CLAIMS

1. A heterotandem bicyclic peptide complex comprising:

(a) a first peptide ligand which binds to a component present on an immune cell; conjugated via a linker to

(b) a second peptide ligand which binds to a component present on a cancer cell; wherein each of said peptide ligands comprises a polypeptide comprising at least three cysteine residues, separated by at least two loop sequences, and a molecular scaffold which forms covalent bonds with the cysteine residues of the polypeptide such that at least two polypeptide loops are formed on the molecular scaffold.

2. The heterotandem bicyclic peptide complex as defined in claim 1, wherein the immune cell is selected from: white blood cells; lymphocytes (e.g. T lymphocytes or T cells, B cells or natural killer cells); CD8+ or CD4+ T cells~~;~~, for example CD8+ T cells; dendritic cells, follicular dendritic cells and granulocytes.

3. The heterotandem bicyclic peptide complex as defined in claim 1 or claim 2, wherein the component present on an immune cell is CD137.

4. The heterotandem bicyclic peptide complex as defined in any one of claims 1 to 3, wherein the first peptide ligand comprises a CD137 binding bicyclic peptide ligand.

5. The heterotandem bicyclic peptide complex as defined in claim 4, wherein the CD137 binding bicyclic peptide ligand comprises an amino acid sequence selected from:

C_iIEEGQYC_{ii}FADPY[Nle]C_{iii} (SEQ ID NO: 1);

C_i[tBuAla]PE[D-Ala]PYC_{ii}FADPY[Nle]C_{iii} (SEQ ID NO: 3);

C_iIEEGQYC_{ii}F[D-Ala]DPY[Nle]C_{iii} (SEQ ID NO: 4);

C_i[tBuAla]PK[D-Ala]PYC_{ii}FADPY[Nle]C_{iii} (SEQ ID NO: 5);

C_i[tBuAla]PE[D-Lys]PYC_{ii}FADPY[Nle]C_{iii} (SEQ ID NO: 6);

C_i[tBuAla]P[K(PYA)][D-Ala]PYC_{ii}FADPY[Nle]C_{iii} (SEQ ID NO: 7);

C_i[tBuAla]PE[D-Lys(PYA)]PYC_{ii}FADPY[Nle]C_{iii} (SEQ ID NO: 8);

C_iIEE[D-Lys(PYA)]QYC_{ii}FADPY(Nle)C_{iii} (SEQ ID NO: 9); and

[dC_i][dI][dE][dE][K(PYA)][dQ][dY][dC_{ii}][dF][dA][dD][dP][dY][dNle][dC_{iii}] (SEQ ID NO: 10);

wherein C_i, C_{ii} and C_{iii} represent first, second and third cysteine residues, respectively, Nle represents norleucine, tBuAla represents t-butyl-alanine, PYA represents 4-pentynoic acid, or a pharmaceutically acceptable salt thereof.

6. The heterotandem bicyclic peptide complex as defined in claim 5, wherein the CD137 binding bicyclic peptide ligand comprises N- and C-terminal modifications and comprises:

Ac-A-(SEQ ID NO: 1)-Dap (hereinafter referred to as BCY7732);

Ac-A-(SEQ ID NO: 1)-Dap(PYA) (hereinafter referred to as BCY7741);

Ac-(SEQ ID NO: 3)-Dap (hereinafter referred to as BCY9172);

Ac-(SEQ ID NO: 3)-Dap(PYA) (hereinafter referred to as BCY11014);

Ac-A-(SEQ ID NO: 4)-Dap (hereinafter referred to as BCY8045);

Ac-(SEQ ID NO: 5)-A (hereinafter referred to as BCY8919);

Ac-(SEQ ID NO: 6)-A (hereinafter referred to as BCY8920);

Ac-(SEQ ID NO: 7)-A (hereinafter referred to as BCY8927);

Ac-(SEQ ID NO: 8)-A (hereinafter referred to as BCY8928);

Ac-A-(SEQ ID NO: 9)-A (hereinafter referred to as BCY7744); and

Ac-[dA]-(SEQ ID NO: 10)-[dA]-NH_2 (hereinafter referred to as BCY11506);

wherein Ac represents an acetyl group, Dap represents diaminopropionic acid and PYA represents 4-pentynoic acid, or a pharmaceutically acceptable salt thereof.

7. The heterotandem bicyclic peptide complex as defined in any one of claims 1 to 6, wherein the cancer cell is selected from an HT1080, SC-OV-3, PC3, H1376, NCI-H292, LnCap, MC38 and RKO tumor cell.

8. The heterotandem bicyclic peptide complex as defined in any one of claims 1 to 7, wherein the component present on a cancer cell is EphA2.

9. The heterotandem bicyclic peptide complex as defined in any one of claims 1 to 8, wherein the second peptide ligand comprises an EphA2 binding bicyclic peptide ligand.

10. The heterotandem bicyclic peptide complex as defined in claim 9, wherein the EphA2 binding bicyclic peptide ligand comprises an amino acid sequence selected from:

C_i[HyP]LVNPLC_{ii}LHP[dD]W[HArg]C_{iii} (SEQ ID NO: 2); and

C_iLWDPTPC$_{ii}$ANLHL[HArg]C_{iii} (SEQ ID NO: 11);

wherein C_i, C_{ii} and C_{iii} represent first, second and third cysteine residues, respectively, HyP represents hydroxyproline, dD represents aspartic acid in D-configuration and HArg represents homoarginine, or a pharmaceutically acceptable salt thereof.

11. The heterotandem bicyclic peptide complex as defined in claim 10, wherein the EphA2 binding bicyclic peptide ligand comprises N-terminal modifications and comprises:

A-HArg-D-(SEQ ID NO: 2) (hereinafter referred to as BCY9594);

[B-Ala]-[Sar_{10}]-A-[HArg]-D-(SEQ ID NO: 2) (hereinafter referred to as BCY6099);

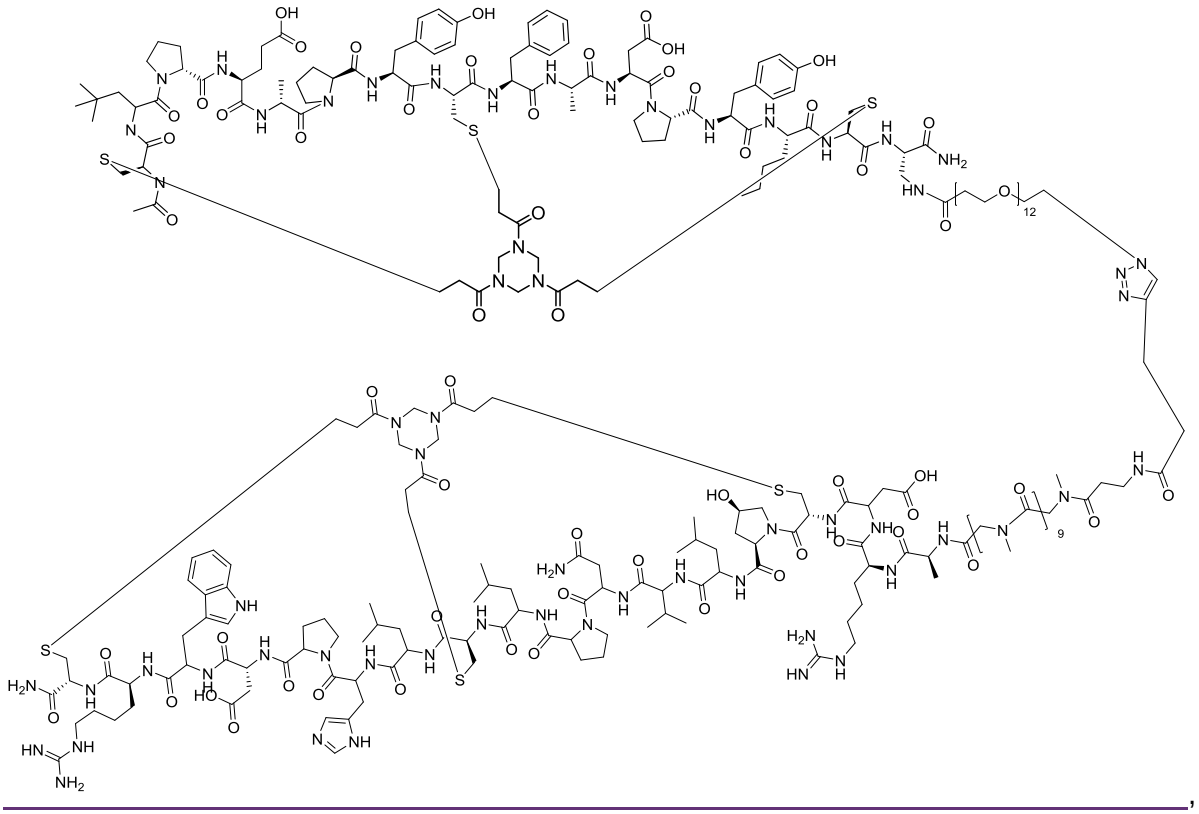
[PYA]-[B-Ala]-[Sar_{10}]-A-[HArg]-D-(SEQ ID NO: 2) (hereinafter referred to as BCY6169); and

[PYA]-[B-Ala]-[Sar_{10}]-VGP-(SEQ ID NO: 11) (hereinafter referred to as BCY8941);

wherein HArg represents homoarginine, PYA represents 4-pentynoic acid, Sar_{10} represents 10 sarcosine units, B-Ala represents beta-alanine, or a pharmaceutically acceptable salt thereof.

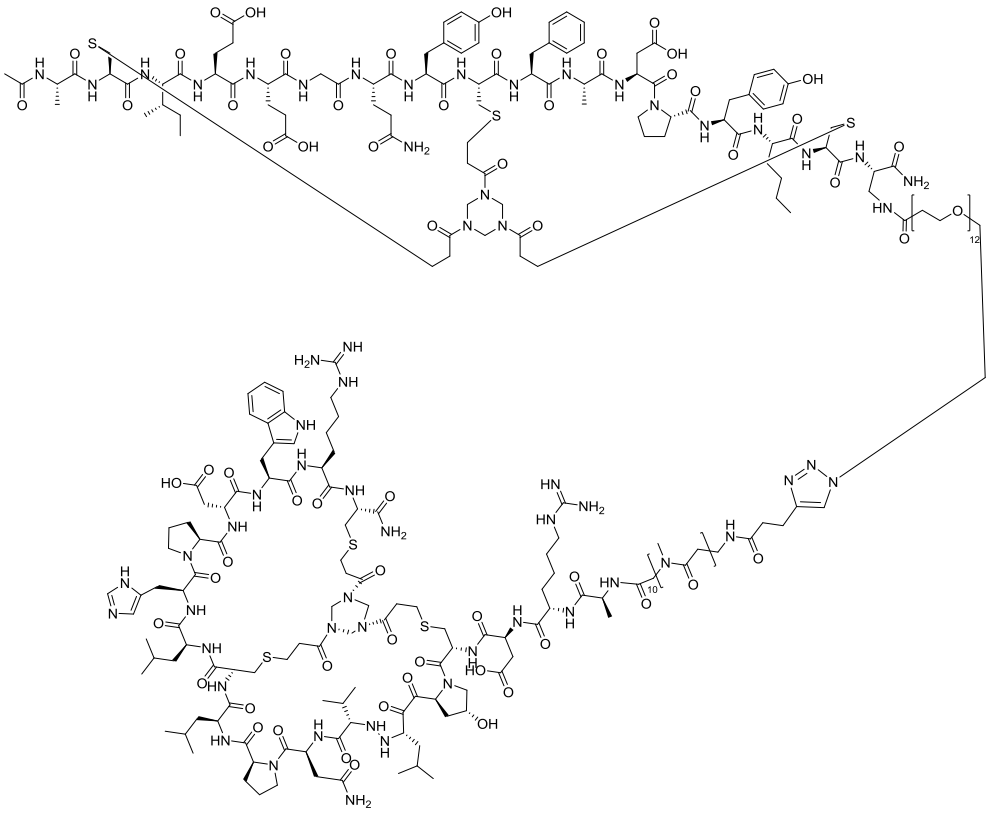
12. The heterotandem bicyclic peptide complex as defined in any one of claims 9 to 11 which is a CD137/EphA2 complex selected from:

BCY9173



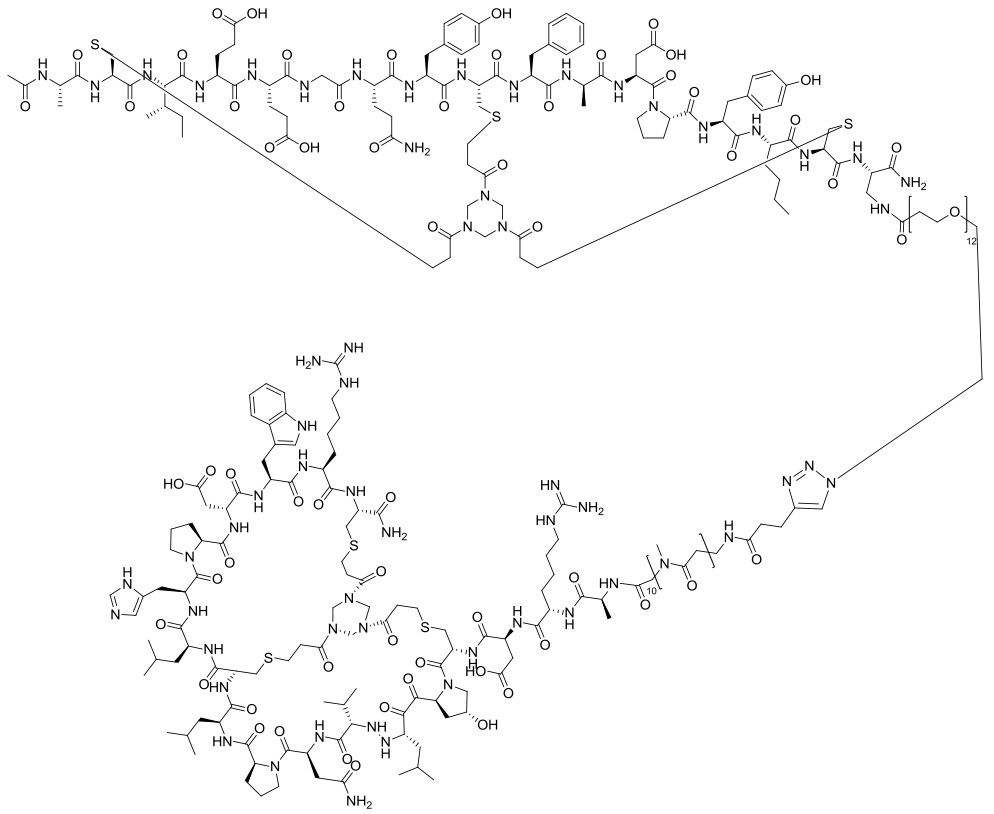
,

BCY7985



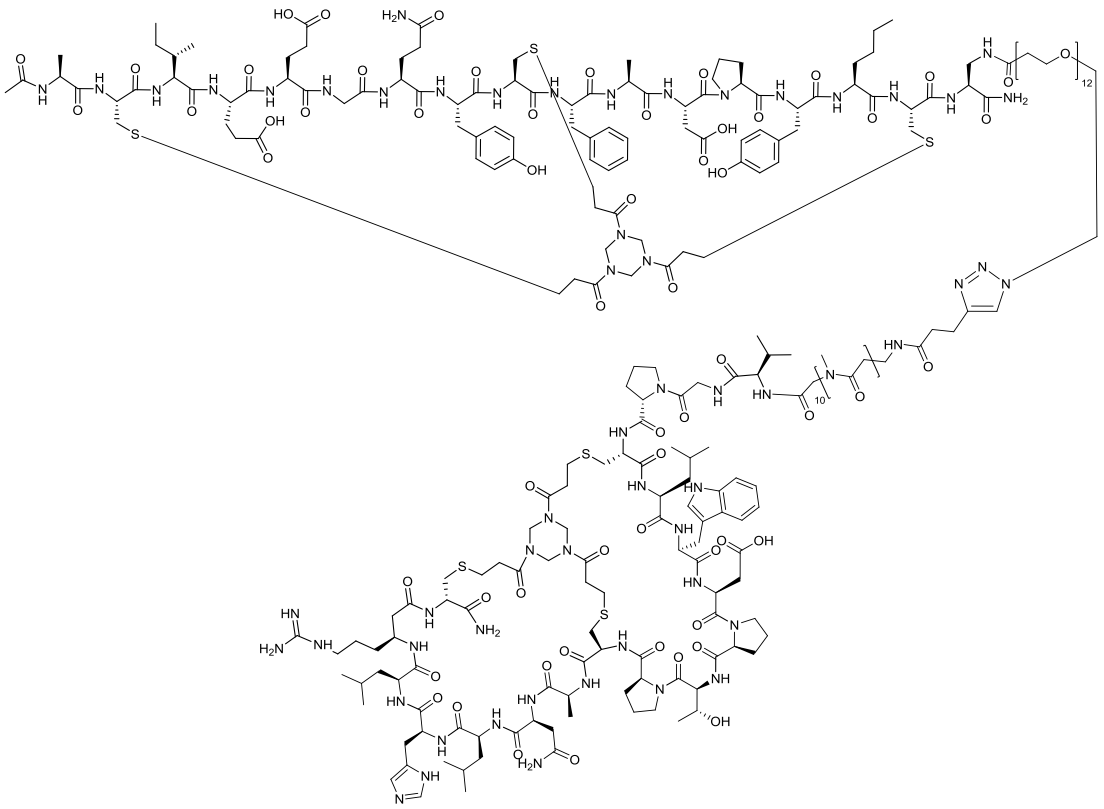
,

BCY8942



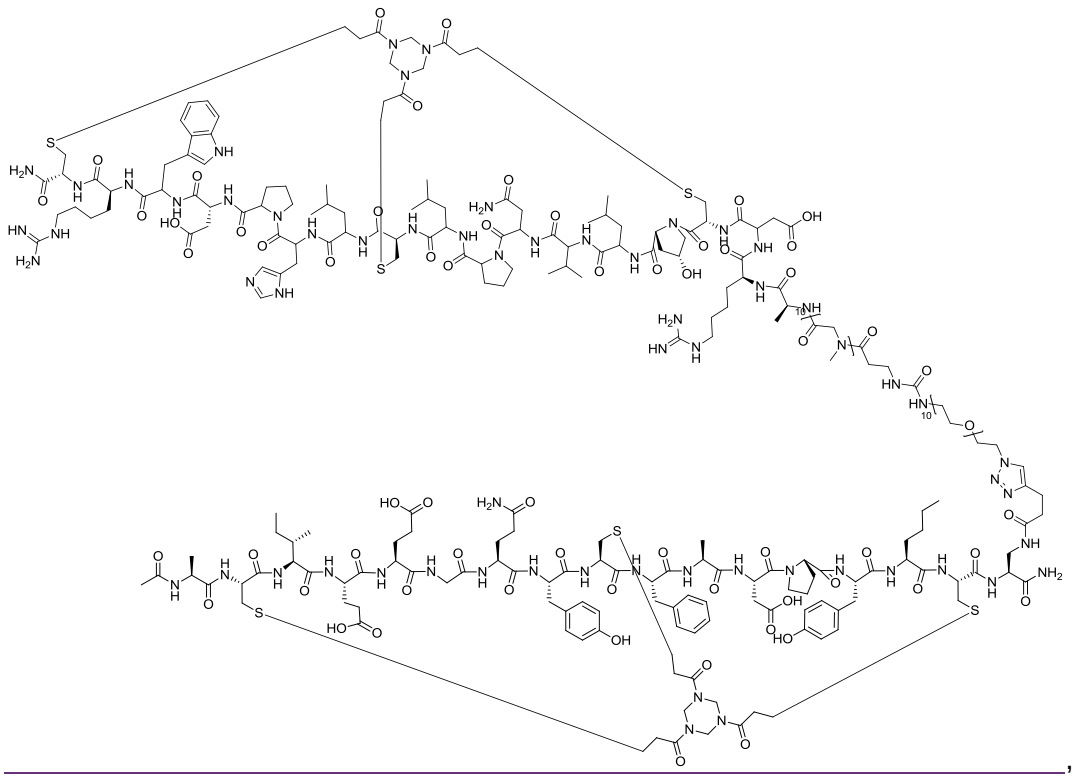
,

BCY8943



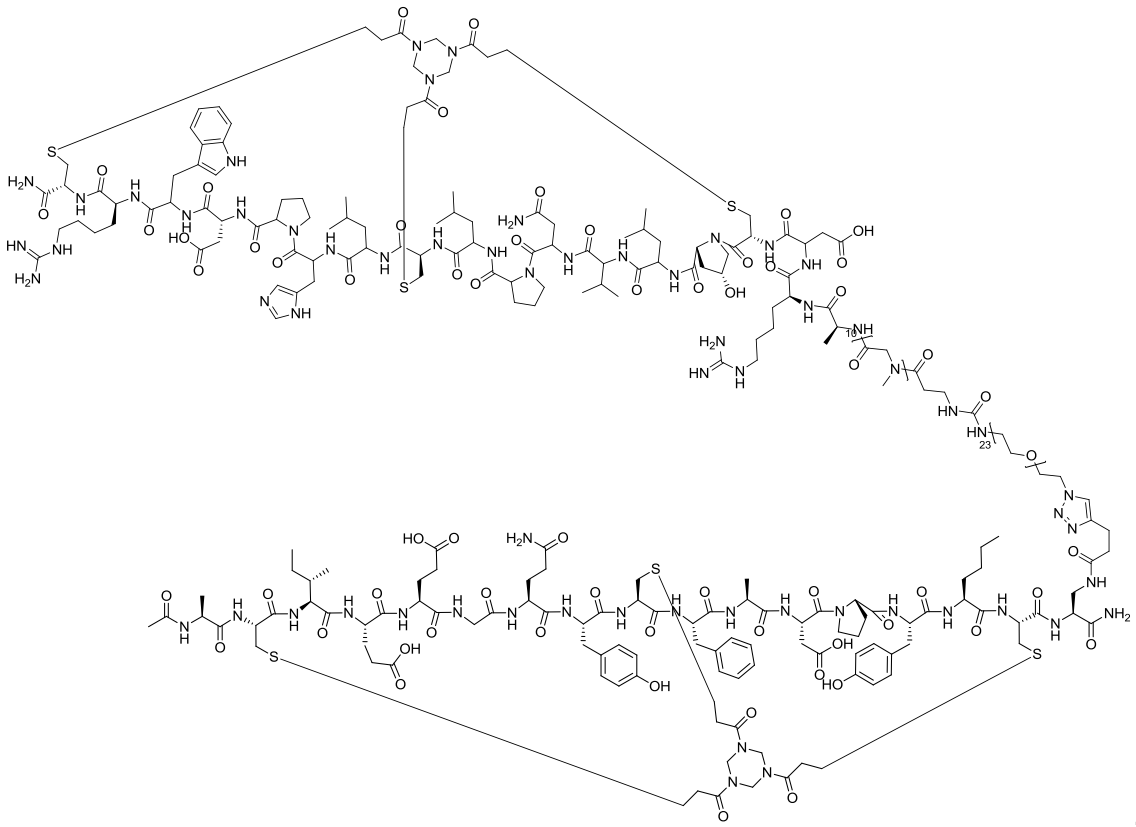
,

BCY9647



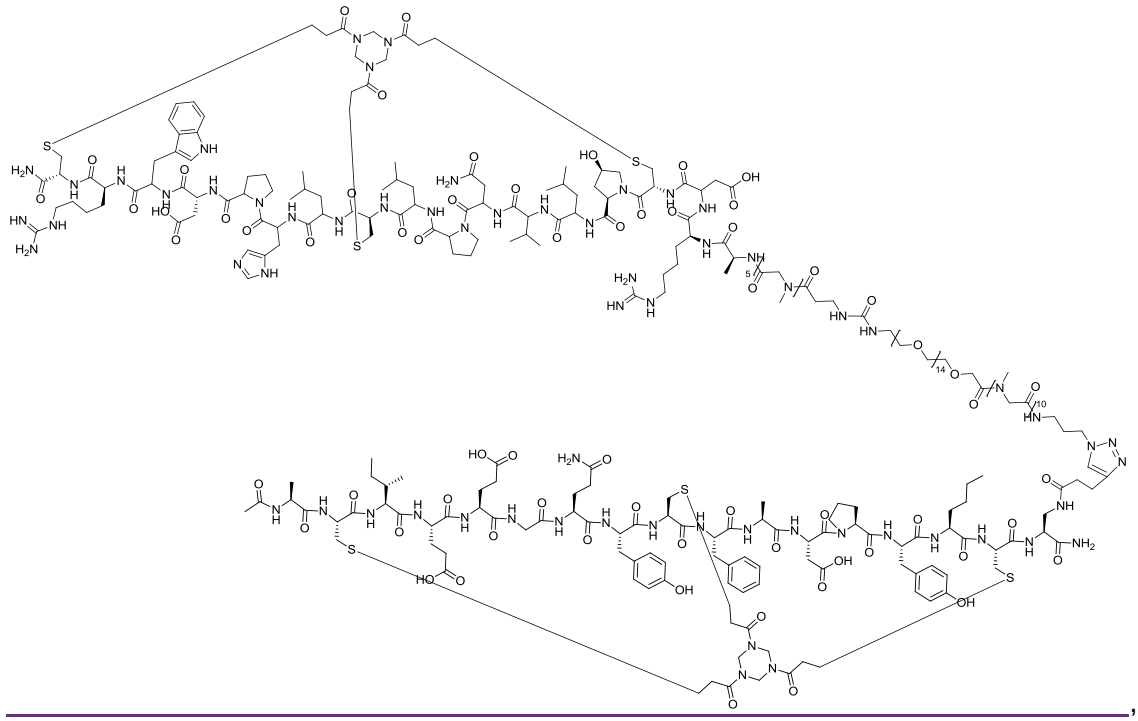
,

BCY9648



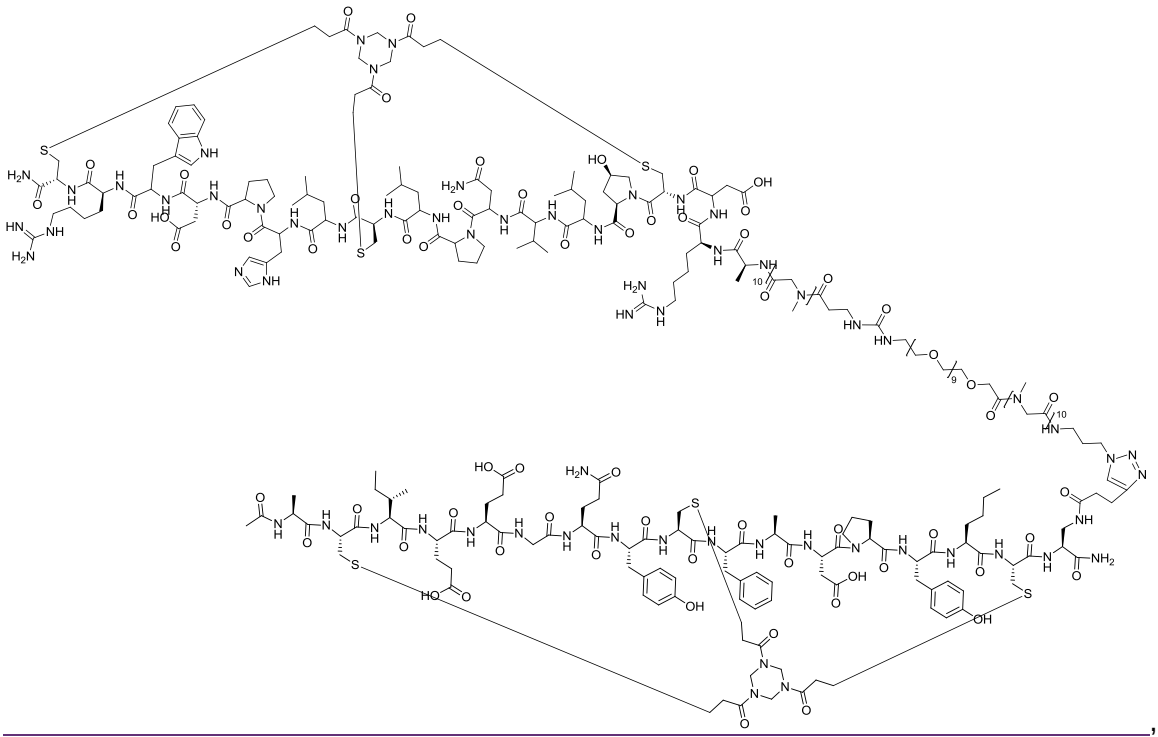
,

BCY9655



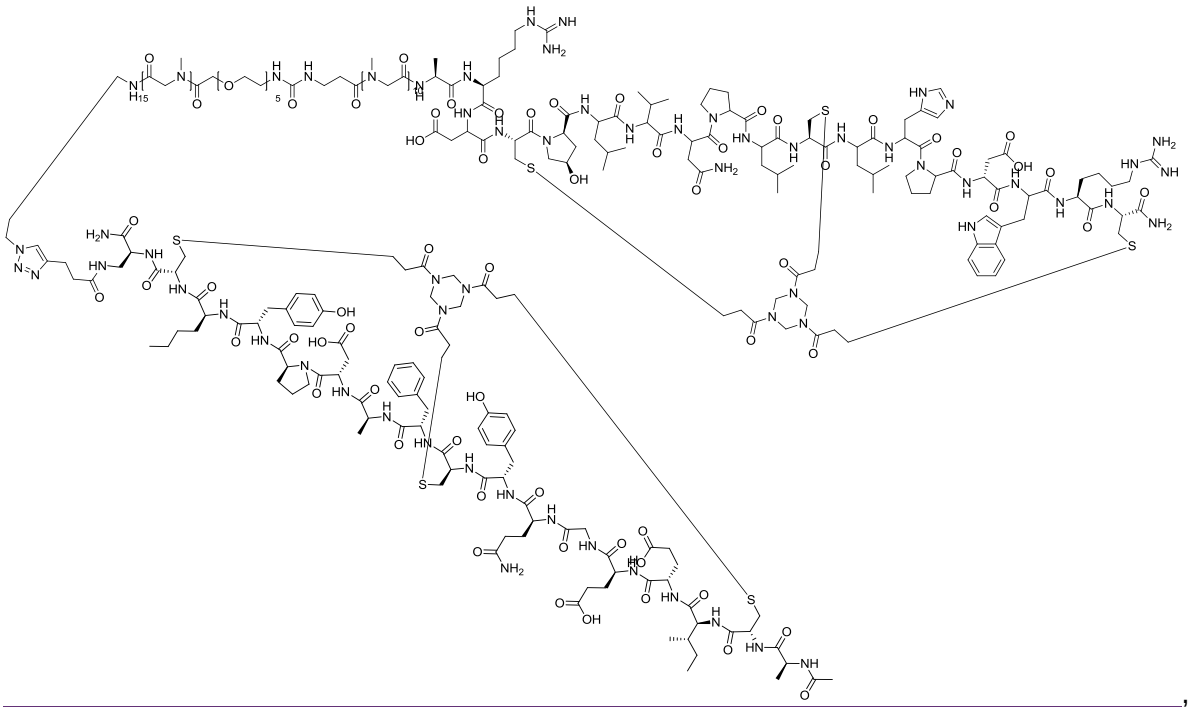
,

BCY9656



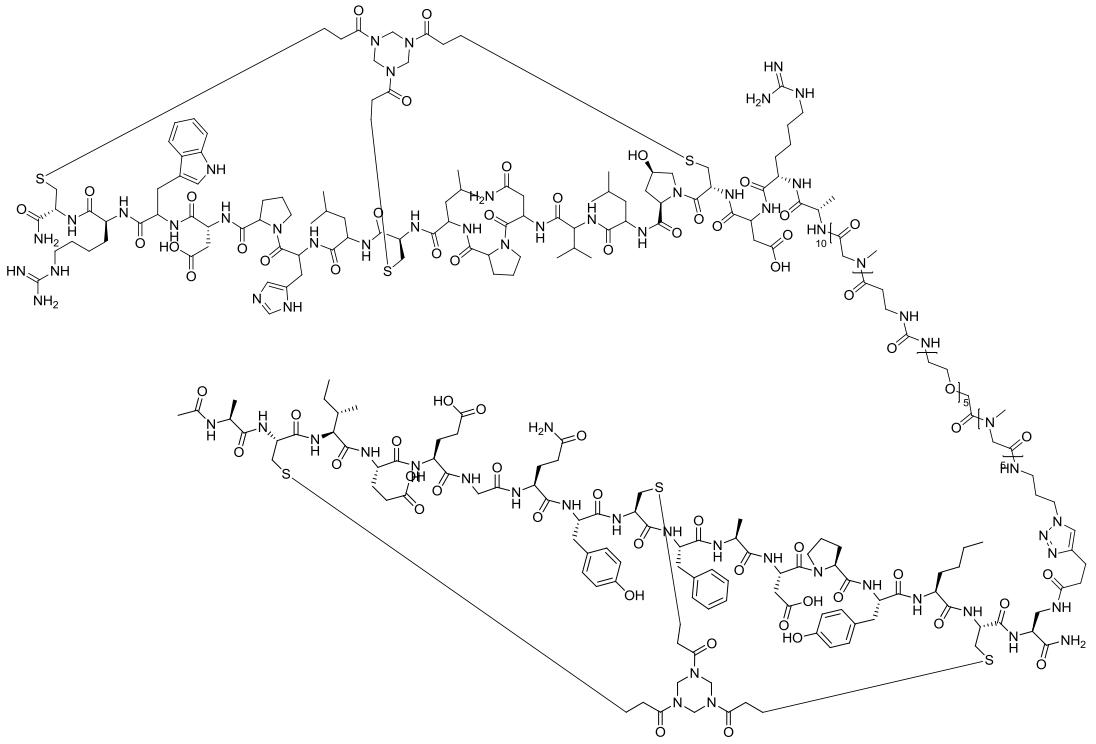
,

BCY9657



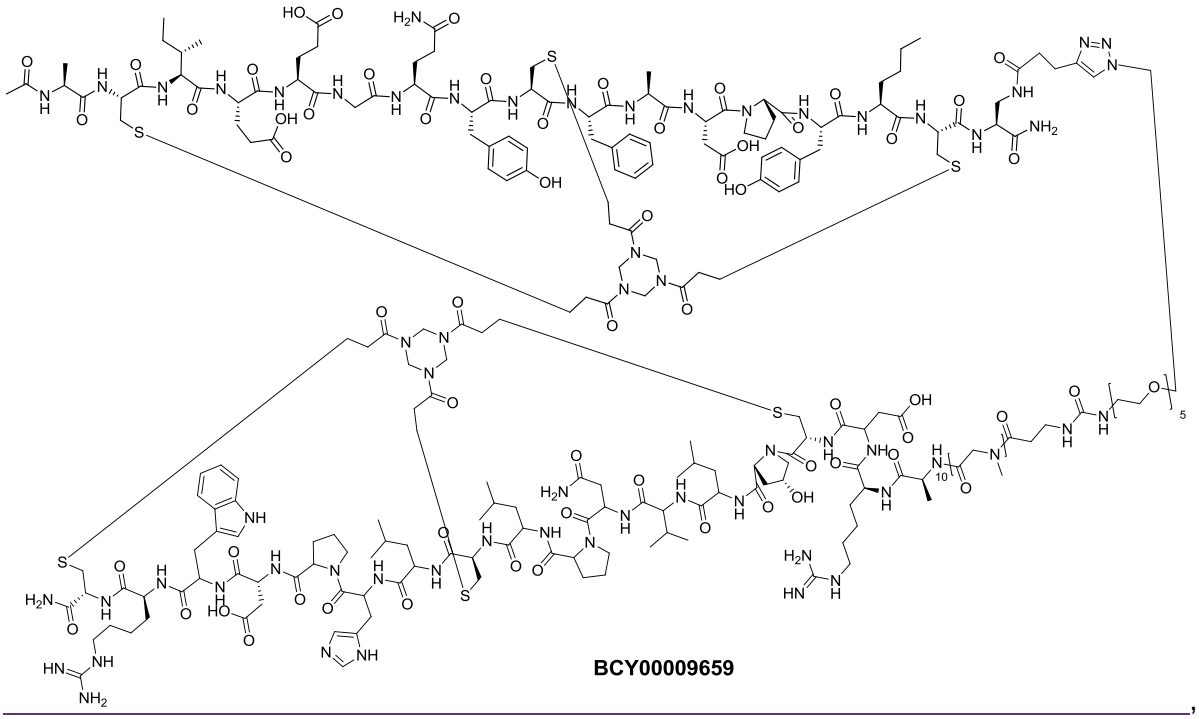
,

BCY9658



,

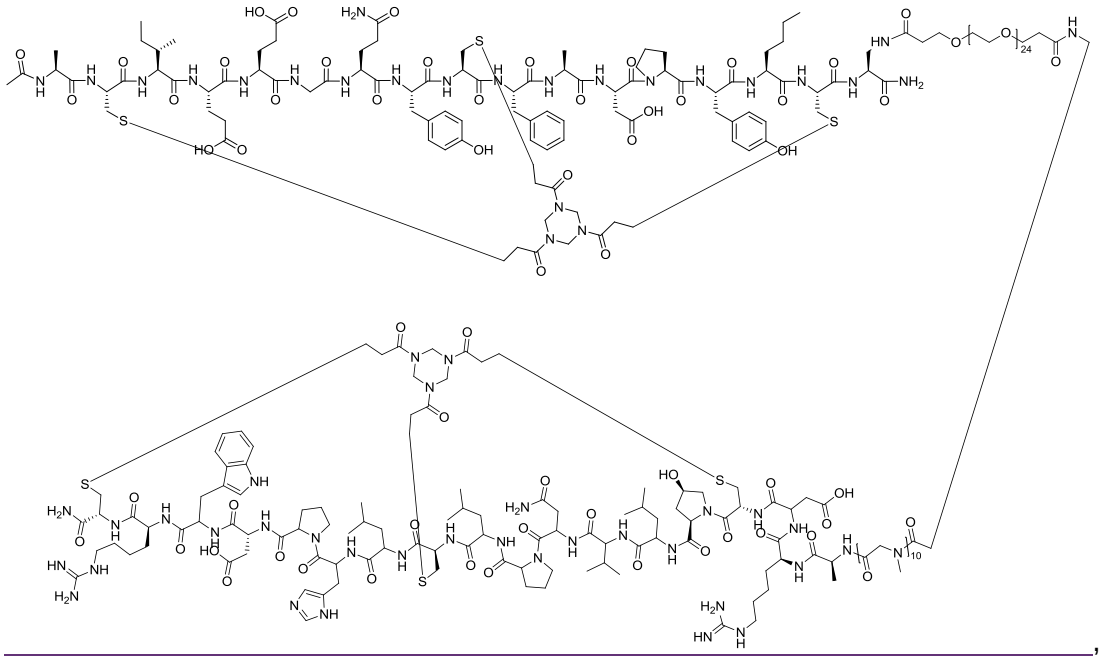
BCY9659



BCY00009659

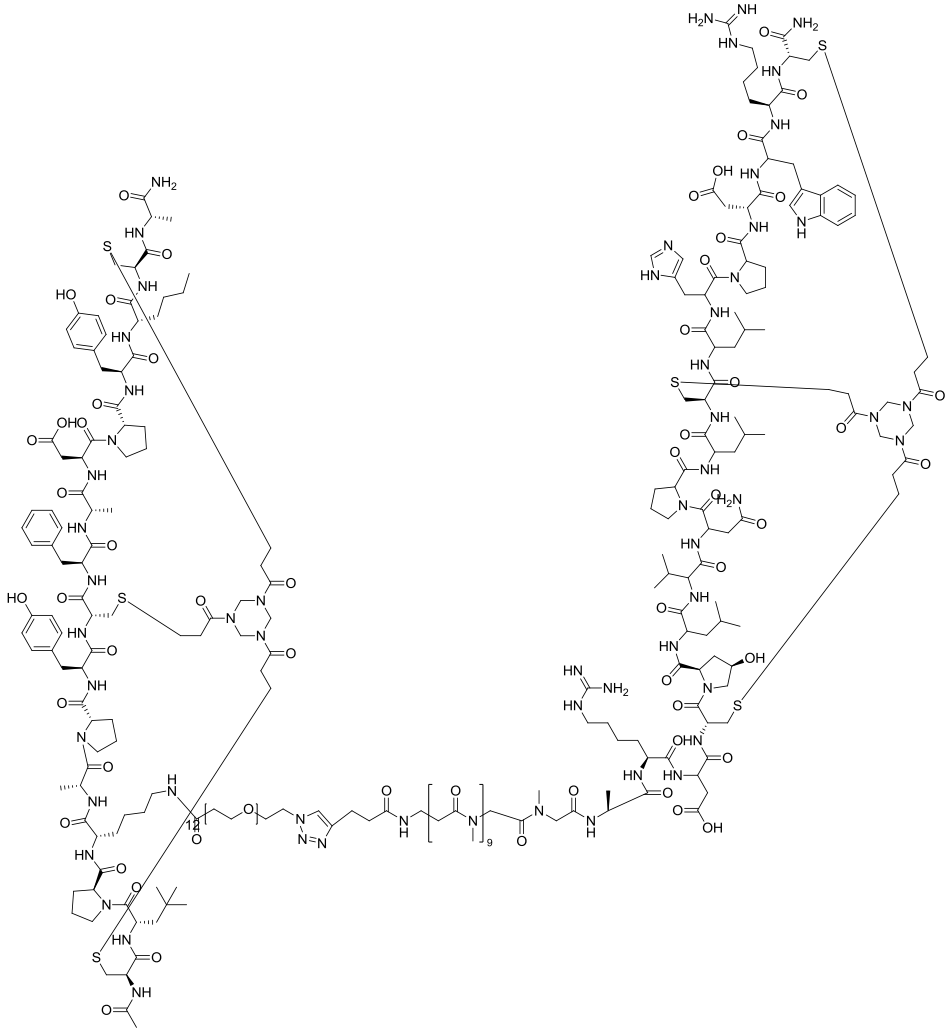
,

BCY9758



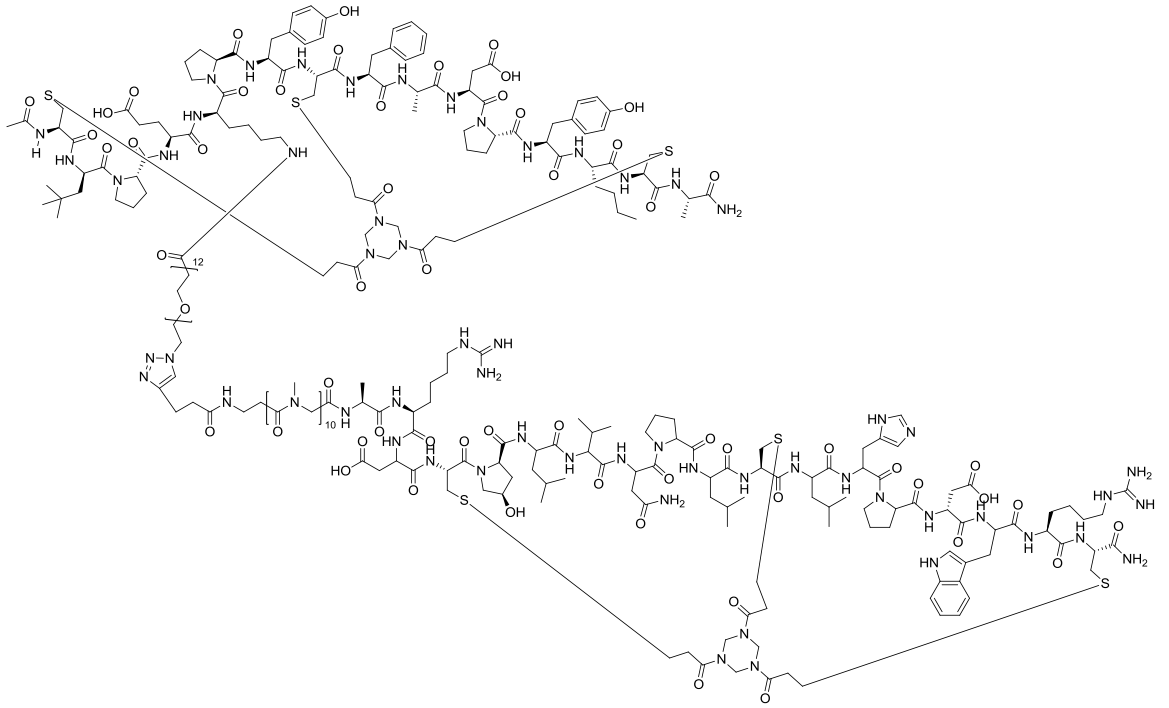
,

BCY10568



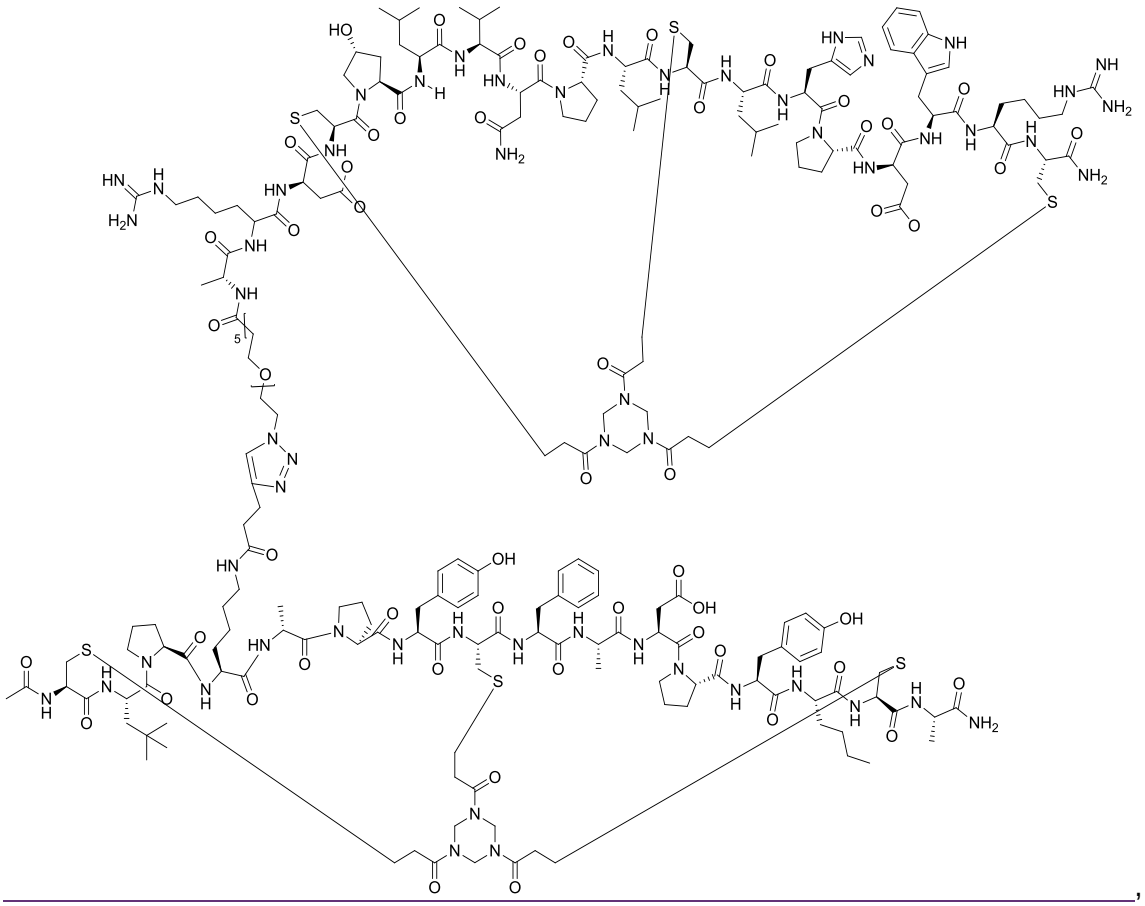
,

BCY10570



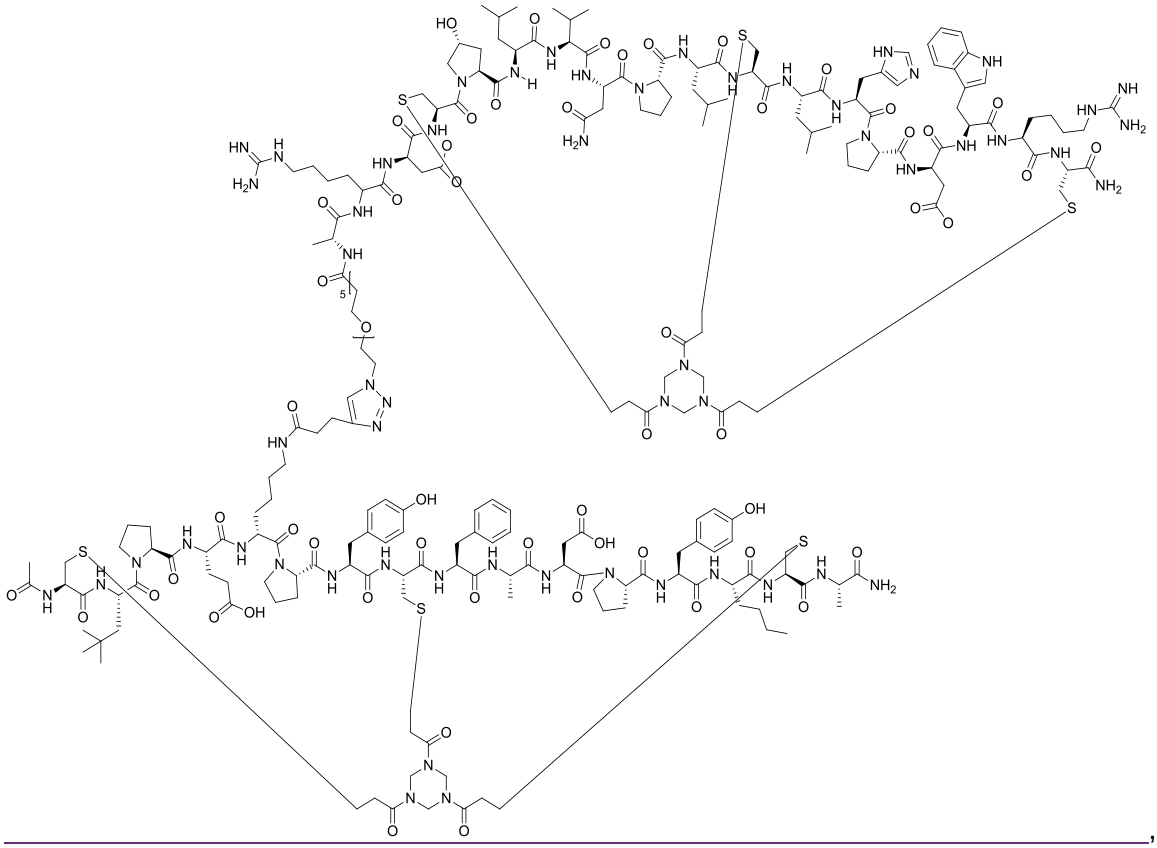
,

BCY10574



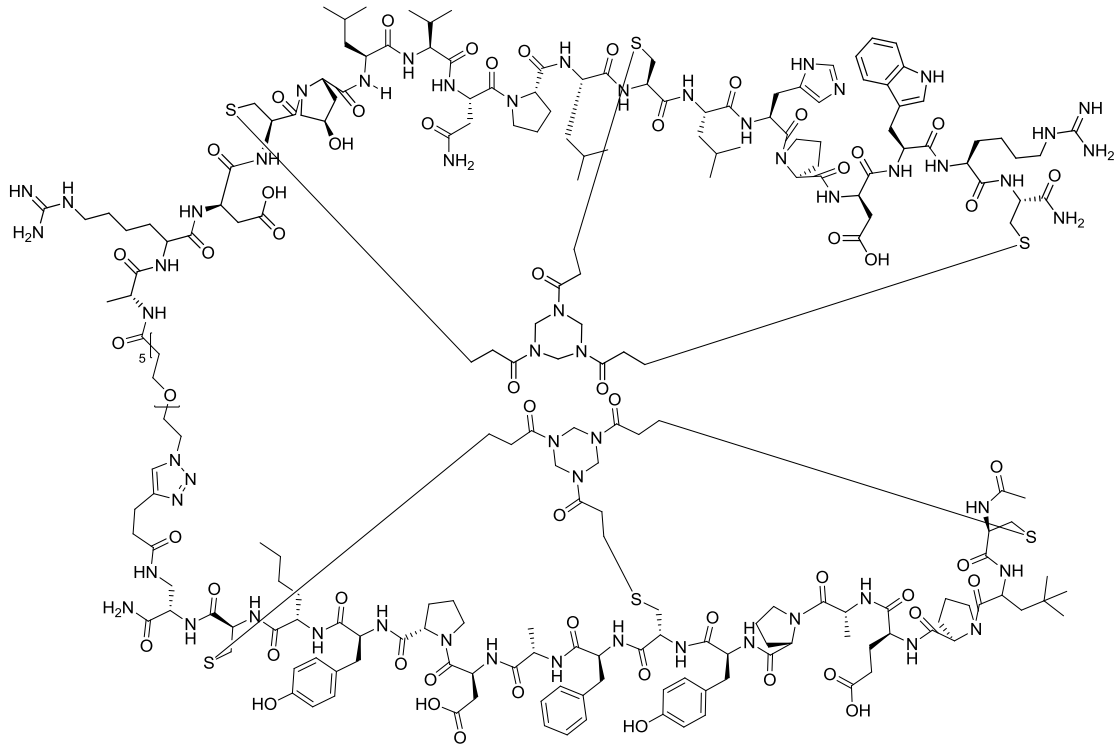
,

BCY10575



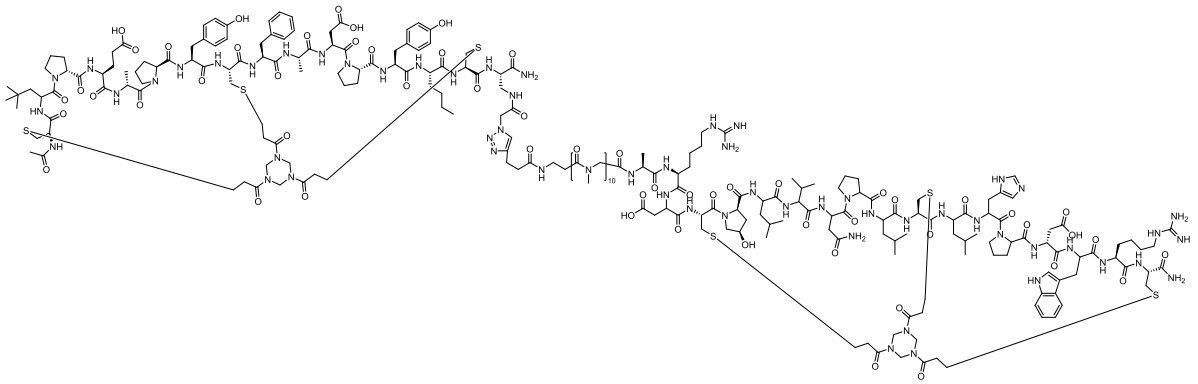
,

BCY10576



, and

BCY10577



.

13. The heterotandem bicyclic peptide complex as defined in any one of claims 1 to 7, wherein the component present on a cancer cell is PD-L1.

14. The heterotandem bicyclic peptide complex as defined in any one of claims 1 to 7 and 13, wherein the second peptide ligand comprises PD-L1 binding bicyclic peptide ligand.

15. The heterotandem bicyclic peptide complex as defined in claim 14, wherein the PD-L1 binding bicyclic peptide ligand comprises an amino acid sequence selected from:

C_i[HArg]DWC_{ii}HWTFSHGHPC_{iii} (SEQ ID NO: 12);

C_iSAGWLTMC_{ii}QKLHLC_{iii} (SEQ ID NO: 13); and

C_iSAGWLTMC_{ii}Q[K(PYA)]LHLC_{iii} (SEQ ID NO: 14);

wherein C_i, C_{ii} and C_{iii} represent first, second and third cysteine residues, respectively, HArg represents homoarginine and PYA represents 4-pentynoic acid, or a pharmaceutically acceptable salt thereof.

16. The heterotandem bicyclic peptide complex as defined in claim 15, wherein the PD-L1 binding bicyclic peptide ligand comprises N-terminal and/or C-terminal modifications and comprises:

[PYA]-[B-Ala]-[Sar_{10}]-(SEQ ID NO: 12) (hereinafter referred to as BCY8938);

[PYA]-[B-Ala]-[Sar_{10}]-SDK-(SEQ ID NO: 13) (hereinafter referred to as BCY10043);

NH_2-SDK-(SEQ ID NO: 13)-[Sar_{10}]-[K(PYA)] (hereinafter referred to as BCY10044);

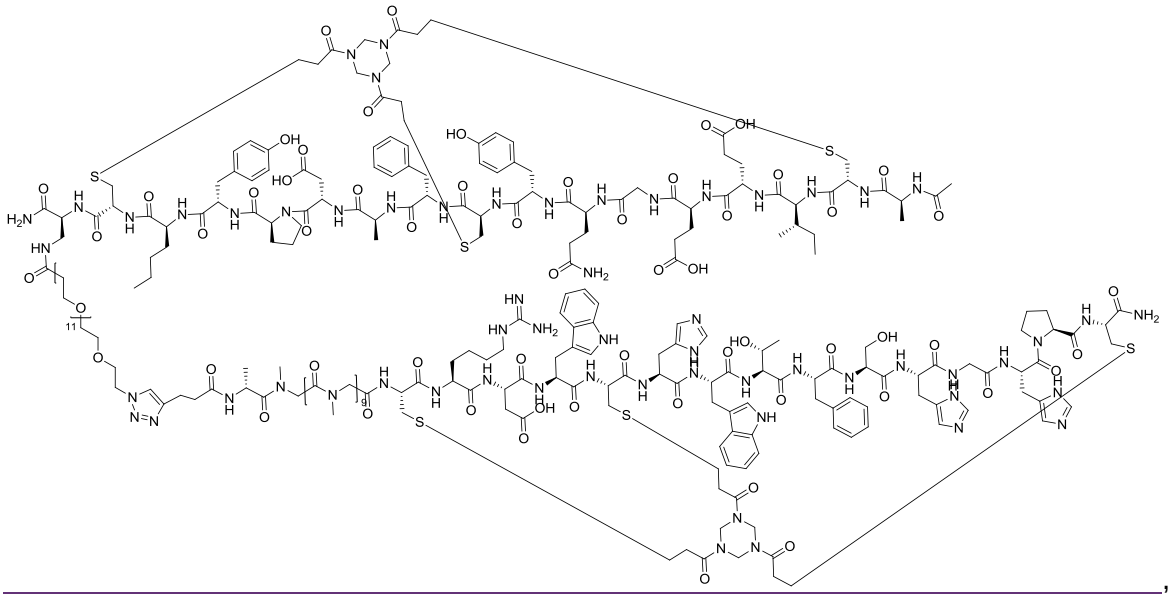
NH_2-SDK-(SEQ ID NO: 14) (hereinafter referred to as BCY10045); and

Ac-SDK-(SEQ ID NO: 14)-PSH (hereinafter referred to as BCY10861);

wherein PYA represents 4-pentynoic acid, B-Ala represents beta-alanine, Sar_{10} represents 10 sarcosine units, or a pharmaceutically acceptable salt thereof.

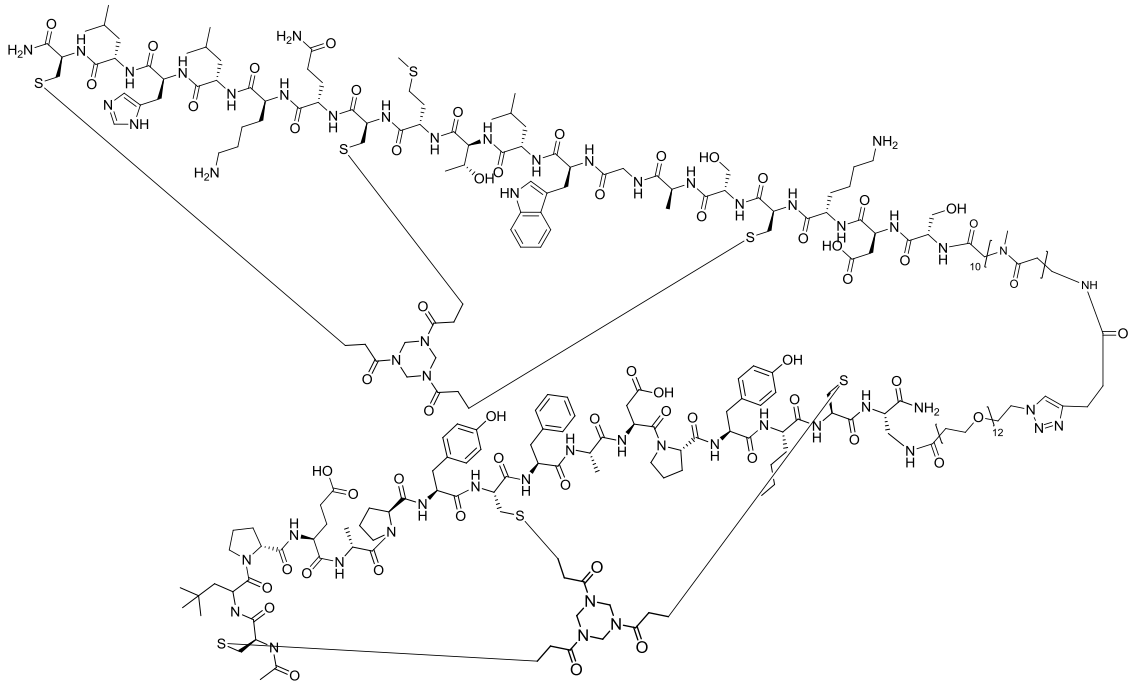
17. The heterotandem bicyclic peptide complex as defined in any one of claims 14 to 16 which is a CD137/PD-L1 complex selected from:

BCY8939



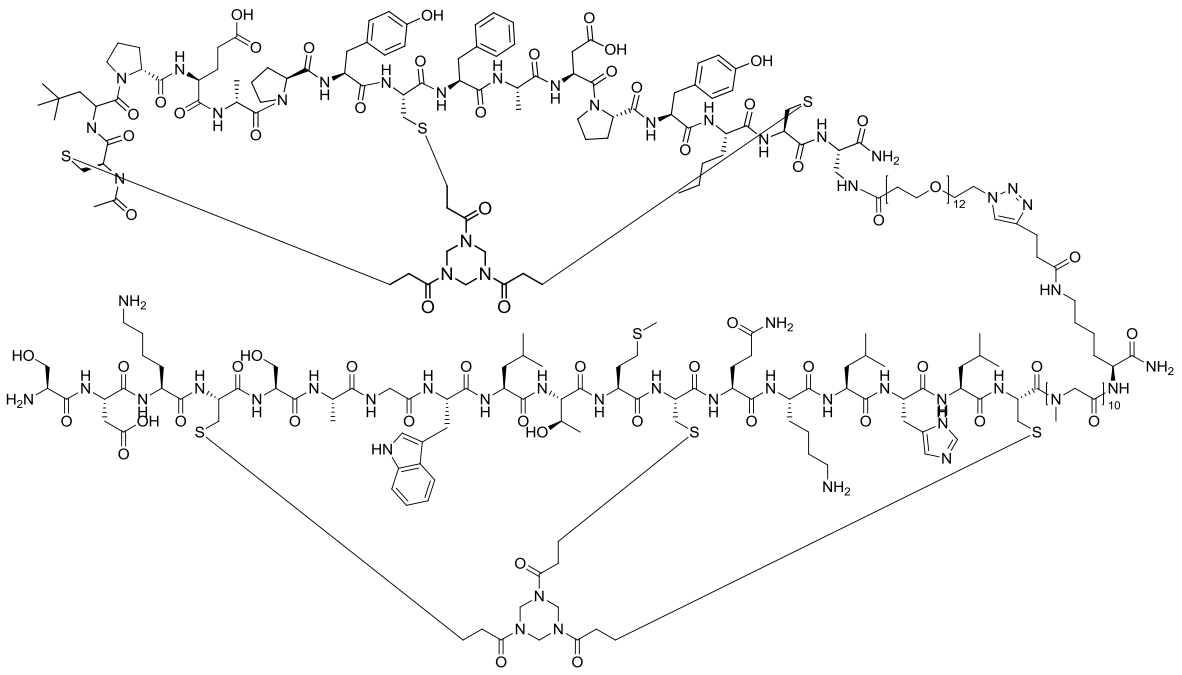
,

BCY10580



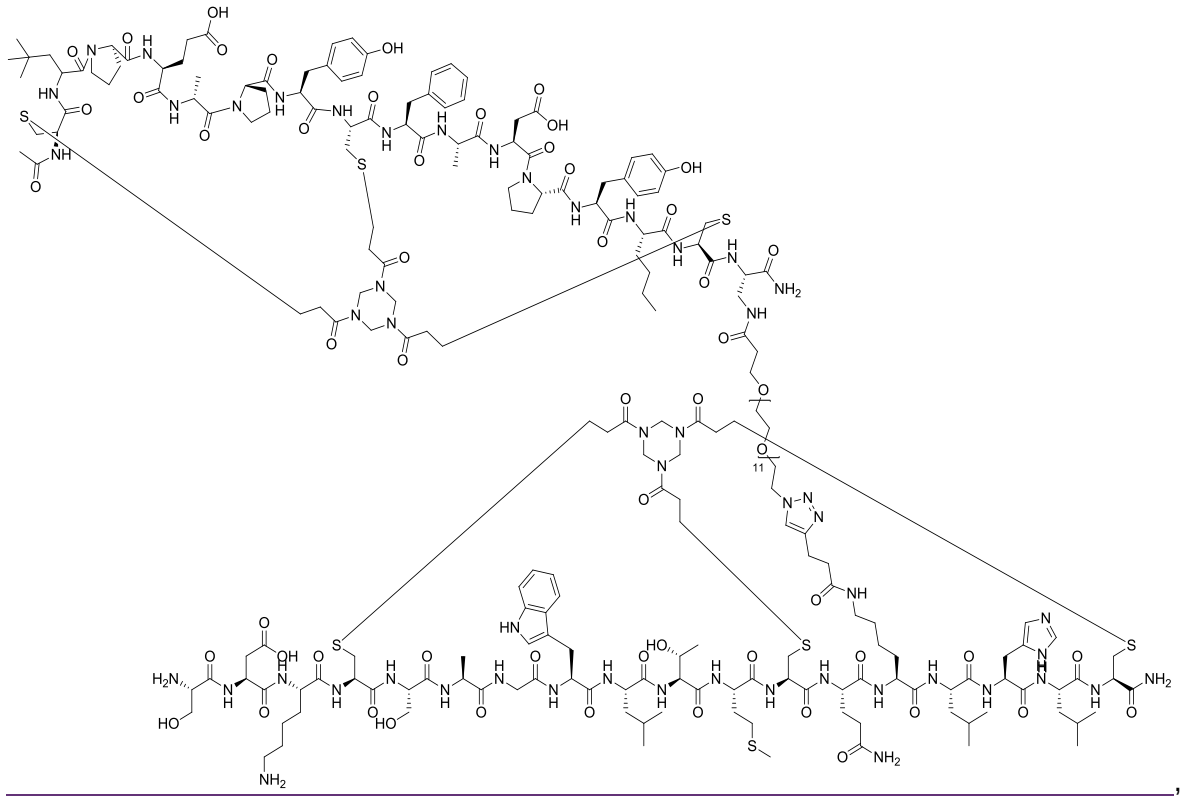
,

BCY10581



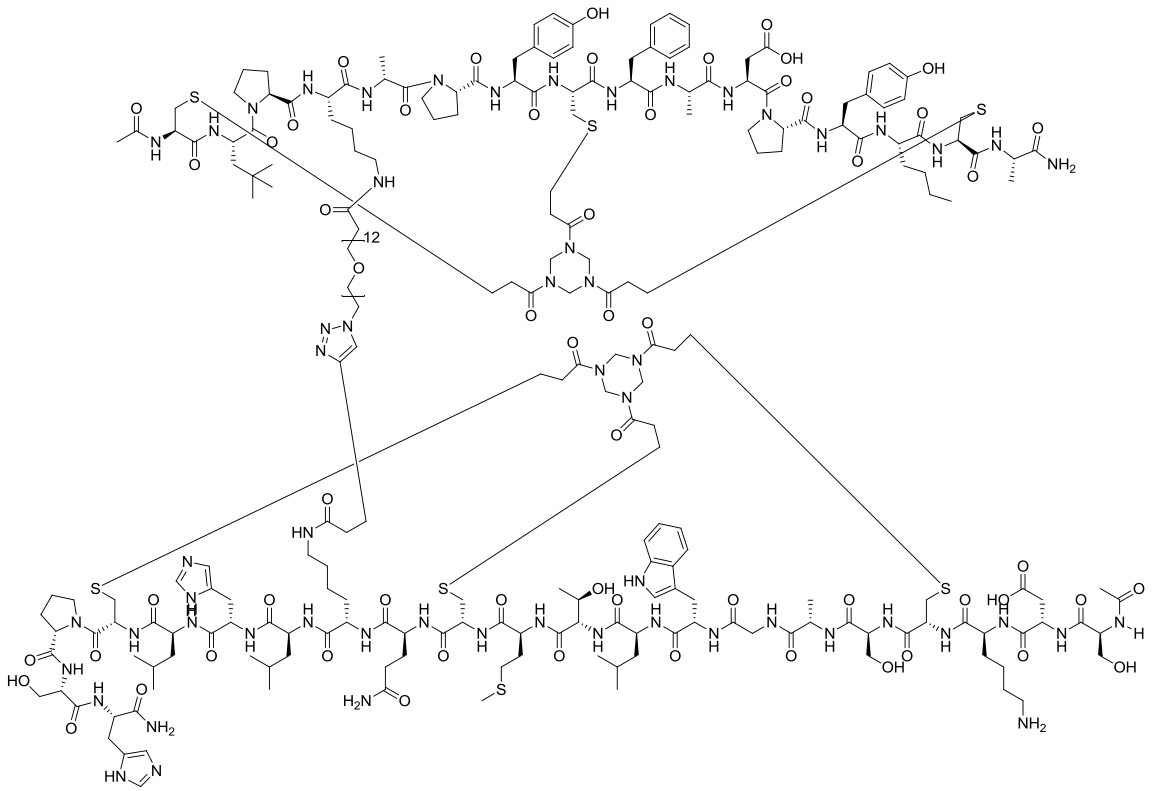
,

BCY10582



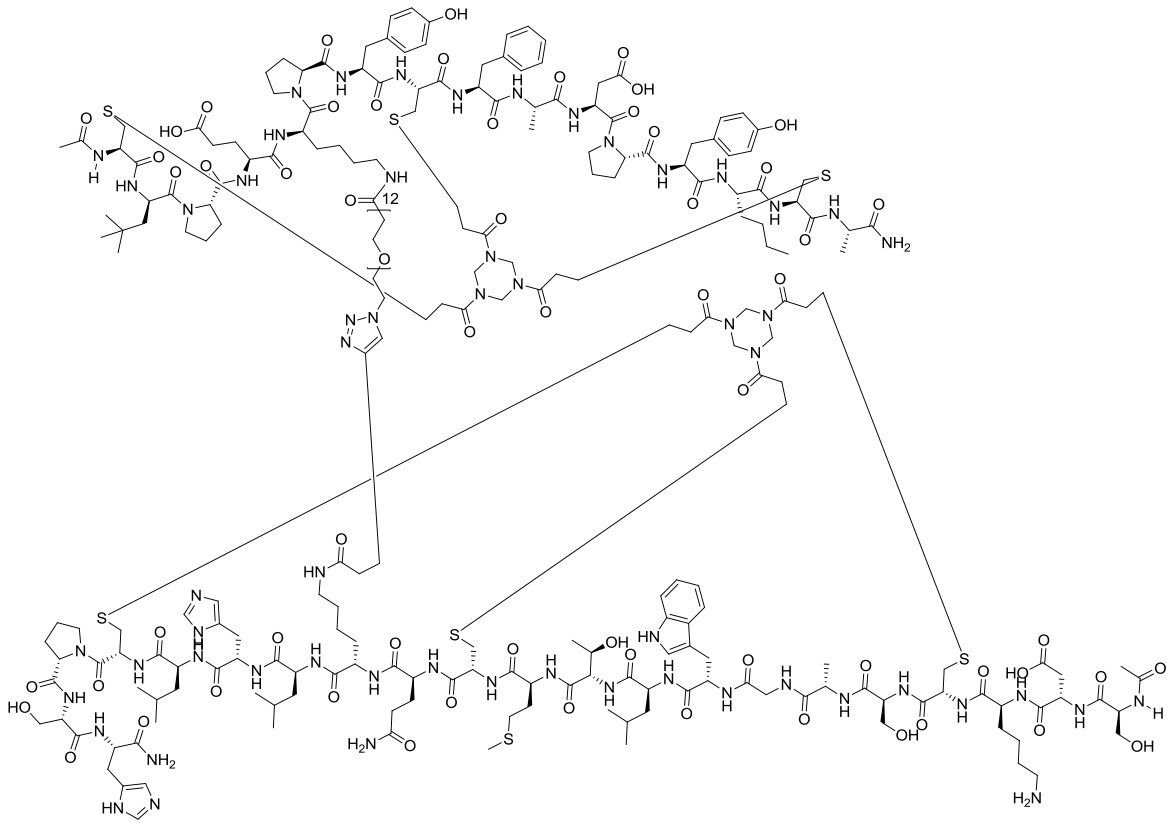
,

BCY11017



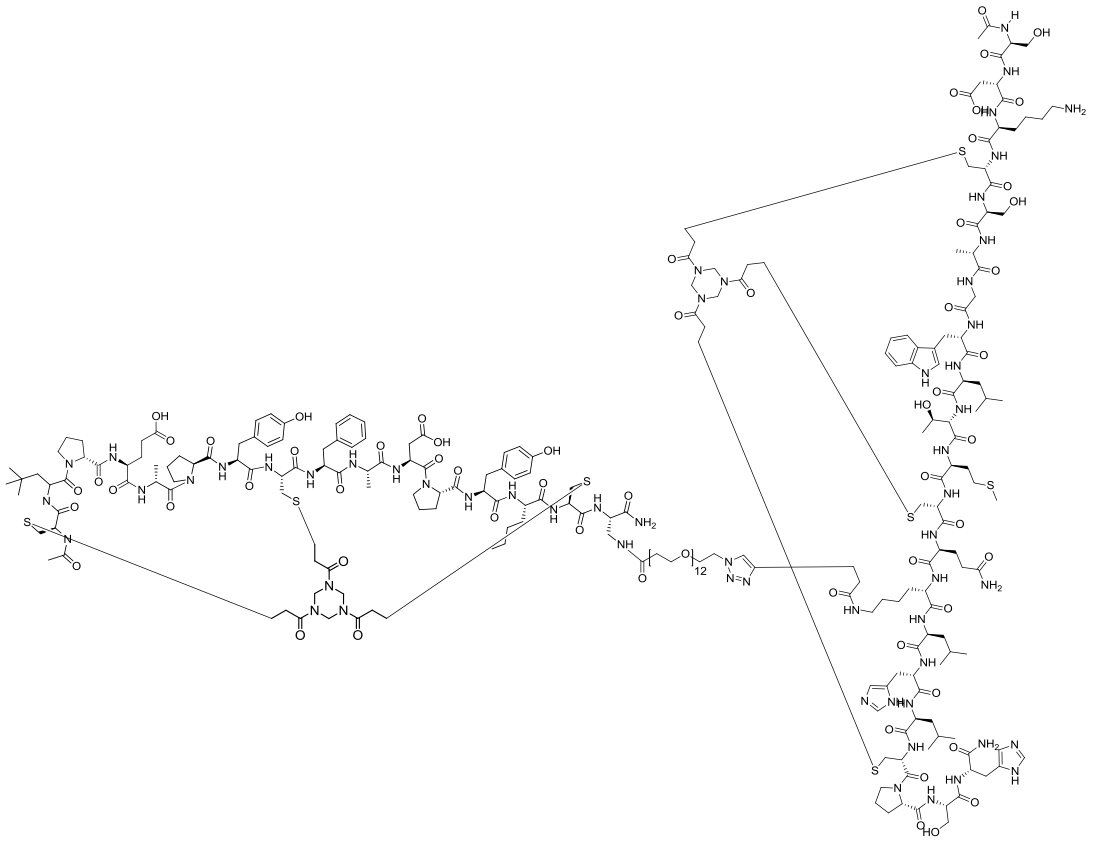
,

BCY11018



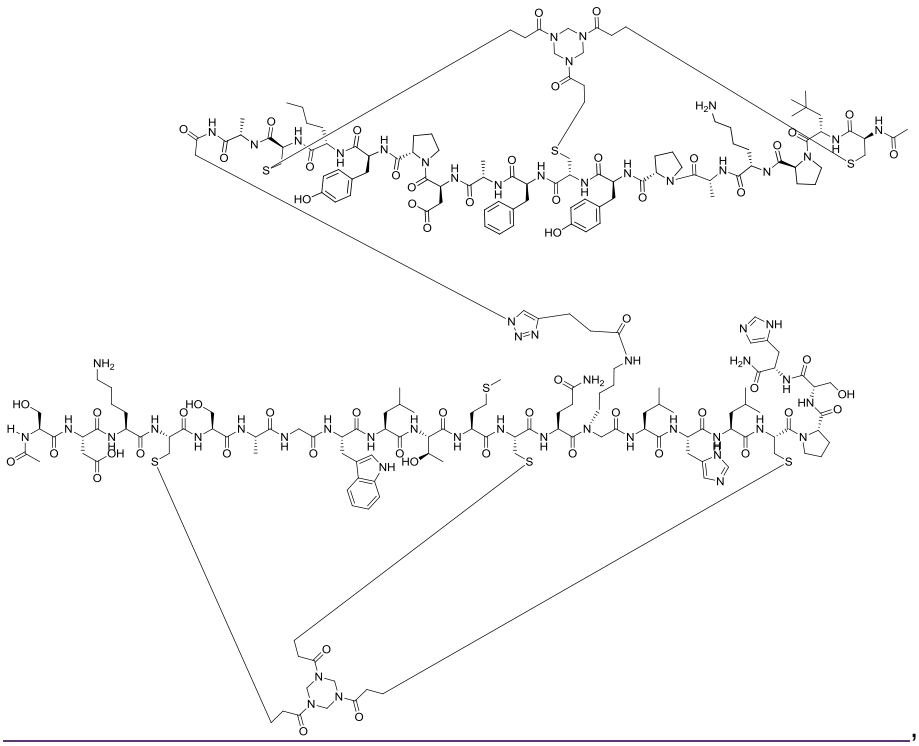
,

BCY11019



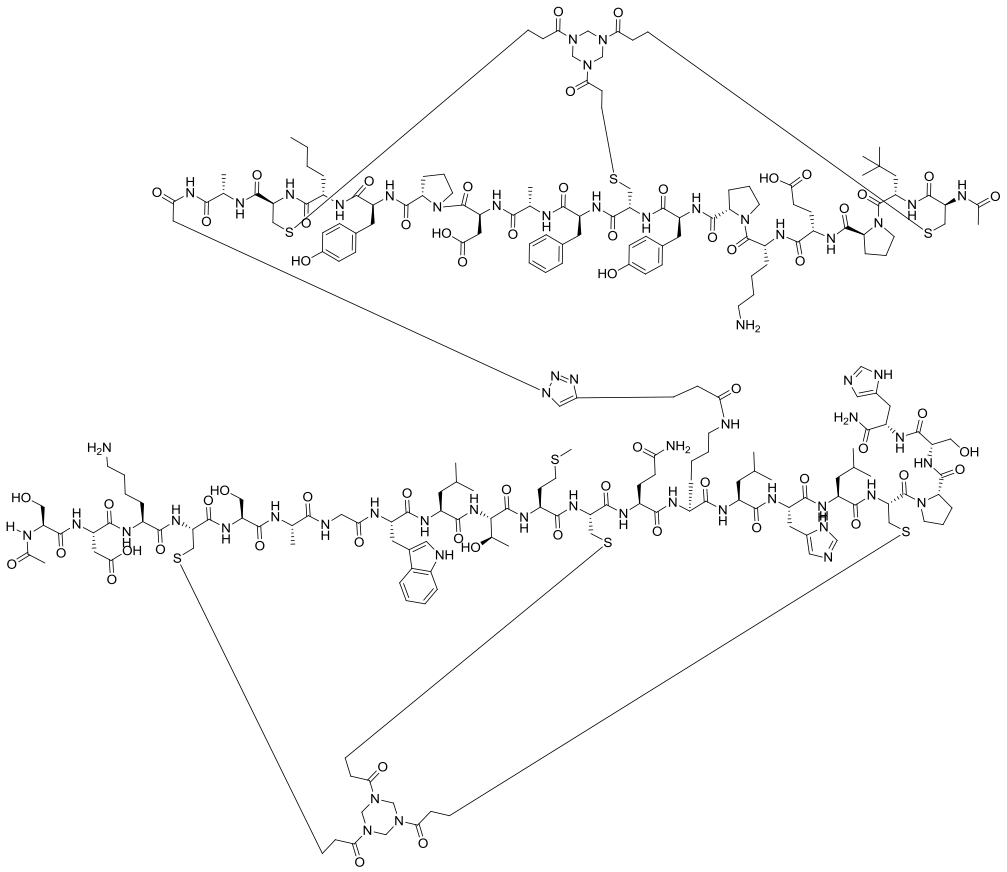
,

BCY11376



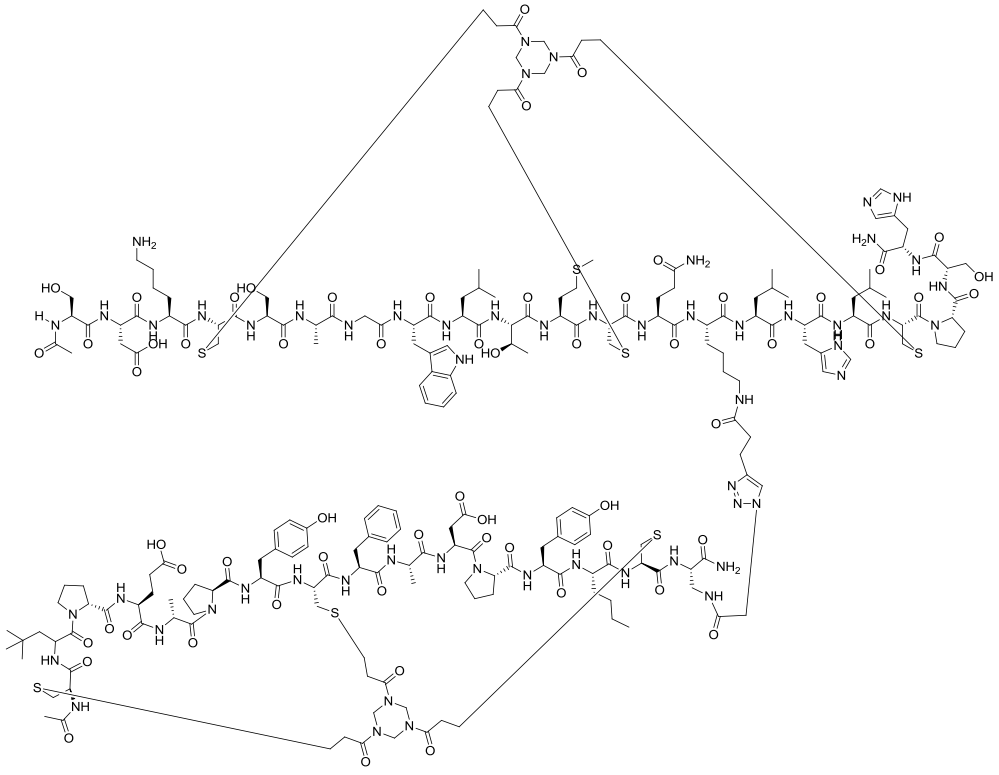
,

BCY11377



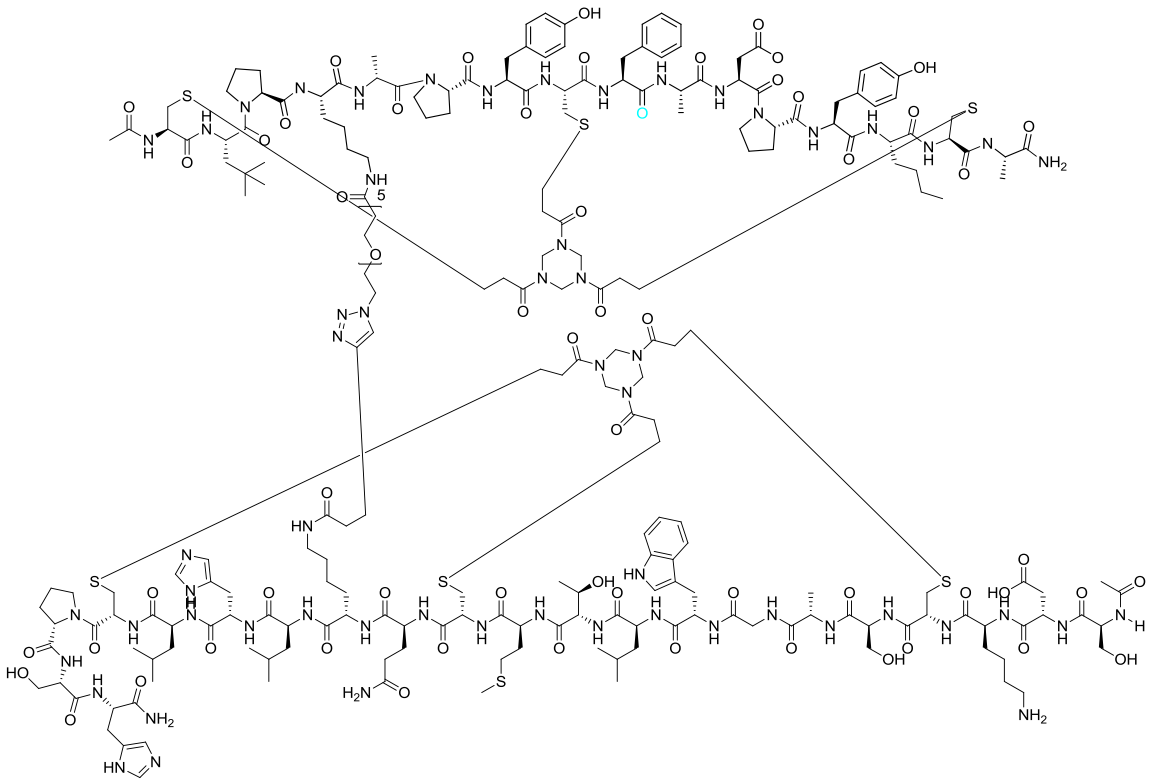
,

BCY11378



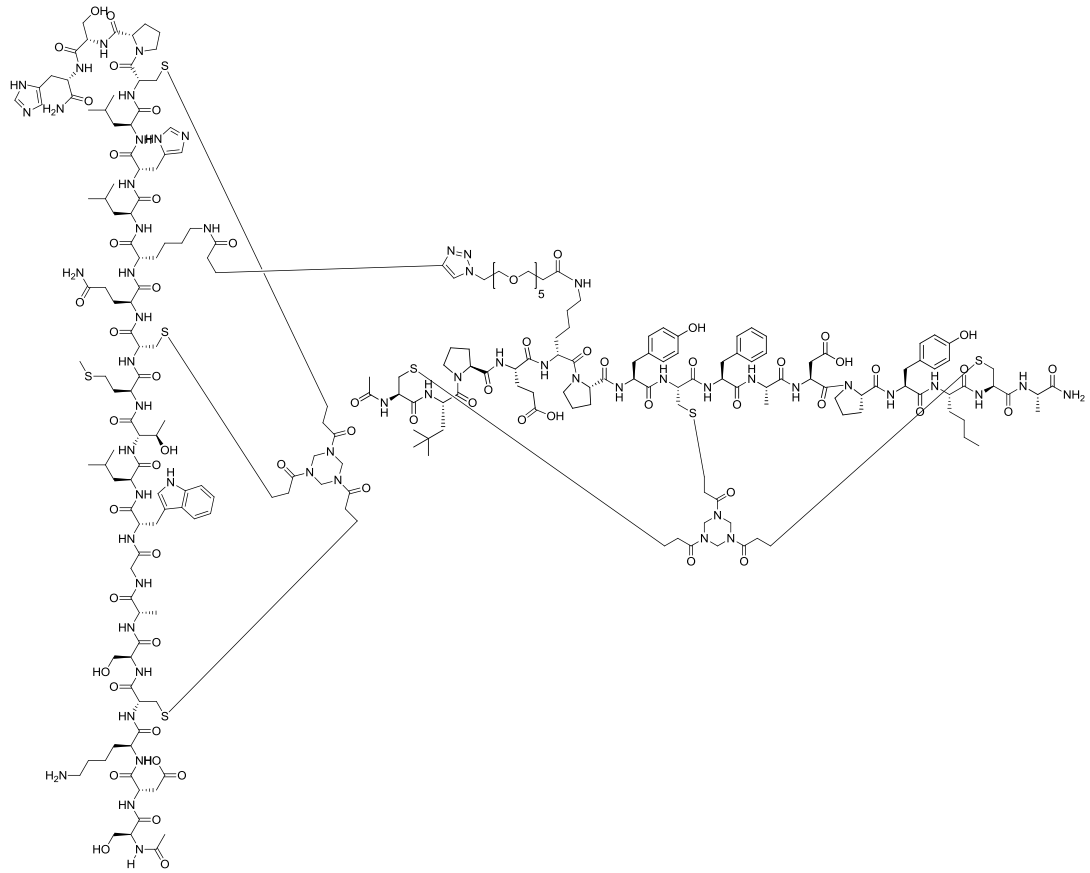
,

BCY11379



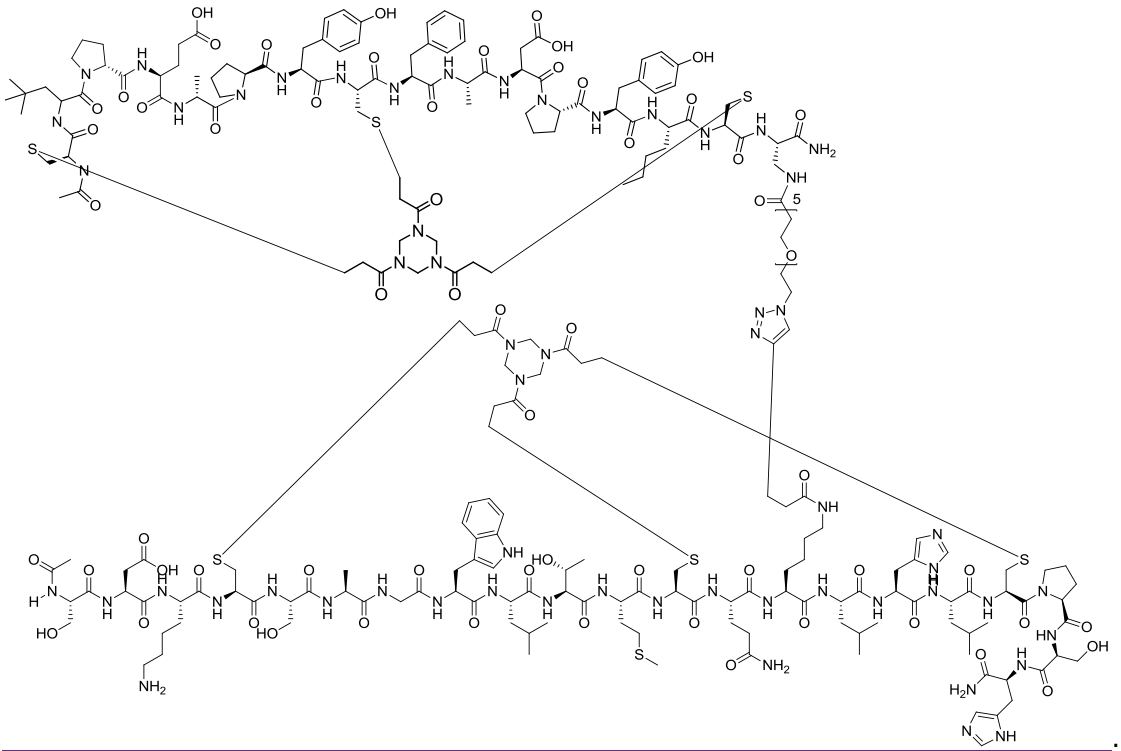
,

BCY11380



, and

BCY11381



.

18. The heterotandem bicyclic peptide complex as defined in any one of claims 1 to 7, wherein the component present on a cancer cell is Nectin-4.

19. The heterotandem bicyclic peptide complex as defined in any one of claims 1 to 7 and 18, wherein the second peptide ligand comprises Nectin-4 binding bicyclic peptide ligand.

20. The heterotandem bicyclic peptide complex as defined in claim 19, wherein the Nectin-4 binding bicyclic peptide ligand comprises an amino acid sequence selected from:

$C_iP[1Nal][dD]C_{ii}M[HArg]DWSTP[HyP]WC_{iii}$ (SEQ ID NO: 15; hereinafter referred to as BCY8116);

$C_iP[1Nal][dD]C_{ii}M[HArg]D[dW]STP[HyP][dW]C_{iii}$ (SEQ ID NO: 16; hereinafter referred to as BCY11415); and

$C_iP[1Nal][dK](Sar_{10}\text{-}(B\text{-}Ala))C_{ii}M[HArg]DWSTP[HyP]WC_{iii}$ (SEQ ID NO: 17);

$C_iPFGC_{ii}M[HArg]DWSTP[HyP]WC_{iii}$ (SEQ ID NO: 18; hereinafter referred to as BCY11414);

wherein C_i, C_{ii} and C_{iii} represent first, second and third cysteine residues, respectively, 1Nal represents 1-naphthylalanine, HArg represents homoarginine, HyP represents hydroxyproline, Sar_{10} represents 10 sarcosine units, B-Ala represents beta-alanine, or a pharmaceutically acceptable salt thereof.

21. The heterotandem bicyclic peptide complex as defined in claim 20, wherein the Nectin-4 binding bicyclic peptide ligand optionally comprises N-terminal modifications and comprises:

SEQ ID NO: 15 (hereinafter referred to as BCY8116);

[PYA]-[B-Ala]-[Sar_{10}]-(SEQ ID NO: 15) (hereinafter referred to as BCY8846);

SEQ ID NO: 16 (hereinafter referred to as BCY11415);

[PYA]-[B-Ala]-[Sar_{10}]-(SEQ ID NO: 16) (hereinafter referred to as BCY11942);

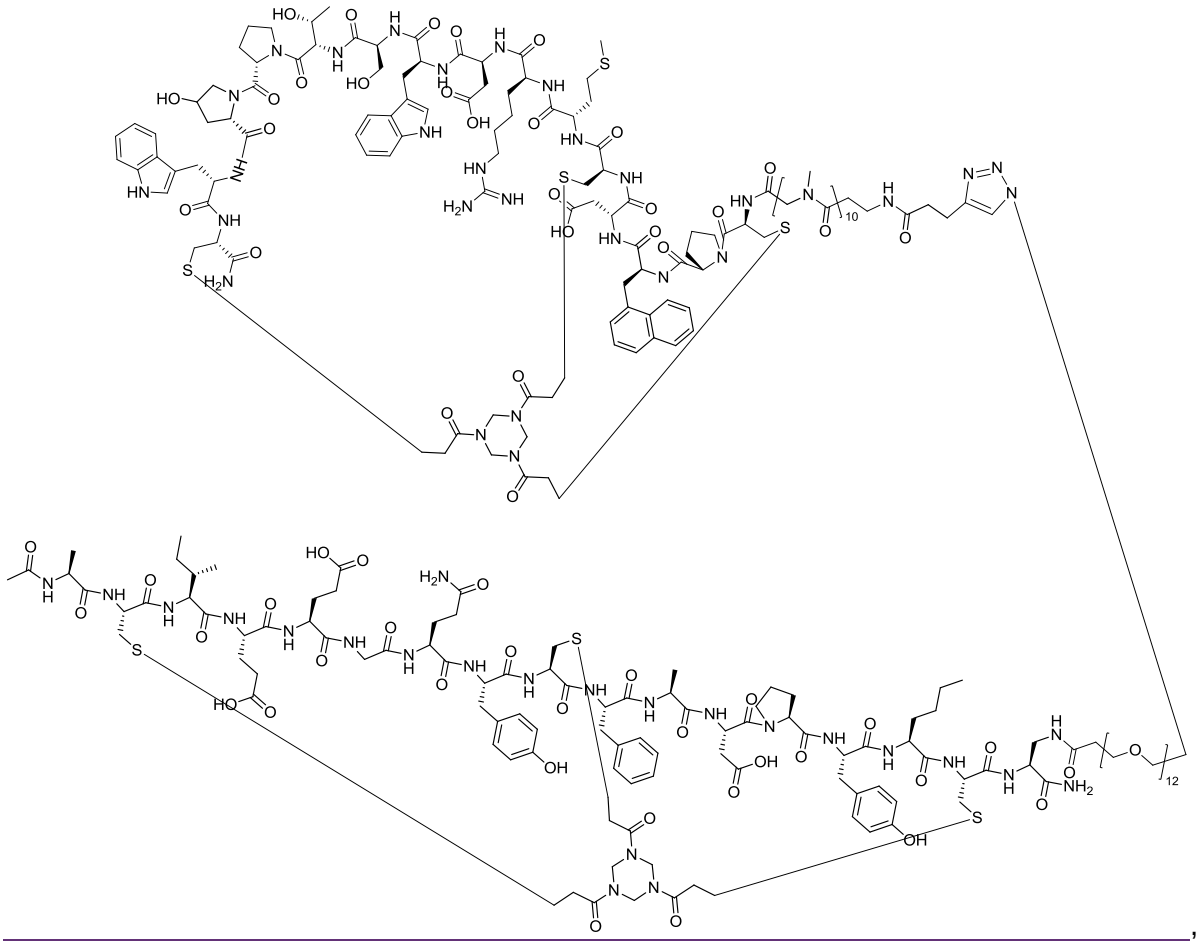
Ac-(SEQ ID NO: 17) (hereinafter referred to as BCY8831); and

SEQ ID NO: 18 (hereinafter referred to as BCY11414);

wherein PYA represents 4-pentynoic acid, B-Ala represents beta-alanine, Sar_{10} represents 10 sarcosine units, or a pharmaceutically acceptable salt thereof.

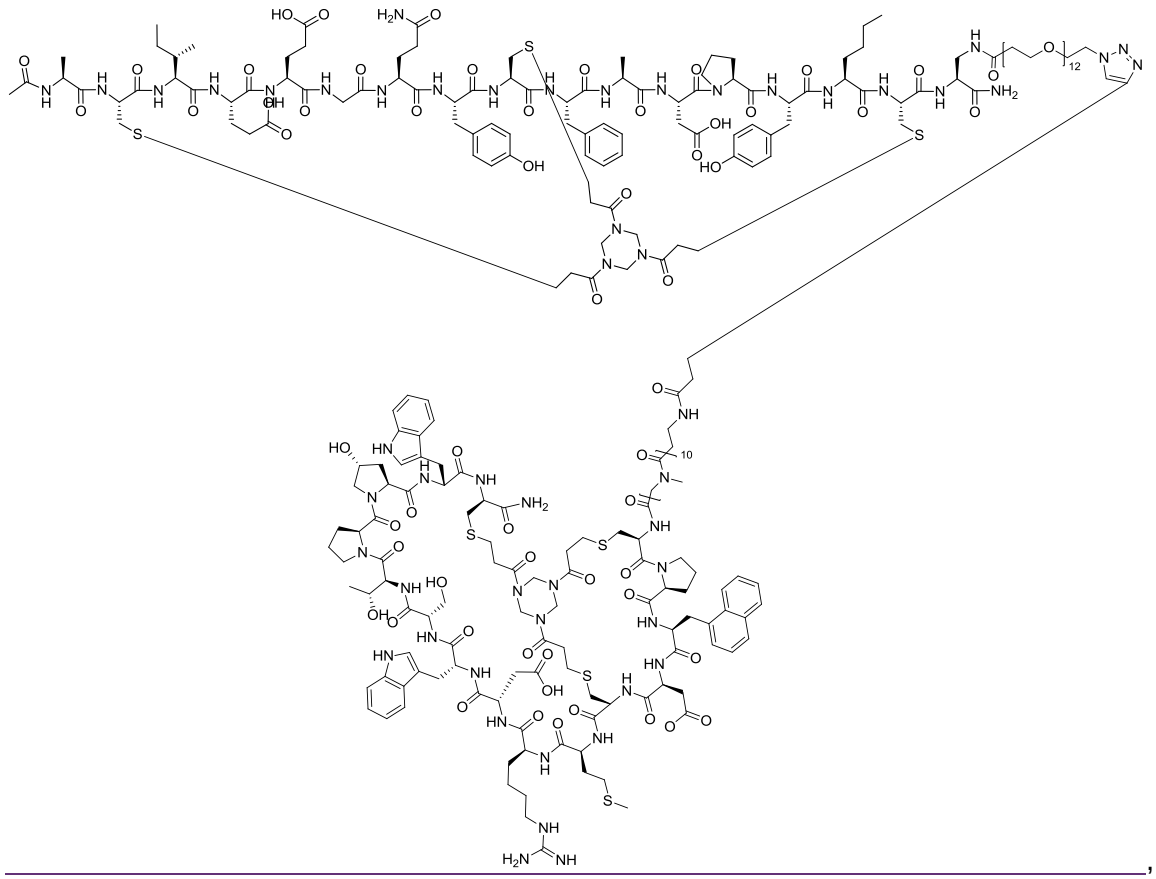
22. The heterotandem bicyclic peptide complex as defined in any one of claims 19 to 21 which is a CD137/Nectin-4 complex selected from:

BCY8854



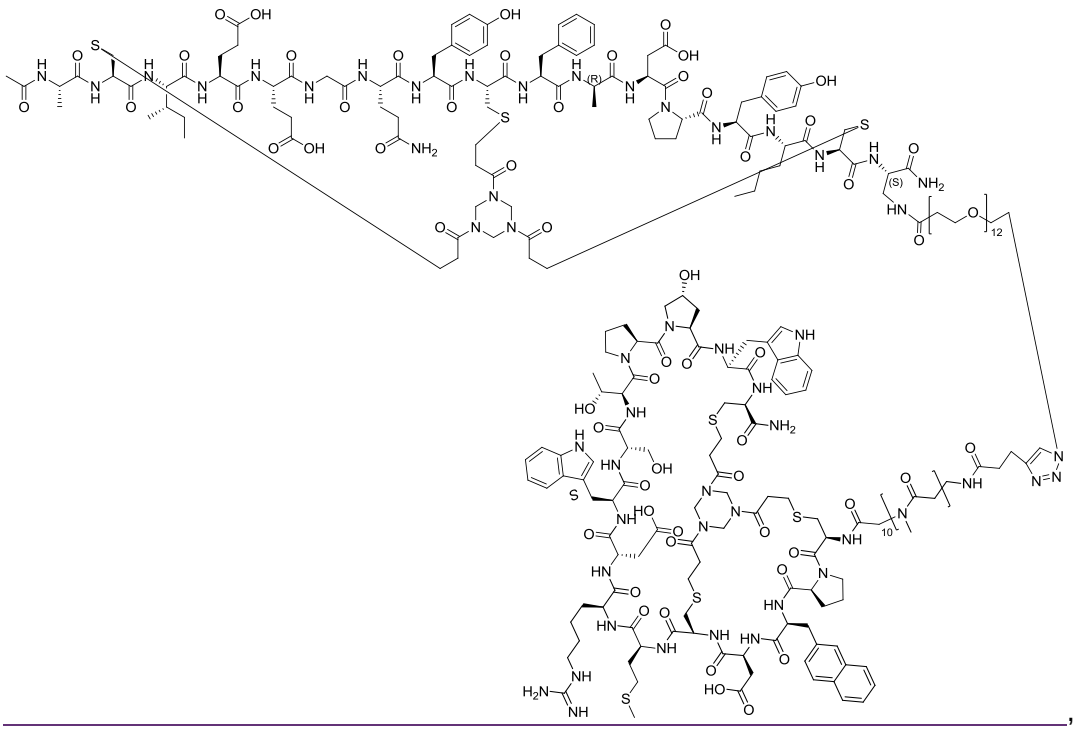
,

BCY9350



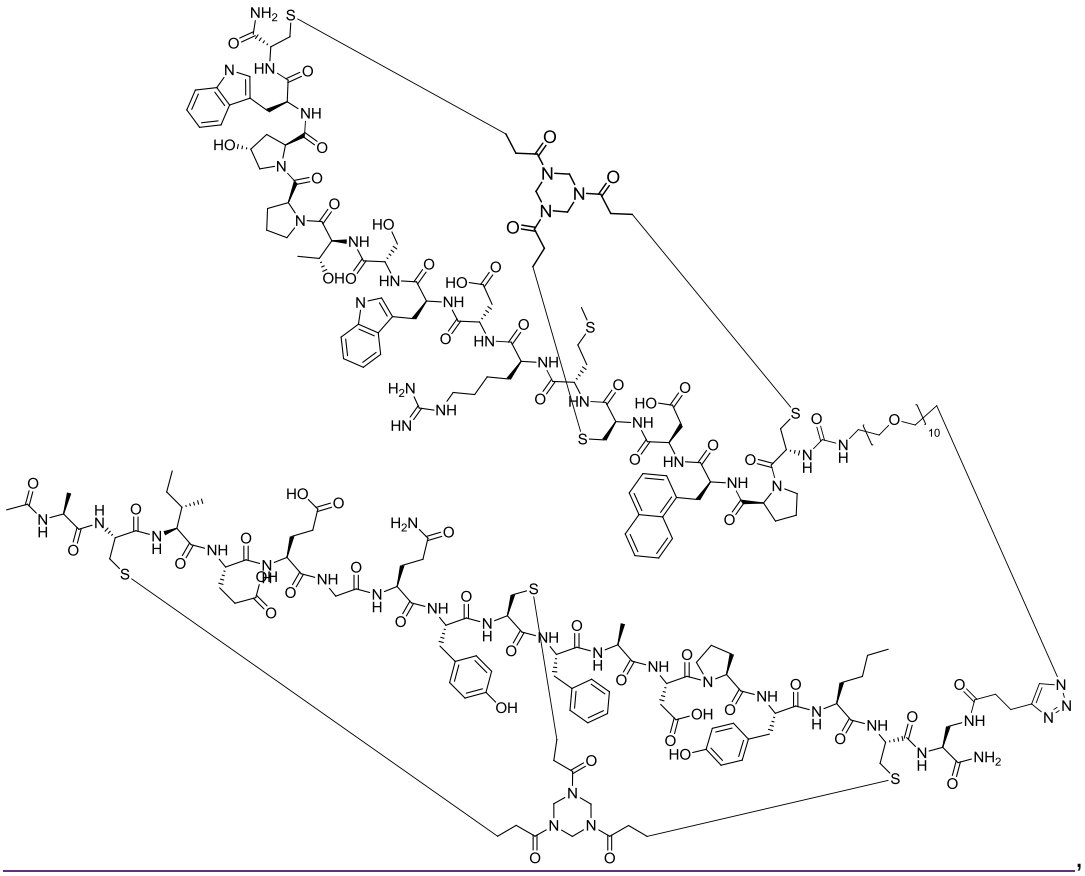
,

BCY9351



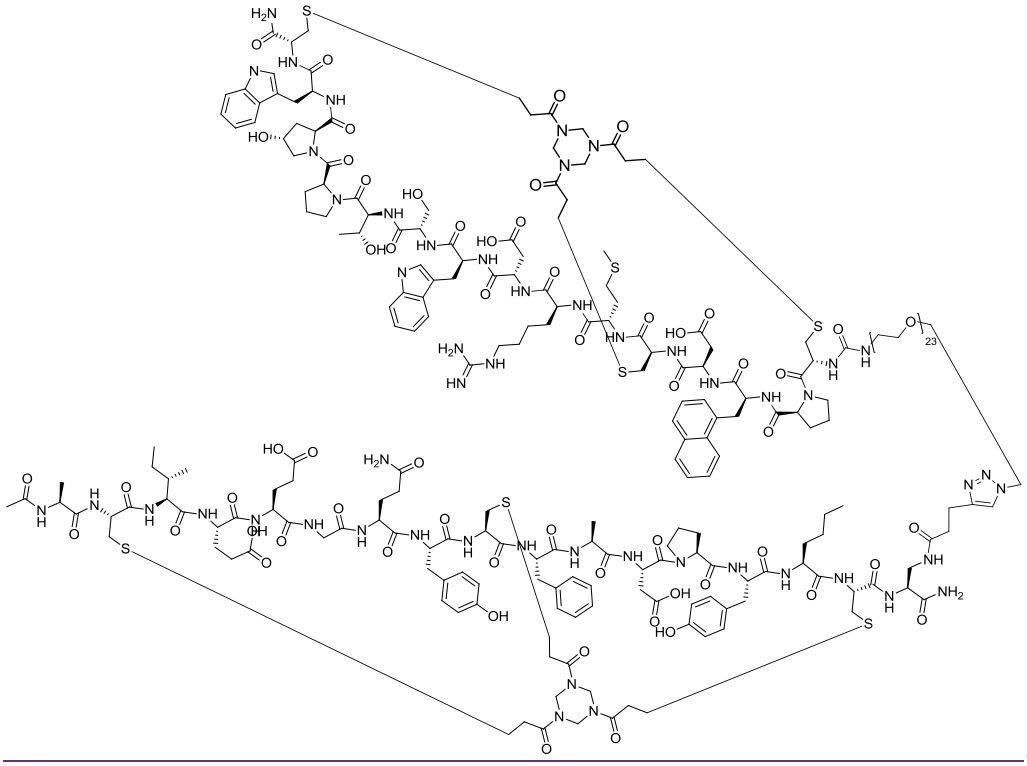
,

BCY9399



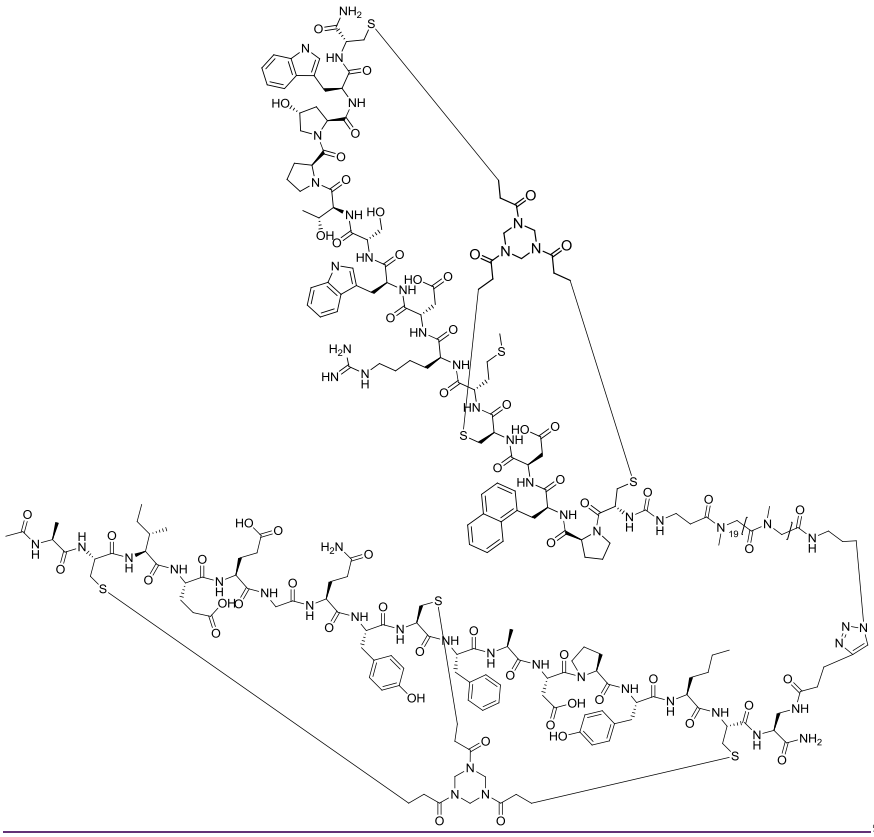
,

BCY9400



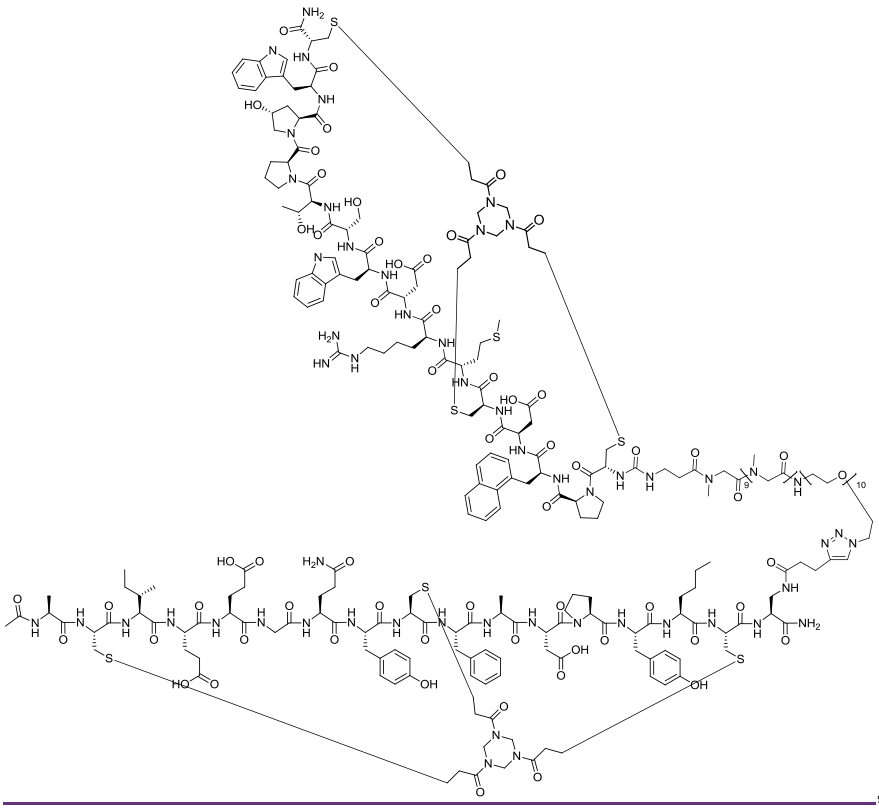
,

BCY9401



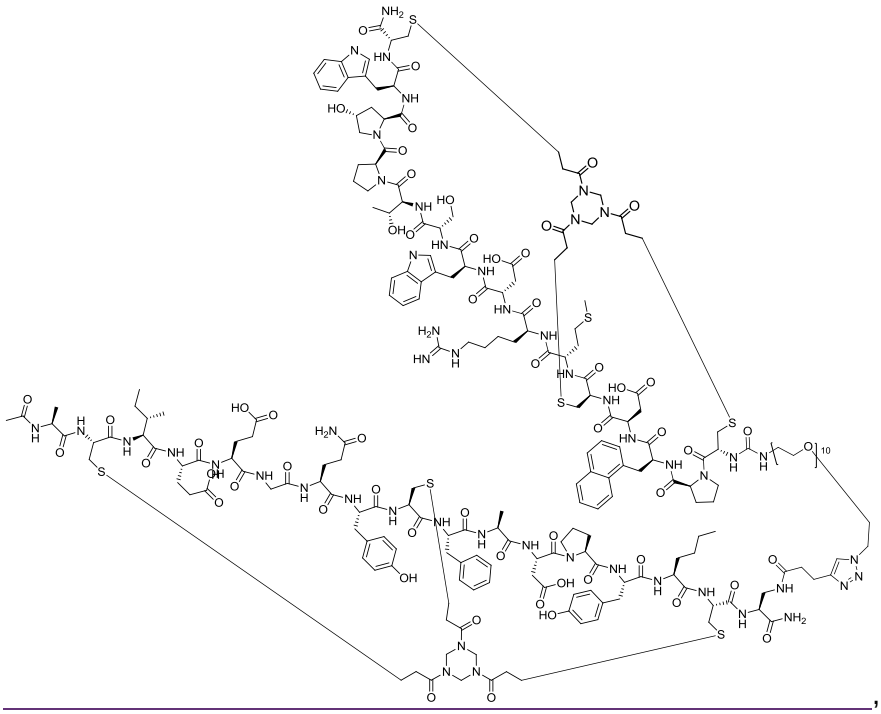
,

BCY9403



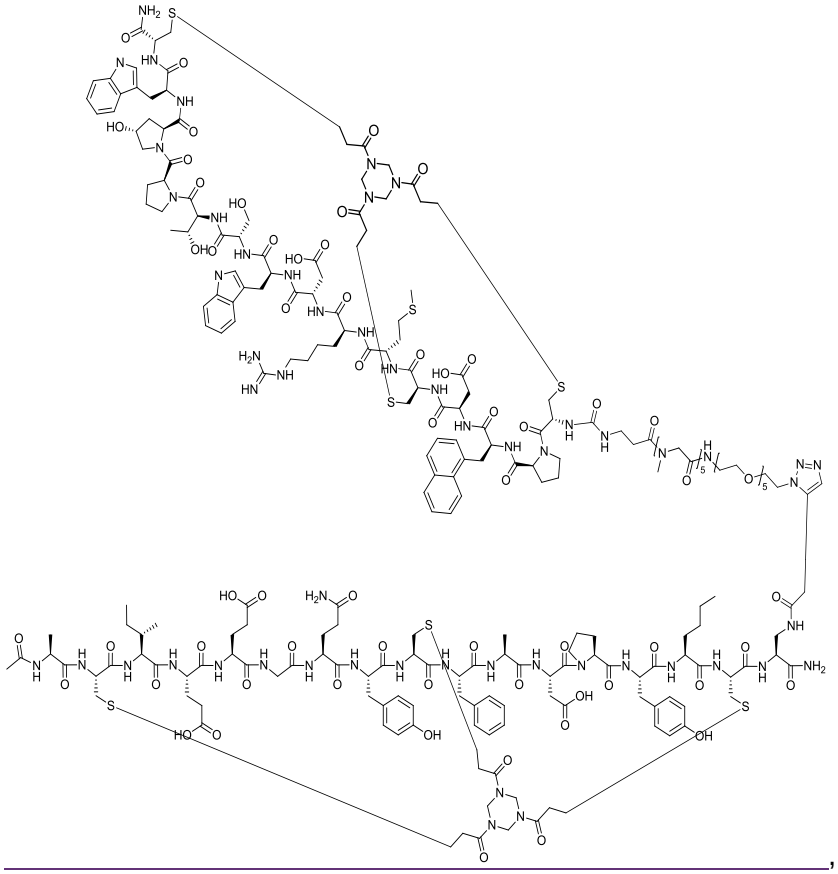
,

BCY9405



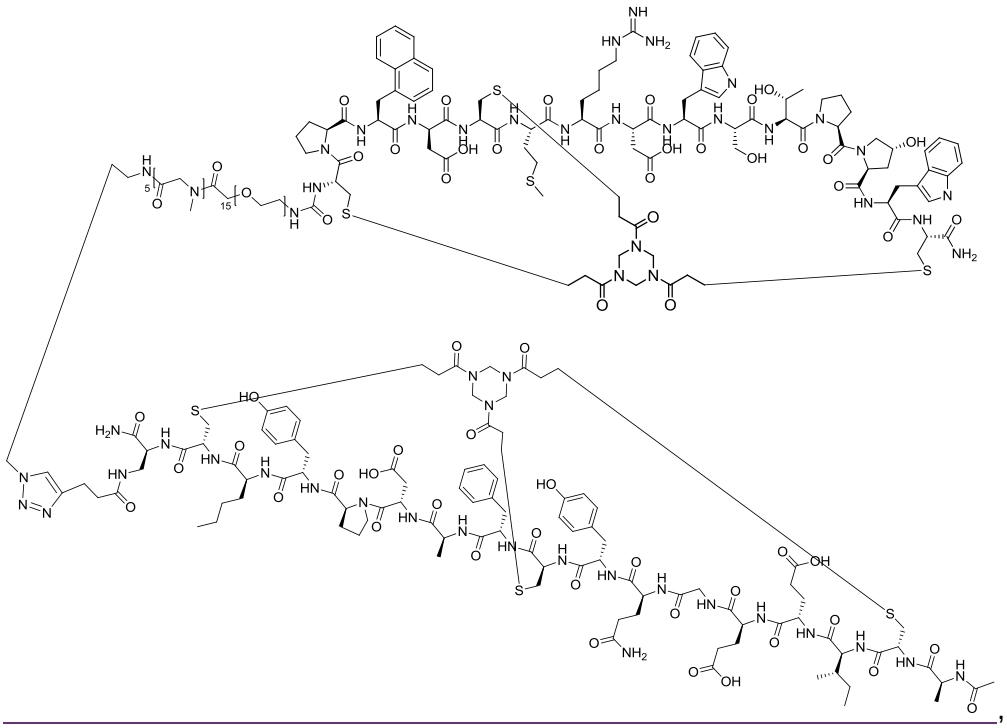
,

BCY9406

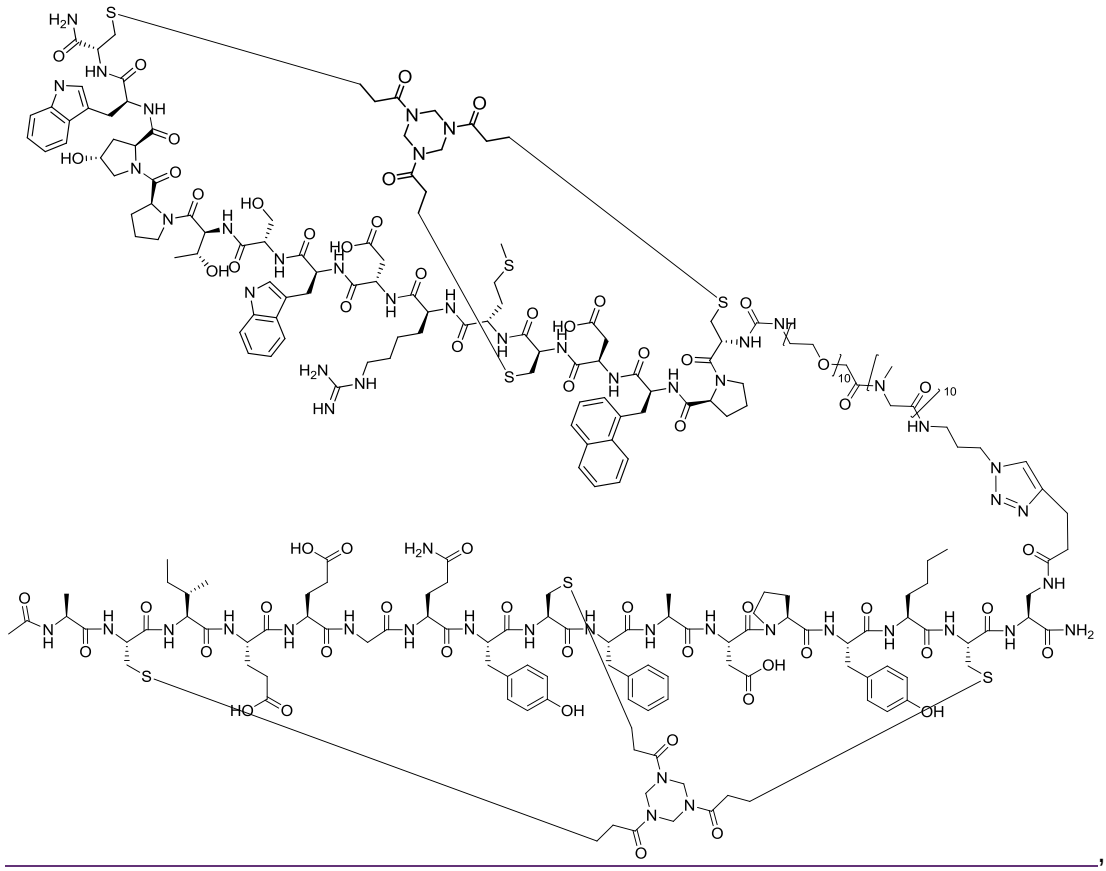


,

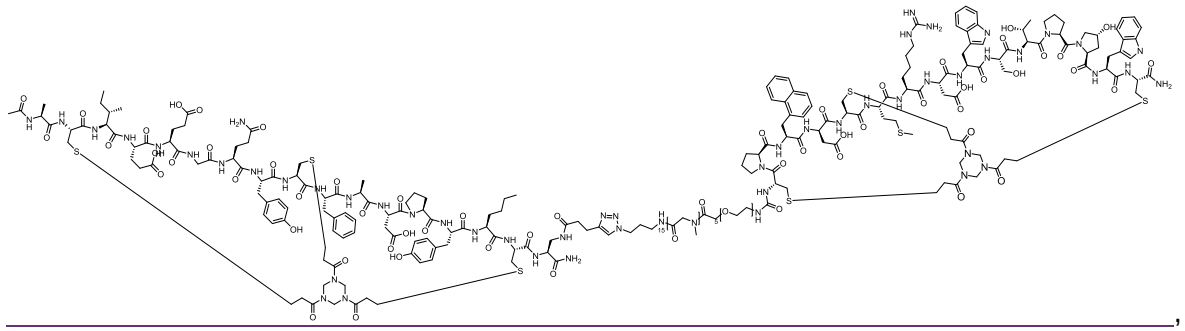
BCY9407



BCY9408

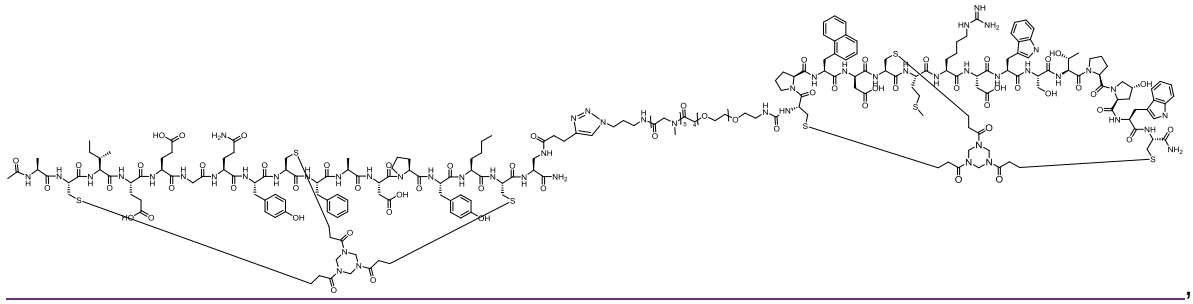


BCY9409



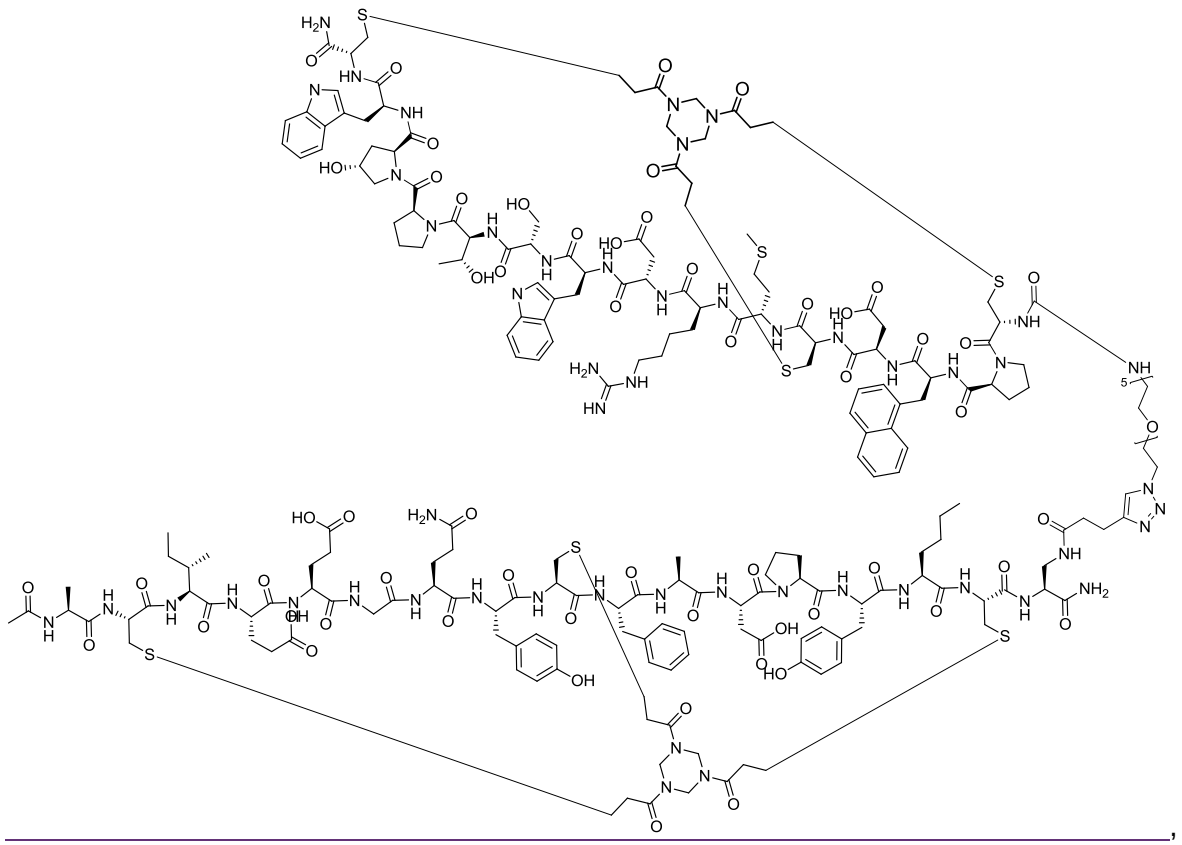
,

BCY9410



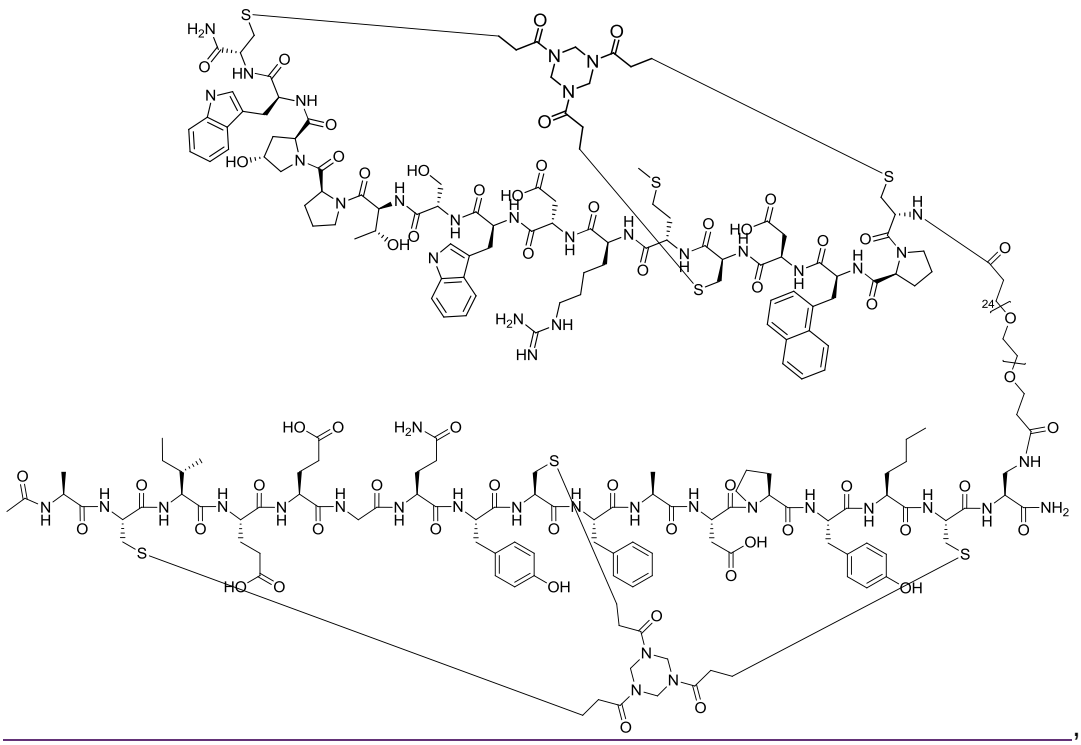
,

BCY9411



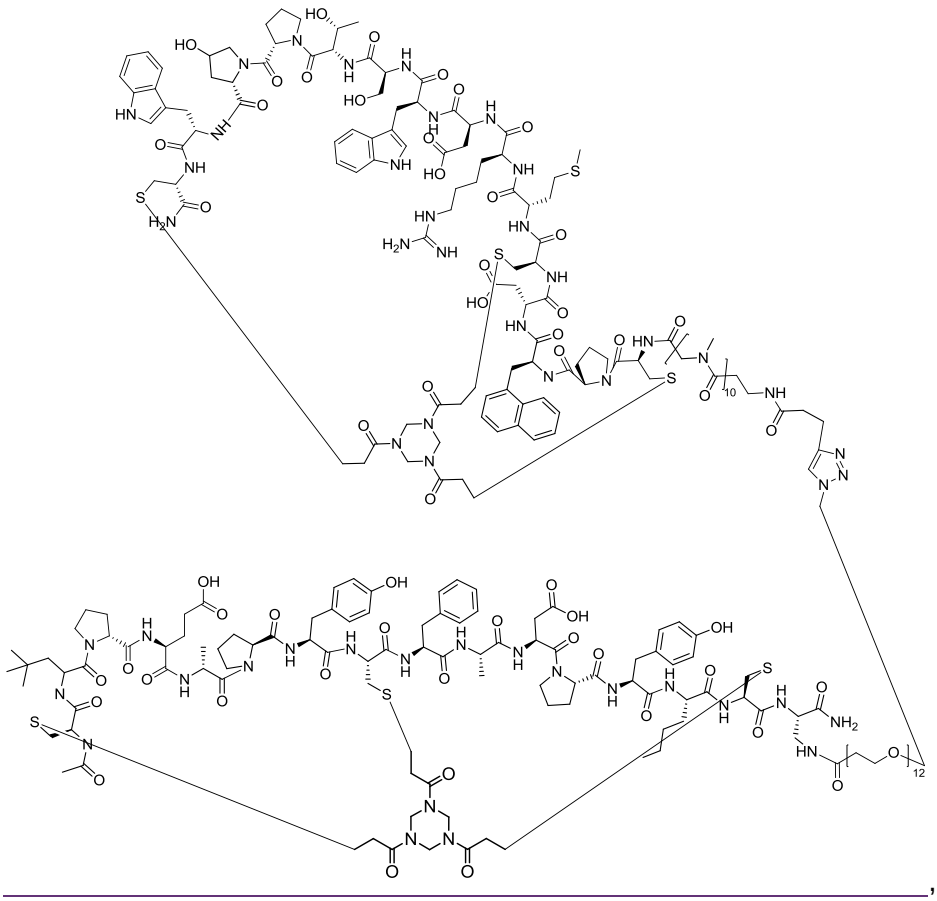
,

BCY9759



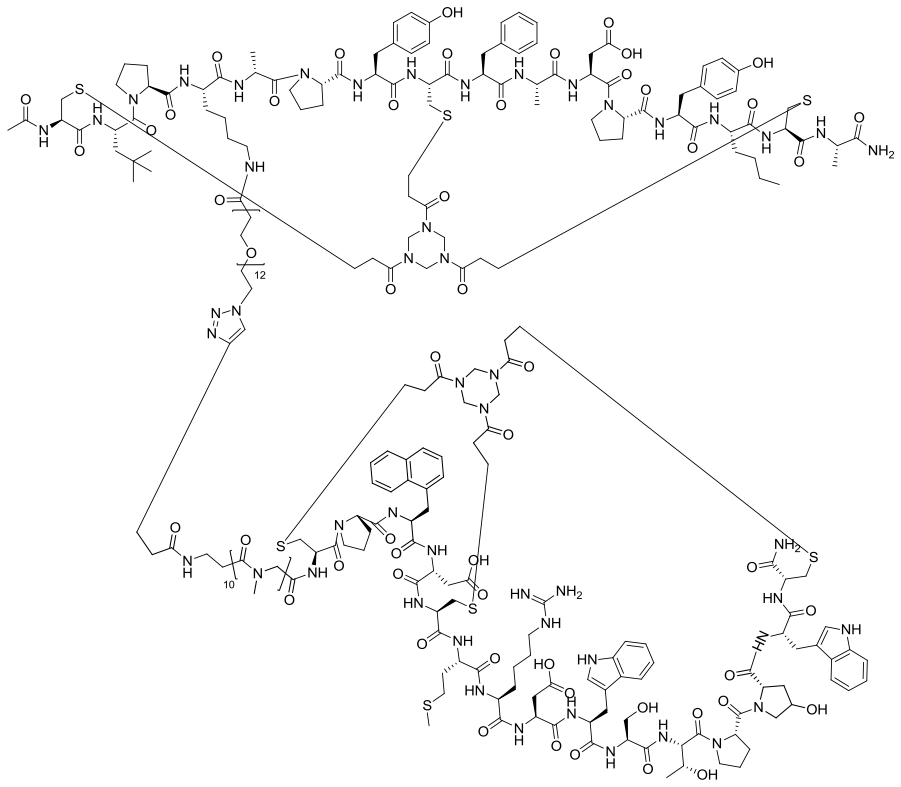
,

BCY10000



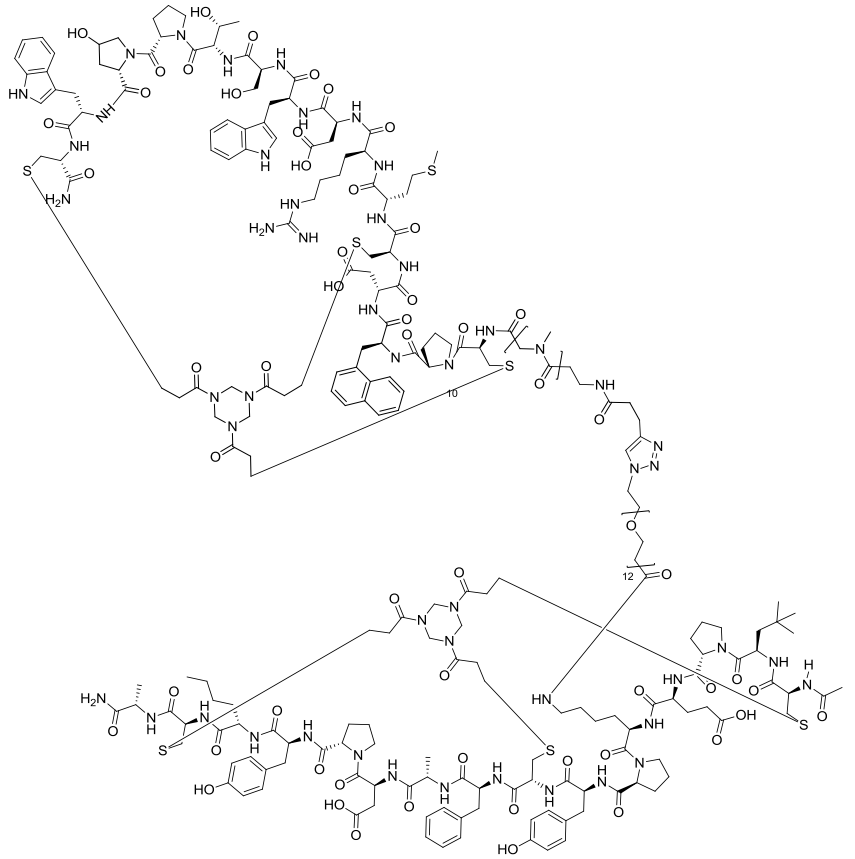
,

BCY10567



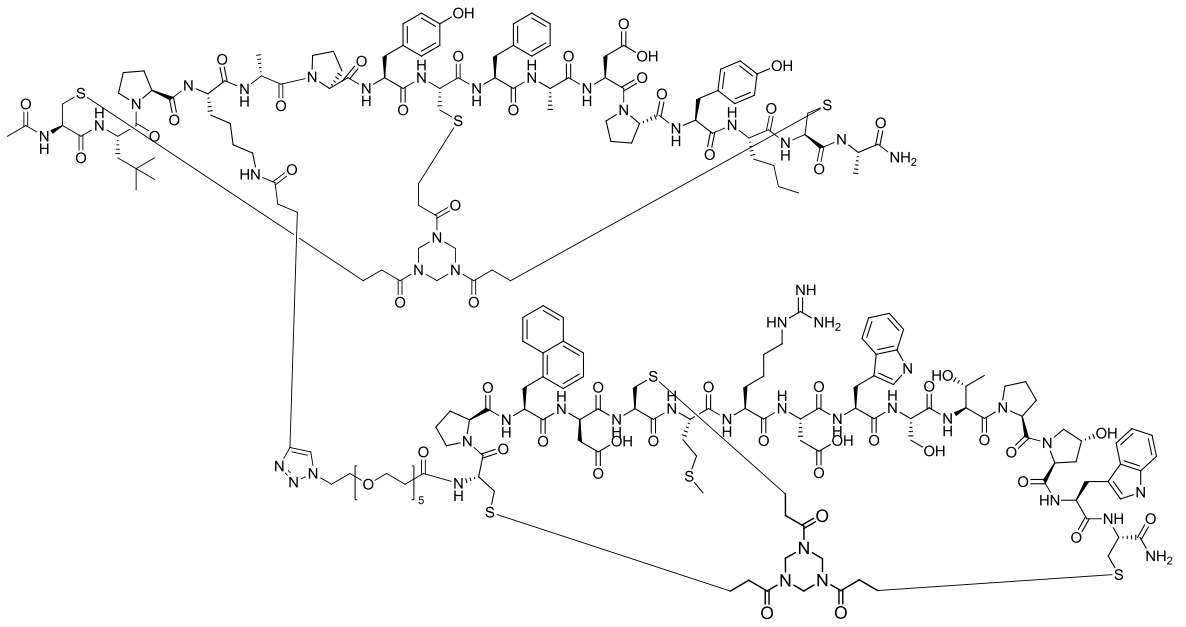
,

BCY10569



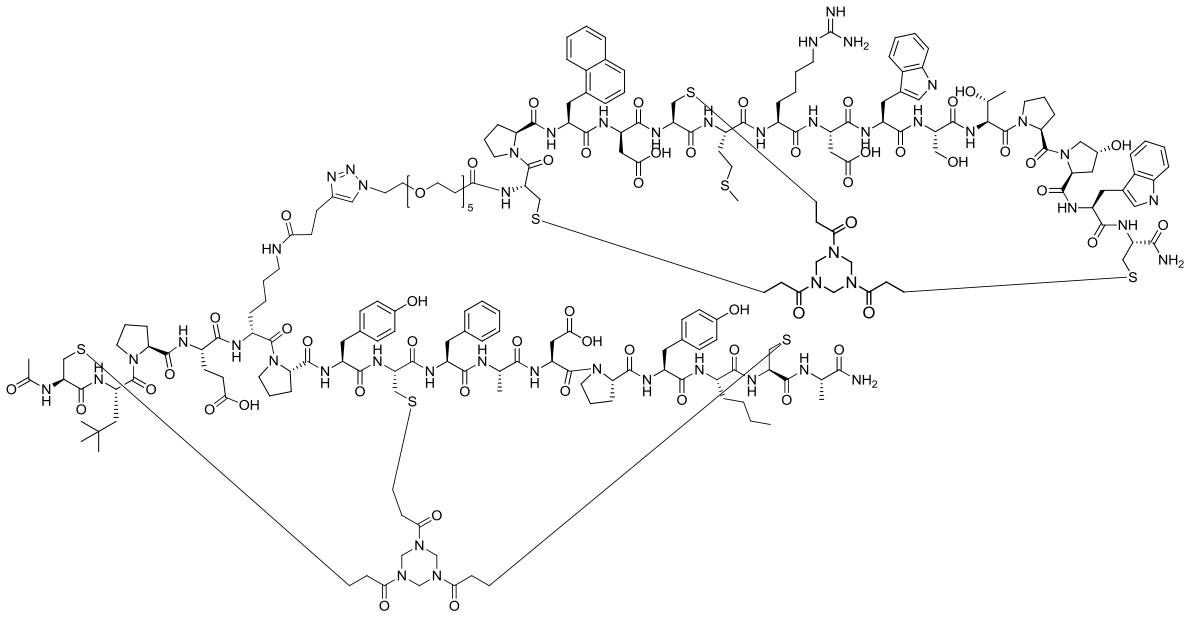
,

BCY10571



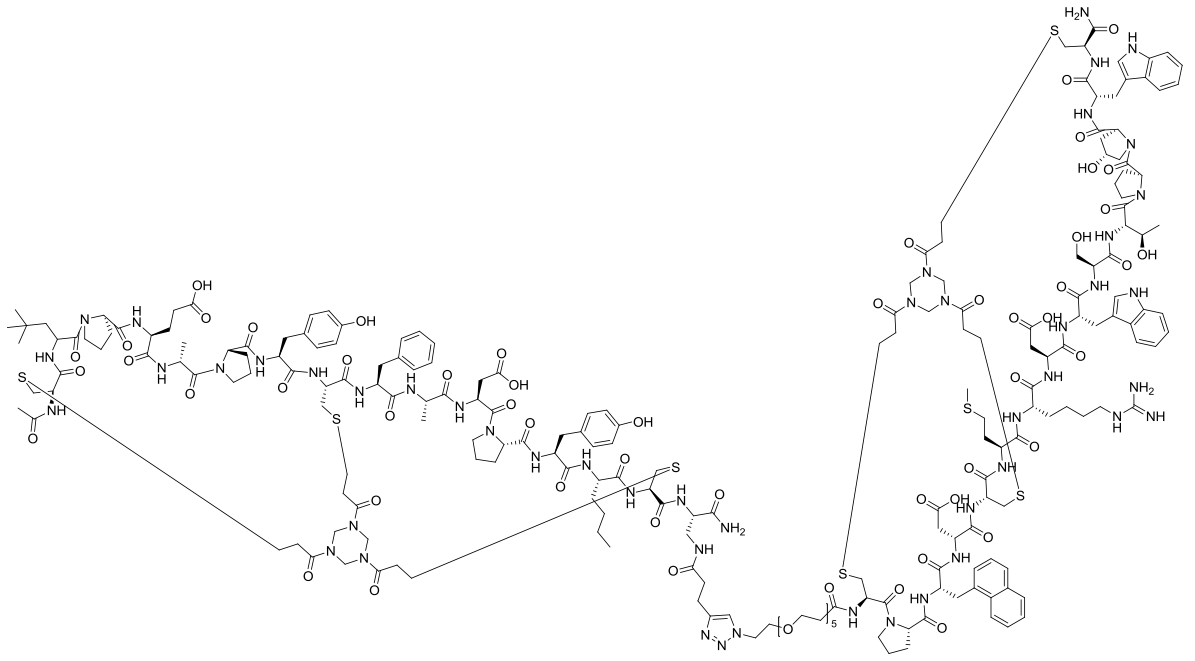
,

BCY10572



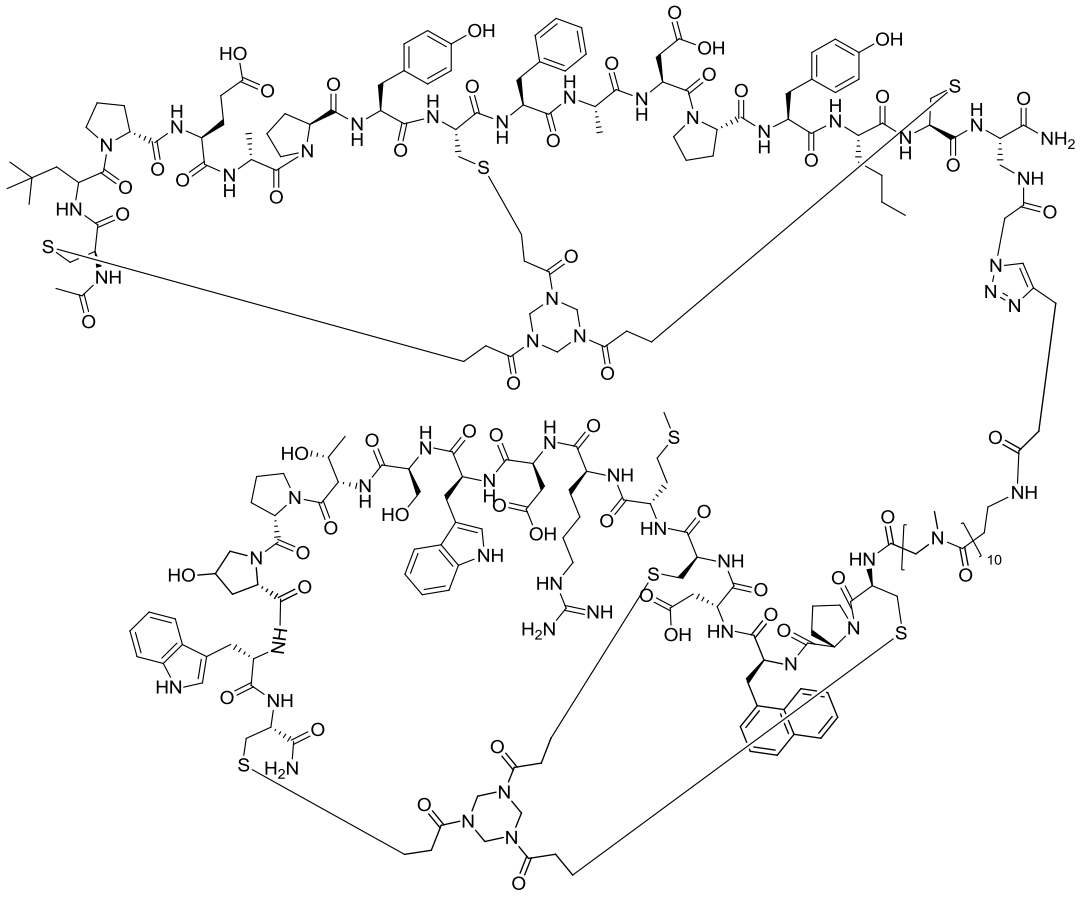
,

BCY10573

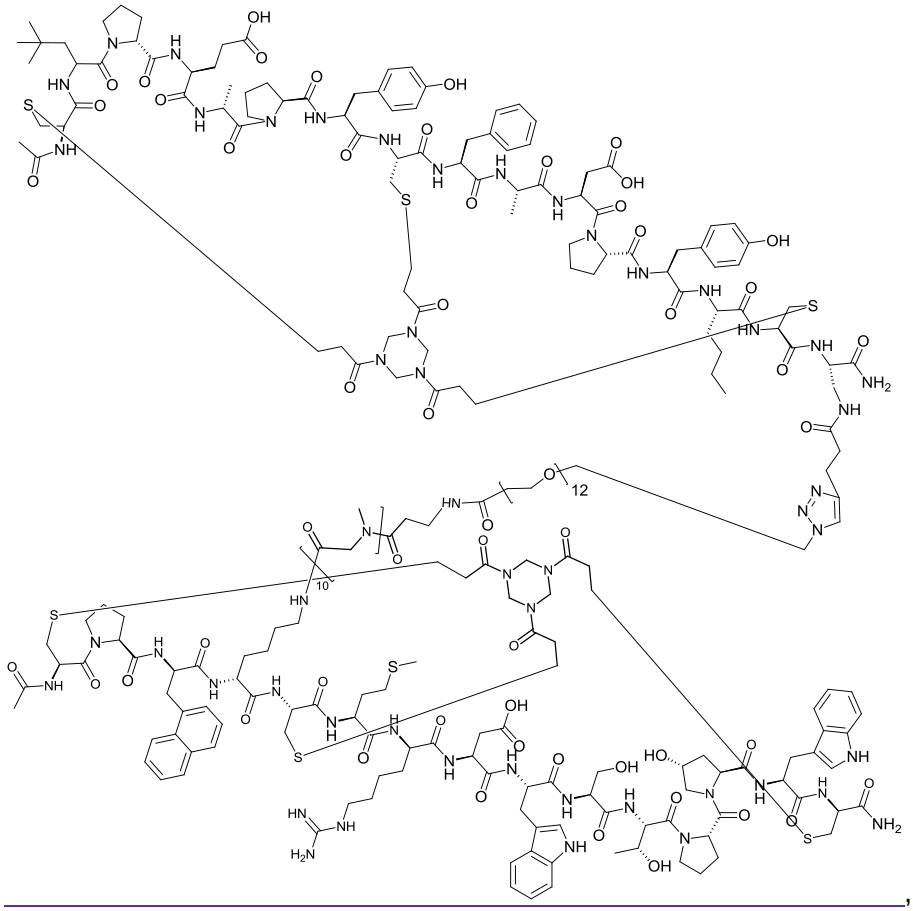


,

BCY10578

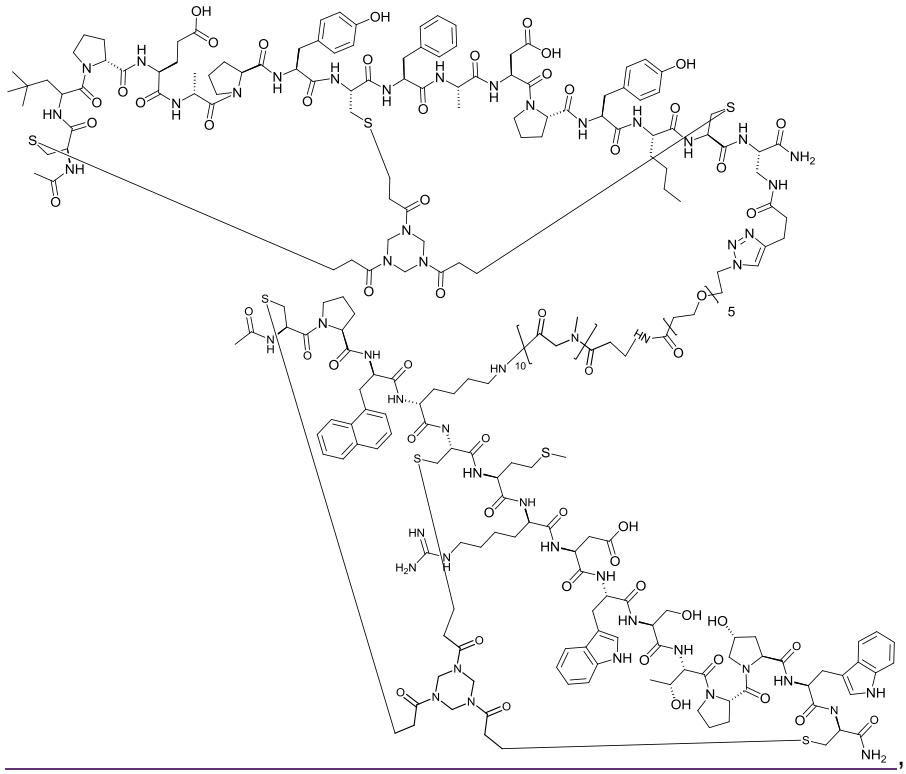


BCY10917



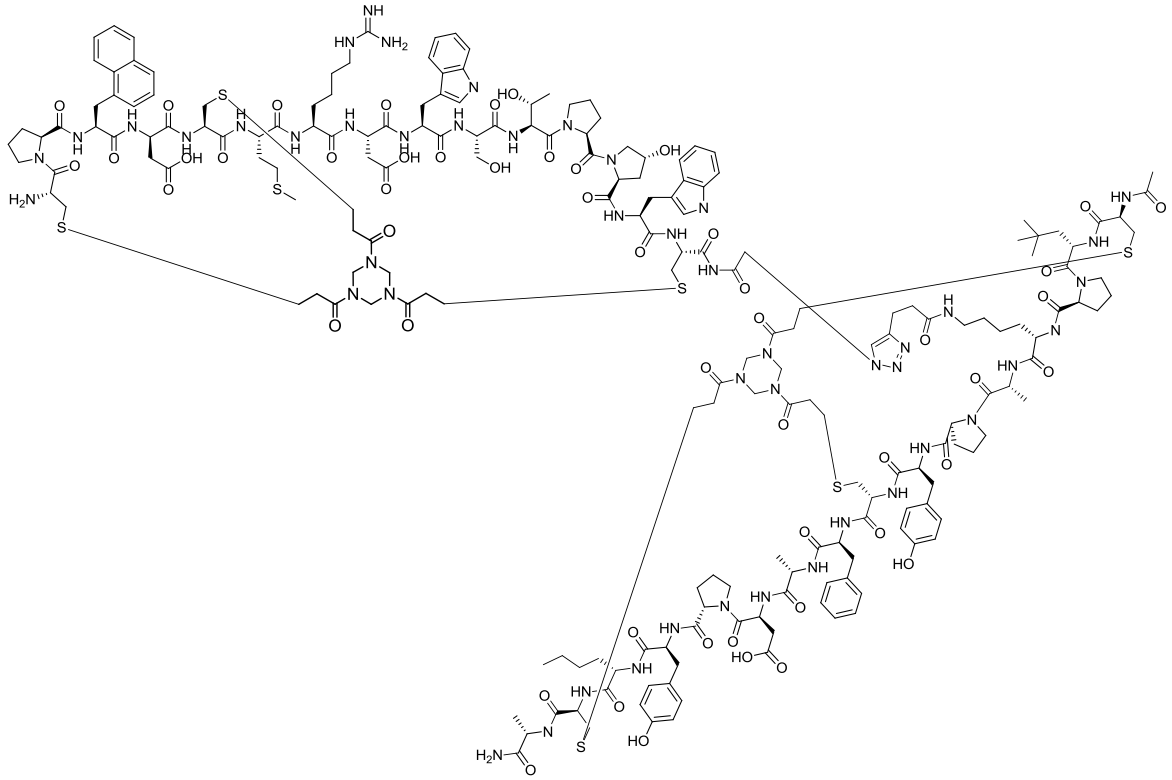
,

BCY11020



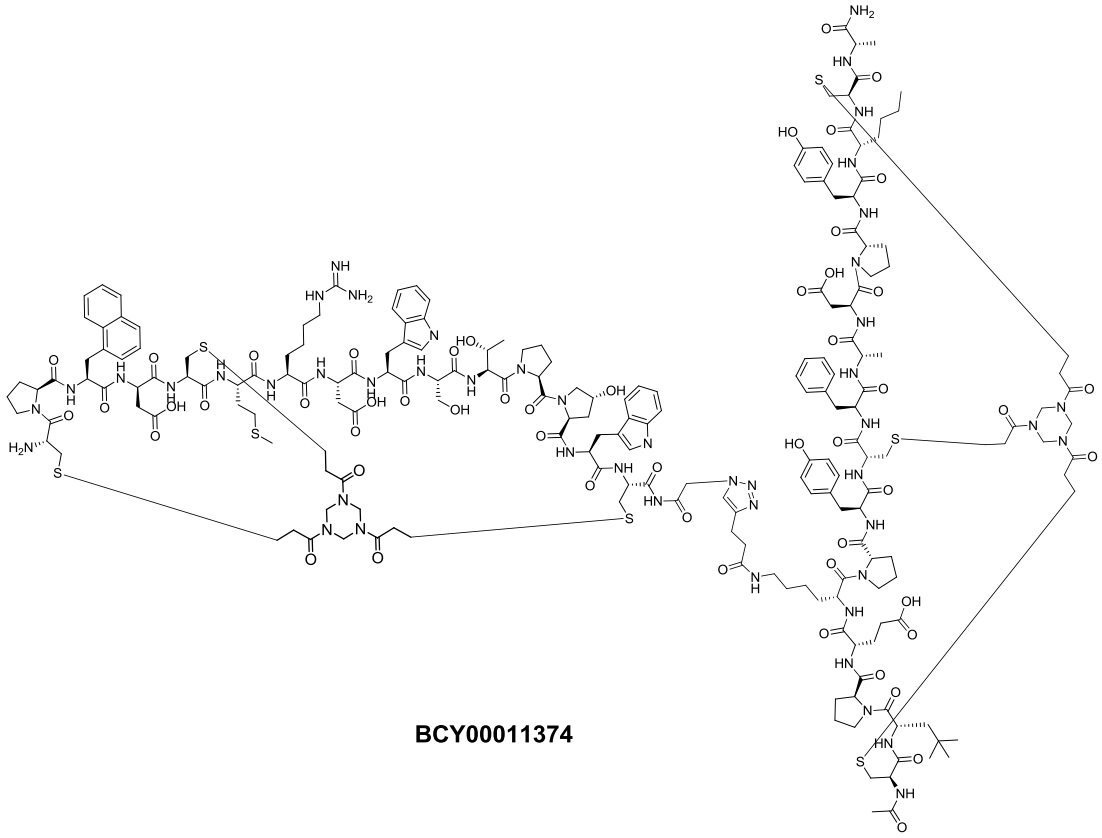
,

BCY11373



,

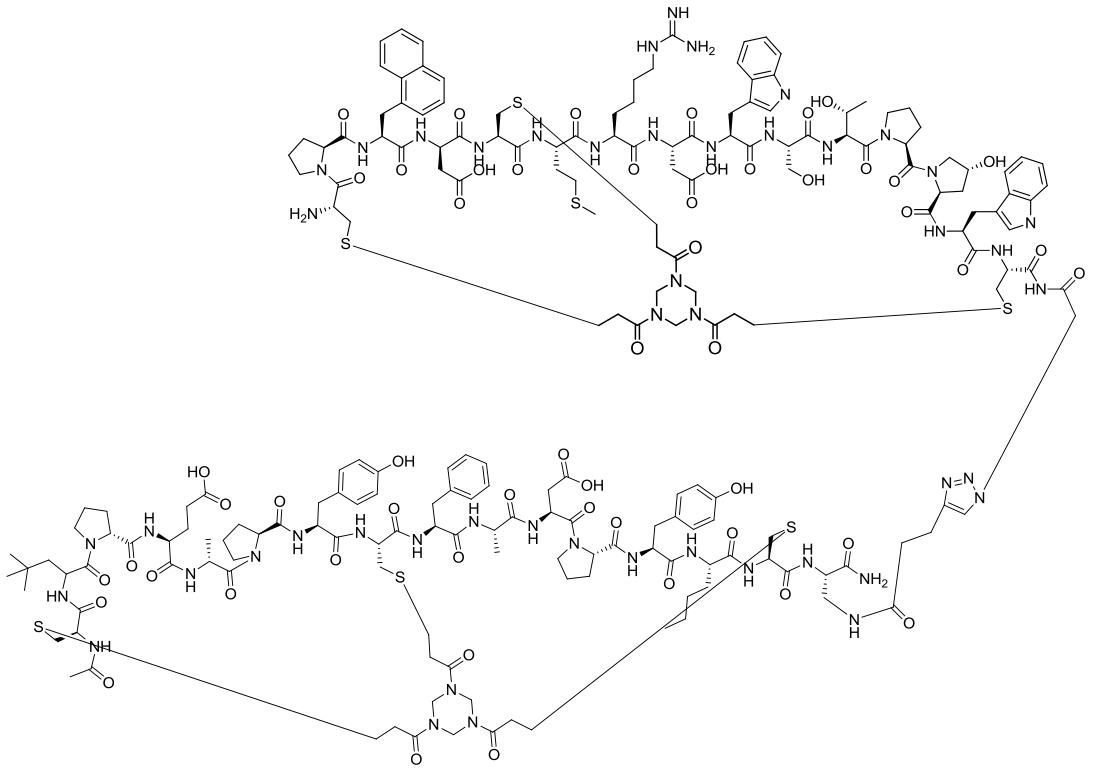
BCY11374



BCY00011374

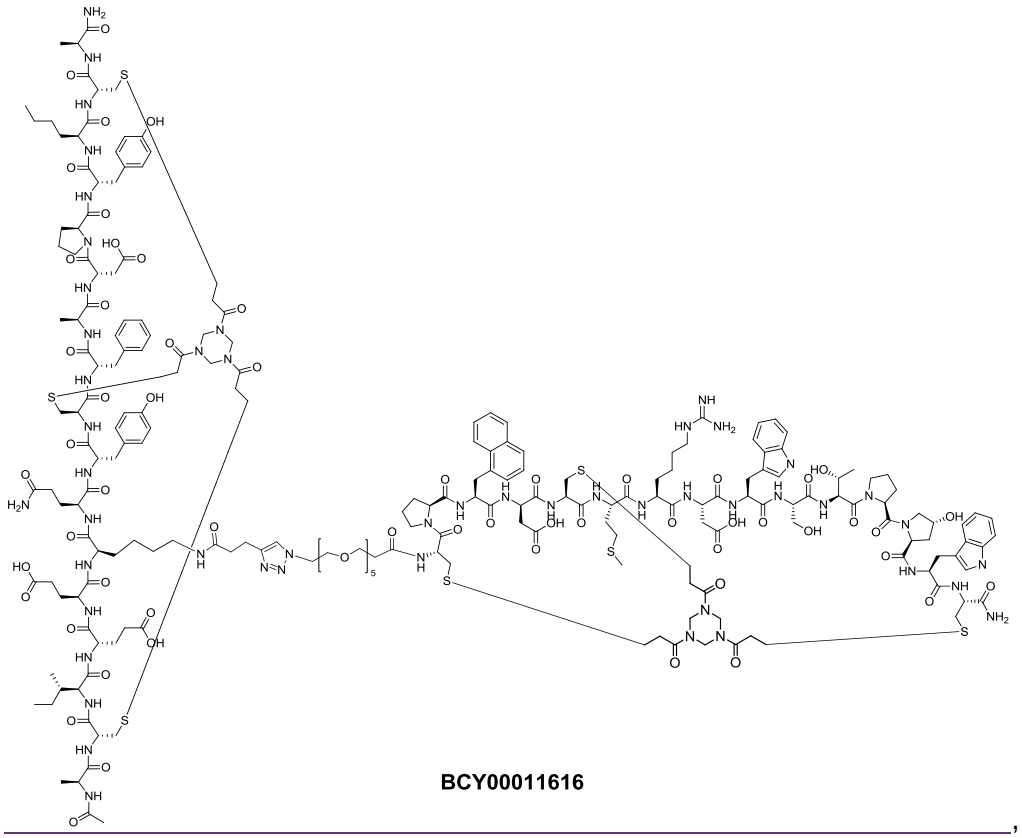
,

BCY11375



,

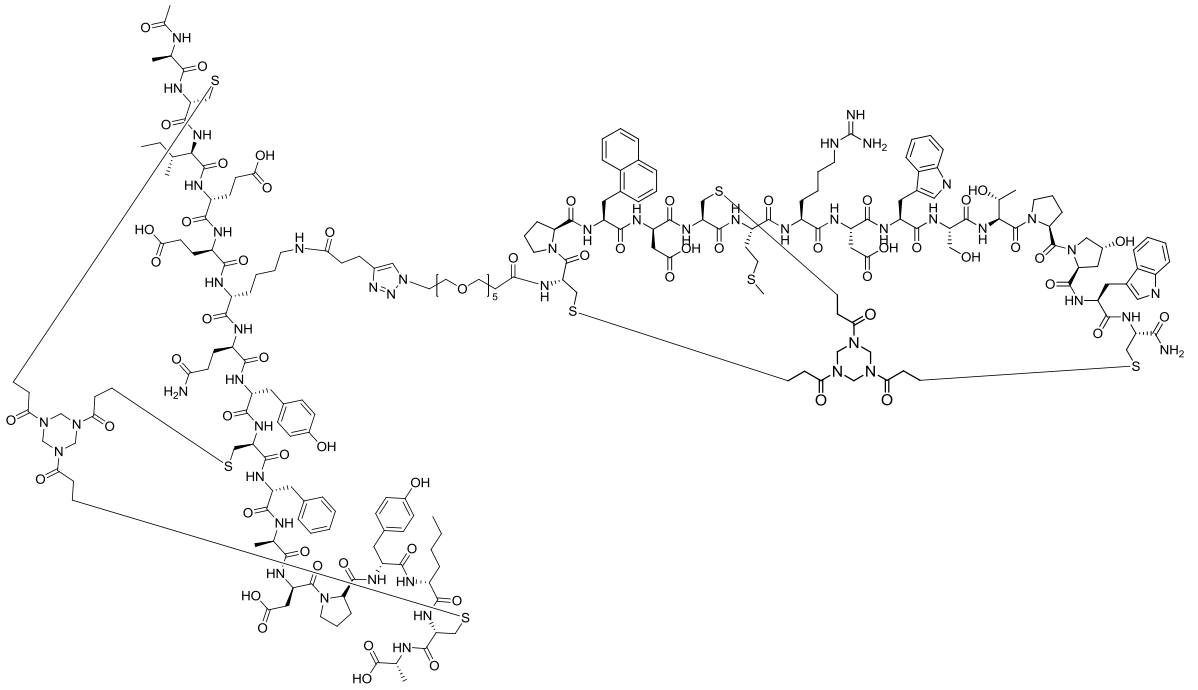
BCY11616



BCY00011616

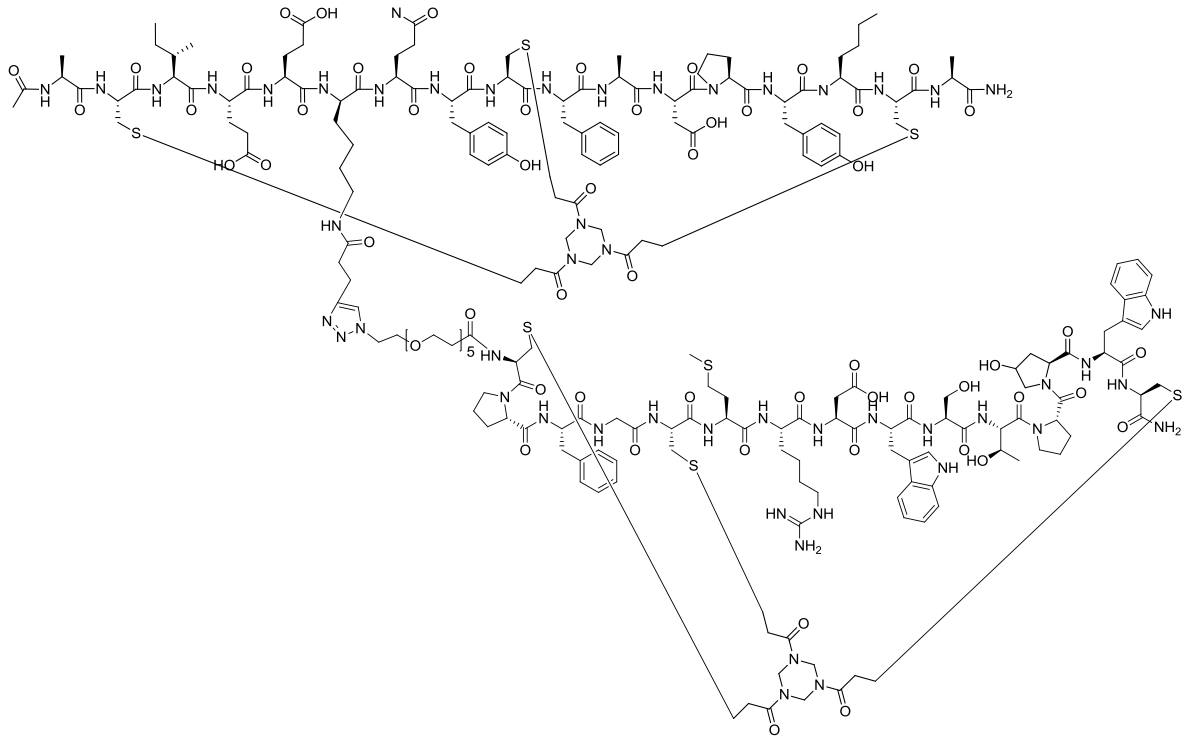
,

BCY11617



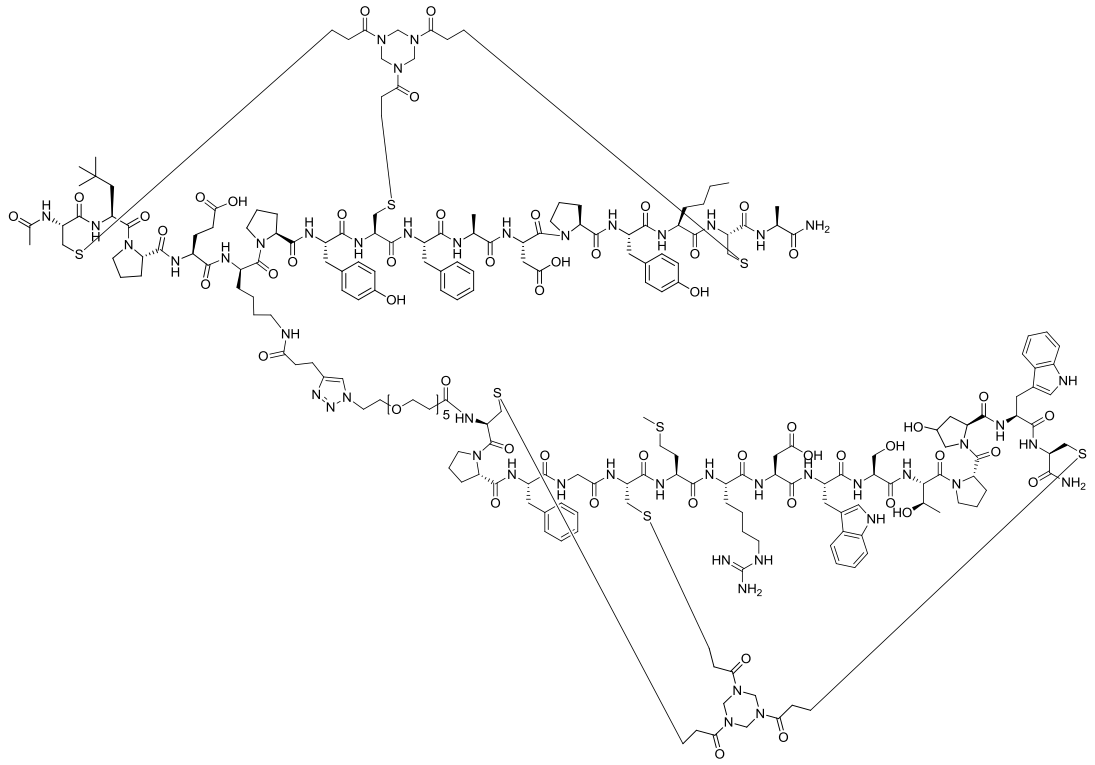
,

BCY11857



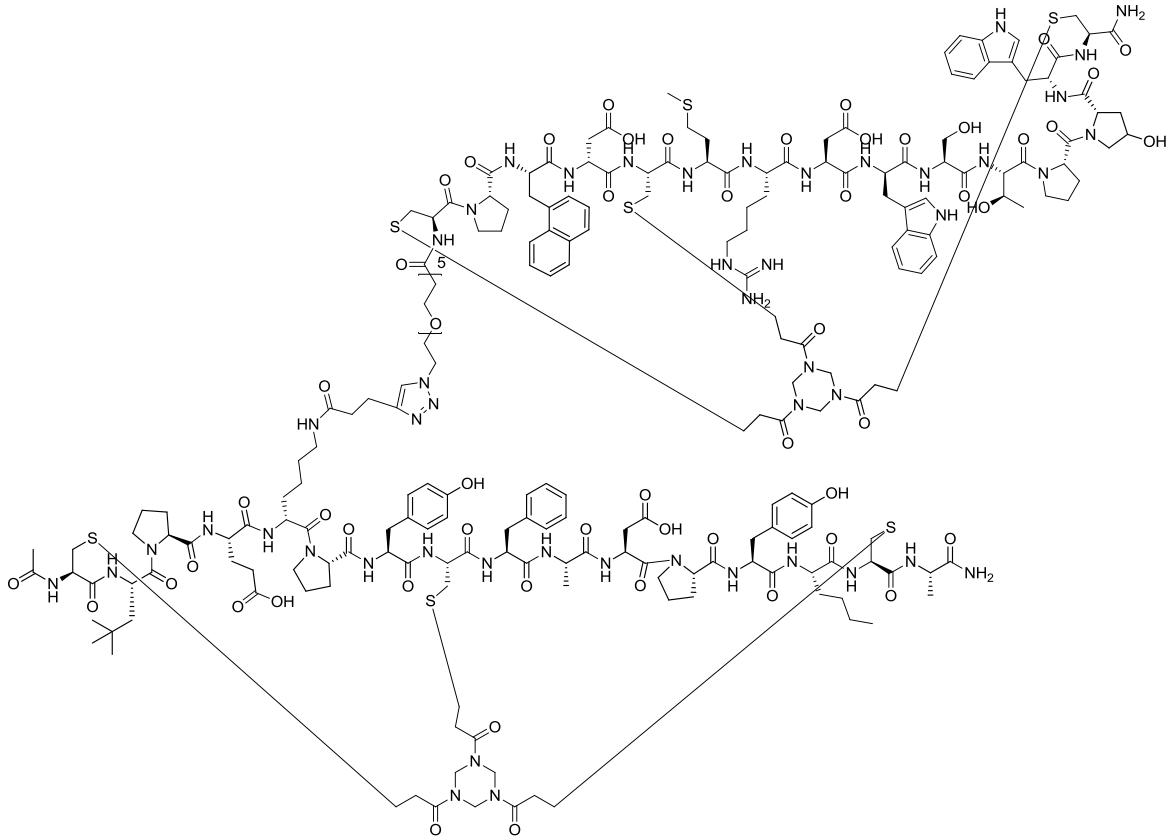
,

BCY11858



, and

BCY11859



.

23. The heterotandem bicyclic peptide complex as defined in any one of claims 1 to 7, wherein the component present on a cancer cell is PSMA.

24. The heterotandem bicyclic peptide complex as defined in any one of claims 1 to 7 and 23, wherein the second peptide ligand comprises PSMA binding bicyclic peptide ligand.

25. The heterotandem bicyclic peptide complex as defined in any one of claims 1 to 24, wherein the linker is selected from: -CH_2-, -PEG_5-, -PEG_{10}-, -PEG_{12}-, -PEG_{23}-, -PEG_{24}-, -PEG_{15}-Sar_5-, -PEG_{10}-Sar_{10}-, -PEG_5-Sar_{15}-, -PEG_5-Sar_5-, -B-Ala-Sar_{20}-, -B-Ala-Sar_{10}-PEG_{10}-, -B-Ala-Sar_5-PEG_{15}- and -B-Ala-Sar_5-PEG_5-..

26. The heterotandem bicyclic peptide complex as defined in any one of claims 1 to 25, wherein the molecular scaffold is ~~selected from~~ 1,1',1''-(1,3,5-triazinane-1,3,5-triyl)triprop-2-en-1-one (TATA).

27. The heterotandem bicyclic peptide complex as defined in any one of claims 1 to 26, wherein the pharmaceutically acceptable salt is selected from the free acid or the sodium, potassium, calcium, ammonium salt.

28. A pharmaceutical composition which comprises the heterotandem bicyclic peptide complex of any one of claims 1 to 27 in combination with one or more pharmaceutically acceptable excipients.

29. The heterotandem bicyclic peptide complex as defined in any one of claims 1 to 27 for use in preventing, suppressing or treating cancer.