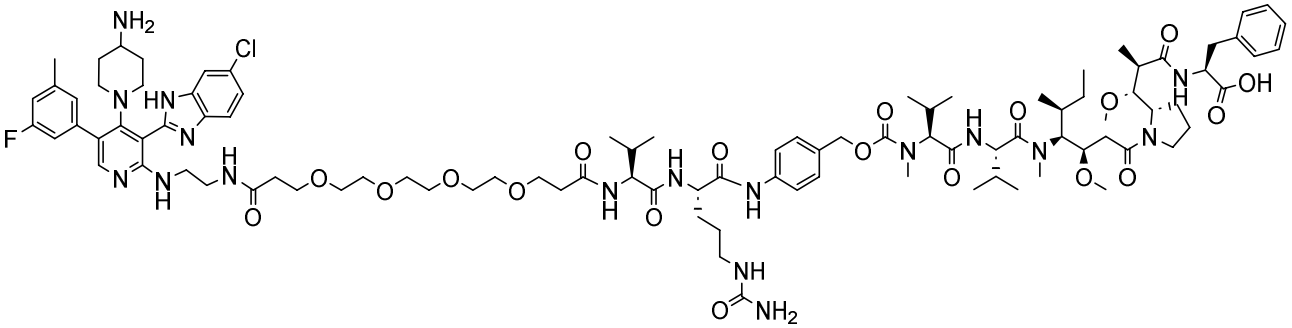

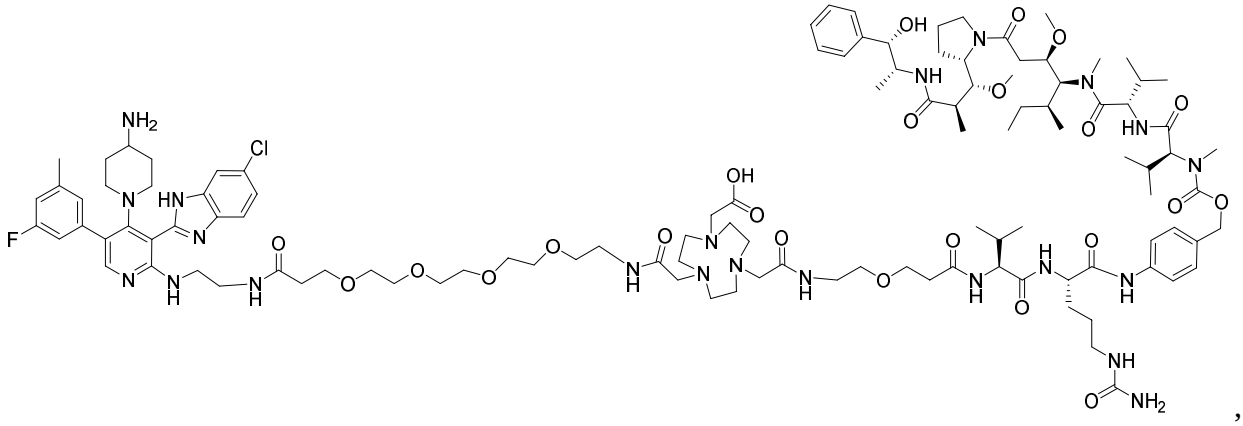

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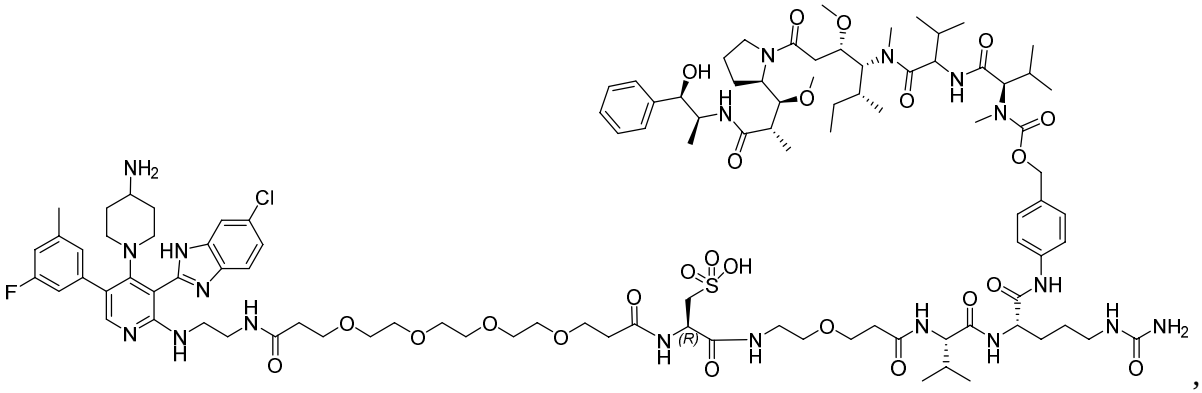

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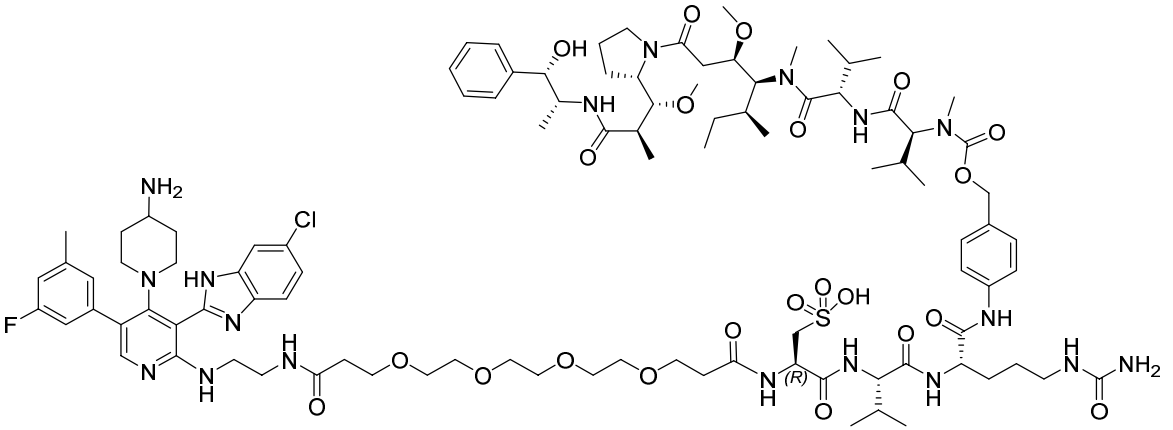

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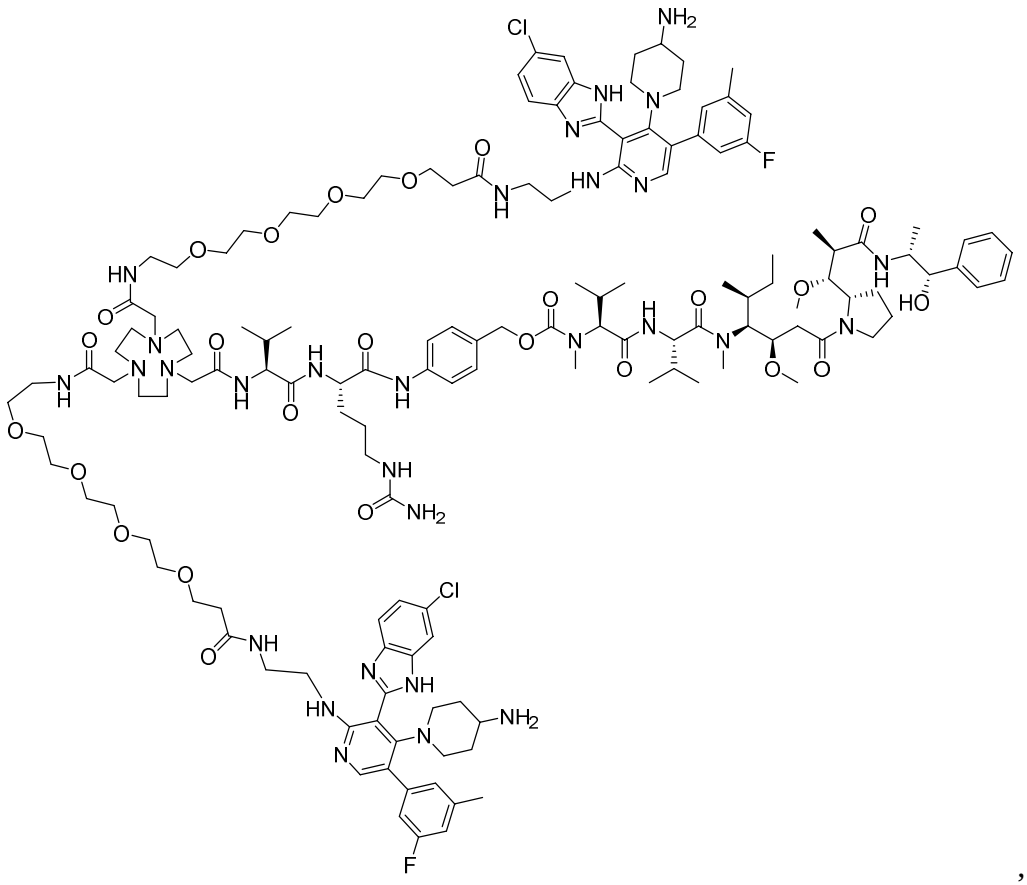

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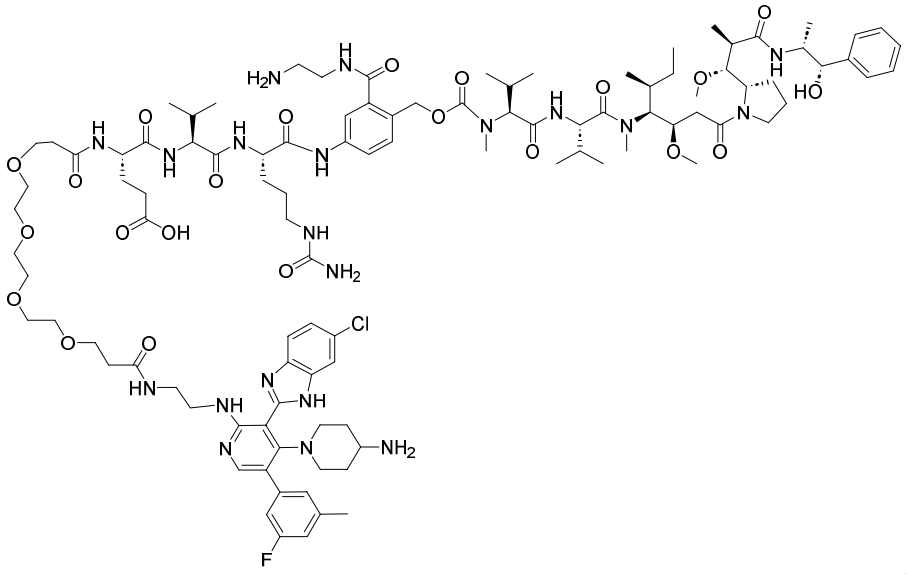

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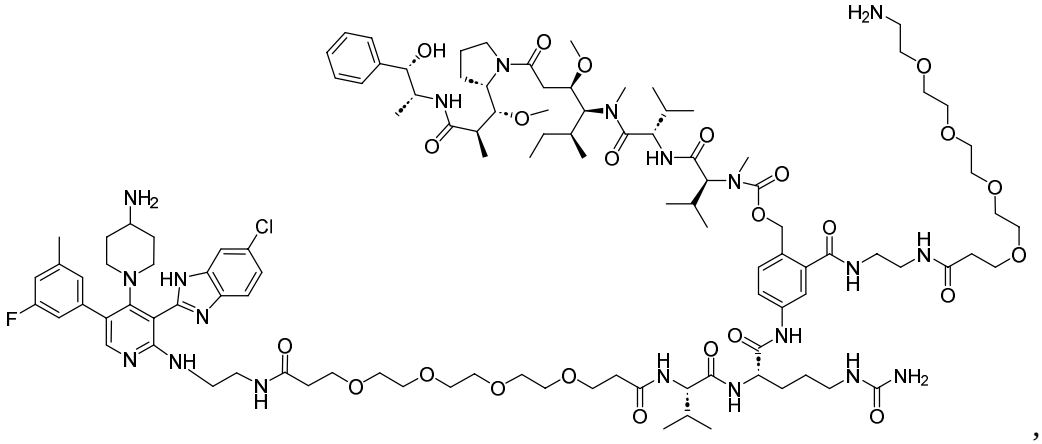

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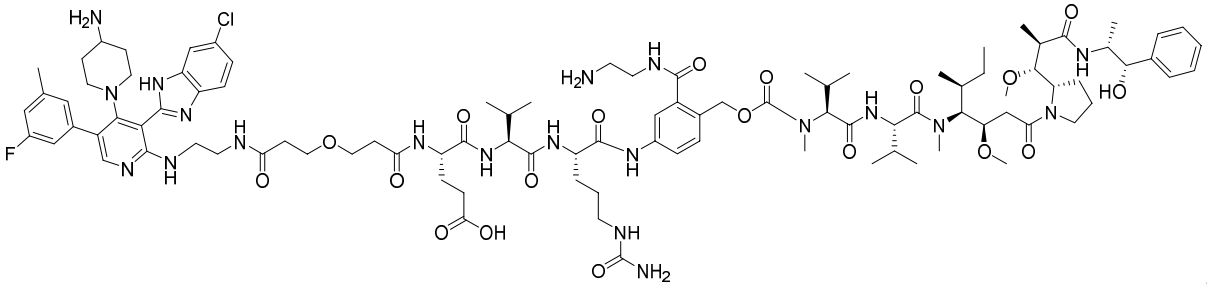

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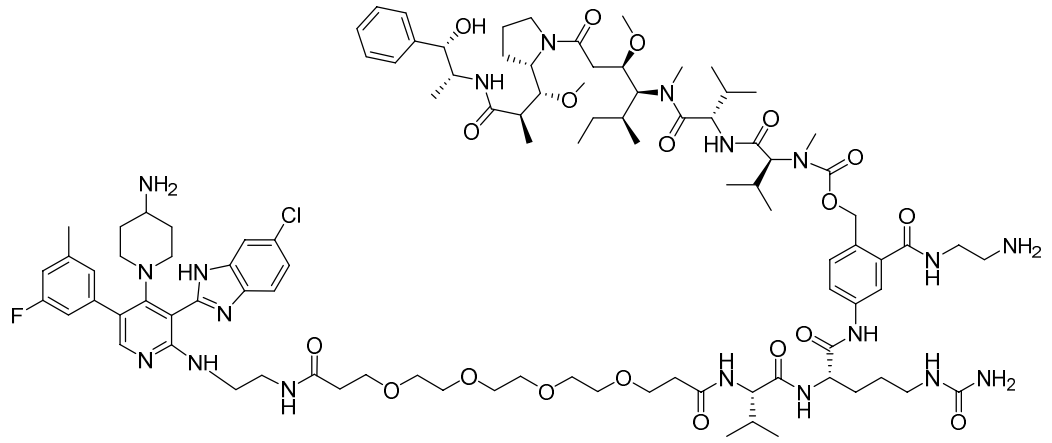

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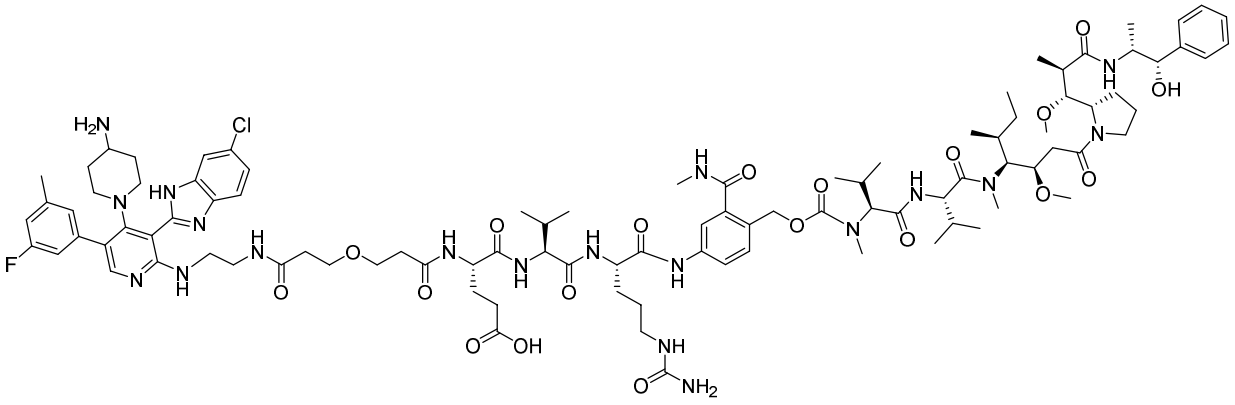

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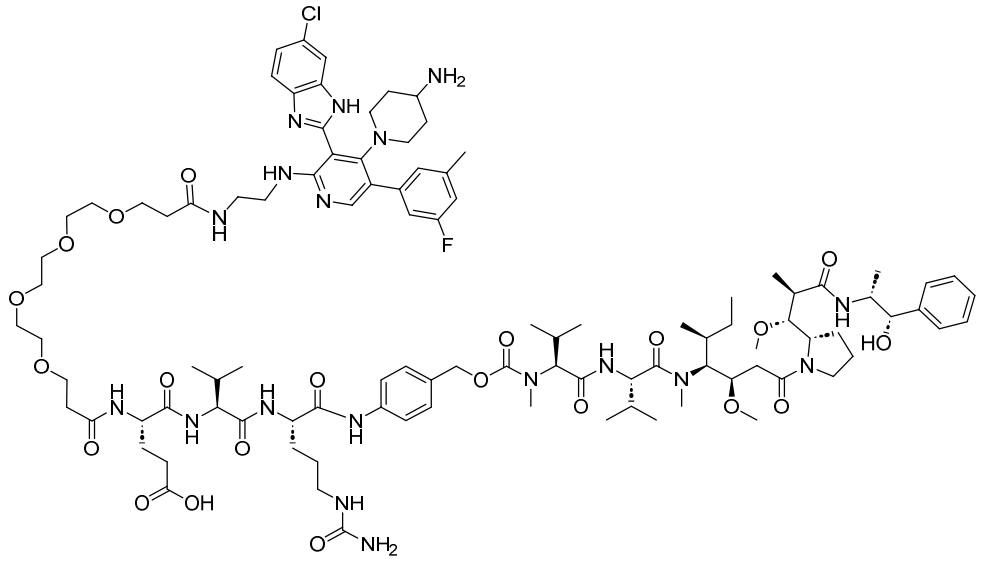

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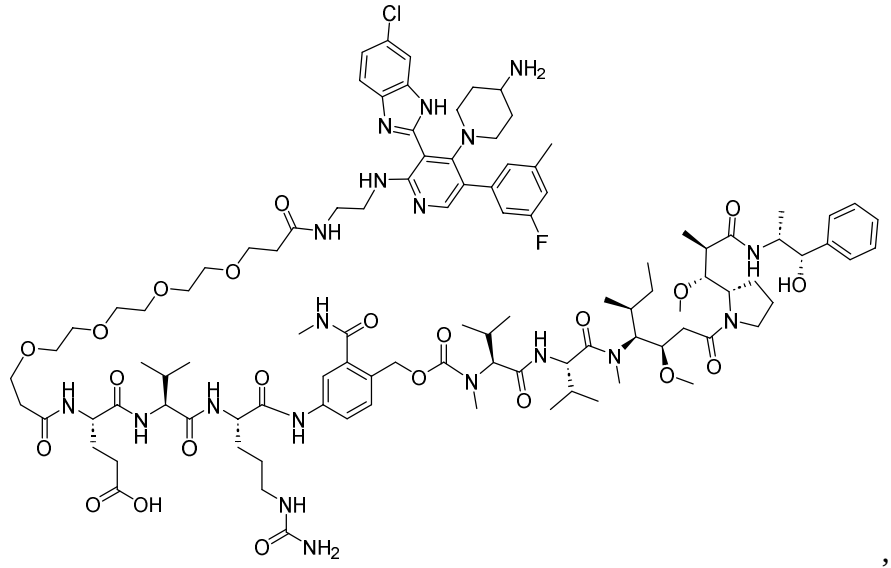

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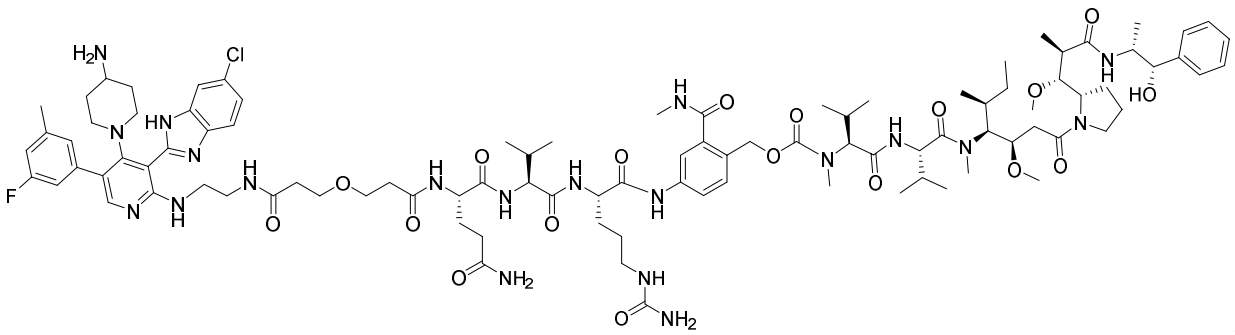

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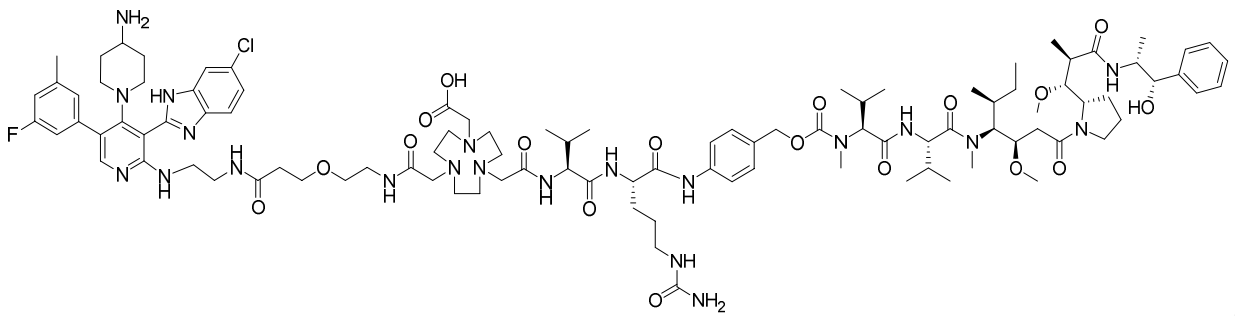

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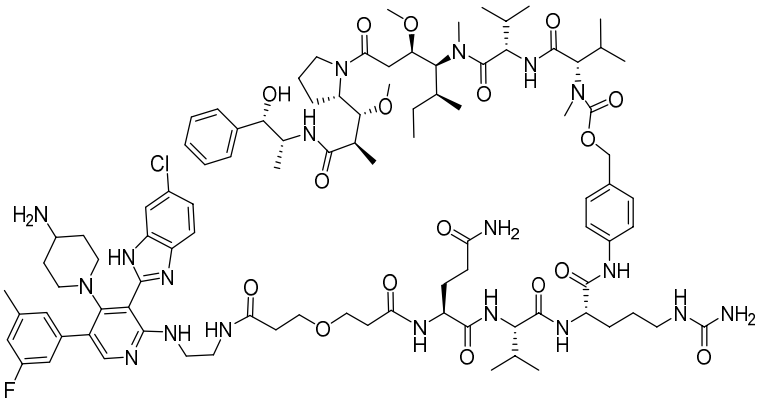

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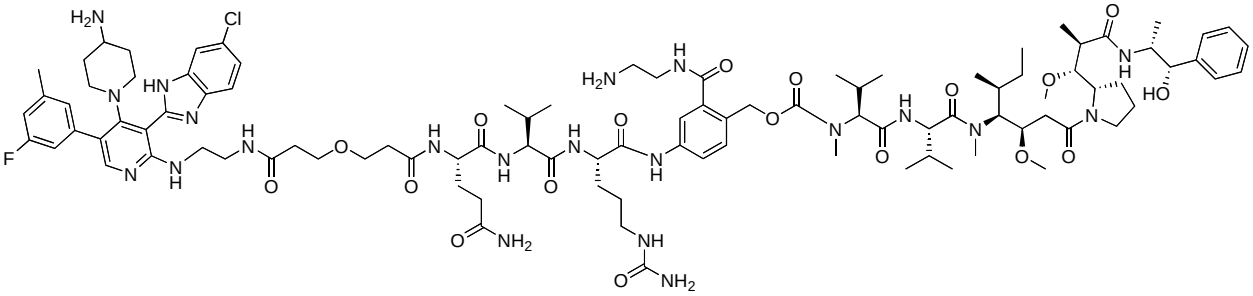

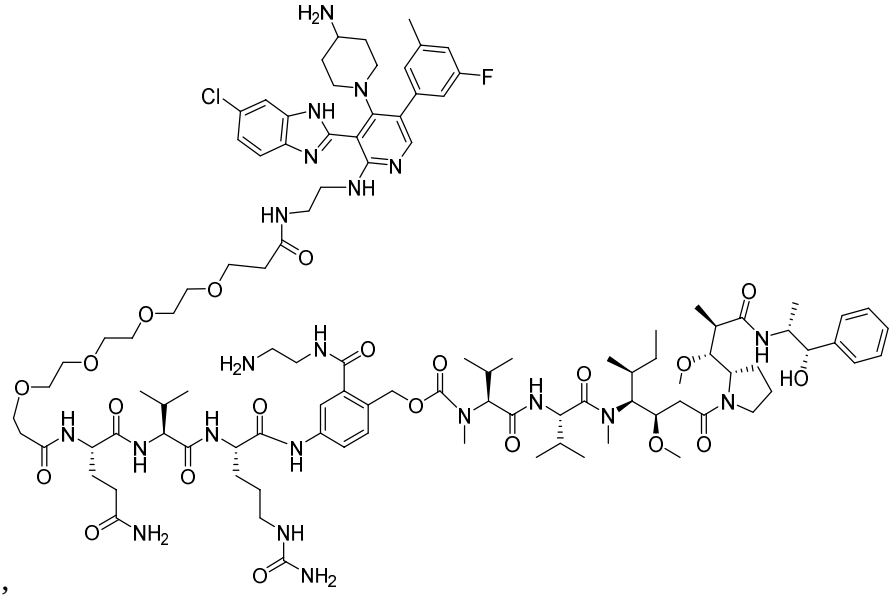

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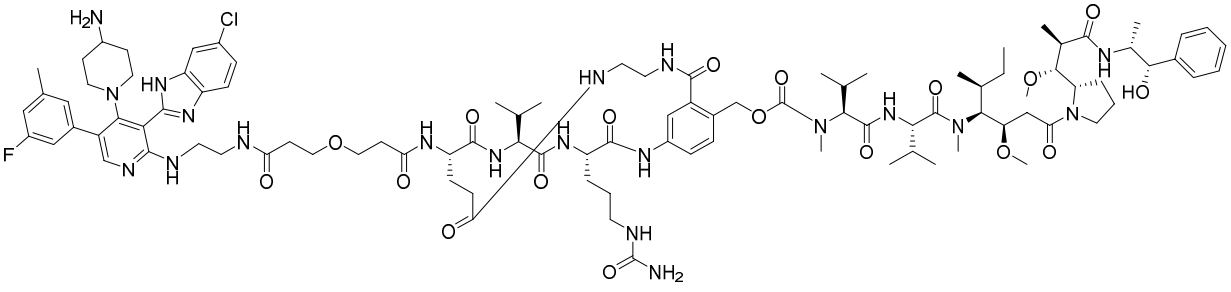

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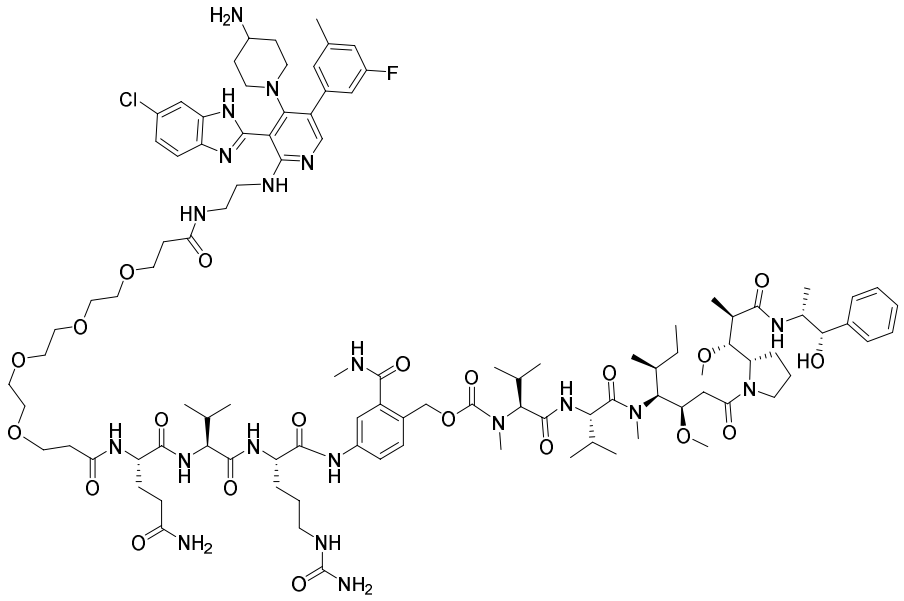

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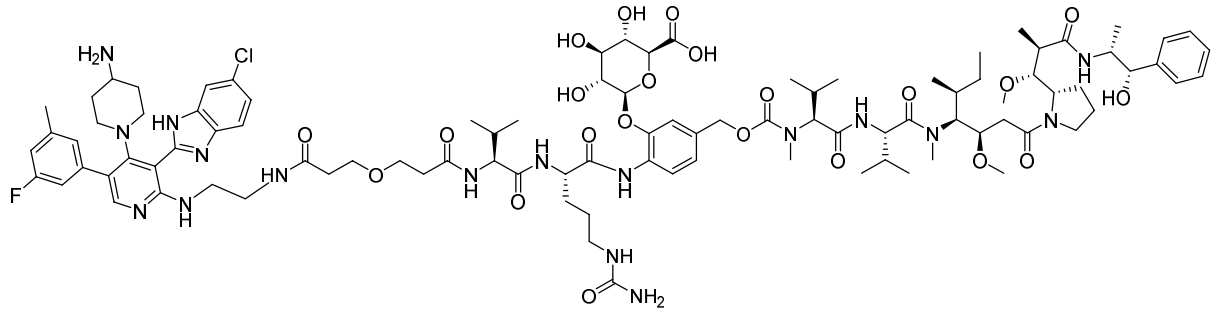

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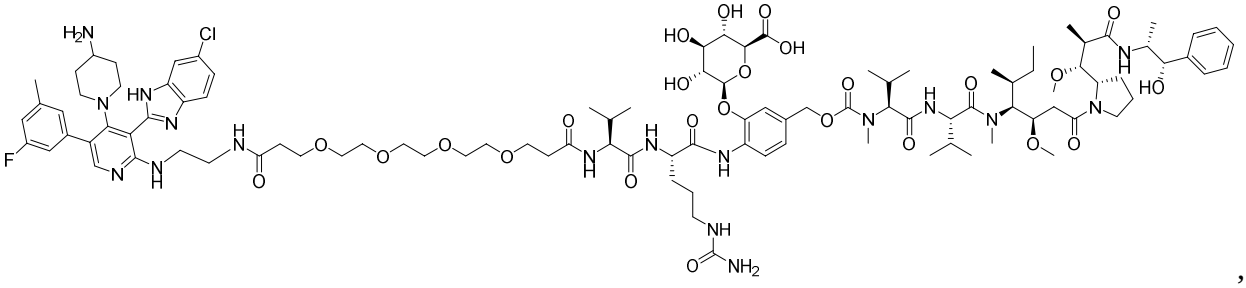

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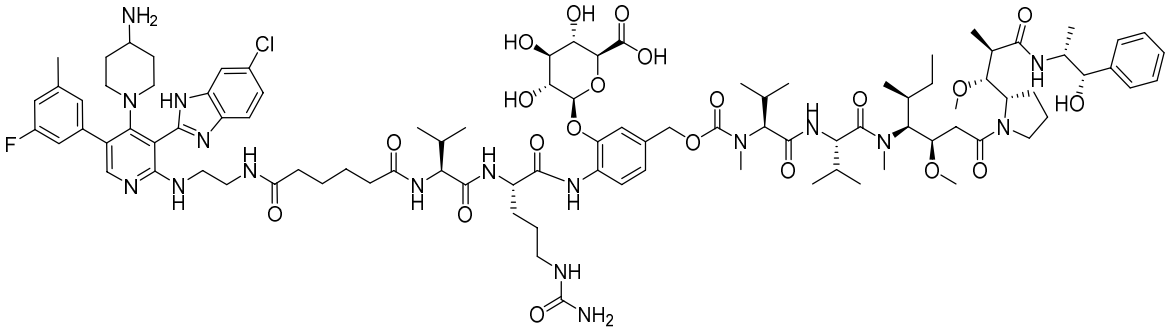

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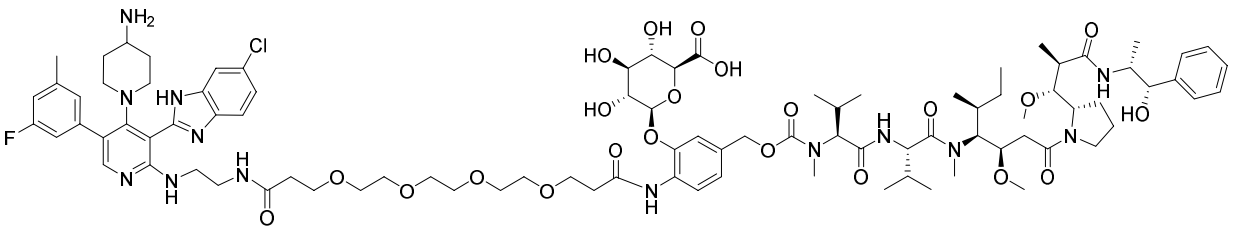

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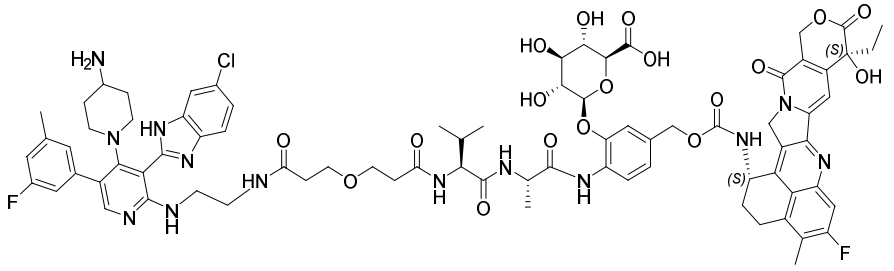

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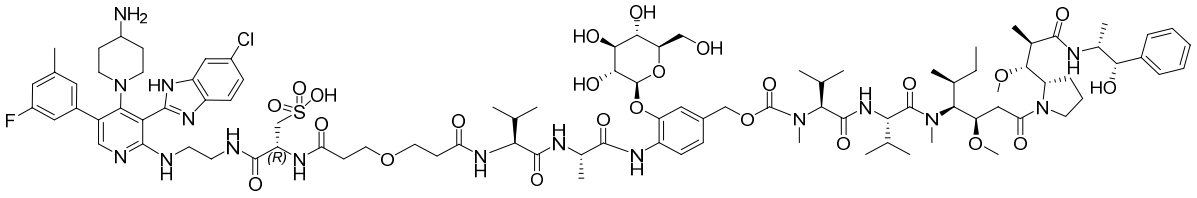

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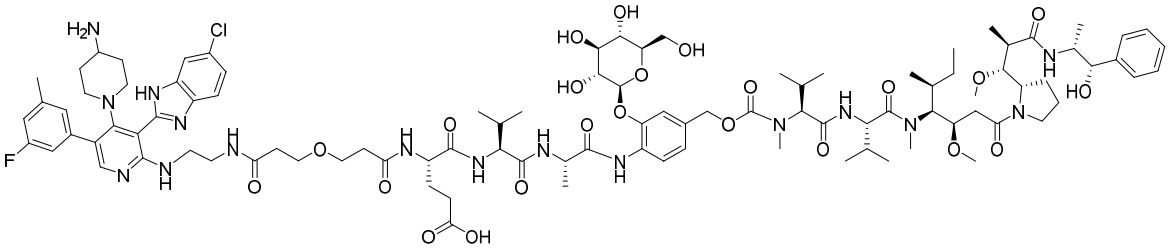

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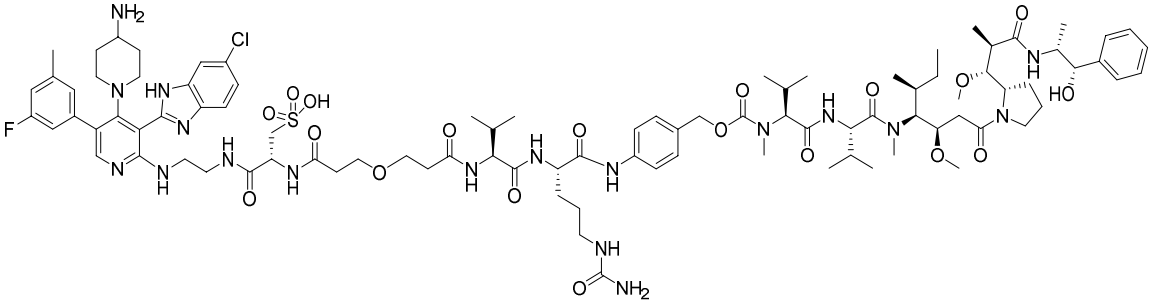

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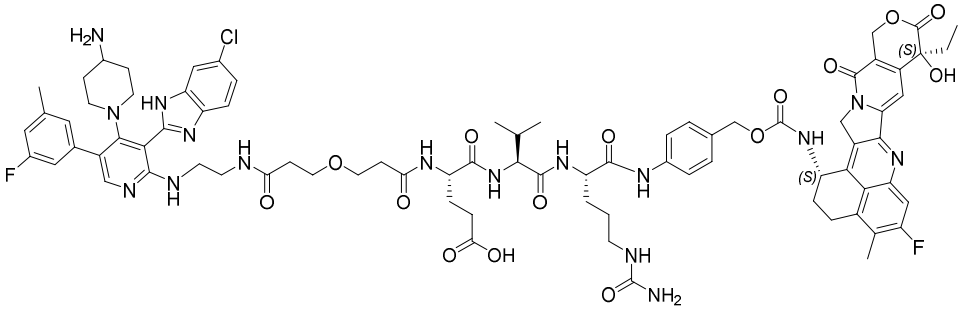

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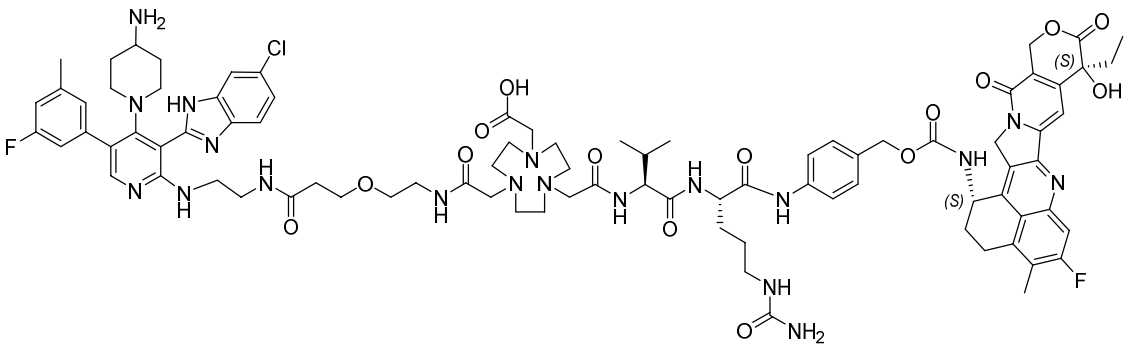

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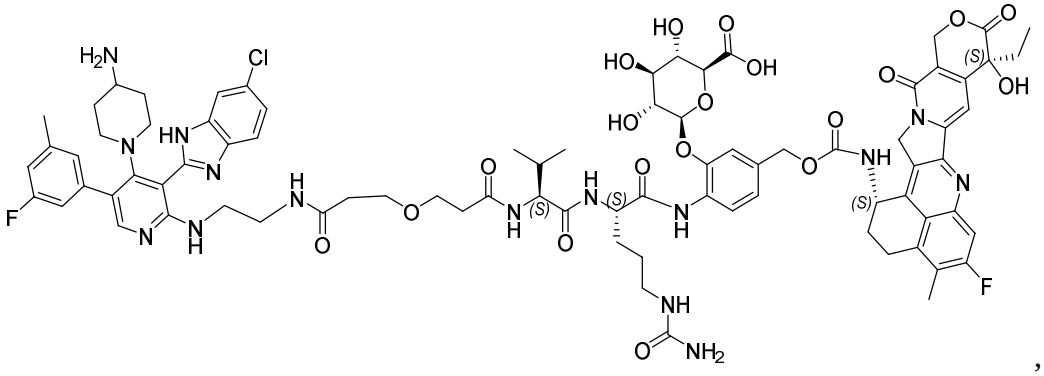

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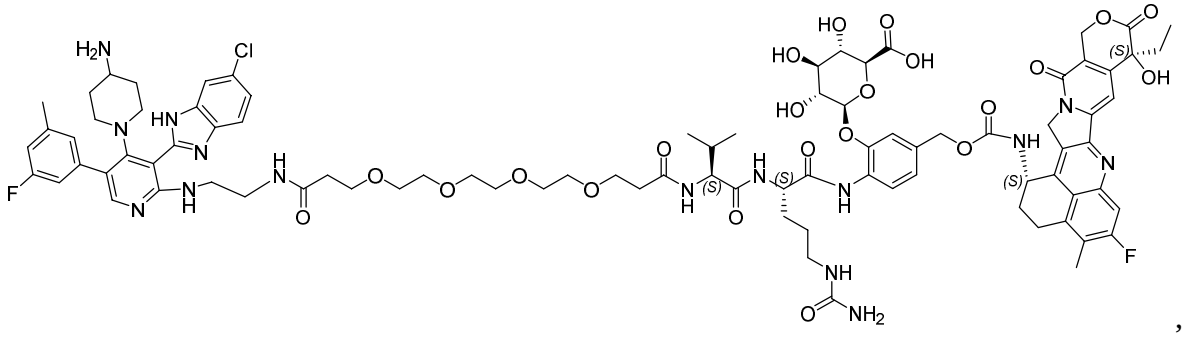

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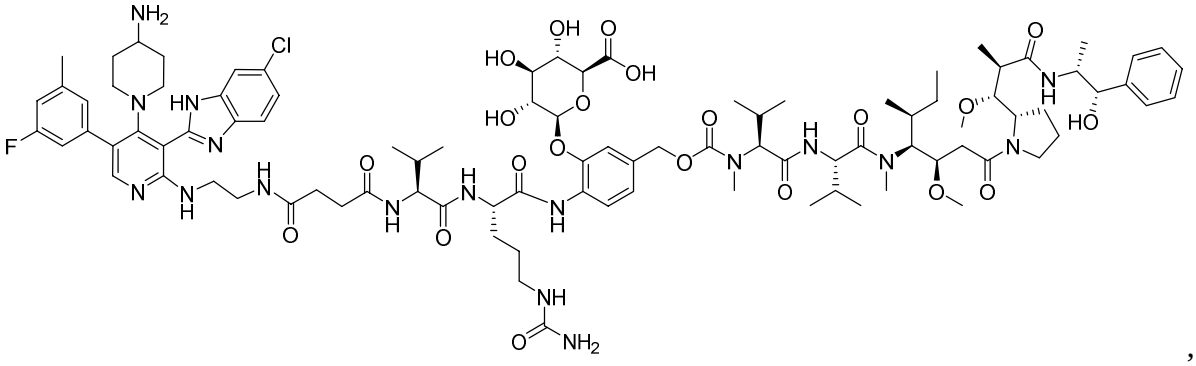

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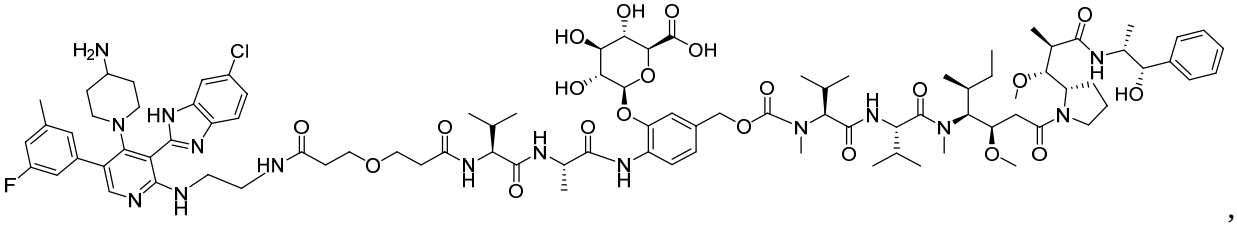

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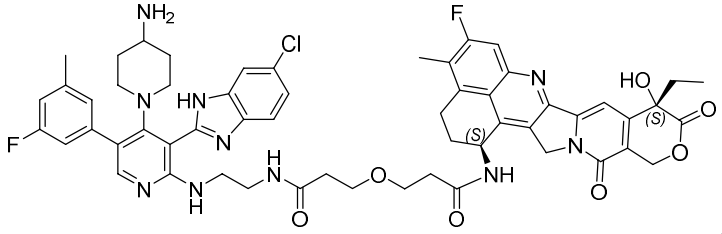

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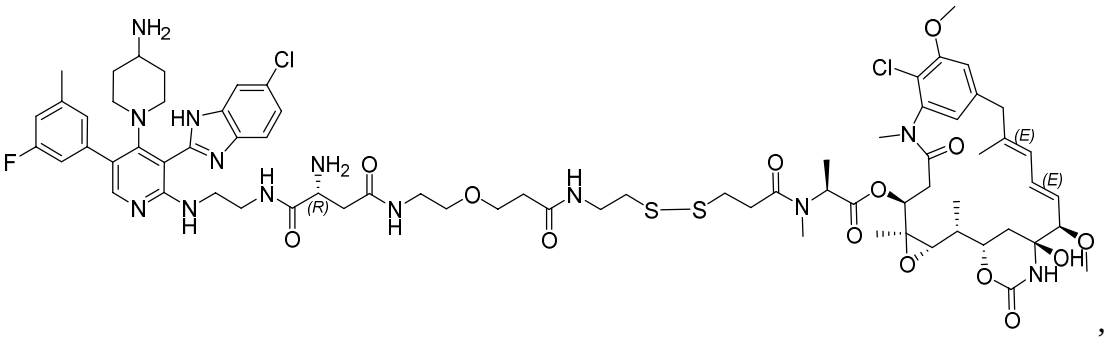

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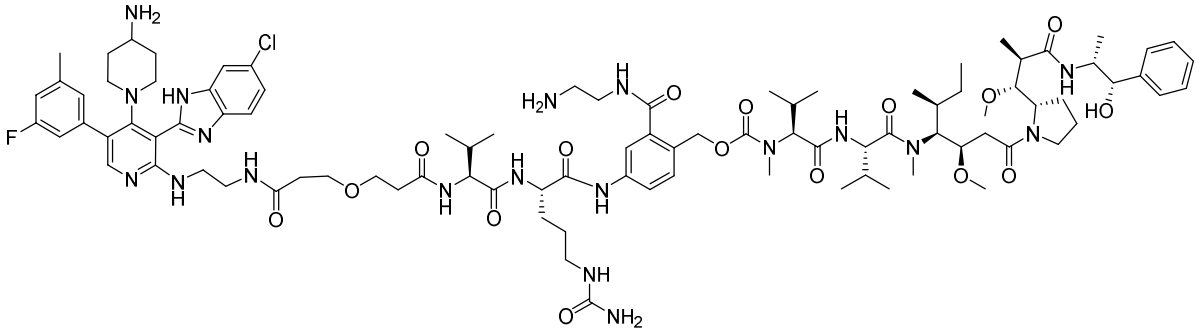

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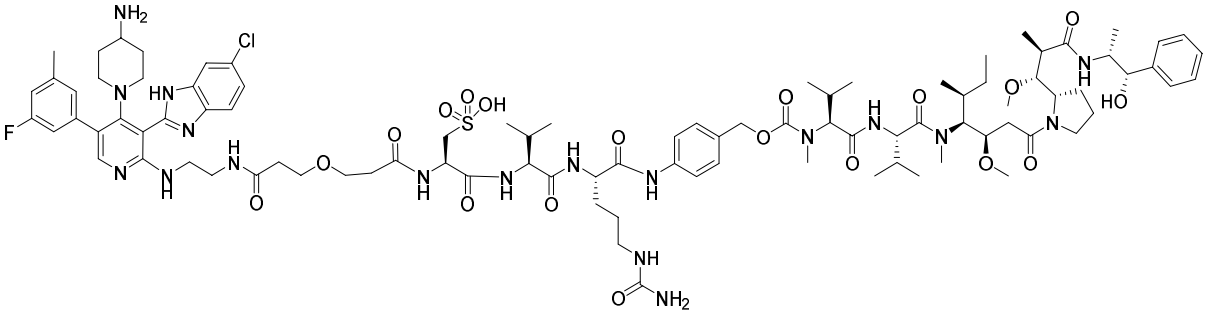

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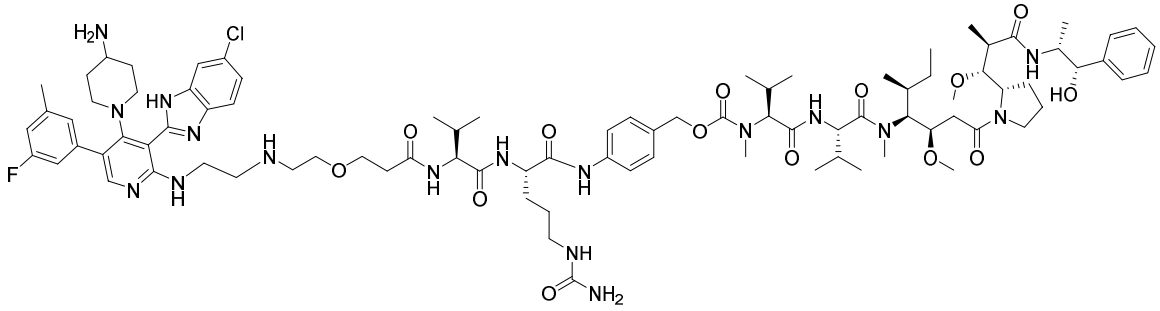

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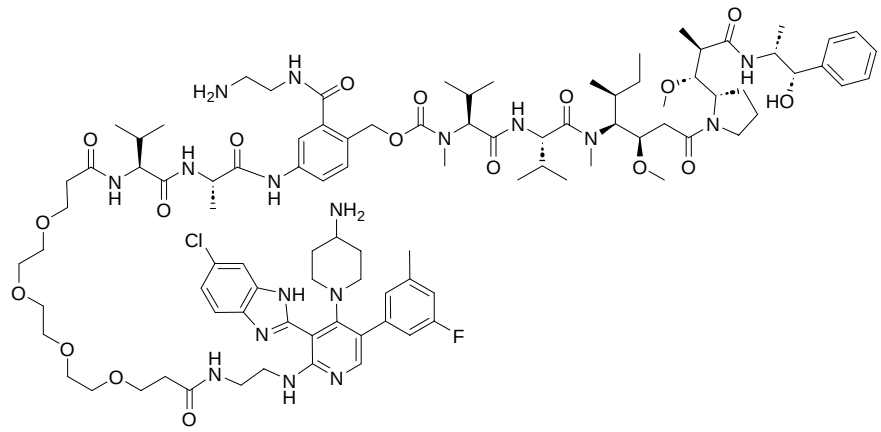

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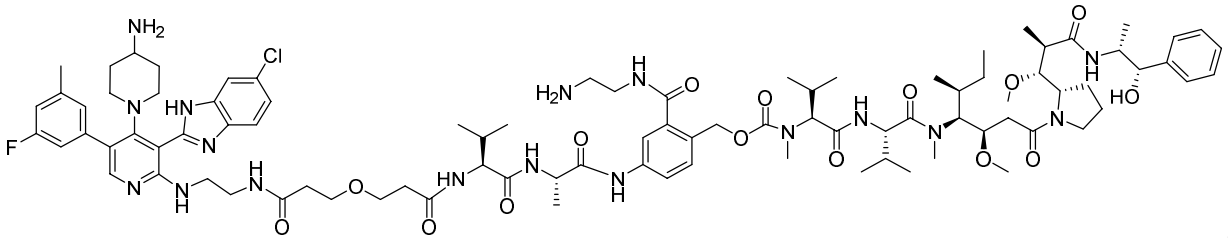

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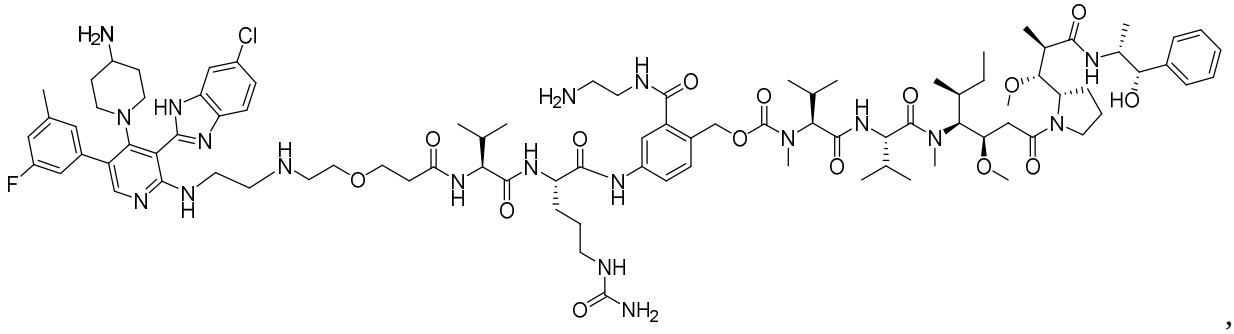

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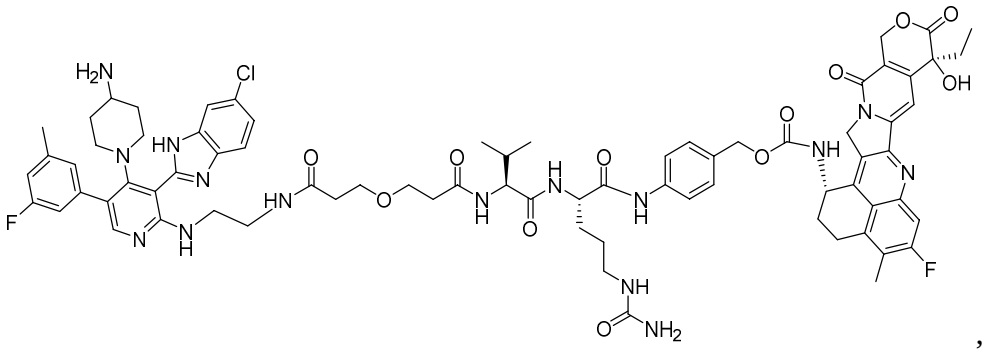

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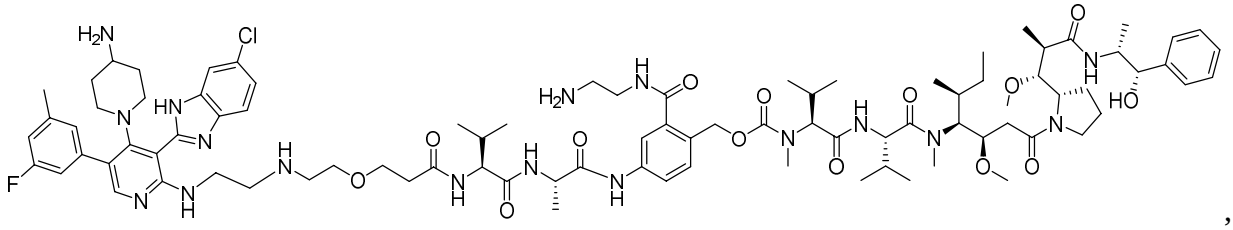

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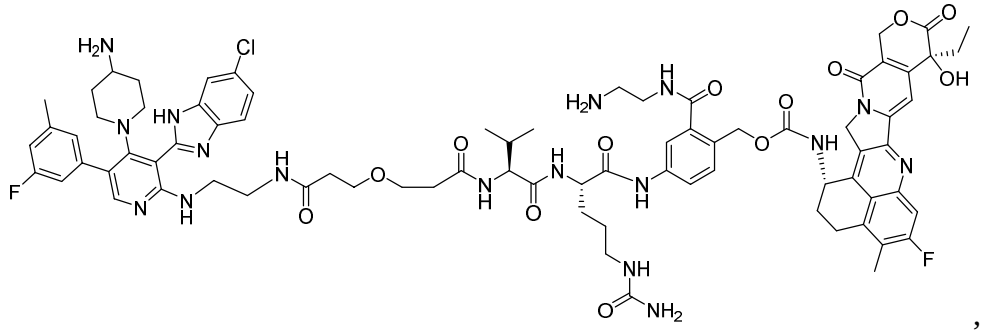

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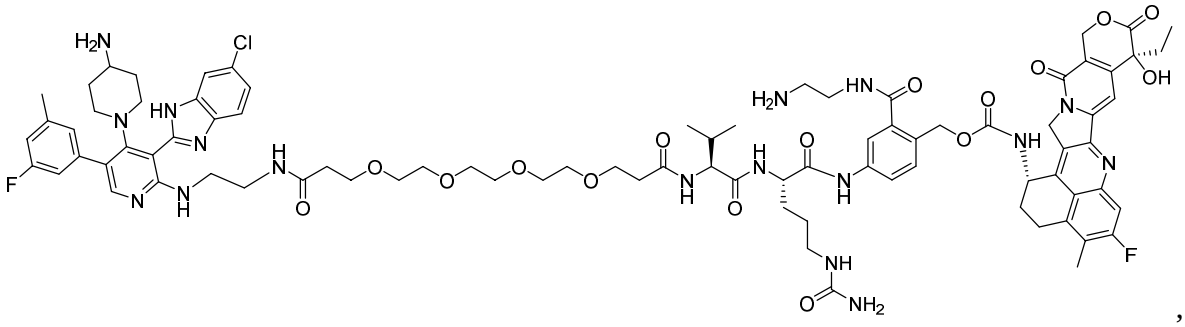

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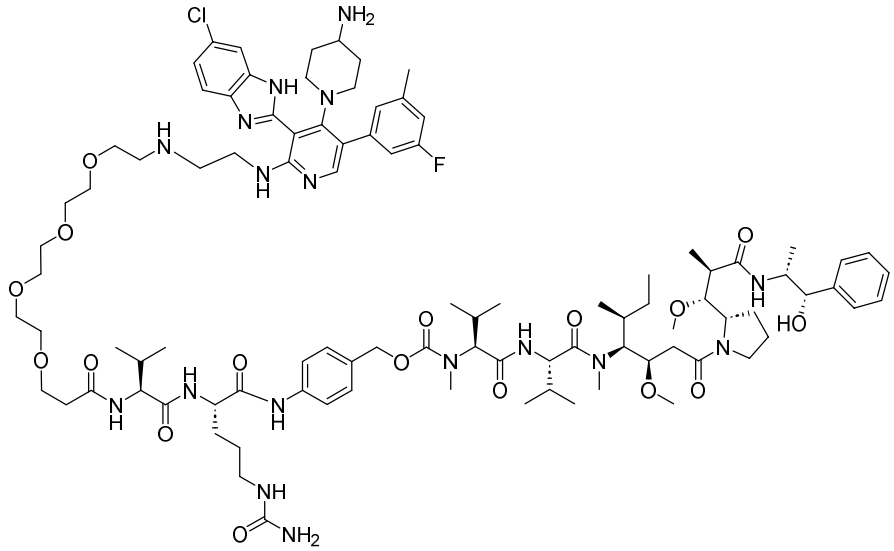

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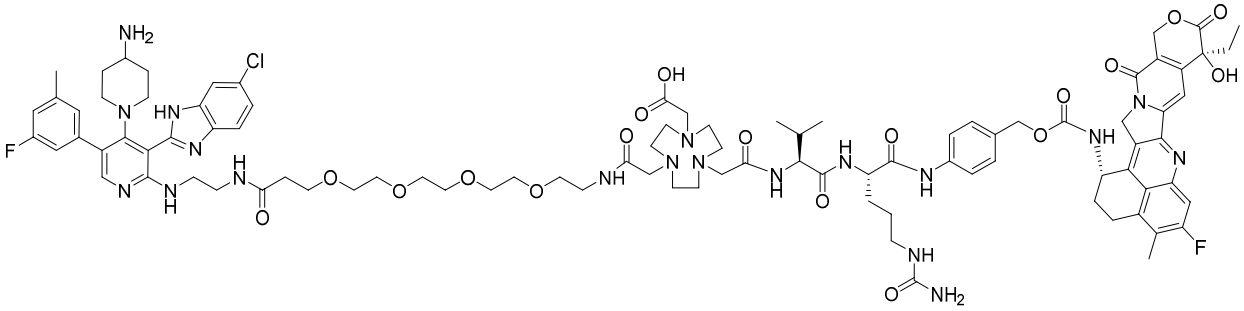

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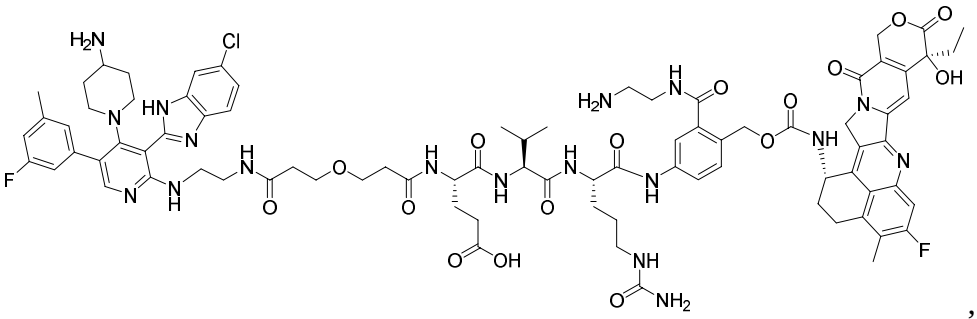

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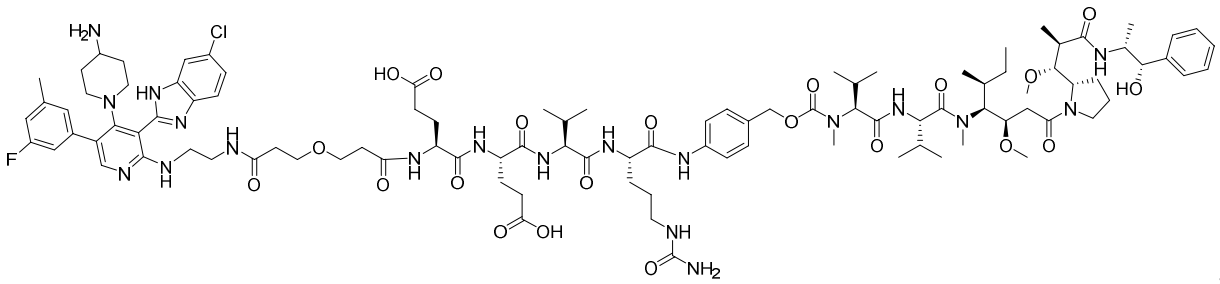

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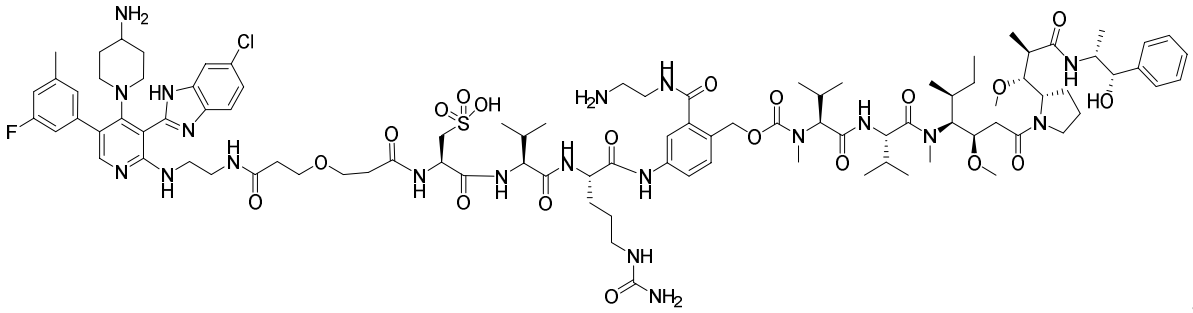

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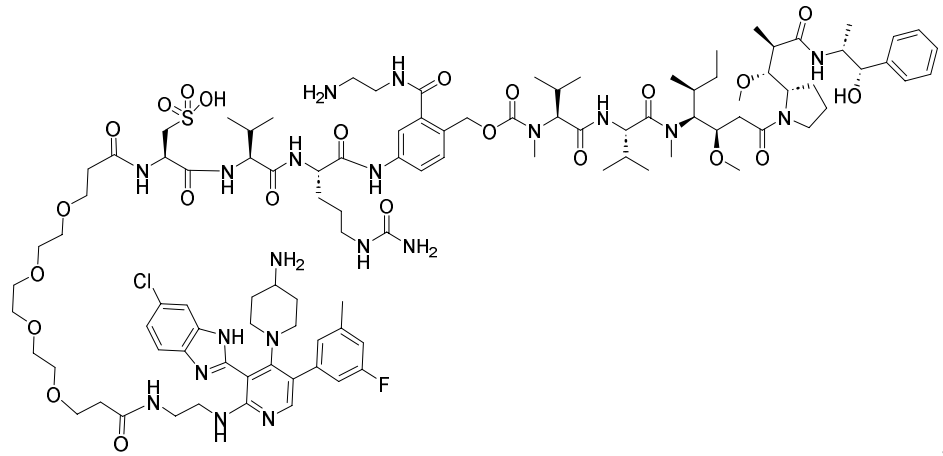

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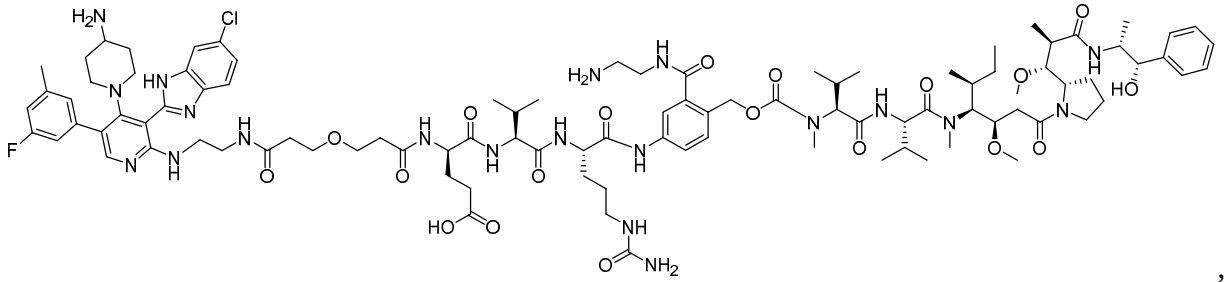

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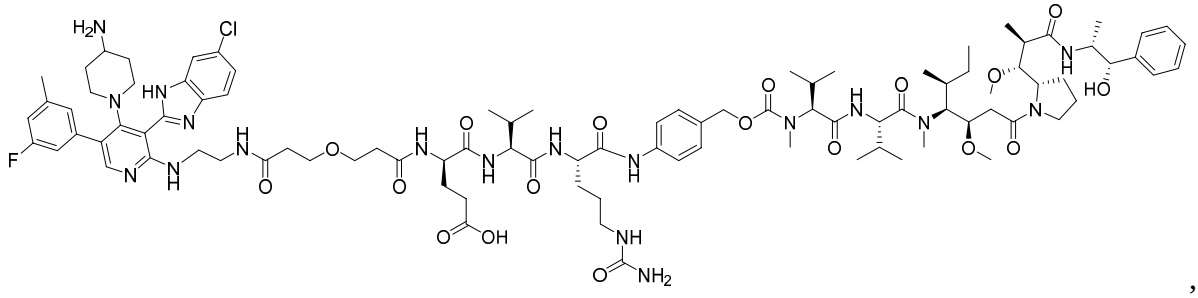

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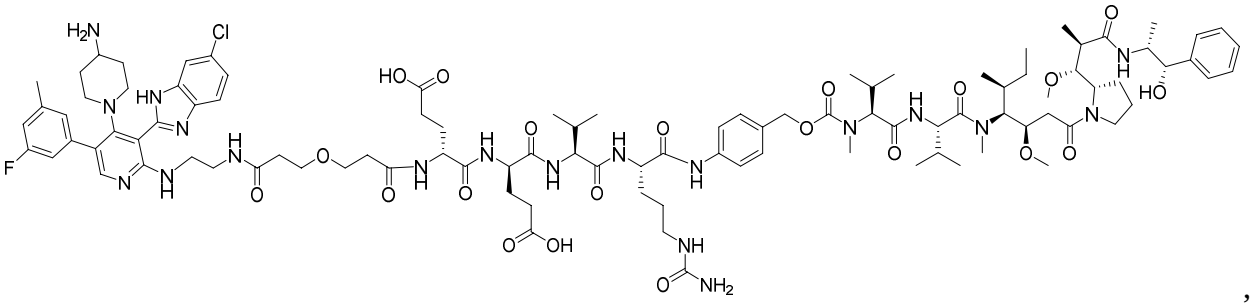

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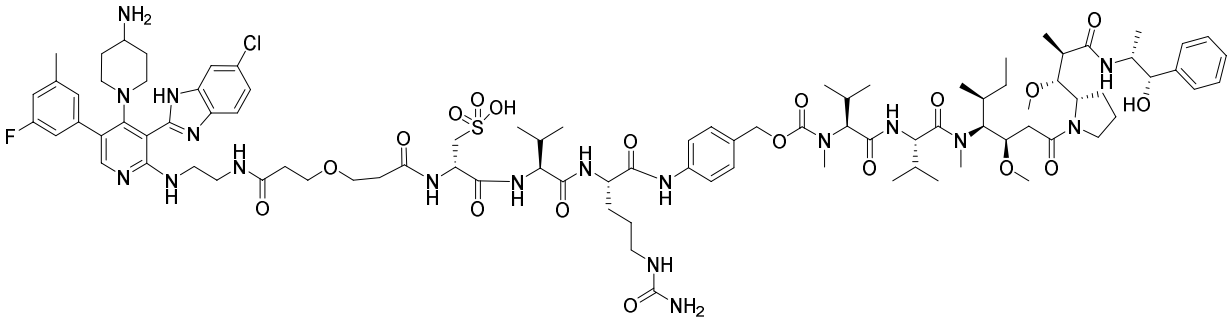

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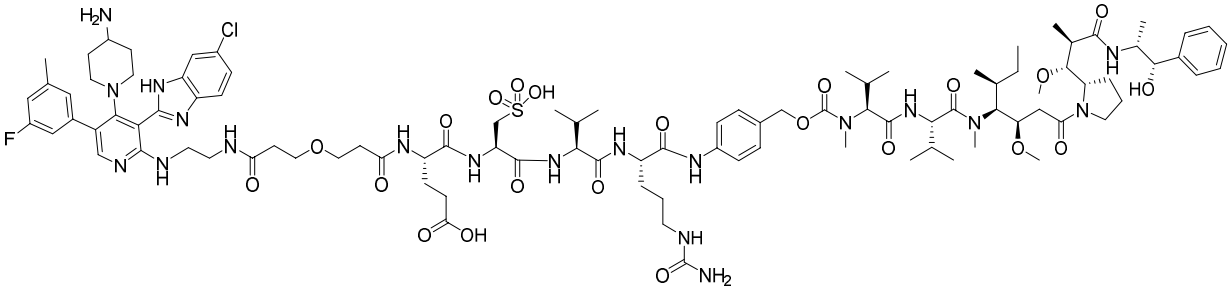

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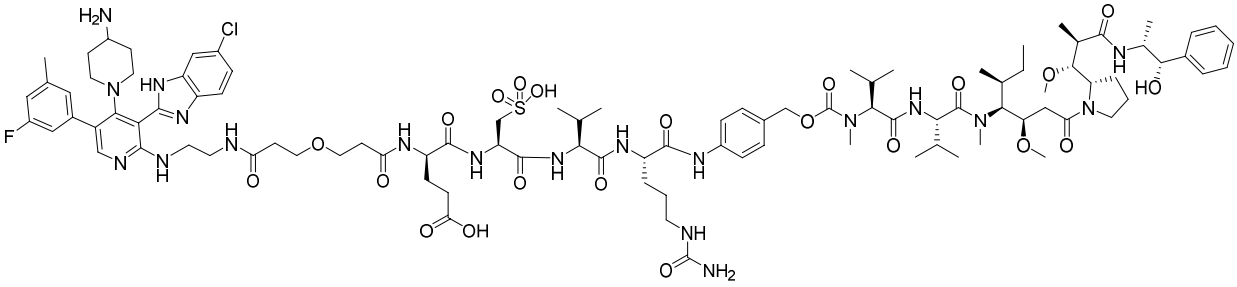

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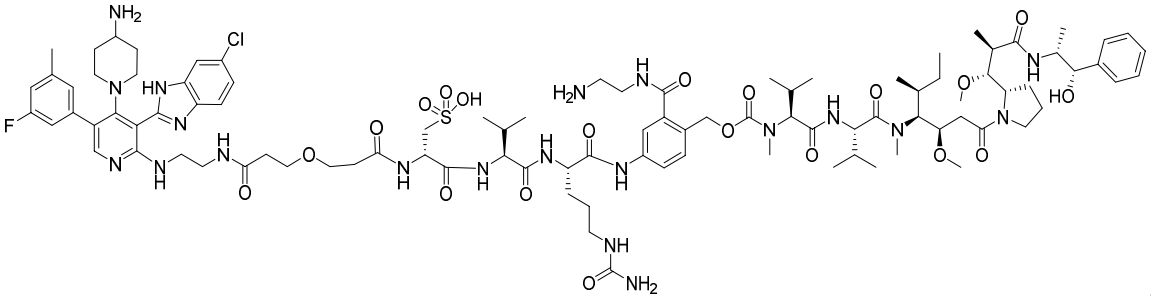

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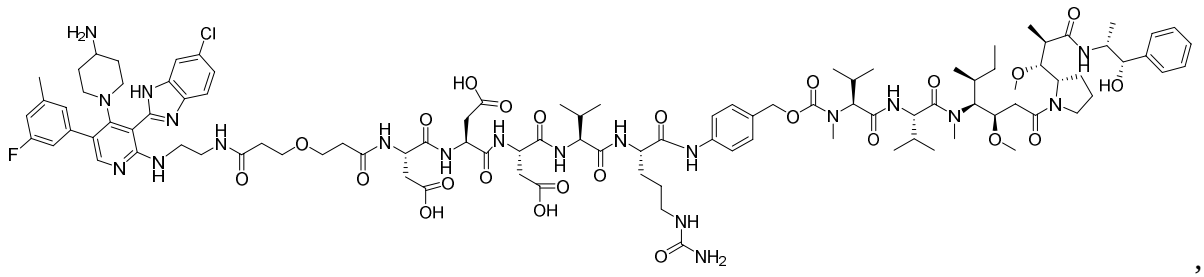

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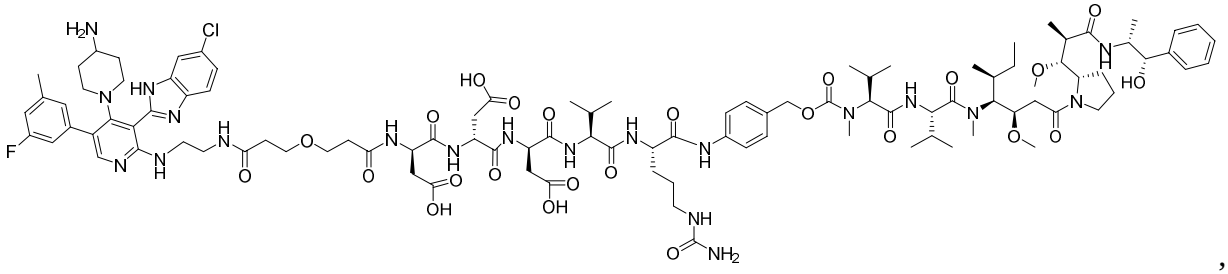

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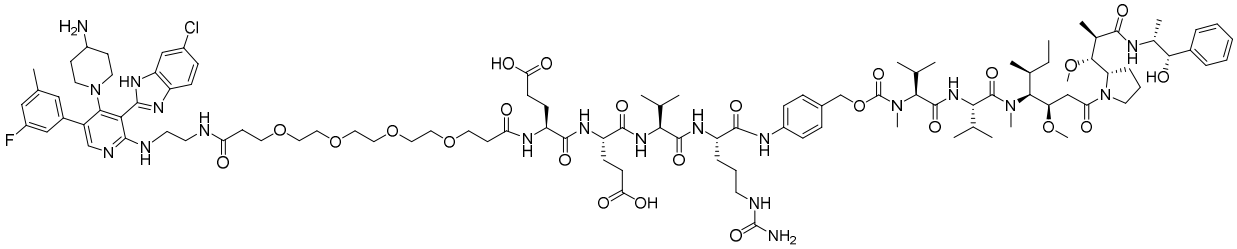

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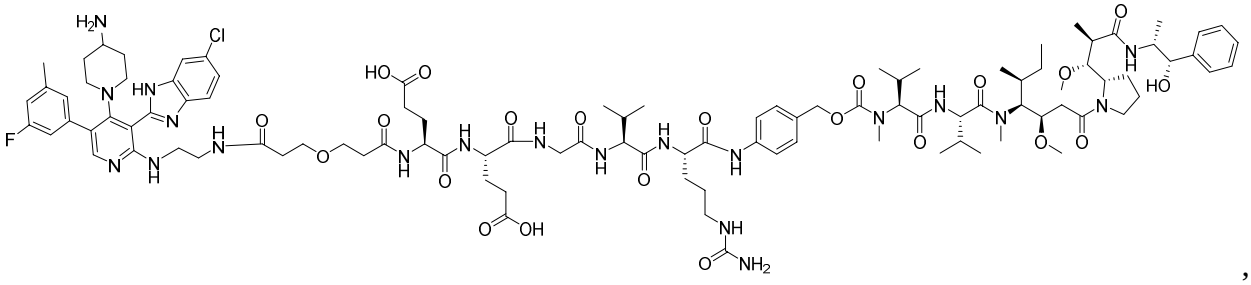

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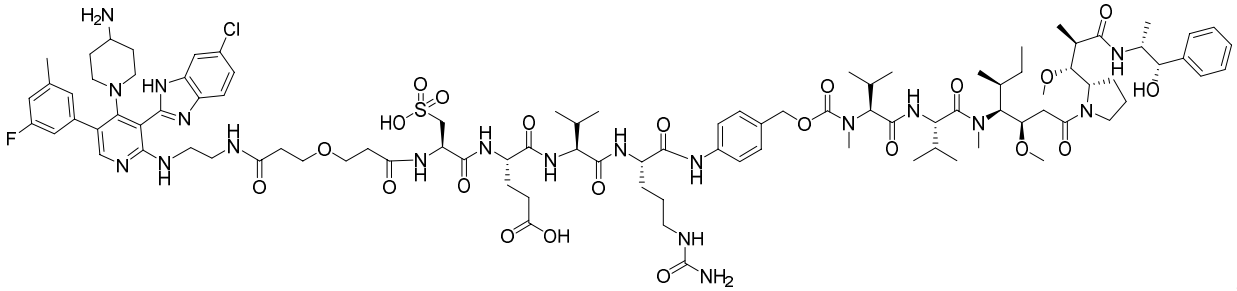

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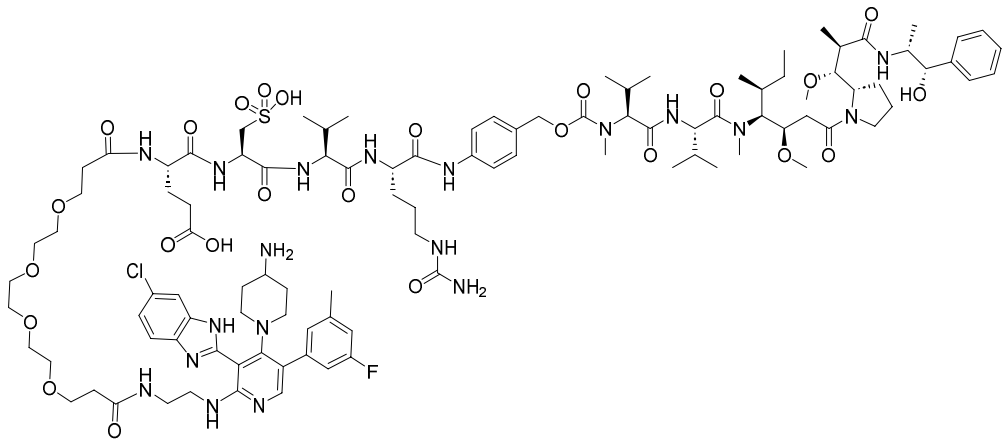

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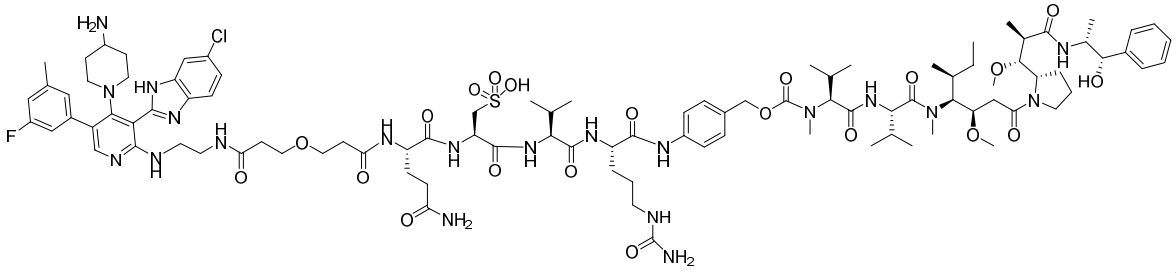

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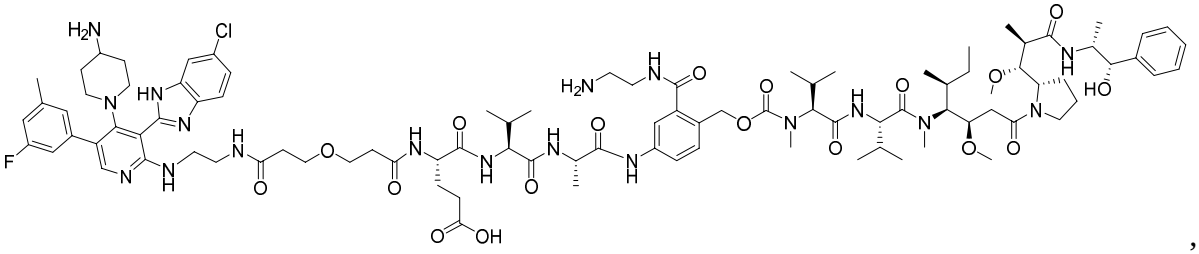

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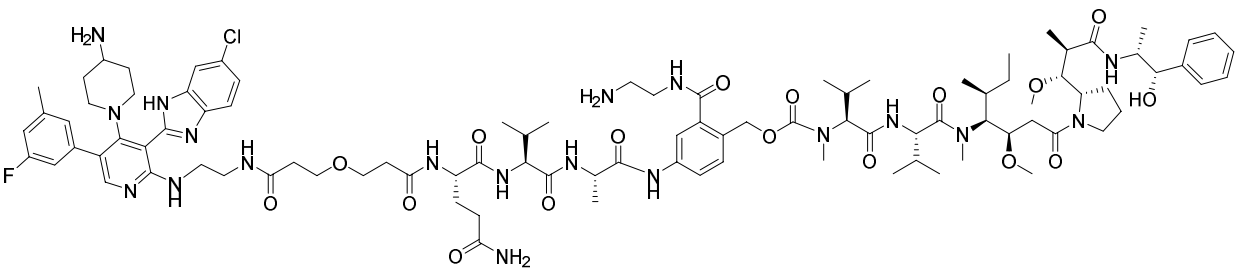

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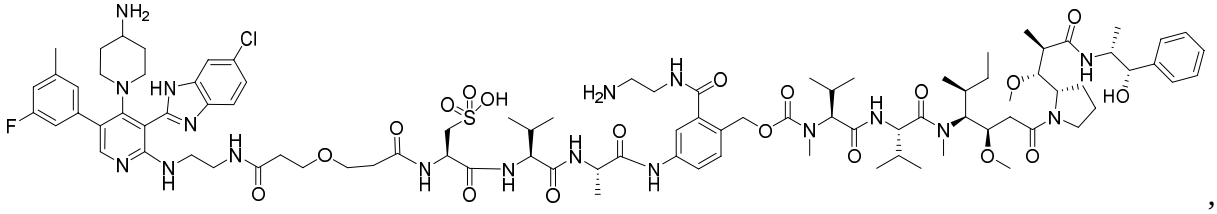

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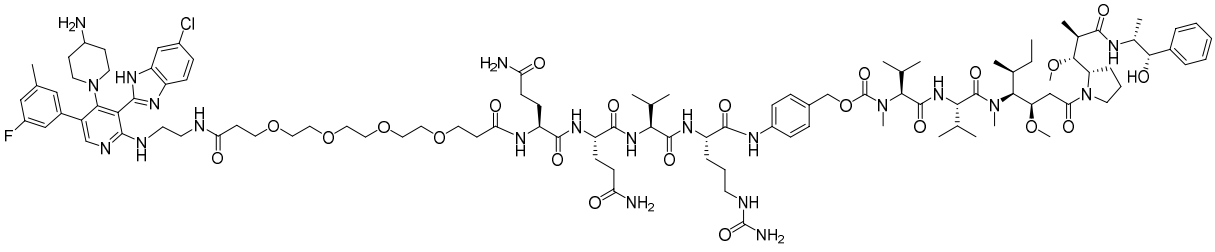

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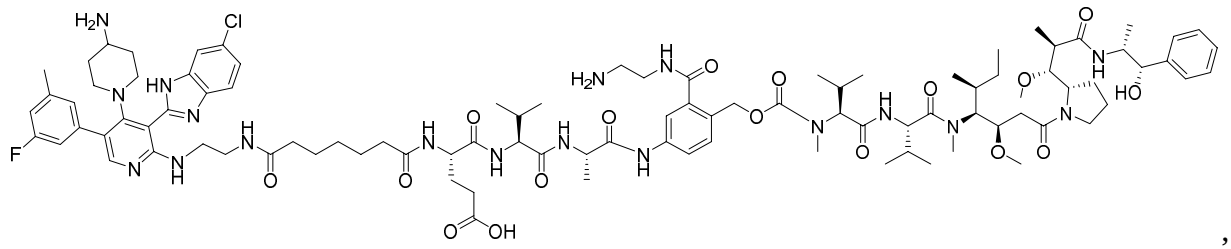

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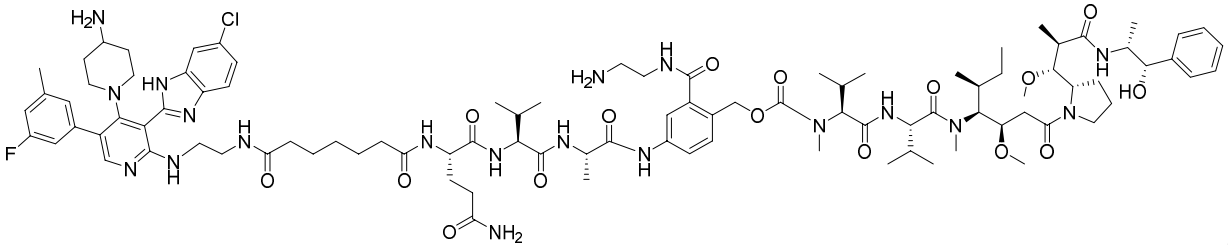

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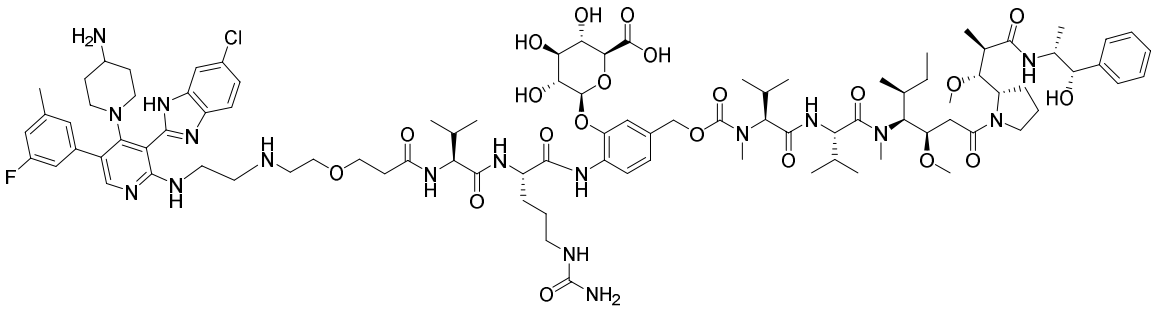

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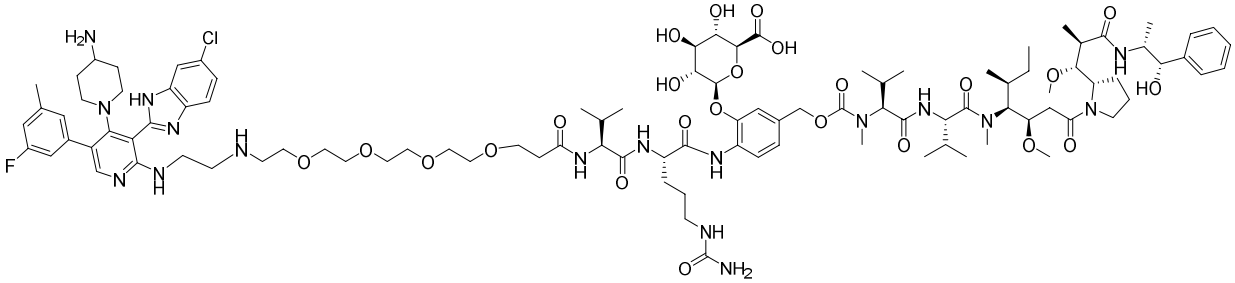

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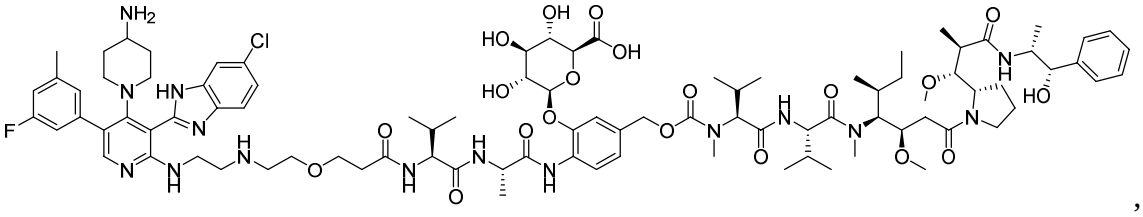

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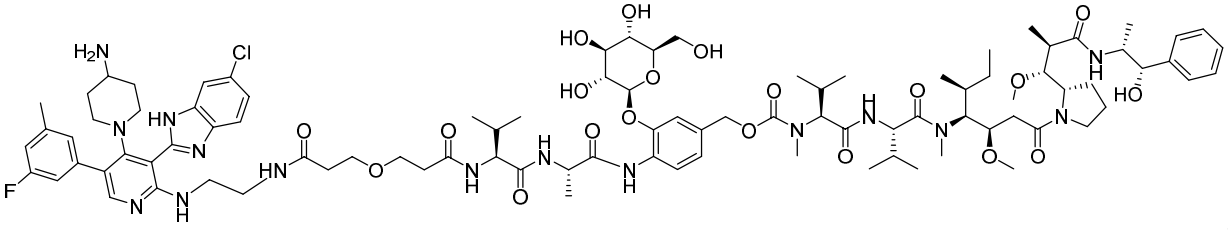

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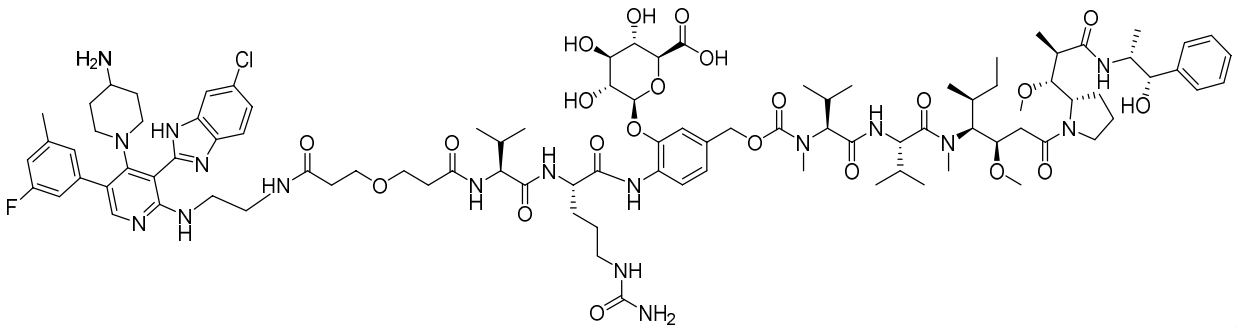

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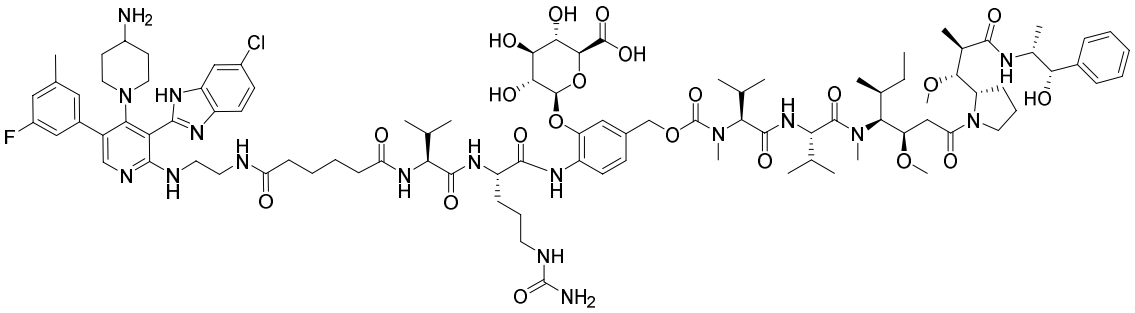

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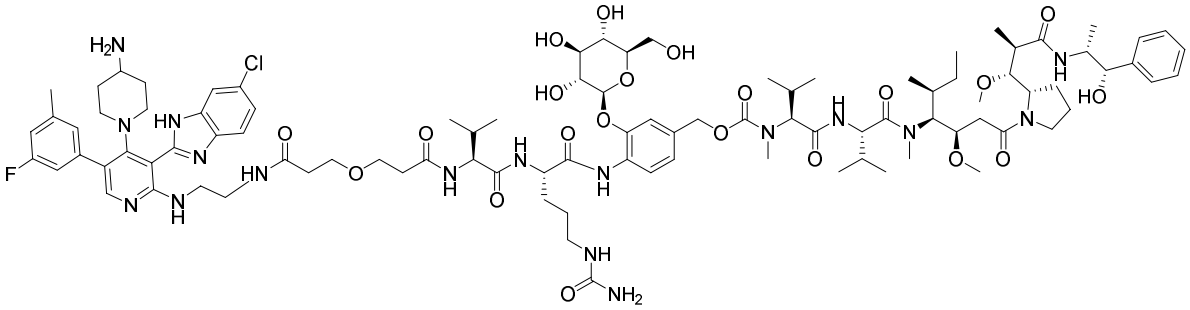

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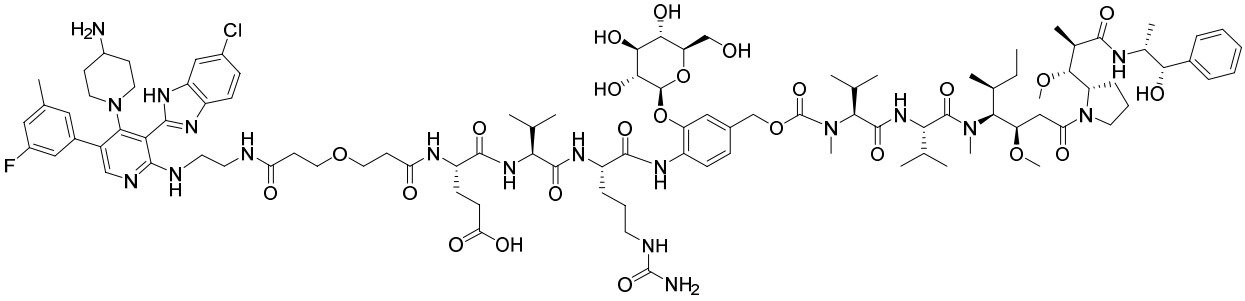

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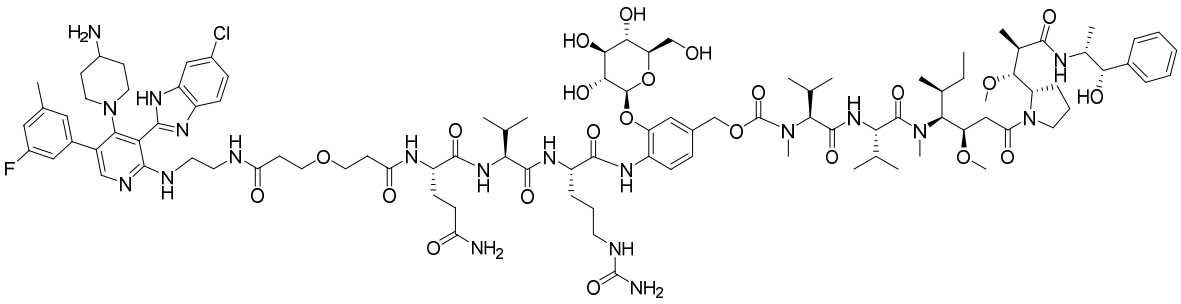

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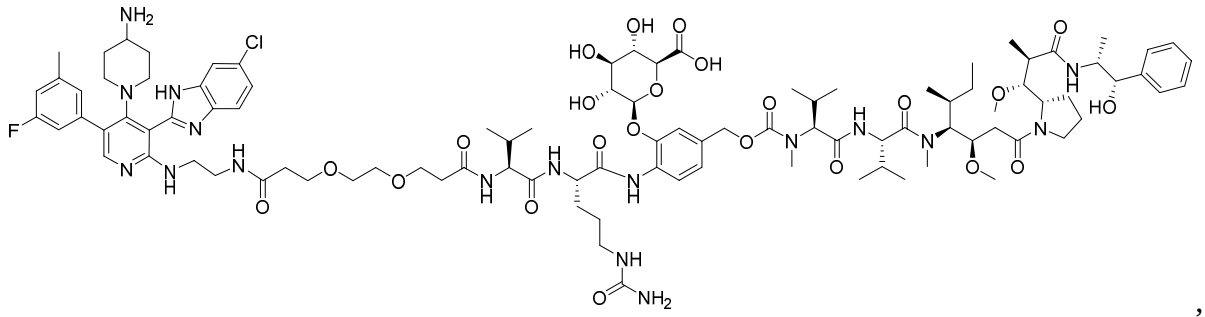

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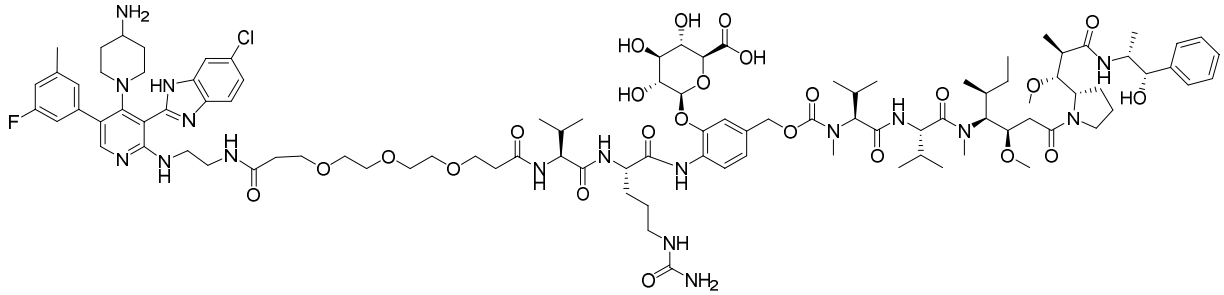

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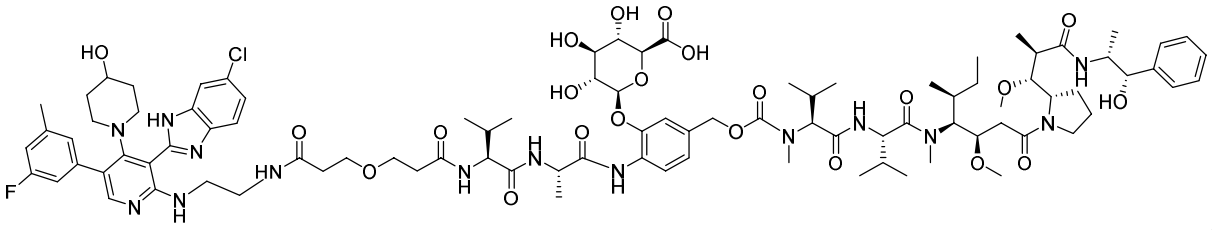

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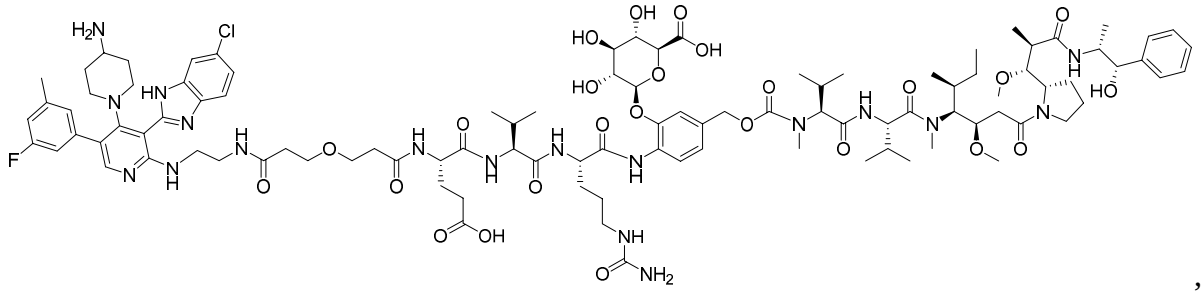

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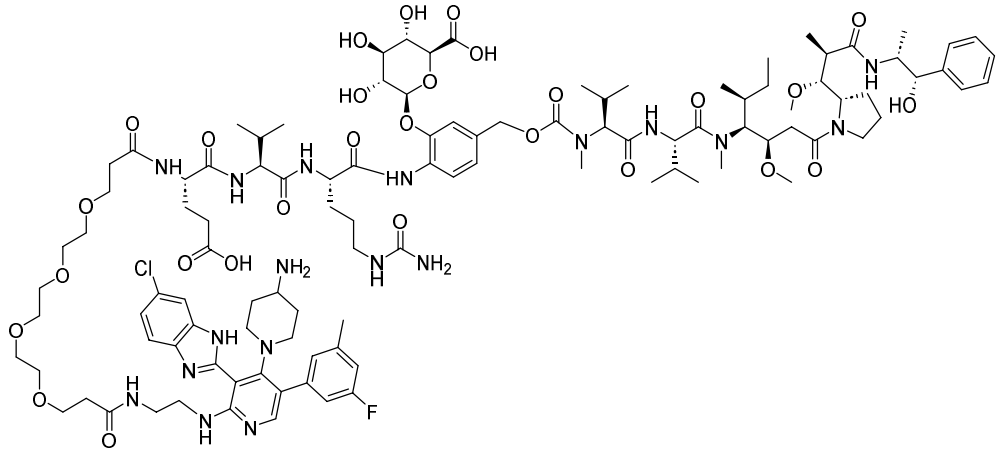

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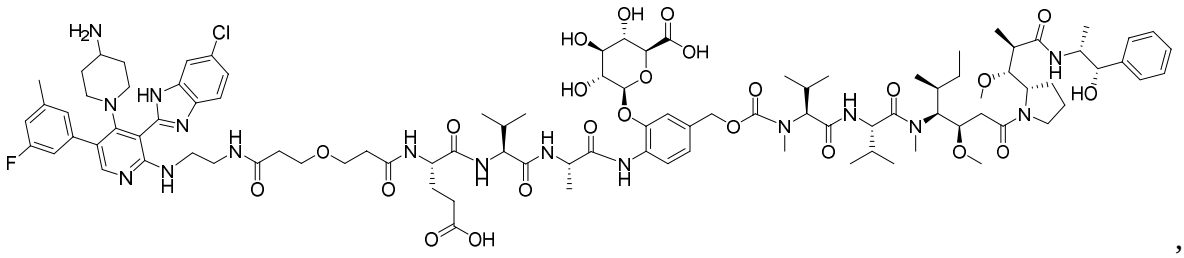

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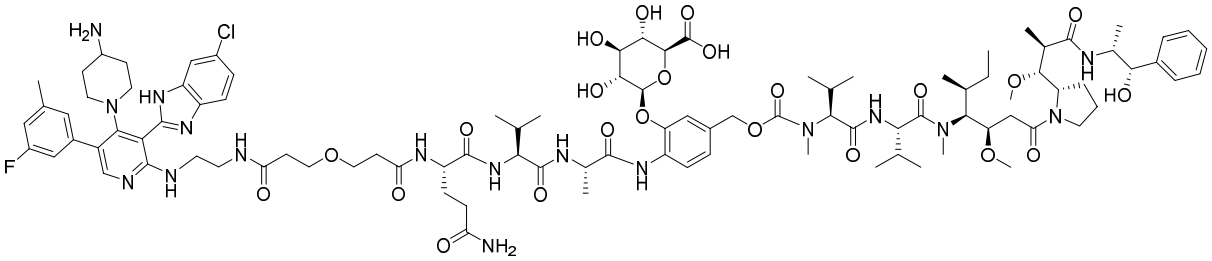

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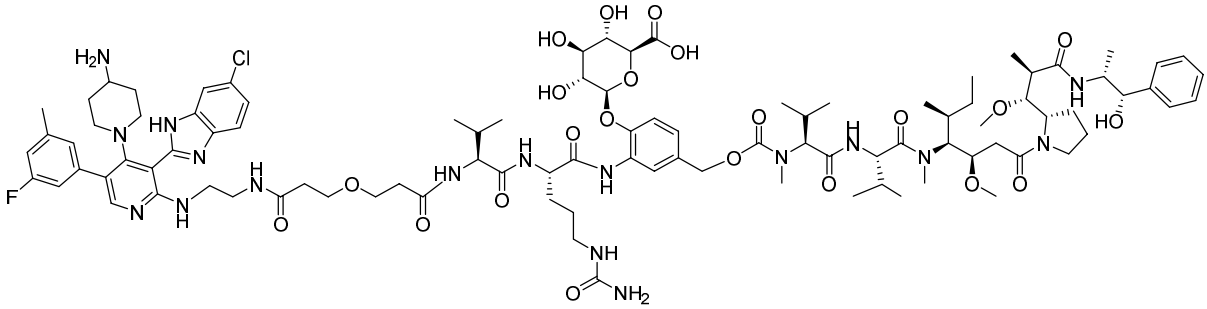

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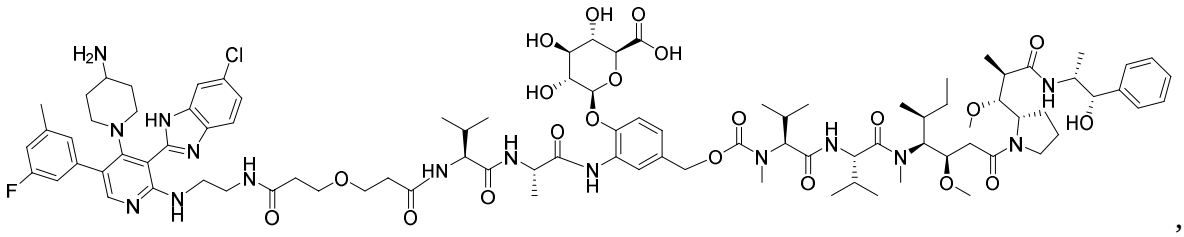

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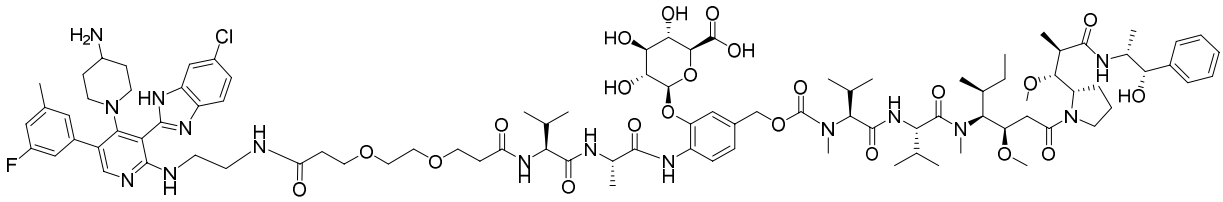

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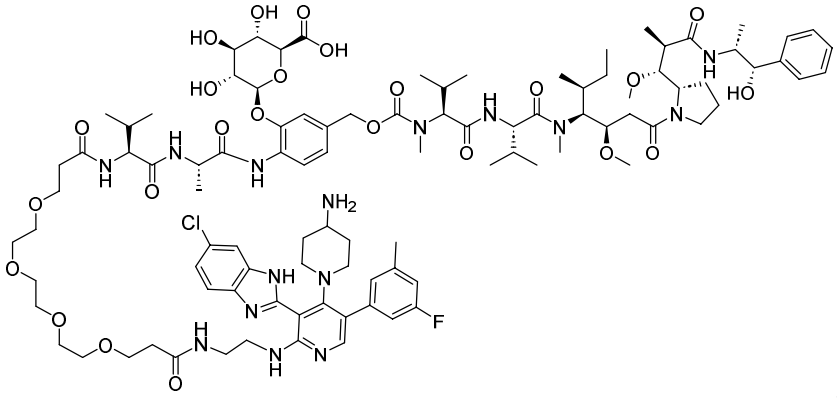

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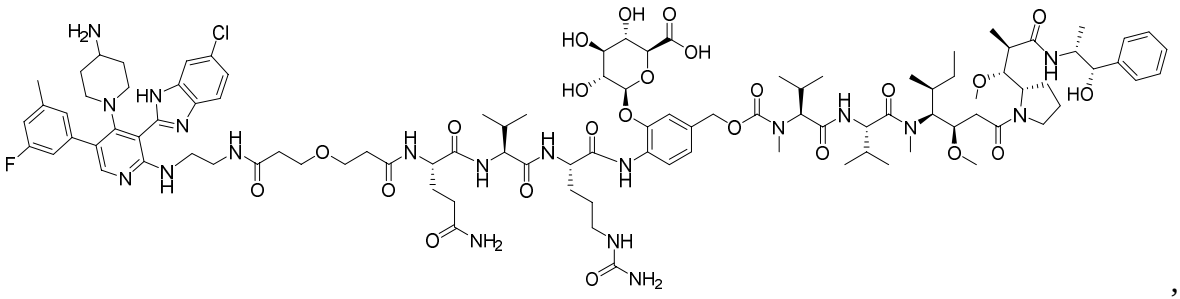

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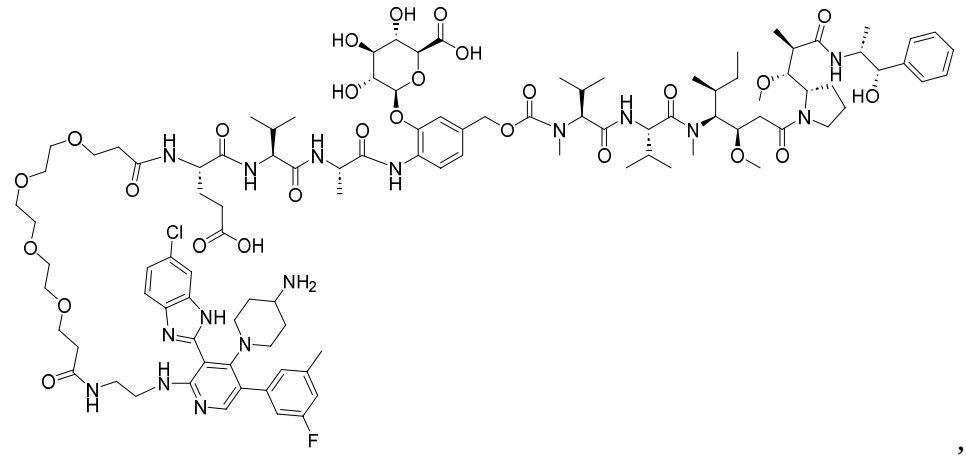

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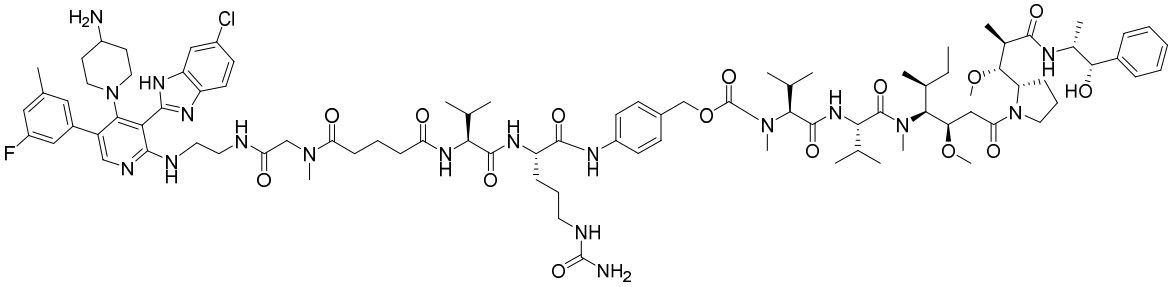

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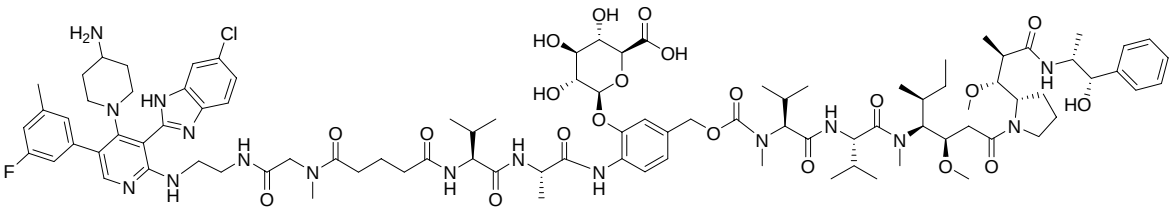

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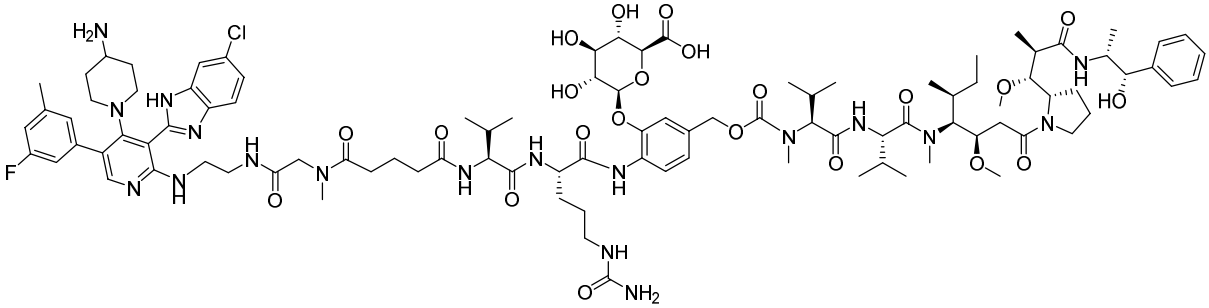

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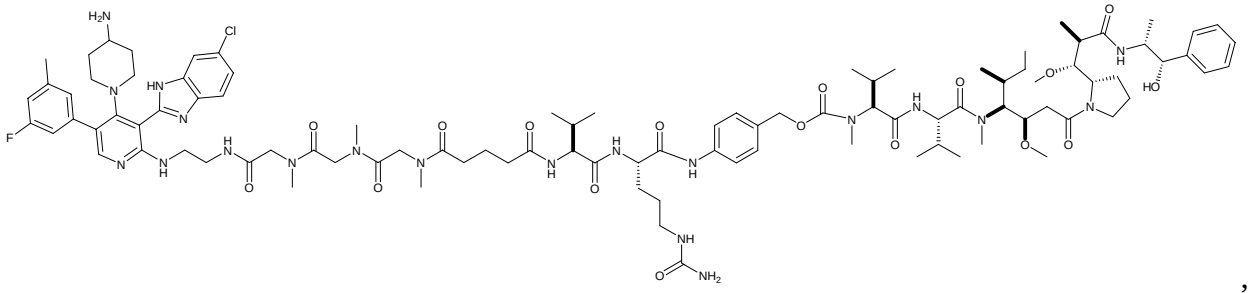

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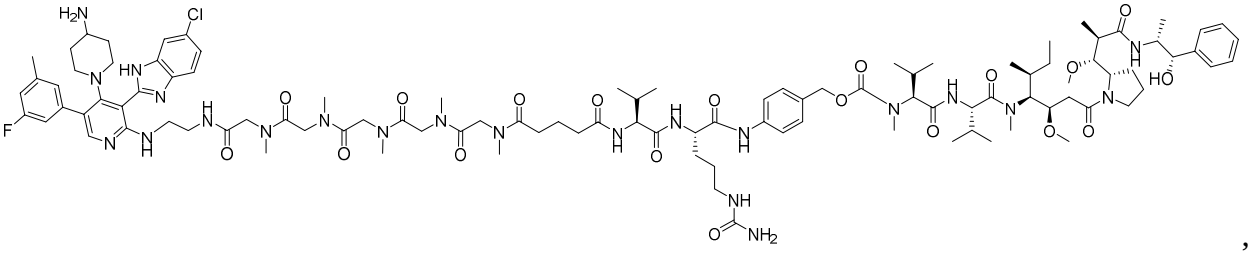

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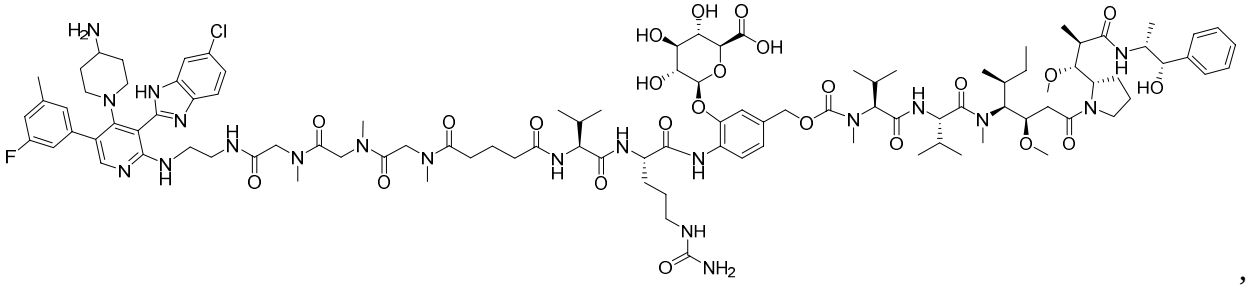

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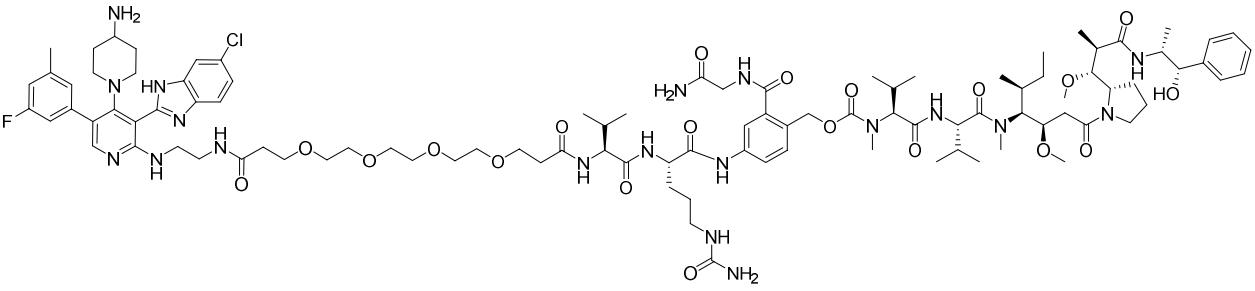

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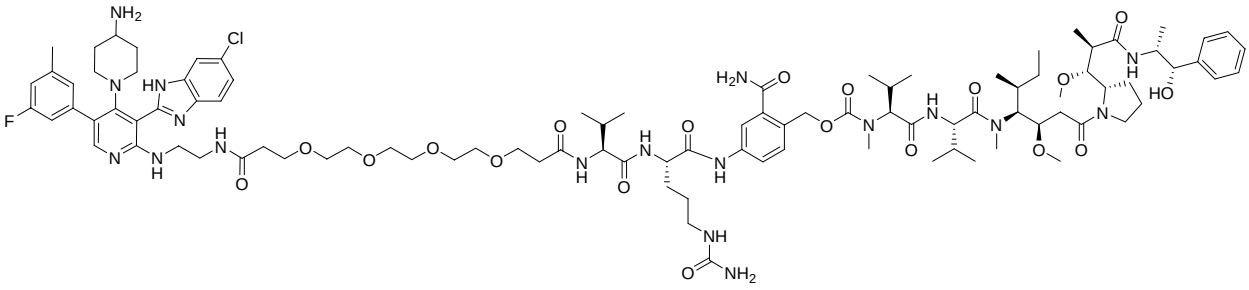

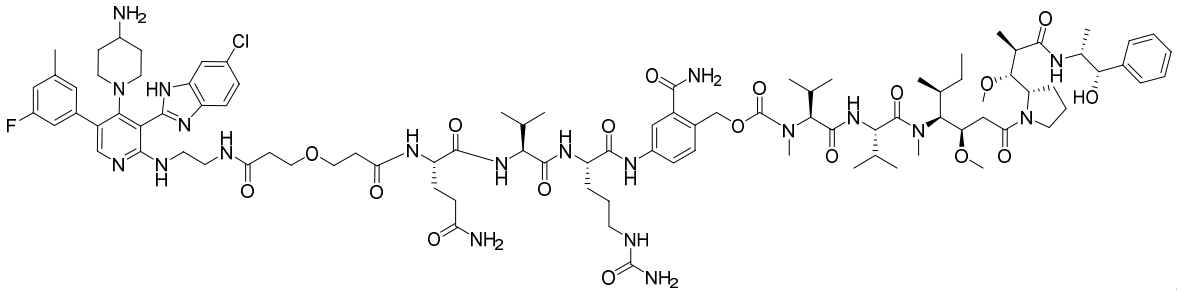

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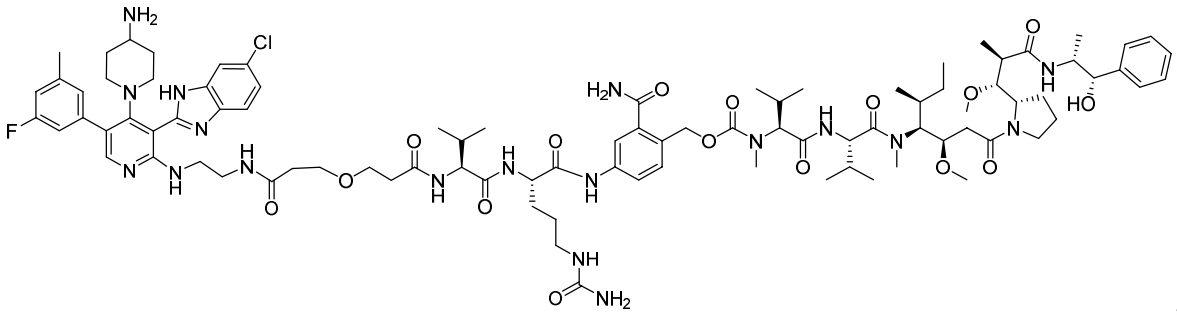

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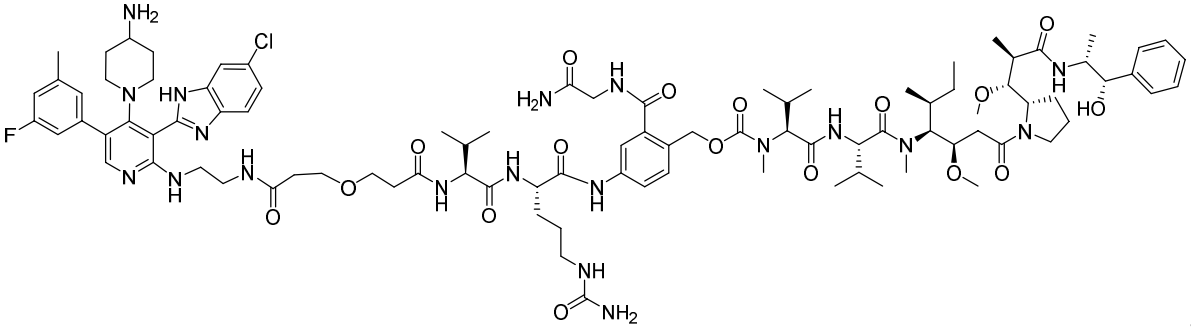

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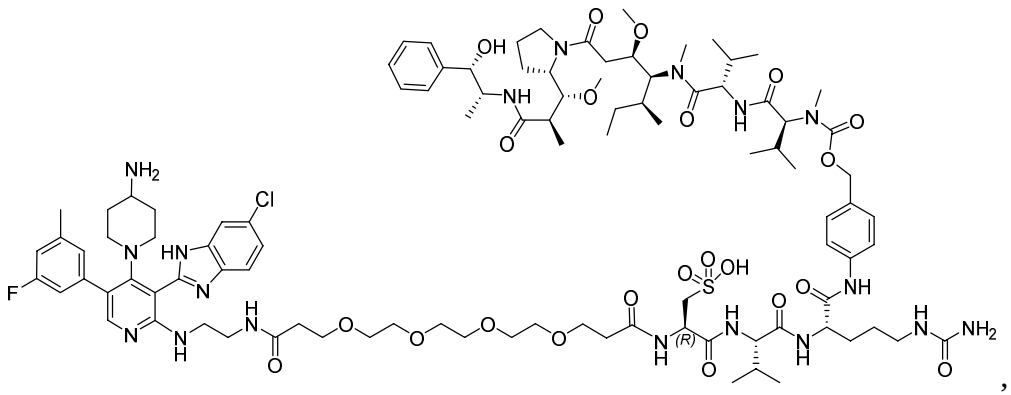

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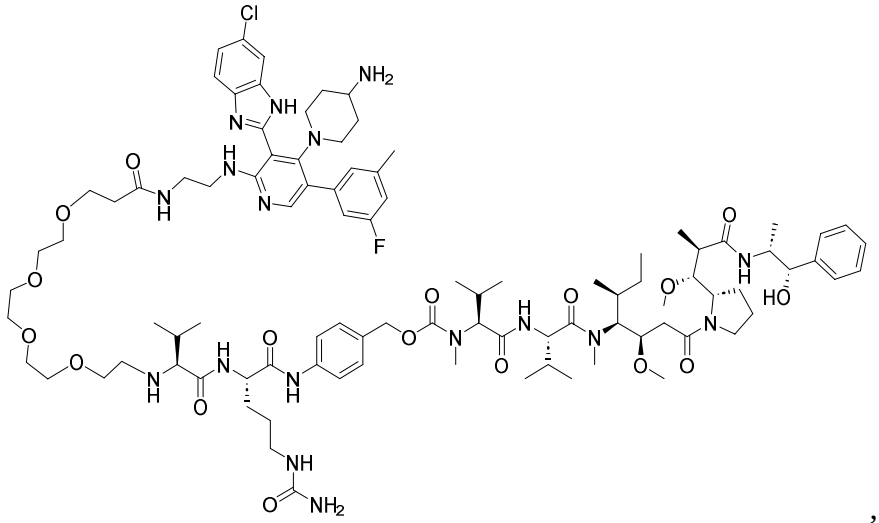

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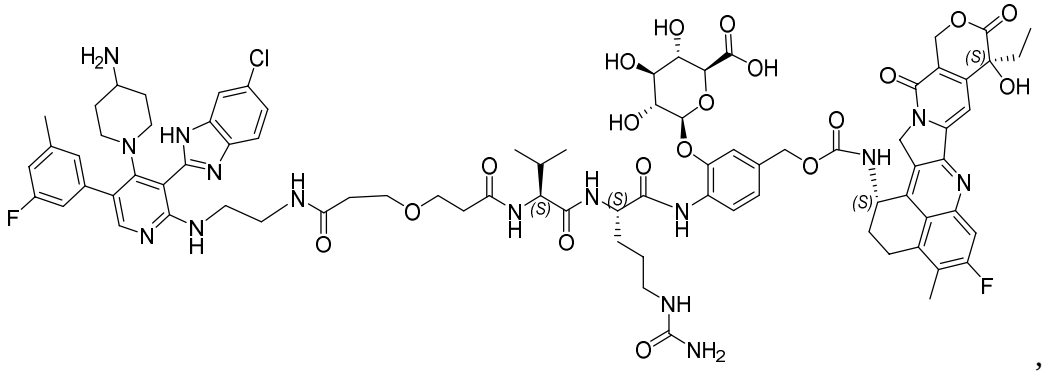

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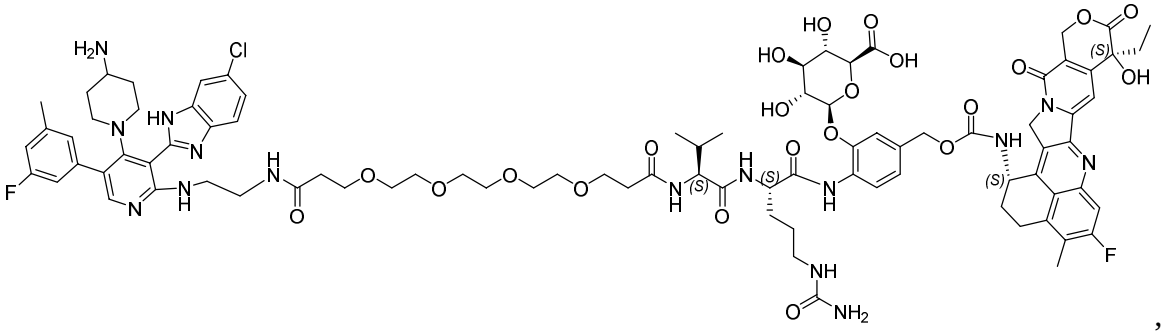

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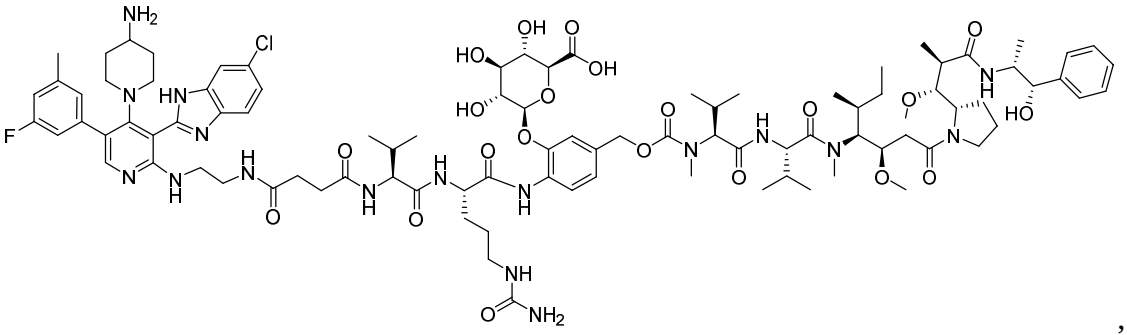

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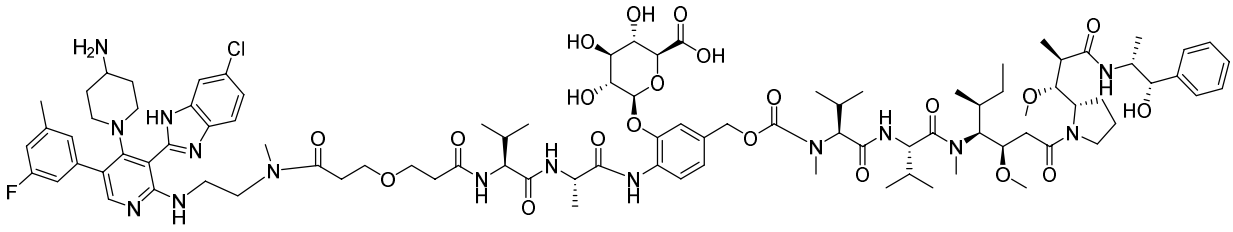

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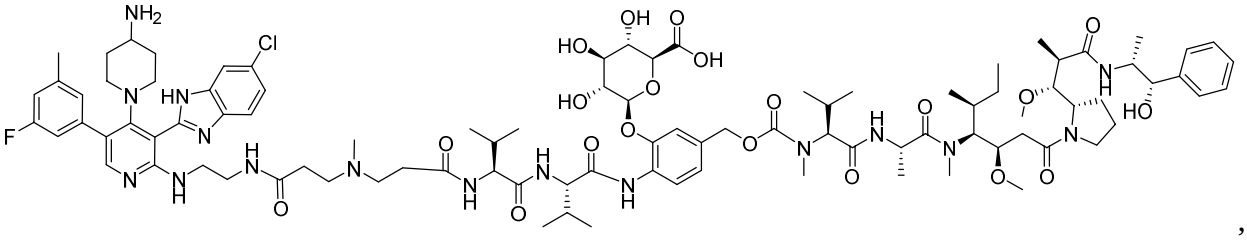

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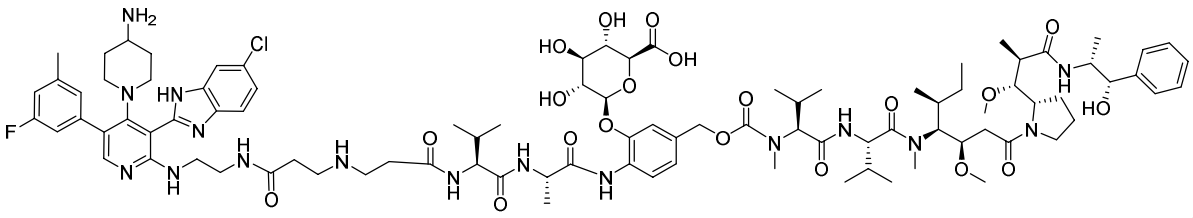

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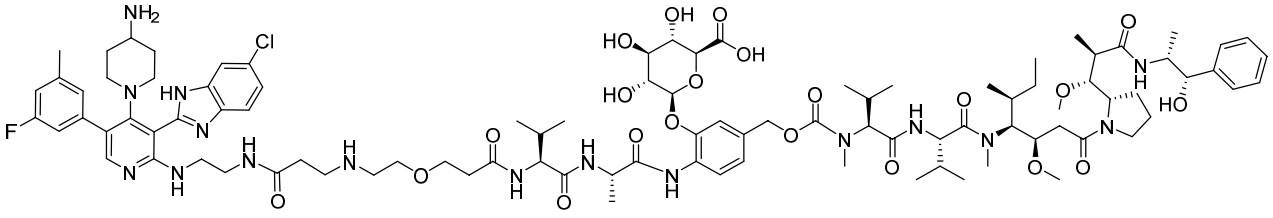

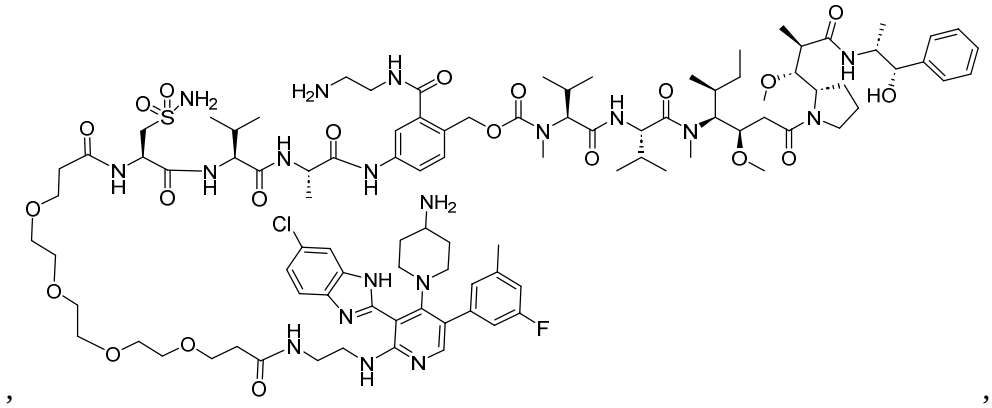

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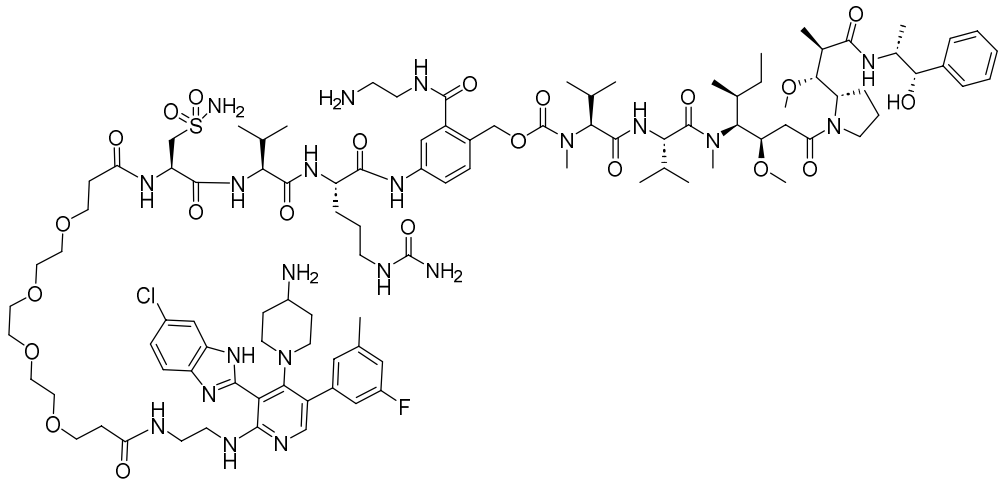

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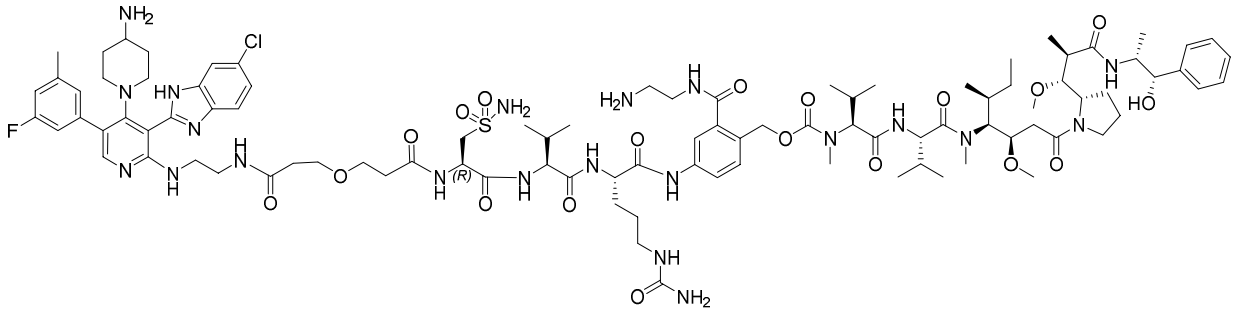

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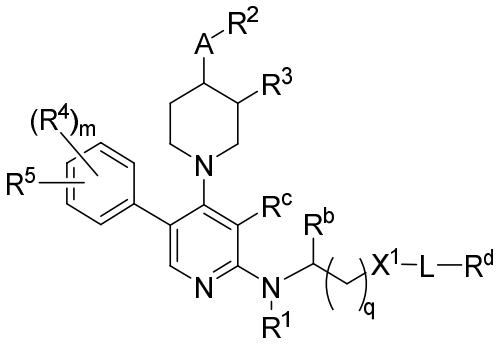
26. A compound that has the structure of Formula (A), or a pharmaceutically acceptable salt thereof:



Formula (A)

wherein:

A is -N(H)- or -O-;

X^1 is $-N(R^a)-$, -O-, -C(=O)-, $-C(=O)N(R^a)-$, -S(=O)-, $-(CH_2)C(R^a)=N-O-(CH_2)-$;

R^a is hydrogen or C_1-C_6alkyl;

R^b is hydrogen or C_1-C_6alkyl;

or when both R^a and R^b are present then R^a and R^b are taken together with the intervening atoms to which they are attached to form a piperidine or pyrrolidine;

q is 1, 2, or 3;

R^1 is hydrogen;

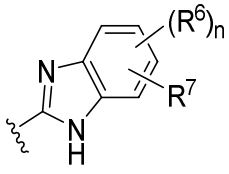
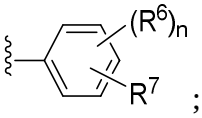
R^2 is hydrogen or C_1-C_6alkyl;

R^3 is hydrogen, $-OR^8$, $-N(R^8)_2$, -CN, halogen, C_1-C_6 alkyl, or C_1-C_6fluoroalkyl;

or R^2 and R^3 are taken together with the intervening atoms to which they are attached to form a morpholine;

each R^4 and R^5 is independently hydrogen, halogen, C_1-C_6alkyl, C_1-C_6fluoroalkyl, substituted or unsubstituted C_1-C_6heteroalkyl, -CN, $-N(R^8)_2$, or $-OR^8$;

m is 1, 2, or 3;

R^c is  or  ;

each R^6 and R^7 is independently hydrogen, halogen, C_1-C_4alkyl, C_1-C_4fluoroalkyl, C_2-C_4alkenyl, C_2-C_4alkynyl, substituted or unsubstituted C_1-C_6heteroalkyl, substituted or unsubstituted phenyl, substituted or unsubstituted C_3-C_6cycloalkyl, -CN, $-OR^8$, $-CO_2R^8$, $-C(=O)N(R^8)_2$, $-N(R^8)_2$, $-NR^8C(=O)R^9$, $-NR^8C(=O)OR^9$, $-SR^8$, $-S(=O)R^9$, $-SO_2R^9$, or $-SO_2N(R^8)_2$;

n is 1, 2, or 3;

each R^8 is independently hydrogen, C_1-C_4alkyl, C_1-C_4fluoroalkyl, substituted or unsubstituted C_1-C_4heteroalkyl;

each R^9 is independently C_1-C_4alkyl, C_1-C_4fluoroalkyl, substituted or unsubstituted C_1-C_4heteroalkyl;

L is -L^1-L^2-;

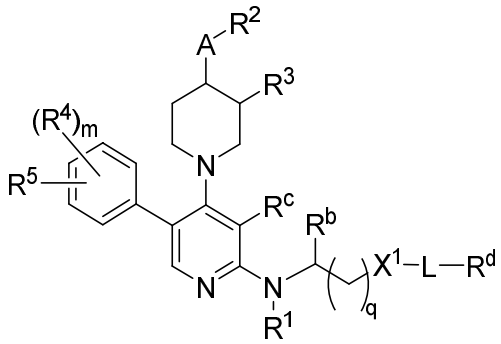
L^1 is an optional spacer;

L^2 is an optional linker;

wherein at least one of L^1 or L^2 is present;

R^d is a payload moiety comprising a chelating moiety or a radionuclide complex thereof.

27. A compound that has the structure of Formula (A), or a pharmaceutically acceptable salt thereof:



Formula (A)

wherein:

A is -N(H)- or -O-;

X^1 is -N(R^a)-, -O-, -C(=O)-, -C(=O)N(R^a)-, -S(=O)-, -(CH_2)C(R^a)=N-O-(CH_2)-;

R^a is hydrogen or C_1-C_6alkyl;

R^b is hydrogen or C_1-C_6alkyl;

or when both R^a and R^b are present then R^a and R^b are taken together with the intervening atoms to which they are attached to form a piperidine or pyrrolidine;

q is 1, 2, or 3;

R^1 is hydrogen;

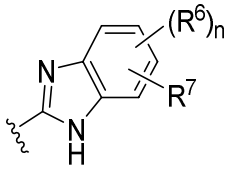
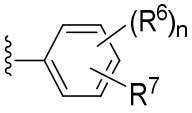
R^2 is hydrogen or C_1-C_6alkyl;

R^3 is hydrogen, -OR^8, -N(R^8)$_2$, -CN, halogen, C_1-C_6 alkyl, or C_1-C_6fluoroalkyl;

or R^2 and R^3 are taken together with the intervening atoms to which they are attached to form a morpholine;

each R^4 and R^5 is independently hydrogen, halogen, C_1-C_6alkyl, C_1-C_6fluoroalkyl, substituted or unsubstituted C_1-C_6heteroalkyl, -CN, -N(R^8)$_2$, or -OR^8;

m is 1, 2, or 3;

R^c is  or  ;

each R^6 and R^7 is independently hydrogen, halogen, C_1-C_4alkyl, C_1-C_4fluoroalkyl, C_2-C_4alkenyl, C_2-C_4alkynyl, substituted or unsubstituted C_1-C_6heteroalkyl, substituted or unsubstituted phenyl, substituted or unsubstituted C_3-C_6cycloalkyl, -CN, -OR^8, -CO_2R^8, -$C(=O)N(R^8)_2$, -$N(R^8)_2$, -$NR^8C(=O)R^9$, -$NR^8C(=O)OR^9$, -SR^8, -$S(=O)R^9$, -SO_2R^9, or -$SO_2N(R^8)_2$;

n is 1, 2, or 3;

each R^8 is independently hydrogen, C_1-C_4alkyl, C_1-C_4fluoroalkyl, substituted or unsubstituted C_1-C_4heteroalkyl;

each R^9 is independently C_1-C_4alkyl, C_1-C_4fluoroalkyl, substituted or unsubstituted C_1-C_4heteroalkyl;

L is -L^1-L^2-;

L^1 is an optional spacer;

L^2 is an optional linker;

wherein at least one of L^1 or L^2 is present;

R^d is a payload moiety comprising: a chelating moiety or a radionuclide complex thereof.

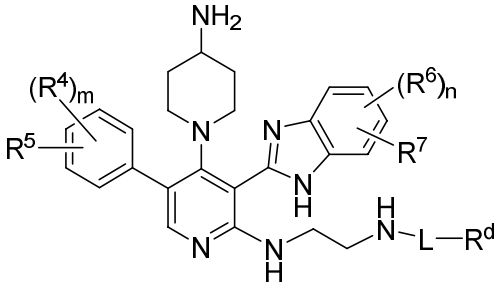
28. The compound of any one of claims 26-27, or a pharmaceutically acceptable salt thereof, wherein R^2 is hydrogen; R^3 is hydrogen -OH, or -OCH_3; or R^2 and R^3 are taken together with the intervening atoms to which they are attached to form a morpholine.

29. The compound of any one of claims 26-28, or a pharmaceutically acceptable salt thereof, wherein each R^4 and R^5 is independently hydrogen, F, Cl, Br, C_1-C_4alkyl, C_1-C_4fluoroalkyl, -CN, -$N(R^7)_2$, or -OR^7.

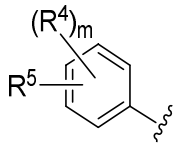
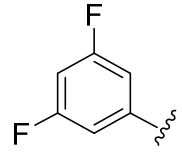
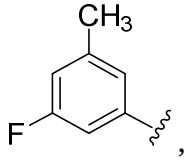
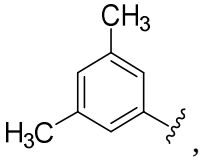
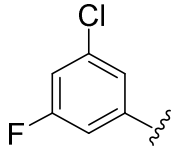
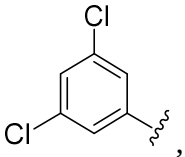
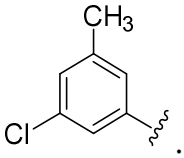
30. The compound of any one of claims 26-29, or a pharmaceutically acceptable salt thereof, wherein each R^4 and R^5 is independently hydrogen, F, Cl, Br, -CH_3, -CH_2F, -CHF_2, -CF_3, -CN, -NH_2, -$NHCH_3$, -$N(CH_3)_2$, -OH, -OCH_3, or -OCF_3.

31. The compound of any one of claims 26-30, or a pharmaceutically acceptable salt thereof, wherein A is -N(H)-; R^a is hydrogen, -CH_3, or -CH_2CH_3; R^b is hydrogen, -CH_3, or -CH_2CH_3; or when both R^a and R^b are present then R^a and R^b are taken together with the intervening atoms to which they are attached to form a piperidine; and R^1 is hydrogen, -CH_3, or -CH_2CH_3.

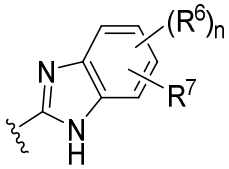
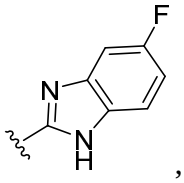
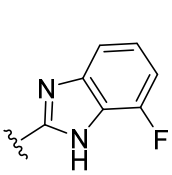
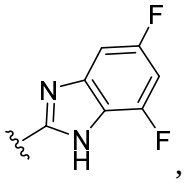
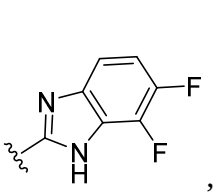
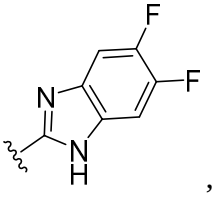
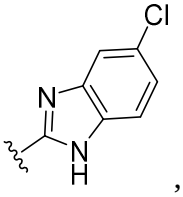
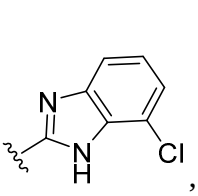
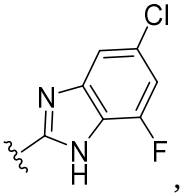
32. The compound of any one of claims 26-31, or a pharmaceutically acceptable salt thereof, wherein the compound has the structure of Formula (II), or a pharmaceutically acceptable salt thereof:

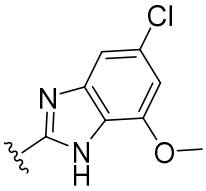
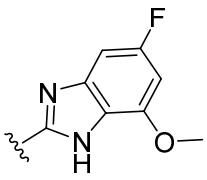
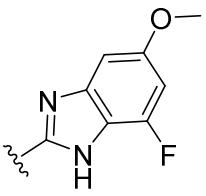
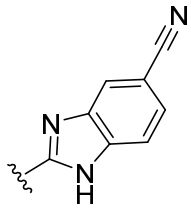
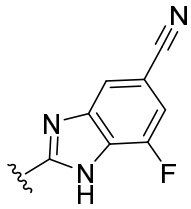


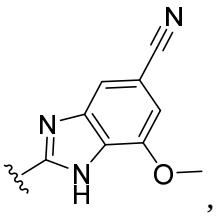
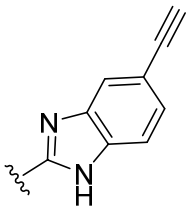
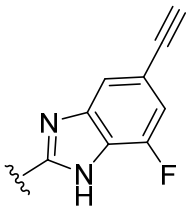
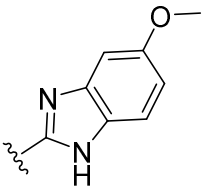
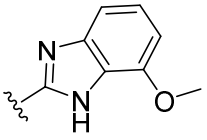
Formula (II).

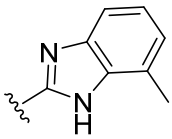
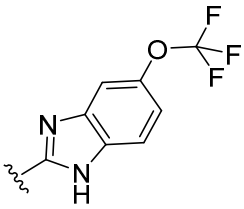
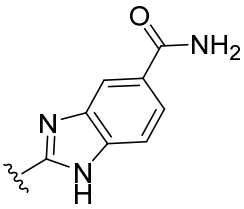
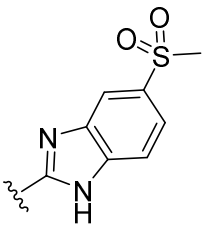
33. The compound of any one of claims 26-32, or a pharmaceutically acceptable salt thereof, wherein  is  ,  ,  ,  ,  , or  .

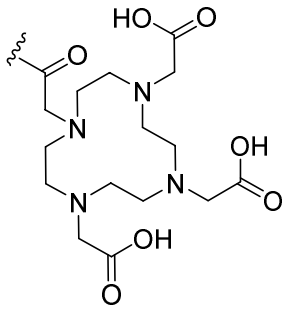
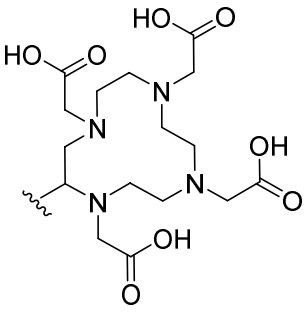
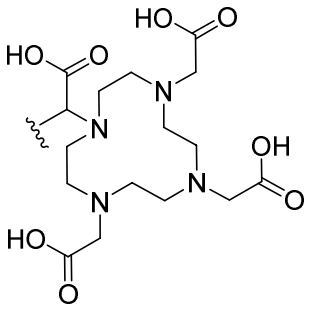
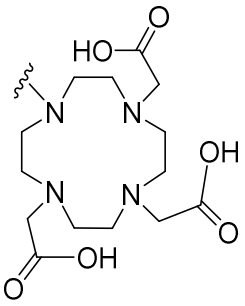
34. The compound of any one of claims 26-33, or a pharmaceutically acceptable salt thereof, wherein each R^6 and R^7 is independently hydrogen, F, Cl, Br, $-CH_3$, $-CH_2CH_3$, $-CO_2H$, $-CO_2CH_3$, $-CO_2CH_2CH_3$, $-CH_2F$, $-CHF_2$, $-CF_3$, $-CH=CH_2$, $-C\equiv CH$, $-CN$, $-OH$, $-OCH_3$, $-OCH_2CH_3$, $-OCF_3$, $-C(=O)NH_2$, $-C(=O)NHCH_3$, $-C(=O)N(CH_3)_2$, $-NH_2$, $-NHCH_3$, $-N(CH_3)_2$, $-NHC(=O)CH_3$, $-NCH_3C(=O)CH_3$, $-SO_2CH_3$, $-SO_2NH_2$, $-SO_2NHCH_3$, or $-SO_2N(CH_3)_2$.

35. The compound of any one of claims 26-34, or a pharmaceutically acceptable salt thereof, wherein  is  ,  ,  ,  ,  ,  ,  ,  ,

 ,  ,  ,  ,  ,

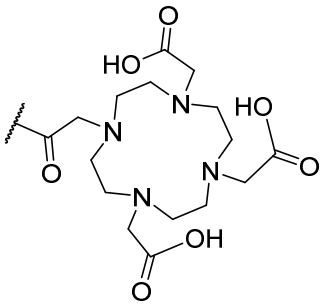
 ,  ,  ,  ,  ,

 ,  ,  , or  .

36. The compound of any one of claim 26-35, or a pharmaceutically acceptable salt thereof, wherein, R^d is  ,  ,  , or  ; or a radionuclide complex thereof.

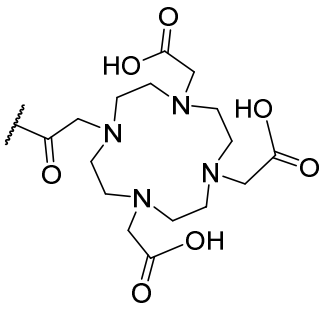
37. The compound of any one of claims 26-35, or a pharmaceutically acceptable salt thereof, wherein L-R^d is: -CH_2CH_2NH-R^d, -C(=O)CH_2NH-R^d, -C(=O)CH_2CH_2NH-R^d, -$CH_2CH_2(OCH_2CH_2)_2NH$-R^d, -$CH_2CH_2(OCH_2CH_2)_3NH$-R^d, -$CH_2CH_2(OCH_2CH_2)_4NH$-R^d, -$CH_2CH_2(OCH_2CH_2)_5NH$-R^d, -$CH_2CH_2(OCH_2CH_2)_6NH$-R^d, -$CH_2CH_2(OCH_2CH_2)_7NH$-R^d, -$CH_2CH_2(OCH_2CH_2)_8NH$-R^d, -C(=O)$CH_2CH_2(OCH_2CH_2)_2NH$-R^d, -C(=O)$CH_2CH_2(OCH_2CH_2)_3NH$-R^d, -C(=O)$CH_2CH_2(OCH_2CH_2)_4NH$-R^d, -C(=O)$CH_2CH_2(OCH_2CH_2)_5NH$-R^d, -C(=O)$CH_2CH_2(OCH_2CH_2)_6NH$-R^d, -

$C(=O)CH_2CH_2(OCH_2CH_2)_7NH\text{-}R^d$, or $\text{-}C(=O)CH_2CH_2(OCH_2CH_2)_8NH\text{-}R^d$;



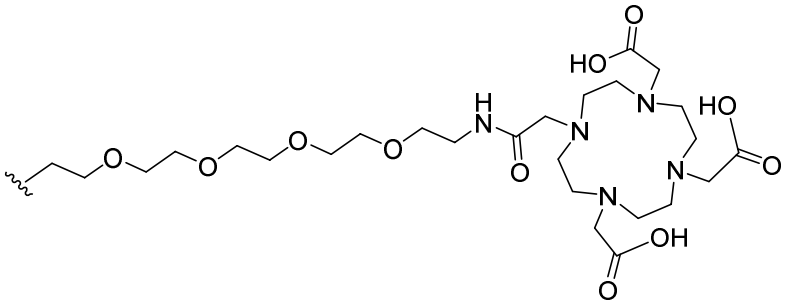
R^d is , or a radionuclide complex thereof.

38. The compound of any one of claim 26-35, or a pharmaceutically acceptable salt thereof, wherein, $\text{-}L^1\text{-}R^d$ is: -(PEG2)NH-R^d, -(PEG3)NH-R^d, -(PEG4)NH-R^d, -(PEG5)NH-R^d, -(PEG6)NH-R^d, -(PEG7)NH-R^d, -(PEG8)NH-R^d, -C(=O)(PEG2)NH-R^d, -C(=O)(PEG3)NH-R^d, -C(=O)(PEG4)NH-R^d, -C(=O)(PEG5)NH-R^d, -C(=O)(PEG6)NH-R^d, -C(=O)(PEG7)NH-R^d, or -C(=O)(PEG8)NH-R^d;

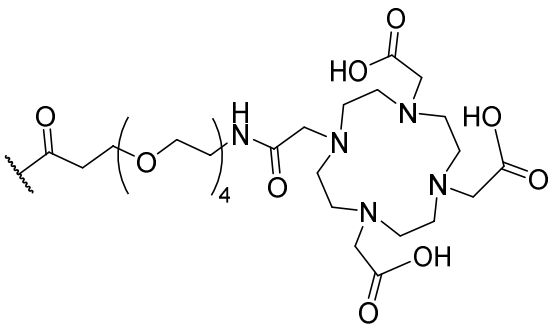


R^d is , or a radionuclide complex thereof.

39. The compound of any one of claim 26-35, or a pharmaceutically acceptable salt thereof,



wherein, $\text{-}L^1\text{-}R^d$ is: ,



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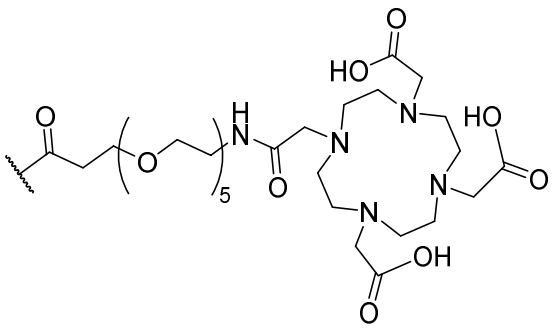

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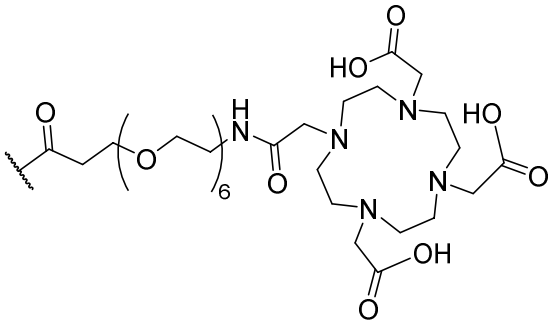
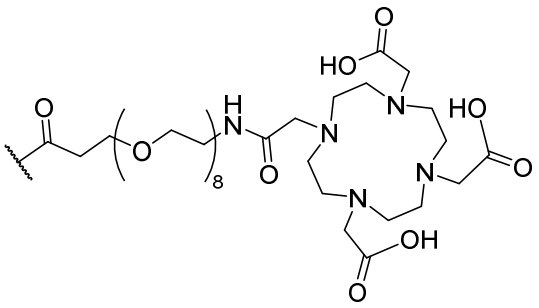


, or



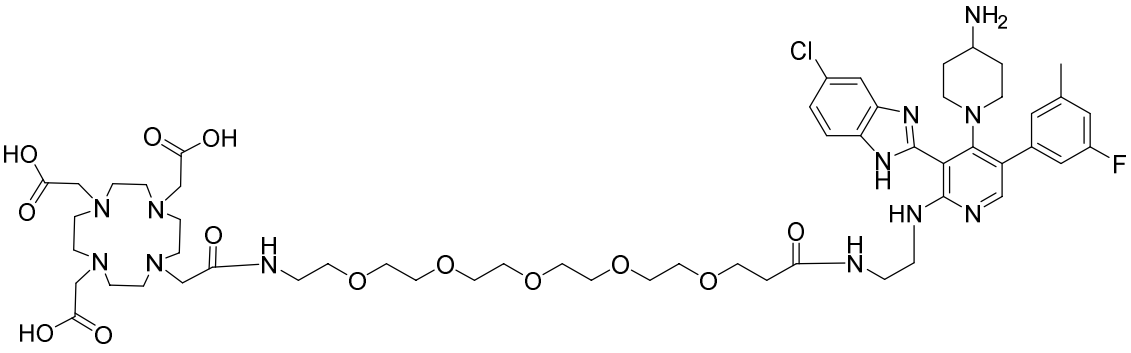
,

or a radionuclide complex thereof.

40. The compound of any one of claim 26-39, or a pharmaceutically acceptable salt thereof, wherein, the radionuclide of the radionuclide complex is copper-64 (^{64}Cu), 67-copper (^{67}Cu), 111-indium (^{111}In), 115-indium (^{115}In), 67-gallium (^{67}Ga), 68-gallium (^{68}Ga), 225-actinium (^{225}Ac), 175-lutetium (^{175}Lu), 177-lutetium (^{177}Lu), or 212-lead (^{212}Pb).

41. The compound of any one of claim 26-39, or a pharmaceutically acceptable salt thereof, wherein, the radionuclide of the radionuclide complex is 111-indium (^{111}In), 115-indium (^{115}In), 67-gallium (^{67}Ga), 68-gallium (^{68}Ga), 225-actinium (^{225}Ac), 175-lutetium (^{175}Lu), or 177-lutetium (^{177}Lu).

42. A compound, or pharmaceutically salt thereof, selected from the group consisting of:



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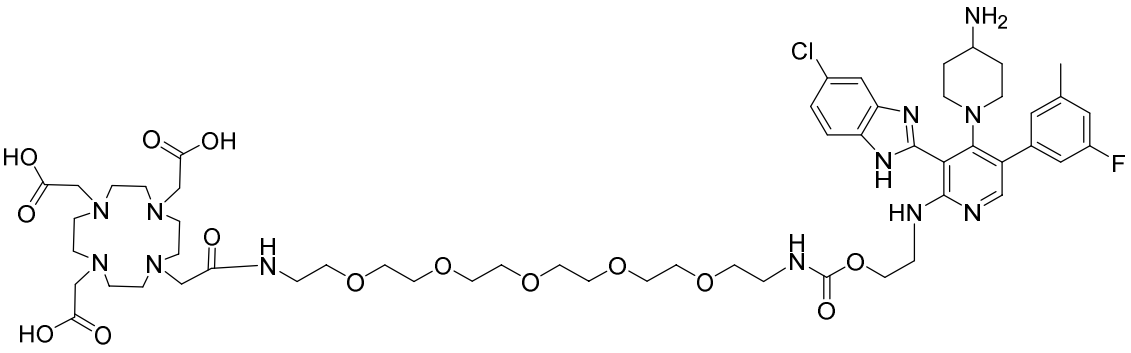

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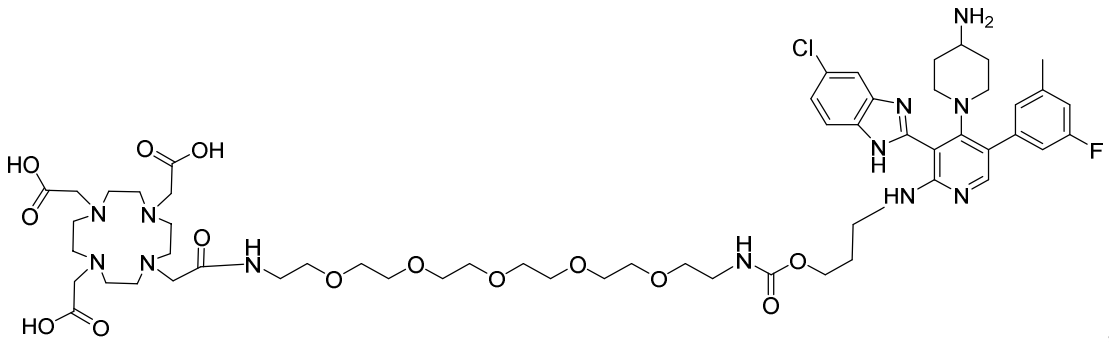
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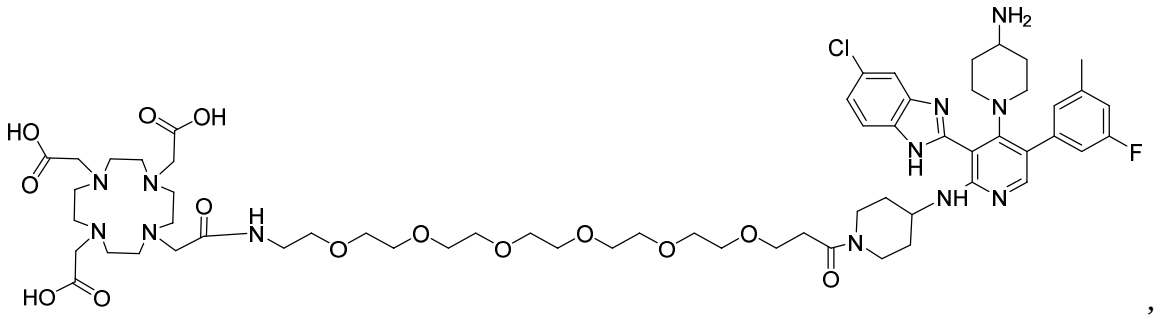
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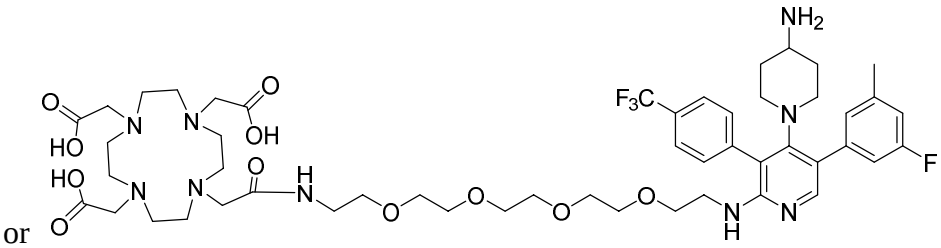
or .

43. A pharmaceutical composition comprising a compound of any one of claims 1-42, or a pharmaceutically acceptable salt thereof, and at least one pharmaceutically acceptable excipient.

44. Use of a compound of any one of claims 1-42, or a pharmaceutically acceptable salt thereof in the manufacture of a medicament for the treatment of cancer in a mammal.

45. Use of a compound of any one of claims 1-42, or a pharmaceutically acceptable salt thereof in the manufacture of a medicament for treating tumors in a mammal.

46. The use of any one of claims 44-45, wherein the mammal has anal cancer, bladder cancer, bowel cancer, brain cancer, breast cancer, colon cancer, colorectal cancer, endometrial cancer, esophageal cancer, gallbladder cancer, gastric cancer, heart cancer, kidney cancer, lung cancer, liver cancer, melanoma, uterine cancer, lymphoma, ovarian cancer, pancreatic cancer, prostate cancer, thymus cancer, pheochromocytoma, medullary thyroid carcinoma, or head & neck cancer.

47. The use of any one of claims 44-45, wherein the mammal has an endocrine cancer.

48. The use of claim 47, wherein the endocrine cancer comprises adrenal tumors, neuroendocrine tumors, parathyroid tumors, pituitary tumors, or thyroid tumors.

49. The use of any one of claims 44-45, wherein the mammal has neuroendocrine tumors.

50. The use of any one of claims 44-45, wherein the mammal has somatostatin receptor-positive gastroenteropancreatic neuroendocrine tumors (GEP-NETs).

51. Use of a compound of any one of claims 1-42, or a pharmaceutically acceptable salt thereof in the manufacture of a medicament for targeted delivery of a chemotherapeutic to tumors in a mammal.

52. Use of a compound of any one of claims 1-42, or a pharmaceutically acceptable salt thereof in the manufacture of a medicament for killing tumors that overexpress the somatostatin subtype-2 receptor (SST2R) in a mammal.