6. The insulin receptor partial agonist of claim 1, wherein the insulin receptor partial agonist comprises a first and second insulins or insulin analogs, which are independently selected from the group consisting of native human insulin, insulin lispro, insulin aspart, desB30 insulin, and insulin glargine.

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7. An insulin receptor partial agonist comprising the formula

$$D^1\text{-}L\text{-}D^2$$

wherein D^1 and D^2 are each independently an insulin or insulin analog polypeptide,

wherein each insulin polypeptide is a heterodimer comprising an A-chain polypeptide and a B-chain polypeptide linked together through interchain disulfide bonds;

L is a linking moiety wherein one end of the linker moiety is attached to an amino acid residue at or near the carboxyl group of D^1 and the other end of the linker moiety is attached to an amino acid residue at or near the carboxyl end of D^2 with the proviso that L does not include a disulfide linkage; and

wherein the first and second insulin or insulin analog polypeptides include a substituent attached to the amino terminus of the A-chain polypeptide and the B-chain polypeptide;

or

an insulin receptor partial agonist comprising:

a first insulin or insulin analog heterodimer and a second insulin or insulin analog heterodimer each heterodimer including an A-chain polypeptide and a B-chain polypeptide, wherein the A-chain polypeptide and the B-chain polypeptide are linked together through interchain disulfide bonds;

wherein the first and second insulin or insulin analog heterodimers are covalently linked together through a linking moiety joining the side chain of an amino acid at or near the carboxy terminus of the two respective B-chain polypeptides; and

optionally wherein the amino terminus of at least one of the A-chain polypeptides and the B-chain polypeptides of the first insulin polypeptide or second insulin polypeptide is covalently linked to a substituent,

with the proviso that (1) the linking moiety does not include a disulfide bond and (2) when the amino terminus of the A-chain polypeptide and the B-chain polypeptide do not include a substituent then the linking moiety is not an oxalyl (C2) moiety, a suberyol (C8) moiety, or a dodecanedioyl (C12) moiety; or

an insulin receptor partial agonist comprising the formula

$$D^1\text{-}L\text{-}D^2$$

wherein D^1 and D^2 are each independently an insulin or insulin analog polypeptide, wherein each insulin polypeptide is a heterodimer comprising an A-chain polypeptide and a B-chain polypeptide linked together through interchain disulfide bonds;

L is a linking moiety wherein one end of the linker moiety is attached to an amino acid residue at or near the carboxyl group of D^1 and the other end of the linker moiety is attached to an amino acid residue at or near the carboxyl end of D^2 with the proviso that L does not include a disulfide linkage; and

optionally, wherein at least one of D^1 or D^2 includes a substituent attached to the amino terminus of the A-chain polypeptide or the B-chain polypeptide of D^1 or D^2;

with the proviso that (1) the linking moiety does not include a disulfide bond and (2) when the insulin or insulin analog is not a human insulin or insulin analog and the amino terminus of the A-chain polypeptide and the B-chain polypeptide do not include a substituent then the linking moiety is not an oxalyl (C2) moiety, a suberyol (C8) moiety, or a dodecanedioyl (C12) moiety; or

an insulin analog dimer comprising:

a first insulin analog heterodimer and a second insulin or insulin analog heterodimer each heterodimer including an A-chain polypeptide and a B-chain polypeptide, wherein the A-chain polypeptide and the B-chain polypeptide are linked together through interchain disulfide bonds;

wherein the first and second insulin or insulin analog heterodimers are covalently linked together through a linking moiety joining the side chain of an amino acid at or near the carboxy terminus of the two respective B-chain polypeptides;

wherein the insulin analog is selected from insulin lispro, insulin aspart, desB30 insulin, and insulin glargine; and

optionally wherein the amino terminus of at least one of the A-chain polypeptides and the B-chain polypeptides of the first insulin polypeptide or second insulin polypeptide is covalently linked to a substituent,

with the proviso that the linking moiety does not include a disulfide bond; or

an insulin analog dimer comprising the formula

$$D^1\text{-}L\text{-}D^2$$

wherein D^1 and D^2 are each independently an insulin or insulin analog polypeptide, wherein each insulin polypeptide is a heterodimer comprising an A-chain polypeptide and a B-chain polypeptide linked together through interchain disulfide bonds;

L is a linking moiety wherein one end of the linker moiety is attached to an amino acid residue at or near the carboxyl group of D^1 and the other end of the linker moiety is attached to an amino acid residue residue at or near the carboxyl end of D^2 with the proviso that L does not include a disulfide linkage;

wherein the insulin analog is selected from insulin lispro, insulin aspart, desB30 insulin, and insulin glargine; and

optionally, wherein at least one of D^1 or D^2 includes a substituent attached to the amino terminus of the A-chain polypeptide or the B-chain polypeptide of D^1 or D^2;

with the proviso that the linking moiety does not include a disulfide bond.

8. The insulin receptor partial agonist of claim 7, wherein the insulin receptor partial agonist comprises a D^1 and D^2 which are the same or a D^1 and D^2 which are different.

9. The insulin receptor partial agonist of claim 7, wherein the insulin receptor partial agonist comprises a linking moiety that covalently links D^1 and D^2 via the epsilon amino group of a lysine residue at or near the carboxy terminus of D^1 and D^2.

10. The insulin receptor partial agonist of claim 7, wherein the insulin receptor partial agonist comprises a substituent which has a general formula RC(O)-, where R

can be R'CH2, R'NH, R'O, and R' can be H, linear alkyl chain, amino acid, peptide, polyethylene glycol (PEG), and a saccharide.

11. The insulin receptor partial agonist of claim 7, wherein the insulin receptor partial agonist comprises a substituent selected from the group consisting of acetyl, phenylacetyl , carbamoyl, *N*-alkyl carbamoyl, isobutyl, methoxy acetyl, glycine, aminoethylglucose (AEG), AEG-C6, PEG1, PEG2, *N*-dimethyl, and alkoxycarbonyl.

12. The insulin receptor partial agonist of claim 7, wherein insulin receptor partial agonist comprises a D^1 and D^2 which are independently selected from the group consisting of native human insulin, insulin lispro, insulin aspart, desB30 insulin, and insulin glargine.

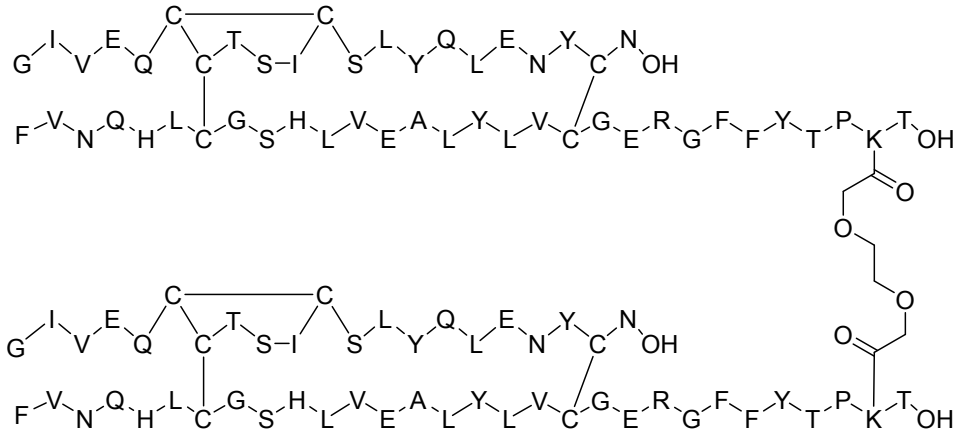
13. The insulin receptor partial agonist of claim 7, wherein each A-chain polypeptide independently comprises the amino acid sequence $GX_2X_3EQCCX_8SICSLYQLX_{17}NX_{19}CX_{23}$ (SEQ ID NO:3) and each B-chain polypeptide independently comprises the amino acid sequence $X_{25}LCGX_{29}X_{30}LVEALYLVCGERGFX27YTX_{31}X_{32}$ (SEQ ID NO:4) or $X_{22}VNQX_{25}X_{26}CGX_{29}X_{30}LVEALYLVCGERGFX_{27}YTX_{31}X_{32}X_{33}X_{34}X_{35}$ (SEQ ID NO:5) wherein X_2 is isoleucine or threonine; X_3 is valine, glycine, or leucine; X_8 is threonine or histidine; X_{17} is glutamic acid or glutamine; X_{19} is tyrosine, 4-methoxy-phenylalanine, alanine, or 4-amino phenylalanine; X_{23} is asparagine or glycine; X_{22} is or phenylalanine and desamino-phenylalanine; X_{25} is histidine or threonine; X26 is leucine or glycine; X_{27} is phenylalanine or aspartic acid; X_{29} is alanine, glycine, or serine; X_{30} is histidine, aspartic acid, glutamic acid, homocysteic acid, or cysteic acid; X_{31} is aspartic acid, proline, or lysine; X_{32} is lysine or proline; X_{33} is threonine, alanine, or absent; X_{34} is arginine or absent; and X_{35} is arginine or absent; with the proviso at least one of X_{31} or X_{32} is lysine.

14. The insulin receptor partial agonist of claim 7, wherein the linking moiety comprises a bivalent, straight or branched, saturated or unsaturated, optionally substituted C1-C20 hydrocarbon chain wherein one or more methylene units are optionally and independently replaced by -O-, -S-, -N(R)-, -C(O)-, C(O)O-, OC(O)-, -N(R)C(O)-, -C(O)N(R)-, -S(O)-, -$S(O)_2$-, -N(R)SO_2-, SO_2N(R)-, a heterocyclic group, an aryl group, or a heteroaryl group, wherein each occurrence of R independently comprises hydrogen, a suitable protecting group, an acyl moiety, arylalkyl moiety, aliphatic moiety, aryl moiety, heteroaryl moiety, or heteroaliphatic moiety, and poly(ethylene glycol) (PEG).

15. The insulin receptor partial agonist of claim 7, wherein the linking moiety comprises an alkyldioyl, -C(O)$(CH_2)_n$C(O)-, wherein n = 0-4, an acyl moiety, -C(O)RC(O)-, where R is alkyl chain, poly(ethylene glycol) (PEG) chain, amide-containing chain, triazole(s)-containing chain, cyclooctyne-containing moiety, a substituted acyl chain, or a polyethylene glycol (PEG) chain.

16. A composition comprising the insulin receptor partial agonist of any one of the above claims and a pharmaceutically acceptable carrier.

17. A compound selected from the group consisting of



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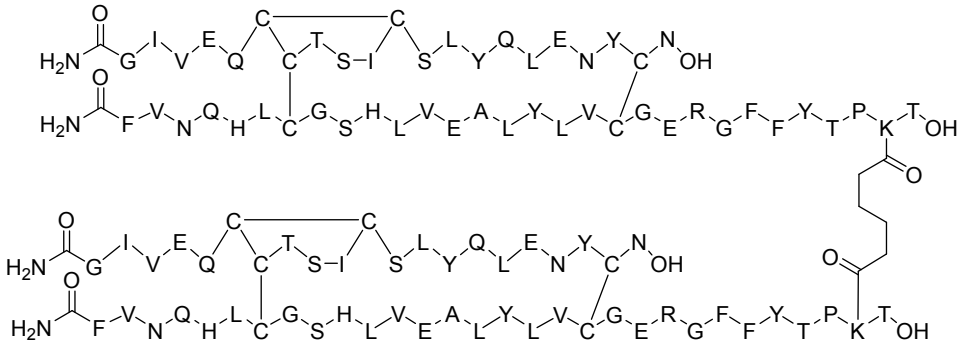

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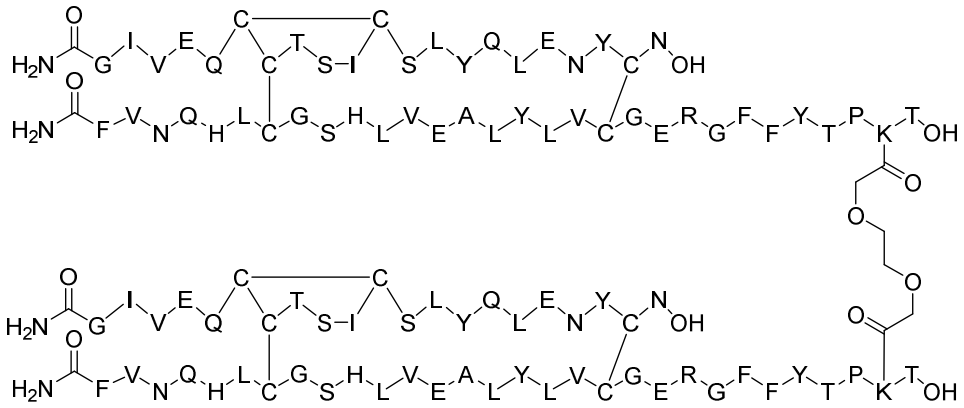

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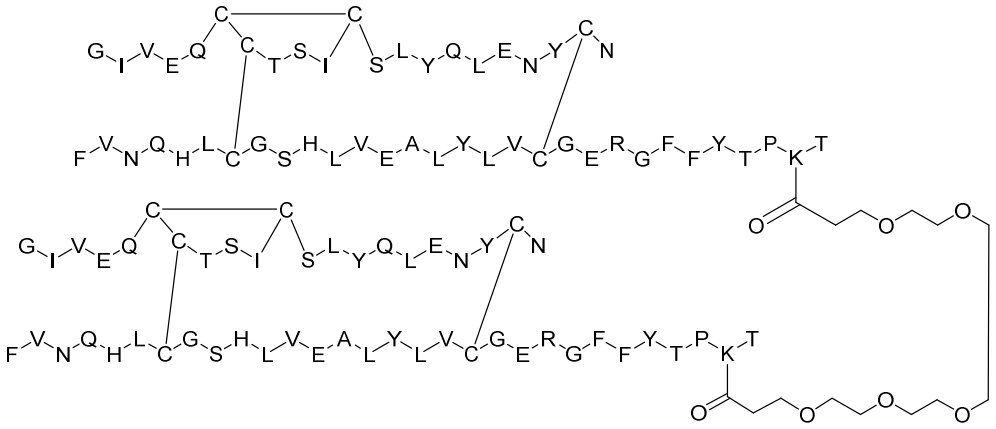

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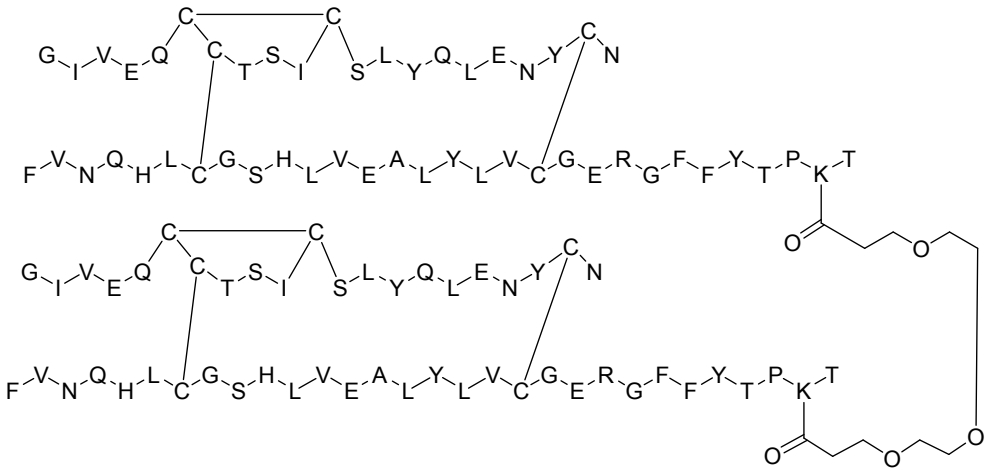

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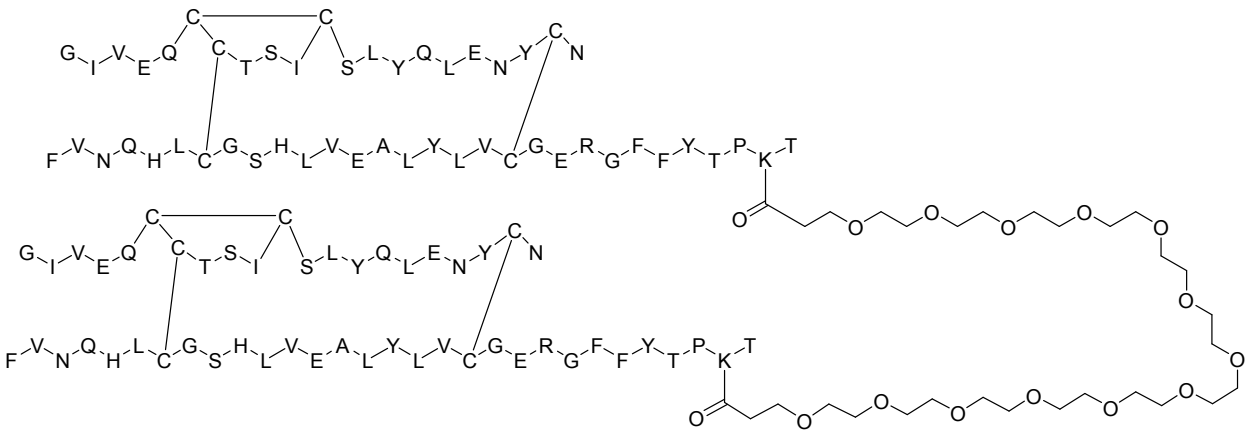

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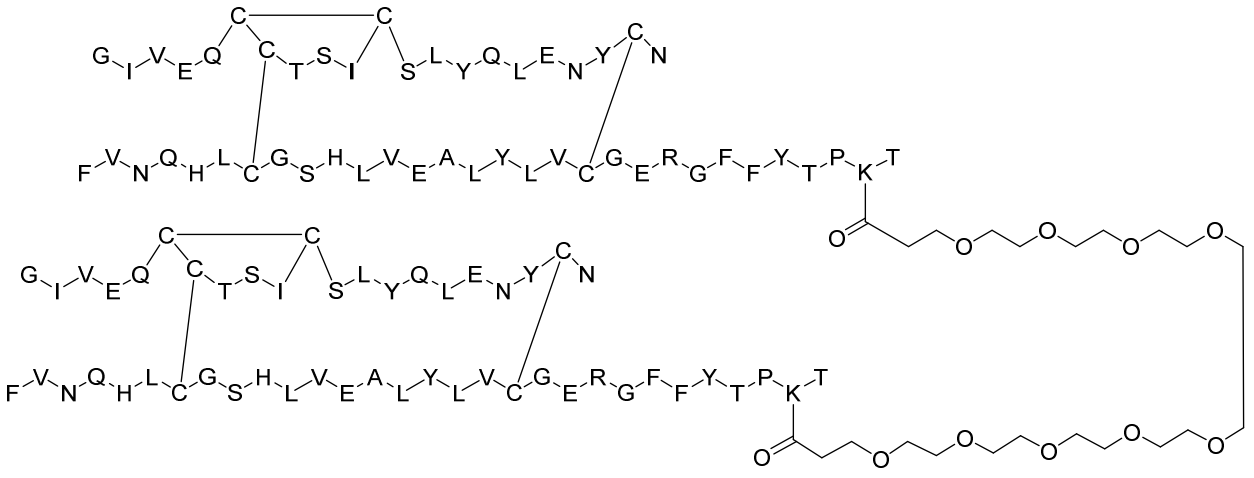

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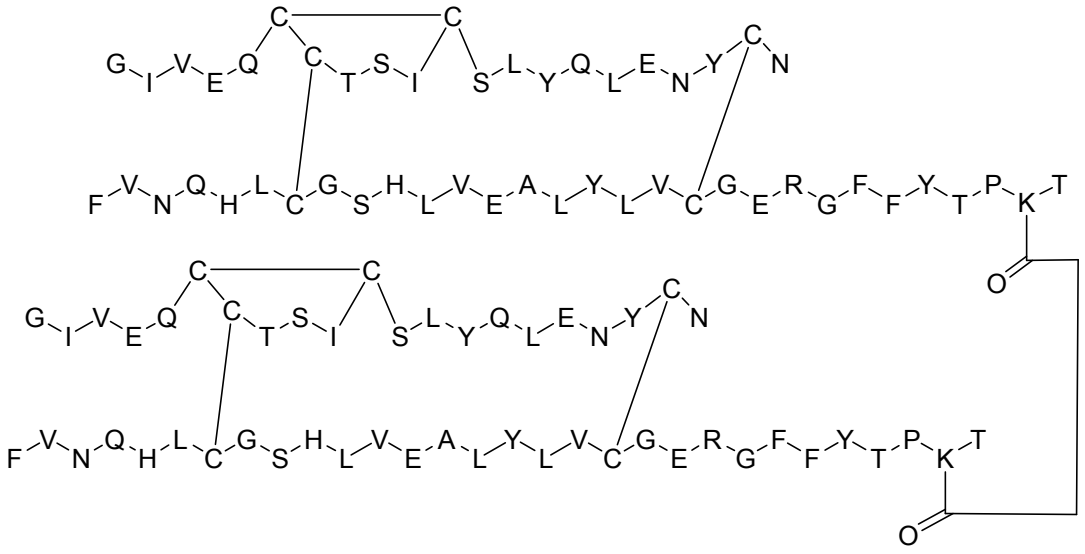
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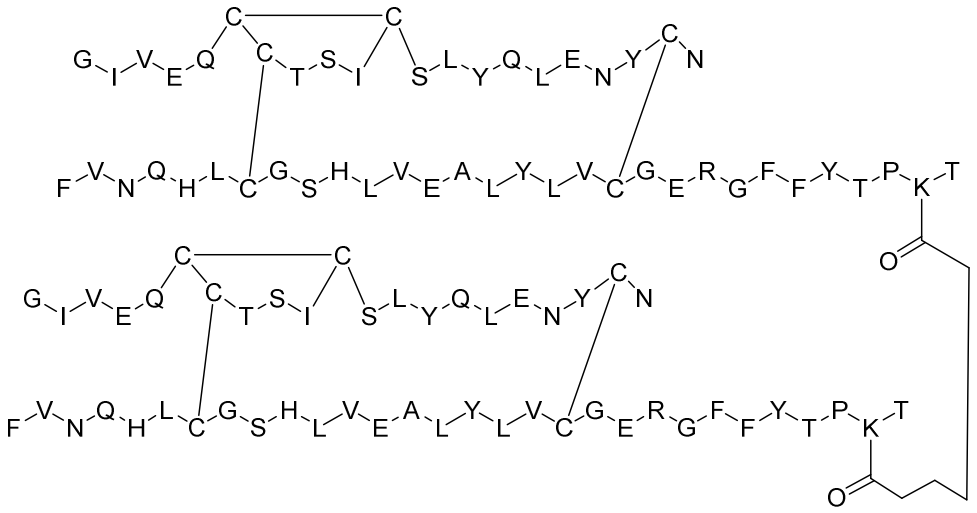

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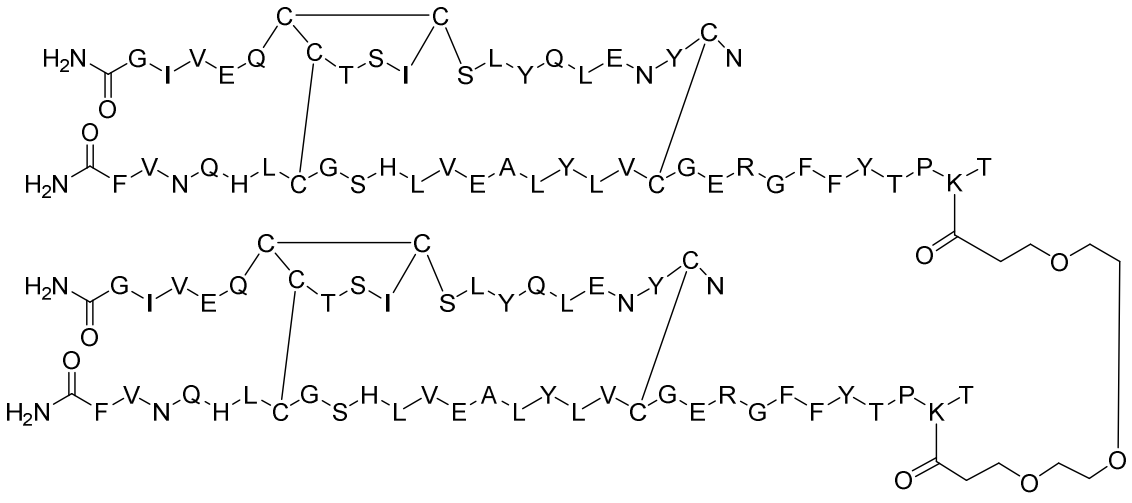

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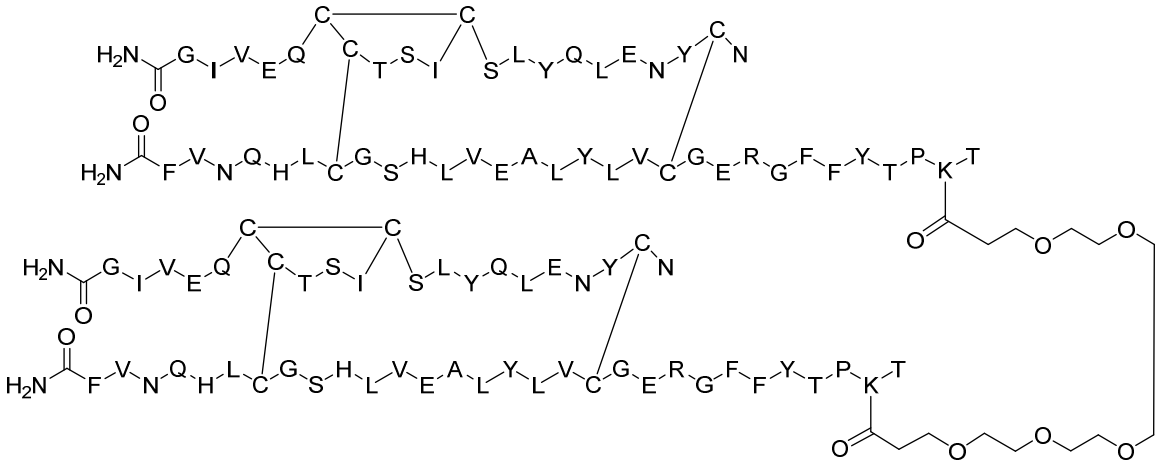

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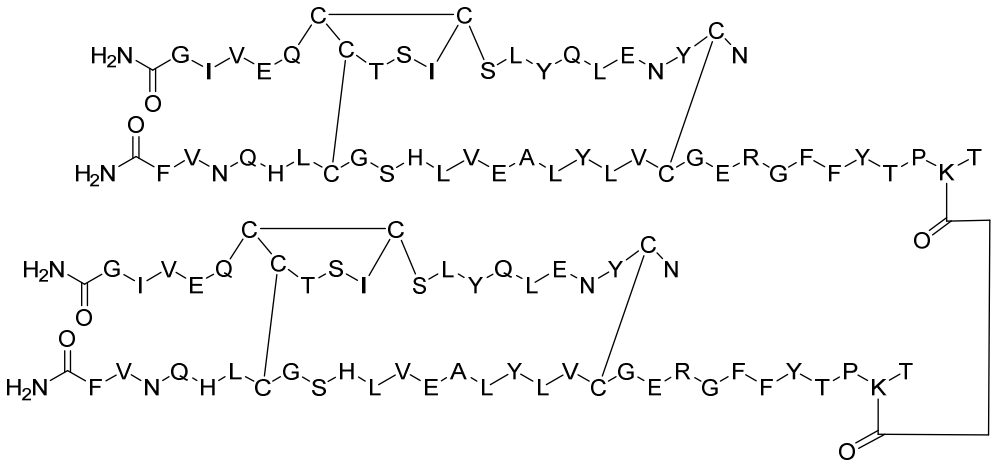

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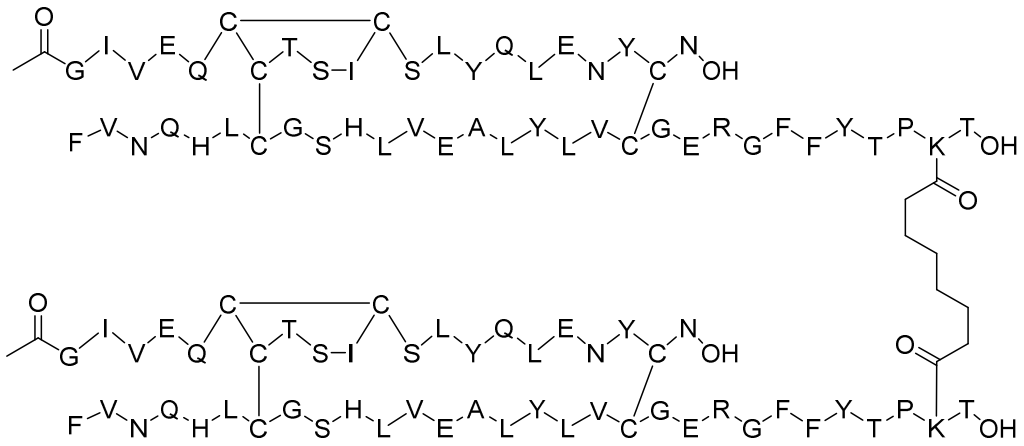

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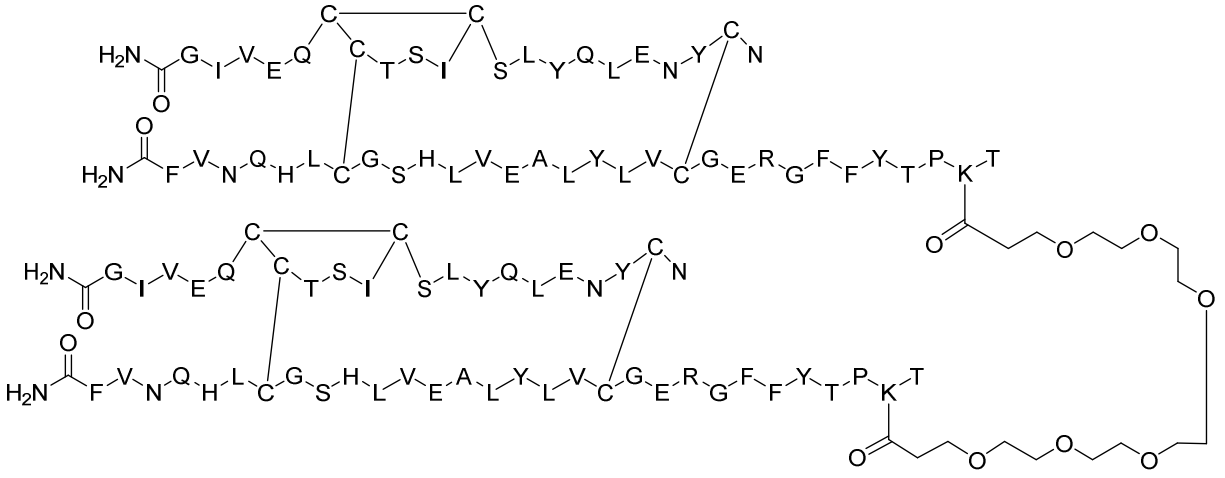

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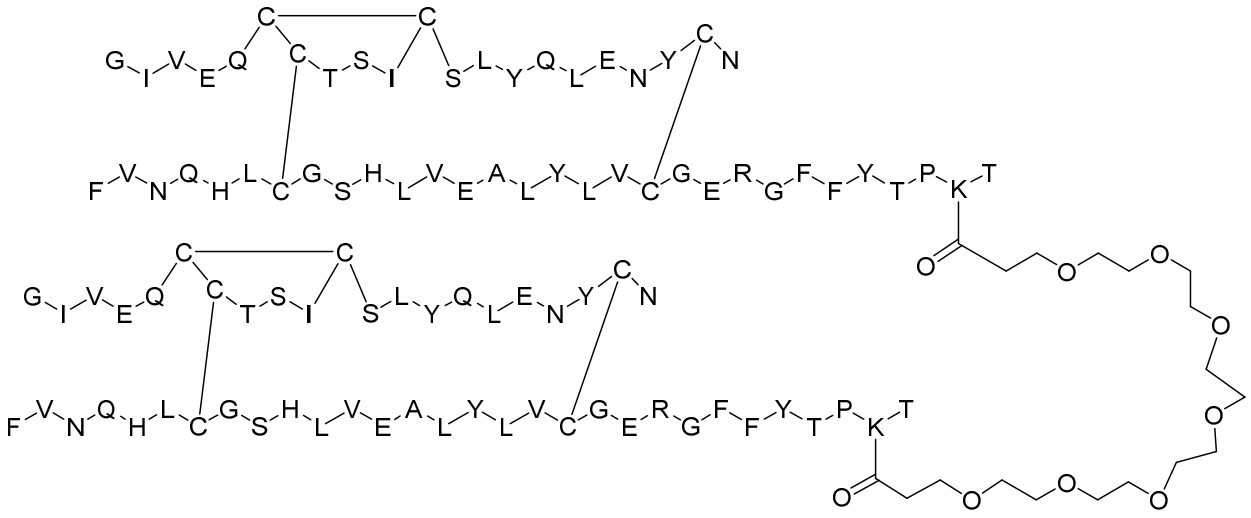

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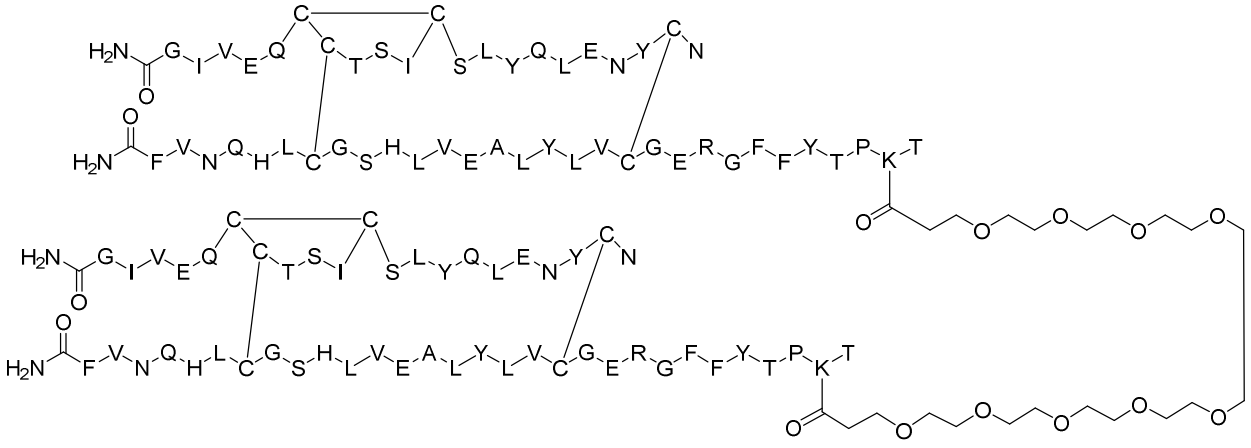

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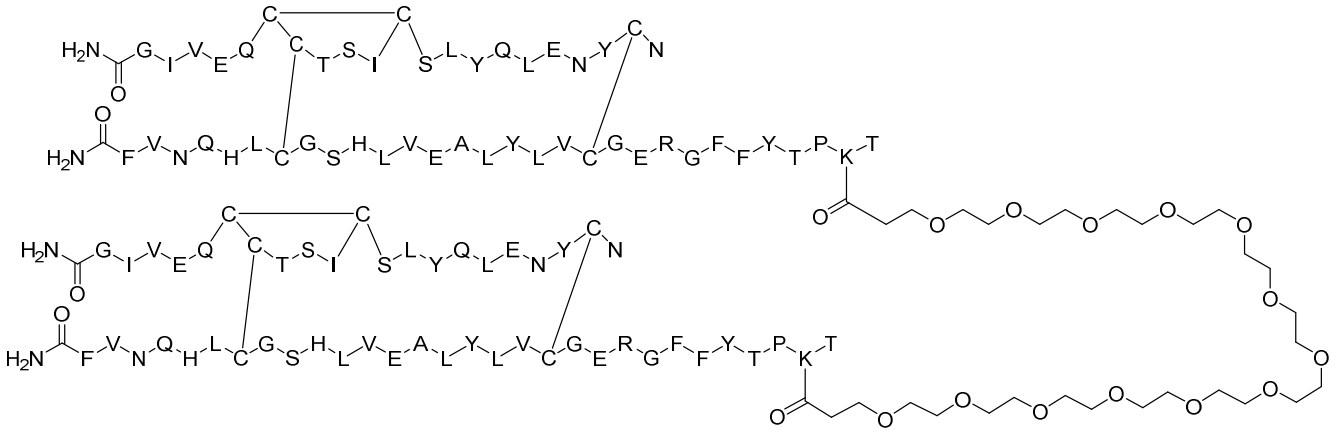

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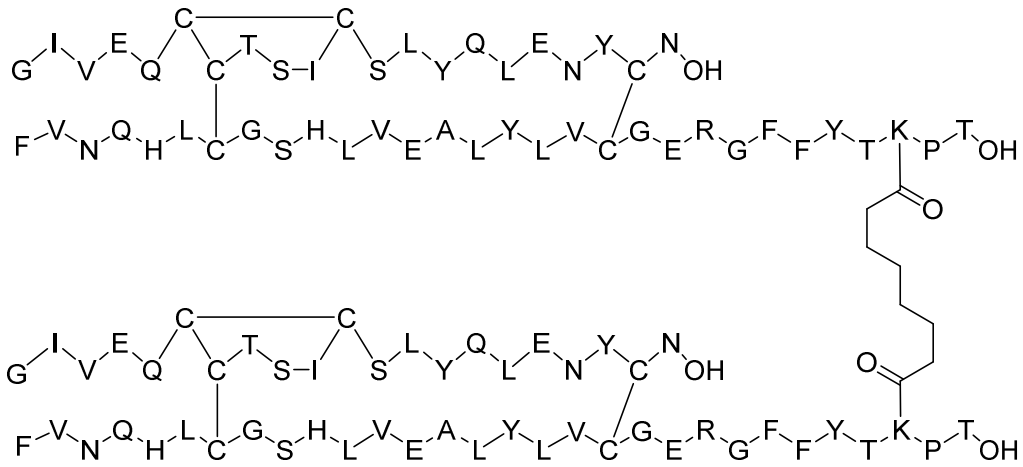

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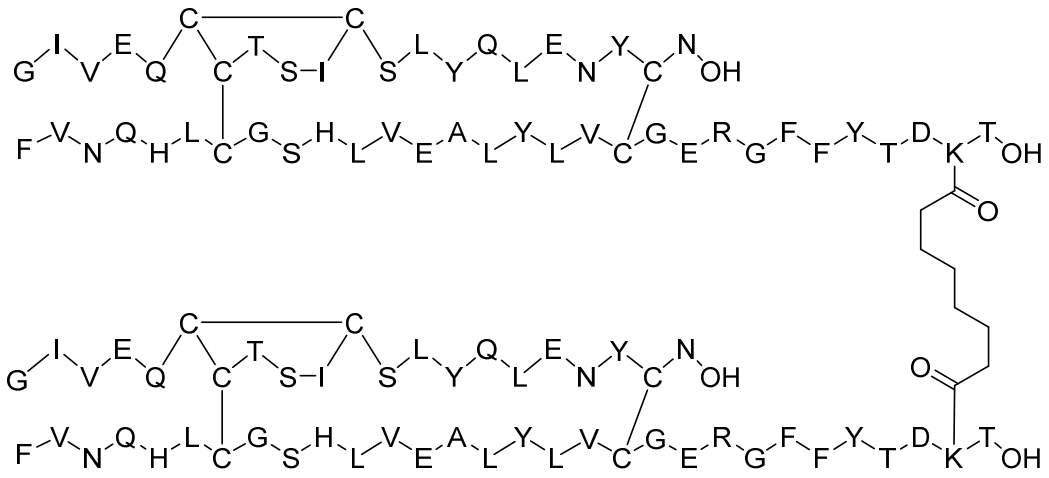

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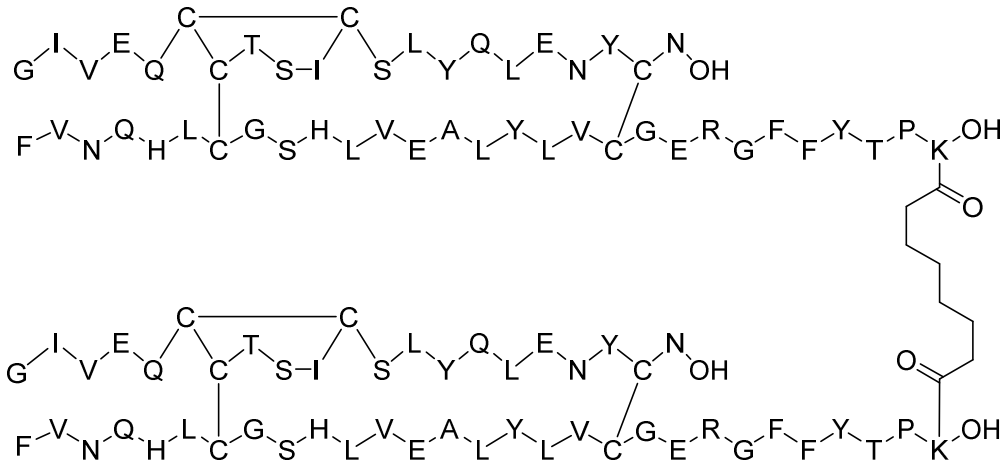

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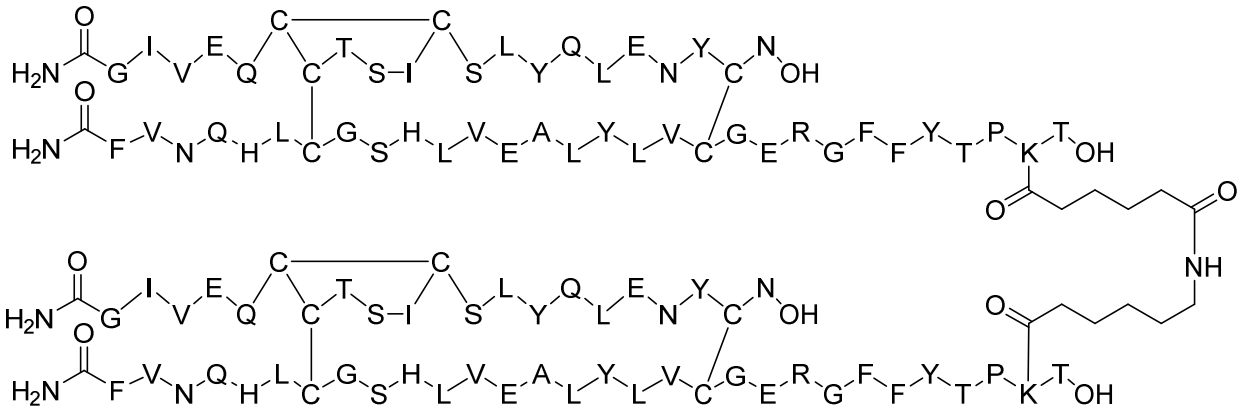

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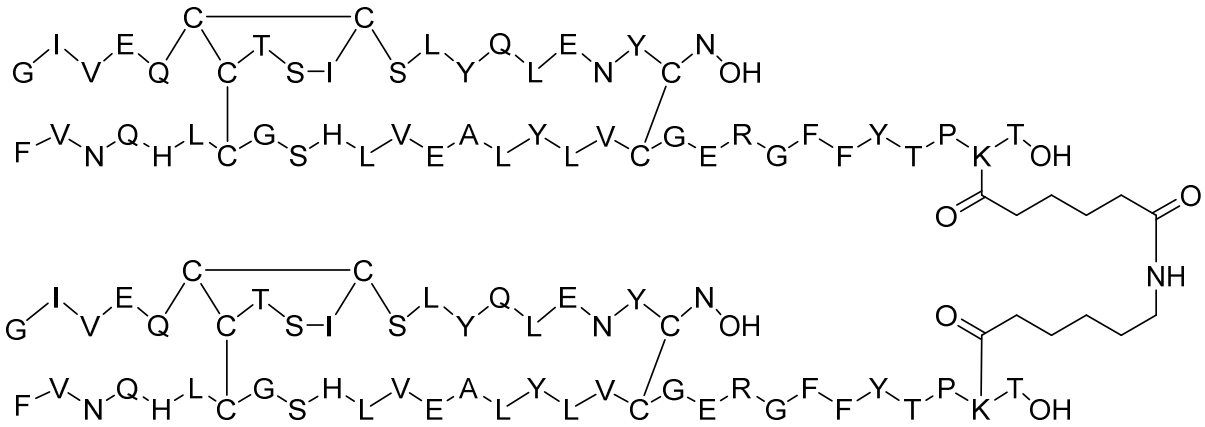

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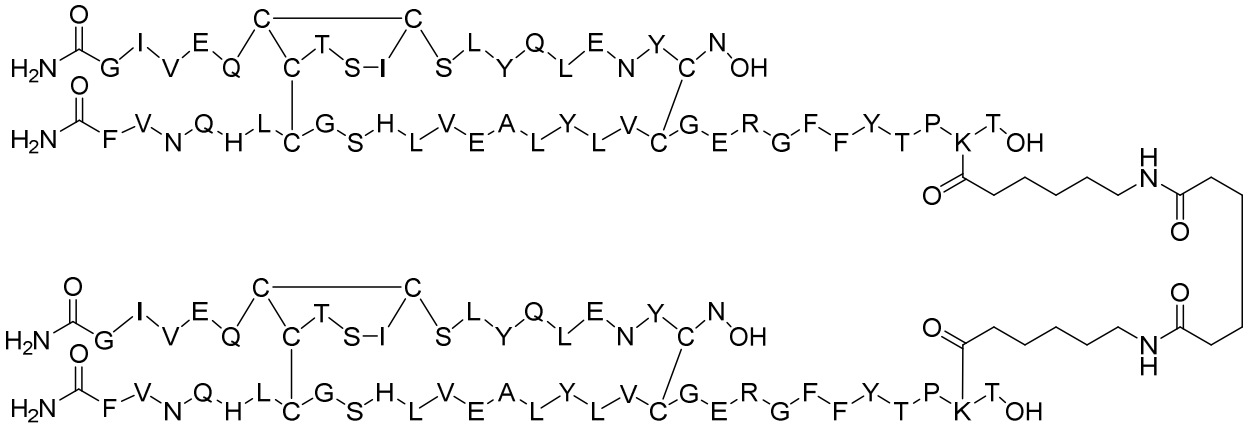

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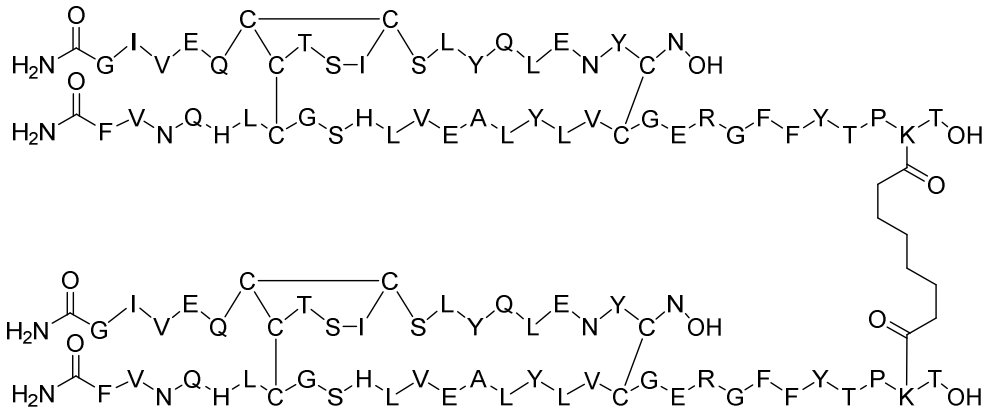

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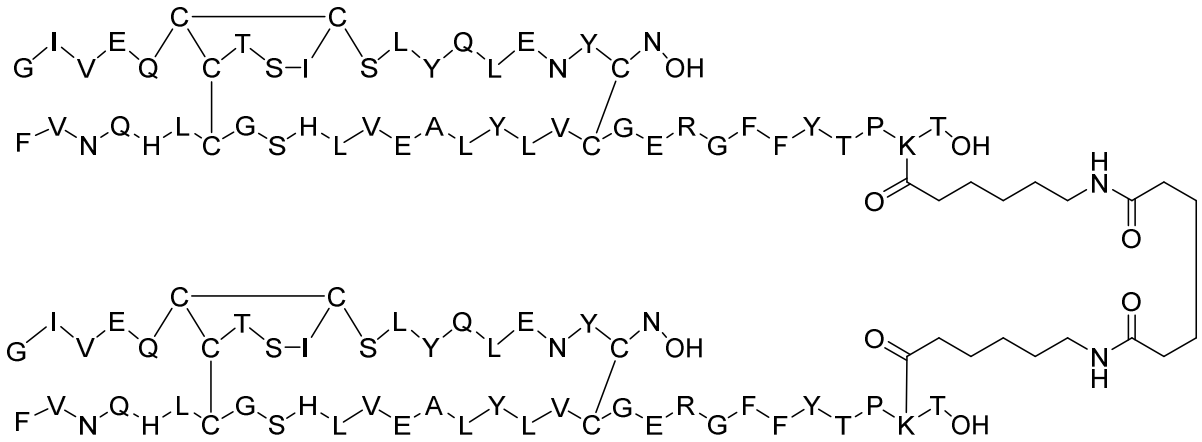

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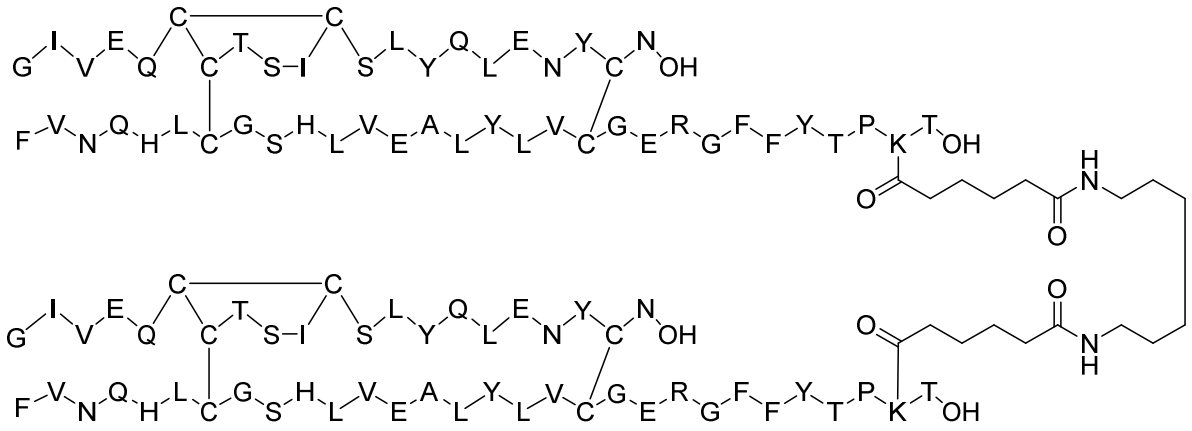

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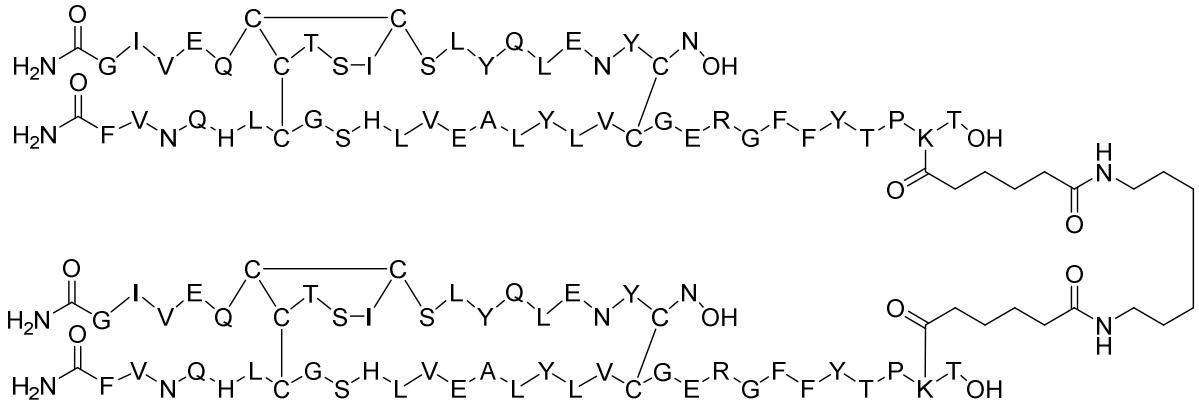

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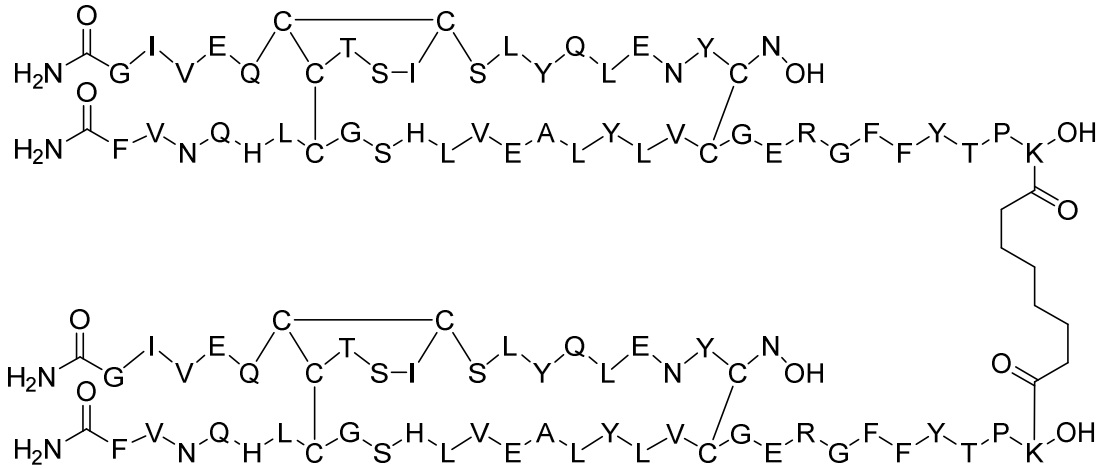

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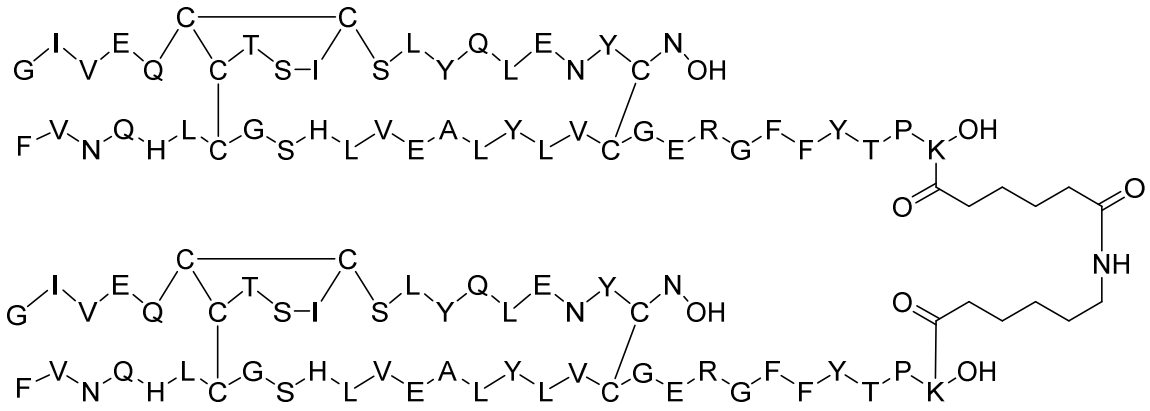

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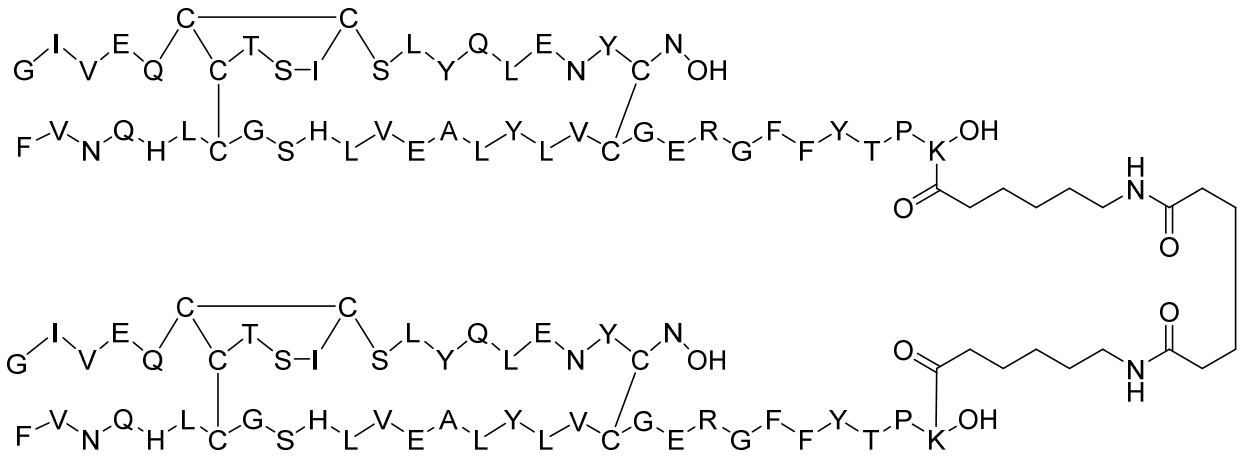

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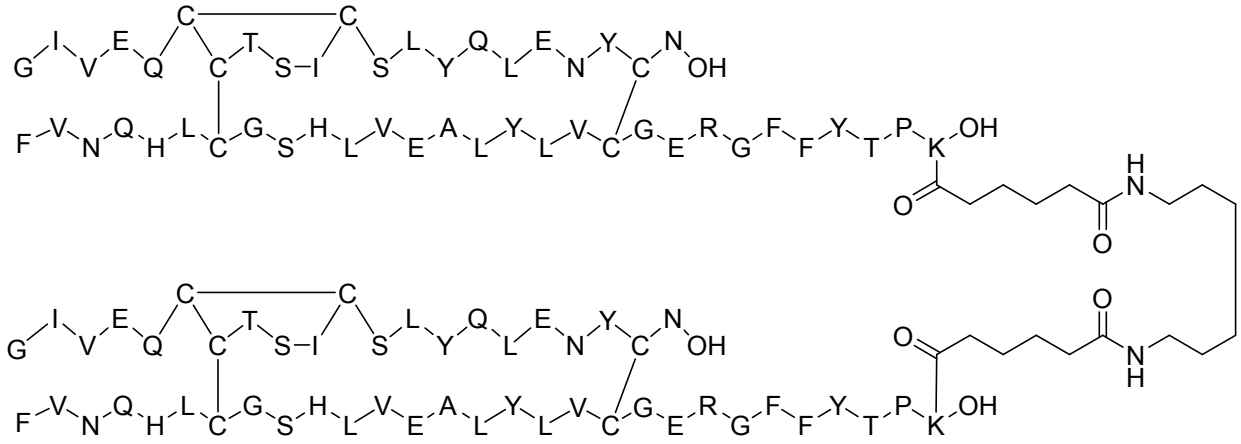

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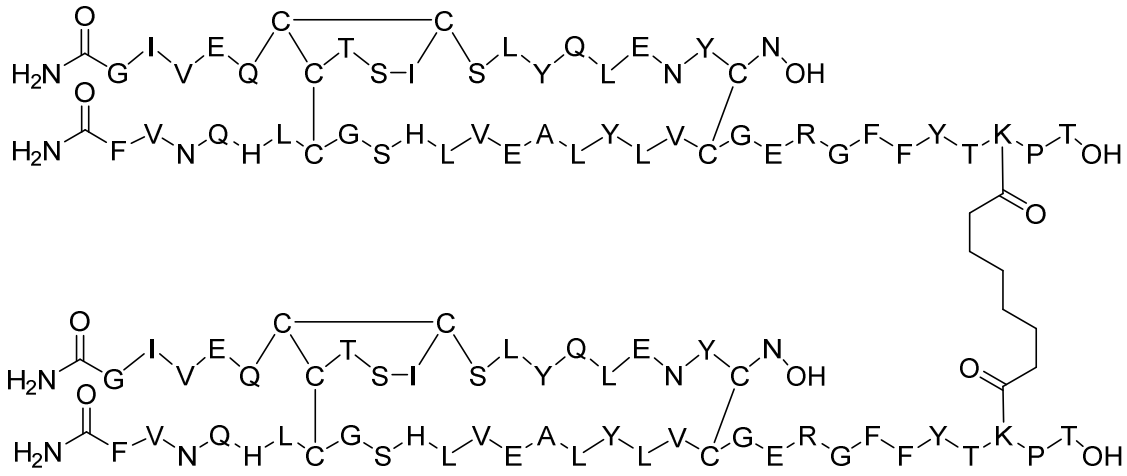

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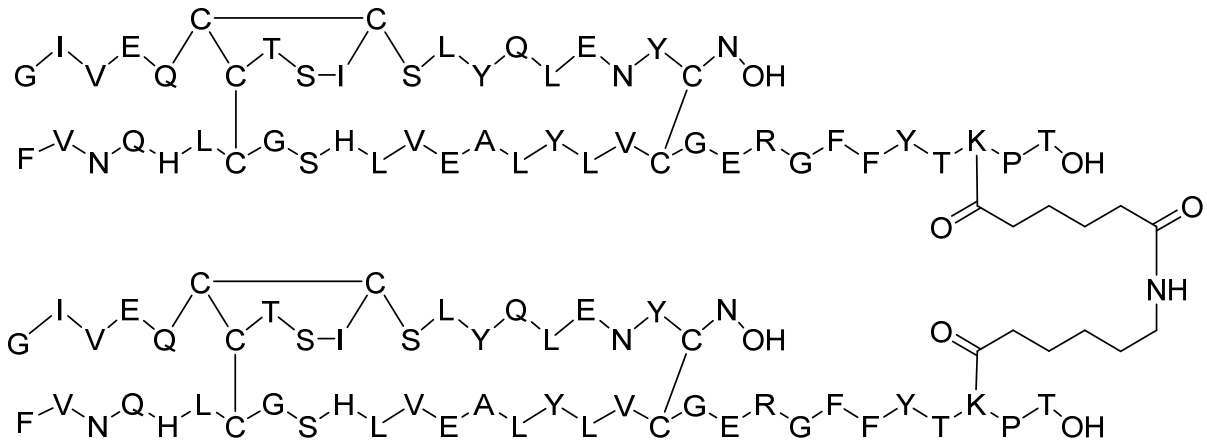

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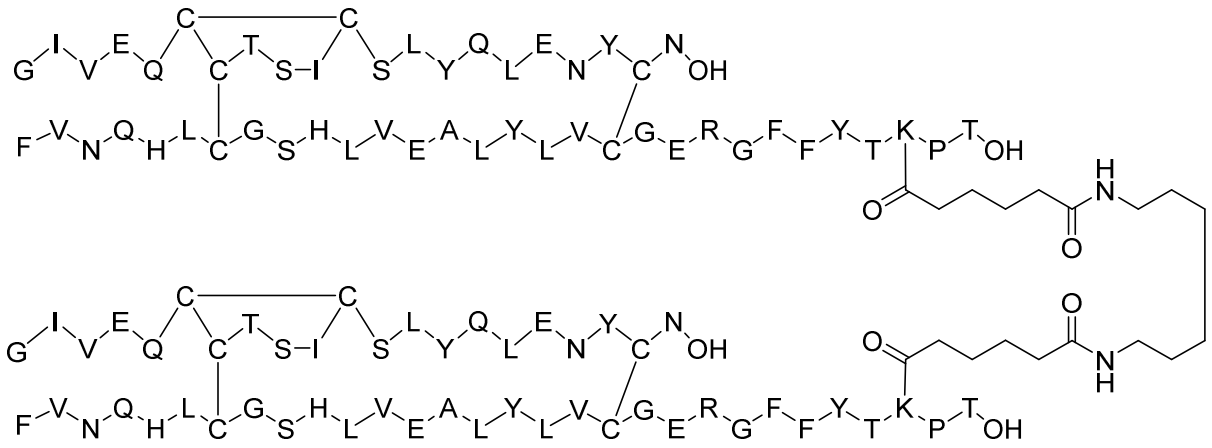

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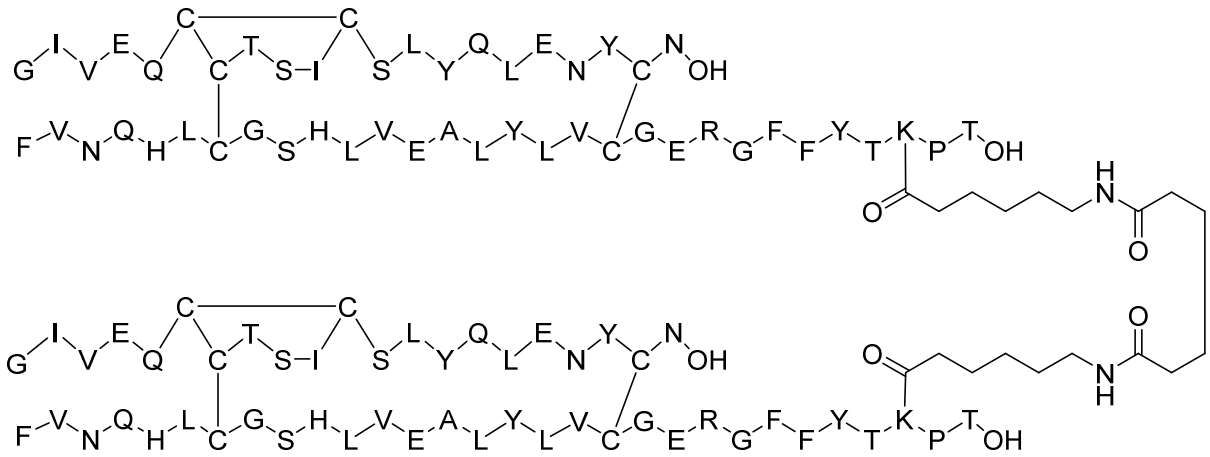

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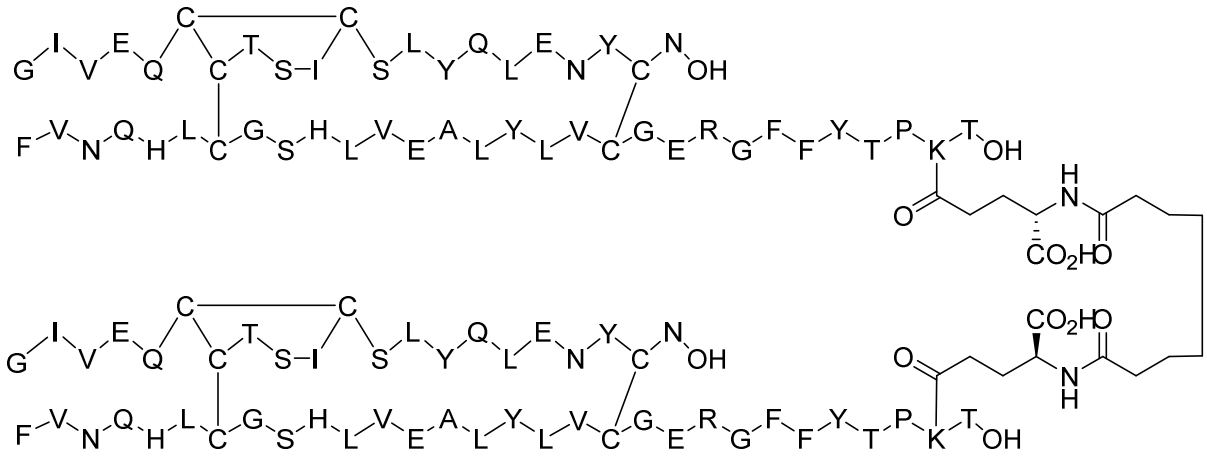

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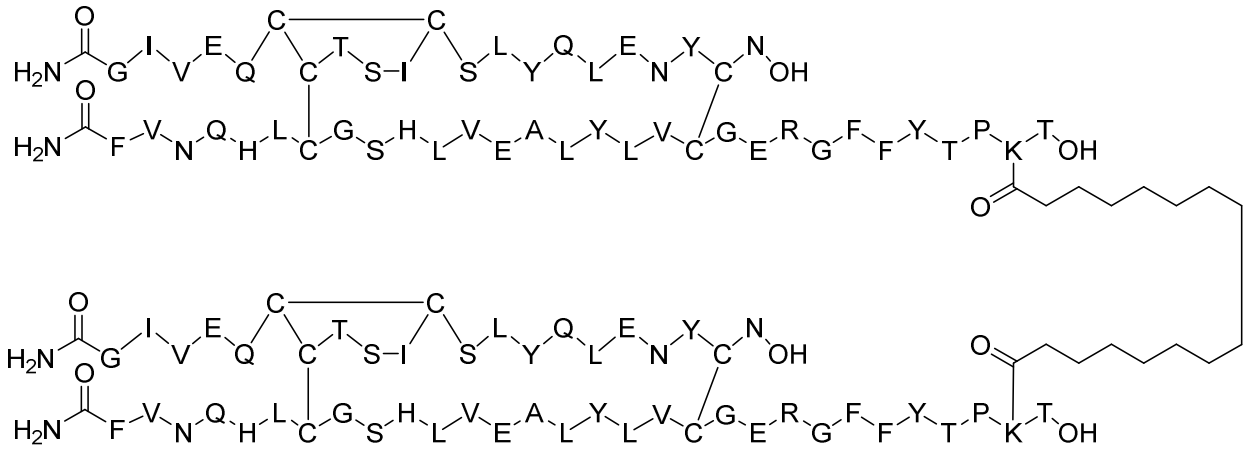

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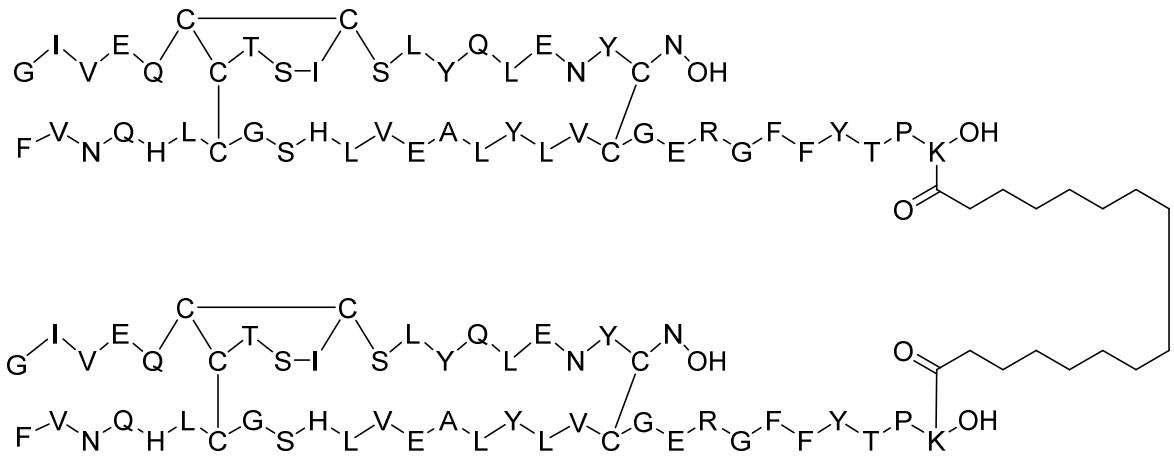

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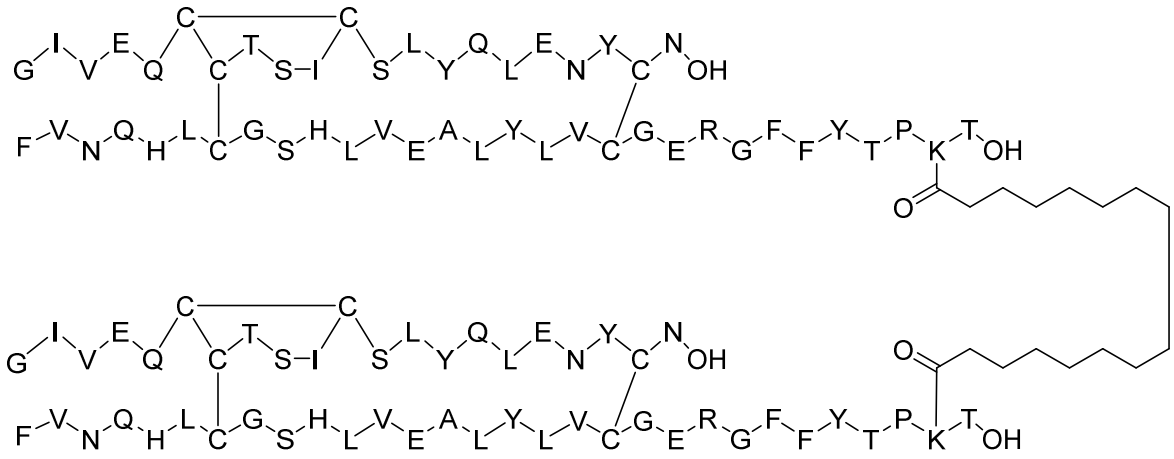

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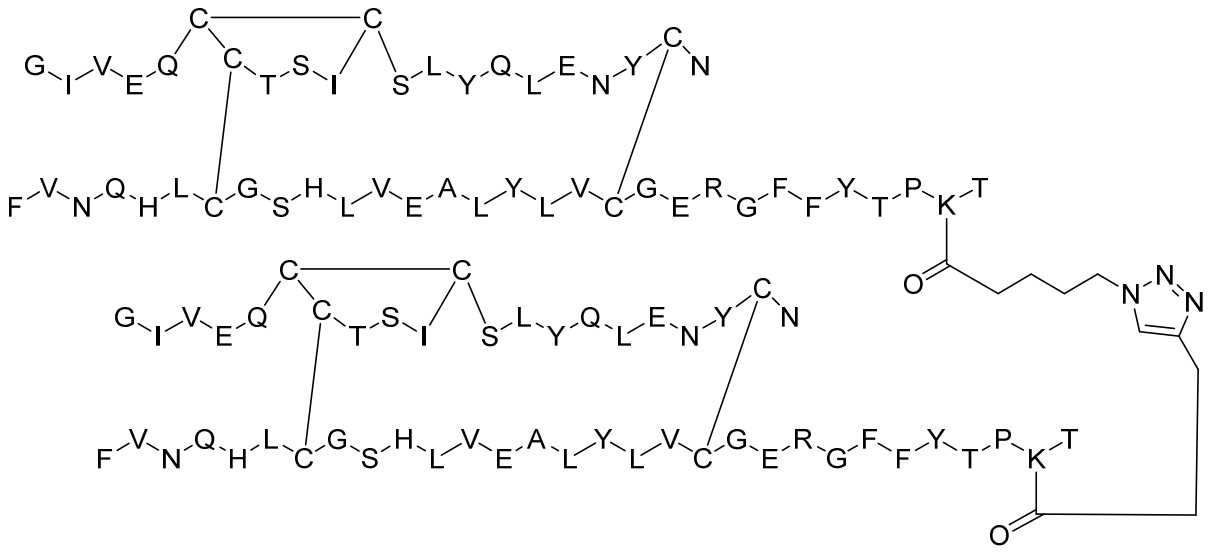

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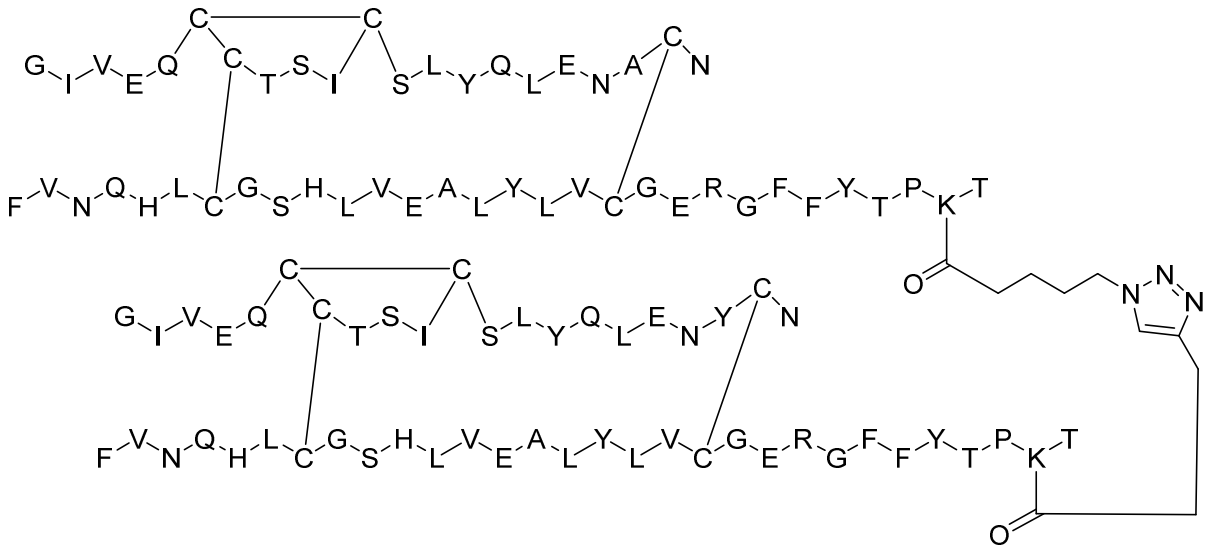

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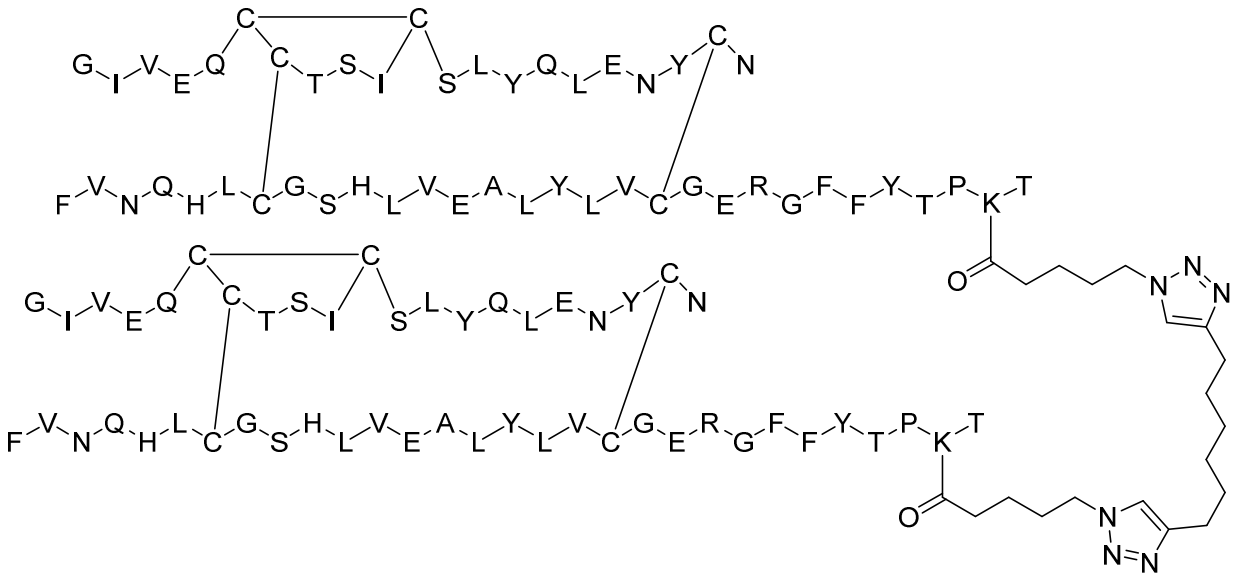

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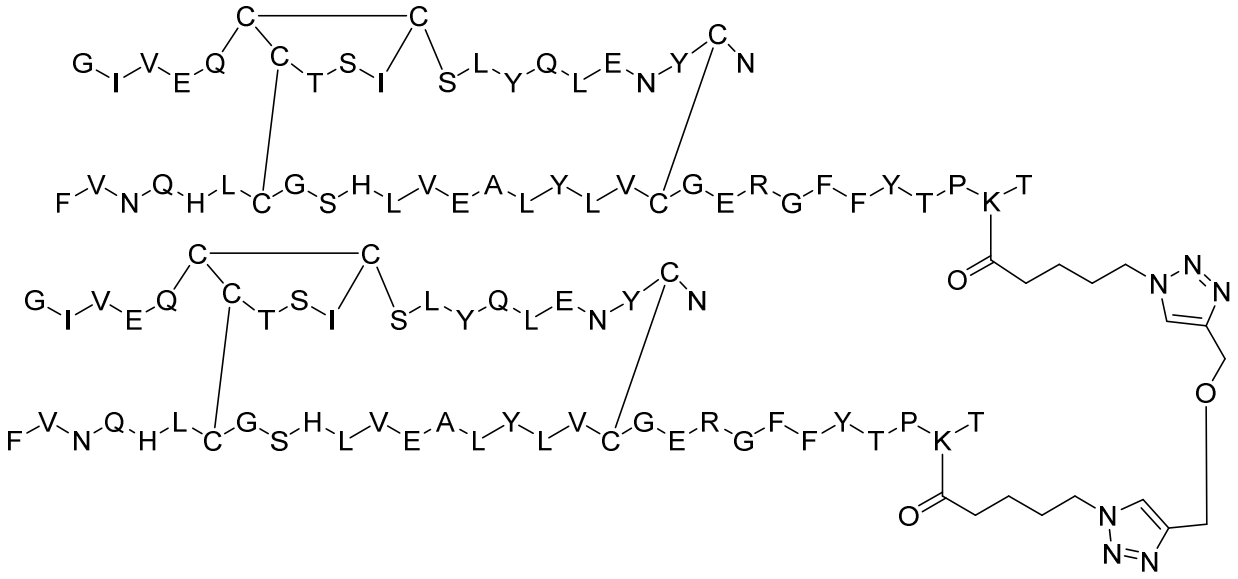

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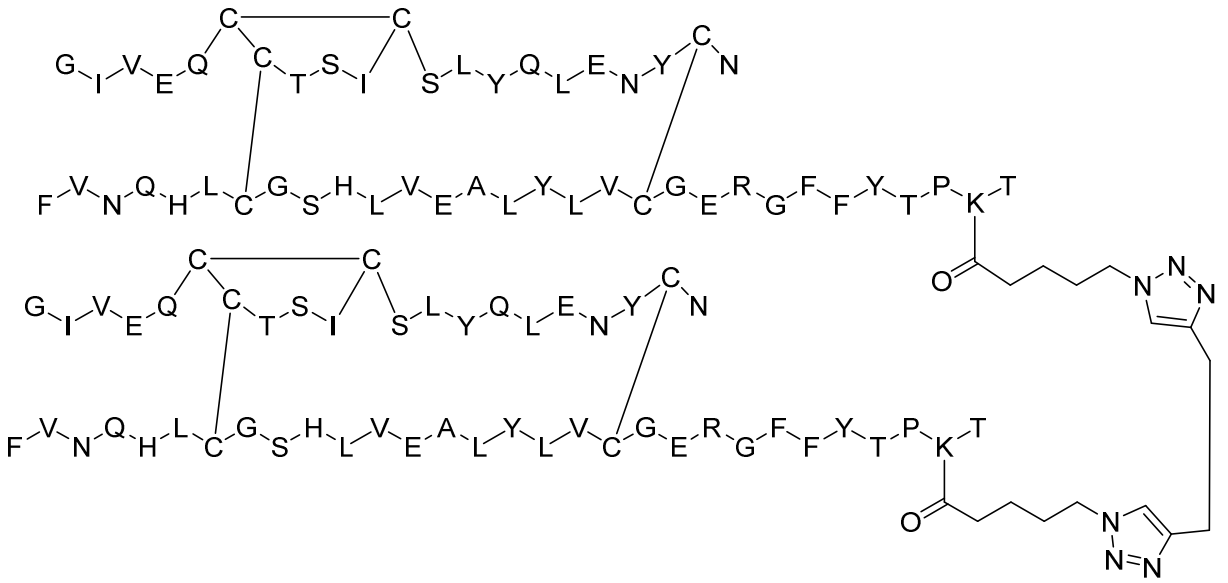

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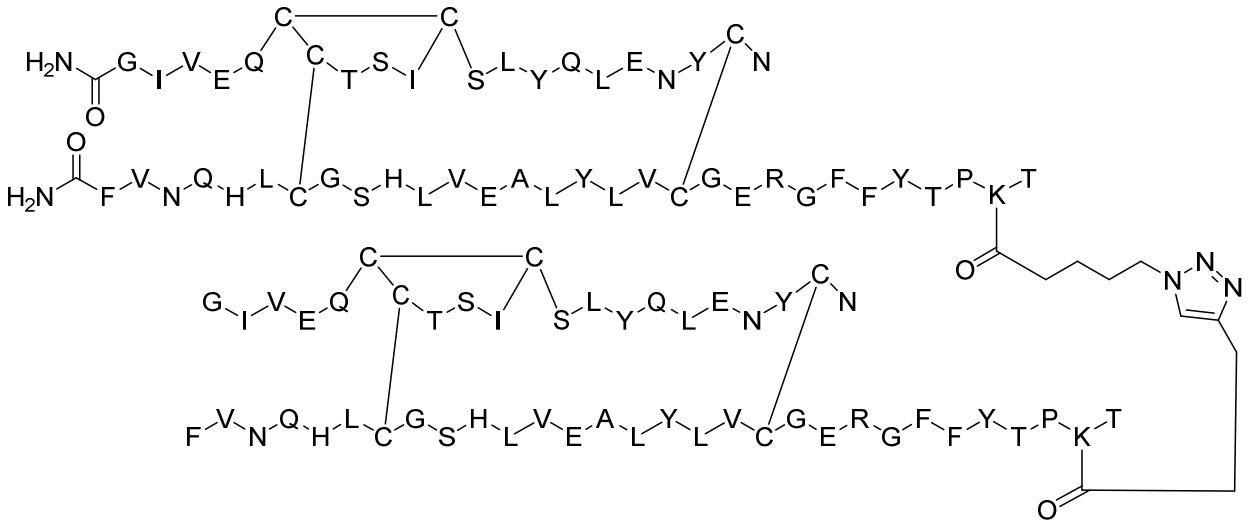

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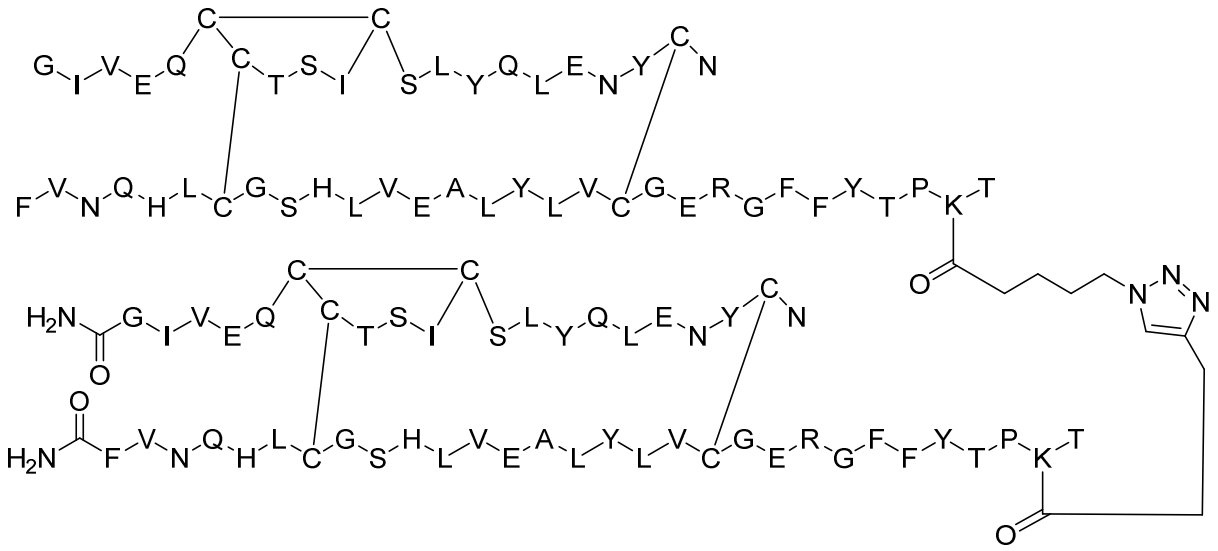

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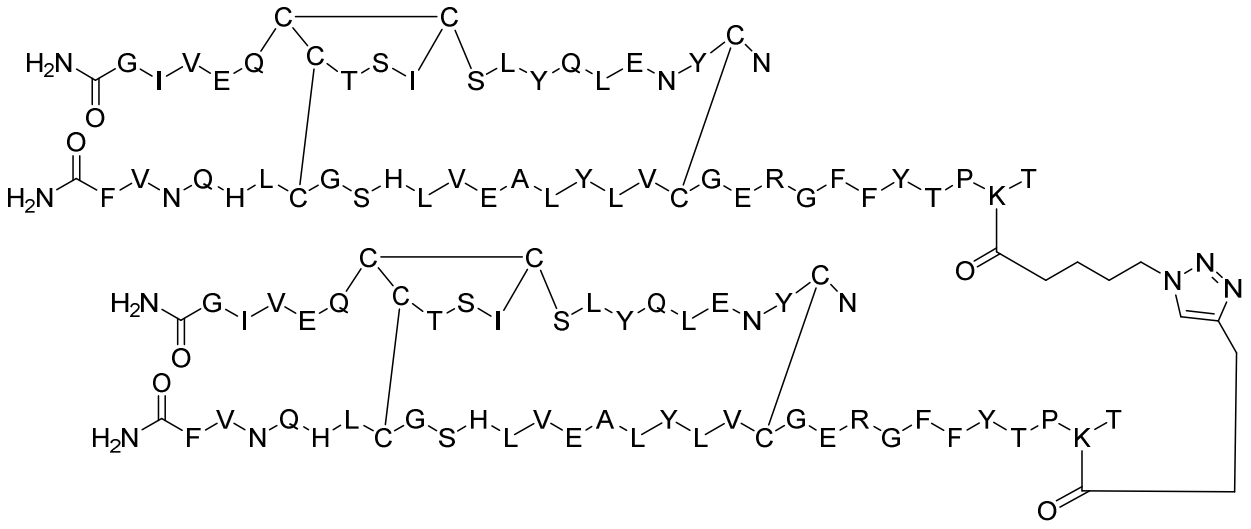

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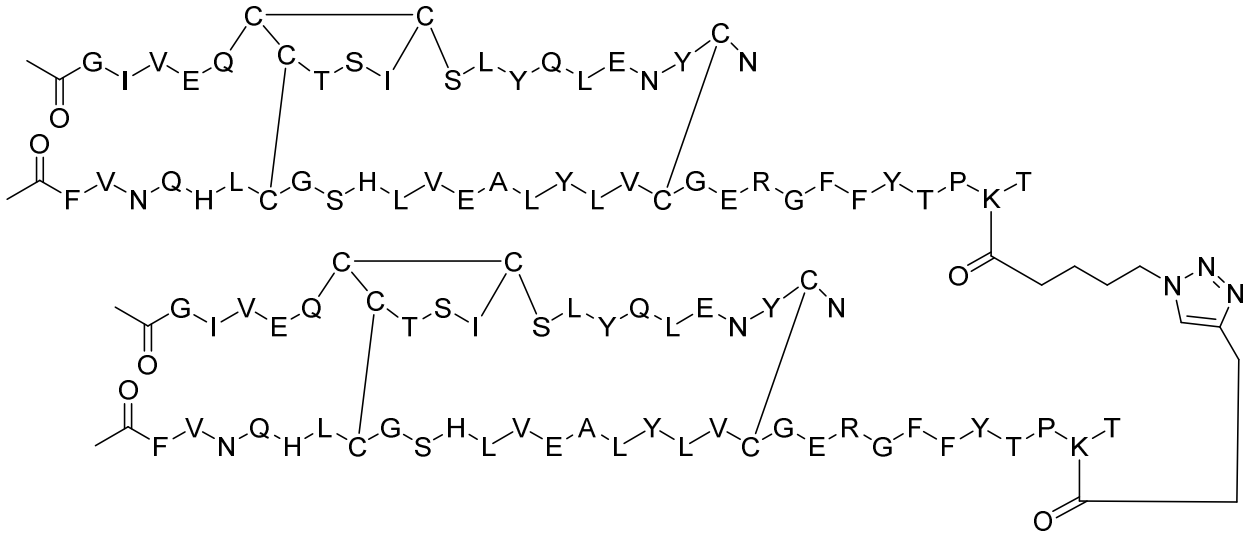

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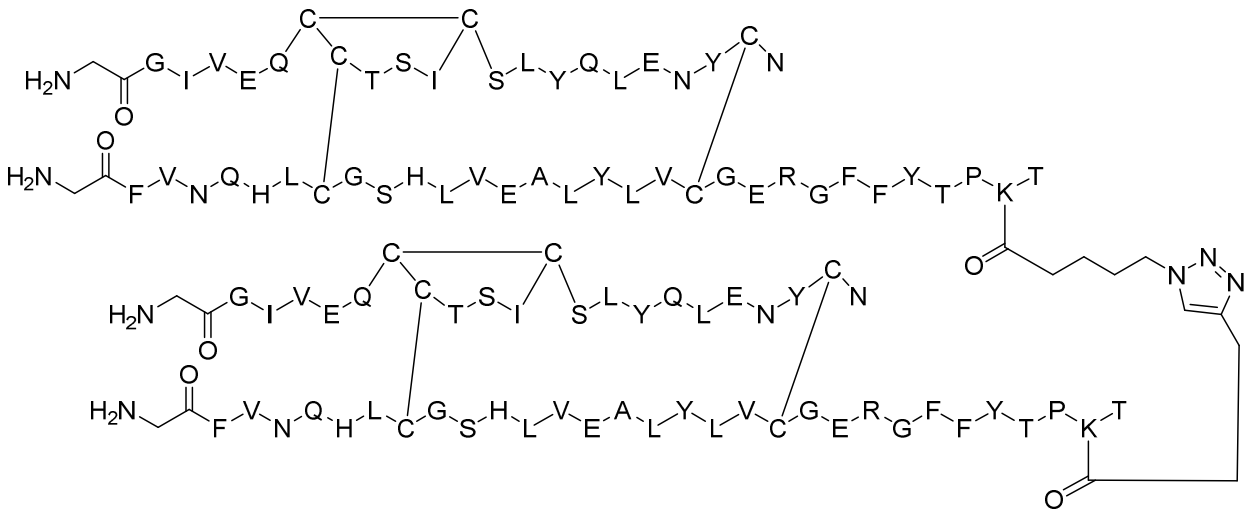

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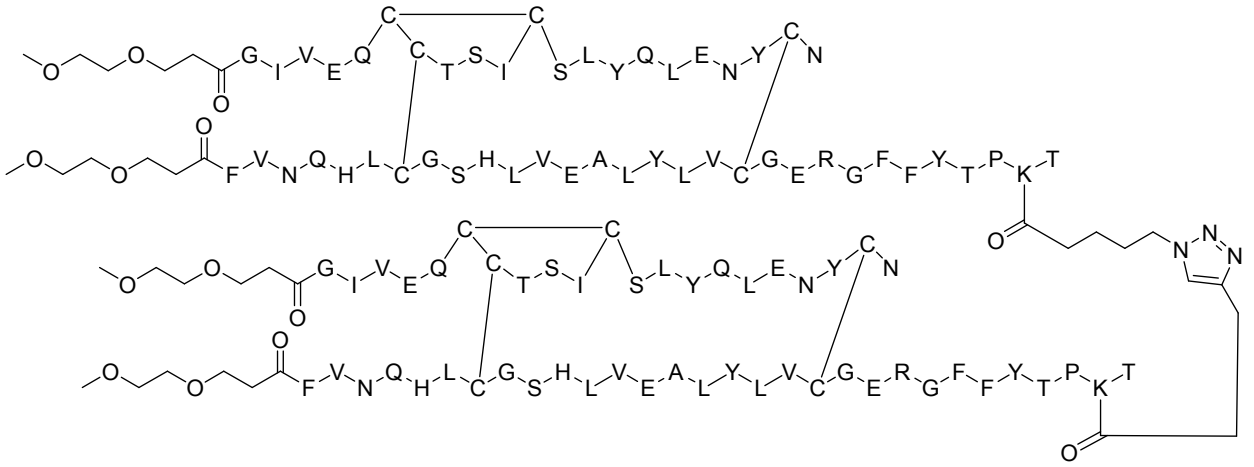

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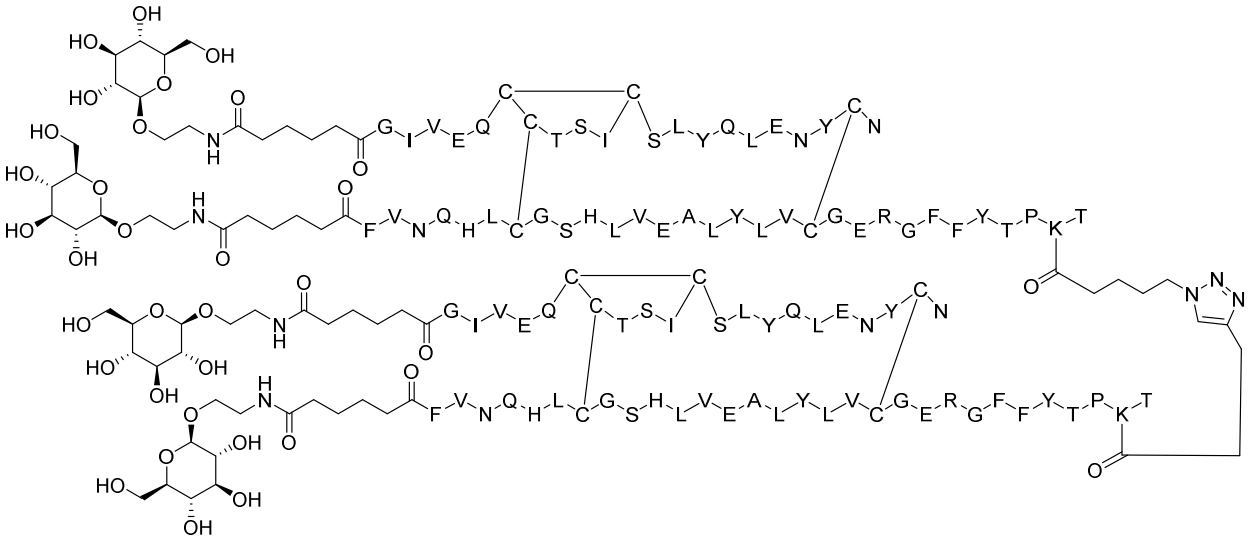

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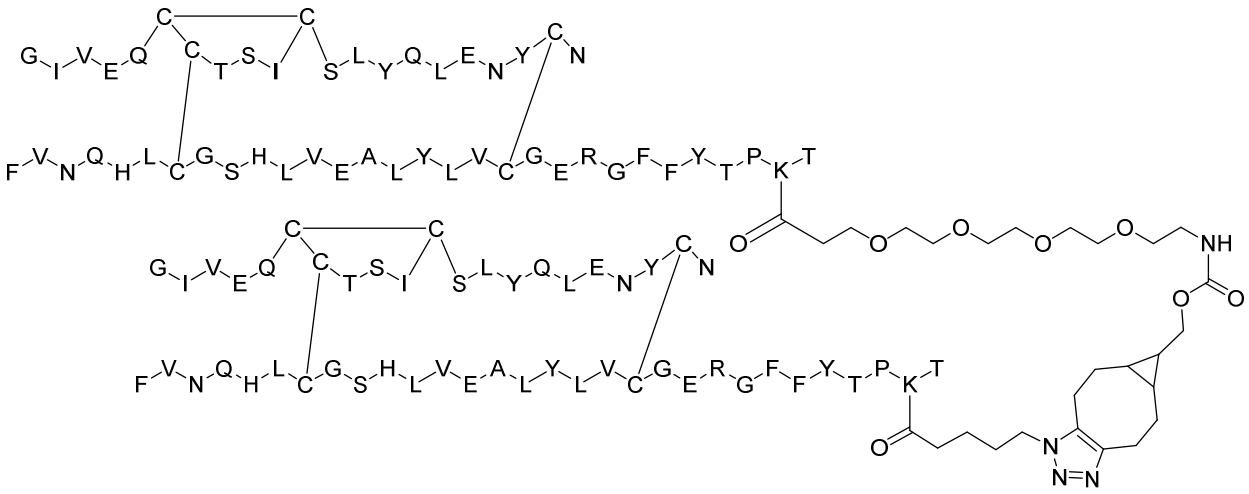

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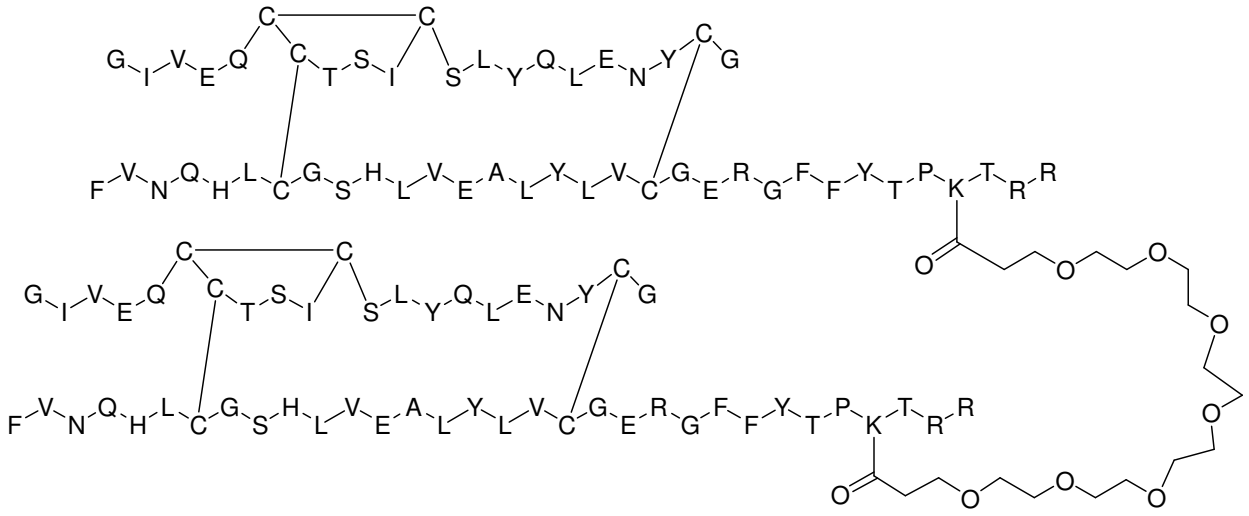

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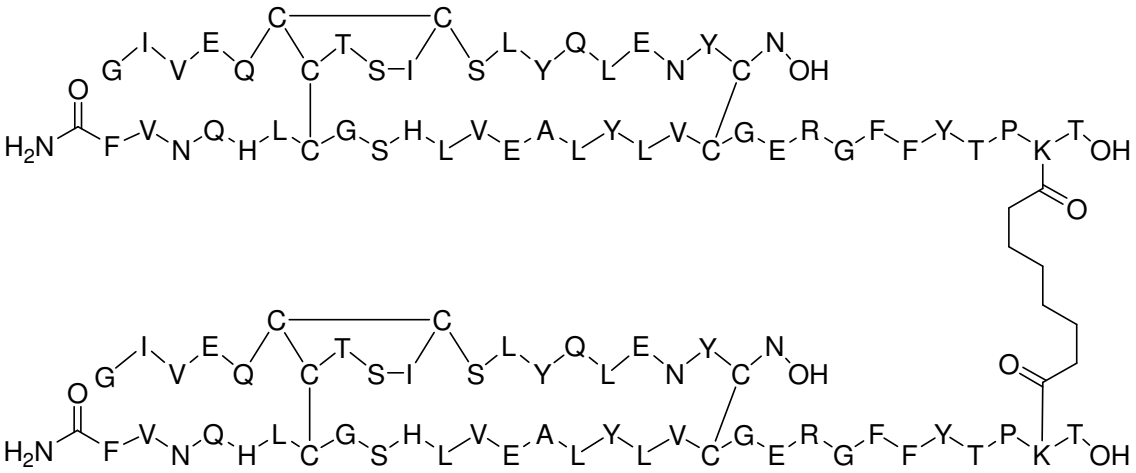

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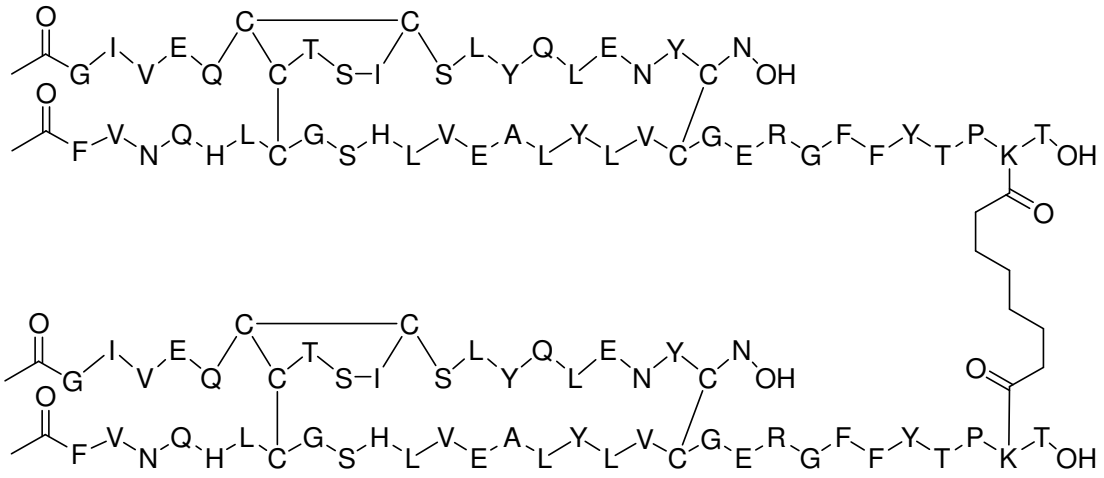

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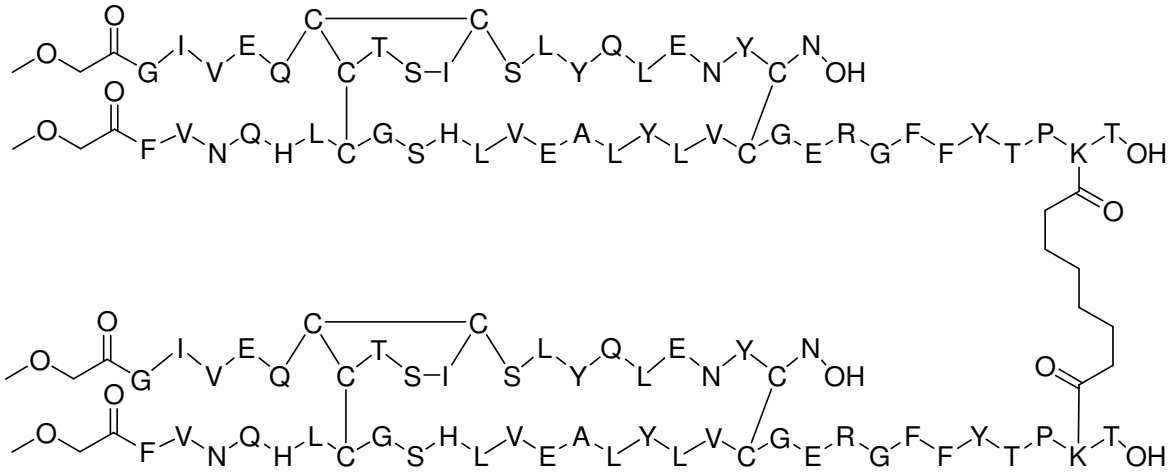

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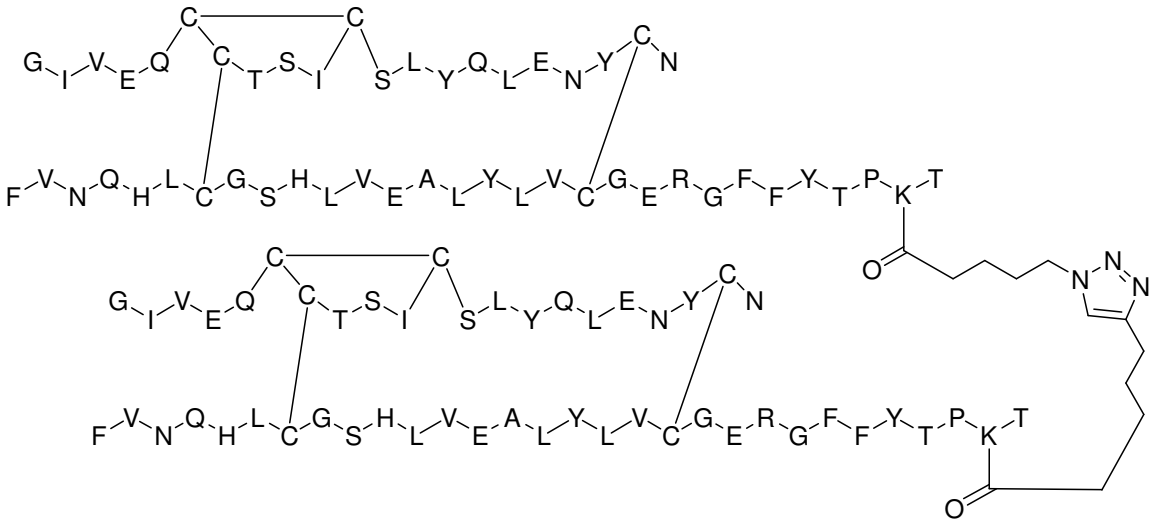

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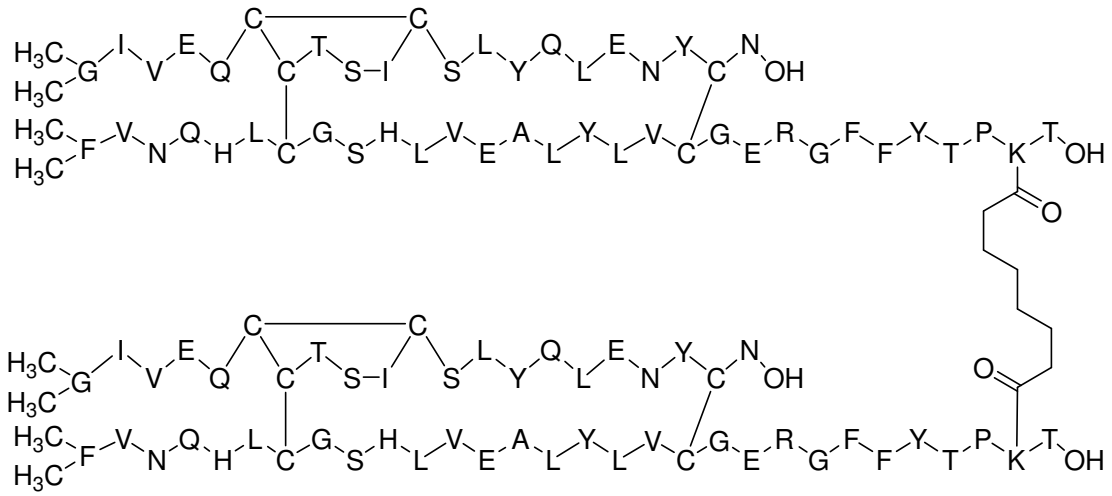

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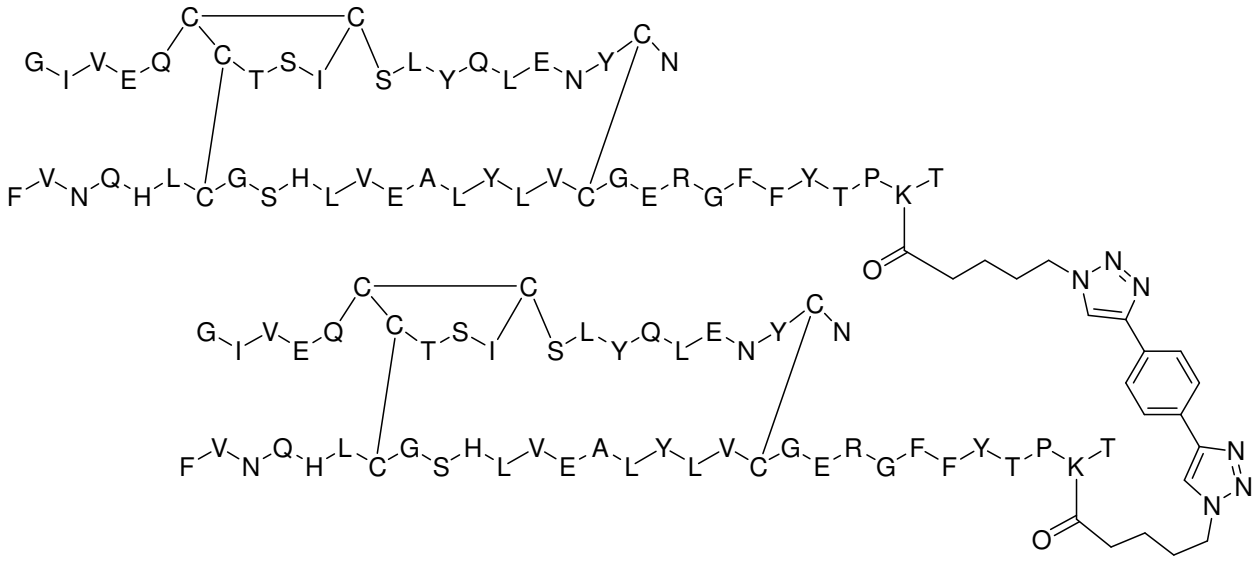

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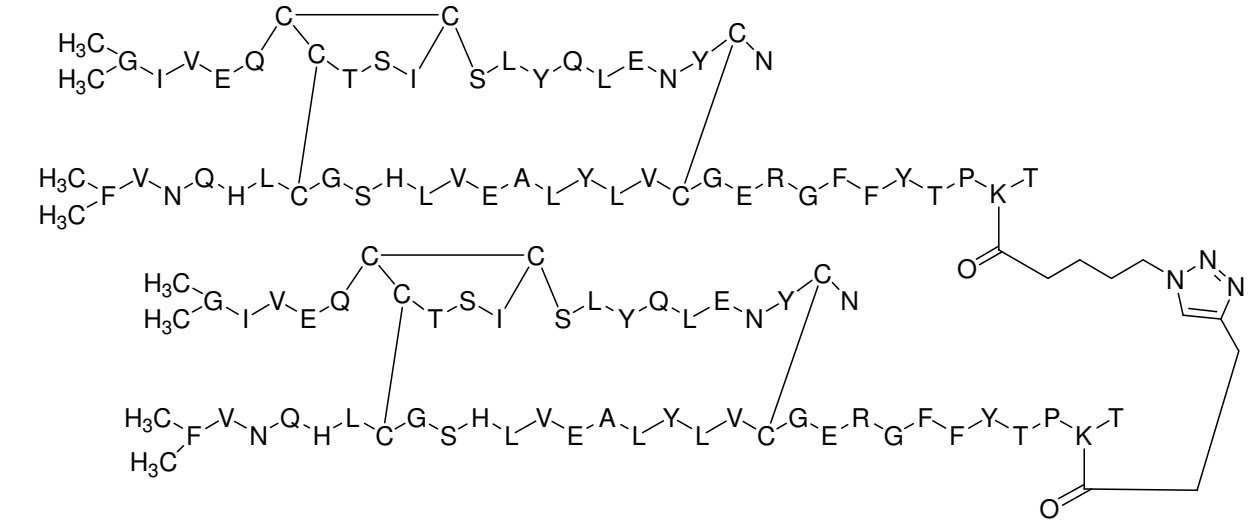

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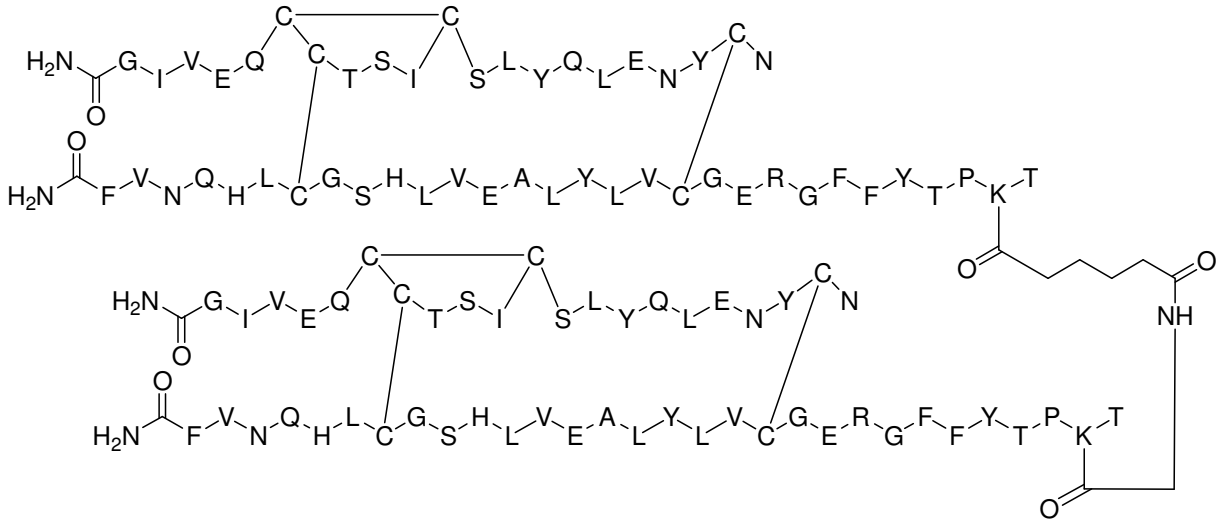

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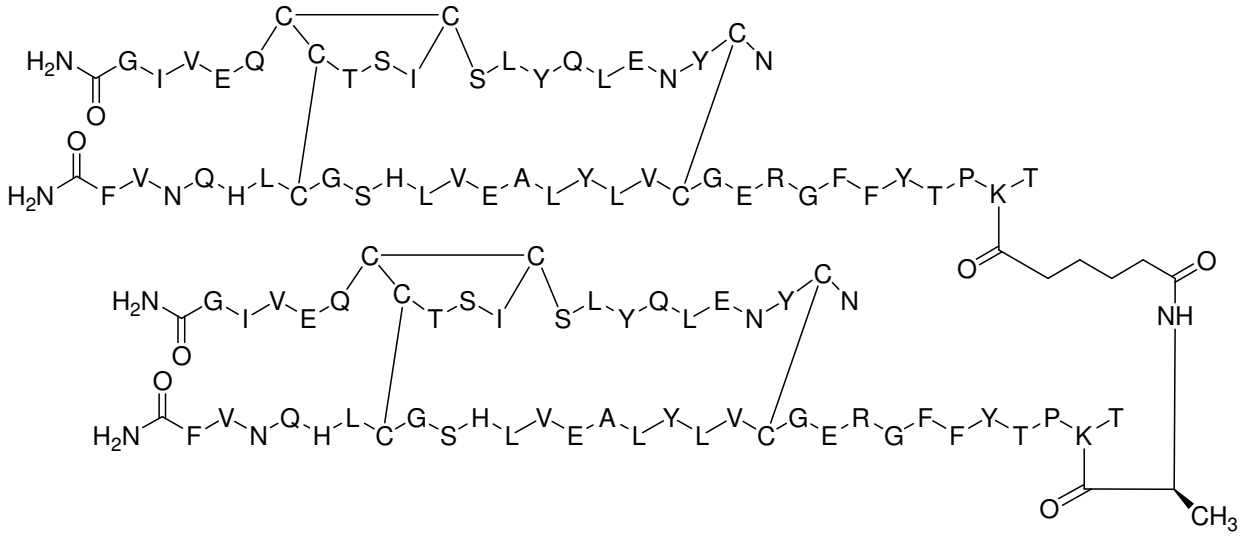

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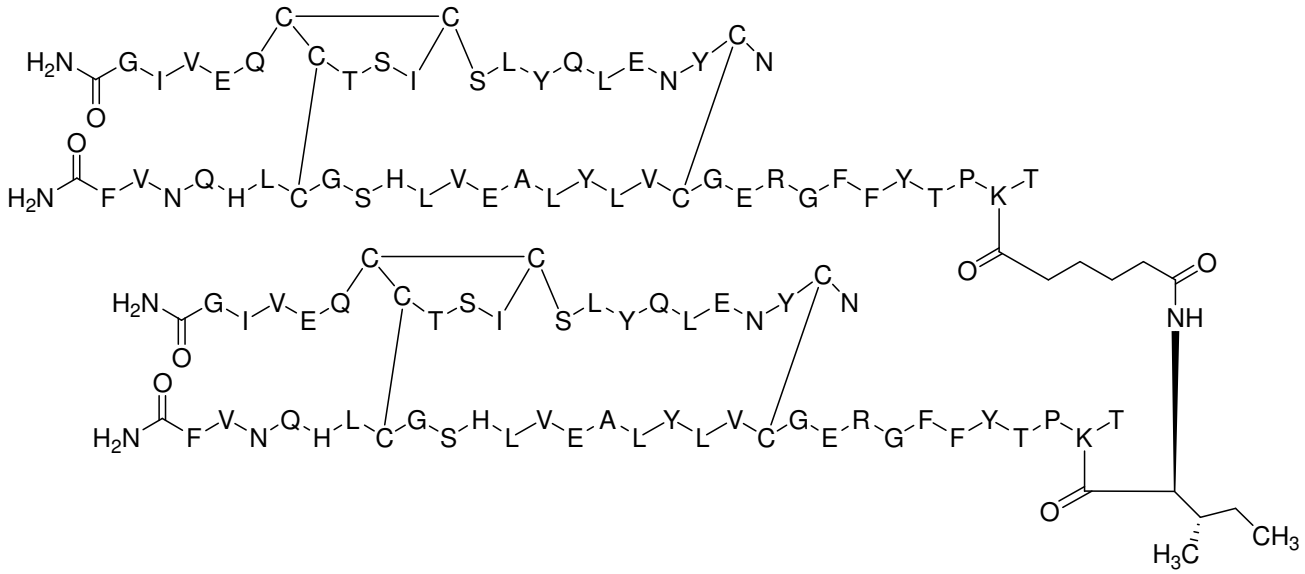

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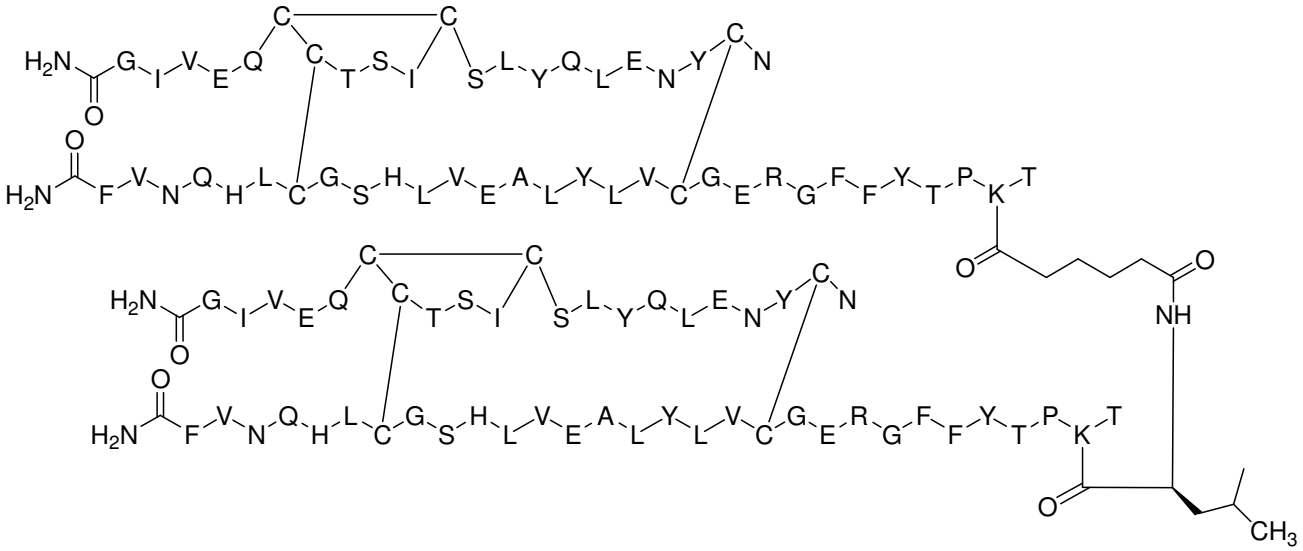

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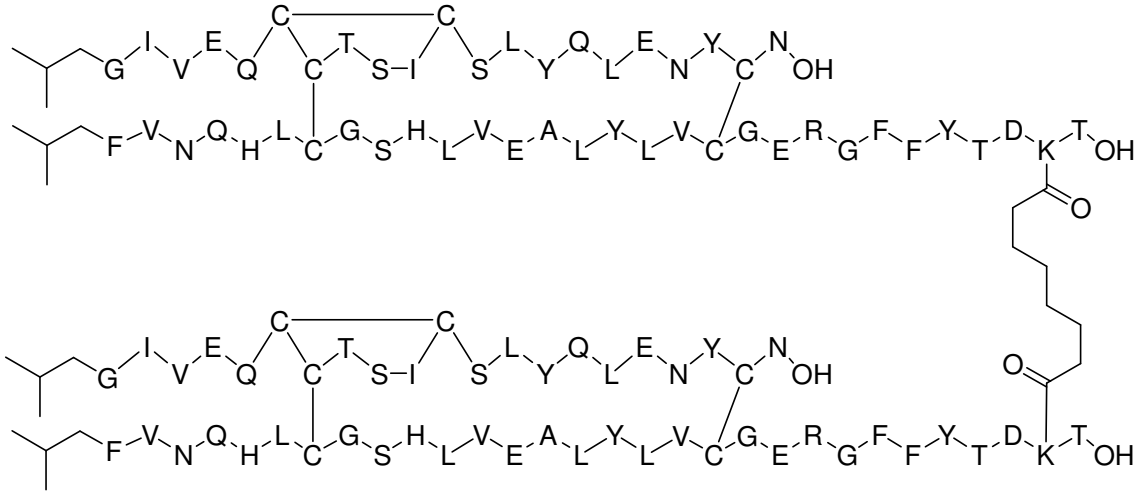

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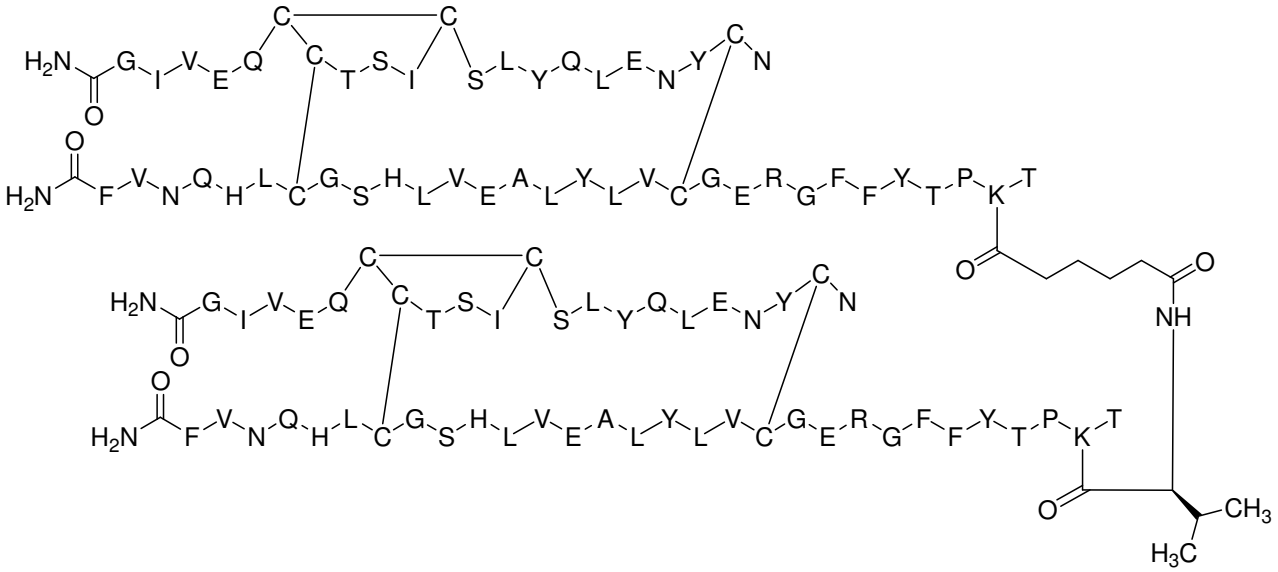

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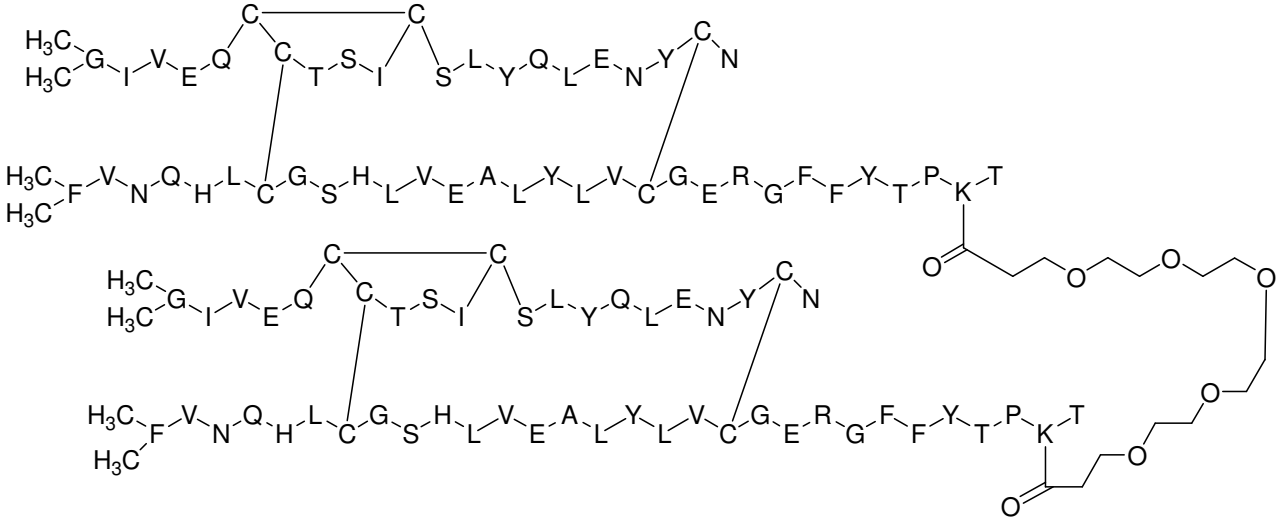

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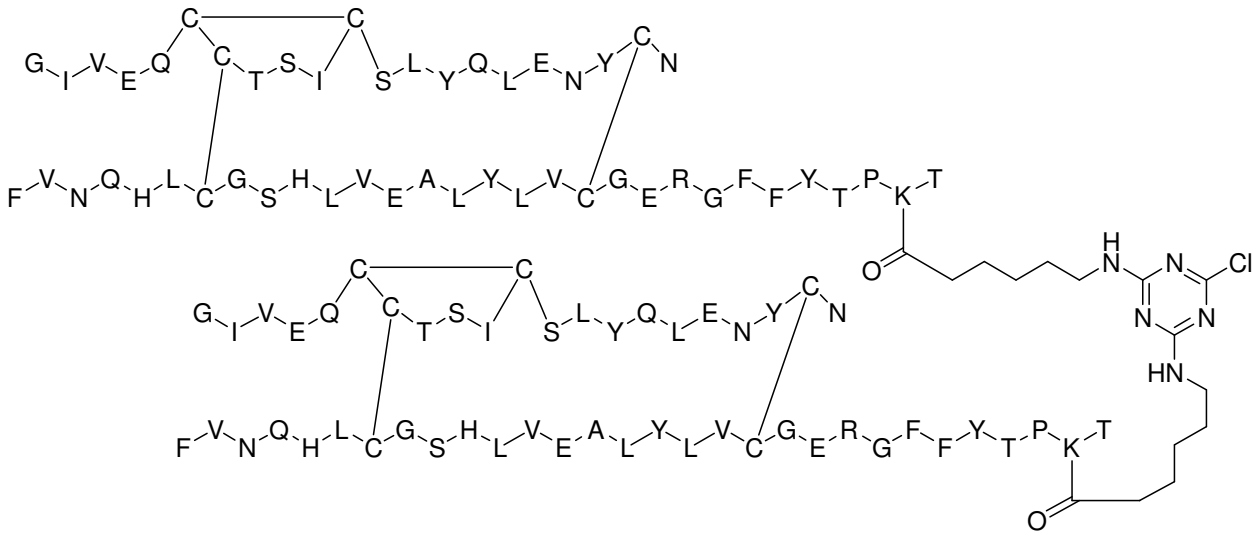

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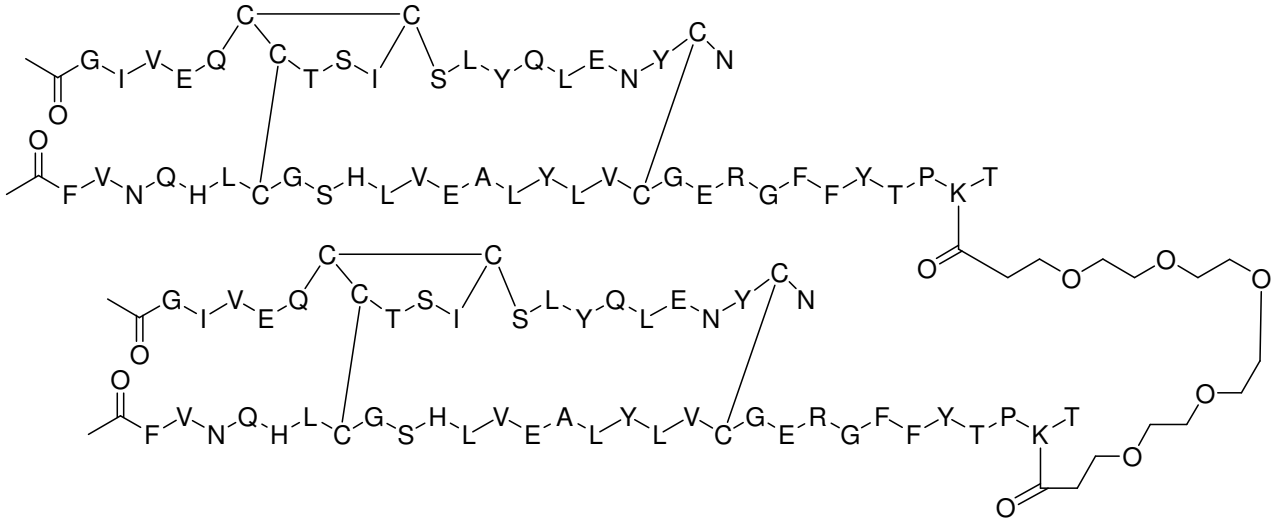

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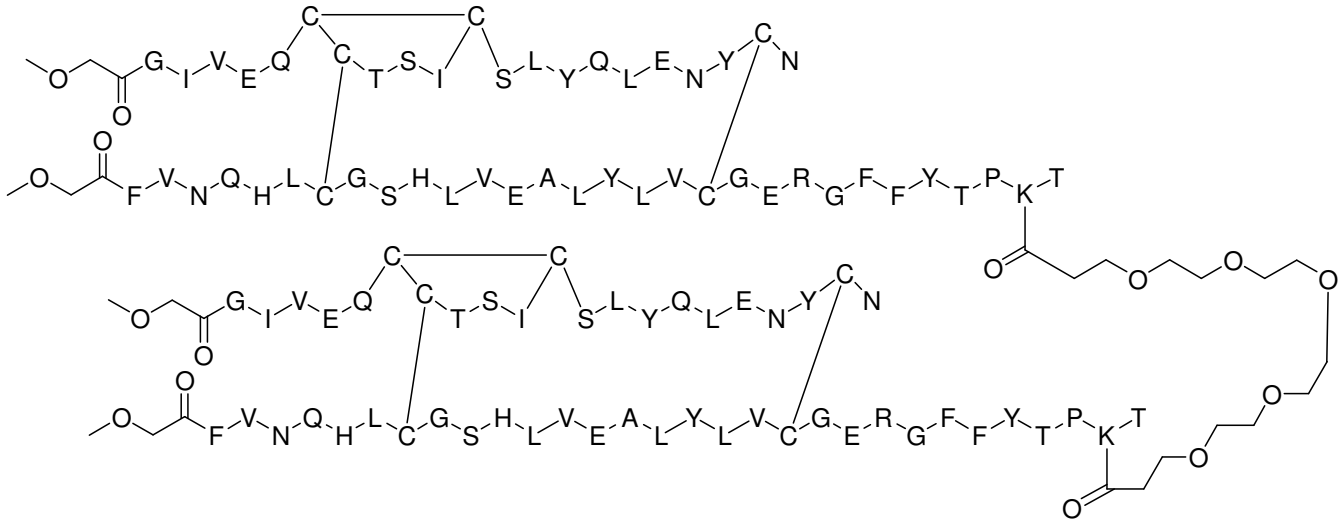

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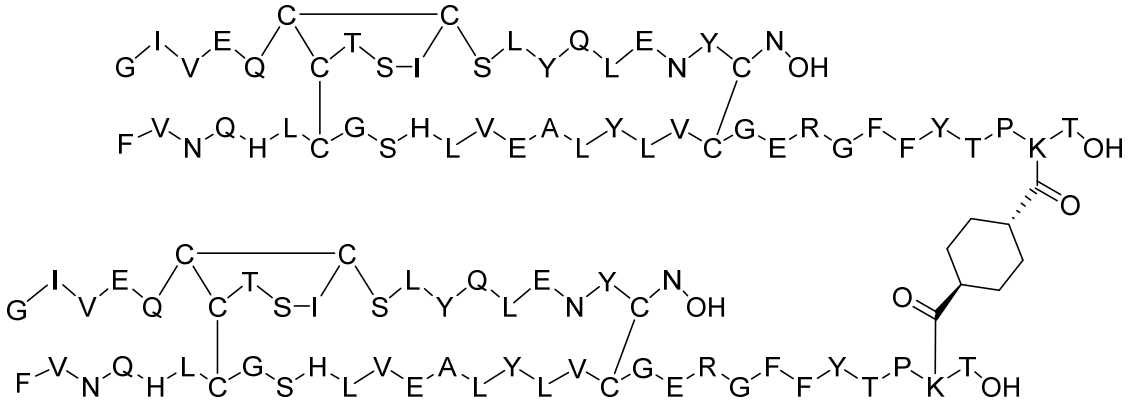

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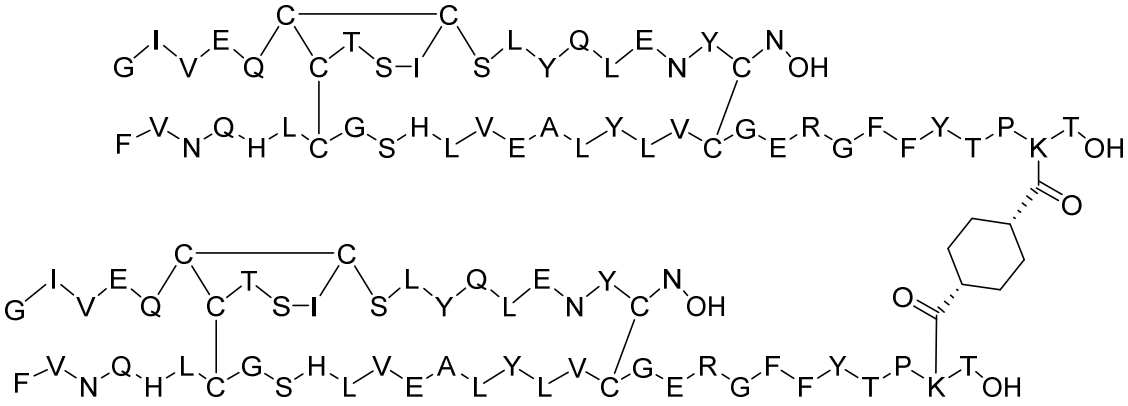

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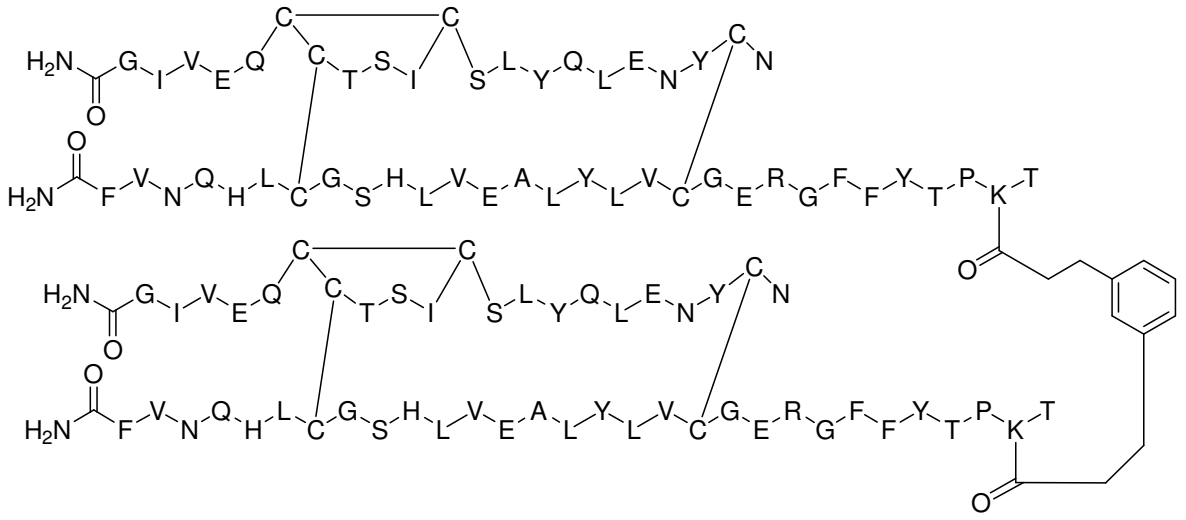

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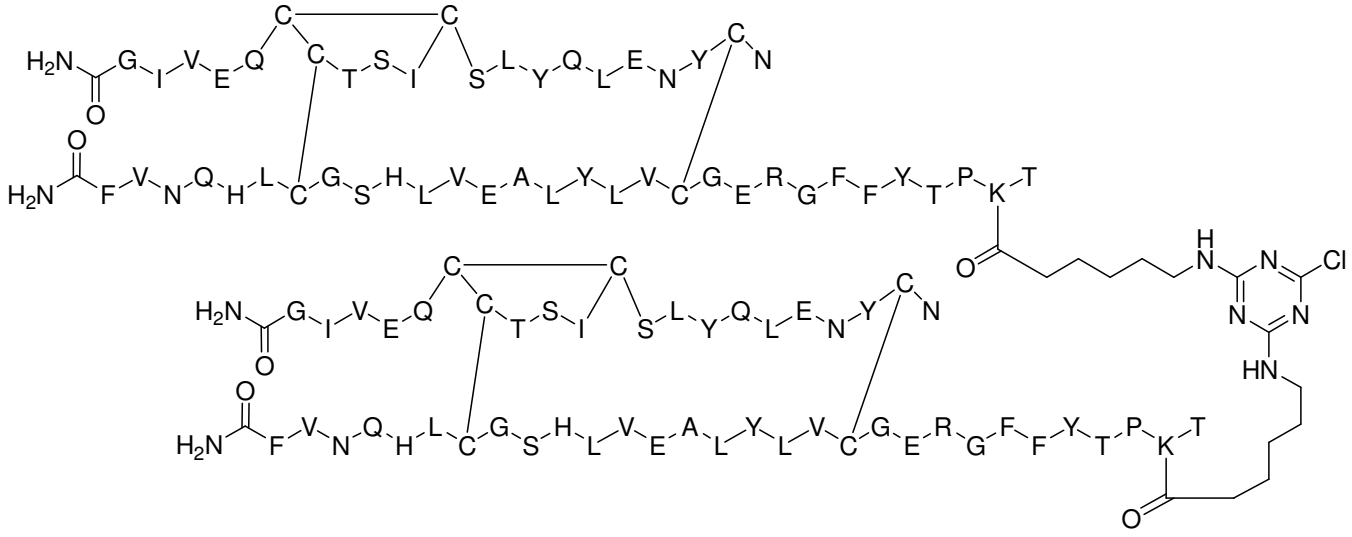

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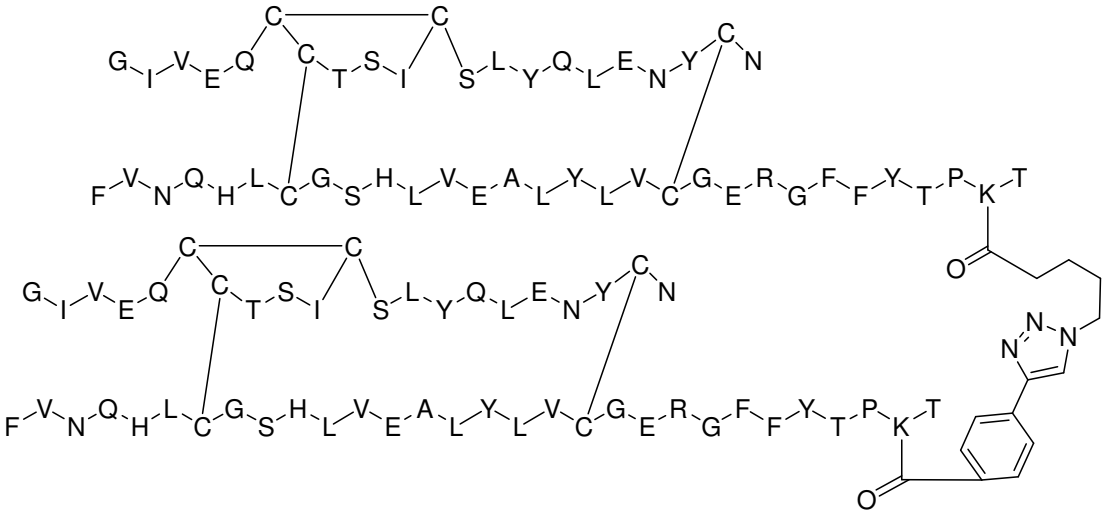

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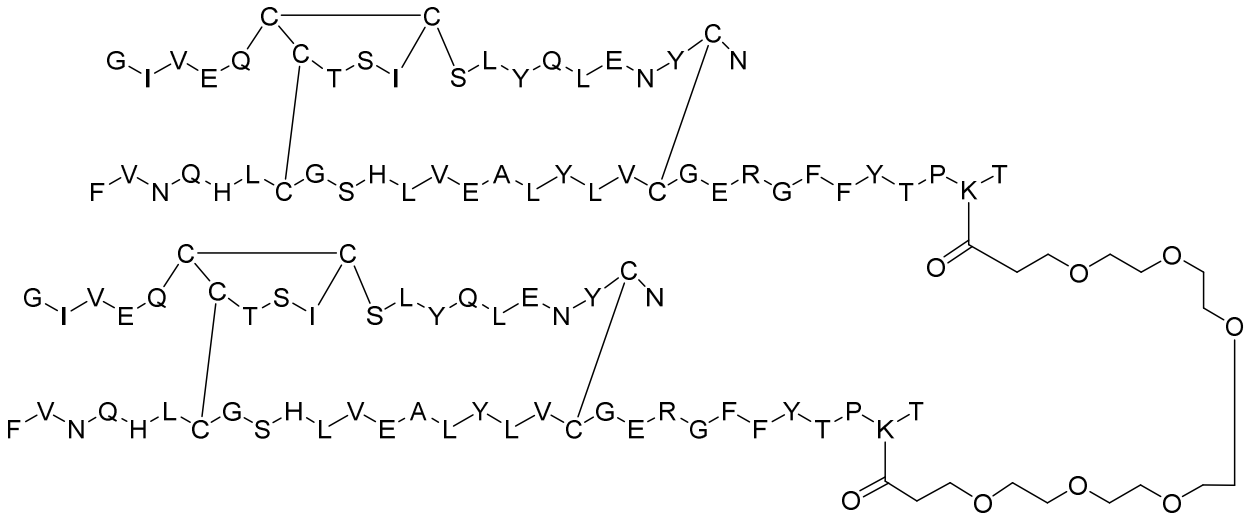

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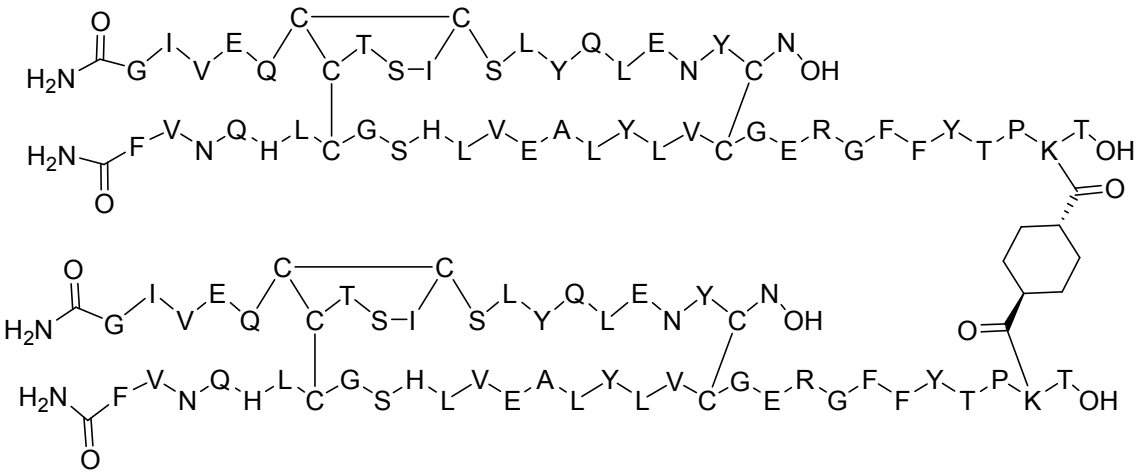

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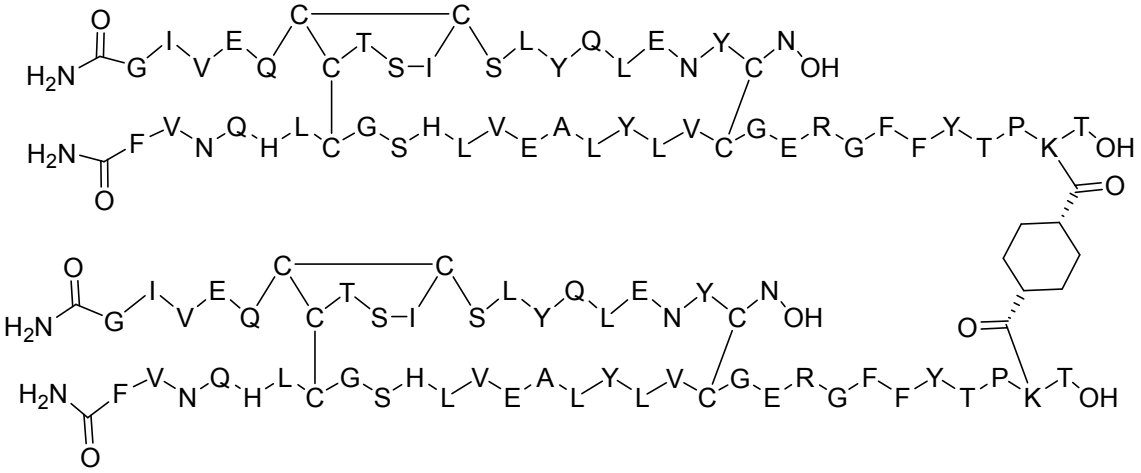

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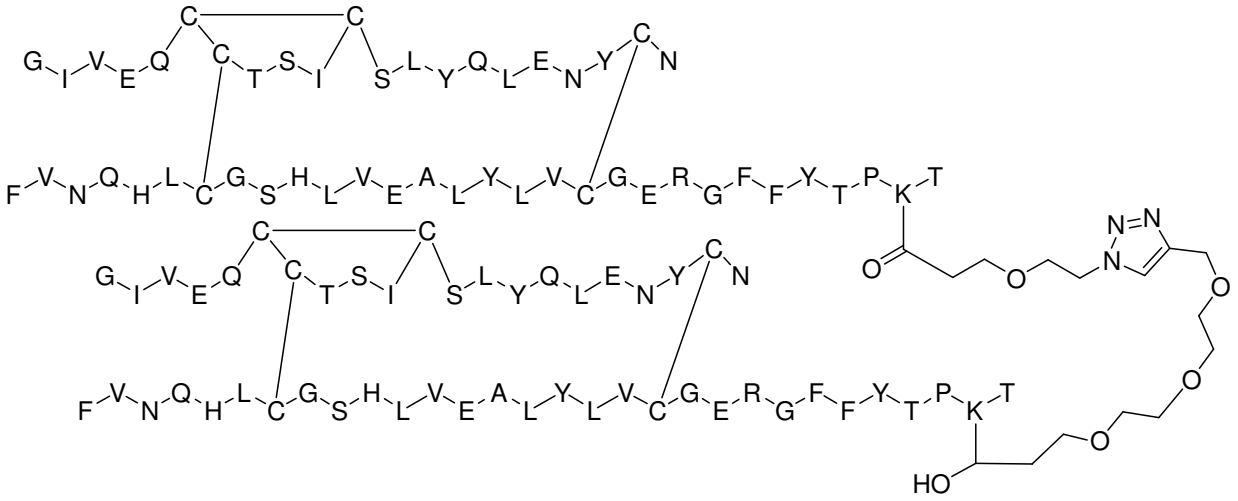

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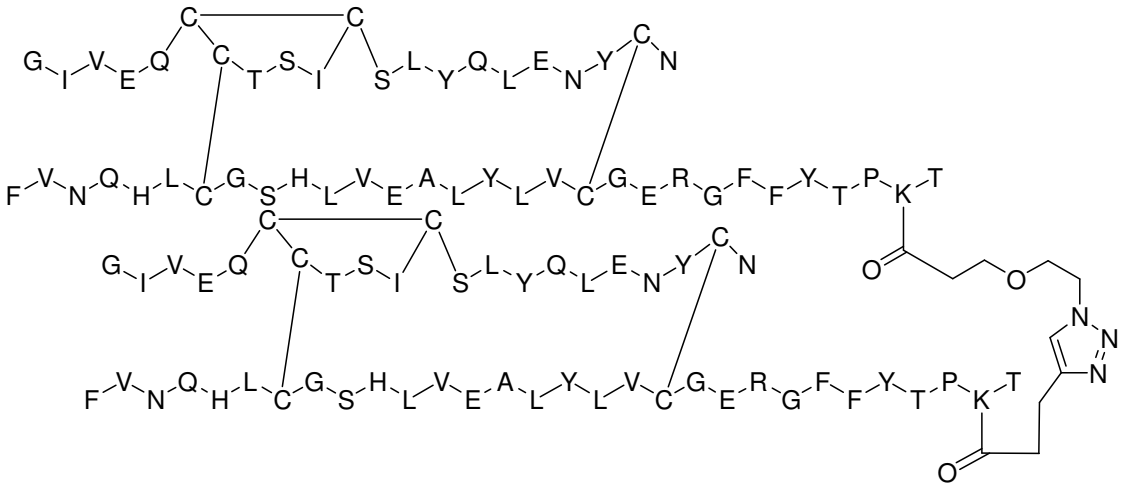

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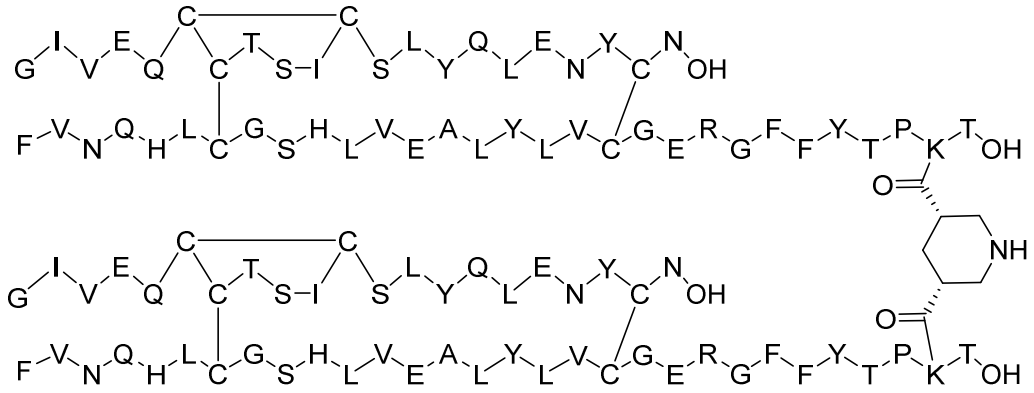

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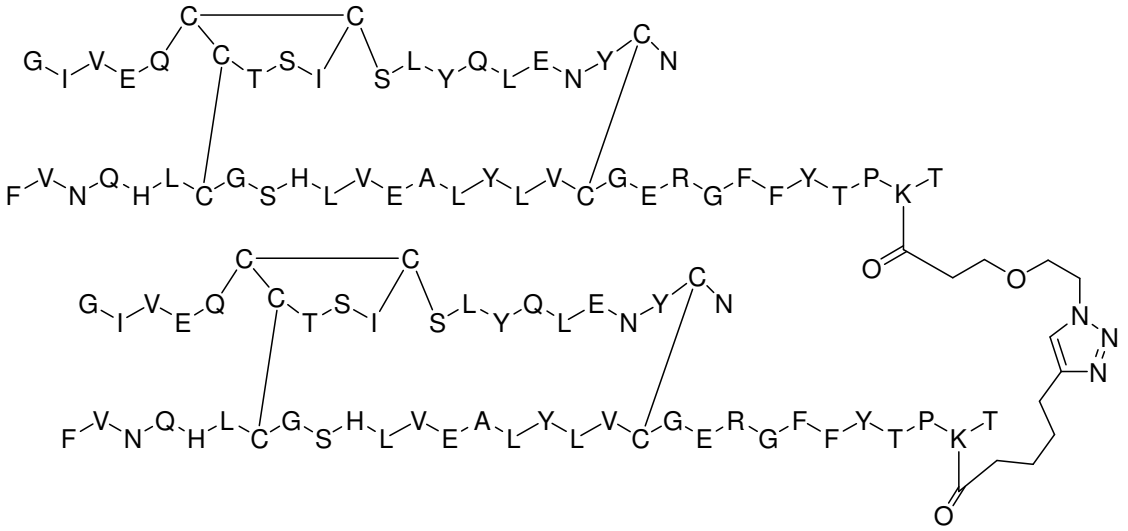

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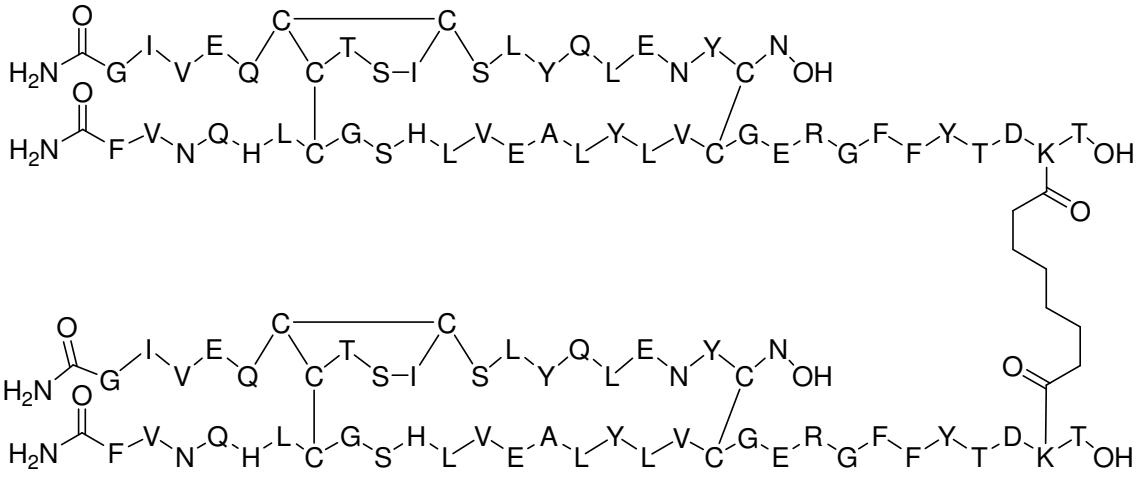

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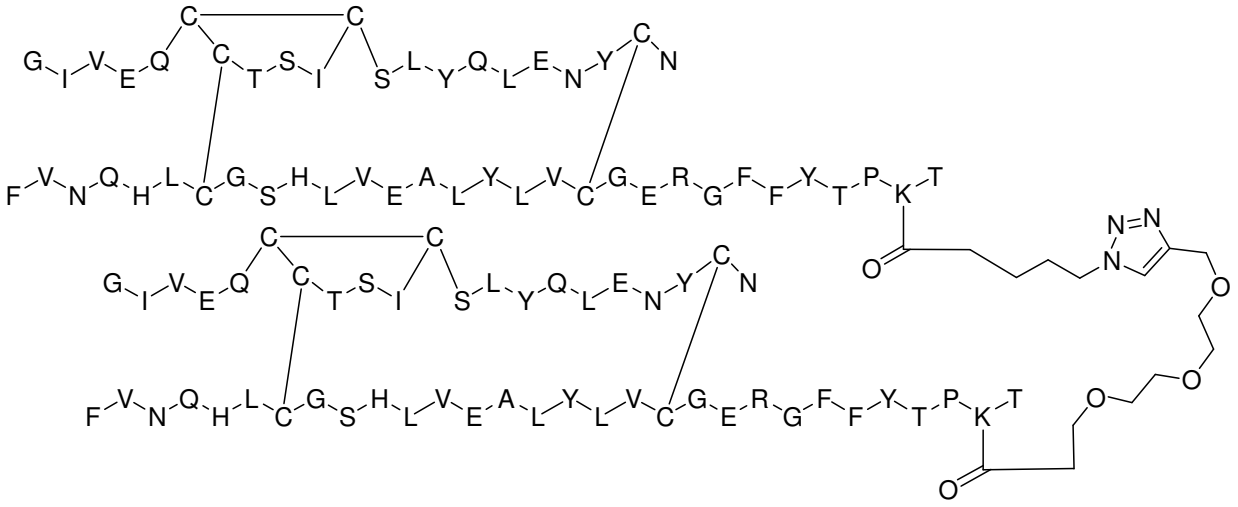

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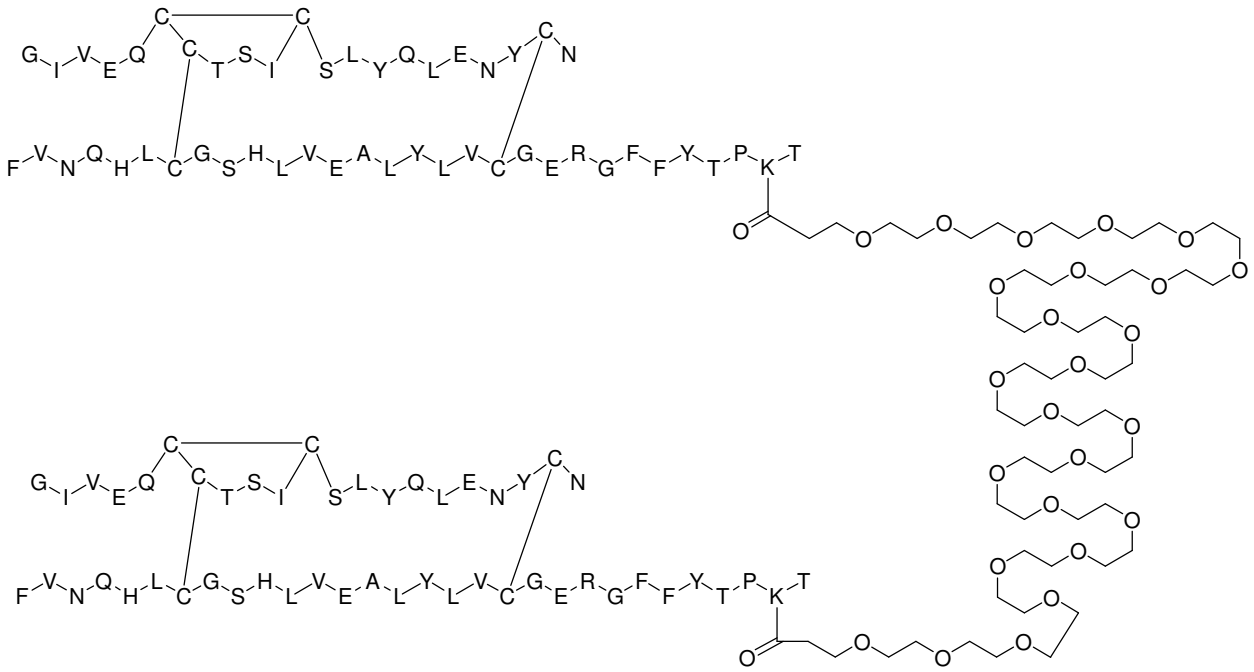

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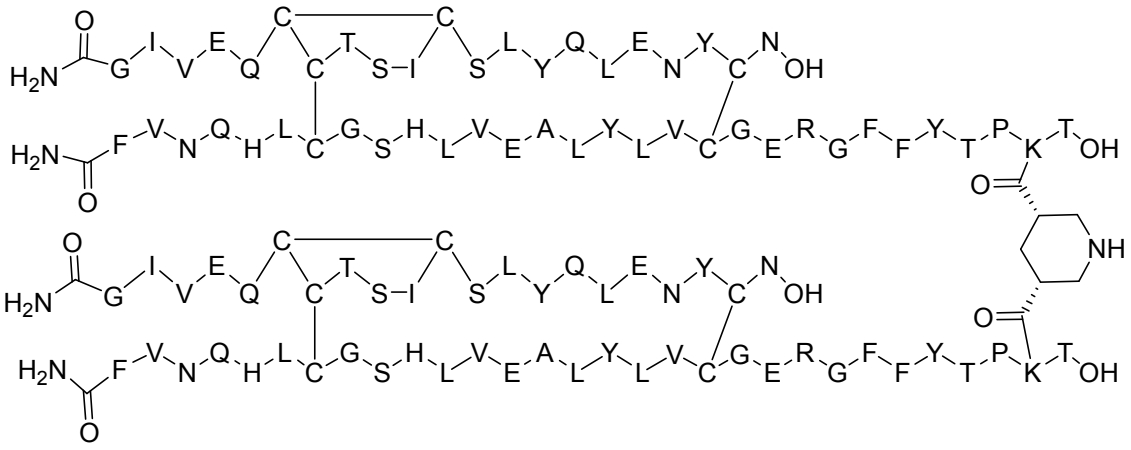

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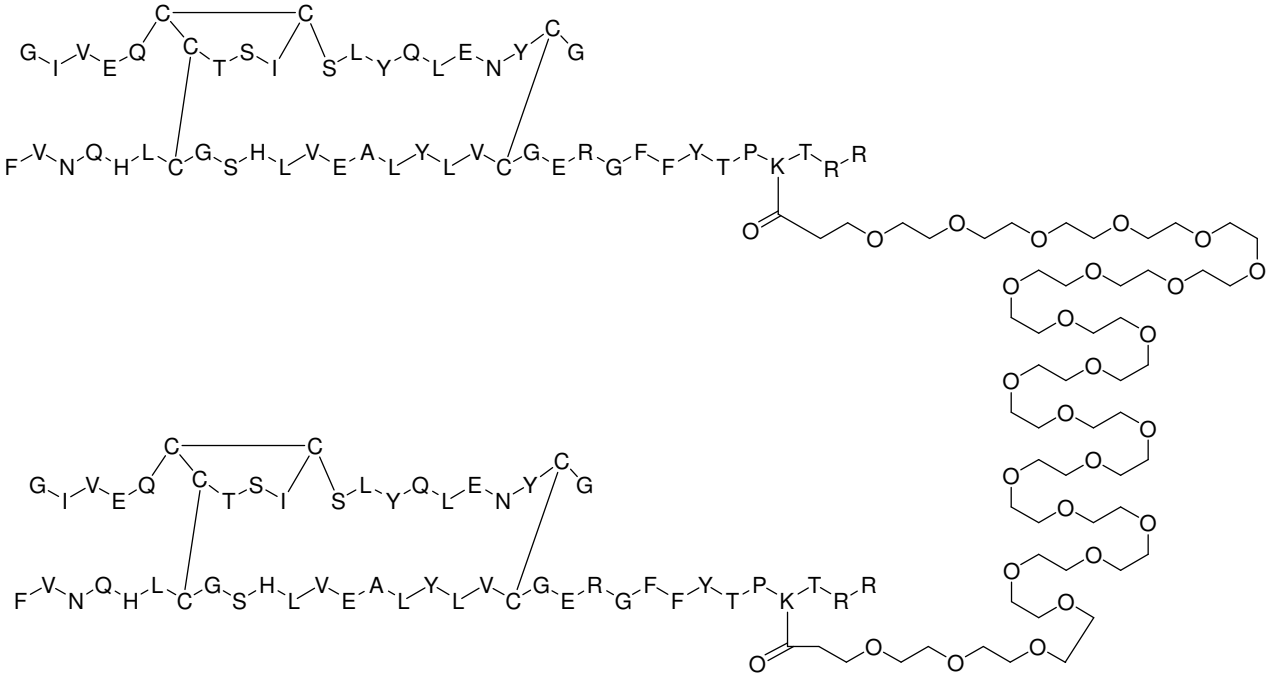

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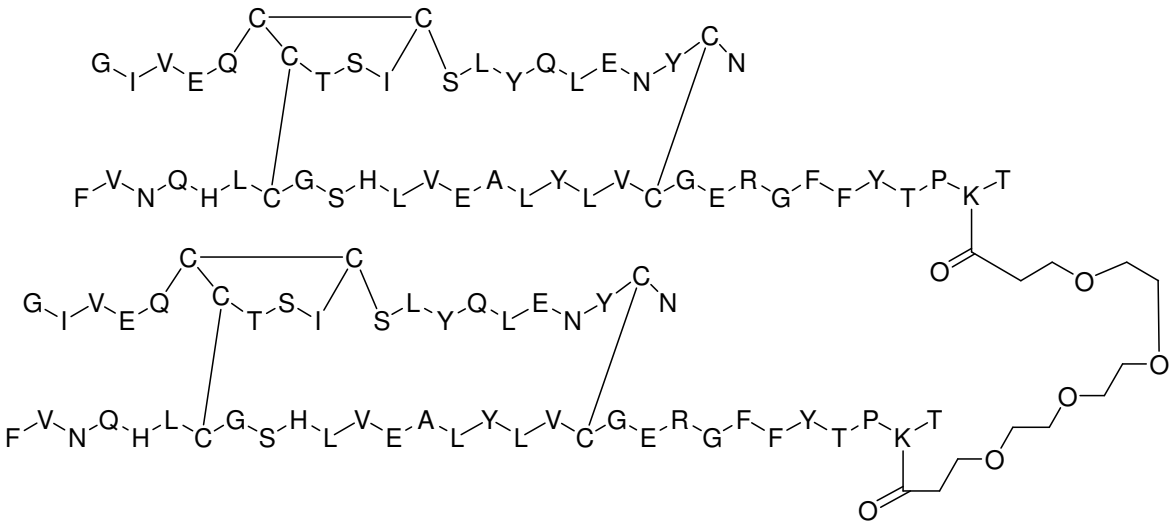

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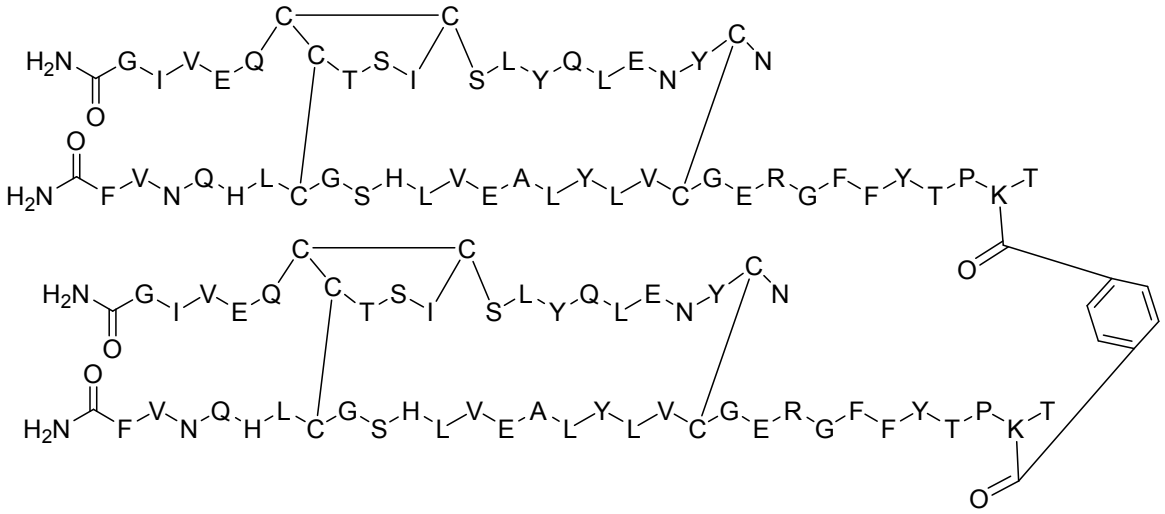

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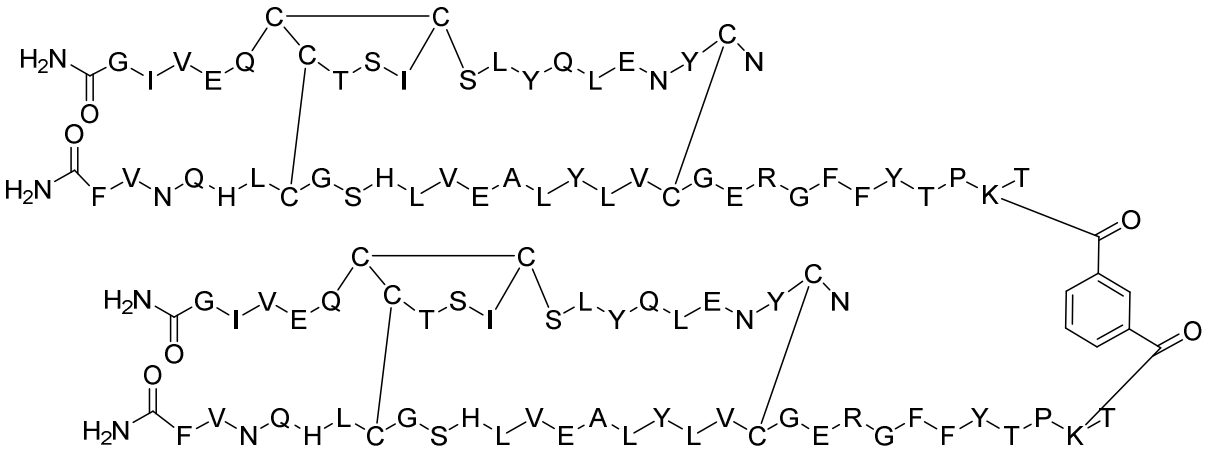

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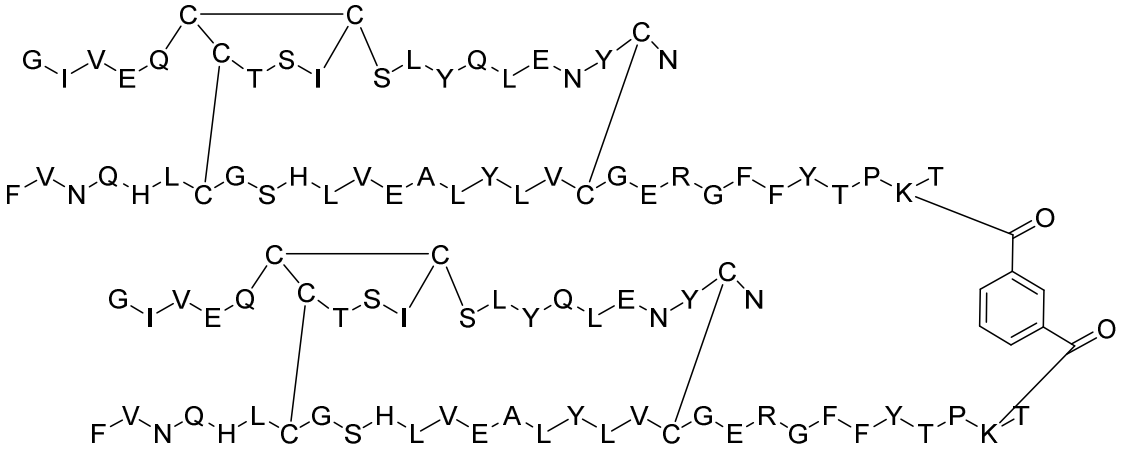

Dimer 91;

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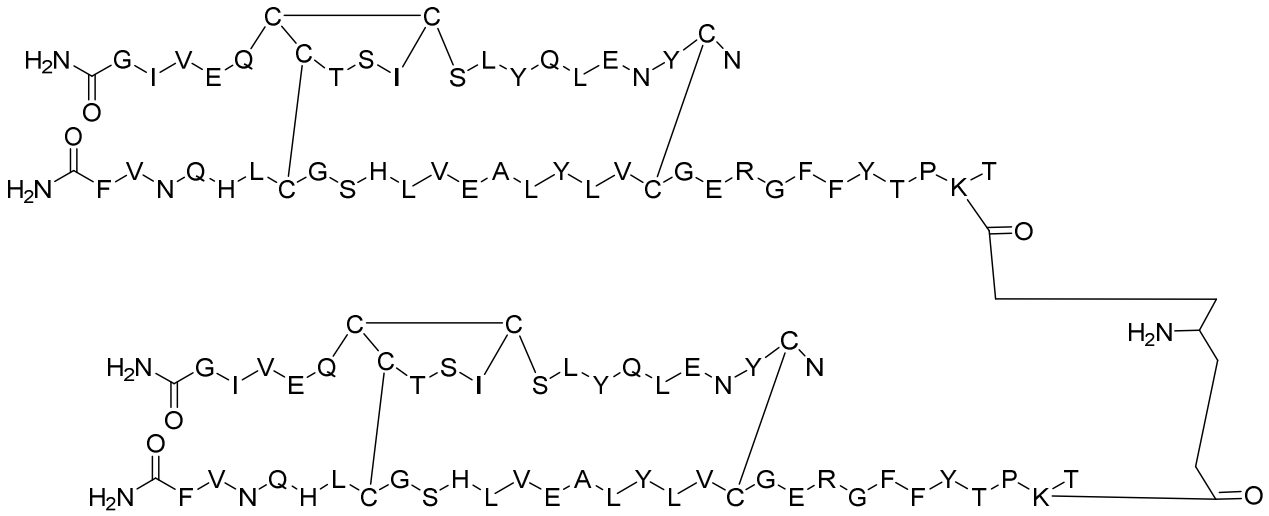
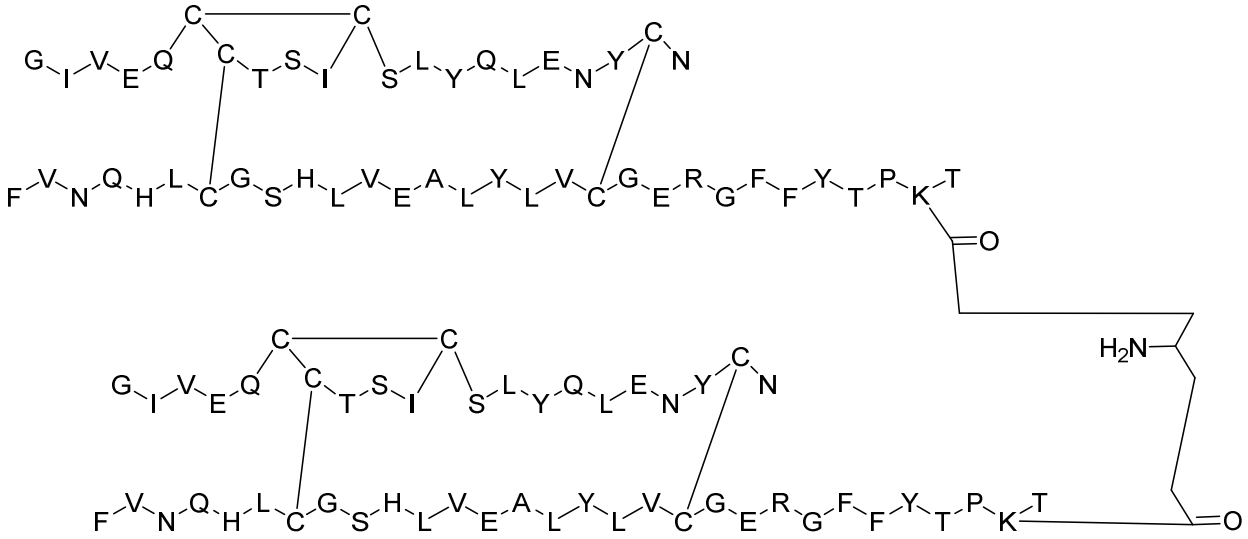


Dimer 93; or



Dimer 94

wherein the disulfide linkages between the Cys_6 and Cys_{11} residues of the A-chain polypeptide and the disulfide linkages between the Cys_7 and Cys_{20} of the A-chain to the Cys_7 and Cys_{19} of the B-chain polypeptide, respectively, are represented by the solid line therebetween; wherein the linking moieties are covalently linked to the epsilon amino acid of the shown lysine residue, wherein the A-chain polypeptide for **Dimers 1-40**, **42-52**, **54-86**, and **88-94** has the amino acid sequence shown in SEQ ID NO:1; the A-chain polypeptide for **Dimer 56** has the amino acid sequence shown for SEQ ID NO:11; the B-chain polypeptide for **Dimers 1-17**, **21-27**, **36**, **37**, **39-40**, and **42-52**, **54-82**, **84-86**, and **88-94** has the amino acid sequence shown in SEQ ID NO:2; the B-chain polypeptide for **Dimers 18** and **32-35** has the amino acid sequence

shown in SEQ ID NO:6; the B-chain polypeptide for **Dimers 19** and **83** has the amino acid sequence shown in SEQ ID NO:9; the B-chain polypeptide for **Dimers 20**, **28-31**, and **38** has the amino acid sequence shown in SEQ ID NO:10; and the A-chain polypeptide and B-chain polypeptide for **Dimers 53** and **87** are SEQ ID NO:7 and SEQ ID NO:8, respectively.

18. An insulin dimer comprising:

a first B29 or B28 Lys of a first insulin heterodimer molecule having a first A-chain polypeptide and first B-chain polypeptide and a second B29 or B28 Lys of a second insulin heterodimer having a second A-chain polypeptide and second B-chain polypeptide conjugated

together by a bifunctional linker selected from the group consisting **Linker 1**, **Linker 2**, **Linker 3**, **Linker 10**, **Linker 11**, **Liner 12**, **Linker 13**, **Linker 14**, **Linker 15**, **Linker 16**, **Linker 17**, **Linker 18**, **Linker 19**, **Linker 20**, **Linker 21**, **Linker 22**, **Linker 23**, **Linker 24**, **Linker 25**, **Linker 26**, **Linker 27**, **Linker 28**, **Linker 29**, **Linker 30**, **Linker 31**, **Linker 32**, **Linker 33**, **Linker 34**, **Linker 35**, **Linker 36**, **Linker 37**, **Linker 38**, **Linker 39**, **Linker 40**, **Linker 41**, **Linker 42**, **Linker 43**, **Linker 44**, **Linker 45**, **Linker 46**, **Linker 47**, **Linker 48**, **Linker 49**, and **Linker 50** with the proviso that when the bifunctional linker is **Linker 10**, **Linker 11**, **Linker 12**, **Linker 13**, or **Linker 14**, at least one of the first or second A-chain or B-chain polypeptides is conjugated at its *N*-terminal amino acid to a substituent or at least the *N*-terminal amino acids of the first insulin heterodimer molecule are conjugated to a substituent or the *N*-terminal amino acids of both the first insulin heterodimer and second insulin heterodimer are conjugated to a substituent; or

or

an insulin receptor partial agonist comprising:

a first insulin or insulin analog heterodimer and a second insulin or insulin analog heterodimer each heterodimer including an A-chain polypeptide and a B-chain polypeptide, wherein the A-chain polypeptide and the B-chain polypeptide are linked together through interchain disulfide bonds;

wherein the first and second insulin or insulin analog heterodimers are covalently linked together through a linking moiety joining the side chain of an amino acid at or near the carboxy terminus of the two respective B-chain polypeptides; and

optionally wherein the amino terminus of at least one of the A-chain polypeptides and the B-chain polypeptides of the first insulin polypeptide or second insulin polypeptide is covalently linked to a substituent,

with the proviso that (1) the linking moiety does not include a disulfide bond and (2) when the amino terminus of the A-chain polypeptide and the B-chain polypeptide do not include a substituent then the linking moiety is not an oxalyl (C2) moiety, a suberyol (C8) moiety, or a dodecanedioyl (C12) moiety; or

an insulin receptor partial agonist comprising the formula

$$D^1\text{-}L\text{-}D^2$$

wherein D^1 and D^2 are each independently an insulin or insulin analog polypeptide, wherein each insulin polypeptide is a heterodimer comprising an A-chain polypeptide and a B-chain polypeptide linked together through interchain disulfide bonds;

L is a linking moiety wherein one end of the linker moiety is attached to an amino acid residue at or near the carboxyl group of D^1 and the other end of the linker moiety is attached to an amino acid residue at or near the carboxyl end of D^2 with the proviso that L does not include a disulfide linkage; and

optionally, wherein at least one of D^1 or D^2 includes a substituent attached to the amino terminus of the A-chain polypeptide or the B-chain polypeptide of D^1 or D^2;

with the proviso that (1) the linking moiety does not include a disulfide bond and (2) when the insulin or insulin analog is not a human insulin or insulin analog and the amino terminus of the A-chain polypeptide and the B-chain polypeptide do not include a substituent then the linking moiety is not an oxalyl (C2) moiety, a suberyol (C8) moiety, or a dodecanedioyl (C12) moiety; or

an insulin analog dimer comprising:

a first insulin analog heterodimer and a second insulin or insulin analog heterodimer each heterodimer including an A-chain polypeptide and a B-chain polypeptide, wherein the A-chain polypeptide and the B-chain polypeptide are linked together through interchain disulfide bonds;

wherein the first and second insulin or insulin analog heterodimers are covalently linked together through a linking moiety joining the side chain of an amino acid at or near the carboxy terminus of the two respective B-chain polypeptides;

wherein the insulin analog is selected from insulin lispro, insulin aspart, desB30 insulin, and insulin glargine; and

optionally wherein the amino terminus of at least one of the A-chain polypeptides and the B-chain polypeptides of the first insulin polypeptide or second insulin polypeptide is covalently linked to a substituent,

with the proviso that the linking moiety does not include a disulfide bond; or

an insulin analog dimer comprising the formula

D^1-L-D^2

wherein D^1 and D^2 are each independently an insulin or insulin analog polypeptide, wherein each insulin polypeptide is a heterodimer comprising an A-chain polypeptide and a B-chain polypeptide linked together through interchain disulfide bonds;

L is a linking moiety wherein one end of the linker moiety is attached to an amino acid residue at or near the carboxyl group of D^1 and the other end of the linker moiety is attached to an amino acid residue residue at or near the carboxyl end of D^2 with the proviso that L does not include a disulfide linkage;

wherein the insulin analog is selected from insulin lispro, insulin aspart, desB30 insulin, and insulin glargine; and

optionally, wherein at least one of D^1 or D^2 includes a substituent attached to the amino terminus of the A-chain polypeptide or the B-chain polypeptide of D^1 or D^2;

with the proviso that the linking moiety does not include a disulfide bond.

19. The insulin dimer of claim 18, wherein the substituent comprises an *N*-hydroxysuccinimide ester linked to a group having the general formula RC(O)-, where R can be R'CH_2, R'NH, R'O, and R' can be H, linear alkyl chain, amino acid, peptide, polyethylene glycol (PEG), saccharides.

20. The insulin dimer of claim 18, wherein the substituent is a carbamoyl group, acetyl group, glycine, methyl group, methoxy group, dimethyl group, isobutyl group, PEG1 group, AEG group, AEG-C6 alkyl group, or PEG2 group.

21. A composition comprising one or more compounds of claim 17 or the insulin dimer of any one of claims 18 to 20 and a pharmaceutically acceptable carrier.

22. A composition of claim 16 or claim 21 for use in the treatment of diabetes.

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23. The composition of claim 22, wherein the diabetes is Type 1 diabetes, Type 2 diabetes, or gestational diabetes.

24. Use of a composition of claim 16 or claim 21 for the manufacture of a medicament for the treatment of diabetes.

25. The use of claim 24, wherein the diabetes is Type 1 diabetes, Type 2 diabetes, or gestational diabetes.