

PEPTIDE INHIBITORS OF INTERLEUKIN-23 RECEPTOR

CROSS-REFERENCE TO RELATED APPLICATIONS

This application claims the benefit of U.S. Provisional Application No. 63/480,038 filed
5 January 16, 2023, which is herein incorporated by reference in its entirety.

INCORPORATION OF SEQUENCE LISTING

The sequence listing in ST.26 XML format entitled 739650_NTT-4248PC_SL.xml,
created on January 12, 2024, comprising 1,212,736 bytes, prepared according to 37 CFR 1.822
to 1.824, submitted concurrently with the filing of this application, is incorporated herein by
10 reference in its entirety.

BACKGROUND

The interleukin-23 (IL-23) cytokine is a heterodimer composed of a unique p19 subunit
and the p40 subunit shared with IL-12, which is a cytokine involved in the development of
interferon- γ (IFN- γ)-producing T helper 1 (T_H1) cells. Although IL-23 and IL-12 both contain
15 the p40 subunit, they have different phenotypic properties. For example, animals deficient in IL-
12 are susceptible to inflammatory autoimmune diseases, whereas IL-23 deficient animals are
resistant to these diseases, presumably due to a reduced number of CD4⁺ T cells producing IL-6,
IL-17, and TNF in the CNS of IL-23-deficient animals. IL-23 binds to IL-23R, which is a
heterodimeric receptor composed of IL-12R β 1 and IL-23R subunits. Binding of IL-23 to IL-23R
20 activates the Jak-Stat signaling molecules Jak2, Tyk2, Stat1, Stat 3, Stat 4, and Stat 5, although
Stat4 activation is substantially weaker and different DNA-binding Stat complexes form in
response to IL-23 as compared with IL-12. IL-23R associates constitutively with Jak2 and in a
ligand-dependent manner with Stat3. In contrast to IL-12, which acts mainly on naive CD4(+) T
cells, IL-23 preferentially acts on memory CD4(+) T cells.

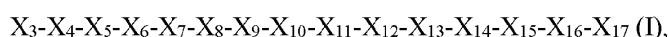
25 IL-23 has been implicated as playing a crucial role in the pathogenesis of autoimmune
inflammation and related diseases and disorders, such as multiple sclerosis, asthma, rheumatoid
arthritis, psoriasis, and inflammatory bowel diseases (IBDs) such as ulcerative colitis and
Crohn's disease. Studies in acute and chronic mouse models of IBDs revealed a primary role of
interleukin-23 receptor (IL-23R) and downstream effector cytokines in disease pathogenesis.
30 IL-23R is expressed on various adaptive and innate immune cells including Th17 cells,
 $\gamma\delta$ T cells, natural killer (NK) cells, dendritic cells, macrophages, and innate lymphoid cells,
which are found abundantly in the intestine. At the intestine mucosal surface, the gene
expression and protein levels of IL-23R are found to be elevated in IBD patients. It is believed
that IL-23 mediates this effect by promoting the development of a pathogenic CD4⁺ T cell
35 population that produces IL-6, IL-17, and tumor necrosis factor (TNF).

Accordingly, there remains a need for compositions that bind IL-23R to inhibit IL-23 binding and signaling in a patient.

BRIEF SUMMARY

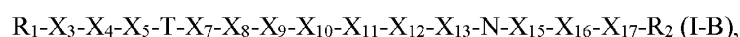
5 Provided herein are peptide inhibitors of the interleukin-23 receptor (IL-23R) or pharmaceutically acceptable salts thereof, corresponding pharmaceutical compositions, and methods and/or uses of the IL-23R inhibitors for the treatment of inflammatory diseases, autoimmune diseases, and/or related disorders.

10 In particular, the present disclosure provides a peptide of Formula (I), comprising the amino acid sequence:



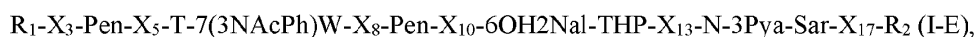
or a pharmaceutically acceptable salt thereof, wherein each of X₃, X₄, X₅, X₆, X₇, X₈, X₉, X₁₀, X₁₁, X₁₂, X₁₃, X₁₄, X₁₅, X₁₆, and X₁₇ are defined herein.

15 In some embodiments, the present disclosure provides a peptide of Formula (I-B), comprising the amino acid sequence:



or a pharmaceutically acceptable salt thereof, wherein each of R₁, X₃, X₄, X₅, X₇, X₈, X₉, X₁₀, X₁₁, X₁₂, X₁₃, X₁₅, X₁₆, X₁₇, and R₂ are defined herein.

20 In some embodiments, the present disclosure provides a peptide of Formula (I-E), comprising the amino acid sequence:



or a pharmaceutically acceptable salt thereof, wherein each of R₁, X₃, X₅, X₈, X₁₀, X₁₃, X₁₇, and R₂ are defined herein.

25 The present disclosure further provides a pharmaceutical composition comprising a peptide described herein, or a pharmaceutically acceptable salt thereof, and a pharmaceutically acceptable carrier.

30 The present disclosure still further provides a method for treating a disease or disorder associated with Interleukin 23 (IL-23)/Interleukin 23 Receptor (IL-23R), comprising administering to a subject in need thereof a therapeutically effective amount of a peptide or a pharmaceutical composition described herein. In some embodiments, the disease or disorder is selected from ulcerative colitis (UC), Crohn's disease (CD), psoriasis (PsO), and psoriatic arthritis (PsA).

DETAILED DESCRIPTION

Provided herein are peptide inhibitors of IL-23R, and pharmaceutically acceptable salts thereof, corresponding pharmaceutical compositions, and methods and/or uses for the treatment of inflammatory diseases, autoimmune diseases, and/or related disorders. The peptide inhibitors of the present disclosure may exhibit enhanced properties, such as longer in vivo half-life, compared to the corresponding cyclic peptide inhibitor of IL-23R without a cyclic structure.

Peptide molecules that modulate the interactions of IL-23R with IL-23 represent a convenient and cost-efficient treatment for autoimmune diseases when used as an oral therapeutic. To achieve high binding interactions with the IL-23 receptor, it is critical to maintain several amino acid residues at selected positions as shown in the peptide molecules described herein. In addition, peptide molecules having a hydroxy substituted naphthalene at the X₁₁ position can provide higher potency than peptide molecules without such a feature. Therefore, the peptide molecules described herein represent a series of more potent and efficient therapeutics for inhibiting IL-23R.

Definitions

Unless otherwise defined herein, scientific and technical terms used in this application shall have the meanings that are commonly understood by those of ordinary skill in the art.

As used in the specification and in the claims, the “comprise(s),” “comprising,” “include(s),” “having,” “has,” “can,” “contain(s),” and variants thereof, as used herein, are intended to be open-ended transitional phrases, terms, or words that require the presence of the named features, groups, ingredients, or steps and does not exclude the presence of additional features, groups, ingredients, or steps. For example, the language “a peptide of Formula (I), comprising the amino acid sequence: X₃-X₄-X₅-X₆-X₇-X₈-X₉-X₁₀-X₁₁-X₁₂-X₁₃-X₁₄-X₁₅-X₁₆-X₁₇ (I),” means that in addition to amino acids X₃ through X₁₇, the peptide may include but is not limited to additional amino acids attached to the N-terminus, additional amino acids attached to the C-terminus, N-terminal or C-terminal capping groups, chemical or biological moieties (including but not limited to, for example, lipophilic substituents, antibodies, imaging agents, etc.) conjugated to the peptide at any location, and the like. The term “comprise(s),” “comprising,” “include(s),” “having,” “has,” “can,” or “contain(s),” can include embodiments encompassed by the term “consisting essentially of” or “consisting of.”

The terms “peptide,” “polypeptide,” and “protein” are used interchangeably herein and typically refer to a molecule comprising a chain of two or more amino acids (e.g., L-amino acids, D-amino acids, modified amino acids, amino acid analogs, amino acid mimetics, etc.).

Naturally-occurring L-amino acids are represented by the conventional three-letter or capitalized one-letter amino acid designations of Table 1. The corresponding D-amino acids are represented by lower-case one-letter amino acid designations or by the three-letter or capitalized one letter amino acid designations of Table 1 preceded by the letter “D” (e.g., r, dR, or D-Arg).

5 **Table 1:** Naturally-occurring amino acids

G	Glycine	Gly	P	Proline	Pro
A	Alanine	Ala	V	Valine	Val
L	Leucine	Leu	I	Isoleucine	Ile
M	Methionine	Met	C	Cysteine	Cys
F	Phenylalanine	Phe	Y	Tyrosine	Tyr
W	Tryptophan	Trp	H	Histidine	His
K	Lysine	Lys	R	Arginine	Arg
Q	Glutamine	Gln	N	Asparagine	Asn
E	Glutamic Acid	Glu	D	Aspartic Acid	Asp
S	Serine	Ser	T	Threonine	Thr

The term “L-amino acid,” as used herein, refers to the “L” isomeric form of an amino acid, and conversely the term “D-amino acid” refers to the “D” isomeric form of an amino acid (e.g., (D)Asp or D-Asp; (D)Phe or D-Phe). D-amino acids may be indicated as customary in lower case when referred to using single-letter abbreviations. For example, D-arginine can be represented as “arg” or “r.” Alternatively, a lower case “d” in front of an amino acid can be used to indicate that it is of the D isomeric form, for example D-lysine can be represented by dK.

In the case of less common or non-naturally occurring amino acids, unless they are referred to by their full name (e.g., sarcosine, ornithine, etc.), frequently employed three- or four-character codes are employed for residues thereof, including, Sar or Sarc (sarcosine, i.e., N-methylglycine), Aib (α -aminoisobutyric acid), Dab (2,4-diaminobutanoic acid), Dapa (2,3-diaminopropanoic acid), γ -Glu (γ -glutamic acid), Gaba (γ -aminobutanoic acid), β -Pro (pyrrolidine-3-carboxylic acid), and Abu (2-aminobutyric acid).

Amino acids of the D-isomeric form may be located at any of the positions in the IL-23R inhibitors set forth herein (e.g., any of X₃-X₁₇ appearing in the molecule). In some embodiments, amino acids of the D-isomeric form may be located only at any one or more of X₃, X₅, X₆, X₈, X₁₃, and optionally one additional position. In other embodiments, amino acids of the D-isomeric form may be located only at any one or more of X₃, X₈, X₁₃, and optionally one additional position. In other embodiments, amino acids of the D-isomeric form may be located only at any one or more of X₈, X₁₃, and optionally one additional position. In other embodiments, amino acids of the D-isomeric form may be located only at X₃ and optionally one additional position. In other embodiments, amino acids of the D-isomeric form may be located

only at X₃, and optionally two or three additional positions. In other embodiments, amino acids of the D-isomeric form may be located at only one or two of positions X₃ to X₁₇ appearing in the IL-23R inhibitors set forth herein. In other embodiments, amino acids of the D-isomeric form may be located at only three or four of positions X₃ to X₁₇ appearing in the IL-23R inhibitors set forth herein. For example, an IL-23R inhibitor set forth herein having only positions X₃ to X₁₅ present may have amino acids of the D-form present in three or four of those positions. In other embodiments, amino acids of the D-isomeric form may be located at only five or six of positions X₃ to X₁₇ appearing in the IL-23R inhibitors set forth herein.

Peptides may be naturally occurring, synthetically produced, or recombinantly expressed. Peptides may also comprise additional groups modifying the amino acid chain, for example, functional groups added via post-translational modification. Examples of post-translation modifications include, but are not limited to, acetylation, alkylation (including, methylation), biotinylation, glutamylation, glycylation, glycosylation, isoprenylation, lipoylation, phosphopantetheinylation, phosphorylation, selenation, and C-terminal amidation. The term peptide also includes peptides comprising modifications of the amino terminus and/or the carboxy terminus. Modifications of the terminal amino group include, but are not limited to, des-amino, N-lower alkyl, N-di-lower alkyl, and N-acyl modifications. Modifications of the terminal carboxy group include, but are not limited to, amide, lower alkyl amide, dialkyl amide, and lower alkyl ester modifications (e.g., wherein lower alkyl is C1-C4 alkyl). The term peptide also includes modifications, such as but not limited to those described above, of amino acids falling between the amino and carboxy termini.

As is clear to the skilled artisan, the peptide sequences disclosed herein are shown proceeding from left to right, with the left end of the sequence being the N-terminus of the peptide and the right end of the sequence being the C-terminus of the peptide. Among sequences disclosed herein are sequences incorporating either an “-OH” moiety or an “-NH₂” moiety at the carboxy terminus (C-terminus) of the sequence. In such cases, and unless otherwise indicated, an “-OH” or an “-NH₂” moiety at the C-terminus of the sequence indicates a hydroxy group or an amino group, corresponding to the presence of a carboxylic acid (COOH) or an amido (CONH₂) group at the C-terminus, respectively. In each sequence of the disclosure, a C-terminal “-OH” moiety may be substituted for a C-terminal “-NH₂” moiety, and vice-versa.

The phrase “amino acid,” “amino acid residue,” or “residue” as used herein refers to an amino acid, a modified amino acid, an amino acid analog, or an amino acid mimetic that is incorporated into a peptide by an amide bond or an amide bond mimetic.

Unless indicated otherwise the names of naturally occurring and non-naturally occurring aminoacyl residues used herein follow the naming conventions suggested by the

IUPAC Commission on the Nomenclature of Organic Chemistry and the IUPAC-IUB Commission on Biochemical Nomenclature as set out in “Nomenclature of α -Amino Acids (Recommendations, 1974)” *Biochemistry*, 14(2), (1975). To the extent that the names and abbreviations of amino acids and aminoacyl residues employed in this specification and
5 appended claims differ from those suggestions, they will be made clear to the reader. In sequences of amino acids that represent IL-23 inhibitors the individual amino acids are separated by a hyphen “-” or brackets e.g, lysine is shown as [K].

One of skill in the art will appreciate that certain amino acids and other chemical moieties are modified when bound to another molecule. For example, an amino acid side chain
10 may be modified when it forms an intramolecular bridge with another amino acid side chain, e.g., one or more hydrogens may be removed or replaced by the bond.

The term “therapeutically effective amount” or “pharmaceutically effective amount” means that amount of active peptide or pharmaceutical agent that elicits the biological or medicinal response in a tissue system, animal or human, that is being sought by a researcher,
15 veterinarian, medical doctor, or other clinician, which includes preventing, treating or ameliorating the symptoms of a syndrome, disorder or disease being treated.

The term “pharmaceutically acceptable” means approved or approvable by a regulatory agency of Federal or a state government or the corresponding agency in countries other than the United States, or that is listed in the U. S. Pharmacopoeia or other generally recognized
20 pharmacopoeia for use in animals, and more particularly, in humans.

“Pharmaceutically acceptable excipient” includes without limitation any adjuvant, carrier, excipient, glidant, sweetening agent, diluent, preservative, dye/colorant, flavor enhancer, surfactant, wetting agent, dispersing agent, suspending agent, stabilizer, isotonic agent, solvent, or emulsifier which has been approved by the United States Food and Drug Administration as
25 being acceptable for use in humans or domestic animals.

“Composition” or “pharmaceutical composition” as used herein is intended to encompass a product comprising the specified active pharmaceutical ingredient (API) (i.e., a peptide of the present disclosure), which may include pharmaceutically acceptable excipients, carriers or diluents as described herein, such as in specified amounts defined throughout the
30 disclosure.

Compositions or pharmaceutical compositions of the present disclosure may be in different pharmaceutically acceptable forms, which may include, but are not limited to a liquid composition, a tablet or matrix composition, a capsule composition, etc.. When the composition is a tablet composition, the tablet may include, but is not limited to different layers two or more

different phases, including an internal phase and an external phase that can comprise a core. The tablet composition can also include, but is not limited to one or more coatings.

Provided are also pharmaceutically acceptable salts and tautomeric forms of the peptides described herein.

- 5 A “pharmaceutically acceptable salt” is intended to mean a salt of a free acid or base of peptides represented by Formula (I) that are non-toxic, biologically tolerable, or otherwise biologically suitable for administration to the subject. It should possess the desired pharmacological activity of the parent compound. See, generally, G.S. Paulekuhn, et al., “Trends in Active Pharmaceutical Ingredient Salt Selection based on Analysis of the Orange Book Database”, *J. Med. Chem.*, **2007**, 50:6665–72, S.M. Berge, et al., “Pharmaceutical Salts”, *J Pharm Sci.*, **1977**, 66:1-19, and *Handbook of Pharmaceutical Salts, Properties, Selection, and Use*, Stahl and Wermuth, Eds., Wiley-VCH and VHCA, Zurich, **2002**. Examples of pharmaceutically acceptable salts are those that are pharmacologically effective and suitable for contact with the tissues of patients without undue toxicity, irritation, or allergic response. A
- 10 peptide of Formula (I) may possess a sufficiently acidic group, a sufficiently basic group, or both types of functional groups, and accordingly react with a number of inorganic or organic bases, and inorganic and organic acids, to form a pharmaceutically acceptable salt.

- The IL-23R inhibitors of the present disclosure, pharmaceutically acceptable salts, and/or other forms thereof may contain one or more asymmetric centers and may thus give rise
- 20 to enantiomers, diastereomers, and other stereoisomeric forms that may be defined, in terms of absolute stereochemistry, as (*R*)- or (*S*)- or as (*D*)- or (*L*)- for amino acids. The present disclosure is meant to include all such possible isomers, as well as their racemic and optically pure forms of the IL-23R inhibitors of the present disclosure. Optically active (+) and (–), (*R*)- and (*S*)-, or (*D*)- and (*L*)- isomers may be prepared using chiral synthons or chiral reagents,
- 25 or resolved using conventional techniques, for example, chromatography and fractional crystallization. Conventional techniques for the preparation/isolation of individual enantiomers include chiral synthesis from a suitable optically pure precursor or resolution of the racemate (or the racemate of a salt or derivative) using, for example, chiral high pressure liquid chromatography (HPLC). When the compounds described herein contain olefinic double bonds
- 30 or other centers of geometric asymmetry, and unless specified otherwise, it is intended that the compounds include both *E* and *Z* geometric isomers. Likewise, all tautomeric forms are also intended to be included. Where compounds are represented in their chiral form, it is understood that the aspect encompasses, but is not limited to, the specific diastereomerically or enantiomerically enriched form. Where chirality is not specified but is present, it is understood

that the aspect is directed to either the specific diastereomerically or enantiomerically enriched form; or a racemic or scalemic mixture of such compound(s).

“Racemates” refers to a mixture of enantiomers. The mixture can include equal or unequal amounts of each enantiomer.

5 “Stereoisomer” and “stereoisomers” refer to compounds that differ in the chirality of one or more stereo centers. Stereoisomers include enantiomers and diastereomers. The compounds may exist in stereoisomeric form if they possess one or more asymmetric centers or a double bond with asymmetric substitution and, therefore, can be produced as individual stereoisomers or as mixtures. Unless otherwise indicated, the description is intended to include
10 individual stereoisomers as well as mixtures. The methods for the determination of stereochemistry and the separation of stereoisomers are well-known in the art (see, e.g., Chapter 4 of Advanced Organic Chemistry, 4th ed., J. March, John Wiley and Sons, New York, 1992).

“Diastereoisomers” are stereoisomers that have at least two asymmetric atoms, but which are not mirror images of each other.

15 “Enantiomers” are a pair of stereoisomers that are non-superimposable mirror images of each other. A “racemic” mixture is a 1:1 mixture of a pair of enantiomers. A “scalemic” mixture of enantiomers is mixture of enantiomers at a ratio other than 1:1.

“Tautomer” refers to alternate forms of a compound that differ in the position of a proton, such as enol-keto and imine-enamine tautomers, or the tautomeric forms of heteroaryl
20 groups containing a ring atom attached to both a ring -NH- and a ring =N- such as pyrazoles, imidazoles, benzimidazoles, triazoles, and tetrazoles.

The term “administering” with respect to the methods of the present disclosure, means a method for therapeutically or prophylactically preventing, treating or ameliorating a syndrome, disorder or disease as described herein by using a compound of the disclosure, or
25 pharmaceutically acceptable salt thereof, composition thereof, or medicament thereof. Such methods include administering a therapeutically effective amount of a peptide of the disclosure, or pharmaceutically acceptable salt thereof, composition thereof, or medicament thereof, at different times during the course of a therapy or concurrently or sequentially as a combination therapy.

30 “Patient” or “subject,” which are used interchangeably, refer to a living organism, preferably a mammal, most preferably a human, whom will be or has been treated by a method according to an embodiment of the application. Examples of mammals include, but are not limited to, cows, horses, sheep, pigs, cats, dogs, mice, rats, rabbits, guinea pigs, non-human primates (NHPs) such as monkeys or apes, humans, etc., more preferably a human.

As used herein, the term “treatment” or “treating,” is defined as the application or administration of a therapeutic agent, i.e., a compound of the present disclosure (alone or in combination with another pharmaceutical agent), to a patient, or application or administration of a therapeutic agent to an isolated tissue or cell line from a patient (e.g., for diagnosis or ex vivo applications), who has a disorder or disease as described herein, a symptom thereof; or the potential to develop such disorder or disease, where the purpose of the application or administration is to cure, heal, alleviate, relieve, alter, remedy, ameliorate, improve or affect the disorder or disease, its symptoms, or the potential to develop said disorder or disease. Such treatments may be specifically tailored or modified, based on knowledge obtained from the field of pharmacogenomics.

As used herein, the term “prevent” or “prevention” means no disorder or disease development if none had occurred, or no further disorder or disease development if there had already been development of the disorder or disease. Also considered is the ability of one to prevent some or all of the symptoms associated with the disorder or disease.

Unless defined otherwise, all technical and scientific terms used herein have the same meaning as commonly or conventionally understood by one of ordinary skill in the art. In the chemical arts a dash at the front or end of a chemical group is a matter of convenience; chemical groups may be depicted with or without one or more dashes without losing their ordinary meaning. A wavy line drawn through a line in a structure indicates a point of attachment of a group. A dashed line indicates an optional bond. Unless chemically or structurally required, no directionality is indicated or implied by the order in which a chemical group is written or the point at which it is attached to the remainder of the molecule. For instance, the group “-SO₂CH₂-” is equivalent to “-CH₂SO₂-” and both may be connected in either direction. Similarly, an “arylalkyl” group, for example, may be attached to the remainder of the molecule at either an aryl or an alkyl portion of the group. A prefix such as “C_{u-v}” or (C_u-C_v) indicates that the following group has from u to v carbon atoms. For example, “C₁₋₆alkyl” and “C₁-C₆ alkyl” both indicate that the alkyl group has from 1 to 6 carbon atoms.

The term “alkyl” is a straight or branched saturated hydrocarbon. For example, an alkyl group can have 1 to 10 carbon atoms (i.e., (C₁-C₁₀)alkyl), 1 to 5 carbon atoms (i.e., (C₁-C₅)alkyl), 1 to 4 carbon atoms (i.e., (C₁-C₄)alkyl), or 1 to 3 carbon atoms (i.e., (C₁-C₃)alkyl). Examples of alkyl groups include, but are not limited to, methyl (Me, -CH₃), ethyl (Et, -CH₂CH₃), 1-propyl (*n*-Pr, *n*-propyl, -CH₂CH₂CH₃), isopropyl (*i*-Pr, *i*-propyl, -CH(CH₃)₂), 1-butyl (*n*-bu, *n*-butyl, -CH₂CH₂CH₂CH₃), 2-butyl (*s*-bu, *s*-butyl, -CH(CH₃)CH₂CH₃), *tert*-butyl (*t*-bu, *t*-butyl, -CH(CH₃)₃), 1-pentyl (*n*-pentyl, -CH₂CH₂CH₂CH₂CH₃), 2-pentyl (-CH(CH₃)CH₂CH₂CH₃), neopentyl (-CH₂C(CH₃)₃), 1-hexyl (-CH₂CH₂CH₂CH₂CH₂CH₃), 2-hexyl (-

CH(CH₃)CH₂CH₂CH₂CH₃), heptyl (-(CH₂)₆CH₃), octyl (-(CH₂)₇CH₃), 2,2,4-trimethylpentyl (-(CH₂C(CH₃)₂CH₂CH(CH₃)₂), nonyl (-(CH₂)₈CH₃), decyl (-(CH₂)₉CH₃), undecyl (-(CH₂)₁₀CH₃), and dodecyl (-(CH₂)₁₁CH₃). In an embodiment, alkyl refers to C₍₁₋₆₎alkyl. In another embodiment, alkyl refers to C₍₁₋₄₎alkyl. In another embodiment, alkyl refers to C₍₁₋₃₎alkyl.

5 The term “alkylene” refers to a bivalent alkyl group. For example, an alkylene group can have 1 to 10 carbon atoms (i.e., (C₁-C₁₀)alkylene), 1 to 5 carbon atoms (i.e., (C₁-C₅)alkylene), 1 to 2 carbon atoms (i.e., (C₁-C₂)alkylene), or 1 carbon atom (i.e., (C₁)alkylene). Examples of alkylene groups include, but are not limited to, methylene (-CH₂-), ethylene (-CH₂CH₂-), *n*-propylene (-CH₂CH₂CH₂-), *n*-butylene (-CH₂CH₂CH₂CH₂-), etc.

10 The term “halo” or “halogen” refers to bromo (-Br), chloro (-Cl), fluoro (-F), or iodo (-I). In an embodiment, halo refers to fluoro.

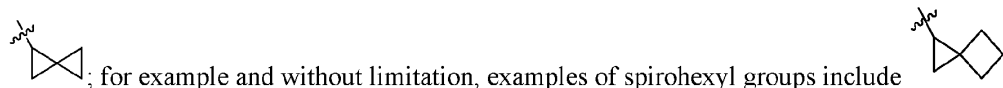
 The term “haloalkyl” refers to a straight- or branched-chain alkyl group having from 1 to 12 carbon atoms, 1 to 6 carbon atoms, 1 to 4 carbon atoms, or 1 to 3 carbon atoms in the chain optionally substituting one or more H with halo. Examples of “haloalkyl” groups include

15 trifluoromethyl (CF₃), difluoromethyl (CF₂H), monofluoromethyl (CH₂F), pentafluoroethyl (CF₂CF₃), tetrafluoroethyl (CHFCH₂F), monofluoroethyl (CH₂CH₂F), trifluoroethyl (CH₂CF₃), tetrafluorotrifluoromethylethyl (CF(CF₃)₂), and groups that in light of the ordinary skill in the art and the teachings provided herein would be considered equivalent to any one of the foregoing examples. In an embodiment, haloalkyl refers to C₍₁₋₆₎haloalkyl. In another embodiment,

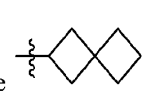
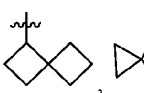
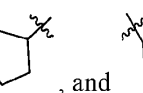
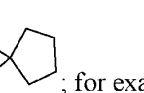
20 haloalkyl refers to C₍₁₋₄₎haloalkyl. In another embodiment, alkyl refers to C₍₁₋₃₎haloalkyl.

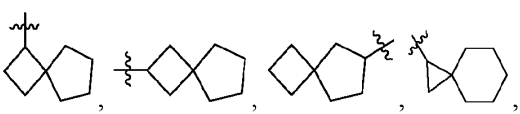
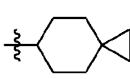
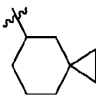
 The term “cycloalkyl” refers to a saturated or partially unsaturated all carbon ring system having 3 to 8 carbon atoms (i.e., C₍₃₋₈₎cycloalkyl), and preferably 3 to 6 carbon atoms (i.e., C₍₃₋₆₎cycloalkyl), wherein the cycloalkyl ring system has a single ring or multiple rings in a spirocyclic or bicyclic form. Exemplary cycloalkyls include, but are not limited to, cyclopropyl,

25 cyclobutyl, cyclopentyl, cyclohexyl, cycloheptyl, and cyclooctyl. Unless otherwise stated specifically in the specification, a cycloalkyl group may be unsubstituted or substituted. Some cycloalkyl groups may exist as spirocycloalkyls, wherein two cycloalkyl rings are fused through a single carbon atom; for example and without limitation, an example of a spirocycloalkyl group is



30 , and ; for example and without limitation examples of cycloheptyl groups

include , , , and ; for example and without limitation

examples of cyclooctyl groups include , , and . Unless otherwise stated specifically in the specification, a spirocycloalkyl group may be unsubstituted or substituted. Bicyclic cycloalkyl ring systems also

include , , or .

- 5 The term “heterocycle” or “heterocyclyl” refers to a saturated or partially unsaturated ring system that has at least one atom other than carbon in the ring system, wherein the atom is selected from the group consisting of oxygen, nitrogen and sulfur. The heterocyclyl group may, for example, consist of a single ring or multiple rings (e.g., in the form of a spirocyclic or bicyclic ring system). Exemplary heterocycles include, but are not limited to oxetanyl, aziridinyl, azetidiny, pyrrolidinyl, piperidinyl, piperazinyl, morpholinyl, tetrahydropyranyl, tetrahydrofuranly, and thiomorpholinyl.

10 The term “heteroaryl” refers to a single aromatic ring that has at least one atom other than carbon in the ring, wherein the atom is selected from the group consisting of oxygen, nitrogen and sulfur. The term “heteroaryl” includes single aromatic rings of from 1 to 6 carbon atoms and 1 to 4 heteroatoms selected from the group consisting of oxygen, nitrogen and sulfur. Exemplary heteroaryl ring systems include but are not limited to pyridinyl, pyrimidinyl, pyrazinyl, pyridazinyl, pyrimidinyl, pyrazolyl, oxazolyl, oxadiazolyl, isoxazolyl, triazolyl, imidazolyl, tetrazolyl, thienyl, thiazolyl, isothiazolyl, thiadiazolyl, or furyl.

20 Furthermore, it is intended that within the scope of the present invention, any element, in particular when mentioned in relation to a peptide of the disclosure, or pharmaceutically acceptable salt thereof, shall comprise all isotopes and isotopic mixtures of said element, either naturally occurring or synthetically produced, either with natural abundance or in an isotopically enriched form. For example, a reference to hydrogen includes within its scope ^1H , ^2H (*i.e.*, deuterium or D), and ^3H (*i.e.*, tritium or T). In some embodiments, the compounds described herein include a ^2H (*i.e.*, deuterium) isotope. By way of example, the group denoted $-\text{C}_{(1-6)}\text{alkyl}$ includes not only $-\text{CH}_3$, but also CD_3 ; not only CH_2CH_3 , but also CD_2CD_3 , *etc.* Similarly, references to carbon and oxygen include within their scope respectively ^{12}C , ^{13}C and ^{14}C and ^{15}O and ^{16}O and ^{17}O and ^{18}O . The isotopes may be radioactive or non-radioactive. Radiolabelled compounds of the disclosure may include a radioactive isotope selected from the group

comprising ^3H , ^{11}C , ^{18}F , ^{35}S , ^{122}I , ^{123}I , ^{125}I , ^{131}I , ^{75}Br , ^{76}Br , ^{77}Br and ^{82}Br . Preferably, the radioactive isotope is selected from the group of ^3H , ^{11}C and ^{18}F .

Abbreviation, “(V/V)” refers to the phrase “volume for volume”, i.e., the proportion of a particular substance within a mixture, as measured by volume or a volume amount of a component of the composition disclosed herein relative to the total volume amount of the composition. Accordingly, the quantity is unit less and represents a volume percentage amount of a component relative to the total volume of the composition. For example, a 2% (V/V) solvent mixture can indicate 2 mL of one solvent is present in 100 mL of the solvent mixture.

Systemic routes of administration as conventionally understood in the medicinal or pharmaceutical arts, refer to or are defined as a route of administration of drug, a pharmaceutical composition or formulation, or other substance into the circulatory system so that various body tissues and organs are exposed to the drug, formulation or other substance. As conventionally understood in the art, administration can take place orally (where drug or oral preparations are taken by mouth, and absorbed via the gastrointestinal tract), via enteral administration (absorption of the drug also occurs through the gastrointestinal tract) or parenteral administration (generally injection, infusion, or implantation, etc).

“Bioavailability” refers to the extent and rate at which the active moiety (drug or metabolite) enters systemic circulation, thereby accessing the site of action. Bioavailability of a drug could be impacted by the factors such as properties of the dosage form and properties of the drug.

“Digestive tract tissue” as used herein refers to all the tissues that comprise the organs of the alimentary canal. For example only, and without limitation, “digestive tract tissue” includes tissues of the mouth, esophagus, stomach, small intestine, large intestine, duodenum, and anus.

25

Compounds

The present disclosure provides a peptide inhibitor of interleukin-23 receptor. In particular, the present disclosure provides a peptide of Formula (I), comprising the amino acid sequence:

30 $\text{X}_3\text{-X}_4\text{-X}_5\text{-X}_6\text{-X}_7\text{-X}_8\text{-X}_9\text{-X}_{10}\text{-X}_{11}\text{-X}_{12}\text{-X}_{13}\text{-X}_{14}\text{-X}_{15}\text{-X}_{16}\text{-X}_{17}$ (I),

or a pharmaceutically acceptable salt thereof, wherein:

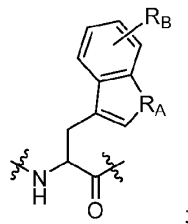
X_3 is any amino acid or absent;

X_4 is any amino acid;

X_5 is any amino acid;

35 X_6 is any amino acid;

X₇ is:



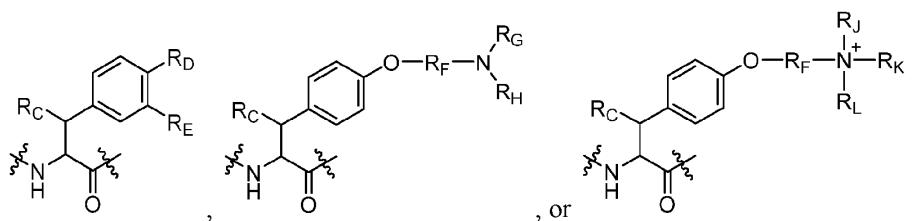
R_A is O, NH, N-C₍₁₋₅₎alkyl, or S;

R_B is -H, halo, C₍₁₋₃₎alkyl, or phenyl, wherein the phenyl is optionally substituted with one -N(H)C(O)C₍₁₋₃₎alkyl group;

X₈ is any amino acid;

X₉ is any amino acid;

X₁₀ is:



R_C is -H or -C₍₁₋₃₎alkyl;

R_D is -H, -OH, -CN, -C₍₁₋₃₎alkyl, -OC₍₁₋₃₎alkyl, -OC₍₁₋₃₎alkyl-(5-membered heteroaryl), -C(O)NH₂, or heterocyclyl, wherein the -OC₍₁₋₃₎alkyl-(5-membered heteroaryl) is optionally substituted with a polyethylene glycol chain, and wherein the heterocyclyl is optionally substituted with one -C(O)NH₂ group;

R_E is -H or halo;

R_F is -C₍₁₋₆₎alkylene or a bivalent polyethylene glycol chain;

R_G is -H, -C₍₁₋₃₎alkyl, or a bond to the amino acid at X₅ or X₁₃;

R_H is -H, -C₍₁₋₃₎alkyl, -C(NH)NH₂, -C(O)-R_{H1};

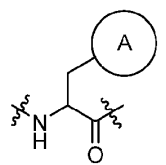
or R_G and R_H taken together with the nitrogen atom to which they are attached form a 5- to 8-membered heterocyclyl group;

R_{H1} is -C₍₁₋₅₎alkyl, -OC₍₁₋₅₎alkyl, -C₍₁₋₃₎alkyl-phenyl, -phenyl-C₍₁₋₃₎alkyl-N(H)-S(O)₂-C₍₁₋₃₎alkyl, or a polyethylene glycol chain, wherein the -C₍₁₋₃₎alkyl-phenyl is optionally substituted with one to three groups selected from halo and -OH;

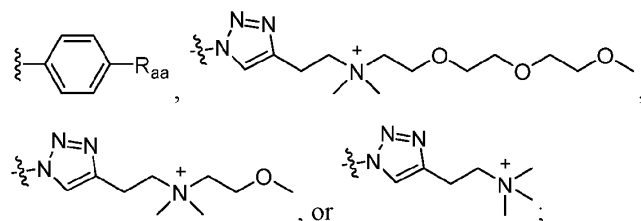
R_J, R_K, and R_L are each, independently, C₍₁₋₃₎alkyl;

or R_J and R_K taken together with the nitrogen atom to which they are attached form a 5- to 8-membered heterocyclyl group;

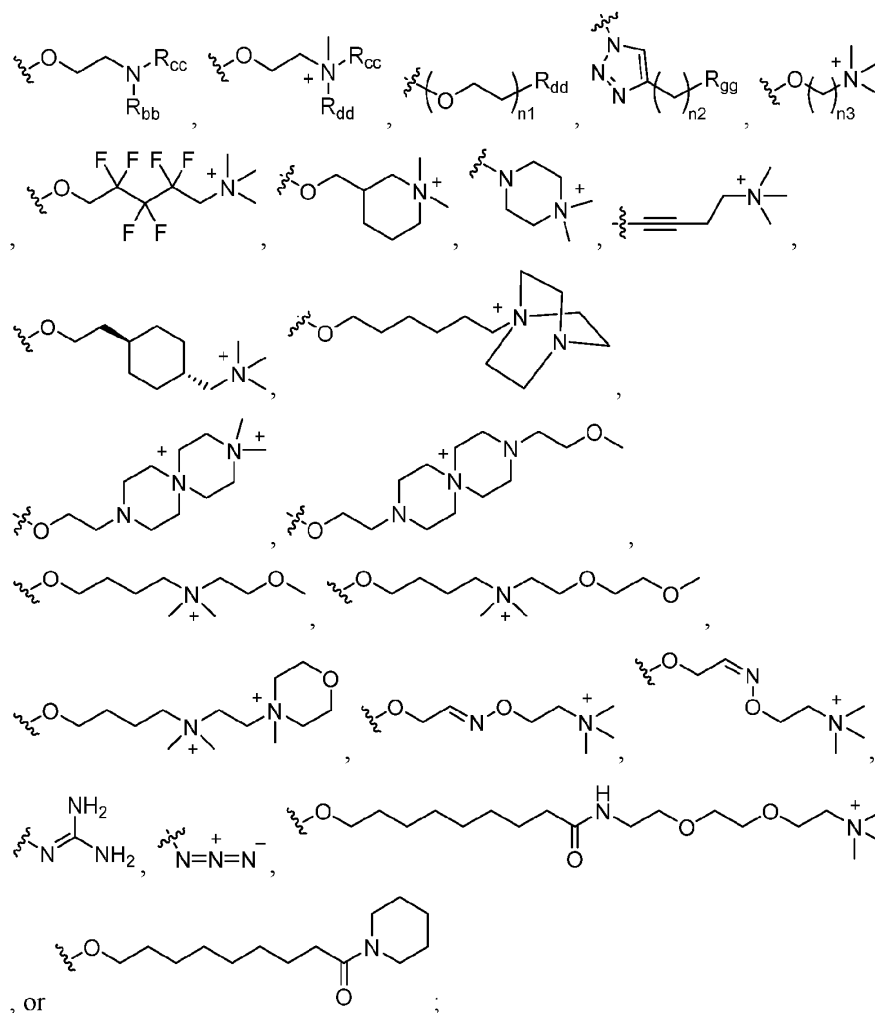
or X₁₀ is:



A is

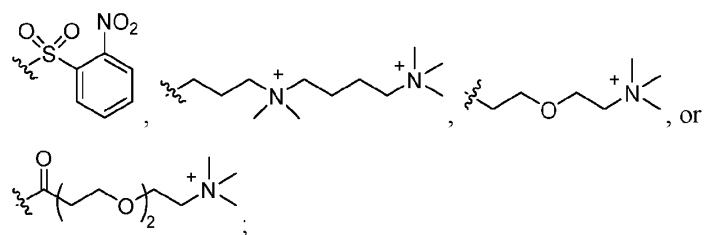


5 R_{aa} is $-\text{OCHF}_2$, $-\text{O}(\text{CH}_2)_9\text{CO}_2\text{H}$,

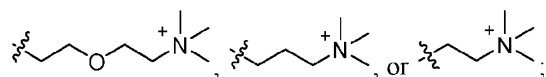


10

15 R_{bb} is $-\text{H}$, $-\text{CH}_3$, $-\text{C}(\text{O})\text{CH}_3$, $-\text{C}(\text{NH})\text{NH}_2$, $-(\text{CH}_2)_3\text{O}(\text{CH}_2)_2\text{OCH}_3$, $-\text{CH}_2\text{CH}_2\text{OCH}_3$, $-(\text{CH}_2\text{CH}_2\text{O})_3\text{CH}_3$, $-(\text{CH}_2\text{CH}_2\text{O})_6\text{CH}_3$,

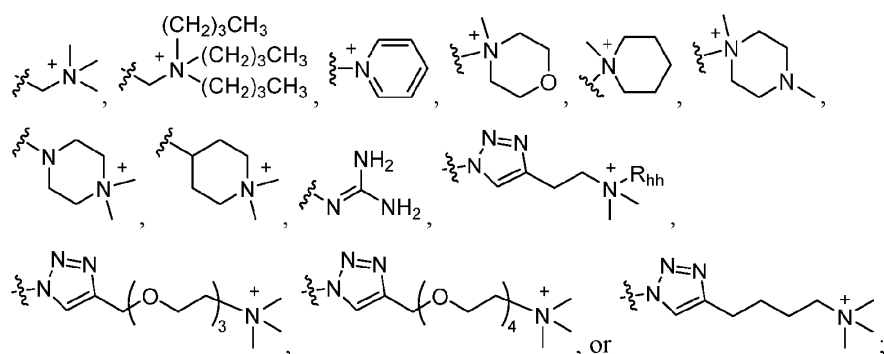


R_{cc} is -H, -CH₃, -(CH₂)₃O(CH₂)₂OCH₃,



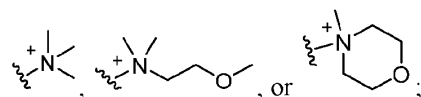
5 n_1 is 1, 2, or 3;

R_{dd} is



10 n_2 is 1, 2, 3, 4, or 5;

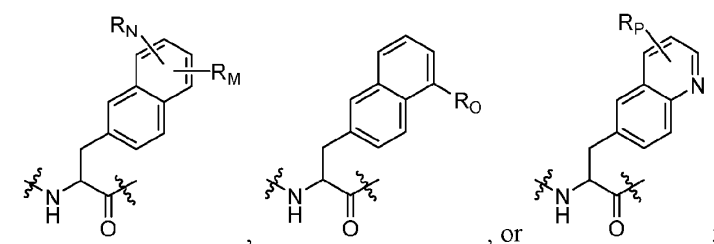
R_{gg} is -OCH₃,



n_3 is 3, 4, 5, 6, or 8;

R_{hh} is -H, -(CH₂)₇CH₃, -(CH₂)₁₅CH₃, -(CH₂)₂OCH₃, or -(CH₂CH₂O)₃CH₃;

15 X_{11} is:



R_M is halo, -OH, -C₍₁₋₃₎alkyl, -OC(O)C₍₁₋₃₎haloalkyl, phenyl, or 5- to 6-membered heteroaryl, wherein the phenyl and 5- to 6-membered heteroaryl are each optionally substituted with one to three groups selected from -OH, -OC₍₁₋₃₎alkyl, -C₍₁₋₃₎haloalkyl, and 3- to 6-membered heterocyclyl;

R_N is -H or -OH;

R_O is $-\text{OC}_{(1-3)}\text{alkyl}$ or $-\text{C}(\text{O})\text{NH}_2$;

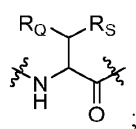
R_P is halo, -OH, $-\text{C}_{(1-3)}\text{alkyl}$, $-\text{OC}_{(1-3)}\text{alkyl}$, $-\text{C}(\text{O})\text{NH}_2$, $-\text{OC}(\text{O})\text{C}_{(1-3)}\text{haloalkyl}$, phenyl, or 5- to 6-membered heteroaryl, wherein the phenyl and 5- to 6-membered heteroaryl are each optionally substituted with one to three groups selected from -OH, $-\text{OC}_{(1-3)}\text{alkyl}$, $-\text{C}_{(1-3)}\text{haloalkyl}$, and 3- to 6-membered heterocyclyl;

X_{12} is any amino acid;

X_{13} is any amino acid;

X_{14} is any amino acid;

10 X_{15} is Ala, THP, or



R_Q is -H or $-\text{C}_{(1-3)}\text{alkyl}$;

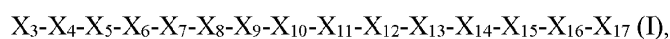
R_S is phenyl or 5- to 6-membered heteroaryl, each of which is optionally substituted with one $-\text{C}(\text{O})\text{NH}_2$ group;

15 X_{16} is any amino acid or absent; and

X_{17} is any amino acid or absent;

wherein the peptide is cyclized to form a first ring, wherein the first ring comprises 4-11 or 14 amino acids.

In some embodiments, the present disclosure provides a peptide of Formula (I), comprising the amino acid sequence:



or a pharmaceutically acceptable salt thereof, wherein:

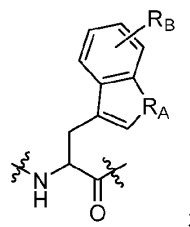
X_3 is any amino acid or absent;

X_4 is an amino acid that is linked to the amino acid at X_9 ;

25 X_5 is any amino acid;

X_6 is any amino acid;

X_7 is:



R_A is O, NH, $\text{N}-\text{C}_{(1-5)}\text{alkyl}$, or S;

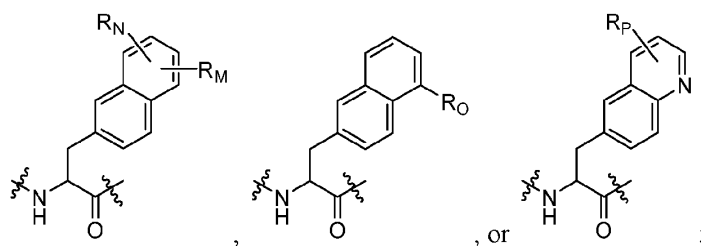
R_B is -H, halo, $C_{(1-3)}$ alkyl, or phenyl, wherein the phenyl is optionally substituted with one -N(H)C(O) $C_{(1-3)}$ alkyl group;

X_8 is any amino acid;

X_9 is an amino acid that is linked to the amino acid at X_4 ;

5 X_{10} is a substituted or unsubstituted aromatic amino acid;

X_{11} is:



R_M is halo, -OH, $-C_{(1-3)}$ alkyl, $-OC(O)C_{(1-3)}$ haloalkyl, phenyl, or 5- to 6-membered heteroaryl, wherein the phenyl and 5- to 6-membered heteroaryl are each optionally substituted
10 with one to three groups selected from -OH, $-OC_{(1-3)}$ alkyl, $-C_{(1-3)}$ haloalkyl, and 3- to 6-membered heterocyclyl;

R_N is -H or -OH;

R_O is $-OC_{(1-3)}$ alkyl or $-C(O)NH_2$;

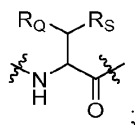
R_P is halo, -OH, $-C_{(1-3)}$ alkyl, $-OC_{(1-3)}$ alkyl, $-C(O)NH_2$, $-OC(O)C_{(1-3)}$ haloalkyl, phenyl, or
15 5- to 6-membered heteroaryl, wherein the phenyl and 5- to 6-membered heteroaryl are each optionally substituted with one to three groups selected from -OH, $-OC_{(1-3)}$ alkyl, $-C_{(1-3)}$ haloalkyl, and 3- to 6-membered heterocyclyl;

X_{12} is any amino acid;

X_{13} is any amino acid;

20 X_{14} is any amino acid;

X_{15} is Ala, THP, or



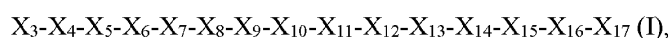
R_Q is -H or $-C_{(1-3)}$ alkyl;

R_S is phenyl or 5- to 6-membered heteroaryl, each of which is optionally substituted with
25 one $-C(O)NH_2$ group;

X_{16} is any amino acid or absent; and

X_{17} is any amino acid or absent.

In some embodiments, the present disclosure provides a peptide of Formula (I), comprising the amino acid sequence:



or a pharmaceutically acceptable salt thereof, wherein:

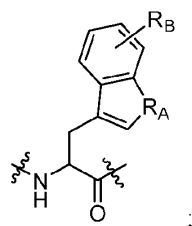
5 X_3 is any amino acid or absent;

X_4 is an amino acid that is linked to the amino acid at X_9 ;

X_5 is any amino acid;

X_6 is any amino acid;

X_7 is:



10

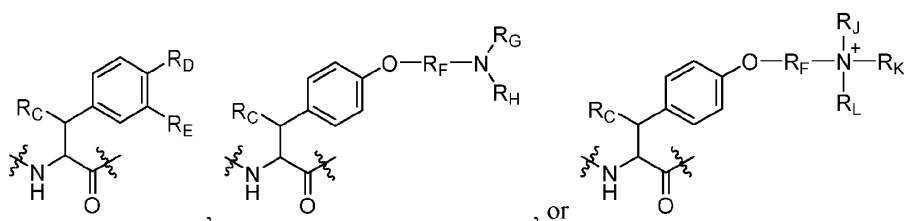
R_A is O, NH, N- $C_{(1-5)}$ alkyl, or S;

R_B is -H, halo, $C_{(1-3)}$ alkyl, or phenyl, wherein the phenyl is optionally substituted with one -N(H)C(O) $C_{(1-3)}$ alkyl group;

X_8 is any amino acid;

15 X_9 is an amino acid that is linked to the amino acid at X_4 ;

X_{10} is:



R_C is -H or $-C_{(1-3)}$ alkyl;

20 R_D is -H, -OH, -CN, $-C_{(1-3)}$ alkyl, $-OC_{(1-3)}$ alkyl, $-OC_{(1-3)}$ alkyl-(5-membered heteroaryl), -C(O)NH₂, or heterocyclyl, wherein the $-OC_{(1-3)}$ alkyl-(5-membered heteroaryl) is optionally substituted with a polyethylene glycol chain, and wherein the heterocyclyl is optionally substituted with one -C(O)NH₂ group;

R_E is -H or halo;

R_F is $-C_{(1-6)}$ alkylene or a bivalent polyethylene glycol chain;

25 R_G is -H, $-C_{(1-3)}$ alkyl, or a bond to the amino acid at X_5 or X_{13} ;

R_H is -H, $-C_{(1-3)}$ alkyl, -C(NH)NH₂, -C(O)- R_{H1} ;

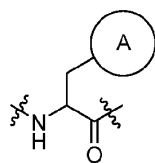
or R_G and R_H taken together with the nitrogen atom to which they are attached form a 5- to 8-membered heterocyclyl group;

R_{H1} is $-C_{(1-5)}\text{alkyl}$, $-\text{OC}_{(1-5)}\text{alkyl}$, $-C_{(1-3)}\text{alkyl-phenyl}$, $-\text{phenyl-}C_{(1-3)}\text{alkyl-N(H)-S(O)}_2\text{-}C_{(1-3)}\text{alkyl}$, or a polyethylene glycol chain, wherein the $-C_{(1-3)}\text{alkyl-phenyl}$ is optionally substituted
5 with one to three groups selected from halo and $-\text{OH}$;

R_J , R_K , and R_L are each, independently, $C_{(1-3)}\text{alkyl}$;

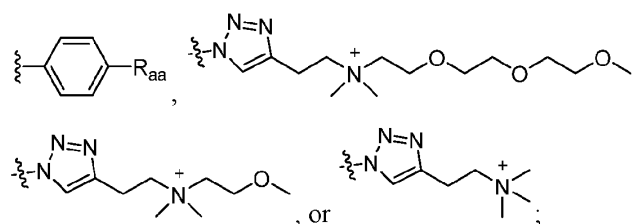
or R_J and R_K taken together with the nitrogen atom to which they are attached form a 5- to 8-membered heterocyclyl group;

or X_{10} is



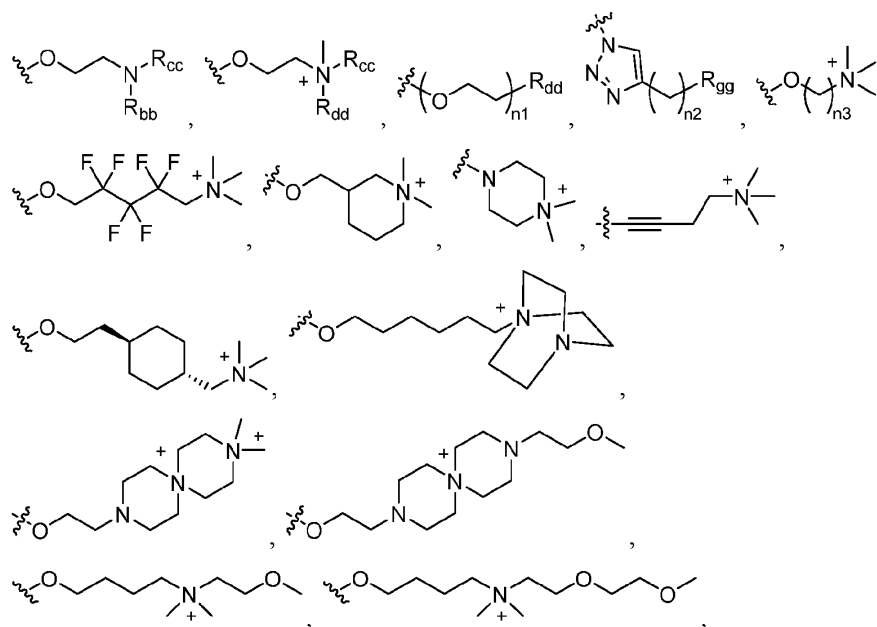
10

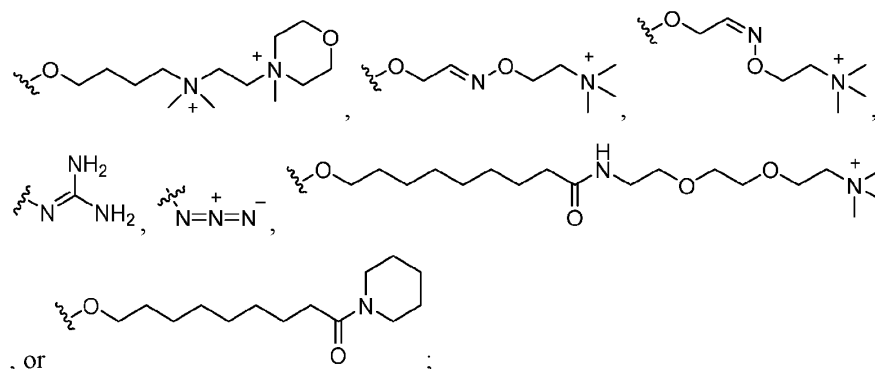
A is



R_{aa} is $-\text{OCHF}_2$, $-\text{O}(\text{CH}_2)_9\text{CO}_2\text{H}$,

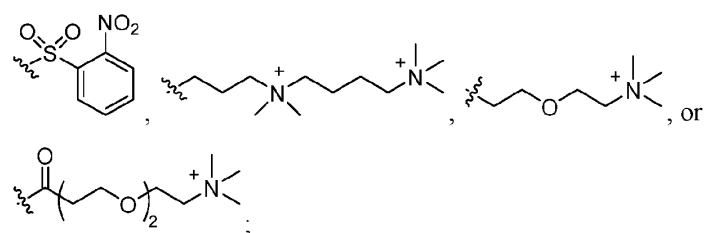
15



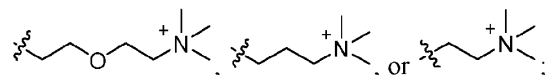


R_{bb} is -H, -CH₃, -C(O)CH₃, -C(NH)NH₂, -(CH₂)₃O(CH₂)₂OCH₃, -CH₂CH₂OCH₃, -

5 (CH₂CH₂O)₃CH₃, -(CH₂CH₂O)₆CH₃,

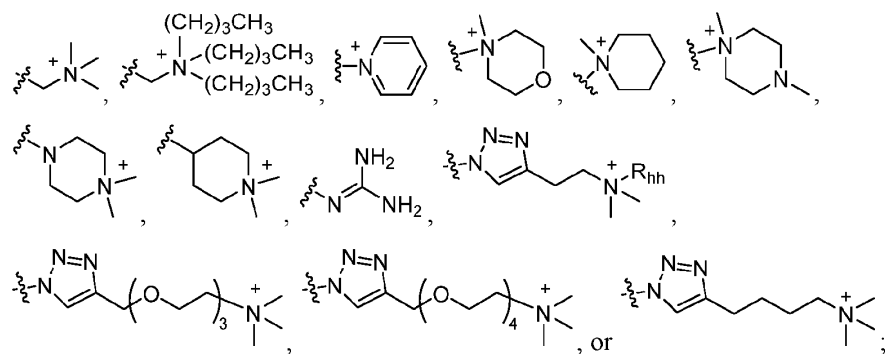


R_{cc} is -H, -CH₃, -(CH₂)₃O(CH₂)₂OCH₃,



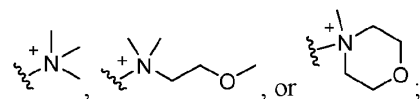
10 n_1 is 1, 2, or 3;

R_{dd} is



15 n_2 is 1, 2, 3, 4, or 5;

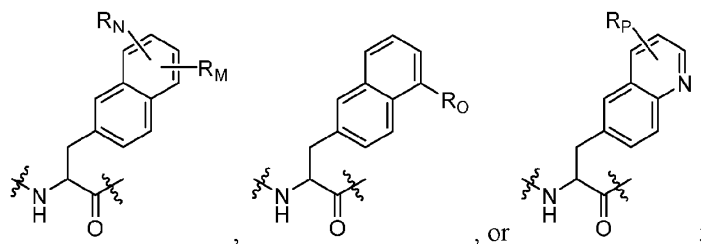
R_{gg} is -OCH₃,



n_3 is 3, 4, 5, 6, or 8;

R_{hh} is -H, -(CH₂)₇CH₃, -(CH₂)₁₅CH₃, -(CH₂)₂OCH₃, or -(CH₂CH₂O)₃CH₃;

X₁₁ is:



R_M is halo, -OH, -C₍₁₋₃₎alkyl, -OC(O)C₍₁₋₃₎haloalkyl, phenyl, or 5- to 6-membered heteroaryl, wherein the phenyl and 5- to 6-membered heteroaryl are each optionally substituted
5 with one to three groups selected from -OH, -OC₍₁₋₃₎alkyl, -C₍₁₋₃₎haloalkyl, and 3- to 6-membered heterocyclyl;

R_N is -H or -OH;

R_O is -OC₍₁₋₃₎alkyl or -C(O)NH₂;

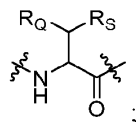
R_P is halo, -OH, -C₍₁₋₃₎alkyl, -OC₍₁₋₃₎alkyl, -C(O)NH₂, -OC(O)C₍₁₋₃₎haloalkyl, phenyl, or
10 5- to 6-membered heteroaryl, wherein the phenyl and 5- to 6-membered heteroaryl are each optionally substituted with one to three groups selected from -OH, -OC₍₁₋₃₎alkyl, -C₍₁₋₃₎haloalkyl, and 3- to 6-membered heterocyclyl;

X₁₂ is any amino acid;

X₁₃ is any amino acid;

15 X₁₄ is any amino acid;

X₁₅ is Ala, THP, or



R_Q is -H or -C₍₁₋₃₎alkyl;

R_S is phenyl or 5- to 6-membered heteroaryl, each of which is optionally substituted with
20 one -C(O)NH₂ group;

X₁₆ is any amino acid or absent; and

X₁₇ is any amino acid or absent.

In some embodiments, the present disclosure provides a peptide of Formula (I),
comprising the amino acid sequence:

25 X₃-X₄-X₅-X₆-X₇-X₈-X₉-X₁₀-X₁₁-X₁₂-X₁₃-X₁₄-X₁₅-X₁₆-X₁₇ (I),

or a pharmaceutically acceptable salt thereof, wherein:

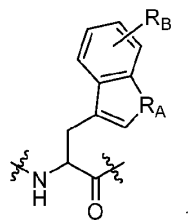
X₃ is any amino acid or absent;

X₄ is any amino acid;

X₅ is any amino acid;

X₆ is any amino acid;

X₇ is:



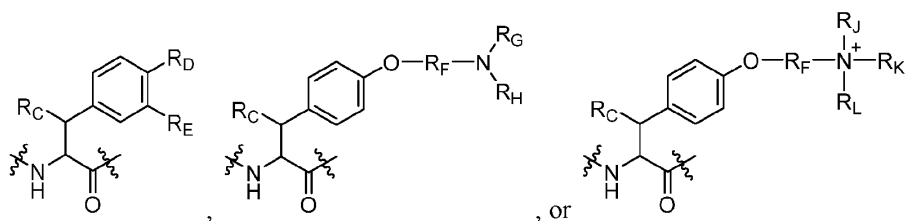
5 RA is O, NH, N-C₍₁₋₅₎alkyl, or S;

RB is -H, halo, C₍₁₋₃₎alkyl, or phenyl, wherein the phenyl is optionally substituted with one -N(H)C(O)C₍₁₋₃₎alkyl group;

X₈ is any amino acid;

X₉ is any amino acid;

10 X₁₀ is:



RC is -H or -C₍₁₋₃₎alkyl;

RD is -H, -OH, -CN, -C₍₁₋₃₎alkyl, -OC₍₁₋₃₎alkyl, -OC₍₁₋₃₎alkyl-(5-membered heteroaryl), -C(O)NH₂, or heterocyclyl, wherein the -OC₍₁₋₃₎alkyl-(5-membered heteroaryl) is optionally substituted with a polyethylene glycol chain, and wherein the heterocyclyl is optionally substituted with one -C(O)NH₂ group;

RE is -H or halo;

RF is -C₍₁₋₆₎alkylene or a bivalent polyethylene glycol chain;

RG is -H, -C₍₁₋₃₎alkyl, or a bond to the amino acid at X₅ or X₁₃;

20 RH is -H, -C₍₁₋₃₎alkyl, -C(NH)NH₂, -C(O)-RH₁;

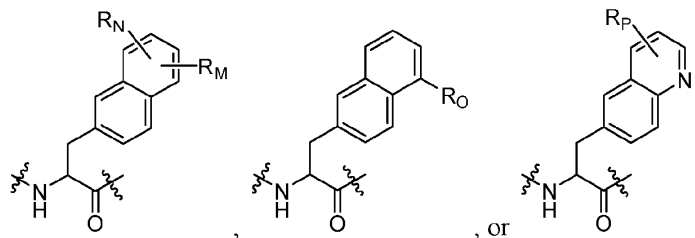
or RG and RH taken together with the nitrogen atom to which they are attached form a 5- to 8-membered heterocyclyl group;

RH₁ is -C₍₁₋₅₎alkyl, -OC₍₁₋₅₎alkyl, -C₍₁₋₃₎alkyl-phenyl, -phenyl-C₍₁₋₃₎alkyl-N(H)-S(O)₂-C₍₁₋₃₎alkyl, or a polyethylene glycol chain, wherein the -C₍₁₋₃₎alkyl-phenyl is optionally substituted with one to three groups selected from halo and -OH;

RJ, RK, and RL are each, independently, C₍₁₋₃₎alkyl;

or R_J and R_K taken together with the nitrogen atom to which they are attached form a 5- to 8-membered heterocyclyl group;

X_{11} is:



- 5 R_M is halo, -OH, $-C_{(1-3)}\text{alkyl}$, $-\text{OC(O)}C_{(1-3)}\text{haloalkyl}$, phenyl, or 5- to 6-membered heteroaryl, wherein the phenyl and 5- to 6-membered heteroaryl are each optionally substituted with one to three groups selected from -OH, $-\text{OC}_{(1-3)}\text{alkyl}$, $-C_{(1-3)}\text{haloalkyl}$, and 3- to 6-membered heterocyclyl;

R_N is -H or -OH;

- 10 R_O is $-\text{OC}_{(1-3)}\text{alkyl}$ or $-\text{C(O)NH}_2$;

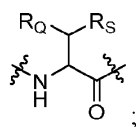
R_P is halo, -OH, $-C_{(1-3)}\text{alkyl}$, $-\text{OC}_{(1-3)}\text{alkyl}$, $-\text{C(O)NH}_2$, $-\text{OC(O)}C_{(1-3)}\text{haloalkyl}$, phenyl, or 5- to 6-membered heteroaryl, wherein the phenyl and 5- to 6-membered heteroaryl are each optionally substituted with one to three groups selected from -OH, $-\text{OC}_{(1-3)}\text{alkyl}$, $-C_{(1-3)}\text{haloalkyl}$, and 3- to 6-membered heterocyclyl;

- 15 X_{12} is any amino acid;

X_{13} is any amino acid;

X_{14} is any amino acid;

X_{15} is Ala, THP, or



- 20 R_Q is -H or $-C_{(1-3)}\text{alkyl}$;

R_S is phenyl or 5- to 6-membered heteroaryl, each of which is optionally substituted with one $-\text{C(O)NH}_2$ group;

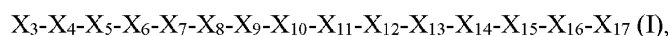
X_{16} is any amino acid or absent; and

X_{17} is any amino acid or absent;

- 25 X_{18} is any amino acid or absent;

wherein the peptide is cyclized to form a first ring, wherein the first ring comprises 4-11 or 14 amino acids.

In some embodiments, the present disclosure provides a peptide of Formula (I), comprising the amino acid sequence:



or a pharmaceutically acceptable salt thereof, wherein:

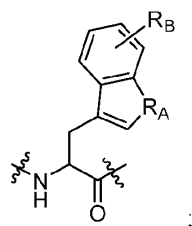
5 X_3 is any amino acid or absent;

X_4 is an amino acid that is linked to the amino acid at X_9 ;

X_5 is any amino acid;

X_6 is any amino acid;

X_7 is:



10

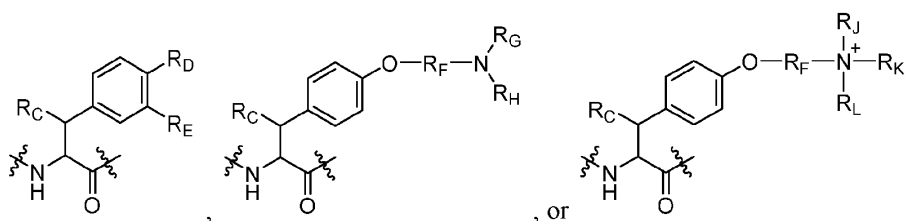
R_A is O, NH, N- $C_{(1-5)}$ alkyl, or S;

R_B is -H, halo, $C_{(1-3)}$ alkyl, or phenyl, wherein the phenyl is optionally substituted with one -N(H)C(O) $C_{(1-3)}$ alkyl group;

X_8 is any amino acid;

15 X_9 is an amino acid that is linked to the amino acid at X_4 ;

X_{10} is:



R_C is -H or $-C_{(1-3)}$ alkyl;

20 R_D is -H, -OH, -CN, $-C_{(1-3)}$ alkyl, $-OC_{(1-3)}$ alkyl, $-OC_{(1-3)}$ alkyl-(5-membered heteroaryl), -C(O)NH₂, or heterocyclyl, wherein the $-OC_{(1-3)}$ alkyl-(5-membered heteroaryl) is optionally substituted with a polyethylene glycol chain, and wherein the heterocyclyl is optionally substituted with one -C(O)NH₂ group;

R_E is -H or halo;

R_F is $-C_{(1-6)}$ alkylene or a bivalent polyethylene glycol chain;

25 R_G is -H, $-C_{(1-3)}$ alkyl, or a bond to the amino acid at X_5 or X_{13} ;

R_H is -H, $-C_{(1-3)}$ alkyl, -C(NH)NH₂, -C(O)- R_{H1} ;

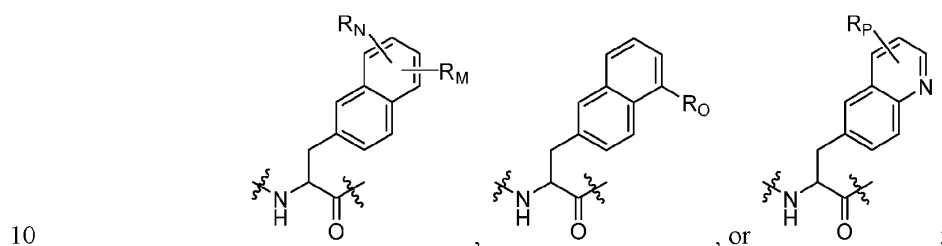
or R_G and R_H taken together with the nitrogen atom to which they are attached form a 5- to 8-membered heterocyclyl group;

R_{H1} is $-C_{(1-5)}\text{alkyl}$, $-\text{OC}_{(1-5)}\text{alkyl}$, $-C_{(1-3)}\text{alkyl-phenyl}$, $-\text{phenyl-}C_{(1-3)}\text{alkyl-N(H)-S(O)}_2-C_{(1-3)}\text{alkyl}$, or a polyethylene glycol chain, wherein the $-C_{(1-3)}\text{alkyl-phenyl}$ is optionally substituted
5 with one to three groups selected from halo and $-\text{OH}$;

R_J , R_K , and R_L are each, independently, $C_{(1-3)}\text{alkyl}$;

or R_J and R_K taken together with the nitrogen atom to which they are attached form a 5- to 8-membered heterocyclyl group;

X_{11} is:



R_M is halo, $-\text{OH}$, $-C_{(1-3)}\text{alkyl}$, $-\text{OC(O)}C_{(1-3)}\text{haloalkyl}$, phenyl, or 5- to 6-membered heteroaryl, wherein the phenyl and 5- to 6-membered heteroaryl are each optionally substituted with one to three groups selected from $-\text{OH}$, $-\text{OC}_{(1-3)}\text{alkyl}$, $-C_{(1-3)}\text{haloalkyl}$, and 3- to 6-membered heterocyclyl;

15 R_N is $-\text{H}$ or $-\text{OH}$;

R_O is $-\text{OC}_{(1-3)}\text{alkyl}$ or $-\text{C(O)NH}_2$;

R_P is halo, $-\text{OH}$, $-C_{(1-3)}\text{alkyl}$, $-\text{OC}_{(1-3)}\text{alkyl}$, $-\text{C(O)NH}_2$, $-\text{OC(O)}C_{(1-3)}\text{haloalkyl}$, phenyl, or 5- to 6-membered heteroaryl, wherein the phenyl and 5- to 6-membered heteroaryl are each optionally substituted with one to three groups selected from $-\text{OH}$, $-\text{OC}_{(1-3)}\text{alkyl}$, $-C_{(1-3)}\text{haloalkyl}$,
20 and 3- to 6-membered heterocyclyl;

X_{12} is any amino acid;

X_{13} is any amino acid;

X_{14} is any amino acid;

X_{15} is Ala, THP, or



R_Q is $-\text{H}$ or $-C_{(1-3)}\text{alkyl}$;

R_S is phenyl or 5- to 6-membered heteroaryl, each of which is optionally substituted with one $-\text{C(O)NH}_2$ group;

X₁₆ is any amino acid or absent; and

X₁₇ is any amino acid or absent.

In some embodiments, the peptide is not MeCO-Pen-N-T-7MeW-K(Ac)-Pen-AEF-6OHQui-THP-E-N-3Py-a-Sar-CONH₂.

5 The linear form structure of Formula (I) is intended for exemplary and non-limiting purposes, which will be apparent from examples set forth and exemplified throughout the instant specification, e.g., where each such structure may be longer or shorter than the length of eighteen amino acids and/or other corresponding chemical moieties or functional group substituents as defined herein.

10 In some embodiments, the peptide comprises an amino acid sequence selected from the group consisting of:

R₁-X₃-X₄-X₅-X₆-X₇-X₈-X₉-X₁₀-X₁₁-X₁₂-X₁₃-X₁₄-X₁₅-X₁₆-X₁₇ (I-A1),

X₃-X₄-X₅-X₆-X₇-X₈-X₉-X₁₀-X₁₁-X₁₂-X₁₃-X₁₄-X₁₅-X₁₆-X₁₇-R₂ (I-A2), and

R₁-X₃-X₄-X₅-X₆-X₇-X₈-X₉-X₁₀-X₁₁-X₁₂-X₁₃-X₁₄-X₁₅-X₁₆-X₁₇-R₂ (I-A3),

15 or a pharmaceutically acceptable salt thereof.

R₁ represents the N-terminal end of the peptide, which may be, for example, a hydrogen or a chemical moiety or functional group substituted on the amino group (e.g., an acetate group).

20 Similarly, R₂ represents the carboxyl end, which may be, for example the OH of the carboxyl or a chemical moiety or functional group attached thereto or substituted for the OH group (e.g., an amino group to give a terminal amide, e.g., -CONH₂);

In some embodiments, R₁ is 5cpaCO, CF₃CO, CF₃Propylamide, EtCO, MeCO, a polyethylene glycol chain, or a lipophilic substituent, or R₁ is an alkyl or polyethylene glycol chain linked to the amino acid at X₁₃; and

25 R₂ is CONH₂, CO(DiFPip), CON(Me)₂, a polyethylene glycol chain, or a lipophilic substituent.

In some embodiments, the peptide comprises an amino acid sequence of Formula (I-A1):

R₁-X₃-X₄-X₅-X₆-X₇-X₈-X₉-X₁₀-X₁₁-X₁₂-X₁₃-X₁₄-X₁₅-X₁₆-X₁₇ (I-A1),

or a pharmaceutically acceptable salt thereof, wherein:

30 R₁ is 5cpaCO, CF₃CO, CF₃Propylamide, EtCO, MeCO, a polyethylene glycol chain, or a lipophilic substituent, or R₁ is an alkyl or polyethylene glycol chain linked to the amino acid at X₁₃.

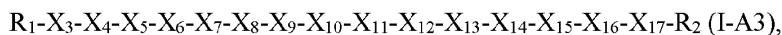
In some embodiments, the peptide comprises an amino acid sequence of Formula (I-A2):

X₃-X₄-X₅-X₆-X₇-X₈-X₉-X₁₀-X₁₁-X₁₂-X₁₃-X₁₄-X₁₅-X₁₆-X₁₇-R₂ (I-A2),

or a pharmaceutically acceptable salt thereof, wherein:

R₂ is CONH₂, CO(DiFPip), CON(Me)₂, a polyethylene glycol chain, or a lipophilic substituent.

In some embodiments, the peptide comprises an amino acid sequence of Formula (I-A3):



5 or a pharmaceutically acceptable salt thereof, wherein:

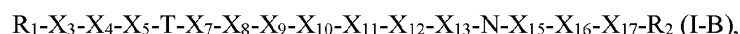
R₁ is 5cpaCO, CF₃CO, CF₃Propylamide, EtCO, MeCO, a polyethylene glycol chain, or a lipophilic substituent, or R₁ is an alkyl or polyethylene glycol chain linked to the amino acid at X₁₃; and

10 R₂ is CONH₂, CO(DiFPip), CON(Me)₂, a polyethylene glycol chain, or a lipophilic substituent.

In some embodiments, the peptide further comprises a linkage between the amino acids at X₃ and X₁₃, between the amino acids at X₅ and X₁₀, between the amino acids at X₁₀ and X₁₃, or between R₁ and the amino acid at X₁₃. In some embodiments, the amino acid at X₃ is linked to the amino acid at X₁₃. In some embodiments, the amino acid at X₅ is linked to the amino acid at X₁₀. In some embodiments, the amino acid at X₁₀ is linked to the amino acid at X₁₃. In some
15 embodiments, R₁ is linked to the amino acid at X₁₃.

In some embodiments, the amino acid at X₃, X₅, X₆, X₈, X₁₂, X₁₃, X₁₄, X₁₆, or X₁₇ is conjugated to a polyethylene glycol chain. In some embodiments, the amino acid at X₃, X₅, X₆, X₈, X₁₂, X₁₃, X₁₄, X₁₆, or X₁₇ is conjugated to a polyethylene glycol chain. In some
20 embodiments, the amino acid at X₃, X₅, X₆, X₈, X₁₂, X₁₃, X₁₄, X₁₆, or X₁₇ is conjugated to a lipophilic substituent.

In some embodiments, the peptide comprises an amino acid sequence of Formula (I-B), comprising the amino acid sequence:



25 or a pharmaceutically acceptable salt thereof, wherein:

R₁ is 5Ava, 5cpaCO, 6Ahx, 7Ahp, CF₃CO, CF₃Propylamide, EtCO, MeCO, PEG₂, PEG₂NMe, Z_{peg}, or Z_{lipid};

X₃ is Dab(COCH₂), K(COCH₂CH₂), hK(Me)₃, K, K(5cpa), K-Z_{peg}, K-Z_{lipid}, K(d), K(Me)₃, Ser(MePEG₂), R, SP₆, or absent;

30 X₄ is 4AminoPro, Abu, aG, aMeC, C, Dap, Pen, Pen(oXyl), Pen(mXyl), Pen(pXyl), or Pra;

X₅ is D, E, hE, K, K(a), K(Ac), K(d), K(G), K(NMe), K(NNs), K-Z_{peg}, K-Z_{lipid}, L, N, N(NMe), N(NMe₂), Q, Q(NMe), or Q(NMe₂);

X₇ is 7(3NacPh)W, 7BrW, 7MeW, BT, or W;

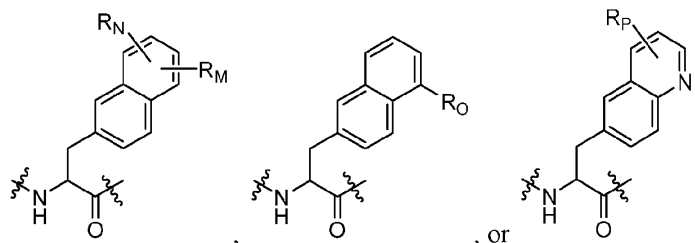
X_8 is Dab(NMeAc), Dab(NMecarn), Dab- Z_{peg} , hK(Me)₃, K(Ac), K(Me)₃, K(NMeAc), NMeK- Z_{peg} , K- Z_{peg} , K- Z_{lipid} , Lys(N+Me₂)- Z_{peg} , Q, or Q(NMe₂);

X_9 is aMeC, aG, C, D, E, hE, Pen, or Dap(N₃);

X_{10} is 4DMPzEF, 4OMeF, AEF, AEF(G), AEF(NMe), AEF(NMe₂), AEF- Z_{peg} ,

5 AEF(NMe)- Z_{peg} , APEG3F, bMeAEF, F, MMoEF, TMAPF, or Y;

X_{11} is:



R_M is halo, -OH, -C₍₁₋₃₎alkyl, -OC(O)C₍₁₋₃₎haloalkyl, phenyl, or 5- to 6-membered heteroaryl, wherein the phenyl and 5- to 6-membered heteroaryl are each optionally substituted
10 with one to three groups selected from -OH, -OC₍₁₋₃₎alkyl, -C₍₁₋₃₎haloalkyl, and 3- to 6-membered heterocyclyl;

R_N is -H or -OH;

R_O is -OC₍₁₋₃₎alkyl or -C(O)NH₂;

R_P is halo, -OH, -C₍₁₋₃₎alkyl, -OC₍₁₋₃₎alkyl, -C(O)NH₂, -OC(O)C₍₁₋₃₎haloalkyl, phenyl, or
15 5- to 6-membered heteroaryl, wherein the phenyl and 5- to 6-membered heteroaryl are each optionally substituted with one to three groups selected from -OH, -OC₍₁₋₃₎alkyl, -C₍₁₋₃₎haloalkyl, and 3- to 6-membered heterocyclyl;

X_{12} is THP, aMeL, diFCpx, or Pip(NMe₂);

X_{13} is C, D, Dab(NMeAc), Dab(NMecarn), E, E(COcPEG3a), hE, K(Ac), K(Me)₃,
20 K(NMeAc), K- Z_{peg} , K- Z_{lipid} , L, or Q(NMe₂);

X_{15} is 3AmPyrazolAla, 3Pya, 5AmPyridinAla, 5MePyridinAla, Ala, ACIPA, aMePhe, H,
or THP;

X_{16} is Sar, NMeK- Z_{lipid} , or absent;

X_{17} is K- Z_{lipid} , NMeK- Z_{lipid} , or absent;

25 R_2 is CONH₂, CO(DiFPip), CON(Me)₂, or Z_{peg} ;

Z_{peg} , independently for each occurrence, is a polyethylene glycol chain;

Z_{lipid} , independently for each occurrence, is a lipophilic substituent;

wherein the peptide is cyclized via a linkage between the residues at X_4 and X_9 ;

wherein:

- (a) when R₁ is 5Ava, 6Ahx, 7Ahp, PEG2, or PEG2NMe, then the peptide further comprises a linkage between the residue at R₁ and a residue selected from E or hE at X₁₃;
- (b) when X₃ is Dab(COCH₂), k(COCH₂CH₂), or Ser(MePEG2), and optionally when X₃ is k, then the peptide further comprises a linkage between the residue at X₃ and a residue selected from C, D, or hE at X₁₃;
- (c) when X₅ is D, E, hE, K, K(a), K(Ac), K(d), K(G), K(NMe), or K(NNs), and optionally when X₅ is K-Z_{peg} or K-Z_{lipid}, then the peptide further comprises a linkage between the residue at X₅ and a residue selected from AEF or AEF(NMe) at X₁₀;
- (d) when X₁₀ is AEF or AEF(NMe), the peptide optionally further comprises a linkage between the residue at X₁₀ and a residue selected from D, E, hE, K, K(a), K(Ac), K(d), K(G), K(NMe), K(NNs), K-Z_{peg}, and K-Z_{lipid} at X₅ or an E residue at X₁₃;
- (e) when X₁₃ is C, D, or hE, and optionally when X₁₃ is E, then the peptide further comprises a linkage between the residue at X₁₃ and a residue selected from 5Ava, 6Ahx, 7Ahp, PEG2, and PEG2NMe at R₁ or a residue selected from Dab(COCH₂), k(COCH₂CH₂), k, and Ser(MePEG2) at X₃ or an AEF residue at X₁₀;
- provided that the peptide comprises no more than one linkage between any one of R₁ and X₁₃, X₃ and X₁₃, X₅ and X₁₀, and X₁₀ and X₁₃.
- In some embodiments, the peptide comprises an amino acid sequence of Formula (I-C):
- $$R_1-X_3-X_4-X_5-T-X_7-X_8-X_9-X_{10}-X_{11}-THP-X_{13}-N-X_{15}-Sar-X_{17}-R_2 \text{ (I-C)},$$
- or a pharmaceutically acceptable salt thereof, wherein:
- R₁ is 5cpaCO, CF₃CO, MeCO, Z_{peg}, or Z_{lipid};
- X₃ is hk(Me)₃, k, k-Z_{peg}, k-Z_{lipid}, k(d), k(Me)₃, K-Z_{peg}, K-Z_{lipid}, r, R, SP6, or absent
- X₄ is 4AminoPro, Abu, aG, aMeC, C, Dap, Pen, Pen(oXyl), Pen(mXyl), Pen(pXyl), or Pra;
- X₅ is D, E, hE, K, K(a), K(Ac), K(d), K(G), K(NMe), K(NNs), K-Z_{peg}, K-Z_{lipid}, N, N(NMe₂), Q, or Q(NMe₂);
- X₇ is 7(3NAcPh)W, 7MeW, or W;
- X₈ is Dab(NMeAc), Dab(NMecarn), Dab-Z_{peg}, K(Ac), K(NMeAc), NMeK-Z_{peg}, K-Z_{peg}, K-Z_{lipid}, Q, or Q(NMe₂);
- X₉ is aMeC, aG, C, D, E, hE, Pen, or Dap(N₃);
- X₁₀ is AEF, AEF(G), AEF(NMe), AEF(NMe₂), AEF-Z_{peg}, AEF(NMe)-Z_{peg}, bMeAEF, MMoEF, or TMAPF;
- X₁₁ is 2Nal6((5CF₃)₃Pyrazole), 6OH₂Nal, 2Nal6(Ph₂OH), 2Nal6(Ph₄(NMorph)), 2Nal6(3Pyrazole), 2Nal6(4OMePh), 5OMe₂Nal, 5amido₂Nal, 5Br₂Nal, 5Me₂Nal, 6MeQui, 6O(COCF₃)₂Nal, 6F₂Nal, 6Br₂Nal, or 7OH₂Nal;

X₁₃ is Dab(NMeAc), Dab(NMecarn), E, K(Ac), K(NMeAc), K-Z_{peg}, or K-Z_{lipid};

X₁₅ is 3Py_a, 5MePyridinAla, or THP;

X₁₇ is K-Z_{lipid}, NMeK-Z_{lipid}, or absent;

R₂ is CONH₂, CON(Me)₂, or Z_{peg};

5 Z_{peg}, independently for each occurrence, is a polyethylene glycol chain;

Z_{lipid}, independently for each occurrence, is a lipophilic substituent;

wherein the peptide is cyclized via a linkage between the residues at X₄ and X₉; and

wherein when X₅ is D, E, hE, K, K(a), K(Ac), K(d), K(G), K(NMe), or K(NNs), and

optionally when X₅ is K-Z_{peg} or K-Z_{lipid}, then the peptide further comprises a linkage between
10 the residue at X₅ and a residue selected from AEF or AEF(NMe) at X₁₀.

In some embodiments, the peptide comprises an amino acid sequence of Formula (I-D):

R₁-X₃-Pen-X₅-T-X₇-X₈-Pen-X₁₀-6OH₂Nal-THP-X₁₃-N-3Py_a-Sar-X₁₇-R₂ (I-D),

or a pharmaceutically acceptable salt thereof, wherein:

R₁ is MeCO, Z_{peg}, or Z_{lipid};

15 X₃ is k-Z_{peg}, k-Z_{lipid}, k(Me)₃, r, or absent

X₅ is D, E, hE, N, N(NMe₂), Q, or Q(NMe₂);

X₇ is 7(3NAcPh)W, 7MeW, or W;

X₈ is K(Ac), K(NMeAc), NMeK-Z_{peg}, K-Z_{peg}, or K-Z_{lipid};

X₁₀ is AEF or TMAPF;

20 X₁₃ is E, K(Ac), K(NMeAc), K-Z_{peg}, or K-Z_{lipid};

X₁₇ is K-Z_{lipid}, NMeK-Z_{lipid}, or absent;

R₂ is CONH₂, CON(Me)₂, or Z_{peg};

Z_{peg}, independently for each occurrence, is a polyethylene glycol chain;

Z_{lipid}, independently for each occurrence, is a lipophilic substituent;

25 wherein the peptide is cyclized via a linkage between the Pen residues at X₄ and X₉; and

wherein when X₅ is D, E, or hE, then the peptide further comprises a linkage between the
residue at X₅ and the AEF residue at X₁₀.

In some embodiments, the peptide comprises an amino acid sequence of Formula (I-E):

R₁-X₃-Pen-X₅-T-7(3NAcPh)W-X₈-Pen-X₁₀-6OH₂Nal-THP-X₁₃-N-3Py_a-Sar-X₁₇-R₂ (I-E),

30 or a pharmaceutically acceptable salt thereof, wherein:

R₁ is MeCO or Z_{peg};

X₃ is r or absent

X₅ is E, N, or N(NMe₂);

X₈ is K(Ac) or K(NMeAc);

35 X₁₀ is AEF or TMAPF;

X₁₃ is E, K(Ac), or K(NMeAc);

X₁₇ is K-Z_{lipid} or absent;

R₂ is CONH₂ or CON(Me)₂;

Z_{peg}, independently for each occurrence, is a polyethylene glycol chain;

5 Z_{lipid}, independently for each occurrence, is a lipophilic substituent;

wherein the peptide is cyclized via a linkage between the Pen residues at X₄ and X₉; and

wherein when X₅ is E then the peptide further comprises a linkage between the E residue at X₅ and the AEF residue at X₁₀.

In some embodiments, the peptide comprises an amino acid sequence of Formula (I-B):

10 R₁-X₃-X₄-X₅-T-X₇-X₈-X₉-X₁₀-X₁₁-X₁₂-X₁₃-N-X₁₅-X₁₆-X₁₇-R₂ (I-B),

or a pharmaceutically acceptable salt thereof, wherein:

R₁ is 5cpaCO, CF₃CO, CF₃Propylamide, EtCO, MeCO, Z_{peg}, or Z_{lipid};

X₃ is hk(Me)₃, k, k(5cpa), k-Z_{peg}, k-Z_{lipid}, k(d), k(Me)₃, K-Z_{peg}, K-Z_{lipid}, r, R, SP6, or absent

15 X₄ is 4AminoPro, Abu, aG, aMeC, C, Dap, Pen, Pen(oXyl), Pen(mXyl), Pen(pXyl), or Pra;

X₅ is K-Z_{peg}, K-Z_{lipid}, L, N, N(NMe₂), Q, or Q(NMe₂);

X₇ is 7(3NAcPh)W, 7BrW, 7MeW, BT, or W;

X₈ is Dab(NMeAc), Dab(NMecarn), Dab-Z_{peg}, hK(Me)₃, K(Ac), K(Me)₃, K(NMeAc),

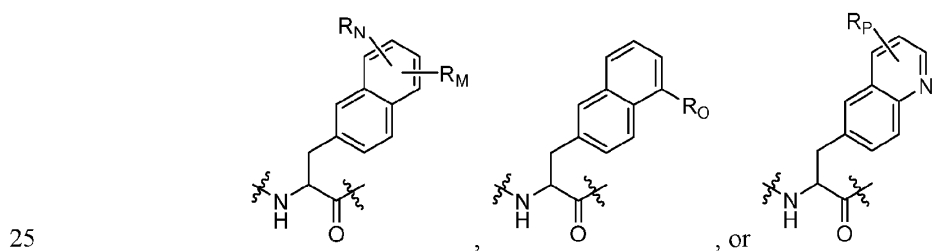
20 NMeK-Z_{peg}, K-Z_{peg}, K-Z_{lipid}, Lys(N⁺Me₂)-Z_{peg}, Q, or Q(NMe₂);

X₉ is aMeC, aG, C, D, E, hE, Pen, or Dap(N₃);

X₁₀ is 4DMPzEF, 4OMeF, AEF, AEF(G), AEF(NMe), AEF(NMe₂), AEF-Z_{peg},

AEF(NMe)-Z_{peg}, APEG3F, bMeAEF, F, MMoEF, TMAPF, or Y;

X₁₁ is:



R_M is halo, -OH, -C₍₁₋₃₎alkyl, -OC(O)C₍₁₋₃₎haloalkyl, phenyl, or 5- to 6-membered heteroaryl, wherein the phenyl and 5- to 6-membered heteroaryl are each optionally substituted with one to three groups selected from -OH, -OC₍₁₋₃₎alkyl, -C₍₁₋₃₎haloalkyl, and 3- to 6-membered heterocycle;

30 R_N is -H or -OH;

R_O is -OC₍₁₋₃₎alkyl or -C(O)NH₂;

R_P is halo, -OH, -C₍₁₋₃₎alkyl, -OC₍₁₋₃₎alkyl, -C(O)NH₂, -OC(O)C₍₁₋₃₎haloalkyl, phenyl, or 5- to 6-membered heteroaryl, wherein the phenyl and 5- to 6-membered heteroaryl are each optionally substituted with one to three groups selected from -OH, -OC₍₁₋₃₎alkyl, -C₍₁₋₃₎haloalkyl, and 3- to 6-membered heterocycle;

X₁₂ is THP, aMeL, diFCpx, or Pip(NMe₂);

X₁₃ is Dab(NMeAc), Dab(NMecarn), E, E(COcPEG3a), K(Ac), K(Me)₃, K(NMeAc), K-Z_{peg}, K-Z_{lipid}, L, or Q(NMe₂);

X₁₅ is 3AmPyrazolAla, 3Pya, 5AmPyridinAla, 5MePyridinAla, Ala, ACIPA, aMePhe, H, or THP;

X₁₆ is Sar, NMeK-Z_{lipid}, or absent;

X₁₇ is K-Z_{lipid}, NMeK-Z_{lipid}, or absent;

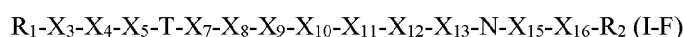
R₂ is CONH₂, CO(DiFPip), CON(Me)₂, or Z_{peg};

Z_{peg}, independently for each occurrence, is a polyethylene glycol chain;

Z_{lipid}, independently for each occurrence, is a lipophilic substituent;

wherein the peptide is cyclized via a linkage between the residues at X₄ and X₉.

In some embodiments, the peptide comprises an amino acid sequence of Formula (I-F):



wherein:

R₁ is 5Ava, 5cpaCO, 6Ahx, 7Ahp, CF₃CO, CF₃Propylamide, EtCO, MeCO, PEG₂, PEG₂NMe, or Z_{peg};

X₃ is Dab(COCH₂), k(COCH₂CH₂), hk(Me)₃, k, k(5cpa), k(d), k(Me)₃, Ser(MePEG₂), r, R, SP₆, or absent;

X₄ is 4AminoPro, Abu, aG, aMeC, C, Dap, Pen, Pen(oXyl), Pen(mXyl), Pen(pXyl), or Pra;

X₅ is D, E, hE, K, K(a), K(Ac), K(d), K(G), K(NMe), K(NNs), K-Z_{peg}, L, N, N(NMe), N(NMe₂), Q, Q(NMe), or Q(NMe₂);

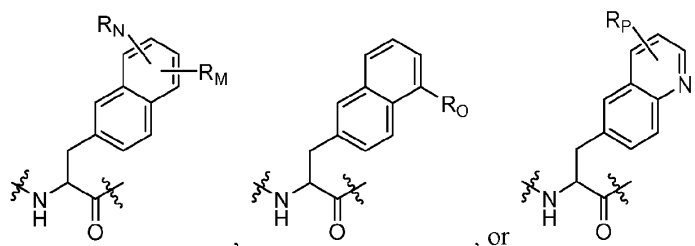
X₇ is 7(3NAcPh)W, 7BrW, 7MeW, BT, or W;

X₈ is Dab(NMeAc), Dab(NMecarn), Dab-Z_{peg}, hK(Me)₃, K(Ac), K(Me)₃, K(NMeAc), NMeK-Z_{peg}, K-Z_{peg}, Lys(N+Me₂)-Z_{peg}, Q, or Q(NMe₂);

X₉ is aMeC, aG, C, D, E, hE, Pen, or Dap(N₃);

X₁₀ is 4DMPzEF, 4OMeF, AEF, AEF(G), AEF(NMe), AEF(NMe₂), AEF-Z_{peg}, AEF(NMe)-Z_{peg}, APEG3F, bMeAEF, F, MMoEF, TMAPF, or Y;

X₁₁ is:



R_M is halo, -OH, -C₍₁₋₃₎alkyl, -OC(O)C₍₁₋₃₎haloalkyl, phenyl, or 5- to 6-membered heteroaryl, wherein the phenyl and 5- to 6-membered heteroaryl are each optionally substituted with one to three groups selected from -OH, -OC₍₁₋₃₎alkyl, -C₍₁₋₃₎haloalkyl, and 3- to 6-membered heterocyclyl;

R_N is -H or -OH;

R_O is -OC₍₁₋₃₎alkyl or -C(O)NH₂;

R_P is halo, -OH, -C₍₁₋₃₎alkyl, -OC₍₁₋₃₎alkyl, -C(O)NH₂, -OC(O)C₍₁₋₃₎haloalkyl, phenyl, or 5- to 6-membered heteroaryl, wherein the phenyl and 5- to 6-membered heteroaryl are each optionally substituted with one to three groups selected from -OH, -OC₍₁₋₃₎alkyl, -C₍₁₋₃₎haloalkyl, and 3- to 6-membered heterocyclyl;

X_{12} is THP, aMeL, diFCpx, or Pip(NMe₂);

X_{13} is C, D, Dab(NMeAc), Dab(NMecam), E, E(COcPEG3a), hE, K(Ac), K(Me)₃, K(NMeAc), K-Z_{peg}, L, or Q(NMe₂);

X_{15} is 3AmPyrazolAla, 3Pya, 5AmPyridinAla, 5MePyridinAla, Ala, ACIPA, aMePhe, H, or THP;

X_{16} is Sar or absent;

R_2 is CONH₂, CO(DiFPip), CON(Me)₂, or Z_{peg};

Z_{peg}, independently for each occurrence, is a polyethylene glycol;

wherein the peptide is cyclized via a linkage between the residues at X_4 and X_9 ;

wherein:

(a) when R_1 is 5Ava, 6Ahx, 7Ahp, PEG2, or PEG2NMe, then the peptide further comprises a linkage between the residue at R_1 and a residue selected from E or hE at X_{13} ;

(b) when X_3 is Dab(COCH₂), k(COCH₂CH₂), or Ser(MePEG2), and optionally when X_3 is k, then the peptide further comprises a linkage between the residue at X_3 and a residue selected from C, D, or hE at X_{13} ;

(c) when X_5 is D, E, hE, K, K(a), K(Ac), K(d), K(G), K(NMe), or K(NNs), and optionally when X_5 is K-Z_{peg}, then the peptide further comprises a linkage between the residue at X_5 and a residue selected from AEF or AEF(NMe) at X_{10} ;

(d) when X_{10} is AEF or AEF(NMe), the peptide optionally further comprises a linkage between the residue at X_{10} and a residue selected from D, E, hE, K, K(a), K(Ac), K(d), K(G), K(NMe), K(NNs), and K- Z_{peg} at X_5 or an E residue at X_{13} ;

(e) when X_{13} is C, D, or hE, and optionally when X_{13} is E, then the peptide further comprises a linkage between the residue at X_{13} and a residue selected from 5Ava, 6Ahx, 7Ahp, PEG2, and PEG2NMe at R_1 or a residue selected from Dab(COCH₂), k(COCH₂CH₂), k, and Ser(MePEG2) at X_3 or an AEF residue at X_{10} ;

provided that the peptide comprises no more than one linkage between any one of R_1 and X_{13} , X_3 and X_{13} , X_5 and X_{10} , and X_{10} and X_{13} .

10 In some embodiments, R_1 is 5Ava, 5cpaCO, 6Ahx, 7Ahp, CF₃CO, CF₃Propylamide, EtCO, MeCO, PEG2, PEG2NMe, Z_{peg} (i.e., a polyethylene glycol chain), or Z_{lipid} (i.e., a lipophilic substituent), wherein the 5Ava, 6Ahx, 7Ahp, PEG2, and PEG2NMe are linked to the amino acid at X_{13} . In some embodiments, R_1 is 5Ava, 5cpaCO, 6Ahx, 7Ahp, CF₃CO, CF₃Propylamide, EtCO, MeCO, PEG2, PEG2NMe, Z_{peg} (i.e., a polyethylene glycol chain), or
15 Z_{lipid} (i.e., a lipophilic substituent), wherein the 5Ava, 6Ahx, 7Ahp, PEG2, and PEG2NMe are linked to a residue selected from E or hE at X_{13} via an amide linkage.

In some embodiments, R_1 is 5Ava, 5cpaCO, 6Ahx, 7Ahp, CF₃CO, CF₃Propylamide, EtCO, MeCO, PEG2, PEG2NMe, a polyethylene glycol chain, or a lipophilic substituent, wherein the 5Ava, 6Ahx, 7Ahp, PEG2, and PEG2NMe are linked to the amino acid at X_{13} . In
20 some embodiments, R_1 is 5Ava, 5cpaCO, 6Ahx, 7Ahp, CF₃CO, CF₃Propylamide, EtCO, MeCO, PEG2, PEG2NMe, a polyethylene glycol chain, or a lipophilic substituent, wherein the 5Ava, 6Ahx, 7Ahp, PEG2, and PEG2NMe are linked to a residue selected from E or hE at X_{13} via an amide linkage.

In some embodiments, R_1 is 5cpaCO, CF₃CO, MeCO, Z_{peg} (i.e., a polyethylene glycol chain), or Z_{lipid} (i.e., a lipophilic substituent). In some embodiments, R_1 is 5cpaCO, CF₃CO, MeCO, cPEG3aCO, or Z_{lipid} . In some embodiments, R_1 is 5cpaCO, CF₃CO, MeCO, or cPEG3aCO. In some embodiments, R_1 is MeCO, Z_{peg} , or Z_{lipid} . In some embodiments, R_1 is MeCO or Z_{peg} . In some embodiments, R_1 is MeCO or cPEG3aCO.

In some embodiments, R_1 is 5cpaCO, CF₃CO, CF₃Propylamide, EtCO, MeCO, Z_{peg} , or
30 Z_{lipid} . In some embodiments, R_1 is 5Ava, 5cpaCO, 6Ahx, 7Ahp, CF₃CO, CF₃Propylamide, EtCO, MeCO, PEG2, PEG2NMe, or Z_{peg} , wherein the 5Ava, 6Ahx, 7Ahp, PEG2, and PEG2NMe are linked to a residue selected from E or hE at X_{13} via an amide linkage.

In some embodiments, R_1 is an alkyl or polyethylene glycol chain linked to the amino acid at X_{13} . In some embodiments, R_1 is 5Ava linked to the amino acid at X_{13} . In some
35 embodiments, X_1 is 5Ava linked to E at X_{13} . In some embodiments, R_1 is 5cpaCO. In some

embodiments, R₁ is 6Ahx linked to the amino acid at X₁₃. In some embodiments, R₁ is 6Ahx linked to E at X₁₃. R₁ is 7Ahp linked to the amino acid at X₁₃. In some embodiments, R₁ is 7Ahp linked to E at X₁₃. In some embodiments, R₁ is CF₃CO. In some embodiments, R₁ is CF₃Propylamide. In some embodiments, R₁ is EtCO. In some embodiments, R₁ is MeCO. In some embodiments, R₁ is PEG₂ linked to the amino acid at X₁₃. In some embodiments, R₁ is PEG₂ linked to hE at X₁₃. In some embodiments, R₁ is PEG₂NMe linked to the amino acid at X₁₃. In some embodiments, R₁ is PEG₂NMe linked to hE at X₁₃. In some embodiments, R₁ is Z_{peg}, i.e., a polyethylene glycol chain. In some embodiments, R₁ is a polyethylene glycol chain terminating in an ammonium or methyl group. In some embodiments, R₁ is cPEG₃aCO. In some embodiments, R₁ is Z_{lipid}, i.e., a lipophilic substituent.

In some embodiments, X₃ is Dab(COCH₂), Dab(NMeAc), Dab(NMecarn), Dab-Z_{peg}, Dab-Z_{lipid}, K(COCH₂CH₂), hK(Me)₃, K, K(5cpa), K(Ac), K(d), K(G), K(Me)₃, K(NMe), K(NMeAc), K(NNs), K-Z_{peg}, K-Z_{lipid}, NMeK-Z_{peg}, NMeK-Z_{lipid}, Ser(MePEG₂), R, SP₆, or absent; wherein the Dab(COCH₂), K(COCH₂CH₂), and Ser(MePEG₂) are linked to the amino acid at X₁₃.

In some embodiments, X₃ is Dab(COCH₂), Dab(NMeAc), Dab(NMecarn), Dab-Z_{peg}, Dab-Z_{lipid}, K(COCH₂CH₂), hK(Me)₃, K, K(5cpa), K(Ac), K(d), K(G), K(Me)₃, K(NMe), K(NMeAc), K(NNs), K-Z_{peg}, K-Z_{lipid}, NMeK-Z_{peg}, NMeK-Z_{lipid}, Ser(MePEG₂), R, SP₆, or absent; wherein the Dab(COCH₂), K(COCH₂CH₂), and Ser(MePEG₂) are linked to the amino acid at X₁₃; and wherein the Dab(COCH₂), Dab(NMeAc), Dab(NMecarn), Dab-Z_{peg}, Dab-Z_{lipid}, K(COCH₂CH₂), hK(Me)₃, K, K(5cpa), K(Ac), K(d), K(G), K(Me)₃, K(NMe), K(NMeAc), K(NNs), K-Z_{peg}, K-Z_{lipid}, NMeK-Z_{peg}, NMeK-Z_{lipid}, Ser(MePEG₂), and R are L amino acids.

In some embodiments, X₃ is dDab(COCH₂), dDab(NMeAc), dDab(NMecarn), dDab-Z_{peg}, dDab-Z_{lipid}, k(COCH₂CH₂), hk(Me)₃, k, k(5cpa), k(Ac), k(d), k(G), k(Me)₃, k(NMe), k(NMeAc), k(NNs), k-Z_{peg}, k-Z_{lipid}, NMek-Z_{peg}, NMek-Z_{lipid}, dSer(MePEG₂), r, SP₆, or absent; wherein the dDab(COCH₂), k(COCH₂CH₂), and dSer(MePEG₂) are linked to the amino acid at X₁₃.

In some embodiments, X₃ is Dab(COCH₂), k(COCH₂CH₂), hk(Me)₃, k, k(5cpa), k-Z_{peg}, k-Z_{lipid}, k(d), k(Me)₃, K-Z_{peg}, K-Z_{lipid}, Ser(MePEG₂), r, R, SP₆, or absent; wherein the Dab(COCH₂), k(COCH₂CH₂), and Ser(MePEG₂) are linked to the amino acid at X₁₃. In some embodiments, X₃ is hk(Me)₃, k, k-Z_{peg}, k-Z_{lipid}, k(d), k(Me)₃, K-Z_{peg}, K-Z_{lipid}, r, R, SP₆, or absent. In some embodiments, X₃ is k-Z_{peg}, k-Z_{lipid}, k(Me)₃, r, or absent. In some embodiments, X₃ is r or absent.

In some embodiments, X₃ is hk(Me)₃, k, k(5cpa), k-Z_{peg}, k-Z_{lipid}, k(d), k(Me)₃, K-Z_{peg}, K-Z_{lipid}, r, R, SP₆, or absent. In some embodiments, X₃ is Dab(COCH₂), k(COCH₂CH₂),

hk(Me)₃, k, k(5cpa), k(d), k(Me)₃, Ser(MePEG2), r, R, SP6, or absent, wherein the Dab(COCH₂), k(COCH₂CH₂), and Ser(MePEG2) are linked to the amino acid at X₁₃.

In some embodiments, X₃ is Dab(COCH₂) linked to the amino acid at X₁₃. In some embodiments, X₃ is Dab(COCH₂) linked to C at X₁₃. In some embodiments, X₃ is Dab(NMeAc). In some embodiments, X₃ is Dab(NMecarn). In some embodiments, X₃ is Dab-Z_{peg}. In some embodiments, X₃ is Dab-Z_{lipid}. In some embodiments, X₃ is K(COCH₂CH₂) linked to the amino acid at X₁₃. In some embodiments, X₃ is K(COCH₂CH₂) linked to C at X₁₃. In some embodiments, X₃ is hK(Me)₃. In some embodiments, X₃ is K. In some embodiments, X₃ is K(5cpa). In some embodiments, X₃ is K(Ac). In some embodiments, X₃ is K(d). In some embodiments, X₃ is K(G). In some embodiments, X₃ is K(Me)₃. In some embodiments, X₃ is K(NMe). In some embodiments, X₃ is K(NMeAc). In some embodiments, X₃ is K(NNs). In some embodiments, X₃ is K-Z_{peg}. In some embodiments, X₃ is K-Z_{lipid}. In some embodiments, X₃ is NMeK-Z_{peg}. In some embodiments, X₃ is NMeK-Z_{lipid}. In some embodiments, X₃ is Ser(MePEG2) linked to the amino acid at X₁₃. In some embodiments, X₃ is Ser(MePEG2) linked to D at X₁₃. In some embodiments, X₃ is R. In some embodiments, X₃ is SP6. In some embodiments, X₃ is absent.

In some embodiments, X₃ is dDab(COCH₂) linked to the amino acid at X₁₃. In some embodiments, X₃ is dDab(COCH₂) linked to C at X₁₃. In some embodiments, X₃ is dDab(NMeAc). In some embodiments, X₃ is dDab(NMecarn). In some embodiments, X₃ is dDab-Z_{peg}. In some embodiments, X₃ is dDab-Z_{lipid}. In some embodiments, X₃ is k(COCH₂CH₂) linked to the amino acid at X₁₃. In some embodiments, X₃ is k(COCH₂CH₂) linked to C at X₁₃. In some embodiments, X₃ is hk(Me)₃. In some embodiments, X₃ is k. In some embodiments, X₃ is k(5cpa). In some embodiments, X₃ is k(Ac). In some embodiments, X₃ is k(d). In some embodiments, X₃ is k(G). In some embodiments, X₃ is k(Me)₃. In some embodiments, X₃ is k(NMe). In some embodiments, X₃ is k(NMeAc). In some embodiments, X₃ is k(NNs). In some embodiments, X₃ is k-Z_{peg}. In some embodiments, X₃ is k-Z_{lipid}. In some embodiments, X₃ is NMek-Z_{peg}. In some embodiments, X₃ is NMek-Z_{lipid}. In some embodiments, X₃ is dSer(MePEG2) linked to the amino acid at X₁₃. In some embodiments, X₃ is dSer(MePEG2) linked to D at X₁₃. In some embodiments, X₃ is r.

In some embodiments, X₄ is 4AminoPro, Abu, aG, aMeC, C, Dap, Pen, Pen(oXyl), Pen(mXyl), Pen(pXyl), or Pra. In some embodiments, X₄ is 4AminoPro, Abu, aG, aMeC, C, Dap, Pen, Pen(oXyl), Pen(mXyl), Pen(pXyl), or Pra, each of which is an L amino acid. In some embodiments, X₄ is 4Amino-d-Pro, dAbu, d-aG, aMe-d-C, c, dDap, dPen, dPen(oXyl), dPen(mXyl), dPen(pXyl), or dPra.

In some embodiments, X₄ is 4AminoPro, aG, Dap, Pen(oXyl), Pen(mXyl), Pen(pXyl), or Pra. In some embodiments, X₄ is Abu, aMeC, C, Pen, Pen(oXyl), Pen(mXyl), or Pen(pXyl). In some embodiments, X₄ is Abu, aMeC, C, or Pen. In some embodiments, X₄ is Abu, C, or Pen. In some embodiments, X₄ is Abu or Pen.

5 In some embodiments, X₄ is 4AminoPro. In some embodiments, X₄ is 4RAminoPro. In some embodiments, X₄ is 4SAminoPro. In some embodiments, X₄ is Abu. In some embodiments, X₄ is aG. In some embodiments, X₄ is aMeC. In some embodiments, X₄ is C. In some embodiments, X₄ is Dap. In some embodiments, X₄ is Pen. In some embodiments, X₄ is Pen(oXyl). In some embodiments, X₄ is Pen(mXyl). In some embodiments, X₄ is Pen(pXyl). In
10 some embodiments, X₄ is Pra.

In some embodiments, X₄ is 4Amino-d-Pro. In some embodiments, X₄ is 4RAmino-d-Pro. In some embodiments, X₄ is 4SAmino-d-Pro. In some embodiments, X₄ is dAbu. In some embodiments, X₄ is d-aG. In some embodiments, X₄ is aMe-d-C. In some embodiments, X₄ is c. In some embodiments, X₄ is dDap. In some embodiments, X₄ is dPen. In some embodiments, X₄ is dPen(oXyl). In some embodiments, X₄ is dPen(mXyl). In some embodiments, X₄ is
15 dPen(pXyl). In some embodiments, X₄ is dPra.

In some embodiments, X₅ is D, E, hE, K, K(5cpa), K(a), K(Ac), K(d), K(G), K(Me)₃, K(NMe), K(NMeAc), K(NNs), K-Z_{peg}, K-Z_{lipid}, NMeK-Z_{peg}, NMeK-Z_{lipid}, L, N, N(NMe), N(NMe₂), Q, Q(NMe), or Q(NMe₂); wherein the D, E, hE, K, K(a), K(Ac), K(d), K(G),
20 K(NMe), and K(NNs) are linked to the amino acid at X₁₀, and optionally wherein the K-Z_{peg} or K-Z_{lipid} are linked to the amino acid at X₁₀. In some embodiments, X₅ is D, E, hE, K, K(5cpa), K(a), K(Ac), K(d), K(G), K(Me)₃, K(NMe), K(NMeAc), K(NNs), K-Z_{peg}, K-Z_{lipid}, NMeK-Z_{peg}, NMeK-Z_{lipid}, L, N, N(NMe), N(NMe₂), Q, Q(NMe), or Q(NMe₂), each of which is an L amino acid; wherein the D, E, hE, K, K(a), K(Ac), K(d), K(G), K(NMe), and K(NNs) are linked to the
25 amino acid at X₁₀, and optionally wherein the K-Z_{peg} or K-Z_{lipid} are linked to the amino acid at X₁₀. In some embodiments, X₅ is d, e, he, k, k(5cpa), k(a), k(Ac), k(d), k(G), k(Me)₃, k(NMe), k(NMeAc), k(NNs), k-Z_{peg}, k-Z_{lipid}, NMeK-Z_{peg}, NMeK-Z_{lipid}, l, n, n(NMe), n(NMe₂), q, q(NMe), or q(NMe₂); wherein the d, e, he, k, k(a), k(Ac), k(d), k(G), k(NMe), and k(NNs) are linked to the amino acid at X₁₀, and optionally wherein the k-Z_{peg} or k-Z_{lipid} are linked to the amino acid at
30 X₁₀.

In some embodiments, X₅ is E, K, K(5cpa), K(a), K(Ac), K(d), K(G), K(Me)₃, K(NMe), K(NMeAc), K(NNs), K-Z_{peg}, K-Z_{lipid}, NMeK-Z_{peg}, NMeK-Z_{lipid}, L, N, N(NMe₂), or Q; wherein the E, K, K(a), K(Ac), K(d), K(G), K(NMe), and K(NNs) are linked to the amino acid at X₁₀, and optionally wherein the K-Z_{peg} or K-Z_{lipid} are linked to the amino acid at X₁₀. In some
35 embodiments, X₅ is D, E, hE, K, K(a), K(Ac), K(d), K(G), K(Nme), K(NNs), K-Z_{peg}, K-Z_{lipid}, L,

- N, N(NMe₂), Q, or Q(NMe₂); wherein the D, E, hE, K, K(a), K(Ac), K(d), K(G), K(NMe), and K(NNs) are linked to the amino acid at X₁₀, and optionally wherein the K-Z_{peg} or K-Z_{lipid} are linked to the amino acid at X₁₀. In some embodiments, X₅ is E, K, K(a), K(Ac), K(d), K(G), K(Nme), K(NNs), K-Z_{peg}, K-Z_{lipid}, L, N, N(NMe₂), Q, or Q(NMe₂); wherein the E, K, K(a), K(Ac), K(d), K(G), K(NMe), and K(NNs) are linked to the amino acid at X₁₀, and optionally wherein the K-Z_{peg} or K-Z_{lipid} are linked to the amino acid at X₁₀. In some embodiments, X₅ is D, E, hE, N, N(NMe₂), Q, or Q(NMe₂), wherein the D, E, and hE are linked to the amino acid at X₁₀. In some embodiments, X₅ is E, N, or N(NMe₂), wherein the E is linked to the amino acid at X₁₀.
- 10 In some embodiments, X₅ is K-Z_{peg}, K-Z_{lipid}, L, N, N(NMe₂), Q, or Q(NMe₂). In some embodiments, X₅ is D, E, hE, K, K(a), K(Ac), K(d), K(G), K(NMe), K(NNs), L, N, N(NMe), N(NMe₂), Q, Q(NMe), or Q(NMe₂); wherein the D, E, hE, K, K(a), K(Ac), K(d), K(G), K(NMe), and K(NNs) are linked to the amino acid at X₁₀.
- 15 In some embodiments, X₅ is D linked to the amino acid at X₁₀. In some embodiments, X₅ is D linked to AEF at X₁₀. In some embodiments, X₅ is D linked to AEF(NMe) at X₁₀. In some embodiments, X₅ is E linked to the amino acid at X₁₀. In some embodiments, X₅ is E linked to AEF at X₁₀. In some embodiments, X₅ is E linked to AEF(NMe) at X₁₀. In some embodiments, X₅ is hE linked to the amino acid at X₁₀. In some embodiments, X₅ is hE linked to AEF at X₁₀. In some embodiments, X₅ is hE linked to AEF(NMe) at X₁₀.
- 20 In some embodiments, X₅ is K linked to the amino acid at X₁₀. In some embodiments, X₅ is K linked to AEF at X₁₀. In some embodiments, X₅ is K linked to AEF(NMe) at X₁₀. In some embodiments, X₅ is K(a) linked to the amino acid at X₁₀. In some embodiments, X₅ is K(a) linked to AEF at X₁₀. In some embodiments, X₅ is K(a) linked to AEF(NMe) at X₁₀. In some embodiments, X₅ is K(Ac) linked to the amino acid at X₁₀. In some embodiments, X₅ is K(Ac) linked to AEF at X₁₀. In some embodiments, X₅ is K(Ac) linked to AEF(NMe) at X₁₀. In some embodiments, X₅ is K(d) linked to the amino acid at X₁₀. In some embodiments, X₅ is K(d) linked to AEF at X₁₀. In some embodiments, X₅ is K(d) linked to AEF(NMe) at X₁₀. In some embodiments, X₅ is K(G) linked to the amino acid at X₁₀. In some embodiments, X₅ is K(G) linked to AEF at X₁₀. In some embodiments, X₅ is K(G) linked to AEF(NMe) at X₁₀. In some embodiments, X₅ is K(NMe) linked to the amino acid at X₁₀. In some embodiments, X₅ is K(NMe) linked to AEF at X₁₀. In some embodiments, X₅ is K(NMe) linked to AEF(NMe) at X₁₀. In some embodiments, X₅ is K(NNs) linked to the amino acid at X₁₀. In some embodiments, X₅ is K(NNs) linked to AEF at X₁₀. In some embodiments, X₅ is K(NNs) linked to AEF(NMe) at X₁₀.

In some embodiments, X₅ is K-Z_{peg}. In some embodiments, X₅ is K-Z_{peg} linked to the amino acid at X₁₀. In some embodiments, X₅ is K-Z_{peg} linked to AEF at X₁₀. In some embodiments, X₅ is K-Z_{peg} linked to AEF(NMe) at X₁₀. In some embodiments, X₅ is K-Z_{lipid}. In some embodiments, X₅ is K-Z_{lipid} linked to the amino acid at X₁₀. In some embodiments, X₅ is K-Z_{lipid} linked to AEF at X₁₀. In some embodiments, X₅ is K-Z_{lipid} linked to AEF(NMe) at X₁₀. In some embodiments, X₅ is L. In some embodiments, X₅ is N. In some embodiments, X₅ is N(NMe). In some embodiments, X₅ is N(NMe₂). In some embodiments, X₅ is Q. In some embodiments, X₅ is Q(NMe). In some embodiments, X₅ is Q(NMe₂).

In some embodiments, X₅ is d linked to the amino acid at X₁₀. In some embodiments, X₅ is d linked to AEF at X₁₀. In some embodiments, X₅ is d linked to AEF(NMe) at X₁₀. In some embodiments, X₅ is e linked to the amino acid at X₁₀. In some embodiments, X₅ is e linked to AEF at X₁₀. In some embodiments, X₅ is e linked to AEF(NMe) at X₁₀. In some embodiments, X₅ is he linked to the amino acid at X₁₀. In some embodiments, X₅ is he linked to AEF at X₁₀. In some embodiments, X₅ is he linked to AEF(NMe) at X₁₀.

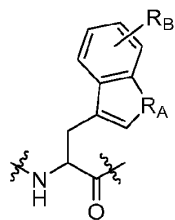
In some embodiments, X₅ is k linked to the amino acid at X₁₀. In some embodiments, X₅ is k linked to AEF at X₁₀. In some embodiments, X₅ is k linked to AEF(NMe) at X₁₀. In some embodiments, X₅ is k(a) linked to the amino acid at X₁₀. In some embodiments, X₅ is k(a) linked to AEF at X₁₀. In some embodiments, X₅ is k(a) linked to AEF(NMe) at X₁₀. In some embodiments, X₅ is k(Ac) linked to the amino acid at X₁₀. In some embodiments, X₅ is k(Ac) linked to AEF at X₁₀. In some embodiments, X₅ is k(Ac) linked to AEF(NMe) at X₁₀. In some embodiments, X₅ is k(d) linked to the amino acid at X₁₀. In some embodiments, X₅ is k(d) linked to AEF at X₁₀. In some embodiments, X₅ is k(d) linked to AEF(NMe) at X₁₀. In some embodiments, X₅ is k(G) linked to the amino acid at X₁₀. In some embodiments, X₅ is k(G) linked to AEF at X₁₀. In some embodiments, X₅ is k(G) linked to AEF(NMe) at X₁₀. In some embodiments, X₅ is k(NMe) linked to the amino acid at X₁₀. In some embodiments, X₅ is k(NMe) linked to AEF at X₁₀. In some embodiments, X₅ is k(NMe) linked to AEF(NMe) at X₁₀. In some embodiments, X₅ is k(NNs) linked to the amino acid at X₁₀. In some embodiments, X₅ is k(NNs) linked to AEF at X₁₀. In some embodiments, X₅ is k(NNs) linked to AEF(NMe) at X₁₀.

In some embodiments, X₅ is k-Z_{peg}. In some embodiments, X₅ is k-Z_{peg} linked to the amino acid at X₁₀. In some embodiments, X₅ is k-Z_{peg} linked to AEF at X₁₀. In some embodiments, X₅ is k-Z_{peg} linked to AEF(NMe) at X₁₀. In some embodiments, X₅ is k-Z_{lipid}. In some embodiments, X₅ is k-Z_{lipid} linked to the amino acid at X₁₀. In some embodiments, X₅ is k-Z_{lipid} linked to AEF at X₁₀. In some embodiments, X₅ is k-Z_{lipid} linked to AEF(NMe) at X₁₀. In some embodiments, X₅ is l. In some embodiments, X₅ is n. In some embodiments, X₅ is n(NMe).

In some embodiments, X₅ is n(NMe₂). In some embodiments, X₅ is q. In some embodiments, X₅ is q(NMe). In some embodiments, X₅ is q(NMe₂).

In some embodiments, X₆ is T. In some embodiments, X₆ is T, wherein the T is an L-amino acid. In some embodiments, X₆ is t.

5 In some embodiments, X₇ is:

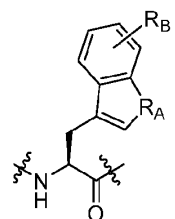


wherein:

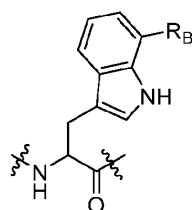
R_A is NH or S; and

R_B is -H, halo, C₍₁₋₃₎alkyl, or phenyl, wherein the phenyl is optionally substituted with
10 one -N(H)C(O)C₍₁₋₃₎alkyl group.

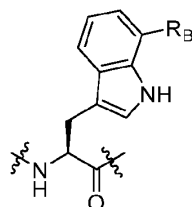
In some embodiments, X₇ is:



In some embodiments, X₇ is:



15 In some embodiments, X₇ is:



In some embodiments, R_B is $C_{(1-3)}$ alkyl or phenyl, wherein the phenyl is optionally substituted with one $-N(H)C(O)C_{(1-3)}$ alkyl group. In some embodiments, R_B is $C_{(1-3)}$ alkyl. In some embodiments, R_B is phenyl substituted with one $-N(H)C(O)C_{(1-3)}$ alkyl group.

In some embodiments, X_7 is 7(3NacPh)W, 7BrW, 7MeW, BT, or W. In some
5 embodiments, X_7 is 7(3NacPh)W, 7BrW, 7MeW, BT, or W, each of which is an L-amino acid. In some embodiments, X_7 is 7(3NacPh)w, 7Brw, 7Mew, dBT, or w.

In some embodiments, X_7 is 7(3NacPh)W or 7MeW.

In some embodiments, X_7 is 7(3NacPh)W. In some embodiments, X_7 is 7BrW. In some
embodiments, X_7 is 7MeW. In some embodiments, X_7 is BT. In some embodiments, X_7 is W.

10 In some embodiments, X_7 is 7(3NacPh)w. In some embodiments, X_7 is 7Brw. In some
embodiments, X_7 is 7Mew. In some embodiments, X_7 is dBT. In some embodiments, X_7 is w.

In some embodiments, X_8 is Dab(NMeAc), Dab(NMecarn), Dab- Z_{peg} , Dab- Z_{lipid} ,
hK(Me)3, K, K(5cpa), K(Ac), K(d), K(G), K(Me)3, K(NMe), K(NMeAc), K(NNs), K- Z_{peg} , K-
 Z_{lipid} , NMeK- Z_{peg} , NMeK- Z_{lipid} , Lys(N+Me2)- Z_{peg} , Lys(N+Me2)- Z_{lipid} , Q, or Q(NMe2). In some
15 embodiments, X_8 is Dab(NMeAc), Dab(NMecarn), Dab- Z_{peg} , Dab- Z_{lipid} , hK(Me)3, K, K(5cpa),
K(Ac), K(d), K(G), K(Me)3, K(NMe), K(NMeAc), K(NNs), K- Z_{peg} , K- Z_{lipid} , NMeK- Z_{peg} ,
NMeK- Z_{lipid} , Lys(N+Me2)- Z_{peg} , Lys(N+Me2)- Z_{lipid} , Q, or Q(NMe2), each of which is an L-
amino acid. In some embodiments, X_8 is dDab(NMeAc), dDab(NMecarn), dDab- Z_{peg} , dDab-
 Z_{lipid} , hK(Me)3, k, k(5cpa), k(Ac), k(d), k(G), k(Me)3, k(NMe), k(NMeAc), k(NNs), k- Z_{peg} , k-
20 Z_{lipid} , NMek- Z_{peg} , NMek- Z_{lipid} , dLys(N+Me2)- Z_{peg} , dLys(N+Me2)- Z_{lipid} , q, or q(NMe2).

In some embodiments, X_8 is Dab(NMeAc), Dab(NMecarn), Dab- Z_{peg} , hK(Me)3, K(Ac),
K(Me)3, K(NMeAc), NMeK- Z_{peg} , K- Z_{peg} , K- Z_{lipid} , Lys(N+Me2)- Z_{peg} , Q, or Q(NMe2).

In some embodiments, X_8 is Dab(NMeAc), Dab(NMecarn), Dab- Z_{peg} , hK(Me)3, K(Ac),
K(Me)3, K(NMeAc), NMeK- Z_{peg} , K- Z_{peg} , Lys(N+Me2)- Z_{peg} , Q, or Q(NMe2). In some
25 embodiments, X_8 is Dab(NMeAc), Dab(NMecarn), Dab- Z_{peg} , K(Ac), K(NMeAc), NMeK- Z_{peg} ,
K- Z_{peg} , K- Z_{lipid} , Q, or Q(NMe2). In some embodiments, X_8 is K(Ac), K(NMeAc), NMeK- Z_{peg} ,
K- Z_{peg} , or K- Z_{lipid} . In some embodiments, X_8 is K(Ac) or K(NMeAc).

In some embodiments, X_8 is Dab(NMeAc). In some embodiments, X_8 is Dab(NMecarn).
In some embodiments, X_8 is Dab- Z_{peg} . In some embodiments, X_8 is Dab- Z_{lipid} . In some
30 embodiments, X_8 is hK(Me)3. In some embodiments, X_8 is K. In some embodiments, X_8 is
K(5cpa). In some embodiments, X_8 is K(Ac). In some embodiments, X_8 is K(d). In some
embodiments, X_8 is K(G). In some embodiments, X_8 is K(Me)3. In some embodiments, X_8 is
K(NMe). In some embodiments, X_8 is K(NMeAc). In some embodiments, X_8 is K(NNs). In
some embodiments, X_8 is K- Z_{peg} . In some embodiments, X_8 is K- Z_{lipid} . In some embodiments,
35 X_8 is NMeK- Z_{peg} . In some embodiments, X_8 is NMeK- Z_{lipid} . In some embodiments, X_8 is

Lys(N+Me2)-Z_{peg}. In some embodiments, X₈ is Lys(N+Me2)-Z_{lipid}. In some embodiments, X₈ is Q. In some embodiments, X₈ is Q(NMe2).

In some embodiments, X₈ is dDab(NMeAc). In some embodiments, X₈ is dDab(NMecarn). In some embodiments, X₈ is dDab-Z_{peg}. In some embodiments, X₈ is dDab-Z_{lipid}. In some embodiments, X₈ is hk(Me)₃. In some embodiments, X₈ is k. In some
 5 embodiments, X₈ is k(5cpa). In some embodiments, X₈ is k(Ac). In some embodiments, X₈ is k(d). In some embodiments, X₈ is k(G). In some embodiments, X₈ is k(Me)₃. In some
 embodiments, X₈ is k(NMe). In some embodiments, X₈ is k(NMeAc). In some embodiments, X₈
 is k(NNs). In some embodiments, X₈ is k-Z_{peg}. In some embodiments, X₈ is k-Z_{lipid}. In some
 10 embodiments, X₈ is NMek-Z_{peg}. In some embodiments, X₈ is NMek-Z_{lipid}. In some
 embodiments, X₈ is dLys(N+Me2)-Z_{peg}. In some embodiments, X₈ is dLys(N+Me2)-Z_{lipid}. In
 some embodiments, X₈ is q. In some embodiments, X₈ is q(NMe2).

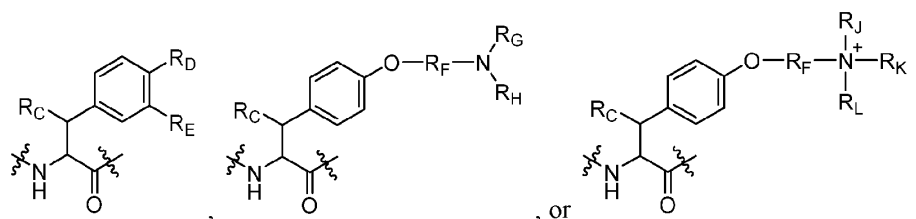
In some embodiments, X₉ is aMeC, aG, C, D, E, hE, Pen, or Dap(N3). In some
 embodiments, X₉ is aMeC, aG, C, D, E, hE, Pen, or Dap(N3), each of which is an L-amino acid.
 15 In some embodiments, X₉ is aMe-d-C, d-aG, c, d, e, he, dPen, or dDap(N3).

In some embodiments, X₉ is aG, D, E, hE, or Dap(N3). In some embodiments, X₉ is
 aMeC, C, or Pen. In some embodiments, X₉ is aMeC or Pen.

In some embodiments, X₉ is aMeC. In some embodiments, X₉ is aG. In some
 embodiments, X₉ is C. In some embodiments, X₉ is D. In some embodiments, X₉ is E. In some
 20 embodiments, X₉ is hE. In some embodiments, X₉ is Pen. In some embodiments, X₉ is Dap(N3).

In some embodiments, X₉ is aMe-d-C. In some embodiments, X₉ is d-aG. In some
 embodiments, X₉ is c. In some embodiments, X₉ is d. In some embodiments, X₉ is e. In some
 embodiments, X₉ is he. In some embodiments, X₉ is dPen. In some embodiments, X₉ is
 dDap(N3).

25 In some embodiments, X₁₀ is:



R_C is -H or -C₍₁₋₃₎alkyl;

R_D is -H, -OH, -CN, -C₍₁₋₃₎alkyl, -OC₍₁₋₃₎alkyl, -OC₍₁₋₃₎alkyl-(5-membered heteroaryl), -
 C(O)NH₂, or heterocyclyl, wherein the -OC₍₁₋₃₎alkyl-(5-membered heteroaryl) is optionally
 30 substituted with a polyethylene glycol chain, and wherein the heterocyclyl is optionally
 substituted with one -C(O)NH₂ group,

R_E is -H or halo;

R_F is $-C_{(1-6)}$ alkylene or a bivalent polyethylene glycol chain;

R_G is -H, $-C_{(1-3)}$ alkyl, or a bond to the amino acid at X_5 or X_{13} ;

R_H is -H, $-C_{(1-3)}$ alkyl, $-C(NH)NH_2$, $-C(O)-R_{H1}$;

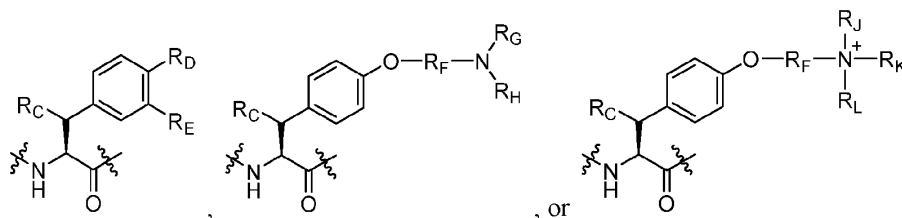
5 or R_G and R_H taken together with the nitrogen atom to which they are attached form a 5- to 8-membered heterocyclyl group;

R_{H1} is $-C_{(1-5)}$ alkyl, $-OC_{(1-5)}$ alkyl, $-C_{(1-3)}$ alkyl-phenyl, -phenyl- $-C_{(1-3)}$ alkyl- $N(H)-S(O)_2-C_{(1-3)}$ alkyl, or a polyethylene glycol chain, wherein the $-C_{(1-3)}$ alkyl-phenyl is optionally substituted with one to three groups selected from halo and -OH;

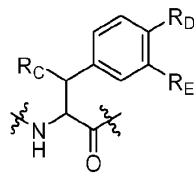
10 R_J , R_K , and R_L are each, independently, $C_{(1-3)}$ alkyl; and

or R_J and R_K taken together with the nitrogen atom to which they are attached form a 5- to 8-membered heterocyclyl group.

In some embodiments, X_{10} is:



15 In some embodiments, X_{10} is



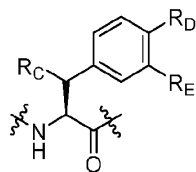
wherein:

R_C is -H or $-C_{(1-3)}$ alkyl;

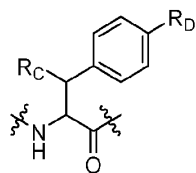
20 R_D is -H, -OH, -CN, $-C_{(1-3)}$ alkyl, $-OC_{(1-3)}$ alkyl, $-OC_{(1-3)}$ alkyl-(5-membered heteroaryl), $-C(O)NH_2$, or heterocyclyl, wherein the $-OC_{(1-3)}$ alkyl-(5-membered heteroaryl) is optionally substituted with a polyethylene glycol chain, and wherein the heterocyclyl is optionally substituted with one $-C(O)NH_2$ group; and

R_E is -H or halo.

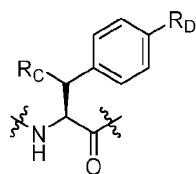
In some embodiments, X_{10} is



In some embodiments, X_{10} is

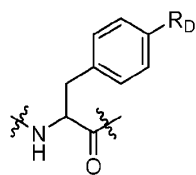


In some embodiments, X_{10} is

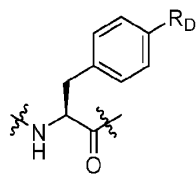


5

In some embodiments, X_{10} is



In some embodiments, X_{10} is



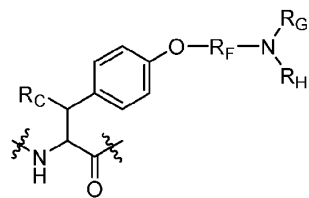
10

In some embodiments, R_C is -H . In some embodiments, R_C is -CH_3 .

In some embodiments, R_D is -H , -OH , or $\text{-OC}_{(1-3)}\text{alkyl}$.

In some embodiments, R_E is -H . In some embodiments, R_E is -F .

In some embodiments, X_{10} is



15 wherein:

R_C is -H or $-C_{(1-3)}\text{alkyl}$;

R_F is $-C_{(1-6)}\text{alkylene}$ or a bivalent polyethylene glycol chain;

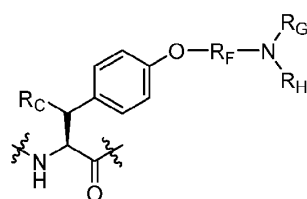
R_G is -H, $-C_{(1-3)}\text{alkyl}$, or a bond to the amino acid at X_5 or X_{13} ;

R_H is -H, $-C_{(1-3)}\text{alkyl}$, $-C(NH)NH_2$, $-C(O)-R_{H1}$;

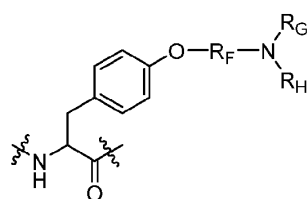
- 5 or R_G and R_H taken together with the nitrogen atom to which they are attached form a 5- to 8-membered heterocycl group; and

R_{H1} is $-C_{(1-5)}\text{alkyl}$, $-OC_{(1-5)}\text{alkyl}$, $-C_{(1-3)}\text{alkyl-phenyl}$, $-\text{phenyl-}C_{(1-3)}\text{alkyl-N(H)-S(O)}_2-C_{(1-3)}\text{alkyl}$, or a polyethylene glycol chain, wherein the $-C_{(1-3)}\text{alkyl-phenyl}$ is optionally substituted with one to three groups selected from halo and -OH.

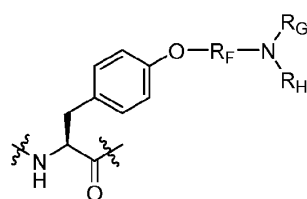
- 10 In some embodiments, X_{10} is



In some embodiments, X_{10} is



In some embodiments, X_{10} is



- 15

In some embodiments, R_C is -H. In some embodiments, R_C is $-CH_3$.

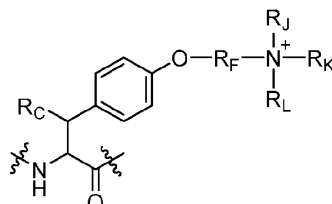
- In some embodiments, R_F is $-C_{(1-6)}\text{alkylene}$. In some embodiments, R_F is a bivalent polyethylene glycol chain having between 1 and 12 polyethylene glycol units. In some embodiments, R_F is a bivalent polyethylene glycol chain having between 1 and 8 polyethylene glycol units. In some embodiments, R_F is a bivalent polyethylene glycol chain having between 1 and 4 polyethylene glycol units.
- 20

In some embodiments, R_G is -H. In some embodiments, R_G is $-CH_3$. In some embodiments, R_G is a bond to the amino acid at X_5 or X_{13} . In some embodiments, R_G is a bond to the amino acid at X_5 . In some embodiments, R_G is a bond to the amino acid at X_{13} .

In some embodiments, R_H is -H. In some embodiments, R_H is -CH₃. In some embodiments, R_H is -C(O)- R_{H1} .

In some embodiments, R_{H1} is a polyethylene glycol chain. In some embodiments, R_{H1} is a polyethylene glycol chain terminating in an ammonium or methyl group.

5 In some embodiments, X_{10} is



wherein:

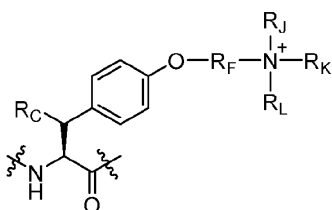
R_C is -H or -C₍₁₋₃₎alkyl;

R_F is -C₍₁₋₆₎alkylene or a bivalent polyethylene glycol chain;

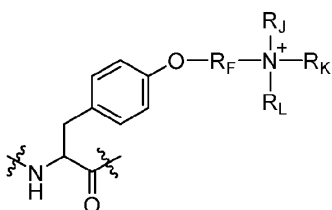
10 R_J , R_K , and R_L are each, independently, C₍₁₋₃₎alkyl;

or R_J and R_K taken together with the nitrogen atom to which they are attached form a 5- to 8-membered heterocyclyl group.

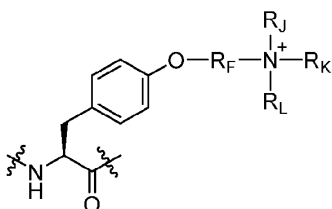
In some embodiments, X_{10} is



15 In some embodiments, X_{10} is



In some embodiments, X_{10} is



In some embodiments, R_C is -H. In some embodiments, R_C is -CH₃.

In some embodiments, R_F is $-C_{(1-6)}$ alkylene. In some embodiments, R_F is a bivalent polyethylene glycol chain having between 1 and 12 polyethylene glycol units. In some embodiments, R_F is a bivalent polyethylene glycol chain having between 1 and 8 polyethylene glycol units. In some embodiments, R_F is a bivalent polyethylene glycol chain having between 1 and 4 polyethylene glycol units.

In some embodiments, R_I , R_K , and R_L are each, independently, methyl.

In some embodiments, X_{10} is 3FTyr, 4AmF, 4CNF, 4DMPzEF, 4OMeF, 4MeF, 4PipPhe, AEF, AEF(Ac), AEF(BH), AEF(Boc), AEF(EtCO), AEF(G), AEF(NMe), AEF(NMe2), AEF(NMe3), AEF(SMSB), AEF- Z_{peg} , AEF(NMe)- Z_{peg} , APEG3F, bMeAEF, F, MMoEF, TMAPF, Y, Y(OTzl), or Y(OTzl(mPEG3)), optionally wherein the AEF or AEF(NMe) is linked to the amino acid at X_5 or the amino acid at X_{13} . In some embodiments, X_{10} is 3FTyr, 4AmF, 4CNF, 4DMPzEF, 4OMeF, 4MeF, 4PipPhe, AEF, AEF(Ac), AEF(BH), AEF(Boc), AEF(EtCO), AEF(G), AEF(NMe), AEF(NMe2), AEF(NMe3), AEF(SMSB), AEF- Z_{peg} , AEF(NMe)- Z_{peg} , APEG3F, bMeAEF, F, MMoEF, TMAPF, Y, Y(OTzl), or Y(OTzl(mPEG3)), each of which is an L-amino acid, optionally wherein the AEF or AEF(NMe) is linked to the amino acid at X_5 or the amino acid at X_{13} . In some embodiments, X_{10} is 3F-d-Tyr, d-4AmF, d-4CNF, d-4DMPzEF, d-4OMeF, d-4MeF, 4Pip-d-Phe, dAEF, dAEF(Ac), dAEF(BH), dAEF(Boc), dAEF(EtCO), dAEF(G), dAEF(NMe), dAEF(NMe2), dAEF(NMe3), dAEF(SMSB), dAEF- Z_{peg} , dAEF(NMe)- Z_{peg} , dAPEG3F, d-bMeAEF, f, dMMoEF, dTMAPF, y, y(OTzl), or y(OTzl(mPEG3)), optionally wherein the dAEF or dAEF(NMe) is linked to the amino acid at X_5 or the amino acid at X_{13} .

In some embodiments, X_{10} is 3FTyr, 4AmF, 4CNF, 4DMPzEF, 4OMeF, 4MeF, 4PipPhe, AEF, AEF(Ac), AEF(BH), AEF(Boc), AEF(EtCO), AEF(G), AEF(NMe), AEF(NMe2), AEF(NMe3), AEF(SMSB), AEF- Z_{peg} , AEF(NMe)- Z_{peg} , APEG3F, bMeAEF, F, MMoEF, TMAPF, Y, Y(OTzl), or Y(OTzl(mPEG3)).

In some embodiments, X_{10} is 4DMPzEF, 4OMeF, AEF, AEF(G), AEF(NMe), AEF(NMe2), AEF- Z_{peg} , AEF(NMe)- Z_{peg} , APEG3F, bMeAEF, F, MMoEF, TMAPF, or Y, optionally wherein the AEF or AEF(NMe) is linked to the amino acid at X_5 or the amino acid at X_{13} . In some embodiments, X_{10} is 4DMPzEF, 4OMeF, AEF, AEF(G), AEF(NMe), AEF(NMe2), AEF- Z_{peg} , AEF(NMe)- Z_{peg} , APEG3F, bMeAEF, F, MMoEF, TMAPF, or Y.

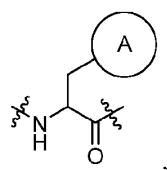
In some embodiments, X_{10} is AEF, AEF(G), AEF(NMe), AEF(NMe2), AEF- Z_{peg} , AEF(NMe)- Z_{peg} , bMeAEF, MMoEF, or TMAPF, optionally wherein the AEF or AEF(NMe) is linked to the amino acid at X_5 or the amino acid at X_{13} . In some embodiments, X_{10} is AEF or TMAPF, optionally wherein the AEF is linked to the amino acid at X_5 or the amino acid at X_{13} . In some embodiments, X_{10} is AEF or TMAPF.

In some embodiments, X₁₀ is 3FTyr. In some embodiments, X₁₀ is 4AmF. In some
embodiments, X₁₀ is 4CNF. In some embodiments, X₁₀ is 4DMPzEF. In some embodiments, X₁₀
is 4OMeF. In some embodiments, X₁₀ is 4MeF. In some embodiments, X₁₀ is 4PipPhe. In some
embodiments, X₁₀ is AEF. In some embodiments, X₁₀ is AEF linked to the amino acid at X₅. In
5 some embodiments, X₁₀ is AEF linked to E at X₅. In some embodiments, X₁₀ is AEF linked to K
at X₅. In some embodiments, X₁₀ is AEF linked to K(a) at X₅. In some embodiments, X₁₀ is AEF
linked to K(Ac) at X₅. In some embodiments, X₁₀ is AEF linked to K(d) at X₅. In some
embodiments, X₁₀ is AEF linked to K(G) at X₅. In some embodiments, X₁₀ is AEF linked to
K(NMe) at X₅. In some embodiments, X₁₀ is AEF linked to K(NNs) at X₅. In some
10 embodiments, X₁₀ is AEF linked to K-Z_{peg} at X₅. In some embodiments, X₁₀ is AEF linked to K-
Z_{lipid} at X₅. In some embodiments, X₁₀ is AEF linked to the amino acid at X₁₃. In some
embodiments, X₁₀ is AEF linked to E at X₁₃. In some embodiments, X₁₀ is AEF(Ac). In some
embodiments, X₁₀ is AEF(BH). In some embodiments, X₁₀ is AEF(Boc). In some embodiments,
X₁₀ is AEF(EtCO). In some embodiments, X₁₀ is AEF(G). In some embodiments, X₁₀ is
15 AEF(NMe). In some embodiments, X₁₀ is AEF(NMe) linked to the amino acid at X₅. In some
embodiments, X₁₀ is AEF(NMe) linked to the amino acid at X₁₃. In some embodiments, X₁₀ is
AEF(NMe₂). In some embodiments, X₁₀ is AEF(NMe₃). In some embodiments, X₁₀ is
AEF(SMSB). In some embodiments, X₁₀ is AEF-Z_{peg}. In some embodiments, X₁₀ is AEF(NMe)-
Z_{peg}. In some embodiments, X₁₀ is APEG3F. In some embodiments, X₁₀ is bMeAEF. In some
20 embodiments, X₁₀ is F. In some embodiments, X₁₀ is MMoEF. In some embodiments, X₁₀ is
TMAPF. In some embodiments, X₁₀ is Y. In some embodiments, X₁₀ is Y(OTzl). In some
embodiments, X₁₀ is Y(OTzl(mPEG3)).

In some embodiments, X₁₀ is 3F-d-Tyr. In some embodiments, X₁₀ is d-4AmF. In some
embodiments, X₁₀ is d-4CNF. In some embodiments, X₁₀ is d-4DMPzEF. In some embodiments,
25 X₁₀ is d-4OMeF. In some embodiments, X₁₀ is d-4MeF. In some embodiments, X₁₀ is 4Pip-d-
Phe. In some embodiments, X₁₀ is dAEF. In some embodiments, X₁₀ is dAEF linked to the
amino acid at X₅. In some embodiments, X₁₀ is dAEF linked to E at X₅. In some embodiments,
X₁₀ is dAEF linked to K at X₅. In some embodiments, X₁₀ is dAEF linked to K(a) at X₅. In some
embodiments, X₁₀ is dAEF linked to K(Ac) at X₅. In some embodiments, X₁₀ is dAEF linked to
30 K(d) at X₅. In some embodiments, X₁₀ is dAEF linked to K(G) at X₅. In some embodiments, X₁₀
is dAEF linked to K(NMe) at X₅. In some embodiments, X₁₀ is dAEF linked to K(NNs) at X₅. In
some embodiments, X₁₀ is dAEF linked to K-Z_{peg} at X₅. In some embodiments, X₁₀ is dAEF
linked to K-Z_{lipid} at X₅. In some embodiments, X₁₀ is dAEF linked to the amino acid at X₁₃. In
some embodiments, X₁₀ is dAEF linked to E at X₁₃. In some embodiments, X₁₀ is dAEF(Ac). In
35 some embodiments, X₁₀ is dAEF(BH). In some embodiments, X₁₀ is dAEF(Boc). In some

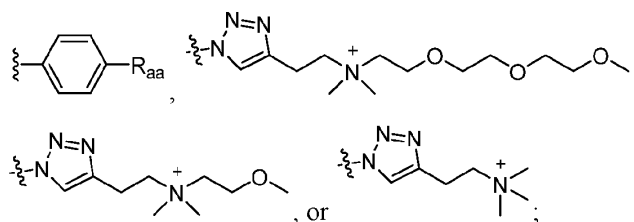
embodiments, X_{10} is dAEF(EtCO). In some embodiments, X_{10} is dAEF(G). In some
embodiments, X_{10} is dAEF(NMe). In some embodiments, X_{10} is dAEF(NMe) linked to the
amino acid at X_5 . In some embodiments, X_{10} is dAEF(NMe) linked to the amino acid at X_{13} . In
some embodiments, X_{10} is dAEF(NMe2). In some embodiments, X_{10} is dAEF(NMe3). In some
5 embodiments, X_{10} is dAEF(SMSB). In some embodiments, X_{10} is dAEF- Z_{peg} . In some
embodiments, X_{10} is dAEF(NMe)- Z_{peg} . In some embodiments, X_{10} is dAPEG3F. In some
embodiments, X_{10} is d-bMeAEF. In some embodiments, X_{10} is f. In some embodiments, X_{10} is
dMMoEF. In some embodiments, X_{10} is dTMAPF. In some embodiments, X_{10} is y. In some
embodiments, X_{10} is y(OTzl). In some embodiments, X_{10} is y(OTzl(mPEG3)).

10 In some embodiments, X_{10} is:



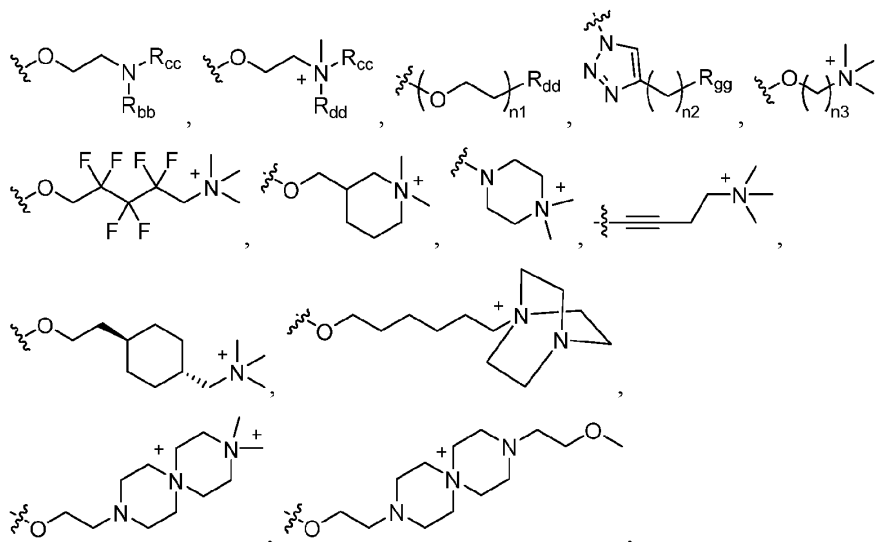
wherein:

A is

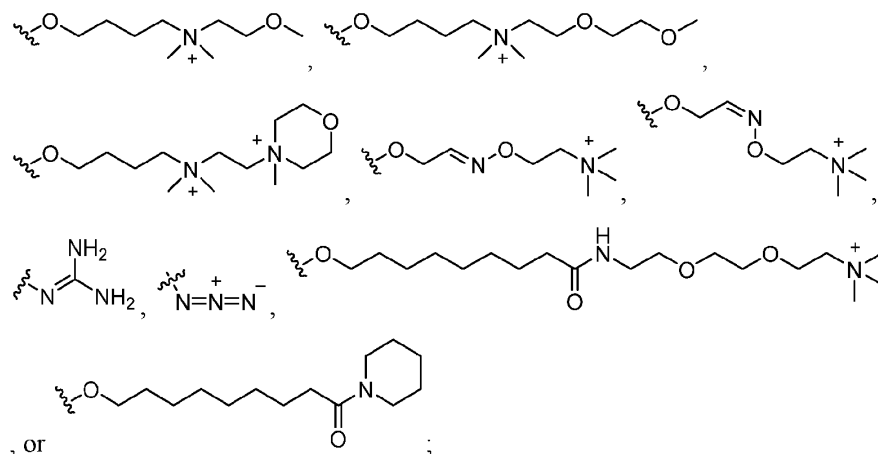


15

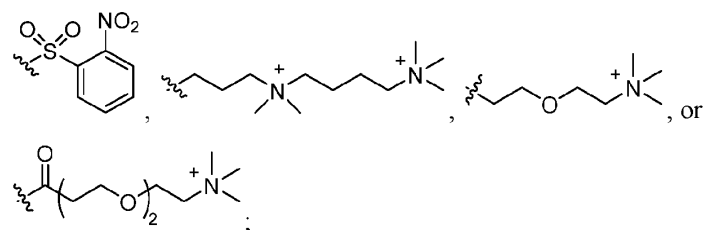
R_{aa} is $-OCHF_2$, $-O(CH_2)_9CO_2H$,



20

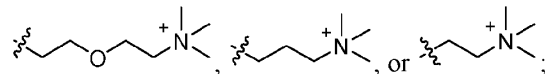


- 5 R_{bb} is -H, -CH₃, -C(O)CH₃, -C(NH)NH₂, -(CH₂)₃O(CH₂)₂OCH₃, -CH₂CH₂OCH₃, -(CH₂CH₂O)₃CH₃, -(CH₂CH₂O)₆CH₃,



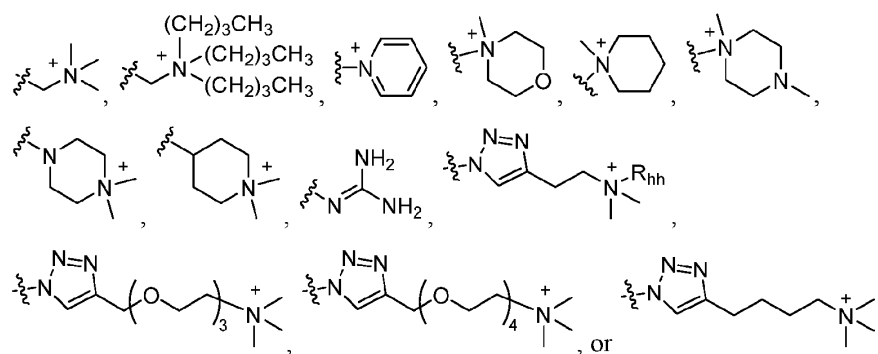
R_{cc} is -H, -CH₃, -(CH₂)₃O(CH₂)₂OCH₃,

10



n_1 is 1, 2, or 3;

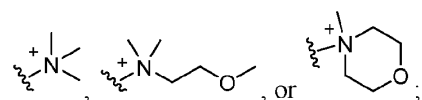
R_{dd} is



15

n_2 is 1, 2, 3, 4, or 5;

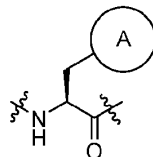
R_{gg} is -OCH₃,



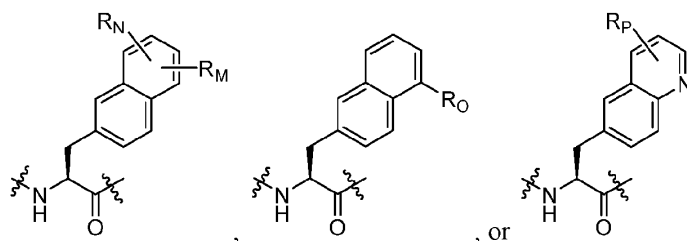
n_3 is 3, 4, 5, 6, or 8; and

R_{hh} is -H, $-(CH_2)_7CH_3$, $-(CH_2)_{15}CH_3$, $-(CH_2)_2OCH_3$, or $-(CH_2CH_2O)_3CH_3$.

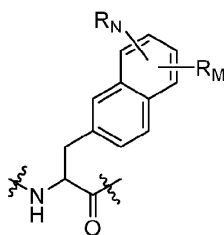
In some embodiments, X_{10} is:



5 In some embodiments, X_{11} is



In some embodiments, X_{11} is

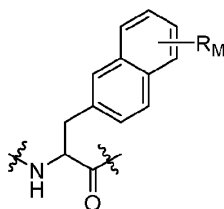


wherein:

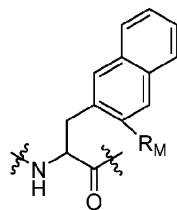
10 R_M is halo, -OH, $-C_{(1-3)}alkyl$, $-OC(O)C_{(1-3)}haloalkyl$, phenyl, or 5- to 6-membered heteroaryl, wherein the phenyl and 5- to 6-membered heteroaryl are each optionally substituted with one to three groups selected from -OH, $-OC_{(1-3)}alkyl$, $-C_{(1-3)}haloalkyl$, and 3- to 6-membered heterocyclyl; and

R_N is -H or -OH.

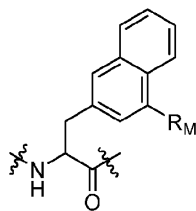
15 In some embodiments, X_{11} is



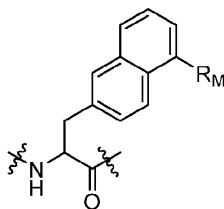
In some embodiments, X_{11} is



In some embodiments, X_{11} is

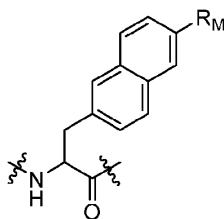


In some embodiments, X_{11} is

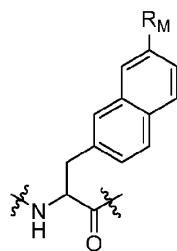


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In some embodiments, X_{11} is

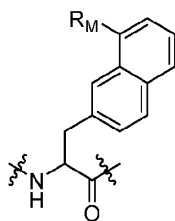


In some embodiments, X_{11} is

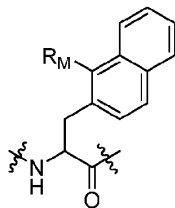


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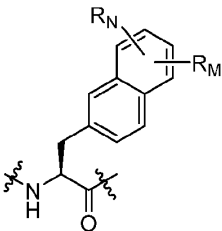
In some embodiments, X_{11} is



In some embodiments, X₁₁ is

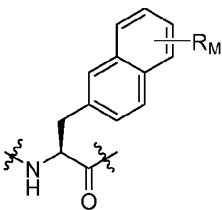


In some embodiments, X₁₁ is

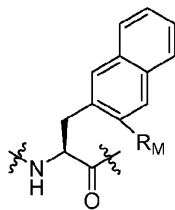


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In some embodiments, X₁₁ is

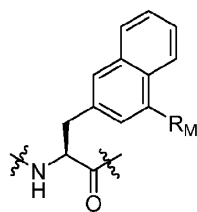


In some embodiments, X₁₁ is

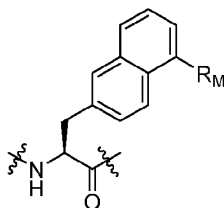


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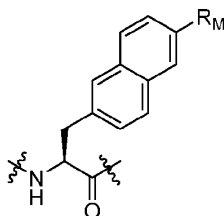
In some embodiments, X₁₁ is



In some embodiments, X_{11} is

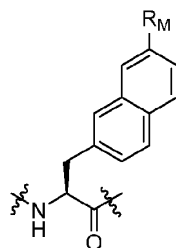


In some embodiments, X_{11} is

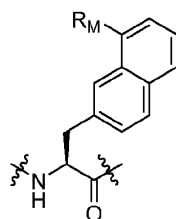


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In some embodiments, X_{11} is

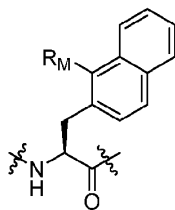


In some embodiments, X_{11} is



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In some embodiments, X_{11} is

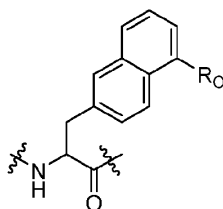


In some embodiments, R_M is -OH, -CH₃, -OC(O)CF₃, phenyl, or 5-membered heteroaryl, wherein the phenyl and 5- to 6-membered heteroaryl are each optionally substituted with one to three groups selected from -OH, -OCH₃, -CF₃, and 6-membered heterocyclyl. In some

5 embodiments, R_M is -OH.

In some embodiments, R_N is -H. In some embodiments, R_N is -OH.

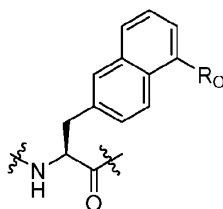
In some embodiments, X_{11} is



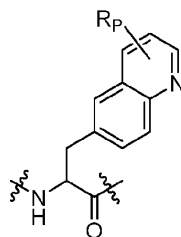
wherein R_O is -OC₍₁₋₃₎alkyl or -C(O)NH₂.

10 In some embodiments, R_O is -OC₍₁₋₃₎alkyl. In some embodiments, R_O is -C(O)NH₂.

In some embodiments, X_{11} is

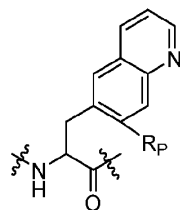


In some embodiments, X_{11} is

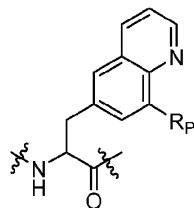


15 wherein R_P is halo, -OH, -C₍₁₋₃₎alkyl, -OC₍₁₋₃₎alkyl, -C(O)NH₂, -OC(O)C₍₁₋₃₎haloalkyl, phenyl, or 5- to 6-membered heteroaryl, wherein the phenyl and 5- to 6-membered heteroaryl are each optionally substituted with one to three groups selected from -OH, -OC₍₁₋₃₎alkyl, -C₍₁₋₃₎haloalkyl, and 3- to 6-membered heterocyclyl.

In some embodiments, X₁₁ is

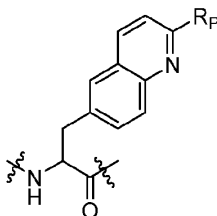


In some embodiments, X₁₁ is

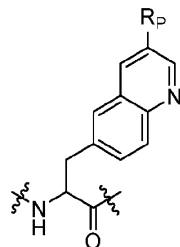


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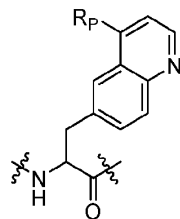
In some embodiments, X₁₁ is



In some embodiments, X₁₁ is

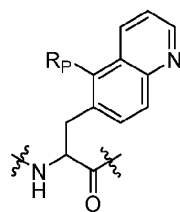


In some embodiments, X₁₁ is

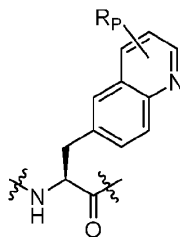


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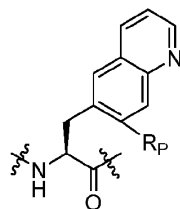
In some embodiments, X₁₁ is



In some embodiments, X_{11} is

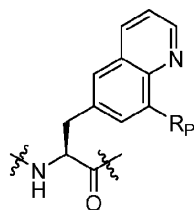


In some embodiments, X_{11} is

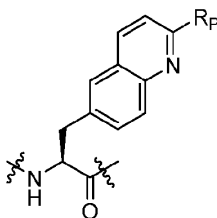


5

In some embodiments, X_{11} is

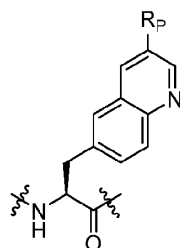


In some embodiments, X_{11} is

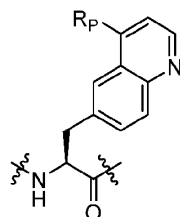


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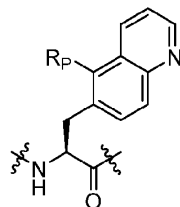
In some embodiments, X_{11} is



In some embodiments, X₁₁ is



In some embodiments, X₁₁ is



5

In some embodiments, R_P is halo, -C₍₁₋₃₎alkyl, -OC₍₁₋₃₎alkyl, -C(O)NH₂, -OC(O)C₍₁₋₃₎haloalkyl, phenyl, or 5- to 6-membered heteroaryl, wherein the phenyl and 5- to 6-membered heteroaryl are each optionally substituted with one to three groups selected from -OH, -OC₍₁₋₃₎alkyl, -C₍₁₋₃₎haloalkyl, and 3- to 6-membered heterocyclyl. In some embodiments, R_P is -OH or -OC₍₁₋₃₎alkyl. In some embodiments, R_P is -OH. In some embodiments, R_P is -OC₍₁₋₃₎alkyl.

In some embodiments, X₁₁ is 2Nal6((5CF3)3Pyrazole), 6OH2Nal, 6OHQui, 2Nal6(Ph2OH), 2Nal6(Ph4(NMorph)), 2Nal6(3Pyrazole), 2Nal6(4OMePh), 5OMe2Nal, 5amido2Nal, 5Br2Nal, 5Me2Nal, 6MeQui, 6O(COCF3)2Nal, 6F2Nal, 6Br2Nal, or 7OH2Nal. In some embodiments, X₁₁ is 2Nal6((5CF3)3Pyrazole), 6OH2Nal, 6OHQui, 2Nal6(Ph2OH), 2Nal6(Ph4(NMorph)), 2Nal6(3Pyrazole), 2Nal6(4OMePh), 5OMe2Nal, 5amido2Nal, 5Br2Nal, 5Me2Nal, 6MeQui, 6O(COCF3)2Nal, 6F2Nal, 6Br2Nal, or 7OH2Nal, each of which is an L-amino acid. In some embodiments, X₁₁ is d-2Nal6((5CF3)3Pyrazole), d-6OH2Nal, d-6OHQui, d-2Nal6(Ph2OH), d-2Nal6(Ph4(NMorph)), d-2Nal6(3Pyrazole), d-2Nal6(4OMePh), d-5OMe2Nal, d-5amido2Nal, d-5Br2Nal, d-5Me2Nal, d-6MeQui, d-6O(COCF3)2Nal, d-6F2Nal, d-6Br2Nal, or d-7OH2Nal.

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In some embodiments, X₁₁ is 2Nal6((5CF3)3Pyrazole), 6OH2Nal, 2Nal6(Ph2OH), 2Nal6(Ph4(NMorph)), 2Nal6(3Pyrazole), 2Nal6(4OMePh), 5OMe2Nal, 5amido2Nal, 5Br2Nal,

5Me2Nal, 6MeQui, 6O(COCF3)2Nal, 6F2Nal, 6Br2Nal, or 7OH2Nal. In some embodiments, X₁₁ is 2Nal6((5CF3)3Pyrazole), 6OH2Nal, 2Nal6(Ph2OH), 2Nal6(Ph4(NMorph)), 2Nal6(3Pyrazole), 2Nal6(4OMePh), 5Br2Nal, 5Me2Nal, 6O(COCF3)2Nal, 6F2Nal, 6Br2Nal, or 7OH2Nal.

- 5 In some embodiments, X₁₁ is 2Nal6((5CF3)3Pyrazole). In some embodiments, X₁₁ is 6OH2Nal. In some embodiments, X₁₁ is 6OHQui. In some embodiments, X₁₁ is 2Nal6(Ph2OH). In some embodiments, X₁₁ is 2Nal6(Ph4(NMorph)). In some embodiments, X₁₁ is 2Nal6(3Pyrazole). In some embodiments, X₁₁ is 2Nal6(4OMePh). In some embodiments, X₁₁ is 5OMe2Nal. In some embodiments, X₁₁ is 5amido2Nal. In some embodiments, X₁₁ is 5Br2Nal.
- 10 In some embodiments, X₁₁ is 5Me2Nal. In some embodiments, X₁₁ is 6MeQui. In some embodiments, X₁₁ is 6O(COCF3)2Nal. In some embodiments, X₁₁ is 6F2Nal. In some embodiments, X₁₁ is 6Br2Nal. In some embodiments, X₁₁ is 7OH2Nal.

- In some embodiments, X₁₁ is d-2Nal6((5CF3)3Pyrazole). In some embodiments, X₁₁ is d-6OH2Nal. In some embodiments, X₁₁ is d-6OHQui. In some embodiments, X₁₁ is d-2Nal6(Ph2OH). In some embodiments, X₁₁ is d-2Nal6(Ph4(NMorph)). In some embodiments, X₁₁ is d-2Nal6(3Pyrazole). In some embodiments, X₁₁ is d-2Nal6(4OMePh). In some embodiments, X₁₁ is d-5OMe2Nal. In some embodiments, X₁₁ is d-5amido2Nal. In some embodiments, X₁₁ is d-5Br2Nal. In some embodiments, X₁₁ is d-5Me2Nal. In some embodiments, X₁₁ is d-6MeQui. In some embodiments, X₁₁ is d-6O(COCF3)2Nal. In some
- 15 2Nal6(Ph2OH). In some embodiments, X₁₁ is d-2Nal6(Ph4(NMorph)). In some embodiments, X₁₁ is d-2Nal6(3Pyrazole). In some embodiments, X₁₁ is d-2Nal6(4OMePh). In some embodiments, X₁₁ is d-5OMe2Nal. In some embodiments, X₁₁ is d-5amido2Nal. In some embodiments, X₁₁ is d-5Br2Nal. In some embodiments, X₁₁ is d-5Me2Nal. In some embodiments, X₁₁ is d-6MeQui. In some embodiments, X₁₁ is d-6O(COCF3)2Nal. In some
- 20 embodiments, X₁₁ is d-6F2Nal. In some embodiments, X₁₁ is d-6Br2Nal. In some embodiments, X₁₁ is d-7OH2Nal.

In some embodiments, X₁₂ is THP, aMeL, diFCpx, or Pip(Nme2). In some embodiments, X₁₂ is THP, aMeL, diFCpx, or Pip(Nme2), wherein the aMeL is an L-amino acid. In some embodiments, X₁₂ is THP, aMeL, diFCpx, or Pip(Nme2).

- 25 In some embodiments, X₁₂ is THP. In some embodiments, X₁₂ is aMeL. In some embodiments, X₁₂ is aMeL. In some embodiments, X₁₂ is diFCpx. In some embodiments, X₁₂ is Pip(Nme2).

- In some embodiments, X₁₃ is C, D, Dab(NMeAc), Dab(NMecarn), Dab-Z_{peg}, Dab-Z_{lipid}, E, E(COcPEG3a), hE, K, K(5cpa), K(Ac), K(d), K(G), K(Me)3, K(NMe), K(NMeAc), K(NNs), K-Z_{peg}, K-Z_{lipid}, NMeK-Z_{peg}, NMeK-Z_{lipid}, L, or Q(NMe2); wherein the C, D, and hE are linked to R₁, the amino acid at X₃, or the amino acid at X₁₀, and optionally wherein the E is linked to R₁, the amino acid at X₃, or the amino acid at X₁₀. In some embodiments, X₁₃ is C, D, Dab(NMeAc), Dab(NMecarn), Dab-Z_{peg}, Dab-Z_{lipid}, E, E(COcPEG3a), hE, K, K(5cpa), K(Ac), K(d), K(G), K(Me)3, K(NMe), K(NMeAc), K(NNs), K-Z_{peg}, K-Z_{lipid}, NMeK-Z_{peg}, NMeK-Z_{lipid}, L, or Q(NMe2), each of which is an L-amino acid; wherein the C, D, and hE are linked to R₁, the
- 30 K-Z_{peg}, K-Z_{lipid}, NMeK-Z_{peg}, NMeK-Z_{lipid}, L, or Q(NMe2); wherein the C, D, and hE are linked to R₁, the amino acid at X₃, or the amino acid at X₁₀, and optionally wherein the E is linked to R₁, the amino acid at X₃, or the amino acid at X₁₀. In some embodiments, X₁₃ is C, D, Dab(NMeAc), Dab(NMecarn), Dab-Z_{peg}, Dab-Z_{lipid}, E, E(COcPEG3a), hE, K, K(5cpa), K(Ac), K(d), K(G), K(Me)3, K(NMe), K(NMeAc), K(NNs), K-Z_{peg}, K-Z_{lipid}, NMeK-Z_{peg}, NMeK-Z_{lipid}, L, or Q(NMe2), each of which is an L-amino acid; wherein the C, D, and hE are linked to R₁, the
- 35 L, or Q(NMe2), each of which is an L-amino acid; wherein the C, D, and hE are linked to R₁, the

amino acid at X₃, or the amino acid at X₁₀, and optionally wherein the E is linked to R₁, the amino acid at X₃, or the amino acid at X₁₀. In some embodiments, X₁₃ is c, d, dDab(NMeAc), dDab(NMecarn), dDab-Z_{peg}, dDab-Z_{lipid}, e, e(COcPEG3a), he, k, k(5cpa), k(Ac), k(d), k(G), k(Me)₃, k(NMe), k(NMeAc), k(NNs), k-Z_{peg}, k-Z_{lipid}, NMek-Z_{peg}, NMek-Z_{lipid}, l, or q(NMe₂);
 5 wherein the c, d, and he are linked to R₁, the amino acid at X₃, or the amino acid at X₁₀, and optionally wherein the e is linked to R₁, the amino acid at X₃, or the amino acid at X₁₀.

In some embodiments, X₁₃ is C, D, Dab(NMeAc), Dab(NMecarn), E, E(COcPEG3a), hE, K(Ac), K(Me)₃, K(NMeAc), K-Z_{peg}, K-Z_{lipid}, L, or Q(NMe₂); wherein the C, D, and hE are linked to R₁, the amino acid at X₃, or the amino acid at X₁₀, and optionally wherein the E is
 10 linked to R₁, the amino acid at X₃, or the amino acid at X₁₀. In some embodiments, X₁₃ is Dab(NMeAc), Dab(NMecarn), E, K(Ac), K(NMeAc), K-Z_{peg}, or K-Z_{lipid}. In some embodiments, X₁₃ is E, K(Ac), K(NMeAc), K-Z_{peg}, or K-Z_{lipid}. In some embodiments, X₁₃ is E, K(Ac), or K(NMeAc). In some embodiments, X₁₃ is E or K(Ac).

In some embodiments, X₁₃ is Dab(NMeAc), Dab(NMecarn), Dab-Z_{peg}, Dab-Z_{lipid}, E,
 15 E(COcPEG3a), K, K(5cpa), K(Ac), K(d), K(G), K(Me)₃, K(NMe), K(NMeAc), K(NNs), K-Z_{peg}, K-Z_{lipid}, NMek-Z_{peg}, NMek-Z_{lipid}, L, or Q(NMe₂). In some embodiments, X₁₃ is Dab(NMeAc), Dab(NMecarn), E, E(COcPEG3a), K(Ac), K(Me)₃, K(NMeAc), K-Z_{peg}, K-Z_{lipid}, L, or Q(NMe₂).

In some embodiments, X₁₃ is C, D, Dab(NMeAc), Dab(NMecarn), Dab-Z_{peg}, E,
 20 E(COcPEG3a), hE, K, K(5cpa), K(Ac), K(d), K(G), K(Me)₃, K(NMe), K(NMeAc), K(NNs), K-Z_{peg}, NMek-Z_{peg}, L, or Q(NMe₂); wherein the C, D, and hE are linked to R₁, the amino acid at X₃, or the amino acid at X₁₀, and optionally wherein the E is linked to R₁, the amino acid at X₃, or the amino acid at X₁₀. In some embodiments, X₁₃ is C, D, Dab(NMeAc), Dab(NMecarn), E, E(COcPEG3a), hE, K(Ac), K(Me)₃, K(NMeAc), K-Z_{peg}, L, or Q(NMe₂); wherein the C, D, and
 25 hE are linked to R₁, the amino acid at X₃, or the amino acid at X₁₀, and optionally wherein the E is linked to R₁, the amino acid at X₃, or the amino acid at X₁₀.

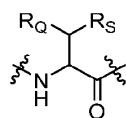
In some embodiments, X₁₃ is C linked to the amino acid at X₃. In some embodiments, X₁₃ is C linked to dK(COCH₂CH₂) at X₃. In some embodiments, X₁₃ is C linked to dab(COCH₂) at X₃. In some embodiments, X₁₃ is D linked to the amino acid at X₃. In some
 30 embodiments, X₁₃ is D linked to ser(MePEG₂) at X₃. In some embodiments, X₁₃ is Dab(NMeAc). In some embodiments, X₁₃ is Dab(NMecarn). In some embodiments, X₁₃ is Dab-Z_{peg}. In some embodiments, X₁₃ is Dab-Z_{lipid}. In some embodiments, X₁₃ is E. In some embodiments, X₁₃ is E linked to R₁. In some embodiments, X₁₃ is E linked to 5Ava at R₁. In some embodiments, X₁₃ is E linked to 6Ahx at R₁. In some embodiments, X₁₃ is E linked to
 35 7Ahp at R₁. In some embodiments, X₁₃ is E linked to the amino acid at X₃. In some

embodiments, X₁₃ is E linked to the amino acid at X₁₀. In some embodiments, X₁₃ is E linked to AEF at X₁₀. In some embodiments, X₁₃ is E(COcPEG3a). In some embodiments, X₁₃ is hE. In some embodiments, X₁₃ is hE linked to R₁. In some embodiments, X₁₃ is hE linked to PEG2 at R₁. In some embodiments, X₁₃ is hE linked to PEG2NMe at R₁. In some embodiments, X₁₃ is hE linked to the amino acid at X₃. In some embodiments, X₁₃ is hE linked to K at X₃. In some
 5 embodiments, X₁₃ is K. In some embodiments, X₁₃ is K(5cpa). In some embodiments, X₁₃ is K(Ac). In some embodiments, X₁₃ is K(d). In some embodiments, X₁₃ is K(G). In some embodiments, X₁₃ is K(Me)₃. In some embodiments, X₁₃ is K(NMe). In some embodiments, X₁₃ is K(NMeAc). In some embodiments, X₁₃ is K(NNs). In some embodiments, X₁₃ is K-Z_{peg}. In
 10 some embodiments, X₁₃ is K-Z_{lipid}. In some embodiments, X₁₃ is NMeK-Z_{peg}. In some embodiments, X₁₃ is NMeK-Z_{lipid}. In some embodiments, X₁₃ is L. In some embodiments, X₁₃ is Q(NMe₂).

In some embodiments, X₁₃ is c linked to the amino acid at X₃. In some embodiments, X₁₃ is c linked to dK(COCH₂CH₂) at X₃. In some embodiments, X₁₃ is c linked to dab(COCH₂) at
 15 X₃. In some embodiments, X₁₃ is d linked to the amino acid at X₃. In some embodiments, X₁₃ is d linked to ser(MePEG2) at X₃. In some embodiments, X₁₃ is dDab(NMeAc). In some embodiments, X₁₃ is dDab(NMecarn). In some embodiments, X₁₃ is dDab-Z_{peg}. In some embodiments, X₁₃ is dDab-Z_{lipid}. In some embodiments, X₁₃ is e. In some embodiments, X₁₃ is e linked to R₁. In some embodiments, X₁₃ is e linked to 5Ava at R₁. In some embodiments, X₁₃ is e
 20 linked to 6Ahx at R₁. In some embodiments, X₁₃ is e linked to 7Ahp at R₁. In some embodiments, X₁₃ is e linked to the amino acid at X₃. In some embodiments, X₁₃ is e linked to the amino acid at X₁₀. In some embodiments, X₁₃ is e linked to AEF at X₁₀. In some embodiments, X₁₃ is e(COcPEG3a). In some embodiments, X₁₃ is he. In some embodiments, X₁₃ is he linked to R₁. In some embodiments, X₁₃ is he linked to PEG2 at R₁. In some embodiments, X₁₃ is he linked to PEG2NMe at R₁. In some embodiments, X₁₃ is he linked to the amino acid at
 25 X₃. In some embodiments, X₁₃ is he linked to K at X₃. In some embodiments, X₁₃ is k. In some embodiments, X₁₃ is k(5cpa). In some embodiments, X₁₃ is k(Ac). In some embodiments, X₁₃ is k(d). In some embodiments, X₁₃ is k(G). In some embodiments, X₁₃ is k(Me)₃. In some embodiments, X₁₃ is k(NMe). In some embodiments, X₁₃ is k(NMeAc). In some embodiments,
 30 X₁₃ is k(NNs). In some embodiments, X₁₃ is k-Z_{peg}. In some embodiments, X₁₃ is k-Z_{lipid}. In some embodiments, X₁₃ is NMek-Z_{peg}. In some embodiments, X₁₃ is NMek-Z_{lipid}. In some embodiments, X₁₃ is l. In some embodiments, X₁₃ is q(NMe₂).

In some embodiments, X₁₄ is N. In some embodiments, X₁₄ is N, wherein the N is an L-amino acid. In some embodiments, X₁₄ is n.

35 In some embodiments, X₁₅ is

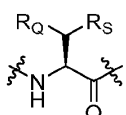


wherein:

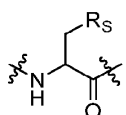
R_Q is -H or -C₍₁₋₃₎alkyl; and

R_S is phenyl or 5- to 6-membered heteroaryl, each of which is optionally substituted with one -C(O)NH₂ group.

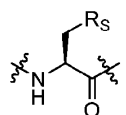
In some embodiments, X_{15} is



In some embodiments, X_{15} is



In some embodiments, X_{15} is



In some embodiments, R_Q is -H. In some embodiments, R_Q is -CH₃.

In some embodiments, R_S is phenyl which is optionally substituted with one -C(O)NH₂ group. In some embodiments, R_S is 5- to 6-membered heteroaryl which is optionally substituted with one -C(O)NH₂ group.

In some embodiments, X_{15} is 3AmPyrazolAla, 3Pya, 5AmPyridinAla, 5MePyridinAla, Ala, ACIPA, aMePhe, H, or THP. In some embodiments, X_{15} is 3AmPyrazolAla, 3Pya, 5AmPyridinAla, 5MePyridinAla, Ala, ACIPA, aMePhe, H, or THP, wherein the 3AmPyrazolAla, 3Pya, 5AmPyridinAla, 5MePyridinAla, Ala, ACIPA, aMePhe, and H are L-amino acids. In some embodiments, X_{15} is 3AmPyrazol-d-Ala, d-3Pya, d-5AmPyridinAla, d-5MePyridinAla, dAla, dACIPA, aMe-d-Phe, h, or THP.

In some embodiments, X_{15} is 3AmPyrazolAla. In some embodiments, X_{15} is 3Pya. In some embodiments, X_{15} is 5AmPyridinAla. In some embodiments, X_{15} is 5MePyridinAla. In some embodiments, X_{15} is Ala. In some embodiments, X_{15} is ACIPA. In some embodiments, X_{15} is aMePhe. In some embodiments, X_{15} is H. In some embodiments, X_{15} is THP.

In some embodiments, X_{15} is 3AmPyrazol-d-Ala. In some embodiments, X_{15} is d-3Pya. In some embodiments, X_{15} is d-5AmPyridinAla. In some embodiments, X_{15} is d-5MePyridinAla.

In some embodiments, X₁₅ is dAla. In some embodiments, X₁₅ is dACIPA. In some embodiments, X₁₅ is aMe-d-Phe. In some embodiments, X₁₅ is h.

In some embodiments, X₁₆ is Sar, Dab-Z_{peg}, Dab-Z_{lipid}, K-Z_{peg}, K-Z_{lipid}, NMeK-Z_{peg}, NMeK-Z_{lipid}, or absent. In some embodiments, X₁₆ is Sar, Dab-Z_{peg}, Dab-Z_{lipid}, K-Z_{peg}, K-Z_{lipid}, NMeK-Z_{peg}, NMeK-Z_{lipid}, or absent, wherein the Dab-Z_{peg}, Dab-Z_{lipid}, K-Z_{peg}, K-Z_{lipid}, NMeK-Z_{peg}, and NMeK-Z_{lipid} are L-amino acids. In some embodiments, X₁₆ is Sar, dDab-Z_{peg}, dDab-Z_{lipid}, k-Z_{peg}, k-Z_{lipid}, NMeK-Z_{peg}, NMeK-Z_{lipid}, or absent.

In some embodiments, X₁₆ is Sar, NMeK-Z_{lipid}, or absent. In some embodiments, X₁₇ is Sar or absent. In some embodiments, X₁₆ is Sar or NMeK-Z_{lipid}.

In some embodiments, X₁₆ is Sar. In some embodiments, X₁₆ is Dab-Z_{peg}. In some embodiments, X₁₆ is Dab-Z_{lipid}. In some embodiments, X₁₆ is K-Z_{peg}. In some embodiments, X₁₆ is K-Z_{lipid}. In some embodiments, X₁₆ is NMeK-Z_{peg}. In some embodiments, X₁₆ is NMeK-Z_{lipid}. In some embodiments, X₁₆ is absent.

In some embodiments, X₁₆ is dDab-Z_{peg}. In some embodiments, X₁₆ is dDab-Z_{lipid}. In some embodiments, X₁₆ is k-Z_{peg}. In some embodiments, X₁₆ is k-Z_{lipid}. In some embodiments, X₁₆ is NMeK-Z_{peg}. In some embodiments, X₁₆ is NMeK-Z_{lipid}.

In some embodiments, X₁₇ is Dab-Z_{peg}, Dab-Z_{lipid}, K-Z_{peg}, K-Z_{lipid}, NMeK-Z_{peg}, NMeK-Z_{lipid}, or absent. In some embodiments, X₁₇ is Dab-Z_{peg}, Dab-Z_{lipid}, K-Z_{peg}, K-Z_{lipid}, NMeK-Z_{peg}, NMeK-Z_{lipid}, or absent, wherein the Dab-Z_{peg}, Dab-Z_{lipid}, K-Z_{peg}, K-Z_{lipid}, NMeK-Z_{peg}, and NMeK-Z_{lipid} are L-amino acids. In some embodiments, X₁₇ is dDab-Z_{peg}, dDab-Z_{lipid}, k-Z_{peg}, k-Z_{lipid}, NMeK-Z_{peg}, NMeK-Z_{lipid}, or absent.

In some embodiments, X₁₇ is Dab-Z_{peg}, Dab-Z_{lipid}, K-Z_{peg}, K-Z_{lipid}, NMeK-Z_{peg}, or NMeK-Z_{lipid}. In some embodiments, X₁₇ is K-Z_{lipid}, NMeK-Z_{lipid}, or absent.

In some embodiments, X₁₇ is Dab-Z_{peg}. In some embodiments, X₁₇ is Dab-Z_{lipid}. In some embodiments, X₁₇ is K-Z_{peg}. In some embodiments, X₁₇ is K-Z_{lipid}. In some embodiments, X₁₇ is NMeK-Z_{peg}. In some embodiments, X₁₇ is NMeK-Z_{lipid}. In some embodiments, X₁₇ is absent.

In some embodiments, X₁₇ is dDab-Z_{peg}. In some embodiments, X₁₇ is dDab-Z_{lipid}. In some embodiments, X₁₇ is k-Z_{peg}. In some embodiments, X₁₇ is k-Z_{lipid}. In some embodiments, X₁₇ is NMeK-Z_{peg}. In some embodiments, X₁₇ is NMeK-Z_{lipid}.

In some embodiments, R₂ is CONH₂, CO(DiFPip), CON(Me)₂, a polyethylene glycol chain terminating in an ammonium or methyl group, or a lipophilic substituent. In some embodiments, R₂ is CONH₂, CO(DiFPip), CON(Me)₂, a polyethylene glycol chain terminating in an ammonium or methyl group, or a lipophilic substituent.

In some embodiments, R_2 is CONH_2 , $\text{CO}(\text{DiFPip})$, $\text{CON}(\text{Me})_2$, or Z_{peg} . In some embodiments, R_2 is CONH_2 , $\text{CON}(\text{Me})_2$, or Z_{peg} . In some embodiments, R_2 is CONH_2 or $\text{CON}(\text{Me})_2$.

In some embodiments, R_2 is CONH_2 . In some embodiments, R_2 is $\text{CO}(\text{DiFPip})$. In some
 5 embodiments, R_2 is $\text{CON}(\text{Me})_2$. In some embodiments, R_2 is Z_{peg} (i.e., a polyethylene glycol chain). In some embodiments, R_2 is Z_{lipid} (i.e., a lipophilic substituent).

When two amino acid positions in the peptide molecule are linked to form a ring, the linker between the α -carbon of one amino acid position and the α -carbon of the other amino acid position can be less than 30, 28, 26, 24, 22, 20, 18, 16, 14, 12, 10, 8, 6, or 4 Angstroms ($\text{\AA}$). In
 10 some embodiments, the linker is between 2 and 30 $\text{\AA}$ in length. In some embodiments, the linker is between 4 $\text{\AA}$ and 24 $\text{\AA}$ in length. In some embodiments, the linker is between 4 $\text{\AA}$ and 20 $\text{\AA}$ in length. In some embodiments, the linker is between 10 $\text{\AA}$ and 24 $\text{\AA}$ in length. In some
 15 embodiments, the linker can comprise between 4 and 18 atoms selected from C, N, S, and O. In some embodiments, the linker can comprise one or more cycloalkyl, heterocyclyl, aryl, or
 20 hateroaryl groups. In some embodiments, the linker can consist of C, N, S, O, and H atoms, and comprises between 2 and 16 carbon atoms. In some embodiments, the linker consists of C, N, S, O, and H atoms, and comprises between 4 and 16 atoms selected from C, N, S, and O. In some
 25 embodiments, the linker consists of C, S, and H atoms, and comprises between 4 and 16 atoms selected from C and S. In some embodiments, the linker consists of C, N, S, O, and H atoms, and comprises between 2 and 14 carbon atoms. In some embodiments, the linker consists of C,
 S, and H atoms, and comprises between 2 and 14 carbon atoms. In some embodiments, the linker consists of C, N, S, O, and H atoms, and comprises between 4 and 14 atoms selected from C, N, S, and O. In some embodiments, the linker consists of C, N, S, O, and H atoms, and
 comprises between 4 and 12 atoms selected from C, N, S, and O. In some embodiments, the
 30 linker consists of C, N, S, O, and H atoms, and comprises between 2 and 12 carbon atoms.

In some embodiments, the peptide comprises a linker between the α -carbon of X_4 and the α -carbon of X_9 . In some embodiments, the linker is less than 24 Angstroms ($\text{\AA}$) in length. In
 some embodiments, the linker is less than 20 $\text{\AA}$ in length. In some embodiments, the linker is
 30 between 4 $\text{\AA}$ and 24 $\text{\AA}$ in length. In some embodiments, the linker is between 4 $\text{\AA}$ and 20 $\text{\AA}$ in length. In some embodiments, the linker is between 10 $\text{\AA}$ and 24 $\text{\AA}$ in length. In some
 35 embodiments, the linker can comprise one or more cycloalkyl, heterocyclyl, aryl, or heteroaryl groups. In some embodiments, the linker can comprise one or more heterocyclyl, aryl, or heteroaryl groups. In some embodiments, the linker consists of C, N, S, O, and H atoms, and comprises between 4 and 18 atoms selected from C, N, S, and O. In some embodiments, the
 35 linker consists of C, N, S, O, and H atoms, and comprises between 2 and 16 carbon atoms. In

some embodiments, the linker consists of C, N, S, O, and H atoms, and comprises between 4 and 16 atoms selected from C, N, S, and O. In some embodiments, the linker consists of C, S, and H atoms, and comprises between 4 and 16 atoms selected from C and S. In some embodiments, the linker consists of C, N, S, O, and H atoms, and comprises between 2 and 14 carbon atoms. In some embodiments, the linker consists of C, S, and H atoms, and comprises between 2 and 14 carbon atoms. In some embodiments, the linker consists of C, N, S, O, and H atoms, and comprises between 4 and 14 atoms selected from C, N, S, and O. In some embodiments, the linker consists of C, N, S, O, and H atoms, and comprises between 4 and 12 atoms selected from C, N, S, and O. In some embodiments, the linker consists of C, N, S, O, and H atoms, and comprises between 2 and 12 carbon atoms.

In some embodiments, X₄ is Abu and X₉ is C. In some embodiments, X₄ is Abu and X₉ is aMeC. In some embodiments, X₄ is Abu and X₉ is Pen.

In some embodiments, X₄ is C and X₉ is C. In some embodiments, X₄ is C and X₉ is aMeC. In some embodiments, X₄ is C and X₉ is Pen.

In some embodiments, X₄ is Pen and X₉ is C. In some embodiments, X₄ is Pen and X₉ is aMeC. In some embodiments, X₄ is Pen and X₉ is Pen.

In some embodiments, X₄ is aMeC and X₉ is C. In some embodiments, X₄ is aMeC and X₉ is aMeC. In some embodiments, X₄ is aMeC and X₉ is Pen.

In some embodiments, X₄ is Pen(oXyl) and X₉ is C. In some embodiments, X₄ is Pen(oXyl) and X₉ is aMeC. In some embodiments, X₄ is Pen(oXyl) and X₉ is Pen.

In some embodiments, X₄ is Pen(mXyl) and X₉ is C. In some embodiments, X₄ is Pen(mXyl) and X₉ is aMeC. In some embodiments, X₄ is Pen(mXyl) and X₉ is Pen.

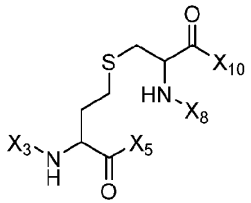
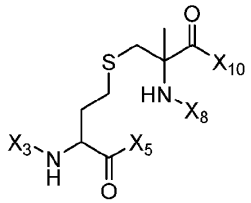
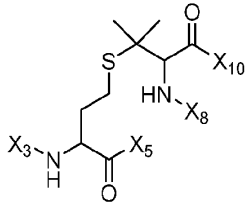
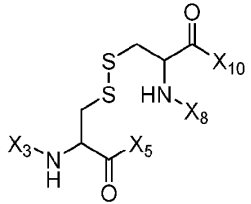
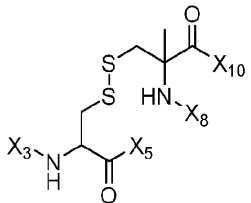
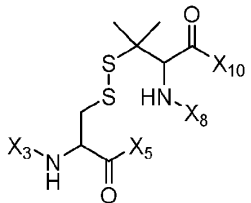
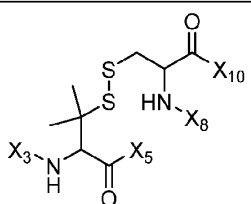
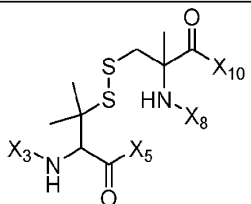
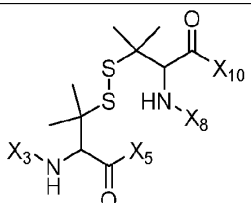
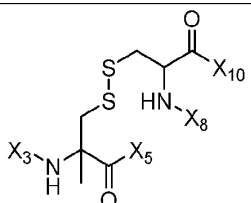
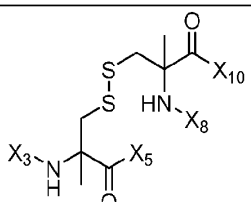
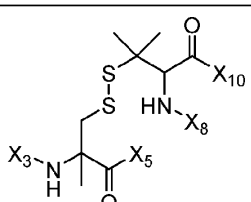
In some embodiments, X₄ is Pen(pXyl) and X₉ is C. In some embodiments, X₄ is Pen(pXyl) and X₉ is aMeC. In some embodiments, X₄ is Pen(pXyl) and X₉ is Pen.

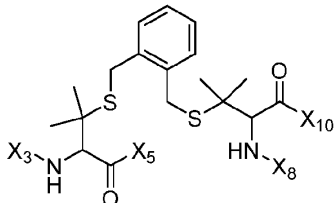
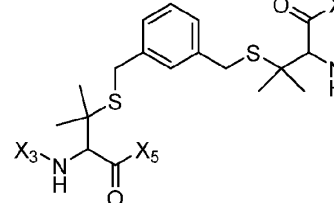
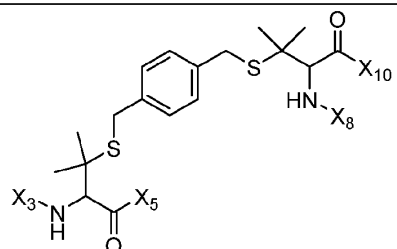
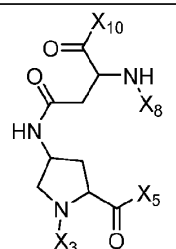
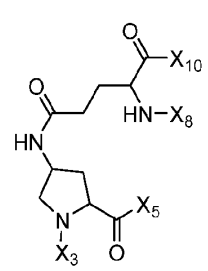
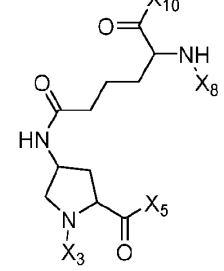
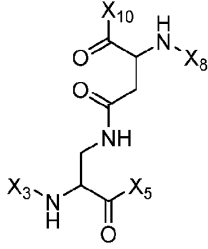
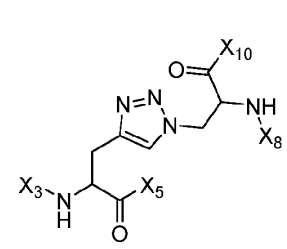
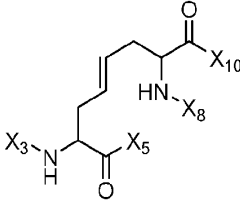
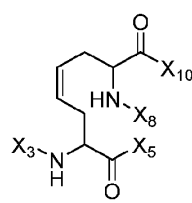
In some embodiments, X₄ is 4AminoPro and X₉ is D. In some embodiments, X₄ is 4AminoPro and X₉ is E. In some embodiments, X₄ is 4AminoPro and X₉ is hE.

In some embodiments, X₄ is Dap and X₉ is D. In some embodiments, X₄ is Dap and X₉ is E. In some embodiments, X₄ is Dap and X₉ is hE.

In some embodiments, X₄ is Pra and X₉ is Dap(N3). In some embodiments, X₄ is aG and X₉ is aG.

In some embodiments, the peptide is cyclized via a linkage between the residues at X₄ and X₉ having a structure selected from the following:

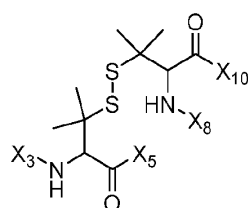
 Abu – C	 Abu – aMeC
 Abu – Pen	 C – C
 C – aMeC	 C – Pen
 Pen – C	 Pen – aMeC
 Pen – Pen	 aMeC – C
	

aMeC – aMeC	aMeC – Pen
 Pen(oXyl) – Pen	 Pen(mXyl) – Pen
 Pen(pXyl) – Pen	 4AminoPro – D
 4AminoPro – E	 4AminoPro – hE
 Dap – D	 Pra – Dap(N3)
 aG – aG.	 aG – aG

In some embodiments, the peptide is cyclized via a linkage between the residues at X₄ and X₉ having a structure selected from the following:

Abu – C	Abu – aMeC
C – aMeC	Pen – Pen.

In some embodiments, the peptide is cyclized via a linkage between the residues at X₄ and X₉ having the following structure:

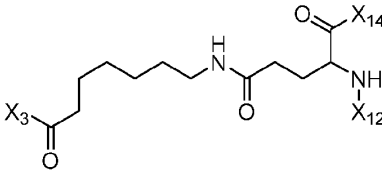
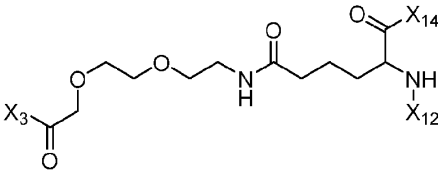
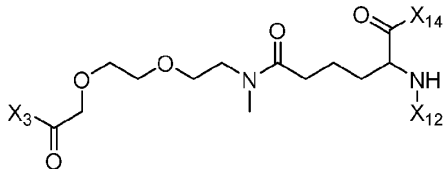


Pen – Pen.

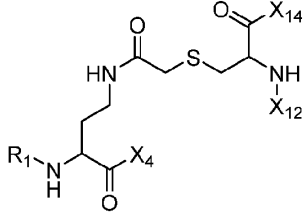
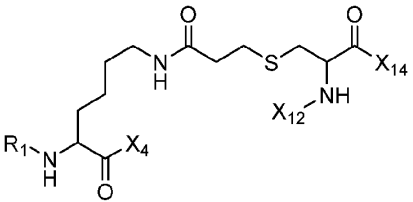
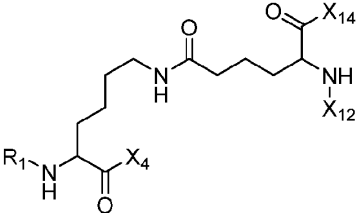
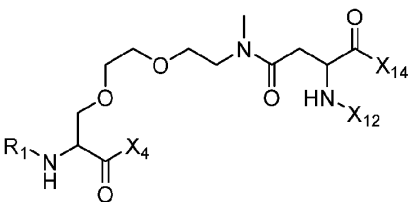
In some embodiments, the peptide comprises one linkage between any one of R₁ and X₁₃, X₃ and X₁₃, X₅ and X₁₀, and X₁₀ and X₁₃. In some embodiments, the peptide comprises no more than one linkage between any one of R₁ and X₁₃, X₃ and X₁₃, X₅ and X₁₀, and X₁₀ and X₁₃.

In some embodiments, the peptide comprises a linkage between R₁ and X₁₃ having a structure selected from the following:

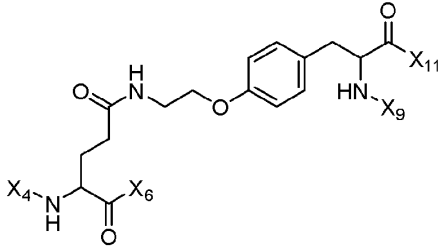
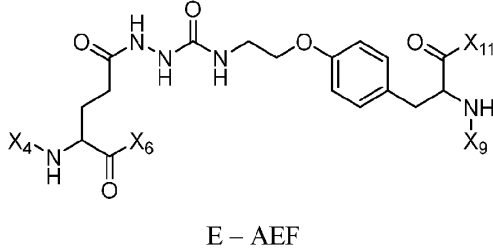
5Ava – E	6Ahx – E
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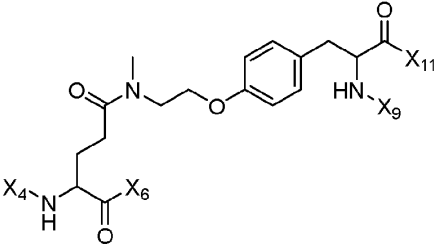
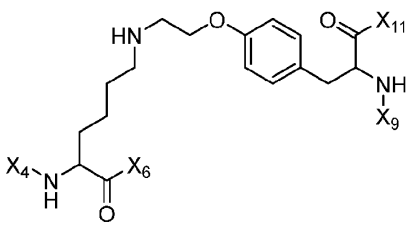
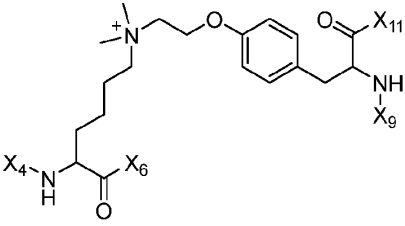
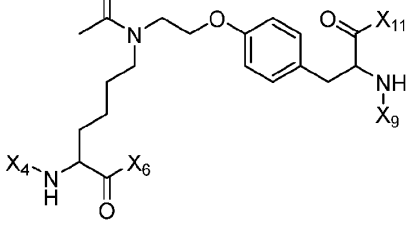
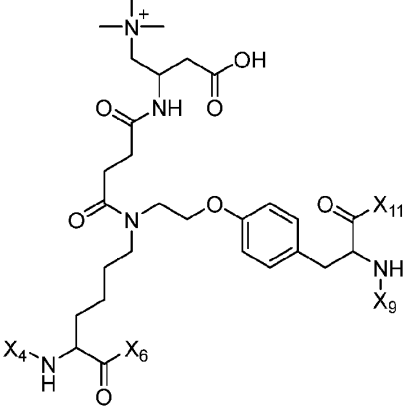
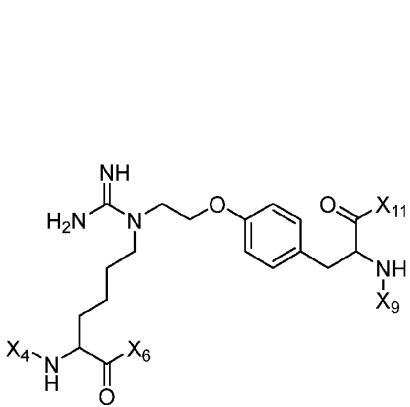
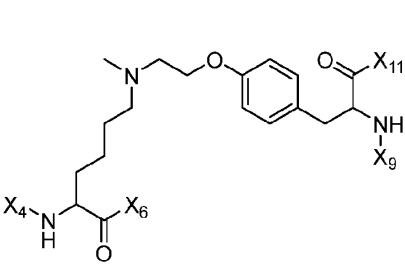
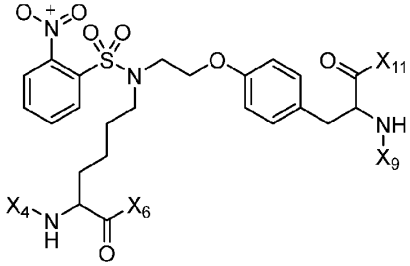
 7Ahp – E	 PEG2 – hE
 PEG2NMe – hE.	

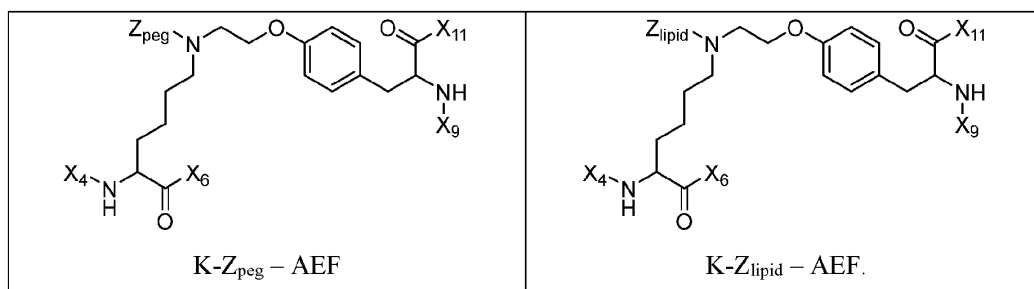
In some embodiments, the peptide comprises a linkage between X₃ and X₁₃ having a structure selected from the following:

 Dab(COCH₂) – C	 K(COCH₂CH₂) – C
 K – hE	 Ser(MePEG₂) – D

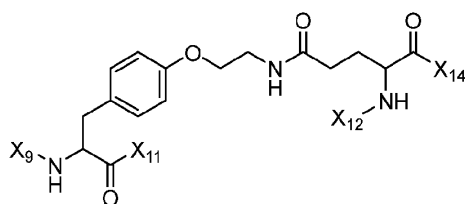
- 5 In some embodiments, the peptide comprises a linkage between X₅ and X₁₀ having a structure selected from the following:

	 E – AEF
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E – AEF	
 E – AEF(NMe)	 K – AEF
 K(a) – AEF	 K(Ac) – AEF
 K(d) – AEF	 K(G) – AEF
 K(NMe) – AEF	 K(NNs) – AEF



In some embodiments, the peptide comprises a linkage between X₁₀ and X₁₃ having the following structure:



5

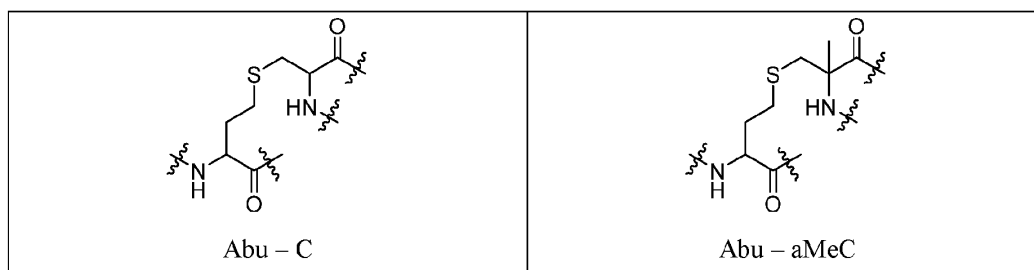
AEF – E.

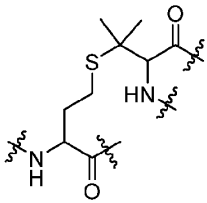
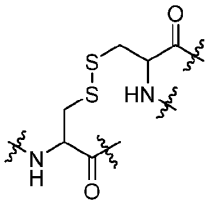
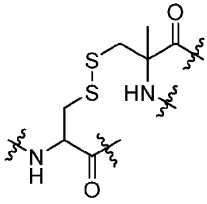
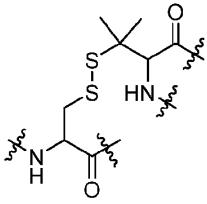
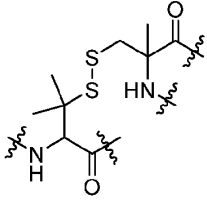
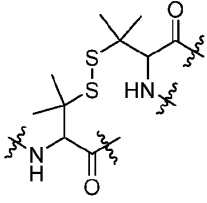
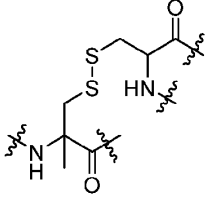
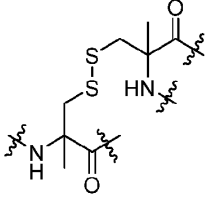
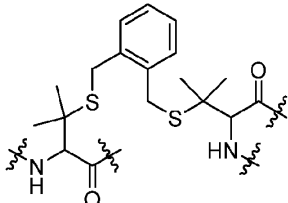
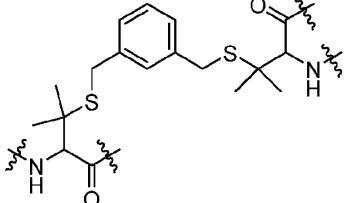
In some embodiments, the peptide is cyclized to form a first ring, wherein the first ring comprises 3 to 14 amino acids. In some embodiments, the peptide is cyclized to form a first ring, wherein the first ring comprises 4-11 or 14 amino acids. In some embodiments, the first ring comprises 4-9 or 11 amino acids. In some embodiments, the first ring comprises 4, 6, or 10 amino acids. In some embodiments, the first ring comprises 4 amino acids. In some embodiments, the first ring comprises 5 amino acids. In some embodiments, the first ring comprises 6 amino acids. In some embodiments, the first ring comprises 7 amino acids. In some embodiments, the first ring comprises 8 amino acids. In some embodiments, the first ring comprises 9 amino acids. In some embodiments, the first ring comprises 10 amino acids. In some embodiments, the first ring comprises 11 amino acids. In some embodiments, the first ring comprises 14 amino acids.

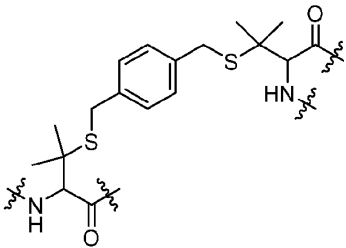
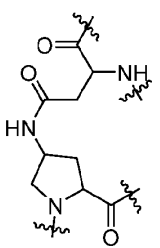
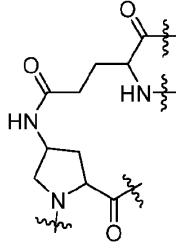
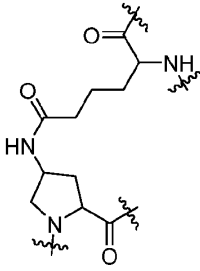
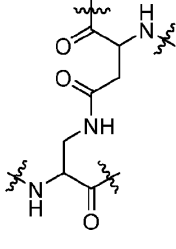
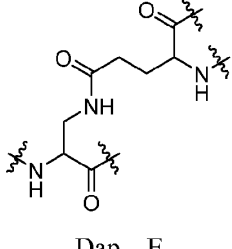
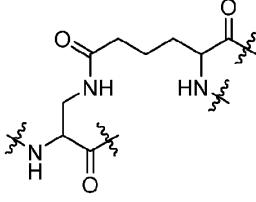
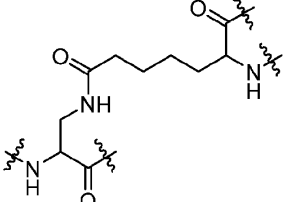
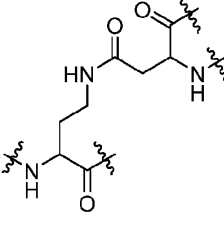
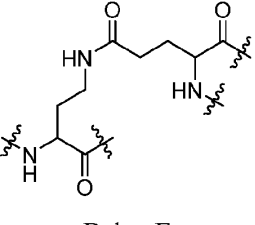
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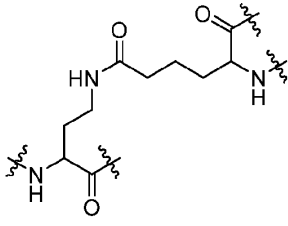
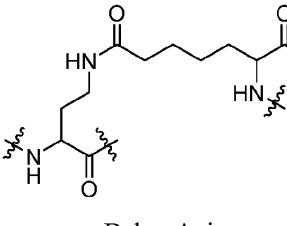
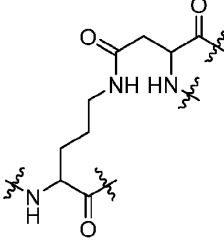
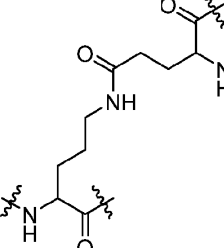
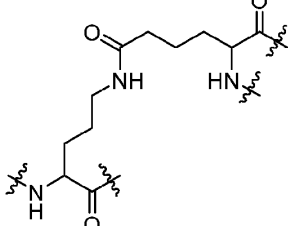
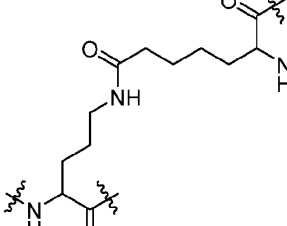
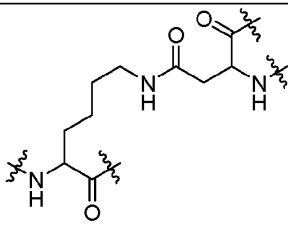
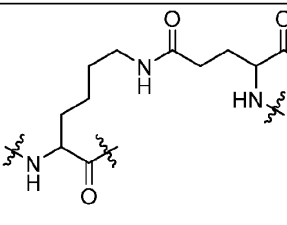
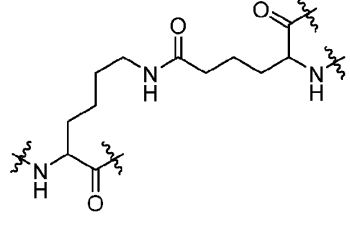
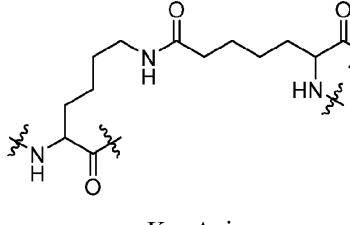
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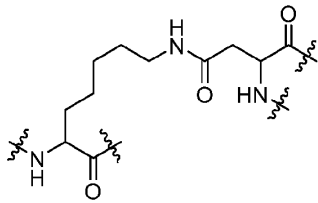
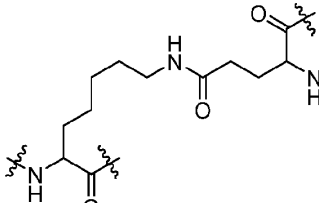
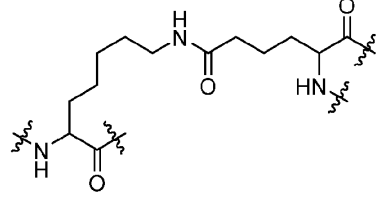
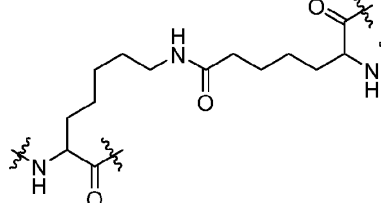
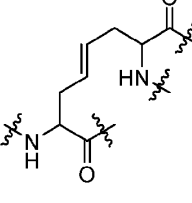
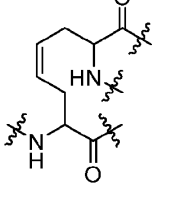
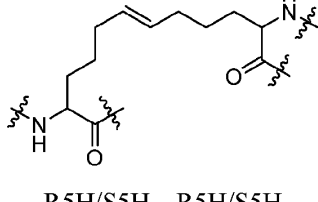
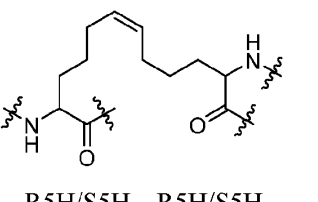
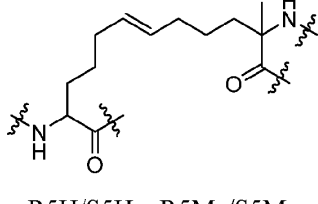
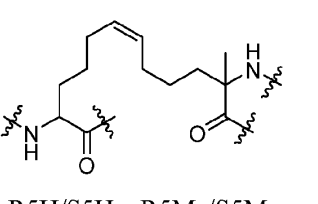
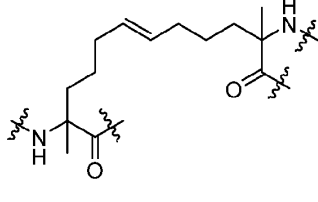
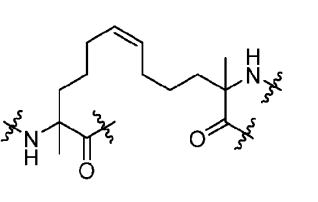
In some embodiments, the first ring comprises a linkage between two amino acids having a structure selected from the following:

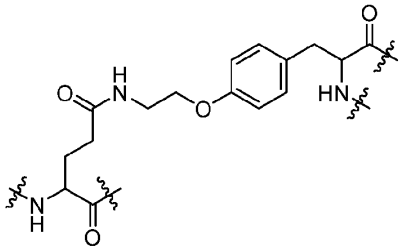
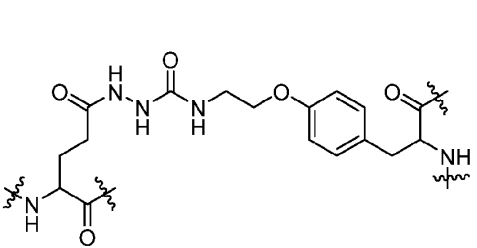
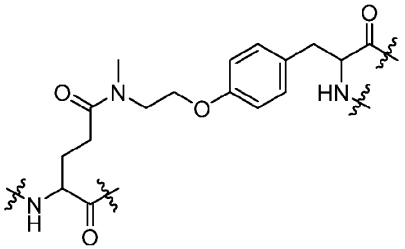
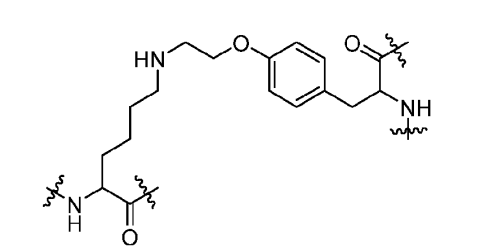
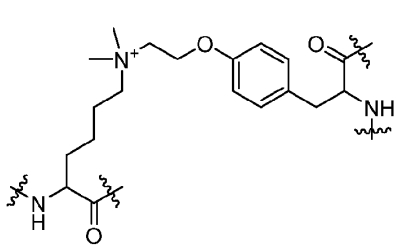
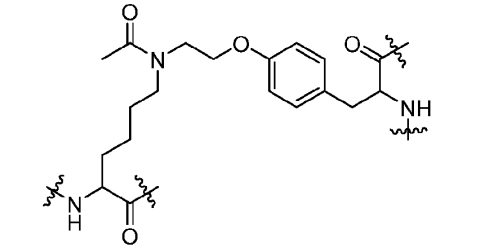
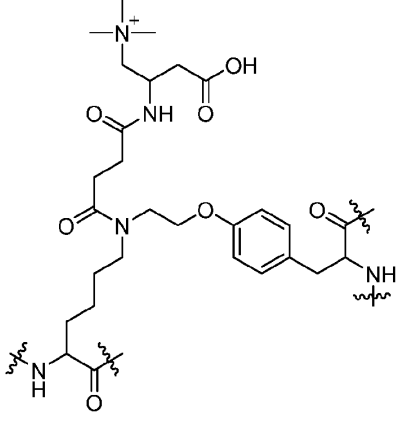
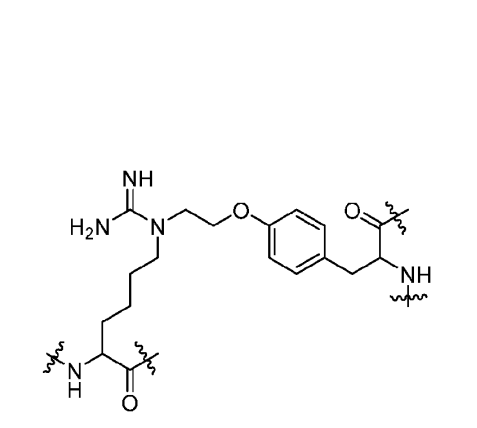


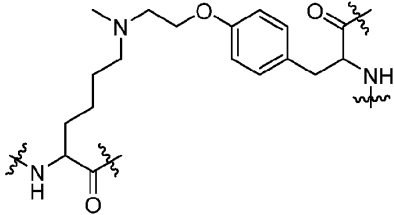
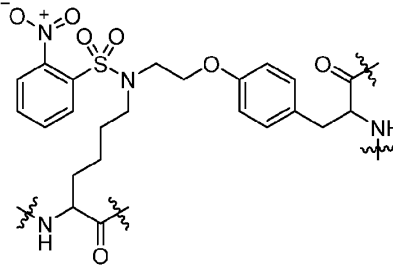
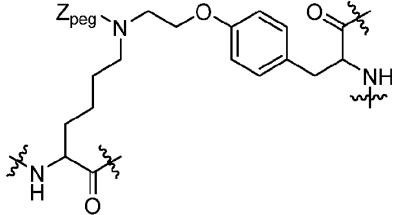
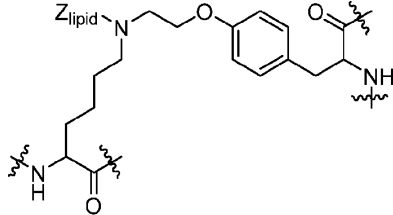
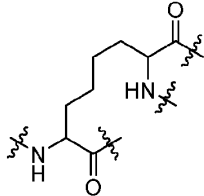
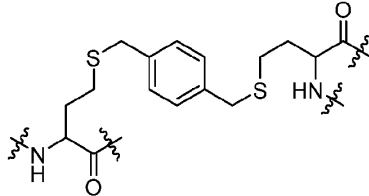
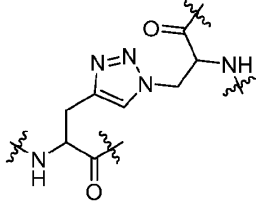
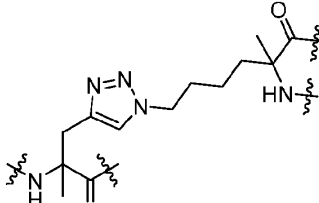
 Abu – Pen	 C – C
 C – aMeC	 C – Pen
 Pen – aMeC	 Pen – Pen
 aMeC – C	 aMeC – aMeC
 Pen(oXyl) – Pen	 Pen(mXyl) – Pen

 Pen(pXyl) – Pen	 4AminoPro – D
 4AminoPro – E	 4AminoPro – hE
 Dap – D	 Dap – E
 Dap – hE	 Dap – Api
 Dab – D	 Dab – E

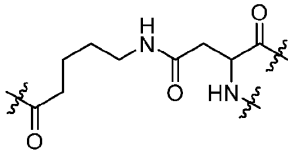
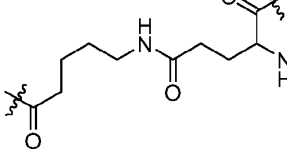
 Dab – hE	 Dab – Api
 Orn – D	 Orn – E
 Orn – hE	 Orn – Api
 K – D	 K – E
 K – hE	 K – Api

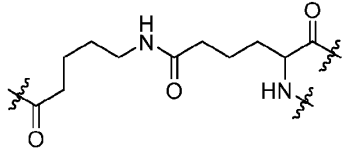
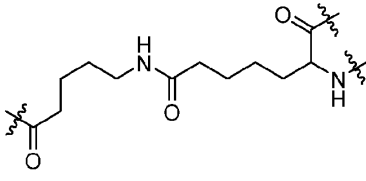
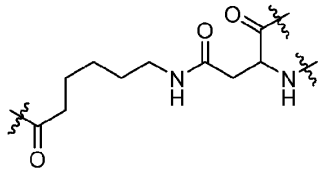
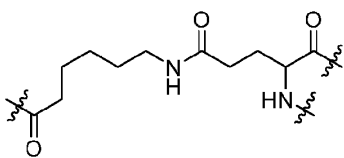
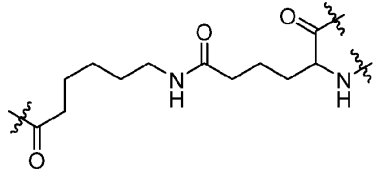
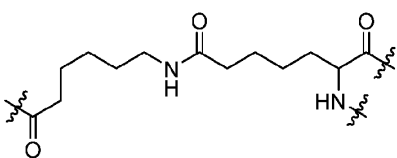
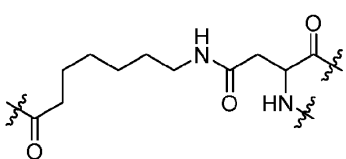
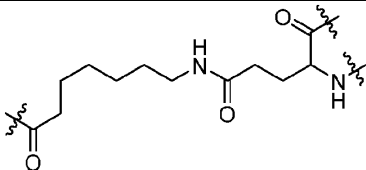
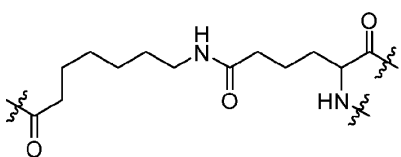
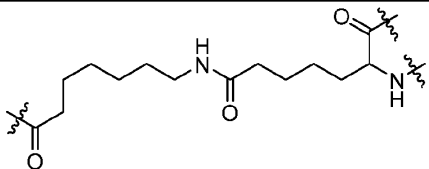
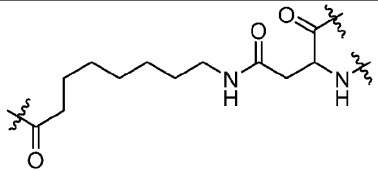
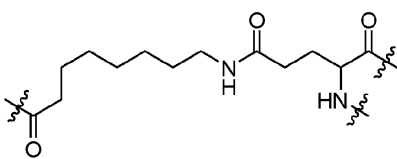
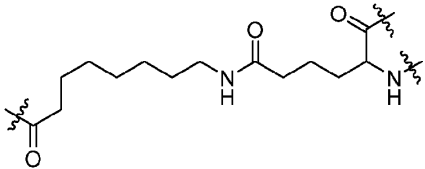
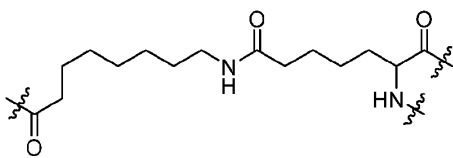
 hK - D	 hK - E
 hK - hE	 hK - Api
 aG - aG	 aG - aG.
 R5H/S5H - R5H/S5H	 R5H/S5H - R5H/S5H
 R5H/S5H - R5Me/S5Me	 R5H/S5H - R5Me/S5Me
 R5Me/S5Me - R5Me/S5Me	 R5Me/S5Me - R5Me/S5Me

 E – AEF	 E – AEF
 E – AEF(NMe)	 K – AEF
 K(a) – AEF	 K(Ac) – AEF
 K(d) – AEF	 K(G) – AEF

 K(NMe) – AEF	 K(NNs) – AEF
 K-Z_{peg} – AEF	 K-Z_{lipid} – AEF.
 hA – hA	 hC(pXyl) – hC
 Pra – Dap(N3)	 aMePra – aMeK(N3)

In some embodiments, the first ring comprises a linkage between the N-terminus of the peptide and an amino acid and has a structure selected from the following:

 5Ava – D	 5Ava – E
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 5Ava – hE	 5Ava – Api
 6Ahx – D	 6Ahx – E
 6Ahx – hE	 6Ahx – Api
 7Ahp – D	 7Ahp – E
 7Ahp – hE	 7Ahp – Api
 8Aoc – D	 8Aoc – E
 8Aoc – hE	 8Aoc – Api

8Aoc – hE	8Aoc – Api
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In some embodiments, the first ring is formed between X₄ and X₉, X₄ and X₁₃, X₅ and X₁₀, X₃ and X₁₃, or X₆ and X₉. In some embodiments, the first ring is formed between X₄ and X₉, X₄ and X₁₃, X₅ and X₁₀, X₃ and X₁₃, or X₆ and X₉ via a linker having one or more groups selected from the group consisting of a disulfide, thioether, amide, olefin, ether, alkylene, and triazole. In some embodiments, the first ring is formed between X₄ and X₉, X₄ and X₁₃, X₅ and X₁₀, X₃ and X₁₃, or X₆ and X₉ via a linker selected from the group consisting of a disulfide, thioether, amide, olefin, and triazole.

In some embodiments, the first ring is formed between X₄ and X₉, X₄ and X₁₃, or X₆ and X₉. In some embodiments, the first ring is formed between X₄ and X₉, X₄ and X₁₃, or X₆ and X₉ via a linker having one or more groups selected from the group consisting of a disulfide, thioether, amide, olefin, ether, alkylene, and triazole. In some embodiments, the first ring is formed between X₄ and X₉, X₄ and X₁₃, or X₆ and X₉ via a linker selected from the group consisting of a disulfide, thioether, amide, olefin, and triazole.

In some embodiments, the first ring is formed between X₄ and X₉. In some embodiments, the first ring is formed between X₄ and X₉ via a linker having one or more groups selected from the group consisting of a disulfide, thioether, amide, olefin, ether, alkylene, and triazole. In some embodiments, the first ring is formed between X₄ and X₉ via a linker selected from the group consisting of a disulfide, thioether, amide, olefin, and triazole.

In some embodiments, the first ring is formed between X₄ and X₁₃. In some embodiments, the first ring is formed between X₄ and X₁₃ via a linker having one or more groups selected from the group consisting of a disulfide, thioether, amide, olefin, ether, alkylene, and triazole. In some embodiments, the first ring is formed between X₄ and X₁₃ via a linker selected from the group consisting of a disulfide, thioether, amide, olefin, and triazole.

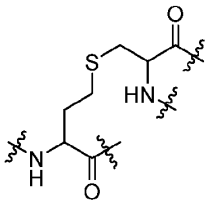
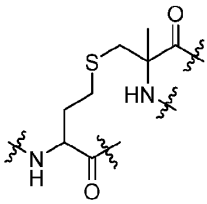
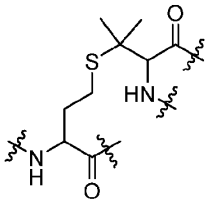
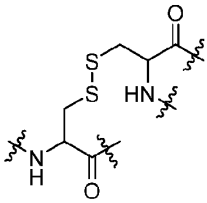
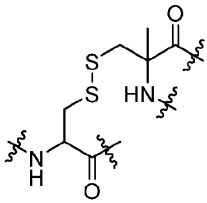
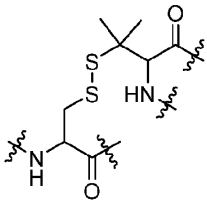
In some embodiments, the first ring is formed between X₅ and X₁₀. In some embodiments, the first ring is formed between X₅ and X₁₀ via a linker having one or more groups selected from the group consisting of a disulfide, thioether, amide, olefin, ether, alkylene, and triazole. In some embodiments, the first ring is formed between X₅ and X₁₀ via a linker selected from the group consisting of a disulfide, thioether, amide, olefin, and triazole.

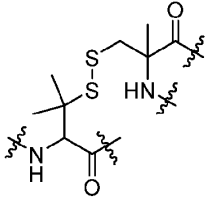
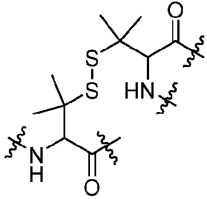
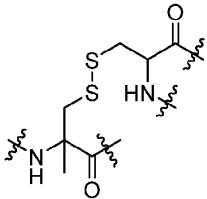
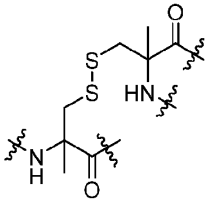
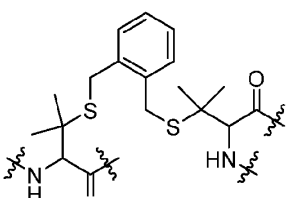
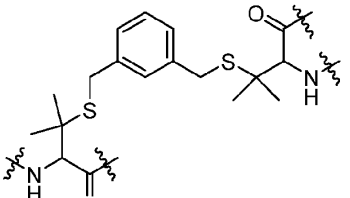
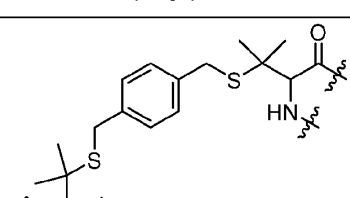
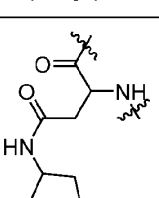
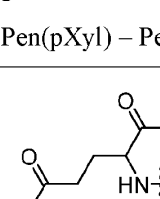
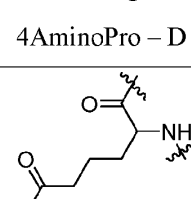
In some embodiments, the first ring is formed between X₃ and X₁₃. In some embodiments, the first ring is formed between X₃ and X₁₃ via a linker having one or more groups selected from the group consisting of a disulfide, thioether, amide, olefin, ether, alkylene, and triazole. In some embodiments, the first ring is formed between X₃ and X₁₃ via a linker selected from the group consisting of a disulfide, thioether, amide, olefin, and triazole.

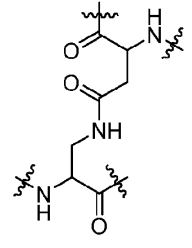
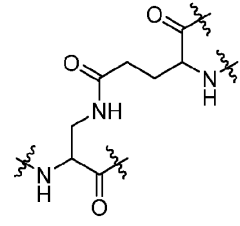
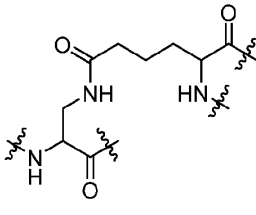
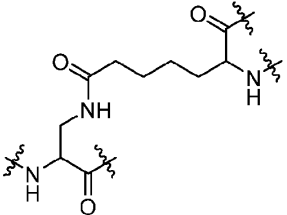
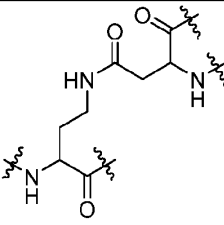
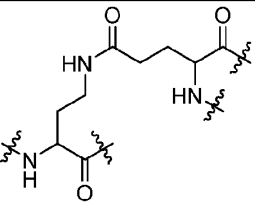
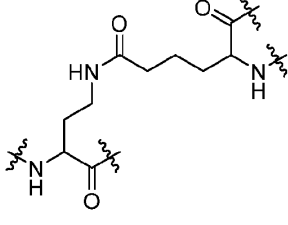
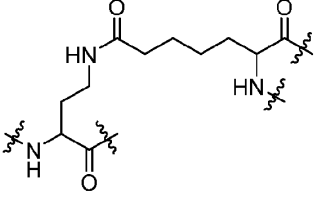
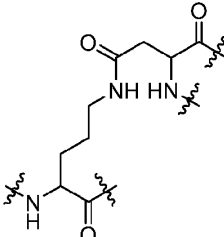
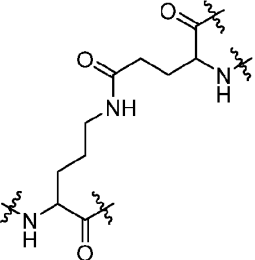
In some embodiments, the first ring is formed between X₆ and X₉. In some embodiments, the first ring is formed between X₆ and X₉ via a linker having one or more groups selected from the group consisting of a disulfide, thioether, amide, olefin, ether, alkylene, and triazole. In some embodiments, the first ring is formed between X₆ and X₉ via a linker selected from the group consisting of a disulfide, thioether, amide, olefin, and triazole.

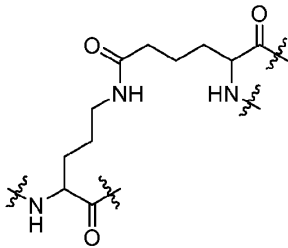
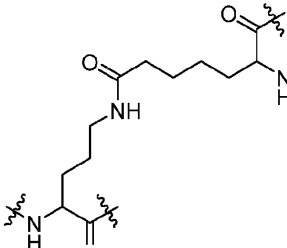
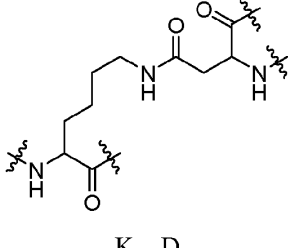
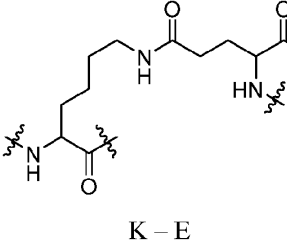
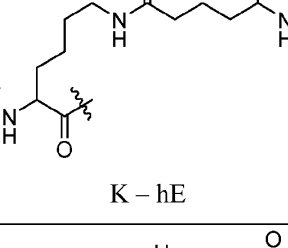
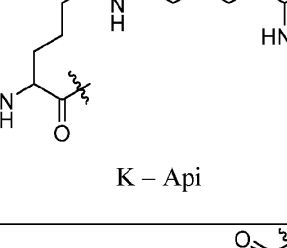
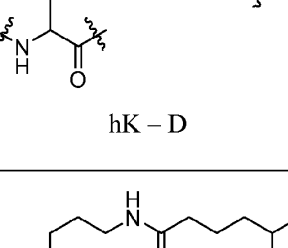
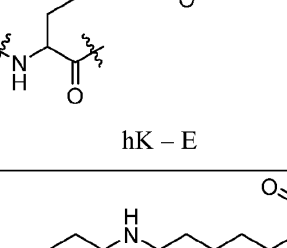
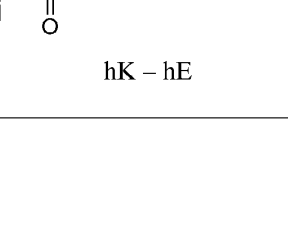
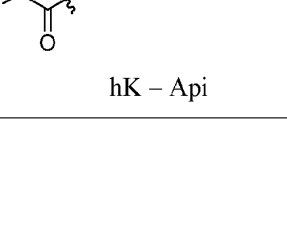
In some embodiments, the peptide is further cyclized to form a second ring, wherein the second ring comprises 3 to 14 amino acids. In some embodiments, the peptide is further cyclized to form a second ring, wherein the second ring comprises 4-11 or 14 amino acids. In some embodiments, the second ring comprises 4-9 or 11 amino acids. In some embodiments, the second ring comprises 4, 6, 10 or 11 amino acids. In some embodiments, the second ring comprises 4 amino acids. In some embodiments, the second ring comprises 5 amino acids. In some embodiments, the second ring comprises 6 amino acids. In some embodiments, the second ring comprises 7 amino acids. In some embodiments, the second ring comprises 8 amino acids. In some embodiments, the second ring comprises 9 amino acids. In some embodiments, the second ring comprises 10 amino acids. In some embodiments, the second ring comprises 11 amino acids. In some embodiments, the second ring comprises 14 amino acids.

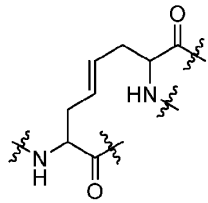
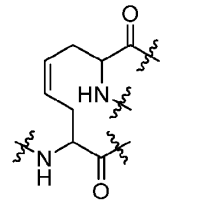
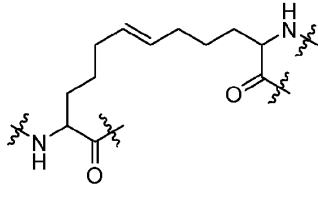
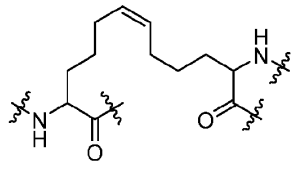
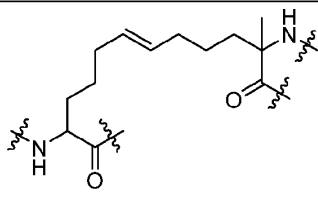
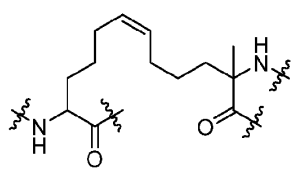
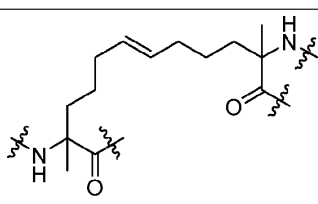
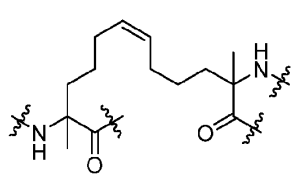
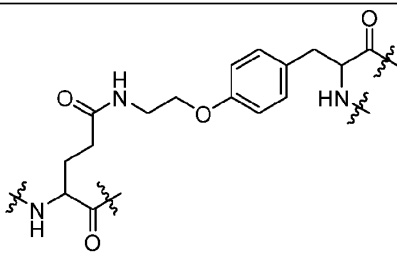
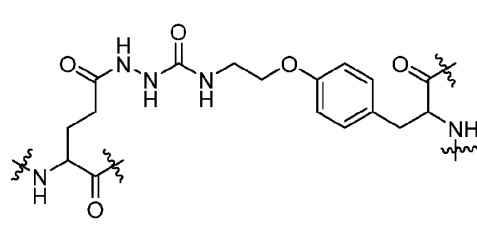
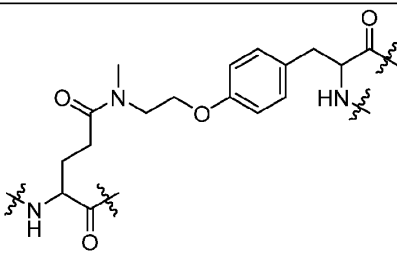
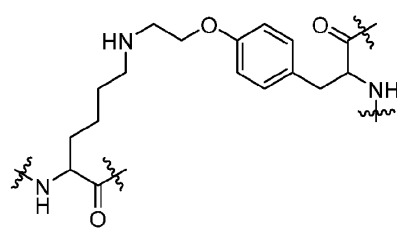
In some embodiments, the second ring comprises a linkage between two amino acids having a structure selected from the following:

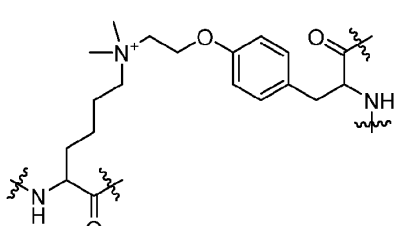
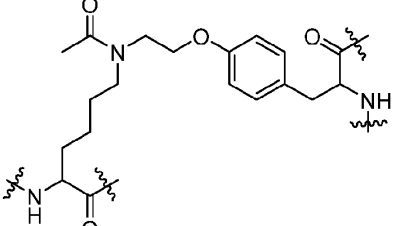
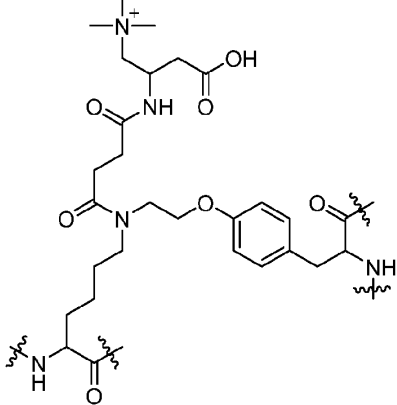
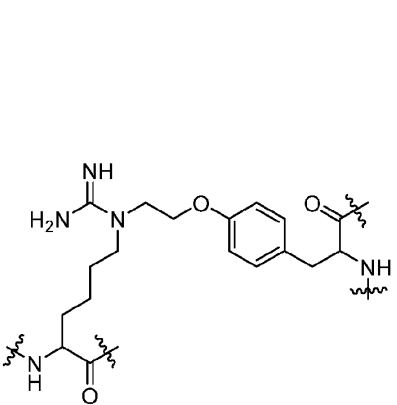
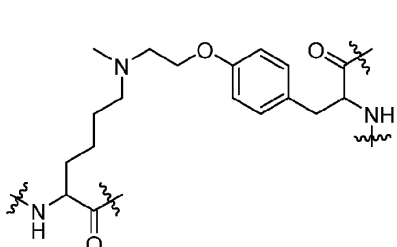
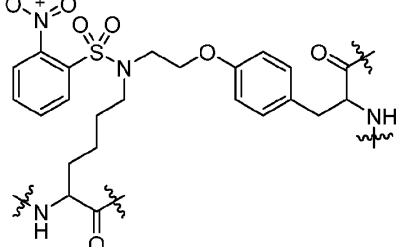
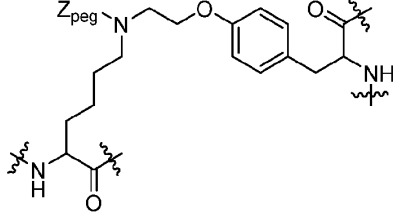
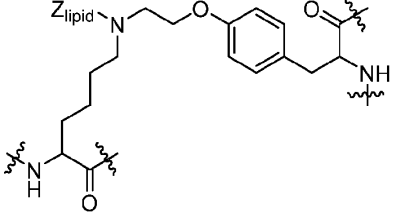
 Abu – C	 Abu – aMeC
 Abu – Pen	 C – C
	

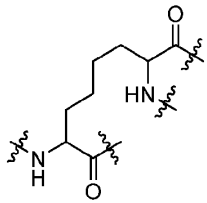
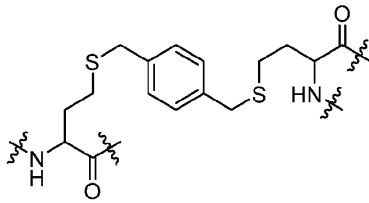
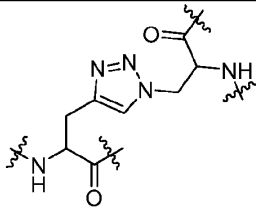
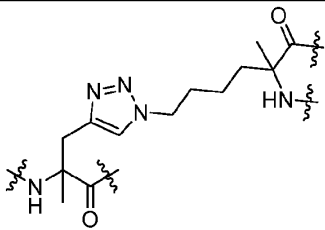
C – aMeC	C – Pen
 Pen – aMeC	 Pen – Pen
 aMeC – C	 aMeC – aMeC
 Pen(oXyl) – Pen	 Pen(mXyl) – Pen
 Pen(pXyl) – Pen	 4AminoPro – D
 4AminoPro – E	 4AminoPro – hE

 Dap – D	 Dap – E
 Dap – hE	 Dap – Api
 Dab – D	 Dab – E
 Dab – hE	 Dab – Api
 Orn – D	 Orn – E

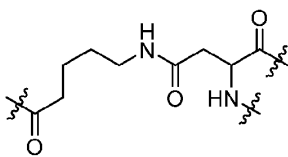
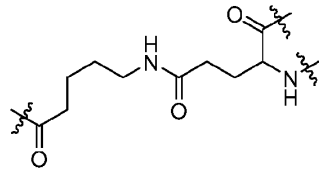
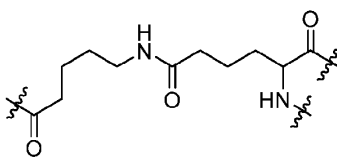
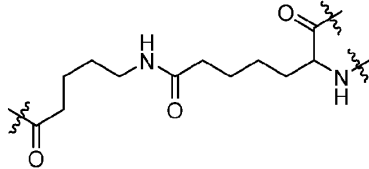
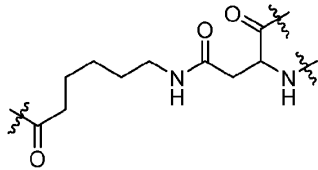
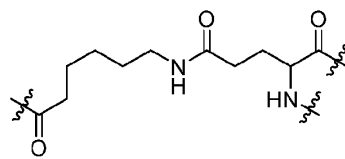
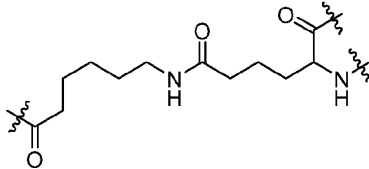
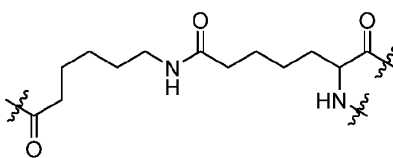
 Orn – hE	 Orn – Api
 K – D	 K – E
 K – hE	 K – Api
 hK – D	 hK – E
 hK – hE	 hK – Api

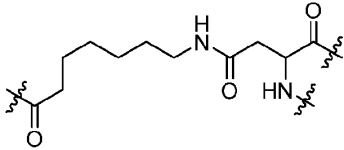
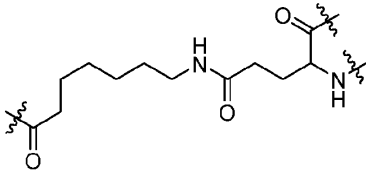
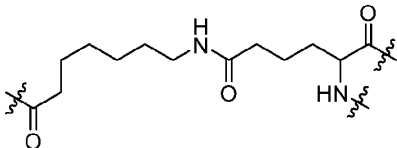
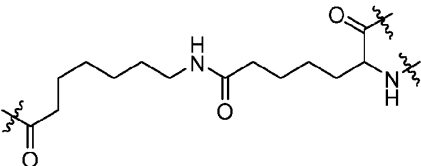
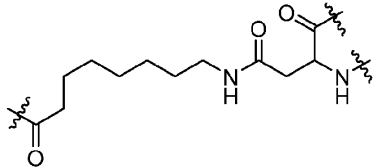
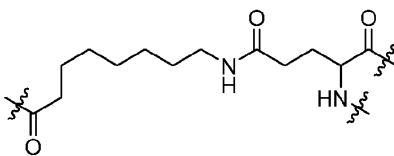
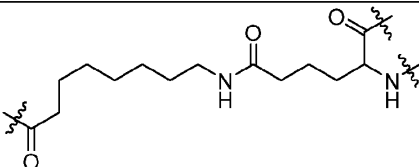
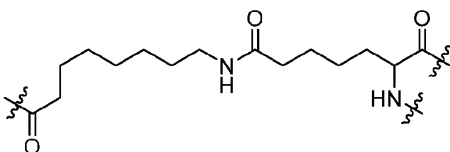
 aG - aG	 aG - aG.
 R5H/S5H - R5H/S5H	 R5H/S5H - R5H/S5H
 R5H/S5H - R5Me/S5Me	 R5H/S5H - R5Me/S5Me
 R5Me/S5Me - R5Me/S5Me	 R5Me/S5Me - R5Me/S5Me
 E - AEF	 E - AEF
 E - AEF	 E - AEF

E – AEF(NMe)	K – AEF
 K(a) – AEF	 K(Ac) – AEF
 K(d) – AEF	 K(G) – AEF
 K(NMe) – AEF	 K(NNs) – AEF
 K-Z_{peg} – AEF	 K-Z_{lipid} – AEF.

 hA – hA	 hC(pXyl) – hC
 Pra – Dap(N3)	 aMePra – aMeK(N3)

In some embodiments, the second ring comprises a linkage between the N-terminus of the peptide and an amino acid and has a structure selected from the following:

 5Ava – D	 5Ava – E
 5Ava – hE	 5Ava – Api
 6Ahx – D	 6Ahx – E
 6Ahx – hE	 6Ahx – Api

 7Ahp – D	 7Ahp – E
 7Ahp – hE	 7Ahp – Api
 8Aoc – D	 8Aoc – E
 8Aoc – hE	 8Aoc – Api

In some embodiments, the second ring is formed between X₄ and X₉, X₄ and X₁₃, X₅ and X₁₀, X₃ and X₁₃, or X₆ and X₉. In some embodiments, the second ring is formed between X₄ and X₉, X₄ and X₁₃, X₅ and X₁₀, X₃ and X₁₃, or X₆ and X₉ via a linker having one or more groups selected from the group consisting of a disulfide, thioether, amide, olefin, ether, alkylene, and triazole. In some embodiments, the second ring is formed between X₄ and X₉, X₄ and X₁₃, X₅ and X₁₀, X₃ and X₁₃, or X₆ and X₉ via a linker selected from the group consisting of a disulfide, thioether, amide, olefin, and triazole.

In some embodiments, the second ring is formed between X₅ and X₁₀ or X₃ and X₁₃. In some embodiments, the second ring is formed between X₅ and X₁₀ or X₃ and X₁₃ via a linker having one or more groups selected from the group consisting of a disulfide, thioether, amide, olefin, ether, alkylene, and triazole. In some embodiments, the second ring is formed between X₅ and X₁₀ or X₃ and X₁₃ via a linker having one or more groups selected from the group consisting of a disulfide, thioether, amide, olefin, and triazole. In some embodiments, the second ring is

formed between X₅ and X₁₀ or X₃ and X₁₃ via a linker selected from the group consisting of a disulfide, thioether, amide, olefin, and triazole.

In some embodiments, the second ring is formed between X₄ and X₉. In some
embodiments, the second ring is formed between X₄ and X₉ via a linker having one or more
5 groups selected from the group consisting of a disulfide, thioether, amide, olefin, ether, alkylene,
and triazole. In some embodiments, the second ring is formed between X₄ and X₉ via a linker
selected from the group consisting of a disulfide, thioether, amide, olefin, and triazole.

In some embodiments, the second ring is formed between X₄ and X₁₃. In some
embodiments, the second ring is formed between X₄ and X₁₃ via a linker having one or more
10 groups selected from the group consisting of a disulfide, thioether, amide, olefin, ether, alkylene,
and triazole. In some embodiments, the second ring is formed between X₄ and X₁₃ via a linker
selected from the group consisting of a disulfide, thioether, amide, olefin, and triazole.

In some embodiments, the second ring is formed between X₅ and X₁₀. In some
embodiments, the second ring is formed between X₅ and X₁₀ via a linker having one or more
15 groups selected from the group consisting of a disulfide, thioether, amide, olefin, ether, alkylene,
and triazole. In some embodiments, the second ring is formed between X₅ and X₁₀ via a linker
selected from the group consisting of a disulfide, thioether, amide, olefin, and triazole.

In some embodiments, the second ring is formed between X₃ and X₁₃. In some
embodiments, the second ring is formed between X₃ and X₁₃ via a linker having one or more
20 groups selected from the group consisting of a disulfide, thioether, amide, olefin, ether, alkylene,
and triazole. In some embodiments, the second ring is formed between X₃ and X₁₃ via a linker
selected from the group consisting of a disulfide, thioether, amide, olefin, and triazole.

In some embodiments, the second ring is formed between X₆ and X₉. In some
embodiments, the second ring is formed between X₆ and X₉ via a linker having one or more
25 groups selected from the group consisting of a disulfide, thioether, amide, olefin, ether, alkylene,
and triazole. In some embodiments, the second ring is formed between X₆ and X₉ via a linker
selected from the group consisting of a disulfide, thioether, amide, olefin, and triazole.

In some embodiments, the second ring is formed between X₁₃ and the N-terminus of the
peptide. In some embodiments, the second ring is formed between X₁₃ and the N-terminus of the
30 peptide via a linker having one or more groups selected from the group consisting of a disulfide,
thioether, amide, olefin, ether, alkylene, and triazole. In some embodiments, the second ring is
formed between X₁₃ and the N-terminus of the peptide via a linker selected from the group
consisting of a disulfide, thioether, amide, olefin, and triazole.

In some embodiments, the first ring is formed between X₄ and X₉ via a linker having one
35 or more groups selected from the group consisting of a disulfide, thioether, amide, olefin, ether,

alkylene, and triazole; and the second ring is formed between X₃ and X₁₃, between X₅ and X₁₀, between X₁₀ and X₁₃, or between X₁₃ and the N-terminus of the peptide via a linker having one or more groups selected from the group consisting of a disulfide, thioether, amide, olefin, ether, alkylene, and triazole.

5 In some embodiments, the first ring is formed between X₄ and X₉ via a linker selected from the group consisting of a disulfide, thioether, amide, olefin, and triazole; and the second ring is formed between X₃ and X₁₃, between X₅ and X₁₀, between X₁₀ and X₁₃, or between X₁₃ and the N-terminus of the peptide via a linker selected from the group consisting of a disulfide, thioether, amide, olefin, and triazole.

10 In some embodiments, the first ring is formed between X₄ and X₁₃ via a linker having one or more groups selected from the group consisting of a disulfide, thioether, amide, olefin, ether, alkylene, and triazole; and the second ring is formed between X₅ and X₁₀ or between X₆ and X₉ via a linker having one or more groups selected from the group consisting of a disulfide, thioether, amide, olefin, ether, alkylene, and triazole.

15 In some embodiments, the first ring is formed between X₄ and X₁₃ via a linker selected from the group consisting of a disulfide, thioether, amide, olefin, and triazole; and the second ring is formed between X₅ and X₁₀ or between X₆ and X₉ via a linker selected from the group consisting of a disulfide, thioether, amide, olefin, and triazole.

20 In some embodiments, the first ring is formed between X₆ and X₉ via a linker having one or more groups selected from the group consisting of a disulfide, thioether, amide, olefin, ether, alkylene, and triazole; and the second ring is formed between X₃ and X₁₃, between X₄ and X₁₃, between X₅ and X₁₀, between X₁₀ and X₁₃, or between X₁₃ and the N-terminus of the peptide via a linker having one or more groups selected from the group consisting of a disulfide, thioether, amide, olefin, ether, alkylene, and triazole.

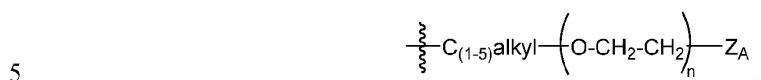
25 In some embodiments, the first ring is formed between X₆ and X₉ via a linker selected from the group consisting of a disulfide, thioether, amide, olefin, and triazole; and the second ring is formed between X₃ and X₁₃, between X₄ and X₁₃, between X₅ and X₁₀, between X₁₀ and X₁₃, or between X₁₃ and the N-terminus of the peptide via a linker selected from the group consisting of a disulfide, thioether, amide, olefin, and triazole.

30 In some embodiments, the peptide comprises at least one polyethylene glycol chain. In some embodiments, the peptide comprises no more than five, no more than four, no more than three, no more than two, or no more than one polyethylene glycol chain.

In some embodiments, each polyethylene glycol chain, independently, terminates in an ammonium group of a methyl group. In some embodiments, the polyethylene glycol chain

terminates in an ammonium group. In some embodiments, the polyethylene glycol chain terminates in a methyl group.

In some embodiments, the peptide comprises a polyethylene glycol chain having the following structure:

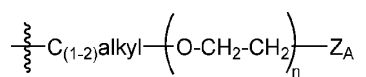


wherein:

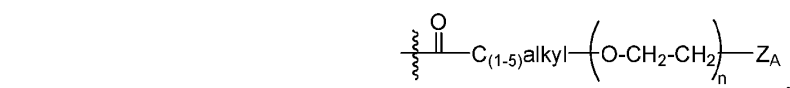
Z_A is $-\text{OCH}_3$ or $-\text{N}^+(\text{CH}_3)_3$; and

n is an integer from 2 to 24.

10 In some embodiments, the peptide comprises a polyethylene glycol chain having the following structure:



In some embodiments, the peptide comprises a polyethylene glycol chain having the following structure:

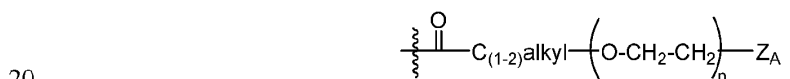


wherein:

Z_A is $-\text{OCH}_3$ or $-\text{N}^+(\text{CH}_3)_3$; and

n is an integer from 2 to 24.

In some embodiments, the peptide comprises a polyethylene glycol chain having the following structure:



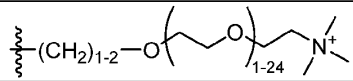
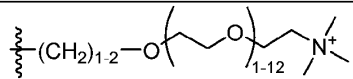
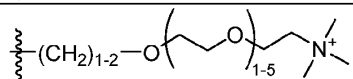
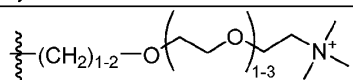
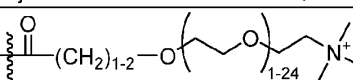
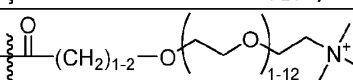
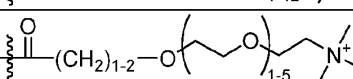
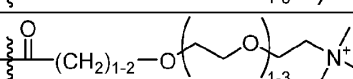
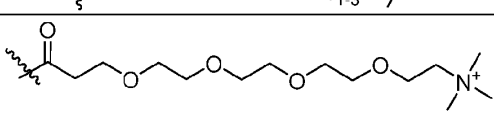
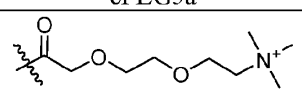
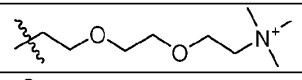
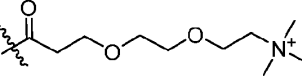
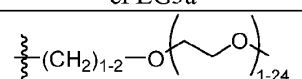
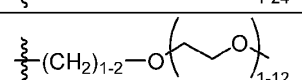
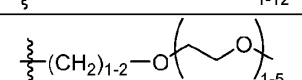
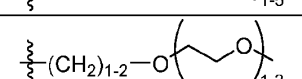
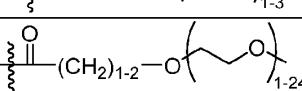
In some embodiments, Z_A is $-\text{OCH}_3$. In some embodiments, Z_A is $-\text{N}^+(\text{CH}_3)_3$.

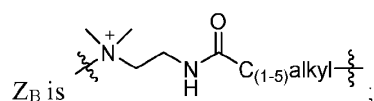
In some embodiments, n is an integer from 2 to 15. In some embodiments, n is an integer from 2 to 5. 2. In some embodiments, n is 2. In some embodiments, n is 3. In some embodiments, n is 4. In some embodiments, n is 5. In some embodiments, n is 6. In some
25 embodiments, n is 7. In some embodiments, n is 8. In some embodiments, n is 9. In some embodiments, n is 10. In some embodiments, n is 11. In some embodiments, n is 12. In some embodiments, n is 14. In some embodiments, n is 14. In some embodiments, n is 15.

In some embodiments, R_1 , R_2 , or any amino acid of the peptide is conjugated to a polyethylene glycol chain.

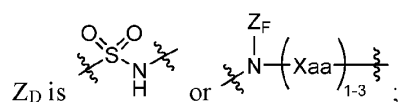
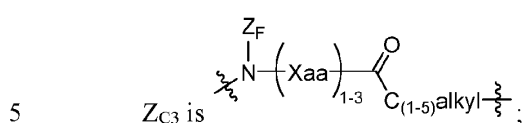
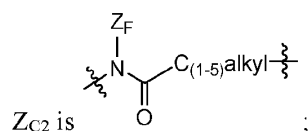
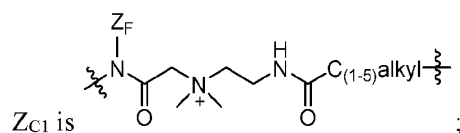
30 Non-limiting examples of polyethylene glycol chains are provided in Table 2.

Table 2. Exemplary polyethylene glycol chains









 cPEG5a


 cPEG3a








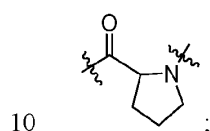
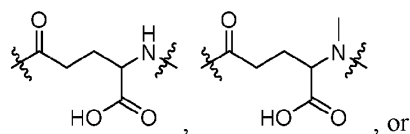
Z_C is Z_{C1} , Z_{C2} , or Z_{C3} ;



Z_E is -H, -COOH, or tetrazolyl;

Z_F is -H or -CH₃;

Xaa is, independently for each occurrence,



p, independently for each occurrence, is 1, 2, 3, 4, 5, or 6;

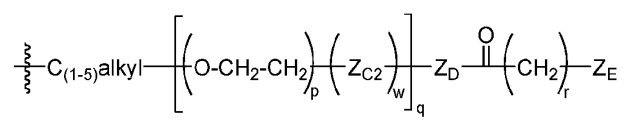
q is 1, 2, 3, 4, 5, or 6;

r is an integer from 6 to 24;

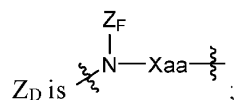
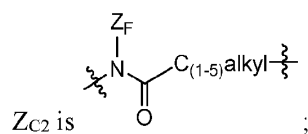
v is 0 or 1; and

15 w, independently for each occurrence, is 0 or 1.

In some embodiments, the peptide comprises a lipophilic substituent having the following structure:

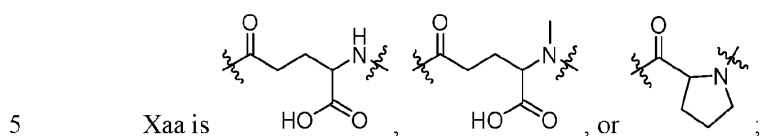


wherein:



Z_E is -H, -COOH, or tetrazolyl;

Z_F is -H or -CH₃;



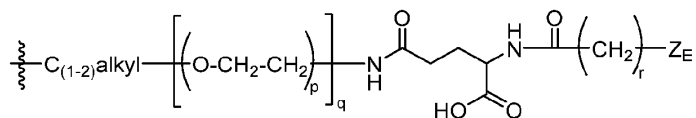
p, independently for each occurrence, is 1, 2, 3, 4, 5, or 6;

q is 1, 2, 3, 4, 5, or 6;

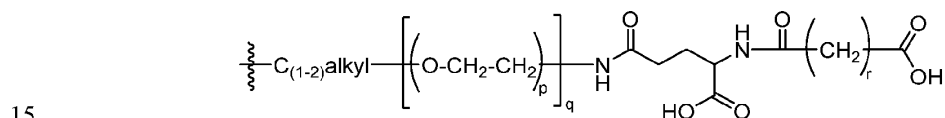
r is an integer from 6 to 24; and

w, independently for each occurrence, is 0 or 1.

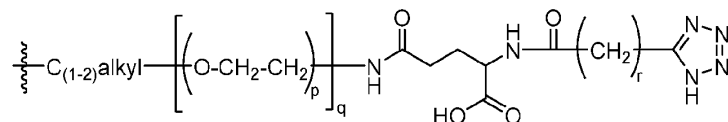
10 In some embodiments, the peptide comprises a lipophilic substituent having the following structure:



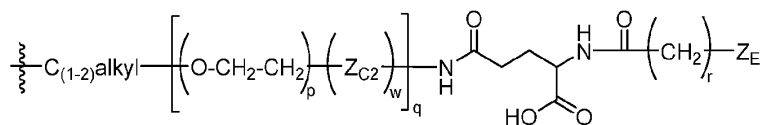
In some embodiments, the peptide comprises a lipophilic substituent having the following structure:



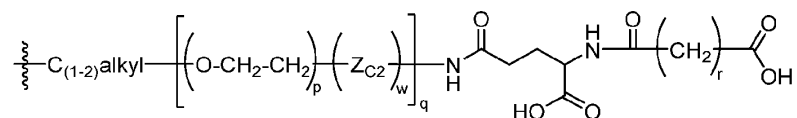
In some embodiments, the peptide comprises a lipophilic substituent having the following structure:



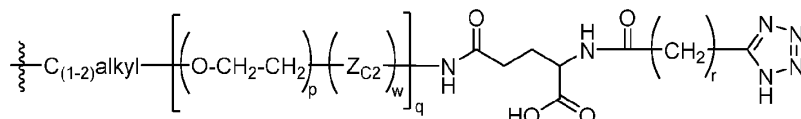
20 In some embodiments, the peptide comprises a lipophilic substituent having the following structure:



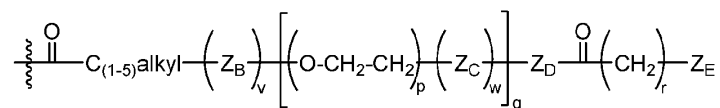
In some embodiments, the peptide comprises a lipophilic substituent having the following structure:



In some embodiments, the peptide comprises a lipophilic substituent having the following structure:

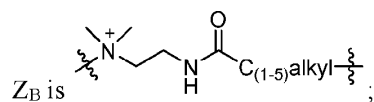


In some embodiments, the peptide comprises a lipophilic substituent having the following structure:

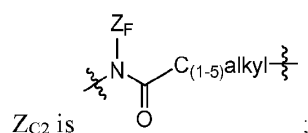
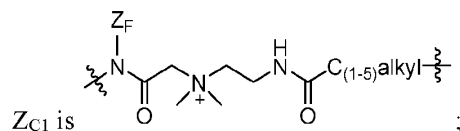


10

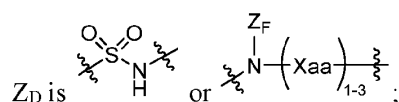
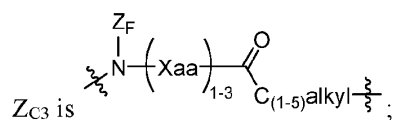
wherein:



Z_C is Z_{C1}, Z_{C2}, or Z_{C3};

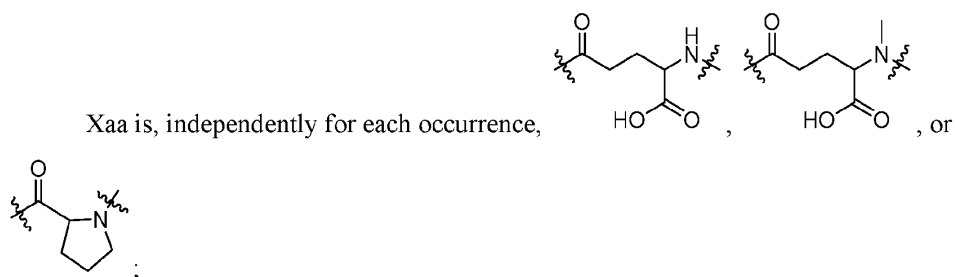


15



Z_E is -H, -COOH, or tetrazolyl;

Z_F is -H or -CH₃;



p, independently for each occurrence, is 1, 2, 3, 4, 5, or 6;

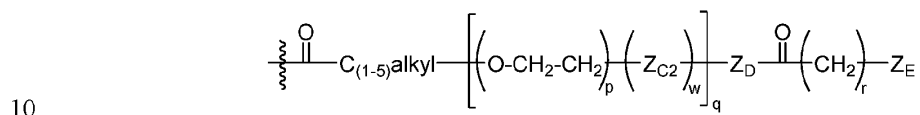
q is 1, 2, 3, 4, 5, or 6;

5 r is an integer from 6 to 24;

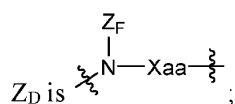
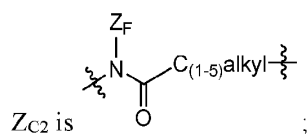
v is 0 or 1; and

w, independently for each occurrence, is 0 or 1.

In some embodiments, the peptide comprises a lipophilic substituent having the following structure:

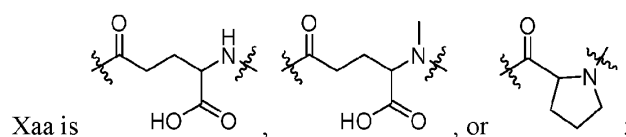


wherein:



ZE is -H, -COOH, or tetrazolyl;

15 ZF is -H or -CH3;



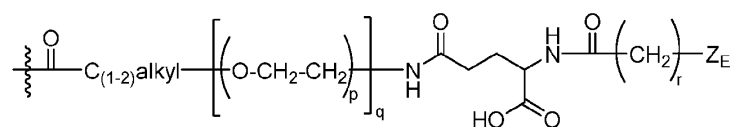
p, independently for each occurrence, is 1, 2, 3, 4, 5, or 6;

q is 1, 2, 3, 4, 5, or 6;

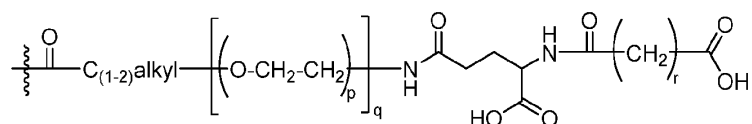
r is an integer from 6 to 24; and

20 w, independently for each occurrence, is 0 or 1.

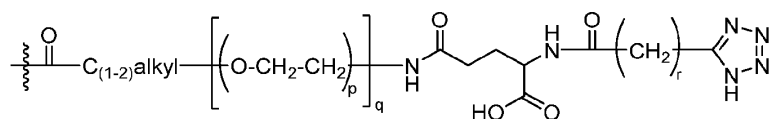
In some embodiments, the peptide comprises a lipophilic substituent having the following structure:



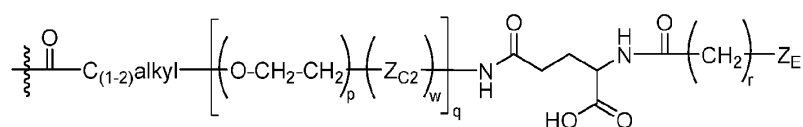
In some embodiments, the peptide comprises a lipophilic substituent having the following structure:



5 In some embodiments, the peptide comprises a lipophilic substituent having the following structure:

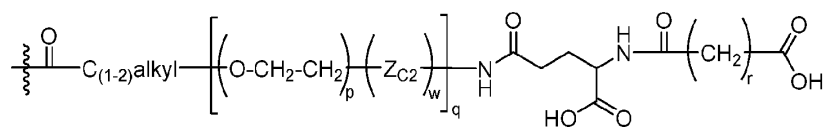


In some embodiments, the peptide comprises a lipophilic substituent having the following structure:

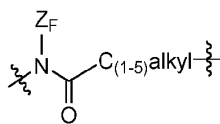
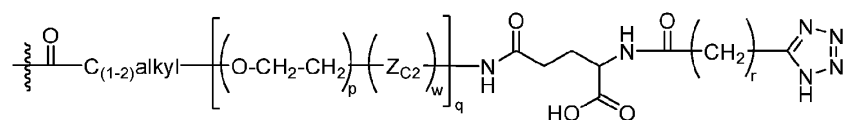


10

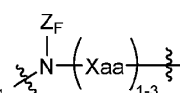
In some embodiments, the peptide comprises a lipophilic substituent having the following structure:



15 In some embodiments, the peptide comprises a lipophilic substituent having the following structure:



In some embodiments, Z_C is

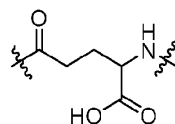


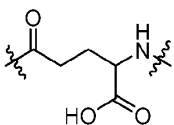
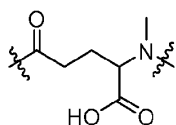
In some embodiments, Z_D is



In some embodiments, Z_E is -H. In some embodiments, Z_E is -COOH. In some embodiments, Z_E is tetrazolyl.

In some embodiments, Z_F is -H. In some embodiments, Z_F is -CH₃.

5 In some embodiments, Xaa is, independently for each occurrence,  or



In some embodiments, Xaa is

In some embodiments, p is 1, 2, 3, or 4. In some embodiments, p is 1. In some
embodiments, p is 2. In some embodiments, p is 3. In some embodiments, p is 4. In some
10 embodiments, p is 5. In some embodiments, p is 6.

In some embodiments, q is 1, 2, 3, or 4. In some embodiments, q is 1. In some
embodiments, q is 2. In some embodiments, q is 3. In some embodiments, q is 4. In some
embodiments, q is 5. In some embodiments, q is 6.

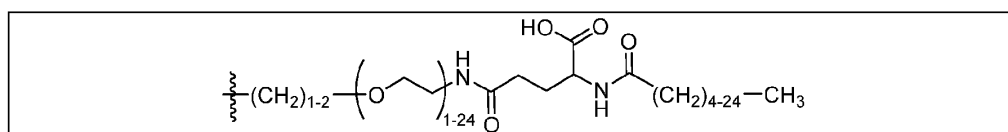
In some embodiments, r is an integer between 10 and 20. In some embodiments, r is 10.
15 In some embodiments, r is 11. In some embodiments, r is 12. In some embodiments, r is 13. In
some embodiments, r is 14. In some embodiments, r is 15. In some embodiments, r is 16. In
some embodiments, r is 17. In some embodiments, r is 18. In some embodiments, r is 19. In
some embodiments, r is 20.

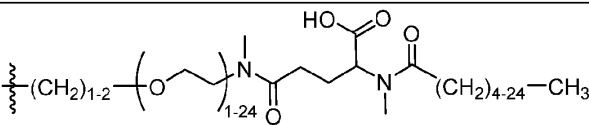
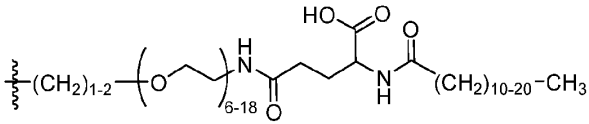
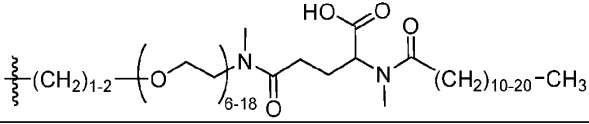
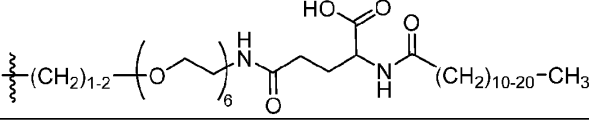
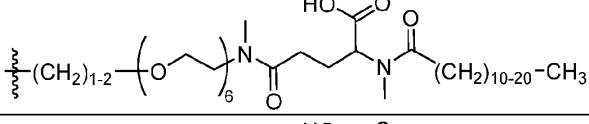
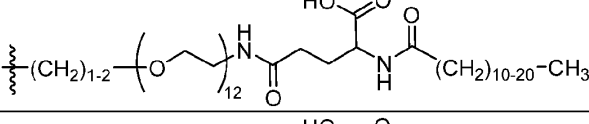
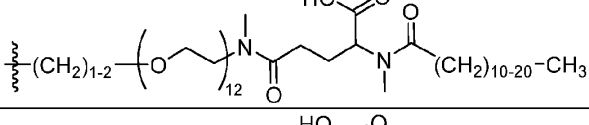
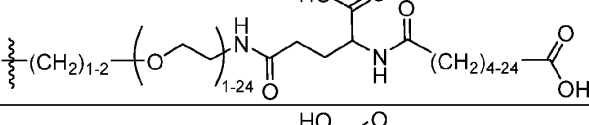
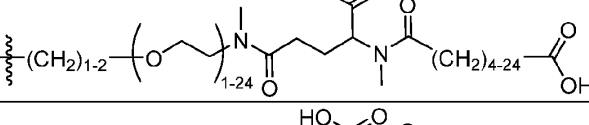
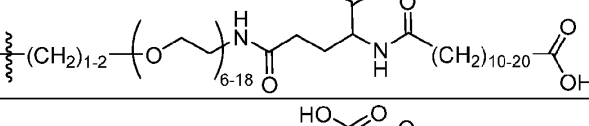
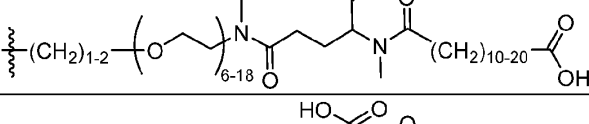
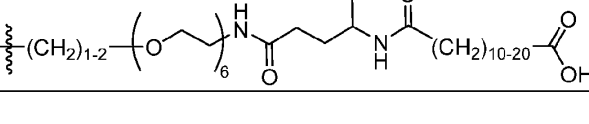
In some embodiments, w is 0. In some embodiments, w is 1.

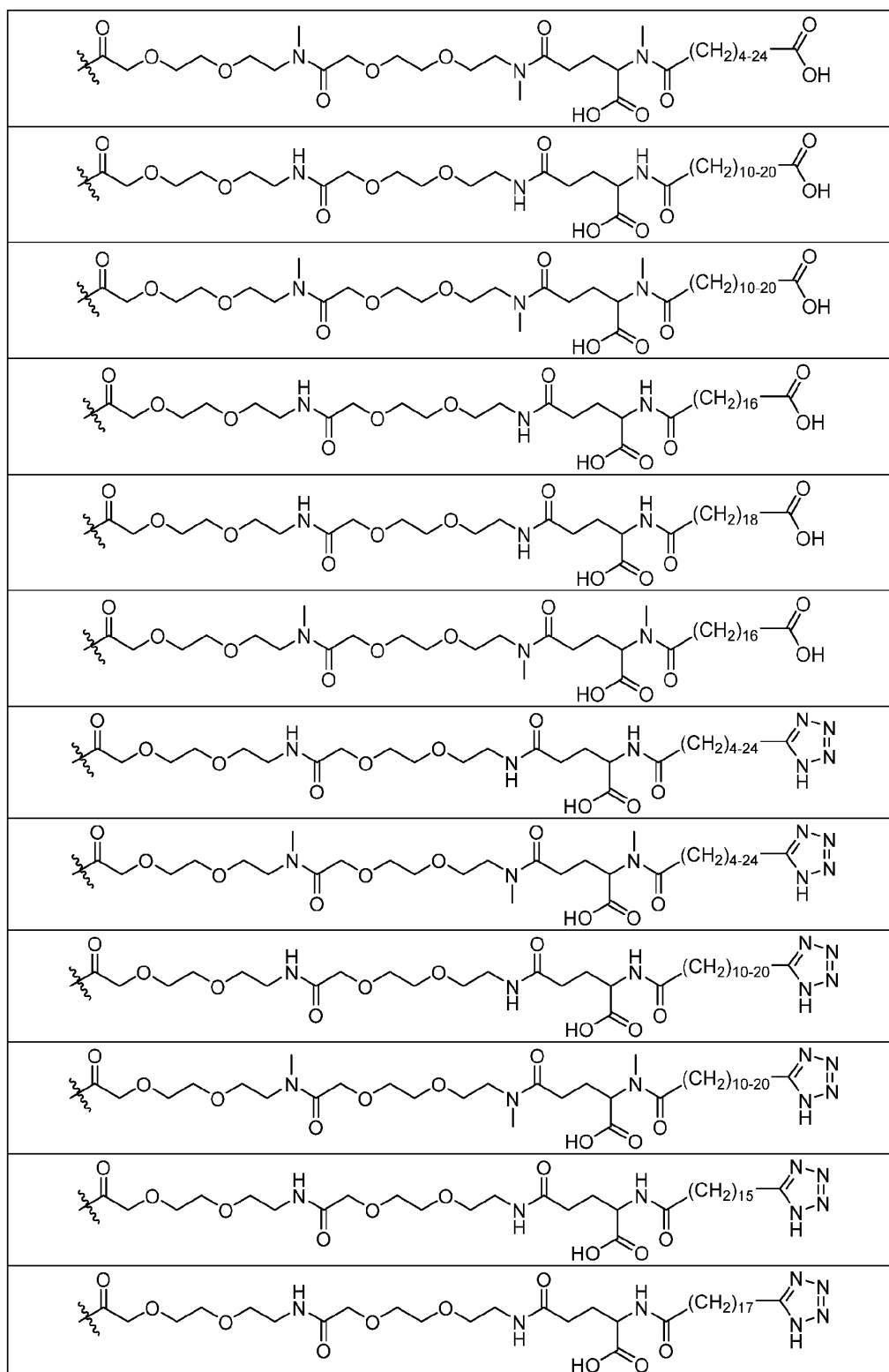
20 In some embodiments, R₁, R₂, or any amino acid of the peptide is conjugated to a
lipophilic substituent.

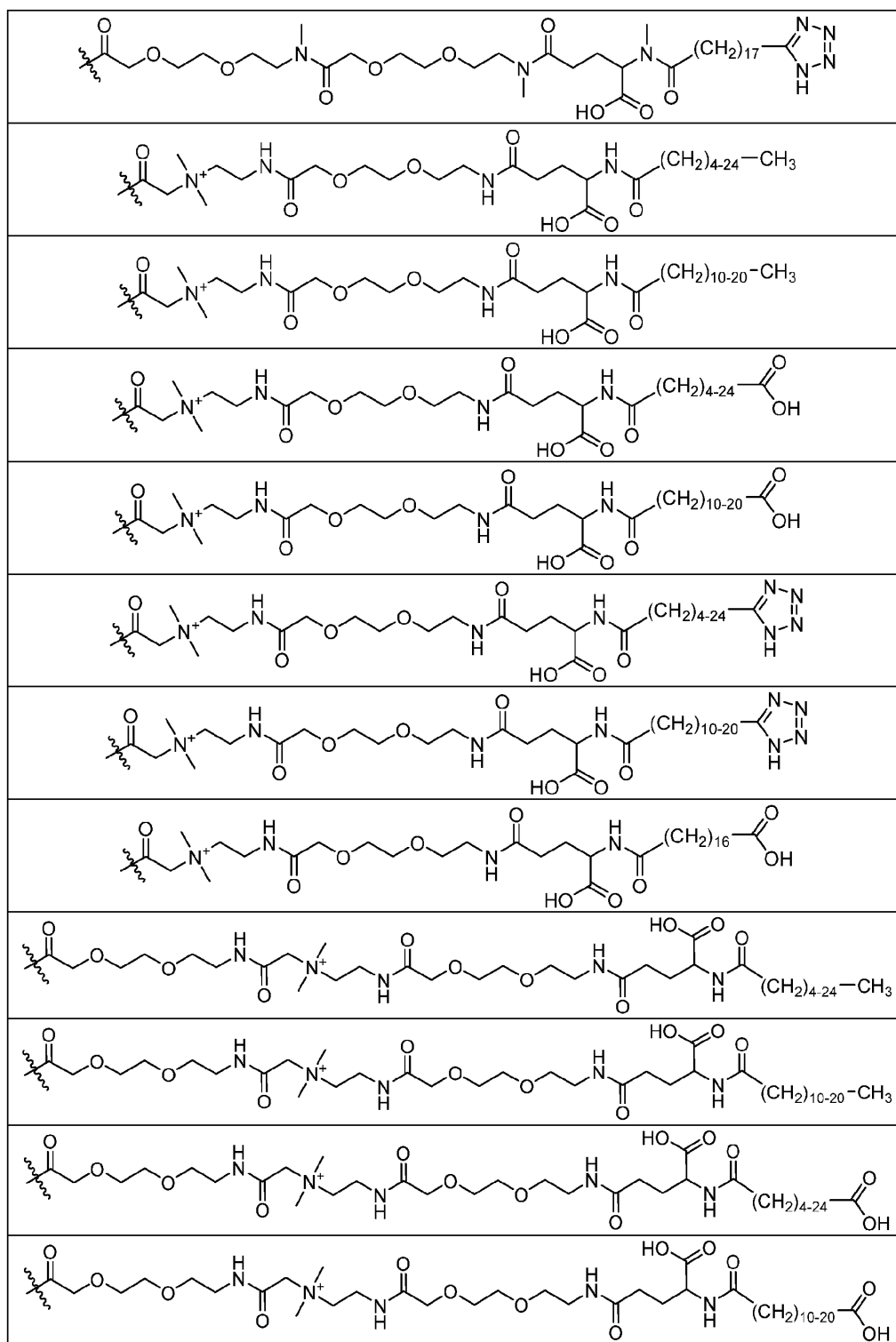
Non-limiting examples of lipophilic substituents are provided in Table 3A.

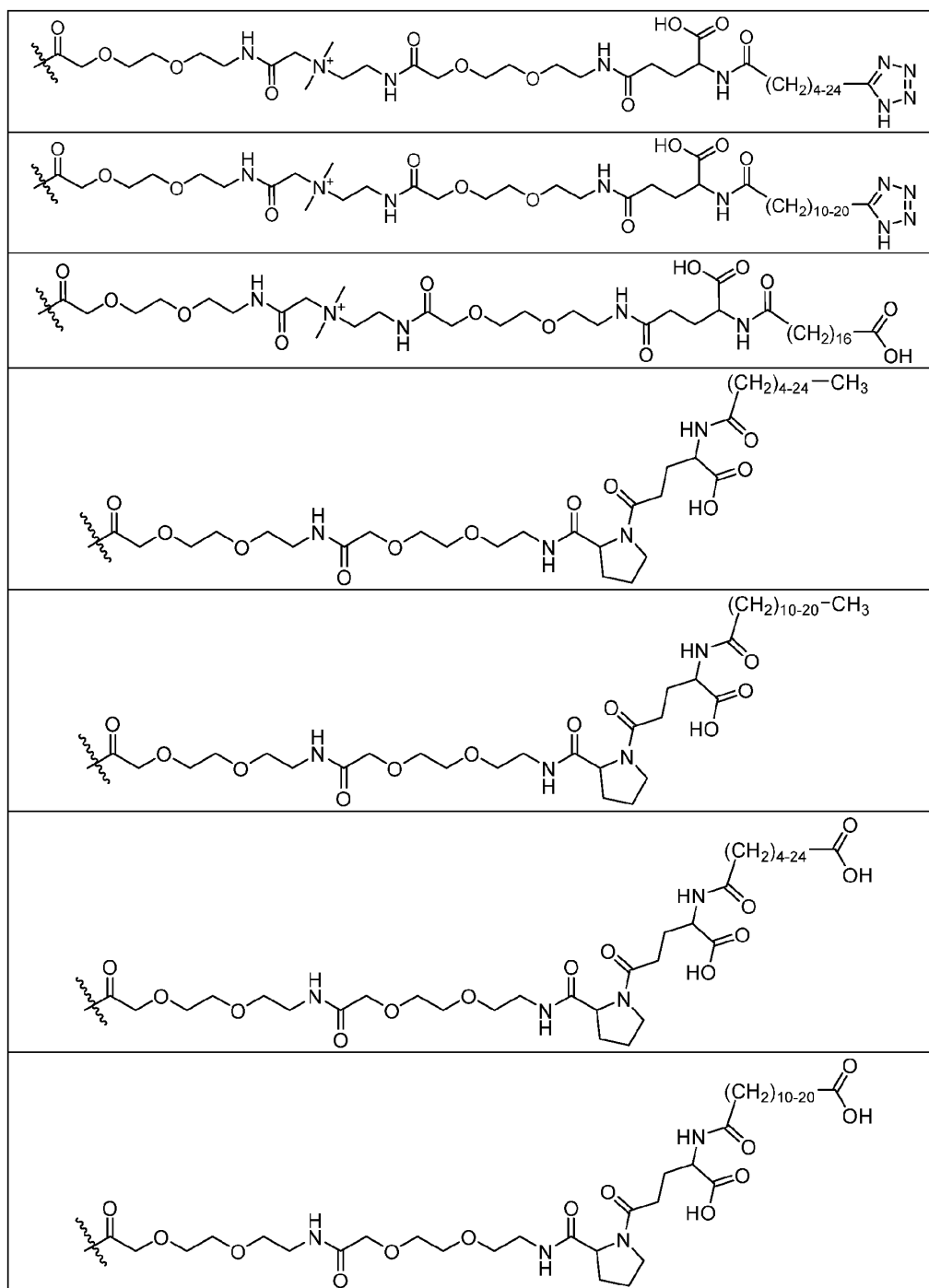
Table 3A. Exemplary lipophilic substituents

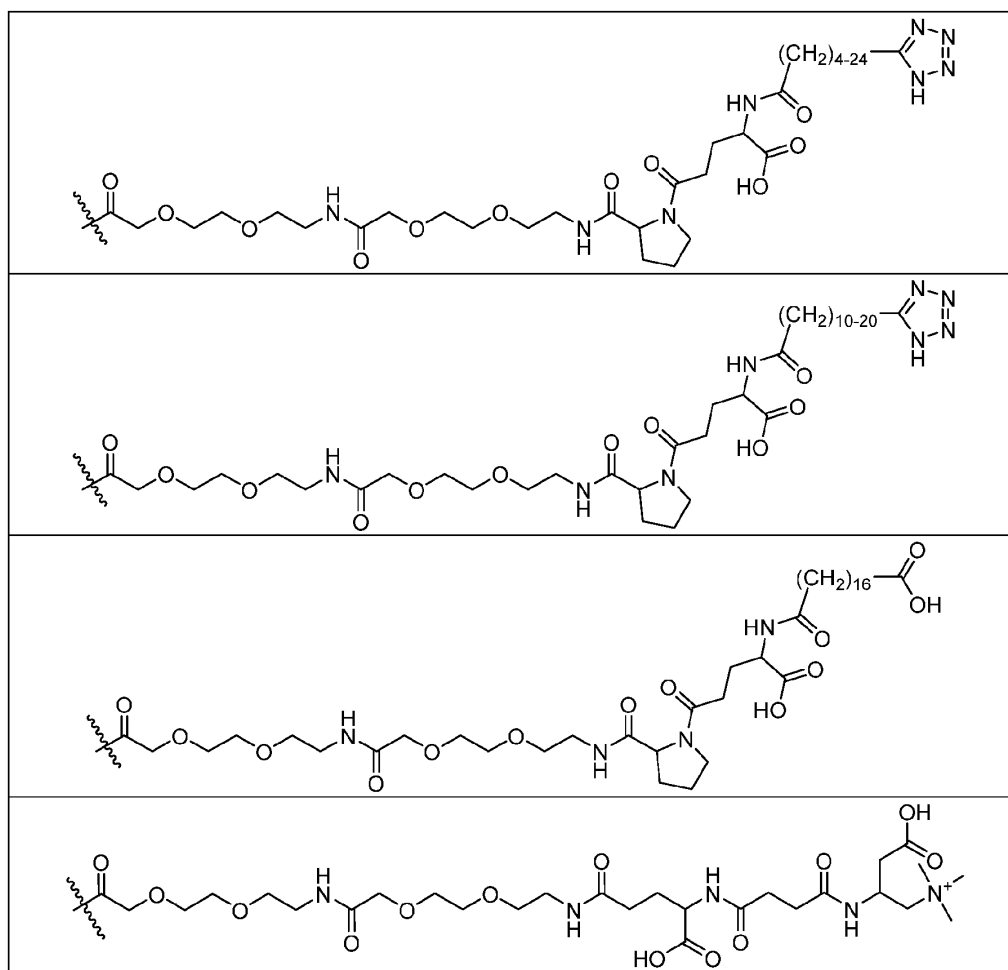




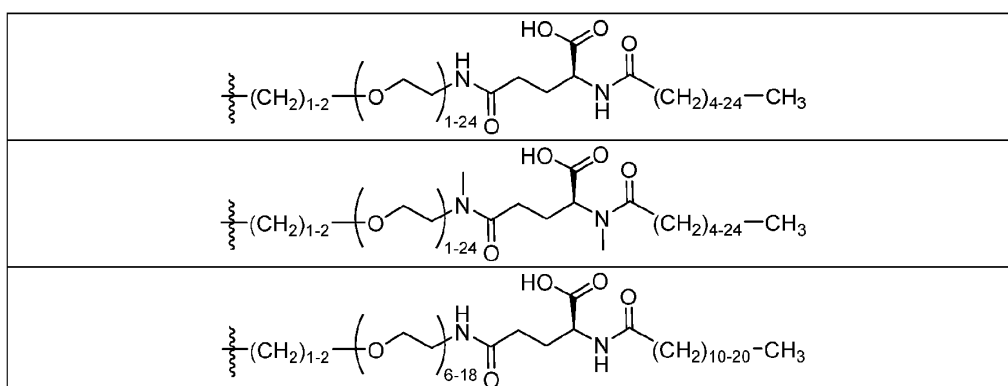


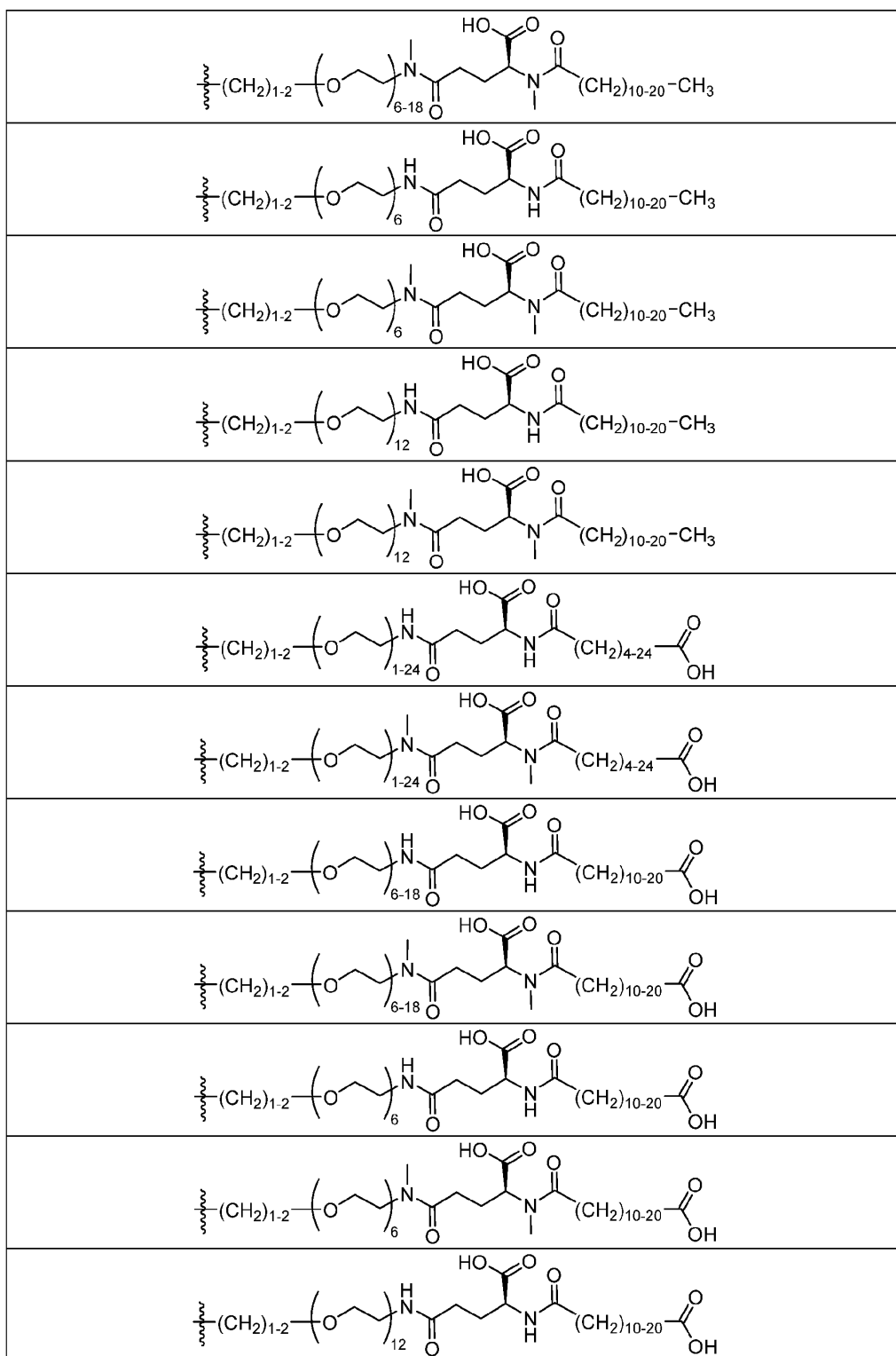




Further non-limiting examples of lipophilic substituents are provided in Table 3B.

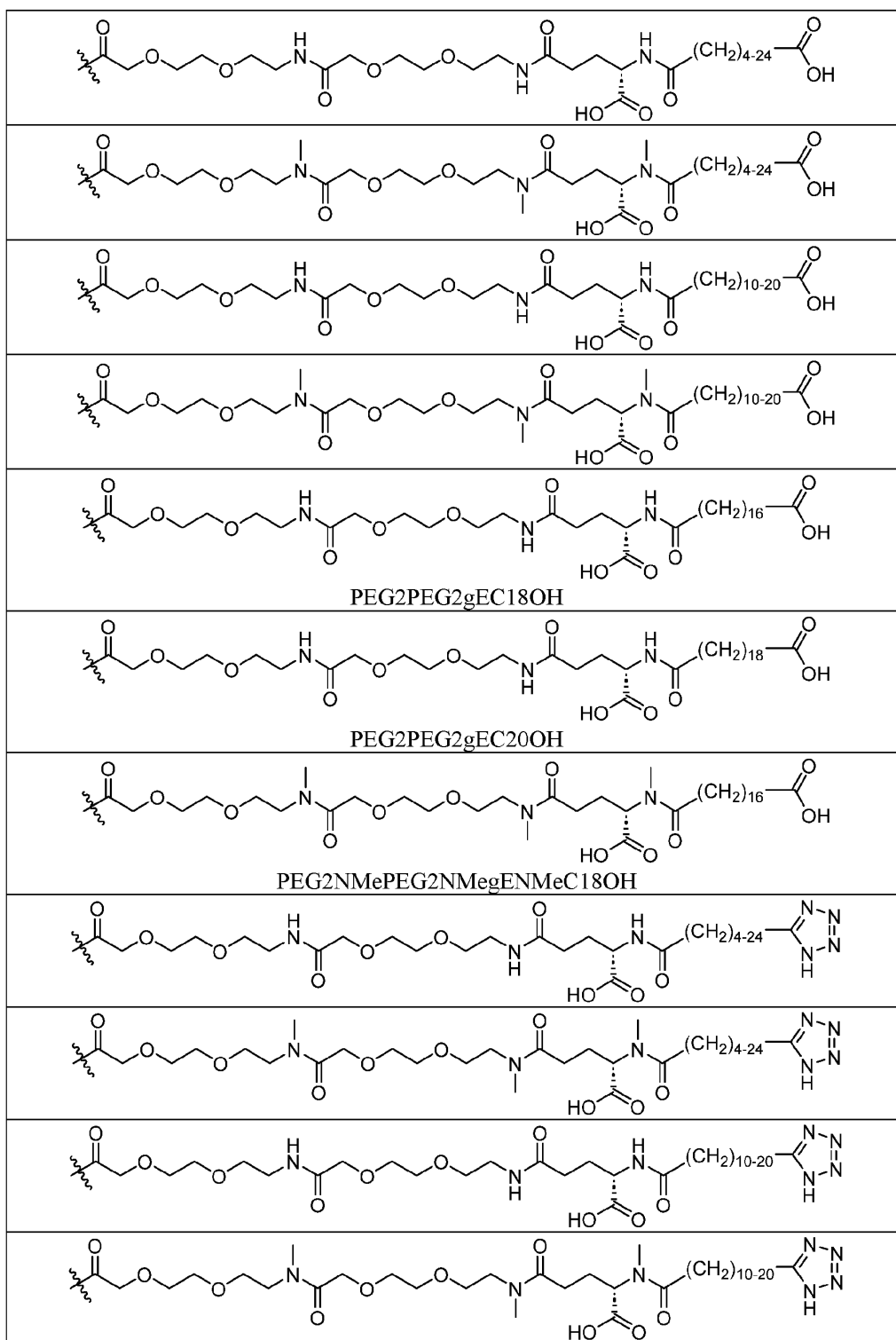
Table 3B. Exemplary lipophilic substituents

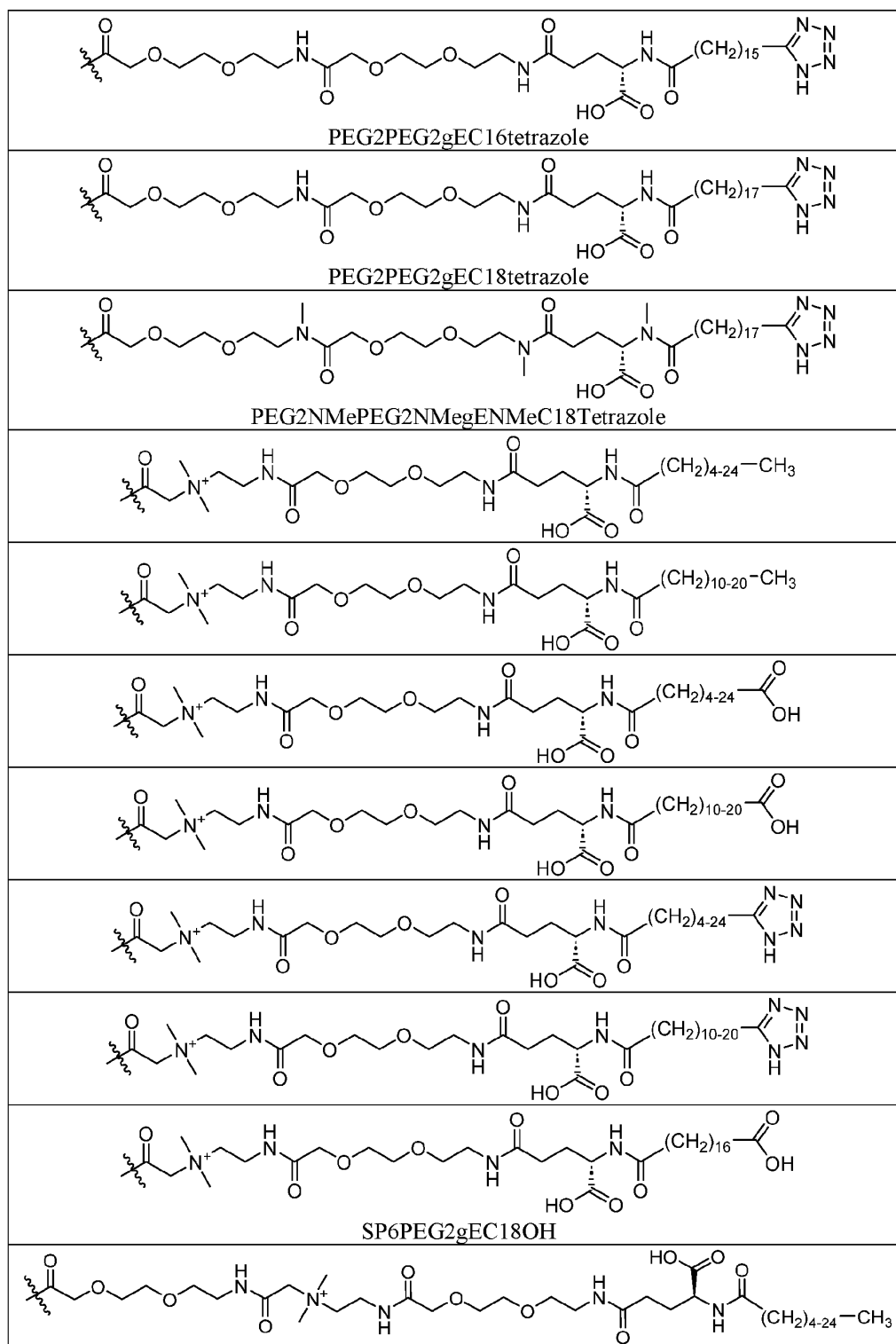


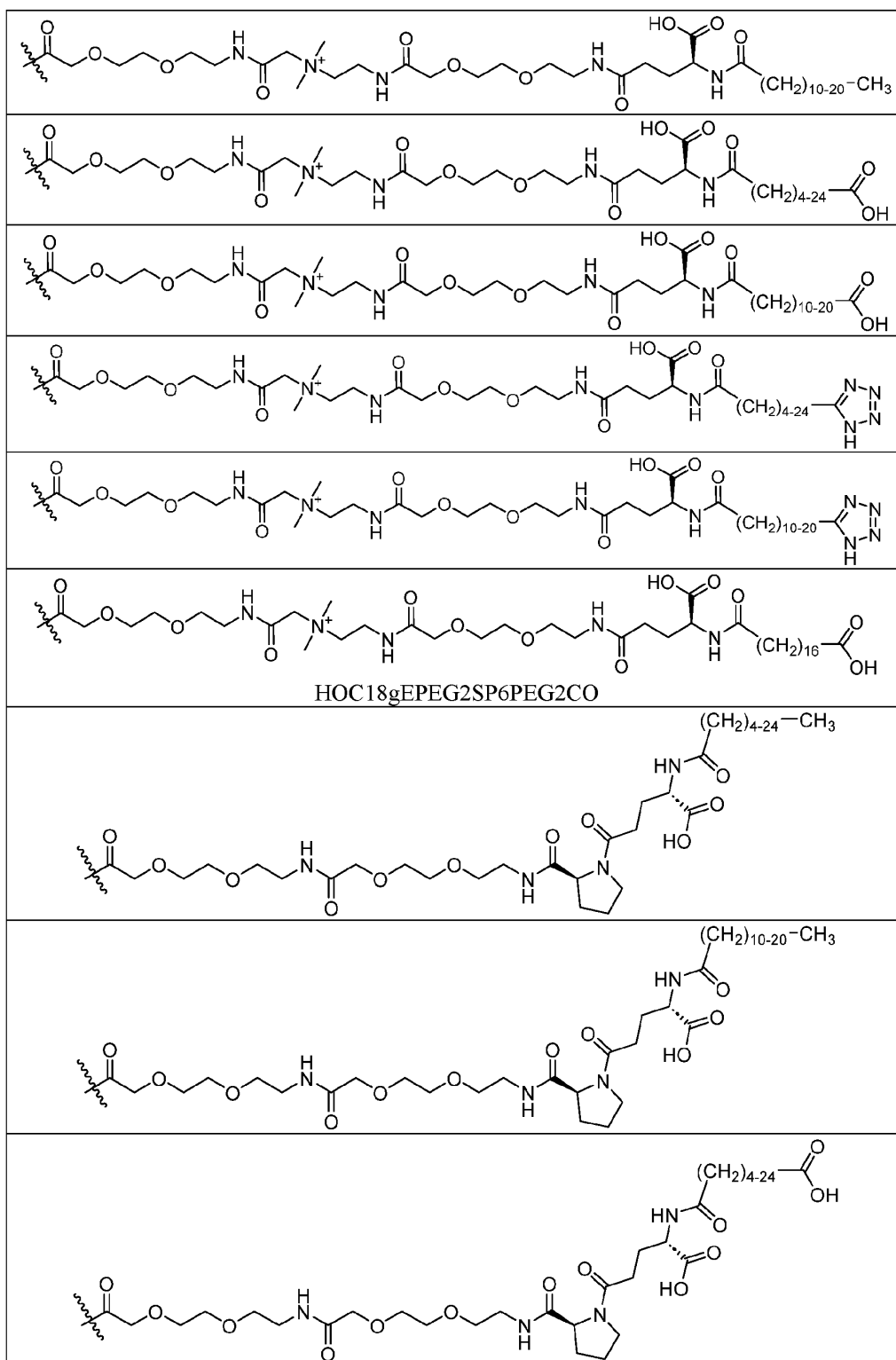


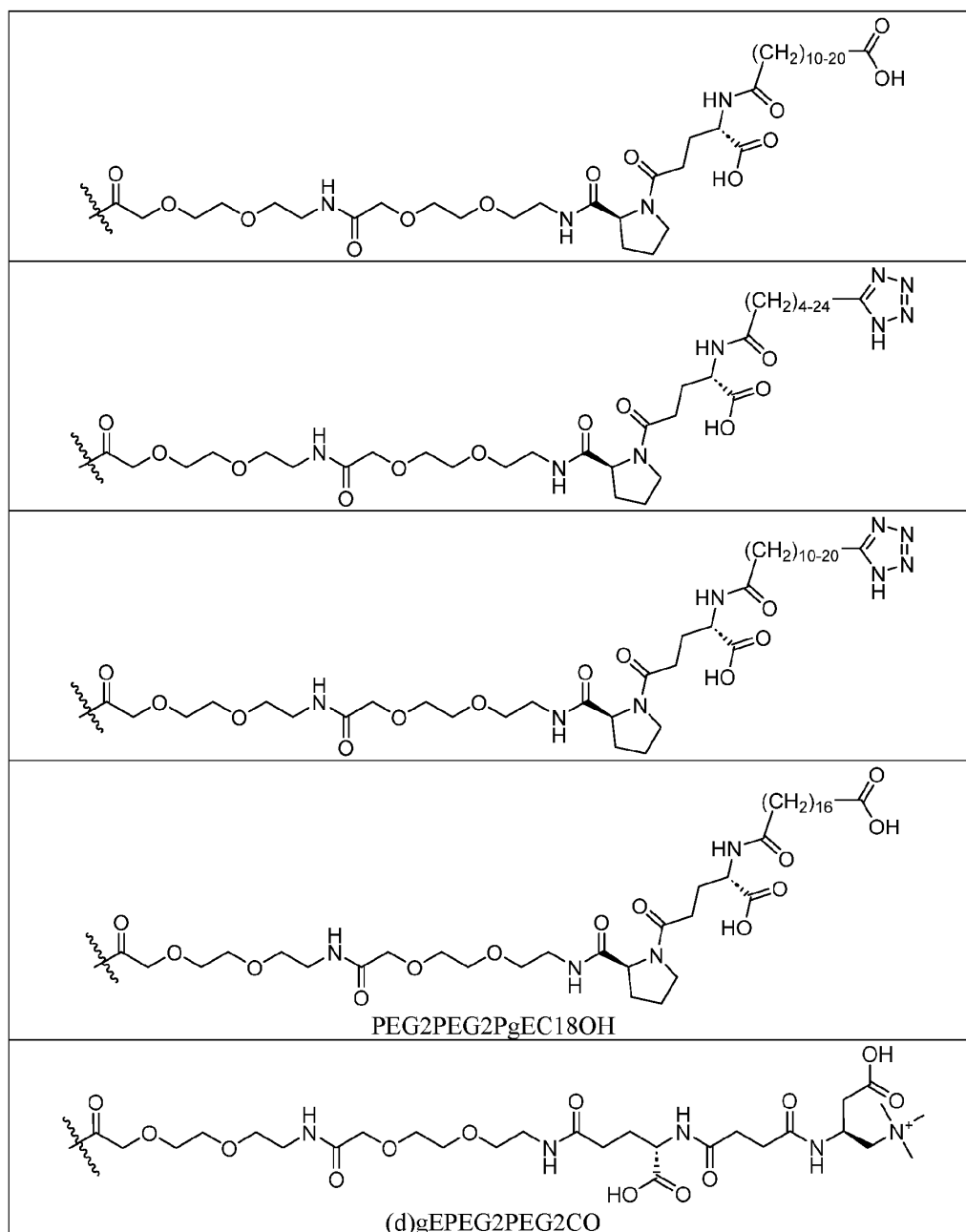
 PEG6gEC18OH, HOC18gEPEG6CO
 PEG12gEC18OH
 PEG12gEC20OH
 PEG12NMegENMeC18OH
 PEG12NMegENMeC20OH

PEG12NMegENMeC18Tetrazole
PEG2PEG2gEC12
PEG2PEG2gEC14









In some embodiments, the peptide comprises a sequence according to any one of the following Formulas:

- 5 $X_3-X_4-X_5-X_6-7\text{MeW}-X_8-X_9-X_{10}-X_{11}-X_{12}-X_{13}-X_{14}-X_{15}-X_{16}-X_{17}$ (I-G1a),
- $X_3-X_4-X_5-X_6-7(3\text{NAcPh})\text{W}-X_8-X_9-X_{10}-X_{11}-X_{12}-X_{13}-X_{14}-X_{15}-X_{16}-X_{17}$ (I-G1b),
- $X_3-X_4-X_5-X_6-X_7-X_8-X_9-\text{AEF}-X_{11}-X_{12}-X_{13}-X_{14}-X_{15}-X_{16}-X_{17}$ (I-H1),
- $X_3-X_4-X_5-X_6-X_7-X_8-X_9-X_{10}-6\text{OH2Nal}-X_{12}-X_{13}-X_{14}-X_{15}-X_{16}-X_{17}$ (I-I1),

- X₃-X₄-X₅-X₆-X₇-X₈-X₉-X₁₀-X₁₁-X₁₂-X₁₃-X₁₄-3PyA-X₁₆-X₁₇ (I-J1),
 X₃-X₄-X₅-X₆-7MeW-X₈-X₉-AEF-6OH2Nal-X₁₂-X₁₃-X₁₄-3PyA-X₁₆-X₁₇ (I-K1a),
 X₃-X₄-X₅-X₆-7(3NAcPh)W-X₈-X₉-AEF-6OH2Nal-X₁₂-X₁₃-X₁₄-3PyA-X₁₆-X₁₇ (I-K1b),
 r-X₄-X₅-X₆-7MeW-X₈-X₉-AEF-6OH2Nal-X₁₂-X₁₃-X₁₄-3PyA-X₁₆-X₁₇ (I-L1a),
 5 r-X₄-X₅-X₆-7(3NAcPh)W-X₈-X₉-AEF-6OH2Nal-X₁₂-X₁₃-X₁₄-3PyA-X₁₆-X₁₇ (I-L1b),
 X₃-Pen-X₅-X₆-7MeW-X₈-Pen-AEF-6OH2Nal-X₁₂-X₁₃-X₁₄-3PyA-X₁₆-X₁₇ (I-M1a),
 X₃-Pen-X₅-X₆-7(3NAcPh)W-X₈-Pen-AEF-6OH2Nal-X₁₂-X₁₃-X₁₄-3PyA-X₁₆-X₁₇ (I-M1b),
 X₃-X₄-X₅-X₆-7MeW-X₈-X₉-AEF-6OH2Nal-X₁₂-X₁₃-X₁₄-3PyA-Sar-X₁₇ (I-N1a),
 10 X₃-X₄-X₅-X₆-7(3NAcPh)W-X₈-X₉-AEF-6OH2Nal-X₁₂-X₁₃-X₁₄-3PyA-Sar-X₁₇ (I-N1b),
 X₃-X₄-X₅-X₆-7MeW-X₈-X₉-AEF-6OH2Nal-X₁₂-X₁₃-X₁₄-3PyA-X₁₆ (I-O1a), or
 X₃-X₄-X₅-X₆-7(3NAcPh)W-X₈-X₉-AEF-6OH2Nal-X₁₂-X₁₃-X₁₄-3PyA-X₁₆ (I-O1b).

In some embodiments, the peptide comprises a sequence according to any one of the following Formulas:

- 15 R₁-X₃-X₄-X₅-T-7MeW-X₈-X₉-X₁₀-X₁₁-X₁₂-X₁₃-N-X₁₅-X₁₆-X₁₇-R₂ (I-G2a),
 R₁-X₃-X₄-X₅-T-7(3NAcPh)W-X₈-X₉-X₁₀-X₁₁-X₁₂-X₁₃-N-X₁₅-X₁₆-X₁₇-R₂ (I-G2b),
 R₁-X₃-X₄-X₅-T-X₇-X₈-X₉-AEF-X₁₁-X₁₂-X₁₃-N-X₁₅-X₁₆-X₁₇-R₂ (I-H2),
 R₁-X₃-X₄-X₅-T-X₇-X₈-X₉-X₁₀-6OH2Nal-X₁₂-X₁₃-N-X₁₅-X₁₆-X₁₇-R₂ (I-I2),
 R₁-X₃-X₄-X₅-T-X₇-X₈-X₉-X₁₀-X₁₁-X₁₂-X₁₃-N-3PyA-X₁₆-X₁₇-R₂ (I-J2),
 20 R₁-X₃-X₄-X₅-T-7MeW-X₈-X₉-AEF-6OH2Nal-X₁₂-X₁₃-N-3PyA-X₁₆-X₁₇-R₂ (I-K2a),
 R₁-X₃-X₄-X₅-T-7(3NAcPh)W-X₈-X₉-AEF-6OH2Nal-X₁₂-X₁₃-N-3PyA-X₁₆-X₁₇-R₂ (I-K2b),
 R₁-r-X₄-X₅-T-7MeW-X₈-X₉-AEF-6OH2Nal-X₁₂-X₁₃-N-3PyA-X₁₆-X₁₇-R₂ (I-L2a),
 R₁-r-X₄-X₅-T-7(3NAcPh)W-X₈-X₉-AEF-6OH2Nal-X₁₂-X₁₃-N-3PyA-X₁₆-X₁₇-R₂ (I-L2b),
 25 R₁-X₃-Pen-X₅-T-7MeW-X₈-Pen-AEF-6OH2Nal-X₁₂-X₁₃-N-3PyA-X₁₆-X₁₇-R₂ (I-M2a),
 R₁-X₃-Pen-X₅-T-7(3NAcPh)W-X₈-Pen-AEF-6OH2Nal-X₁₂-X₁₃-N-3PyA-X₁₆-X₁₇-R₂ (I-M2b),
 R₁-X₃-X₄-X₅-T-7MeW-X₈-X₉-AEF-6OH2Nal-X₁₂-X₁₃-N-3PyA-Sar-X₁₇-R₂ (I-N2a),
 R₁-X₃-X₄-X₅-T-7(3NAcPh)W-X₈-X₉-AEF-6OH2Nal-X₁₂-X₁₃-N-3PyA-Sar-X₁₇-R₂ (I-N2b),
 30 N2b),
 R₁-X₃-X₄-X₅-T-7MeW-X₈-X₉-AEF-6OH2Nal-X₁₂-X₁₃-N-3PyA-X₁₆-R₂ (I-O2a), or
 R₁-X₃-X₄-X₅-T-7(3NAcPh)W-X₈-X₉-AEF-6OH2Nal-X₁₂-X₁₃-N-3PyA-X₁₆-R₂ (I-O2b).

In some embodiments, the amino acid at X₃ is an L-amino acid. In some embodiments, the amino acid at X₃ is a D-amino acid.

In some embodiments, the amino acid at X₄ is an L-amino acid. In some embodiments, the amino acid at X₄ is a D-amino acid.

In some embodiments, the amino acid at X₅ is an L-amino acid. In some embodiments, the amino acid at X₅ is a D-amino acid.

5 In some embodiments, the amino acid at X₆ is an L-amino acid. In some embodiments, the amino acid at X₆ is a D-amino acid.

In some embodiments, the amino acid at X₇ is an L-amino acid. In some embodiments, the amino acid at X₇ is a D-amino acid.

10 In some embodiments, the amino acid at X₈ is an L-amino acid. In some embodiments, the amino acid at X₈ is a D-amino acid.

In some embodiments, the amino acid at X₉ is an L-amino acid. In some embodiments, the amino acid at X₉ is a D-amino acid.

In some embodiments, the amino acid at X₁₀ is an L-amino acid. In some embodiments, the amino acid at X₁₀ is a D-amino acid.

15 In some embodiments, the amino acid at X₁₁ is an L-amino acid. In some embodiments, the amino acid at X₁₁ is a D-amino acid.

In some embodiments, the amino acid at X₁₂ is an L-amino acid. In some embodiments, the amino acid at X₁₂ is a D-amino acid.

20 In some embodiments, the amino acid at X₁₃ is an L-amino acid. In some embodiments, the amino acid at X₁₃ is a D-amino acid.

In some embodiments, the amino acid at X₁₄ is an L-amino acid. In some embodiments, the amino acid at X₁₄ is a D-amino acid.

In some embodiments, the amino acid at X₁₅ is an L-amino acid. In some embodiments, the amino acid at X₁₅ is a D-amino acid.

25 In some embodiments, the amino acid at X₁₆ is an L-amino acid. In some embodiments, the amino acid at X₁₆ is a D-amino acid.

In some embodiments, the amino acid at X₁₇ is an L-amino acid. In some embodiments, the amino acid at X₁₇ is a D-amino acid.

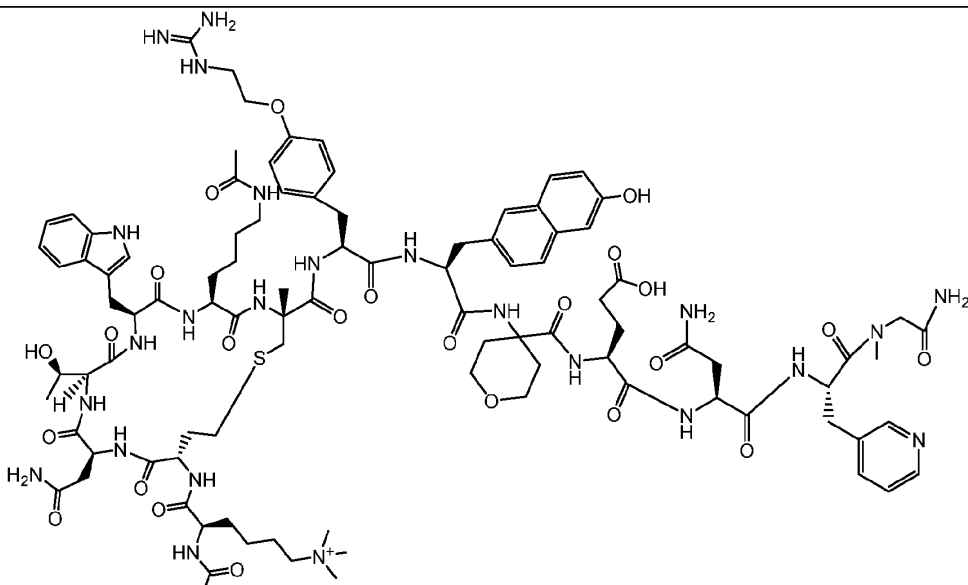
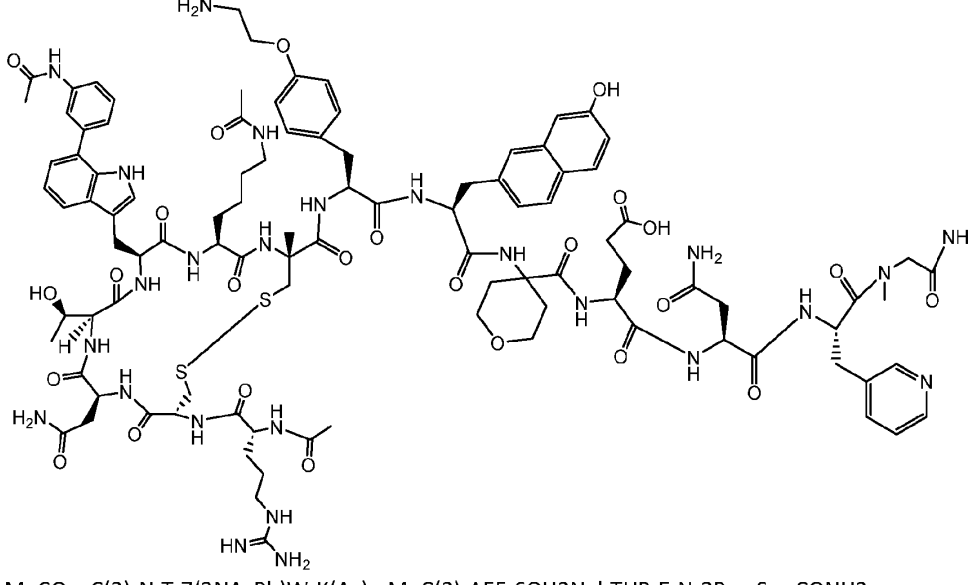
30 In some embodiments, the present disclosure provides a peptide described herein provided the peptide retains activity as an inhibitor of interleukin-23 receptor.

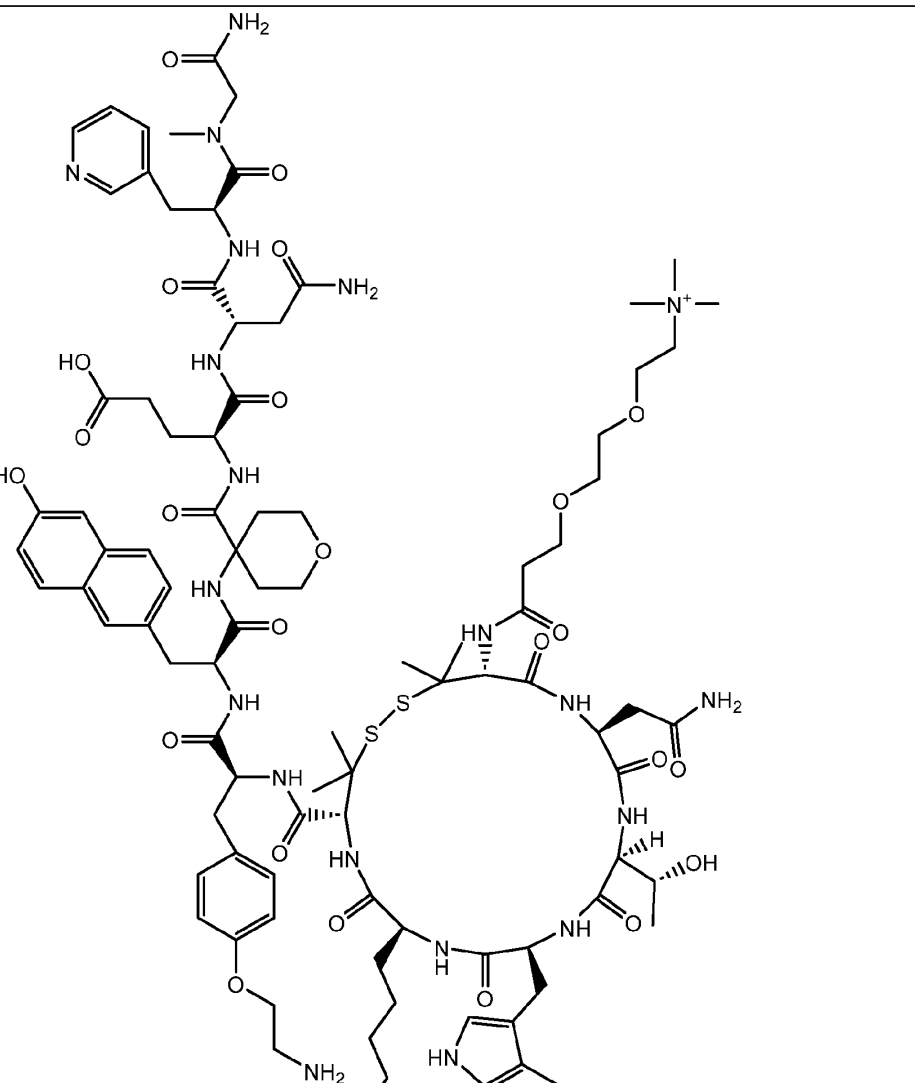
The present disclosure further provides a peptide of any one of SEQ ID NOS: 1-447, as shown in Table 4, or a pharmaceutically acceptable salt thereof.

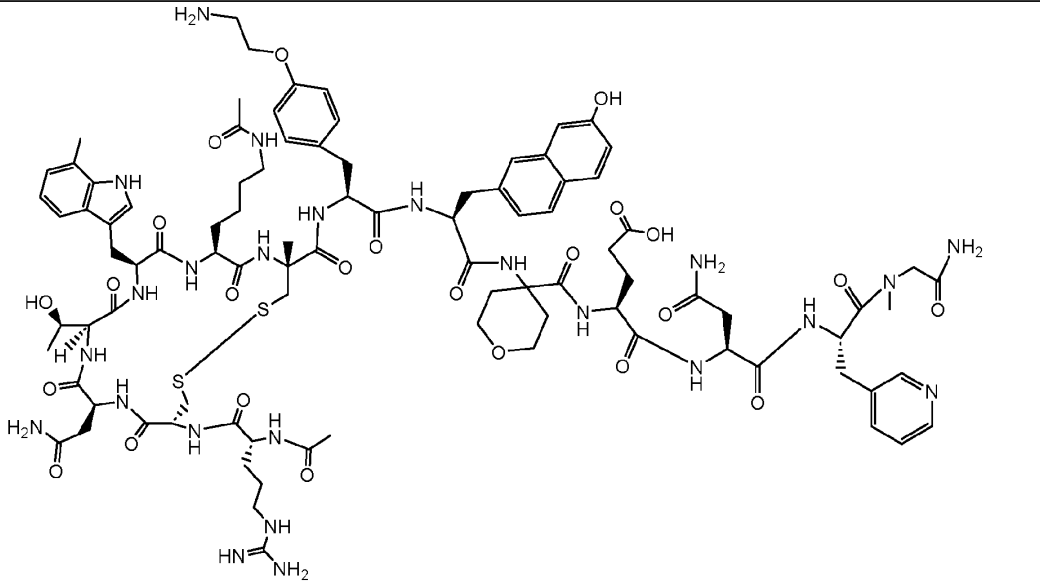
In some embodiments, when the peptide comprises a cationic group (such as a quaternary ammonium moiety), the peptide further comprises a counter-anion, such as, without limitation,

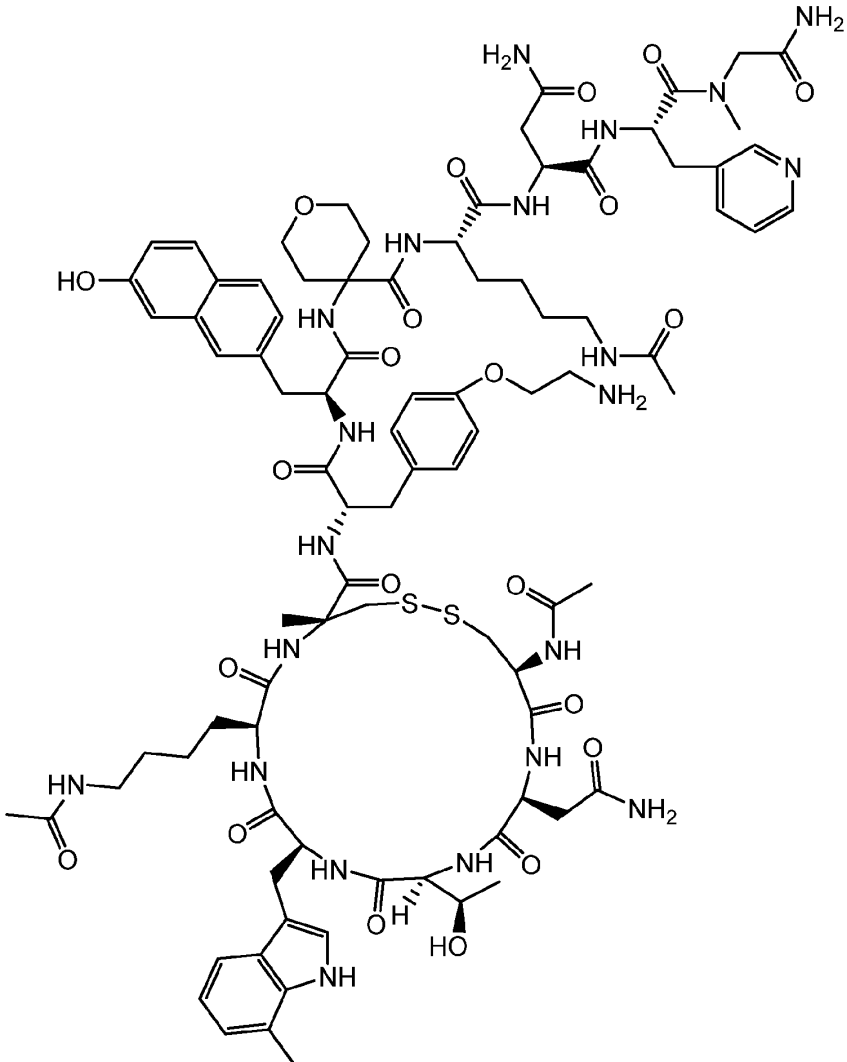
acetate, adipate, benzoate, benzenesulfonate, citrate, decanoate, chloride, lactate, maleate, methanesulfonate, oxalate, pivalate, propionate, succinate, sulfate, tartrate, or trifluoroacetate.

Table 4. Exemplary Peptides

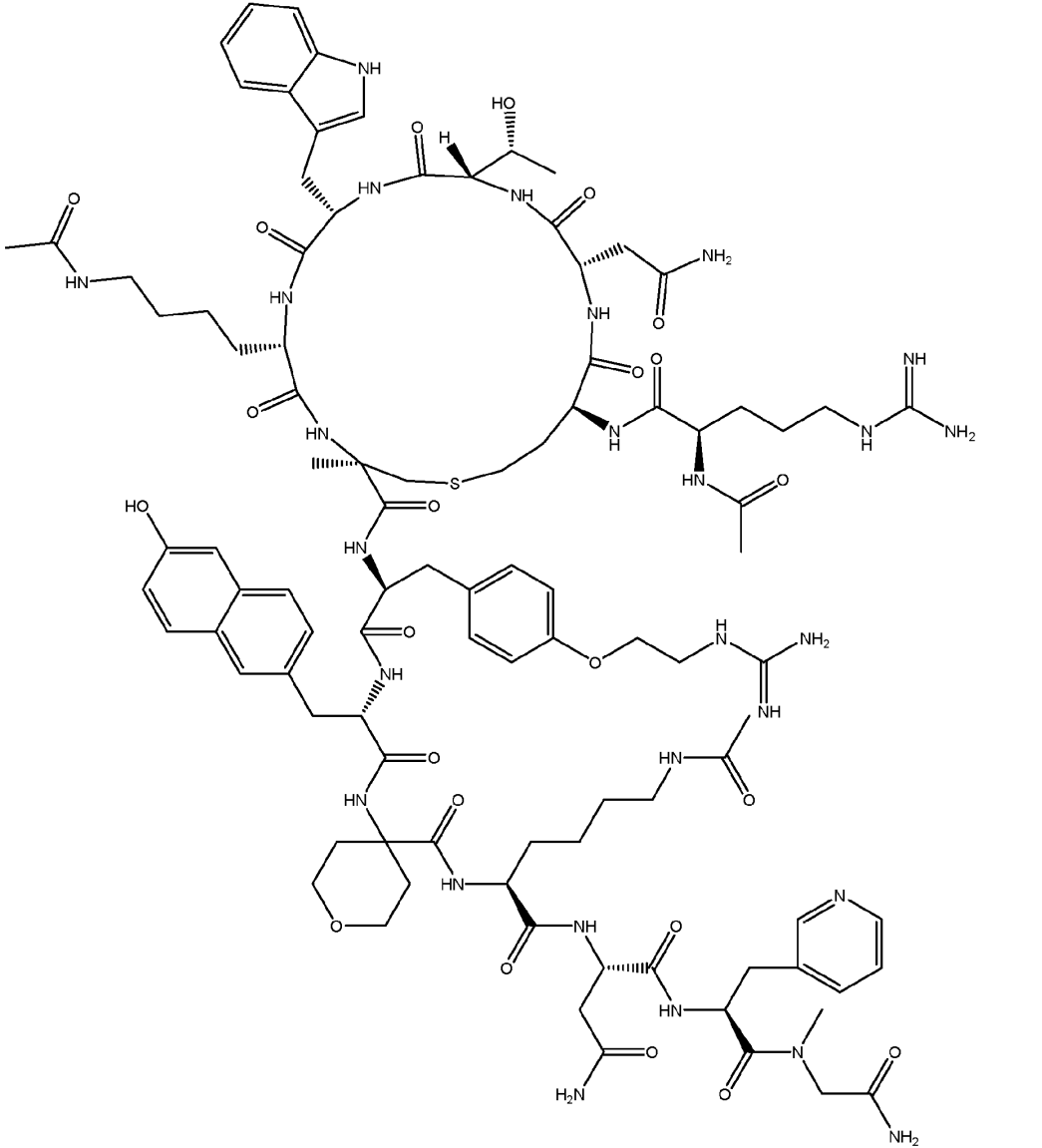
SEQ ID NO	Structure
1	 MeCO-k(Me)3-Abu(1)-N-T-W-K(Ac)-aMeC(1)-AEF(G)-6OH2Nal-THP-E-N-3Pyra-Sar-CONH2
2	 MeCO-r-C(3)-N-T-7(3NAcPh)W-K(Ac)-aMeC(3)-AEF-6OH2Nal-THP-E-N-3Pyra-Sar-CONH2

SEQ ID NO	Structure
3	 cPEG3aCO--Pen(3)-N-T-7MeW-K(Ac)-Pen(3)-AEF-6OH2NaI-THP-E-N-3Pya-Sar--CONH2

SEQ ID NO	Structure
4	 MeCO-r-C(3)-N-T-7MeW-K(Ac)-aMeC(3)-AEF-6OH2Nal-THP-E-N-3Py-Sar--CONH2

SEQ ID NO	Structure
5	 MeCO--C(3)-N-T-7MeW-K(Ac)-aMeC(3)-AEF-6OH2Nal-THP-K(Ac)-N-3Pya-Sar--CONH2

SEQ ID NO	Structure
6	MeCO-r-Abu(1)-N-T-7(3NAcPh)W-K(Ac)-aMeC(1)-AEF-6OH2Nal-THP-E-N-3Pyra-Sar--CONH2

SEQ ID NO	Structure
7	 The chemical structure depicts a large cyclic peptide, specifically a 28-residue macrocycle. The backbone is a continuous chain of amide bonds forming a ring. The side chains are diverse, including an indole ring, a tryptophan residue, a pyridine ring, and several aliphatic chains with functional groups like hydroxyl, amine, and amide. The structure is shown in a 2D representation with stereochemistry indicated by wedges and dashes. The peptide is labeled as MeCO-r-Abu(1)-N-T-W-K(Ac)-aMeC(1)-AEF(G)-6OH2Nal-THP-K(Ac)-N-3Py-Sar--CONH2.

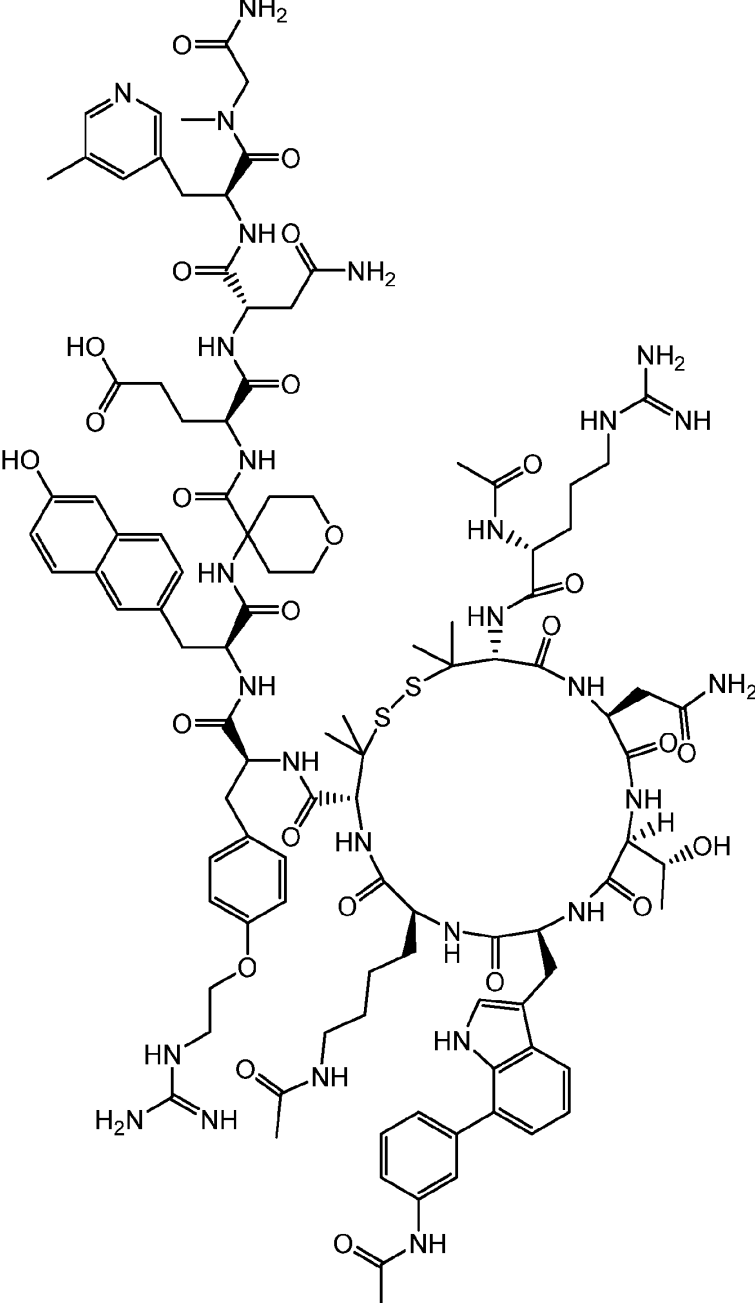
SEQ ID NO	Structure
9	MeCO-Pen(3)-N-T-7(3NAcPh)W-K(Ac)-Pen(3)-AEF(G)-6OH2Nal-THP-E-N-3Pya-Sar-CONH2

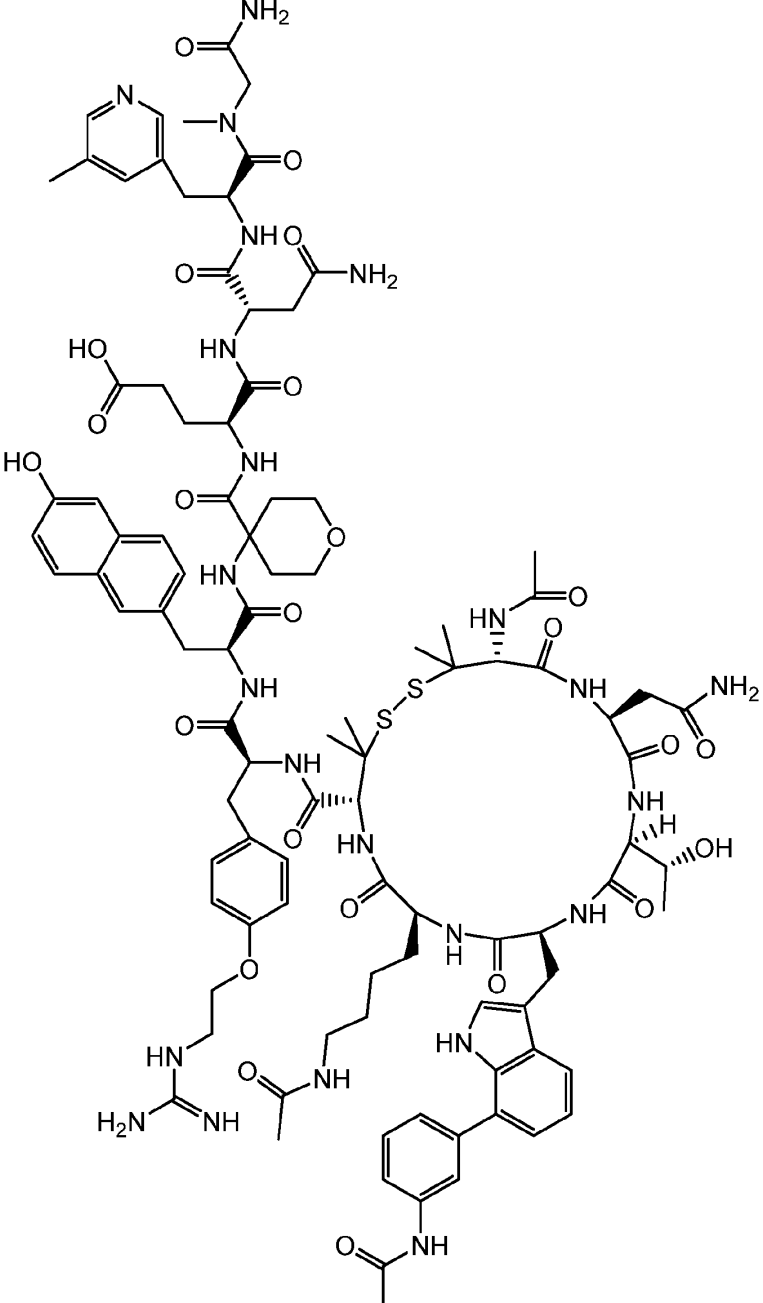
[illegible]

SEQ ID NO	Structure
12	cPEG3aCO-Pen(3)-N-T-7(3NAcPh)W-K(Ac)-Pen(3)-AEF(G)-6OH2NaI-THP-K(NMeAc)-N-5MePyridinAla-Sar-CONH₂

MeCO-Pen(3)-N-T-7(3NAcPh)W-K(Ac)-Pen(3)-AEF(G)-6OH2Nal-THP-K(NMeAc)-N-5MePyridinAla-Sar-CONH2

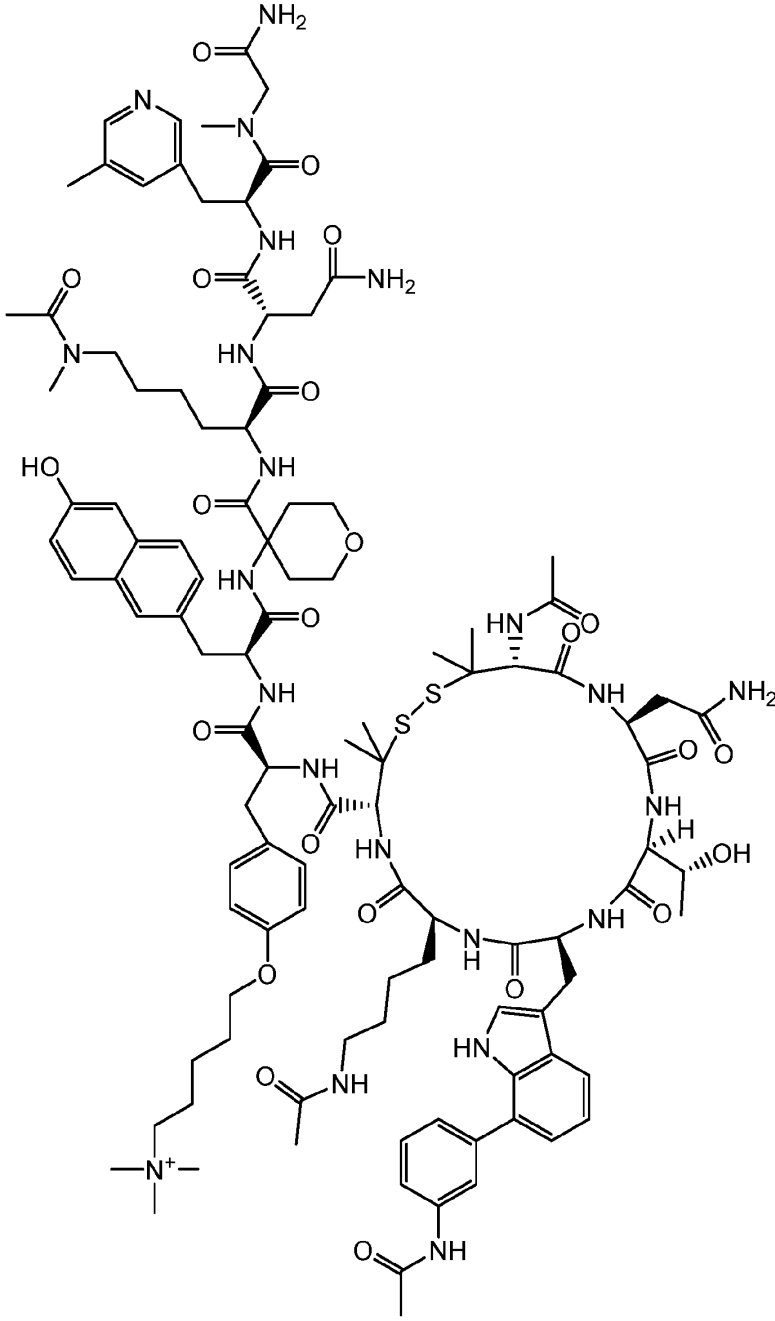
SEQ ID NO	Structure
14	MeCO-Pen(3)-N-T-7(3NAcPh)W-K(Ac)-Pen(3)-AEF(G)-6OH2Nal-THP-K(Ac)-N-5MePyridinAla-Sar-CONH2

SEQ ID NO	Structure
15	 The chemical structure represents a complex cyclic peptide. The backbone is a 16-membered ring with a disulfide bridge (S-S) between two cysteine residues. The side chains are diverse, including: a 5-methylpyridin-2-ylmethyl group, a 3-aminopropionyl group, a 4-aminobutyl group, a 2-aminopropionyl group, a 4-aminobutyl group, a 2-aminopropionyl group, a 4-aminobutyl group, a 2-aminopropionyl group, a 4-aminobutyl group, a 2-aminopropionyl group, a 4-aminobutyl group, a 2-aminopropionyl group, a 4-aminobutyl group, a 2-aminopropionyl group, and a 4-aminobutyl group. The structure is highly detailed, showing stereochemistry and various functional groups. MeCO-r-Pen(3)-N-T-7(3NAcPh)W-K(Ac)-Pen(3)-AEF(G)-6OH2Nal-THP-E-N-5MePyridinAla-Sar-CONH2

SEQ ID NO	Structure
16	 MeCO-Pen(3)-N-T-7(3NAcPh)W-K(Ac)-Pen(3)-AEF(G)-6OH2Nal-THP-E-N-5MePyridinAla-Sar-CONH2

[illegible]

[illegible]

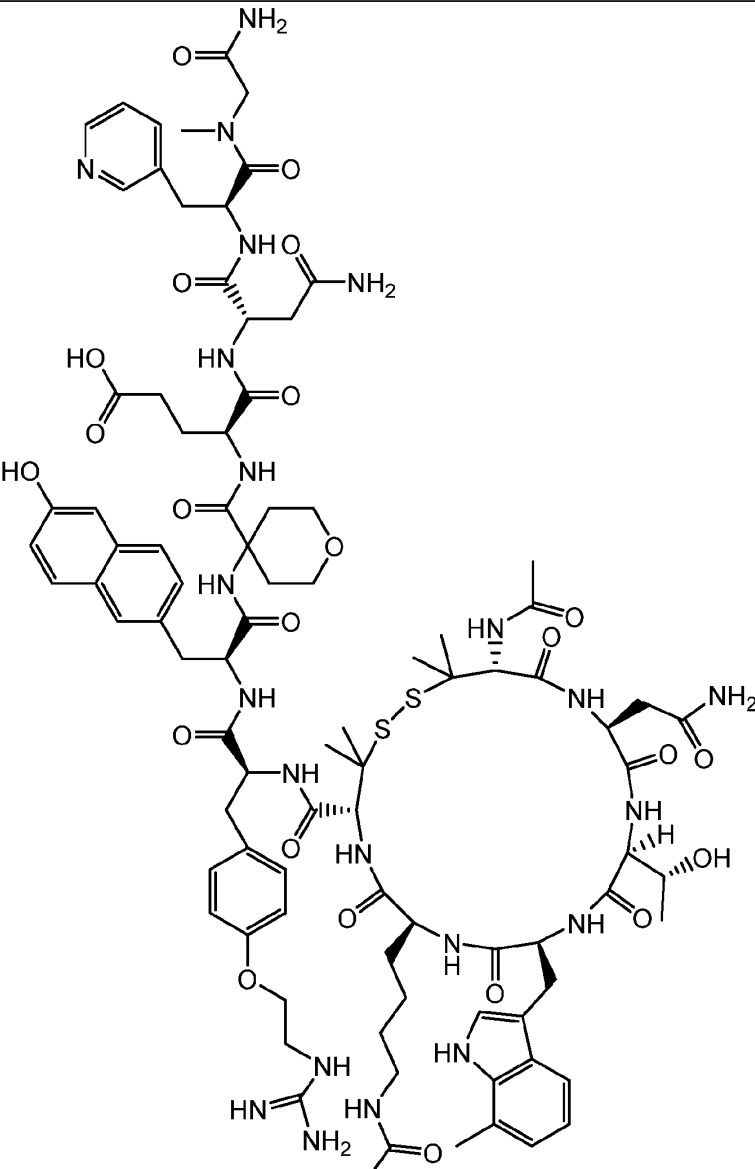
SEQ ID NO	Structure
19	 MeCO-Pen(3)-N-T-7(3NAcPh)W-K(Ac)-Pen(3)-TMAPF-6OH2NaI-THP-K(NMeAc)-N-5MePyridinAla-Sar-CONH2

[illegible]

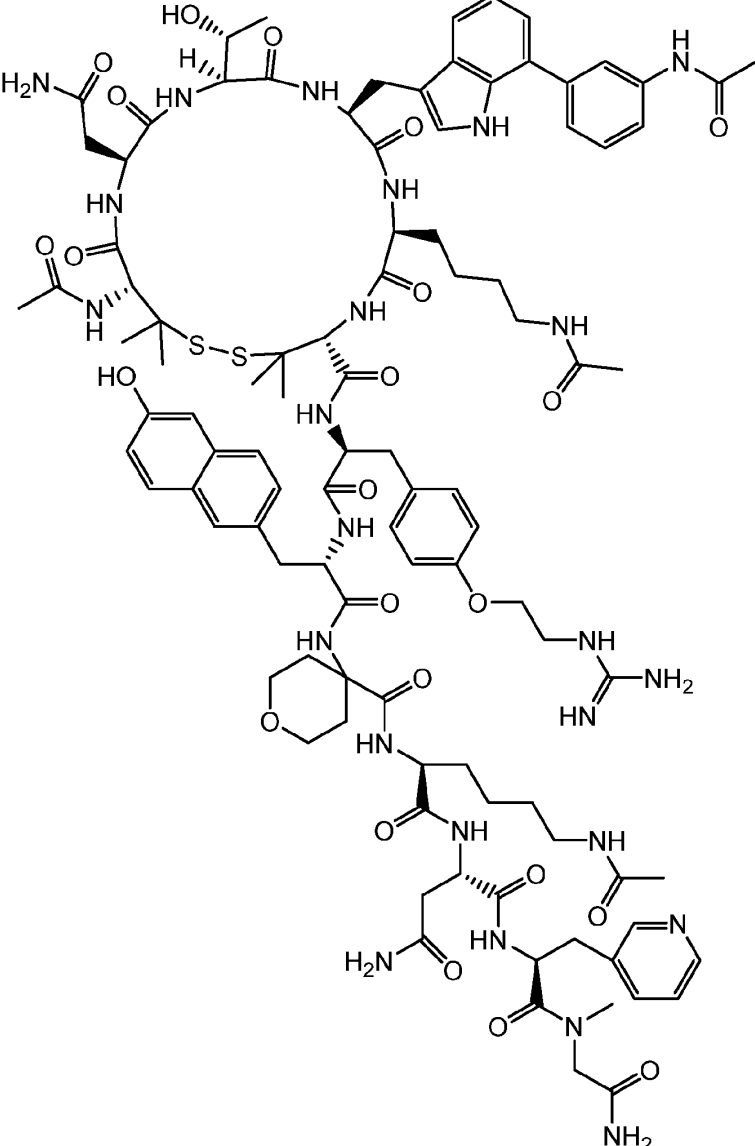
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[illegible]

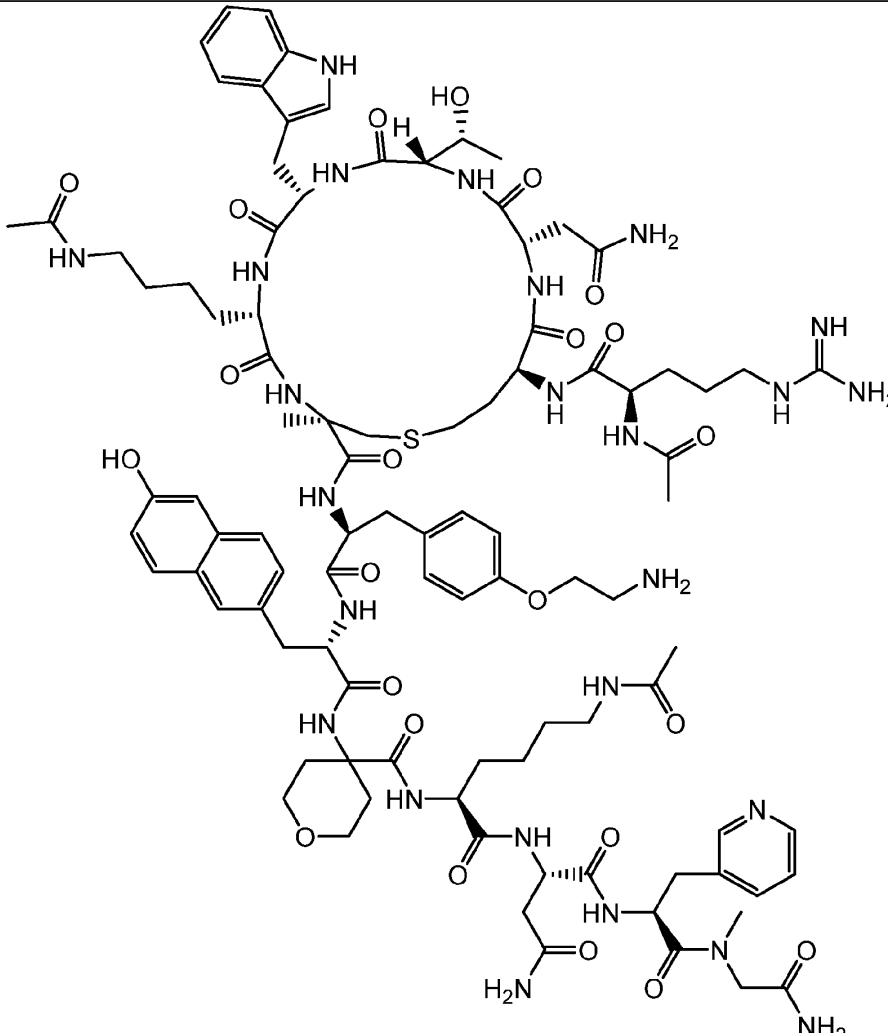
[illegible]

SEQ ID NO	Structure
24	 The chemical structure represents a cyclic peptide with a 12-residue backbone. The residues, starting from the N-terminus and proceeding clockwise, are: 1. N-acetyl-L-proline (Ac-Phe), 2. L-phenylalanine (Phe), 3. L-tyrosine (Tyr), 4. L-tryptophan (Trp), 5. L-tryptophan (Trp), 6. L-tryptophan (Trp), 7. L-tryptophan (Trp), 8. L-tryptophan (Trp), 9. L-tryptophan (Trp), 10. L-tryptophan (Trp), 11. L-tryptophan (Trp), and 12. L-tryptophan (Trp). The side chains include a pyridine ring (Phe), an amide group (Tyr), a hydroxy group (Trp), a thioether group (Trp), and a thioether group (Trp). The structure is highly complex, with multiple amide bonds and a central thioether bridge. MeCO-Pen(3)-N-T-7MeW-K(Ac)-Pen(3)-AEF(G)-6OH2Nal-THP-E-N-3Pya-Sar-CONH2

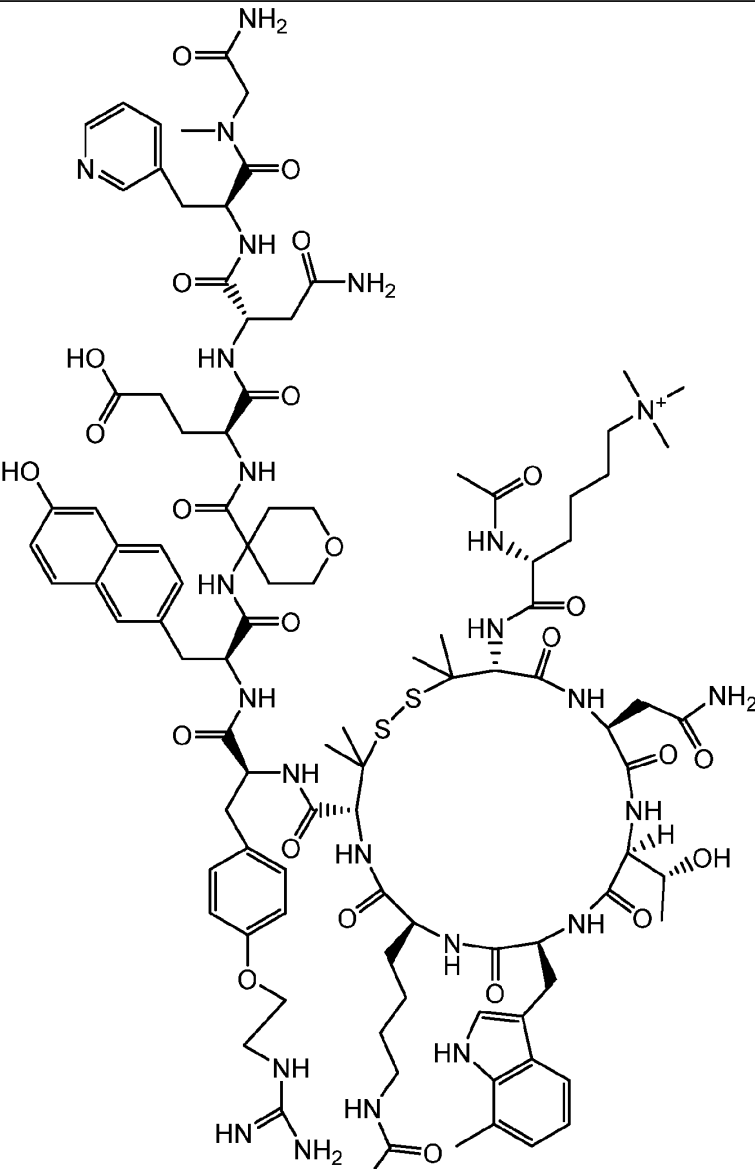
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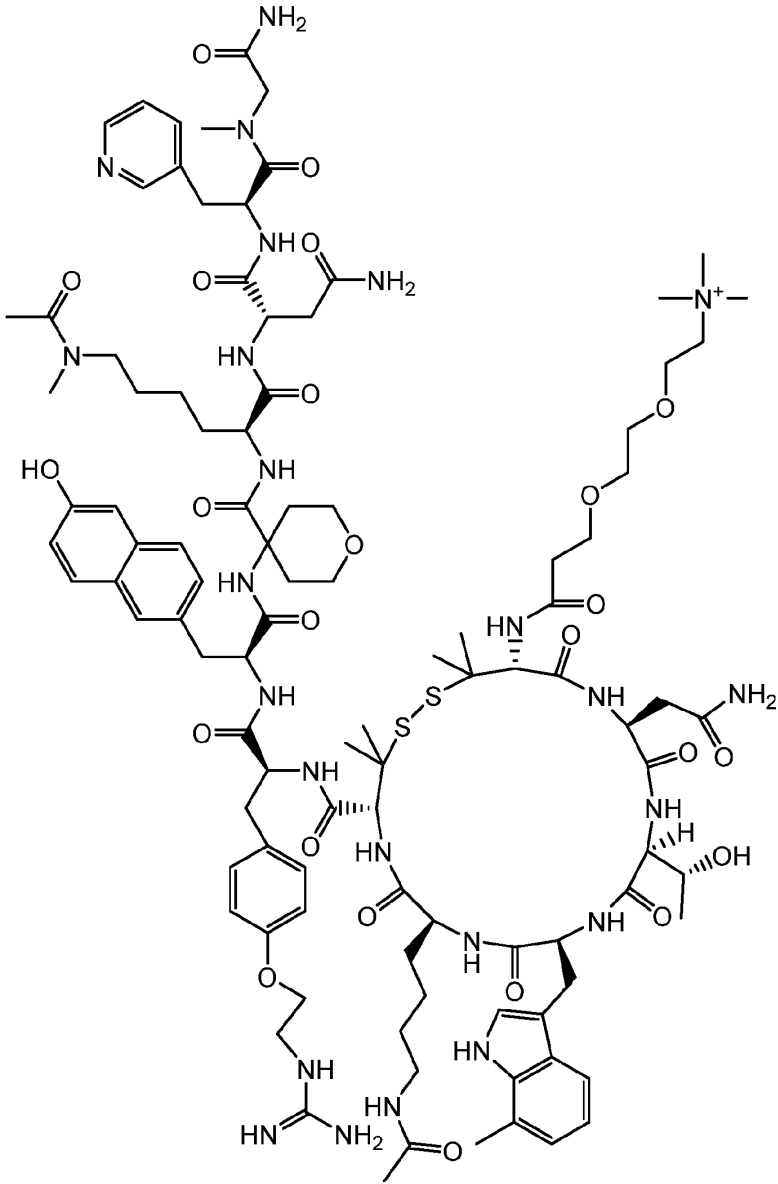
SEQ ID NO	Structure
26	 MeCO-Pen(3)-N-T-7(3NAcPh)W-K(Ac)-Pen(3)-AEF(G)-6OH2Nal-THP-K(Ac)-N-3Pya-Sar-CONH2

SEQ ID NO	Structure
27	MeCO-Pen(3)-N-T-7MeW-K(Ac)-Pen(3)-AEF(G)-6OH2Nal-THP-K(NMeAc)-N-3Pya-Sar-CONH2

SEQ ID NO	Structure
28	 The chemical structure shows a cyclic peptide with a 12-membered ring containing a sulfur atom. The side chains are as follows (starting from the top and moving clockwise): - Indol-3-ylmethyl (indole ring attached to the alpha-carbon) 2-Hydroxyethyl (hydroxyl group on the beta-carbon) - Carbamoylmethyl (CONH₂ group) 4-((2-aminoethoxy)methyl)phenylmethyl (benzene ring with a 2-aminoethoxy group at the para position) 4-((2-aminoethyl)oxy)phenylmethyl (benzene ring with a 2-aminoethyl group at the para position) 2-((2-aminopyridin-3-yl)methyl)-1-methylpyrrolidin-5-ylmethyl (pyridine ring attached to a 1-methylpyrrolidine ring) 2-((2-aminopyridin-3-yl)methyl)-1-methylpyrrolidin-5-ylmethyl (pyridine ring attached to a 1-methylpyrrolidine ring) 4-((2-aminopyridin-3-yl)methyl)-1-methylpyrrolidin-5-ylmethyl (pyridine ring attached to a 1-methylpyrrolidine ring) 2-((2-aminopyridin-3-yl)methyl)-1-methylpyrrolidin-5-ylmethyl (pyridine ring attached to a 1-methylpyrrolidine ring) 2-((2-aminopyridin-3-yl)methyl)-1-methylpyrrolidin-5-ylmethyl (pyridine ring attached to a 1-methylpyrrolidine ring) 2-((2-aminopyridin-3-yl)methyl)-1-methylpyrrolidin-5-ylmethyl (pyridine ring attached to a 1-methylpyrrolidine ring) 2-((2-aminopyridin-3-yl)methyl)-1-methylpyrrolidin-5-ylmethyl (pyridine ring attached to a 1-methylpyrrolidine ring) MeCO-r-Abu(1)-N-T-W-K(Ac)-aMeC(1)-AEF-6OH2Nal-THP-K(Ac)-N-3Pya-Sar-CONH2

[illegible]

SEQ ID NO	Structure
30	 The chemical structure shows a large cyclic peptide backbone with a disulfide bridge (S-S) connecting two side chains. The side chains include a pyridine ring, a naphthalene ring, a quaternary ammonium group (N⁺), and various amide and hydroxyl groups. The structure is highly complex and represents a specific peptide sequence. MeCO-k(Me)3-Pen(3)-N-T-7MeW-K(Ac)-Pen(3)-AEF(G)-6OH2Nal-THP-E-N-3Pya-Sar-CONH2

SEQ ID NO	Structure
31	 cPEG3aCO-Pen(3)-N-T-7MeW-K(Ac)-Pen(3)-AEF(G)-6OH2Nal-THP-K(NMeAc)-N-3Pya-Sar-CONH2

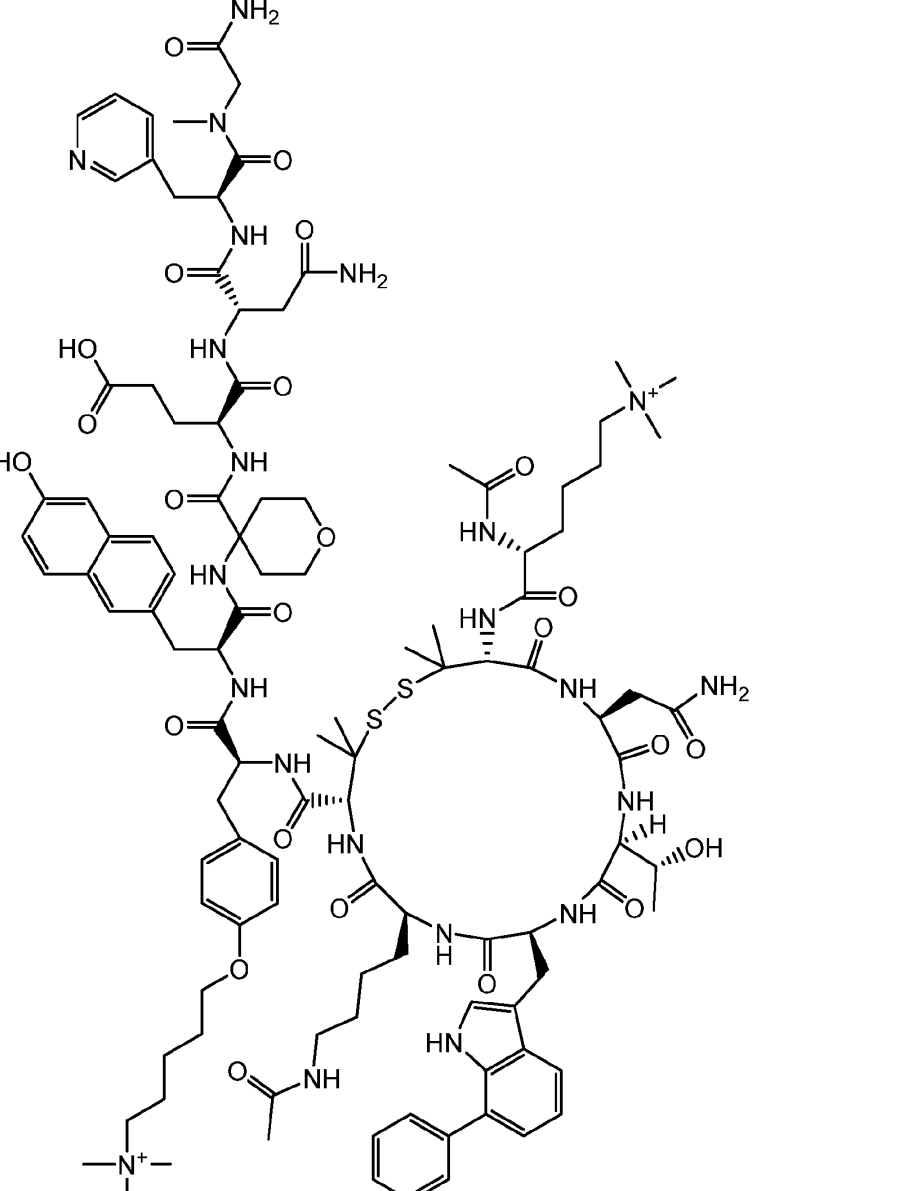
SEQ ID NO	Structure
32	MeCO-r-Pen(3)-N-T-7MeW-K(Ac)-Pen(3)-AEF(G)-6OH2NaI-THP-E-N-3Pya-Sar-CONH2

[illegible]

SEQ ID NO	Structure
34	cPEG3aCO-Pen(3)-N-T-7(3NAcPh)W-K(Ac)-Pen(3)-AEF(G)-6OH₂Nal-THP-K(NMeAc)-N-3Py-Sar-CONH₂

[illegible]

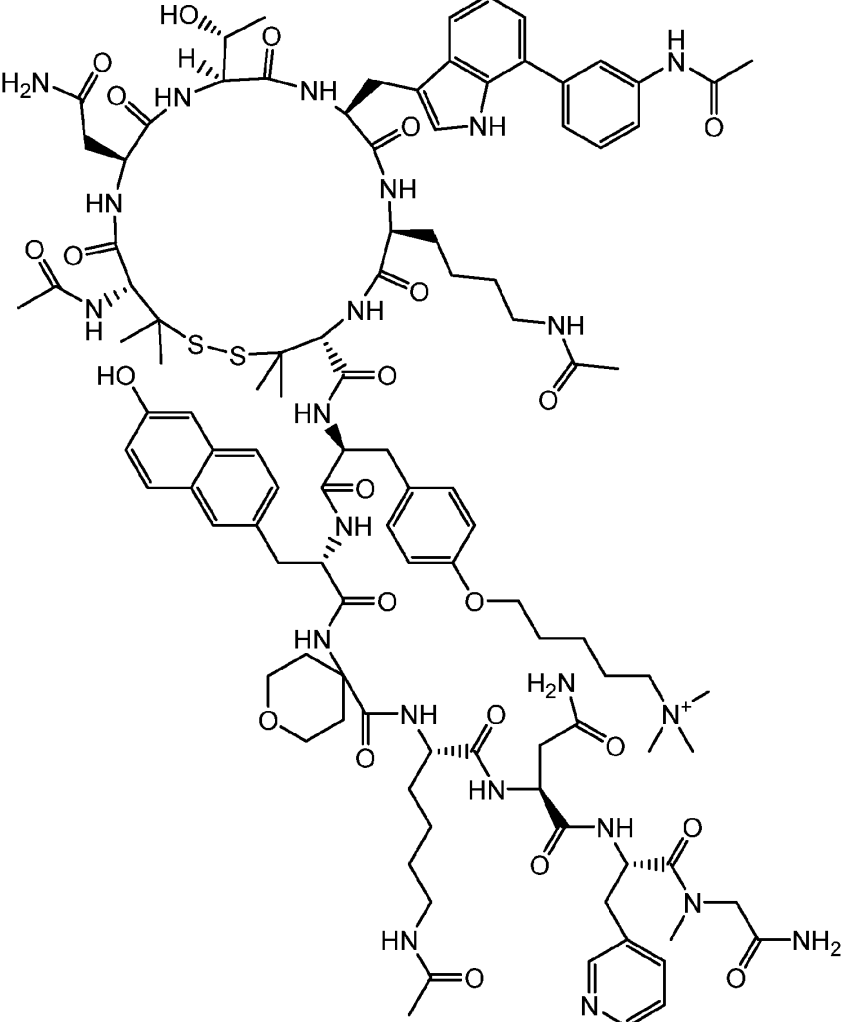
SEQ ID NO	Structure
36	cPEG3aCO-Pen(3)-N-T-7MeW-K(Ac)-Pen(3)-TMAPF-6OH2NaI-THP-K(NMeAc)-N-3Pya-Sar-CONH2

SEQ ID NO	Structure
37	 MeCO-k(Me)³-Pen(3)-N-T-7(3NAcPh)W-K(Ac)-Pen(3)-TMAPF-6OH₂Nal-THP-E-N-3Pya-Sar-CONH₂

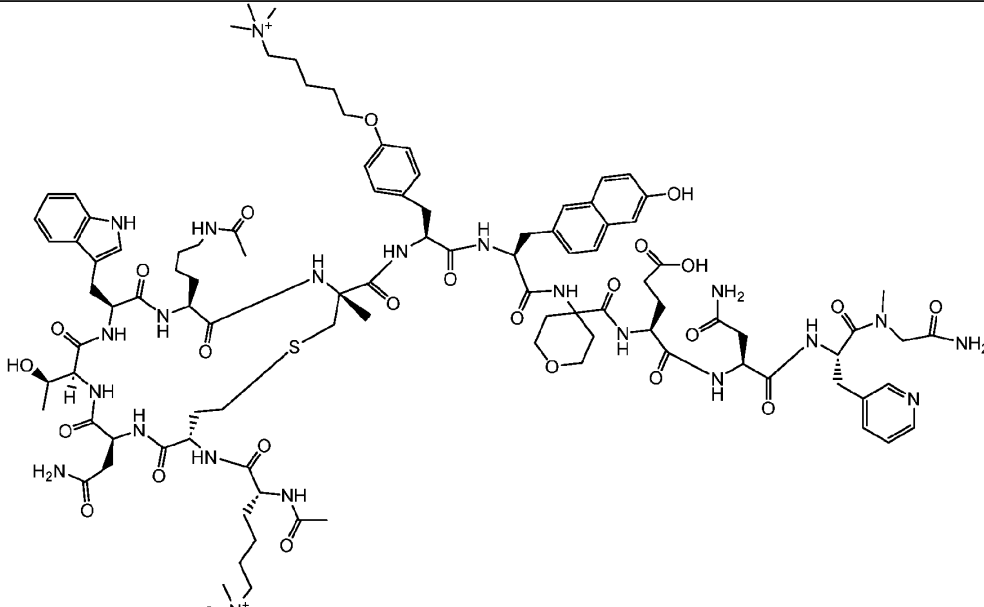
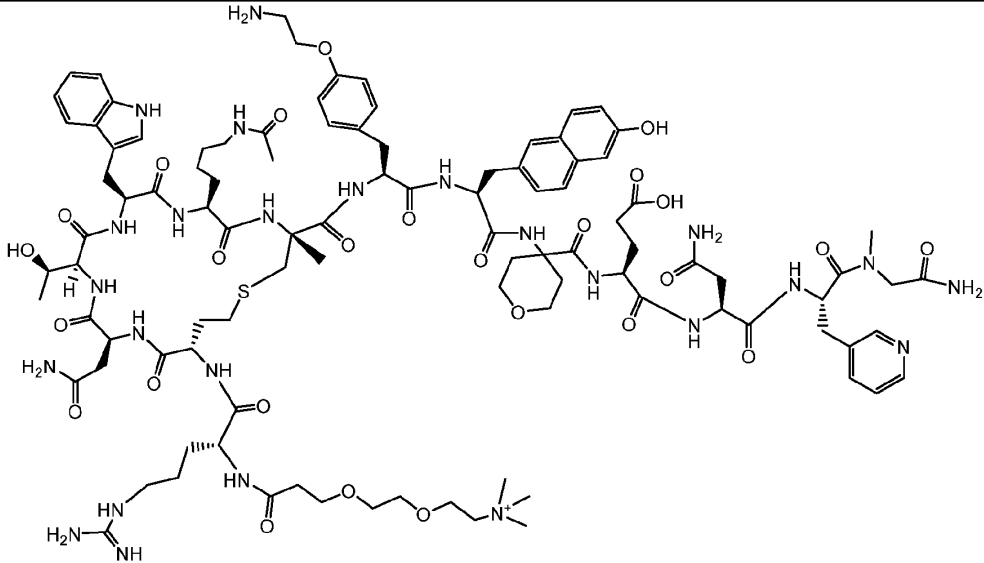
SEQ ID NO	Structure
38	cPEG3aCO-Pen(3)-N-T-7(3NAcPh)W-K(Ac)-Pen(3)-TMAPF-6OH2NaI-THP-K(NMeAc)-N-3Pyra-Sar-CONH2

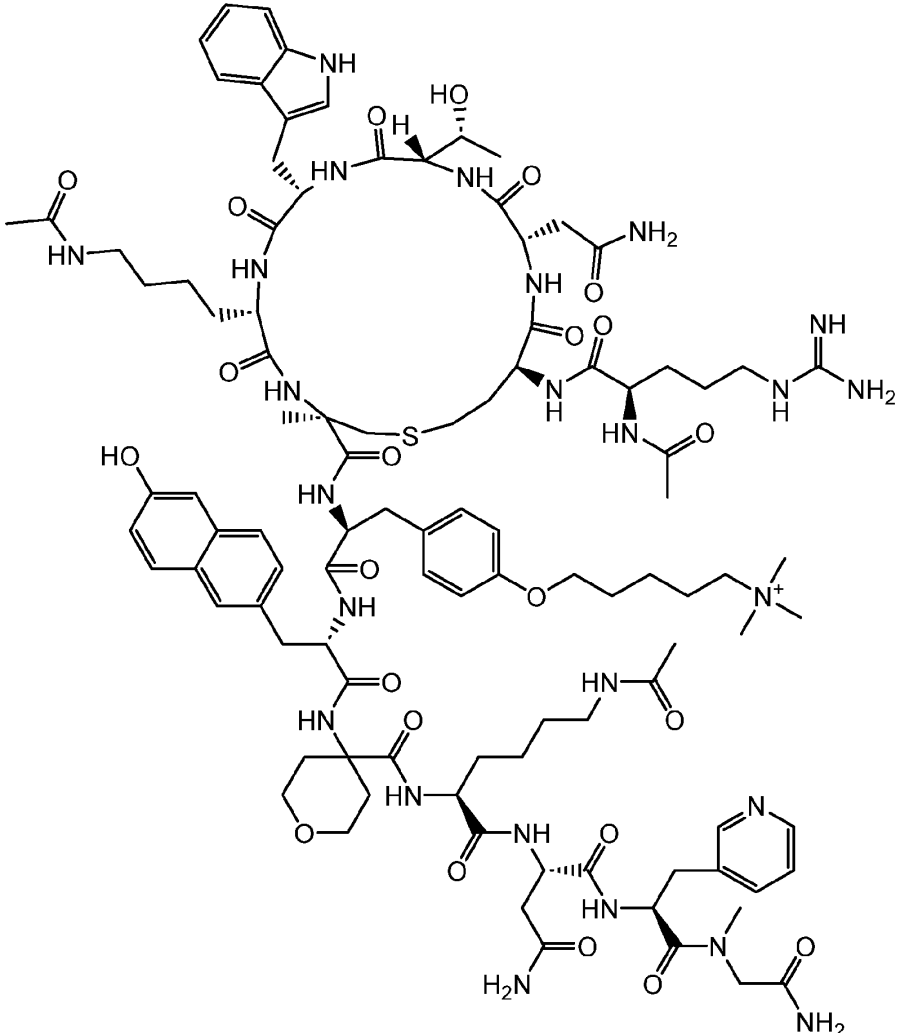
SEQ ID NO	Structure
39	MeCO-r-Pen(3)-N-T-7(3NAcPh)W-K(Ac)-Pen(3)-TMAPF-6OH2Nal-THP-E-N-3Pyra-Sar-CONH2

[illegible]

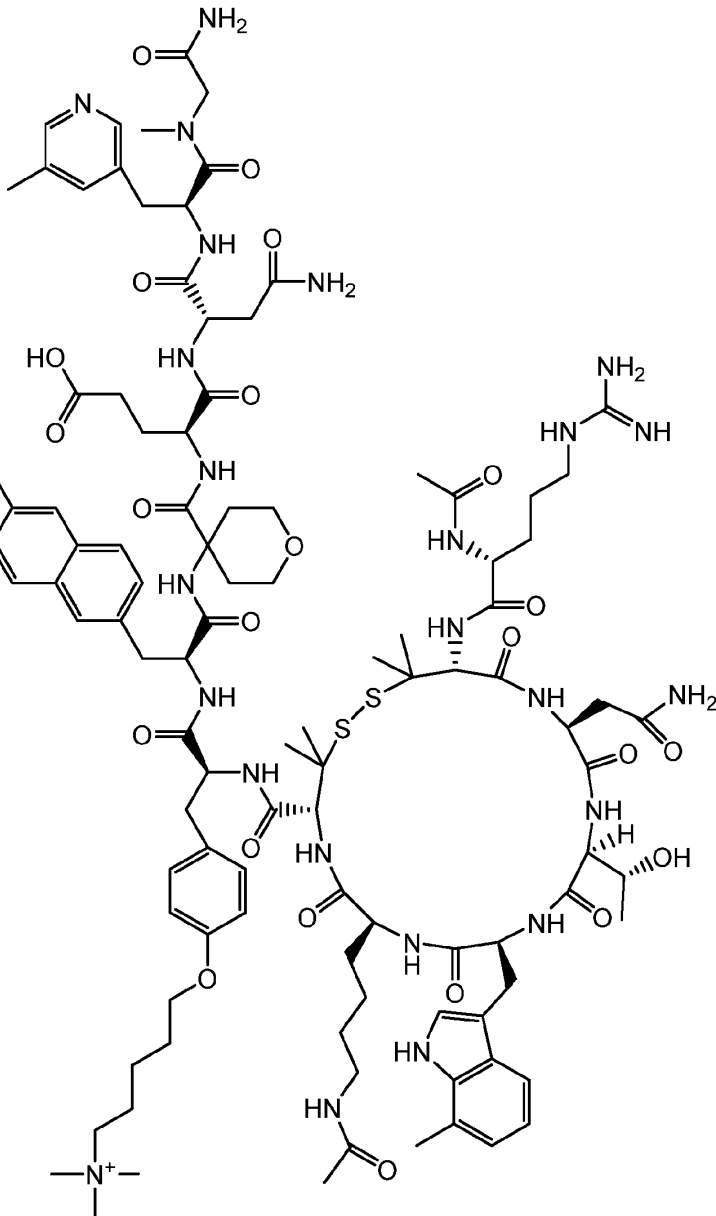
SEQ ID NO	Structure
41	 MeCO-Pen(3)-N-T-7(3NAcPh)W-K(Ac)-Pen(3)-TMAPF-6OH2Nal-THP-K(Ac)-N-3Pyra-Sar-CONH2

SEQ ID NO	Structure
42	Chemical structure of a large cyclic peptide (42). The structure features a central macrocyclic ring with a disulfide bridge (S-S) and a thiazolidine ring. Various side chains are attached to the ring, including a pyridine ring, a naphthol group, a morpholine ring, a thiazolidine ring, and a long alkyl chain with a quaternary ammonium group (N⁺).

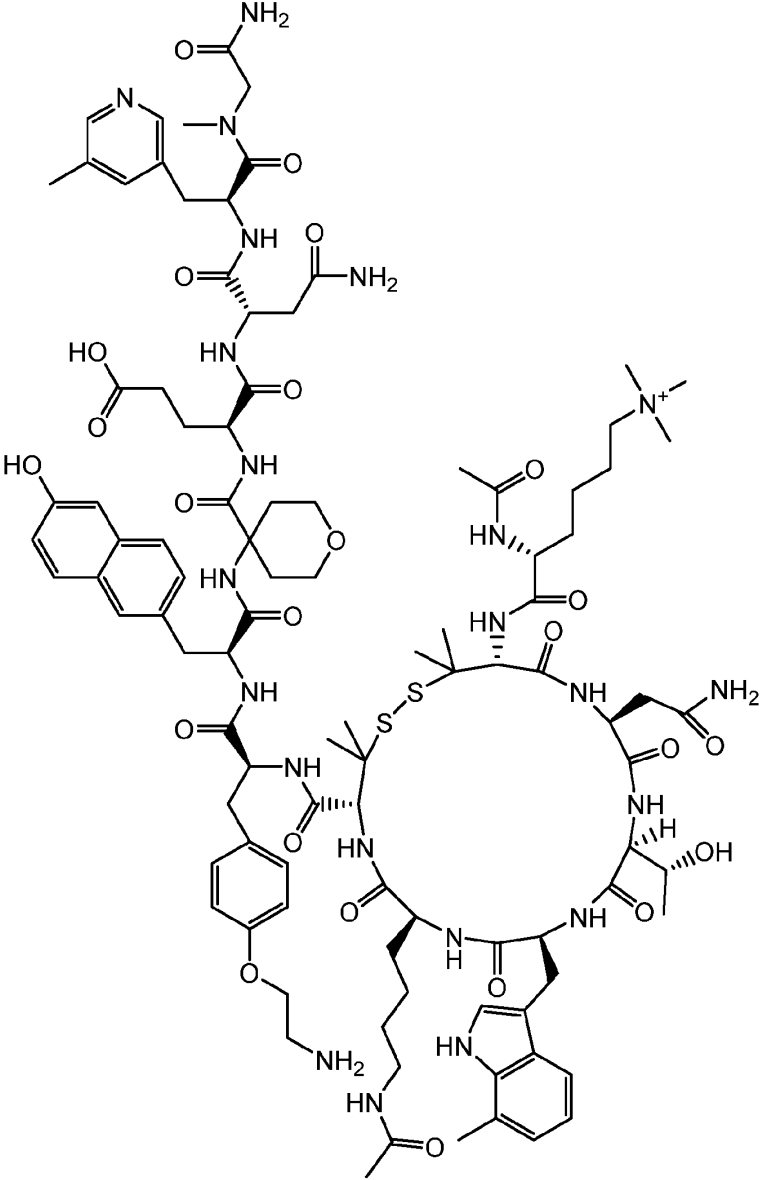
SEQ ID NO	Structure
43	 MeCO-k(Me)₃-Abu(1)-N-T-W-K(Ac)-aMeC(1)-TMAPF-6OH₂Nal-THP-E-N-3Pyra-Sar-CONH₂
44	 cPEG₃aCO-r-Abu(1)-N-T-W-K(Ac)-aMeC(1)-AEF-6OH₂Nal-THP-E-N-3Pyra-Sar--CONH₂

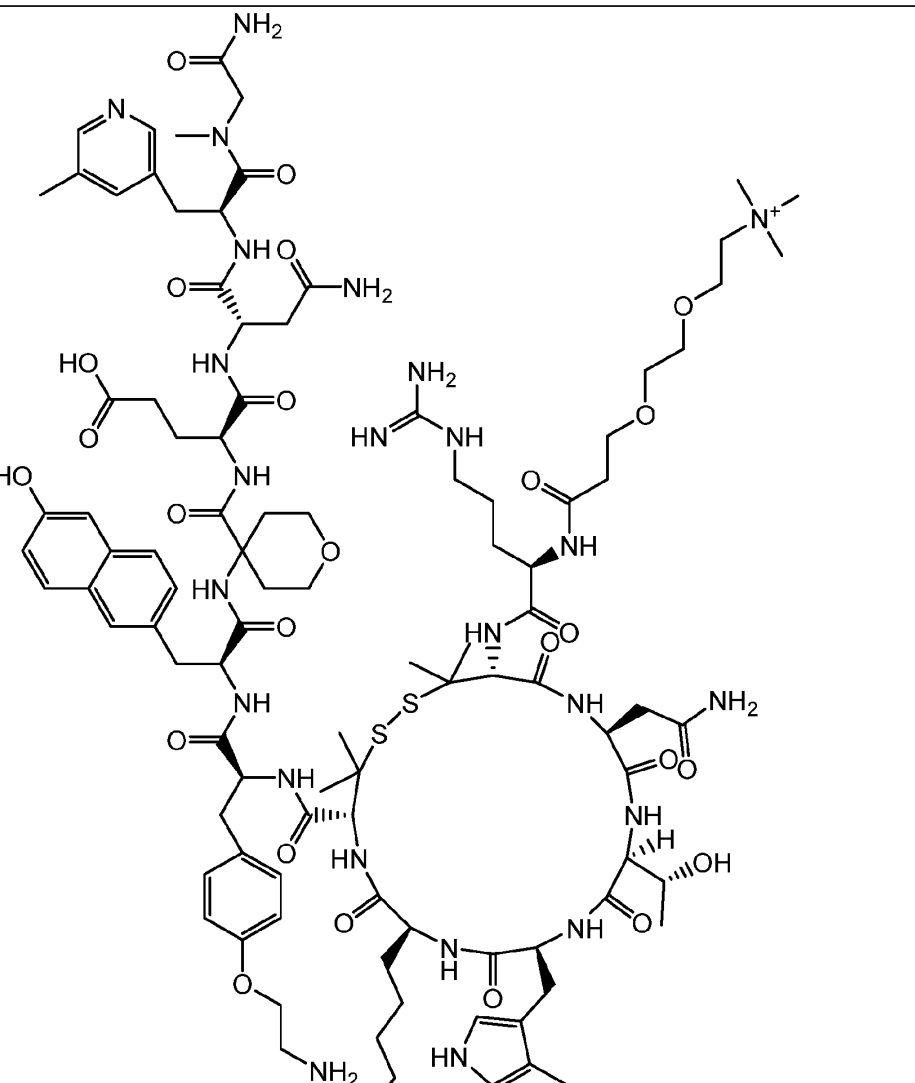
SEQ ID NO	Structure
45	 MeCO-r-Abu(1)-N-T-W-K(Ac)-aMeC(1)-TMAPF-6OH2Nal-THP-K(Ac)-N-3Pya-Sar-CONH2

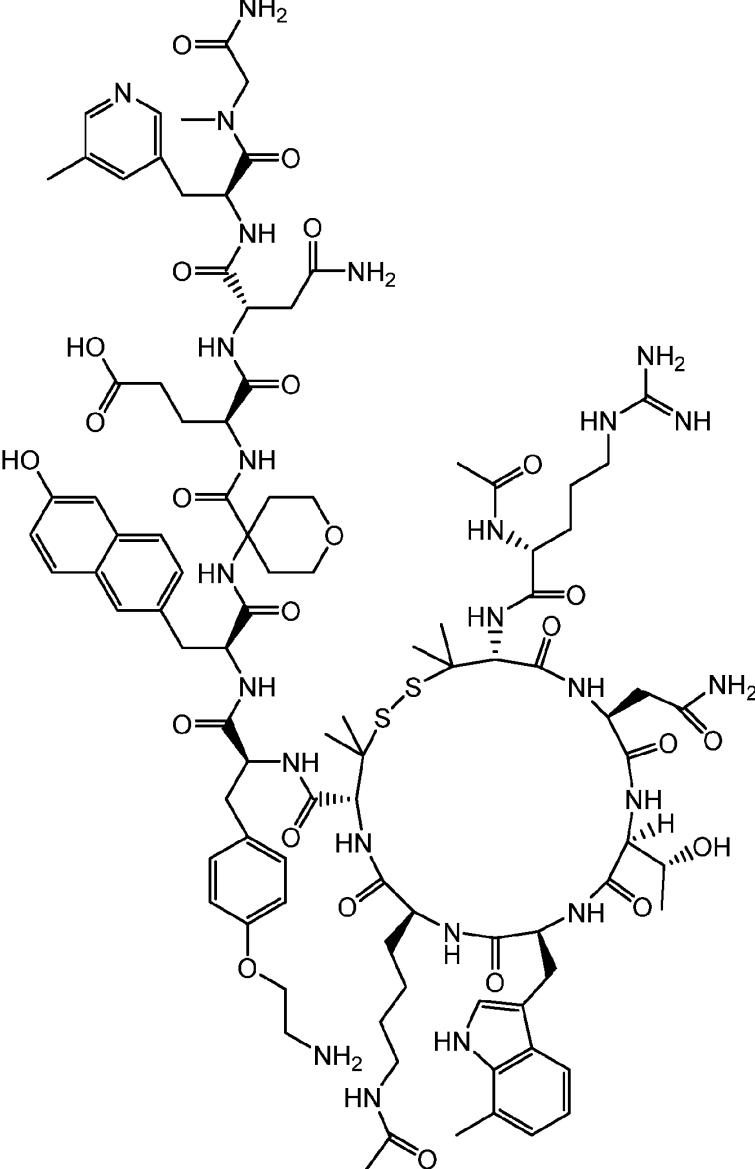
SEQ ID NO	Structure
46	MeCO-r-Abu(1)-N-T-W-K(Ac)-aMeC(1)-TMAPF-6OH2Nal-THP-E-N-3Pya-Sar--CONH2
47	cPEG3aCO-r-Abu(1)-N-T-W-K(Ac)-aMeC(1)-TMAPF-6OH2Nal-THP-E-N-3Pya-Sar-CONH2

SEQ ID NO	Structure
48	 MeCO-r-Pen(3)-N-T-7MeW-K(Ac)-Pen(3)-TMAPF-6OH2NaI-THP-E-N-5MePyridinAla-Sar-CONH2

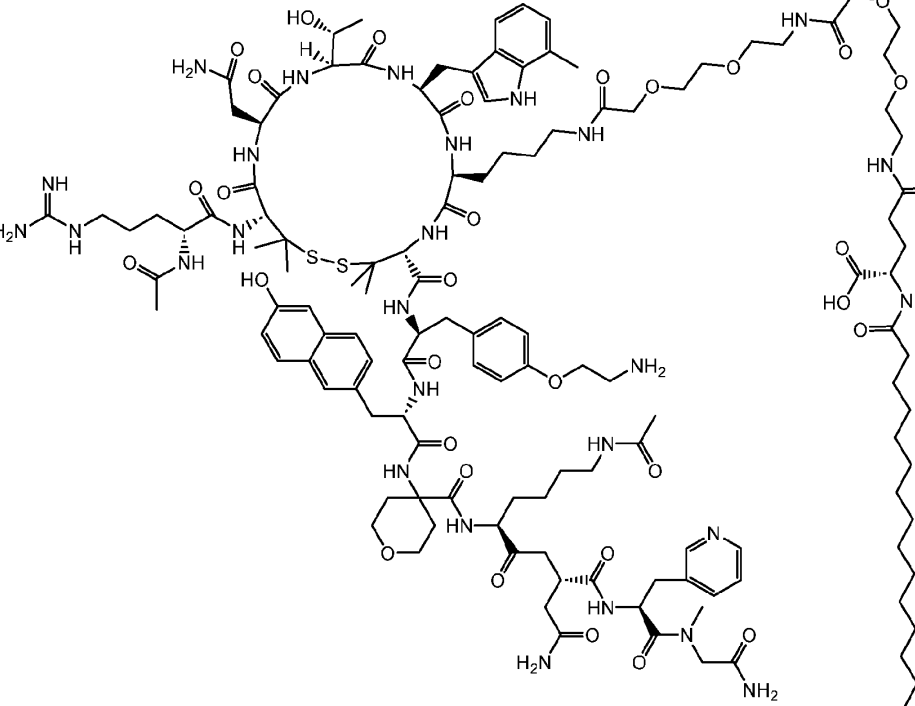
SEQ ID NO	Structure
49	MeCO-r-Pen(3)-N-T-7MeW-K(Ac)-Pen(3)-AEF-6OH2Nal-THP-K(Ac)-N-5MePyridinAla-Sar-CONH2

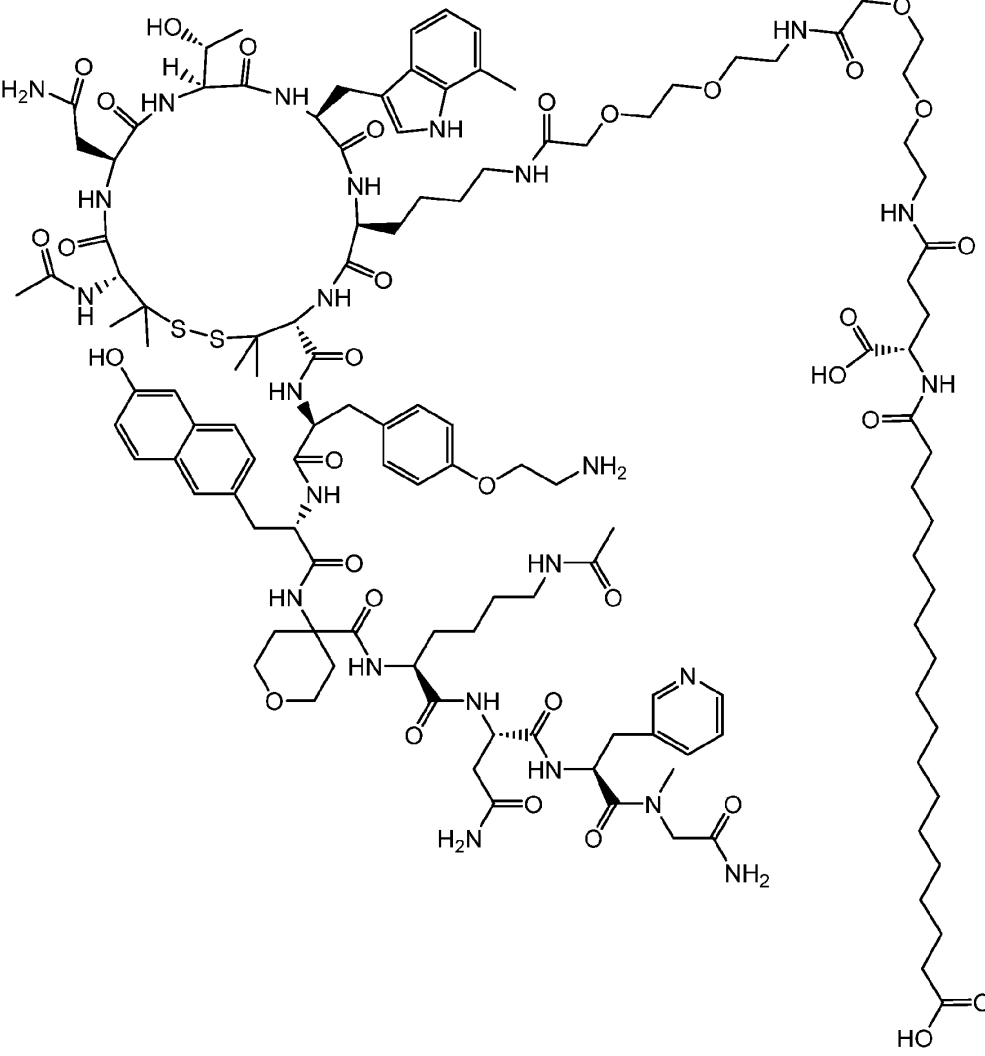
SEQ ID NO	Structure
50	 MeCO-k(Me)3-Pen(3)-N-T-7MeW-K(Ac)-Pen(3)-AEF-6OH2Nal-THP-E-N-5MePyridinAla-Sar-CONH2

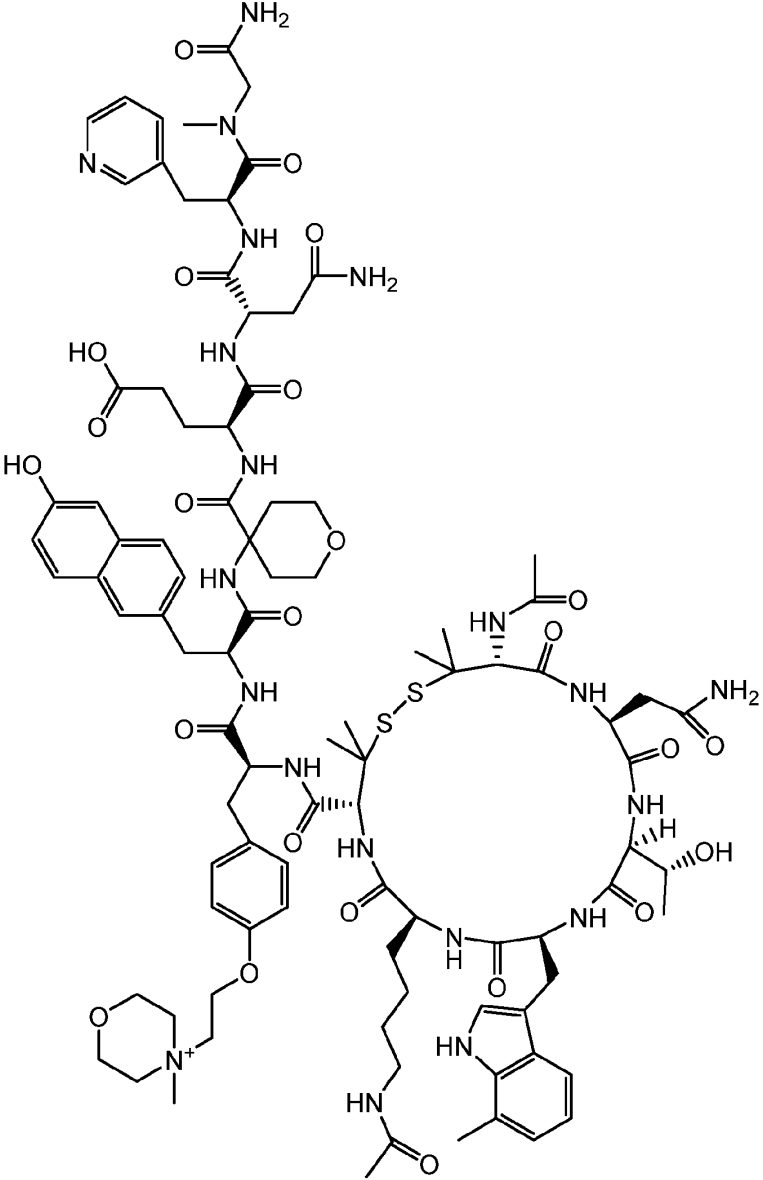
SEQ ID NO	Structure
51	 The structure shows a large cyclic peptide backbone with a disulfide bridge. Various side chains are attached to the backbone, including a pyridine ring, a naphthalene ring, a morpholine ring, and a PEG chain. The peptide is labeled as cPEG3aCO-r-Pen(3)-N-T-7MeW-K(Ac)-Pen(3)-AEF-6OH2NaI-THP-E-N-5MePyridinAla-Sar-CONH2.

SEQ ID NO	Structure
52	 MeCO-r-Pen(3)-N-T-7MeW-K(Ac)-Pen(3)-AEF-6OH2Nal-THP-E-N-5MePyridinAla-Sar-CONH2

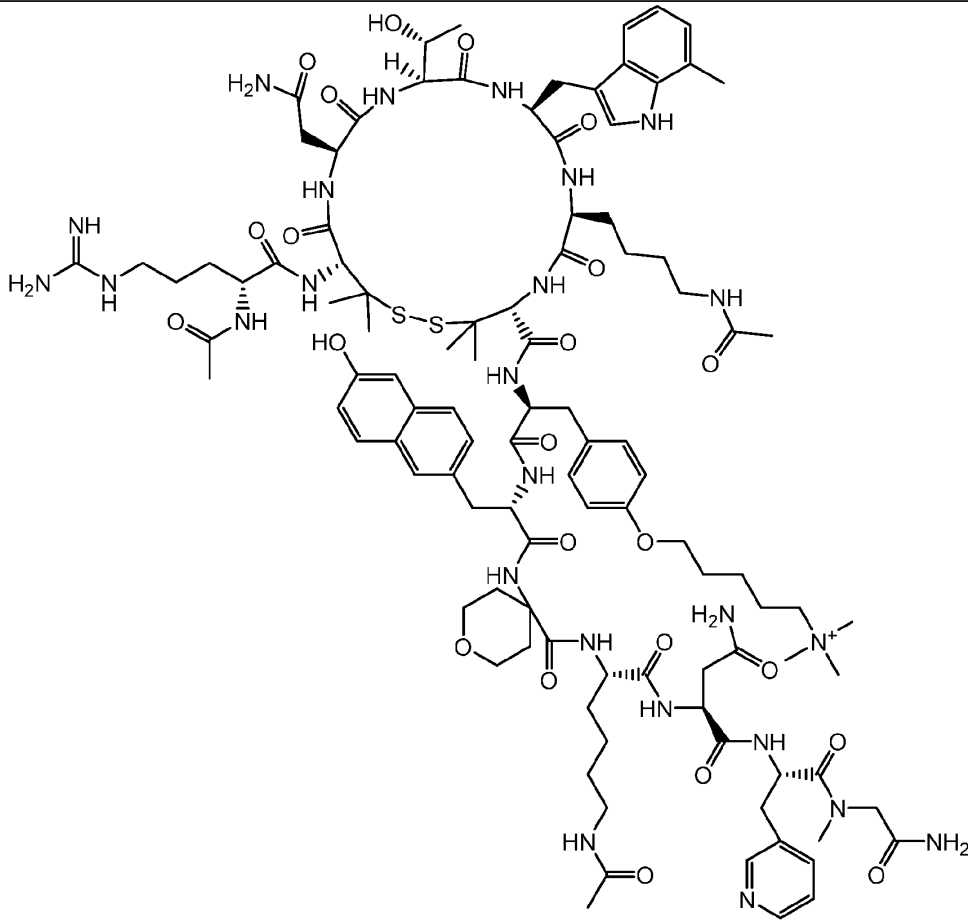
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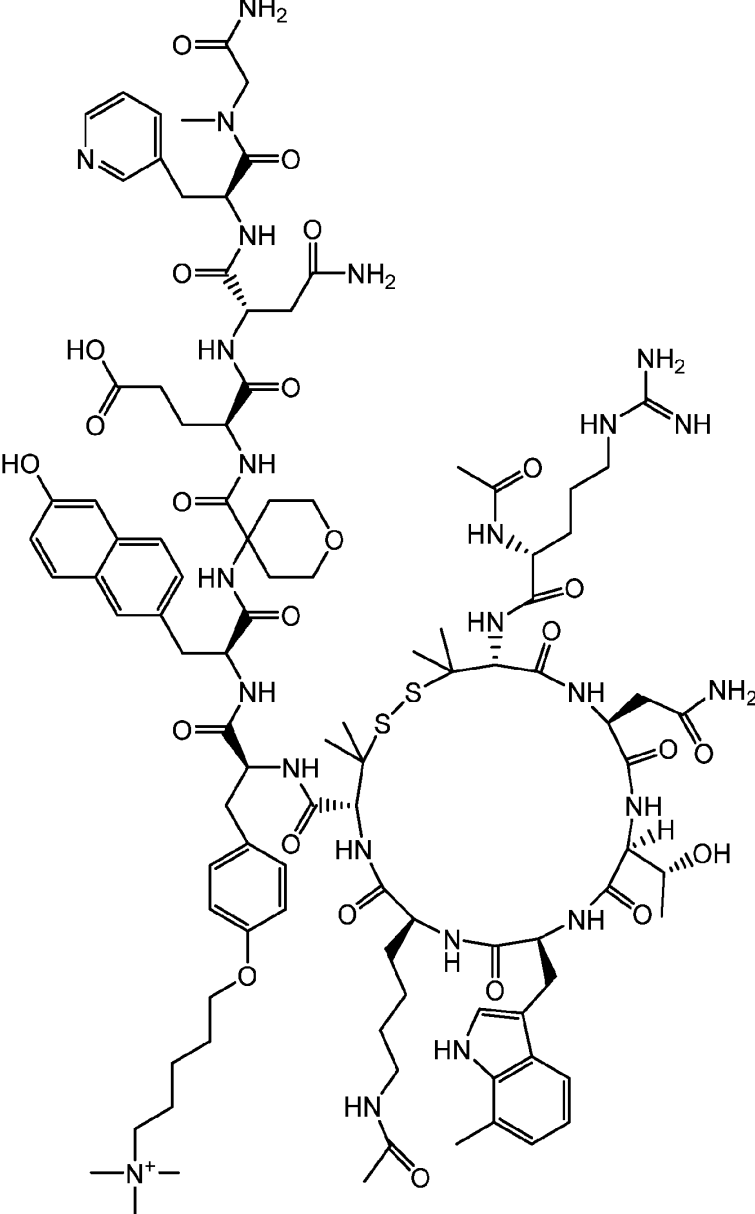
SEQ ID NO	Structure
54	 MeCO-r-Pen(3)-N-T-7MeW-K(PEG2PEG2gEC18OH)-Pen(3)-AEF-6OH2NaI-THP-K(Ac)-N-3Pya-Sar-CONH2

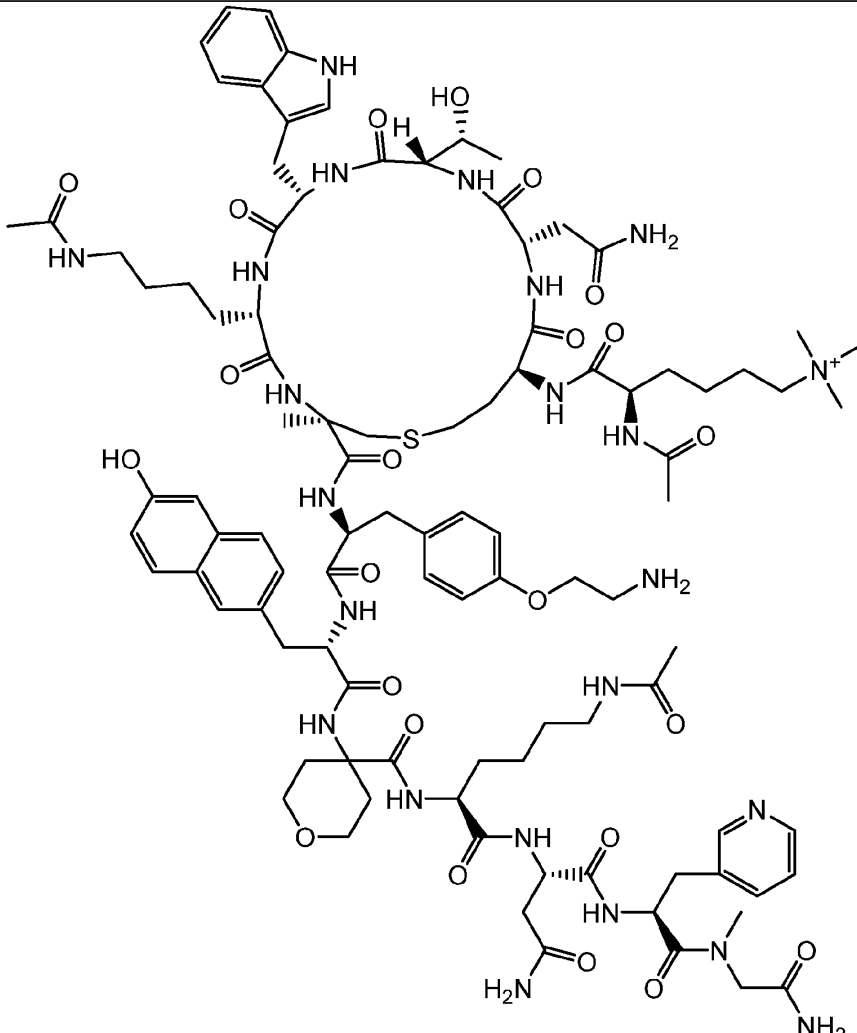
SEQ ID NO	Structure
55	 MeCO-Pen(3)-N-T-7MeW-K(PEG2PEG2gEC18OH)-Pen(3)-AEF-6OH2Nal-THP-K(Ac)-N-3Pya-Sar-CONH2

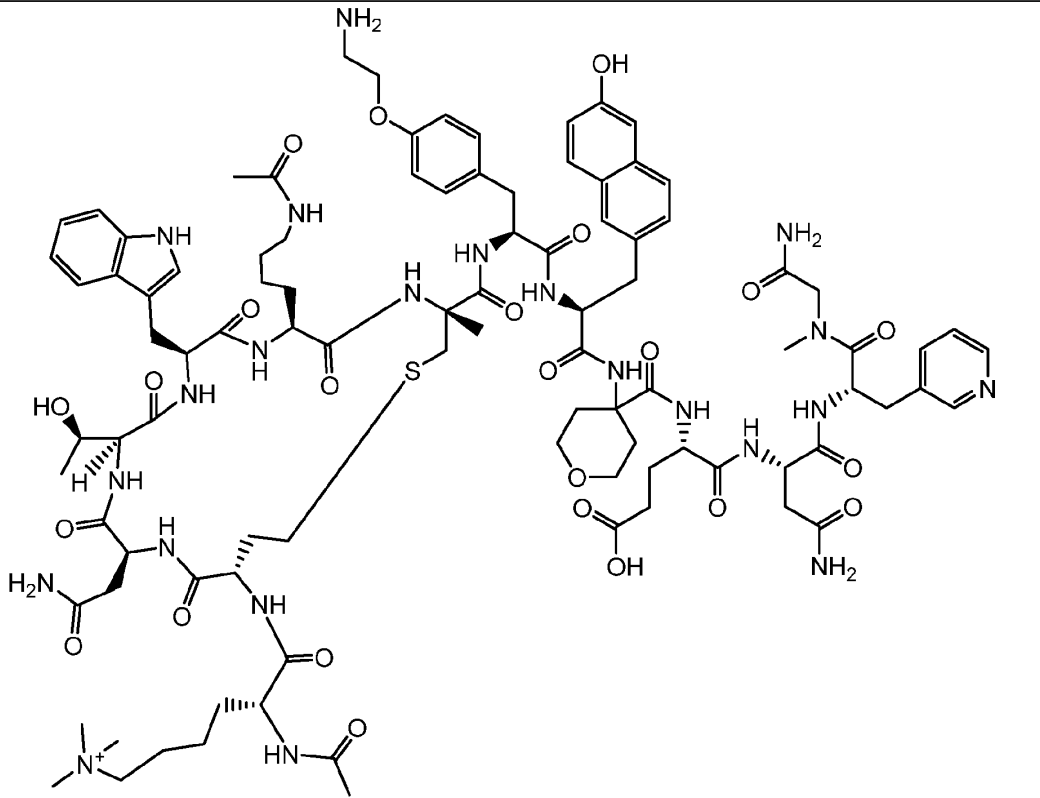
SEQ ID NO	Structure
56	 MeCO-Pen(3)-N-T-7MeW-K(Ac)-Pen(3)-MMoEF-6OH2Nal-THP-E-N-3Pya-Sar-CONH2

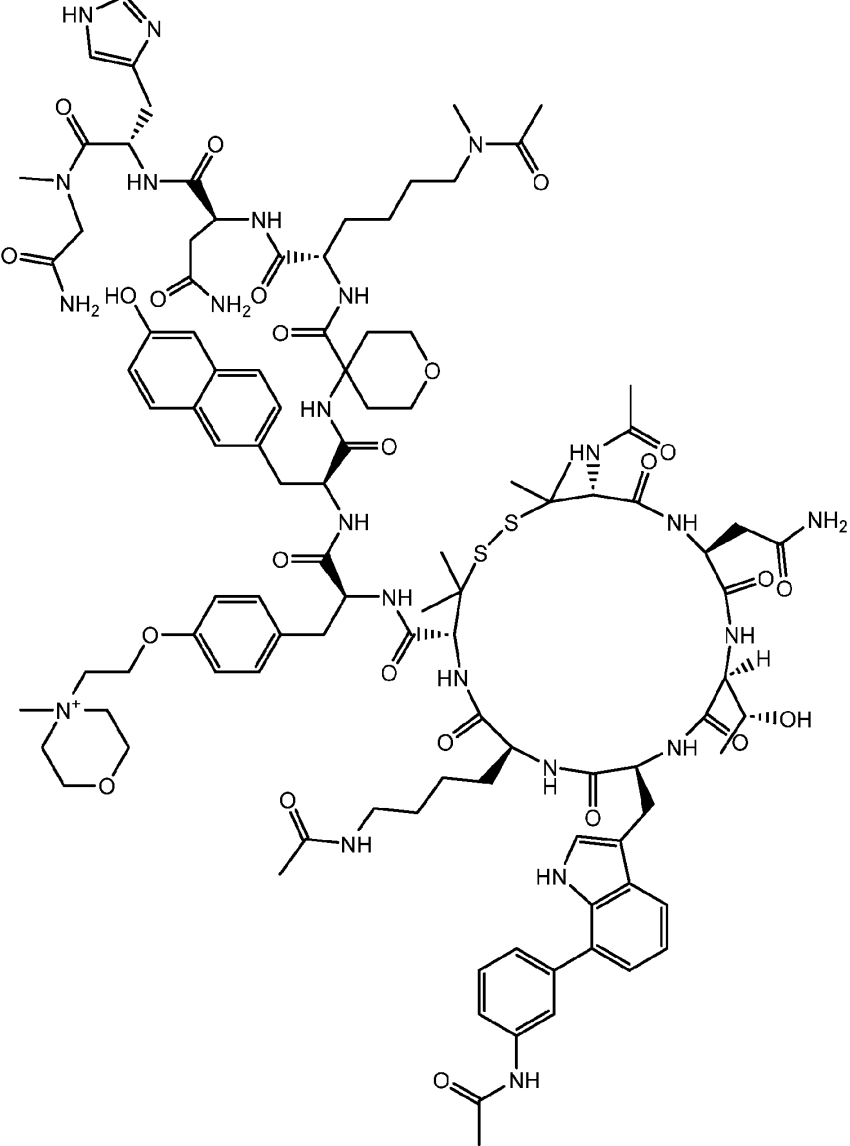
[illegible]

SEQ ID NO	Structure
58	 The chemical structure depicts a large cyclic peptide with a 24-residue backbone. The residues are connected by amide bonds, forming a macrocyclic ring. The side chains are diverse, including aromatic groups (phenyl, naphthyl, indolyl, pyridyl), aliphatic chains, and functional groups like hydroxyl, thiol, and amide. A disulfide bridge is present between two cysteine residues. The structure is labeled with the sequence: MeCO-r-Pen(3)-N-T-7MeW-K(Ac)-Pen(3)-TMAPF-6OH2Nal-THP-K(Ac)-N-3Pya-Sar-CONH2. MeCO-r-Pen(3)-N-T-7MeW-K(Ac)-Pen(3)-TMAPF-6OH2Nal-THP-K(Ac)-N-3Pya-Sar-CONH2

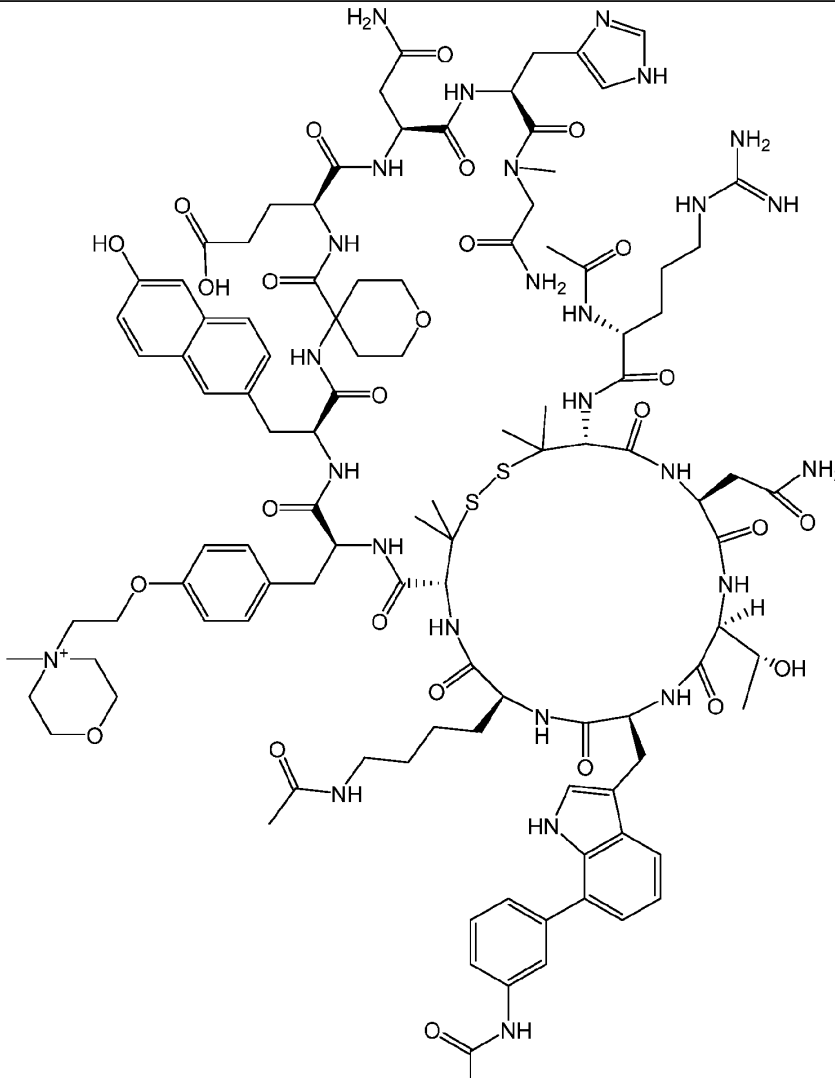
SEQ ID NO	Structure
59	 MeCO-r-Pen(3)-N-T-7MeW-K(Ac)-Pen(3)-TMAPF-6OH2NaI-THP-E-N-3Pya-Sar-CONH2

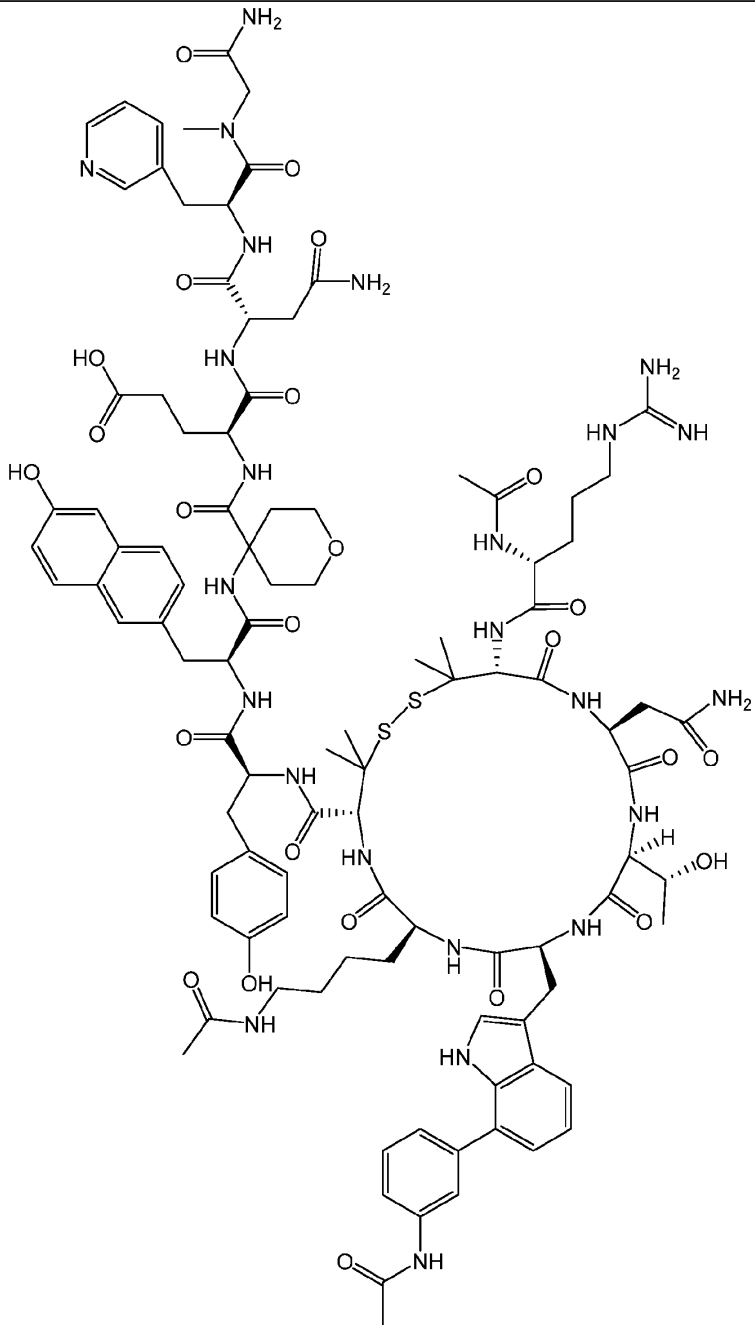
SEQ ID NO	Structure
60	 The chemical structure shows a cyclic peptide with a 16-membered ring containing a thioether bridge. The side chains are: 1. Indol-3-ylmethyl (top left). 2. 2-hydroxyethyl (top). 3. 2-aminoethyl (top right). 4. 2-(dimethylamino)ethyl (right). 5. 2-acetyl-1-methyl-4-aminobutyl (bottom right). 6. 2-(pyridin-3-ylmethyl)-1-methyl-4-aminobutyl (bottom right). 7. 2-amino-3-oxopropyl (bottom). 8. 2-(4-aminophenoxy)ethyl (bottom). 9. 2-(4-hydroxyphenyl)ethyl (bottom left). 10. 2-(4-oxo-4,5,6,7-tetrahydro-2H-pyran-2-yl)ethyl (bottom left). 11. 2-(4-oxo-4,5,6,7-tetrahydro-2H-pyran-2-yl)ethyl (bottom left). 12. 2-(4-oxo-4,5,6,7-tetrahydro-2H-pyran-2-yl)ethyl (bottom left). 13. 2-(4-oxo-4,5,6,7-tetrahydro-2H-pyran-2-yl)ethyl (bottom left). 14. 2-(4-oxo-4,5,6,7-tetrahydro-2H-pyran-2-yl)ethyl (bottom left). 15. 2-(4-oxo-4,5,6,7-tetrahydro-2H-pyran-2-yl)ethyl (bottom left). 16. 2-(4-oxo-4,5,6,7-tetrahydro-2H-pyran-2-yl)ethyl (bottom left). MeCO-k(Me)3-Abu(1)-N-T-W-K(Ac)-aMeC(1)-AEF-6OH2Nal-THP-K(Ac)-N-3Pya-Sar-CONH2

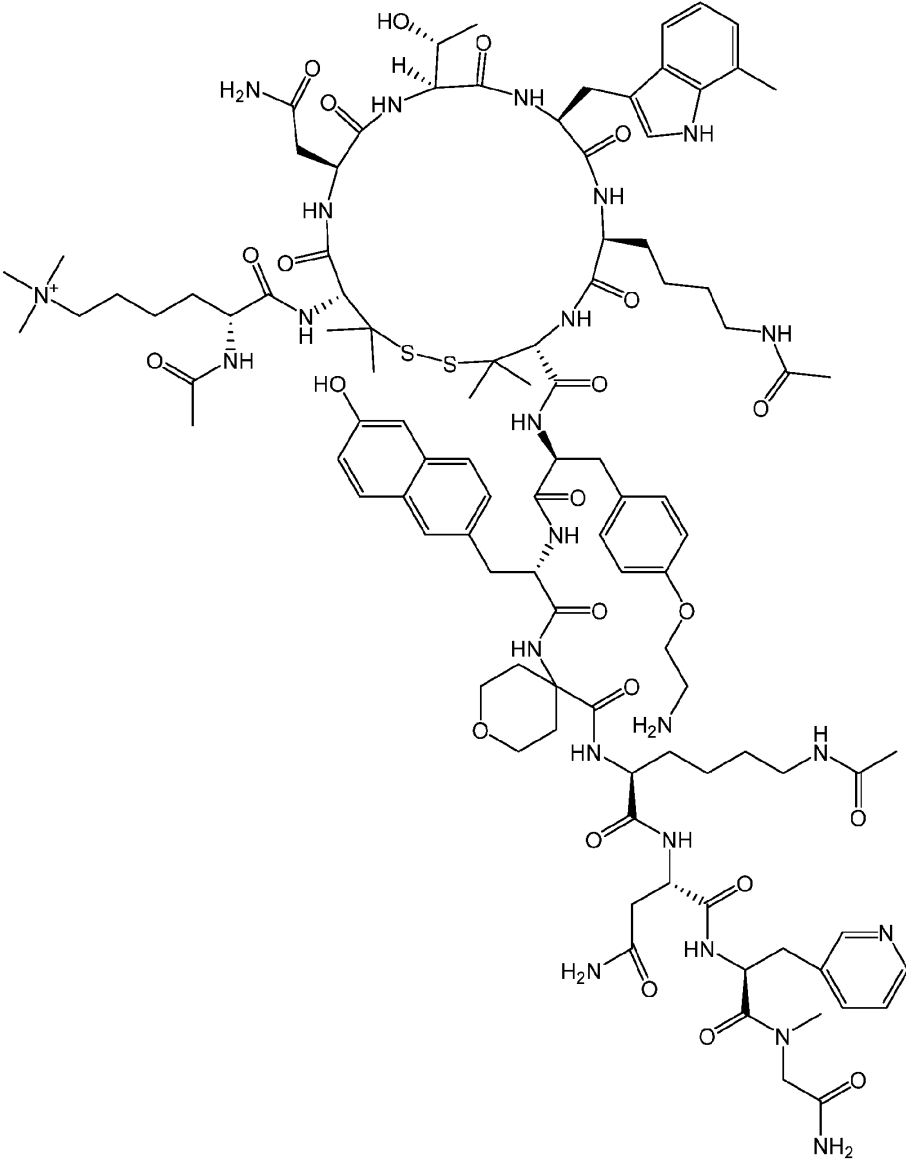
SEQ ID NO	Structure
61	 MeCO-k(Me)3-Abu(1)-N-T-W-K(Ac)-aMeC(1)-AEF-6OH2Nal-THP-E-N-3PyA-Sar-CONH2

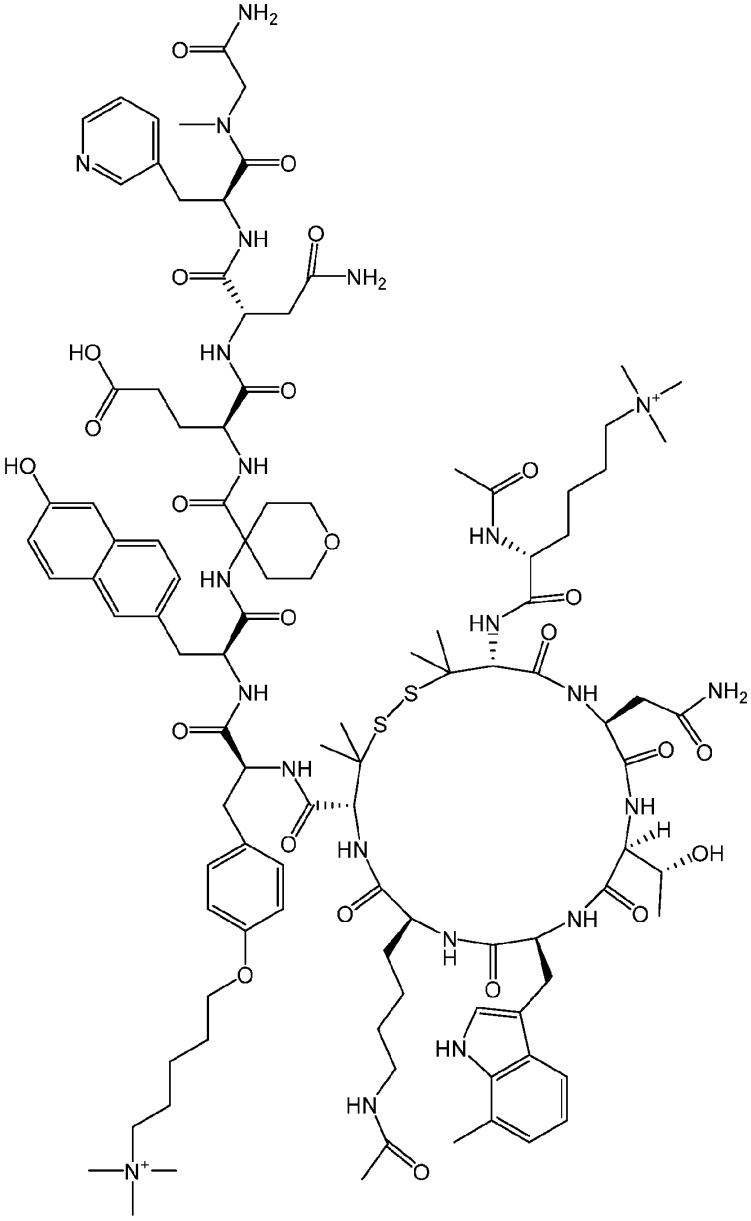
SEQ ID NO	Structure
62	 MeCO-Pen(3)-N-T-7(3NAcPh)W-K(Ac)-Pen(3)-MMoEF-6OH2NaI-THP-K(NMeAc)-N-H-Sar-CONH2

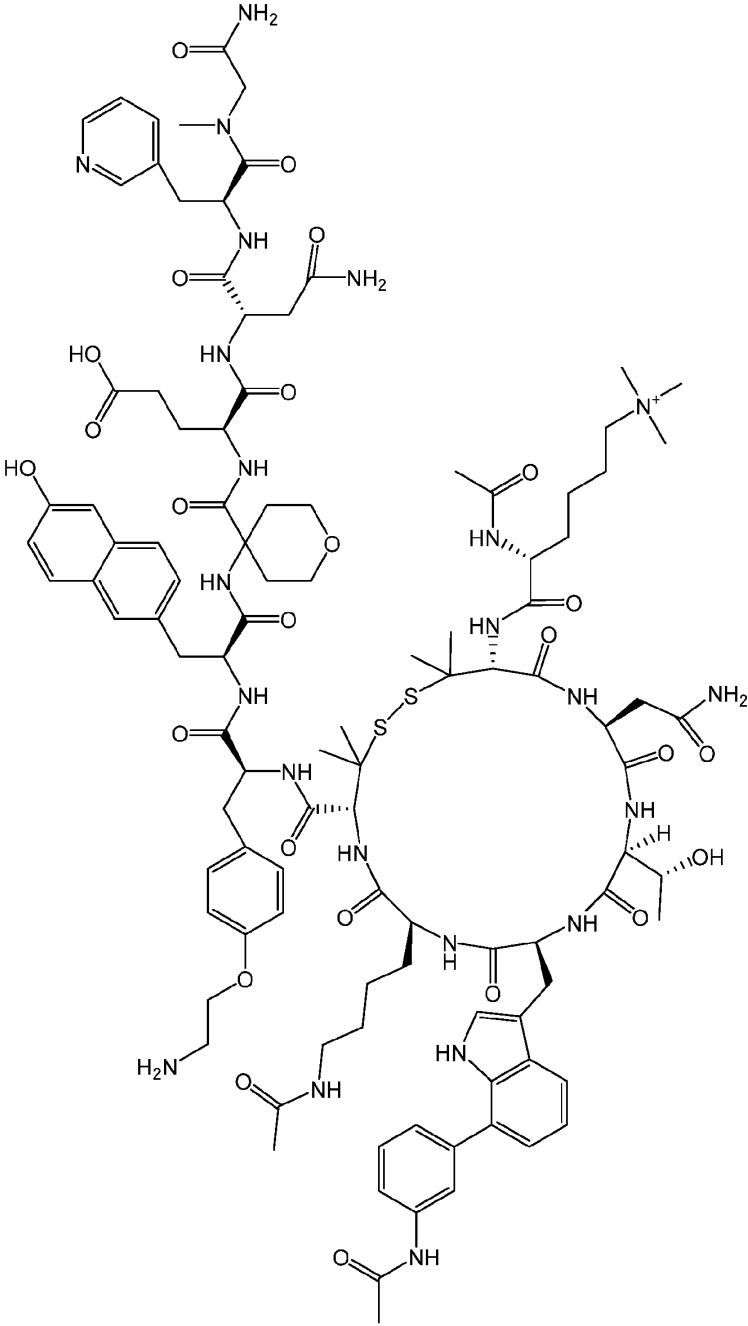
[illegible]

SEQ ID NO	Structure
64	 The structure shows a large cyclic peptide with 32 residues. The backbone is a 32-membered ring with a disulfide bridge between two cysteine residues. The side chains are diverse, including aromatic groups (phenyl, indolyl, tryptophanyl), aliphatic groups (isopropyl, isobutyl, isovaleryl), and functional groups (hydroxyl, carboxyl, amide, guanidino, guanidinoethyl, and a quaternary ammonium group). The sequence is: MeCO-r-Pen(3)-N-T-7(3NAcPh)W-K(Ac)-Pen(3)-MMoEF-6OH2NaI-THP-E-N-H-Sar-CONH2.

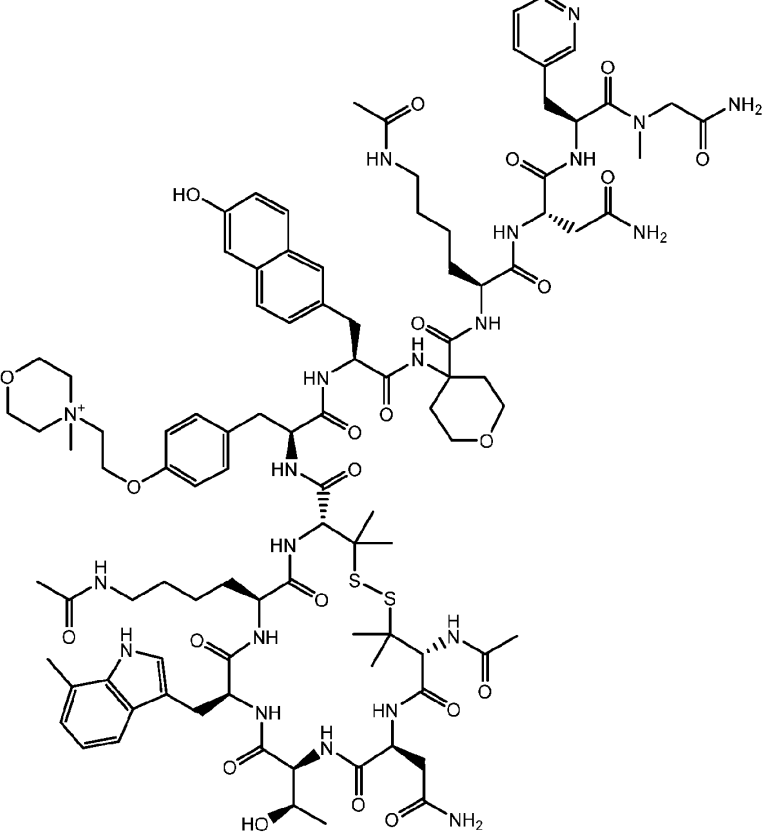
SEQ ID NO	Structure
65	 The chemical structure represents a complex cyclic peptide derivative. It features a 35-residue cyclic backbone with a disulfide bridge (S-S) connecting two cysteine residues. The side chains include a pyridine ring, a 3-acetylphenyl group, a 6-hydroxy-2-naphthyl group, a 3-pyridyl group, and a 3-acetylphenyl group. The structure is highly detailed, showing the stereochemistry of the amino acids and the specific functional groups attached to the peptide backbone. MeCO-r-Pen(3)-N-T-7(3NAcPh)W-K(Ac)-Pen(3)-Y-6OH2Nal-THP-E-N-3Pya-Sar-CONH2

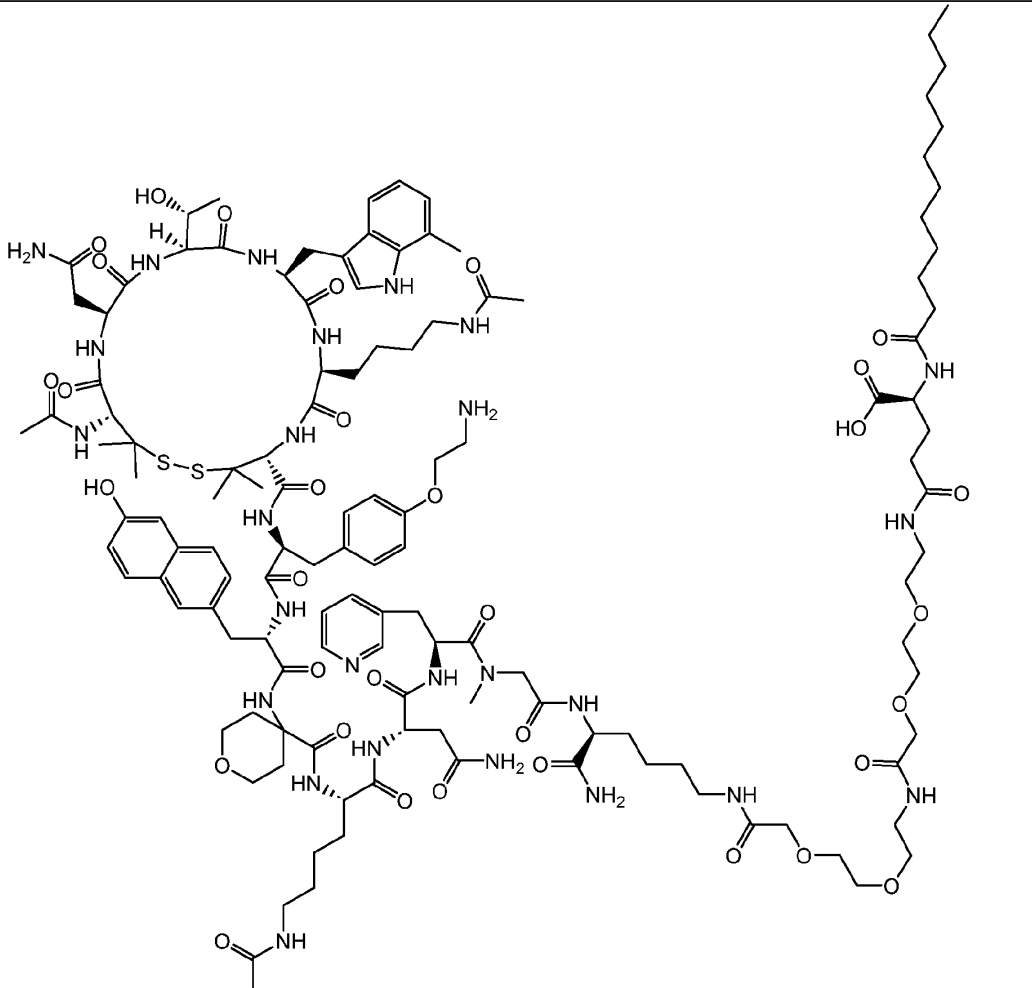
SEQ ID NO	Structure
66	 MeCO-k(Me)3-Pen(3)-N-T-7MeW-K(Ac)-Pen(3)-AEF-6OH2Nal-THP-K(Ac)-N-3Pya-Sar-CONH2

SEQ ID NO	Structure
67	 MeCO-k(Me)₃-Pen(3)-N-T-7MeW-K(Ac)-Pen(3)-TMAPF-6OH₂Nal-THP-E-N-3PyA-Sar-CONH₂

SEQ ID NO	Structure
68	 MeCO-k(Me)3-Pen(3)-N-T-7(3NAcPh)W-K(Ac)-Pen(3)-AEF-6OH2Nal-THP-E-N-3Py-Sar-CONH2

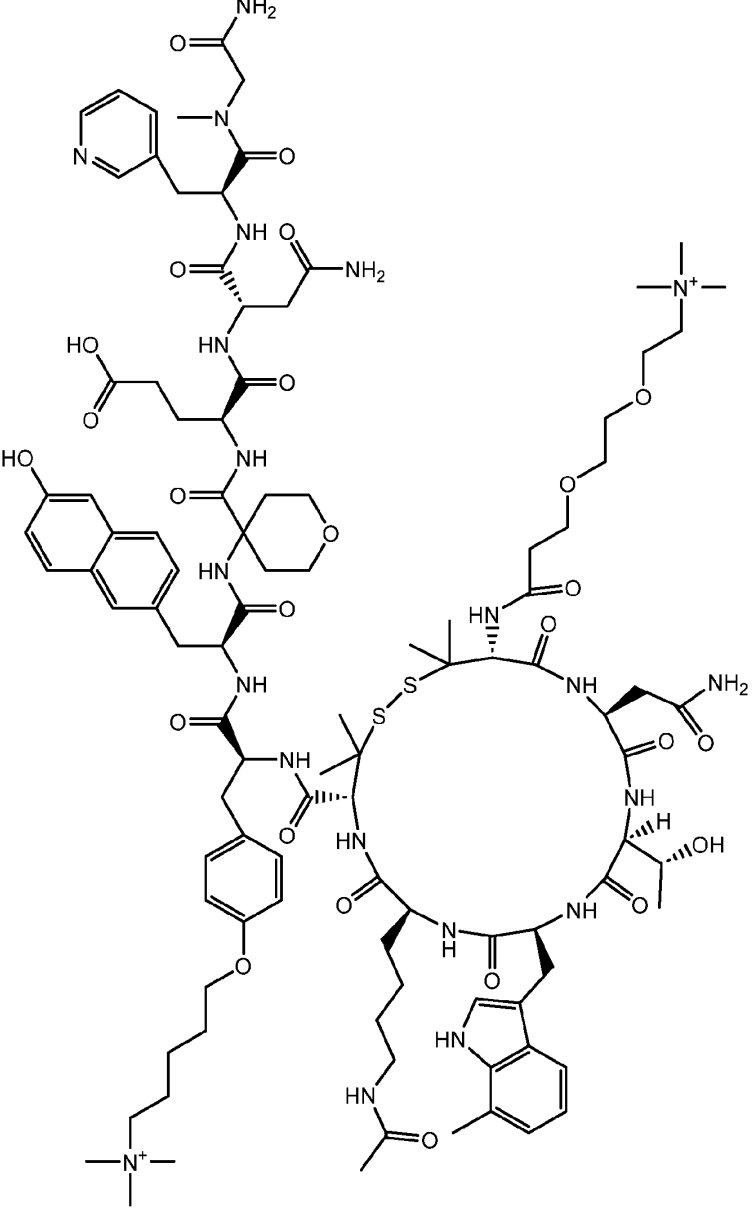
cPEG3aCO-Pen(3)-N-T-7(3NAcPh)W-K(Ac)-Pen(3)-AEF-6OH2Nal-THP-E-N-3Pya-Sar-CONH2

SEQ ID NO	Structure
71	 MeCO-Pen(3)-N-T-7MeW-K(Ac)-Pen(3)-MMoEF-6OH2Nal-THP-K(Ac)-N-3Pya-Sar

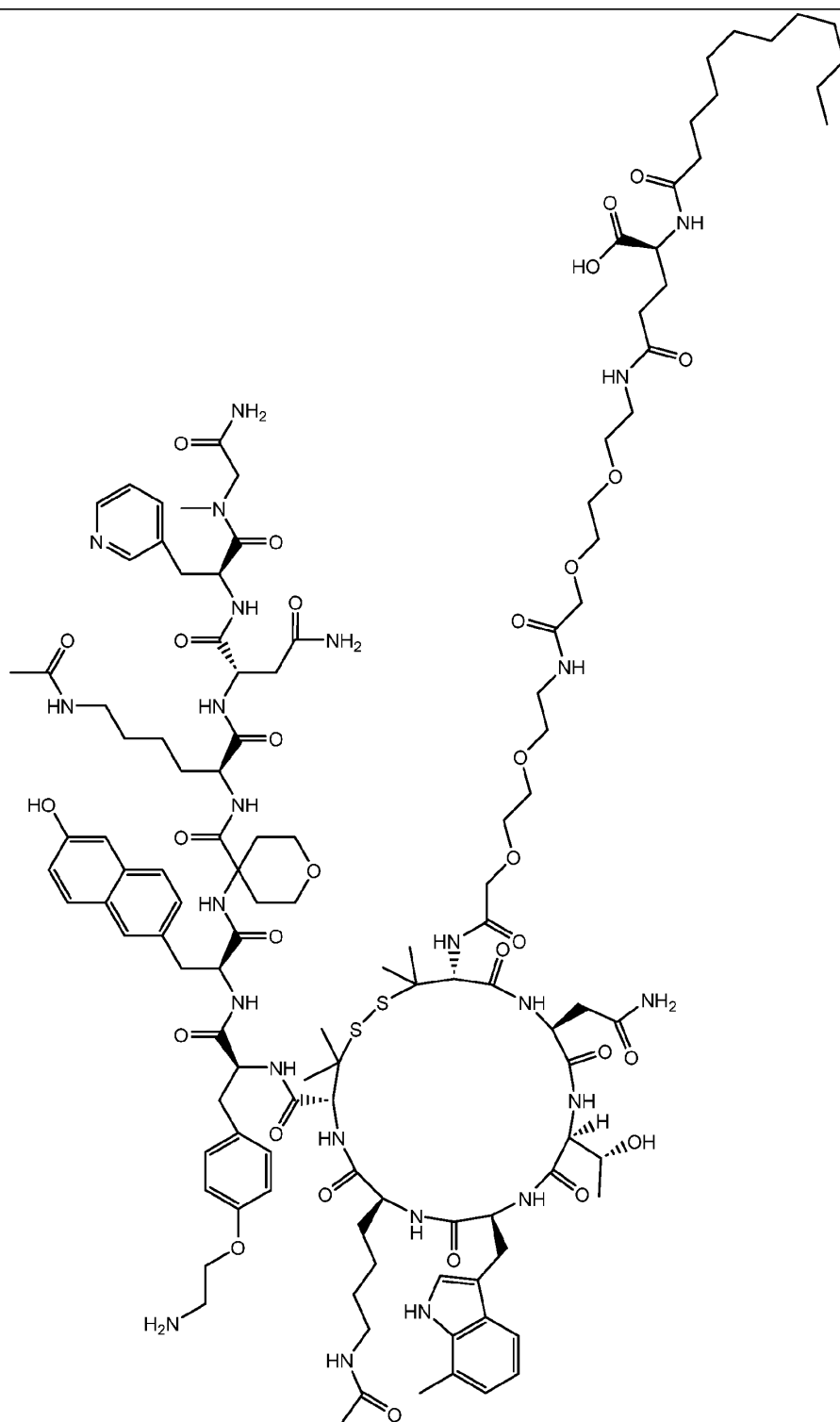
SEQ ID NO	Structure
72	 The chemical structure depicts a large cyclic peptide. The backbone is a 12-membered ring with a disulfide bridge (S-S) between two cysteine residues. The side chains are diverse: one contains a long PEG chain (PEG2PEG2gEC12) terminated with a hydroxyl group; another has a long aliphatic chain with a terminal hydroxyl group; others include aromatic rings (phenyl, naphthyl, pyridine), a morpholine ring, and various amide and ester linkages. Stereochemistry is indicated with wedges and dashes at several chiral centers. MeCO-Pen(3)-N-T-7MeW-K(Ac)-Pen(3)-AEF-6OH2NaI-THP-K(Ac)-N-3Pya-Sar-K(PEG2PEG2gEC12)-CONH2

[illegible]

[illegible]

SEQ ID NO	Structure
75	 cPEG3aCO-Pen(3)-N-T-7MeW-K(Ac)-Pen(3)-TMAPF-6OH2NaI-THP-E-N-3Py-Sar-CONH2

76

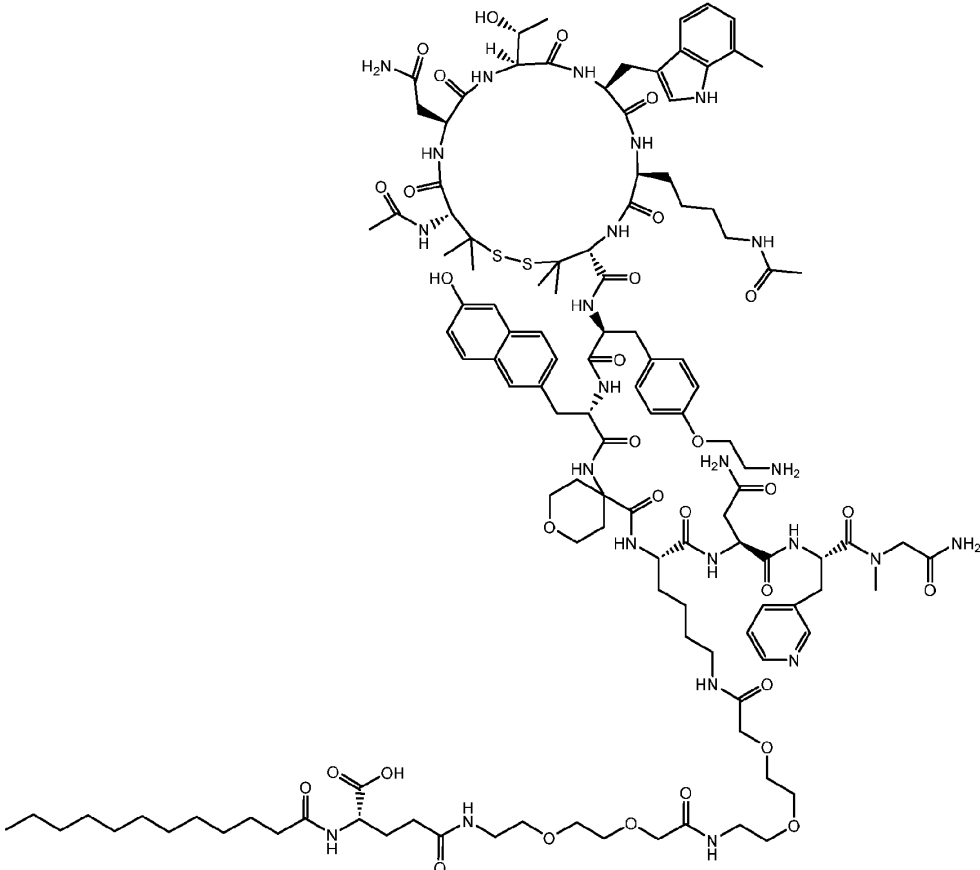


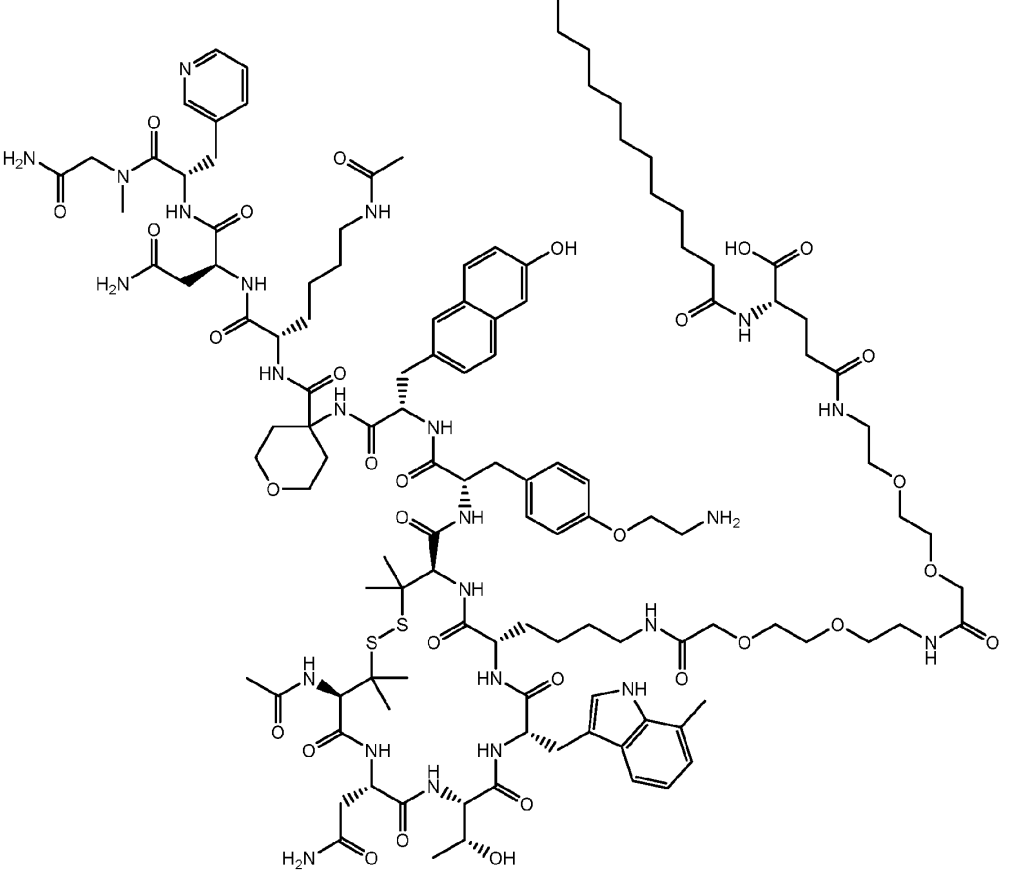
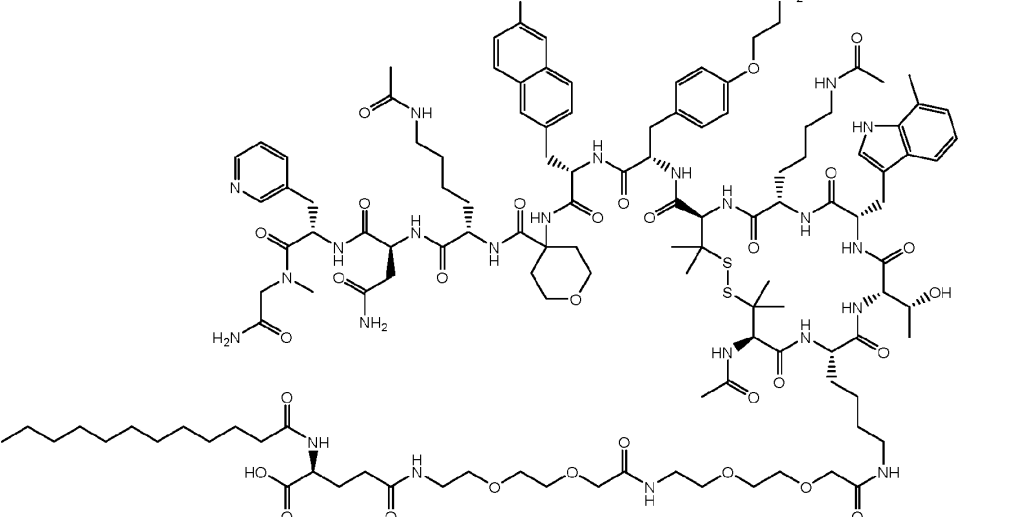
C12gEPEG2PEG2CO-Pen(3)-N-T-7MeW-K(Ac)-Pen(3)-AEF-6OH2Nal-THP-K(Ac)-N-3Pyra-Sar-CONH2

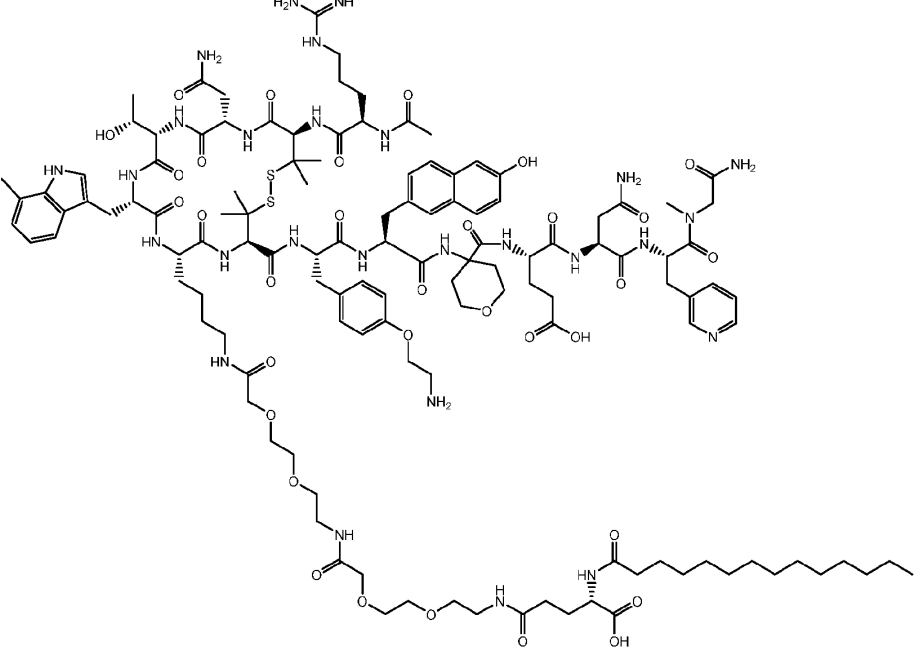
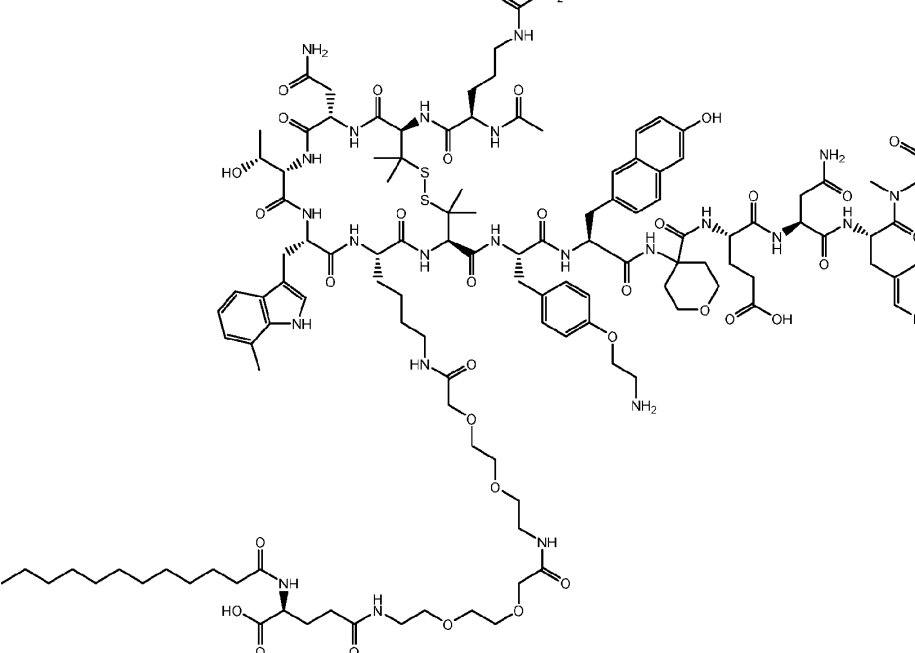
SEQ ID NO	Structure
77	MeCO-r-Pen(3)-N-T-7MeW-K(Ac)-Pen(3)-MMoEF-6OH2NaI-THP-E-N-3PyA-Sar-CONH2

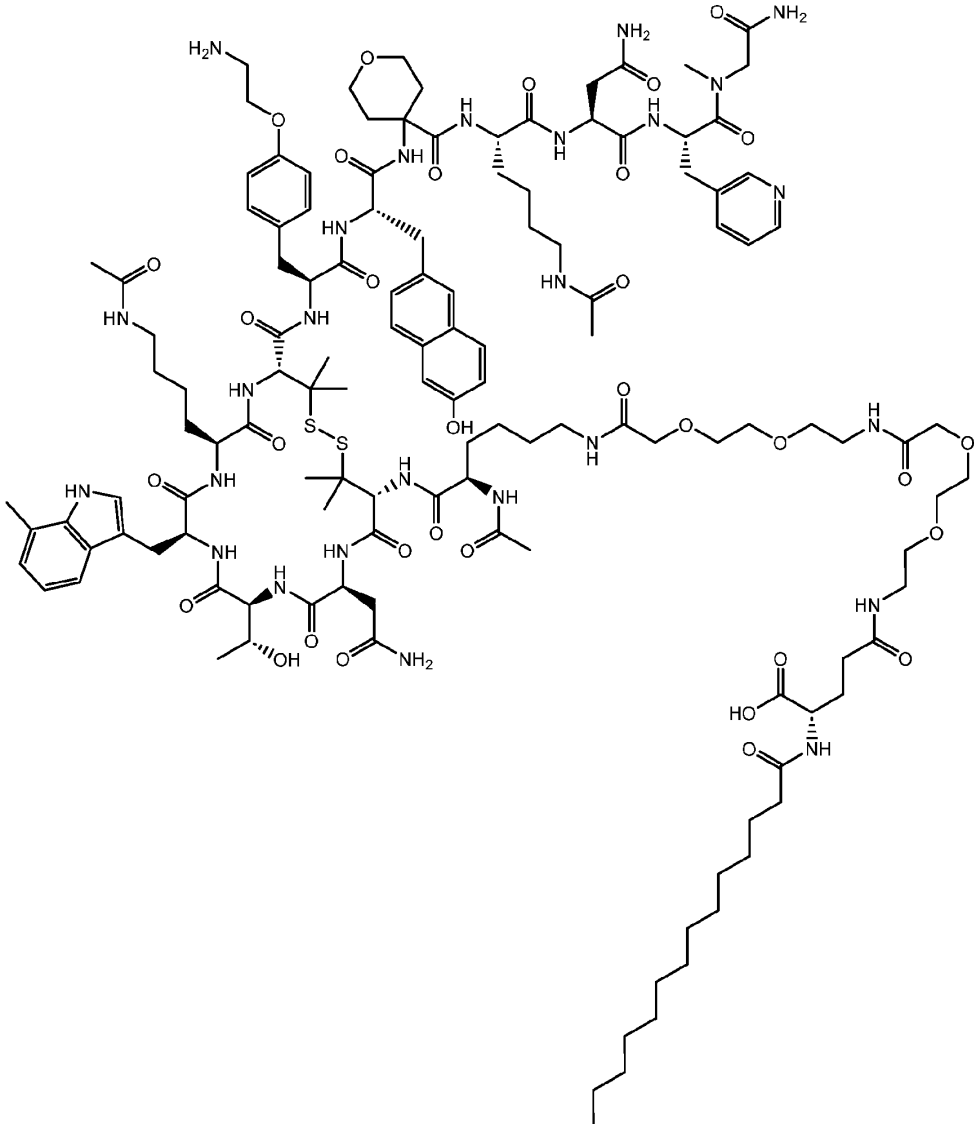
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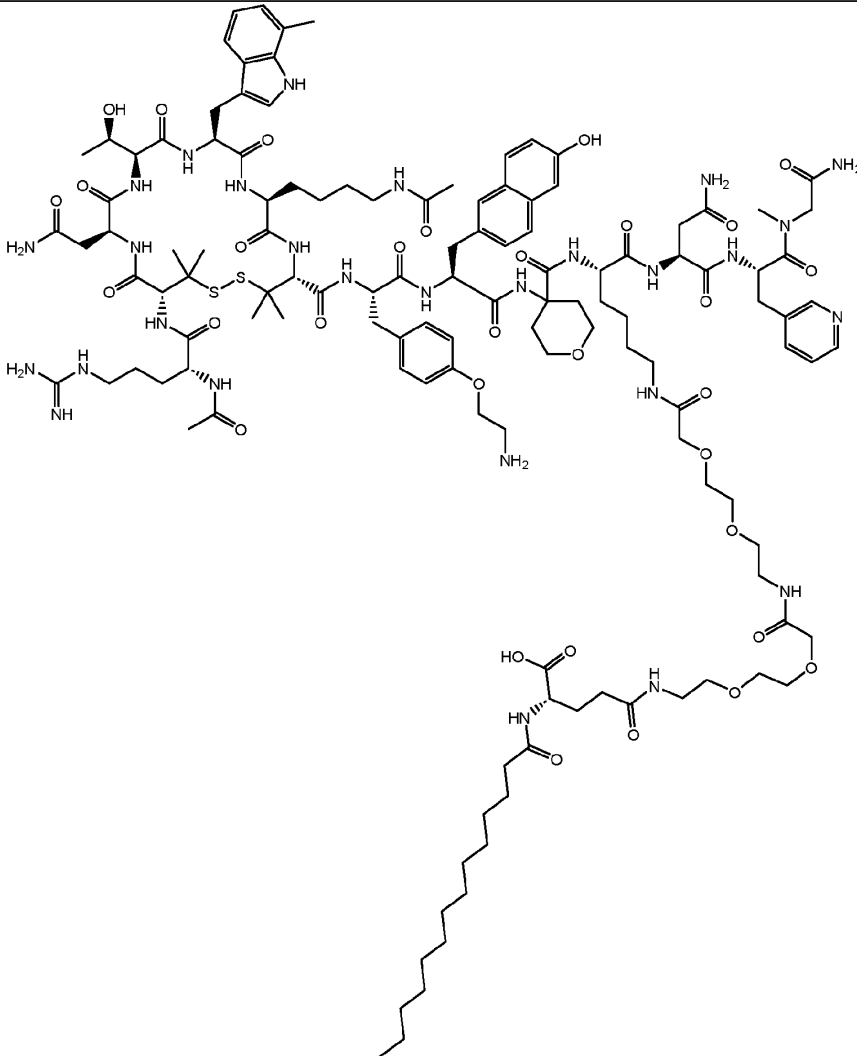
SEQ ID NO	Structure
79	MeCO-Pen(3)-N-T-7MeW-K(Ac)-Pen(3)-TMAPF-6OH2NaI-THP-E-N-3Pva-Sar-CONH2

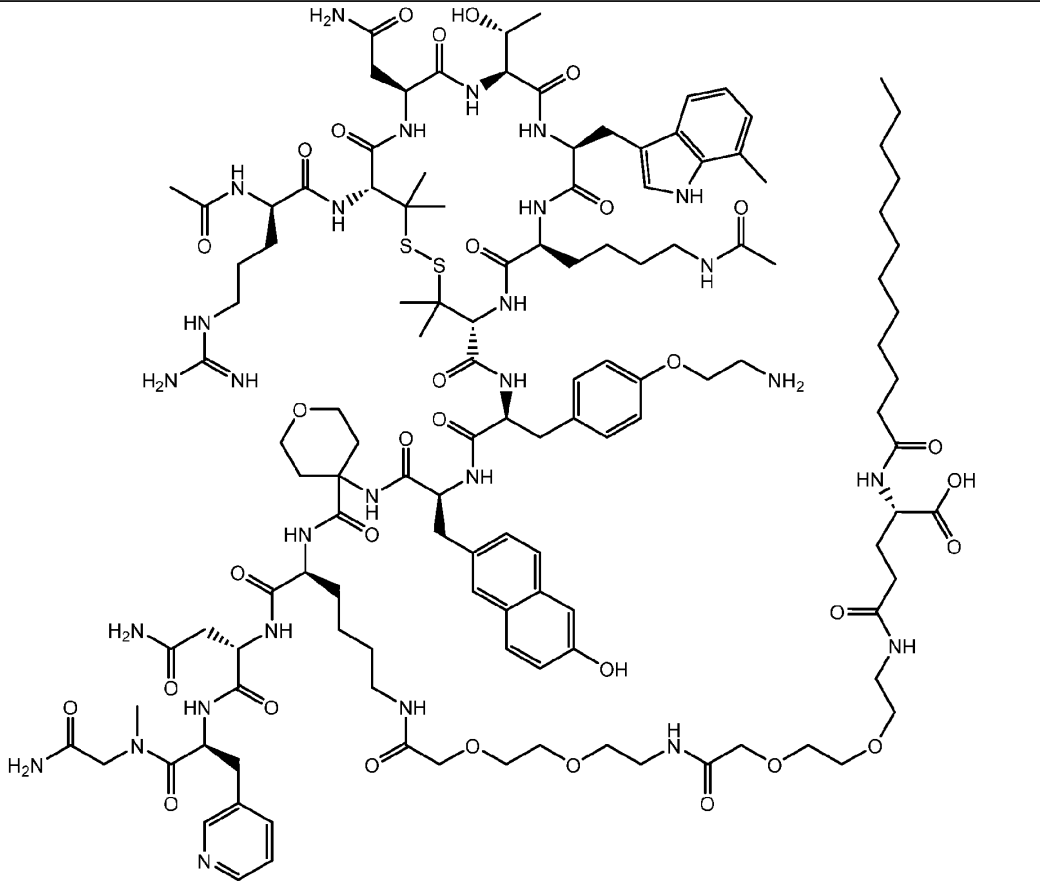
SEQ ID NO	Structure
80	 MeCO-Pen(3)-N-T-7MeW-K(Ac)-Pen(3)-AEF-6OH2NaI-THP-K(PEG2PEG2gEC12)-N-3Pya-Sar-CONH2

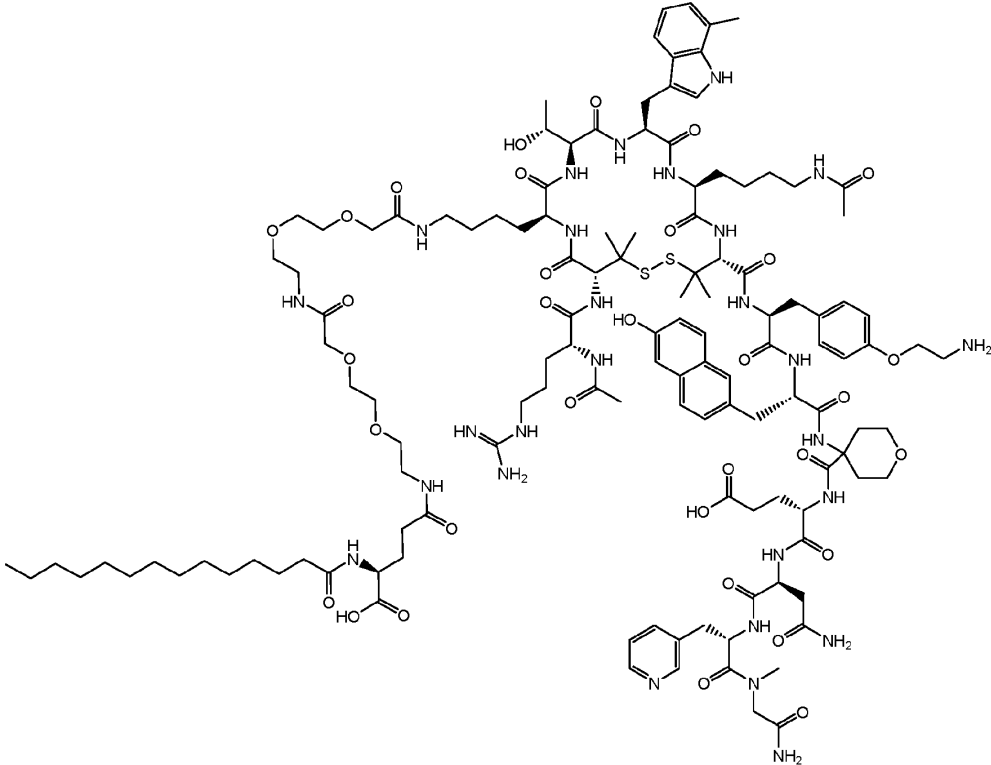
SEQ ID NO	Structure
81	 MeCO-Pen(3)-N-T-7MeW-K(PEG2PEG2gEC12)-Pen(3)-AEF-6OH2Nal-THP-K(Ac)-N-3Pya-Sar
82	 MeCO-Pen(3)-K(PEG2PEG2gEC12)-T-7MeW-K(Ac)-Pen(3)-AEF-6OH2Nal-THP-K(Ac)-N-3Pya-Sar

SEQ ID NO	Structure
83	 MeCO-r-Pen(3)-N-T-7MeW-K(PEG2PEG2gEC14)-Pen(3)-AEF-6OH2Nal-THP-E-N-3Py-Sar-CONH2
84	 MeCO-r-Pen(3)-N-T-7MeW-K(PEG2PEG2gEC12)-Pen(3)-AEF-6OH2Nal-THP-E-N-3Py-Sar-CONH2

SEQ ID NO	Structure
85	 MeCO-k(PEG2PEG2gEC14)-Pen(3)-N-T-7MeW-K(Ac)-Pen(3)-AEF-6OH2Nal-THP-K(Ac)-N-3PyA-Sar-CONH2

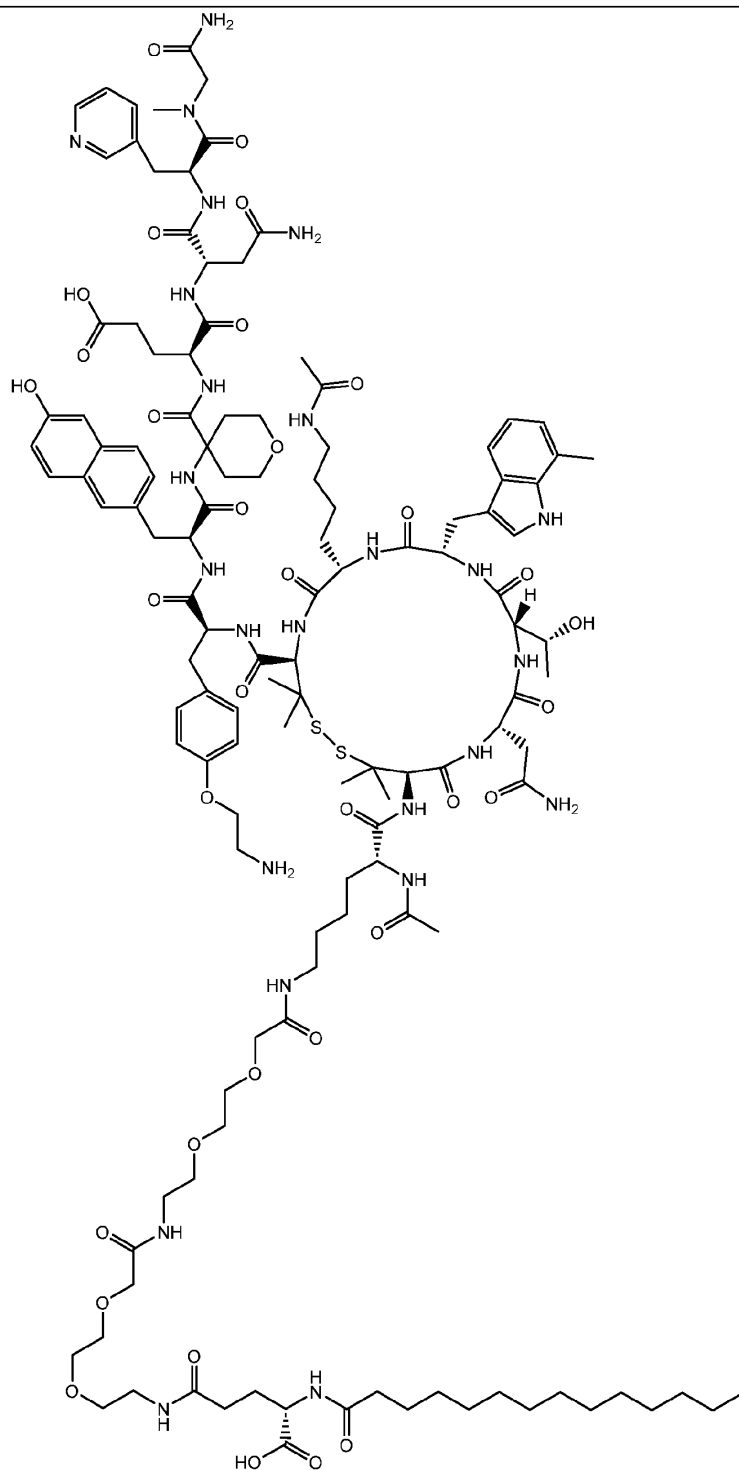
SEQ ID NO	Structure
86	 MeCO-r-Pen(3)-N-T-7MeW-K(Ac)-Pen(3)-AEF-6OH2Nal-THP-K(PEG2PEG2gEC14)-N-3Pya-Sar-CONH2

SEQ ID NO	Structure
87	 MeCO-r-Pen(3)-N-T-7MeW-K(Ac)-Pen(3)-AEF-6OH2Nal-THP-K(PEG2PEG2gEC12)-N-3Pyra-Sar-CONH2

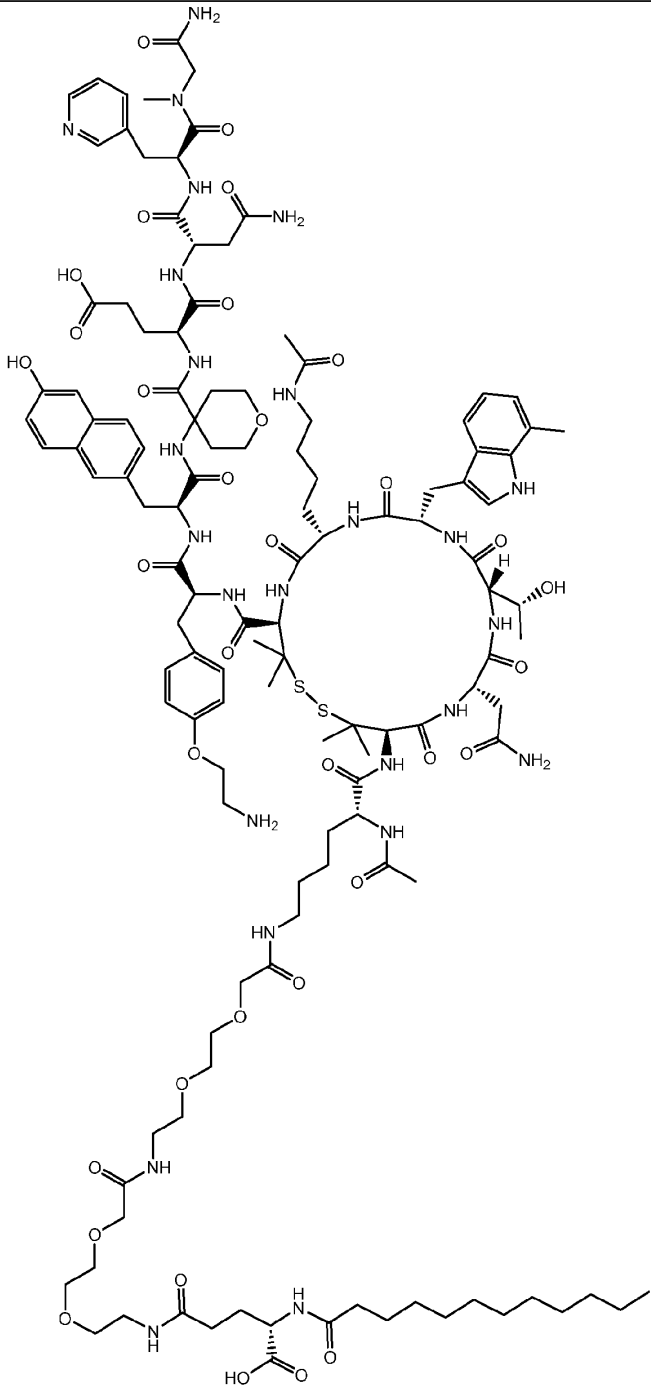
SEQ ID NO	Structure
88	 MeCO-r-Pen(3)-K(PEG2PEG2gEC14)-T-7MeW-K(Ac)-Pen(3)-AEF-6OH2Nal-THP-E-N-3Pya-Sar-CONH2

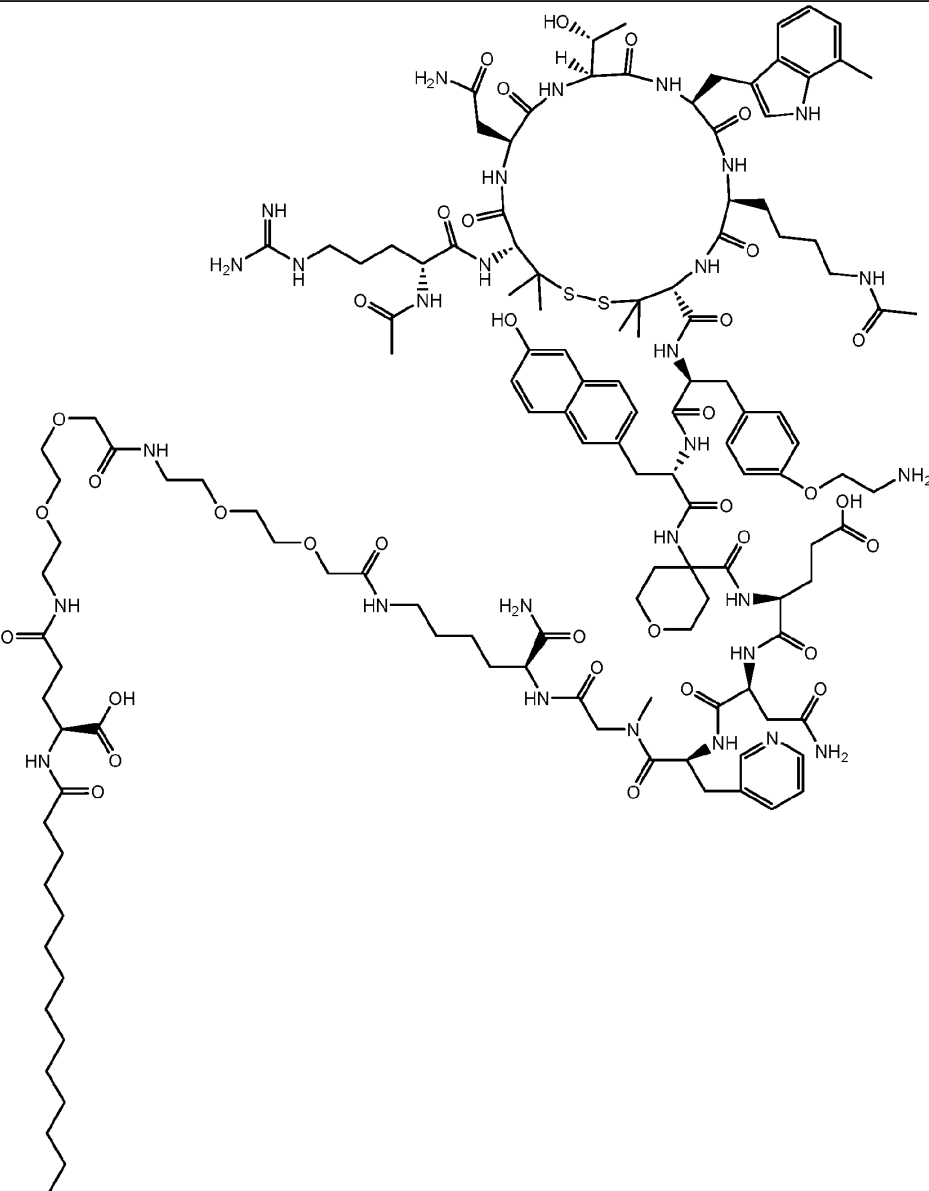
MeCO-r-Pen(3)-K(PEG2PEG2gEC12)-T-7MeW-K(Ac)-Pen(3)-AEF-6OH2Nal-THP-E-N-3Pyra-Sar-CONH2

90



MeCO-k(PEG2PEG2gEC14)-Pen(3)-N-T-7MeW-K(Ac)-Pen(3)-AEF-6OH2Nal-THP-E-N-3Pyra-Sar-CONH2

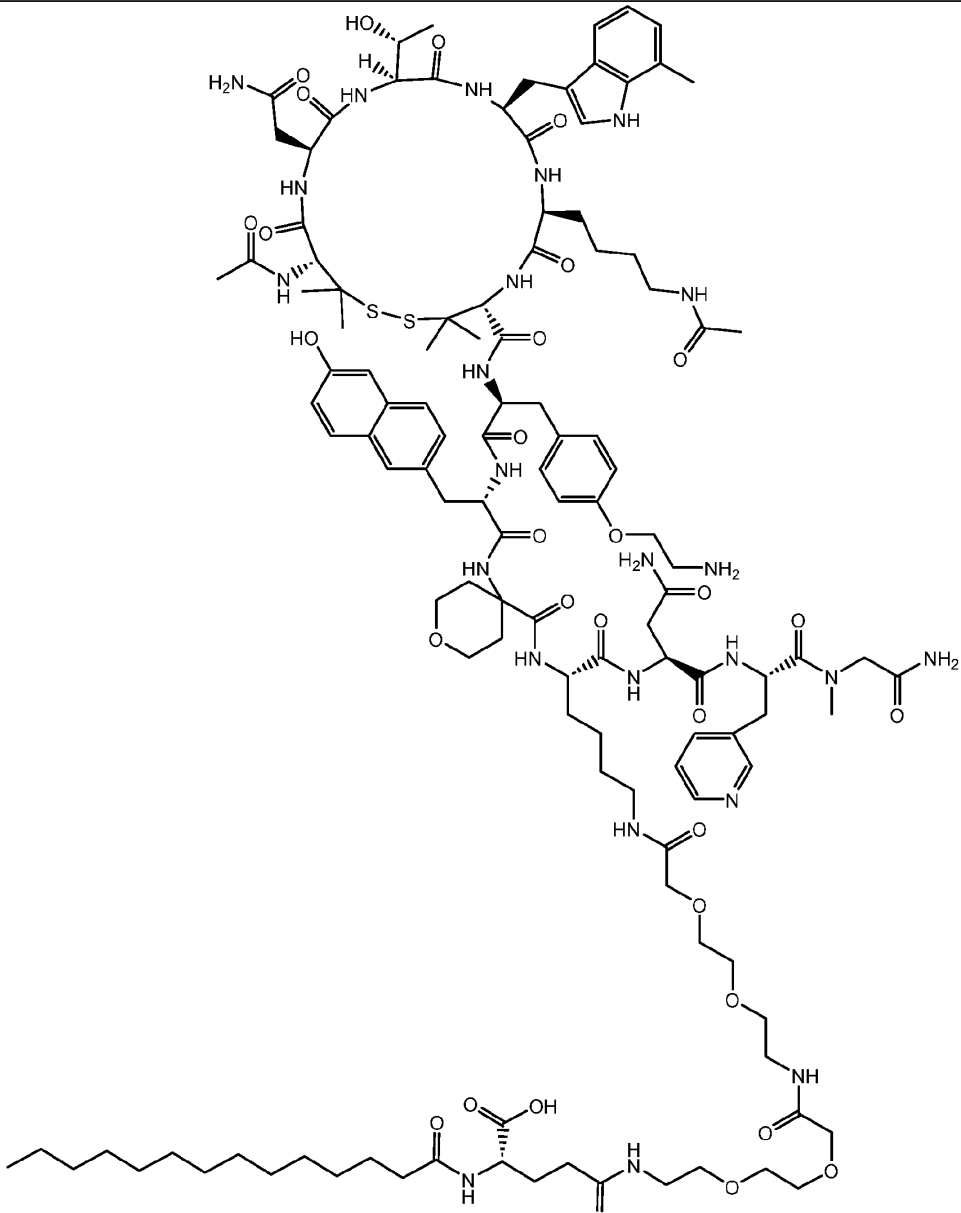
SEQ ID NO	Structure
91	 The chemical structure is a large, complex molecule, likely a peptide or protein derivative. It features a central cyclic core, possibly a macrocycle, with various side chains attached. The side chains include aromatic rings (pyridine, indole, phenol), amide groups, and a long PEG chain. The molecule is highly branched and contains multiple functional groups, including hydroxyl, amino, and carbonyl groups. The structure is drawn in a detailed, skeletal format, showing the connectivity of atoms and the presence of stereochemical centers. MeCO-k(PEG2PEG2gEC12)-Pen(3)-N-T-7MeW-K(Ac)-Pen(3)-AEF-6OH2Nal-THP-E-N-3Pya-Sar-CONH2

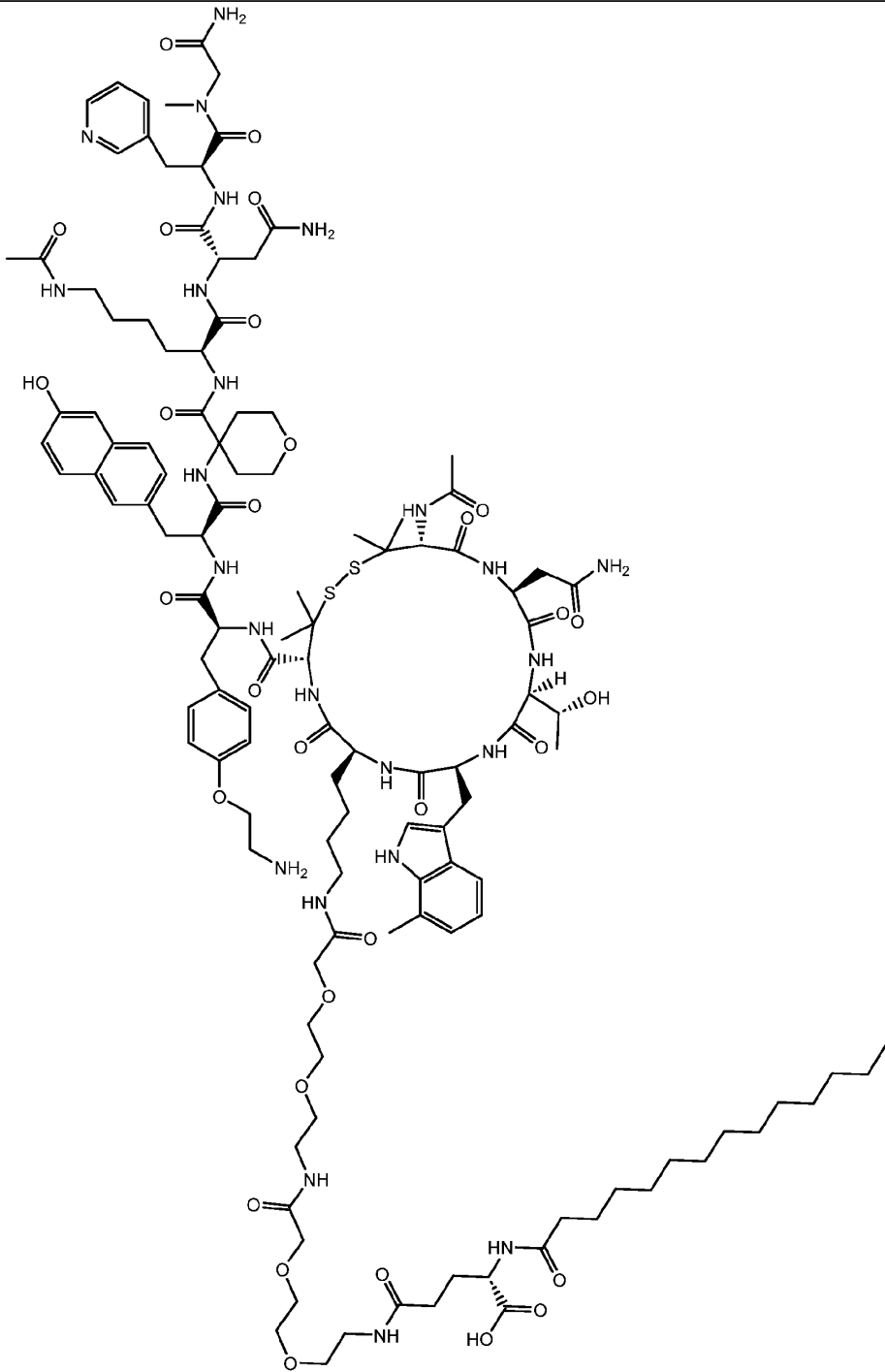
SEQ ID NO	Structure
92	 The chemical structure represents a large, complex peptide molecule, likely a cyclic peptide with multiple side chains and modifications. The main structure is a large, circular ring composed of amino acid residues. Various side chains are attached to the ring, including a long, branched chain with a terminal amine group, a chain with a terminal carboxylic acid group, and a chain with a terminal amide group. The structure also features a disulfide bridge (S-S) and a hydroxyl group (OH). The molecule is highly branched and contains several functional groups, including amides, carboxylic acids, and amines. The structure is drawn in a perspective view, showing the spatial arrangement of the atoms and bonds. MeCO-r-Pen(3)-N-T-7MeW-K(Ac)-Pen(3)-AEF-6OH2Nal-THP-E-N-3Pya-Sar-K(PEG2PEG2gEC14)-CONH2

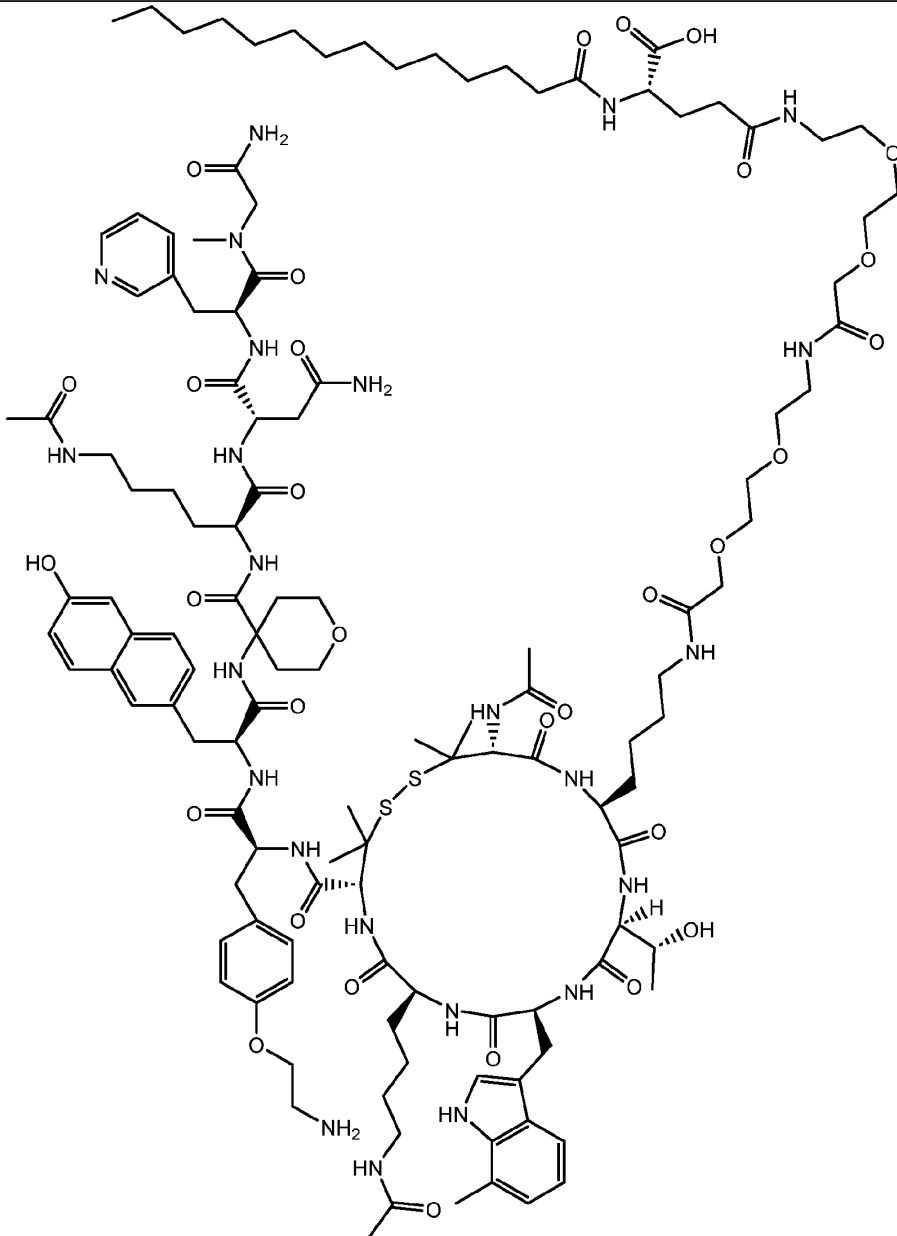
The image displays a complex chemical structure of a macrocyclic peptide. The central feature is a large, circular macrocycle formed by a peptide backbone. Various side chains are attached to the backbone, including a pyridine ring, a naphthyl group, a hydroxyl group, a thiol group, and a long alkyl chain. The structure is highly detailed, showing the stereochemistry of the peptide bonds and the specific functional groups of the side chains.

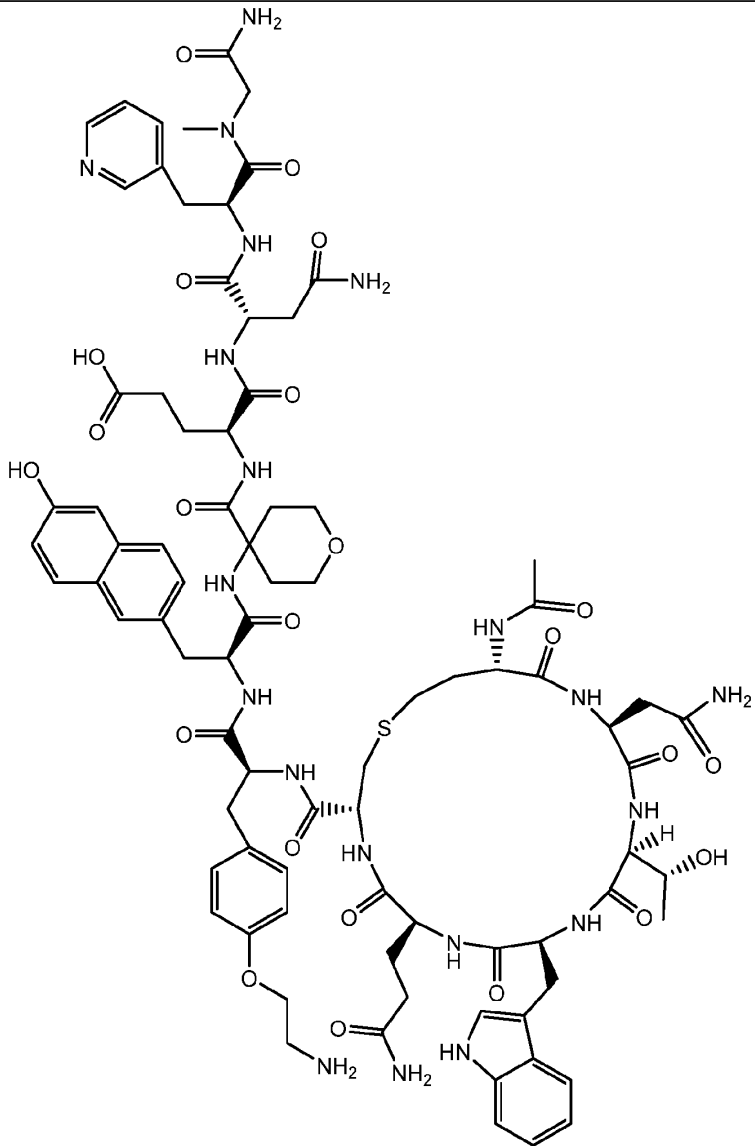
[illegible]

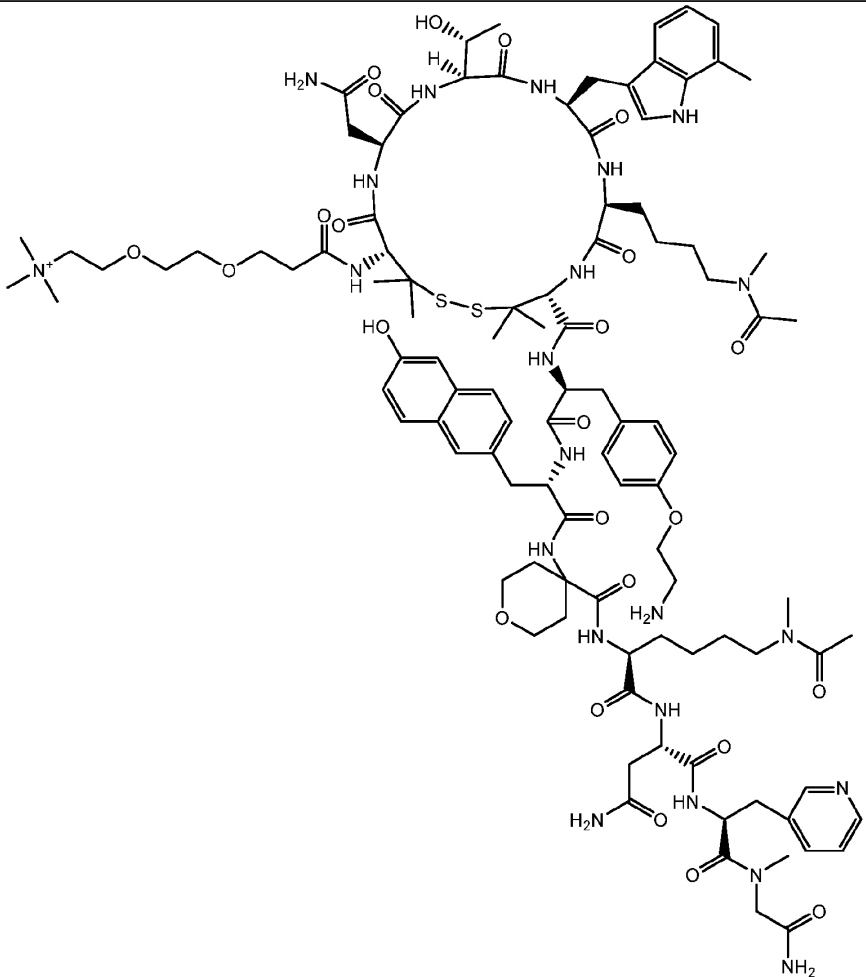
C14gEPEG2PEG2CO-r-Pen(3)-N-T-7MeW-K(Ac)-Pen(3)-AEF-6OH2Nal-THP-E-N-3Pyra-Sar-CONH2

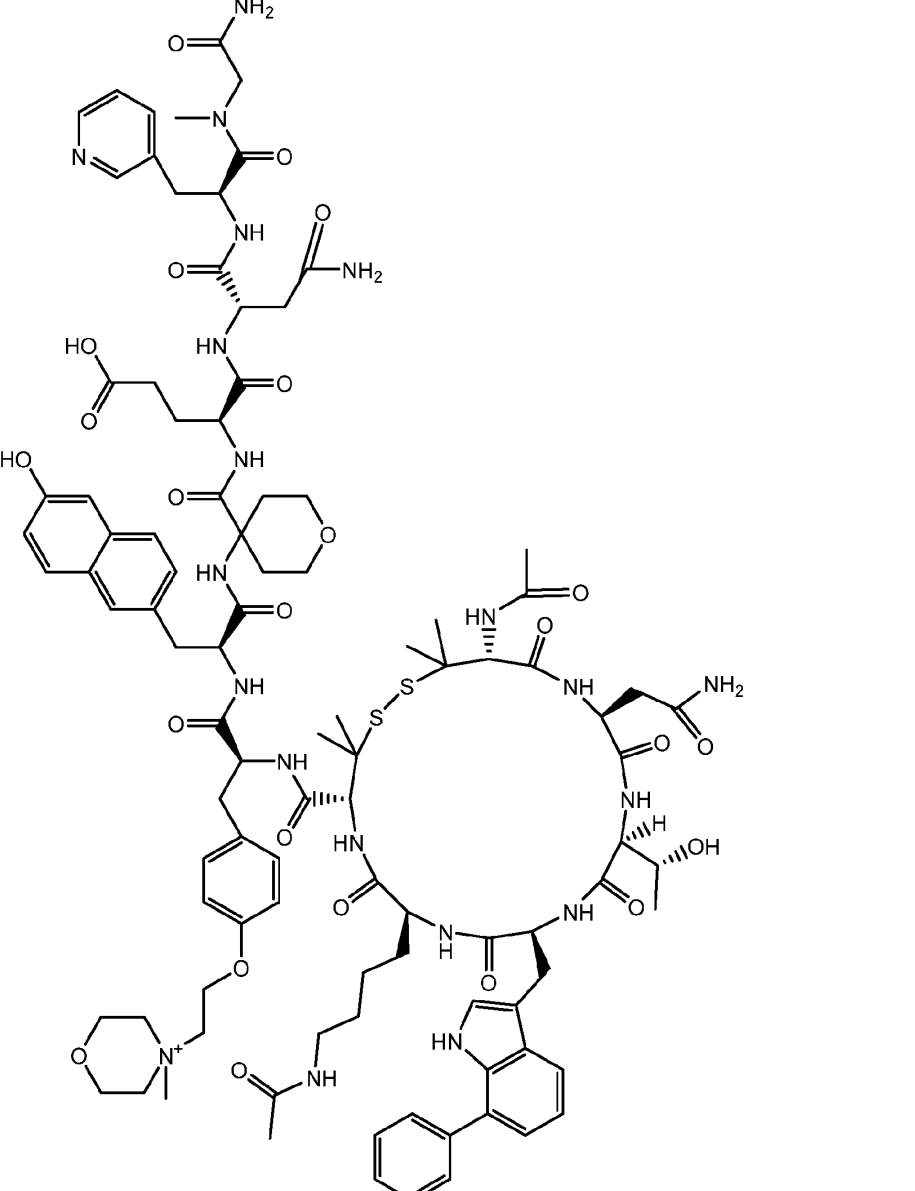
SEQ ID NO	Structure
95	 MeCO-Pen(3)-N-T-7MeW-K(Ac)-Pen(3)-AEF-6OH2NaI-THP-K(PEG2PEG2gEC14)-N-3Pya-Sar-CONH2

SEQ ID NO	Structure
96	 MeCO-Pen(3)-N-T-7MeW-K(PEG2PEG2gEC14)-Pen(3)-AEF-6OH2Nal-THP-K(Ac)-N-3Pya-Sar-CONH2

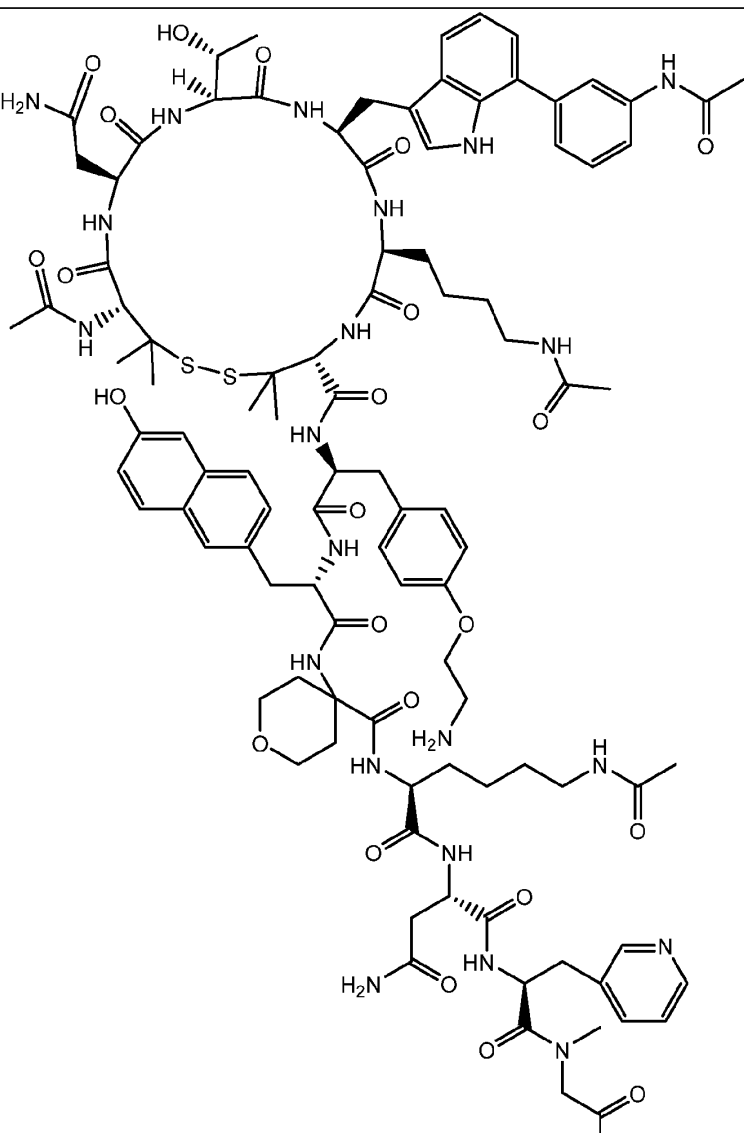
SEQ ID NO	Structure
97	 The chemical structure is a large, complex molecule, likely a peptide or protein derivative. It features a central cyclic core, possibly a macrocycle, with various side chains and functional groups. The structure includes a long, flexible chain with a terminal carboxylic acid group, a pyridine ring, a thiazolidine ring, a hydroxyphenyl group, a thioether bridge, a hydroxyl group, a benzimidazole group, and a long alkyl chain. The molecule is highly branched and contains multiple amide, ester, and ether linkages. MeCO-Pen(3)-K(PEG2PEG2gEC14)-T-7MeW-K(Ac)-Pen(3)-AEF-6OH2NaI-THP-K(Ac)-N-3Pya-Sar-CONH2

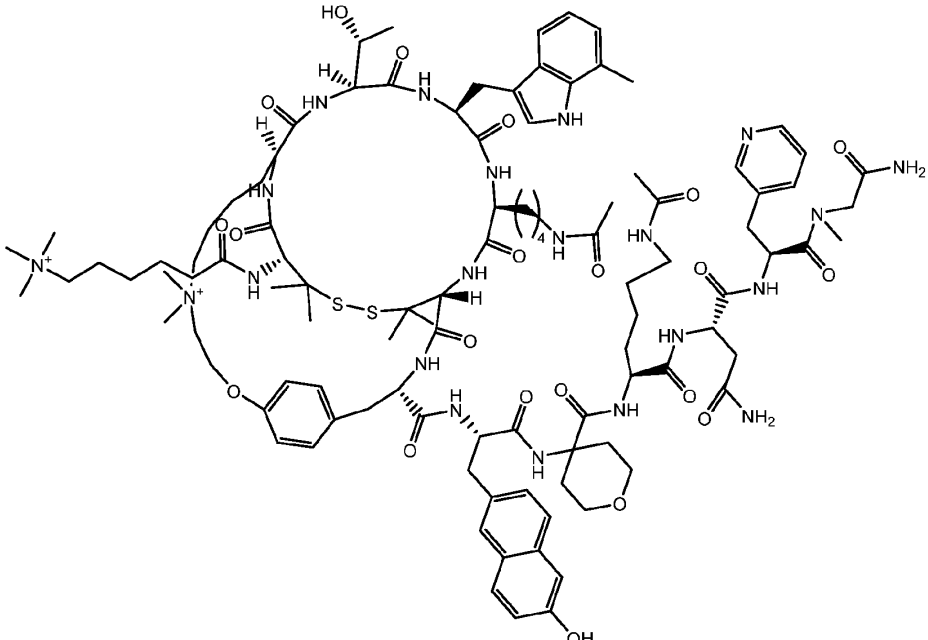
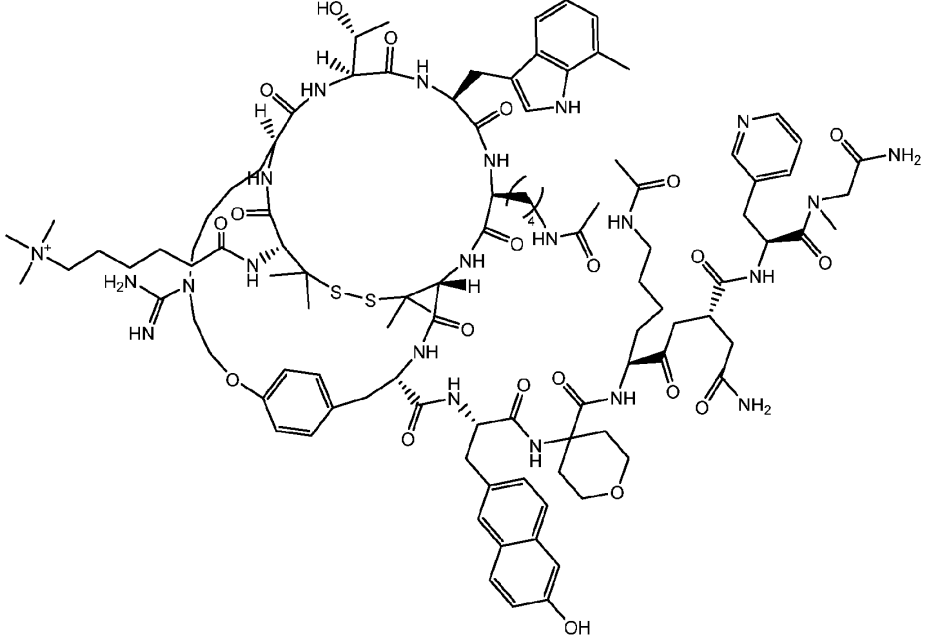
SEQ ID NO	Structure
98	 MeCO-Abu(1)-N-T-W-Q-C(1)-AEF-6OH2Nal-THP-E-N-3PyA-Sar-CONH2

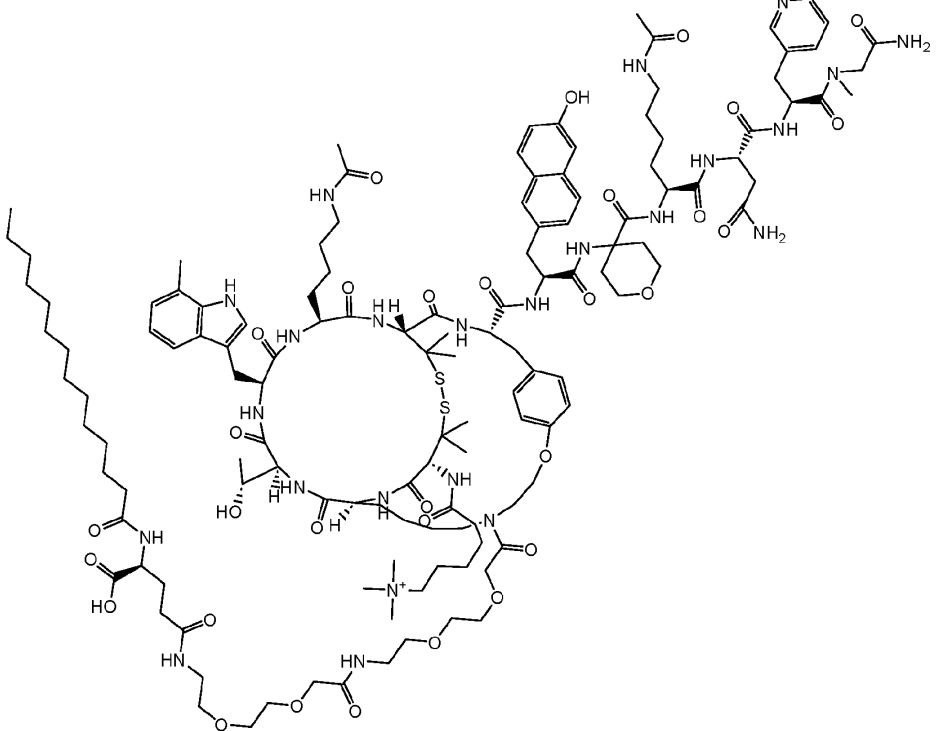
SEQ ID NO	Structure
99	 cPEG3aCO-Pen(3)-N-T-7MeW-K(NMeAc)-Pen(3)-AEF-6OH2NaI-THP-K(NMeAc)-N-3Pya-Sar-CONH2

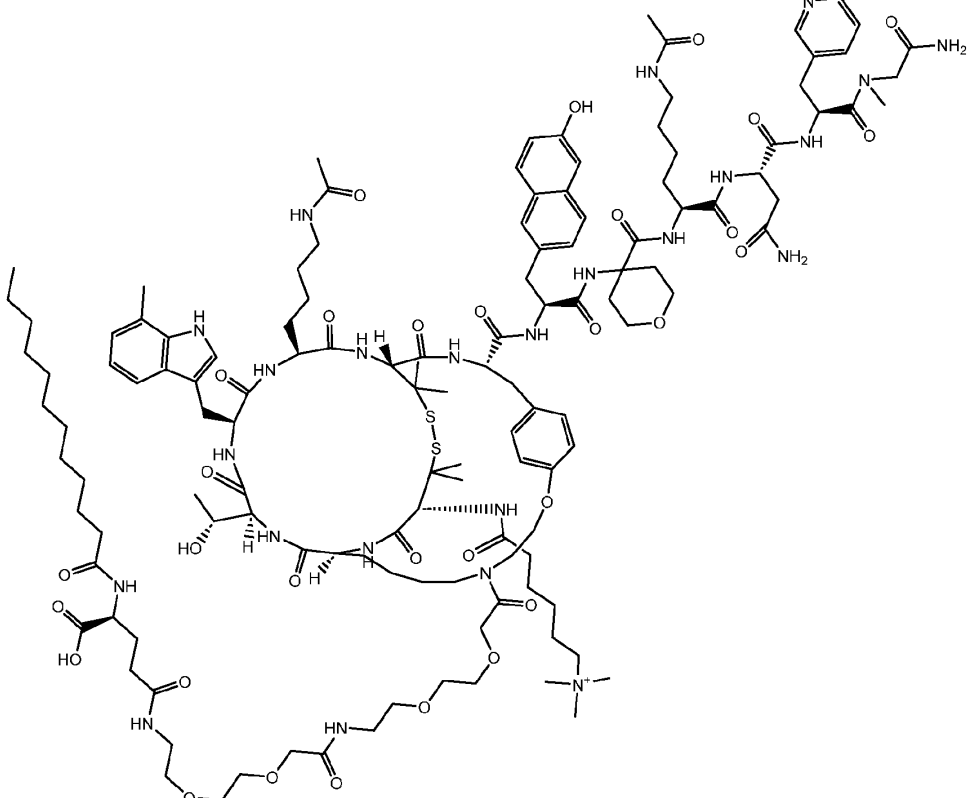
SEQ ID NO	Structure
100	 MeCO-Pen(3)-N-T-7(3NAcPh)W-K(Ac)-Pen(3)-MMoEF-6OH2Nal-THP-E-N-3Pya-Sar-CONH2

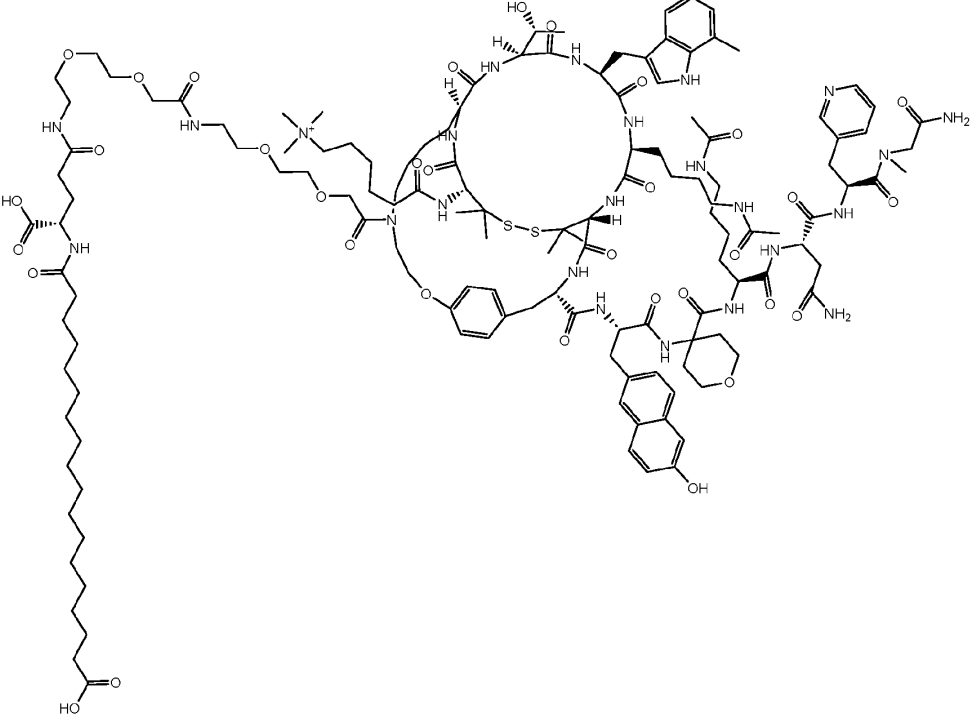
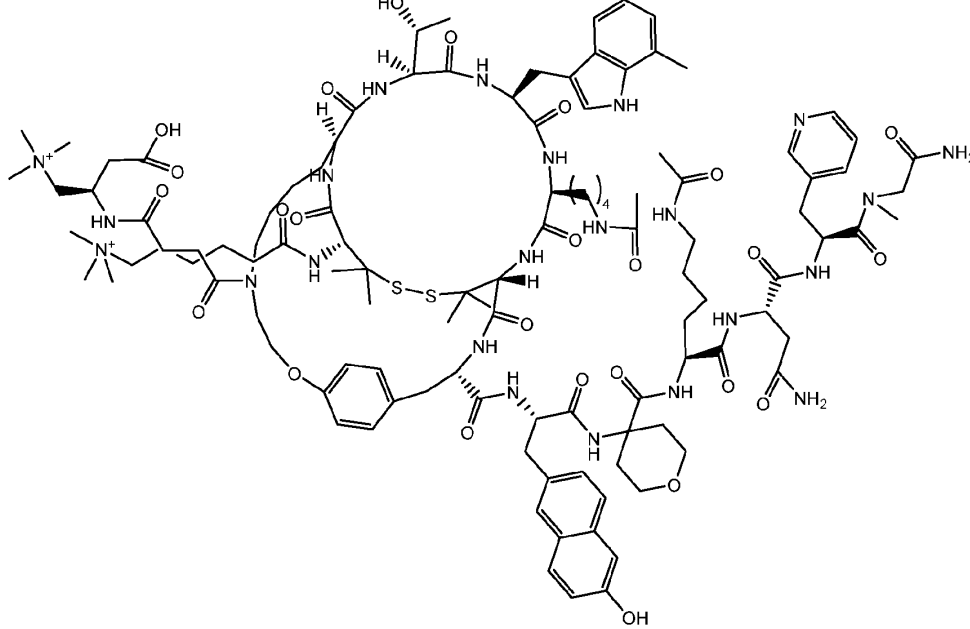
[illegible]

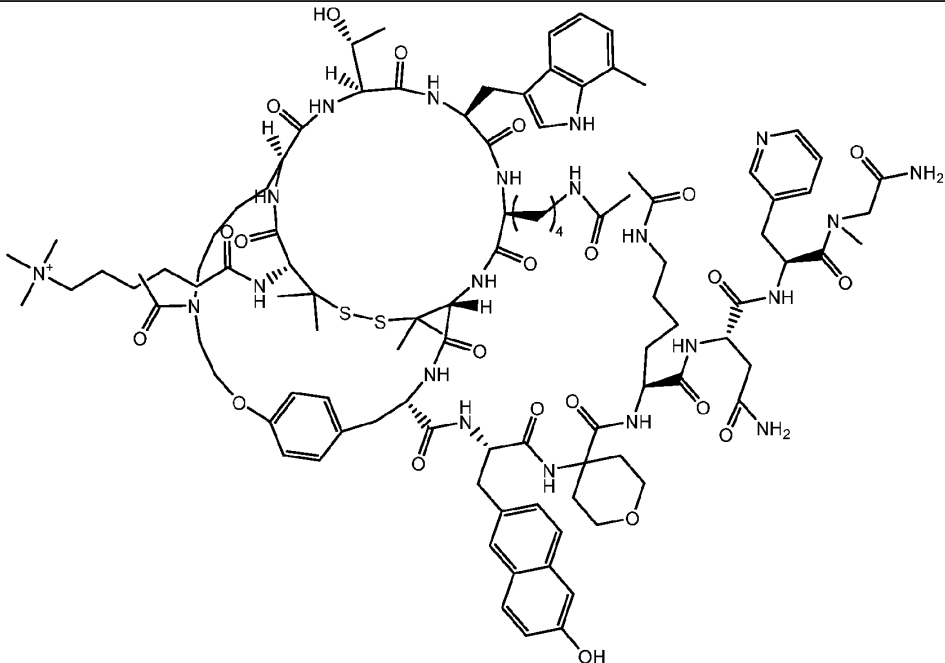
SEQ ID NO	Structure
102	 The structure shows a large cyclic peptide with a central ring and numerous side chains. Key features include: a disulfide bridge (S-S) connecting two cysteine residues; a long aliphatic chain with a terminal amide; a side chain containing a naphthalene ring; a side chain with a phenyl ring and a terminal amide; a side chain with a pyridine ring; and a side chain with a terminal amide and a long aliphatic chain. The peptide backbone is shown with various amide bonds and side chains attached to the ring.

SEQ ID NO	Structure
103	 5cpaCO-Pen(3)-K(a)(5)-T-7MeW-K(Ac)-Pen(3)-AEF(5)-6OH2Nal-THP-K(Ac)-N-3Pya-Sar-CONH2
104	 5cpaCO-Pen(3)-K(G)(5)-T-7MeW-K(Ac)-Pen(3)-AEF(5)-6OH2Nal-THP-K(Ac)-N-3Pya-Sar-CONH2

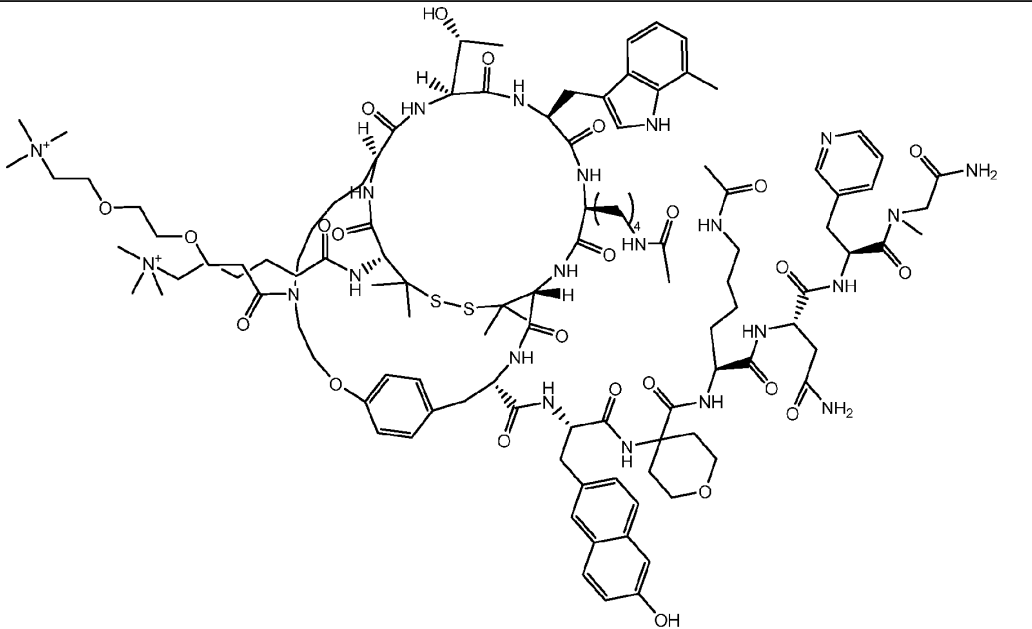
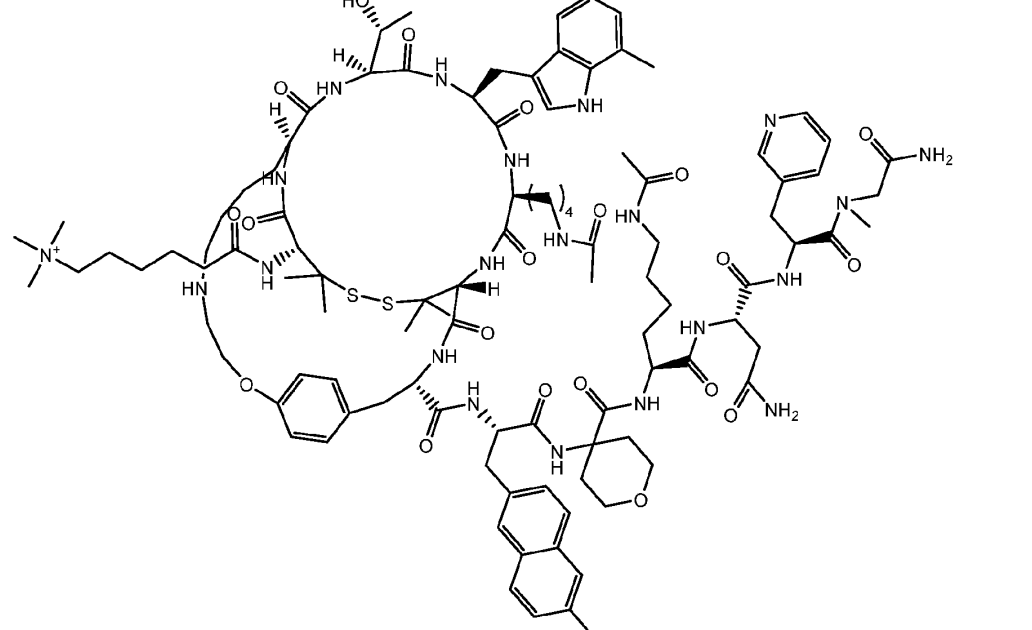
SEQ ID NO	Structure
105	 5cpaCO-Pen(3)-K(PEG2PEG2gEC14)(5)-T-7MeW-K(Ac)-Pen(3)-AEF(5)-6OH2Nal-THP-K(Ac)-N-3Pyra-Sar-CONH2

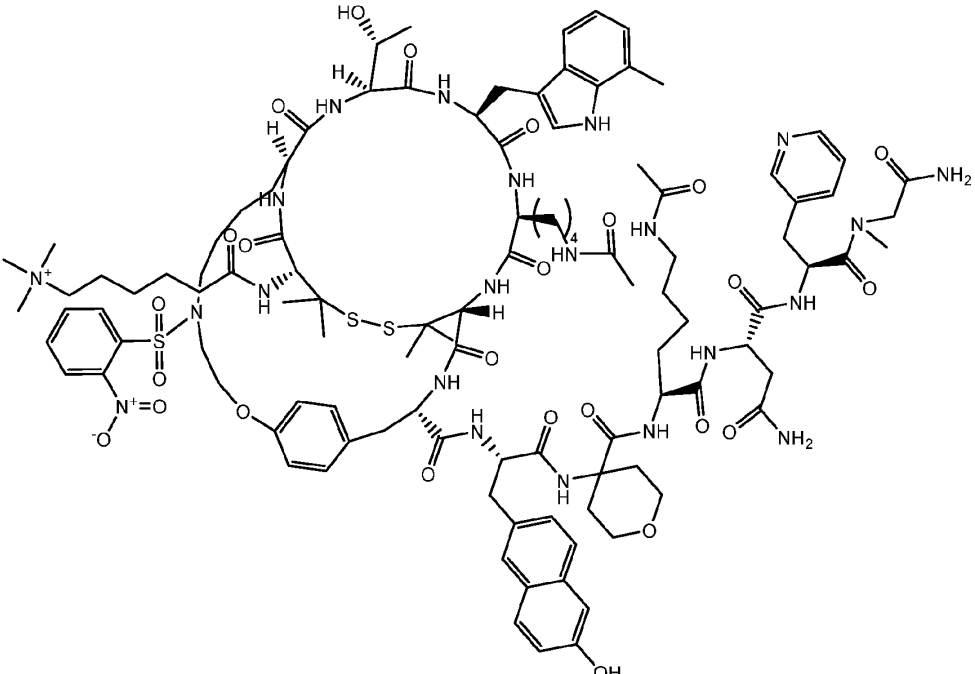
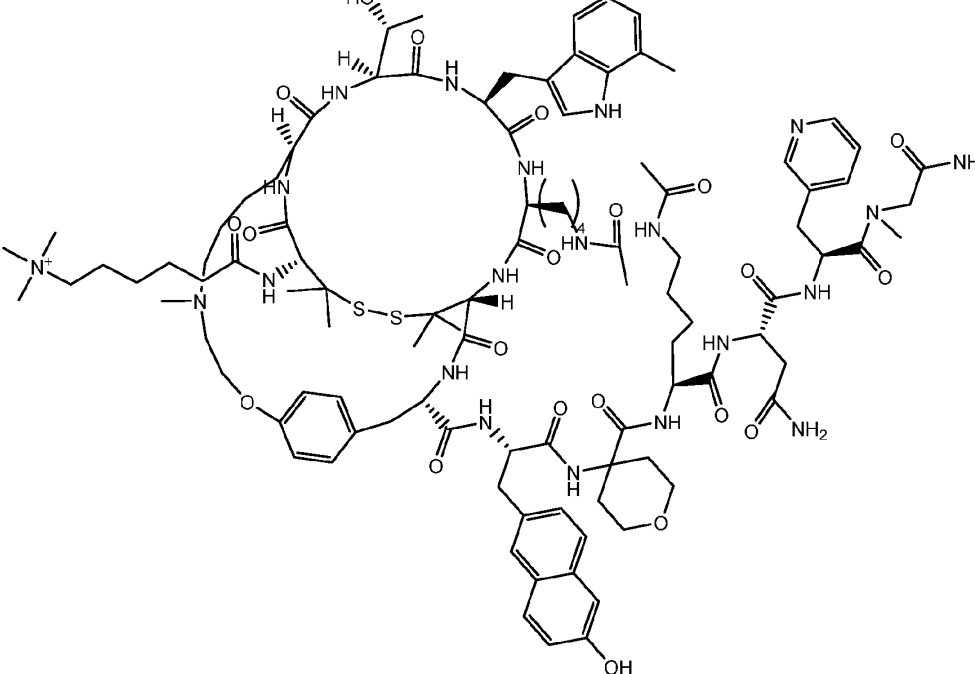
SEQ ID NO	Structure
106	 5cpaCO-Pen(3)-K(PEG2PEG2gEC12)(5)-T-7MeW-K(Ac)-Pen(3)-AEF(5)-6OH2Nal-THP-K(Ac)-N-3PyA-Sar-CONH2

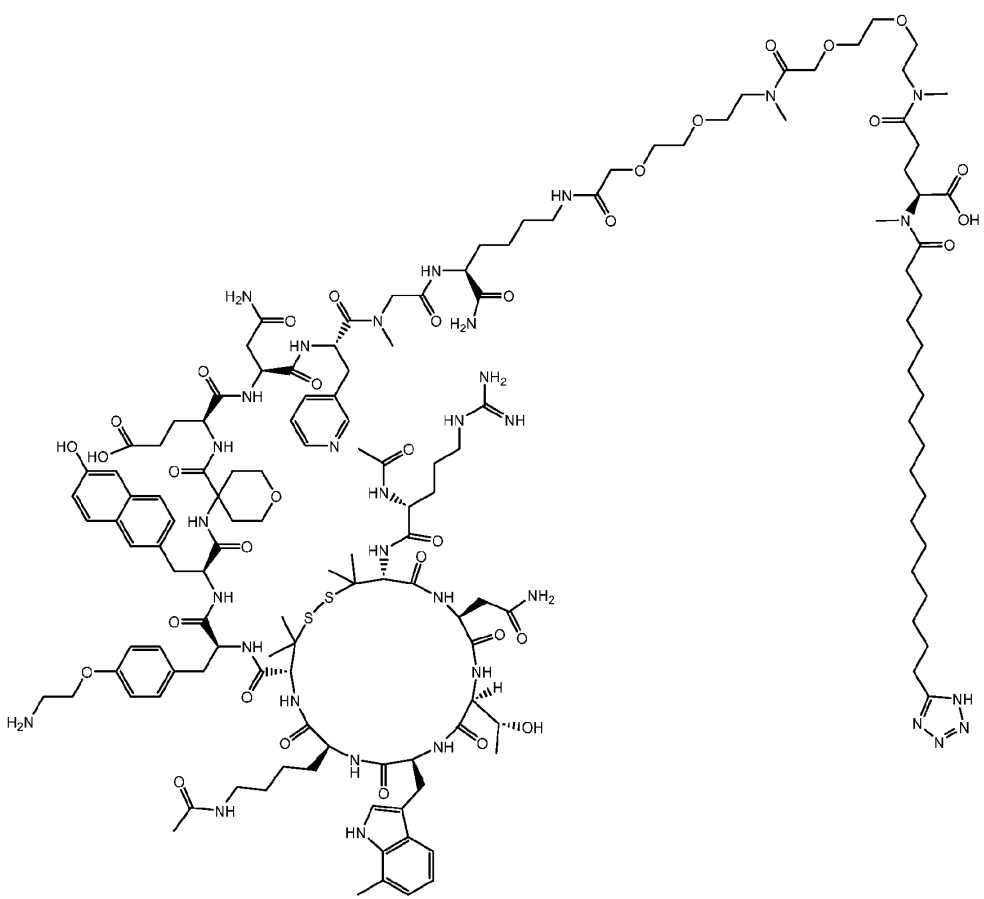
SEQ ID NO	Structure
107	 5cpaCO-Pen(3)-K(PEG2PEG2gEC18OH)(5)-T-7MeW-K(Ac)-Pen(3)-AEF(5)-6OH2Nal-THP-K(Ac)-N-3Pya-Sar-CONH2
108	 5cpaCO-Pen(3)-K(d)(5)-T-7MeW-K(Ac)-Pen(3)-AEF(5)-6OH2Nal-THP-K(Ac)-N-3Pya-Sar-CONH2

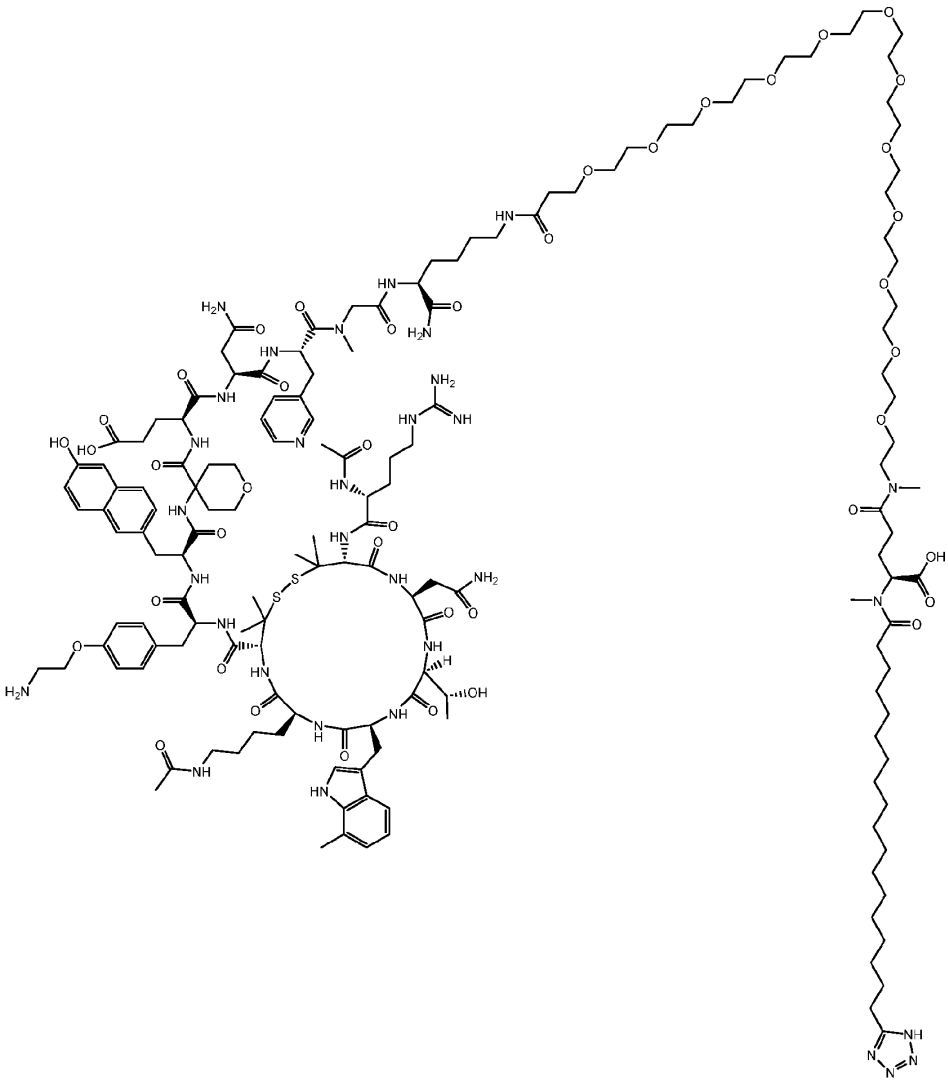
SEQ ID NO	Structure
109	 5cpaCO-Pen(3)-K(Ac)(5)-T-7MeW-K(Ac)-Pen(3)-AEF(5)-6OH2Nal-THP-K(Ac)-N-3Pya-Sar-CONH2

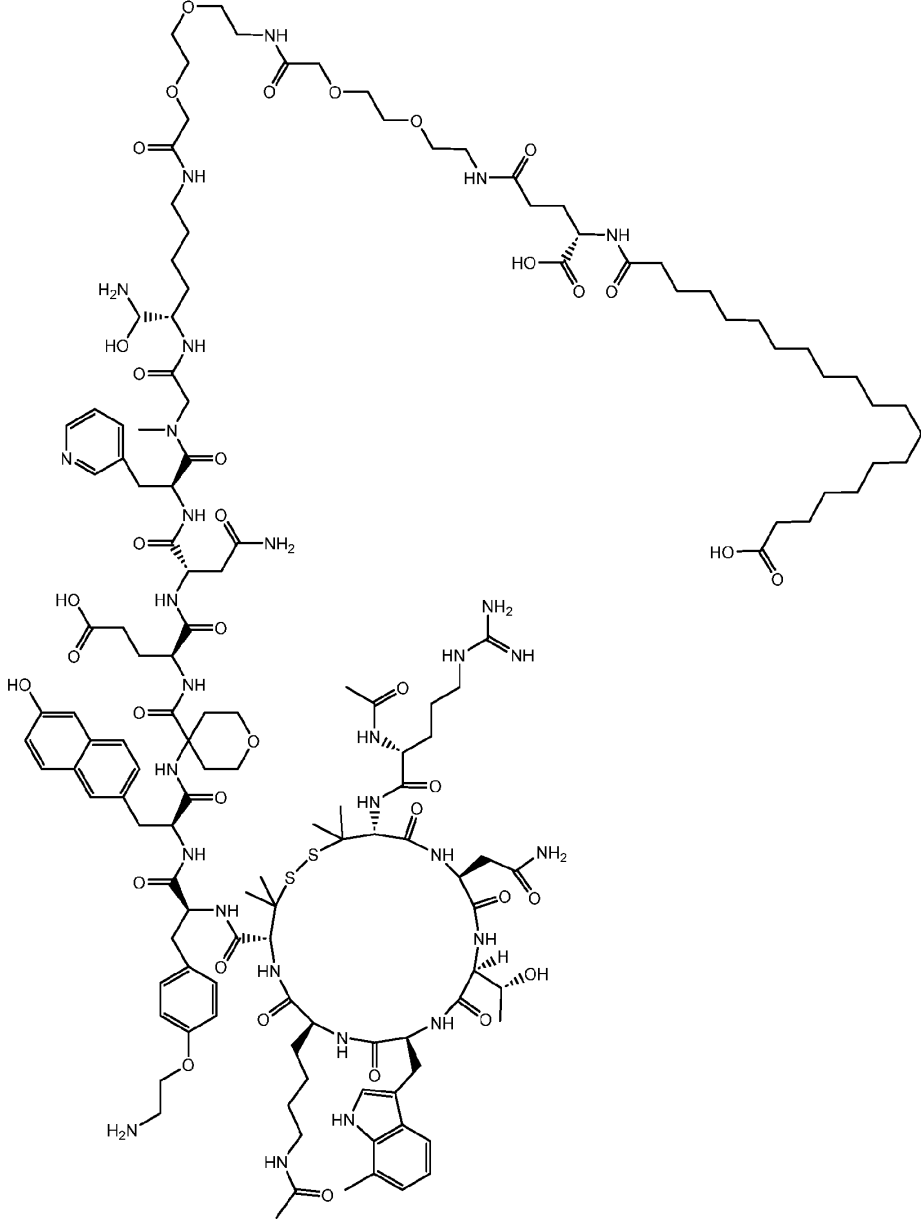
SEQ ID NO	Structure
110	MeCO-r-Pen(3)-N-T-7(3NAcPh)W-K(Ac)-Pen(3)-MMoEF-6OH2NaI-THP-E-N-THP-CONH2

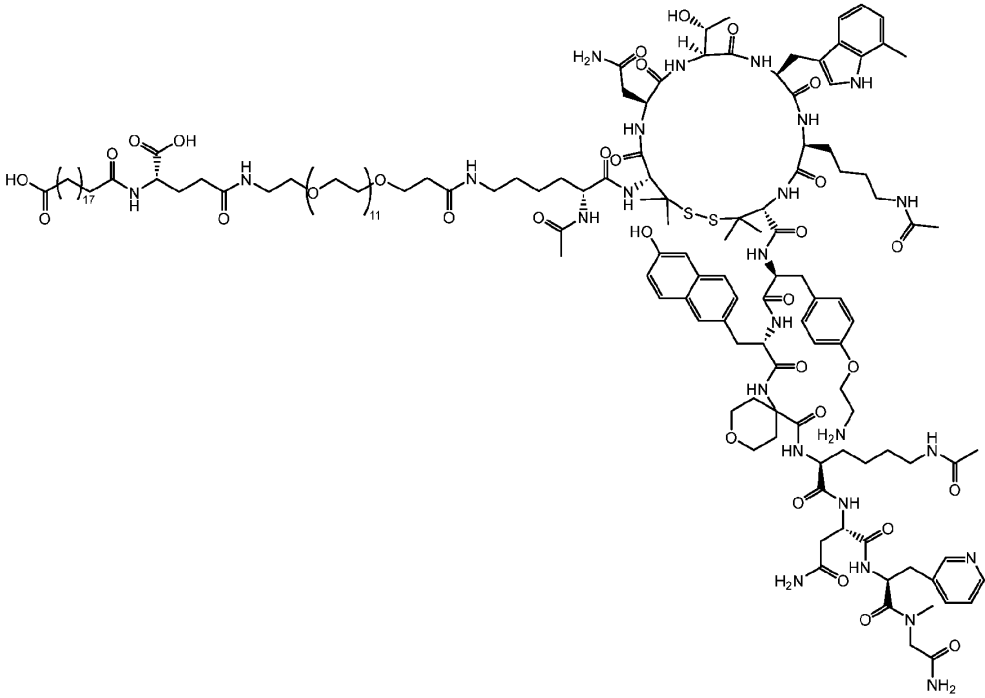
SEQ ID NO	Structure
111	 5cpaCO-Pen(3)-K(cPEG3a)(5)-T-7MeW-K(Ac)-Pen(3)-AEF(5)-6OH2Nal-THP-K(Ac)-N-3Pya-Sar-CONH2
112	 5cpaCO-Pen(3)-K(5)-T-7MeW-K(Ac)-Pen(3)-AEF(5)-6OH2Nal-THP-K(Ac)-N-3Pya-Sar-CONH2

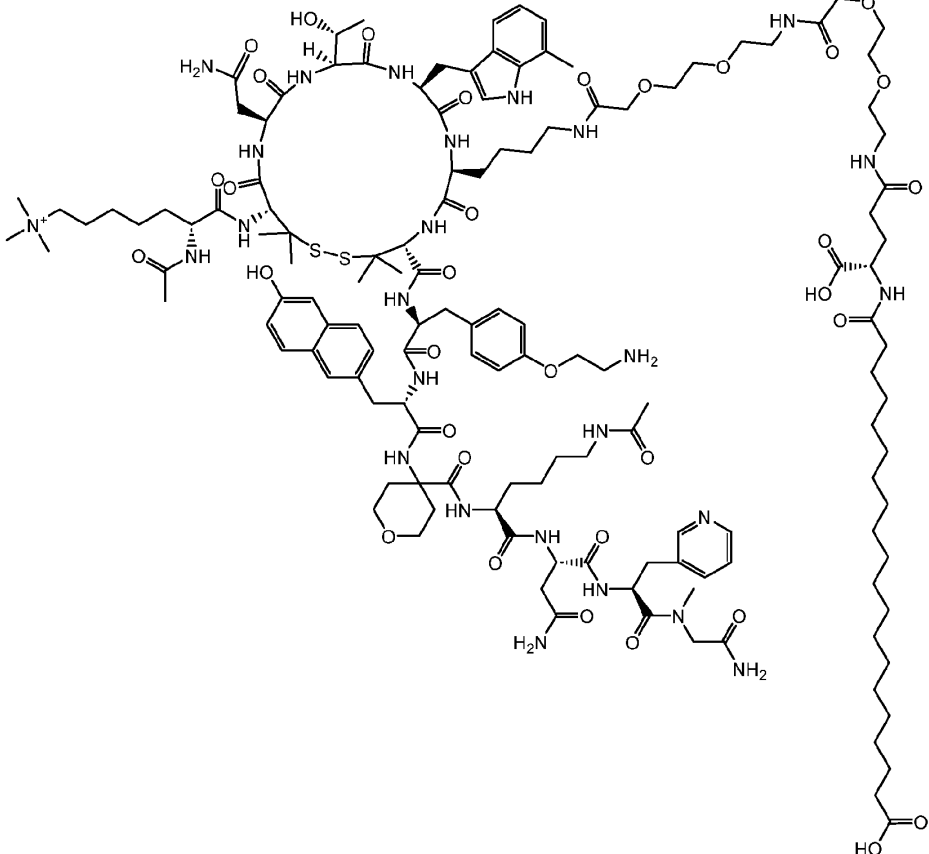
SEQ ID NO	Structure
113	 5cpaCO-Pen(3)-K(NNs)(5)-T-7MeW-K(Ac)-Pen(3)-AEF(5)-6OH2Nal-THP-K(Ac)-N-3Pya-Sar-CONH2
114	 5cpaCO-Pen(3)-K(NMe)(5)-T-7MeW-K(Ac)-Pen(3)-AEF(5)-6OH2Nal-THP-K(Ac)-N-3Pya-Sar-CONH2

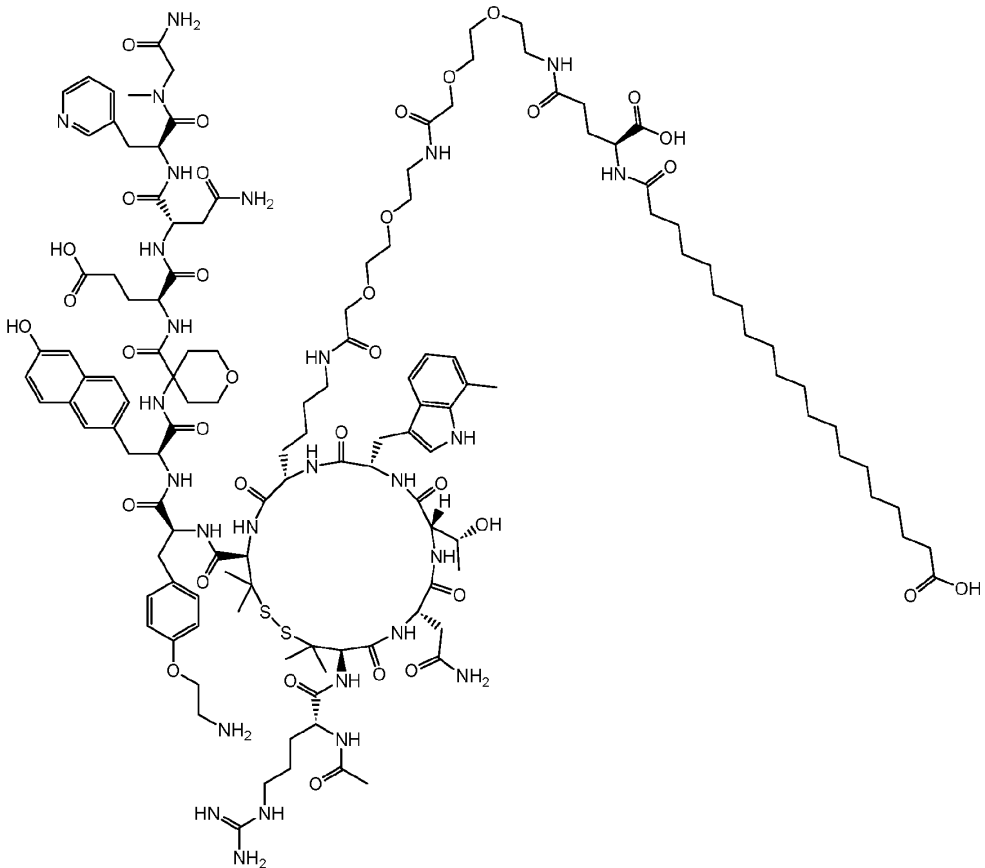
SEQ ID NO	Structure
115	 MeCO-r-Pen(3)-N-T-7MeW-K(Ac)-Pen(3)-AEF-6OH2Nal-THP-E-N-3Pyra-Sar-K(PEG2NMePEG2NMegENMeC18Tetrazole)-CONH2

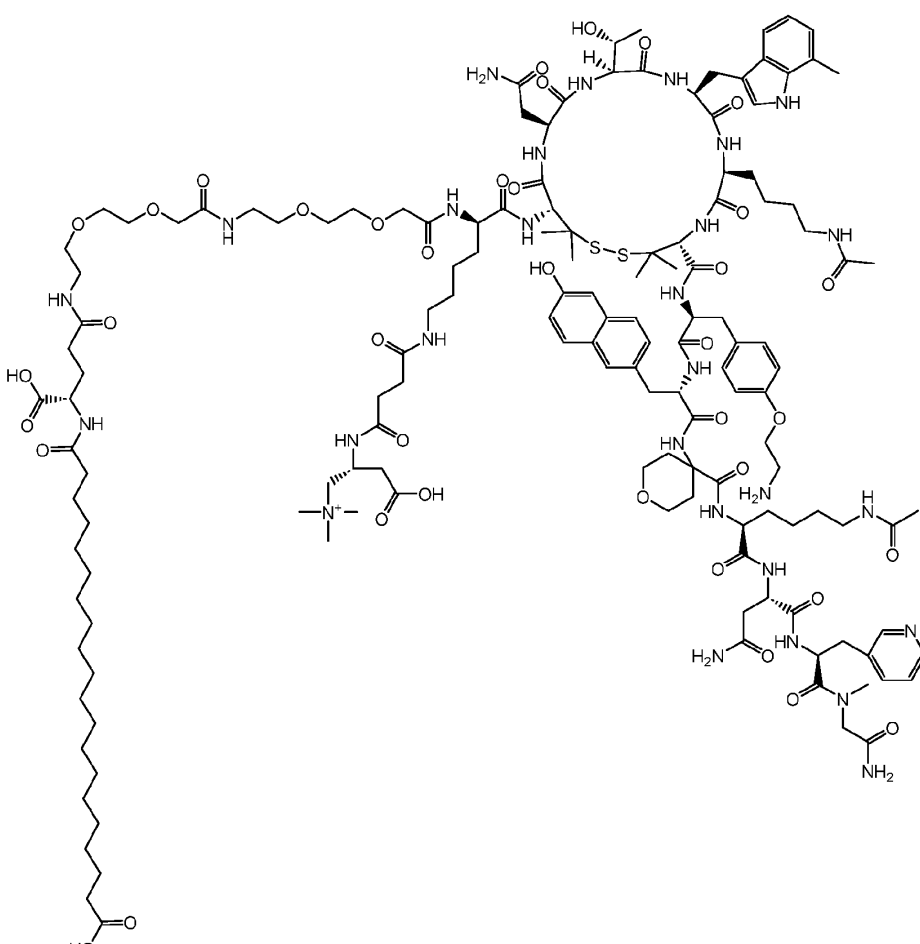
SEQ ID NO	Structure
116	 MeCO-r-Pen(3)-N-T-7MeW-K(Ac)-Pen(3)-AEF-6OH2Nal-THP-E-N-3PyA-Sar-K(PEG12NMegENMeC18Tetrazole)-CONH2

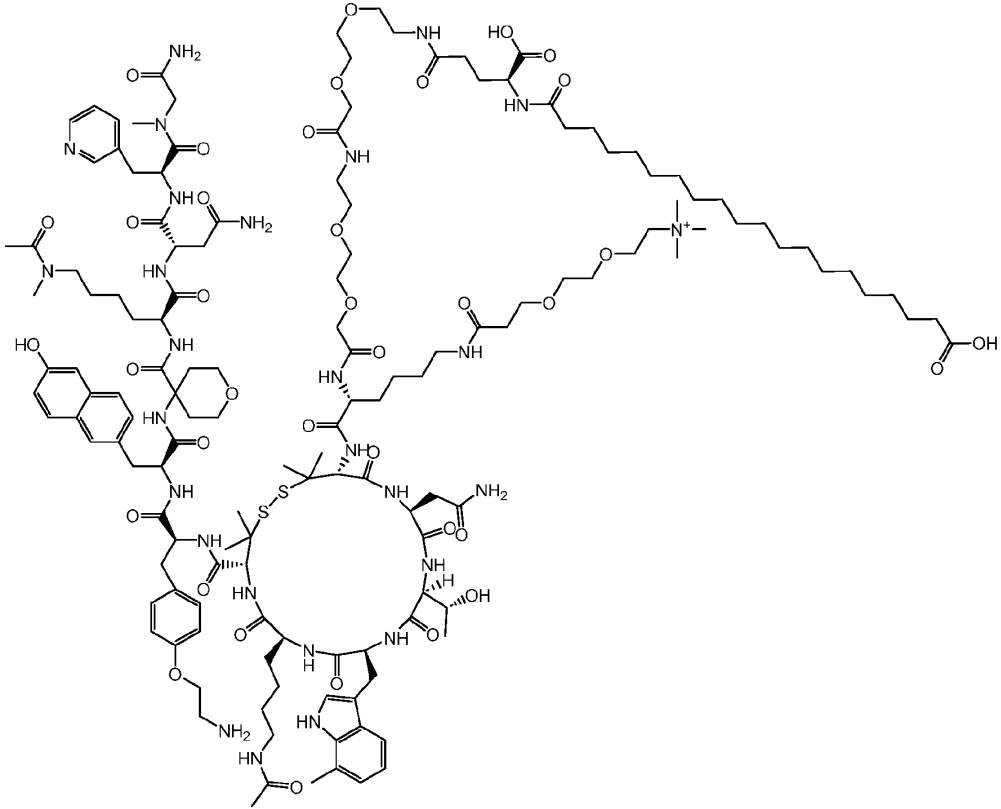
SEQ ID NO	Structure
117	 MeCO-r-Pen(3)-N-T-7MeW-K(Ac)-Pen(3)-AEF-6OH2Nal-THP-E-N-3Pyra-Sar-K(PEG2PEG2gEC20OH)-CONH2

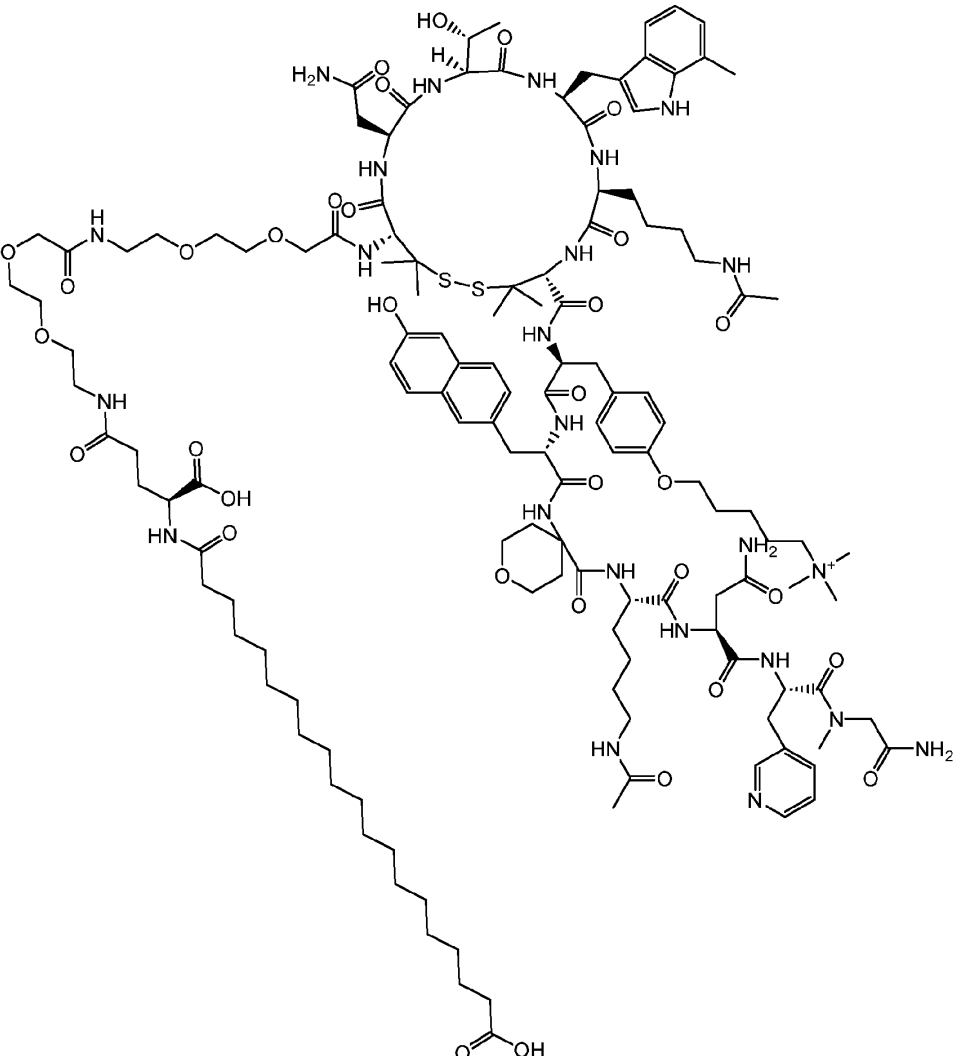
SEQ ID NO	Structure
118	 MeCO-k(PEG12gEC20OH)-Pen(3)-N-T-7MeW-K(Ac)-Pen(3)-AEF-6OH2Nal-THP-K(Ac)-N-3Pya-Sar-CONH2

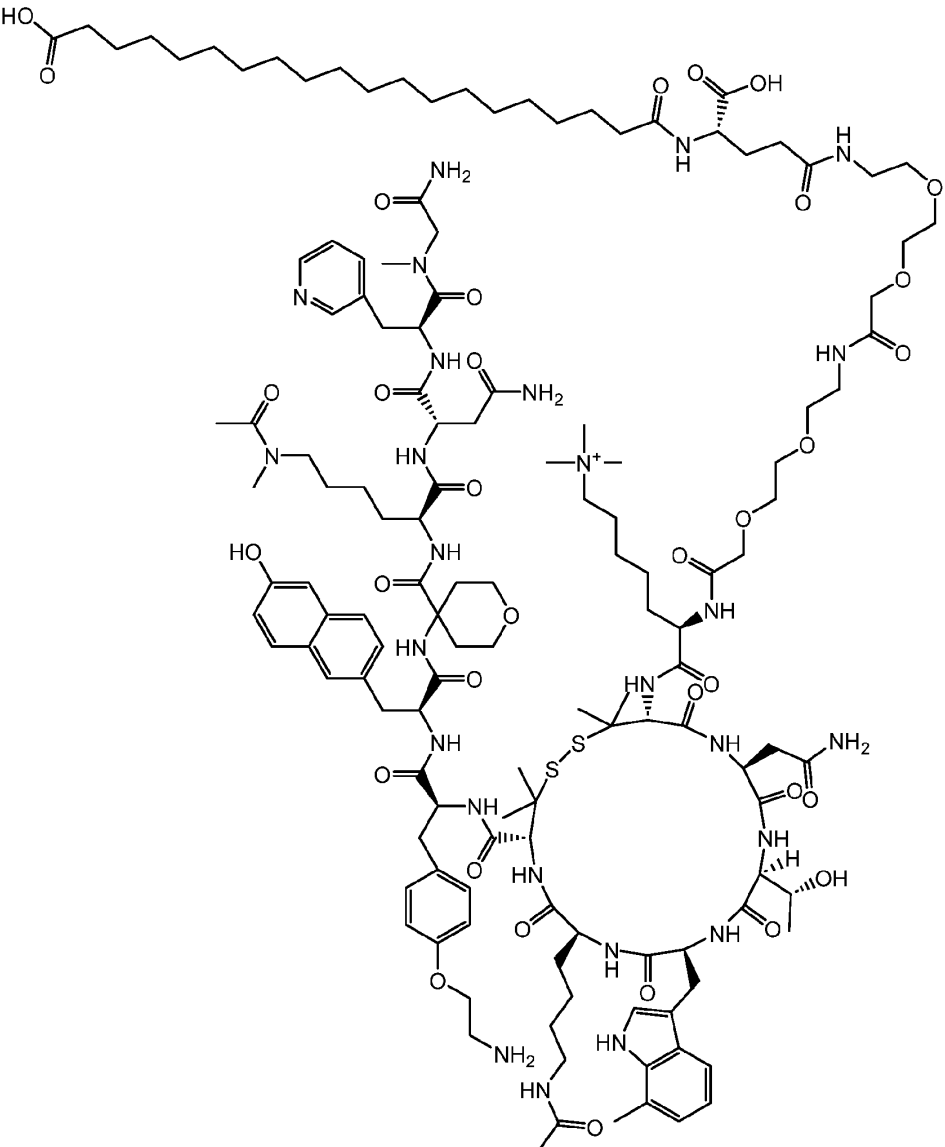
SEQ ID NO	Structure
119	 MeCO-hk(Me)3-Pen(3)-N-T-7MeW-K(PEG2PEG2gEC20OH)-Pen(3)-AEF-6OH2Nal-THP-K(Ac)-N-3Pya-Sar-CONH2

SEQ ID NO	Structure
120	 MeCO-r-Pen(3)-N-T-7MeW-K(PEG2PEG2gEC20OH)-Pen(3)-AEF-6OH2Nal-THP-E-N-3Pya-Sar-CONH2

SEQ ID NO	Structure
121	 HOC20gEPEG2PEG2CO-k(d)-Pen(3)-N-T-7MeW-K(Ac)-Pen(3)-AEF-6OH2NaI-THP-K(Ac)-N-3Pya-Sar-CONH2

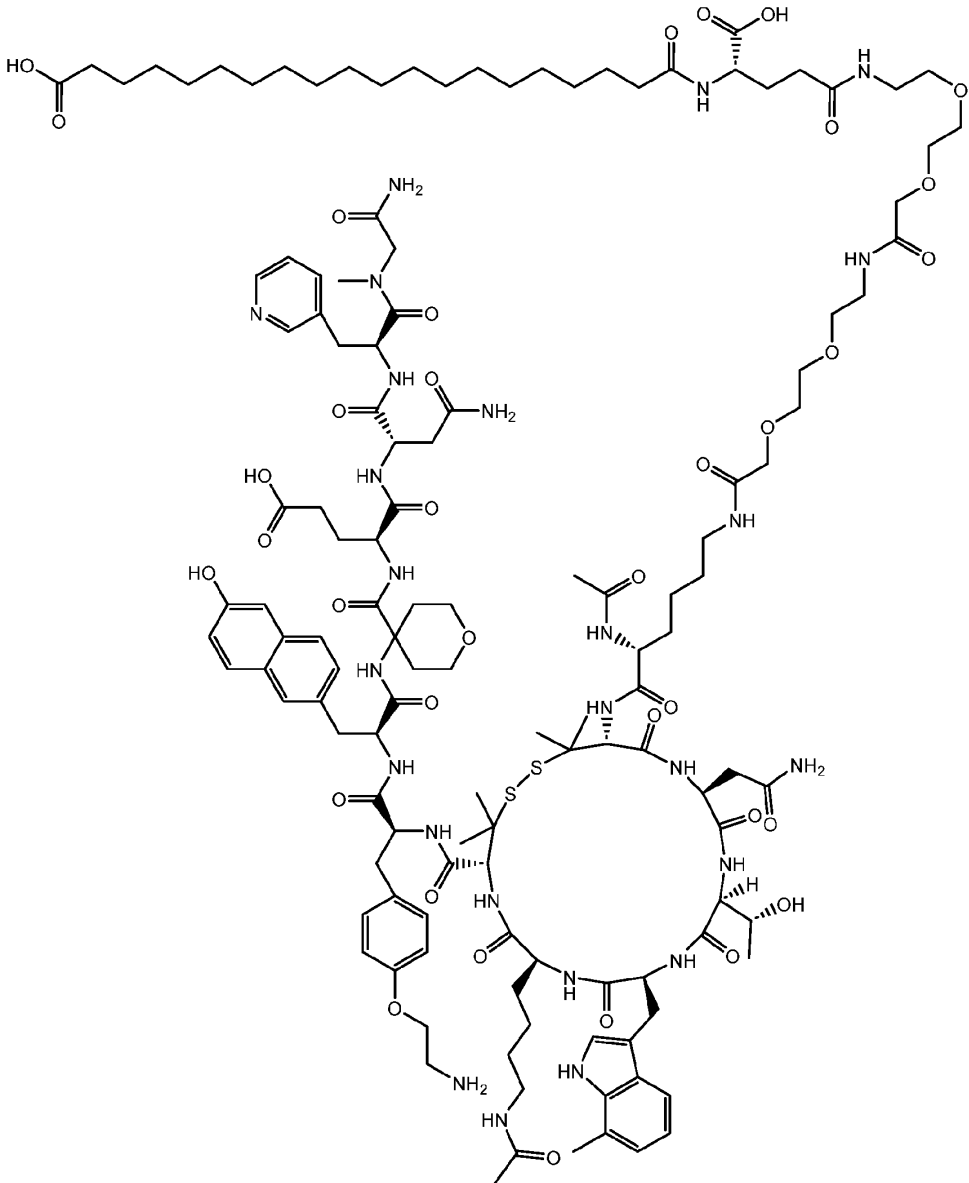
SEQ ID NO	Structure
122	 The chemical structure is a large, complex molecule, likely a peptide or protein derivative. It features a central circular core, possibly a macrocyclic peptide, with various side chains and functional groups. The structure includes a long, flexible chain with a terminal carboxylic acid group (COOH) and a terminal amine group (NH₂). There are also several amide bonds (NH-CO) and a disulfide bridge (S-S) connecting different parts of the molecule. The side chains include a pyridine ring, a phenol group (OH), a thiazolidine ring, and a long alkyl chain. The overall structure is highly branched and complex. HOC20gEPEG2PEG2CO-k(cPEG3a)-Pen(3)-N-T-7MeW-K(Ac)-Pen(3)-AEF-6OH2Nal-THP-K(NMeAc)-N-3Pya-Sar-CONH2

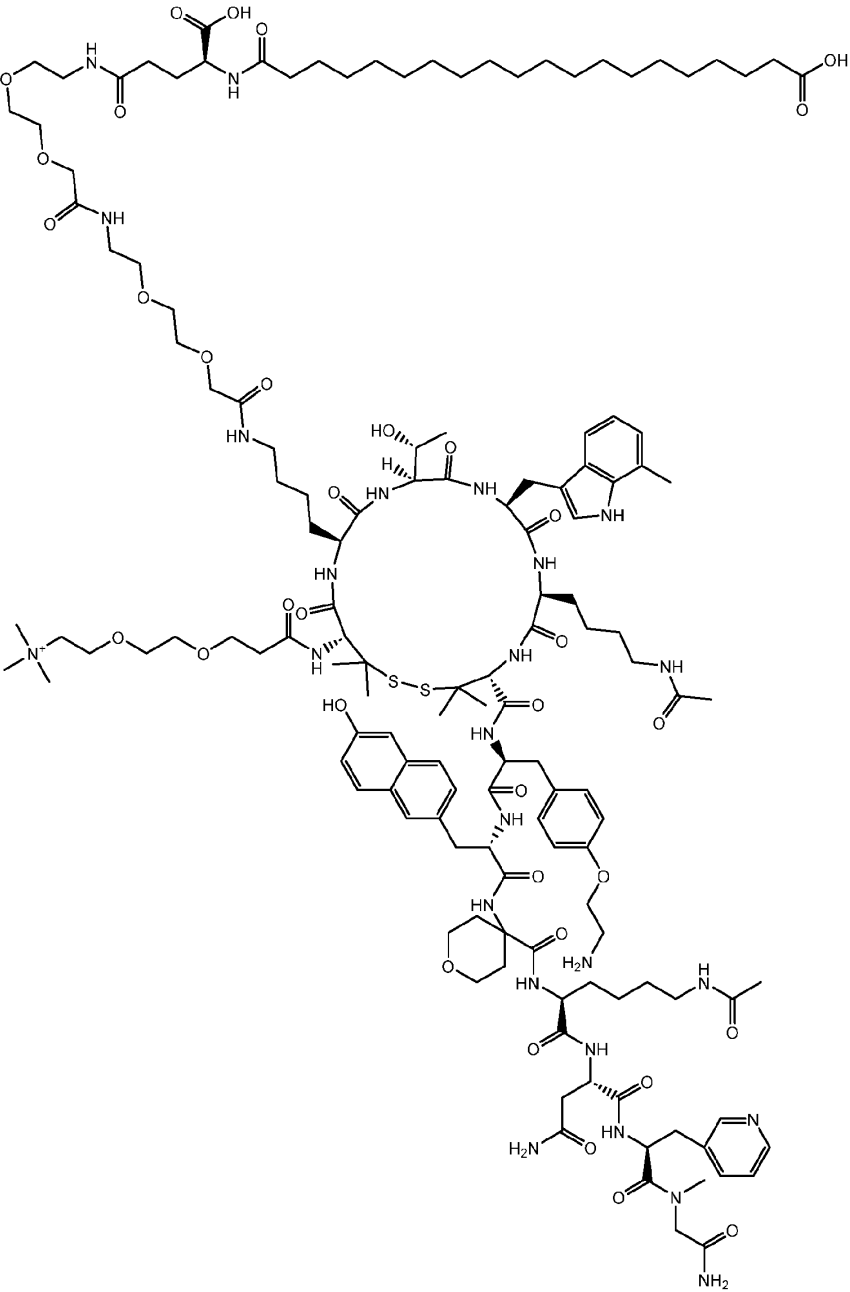
SEQ ID NO	Structure
123	 HOC20gEPEG2PEG2CO-Pen(3)-N-T-7MeW-K(Ac)-Pen(3)-TMAPF-6OH2Nal-THP-K(Ac)-N-3Pya-Sar-CONH2

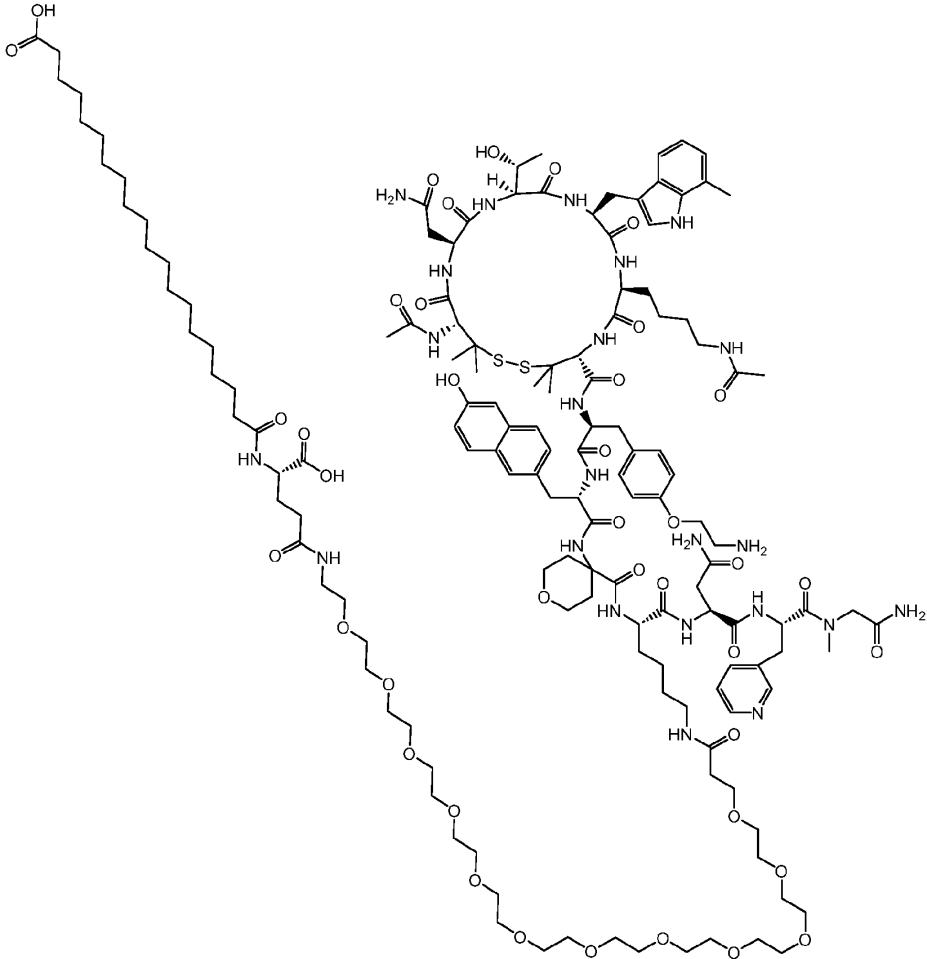
SEQ ID NO	Structure
124	 HOC20gEPEG2PEG2CO-hk(Me)3-Pen(3)-N-T-7MeW-K(Ac)-Pen(3)-AEF-6OH2NaI-THP-K(NMeAc)-N-3Py-Sar-CONH2

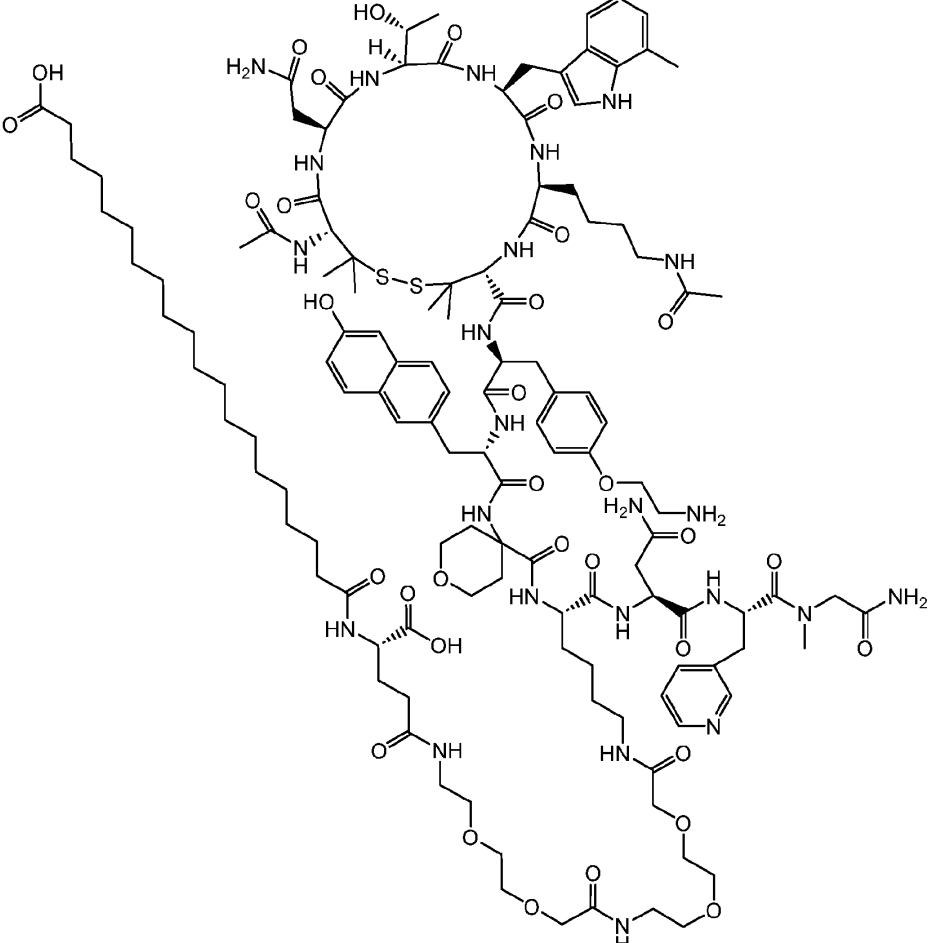
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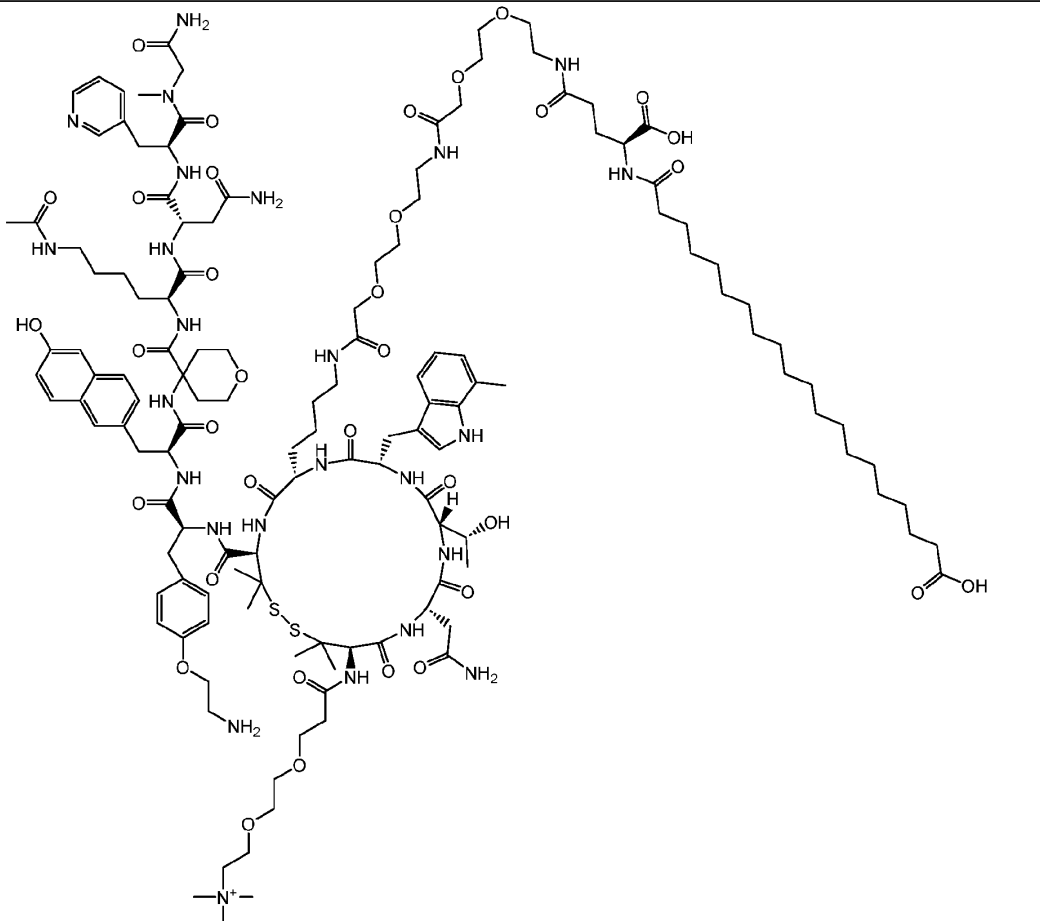
MeCO-r-Pen(3)-N-T-7MeW-K(Ac)-Pen(3)-AEF-6OH₂Nal-THP-E-N-3Pya-Sar-K(PEG12NMegENMeC18OH)-CONH₂

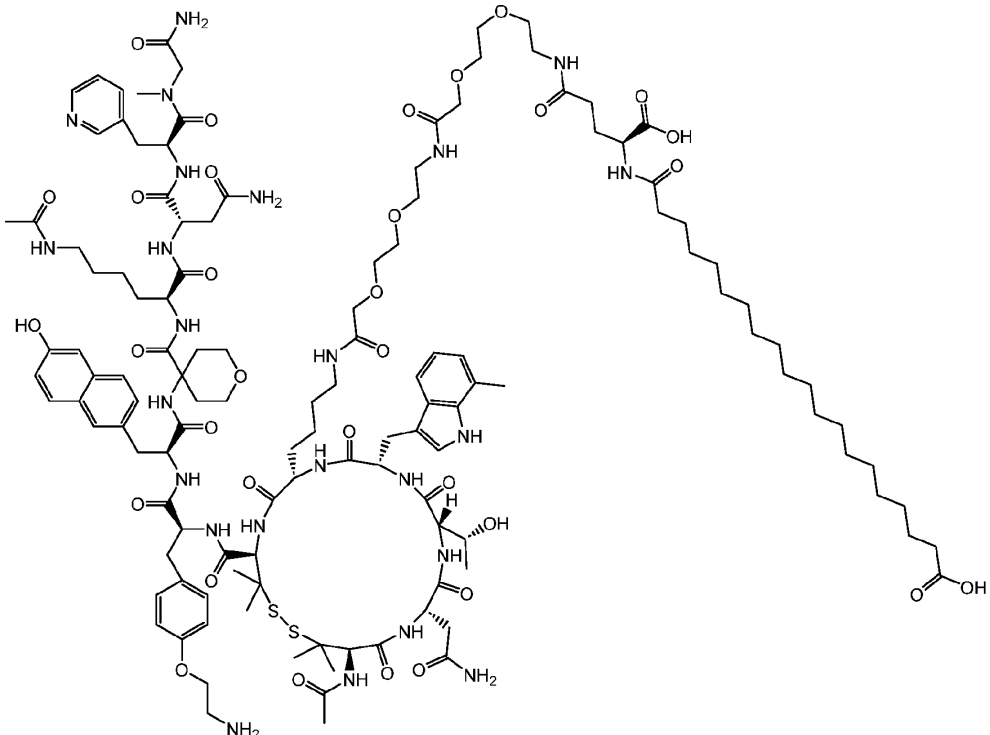
SEQ ID NO	Structure
126	 MeCO-k(PEG2PEG2gEC200H)-Pen(3)-N-T-7MeW-K(Ac)-Pen(3)-AEF-6OH2Nal-THP-E-N-3Pyra-Sar-CONH2

SEQ ID NO	Structure
127	 cPEG3aCO-Pen(3)-K(PEG2PEG2gEC20OH)-T-7MeW-K(Ac)-Pen(3)-AEF-6OH2Nal-THP-K(Ac)-N-3Pya-Sar-CONH2

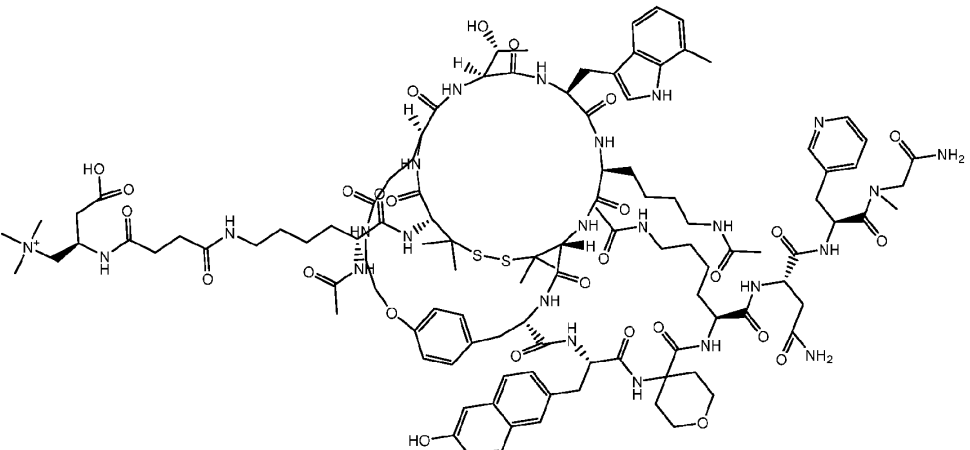
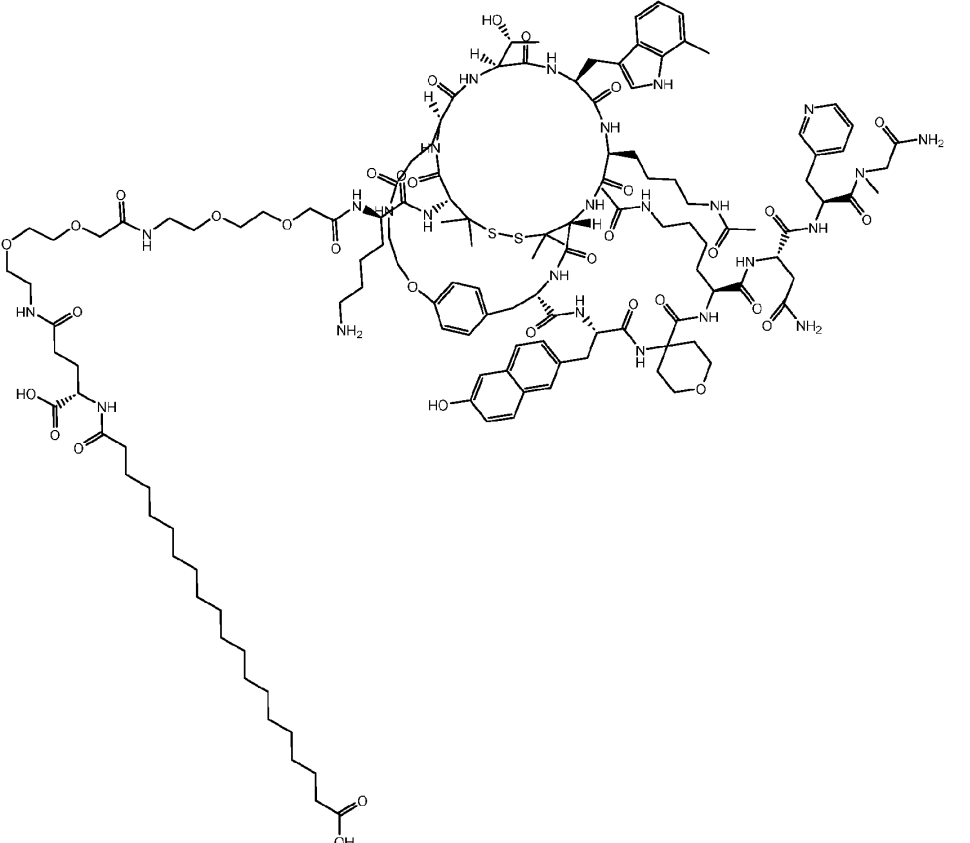
SEQ ID NO	Structure
128	 MeCO-Pen(3)-N-T-7MeW-K(Ac)-Pen(3)-AEF-6OH2NaI-THP-K(PEG12gEC20OH)-N-3Pya-Sar-CONH2

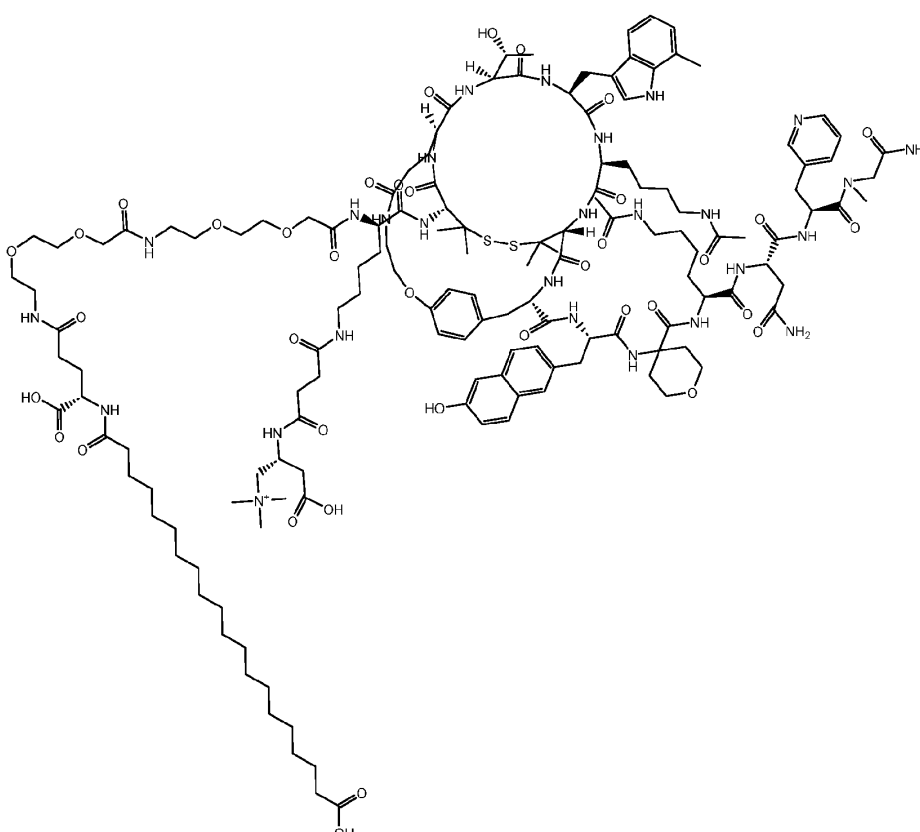
SEQ ID NO	Structure
129	 MeCO-Pen(3)-N-T-7MeW-K(Ac)-Pen(3)-AEF-6OH2NaI-THP-K(PEG2PEG2gEC20OH)-N-3Pya-Sar-CONH2

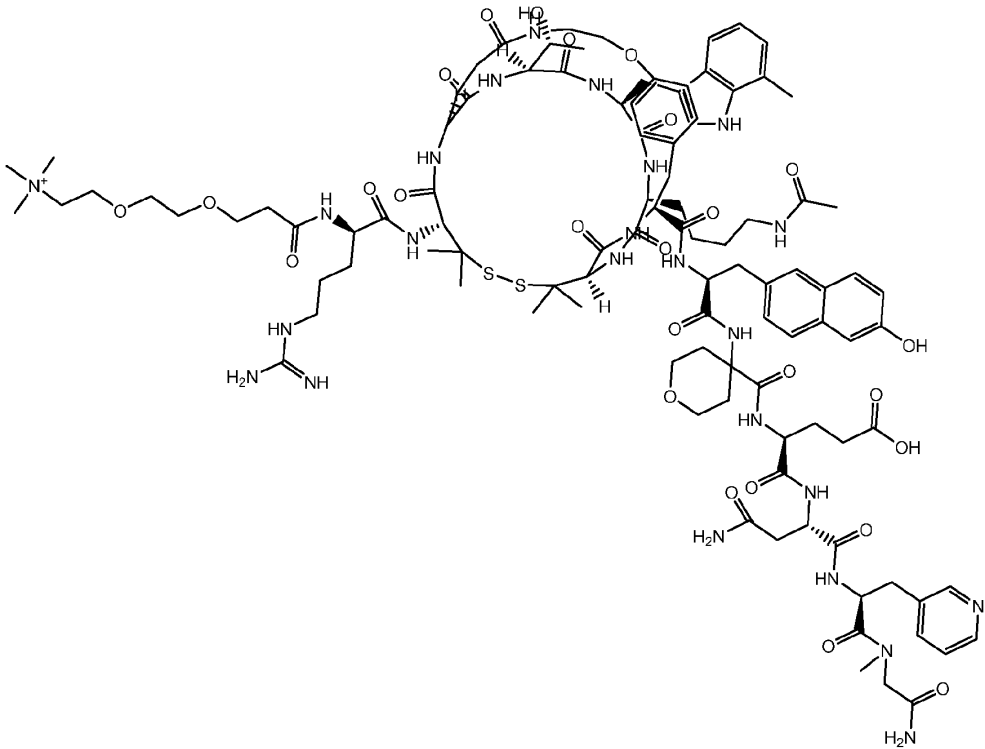
SEQ ID NO	Structure
130	 cPEG3aCO-Pen(3)-N-T-7MeW-K(PEG2PEG2gEC20OH)-Pen(3)-AEF-6OH2Nal-THP-K(Ac)-N-3Pyra-Sar-CONH2

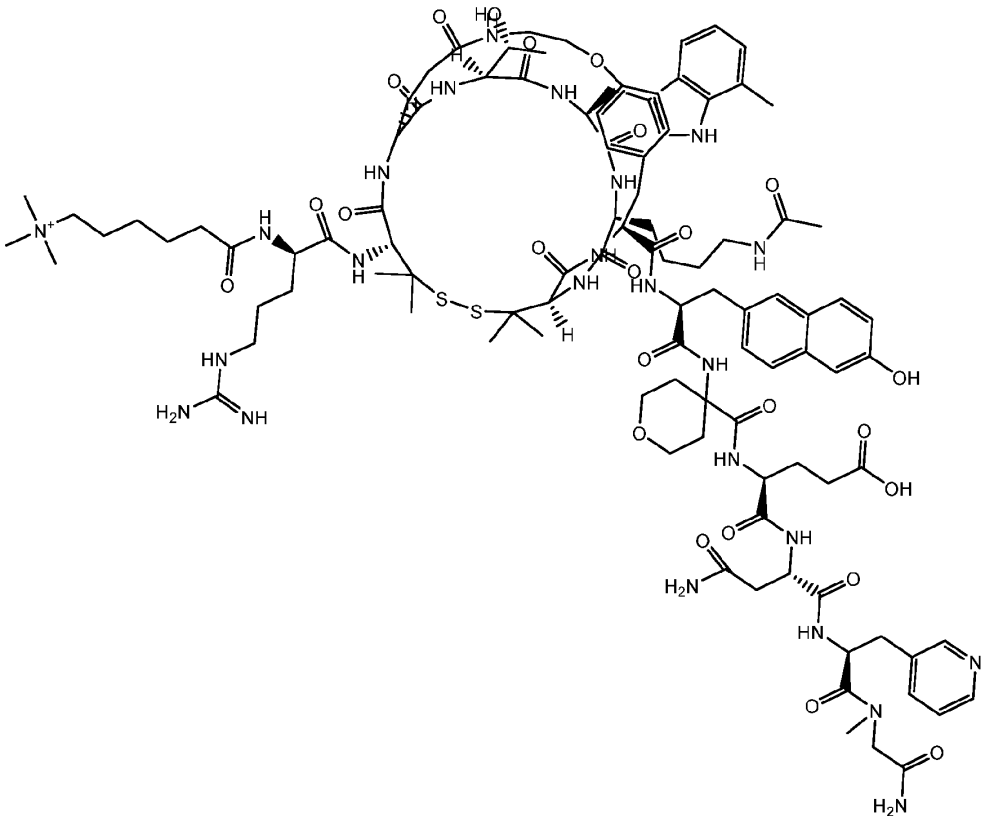
SEQ ID NO	Structure
131	 MeCO-Pen(3)-N-T-7MeW-K(PEG2PEG2gEC20OH)-Pen(3)-AEF-6OH2NaI-THP-K(Ac)-N-3Pya-Sar-CONH2

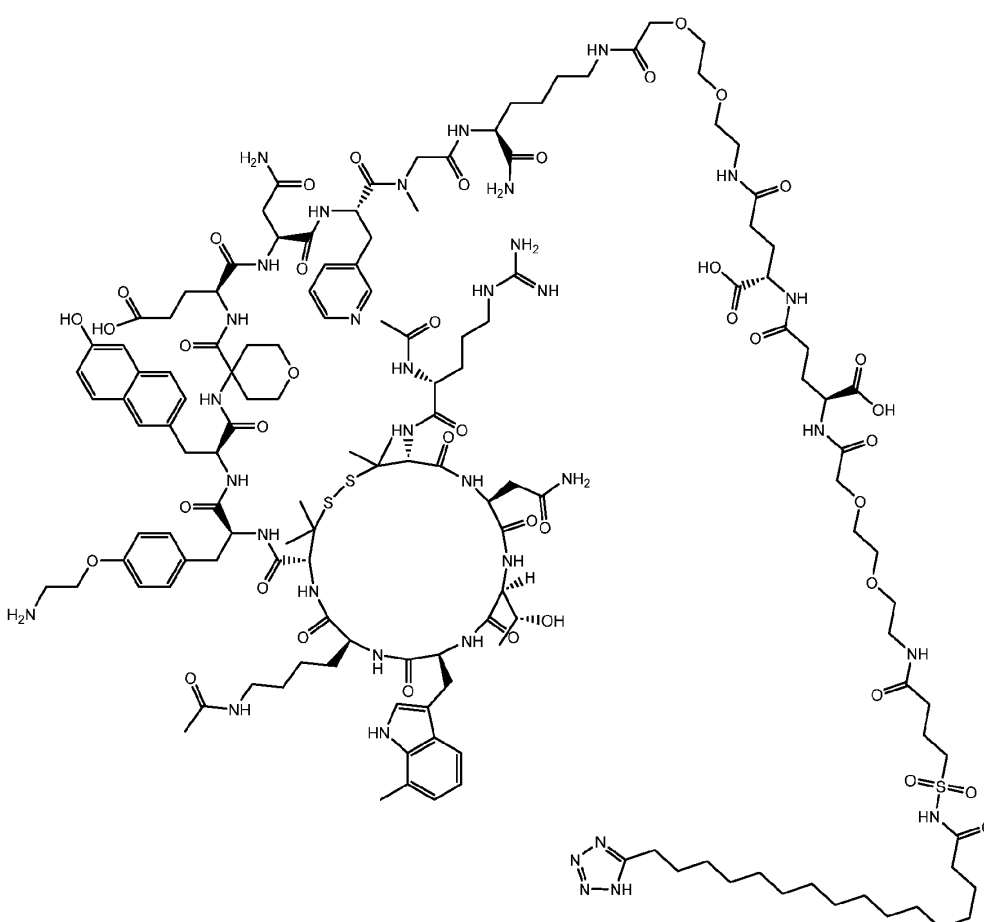
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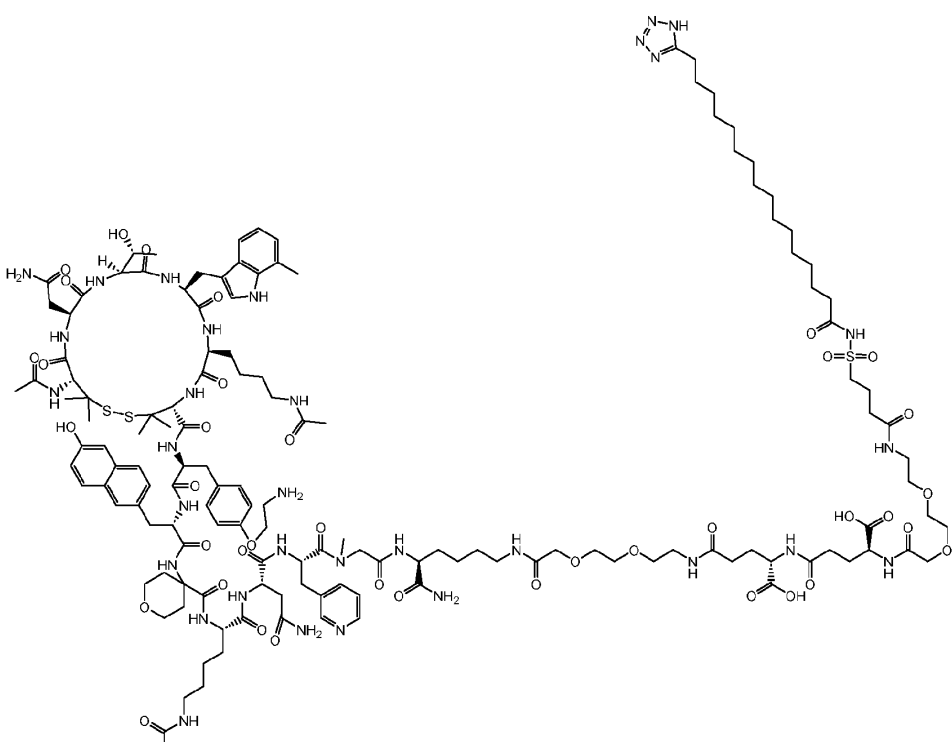
SEQ ID NO	Structure
133	 MeCO-k(d)-Pen(3)-E(2)-T-7MeW-K(Ac)-Pen(3)-AEF(2)-6OH2Nal-THP-K(Ac)-N-3Pyra-Sar-CONH2
134	 HOC20gEPEG2PEG2CO-k-Pen(3)-E(2)-T-7MeW-K(Ac)-Pen(3)-AEF(2)-6OH2Nal-THP-K(Ac)-N-3Pyra-Sar-CONH2

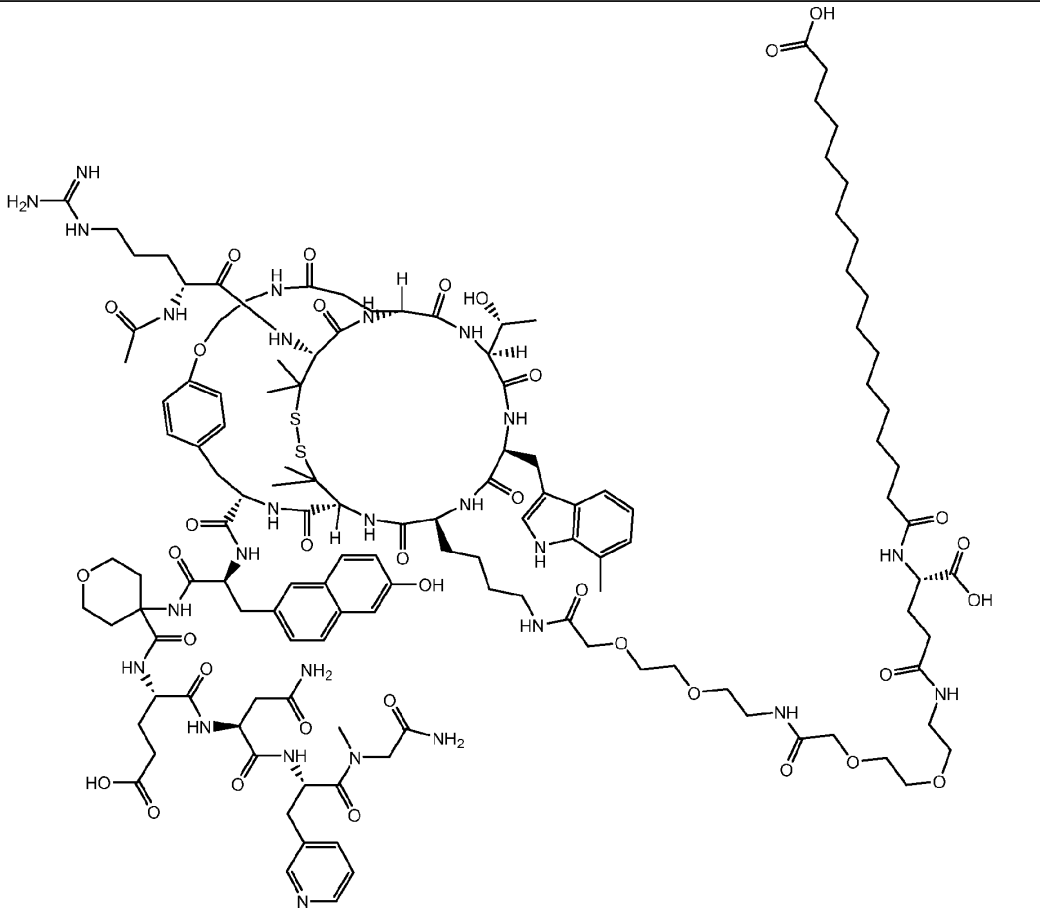
SEQ ID NO	Structure
135	 HOC20gEPEG2PEG2CO-k(d)-Pen(3)-E(2)-T-7MeW-K(Ac)-Pen(3)-AEF(2)-6OH2Nal-THP-K(Ac)-N-3Pyra-Sar-CONH2

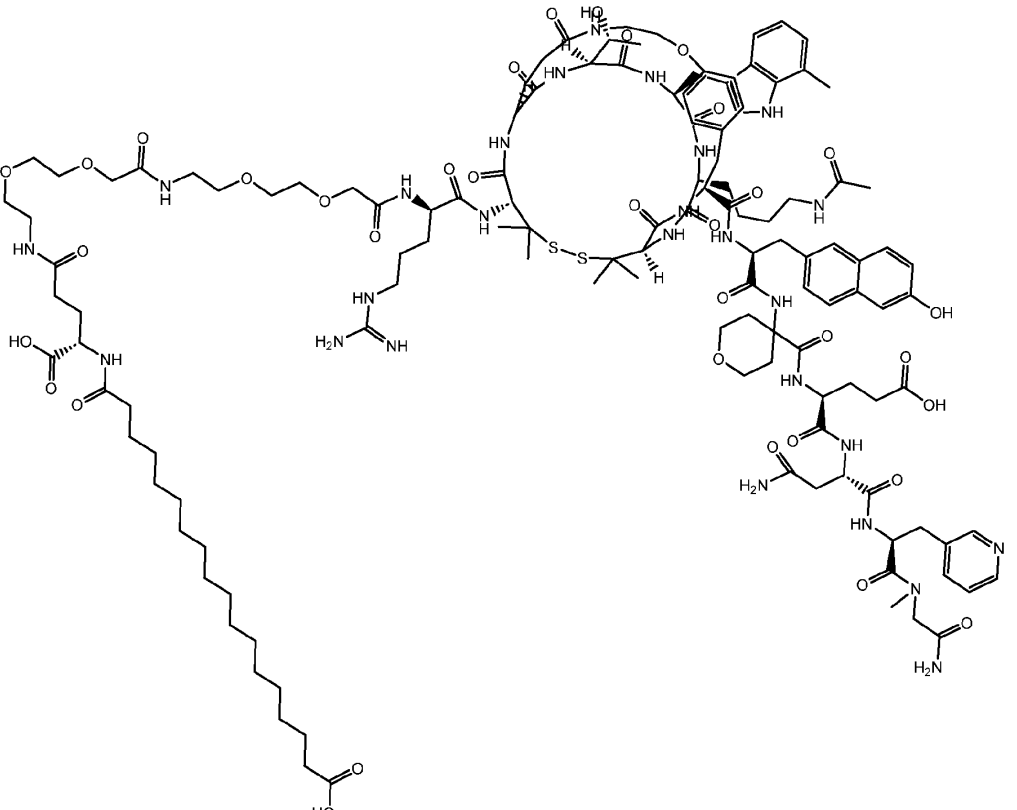
SEQ ID NO	Structure
136	 cPEG3aCO-r-Pen(3)-E(2)-T-7MeW-K(Ac)-Pen(3)-AEF(2)-6OH2Nal-THP-E-N-3Pyra-Sar-CONH2

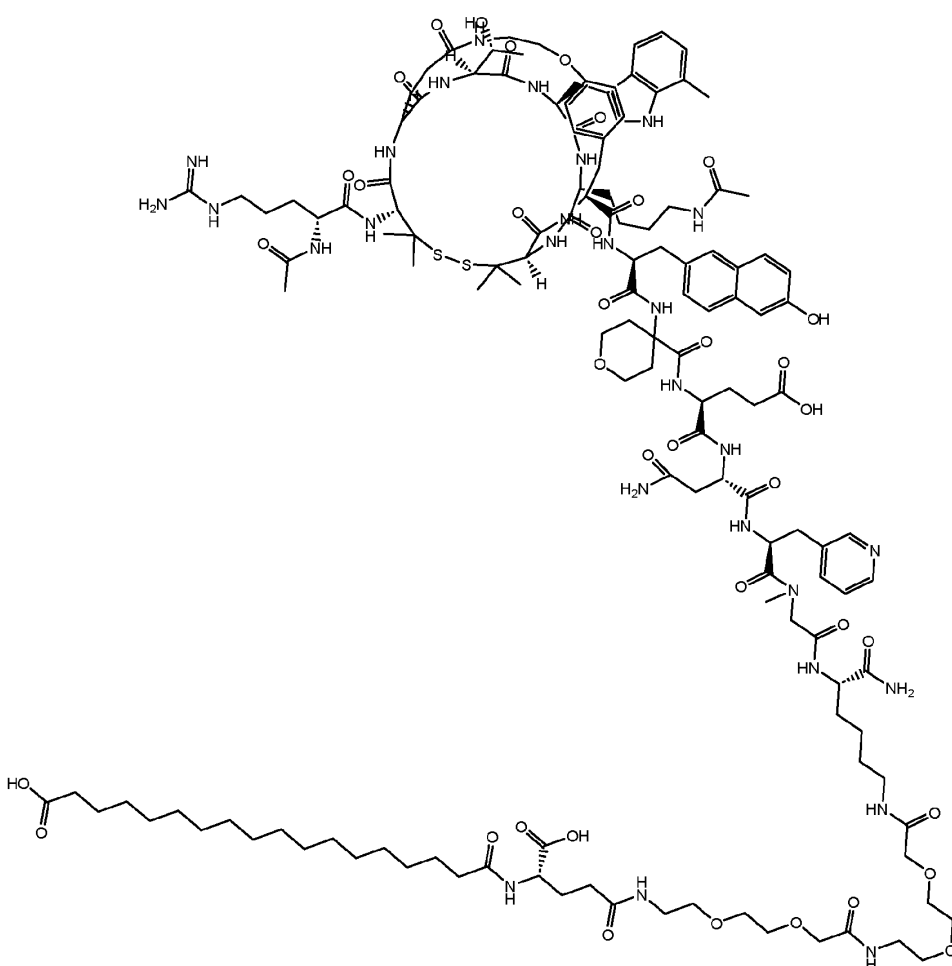
SEQ ID NO	Structure
137	 5cpaCO-r-Pen(3)-E(2)-T-7MeW-K(Ac)-Pen(3)-AEF(2)-6OH2Nal-THP-E-N-3Pya-Sar-CONH2

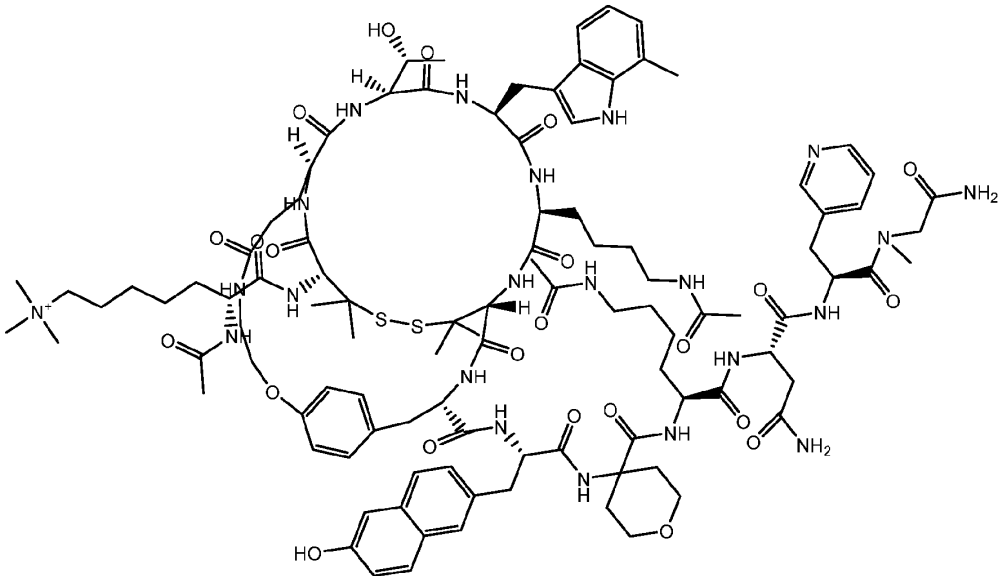
SEQ ID NO	Structure
138	 MeCO-r-Pen(3)-N-T-7MeW-K(Ac)-Pen(3)-AEF-6OH2Nal-THP-E-N-3Pyra-Sar-K(PEG2gEgEPEG24SBC16Tetrazole)-CONH2

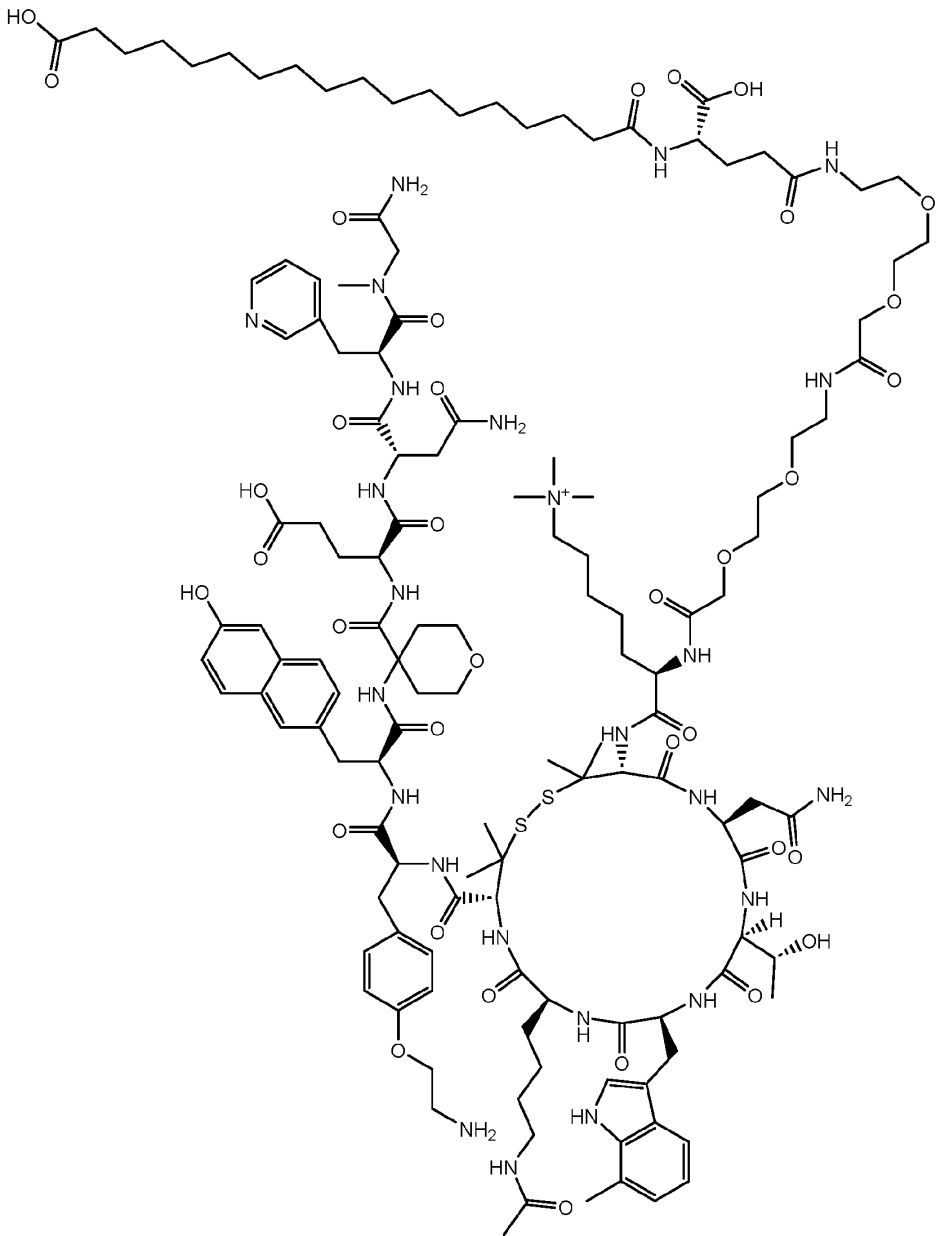
SEQ ID NO	Structure
139	 MeCO-Pen(3)-N-T-7MeW-K(Ac)-Pen(3)-AEF-6OH2Nal-THP-K(Ac)-N-3Pyra-Sar-K(PEG2gEgEPEG24SBC16Tetrazole)-CONH2

SEQ ID NO	Structure
140	 MeCO-r-Pen(3)-E(2)-T-7MeW-K(PEG2PEG2gEC18OH)-Pen(3)-AEF(2)-6OH2NaI-THP-E-N-3PyA-Sar-CONH2

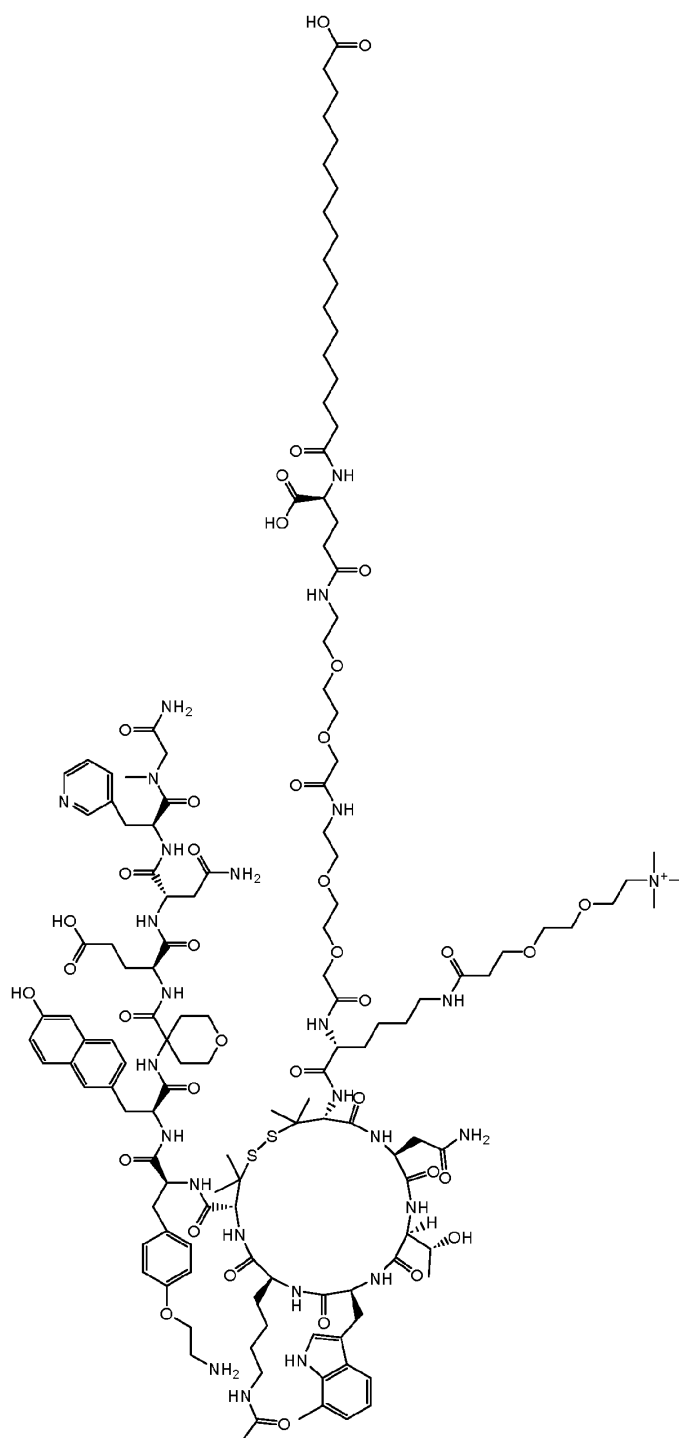
SEQ ID NO	Structure
141	 HOC18gEPEG2PEG2CO-r-Pen(3)-E(2)-T-7MeW-K(Ac)-Pen(3)-AEF(2)-6OH2Nal-THP-E-N-3Py-Sar-CONH2

SEQ ID NO	Structure
142	 MeCO-r-Pen(3)-E(2)-T-7MeW-K(Ac)-Pen(3)-AEF(2)-6OH2Nal-THP-E-N-3Pya-Sar-K(PEG2PEG2gEC18OH)-CONH2

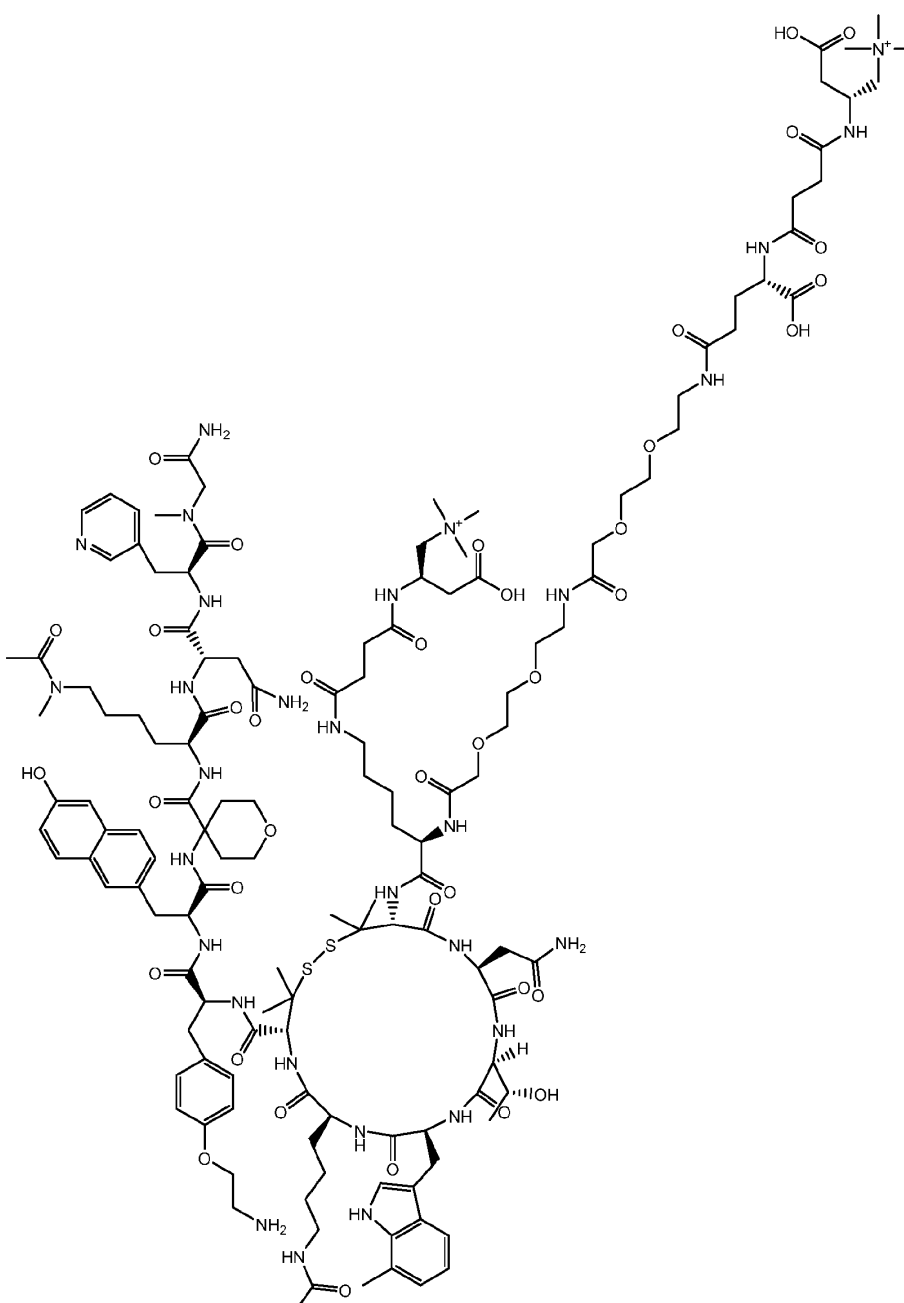
SEQ ID NO	Structure
143	 MeCO-hk(Me)3-Pen(3)-E(2)-T-7MeW-K(Ac)-Pen(3)-AEF(2)-6OH2Nal-THP-K(Ac)-N-3Py-Sar-CONH2

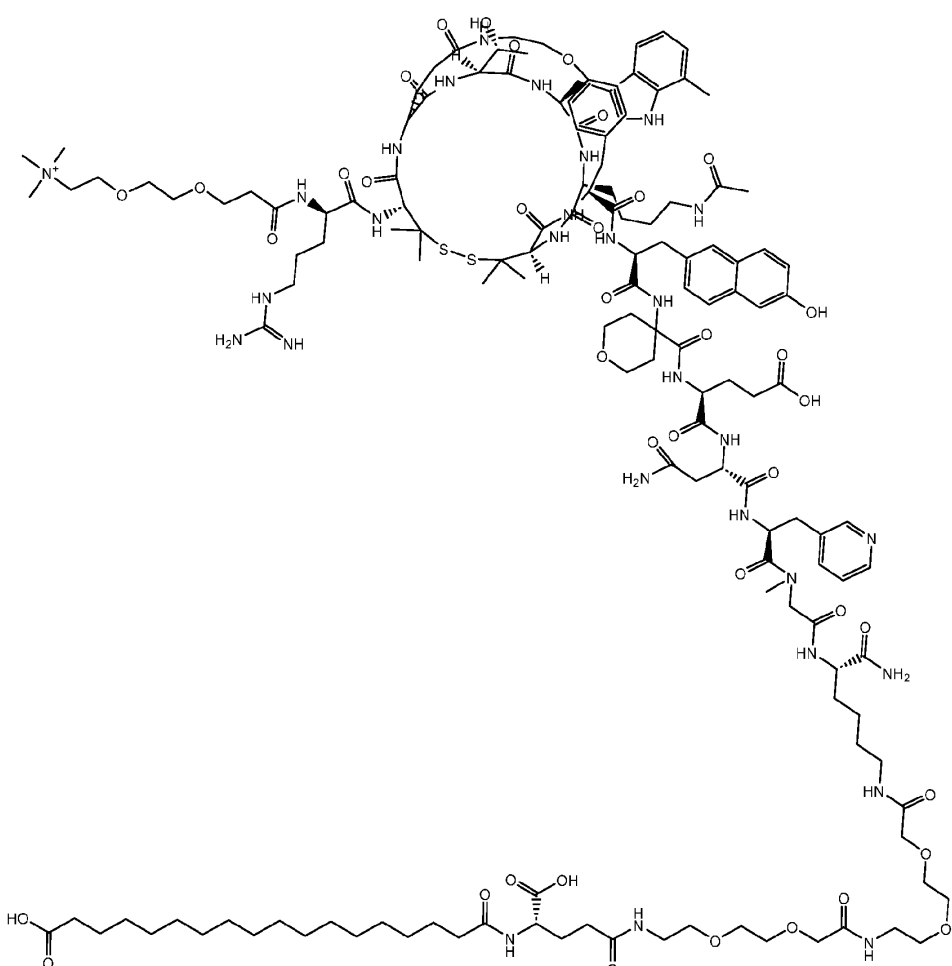
SEQ ID NO	Structure
144	 HOC18gEPEG2PEG2CO-hk(Me)3-Pen(3)-N-T-7MeW-K(Ac)-Pen(3)-AEF-6OH2NaI-THP-E-N-3Pya-Sar-CONH2

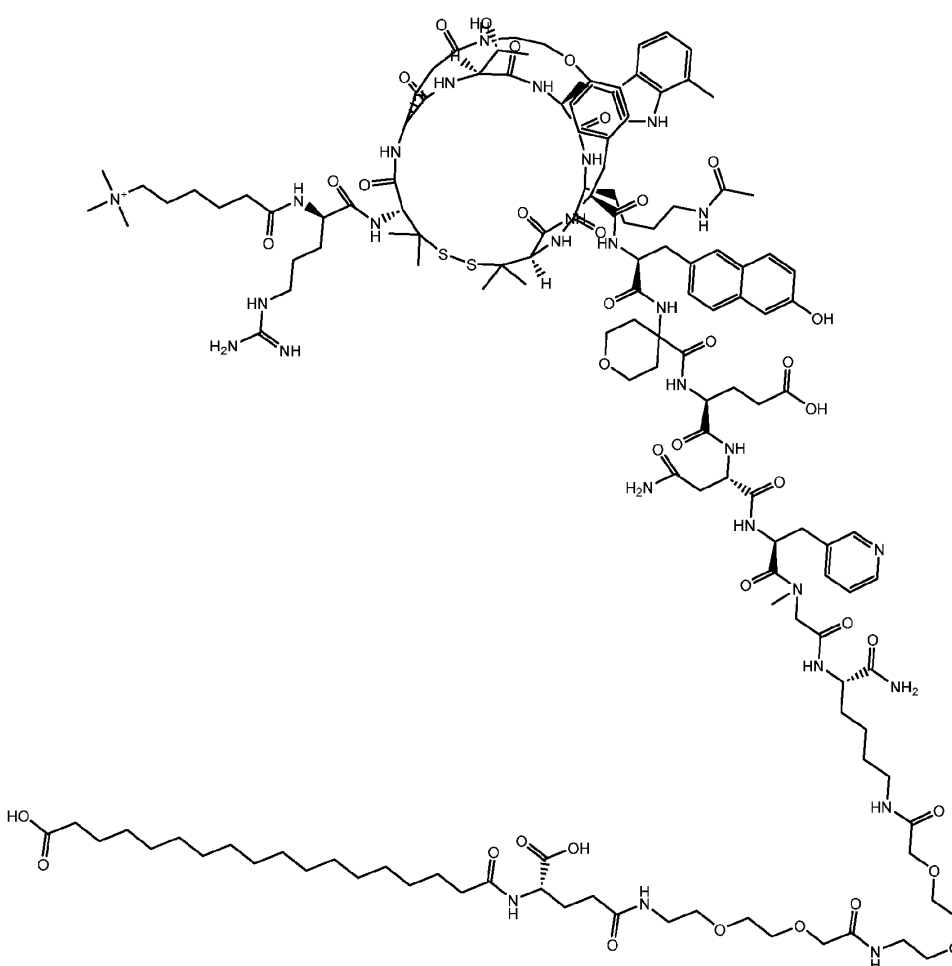
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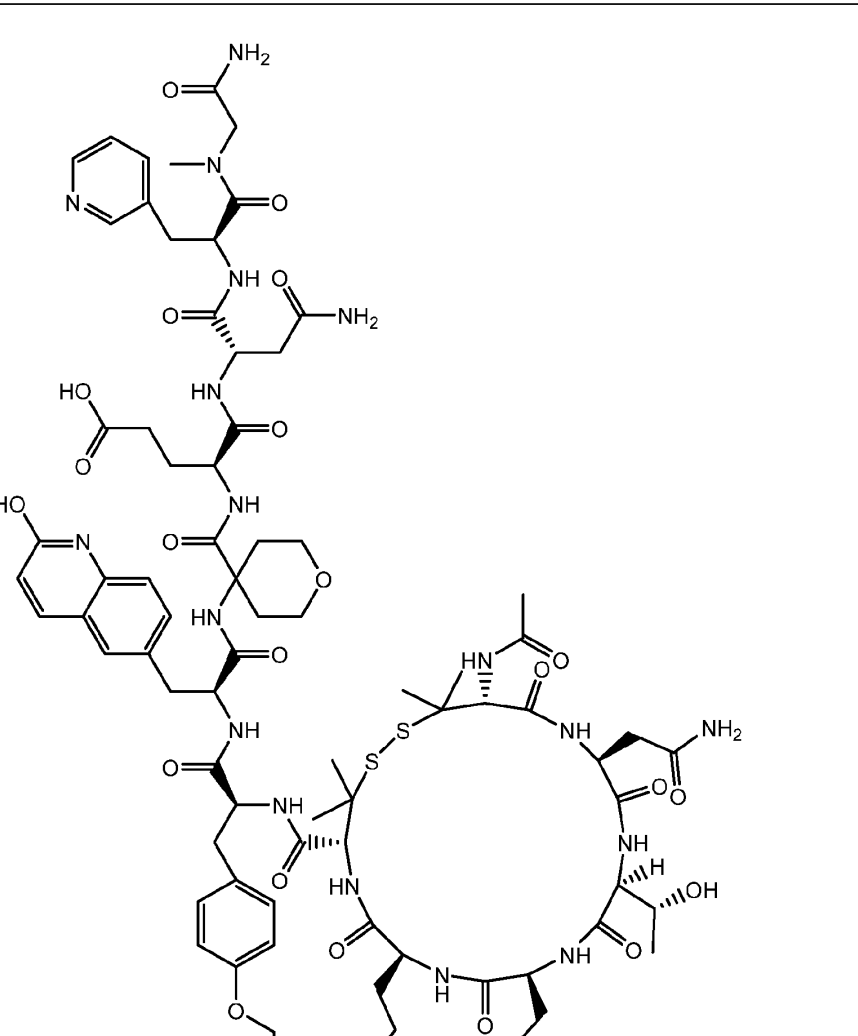


HOC18gEPEG2PEG2CO-k(cPEG3a)-Pen(3)-N-T-7MeW-K(Ac)-Pen(3)-AEF-6OH2Nal-THP-E-N-3Pyra-Sar-CONH2

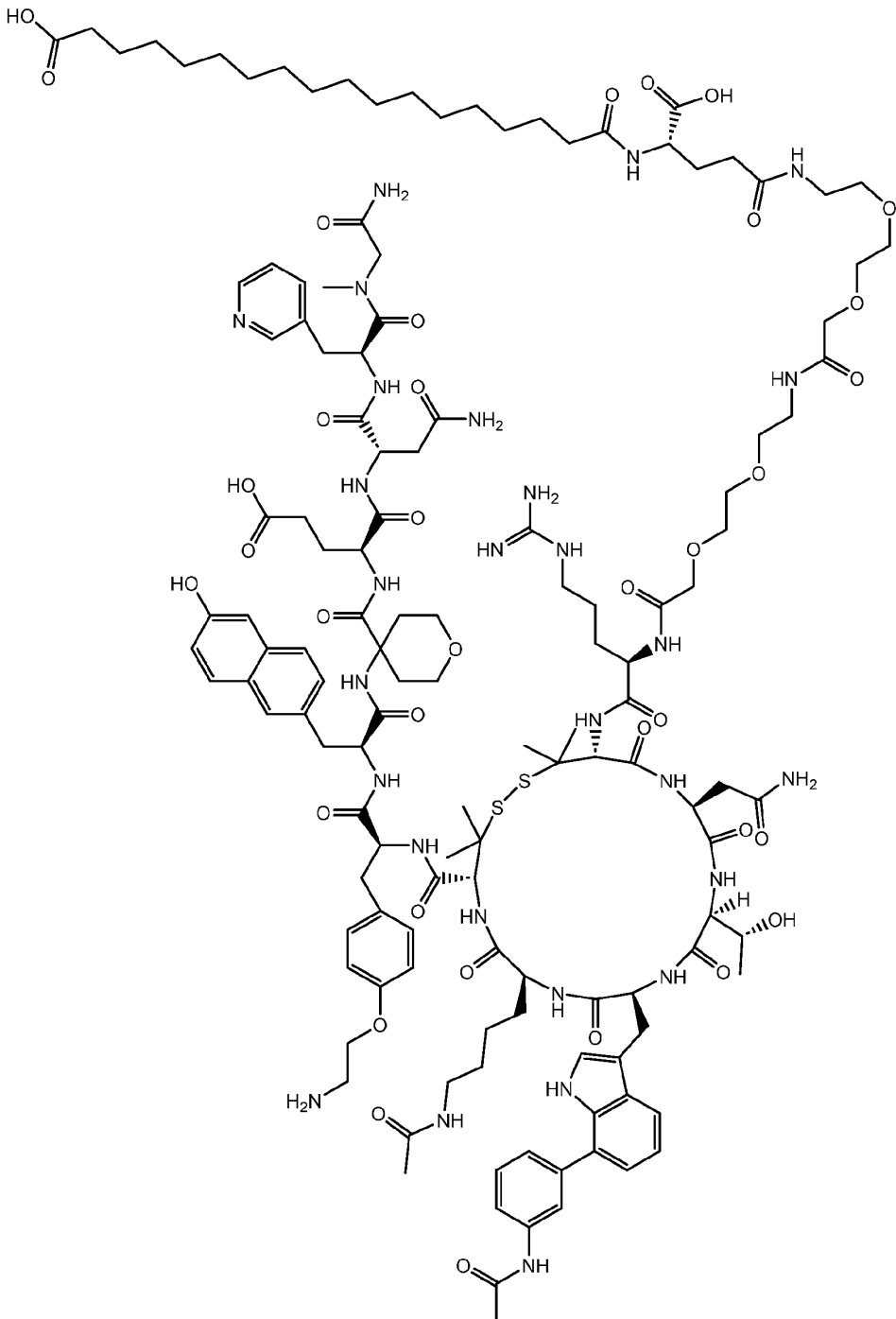
SEQ ID NO	Structure
146	 The chemical structure represents a large, complex peptide molecule, likely a cyclic peptide with multiple side chains and modifications. The structure features a central cyclic core with various side chains, including a long PEG chain, a pyridine ring, a thiazolidine ring, and a thioether bridge. The molecule is highly branched and contains numerous functional groups, including amide bonds, carboxylic acid groups, and a thioether bridge. The structure is shown in a 2D representation, with stereochemistry indicated by wedges and dashes. (d)gEPEG2PEG2CO-k(d)-Pen(3)-N-T-7MeW-K(Ac)-Pen(3)-AEF-6OH2Nal-THP-K(NMeAc)-N-3Pya-Sar-CONH2

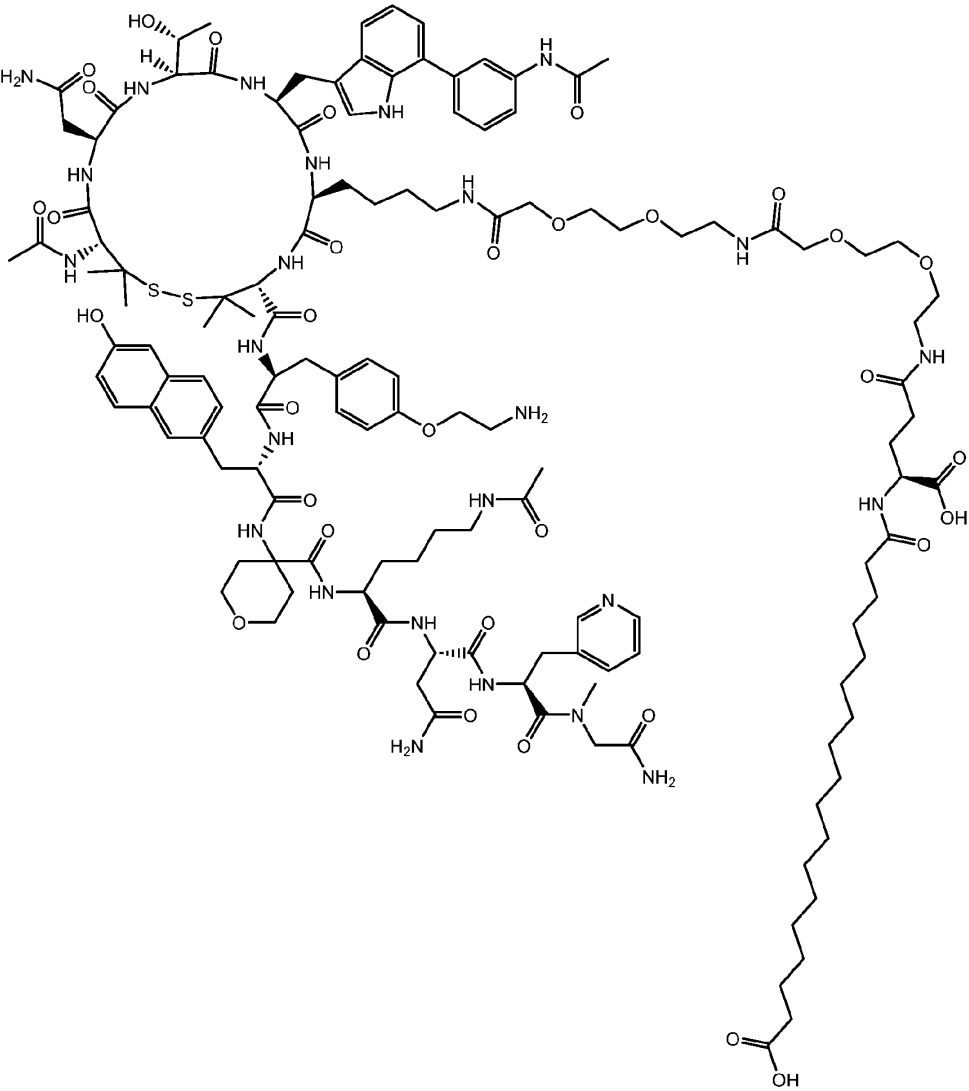
SEQ ID NO	Structure
147	 cPEG3aCO-r-Pen(3)-E(2)-T-7MeW-K(Ac)-Pen(3)-AEF(2)-6OH2Nal-THP-E-N-3Py-Sar-K(PEG2PEG2gEC18OH)-CONH2

SEQ ID NO	Structure
148	 5cpaCO-r-Pen(3)-E(2)-T-7MeW-K(Ac)-Pen(3)-AEF(2)-6OH2NaI-THP-E-N-3Pya-Sar-K(PEG2PEG2gEC18OH)-CONH2

SEQ ID NO	Structure
149	 MeCO-Pen(3)-N-T-7MeW-K(Ac)-Pen(3)-AEF-6OHQui-THP-E-N-3Pva-Sar-CONH2

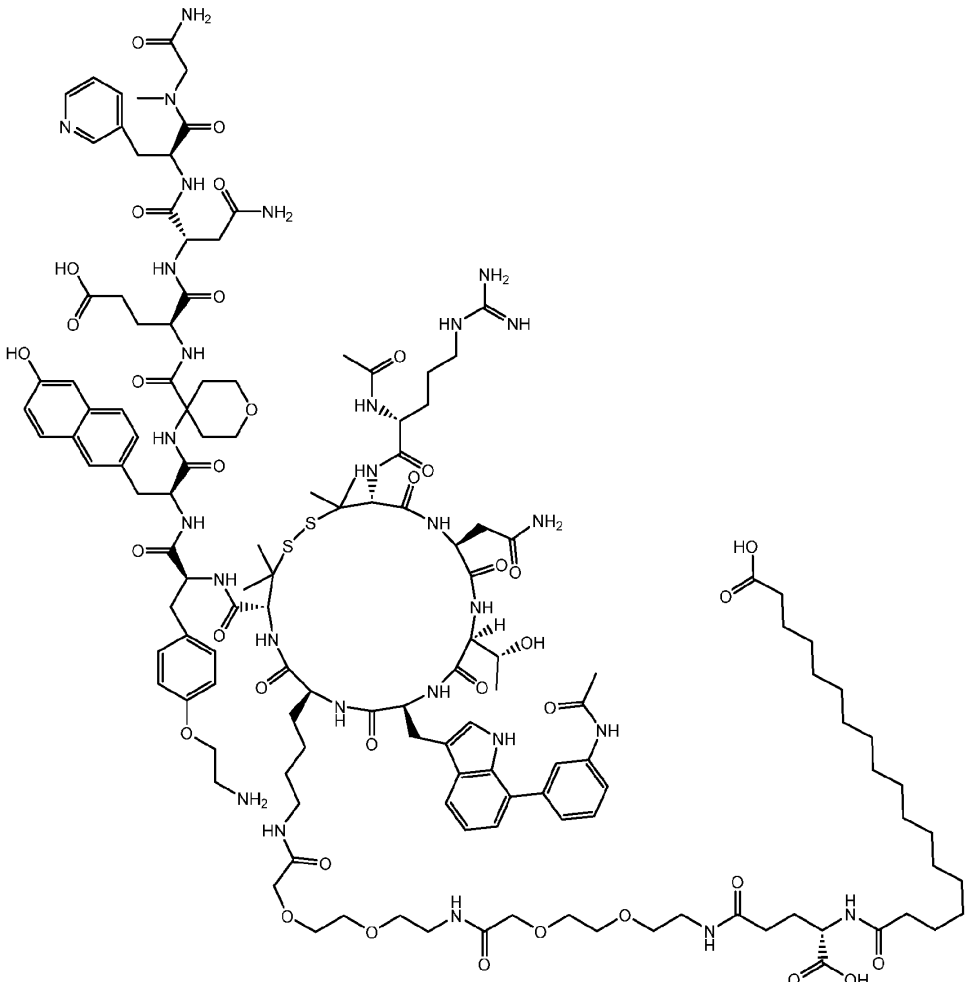
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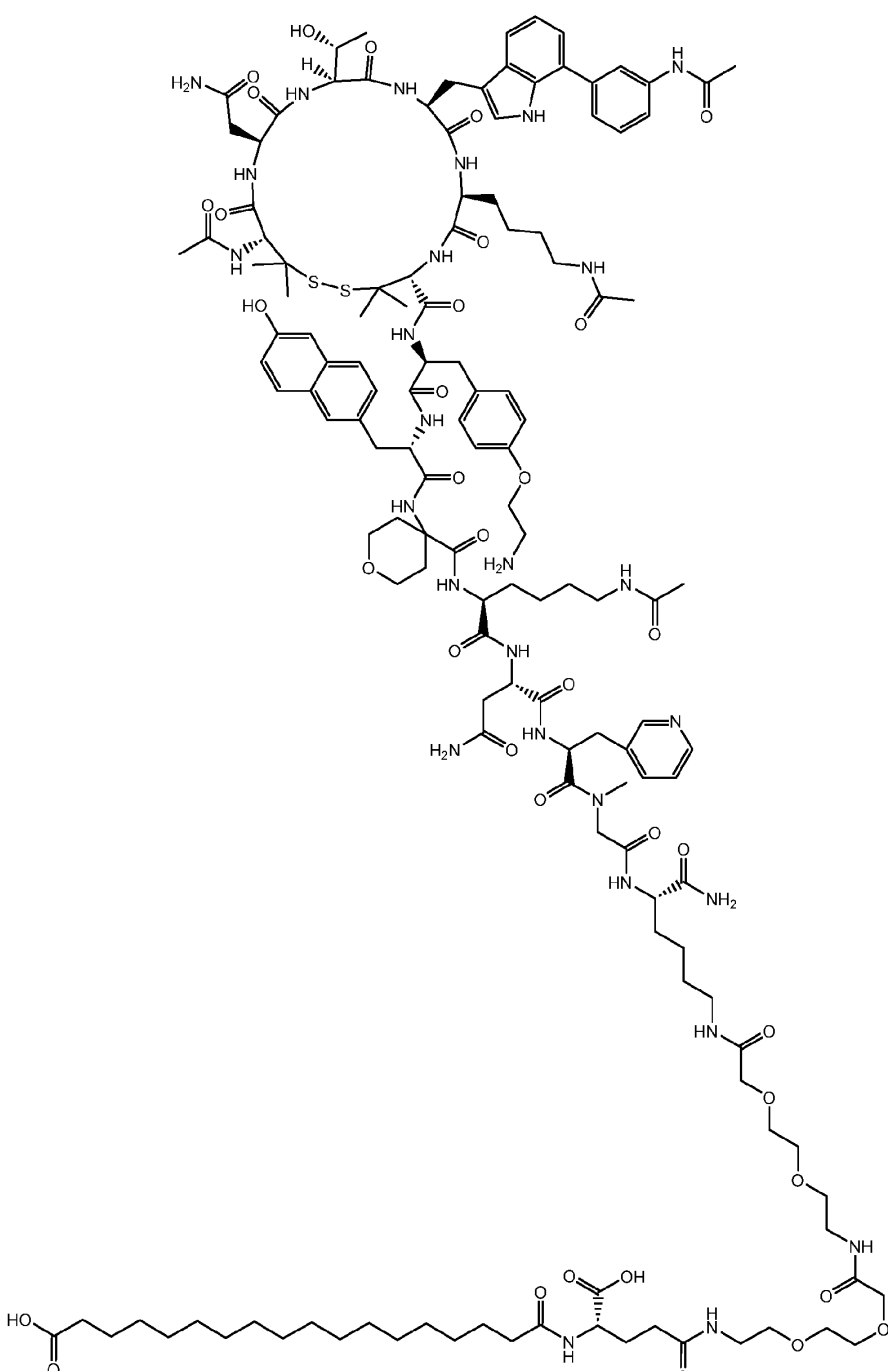
SEQ ID NO	Structure
151	 HOC18gEPEG2PEG2CO-r-Pen(3)-N-T-7(3NAcPh)W-K(Ac)-Pen(3)-AEF-6OH2Nal-THP-E-N-3Pya-Sar-CONH2

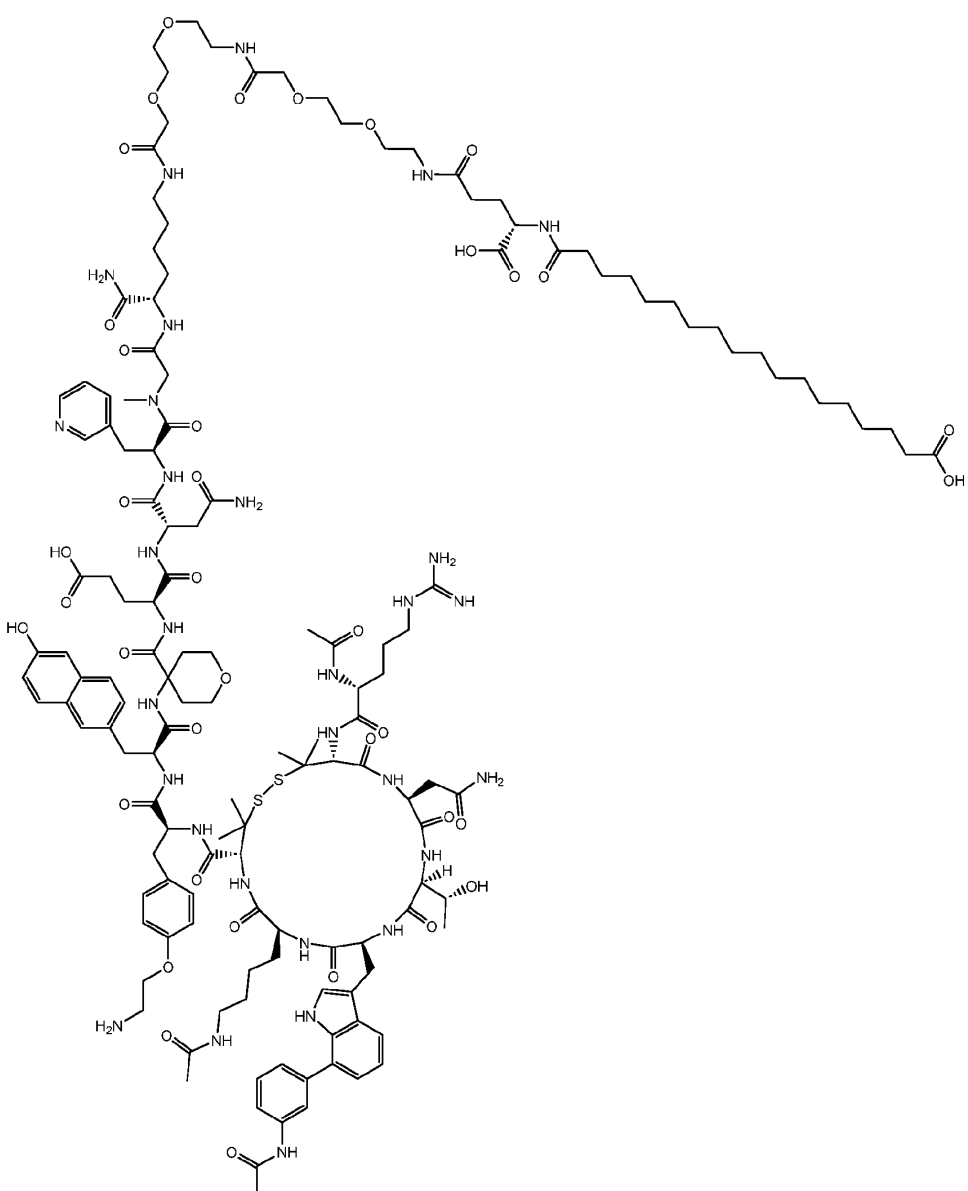
SEQ ID NO	Structure
152	 MeCO-Pen(3)-N-T-7(3NAcPh)W-K(PEG2PEG2gEC18OH)-Pen(3)-AEF-6OH2Nal-THP-K(Ac)-N-3Pyra-Sar-CONH2

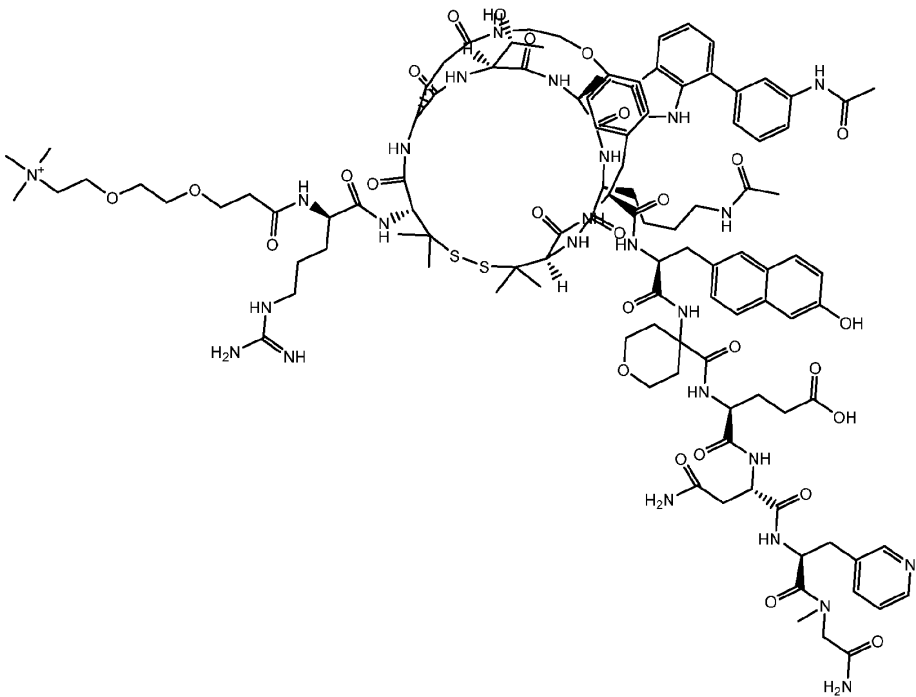
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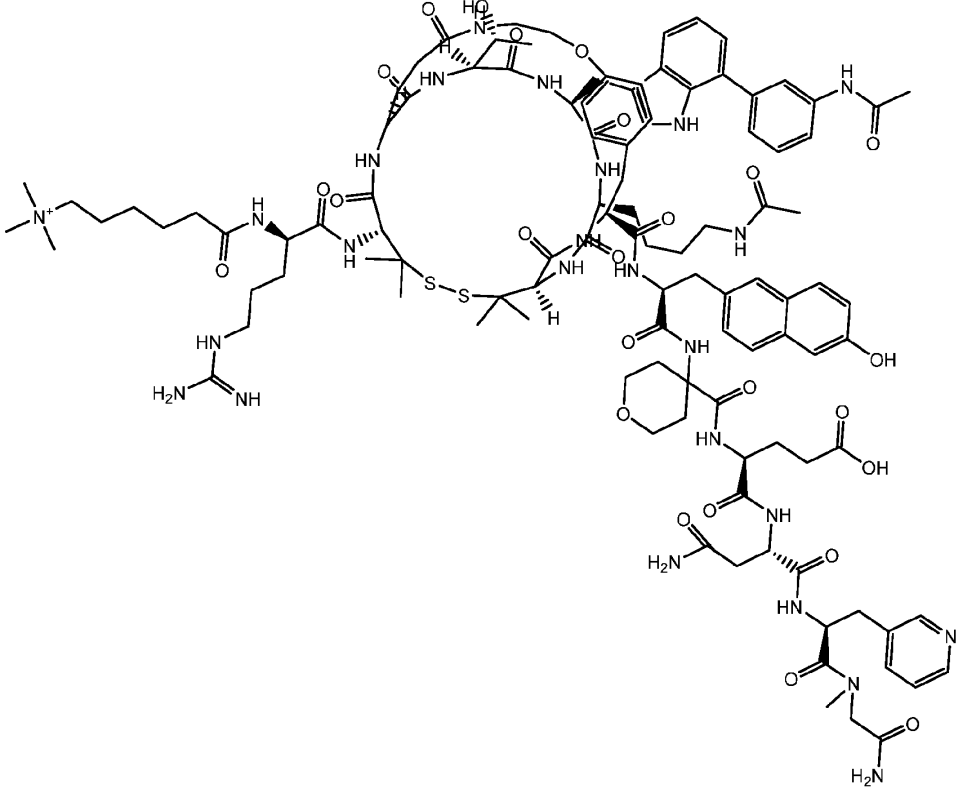
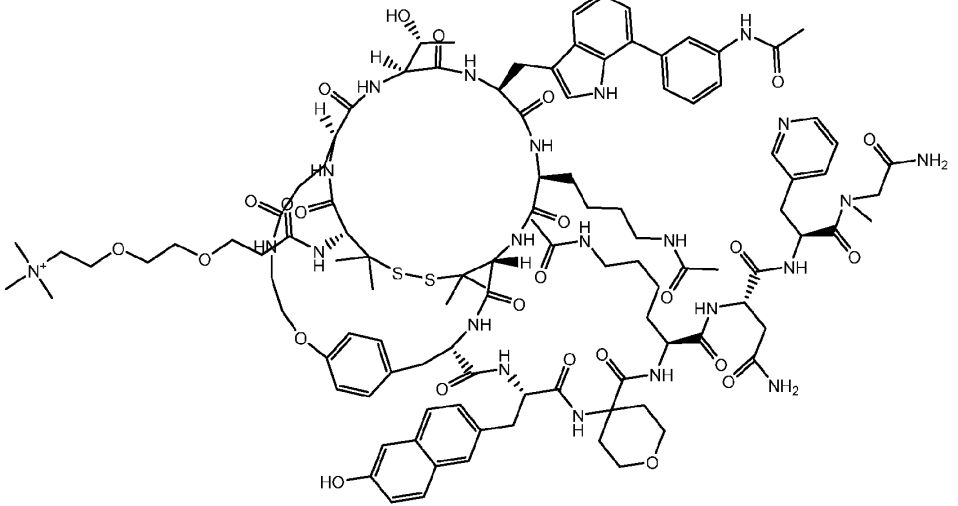
MeCO-Pen(3)-N-T-7(3NAcPh)W-K(Ac)-Pen(3)-AEF-6OH2Nal-THP-K(PEG2PEG2gEC18OH)-N-3PyA-Sar-CONH2

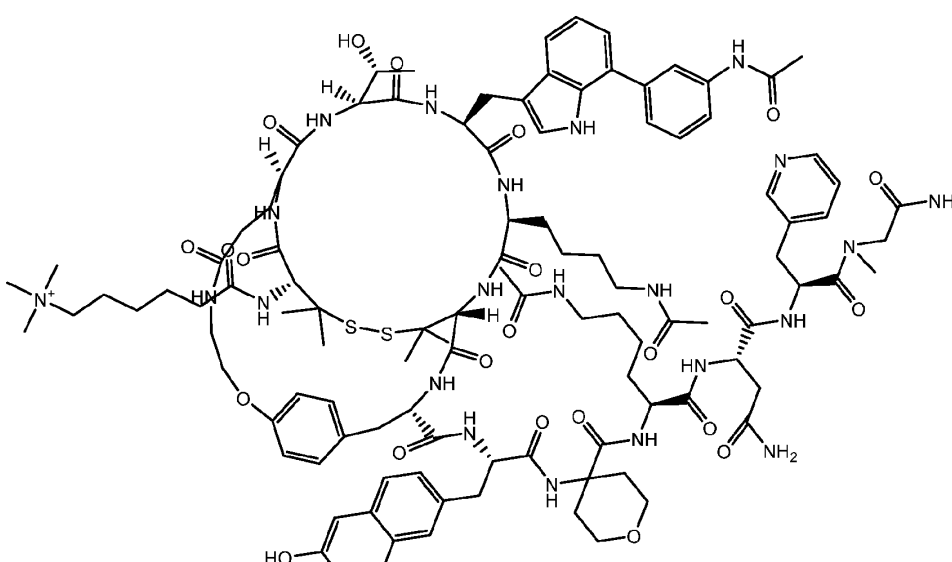
SEQ ID NO	Structure
154	 MeCO-r-Pen(3)-N-T-7(3NAcPh)W-K(PEG2PEG2gEC18OH)-Pen(3)-AEF-6OH2Nal-THP-E-N-3Py-Sar-CONH2

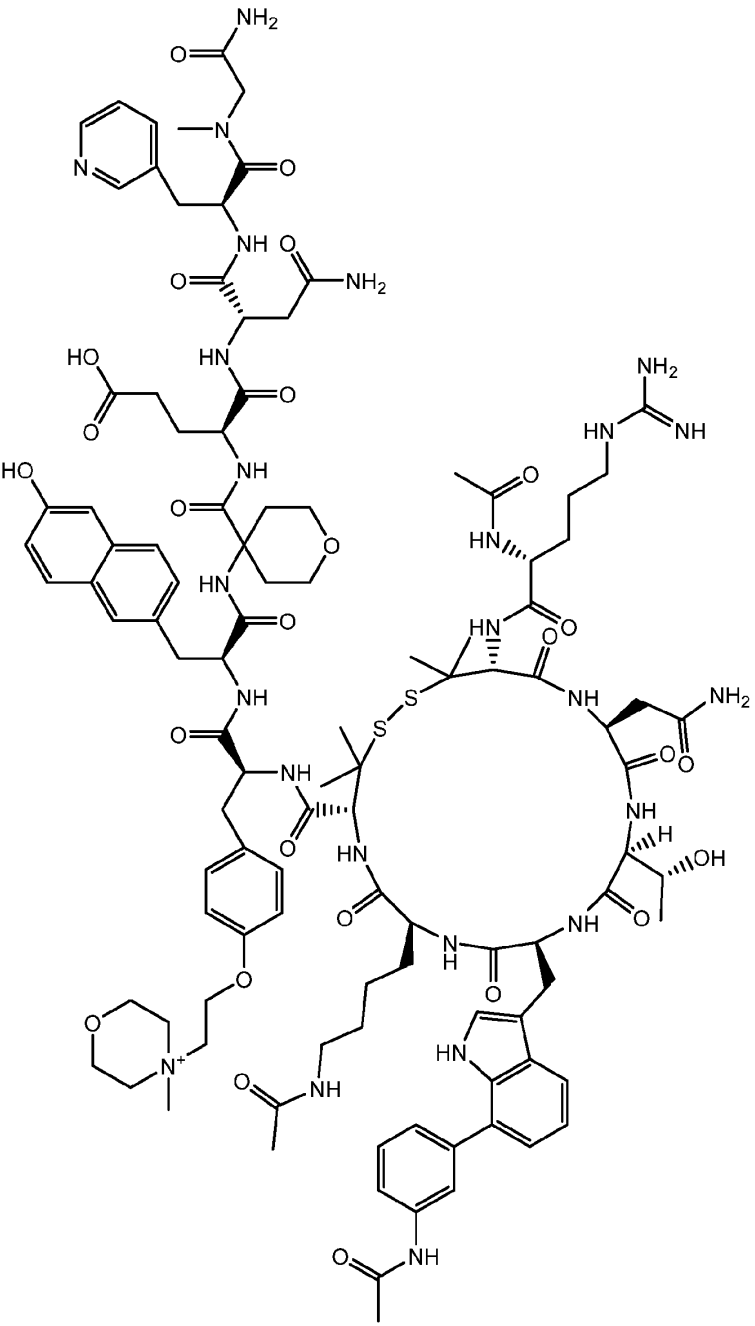
SEQ ID NO	Structure
155	 The chemical structure represents a large, complex peptide molecule, likely a cyclic peptide with multiple side chains and a long PEG linker. The structure is highly branched and includes various functional groups such as amide, ester, and hydroxyl groups. It features a long PEG linker (polyethylene glycol) and a long aliphatic chain. The molecule is composed of several amino acid residues, including Pen(3), N-T-7(3NacPh)W, K(Ac), Pen(3), AEF-6OH2Nal, THP-K(Ac), N-3Pyra-Sar, and K(PEG2PEG2gEC18OH)-CONH2. MeCO-Pen(3)-N-T-7(3NacPh)W-K(Ac)-Pen(3)-AEF-6OH2Nal-THP-K(Ac)-N-3Pyra-Sar-K(PEG2PEG2gEC18OH)-CONH2

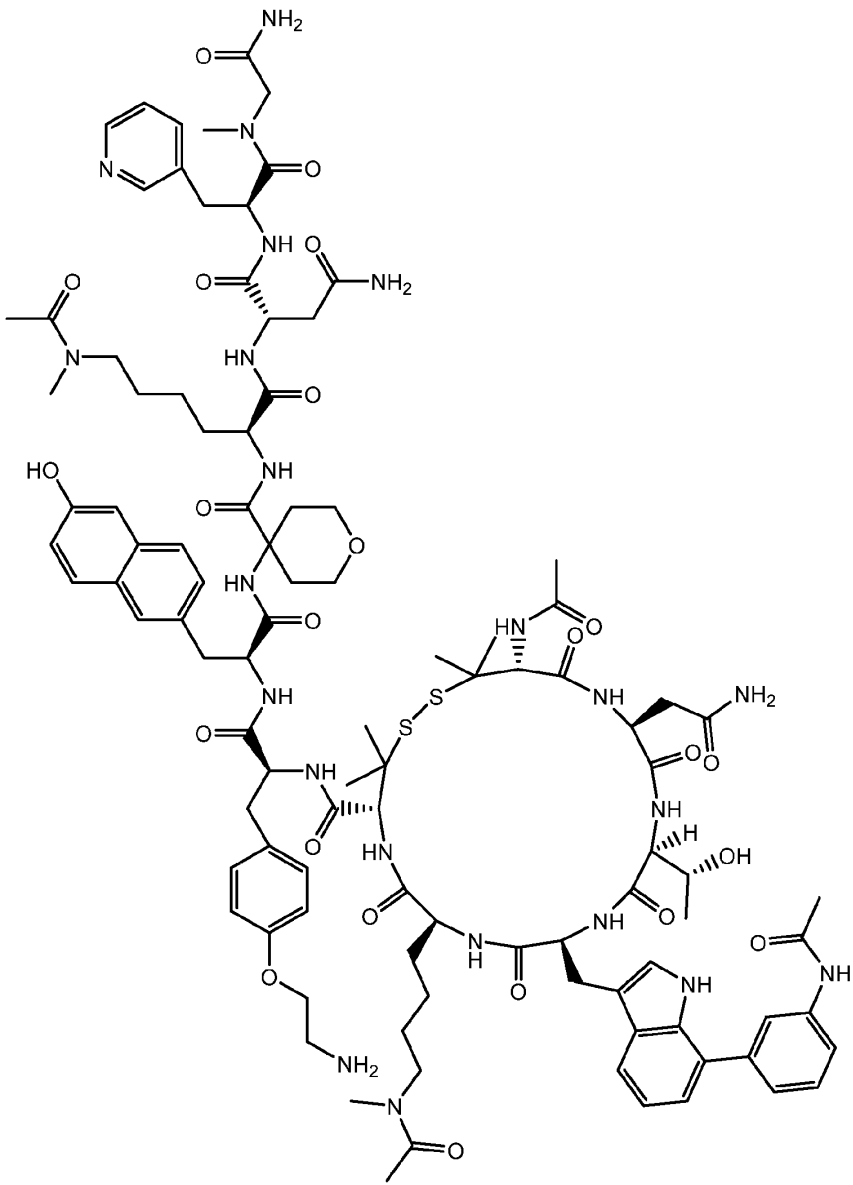
SEQ ID NO	Structure
156	 The chemical structure represents a large, complex peptide molecule, specifically a cyclic peptide with multiple side chains and a long PEG chain. The structure is highly branched and includes various functional groups such as amide, carboxylic acid, and hydroxyl groups. Key features include a long PEG chain (polyethylene glycol) attached to the N-terminus, a cyclic peptide core, and several side chains containing aromatic rings (phenyl, pyridine), hydroxyl groups, and amide bonds. The molecule is labeled as MeCO-r-Pen(3)-N-T-7(3NAcPh)W-K(Ac)-Pen(3)-AEF-6OH2NaI-THP-E-N-3Py-Sar-K(PEG2PEG2gEC18OH)-CONH2.

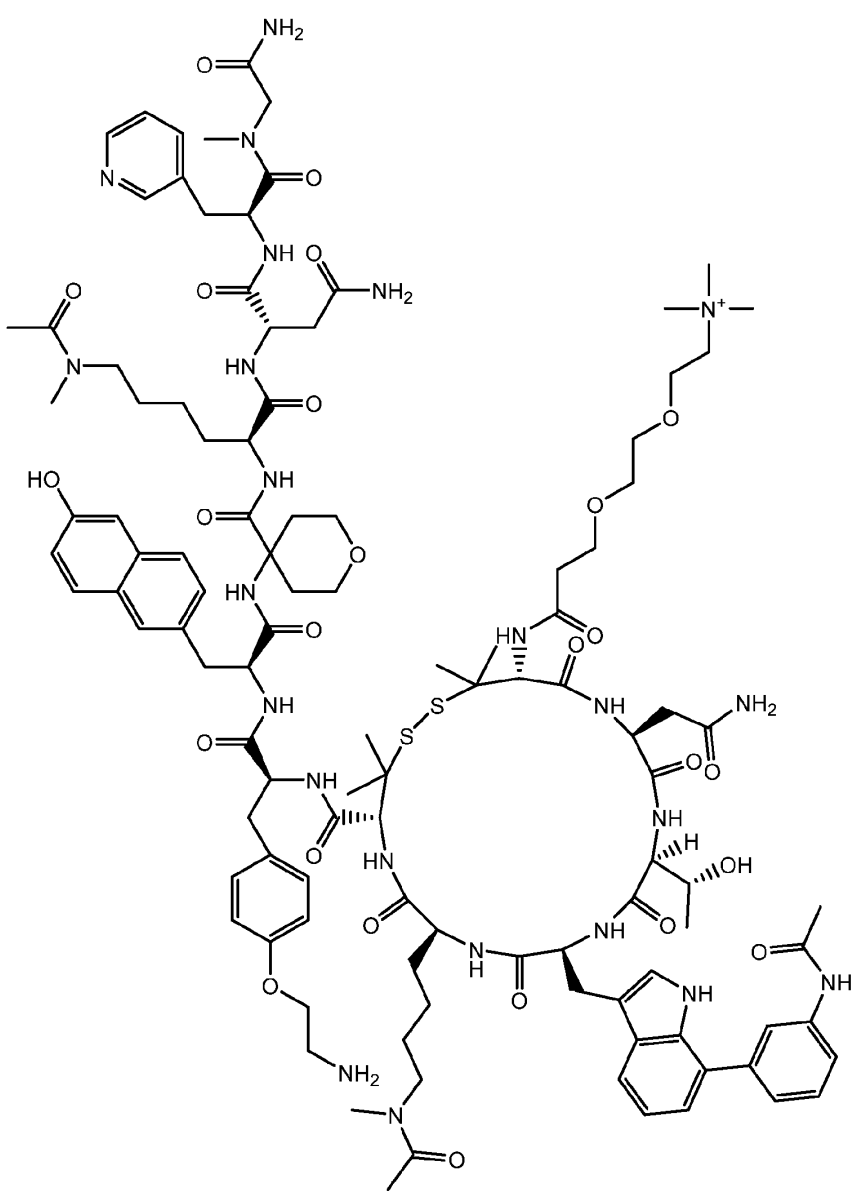
SEQ ID NO	Structure
157	 cPEG3aCO-r-Pen(3)-E(2)-T-7(3NAcPh)W-K(Ac)-Pen(3)-AEF(2)-6OH2Nal-THP-E-N-3Pya-Sar-CONH2

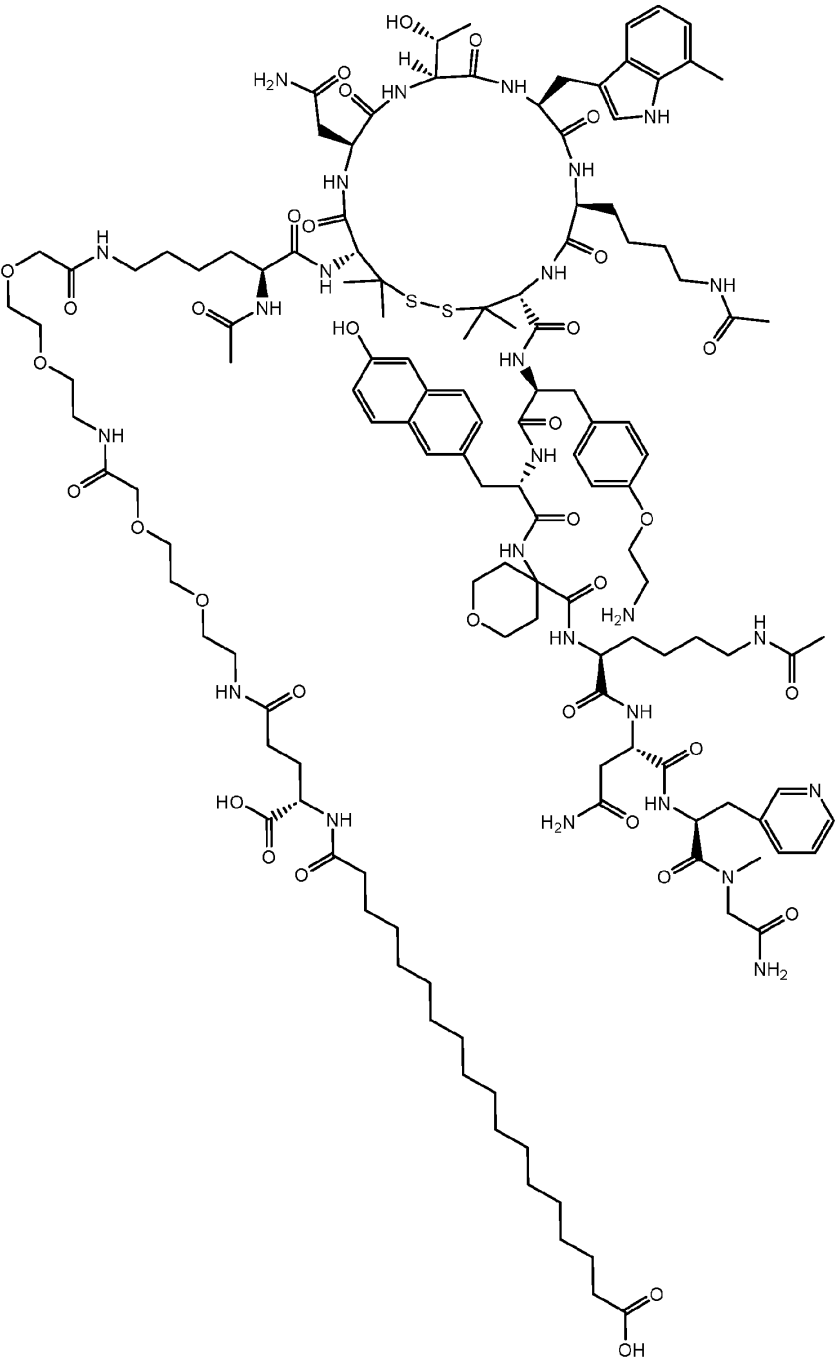
SEQ ID NO	Structure
158	 5cpaCO-r-Pen(3)-E(2)-T-7(3NAcPh)W-K(Ac)-Pen(3)-AEF(2)-6OH2Nal-THP-E-N-3Pya-Sar-CONH2
159	 cPEG3aCO-Pen(3)-E(2)-T-7(3NAcPh)W-K(Ac)-Pen(3)-AEF(2)-6OH2Nal-THP-K(Ac)-N-3Pya-Sar-CONH2

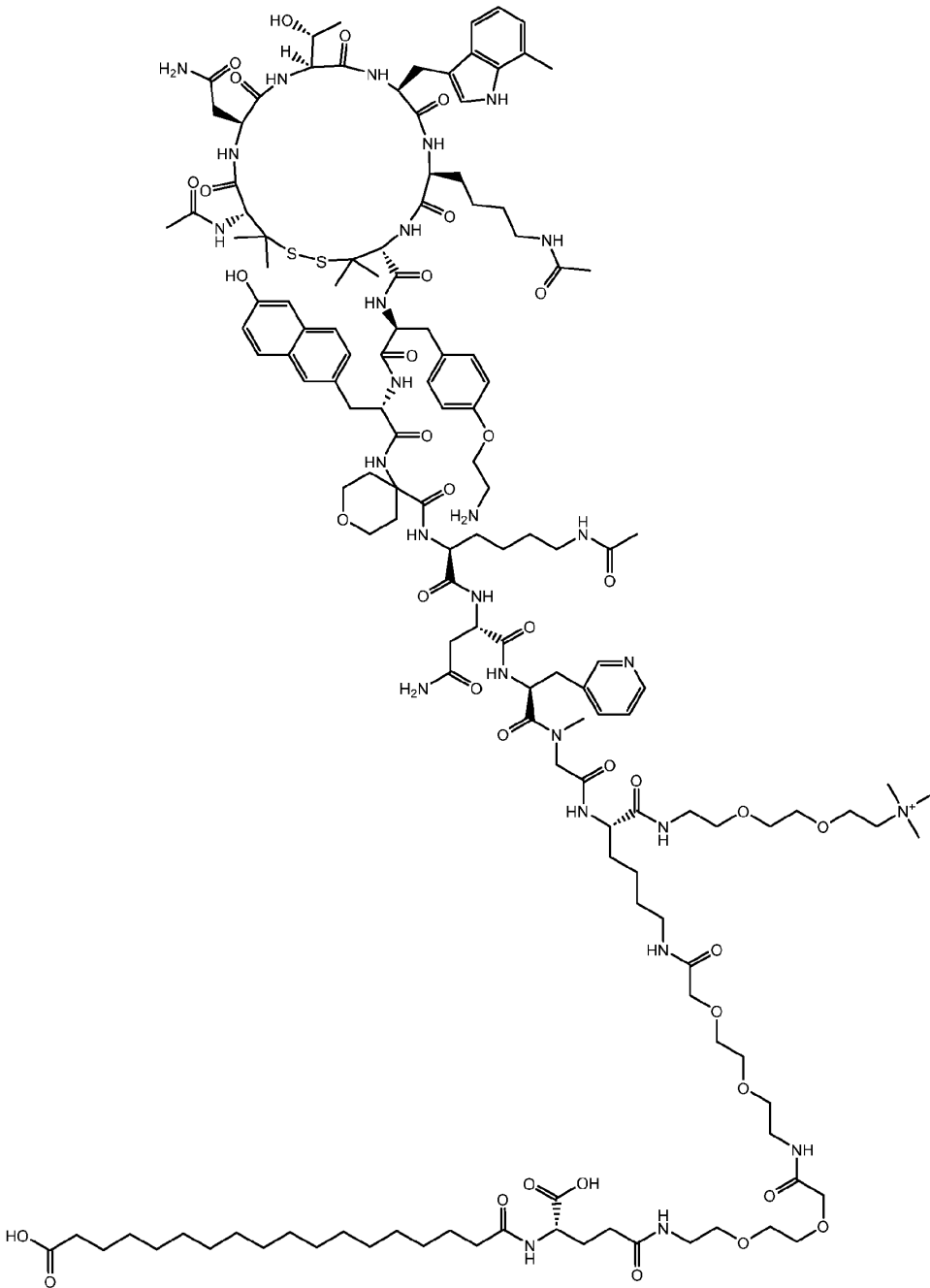
SEQ ID NO	Structure
160	 5cpaCO-Pen(3)-E(2)-T-7(3NAcPh)W-K(Ac)-Pen(3)-AEF(2)-6OH2NaI-THP-K(Ac)-N-3Pya-Sar-CONH2

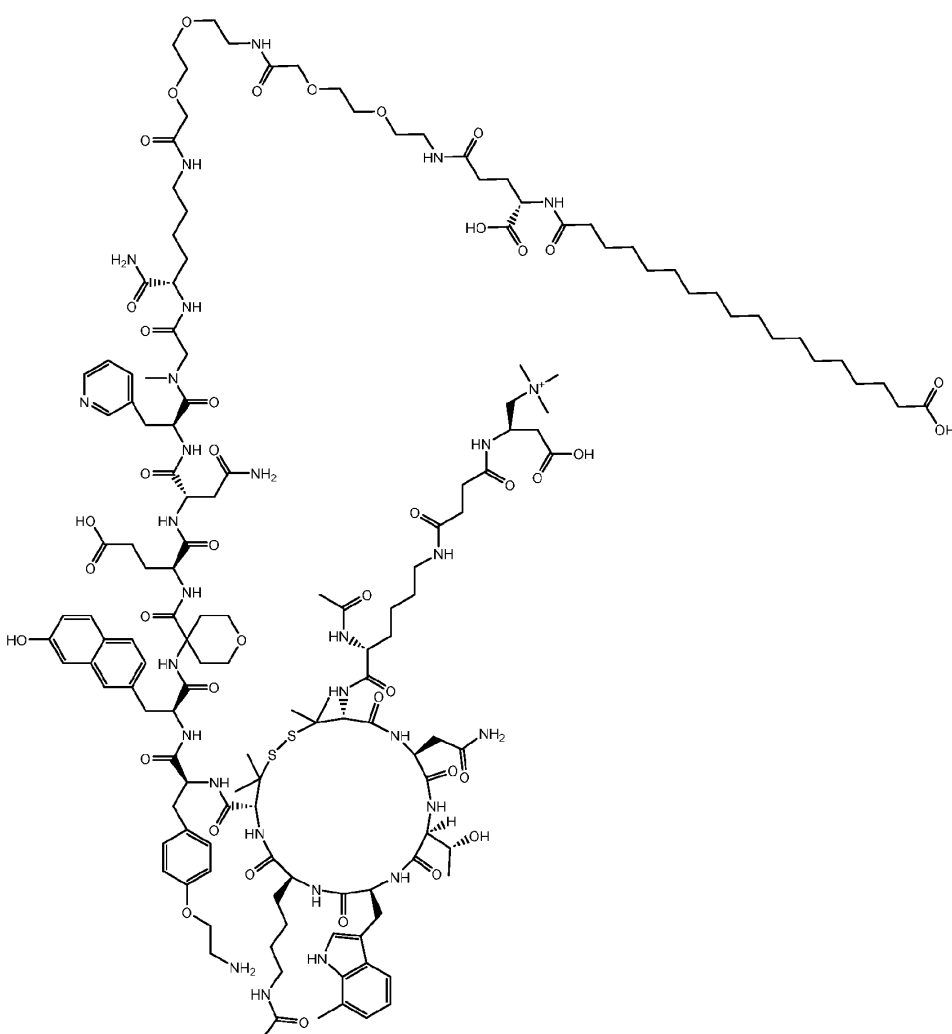
SEQ ID NO	Structure
161	 MeCO-r-Pen(3)-N-T-7(3NAcPh)W-K(Ac)-Pen(3)-MMoEF-6OH2NaI-THP-E-N-3Py-Sar-CONH2

SEQ ID NO	Structure
162	 The chemical structure represents a cyclic peptide with a 16-residue backbone. The residues are: MeCO-Pen(3)-N-T-7(3NAcPh)W-K(NMeAc)-Pen(3)-AEF-6OH2Nal-THP-K(NMeAc)-N-3Pya-Sar-CONH2. The structure features a central 16-membered ring with a disulfide bridge between the 3rd and 13th residues. Various side chains are attached to the ring, including a pyridine ring, an amide group, a hydroxyl group, and a thiazolidine ring. The structure is shown in a 3D representation with stereochemistry indicated by wedges and dashes. MeCO-Pen(3)-N-T-7(3NAcPh)W-K(NMeAc)-Pen(3)-AEF-6OH2Nal-THP-K(NMeAc)-N-3Pya-Sar-CONH2

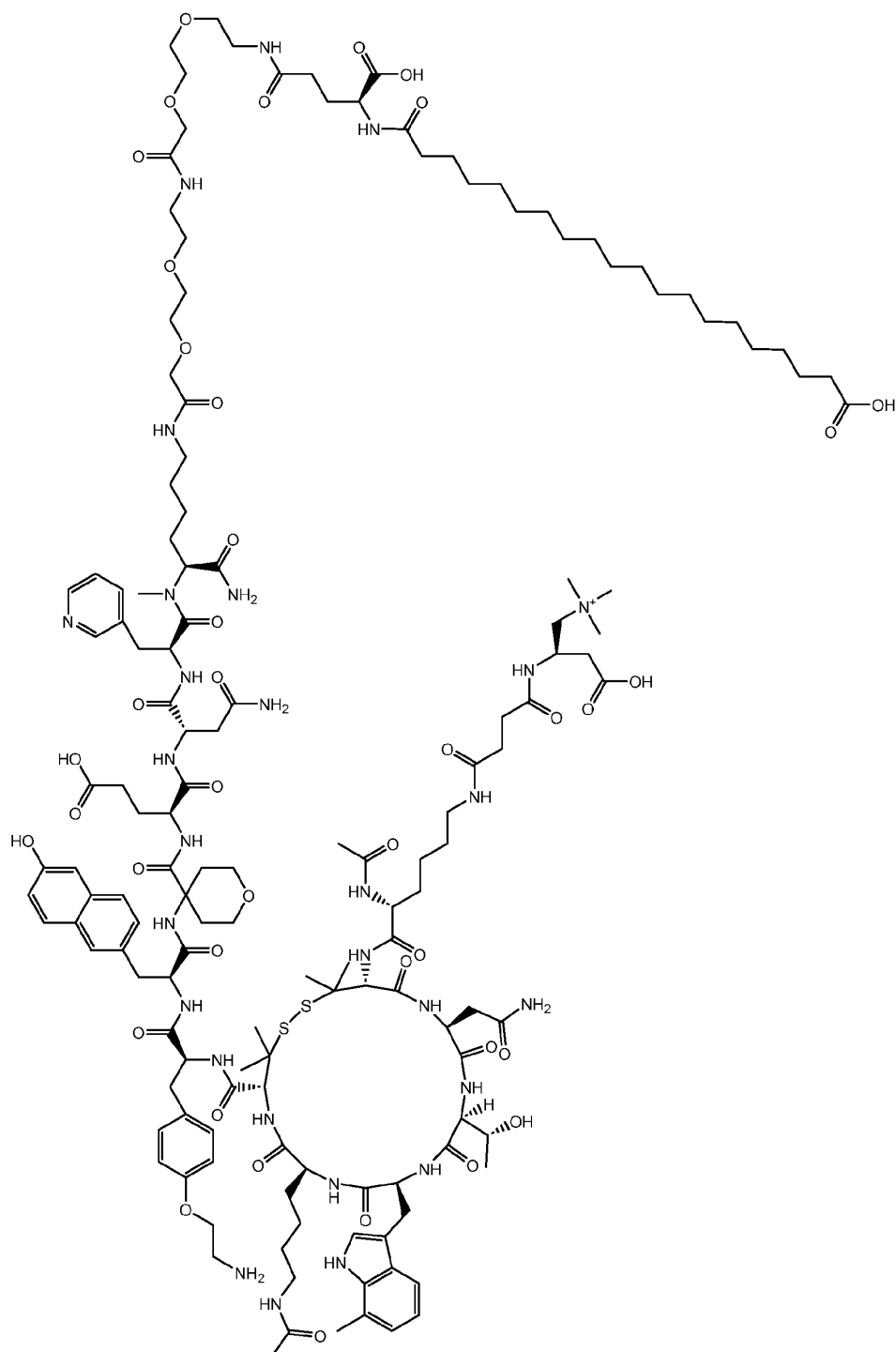
SEQ ID NO	Structure
163	 cPEG3aCO-Pen(3)-N-T-7(3NAcPh)W-K(NMeAc)-Pen(3)-AEF-6OH2Nal-THP-K(NMeAc)-N-3Pya-Sar-CONH2

SEQ ID NO	Structure
164	 The chemical structure represents a large, complex peptide molecule, likely a cyclic peptide with multiple side chains and modifications. The central core is a large, circular ring structure, possibly a macrocyclic peptide, featuring a disulfide bridge (S-S) and various amino acid residues. The structure is highly branched and includes several long, flexible side chains, including a long poly(ethylene glycol) (PEG) chain and a long alkyl chain. The molecule also contains various functional groups, including amide bonds, hydroxyl groups, and a carboxylic acid group. The overall structure is highly complex and appears to be a synthetic or modified natural peptide. MeCO-K(PEG2PEG2gEC18OH)-Pen(3)-N-T-7MeW-K(Ac)-Pen(3)-AEF-6OH2Nal-THP-K(Ac)-N-3Py-Sar-CONH2

SEQ ID NO	Structure
165	 MeCO-Pen(3)-N-T-7MeW-K(Ac)-Pen(3)-AEF-6OH2NaI-THP-K(Ac)-N-3Pya-Sar-K(PEG2PEG2gEC18OH)-CONH(PEG3a)

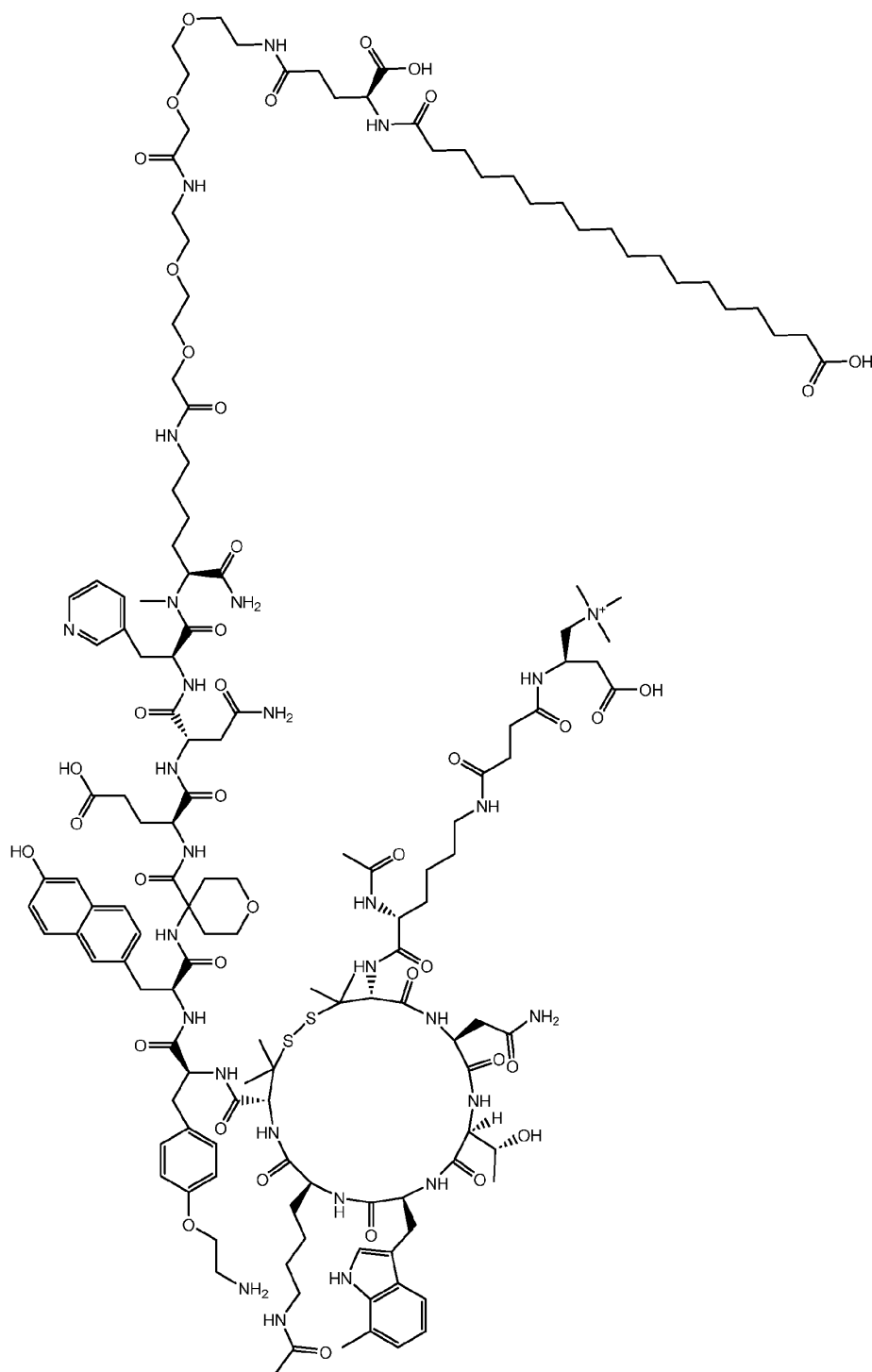
SEQ ID NO	Structure
166	 MeCO-k(d)-Pen(3)-N-T-7MeW-K(Ac)-Pen(3)-AEF-6OH2NaI-THP-E-N-3Py-Sar-K(PEG2PEG2gEC18OH)-CONH2

167

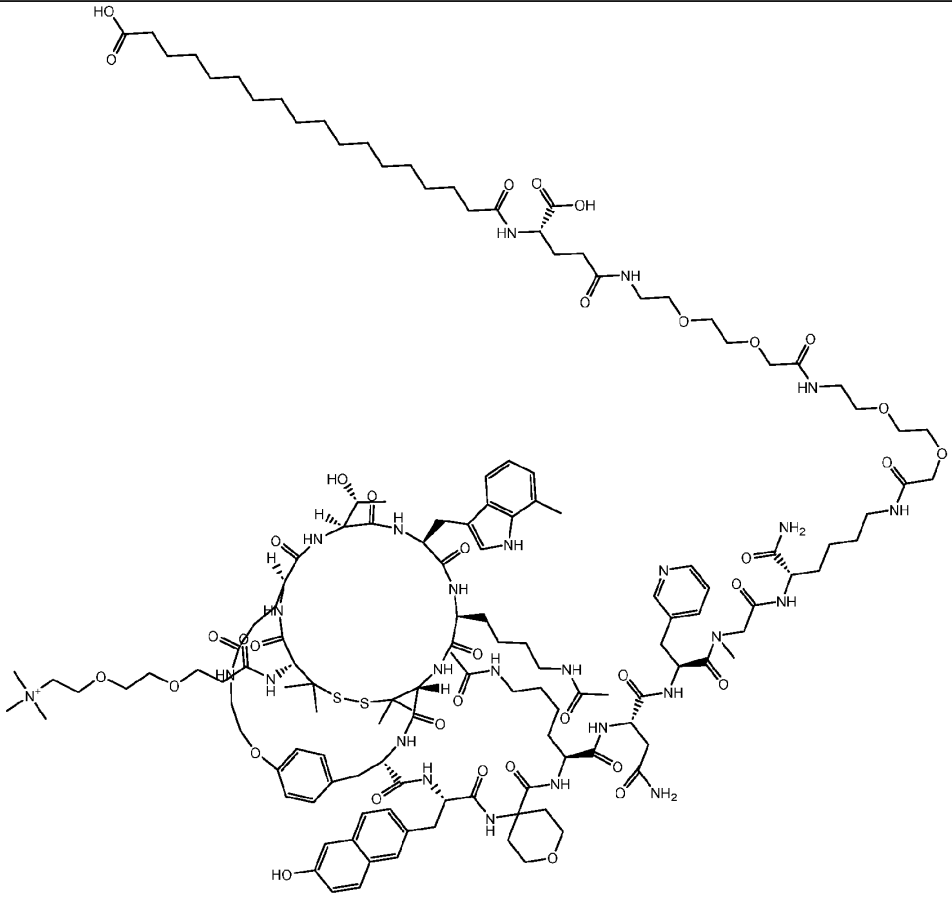


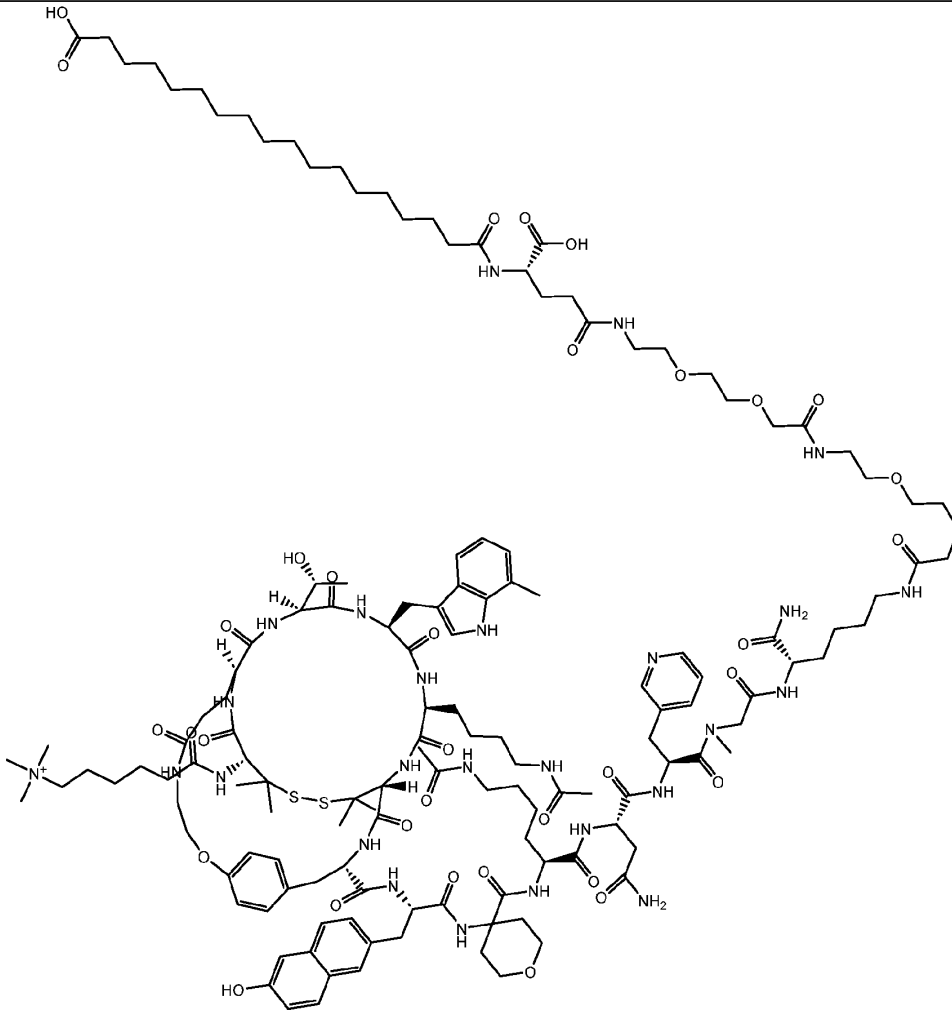
MeCO-k(d)-Pen(3)-N-T-7MeW-K(Ac)-Pen(3)-AEF-6OH₂Nal-THP-E-N-3PyA-NMeK(PEG₂PEG₂gEC₂₀OH)-CONH₂

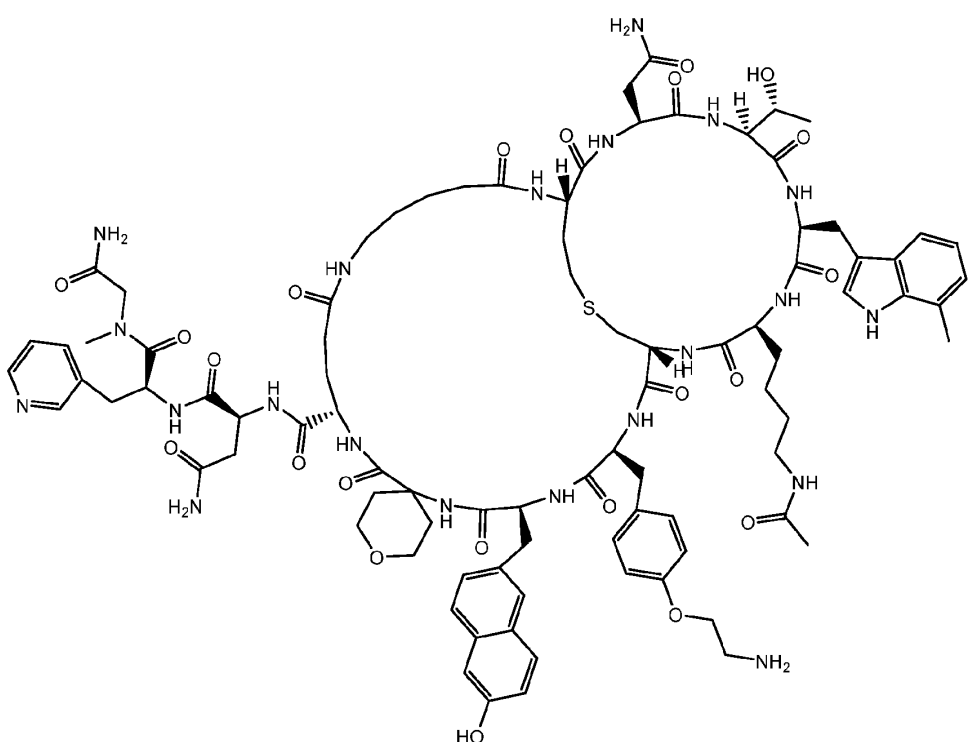
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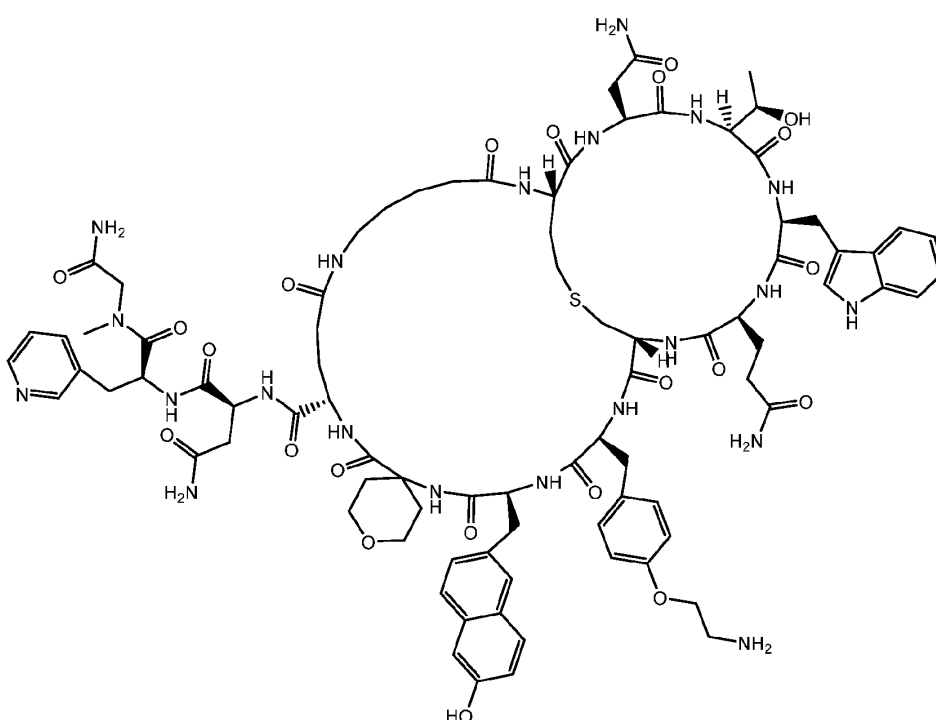


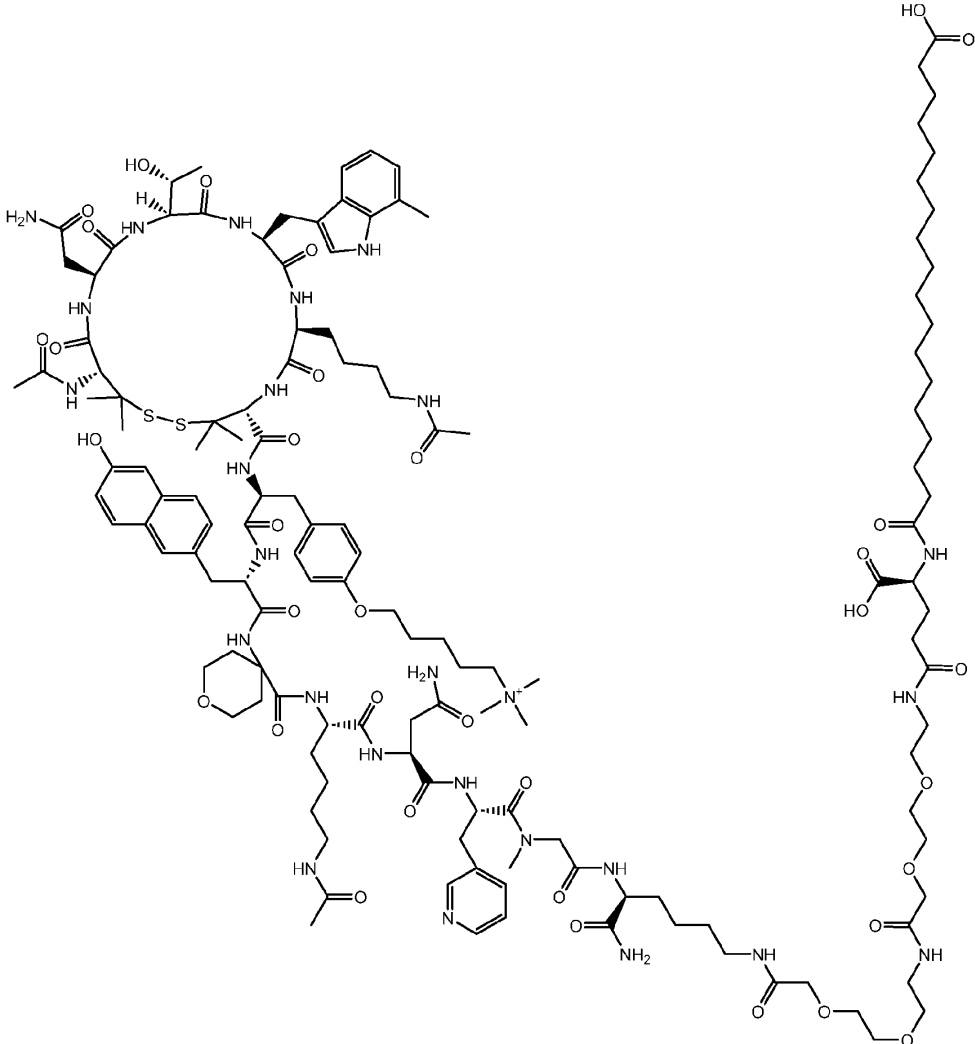
MeCO-k(d)-Pen(3)-N-T-7MeW-K(Ac)-Pen(3)-AEF-6OH₂Nal-THP-E-N-3Py-NMeK(PEG₂PEG₂gEC18OH)-CONH₂

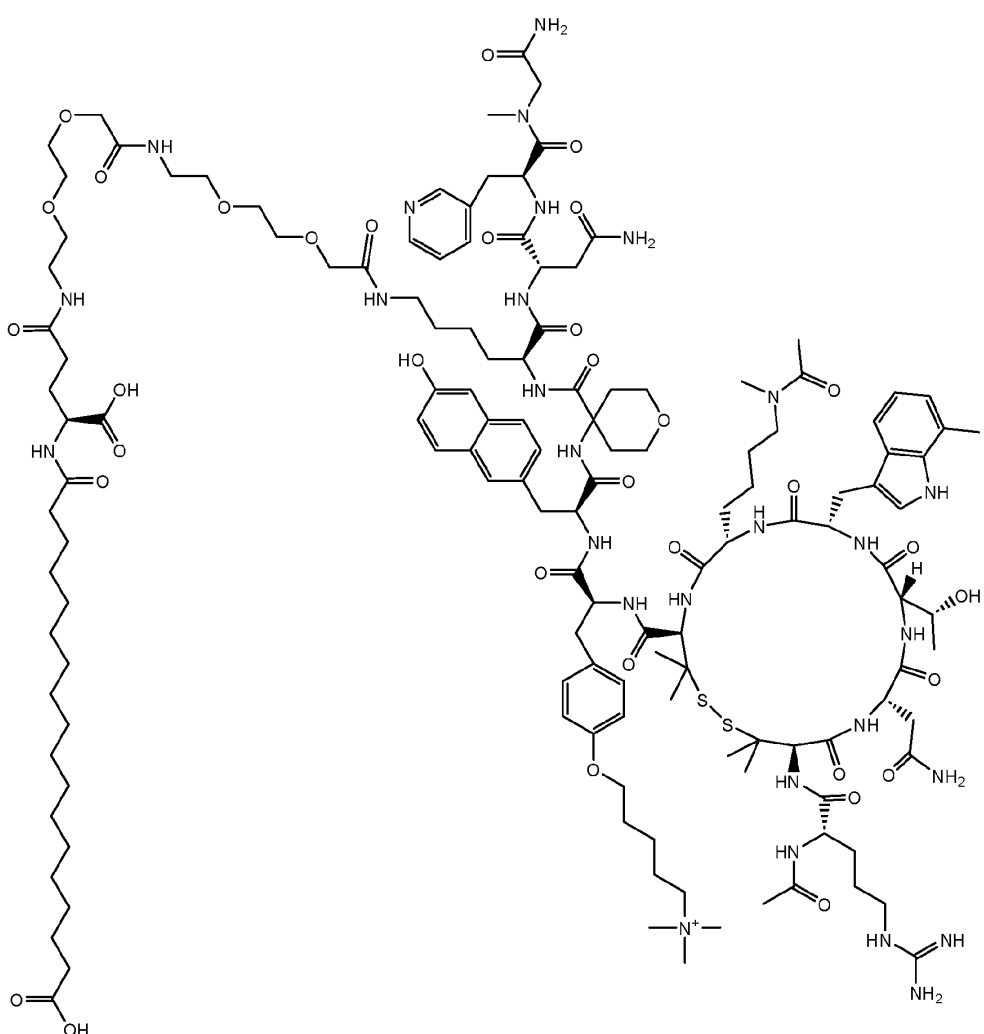
SEQ ID NO	Structure
169	 The chemical structure shows a large cyclic peptide with a central core containing a disulfide bridge. The peptide backbone is composed of various amino acids, including penicillins, threonine, and proline. The side chains are highly diverse, featuring a long PEG chain, a penicillin moiety, a thiazolidine ring, a pyridine ring, and a hydroxyl group. The structure is highly complex and represents a large molecule. cPEG3aCO-Pen(3)-E(2)-T-7MeW-K(Ac)-Pen(3)-AEF(2)-6OH2Nal-THP-K(Ac)-N-3Py-Sar-K(PEG2PEG2gEC18OH)-CONH2

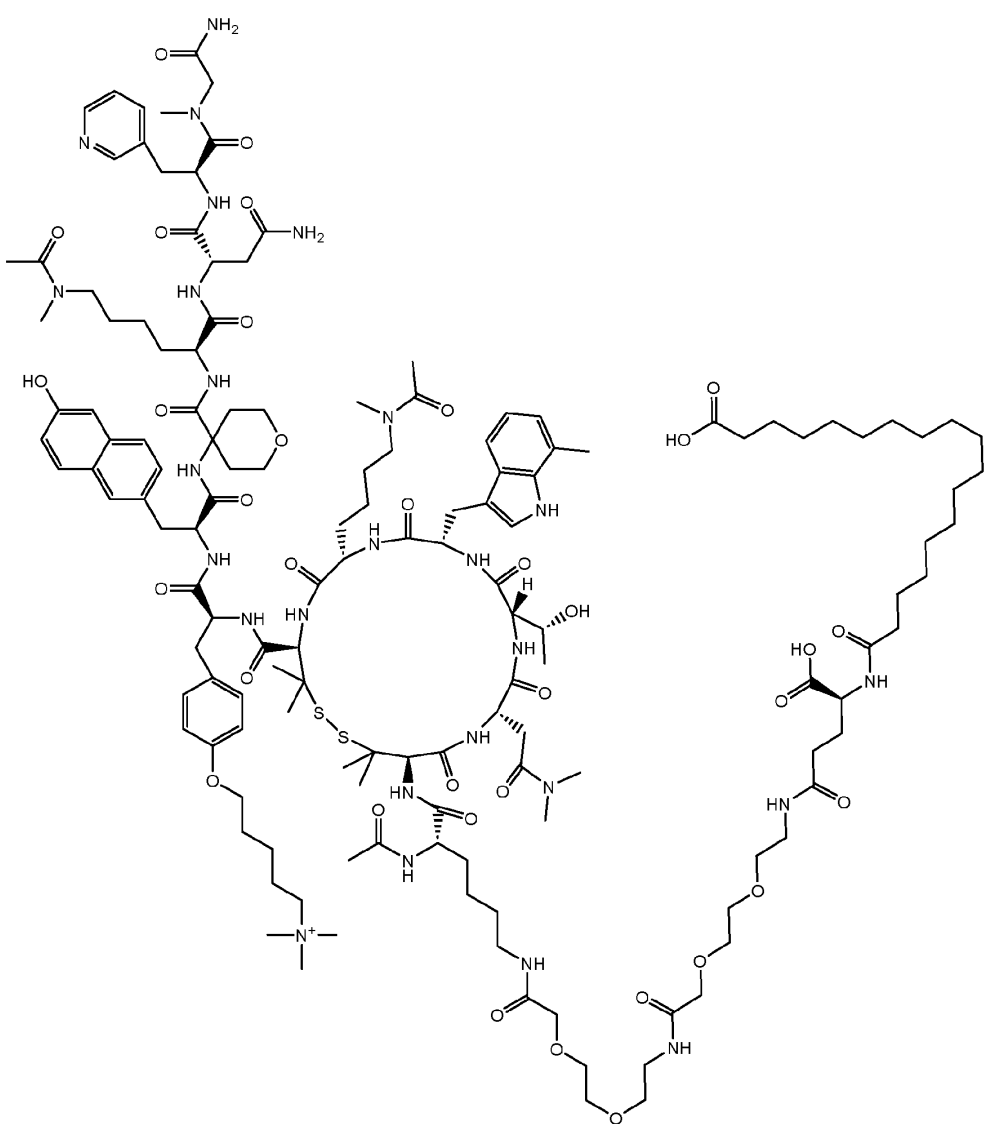
SEQ ID NO	Structure
170	 5cpaCO-Pen(3)-E(2)-T-7MeW-K(Ac)-Pen(3)-AEF(2)-6OH2Nal-THP-K(Ac)-N-3Pyra-Sar-K(PEG2PEG2gEC18OH)-CONH2

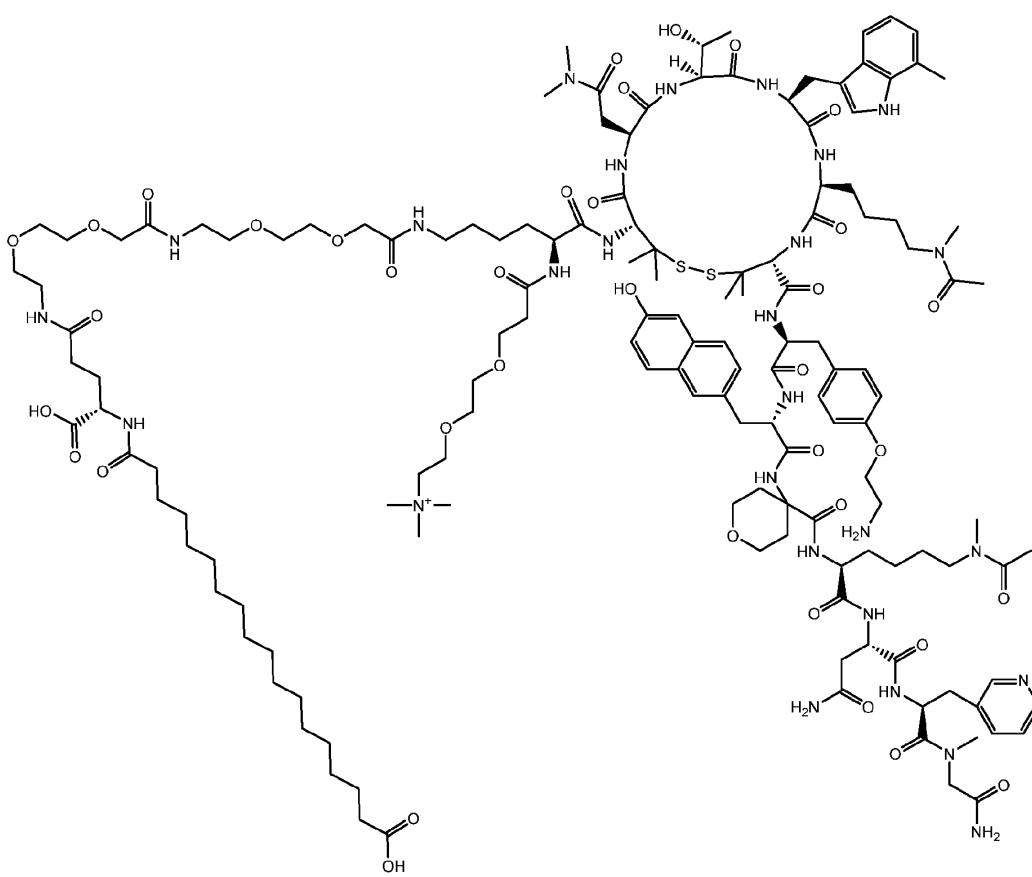
SEQ ID NO	Structure
171	 The chemical structure shows a cyclic peptide with a 12-residue backbone. The residues are: 5Ava(2), Abu(1), N-T, 7MeW, K(Ac), C(1), AEF, 6OH2Nal, THP, E(2), N-3Pya, and Sar. The side chains are: 5Ava(2) (pyridine ring), Abu(1) (amino group), N-T (amide), 7MeW (methyl group), K(Ac) (acetyl group), C(1) (cyclohexyl group), AEF (amino group), 6OH2Nal (naphthalene ring), THP (tetrahydropyran ring), E(2) (amide), N-3Pya (pyridine ring), and Sar (amino group). The structure is a cyclic peptide with a 12-residue backbone. The residues are: 5Ava(2), Abu(1), N-T, 7MeW, K(Ac), C(1), AEF, 6OH2Nal, THP, E(2), N-3Pya, and Sar. The side chains are: 5Ava(2) (pyridine ring), Abu(1) (amino group), N-T (amide), 7MeW (methyl group), K(Ac) (acetyl group), C(1) (cyclohexyl group), AEF (amino group), 6OH2Nal (naphthalene ring), THP (tetrahydropyran ring), E(2) (amide), N-3Pya (pyridine ring), and Sar (amino group). 5Ava(2)-Abu(1)-N-T-7MeW-K(Ac)-C(1)-AEF-6OH2Nal-THP-E(2)-N-3Pya-Sar-CONH2

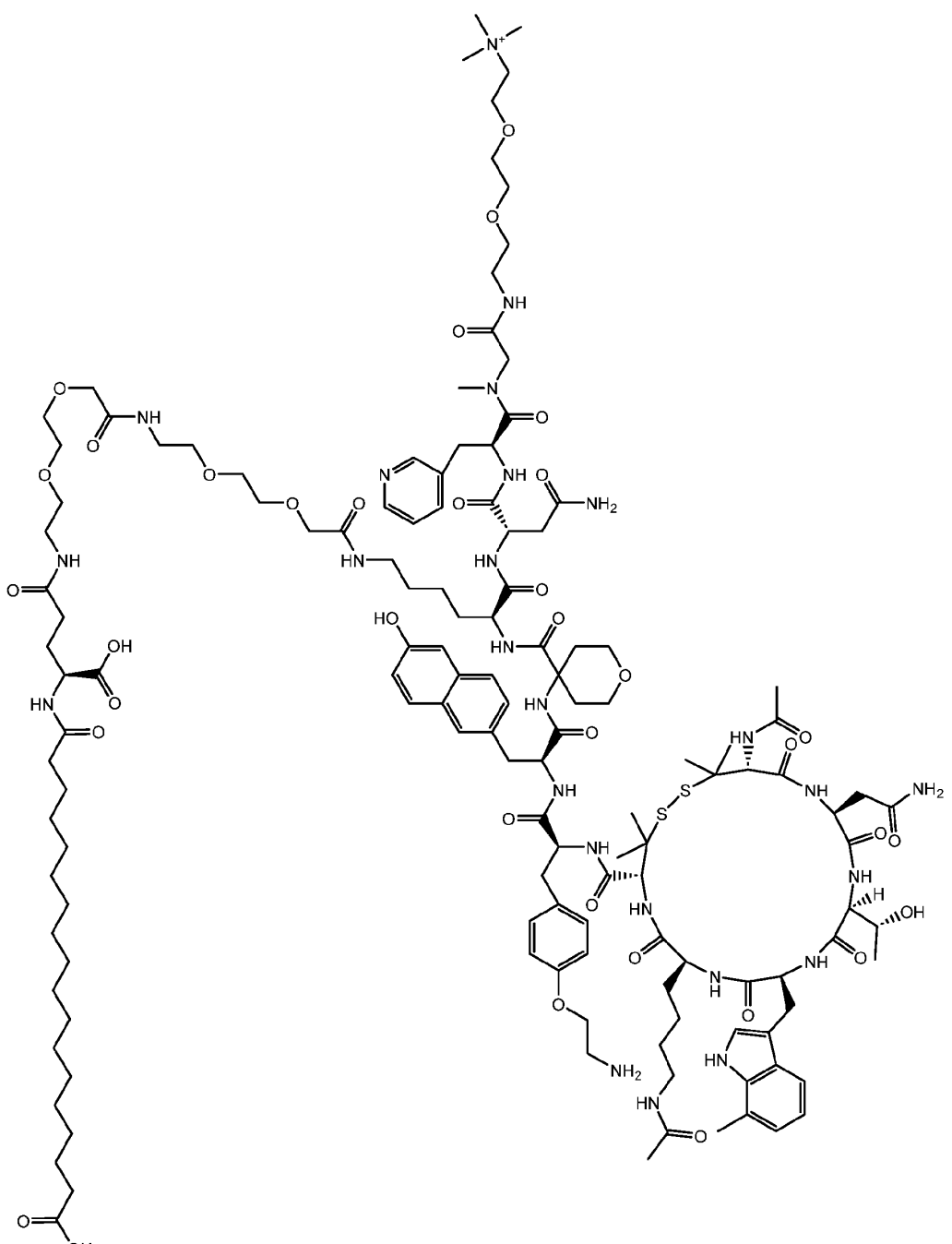
SEQ ID NO	Structure
172	 5Ava(2)-Abu(1)-N-T-W-Q-C(1)-AEF-6OH2NaI-THP-E(2)-N-3Pya-Sar-CONH2

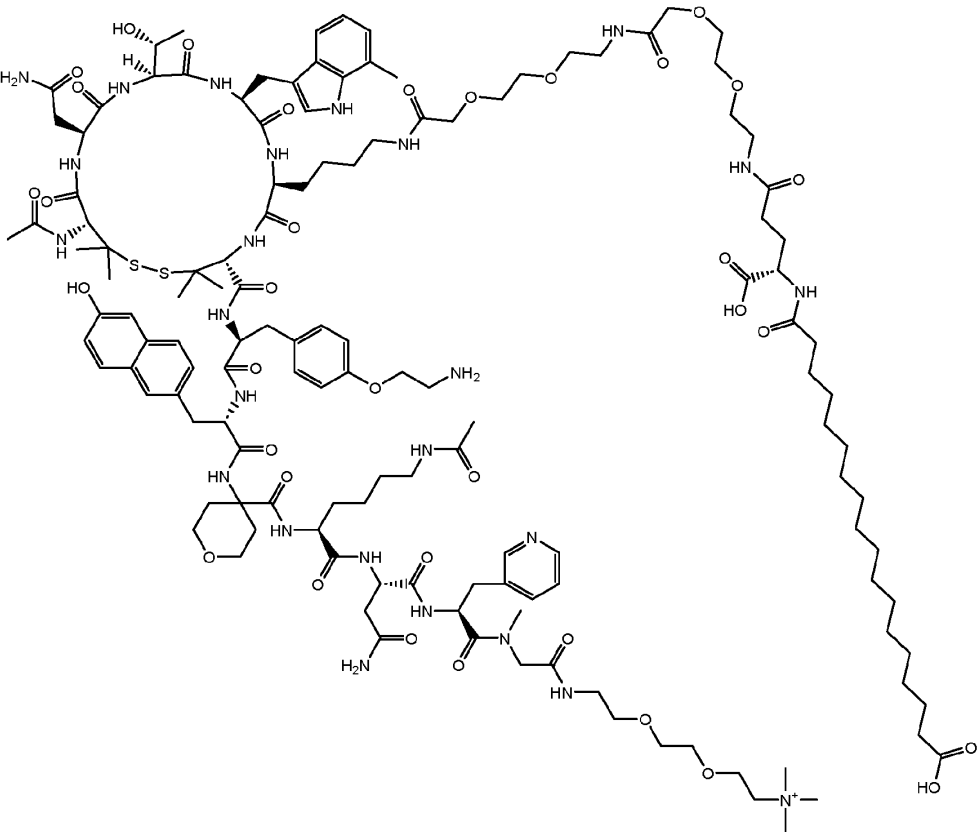
SEQ ID NO	Structure
173	 MeCO-Pen(3)-N-T-7MeW-K(Ac)-Pen(3)-TMAPF-6OH2Nal-THP-K(Ac)-N-3PyA-Sar-K(PEG2PEG2gEC18OH)-CONH2

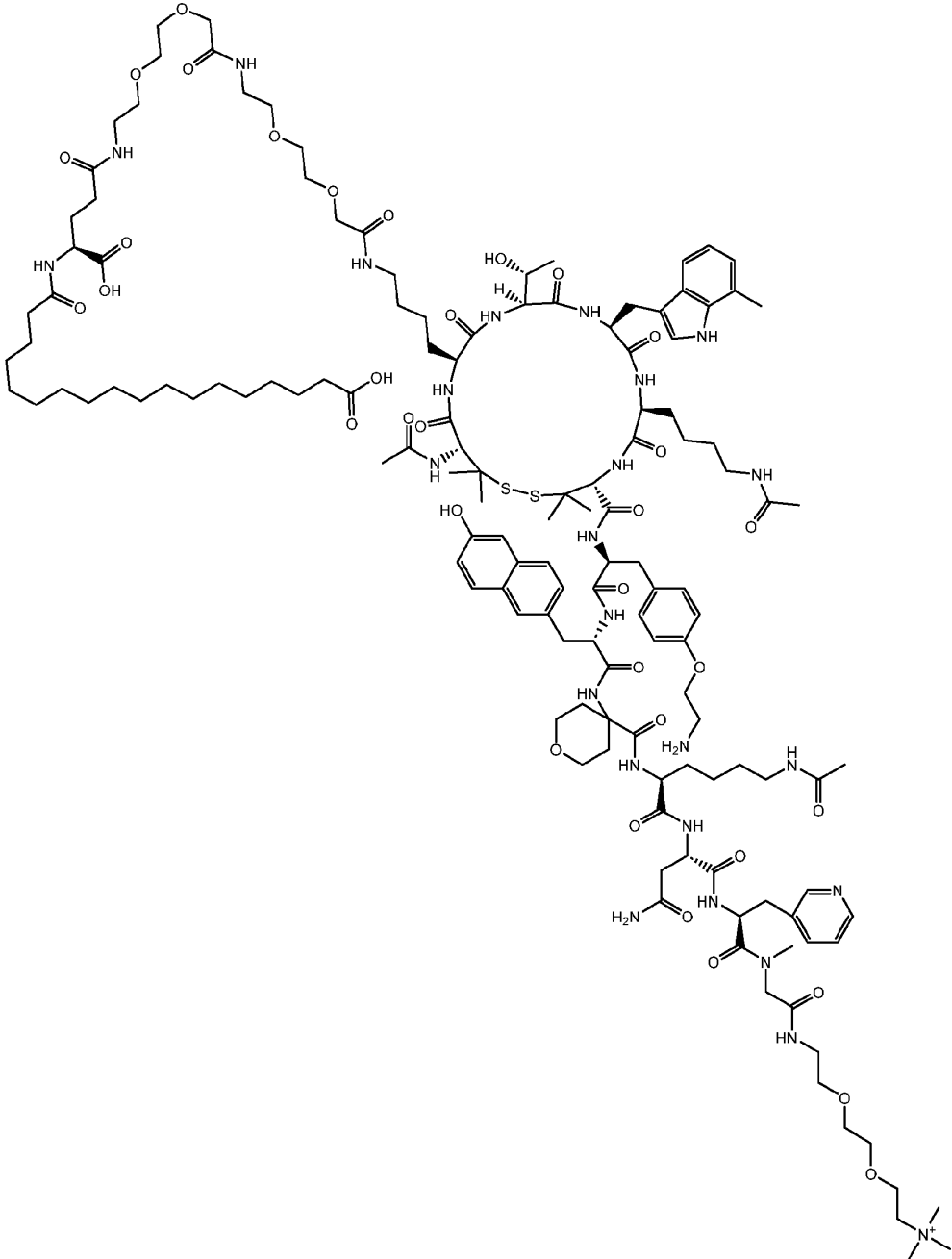
SEQ ID NO	Structure
174	 MeCO-R-Pen(3)-N-T-7MeW-K(NMeAc)-Pen(3)-TMAPF-6OH2Nal-THP-K(PEG2PEG2gEC18OH)-N-3Pya-Sar-CONH2

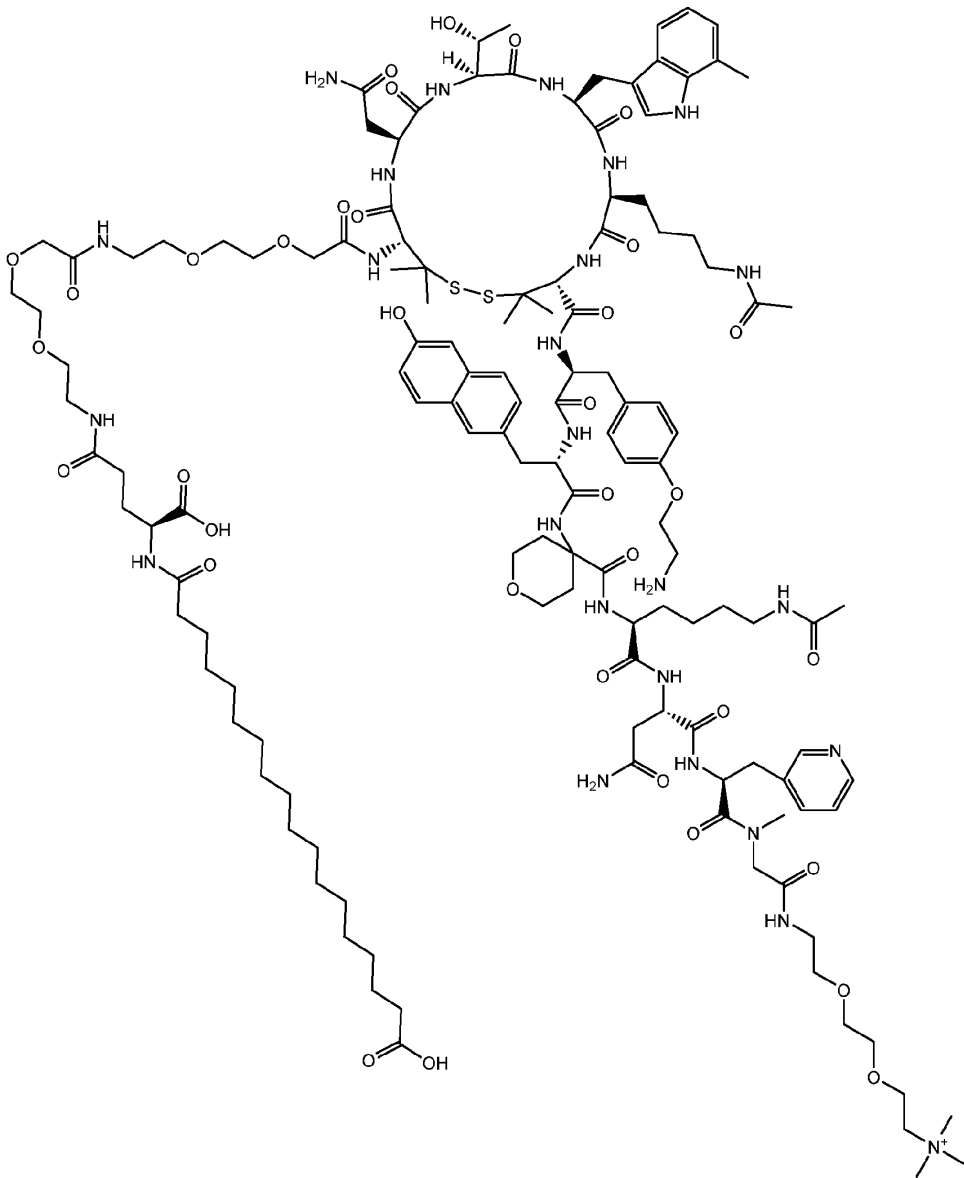
SEQ ID NO	Structure
175	 The chemical structure is a large, complex molecule, likely a peptide or protein derivative. It features a central circular core, possibly a macrocyclic peptide, with various side chains and functional groups. The structure includes a long, flexible chain on the right side, a large, branched structure on the left, and a central core with multiple amide bonds and a disulfide bridge. The molecule is highly branched and contains several aromatic rings, including a pyridine ring and a naphthalene ring. The overall structure is highly complex and appears to be a derivative of a natural peptide or protein. MeCO-K(PEG2PEG2gEC18OH)-Pen(3)-N(N(Me)2)-T-7MeW-K(NMeAc)-Pen(3)-TMAPF-6OH2Nal-THP-K(NMeAc)-N-3Pya-Sar-CONH2

SEQ ID NO	Structure
176	 cPEG3aCO-K(PEG2PEG2gEC18OH)-Pen(3)-N(N(Me)2)-T-7MeW-K(NMeAc)-Pen(3)-AEF-6OH2NaI-THP-K(NMeAc)-N-3PyA-Sar-CONH2

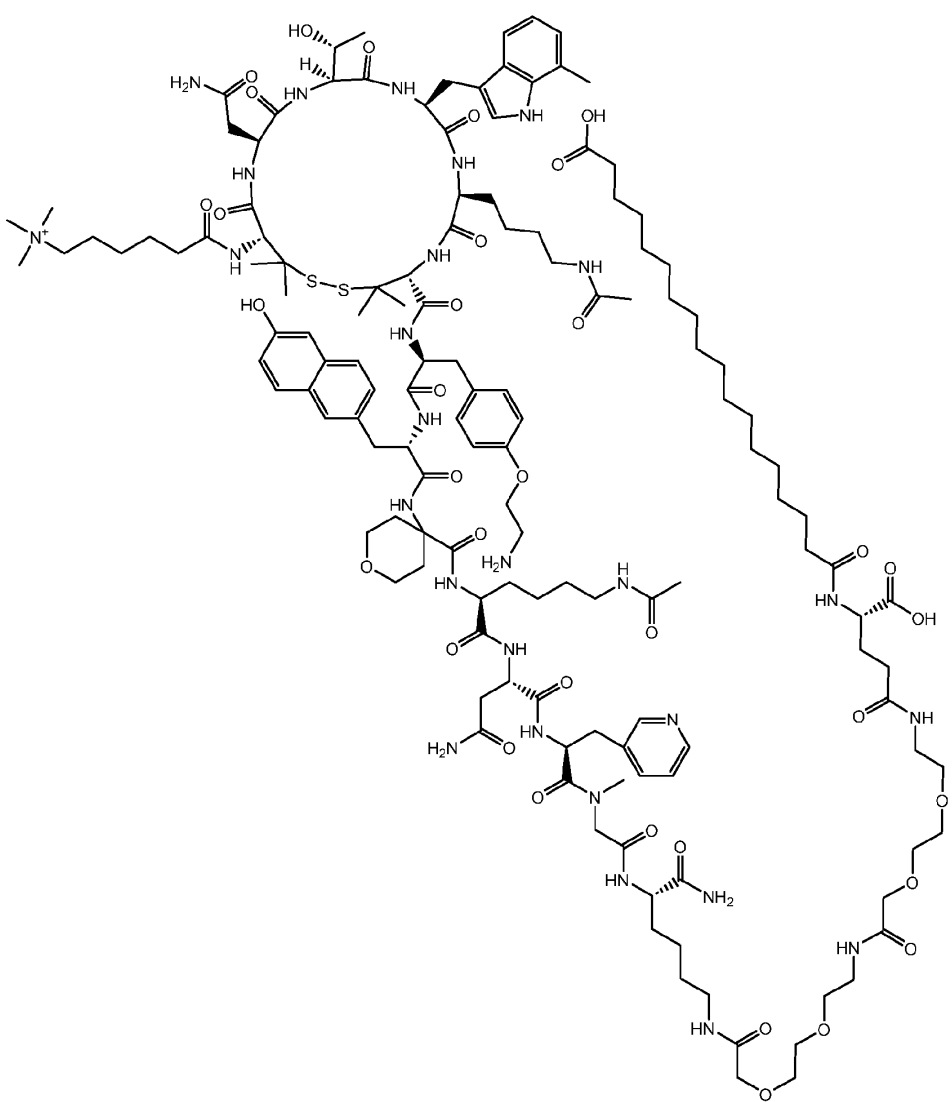
SEQ ID NO	Structure
177	 MeCO-Pen(3)-N-T-7MeW-K(Ac)-Pen(3)-AEF-6OH₂NaI-THP-K(PEG₂PEG₂gEC₁₈OH)-N-3Py-Sar-CONH(PEG₃a)

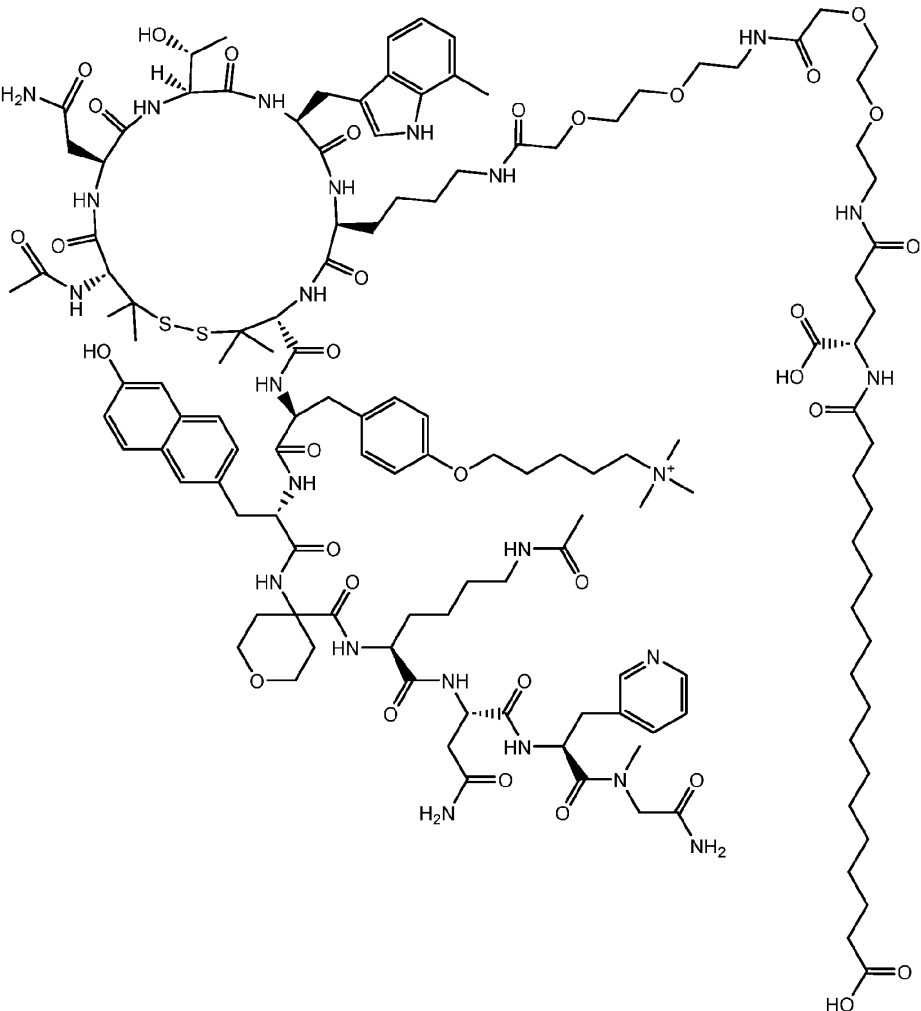
SEQ ID NO	Structure
178	 MeCO-Pen(3)-N-T-7MeW-K(PEG2PEG2gEC18OH)-Pen(3)-AEF-6OH2NaI-THP-K(Ac)-N-3Pyra-Sar-CONH(PEG3a)

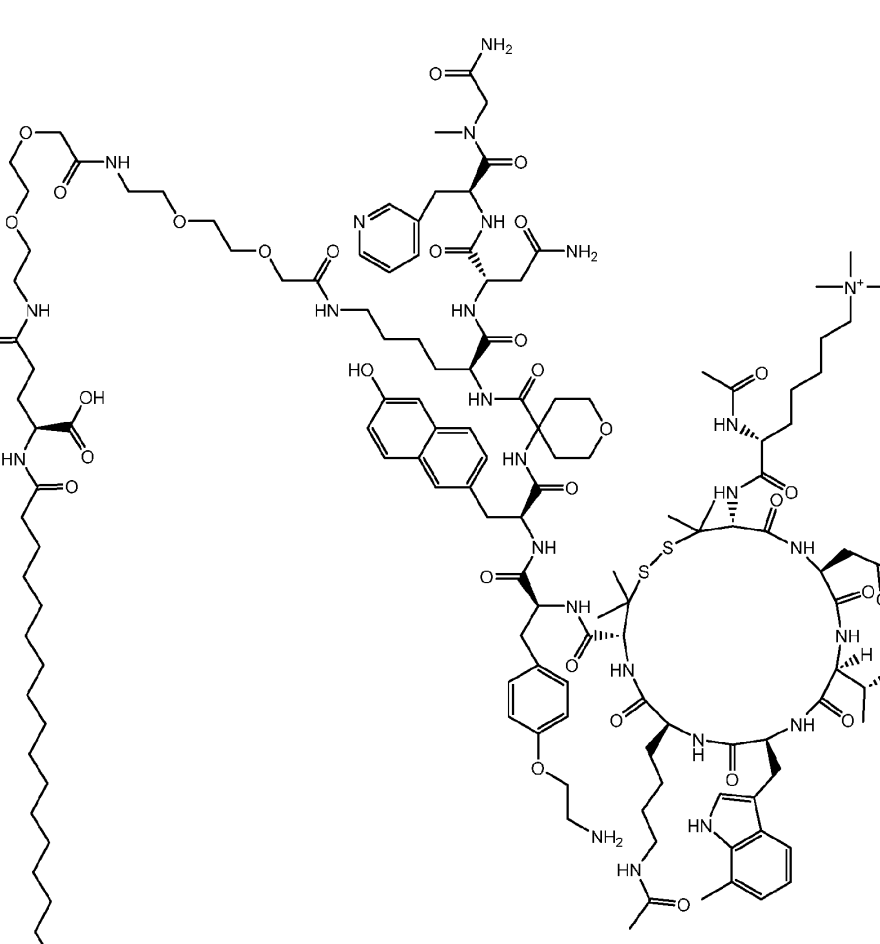
SEQ ID NO	Structure
179	 MeCO-Pen(3)-K(PEG2PEG2gEC18OH)-T-7MeW-K(Ac)-Pen(3)-AEF-6OH2Nal-THP-K(Ac)-N-3Py-Sar-CONH(PEG3a)

SEQ ID NO	Structure
180	 HOC18gEPEG2PEG2CO-Pen(3)-N-T-7MeW-K(Ac)-Pen(3)-AEF-6OH2Nal-THP-K(Ac)-N-3Pyra-Sar-CONH(PEG3a)

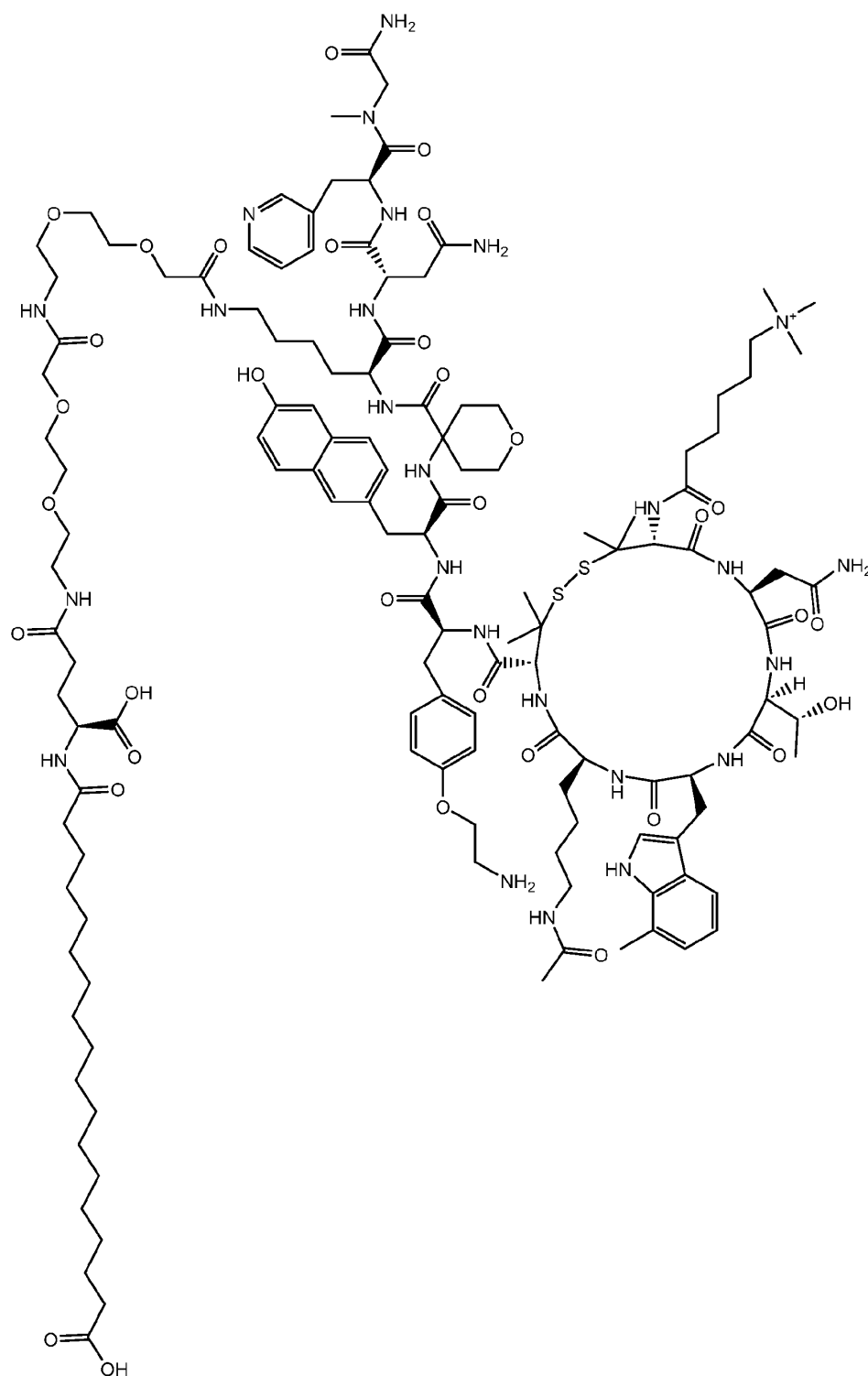
[illegible]

SEQ ID NO	Structure
182	 5cpaCO-Pen(3)-N-T-7MeW-K(Ac)-Pen(3)-AEF-6OH2Nal-THP-K(Ac)-N-3Pya-Sar-K(PEG2PEG2C18OH)-CONH2

SEQ ID NO	Structure
183	 MeCO-Pen(3)-N-T-7MeW-K(PEG2PEG2gEC18OH)-Pen(3)-TMAPF-6OH2Nal-THP-K(Ac)-N-3PyA-Sar-CONH2

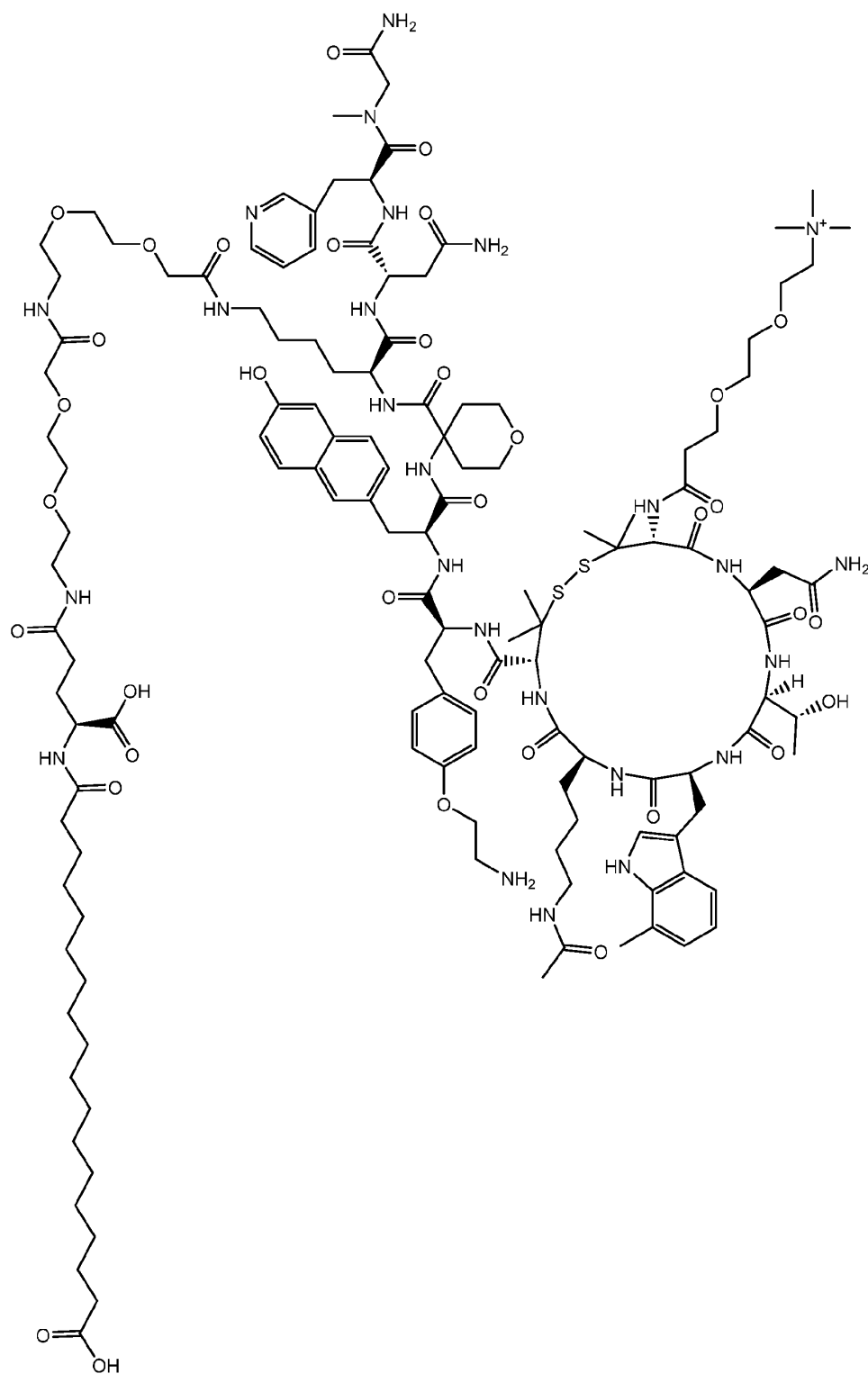
SEQ ID NO	Structure
184	 MeCO-hk(Me)₃-Pen(3)-N-T-7MeW-K(Ac)-Pen(3)-AEF-6OH₂NaI-THP-K(PEG₂PEG₂gEC₁₈OH)-N-3Py_a-Sar-CO₂H

185

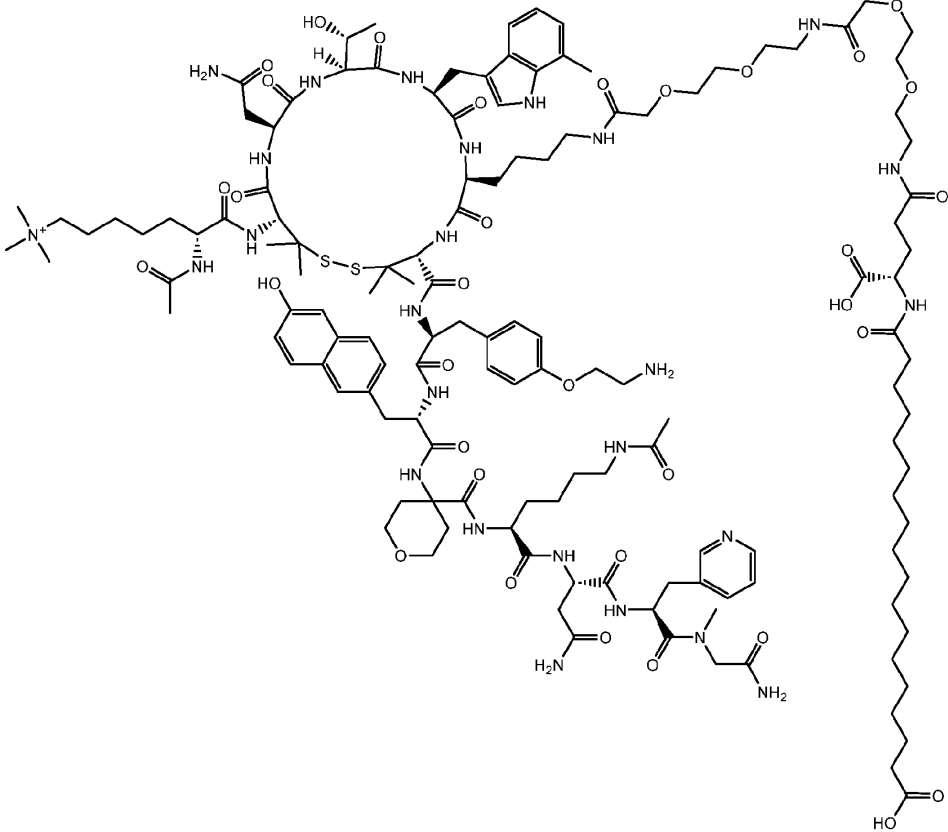


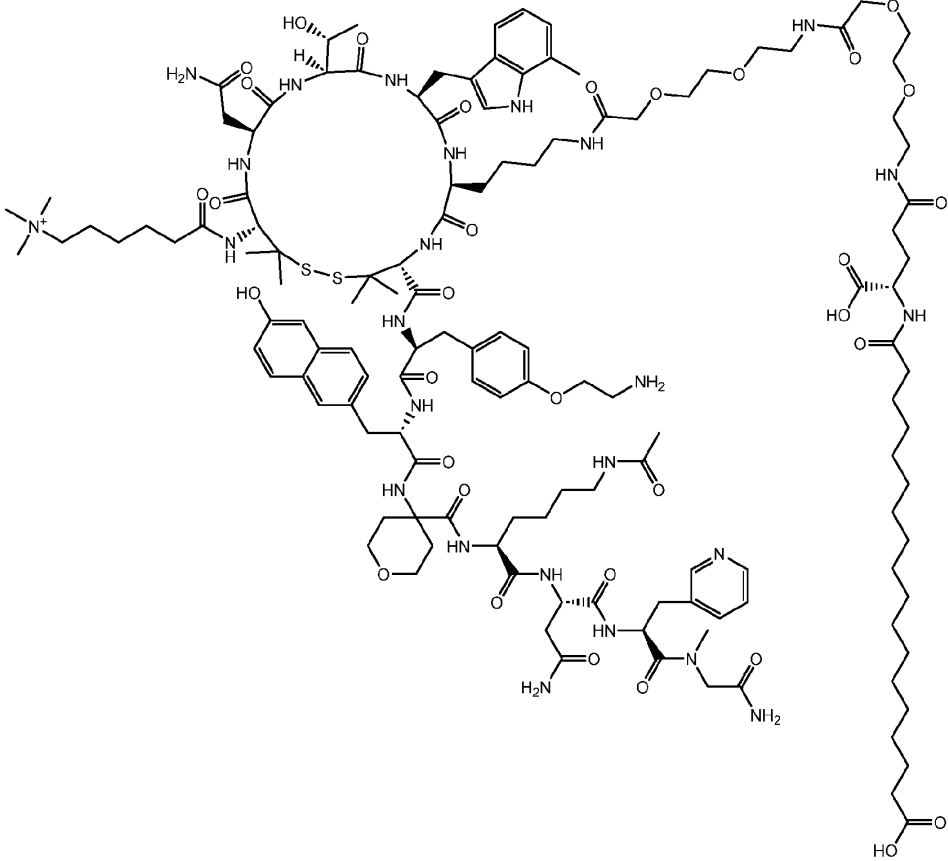
5cpaCO-Pen(3)-N-T-7MeW-K(Ac)-Pen(3)-AEF-6OH2Nal-THP-K(PEG2PEG2gEC18OH)-N-3Pyra-Sar-CONH2

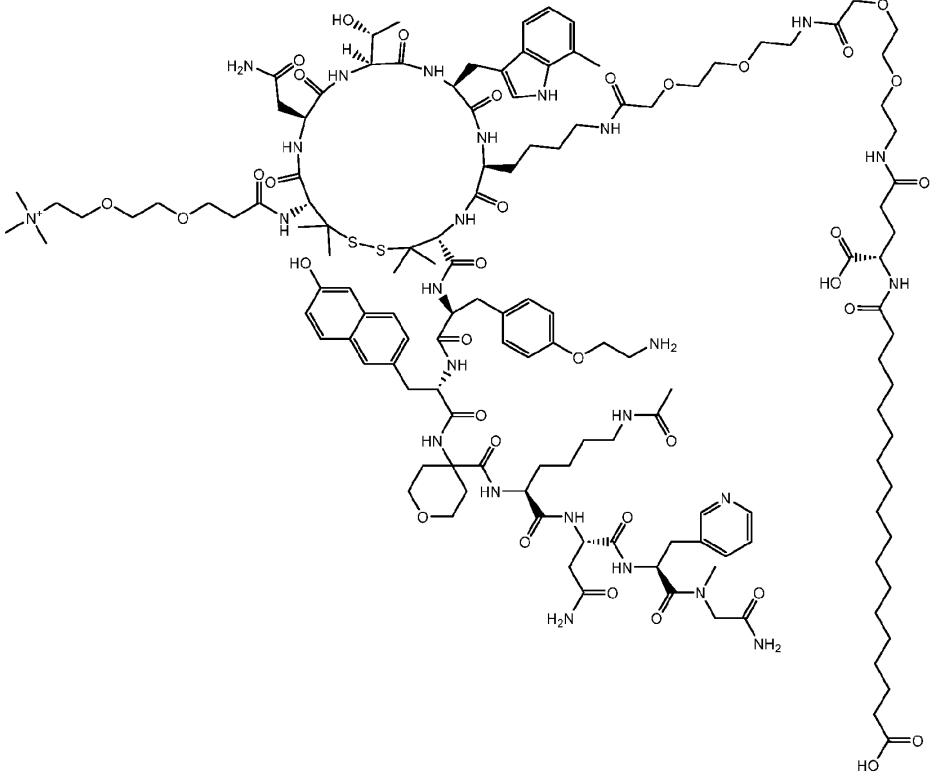
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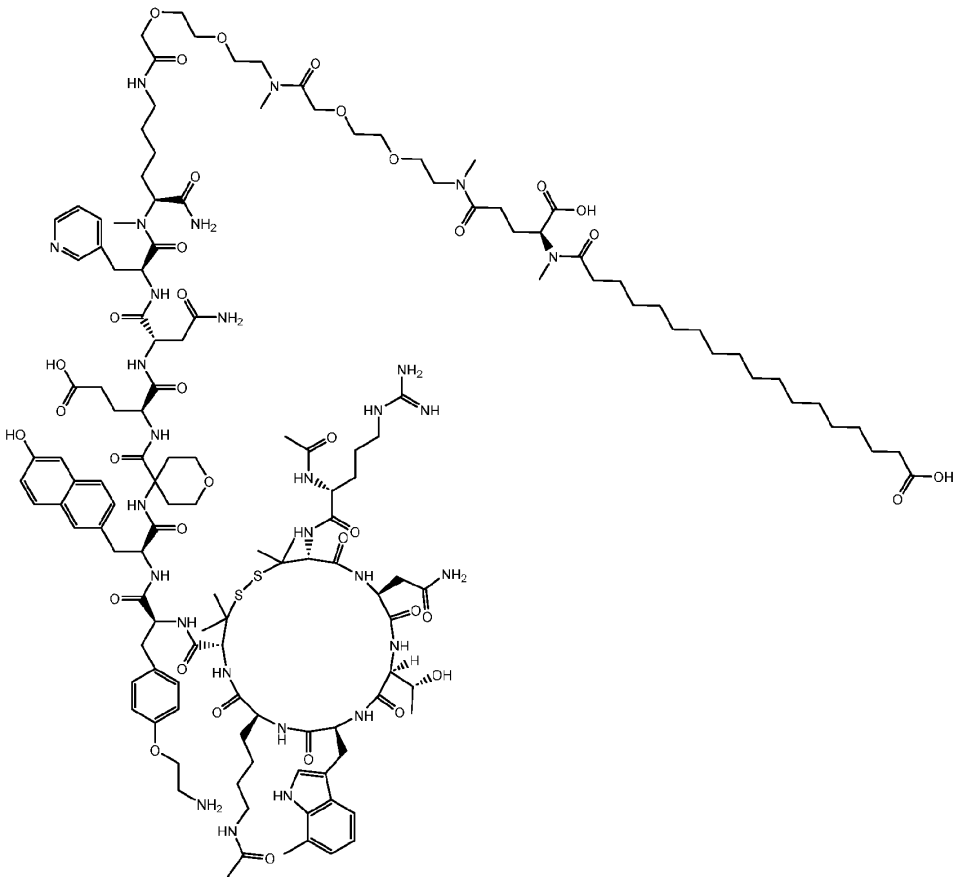


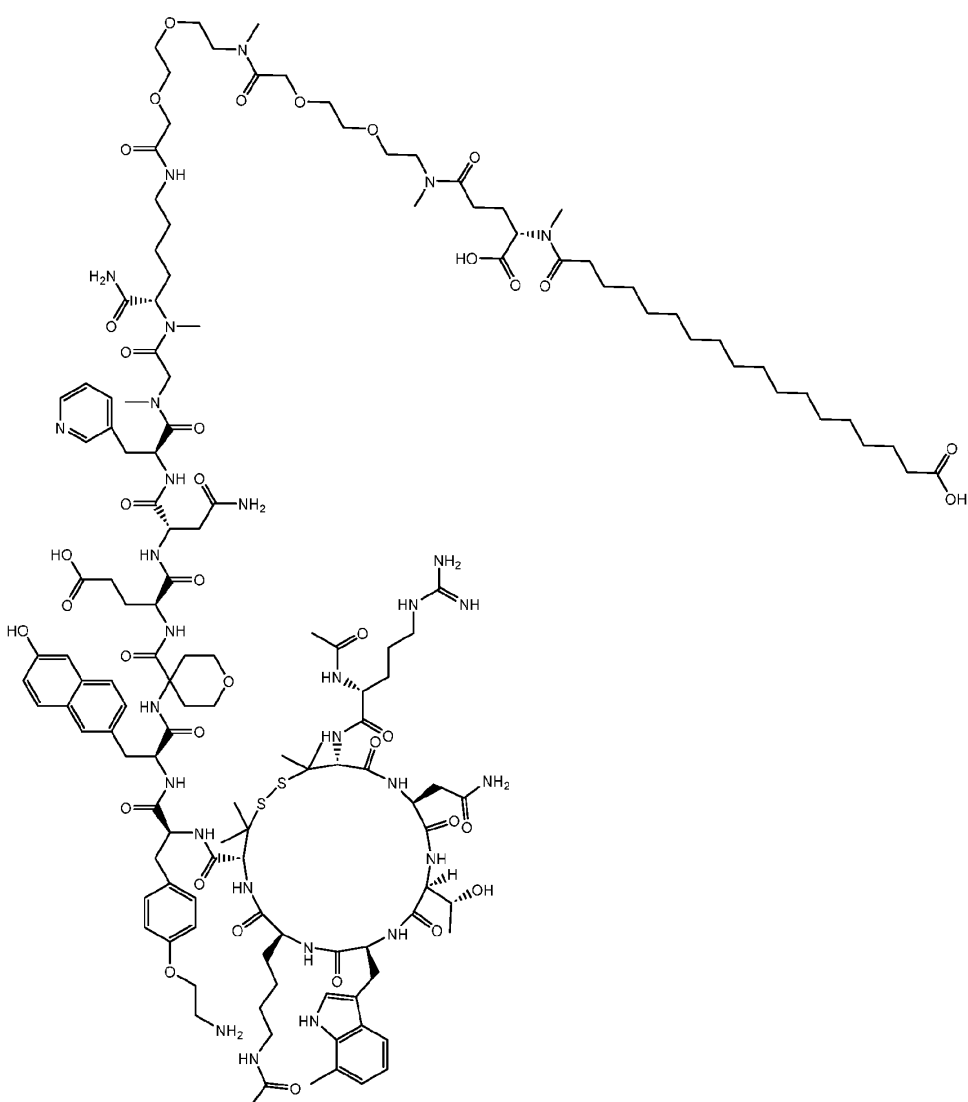
cPEG3aCO-Pen(3)-N-T-7MeW-K(Ac)-Pen(3)-AEF-6OH2Nal-THP-K(PEG2PEG2gEC18OH)-N-3Py-Sar-CONH2

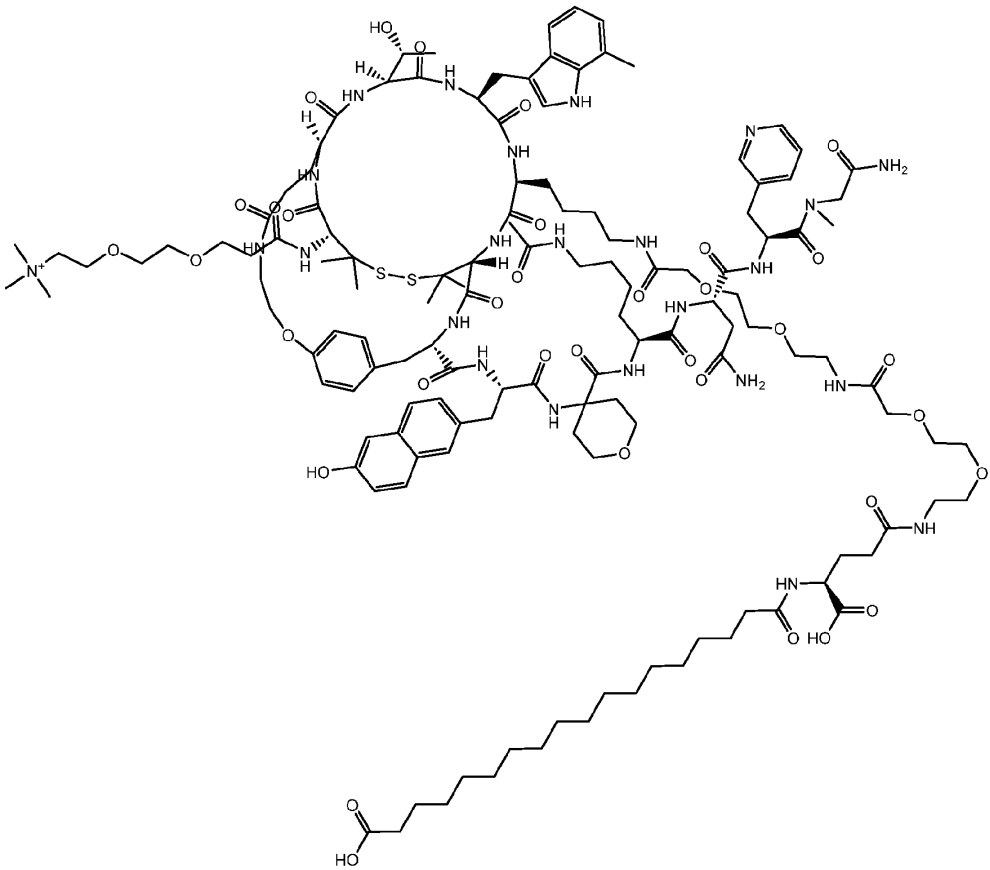
SEQ ID NO	Structure
187	 MeCO-hk(Me)3-Pen(3)-N-T-7MeW-K(PEG2PEG2gEC18OH)-Pen(3)-AEF-6OH2Nal-THP-K(Ac)-N-3Pya-Sar-CONH2

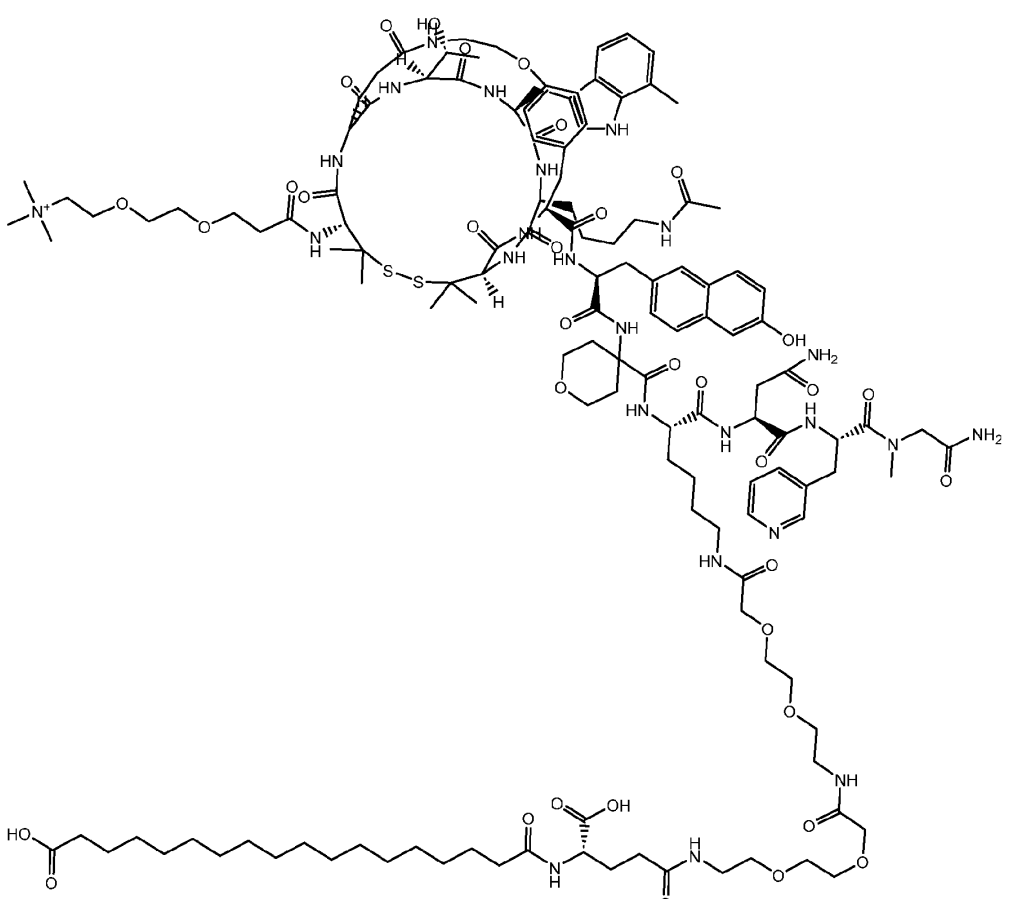
SEQ ID NO	Structure
188	 5cpaCO-Pen(3)-N-T-7MeW-K(PEG2PEG2gEC18OH)-Pen(3)-AEF-6OH2Nal-THP-K(Ac)-N-3Pya-Sar-CONH2

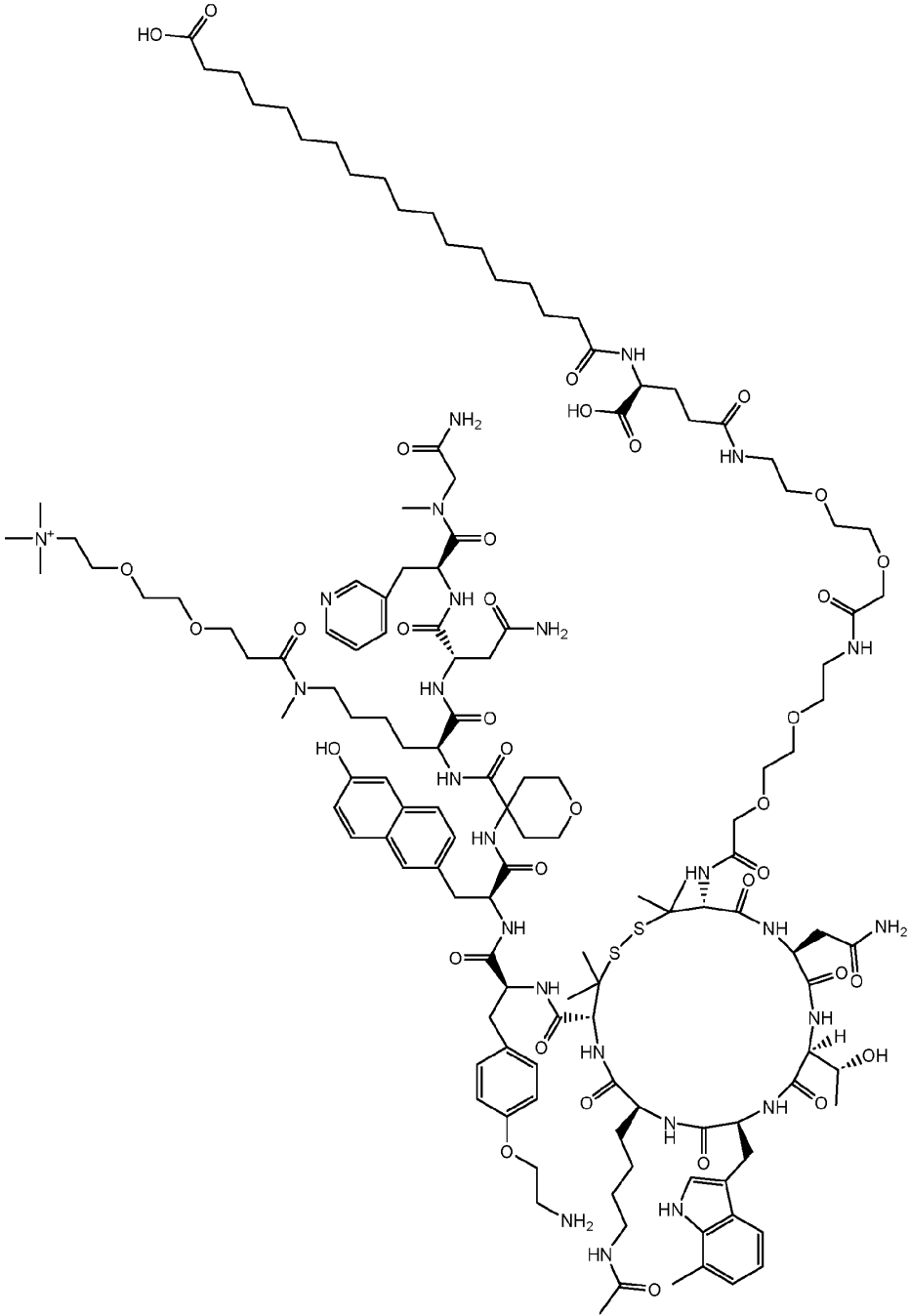
SEQ ID NO	Structure
189	 cPEG3aCO-Pen(3)-N-T-7MeW-K(PEG2PEG2gEC18OH)-Pen(3)-AEF-6OH2Nal-THP-K(Ac)-N-3Pyra-Sar-CONH2

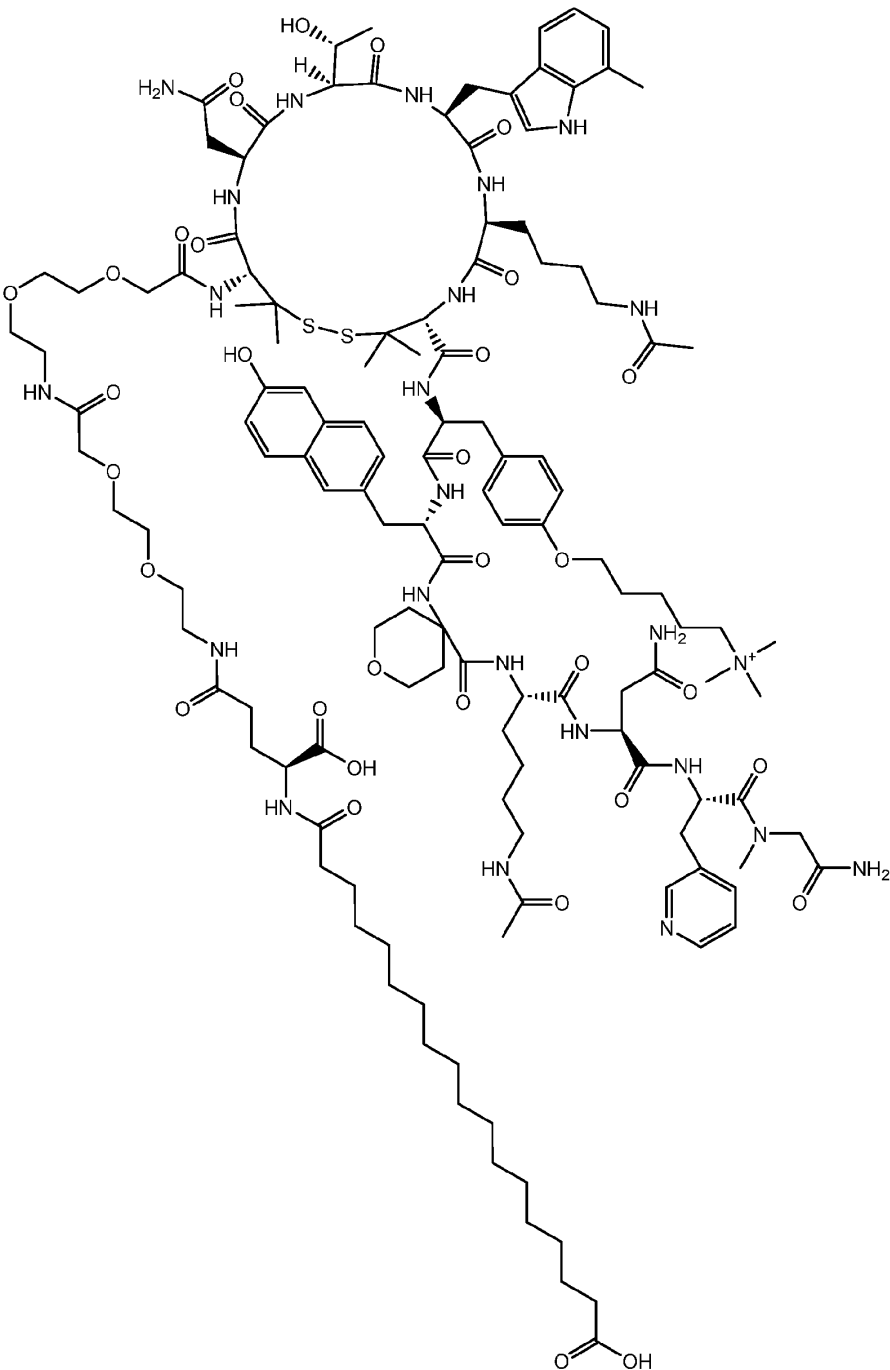
SEQ ID NO	Structure
190	 MeCO-r-Pen(3)-N-T-7MeW-K(Ac)-Pen(3)-AEF-6OH2Nal-THP-E-N-3Py-NMeK(PEG2NMePEG2NMeG2NMeC18OH)-CONH2

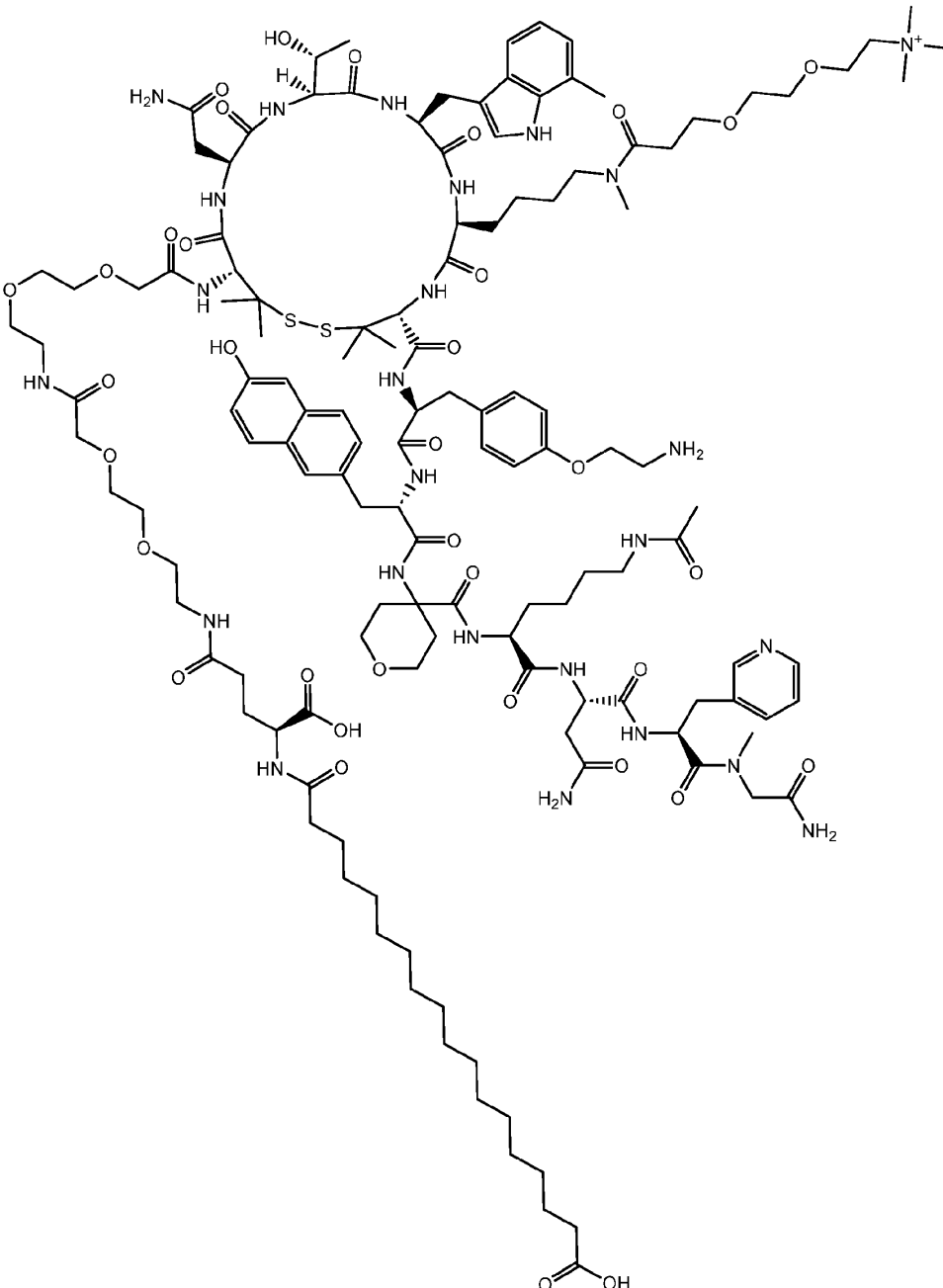
SEQ ID NO	Structure
191	 MeCO-r-Pen(3)-N-T-7MeW-K(Ac)-Pen(3)-AEF-6OH2Nal-THP-E-N-3Pyra-Sar-NMeK(PEG2NMePEG2NMeG18OH)-CONH2

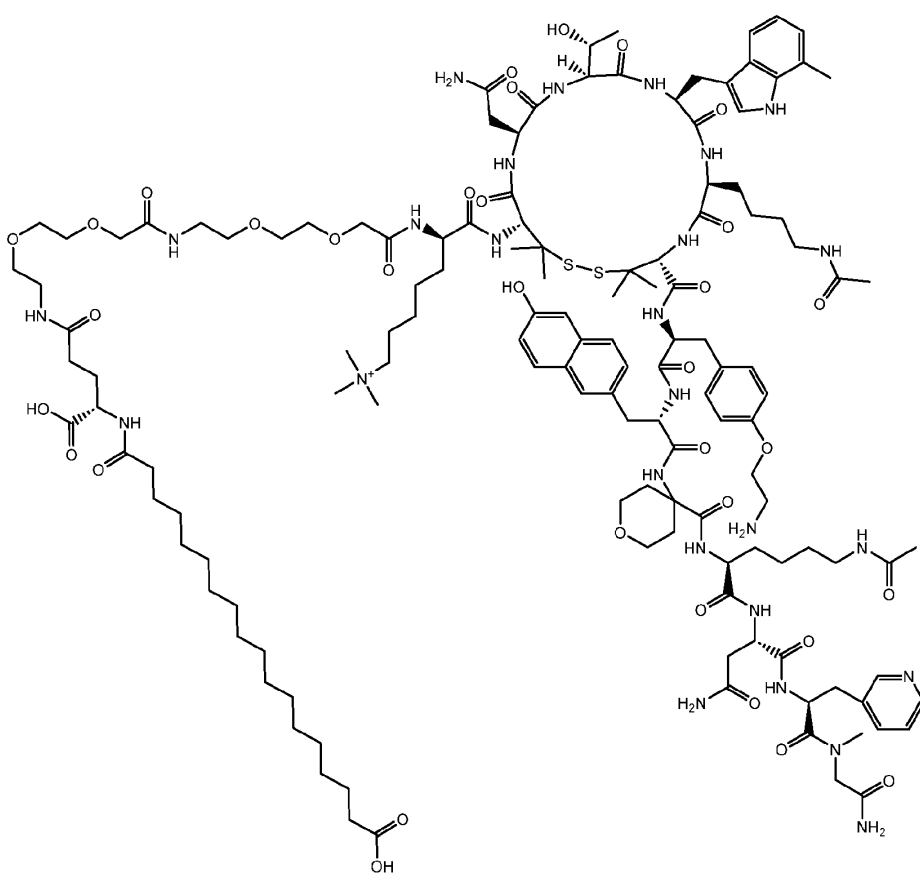
SEQ ID NO	Structure
192	 cPEG3aCO-Pen(3)-E(2)-T-7MeW-K(PEG2PEG2gEC18OH)-Pen(3)-AEF(2)-6OH2NaI-THP-K(Ac)-N-3Pya-Sar-CONH2

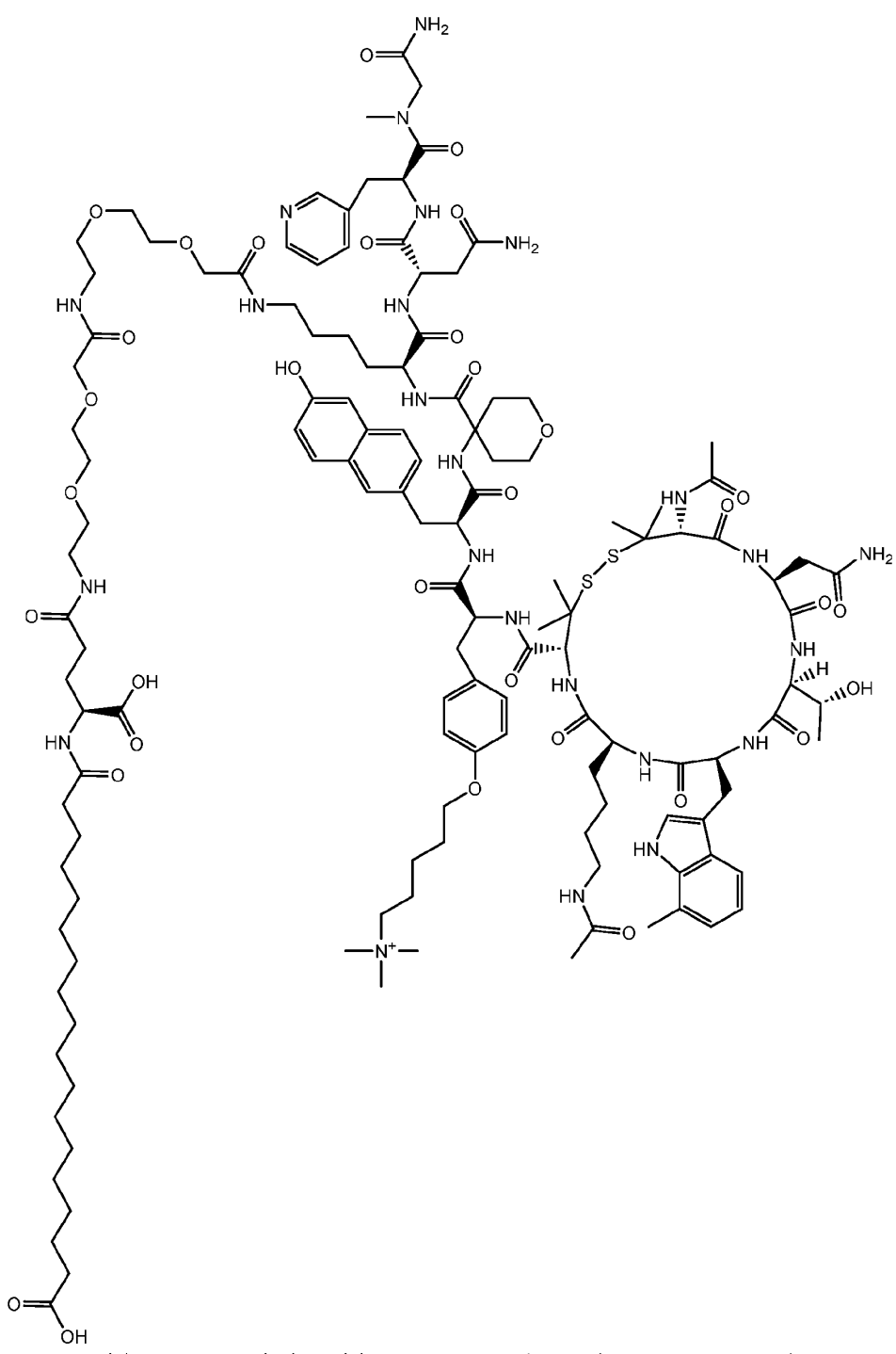
SEQ ID NO	Structure
193	 cPEG3aCO-Pen(3)-E(2)-T-7MeW-K(Ac)-Pen(3)-AEF(2)-6OH2Nal-THP-K(PEG2PEG2gEC18OH)-N-3Py-Sar-CONH2

SEQ ID NO	Structure
194	 HOC18gEPEG2PEG2CO-Pen(3)-N-T-7MeW-K(Ac)-Pen(3)-AEF-6OH2Nal-THP-K(NMecPEG3a)-N-3Py-Sar-CONH2

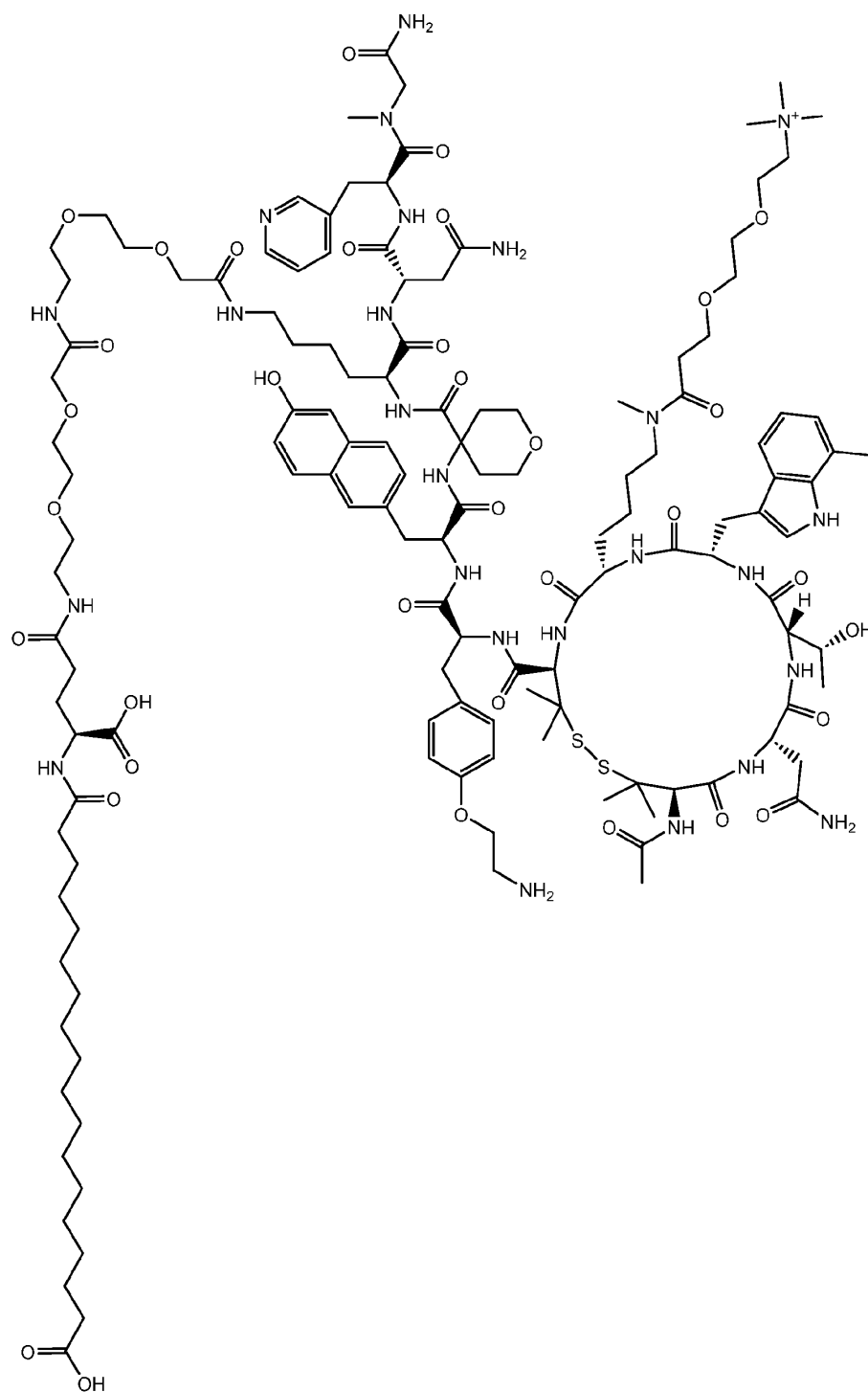
SEQ ID NO	Structure
195	 HOC18gEPEG2PEG2CO-Pen(3)-N-T-7MeW-K(Ac)-Pen(3)-TMAPF-6OH2Nal-THP-K(Ac)-N-3Py-Sar-CONH2

SEQ ID NO	Structure
196	 The chemical structure is a large, complex molecule, likely a peptide or protein derivative. It features a central cyclic core with multiple side chains. Key features include a long alkyl chain, a pyridine ring, and a quaternary ammonium group. The molecule is highly branched and contains various functional groups, including amide, ester, and hydroxyl groups. The structure is drawn in a perspective view, showing the spatial arrangement of the atoms and bonds. HOC18gEPEG2PEG2CO-Pen(3)-N-T-7MeW-K(NMecPEG3a)-Pen(3)-AEF-6OH2Nal-THP-K(Ac)-N-3Pyra-Sar-CONH2

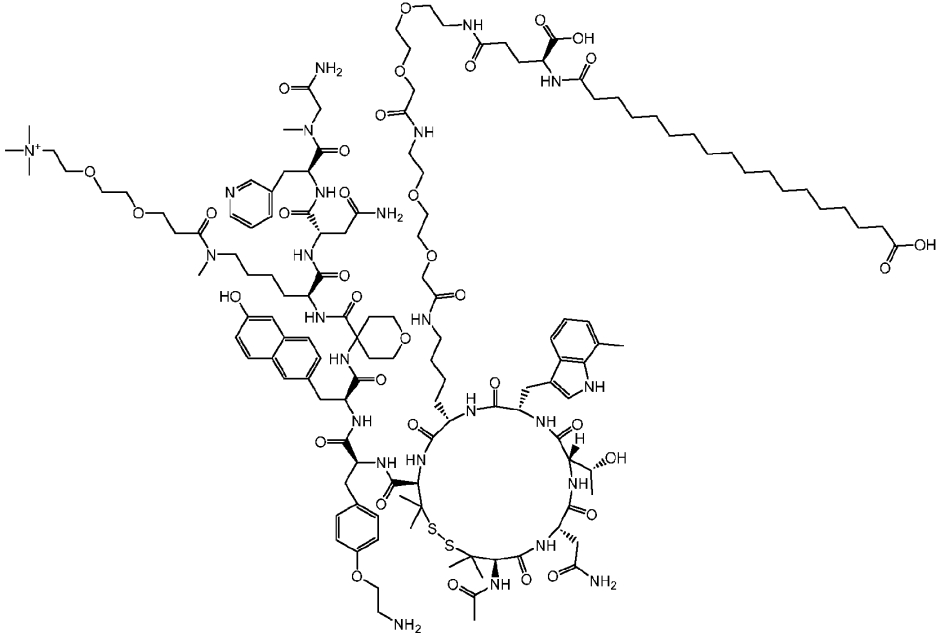
SEQ ID NO	Structure
197	 HOC18gEPEG2PEG2CO-hk(Me)3-Pen(3)-N-T-7MeW-K(Ac)-Pen(3)-AEF-6OH2NaI-THP-K(Ac)-N-3PyA-Sar-CONH2

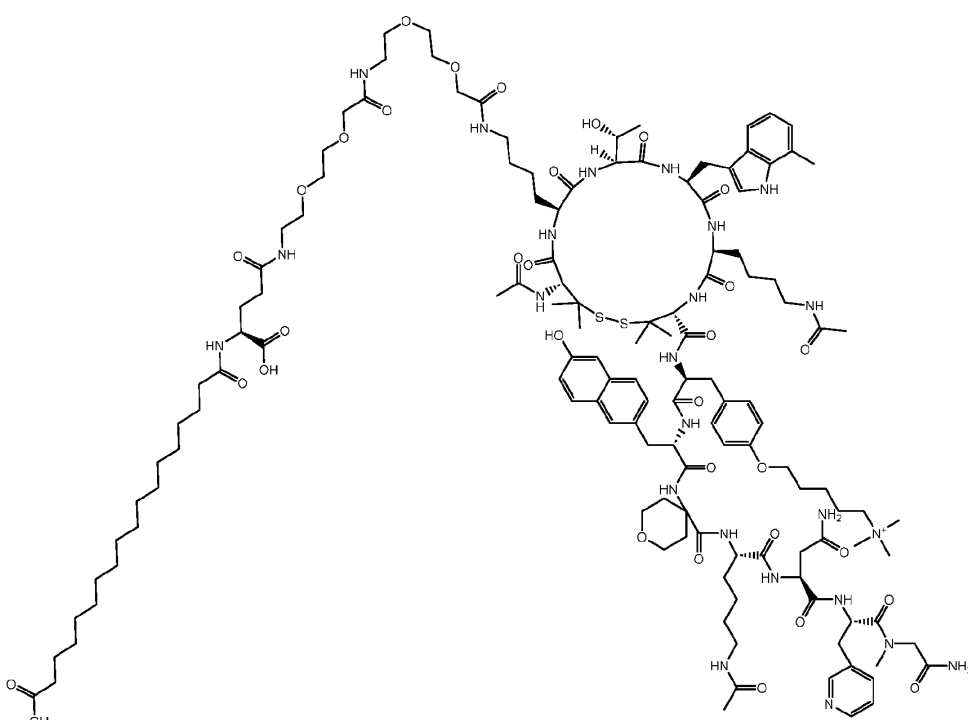
SEQ ID NO	Structure
198	 MeCO-Pen(3)-N-T-7MeW-K(Ac)-Pen(3)-TMAPF-6OH2NaI-THP-K(PEG2PEG2gEC18OH)-N-3PyA-Sar-CONH2

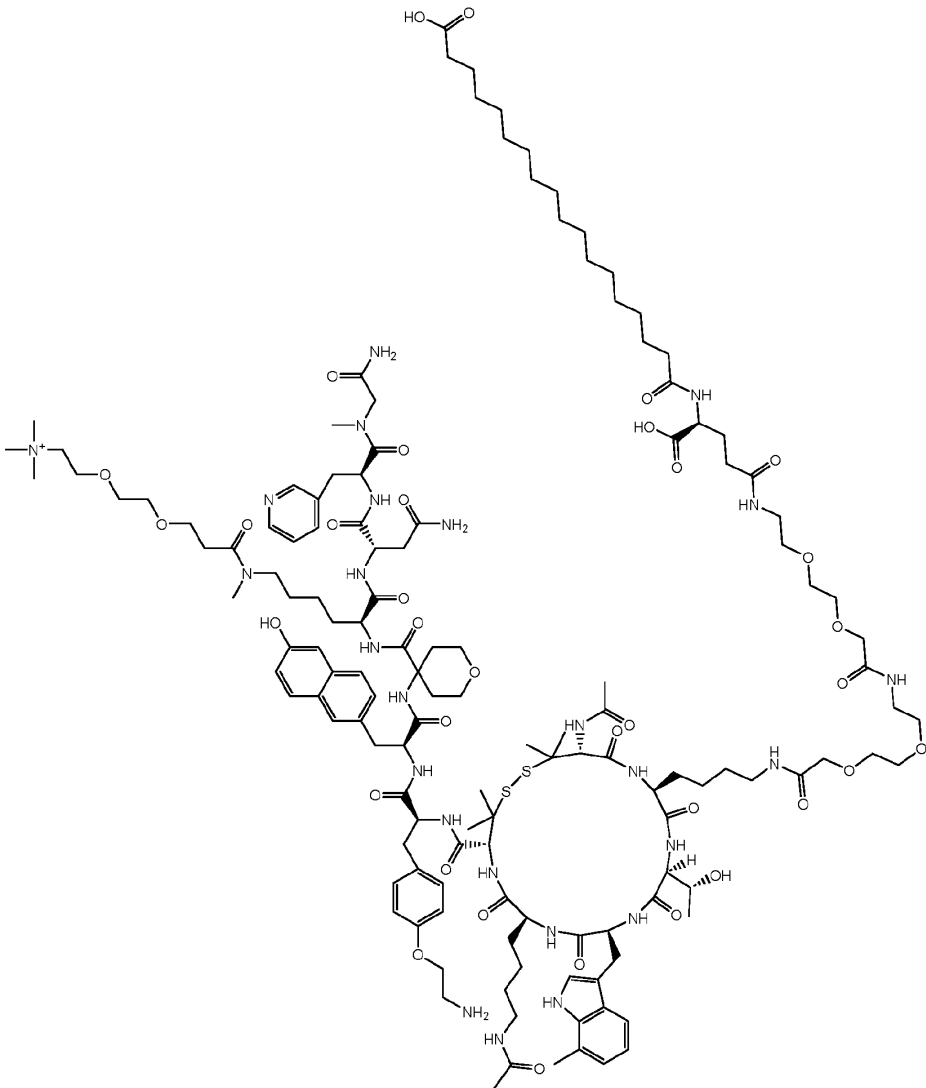
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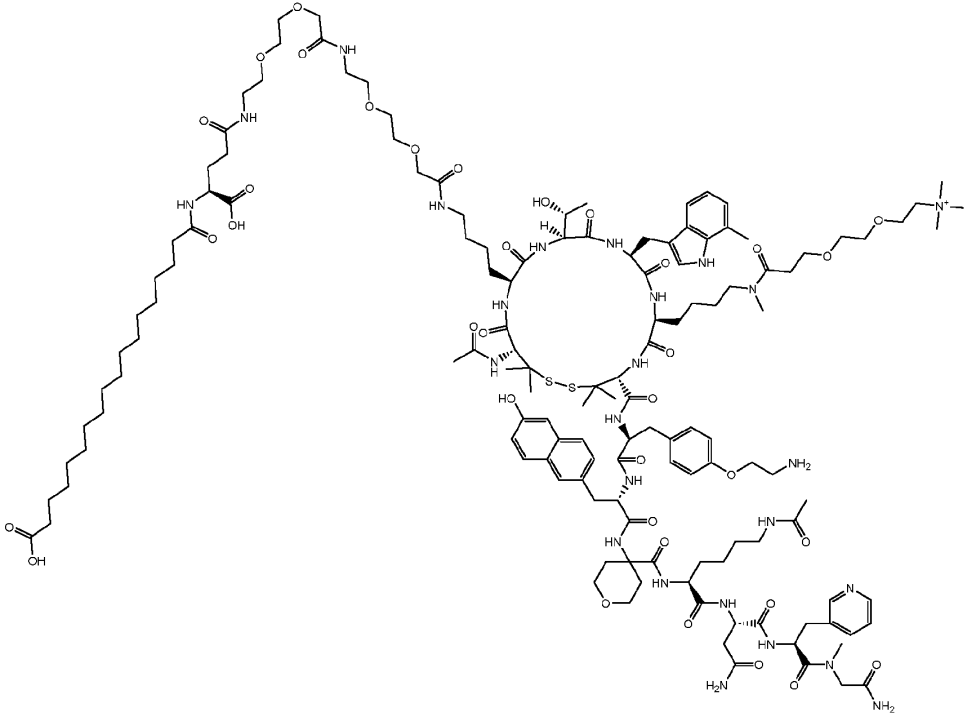


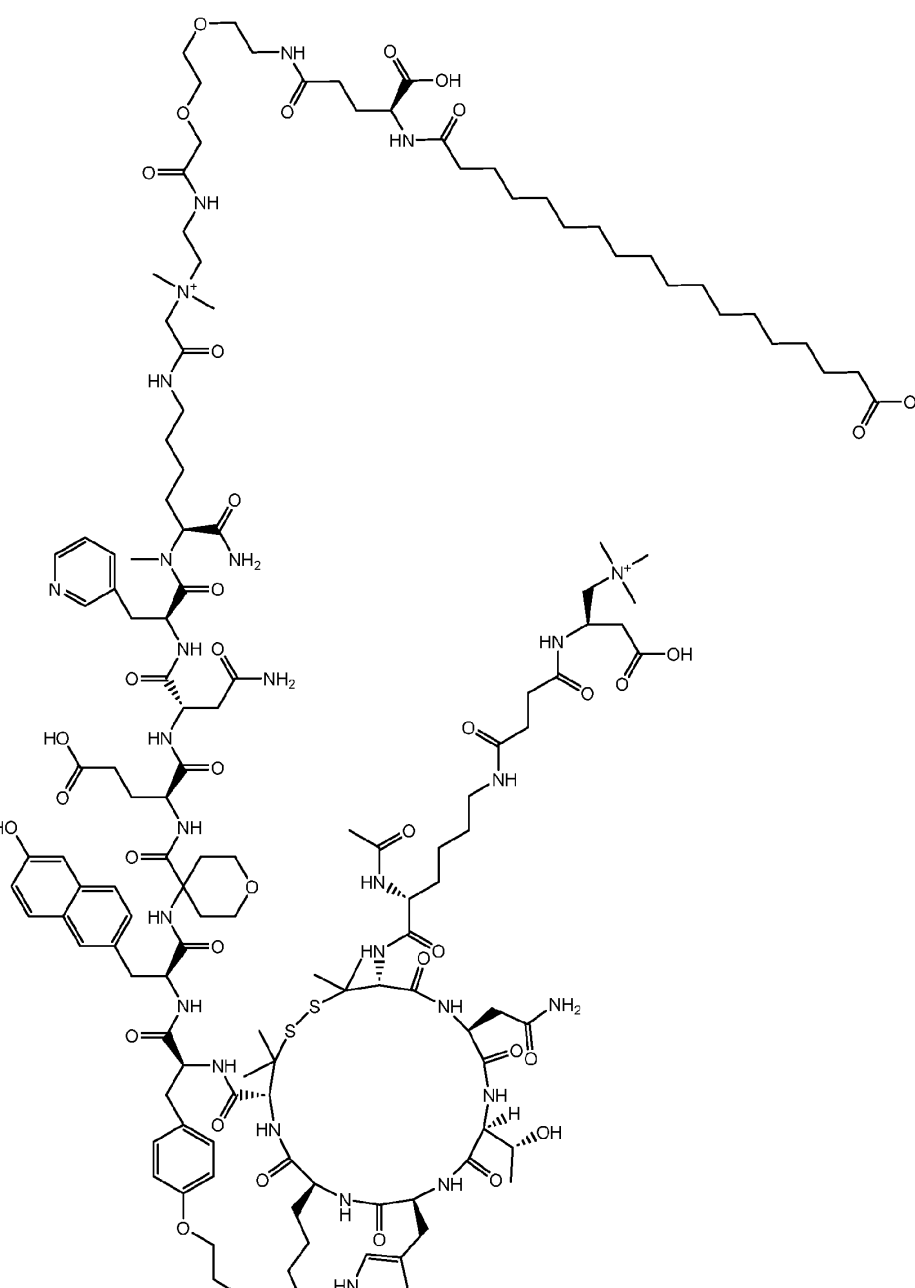
MeCO-Pen(3)-N-T-7MeW-K(NMecPEG3a)-Pen(3)-AEF-6OH2Nal-THP-K(PEG2PEG2gEC18OH)-N-3Py-Sar-CONH2

SEQ ID NO	Structure
200	 MeCO-Pen(3)-N-T-7MeW-K(PEG2PEG2gEC18OH)-Pen(3)-AEF-6OH2NaI-THP-K(NMecPEG3a)-N-3Py-Sar-CONH2

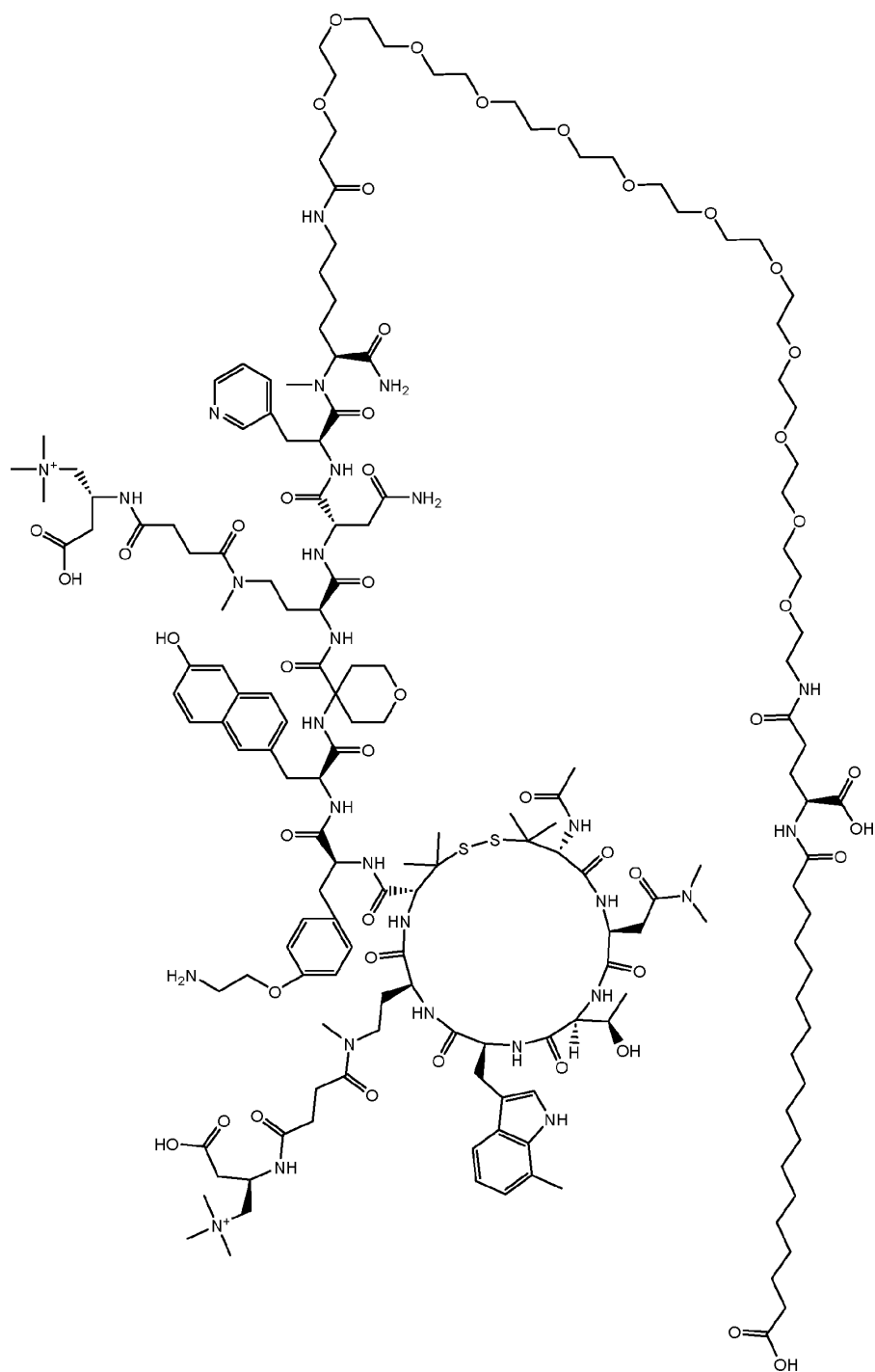
SEQ ID NO	Structure
201	 MeCO-Pen(3)-K(PEG2PEG2gEC18OH)-T-7MeW-K(Ac)-Pen(3)-TMAPF-6OH2NaI-THP-K(Ac)-N-3Pyra-Sar-CONH2

SEQ ID NO	Structure
202	 MeCO-Pen(3)-K(PEG2PEG2gEC18OH)-T-7MeW-K(Ac)-Pen(3)-AEF-6OH2NaI-THP-K(NMecPEG3a)-N-3Py-Sar-CONH2

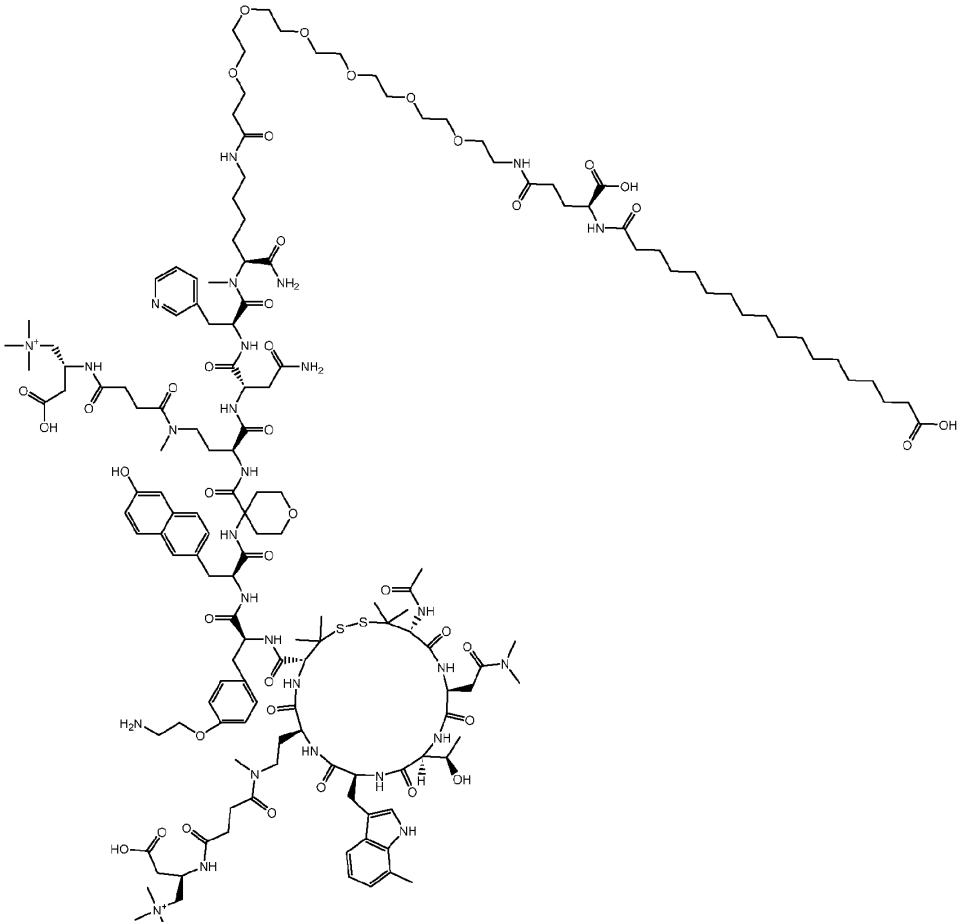
SEQ ID NO	Structure
203	 MeCO-Pen(3)-K(PEG2PEG2gEC18OH)-T-7MeW-K(NMecPEG3a)-Pen(3)-AEF-6OH2NaI-THP-K(Ac)-N-3Py-Sar-CONH2

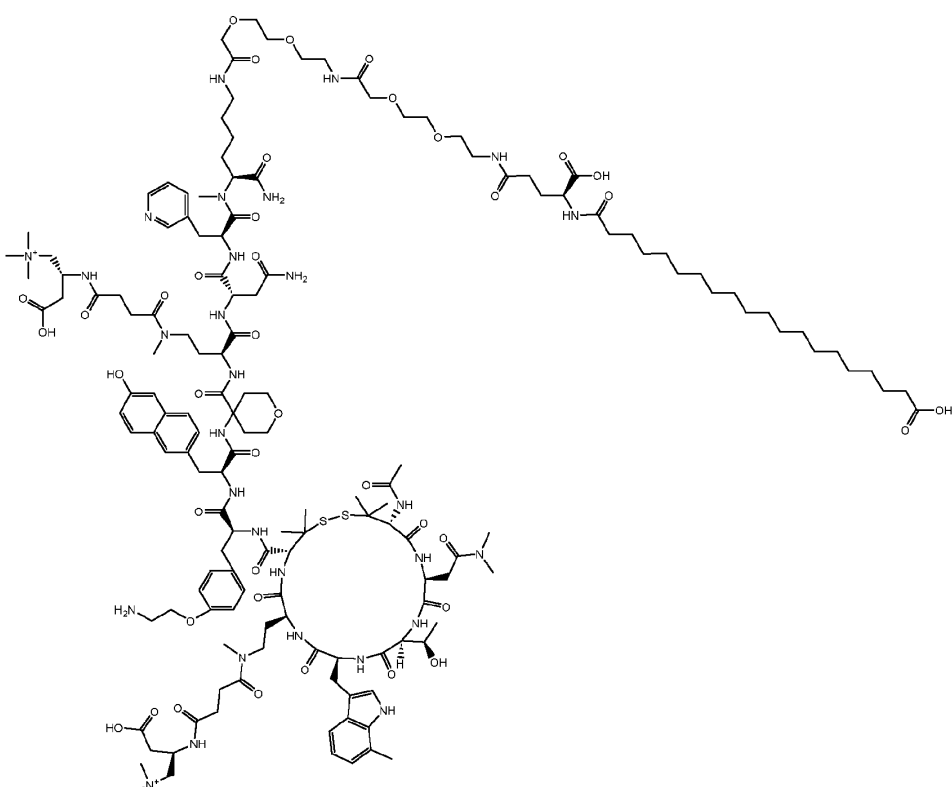
SEQ ID NO	Structure
204	 MeCO-k(d)-Pen(3)-N-T-7MeW-K(Ac)-Pen(3)-AEF-6OH2NaI-THP-E-N-3PyA-NMeK(SP6PEG2gEC18OH)-CONH2

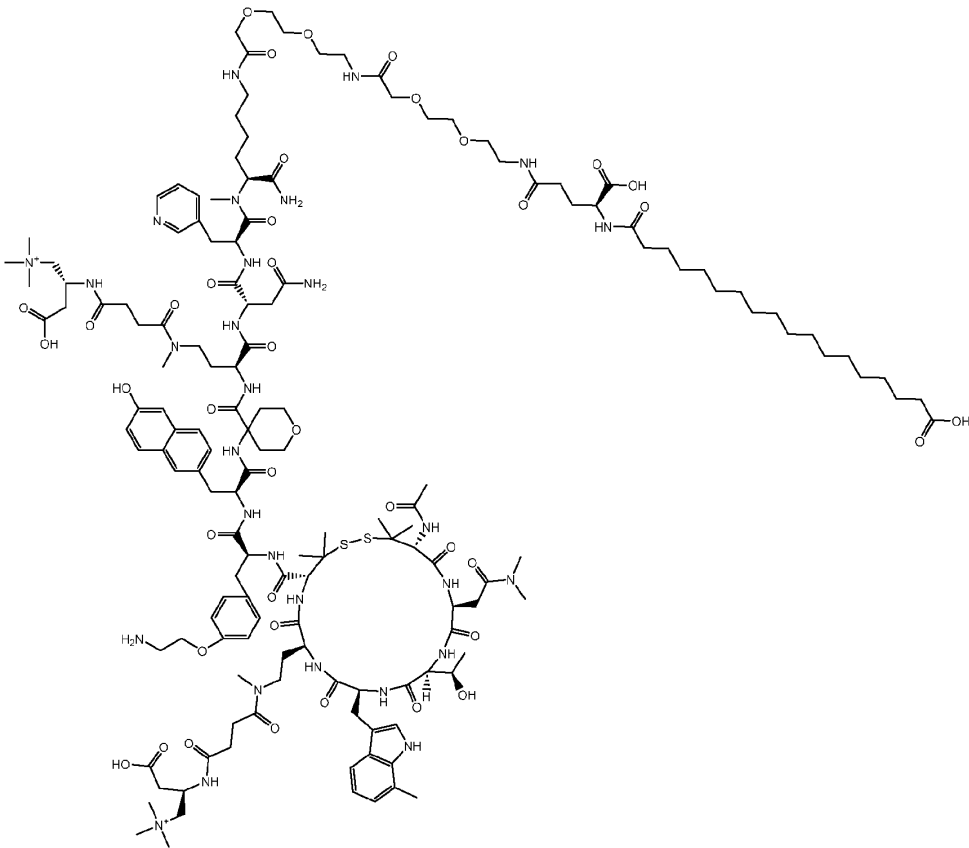
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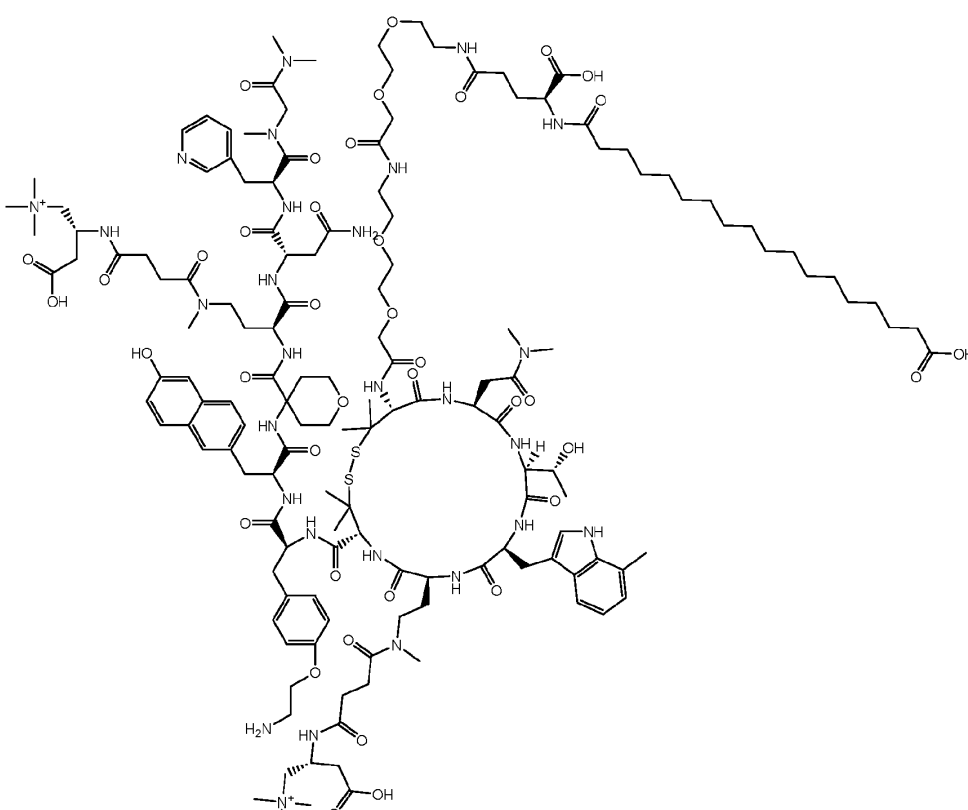


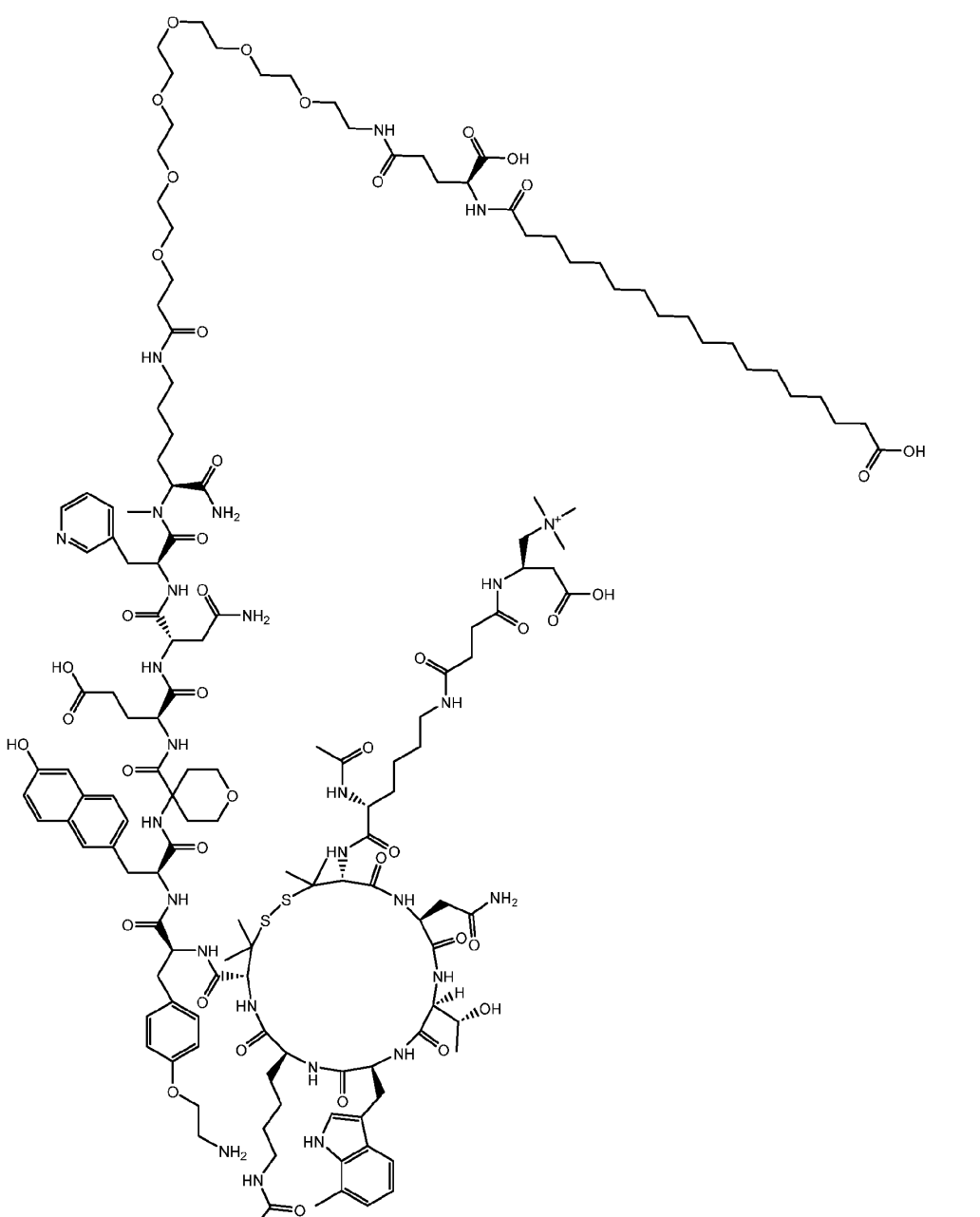
MeCO-Pen(3)-N(N(Me)₂)-T-7MeW-Dab(NMecarn)-Pen(3)-AEF-6OH₂Nal-THP-Dab(NMecarn)-N-3Py-NMeK(PEG12gEC18OH)-CONH₂

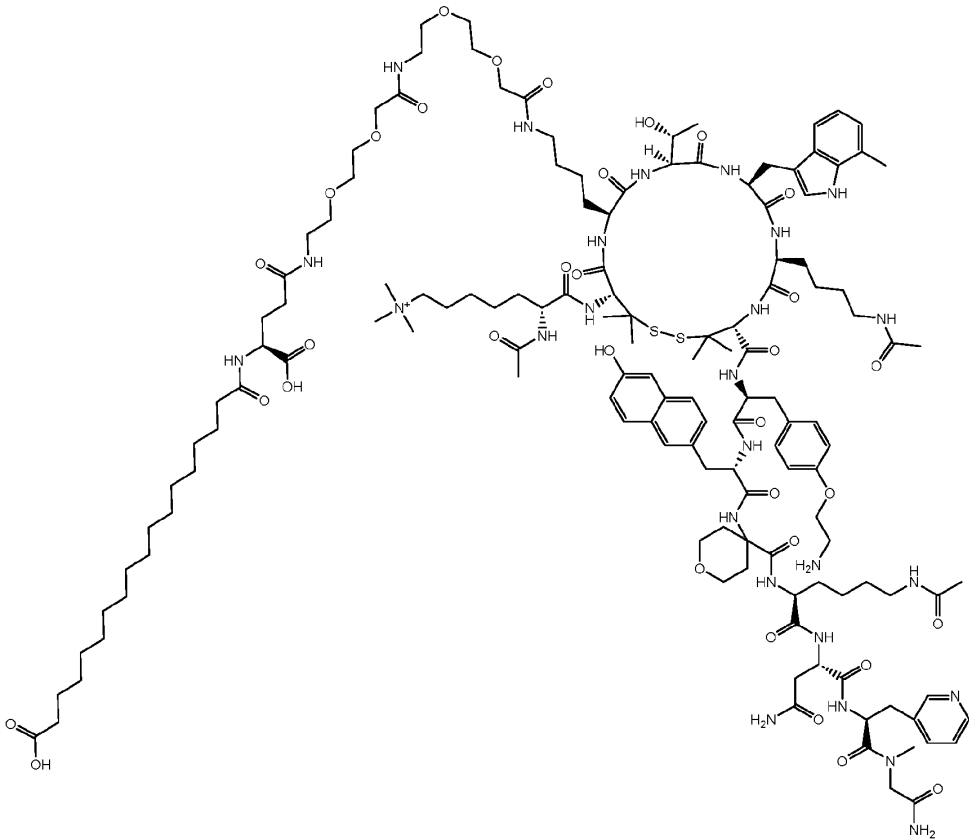
SEQ ID NO	Structure
206	 MeCO-Pen(3)-N(N(Me)2)-T-7MeW-Dab(NMecarn)-Pen(3)-AEF-6OH2Nal-THP-Dab(NMecarn)-N-3Pya-NMeK(PEG6gEC18OH)-CONH2

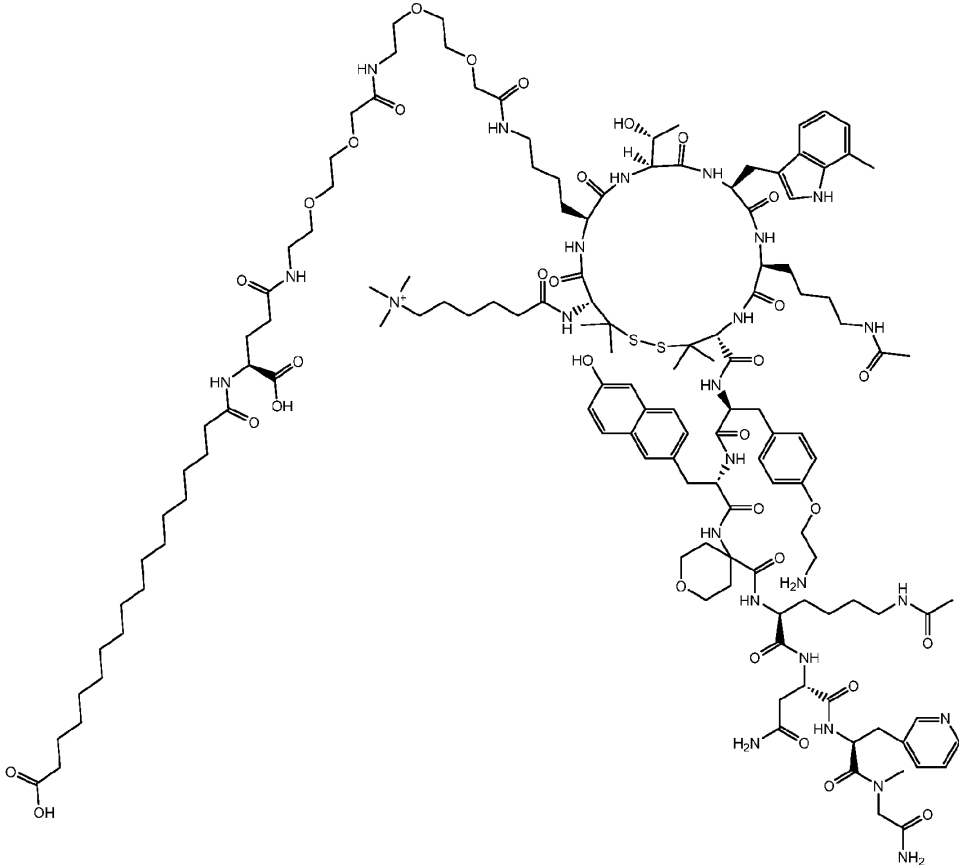
SEQ ID NO	Structure
207	 MeCO-Pen(3)-N(N(Me)₂)-T-7MeW-Dab(NMecarn)-Pen(3)-AEF-6OH₂Nal-THP-Dab(NMecarn)-N-3Py-NMeK(PEG₂PEG₂gEC₂₀OH)-CONH₂

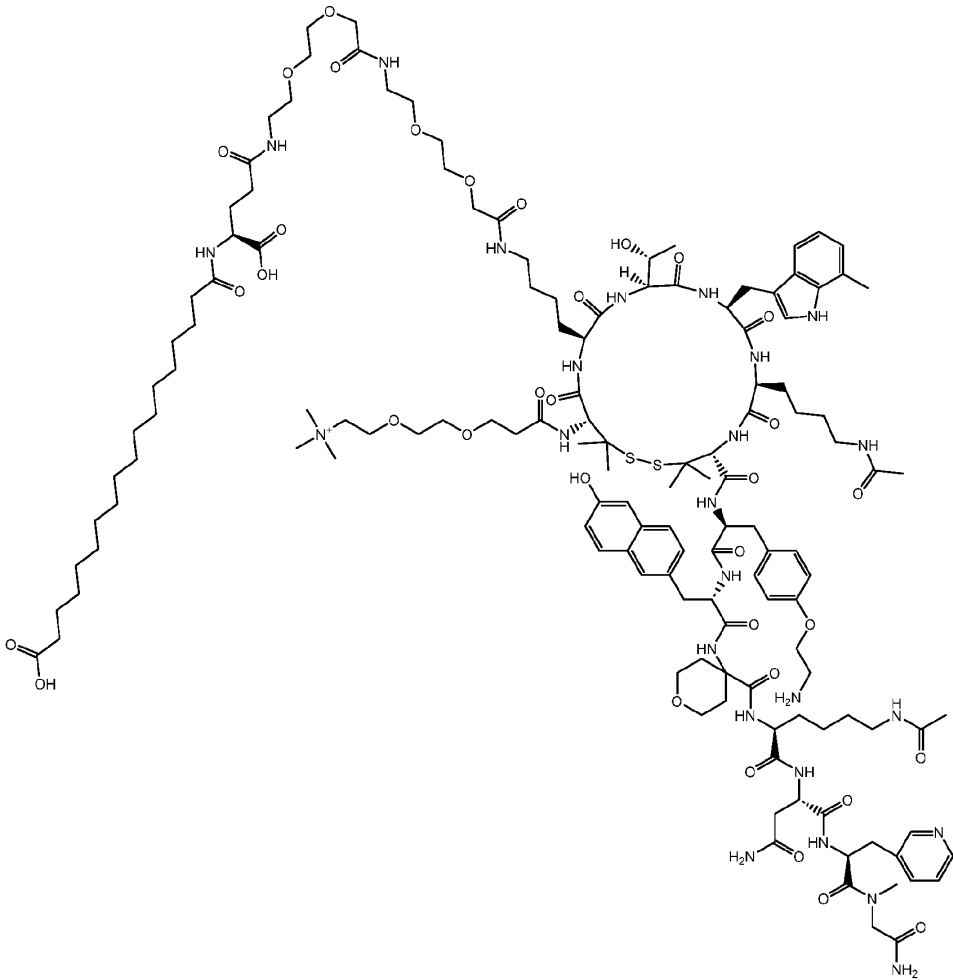
SEQ ID NO	Structure
208	 MeCO-Pen(3)-N(N(Me)2)-T-7MeW-Dab(NMecarn)-Pen(3)-AEF-6OH2Nal-THP-Dab(NMecarn)-N-3Py-NMeK(PEG2PEG2gEC18OH)-CONH2

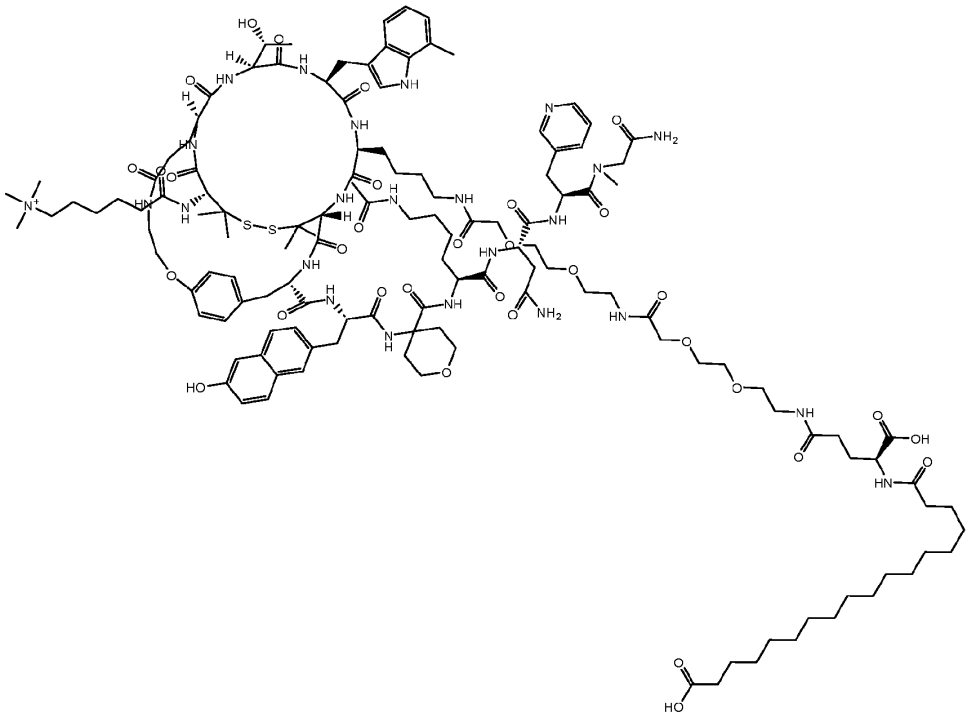
SEQ ID NO	Structure
209	 HOC18gEPEG2PEG2CO-Pen(3)-N(N(Me)2)-T-7MeW-Dab(NMecarn)-Pen(3)-AEF-6OH2Nal-THP-Dab(NMecarn)-N-3Pya-Sar-CON(Me)2

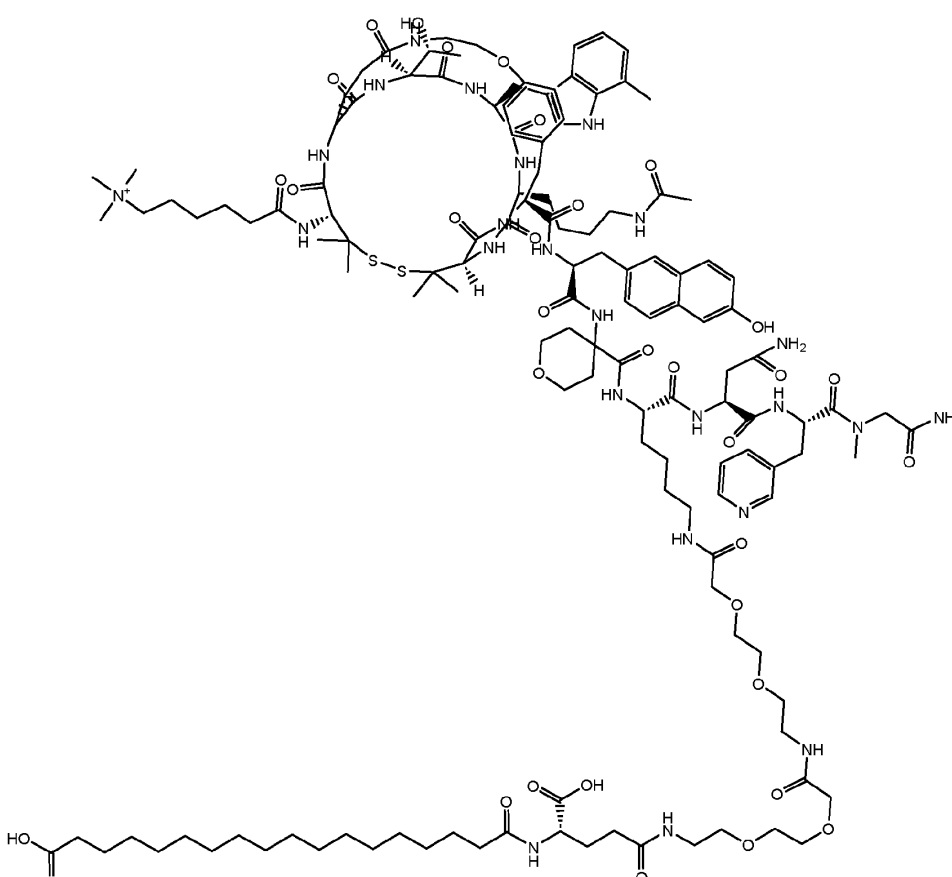
SEQ ID NO	Structure
210	 MeCO-k(d)-Pen(3)-N-T-7MeW-K(Ac)-Pen(3)-AEF-6OH2NaI-THP-E-N-3PyA-NMeK(PEG6gEC18OH)-CONH2

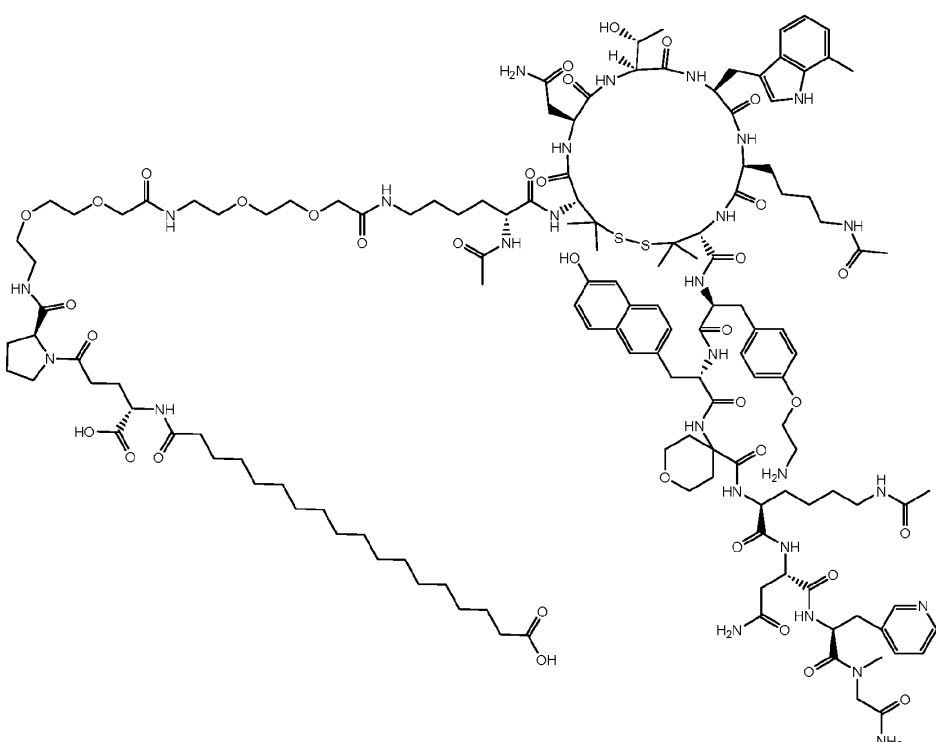
SEQ ID NO	Structure
211	 MeCO-hk(Me)3-Pen(3)-K(PEG2PEG2gEC18OH)-T-7MeW-K(Ac)-Pen(3)-AEF-6OH2Nal-THP-K(Ac)-N-3Py-Sar-CONH2

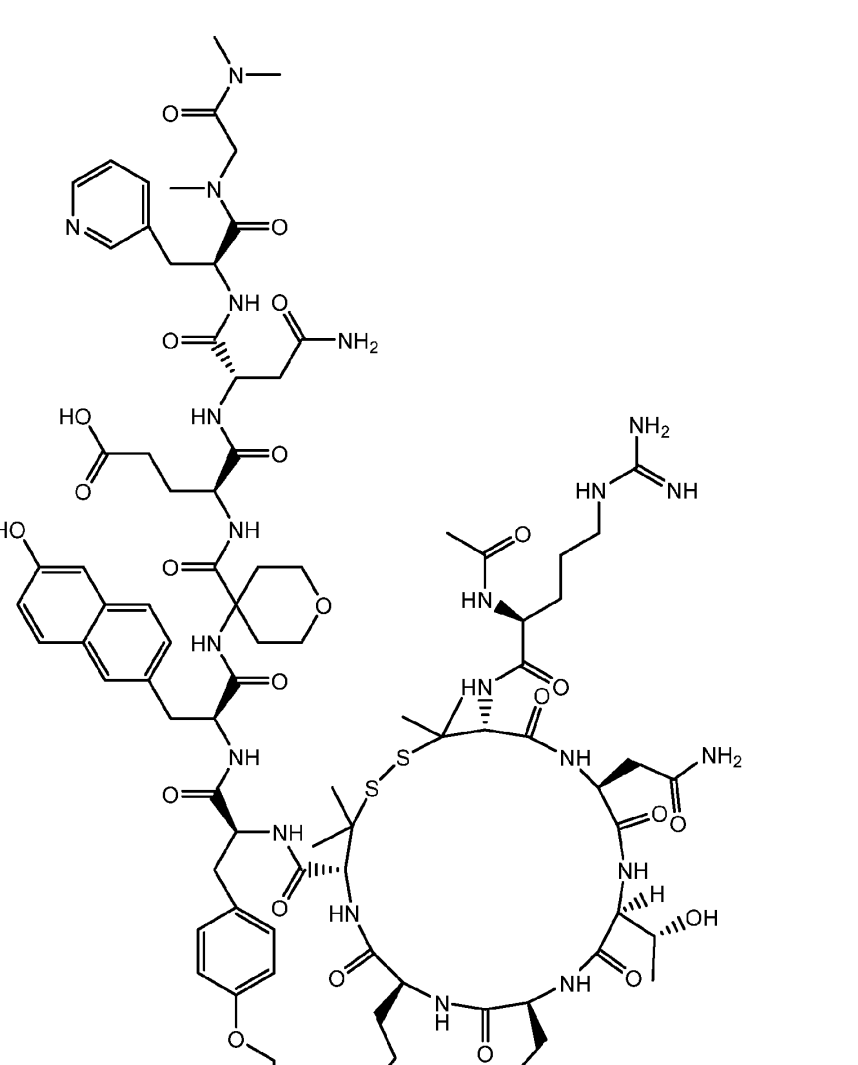
SEQ ID NO	Structure
212	 5cpaCO-Pen(3)-K(PEG2PEG2gEC18OH)-T-7MeW-K(Ac)-Pen(3)-AEF-6OH2NaI-THP-K(Ac)-N-3PyA-Sar-CONH2

SEQ ID NO	Structure
213	 cPEG3aCO-Pen(3)-K(PEG2PEG2gEC18OH)-T-7MeW-K(Ac)-Pen(3)-AEF-6OH2Nal-THP-K(Ac)-N-3Pya-Sar-CONH2

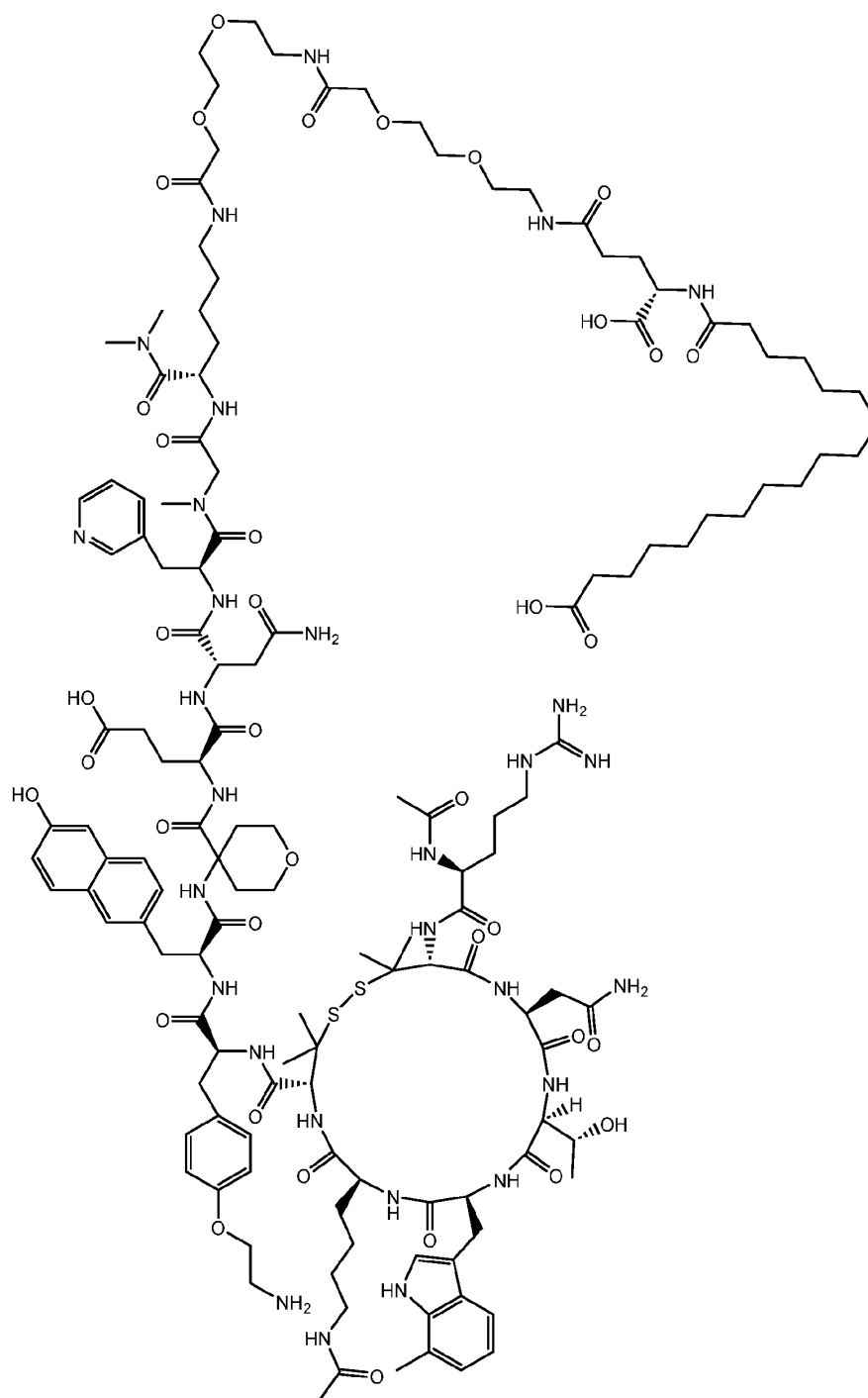
SEQ ID NO	Structure
214	 5cpaCO-Pen(3)-E(2)-T-7MeW-K(PEG2PEG2gEC18OH)-Pen(3)-AEF(2)-6OH2Nal-THP-K(Ac)-N-3Py-Sar-CONH2

SEQ ID NO	Structure
215	 5cpaCO-Pen(3)-E(2)-T-7MeW-K(Ac)-Pen(3)-AEF(2)-6OH2NaI-THP-K(PEG2PEG2gEC18OH)-N-3Pya-Sar-CONH2

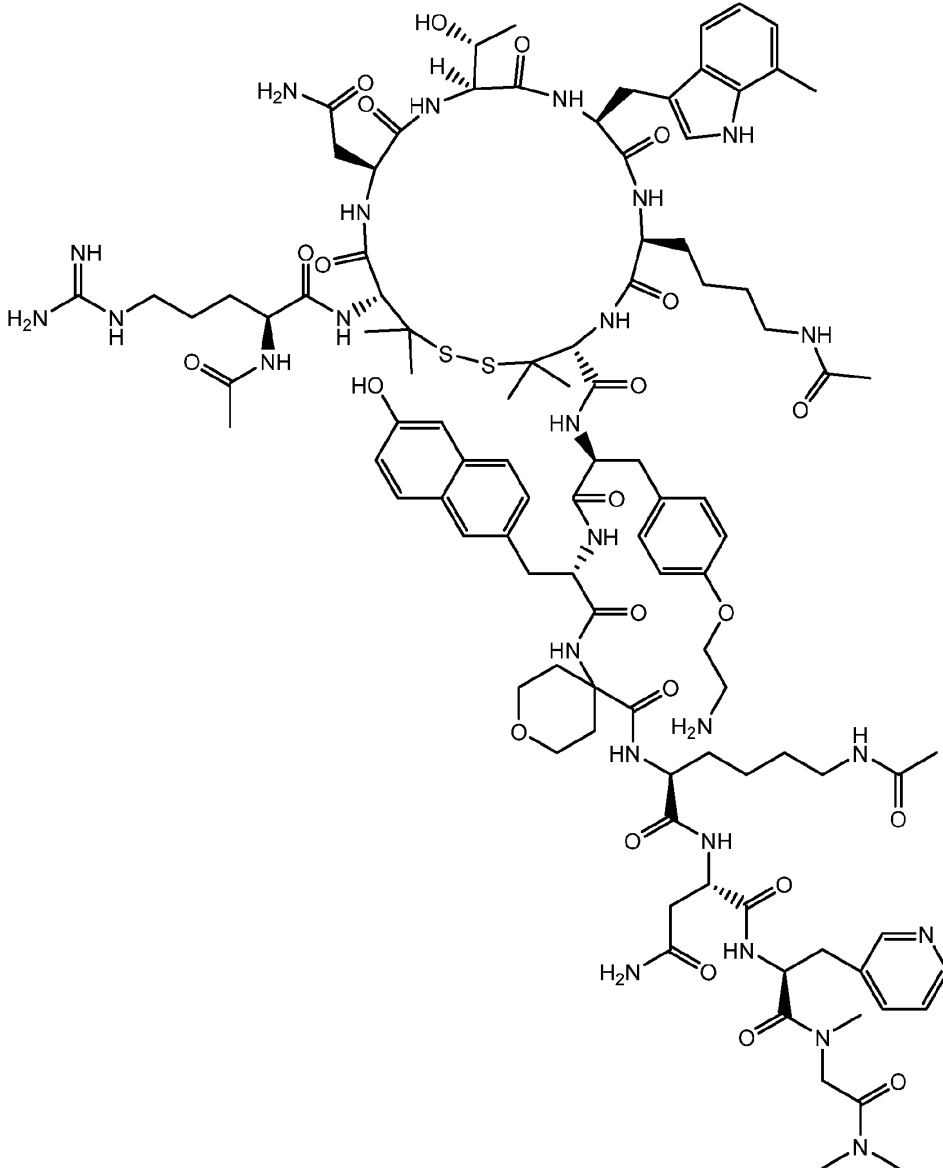
SEQ ID NO	Structure
216	 MeCO-k(PEG2PEG2PgEC18OH)-Pen(3)-N-T-7MeW-K(Ac)-Pen(3)-AEF-6OH2NaI-THP-K(Ac)-N-3PyA-Sar-CONH2

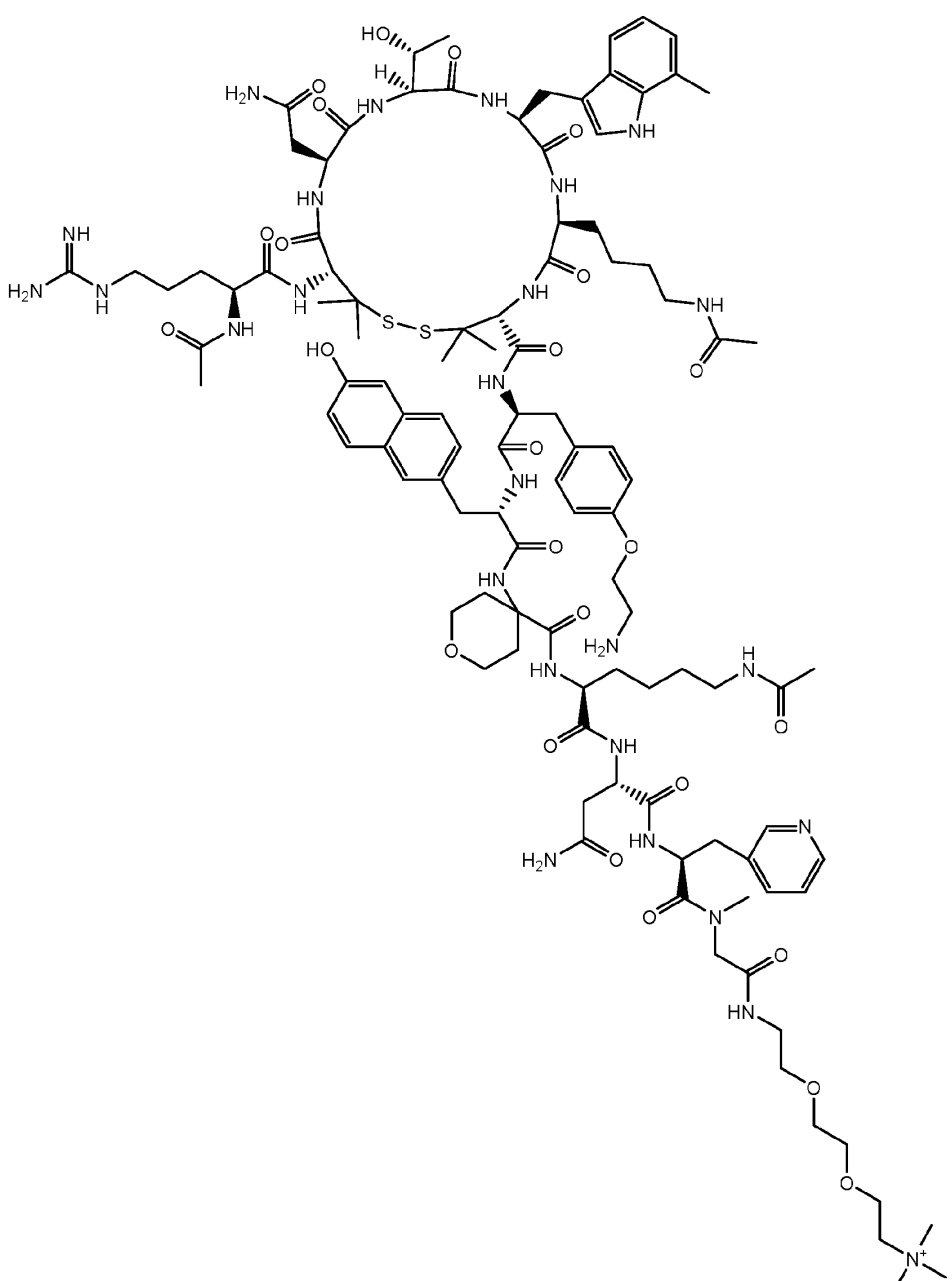
SEQ ID NO	Structure
217	 MeCO-R-Pen(3)-N-T-7MeW-K(Ac)-Pen(3)-AEF-6OH2Nal-THP-E-N-3Pya-Sar-CON(Me)2

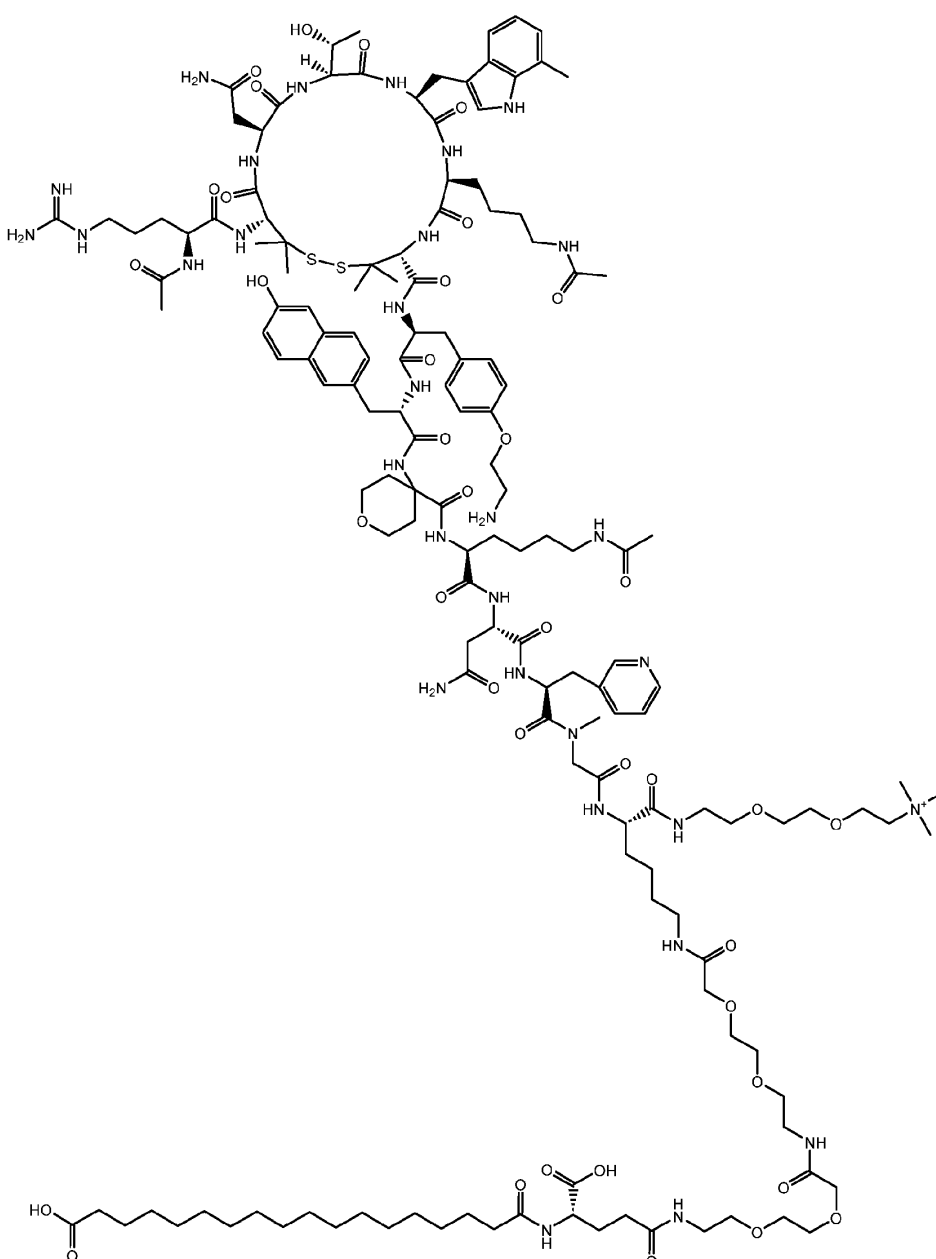
218

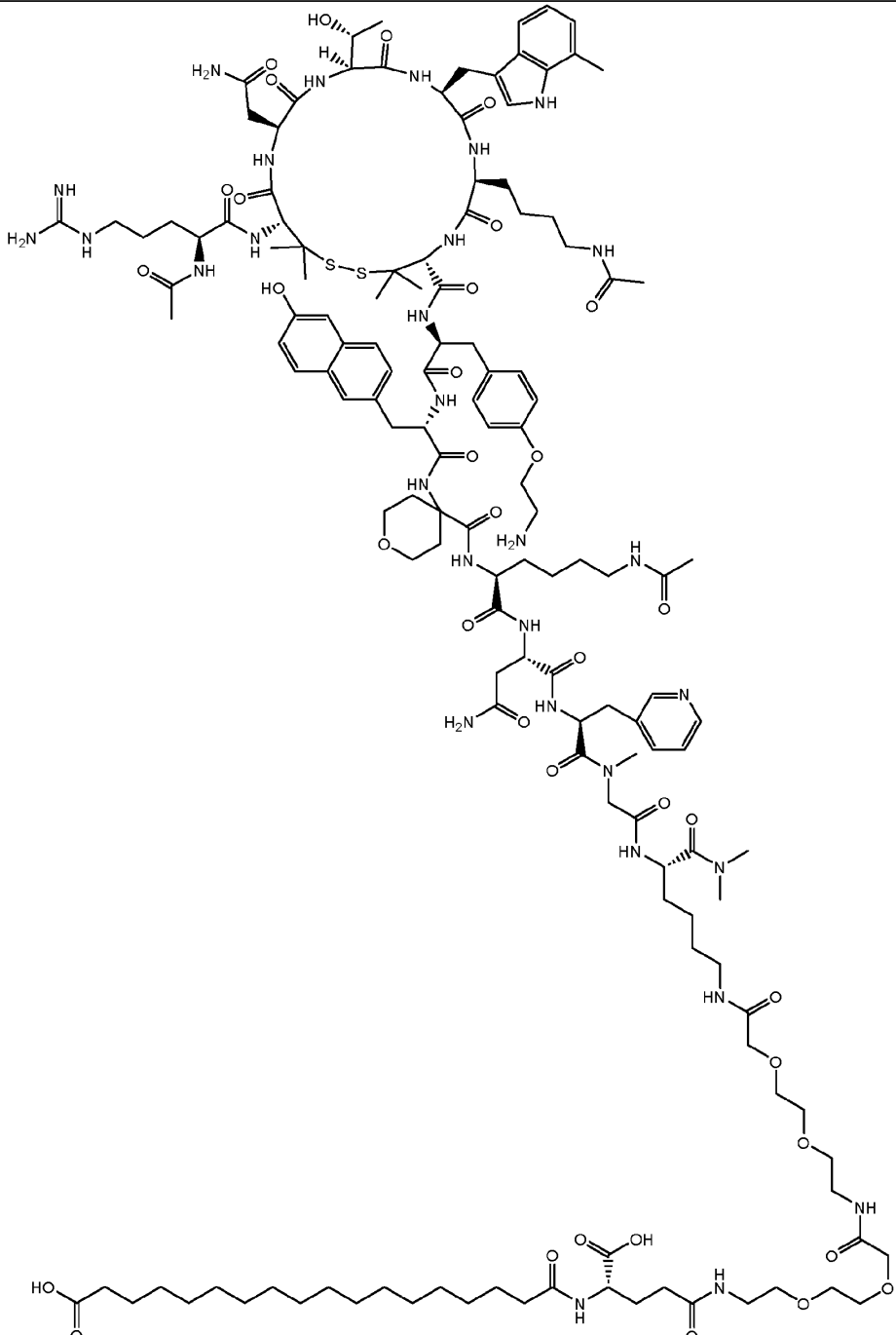


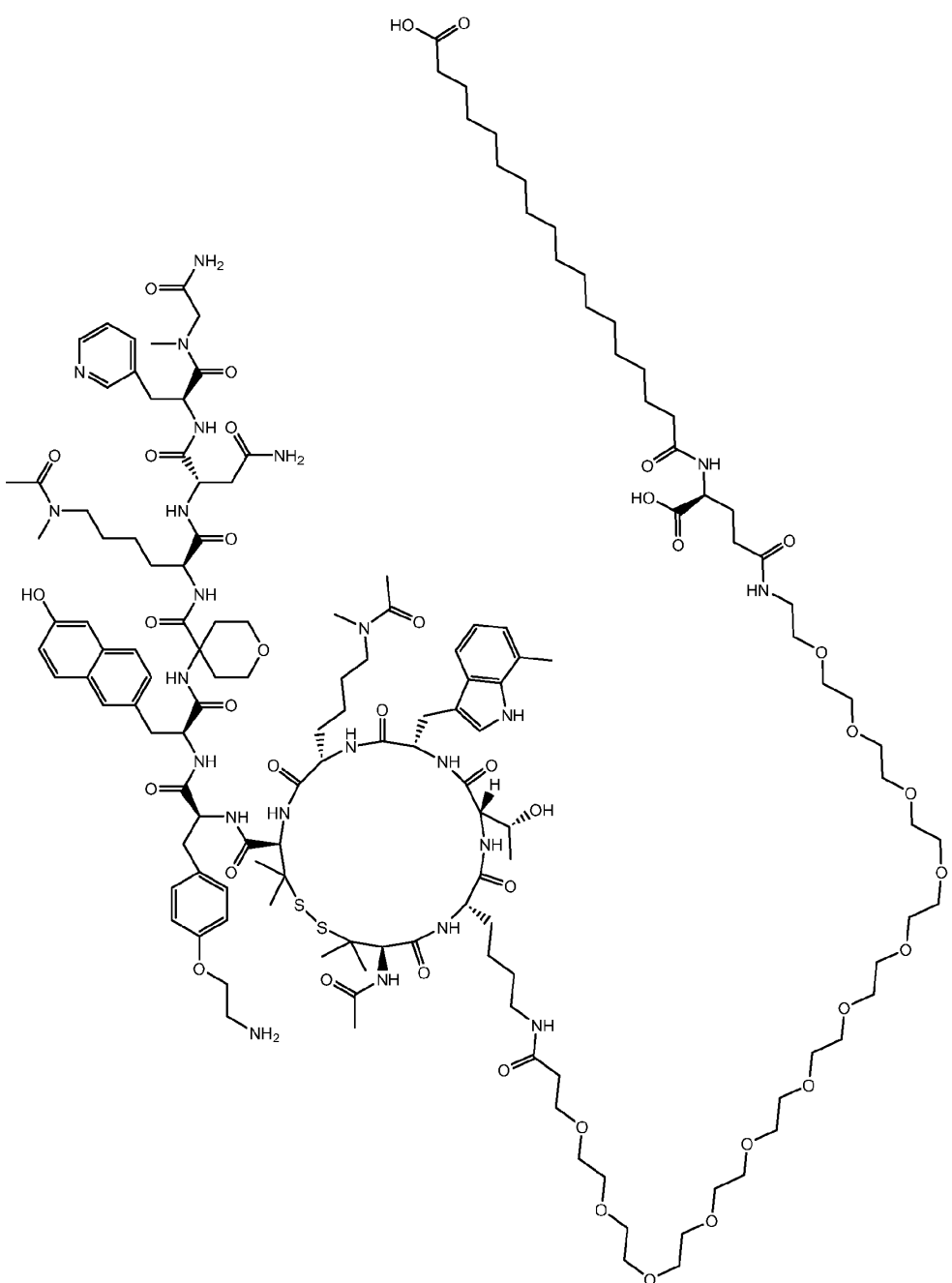
MeCO-R-Pen(3)-N-T-7MeW-K(Ac)-Pen(3)-AEF-6OH2NaI-THP-E-N-3Pya-Sar-K(PEG2PEG2gEC18OH)-CON(Me)2

SEQ ID NO	Structure
219	 MeCO-R-Pen(3)-N-T-7MeW-K(Ac)-Pen(3)-AEF-6OH2Nal-THP-K(Ac)-N-3Pya-Sar-CON(Me)2

SEQ ID NO	Structure
220	 MeCO-R-Pen(3)-N-T-7MeW-K(Ac)-Pen(3)-AEF-6OH2NaI-THP-K(Ac)-N-3Pya-Sar-CONH(PEG3a)

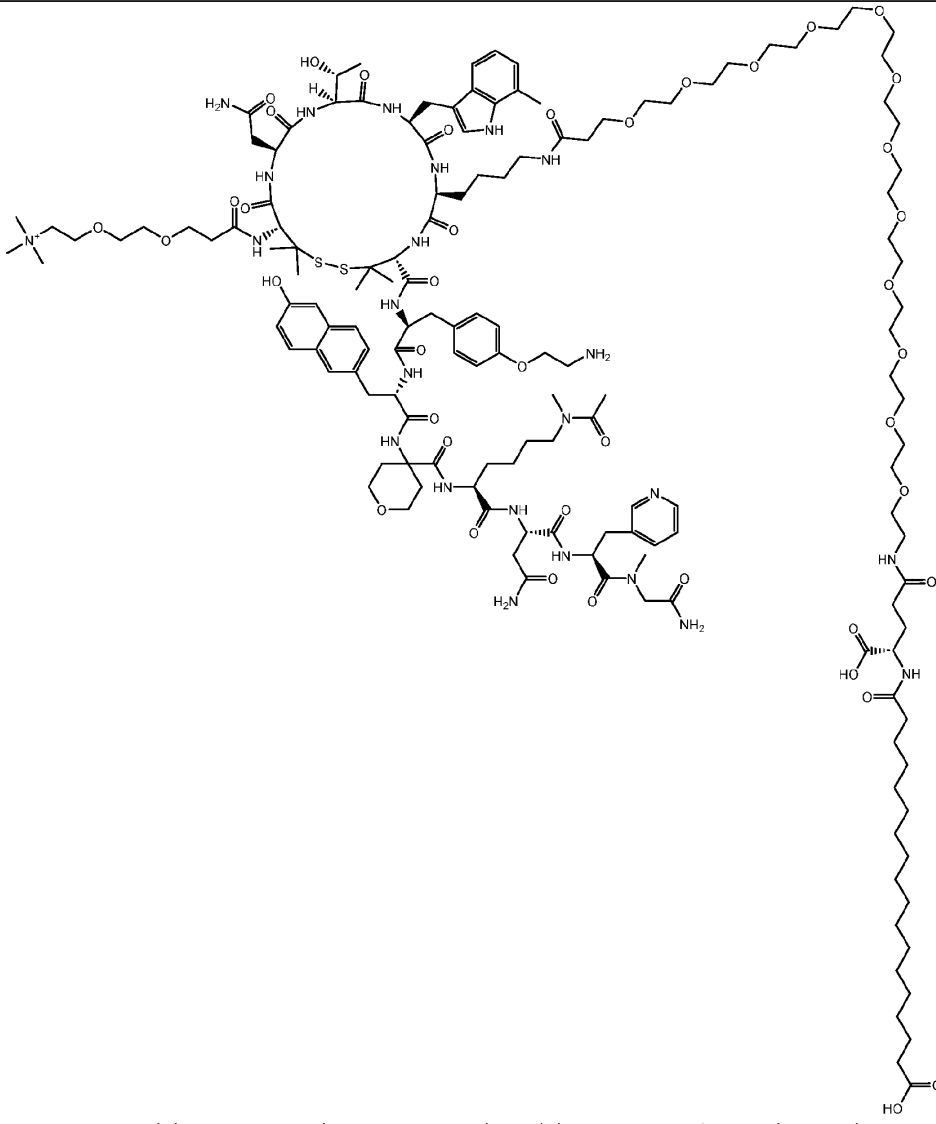
SEQ ID NO	Structure
221	 MeCO-R-Pen(3)-N-T-7MeW-K(Ac)-Pen(3)-AEF-6OH2NaI-THP-K(Ac)-N-3PyA-Sar-K(PEG2PEG2gEC18OH)-CONH(PEG3a)

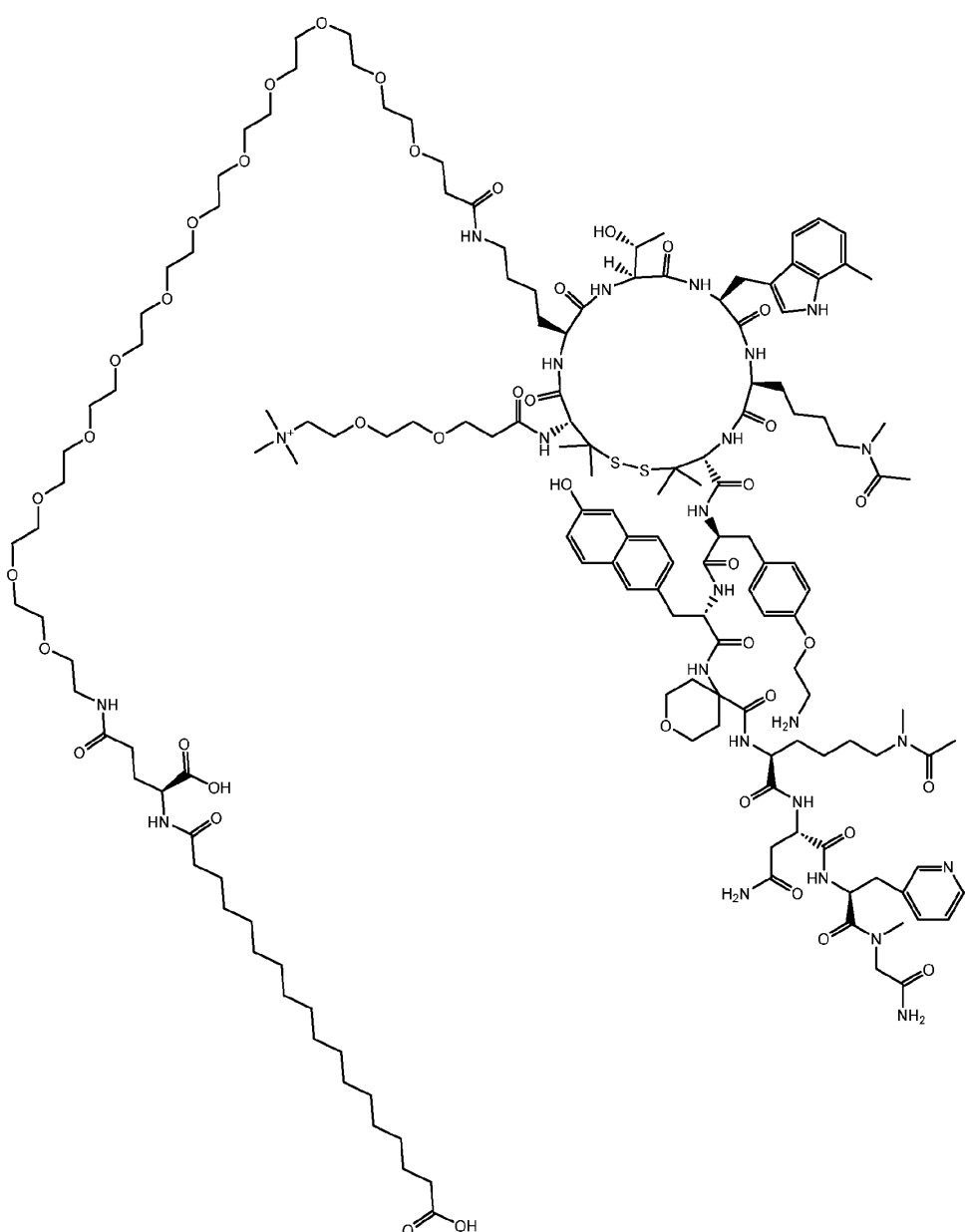
SEQ ID NO	Structure
222	 MeCO-R-Pen(3)-N-T-7MeW-K(Ac)-Pen(3)-AEF-6OH2NaI-THP-K(Ac)-N-3PyA-Sar-K(PEG2PEG2gEC18OH)-CON(Me)2

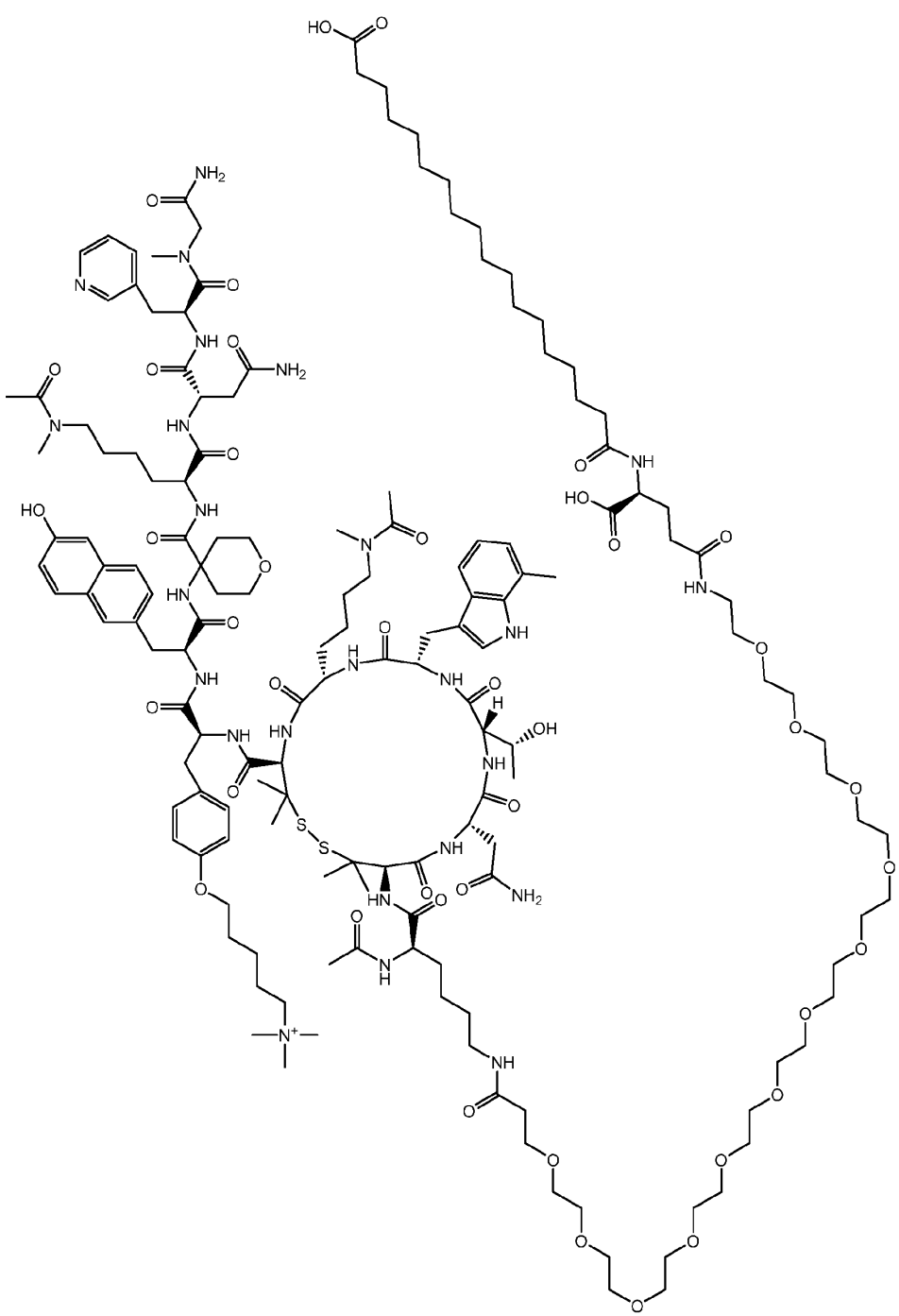
SEQ ID NO	Structure
223	 The chemical structure is a large, complex molecule, likely a peptide or protein derivative. It features a central cyclic core, possibly a macrocycle, with various side chains and functional groups. Key features include: - A long, flexible PEG chain (polyethylene glycol) extending from the right side of the structure. - Aromatic rings, including a pyridine ring and a phenol ring. - Amide groups and carboxylic acid groups. - A central cyclic core with a sulfur atom (S) and a nitrogen atom (N) in the ring. - Various side chains, including a long alkyl chain, a branched chain, and a chain with a hydroxyl group. MeCO-Pen(3)-K(PEG12gEC18OH)-T-7MeW-K(NMeAc)-Pen(3)-AEF-6OH2Nal-THP-K(NMeAc)-N-3Pya-Sar-CONH2

The chemical structure depicts a large macrocyclic molecule. At its core is a 18-membered ring containing several amide and thioether linkages. Attached to this central ring are various side chains, including a long poly(ethylene glycol) (PEG) chain, a long alkyl chain, a long chain with a terminal amine, and a long chain with a terminal carboxylic acid. The molecule also features a central amide group, a long chain with a terminal amine, and a long chain with a terminal carboxylic acid. The structure is highly complex, with multiple functional groups and a large overall size.

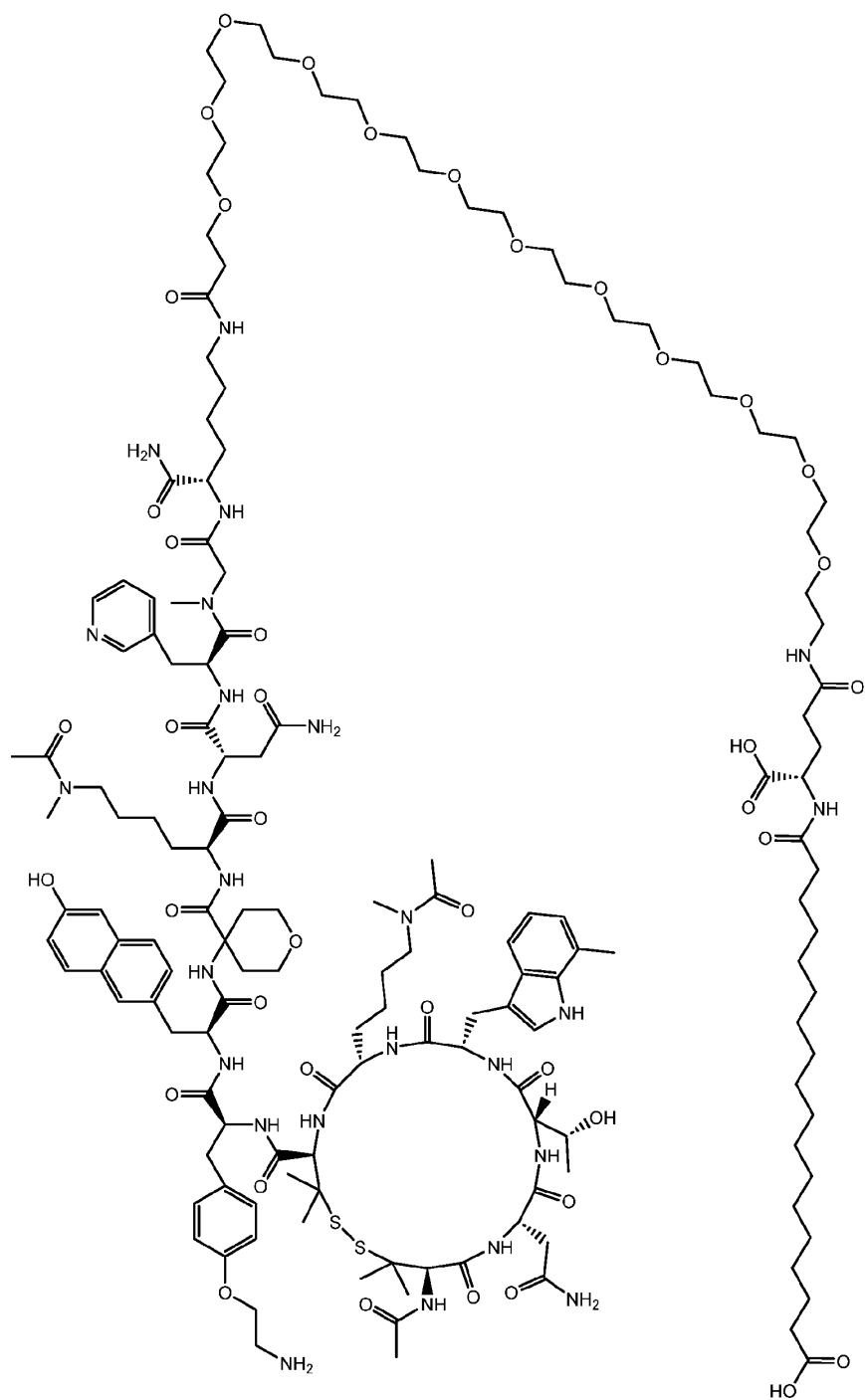
MeCO-Pen(3)-N-T-7MeW-K(NMeAc)-Pen(3)-TMAPF-6OH2NaI-THP-K(NMeAc)-N-3PyA-Sar-K(PEG12gEC18OH)-CONH2

SEQ ID NO	Structure
225	 cPEG3aCO-Pen(3)-N-T-7MeW-K(PEG12gEC18OH)-Pen(3)-AEF-6OH2Nal-THP-K(NMeAc)-N-3Py-Sar-CONH2

SEQ ID NO	Structure
226	 cPEG3aCO-Pen(3)-K(PEG12gEC18OH)-T-7MeW-K(NMeAc)-Pen(3)-AEF-6OH2NaI-THP-K(NMeAc)-N-3Py-Sar-CONH2

SEQ ID NO	Structure
227	 MeCO-k(PEG12gEC18OH)-Pen(3)-N-T-7MeW-K(NMeAc)-Pen(3)-TMAPF-6OH2NaI-THP-K(NMeAc)-N-3PyA-Sar-CONH2

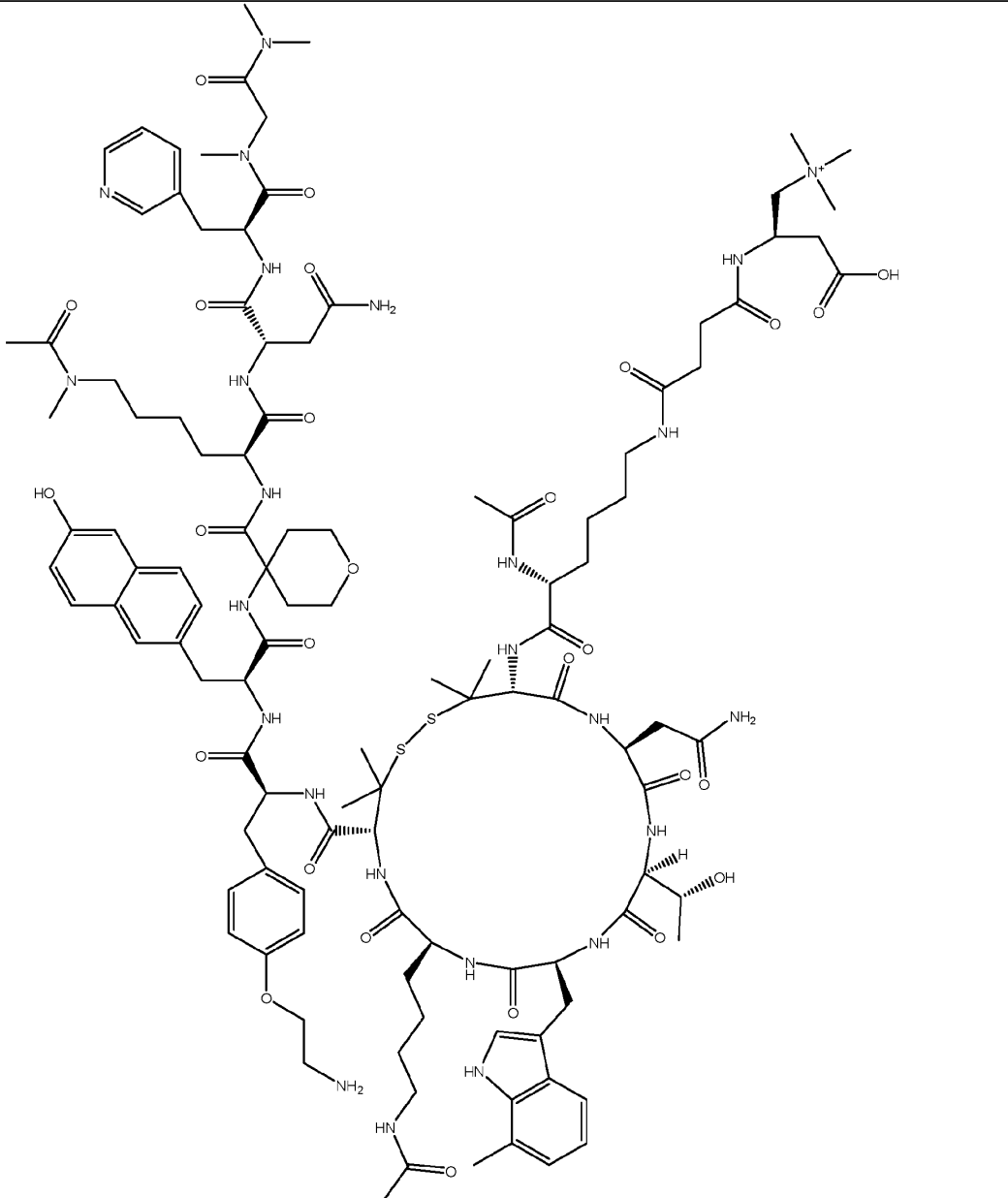
228

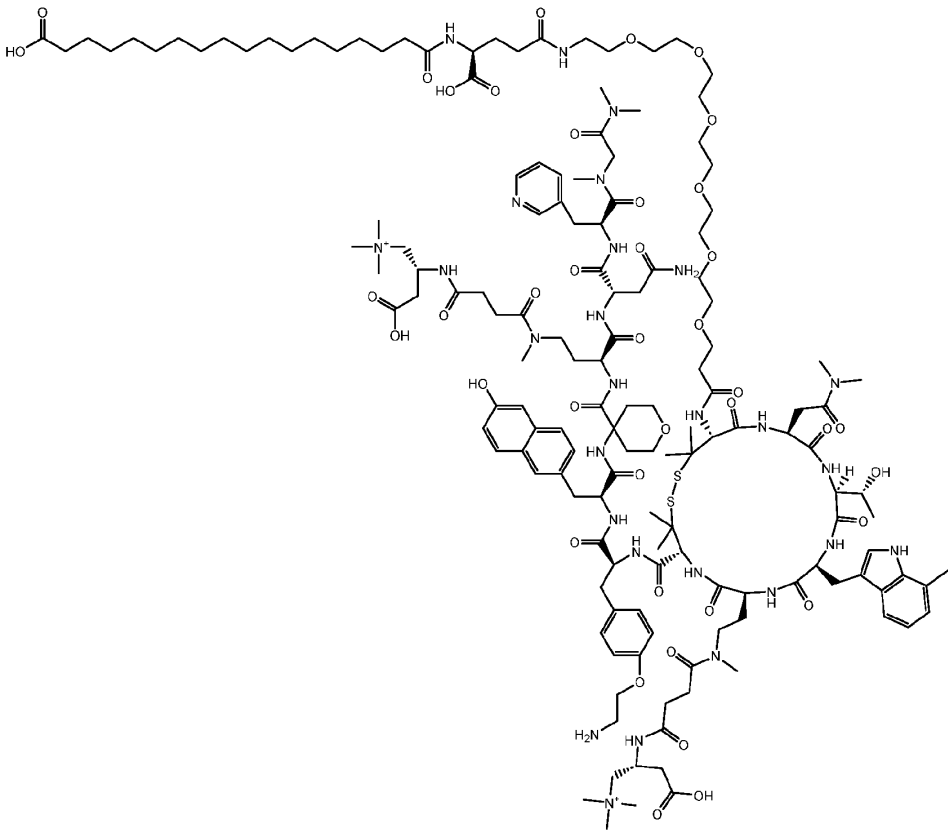


MeCO-Pen(3)-N-T-7MeW-K(NMeAc)-Pen(3)-AEF-6OH2Nal-THP-K(NMeAc)-N-3Pya-Sar-K(PEG12gEC18OH)-CONH2

The image displays a complex chemical structure of a macrocyclic peptide, likely a cyclodextrin derivative. The structure is characterized by a long, winding chain of amino acids connected by amide bonds, forming a large, irregular ring. The chain includes various functional groups, such as hydroxyl (HO) and amine (NH₂) groups, and is decorated with several side chains, including a long alkyl chain, a pyridine ring, a naphthalene ring, and a thiophene ring. The structure is highly detailed, showing the stereochemistry of the amino acids and the specific functional groups attached to the backbone. The overall shape is elongated and somewhat U-shaped, with the chain looping back on itself to form the macrocycle.

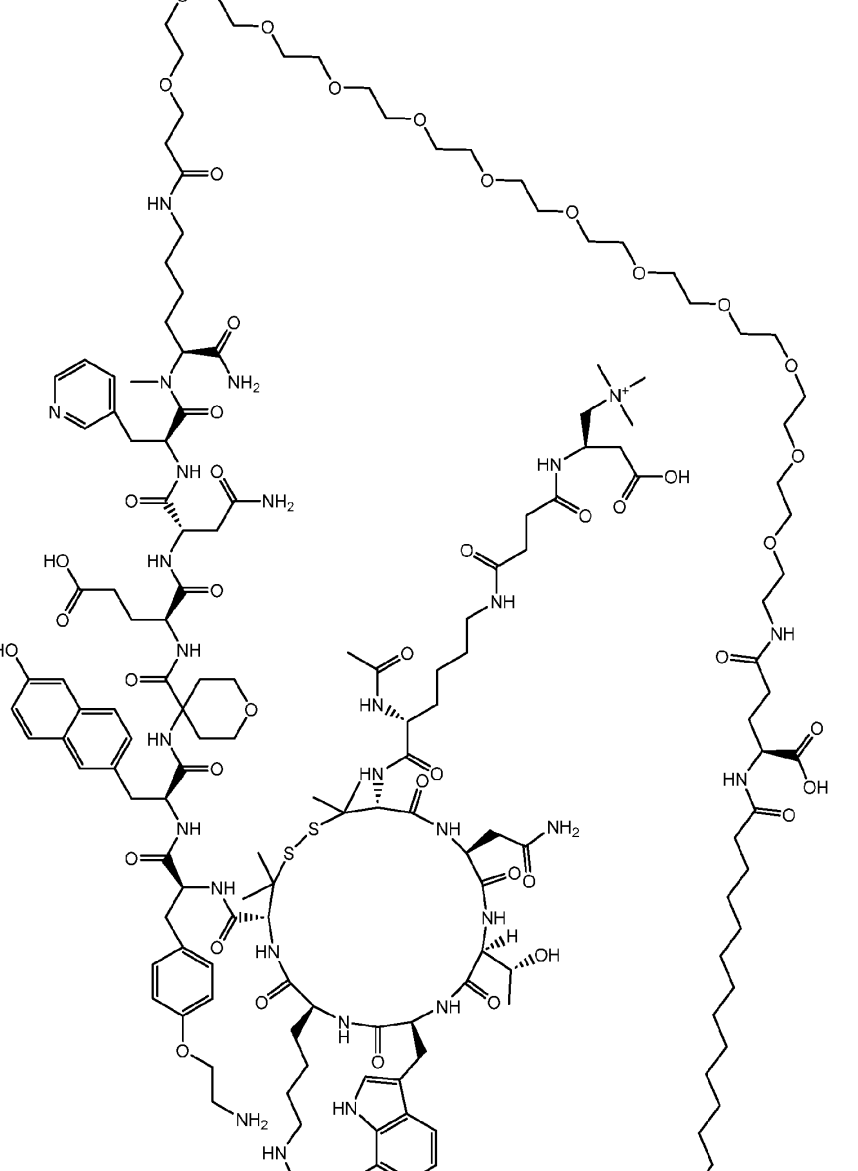
MeCO-k(PEG12gEC18OH)-Pen(3)-N-T-7MeW-K(Ac)-Pen(3)-AEF-6OH2Nal-THP-E-N-3Pya-Sar-CONH2

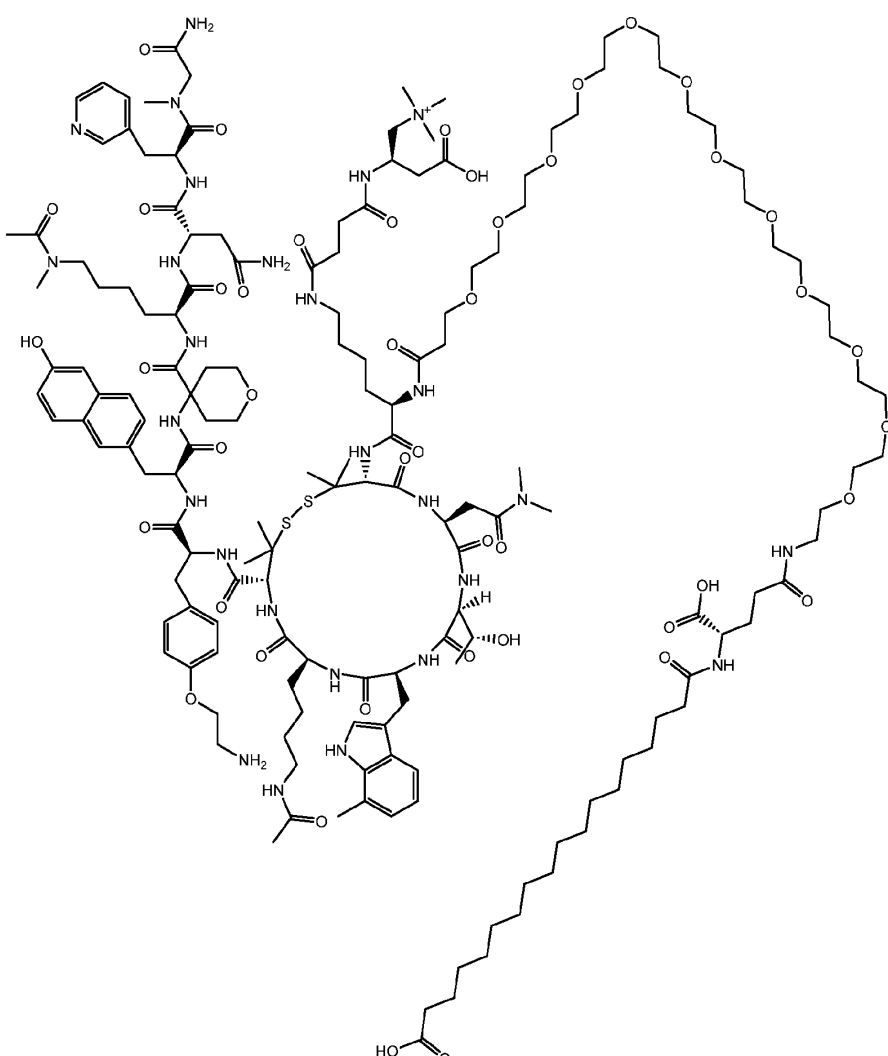
SEQ ID NO	Structure
230	 The chemical structure depicts a large cyclic peptide with a central macrocyclic ring. The ring is composed of several amino acid residues, including Lysine, Arginine, and others, which are linked by amide bonds. The side chains of these residues are highly diverse and complex. Notable features include a long, flexible side chain with a terminal quaternary ammonium group (N⁺), a side chain containing a naphthalene ring system, and another side chain with a pyridine ring. The structure also shows various functional groups such as carboxylic acids, amides, and hydroxyl groups. The overall architecture is highly branched and intricate, typical of a large, specialized peptide molecule. MeCO-k(d)-Pen(3)-N-T-7MeW-K(Ac)-Pen(3)-AEF-6OH2Nal-THP-K(NMeAc)-N-3Pya-Sar-CON(Me)₂

SEQ ID NO	Structure
231	 HOC18gEPEG6CO-Pen(3)-N(N(Me)2)-T-7MeW-Dab(NMecarn)-Pen(3)-AEF-6OH2Nal-THP-Dab(NMecarn)-N-3Py-Sar-CON(Me)2

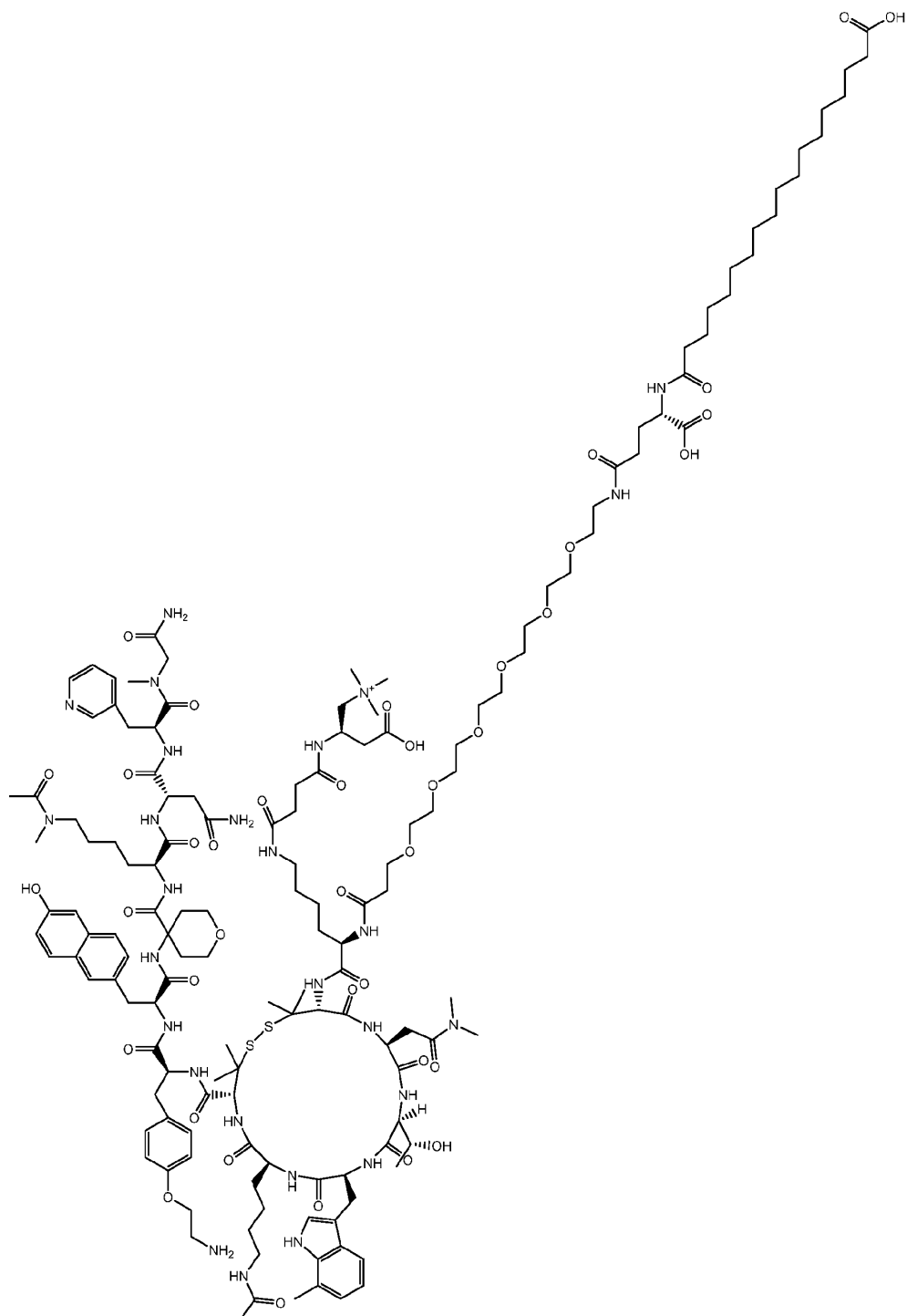
The chemical structure shows a large macrocyclic peptide. The central macrocycle is a 12-membered ring with a sulfur atom and a carbonyl group. It is substituted with various side chains, including a long fatty acid chain (18:1 n-7), a pyridine ring, a fluorophore (4-fluorophenyl), a fluorophore (4-fluorophenyl), and a fluorophore (4-fluorophenyl). The structure also features a long fatty acid chain (18:1 n-7) and a pyridine ring. The side chains are connected to the macrocycle via amide bonds. The structure is highly complex and contains many functional groups, including amide, ester, and ether linkages. The overall structure is a large, multi-functional molecule with a central macrocycle and various side chains.

HOC20gEPEG2PEG2CO-Pen(3)-N(NMe)₂-T-7MeW-Dab(NMecarn)-Pen(3)-AEF-6OH2Nal-THP-Dab(NMecarn)-N-3Py-Sar-CON(Me)₂

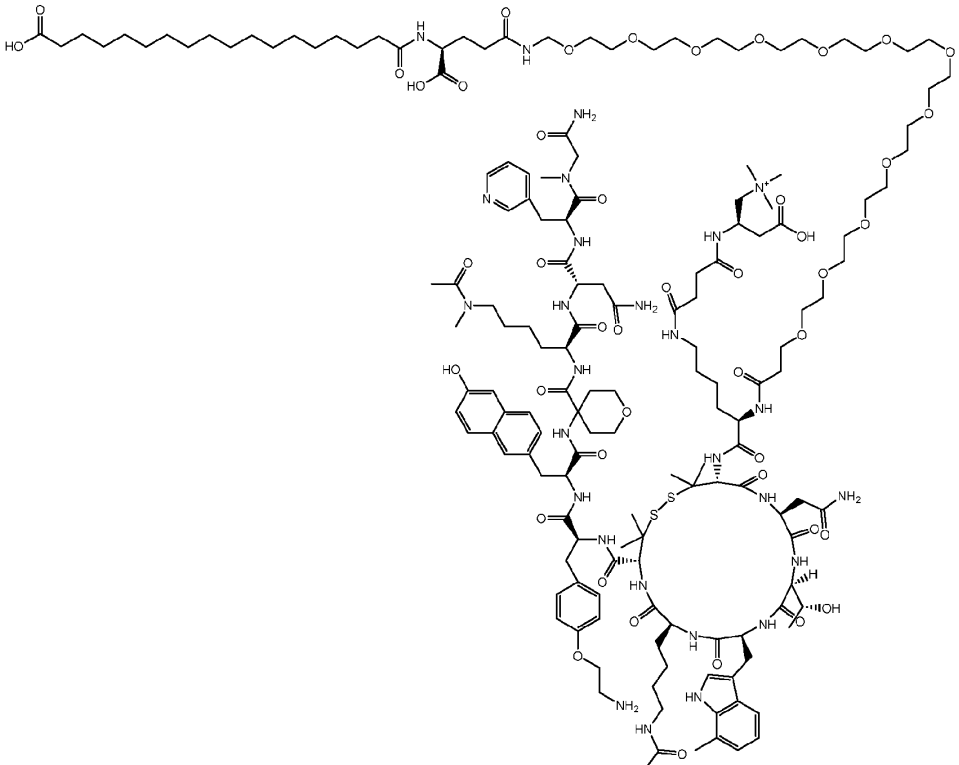
SEQ ID NO	Structure
233	 MeCO-k(d)-Pen(3)-N-T-7MeW-K(Ac)-Pen(3)-AEF-6OH2Nal-THP-E-N-3Pya-NMeK(PEG12gEC18OH)-CONH2

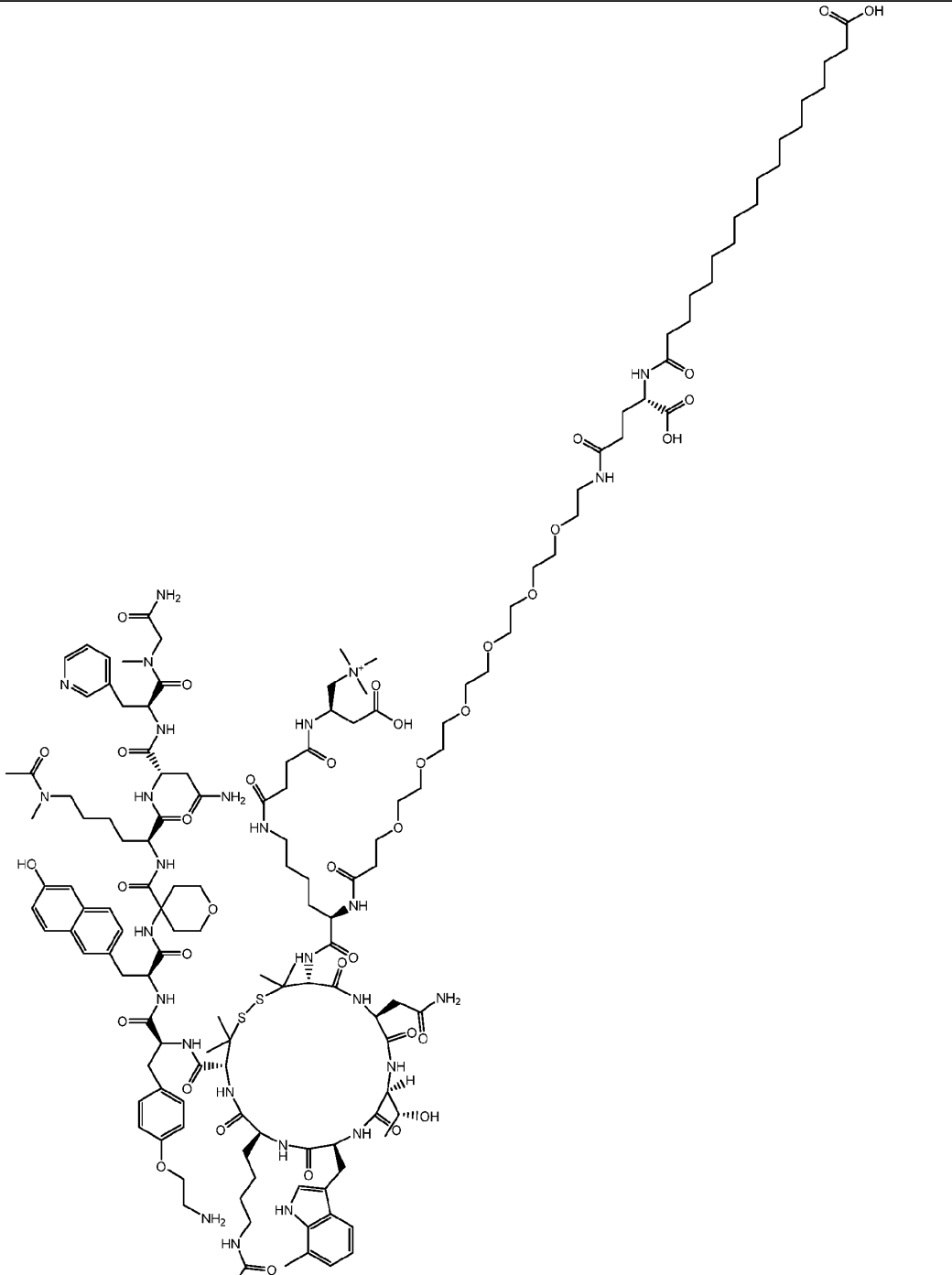
SEQ ID NO	Structure
234	 HOC18gEPEG12CO-k(d)-Pen(3)-N(N(Me)2)-T-7MeW-K(Ac)-Pen(3)-AEF-6OH2Nal-THP-K(NMeAc)-N-3Pya-Sar-CONH2

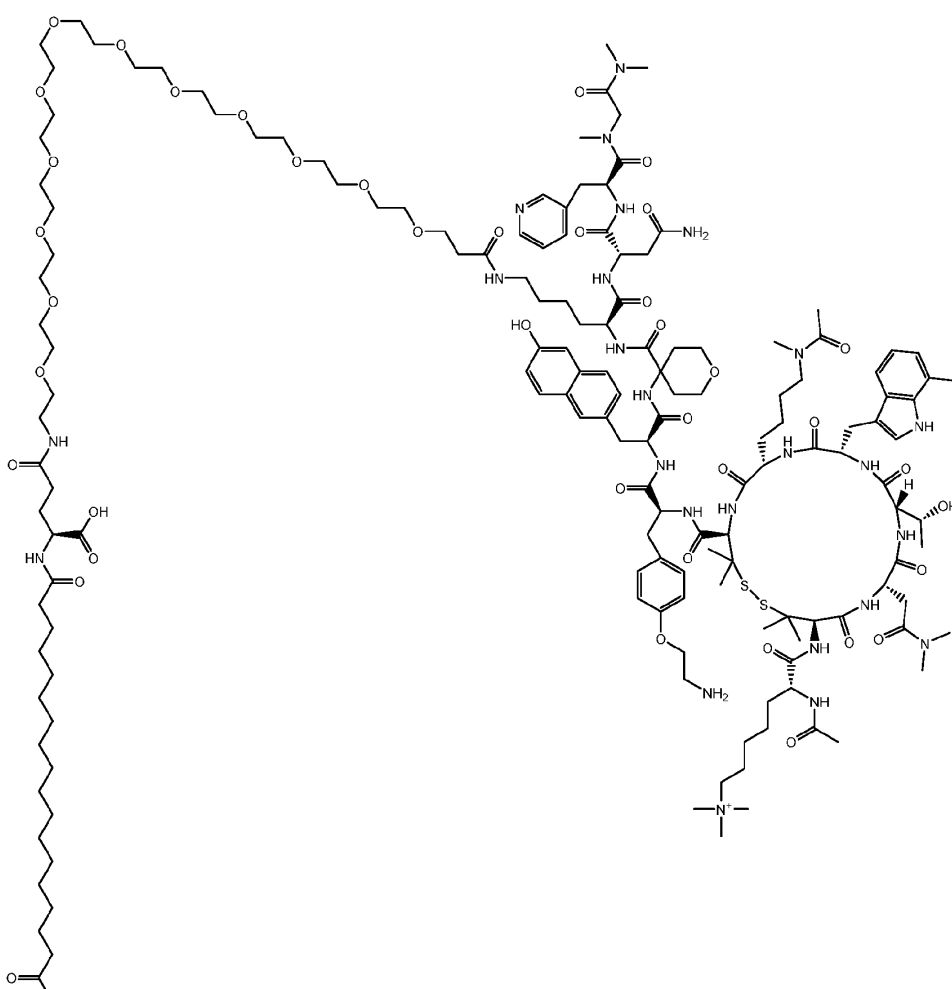
235

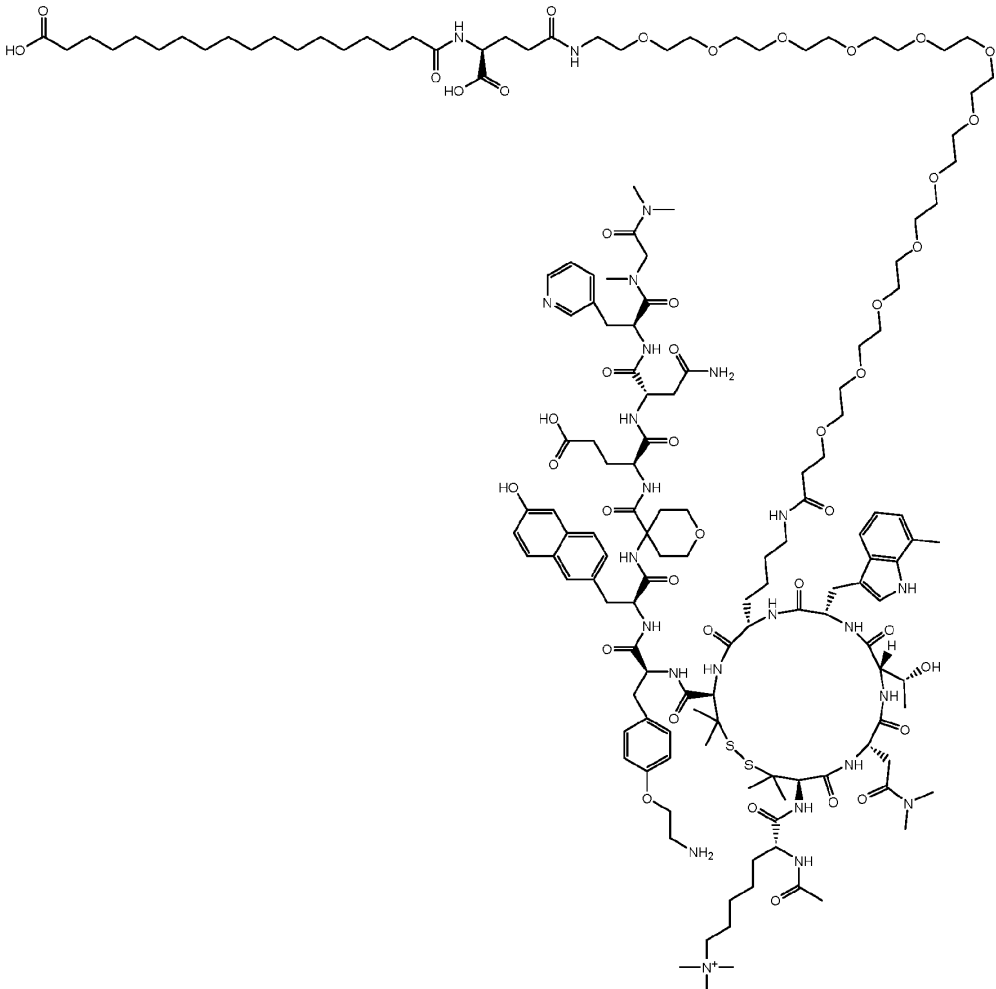


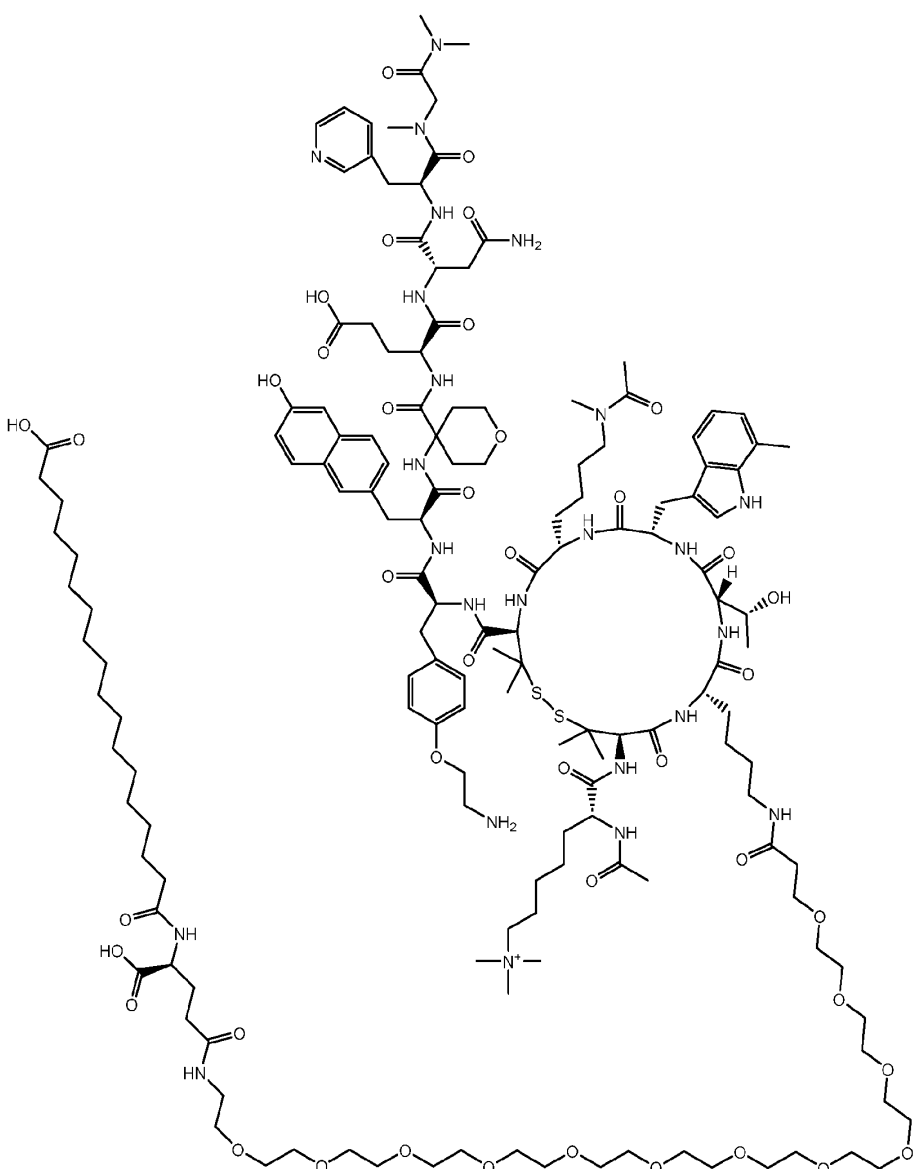
HOC18gEPEG6CO-k(d)-Pen(3)-N(N(Me)2)-T-7MeW-K(Ac)-Pen(3)-AEF-6OH2Nal-THP-K(NMeAc)-N-3Pya-Sar-CONH2

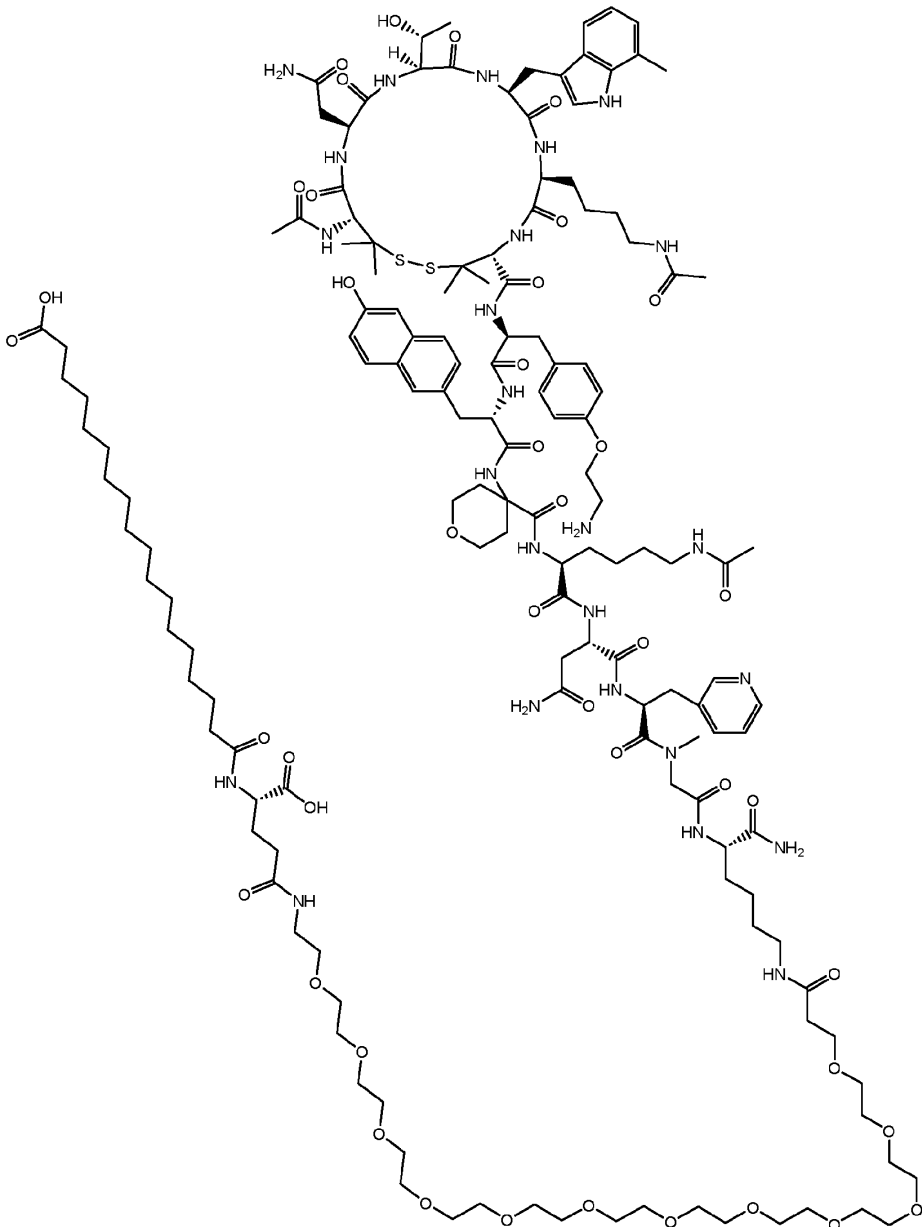
SEQ ID NO	Structure
236	 HOC18gEPEG12CO-k(d)-Pen(3)-N-T-7MeW-K(Ac)-Pen(3)-AEF-6OH2Nal-THP-K(NMeAc)-N-3Pya-Sar-CONH2

SEQ ID NO	Structure
237	 The chemical structure is a highly complex molecule, likely a peptide or protein derivative. It features a central macrocyclic core with various side chains. Key features include a long alkyl chain (HO-C(=O)-(CH₂)₁₈-) attached to a side chain, a pyridine ring, a carboxylic acid group, and a central macrocyclic core with a disulfide bridge. The molecule is labeled with a sequence: HOC18gEPEG6CO-k(d)-Pen(3)-N-T-7MeW-K(Ac)-Pen(3)-AEF-6OH2NaI-THP-K(NMeAc)-N-3PyA-Sar-CONH2.

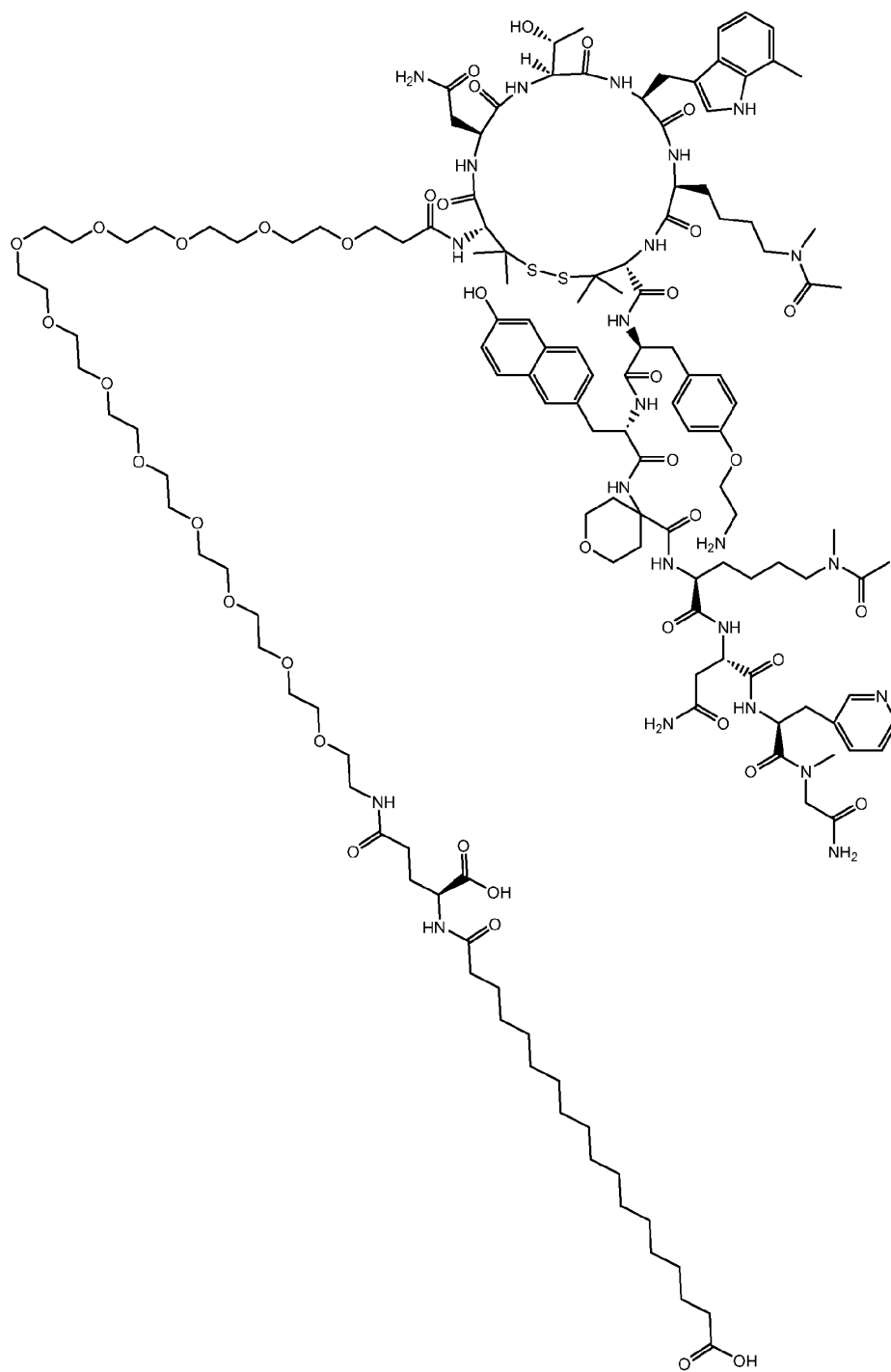
SEQ ID NO	Structure
238	 MeCO-hK(Me)3-Pen(3)-N(N(Me)2)-T-7MeW-K(NMeAc)-Pen(3)-AEF-6OH2Nal-THP-K(PEG12gEC18OH)-N-3Pyra-Sar-CON(Me)2

SEQ ID NO	Structure
239	 MeCO-hk(Me)3-Pen(3)-N(N(Me)2)-T-7MeW-K(PEG12gEC18OH)-Pen(3)-AEF-6OH2Nal-THP-E-N-3Py-Sar-CON(Me)2

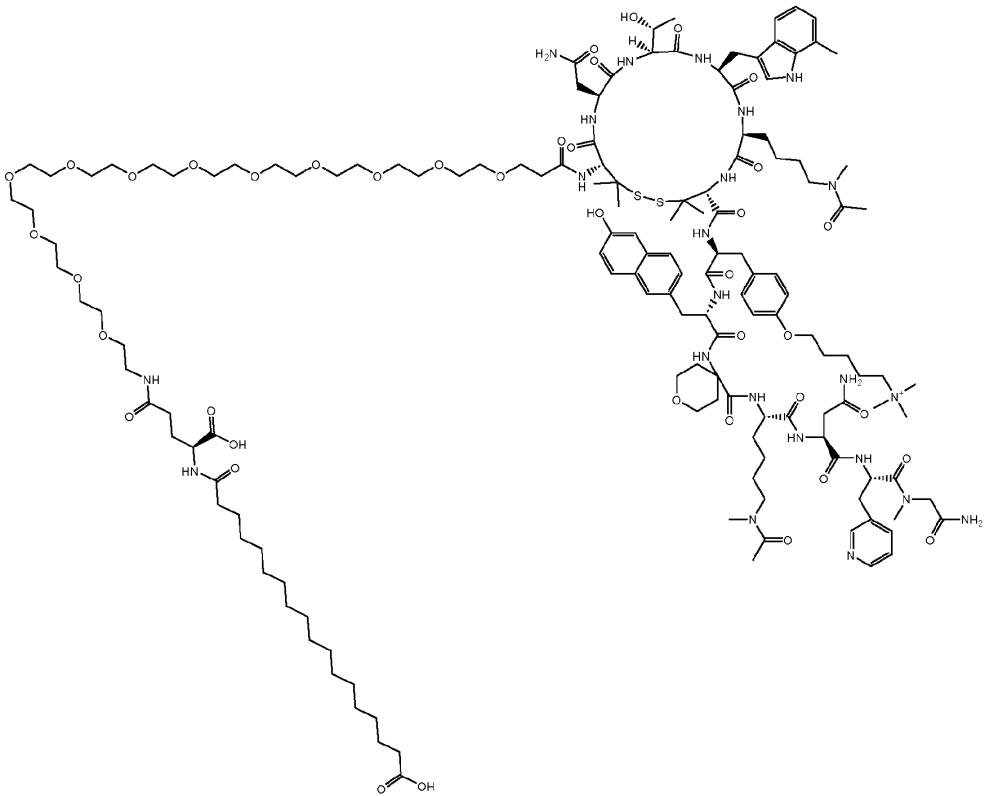
SEQ ID NO	Structure
240	 MeCO-hk(Me)₃-Pen(3)-K(PEG12gEC18OH)-T-7MeW-K(NMeAc)-Pen(3)-AEF-6OH₂Nal-THP-E-N-3Py-Sar-CON(Me)₂

SEQ ID NO	Structure
241	 MeCO-Pen(3)-N-T-7MeW-K(Ac)-Pen(3)-AEF-6OH2Nal-THP-K(Ac)-N-3Pya-Sar-K(PEG12gEC18OH)-CONH2

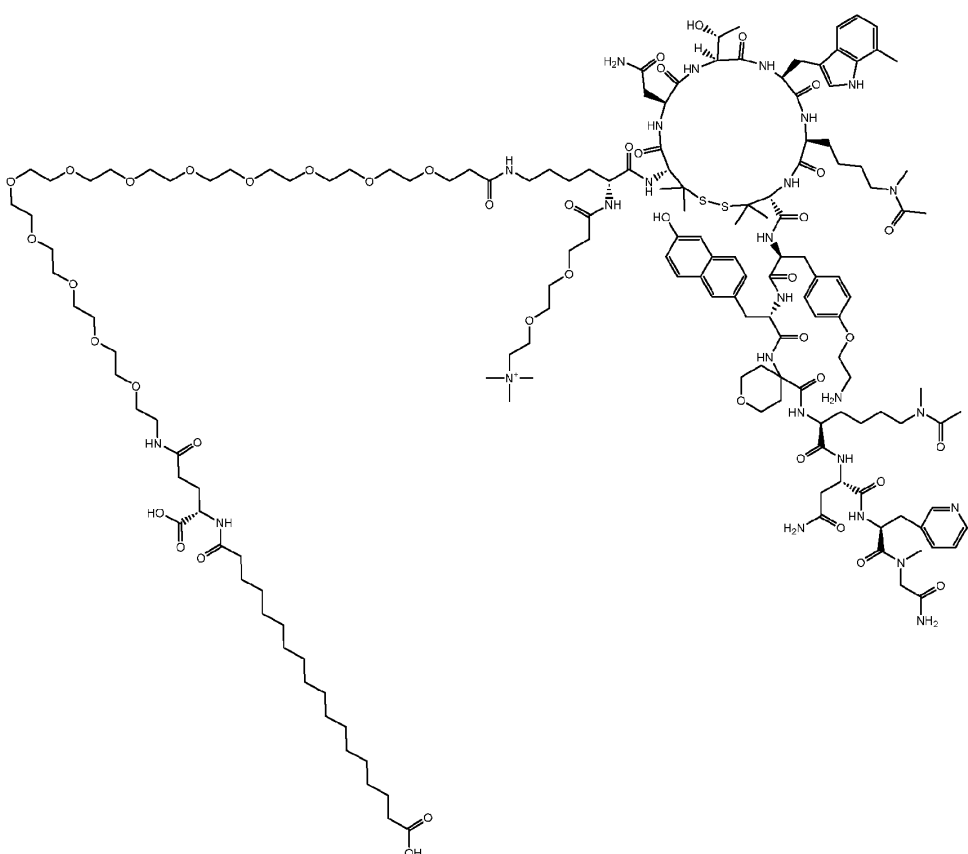
242

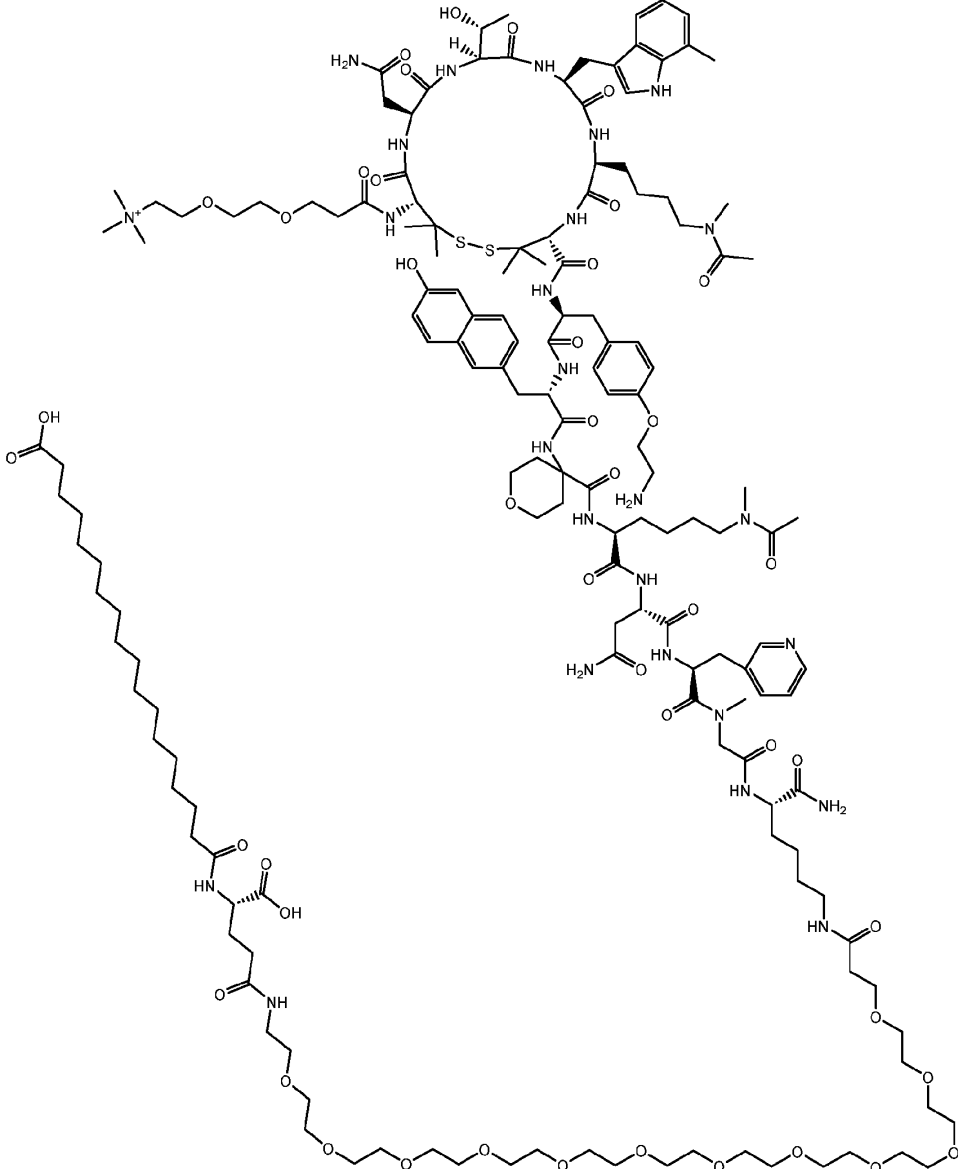


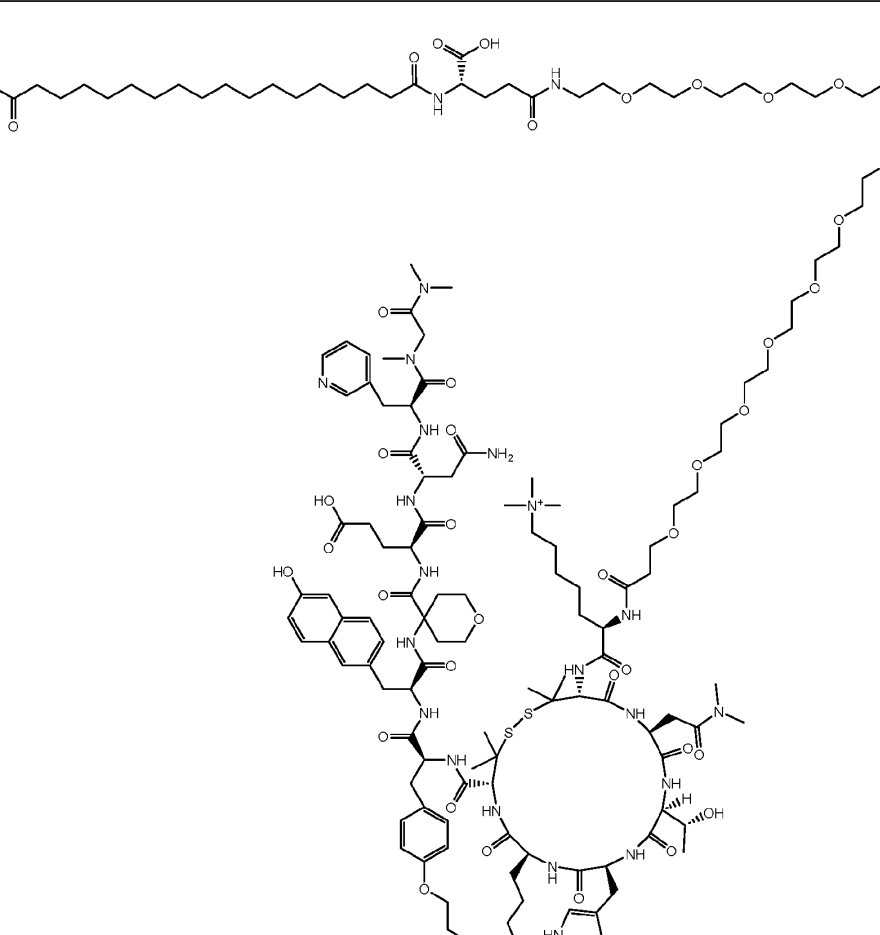
HOC18gEPEG12CO-Pen(3)-N-T-7MeW-K(NMeAc)-Pen(3)-AEF-6OH2Nal-THP-K(NMeAc)-N-3Pya-Sar-CONH₂

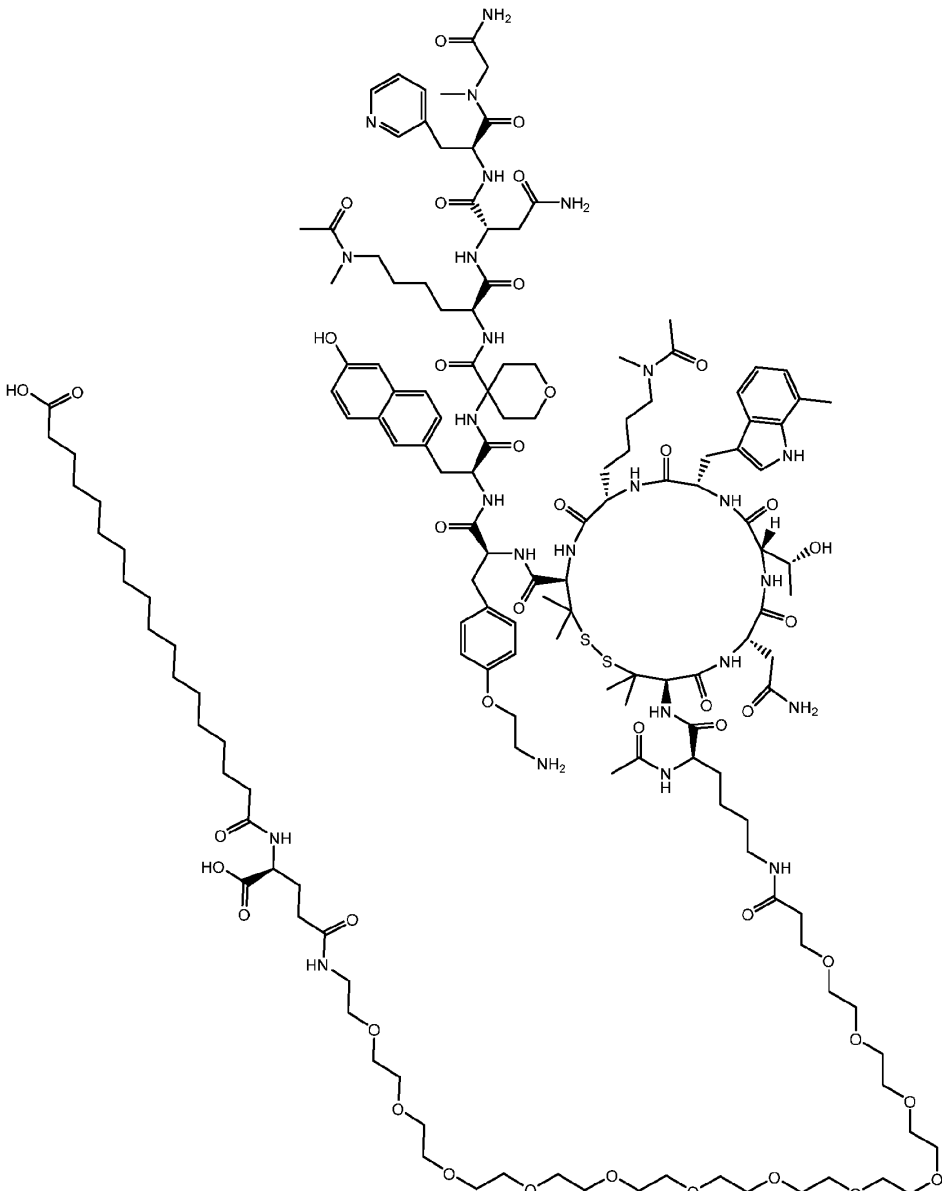
SEQ ID NO	Structure
243	 The chemical structure represents a large cyclic peptide. The backbone is a 12-residue ring. The side chains are as follows, starting from the top and moving clockwise: 1. A long PEG chain (18 units) terminated with a carboxylic acid group. 2. A long alkyl chain (18 units) terminated with a carboxylic acid group. 3. A complex aromatic side chain containing a phenyl ring, a thiazole ring, and a pyridine ring. 4. A side chain containing a thiazole ring and a pyridine ring. 5. A side chain containing a thiazole ring and a pyridine ring. 6. A side chain containing a thiazole ring and a pyridine ring. 7. A side chain containing a thiazole ring and a pyridine ring. 8. A side chain containing a thiazole ring and a pyridine ring. 9. A side chain containing a thiazole ring and a pyridine ring. 10. A side chain containing a thiazole ring and a pyridine ring. 11. A side chain containing a thiazole ring and a pyridine ring. 12. A side chain containing a thiazole ring and a pyridine ring. HOC18gEPEG12CO-Pen(3)-N-T-7MeW-K(NMeAc)-Pen(3)-TMAPF-6OH2Nal-THP-K(NMeAc)-N-3Pya-Sar-CONH2

SEQ ID NO	Structure
244	MeCO-r-Pen(3)-N-T-7MeW-K(Ac)-Pen(3)-AEF-6OH2Nal-THP-E-N-3Pyra-Sar-K(PEG12gEC18OH)-CONH2

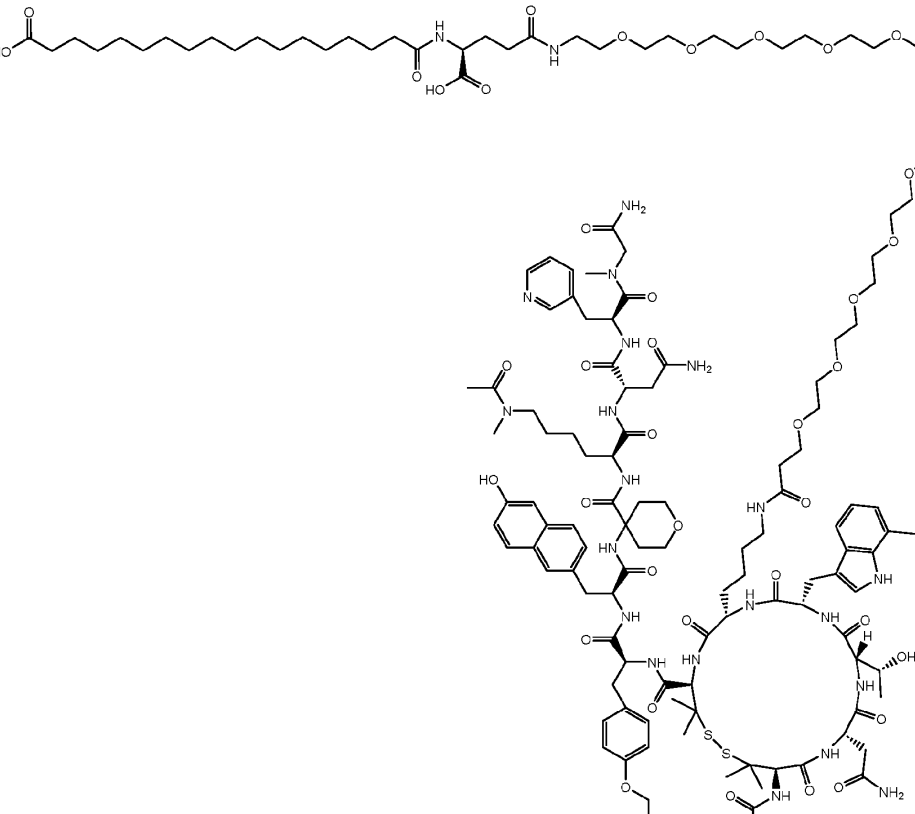
SEQ ID NO	Structure
245	 cPEG3aCO-k(PEG12gEC18OH)-Pen(3)-N-T-7MeW-K(NMeAc)-Pen(3)-AEF-6OH2NaI-THP-K(NMeAc)-N-3Pya-Sar-CONH2

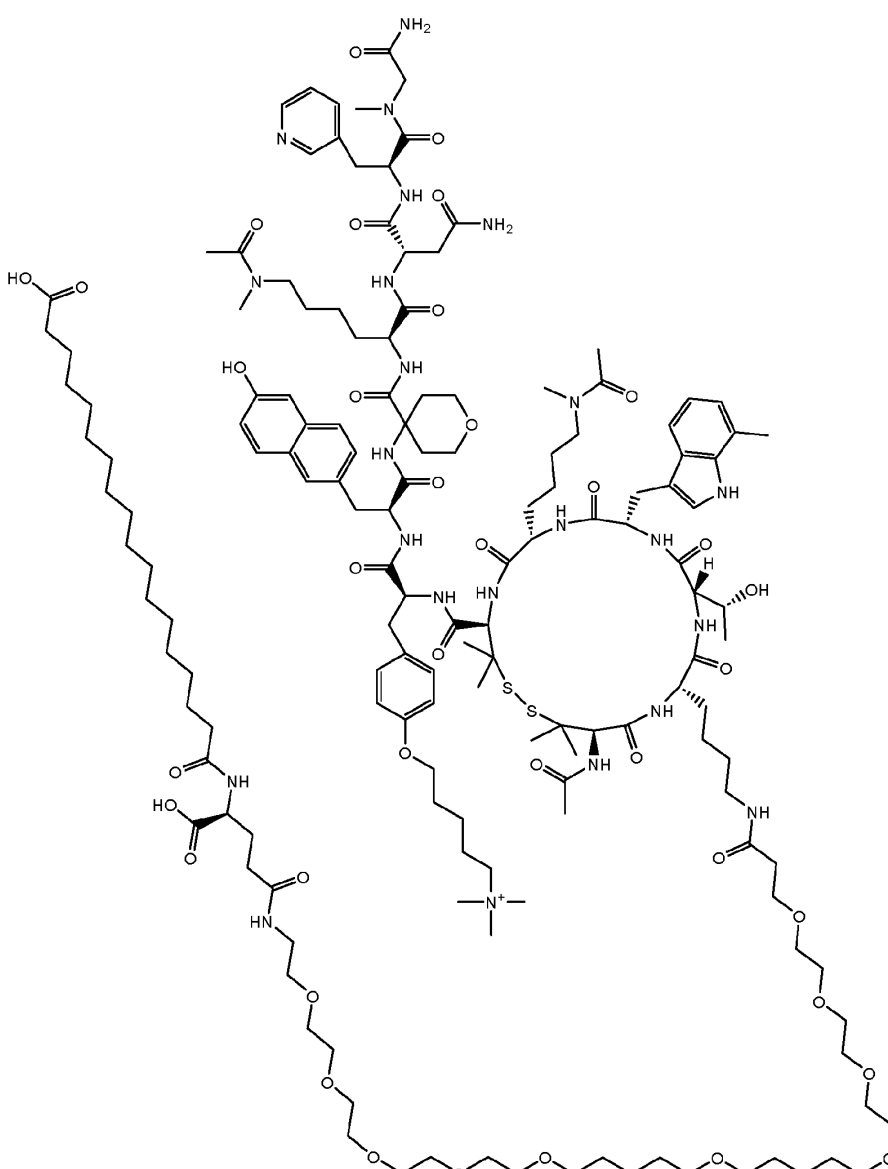
SEQ ID NO	Structure
246	 cPEG3aCO-Pen(3)-N-T-7MeW-K(NMeAc)-Pen(3)-AEF-6OH2Nal-THP-K(NMeAc)-N-3PyA-Sar-K(PEG12gEC18OH)-CONH2

SEQ ID NO	Structure
247	 Chemical structure of a large, complex molecule, likely a peptide or polymer derivative. The structure features a long, flexible chain with multiple amide bonds, a central cyclic structure, and various side chains including a long poly(ethylene glycol) (PEG) chain, a pyridine ring, a naphthalene ring, and a thiazolidine ring. The molecule is highly branched and contains numerous functional groups such as carboxylic acids, amines, and hydroxyl groups.

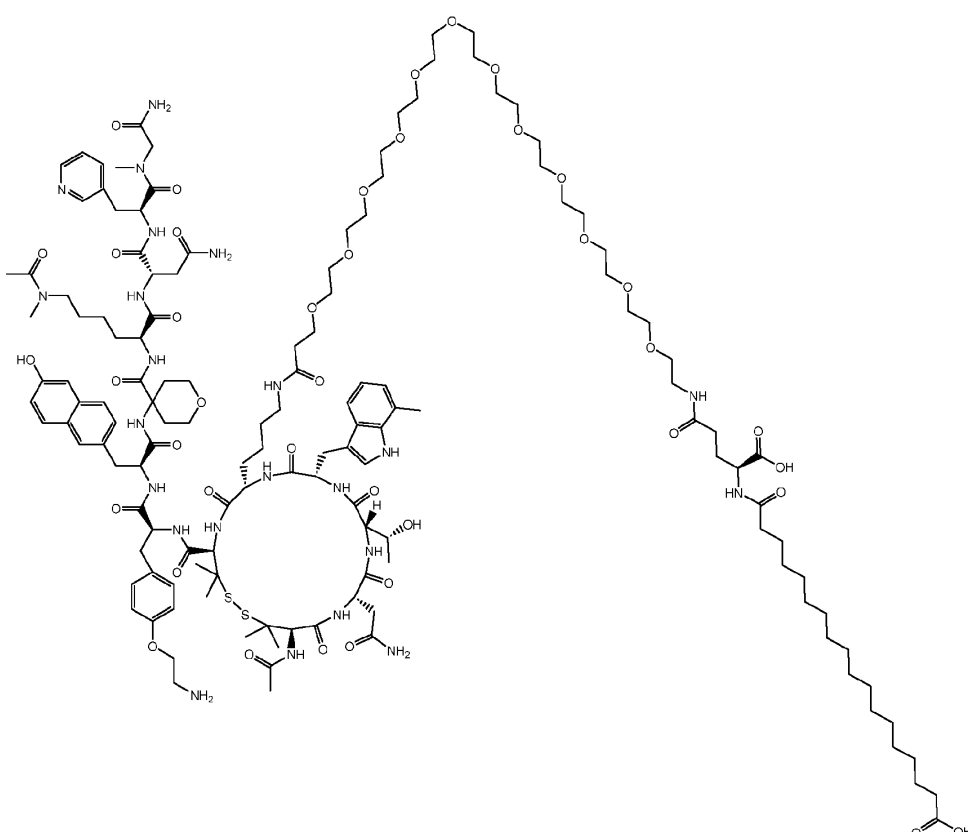
SEQ ID NO	Structure
248	 The chemical structure is a large, complex molecule, likely a peptide or protein derivative. It features a central cyclic core with various side chains. A long PEG chain is attached to the structure, extending from the bottom left towards the center. The molecule includes a thiol group (SH) and a carboxylic acid group (COOH). The structure is highly branched and contains several amide bonds (NH-CO). The side chains include a long alkyl chain, a thiol group, a carboxylic acid group, and a PEG chain. The molecule is highly branched and contains several amide bonds (NH-CO). The side chains include a long alkyl chain, a thiol group, a carboxylic acid group, and a PEG chain. MeCO-k(PEG12gEC18OH)-Pen(3)-N-T-7MeW-K(NMeAc)-Pen(3)-AEF-6OH2NaI-THP-K(NMeAc)-N-3Py-Sar-CONH2

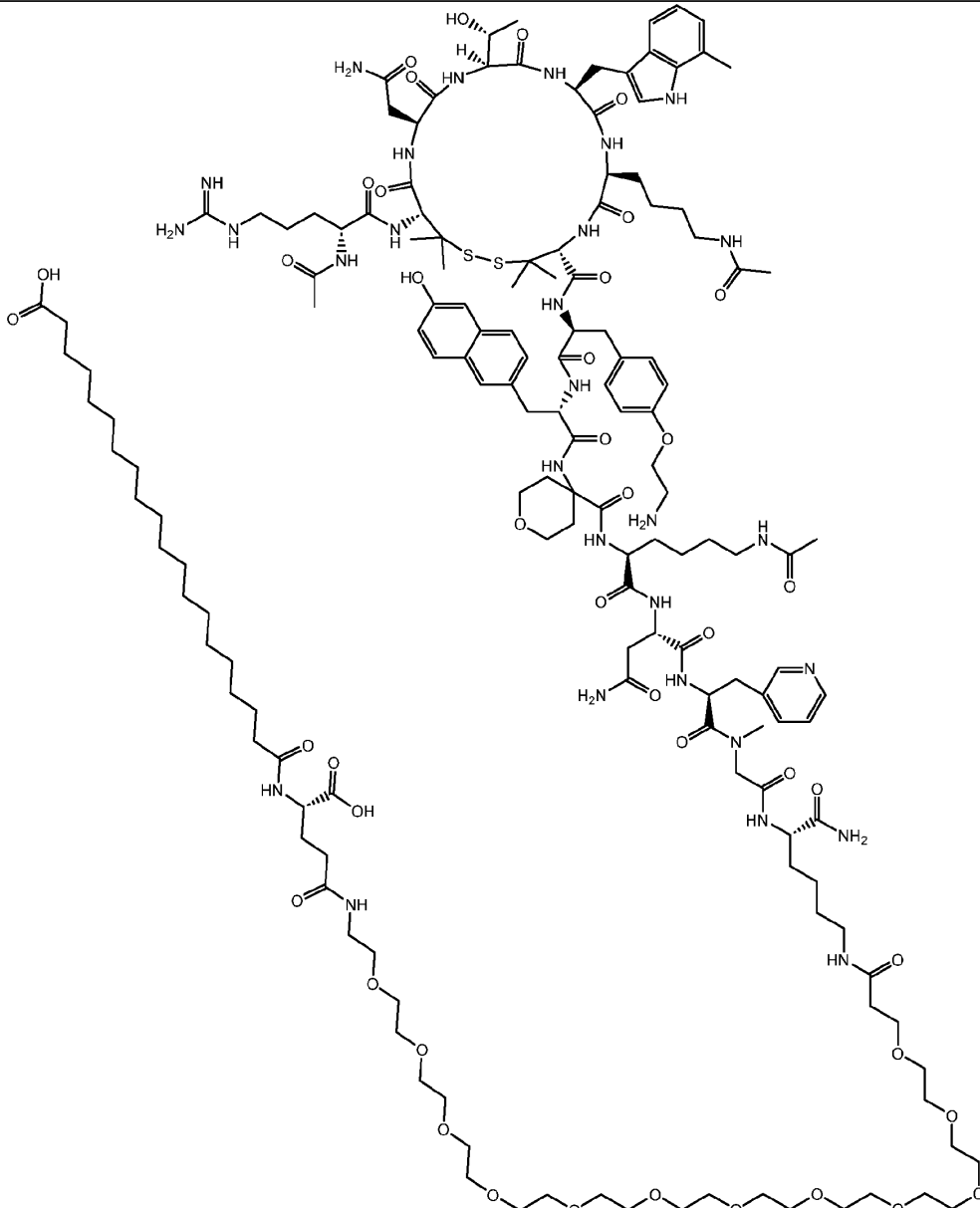
SEQ ID NO	Structure
249	MeCO-Pen(3)-N-T-7MeW-K(NMeAc)-Pen(3)-TMAPF-6OH2NaI-THP-K(PEG12gEC18OH)-N-3Pya-Sar-CONH2

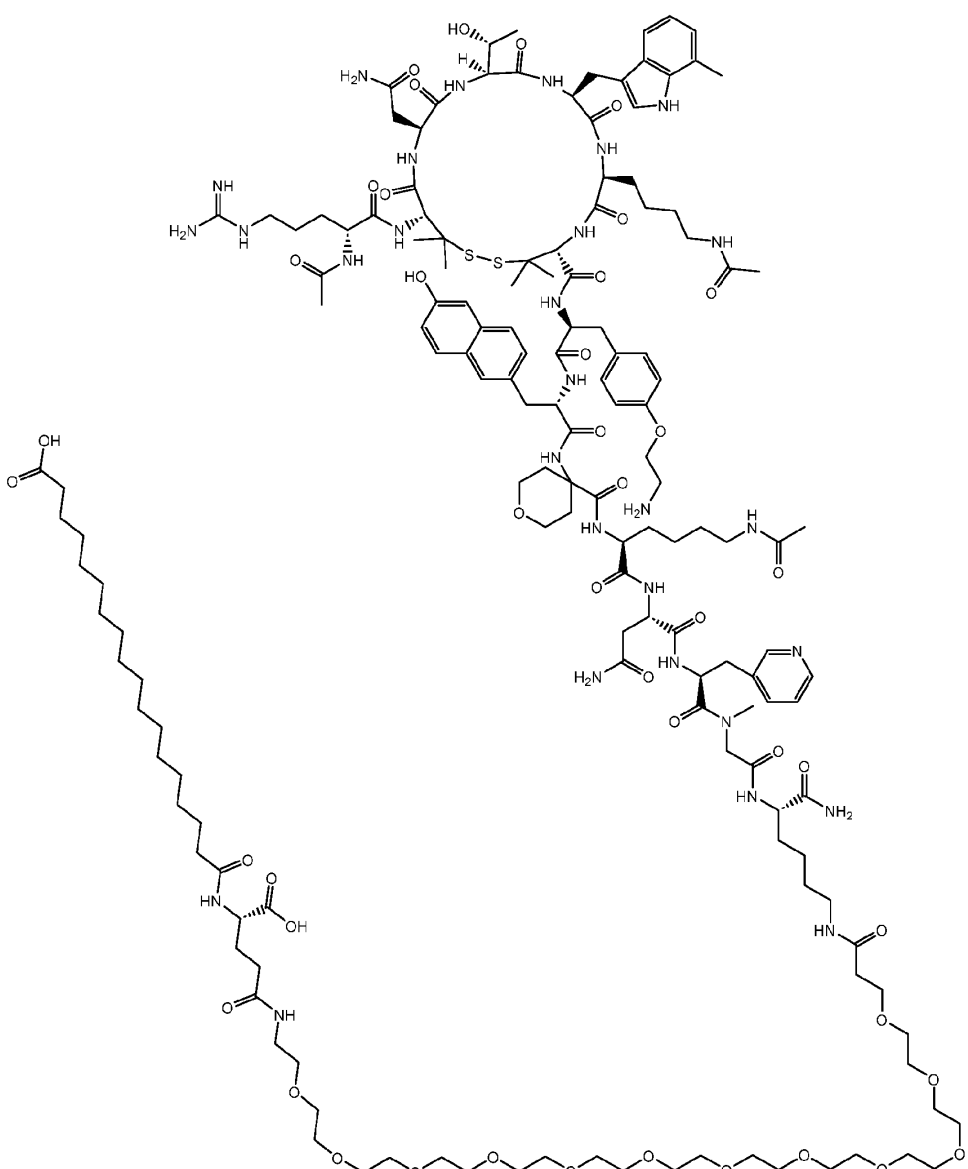
SEQ ID NO	Structure
250	 MeCO-Pen(3)-N-T-7MeW-K(PEG12gEC18OH)-Pen(3)-TMAPF-6OH2NaI-THP-K(NMeAc)-N-3Pya-Sar-CONH2

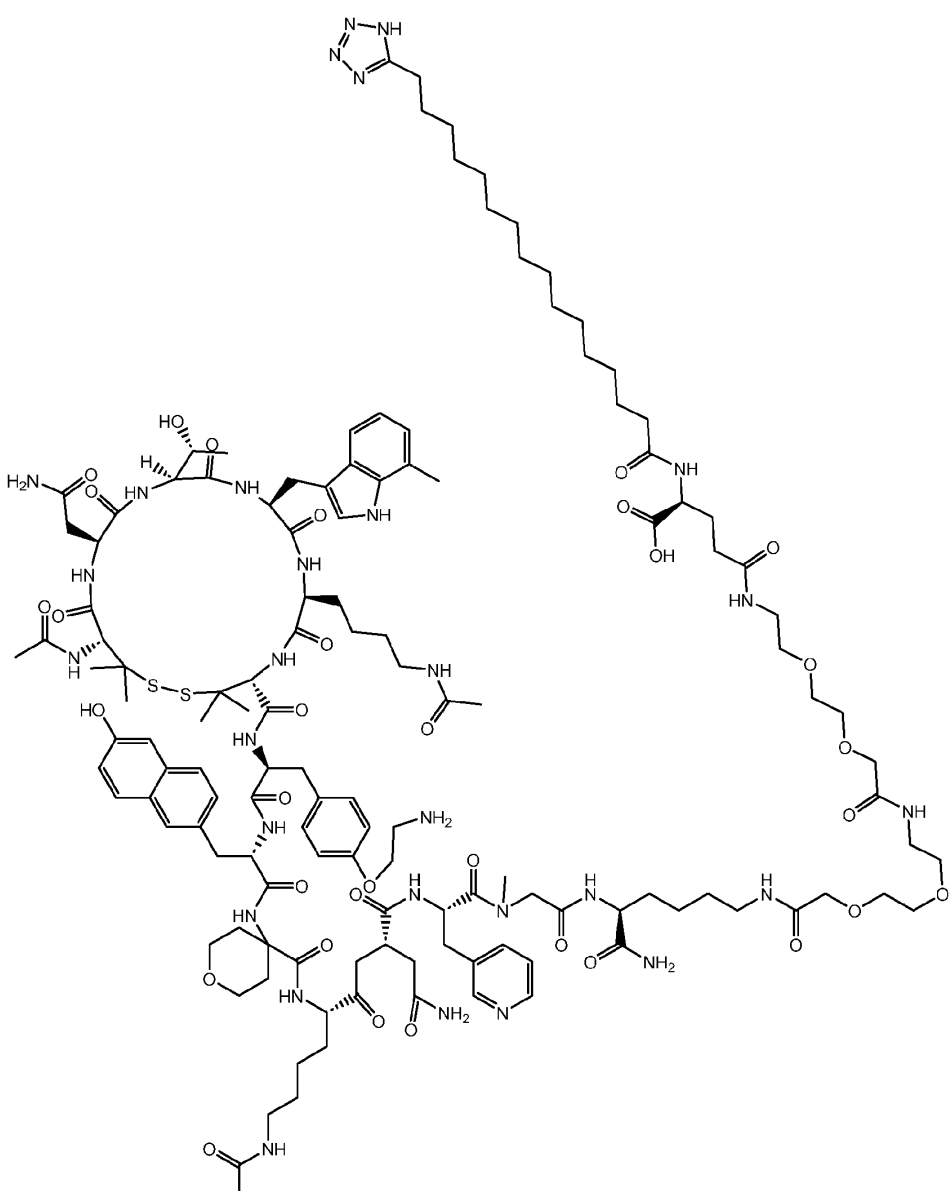
SEQ ID NO	Structure
251	 MeCO-Pen(3)-K(PEG12gEC18OH)-T-7MeW-K(NMeAc)-Pen(3)-TMAPF-6OH2NaI-THP-K(NMeAc)-N-3Pya-Sar-CONH2

SEQ ID NO	Structure
252	MeCO-Pen(3)-N-T-7MeW-K(NMeAc)-Pen(3)-AEF-6OH2NaI-THP-K(PEG12gEC18OH)-N-3Pya-Sar-CONH2

SEQ ID NO	Structure
253	 The chemical structure is a large cyclic peptide. The backbone is a 24-residue ring. The residues, starting from the N-terminus and proceeding clockwise, are: 1. N-Methyl-L-proline (NMePro), 2. L-phenylalanine (Phe), 3. L-phenylalanine (Phe), 4. L-phenylalanine (Phe), 5. L-phenylalanine (Phe), 6. L-phenylalanine (Phe), 7. L-phenylalanine (Phe), 8. L-phenylalanine (Phe), 9. L-phenylalanine (Phe), 10. L-phenylalanine (Phe), 11. L-phenylalanine (Phe), 12. L-phenylalanine (Phe), 13. L-phenylalanine (Phe), 14. L-phenylalanine (Phe), 15. L-phenylalanine (Phe), 16. L-phenylalanine (Phe), 17. L-phenylalanine (Phe), 18. L-phenylalanine (Phe), 19. L-phenylalanine (Phe), 20. L-phenylalanine (Phe), 21. L-phenylalanine (Phe), 22. L-phenylalanine (Phe), 23. L-phenylalanine (Phe), 24. L-phenylalanine (Phe). The side chains include: a PEG12 linker (residue 1), a long alkyl chain (residue 2), a pyridine ring (residue 3), a long alkyl chain (residue 4), a long alkyl chain (residue 5), a long alkyl chain (residue 6), a long alkyl chain (residue 7), a long alkyl chain (residue 8), a long alkyl chain (residue 9), a long alkyl chain (residue 10), a long alkyl chain (residue 11), a long alkyl chain (residue 12), a long alkyl chain (residue 13), a long alkyl chain (residue 14), a long alkyl chain (residue 15), a long alkyl chain (residue 16), a long alkyl chain (residue 17), a long alkyl chain (residue 18), a long alkyl chain (residue 19), a long alkyl chain (residue 20), a long alkyl chain (residue 21), a long alkyl chain (residue 22), a long alkyl chain (residue 23), and a long alkyl chain (residue 24). MeCO-Pen(3)-N-T-7MeW-K(PEG12gEC18OH)-Pen(3)-AEF-6OH2Nal-THP-K(NMeAc)-N-3Pya-Sar-CONH2

SEQ ID NO	Structure
254	 The chemical structure shows a large cyclic peptide with a central core containing a disulfide bridge (S-S) and a hydroxyl group (HO). The peptide is linked to a long PEG12 chain (PEG12gEC20OH) via an amide bond. The side chains include a long alkyl chain (MeCO-r-Pen(3)-N-T-7MeW-K(Ac)-Pen(3)-AEF-6OH2Nal-THP-K(Ac)-N-3Pyra-Sar-K), a pyridine ring, a thiazole ring, and a carboxylic acid group. The structure is highly complex and represents a large molecule. MeCO-r-Pen(3)-N-T-7MeW-K(Ac)-Pen(3)-AEF-6OH2Nal-THP-K(Ac)-N-3Pyra-Sar-K(PEG12gEC20OH)-CONH2

SEQ ID NO	Structure
255	 MeCO-r-Pen(3)-N-T-7MeW-K(Ac)-Pen(3)-AEF-6OH2Nal-THP-K(Ac)-N-3PyA-Sar-K(PEG12gEC18OH)-CONH2

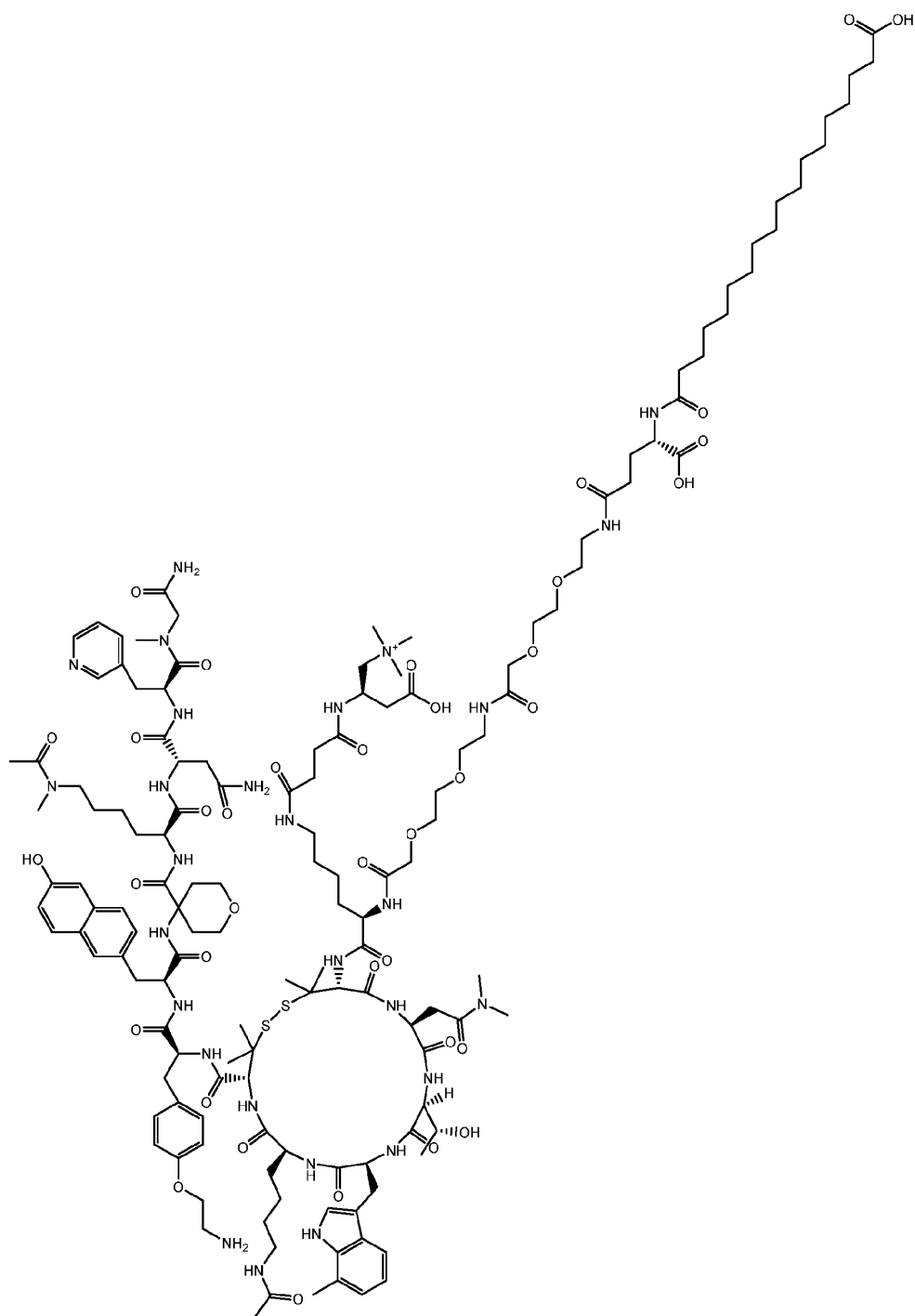
SEQ ID NO	Structure
256	 MeCO-Pen(3)-N-T-7MeW-K(Ac)-Pen(3)-AEF-6OH2Nal-THP-K(Ac)-N-3Pyra-Sar-K(PEG2PEG2gEC16tetrazole)-CONH2

[illegible]

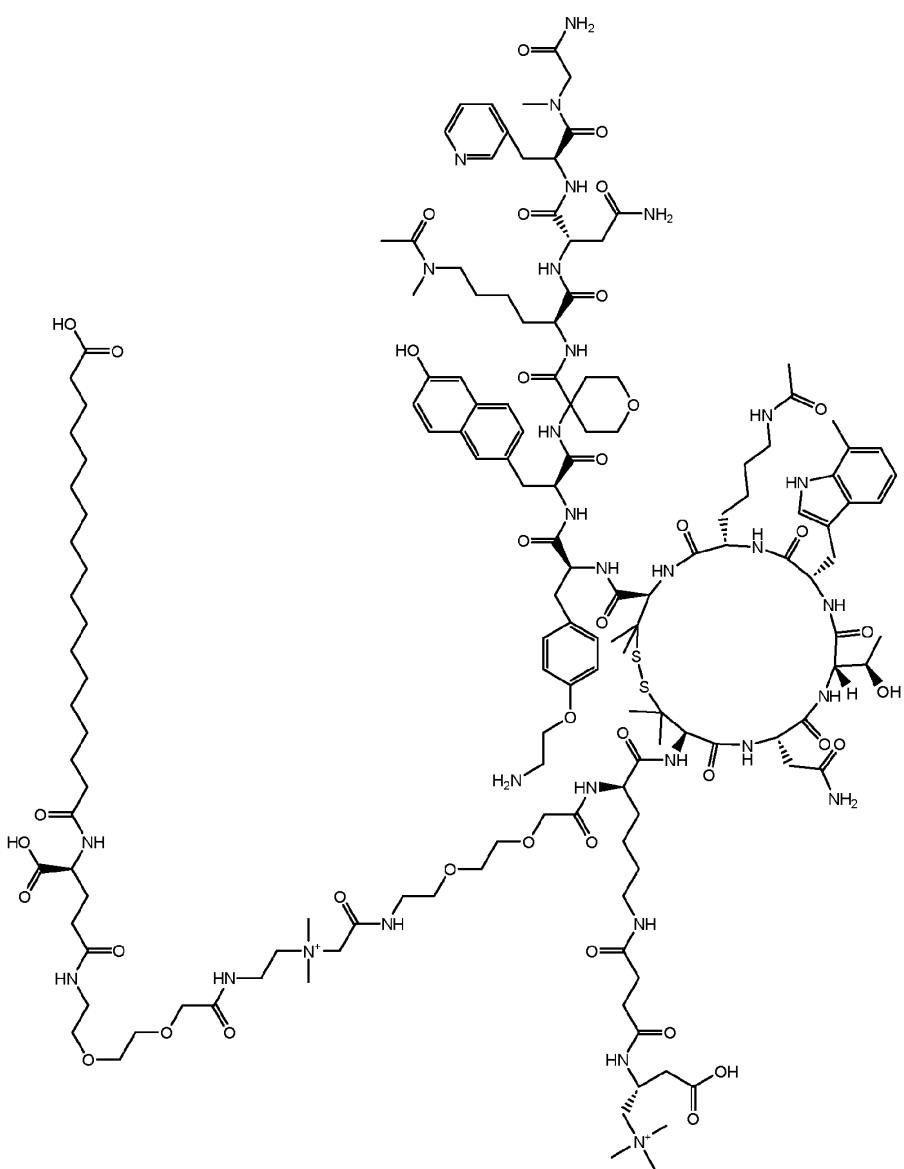
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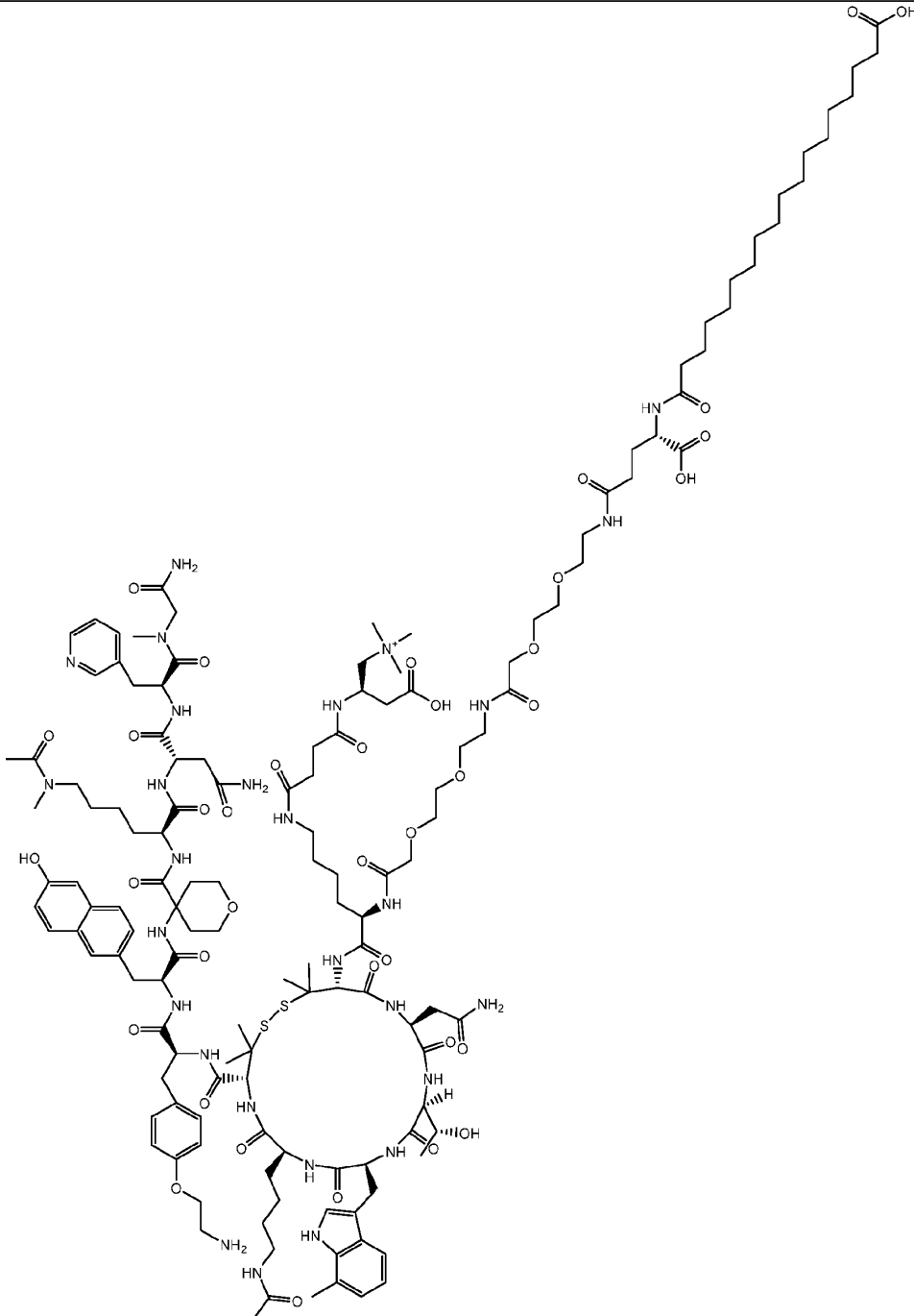
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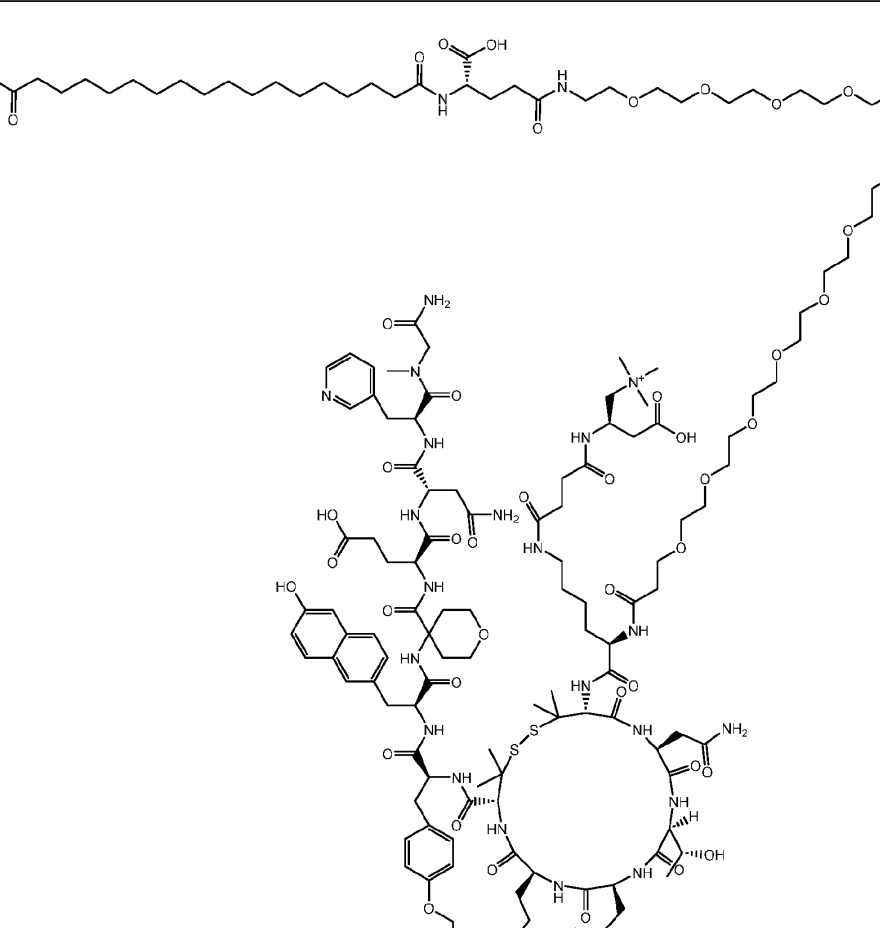


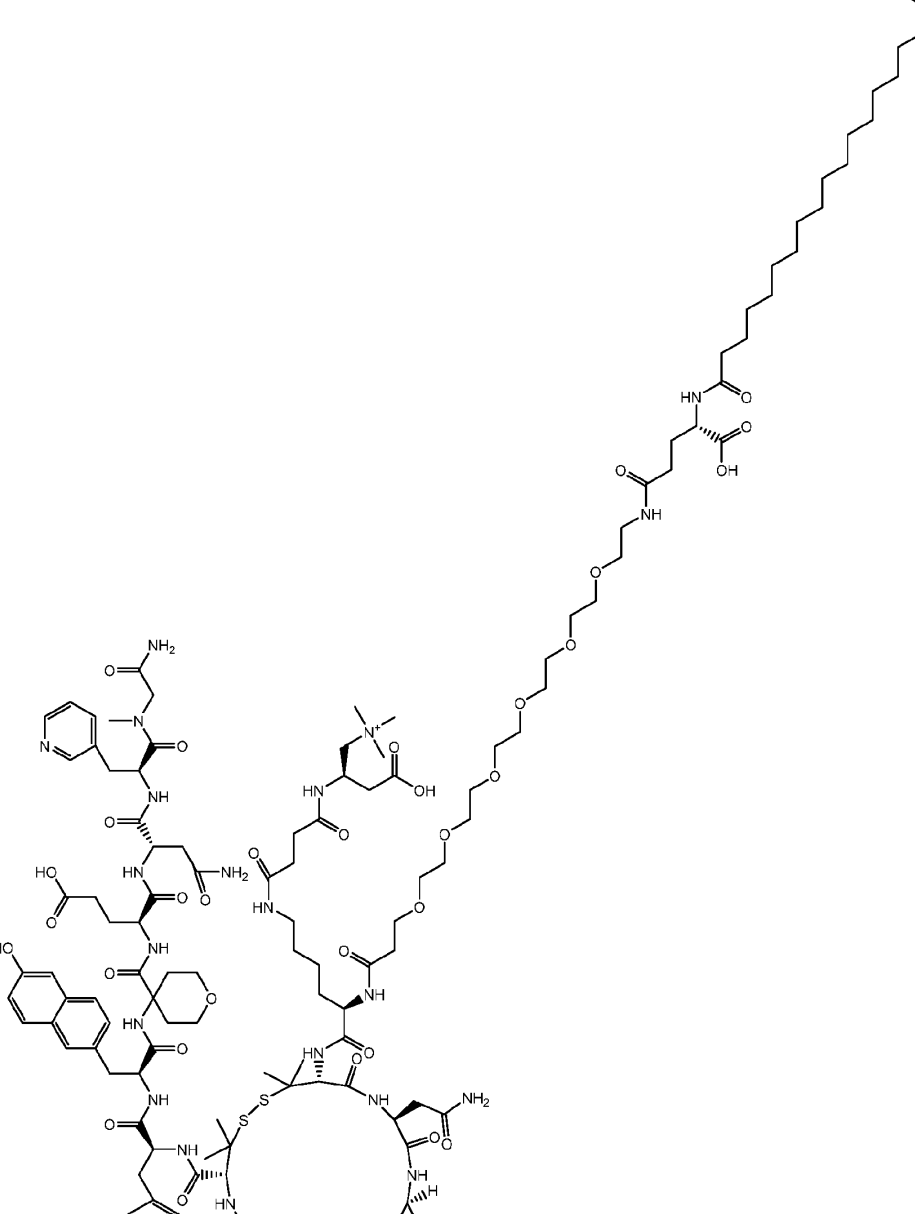
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SEQ ID NO	Structure
260	 HOC18gEPEG2SP6PEG2CO-k(d)-Pen(3)-N-T-7MeW-K(Ac)-Pen(3)-AEF-6OH2Nal-THP-K(NMeAc)-N-3Py-Sar-CONH2

SEQ ID NO	Structure
261	HOC20gEPEG2PEG2CO-k(d)-Pen(3)-N-T-7MeW-K(Ac)-Pen(3)-AEF-6OH2Nal-THP-K(NMeAc)-N-3Py-Sar-CNH2

SEQ ID NO	Structure
262	 HOC18gEPEG2PEG2CO-k(d)-Pen(3)-N-T-7MeW-K(Ac)-Pen(3)-AEF-6OH2NaI-THP-K(NMeAc)-N-3Pyra-Sar-CONH2

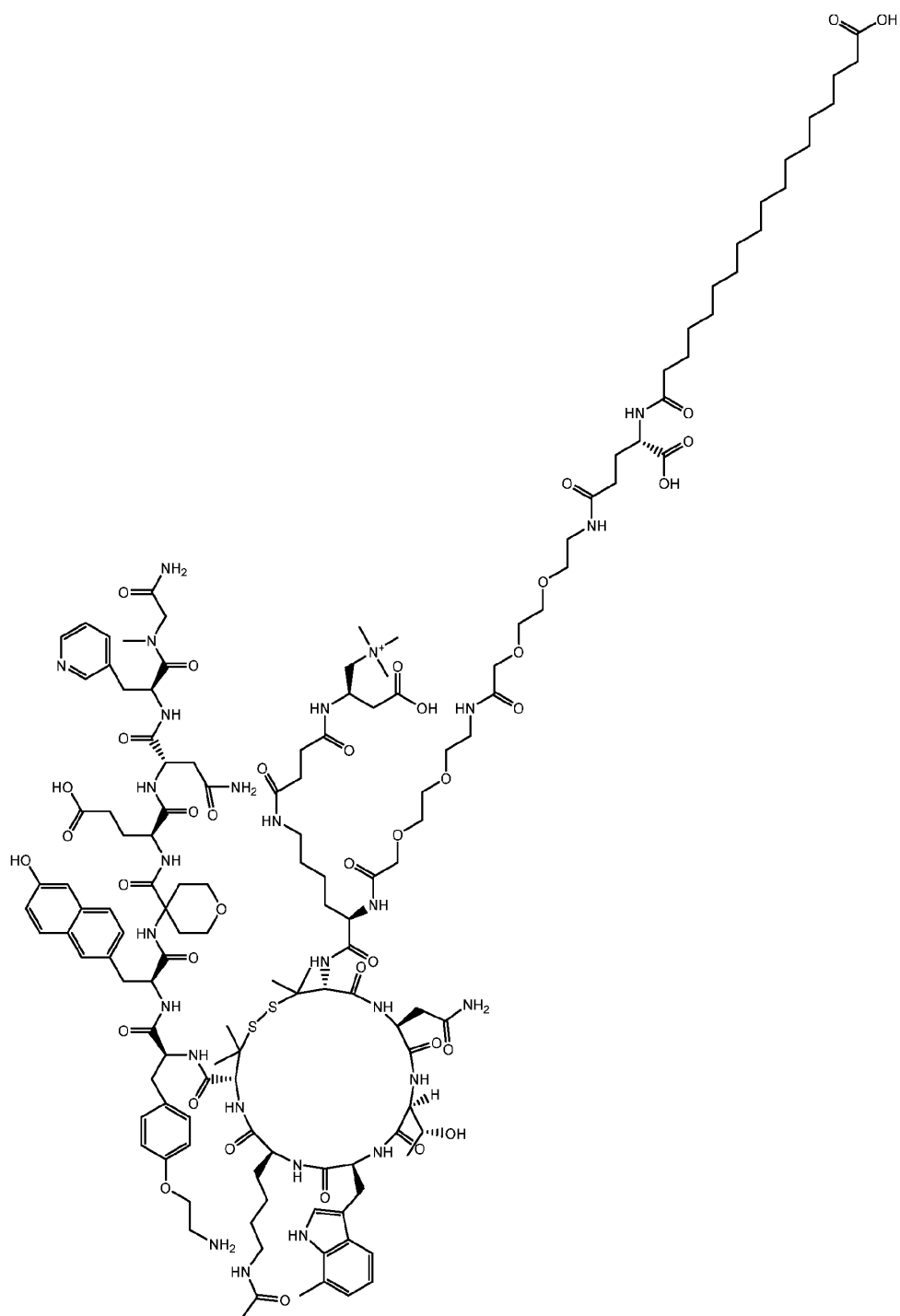
SEQ ID NO	Structure
263	 HOC18gEPEG12CO-k(d)-Pen(3)-N-T-7MeW-K(Ac)-Pen(3)-AEF-6OH2Nal-THP-E-N-3Pya-Sar-CONH2

SEQ ID NO	Structure
264	 Chemical structure of a long, complex peptide chain. The structure features a central backbone with various side chains, including a long alkyl chain, a pyridine ring, a naphthalene ring, and a thiazolidine ring. The structure is highly branched and contains multiple amide bonds and functional groups.

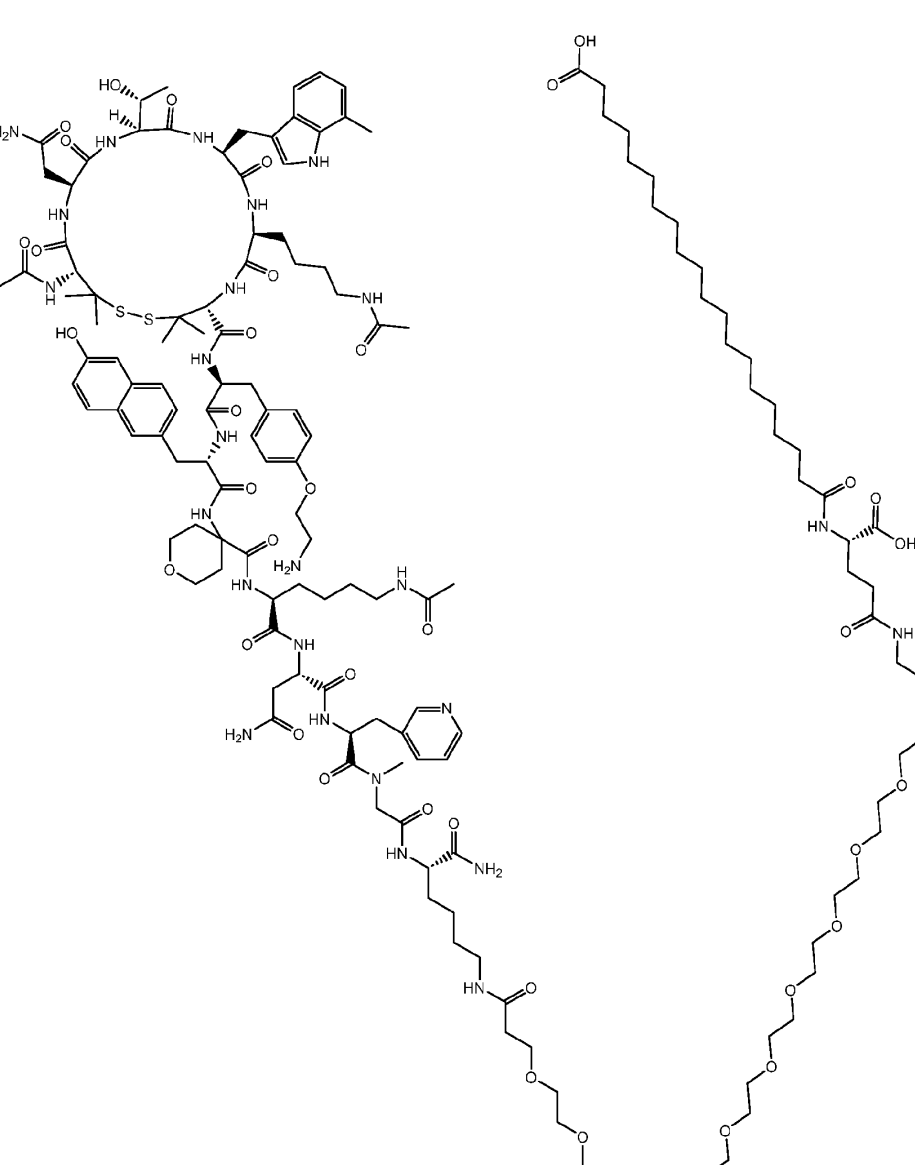
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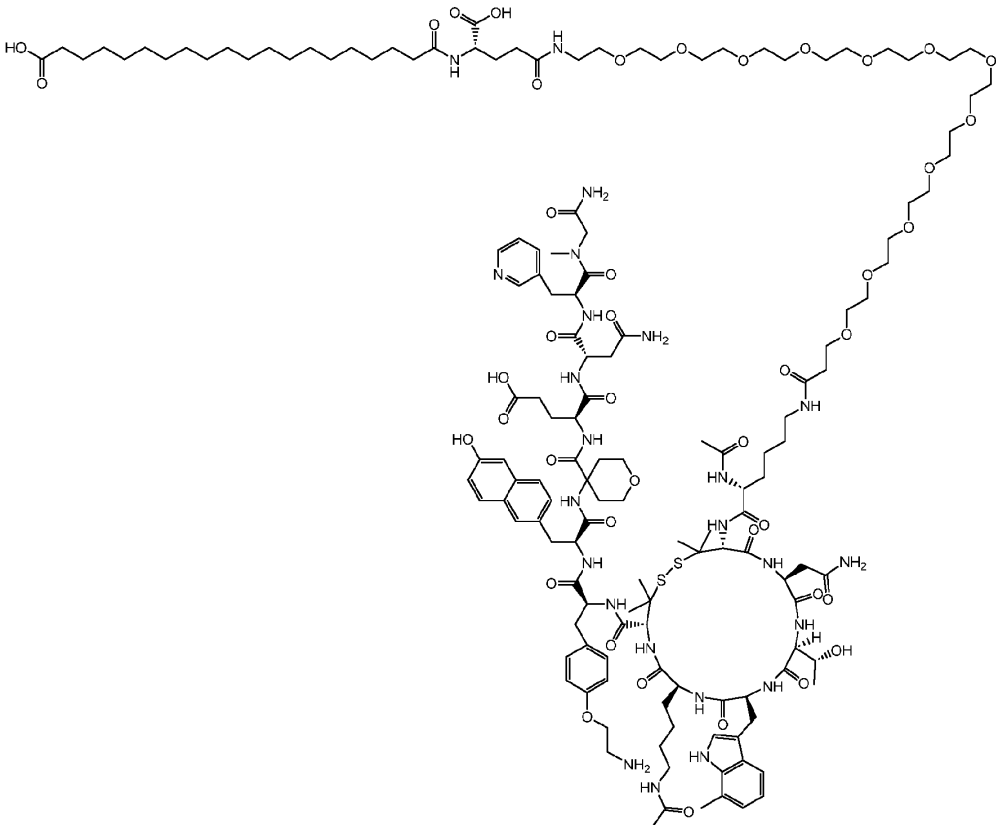
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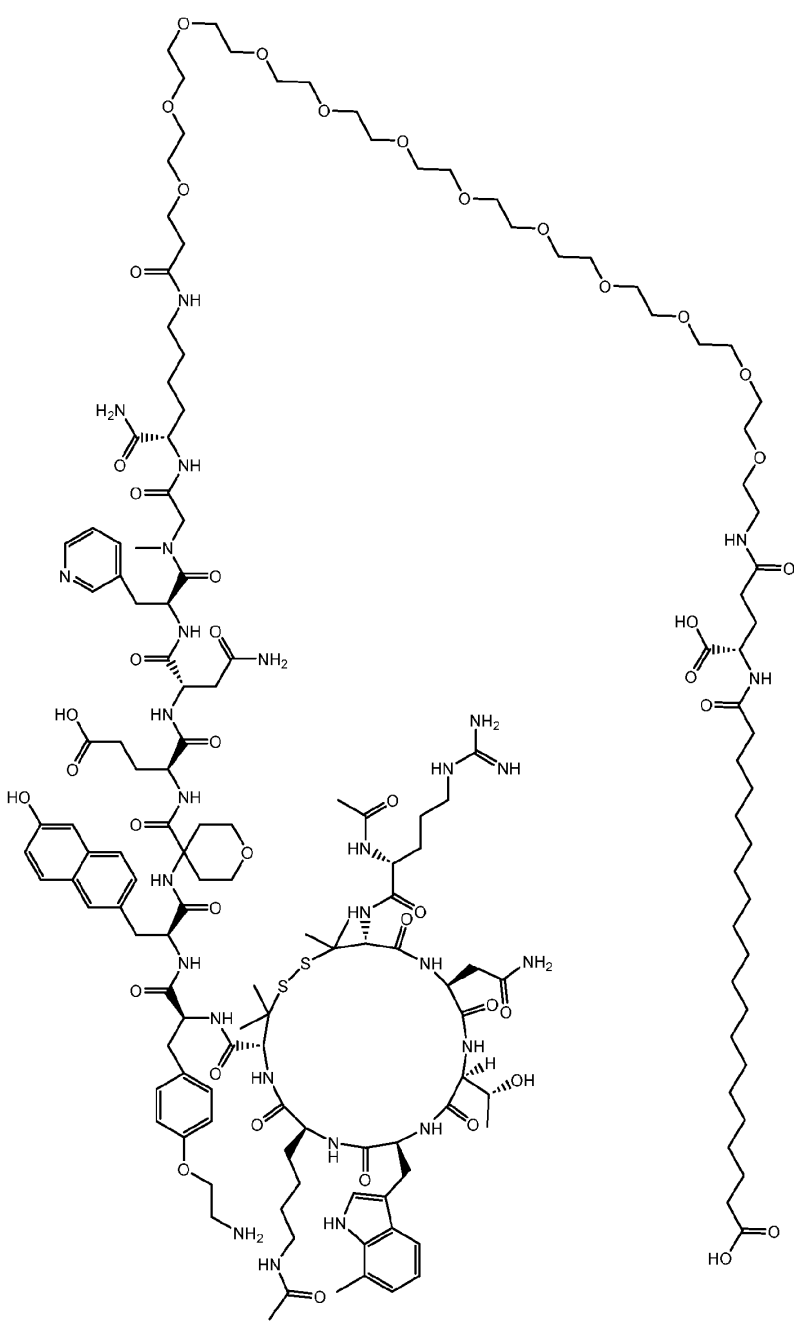
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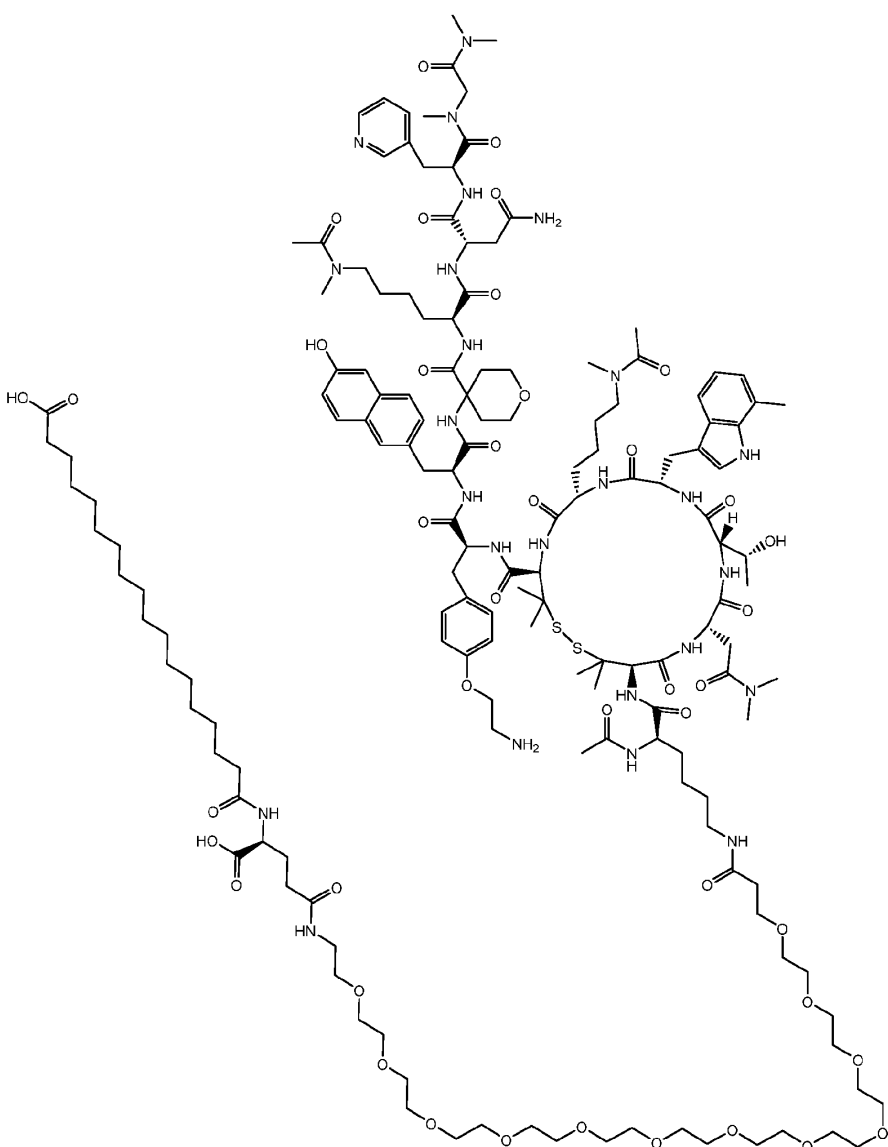


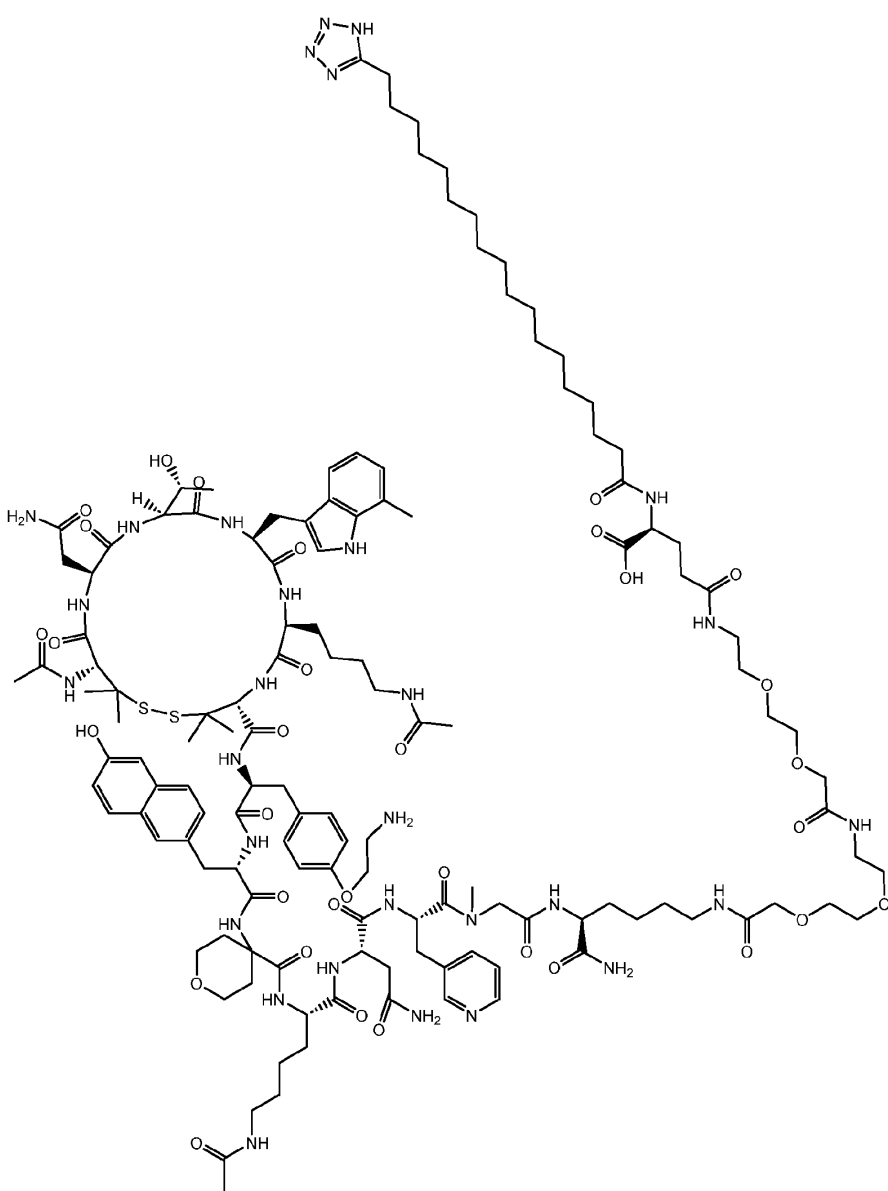
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SEQ ID NO	Structure
267	 The structure shows a large cyclic peptide backbone with a long PEG12 chain (12 repeating units of -CH2CH2O-) attached to one of the residues. The peptide chain includes various side chains, including a long alkyl chain, a phenyl group, a thiazole ring, a pyridine ring, and a carboxylic acid group. The structure is highly complex and represents a large molecule.

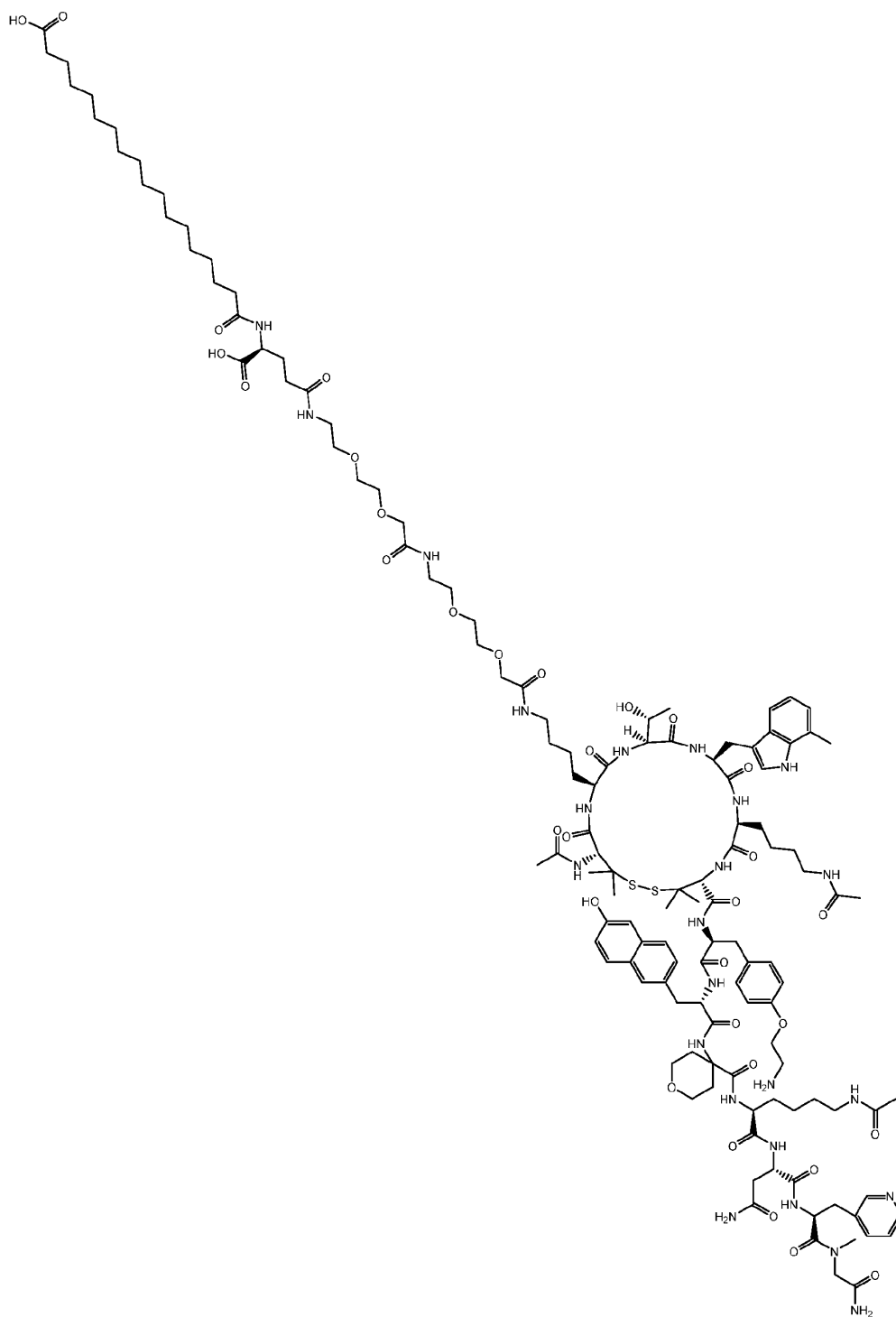
SEQ ID NO	Structure
268	 MeCO-k(PEG12gEC20OH)-Pen(3)-N-T-7MeW-K(Ac)-Pen(3)-AEF-6OH2NaI-THP-E-N-3Pya-Sar-CONH2

SEQ ID NO	Structure
269	 The chemical structure is a large cyclic peptide with a central core and several side chains. The side chains include a PEG12 chain (poly(ethylene glycol) with 12 repeating units), a 6-hydroxy-2-nal chain (6-hydroxy-2-nal), a 3-pyridyl chain (3-pyridyl), and a 20-hydroxy chain (20-hydroxy). The structure is highly complex, featuring multiple amide bonds, hydroxyl groups, and a variety of functional groups. MeCO-r-Pen(3)-N-T-7MeW-K(Ac)-Pen(3)-AEF-6OH2NaI-THP-E-N-3Pyra-Sar-K(PEG12gEC20OH)-CONH2

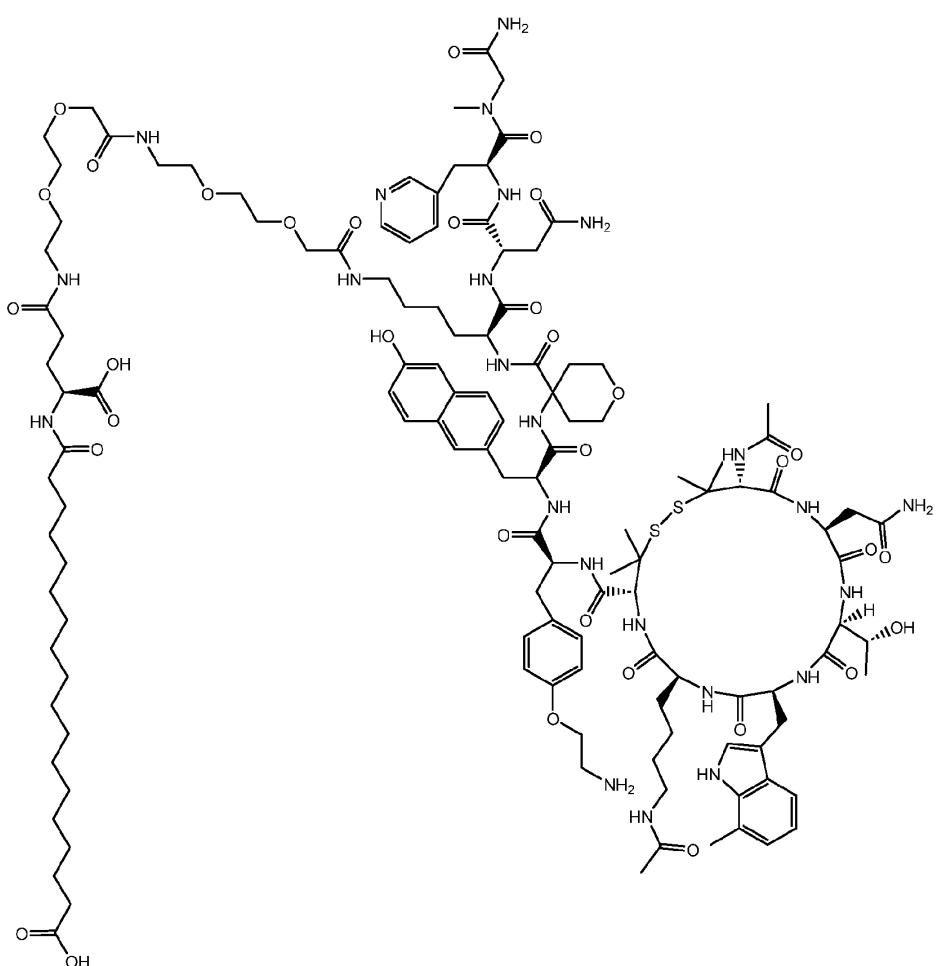
SEQ ID NO	Structure
270	 MeCO-k(PEG12gEC18OH)-Pen(3)-N(N(Me)2)-T-7MeW-K(NMeAc)-Pen(3)-AEF-6OH2NaI-THP-K(NMeAc)-N-3Py-Sar-CON(Me)2

SEQ ID NO	Structure
271	 MeCO-Pen(3)-N-T-7MeW-K(Ac)-Pen(3)-AEF-6OH2Nal-THP-K(Ac)-N-3Pya-Sar-K(PEG2PEG2gEC18tetrazole)-CONH2

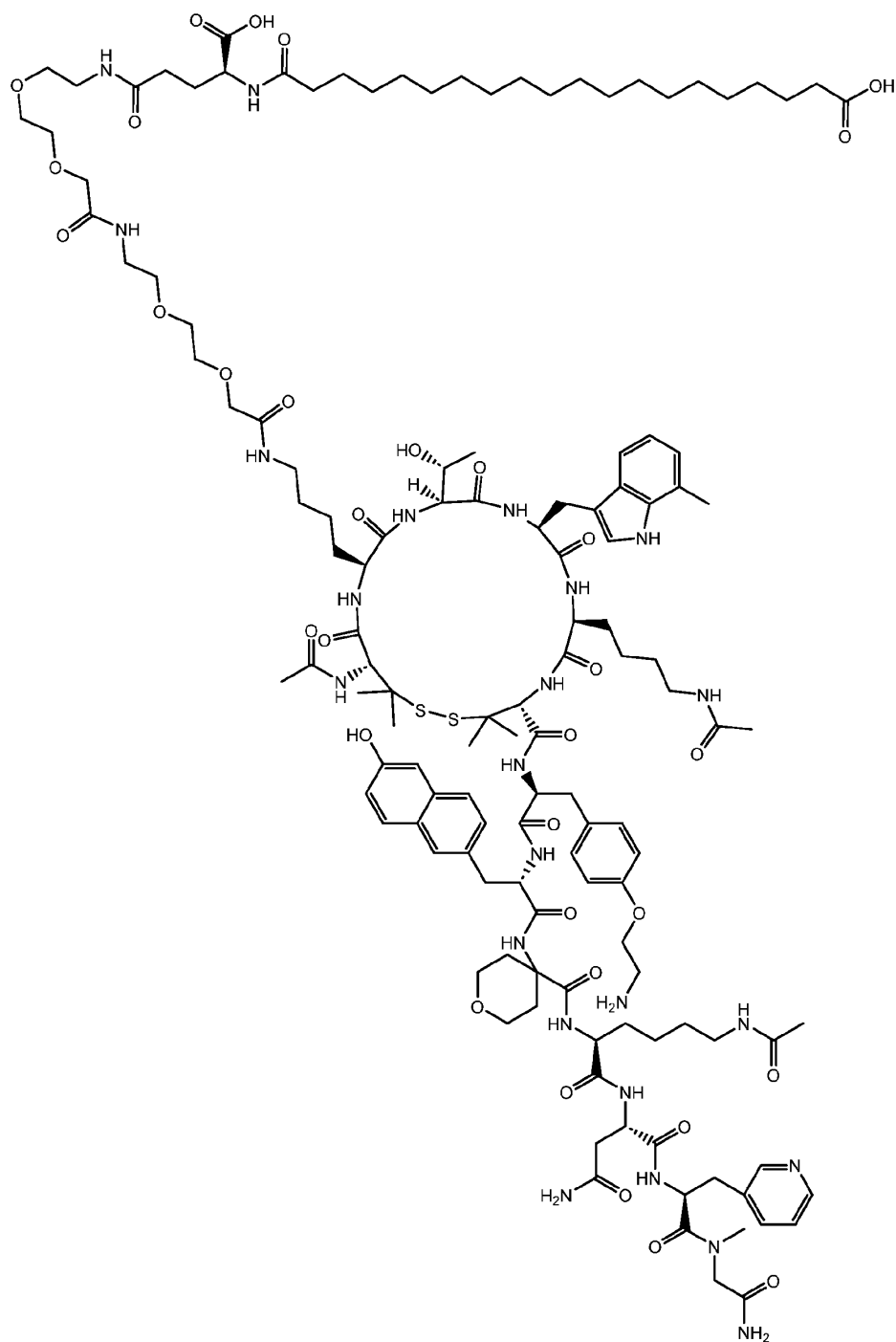
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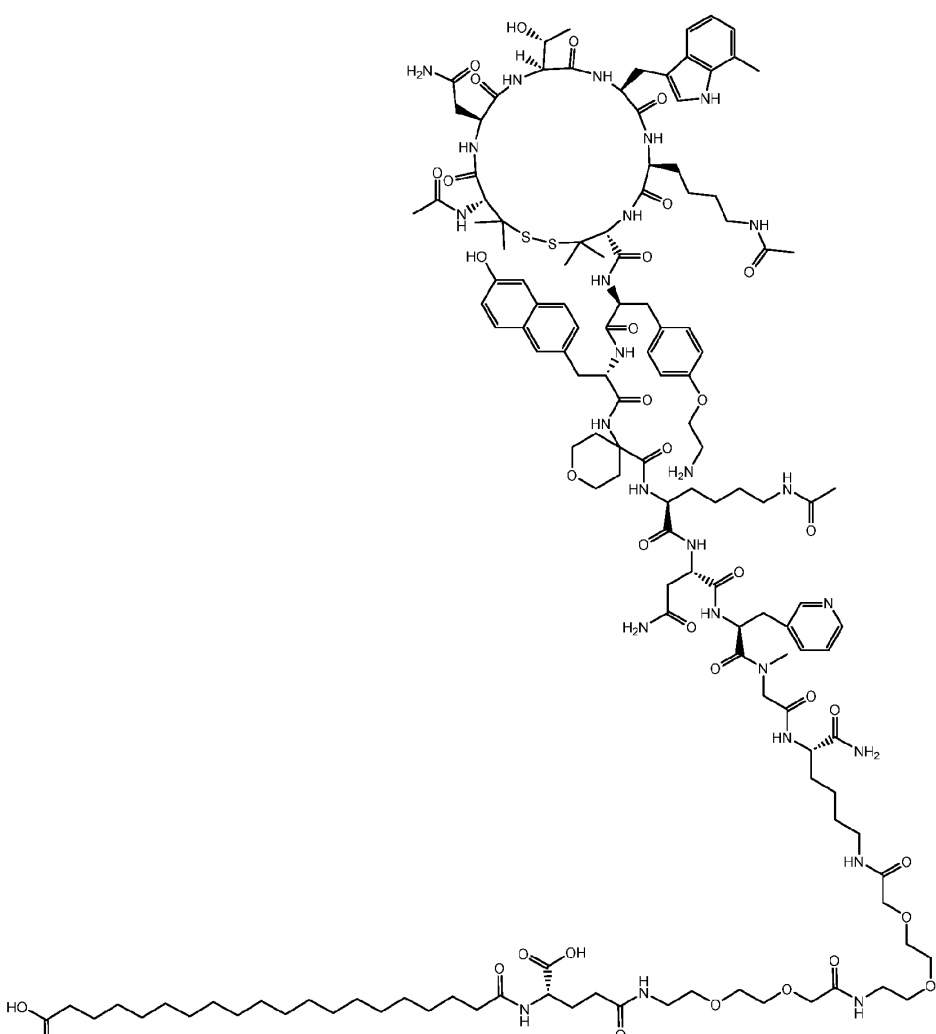
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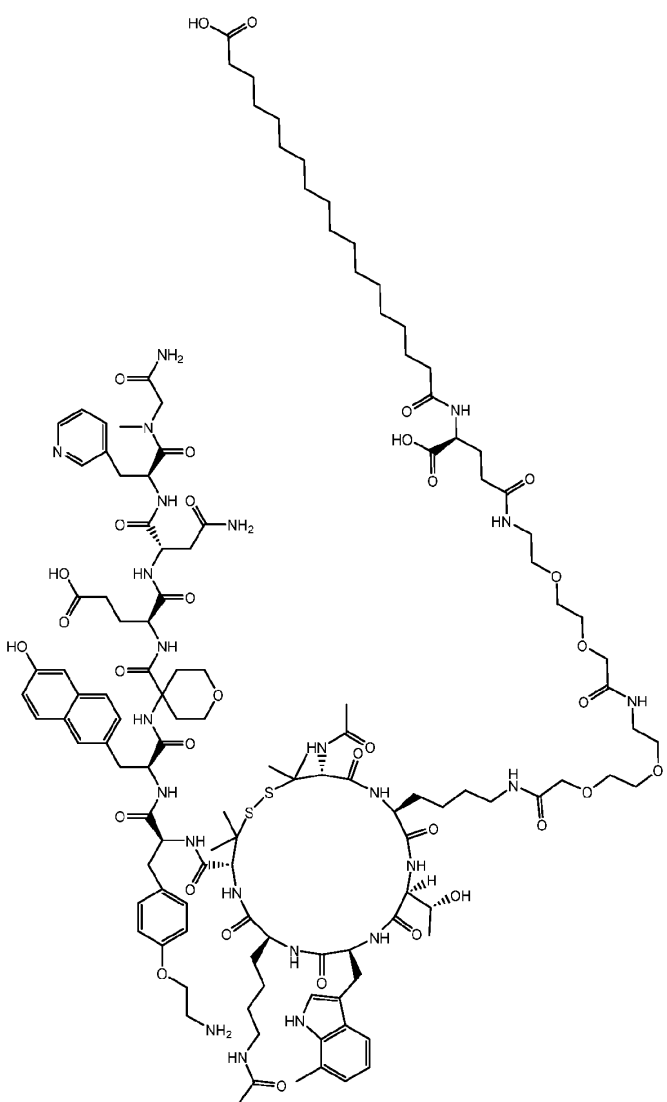
SEQ ID NO	Structure
273	 MeCO-Pen(3)-N-T-7MeW-K(Ac)-Pen(3)-AEF-6OH2NaI-THP-K(PEG2PEG2gEC18OH)-N-3PyA-Sar-CONH2

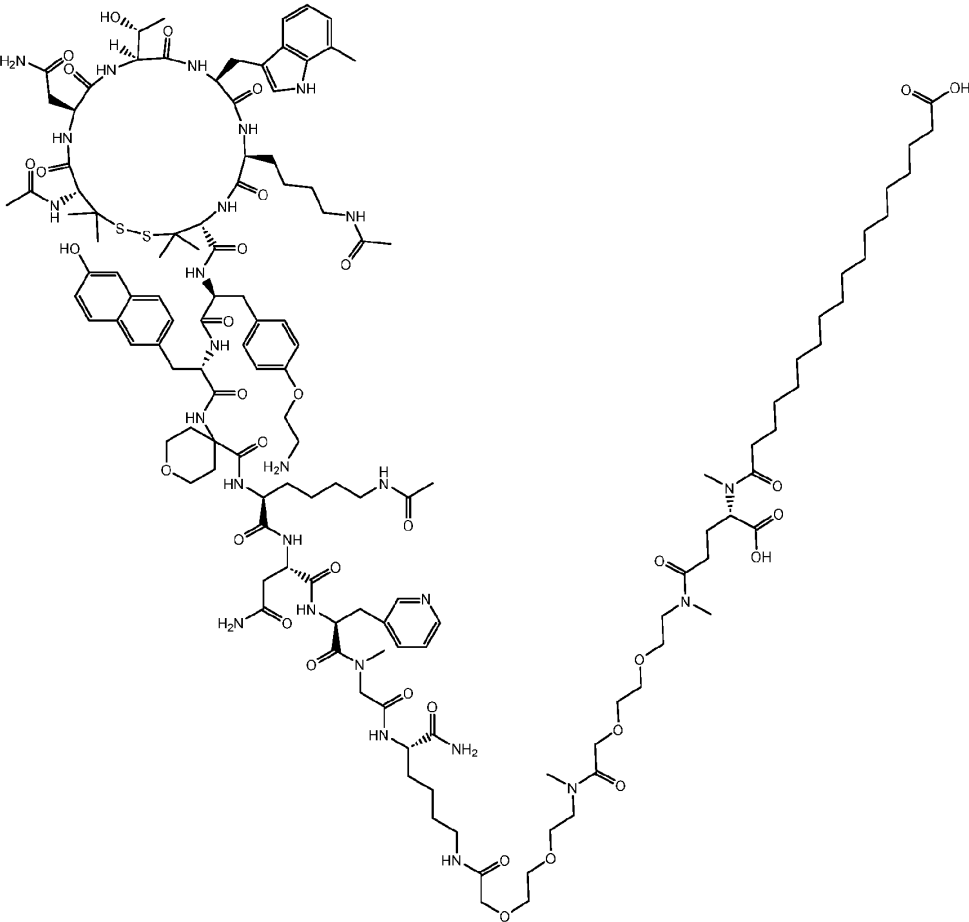
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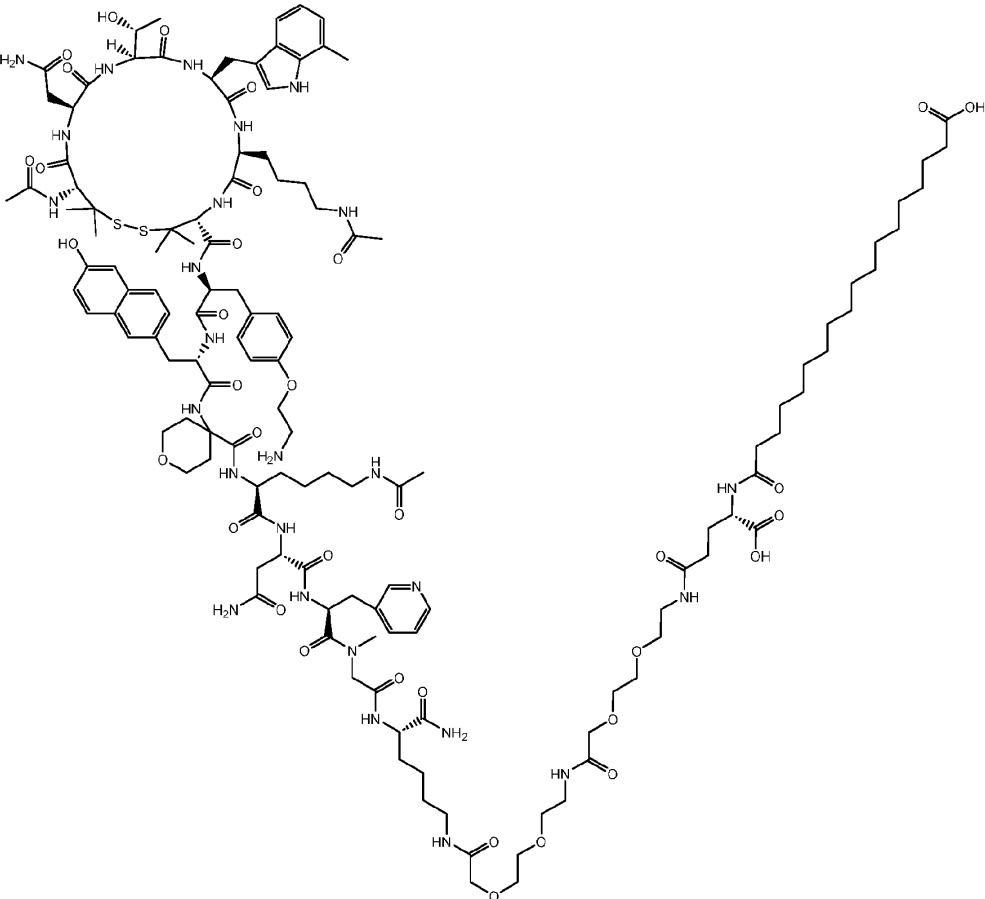


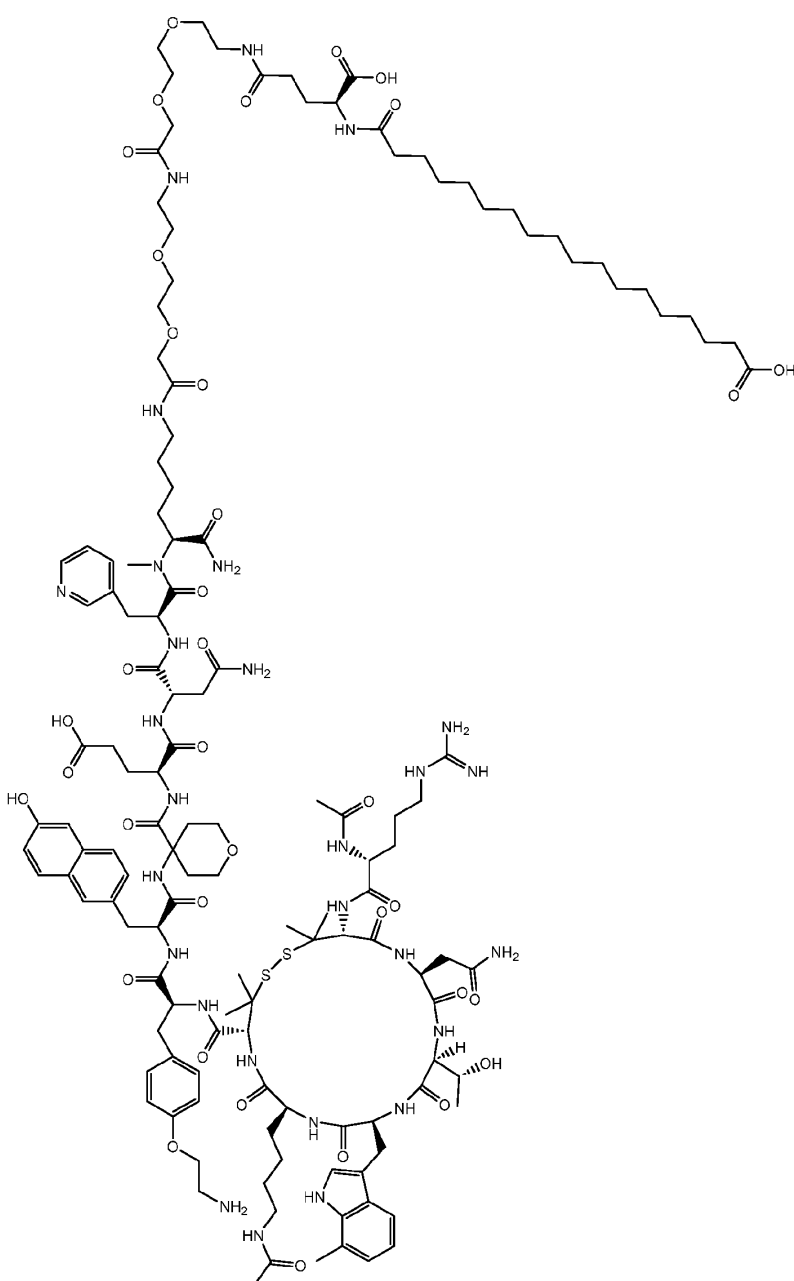
MeCO-Pen(3)-K(PEG2PEG2gEC20OH)-T-7MeW-K(Ac)-Pen(3)-AEF-6OH2Nal-THP-K(Ac)-N-3Py-Sar-CONH2

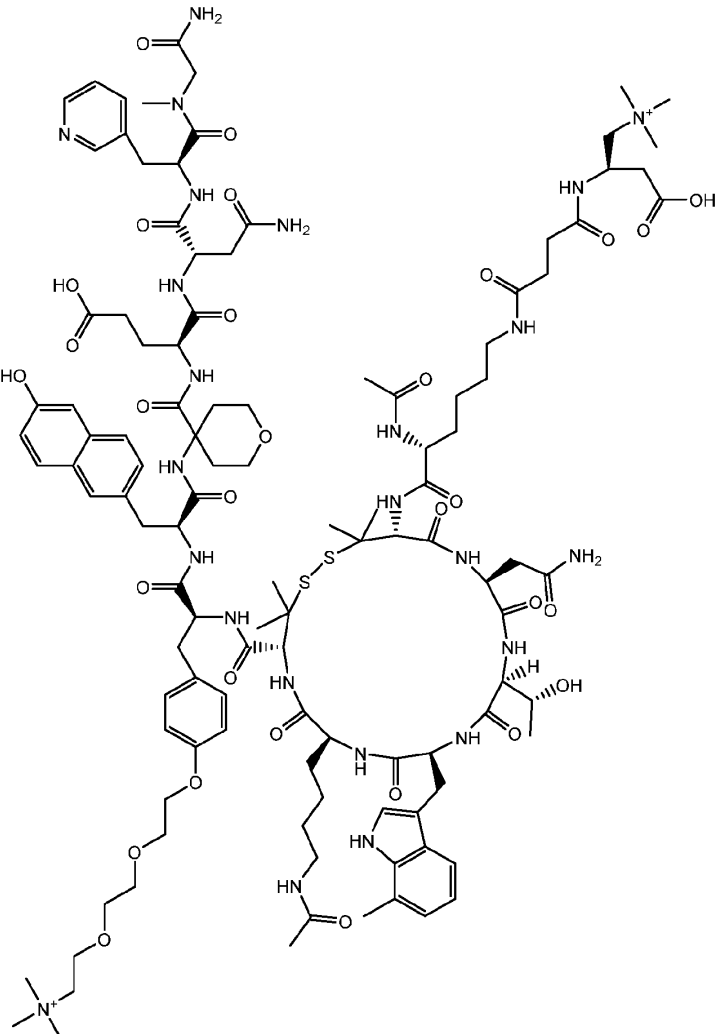
SEQ ID NO	Structure
275	 MeCO-Pen(3)-N-T-7MeW-K(Ac)-Pen(3)-AEF-6OH2NaI-THP-K(Ac)-N-3Pya-Sar-K(PEG2PEG2gEC20OH)-CONH2

SEQ ID NO	Structure
276	 MeCO-Pen(3)-K(PEG2PEG2gEC18OH)-T-7MeW-K(Ac)-Pen(3)-AEF-6OH2Nal-THP-E-N-3Pyra-Sar-CONH2

SEQ ID NO	Structure
277	 MeCO-Pen(3)-N-T-7MeW-K(Ac)-Pen(3)-AEF-6OH2NaI-THP-K(Ac)-N-3Py-Sar-K(PEG2NMePEG2NMeG2NMeC18OH)-CONH2

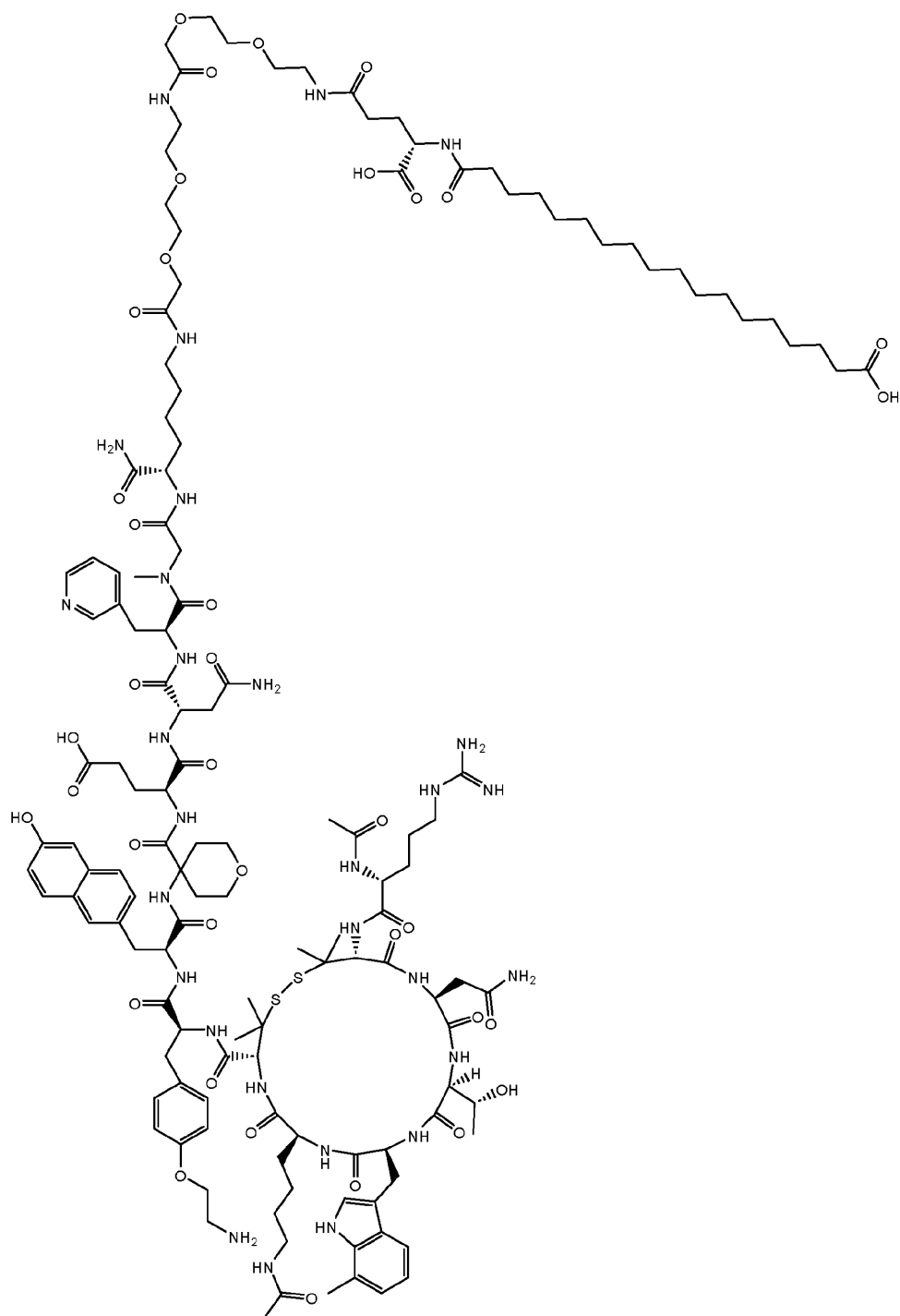
SEQ ID NO	Structure
278	 MeCO-Pen(3)-N-T-7MeW-K(Ac)-Pen(3)-AEF-6OH2NaI-THP-K(Ac)-N-3Pya-Sar-K(PEG2PEG2gEC18OH)-CONH2

SEQ ID NO	Structure
279	 The chemical structure is a large, complex molecule, likely a peptide or protein derivative. It features a central cyclic core, possibly a macrocycle, with various side chains and functional groups. The structure includes a long, branched chain with a terminal carboxylic acid group, a pyridine ring, a thiazolidine ring, a morpholine ring, a phenol group, and a guanidino group. The molecule is highly functionalized with amide, ester, and hydroxyl groups. MeCO-r-Pen(3)-N-T-7MeW-K(Ac)-Pen(3)-AEF-6OH2Nal-THP-E-N-3Py-NMeK(PEG2PEG2gEC18OH)-CONH2

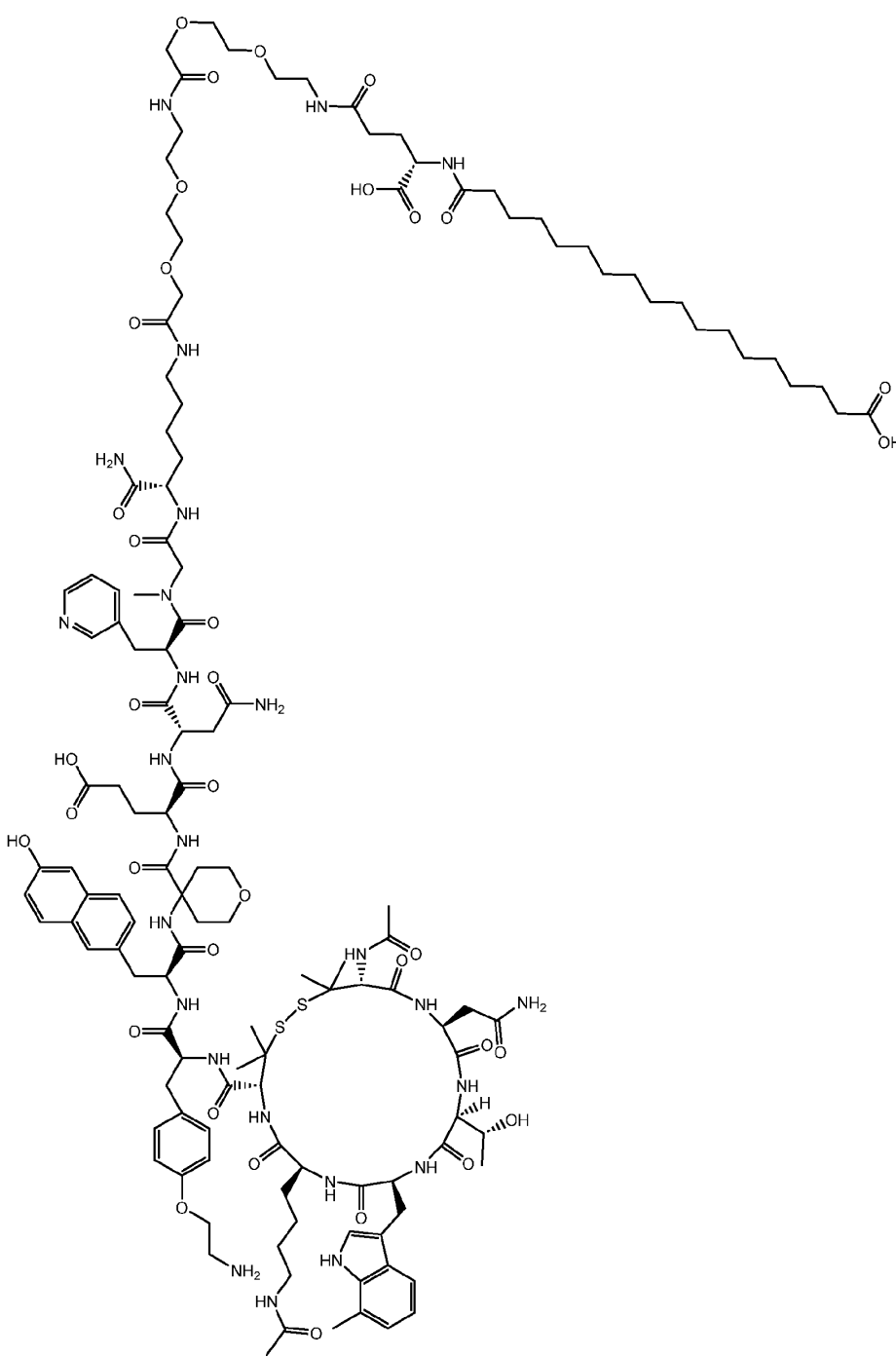
SEQ ID NO	Structure
280	 The chemical structure shows a large cyclic peptide backbone with a disulfide bridge. Various side chains are attached to the backbone, including a pyridine ring, a hydroxyl group, a carboxylic acid, a thiol, and a quaternary ammonium group. The structure is highly complex and represents a specific peptide sequence. MeCO-k(d)-Pen(3)-N-T-7MeW-K(Ac)-Pen(3)-APEG3F-6OH2Nal-THP-E-N-3Pyra-Sar-CONH2

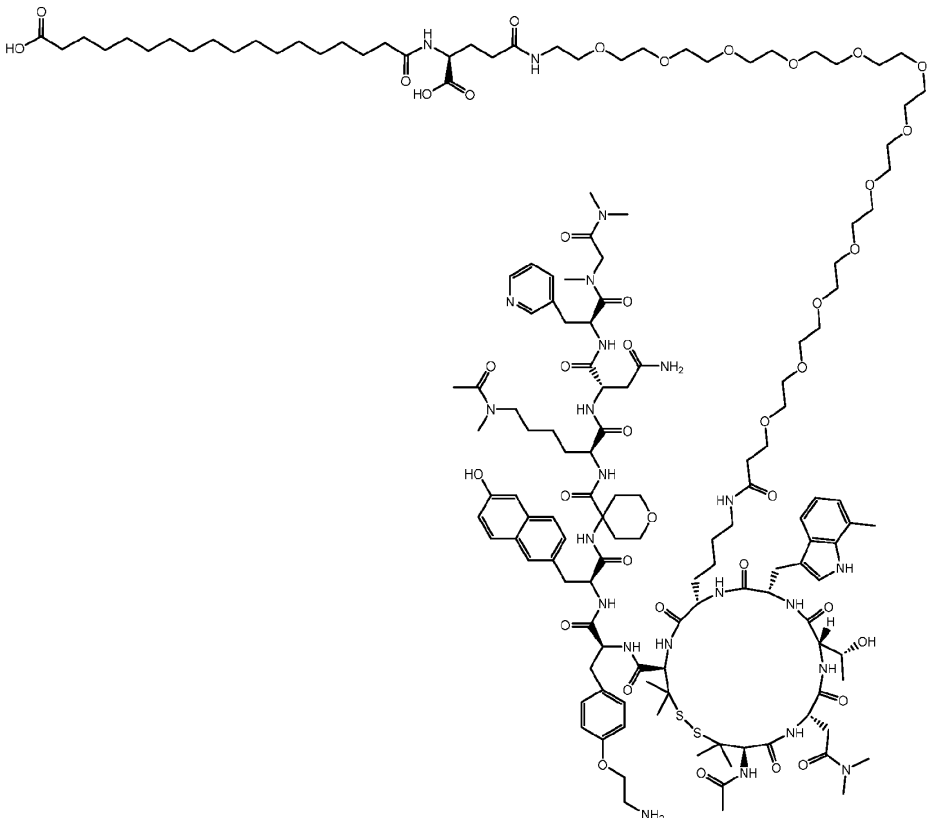
SEQ ID NO	Structure
281	cPEG3aCO-Pen(3)-N(N(Me)₂)-T-7MeW-Lys(N⁺Me₂mPEG3)-Pen(3)-AEF-6OH₂NaI-THP-K(NMeAc)-N-3Pyra-Sar-CONH₂

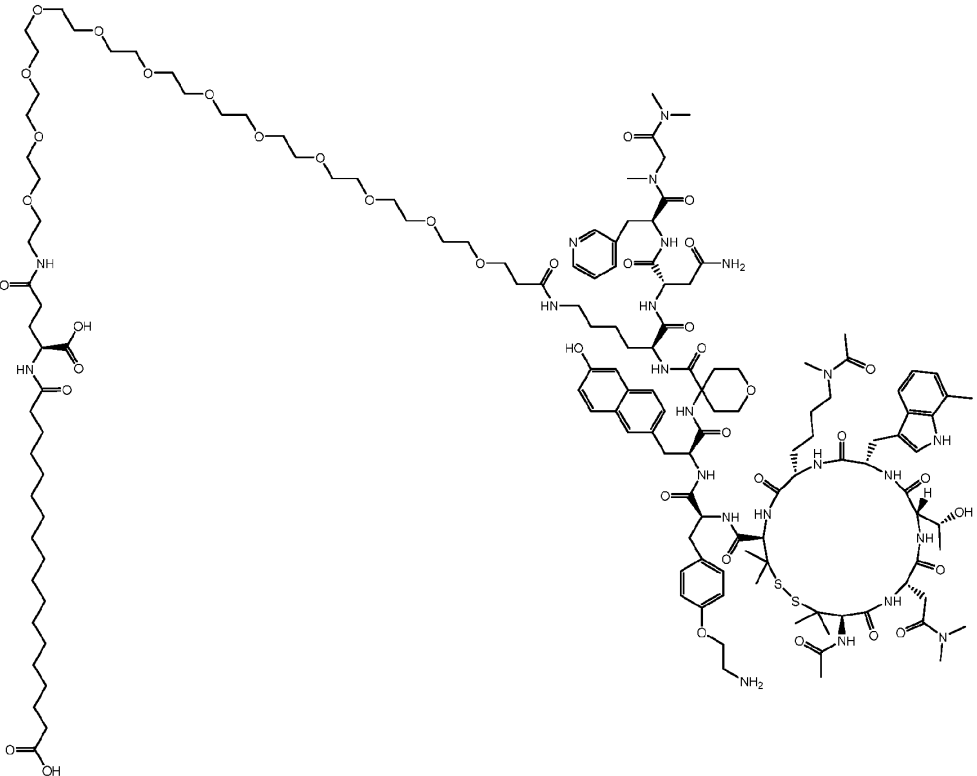
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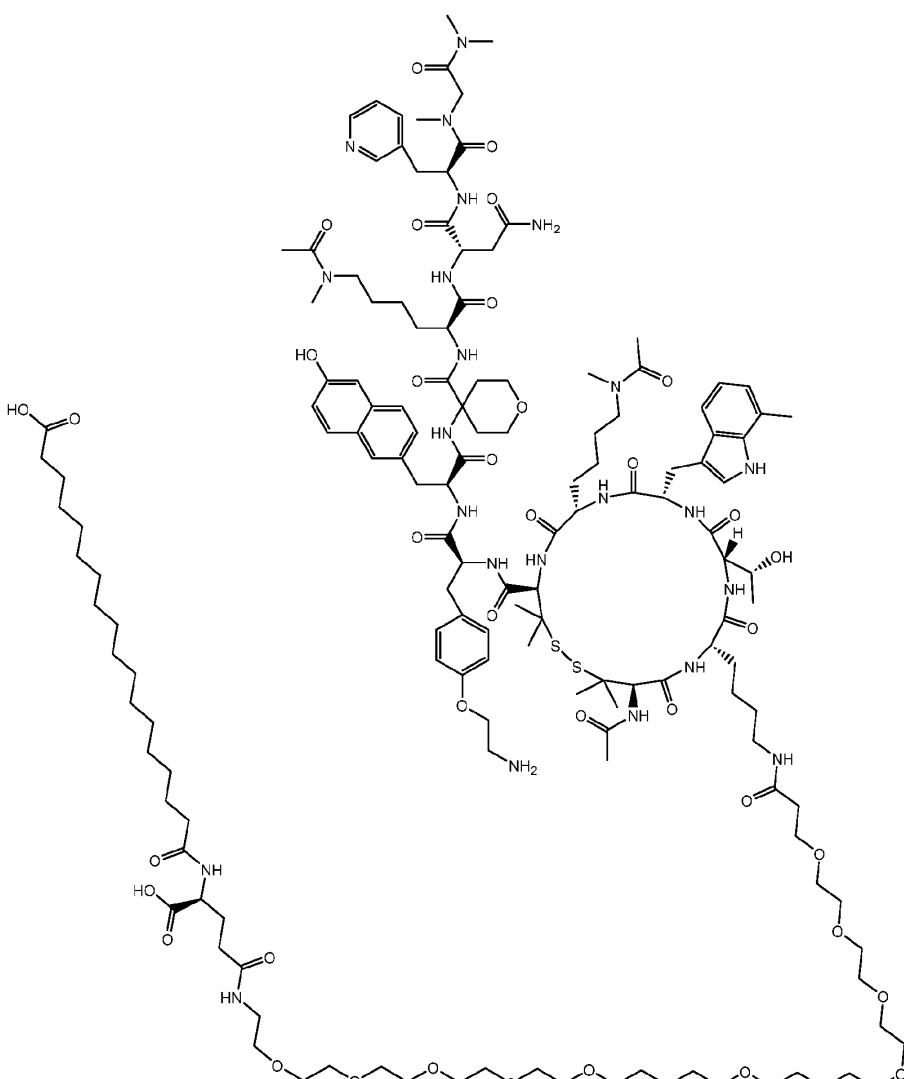


MeCO-r-Pen(3)-N-T-7MeW-K(Ac)-Pen(3)-AEF-6OH₂Nal-THP-E-N-3Pyra-Sar-K(PEG₂PEG₂gEC18OH)-CONH₂

SEQ ID NO	Structure
283	 The chemical structure represents a large, complex peptide molecule, likely a cyclic peptide with multiple side chains and modifications. The structure is highly branched and includes various functional groups, including amide bonds, hydroxyl groups, and a long alkyl chain. The molecule is shown in a 2D representation, with the main chain forming a large, irregular loop. The side chains are attached to the main chain at various points, including a long alkyl chain, a hydroxyl group, and a long alkyl chain. The structure is highly detailed, showing the connectivity of the atoms and the presence of various functional groups. MeCO-Pen(3)-N-T-7MeW-K(Ac)-Pen(3)-AEF-6OH2Nal-THP-E-N-3Pya-Sar-K(PEG2PEG2gEC18OH)-CONH2

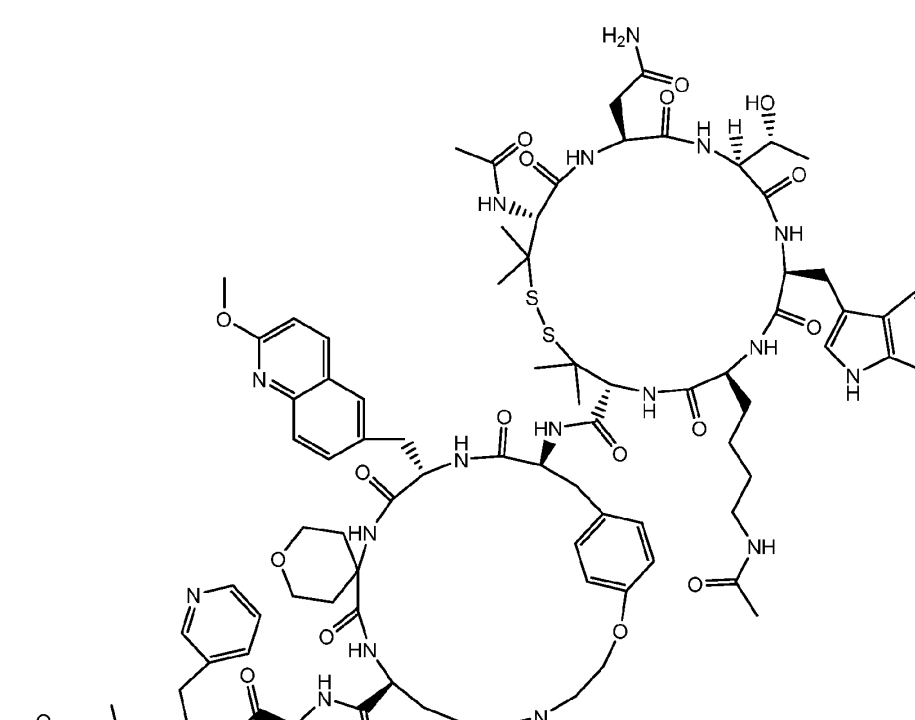
SEQ ID NO	Structure
284	 The chemical structure shows a long-chain peptide derivative. It features a carboxylic acid group at the N-terminus, followed by a long alkyl chain, a PEG linker, and a complex side chain. The side chain includes a pyridine ring, a thiazolidine ring, a hydroxyl group, a thioether bridge, and a thiazolidine ring. The structure is highly branched and contains multiple amide bonds and functional groups. MeCO-Pen(3)-N(N(Me)₂)-T-7MeW-K(PEG12gEC18OH)-Pen(3)-AEF-6OH2NaI-THP-K(NMeAc)-N-3Py-Sar-CON(Me)₂

SEQ ID NO	Structure
285	 MeCO-Pen(3)-N(N(Me)₂)-T-7MeW-K(NMeAc)-Pen(3)-AEF-6OH₂NaI-THP-K(PEG12gEC18OH)-N-3Pyra-Sar-CON(Me)₂

SEQ ID NO	Structure
286	 MeCO-Pen(3)-K(PEG12gEC18OH)-T-7MeW-K(NMeAc)-Pen(3)-AEF-6OH2Nal-THP-K(NMeAc)-N-3PyA-Sar-CON(Me)2

[illegible]

[illegible]

SEQ ID NO	Structure
289	 MeCO-Pen(3)-N-T-7MeW-K(Ac)-Pen(3)-AEF(2)-6MeQui-THP-E(2)-N-3PyA-Sar-CONH2

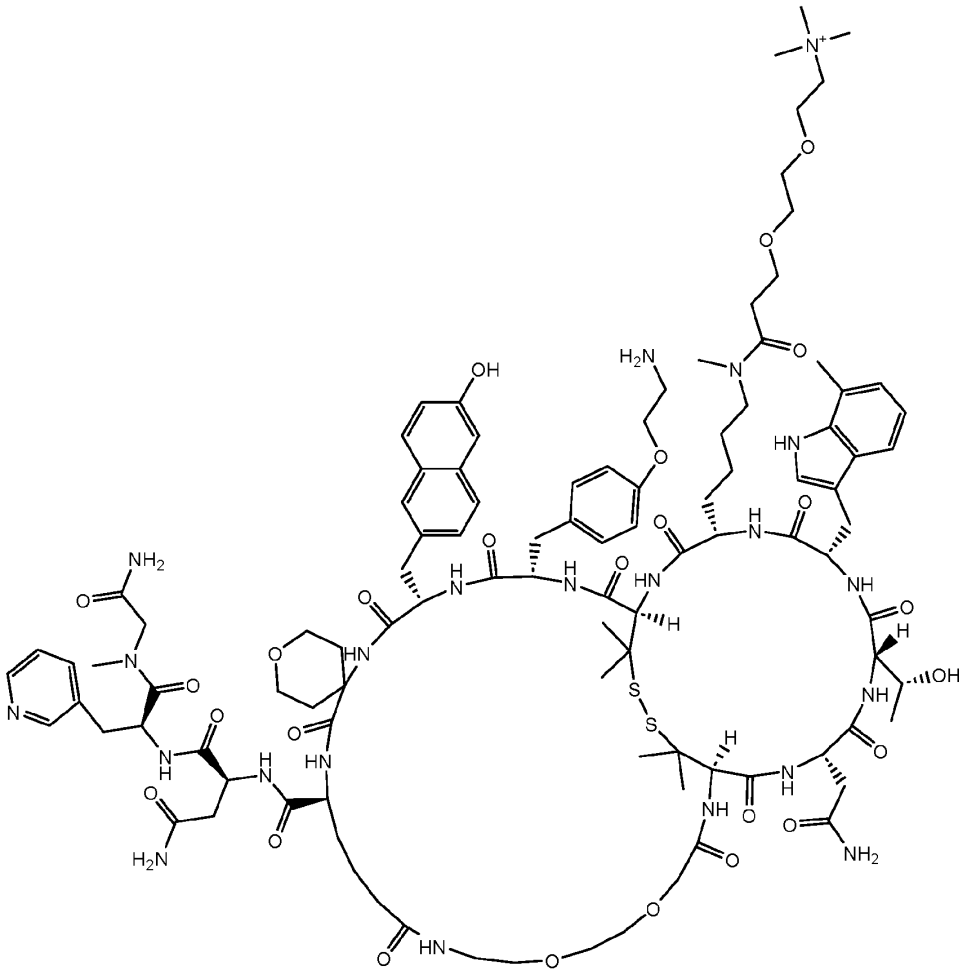
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[illegible]

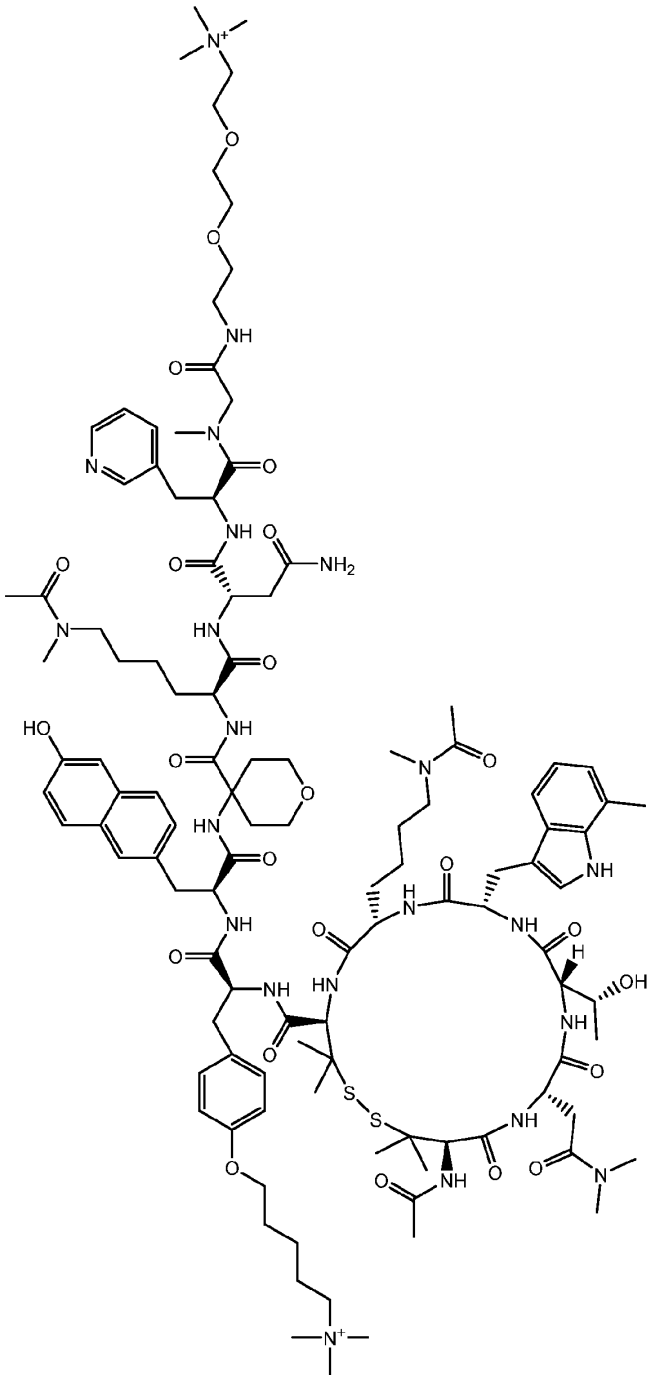
cPEG3aCO-Pen(3)-N(N(Me)2)-T-7MeW-K(NMeAc)-Pen(3)-AEF-6OH2NaI-THP-Dab(NMeAc)-N-3PyA-Sar-CONH(PEG3a)

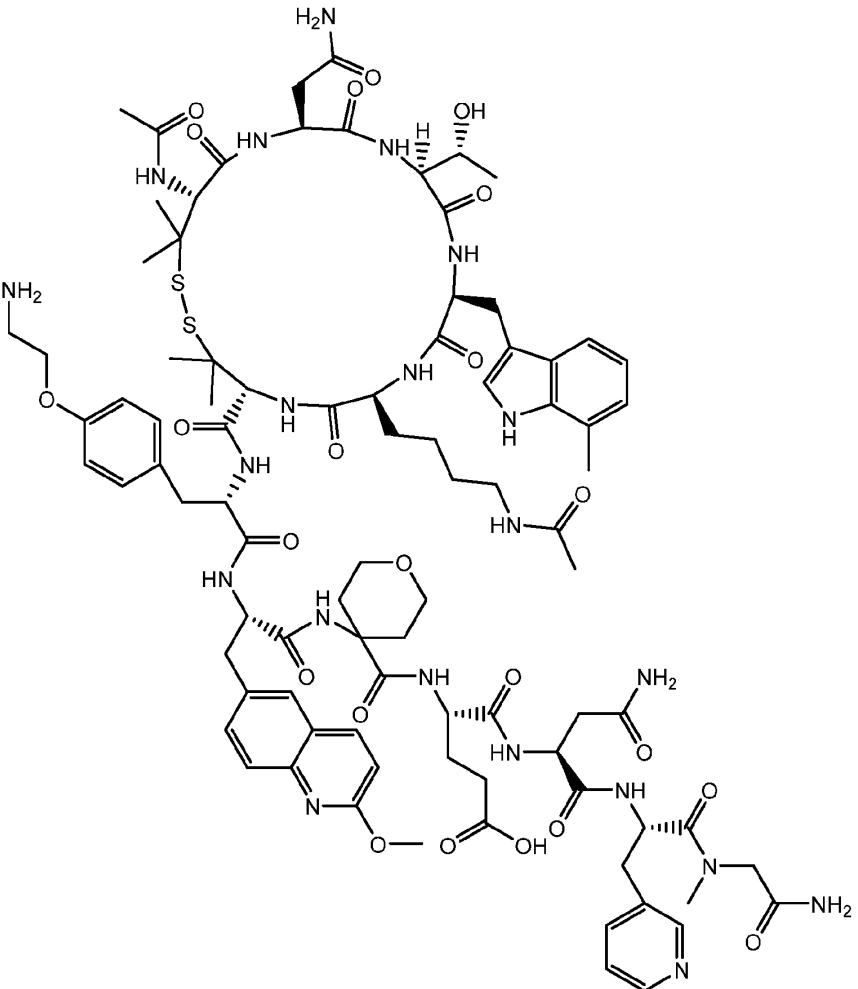
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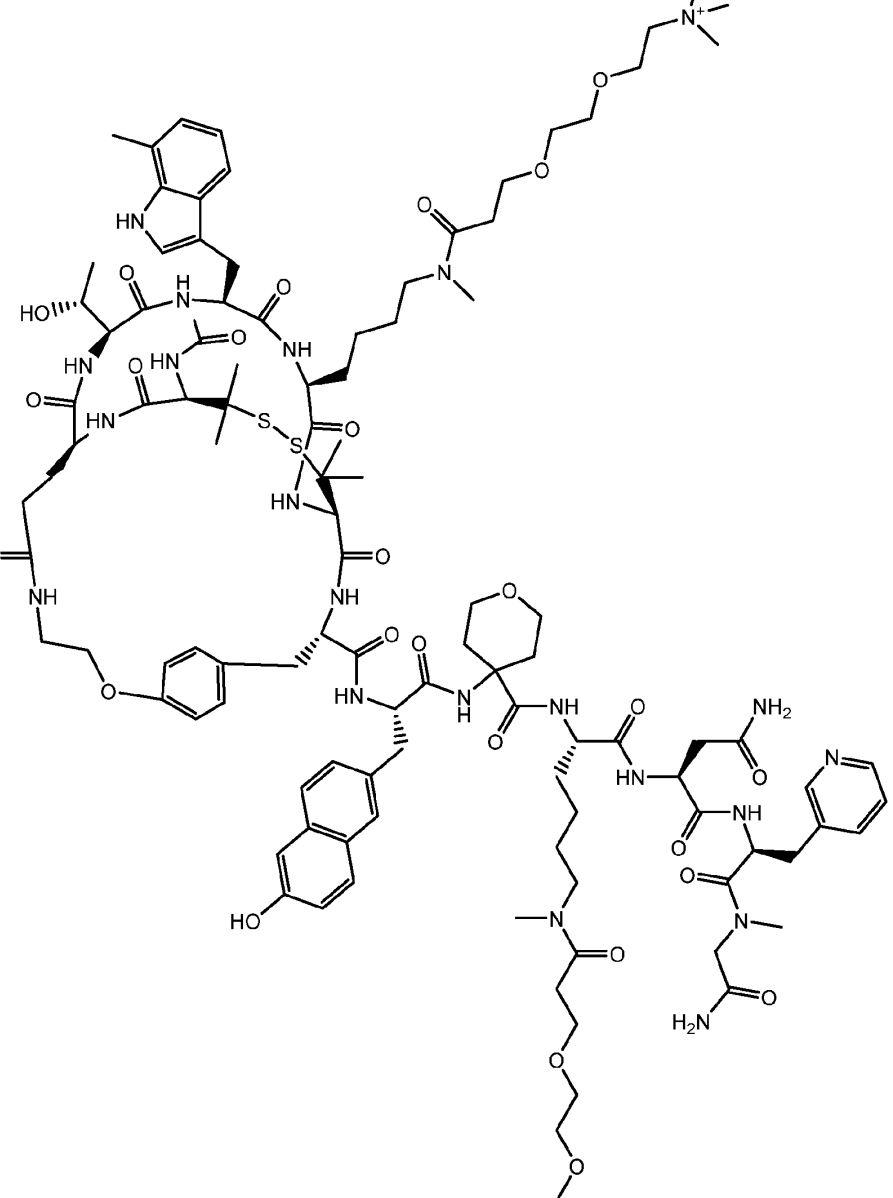
cPEG3aCO-Pen(3)-N(N(Me)₂)-T-7MeW-Lys(N+Me2mPEG3)-Pen(3)-AEF-6OH2NaI-THP-Dab(NMeAc)-N-3PyA-Sar-CONH(PEG3a)

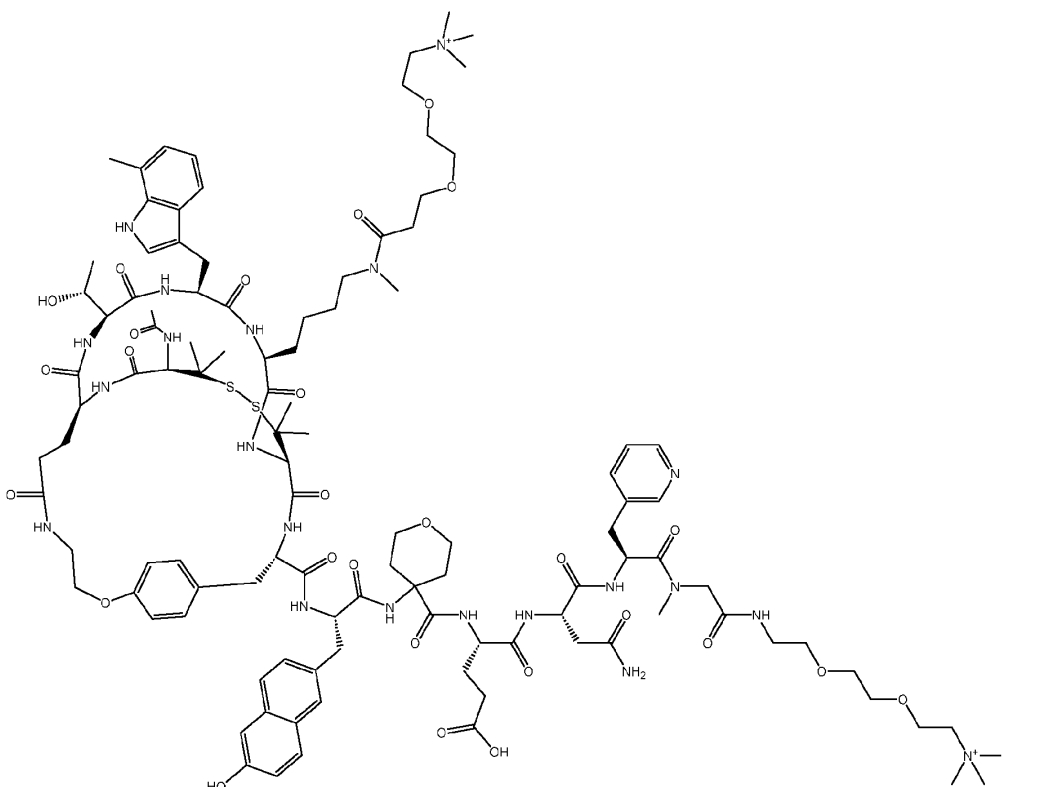
SEQ ID NO	Structure
293	 Chemical structure of a large cyclic peptide, specifically a macrocyclic peptide. The structure features a central ring composed of amino acid residues, including a PEG chain (poly(ethylene glycol)), a naphthyl group, a 6-hydroxy-2-naphthyl group, a 4-aminophenyl group, a 2-pyridyl group, and a 3-pyridyl group. The structure is highly complex, showing multiple amide bonds, hydroxyl groups, and a quaternary ammonium group (N⁺) attached to a long PEG chain. The sequence is identified as PEG2(2)-Pen(3)-N-T-7MeW-K(NMecPEG3a)-Pen(3)-AEF-6OH2Nal-THP-hE(2)-N-3PyA-Sar-CONH2.

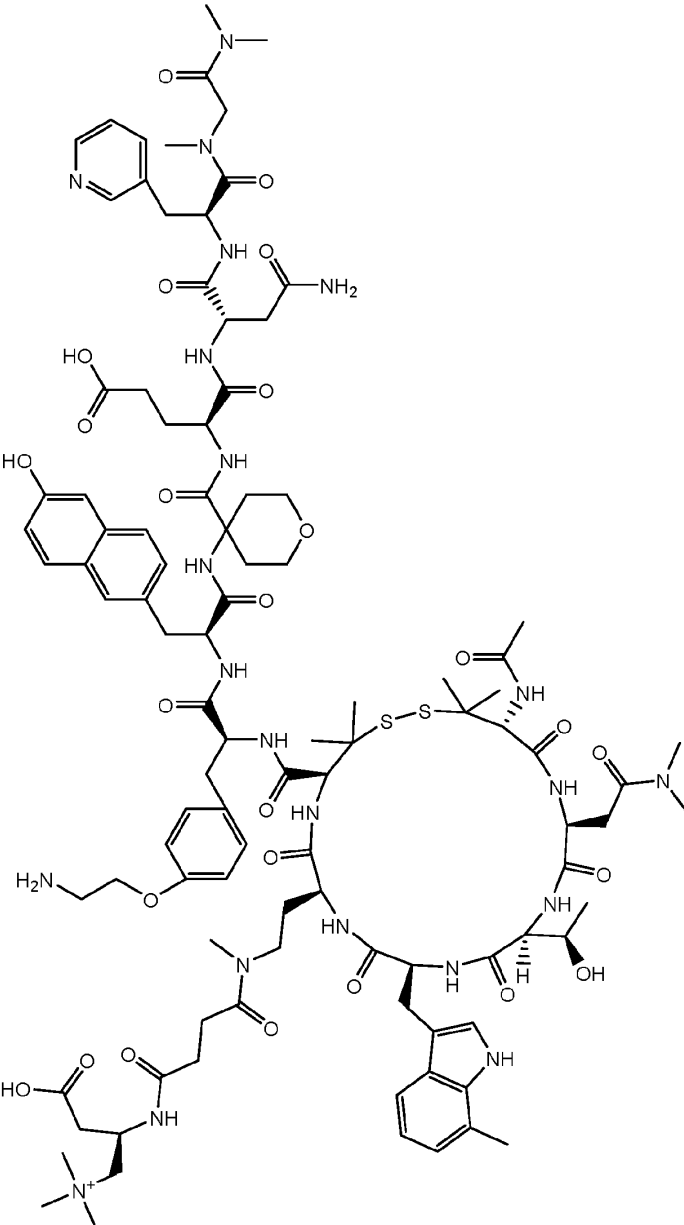
[illegible]

SEQ ID NO	Structure
295	 MeCO-Pen(3)-N(N(Me)₂)-T-7MeW-K(NMeAc)-Pen(3)-TMAPF-6OH₂NaI-THP-K(NMeAc)-N-3Pya-Sar-CONH(PEG3a)

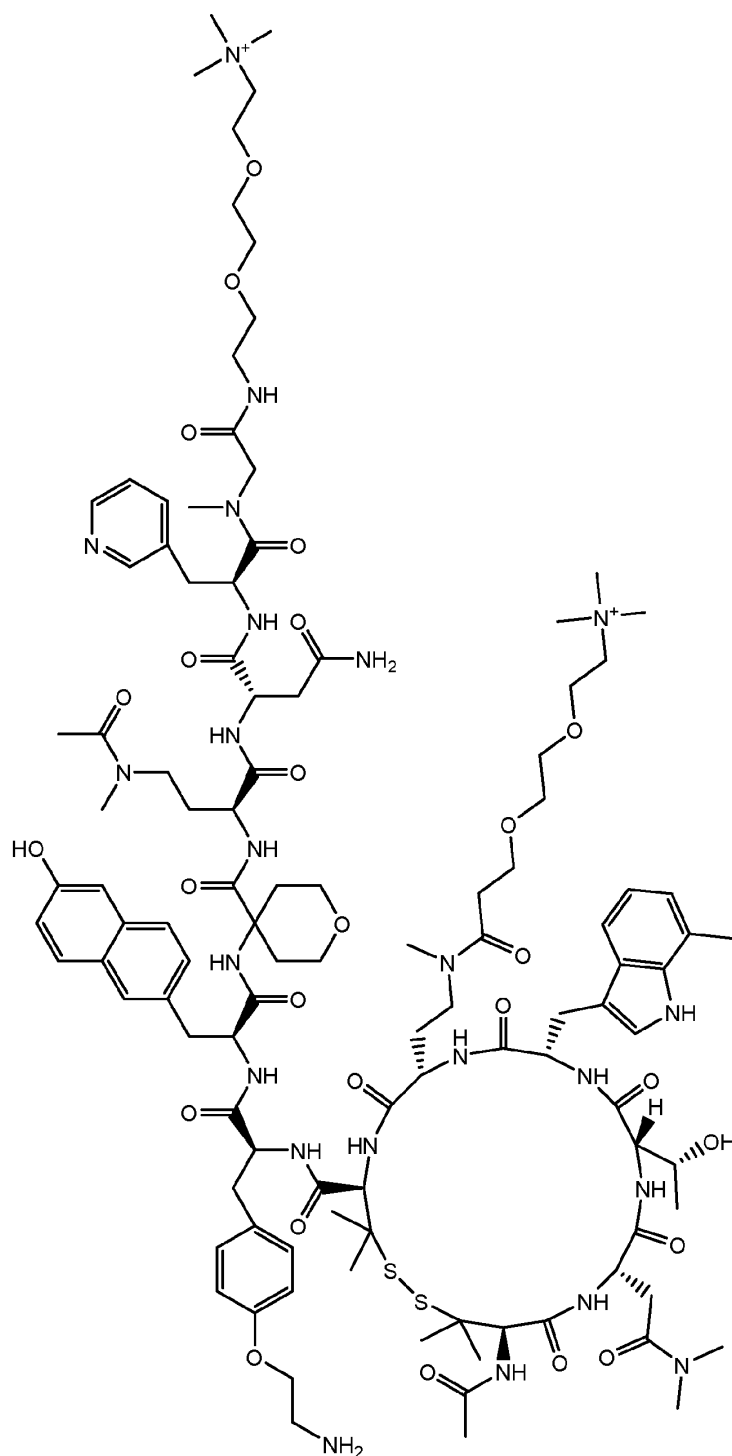
SEQ ID NO	Structure
296	 MeCO-Pen(3)-N-T-7MeW-K(Ac)-Pen(3)-AEF-6MeQui-THP-E-N-3Pya-Sar-CONH₂

SEQ ID NO	Structure
297	 The chemical structure shows a large cyclic peptide backbone with 18 amino acid residues. The residues are: MeCO-Pen(3)-E(2)-T-7MeW-K(NMecPEG3a)-Pen(3)-AEF(2)-6OH2Nal-THP-K(NMecPEG3a)-N-3Pya-Sar-CONH2. The structure is highly complex, featuring a large macrocyclic ring with various side chains, including aromatic rings, aliphatic chains, and charged groups. The structure is drawn in a 2D representation with stereochemistry indicated by wedges and dashes.

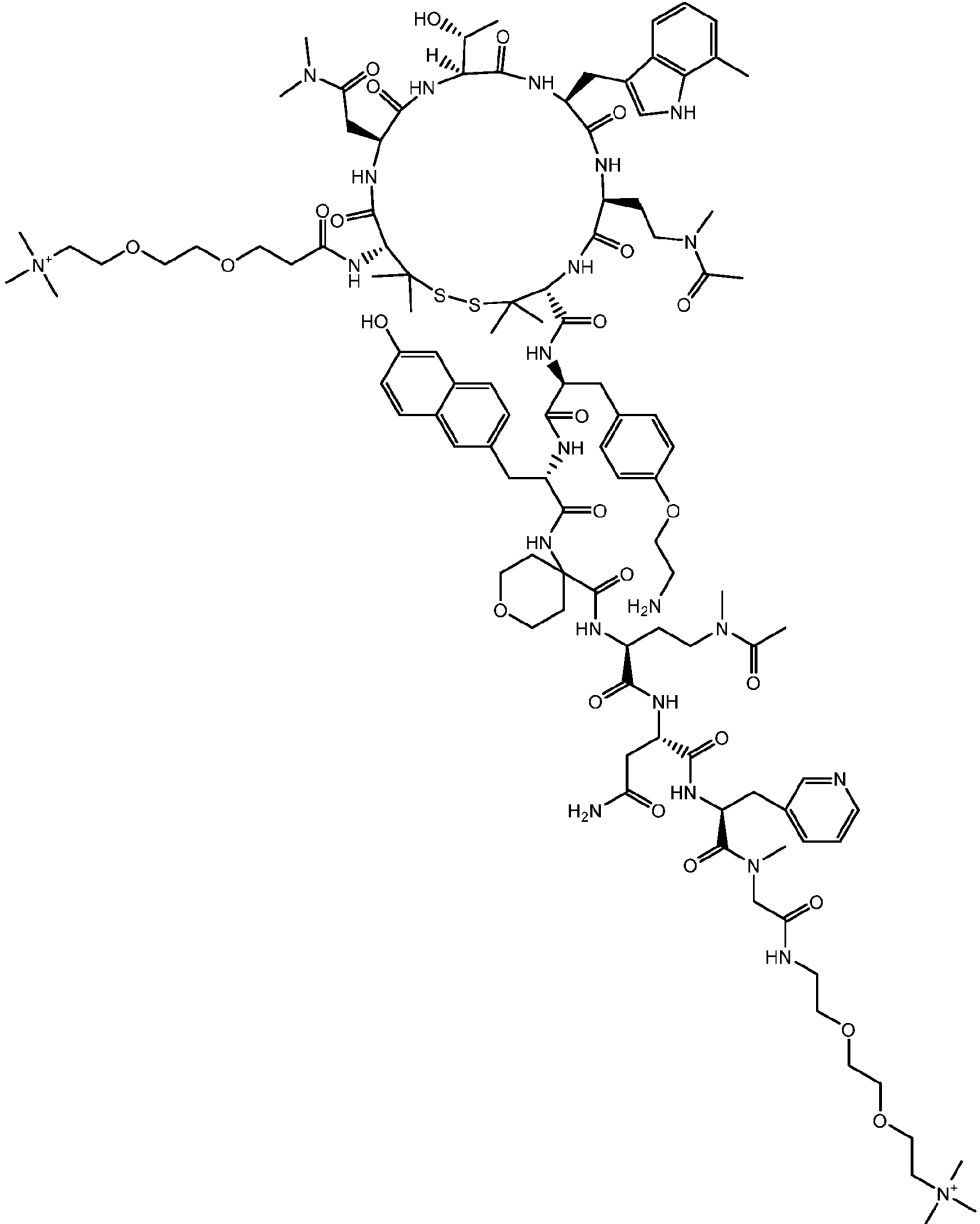
SEQ ID NO	Structure
298	 MeCO-Pen(3)-E(2)-T-7MeW-K(NMecPEG3a)-Pen(3)-AEF(2)-6OH2Nal-THP-E-N-3Py-Sar-CONH(PEG3a)

SEQ ID NO	Structure
299	 The chemical structure depicts a large cyclic peptide with a central 12-membered ring containing a disulfide bridge (S-S). The ring is substituted with several side chains, including a 3-pyridyl group, an amide-linked chain with a terminal amine, a hydroxy acid, a 6-hydroxy-2-naphthyl group, a 4-(2-aminoethoxy)phenyl group, a 3-(dimethylamino)propyl group, a 3-(2-amino-3-methylbutyryl) group, a 3-(2-amino-3-methylbutyryl) group, and a 3-(2-amino-3-methylbutyryl) group. The structure is highly complex, featuring multiple amide bonds, hydroxyl groups, and aromatic systems. MeCO-Pen(3)-N(N(Me)₂)-T-7MeW-Dab(NMecarn)-Pen(3)-AEF-6OH₂Nal-THP-E-N-3Pya-Sar-CON(Me)₂

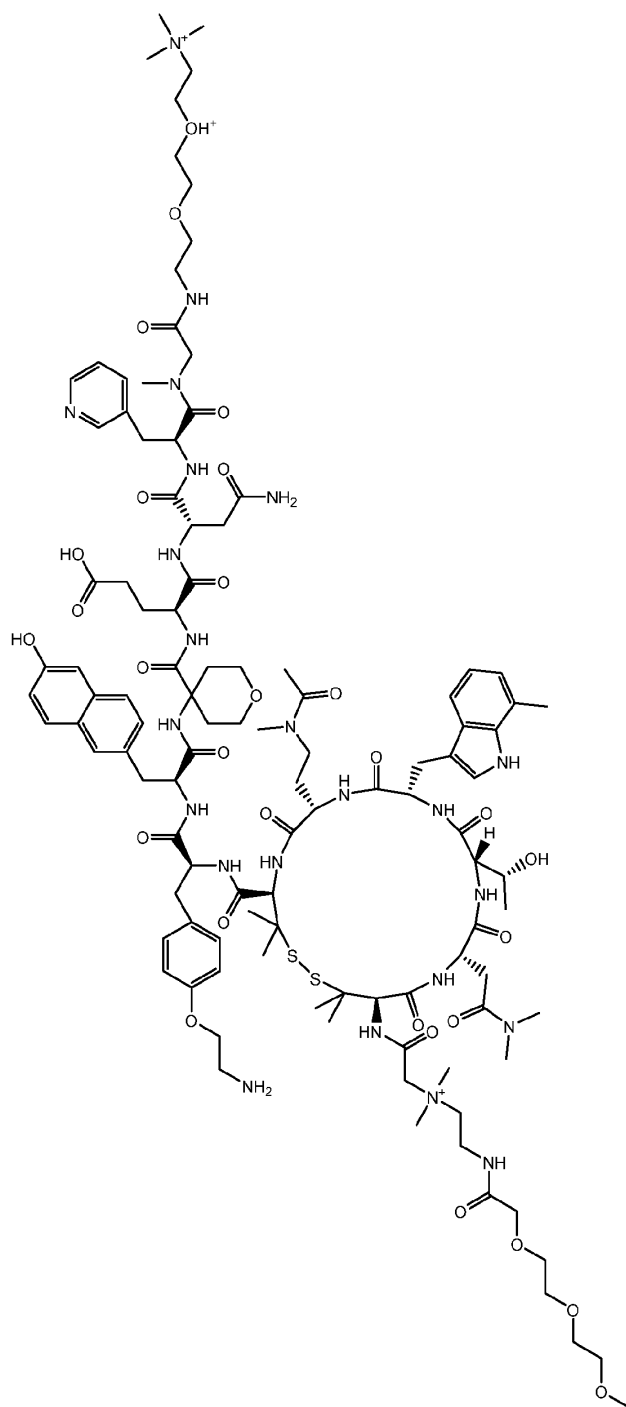
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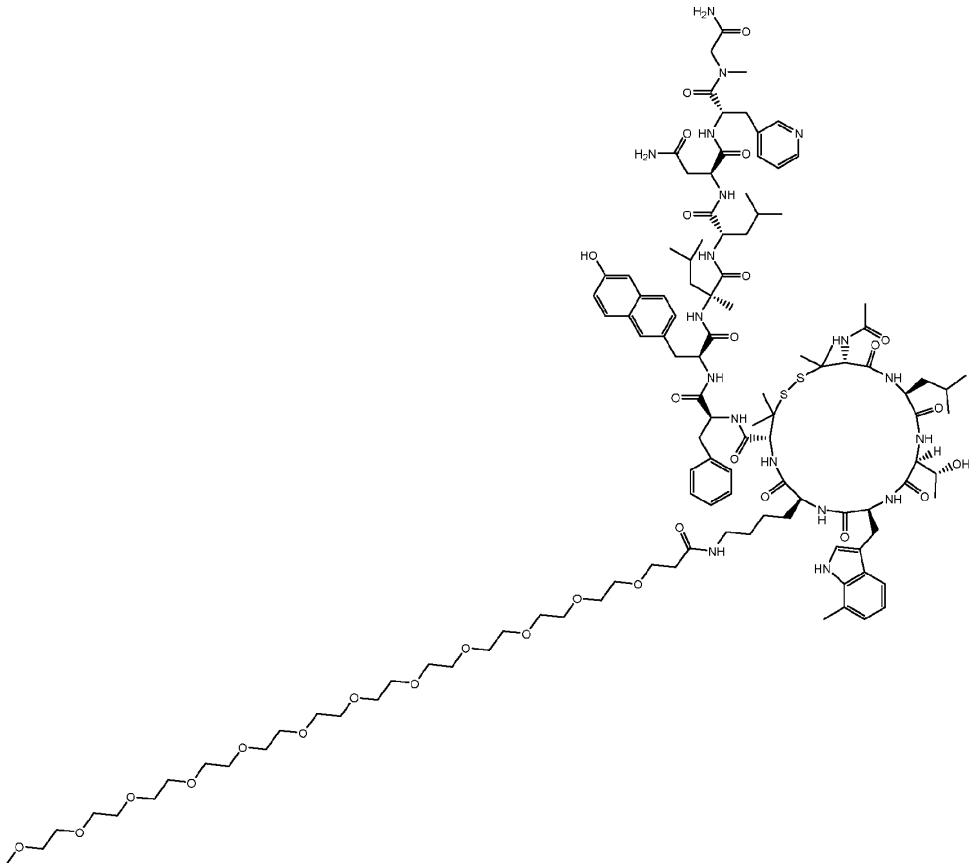
MeCO-Pen(3)-N(N(Me)₂)-T-7MeW-Dab(NMecPEG3a)-Pen(3)-AEF-6OH2Nal-THP-Dab(NMeAc)-N-3Py-Sar-CONH(PEG3a)

SEQ ID NO	Structure
301	 cPEG3aCO-Pen(3)-N(N(Me)2)-T-7MeW-Dab(NMeAc)-Pen(3)-AEF-6OH2NaI-THP-Dab(NMeAc)-N-3Py-Sar-CONH(PEG3a)

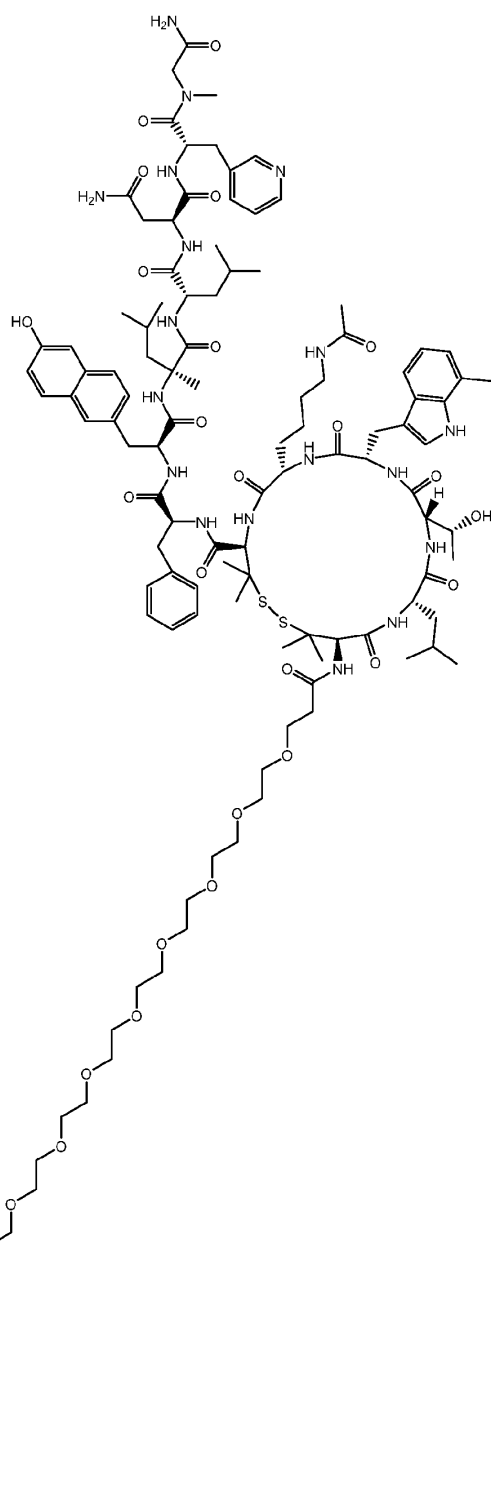
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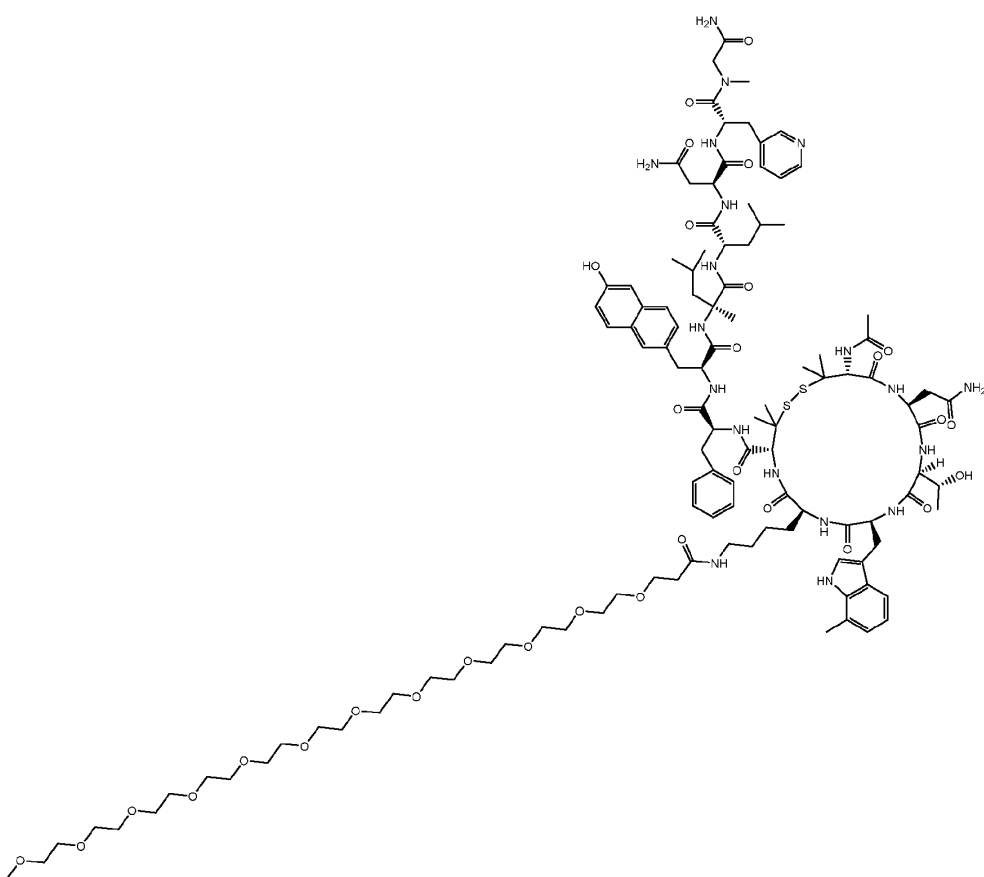
mPEG3CO-SP6-Pen(3)-N(NMe)₂-T-7MeW-Dab(NMeAc)-Pen(3)-AEF-6OH₂Nal-THP-E-N-3Pyra-Sar-CONH(PEG3a)

SEQ ID NO	Structure
303	 The chemical structure shows a long-chain peptide derivative. It begins with a MeCO group, followed by a series of amino acid residues: Pen(3), L, T, 7MeW, K, and a 12-unit mPEG linker. This is followed by another series of residues: Pen(3), F, 6OH2Nal, aMeL, L, N, 3Py, and Sar, which is terminated with a CONH2 group. The structure is highly complex, featuring a large cyclic peptide moiety with a disulfide bridge and various side chains, including a phenol group and a pyridine ring. MeCO-Pen(3)-L-T-7MeW-K(mPEG12)-Pen(3)-F-6OH2Nal-aMeL-L-N-3Py-Sar-CONH2

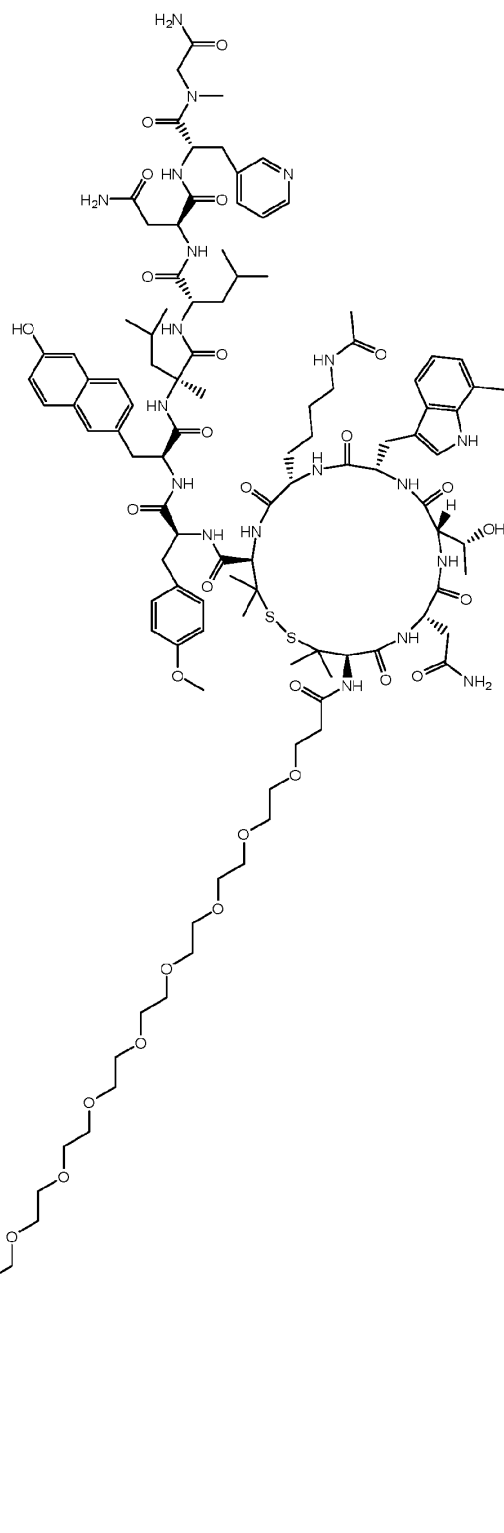
304



mPEG12CO-Pen(3)-L-T-7MeW-K(Ac)-Pen(3)-F-6OH2Nal-aMeL-L-N-3Pya-Sar-CONH2

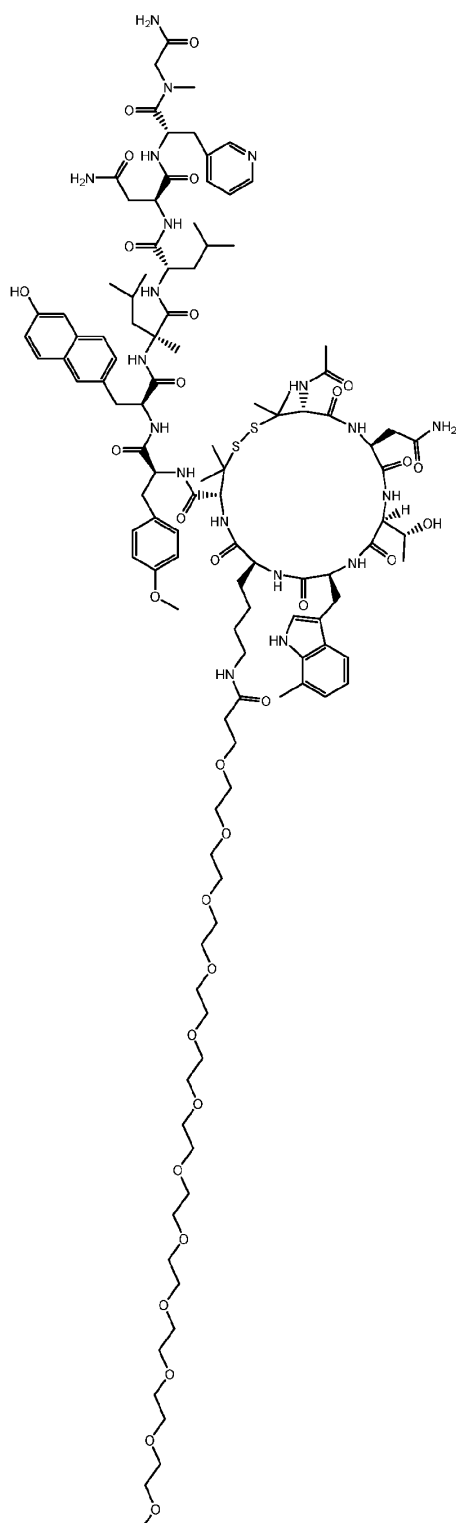
SEQ ID NO	Structure
305	 MeCO-Pen(3)-N-T-7MeW-K(mPEG12)-Pen(3)-F-6OH2Nal-aMeL-L-N-3Pya-Sar-CONH2

306

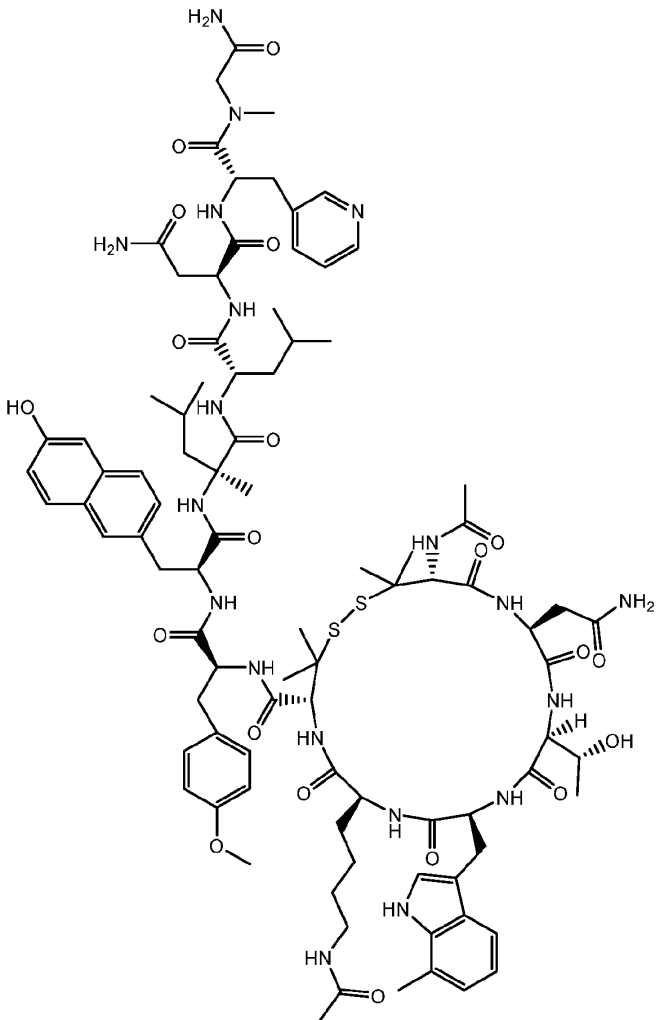


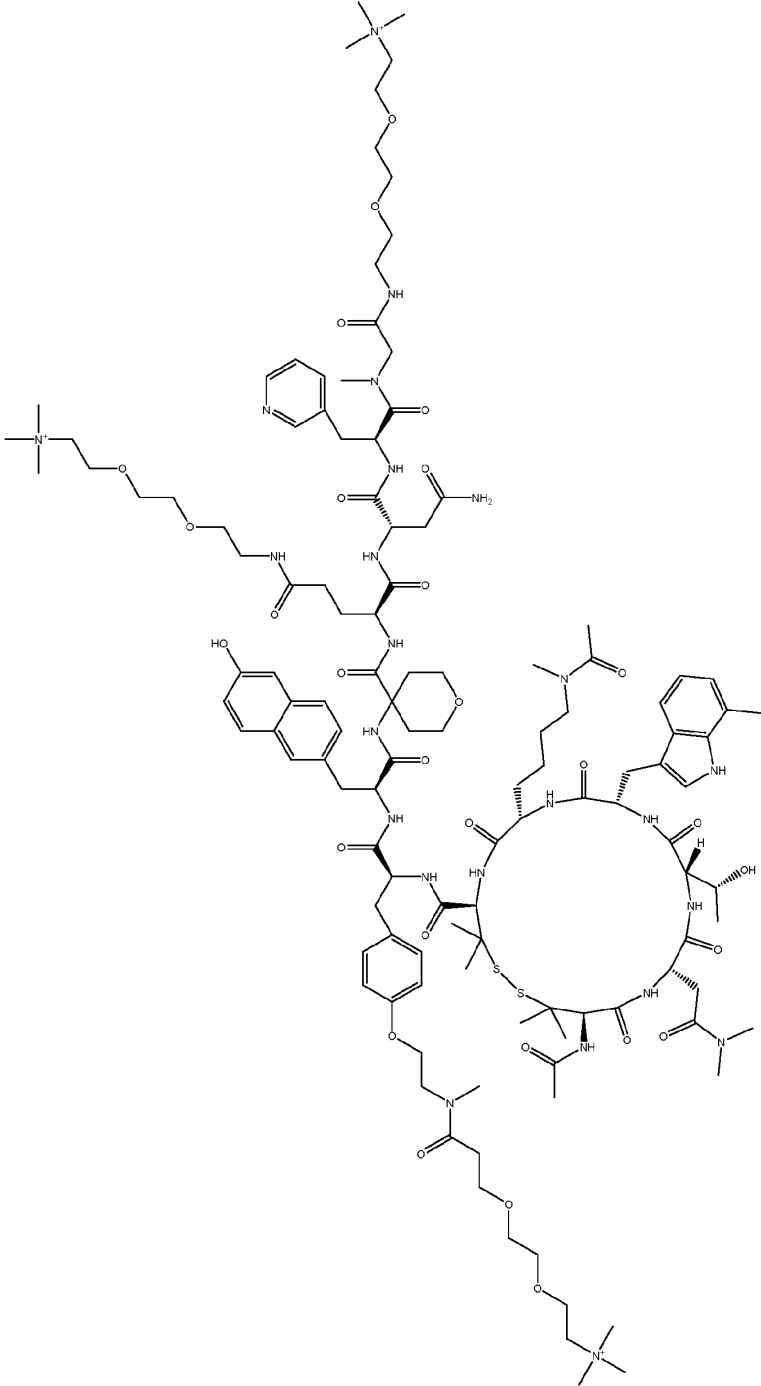
mPEG12CO-Pen(3)-N-T-7MeW-K(Ac)-Pen(3)-4OMeF-6OH2Nal-aMeL-L-N-3Pya-Sar-CONH2

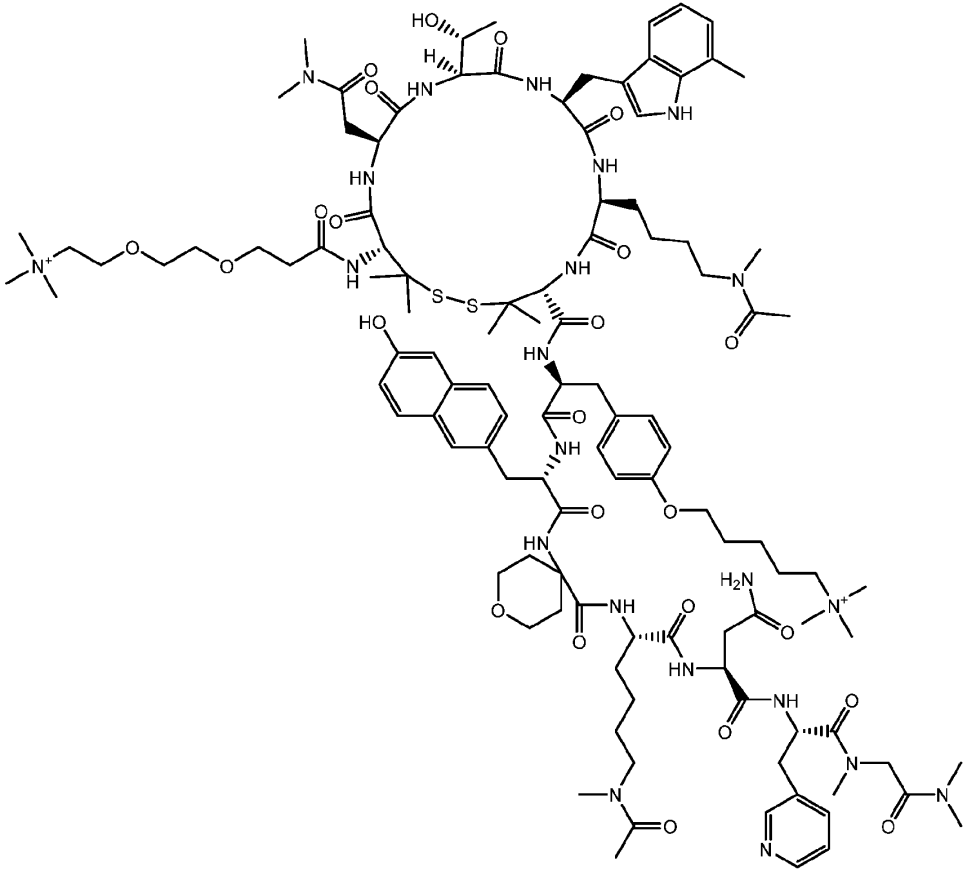
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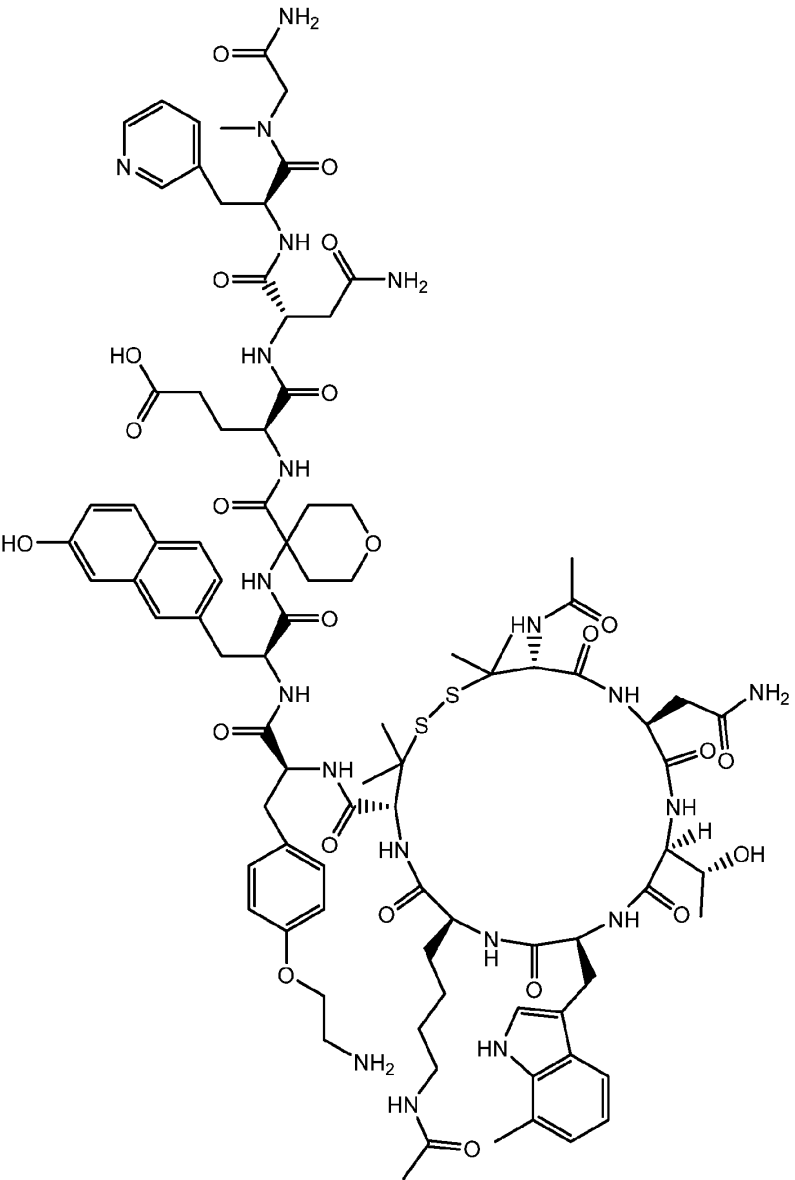


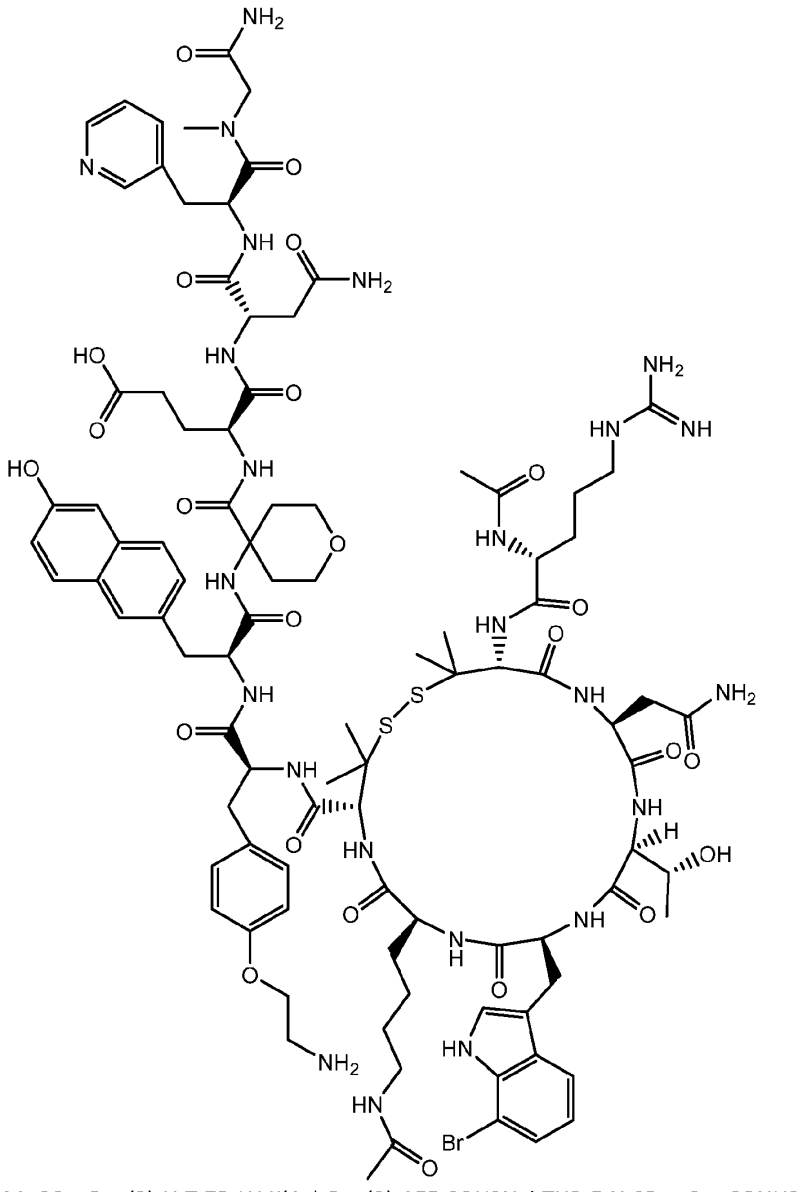
MeCO-Pen(3)-N-T-7MeW-K(mPEG12)-Pen(3)-4OMeF-6OH2Nal-aMeL-L-N-3Pya-Sar-CONH₂

SEQ ID NO	Structure
308	 The chemical structure shows a 12-membered cyclic peptide ring. The ring is composed of amino acid residues connected by amide bonds. The residues, starting from the top and moving clockwise, are: a proline derivative with a methyl group on the nitrogen; a proline derivative with a methyl group on the nitrogen; a proline derivative with a methyl group on the nitrogen; a proline derivative with a methyl group on the nitrogen; a proline derivative with a methyl group on the nitrogen; a proline derivative with a methyl group on the nitrogen; a proline derivative with a methyl group on the nitrogen; a proline derivative with a methyl group on the nitrogen; a proline derivative with a methyl group on the nitrogen; a proline derivative with a methyl group on the nitrogen; a proline derivative with a methyl group on the nitrogen; and a proline derivative with a methyl group on the nitrogen. The side chains of the residues include: a 4-hydroxyphenyl group, a 4-methoxyphenyl group, a 2-pyridyl group, a 2-aminoethyl group, a 2-hydroxyethyl group, a 2-aminoethyl group, a 2-hydroxyethyl group, a 2-aminoethyl group, a 2-hydroxyethyl group, a 2-aminoethyl group, a 2-hydroxyethyl group, and a 2-aminoethyl group. The structure is highly complex and represents a specific peptide sequence. MeCO-Pen(3)-N-T-7MeW-K(Ac)-Pen(3)-4OMeF-6OH2Nal-aMeL-L-N-3Pya-Sar-CONH2

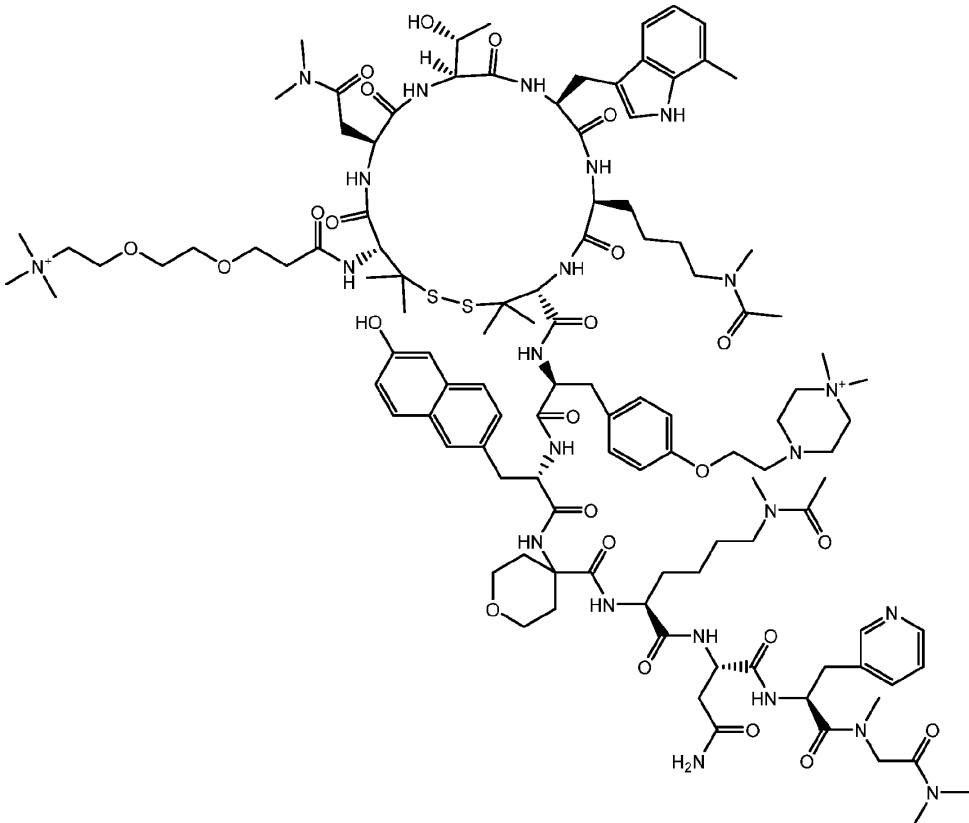
SEQ ID NO	Structure
309	 MeCO-Pen(3)-N(N(Me)2)-T-7MeW-K(NMeAc)-Pen(3)-AEF(NMePEG3a)-6OH2Nal-THP-E(COcPEG3a)-N-3Py-Sar-CONH(PEG3a)

SEQ ID NO	Structure
310	 cPEG3aCO-Pen(3)-N(N(Me)₂)-T-7MeW-K(NMeAc)-Pen(3)-TMAPF-6OH2Nal-THP-K(NMeAc)-N-3Py-Sar-CON(Me)₂

SEQ ID NO	Structure
311	 MeCO-Pen(3)-N-T-7MeW-K(Ac)-Pen(3)-AEF-7OH2NaI-THP-E-N-3Pya-Sar-CONH2

SEQ ID NO	Structure
312	 MeCO-r-Pen(3)-N-T-7BrW-K(Ac)-Pen(3)-AEF-6OH2NaI-THP-E-N-3Py-Sar-CONH2

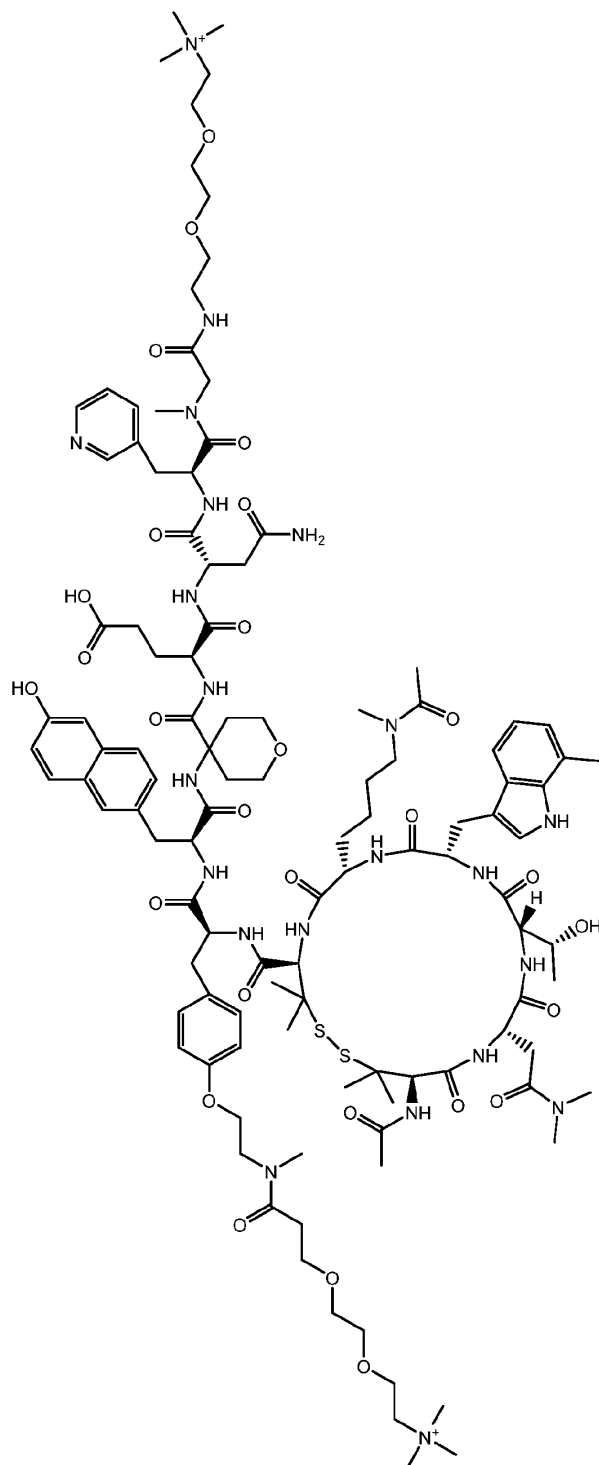
SEQ ID NO	Structure
313	MeCO-Pen(3)-N-T-7BrW-K(Ac)-Pen(3)-AEF-6OH2Nal-THP-E-N-3Pva-Sar-CONH2

SEQ ID NO	Structure
314	 cPEG3aCO-Pen(3)-N(N(Me)2)-T-7MeW-K(NMeAc)-Pen(3)-4DMPzEF-6OH2Nal-THP-K(NMeAc)-N-3Pyra-Sar-CON(Me)2

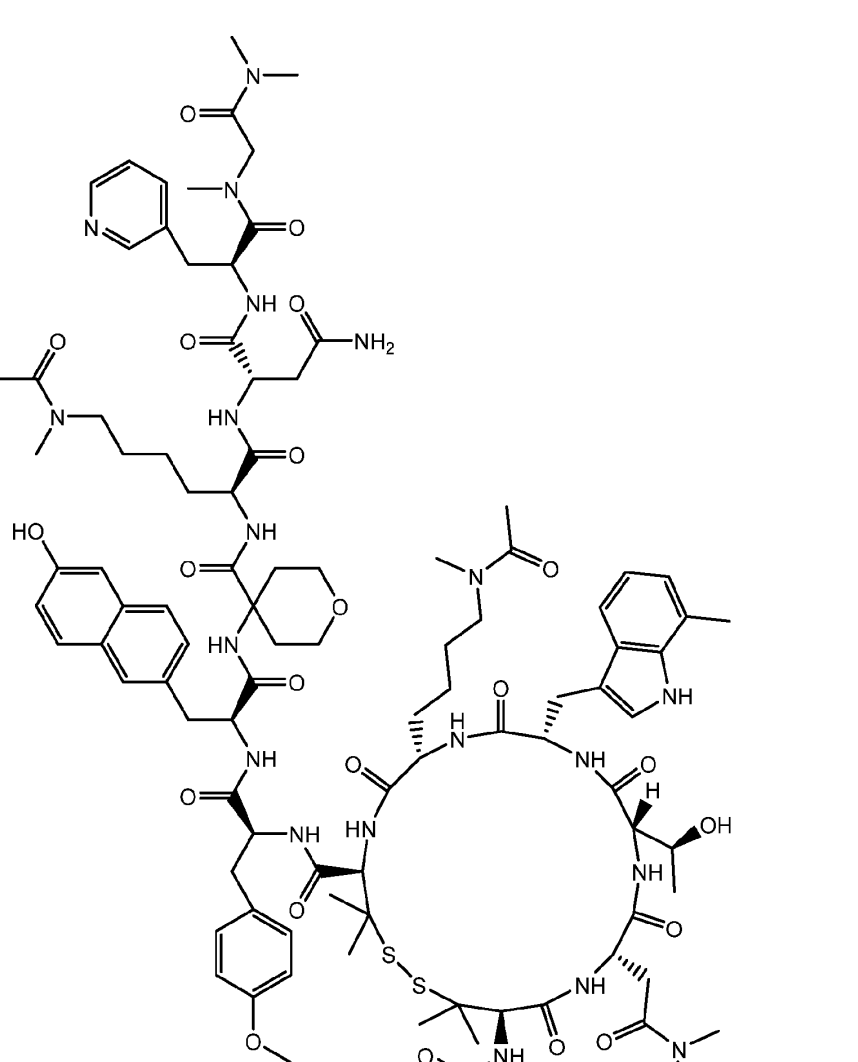
The chemical structure depicts a large macrocyclic molecule with a central ring and several side chains. The macrocycle is a 16-membered ring containing two amide bonds and two sulfonamide groups. The side chains include a quaternary ammonium group (N⁺), a hydroxyl group (OH), a sulfonamide group (SO₂NH₂), and a hydroxyl group (OH). The molecule is highly functionalized and complex.

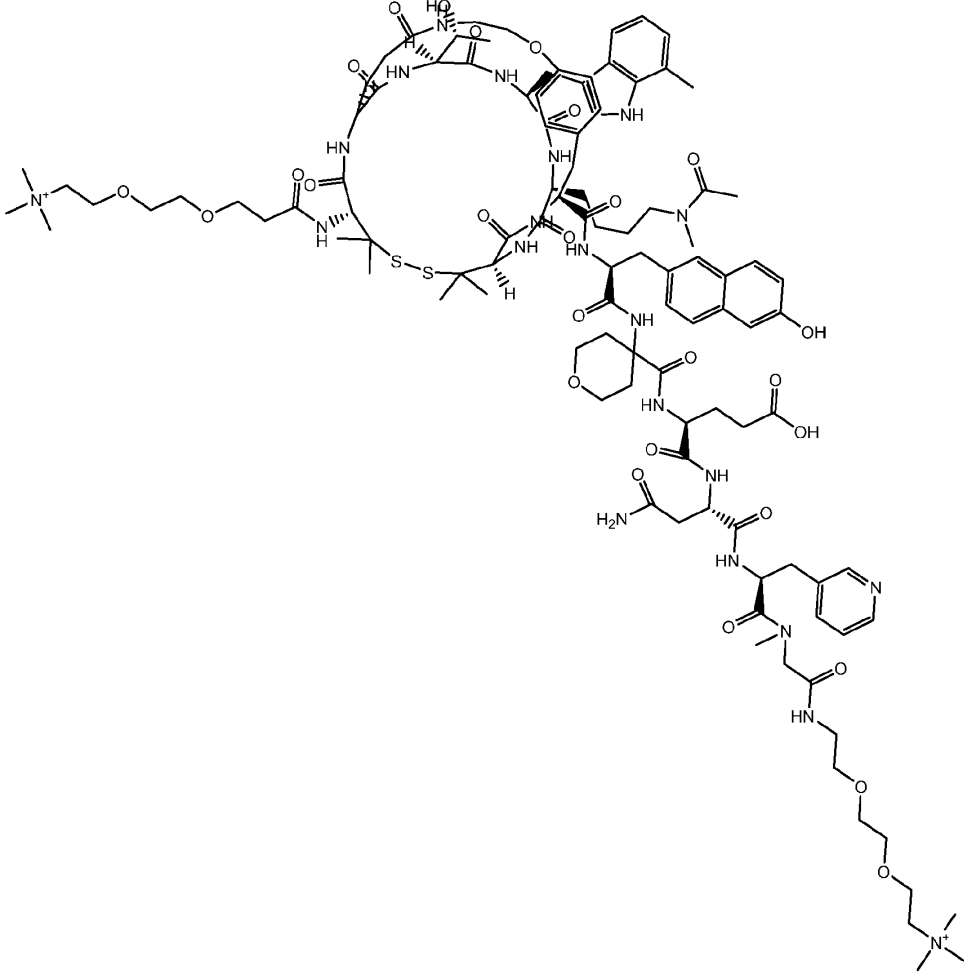
MeCO-Pen(3)-N(NMe₂)-T-7MeW-K(NMeAc)-Pen(3)-AEF(NMePEG3a)-6OH2NaI-THP-K(NMeAc)-N-3Pyra-Sar-CONH(PEG3a)

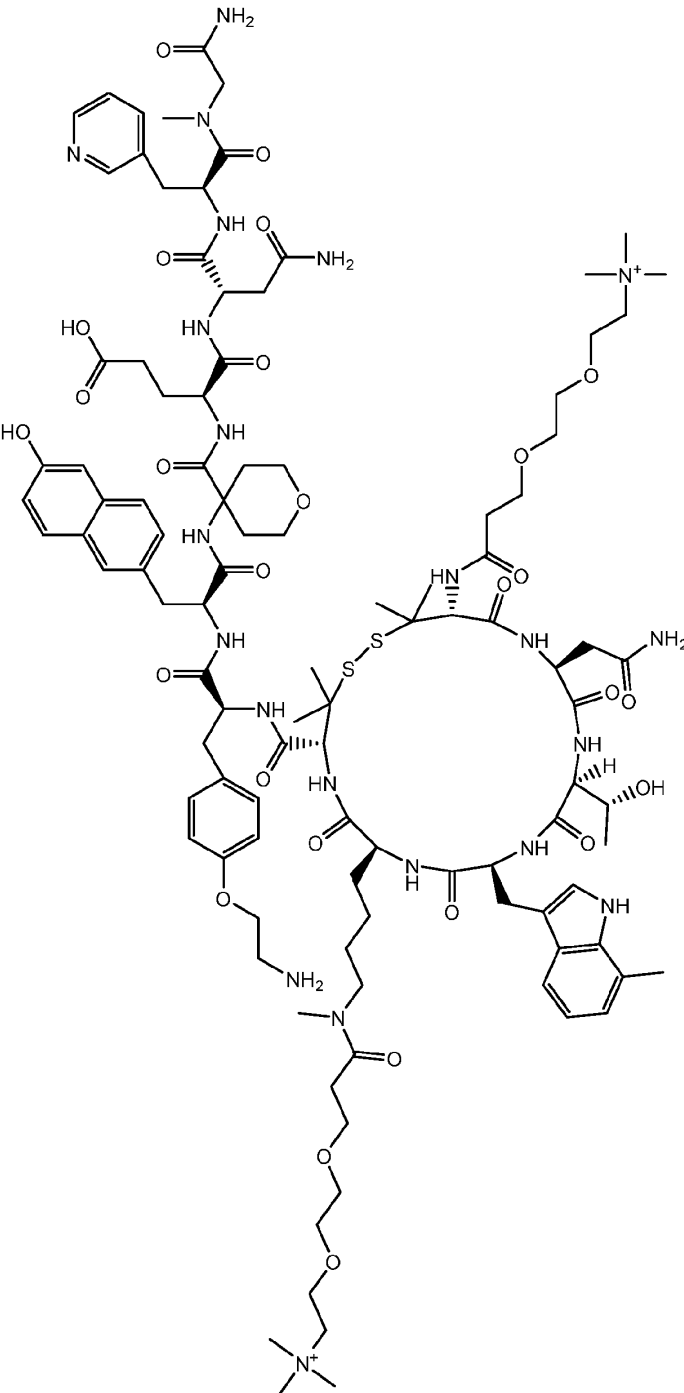
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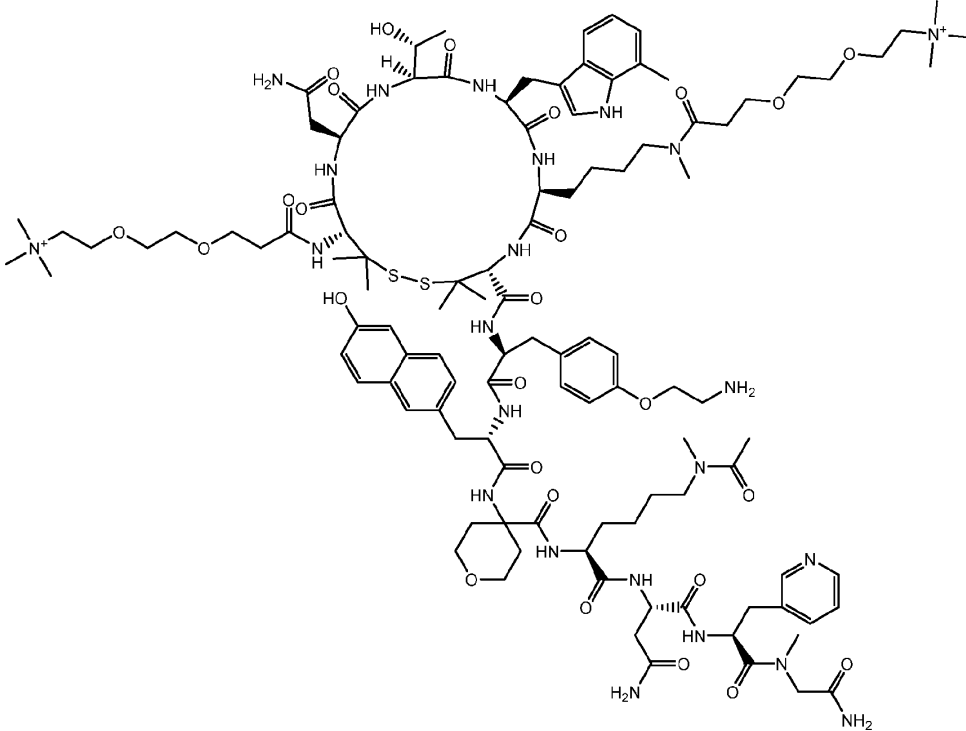


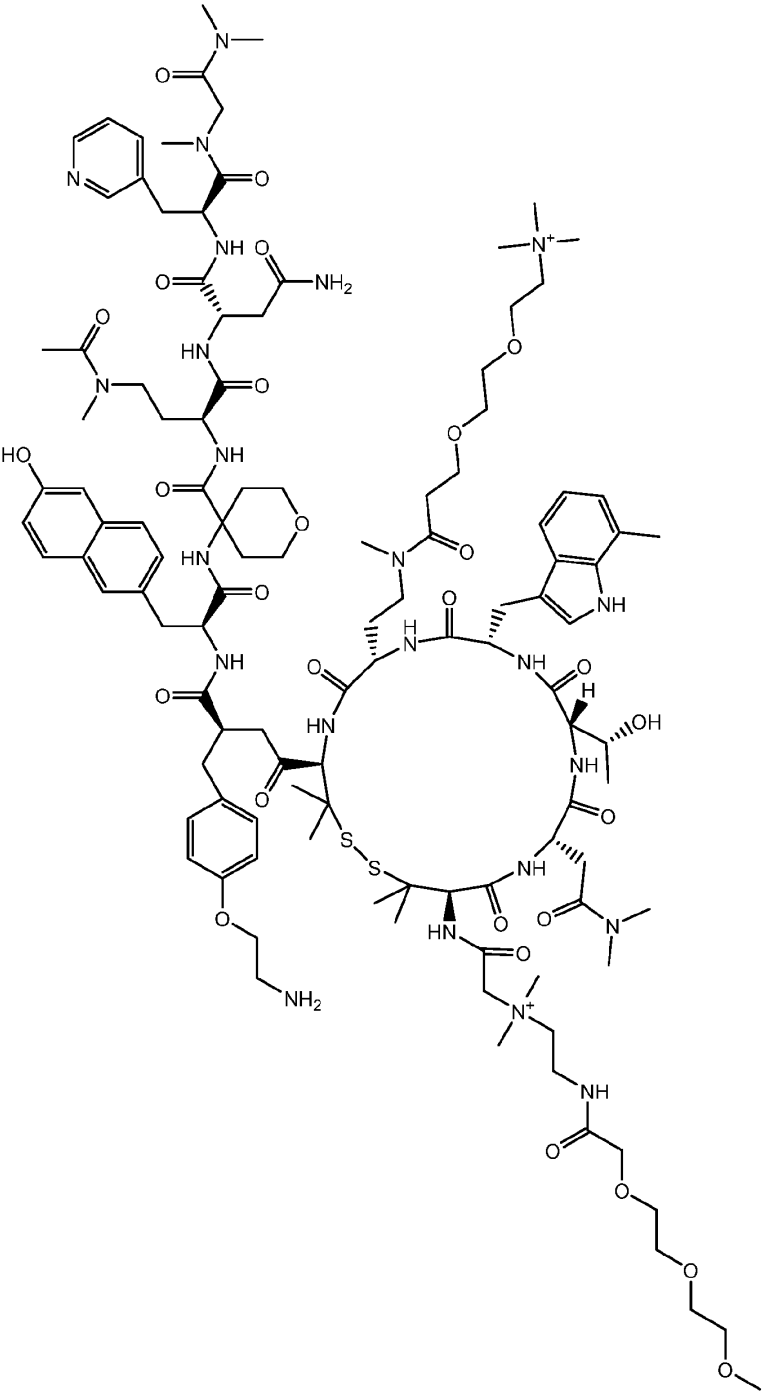
MeCO-Pen(3)-N(NMe₂)-T-7MeW-K(NMeAc)-Pen(3)-AEF(NMePEG3a)-6OH₂NaI-THP-E-N-3Py-Sar-CONH(PEG3a)

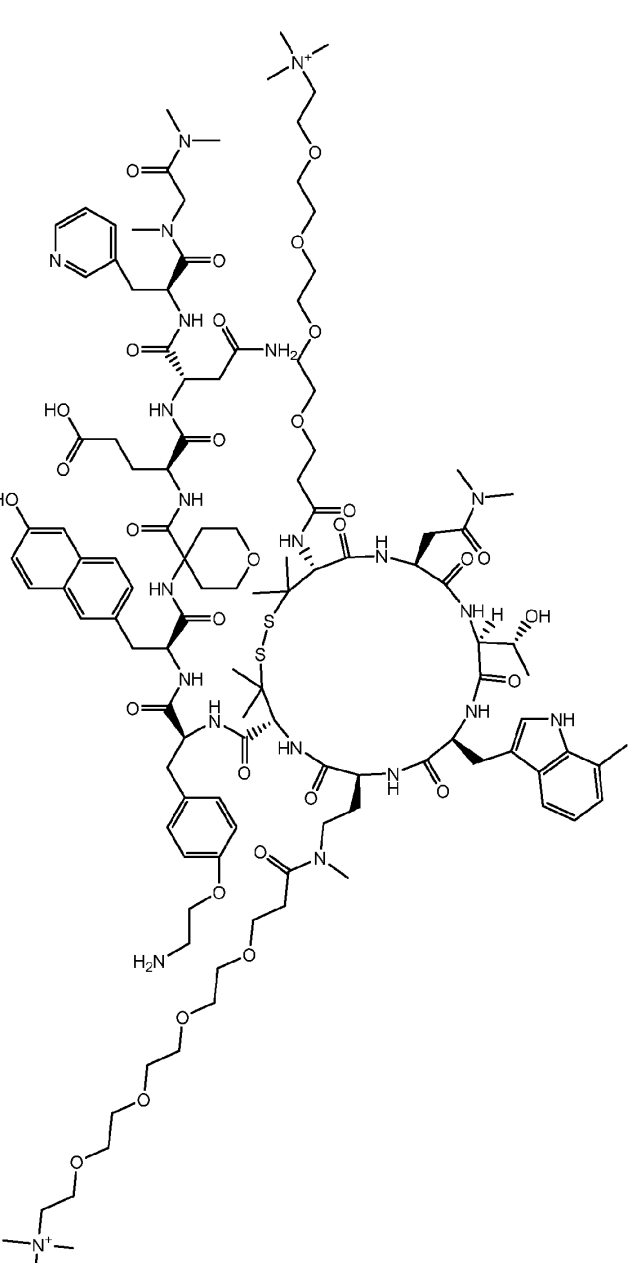
SEQ ID NO	Structure
317	 MeCO-Pen(3)-N(NMe)₂-T-7MeW-K(NMeAc)-Pen(3)-4DMPzEF-6OH₂Nal-THP-K(NMeAc)-N-3Py-Sar-CON(Me)₂

SEQ ID NO	Structure
318	 cPEG3aCO-Pen(3)-E(2)-T-7MeW-K(NMeAc)-Pen(3)-AEF(2)-6OH2Nal-THP-E-N-3Pya-Sar-CONH(PEG3a)

SEQ ID NO	Structure
319	 cPEG3aCO-Pen(3)-N-T-7MeW-K(NMecPEG3a)-Pen(3)-AEF-6OH2Nal-THP-E-N-3Py-Sar-CONH2

SEQ ID NO	Structure
320	 cPEG3aCO-Pen(3)-N-T-7MeW-K(NMecPEG3a)-Pen(3)-AEF-6OH2NaI-THP-K(NMeAc)-N-3PyA-Sar-CONH2

SEQ ID NO	Structure
321	 mPEG3CO-SP6-Pen(3)-N(N(Me)2)-T-7MeW-Dab(NMecPEG3a)-Pen(3)-AEF-6OH2Nal-THP-Dab(NMeAc)-N-3Pyra-Sar-CON(Me)2

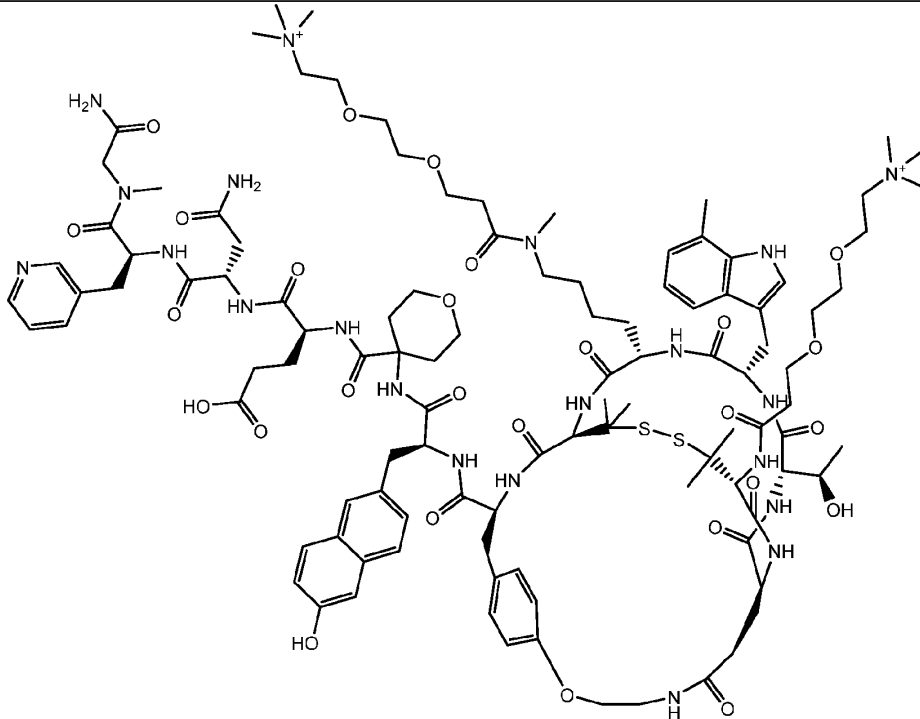
SEQ ID NO	Structure
322	 cPEG5aCO-Pen(3)-N(N(Me)2)-T-7MeW-Dab(NMecPEG5a)-Pen(3)-AEF-6OH2Nal-THP-E-N-3Pyra-Sar-CON(Me)2

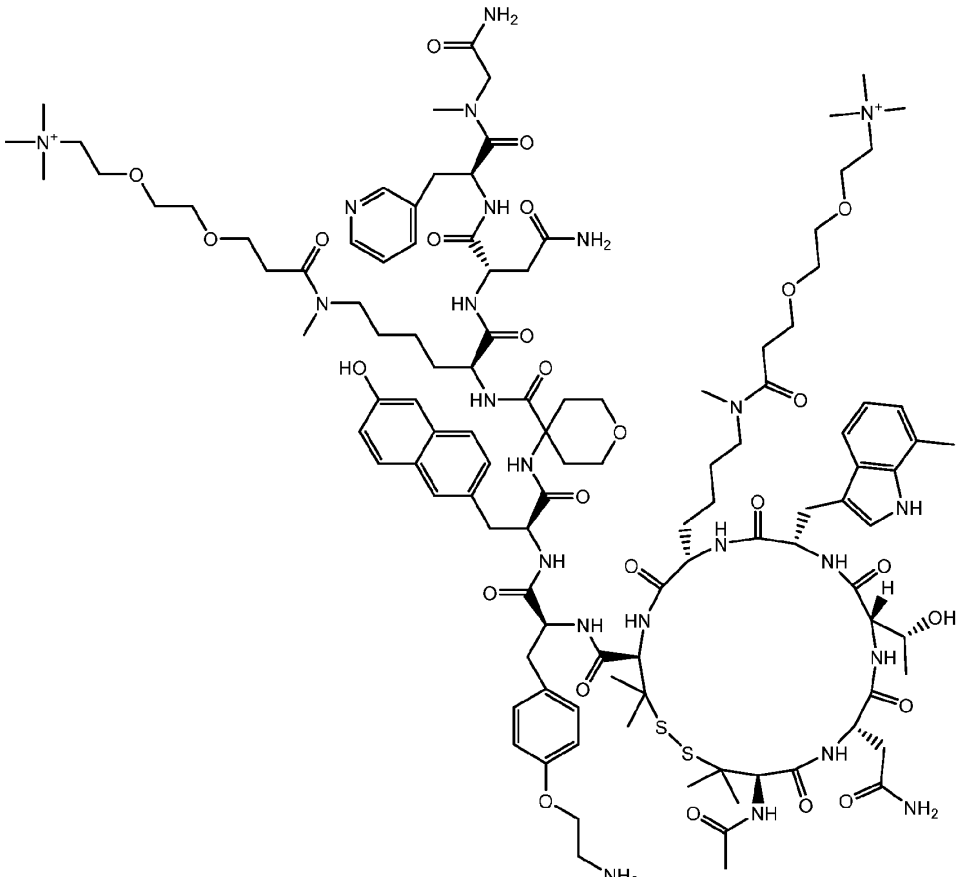
SEQ ID NO	Structure
323	cPEG3aCO-Pen(3)-N(N(Me)₂)-T-7MeW-Dab(NMeAc)-Pen(3)-AEF-6OH₂NaI-THP-E-N-3Pyra-Sar-CONH(PEG3a)

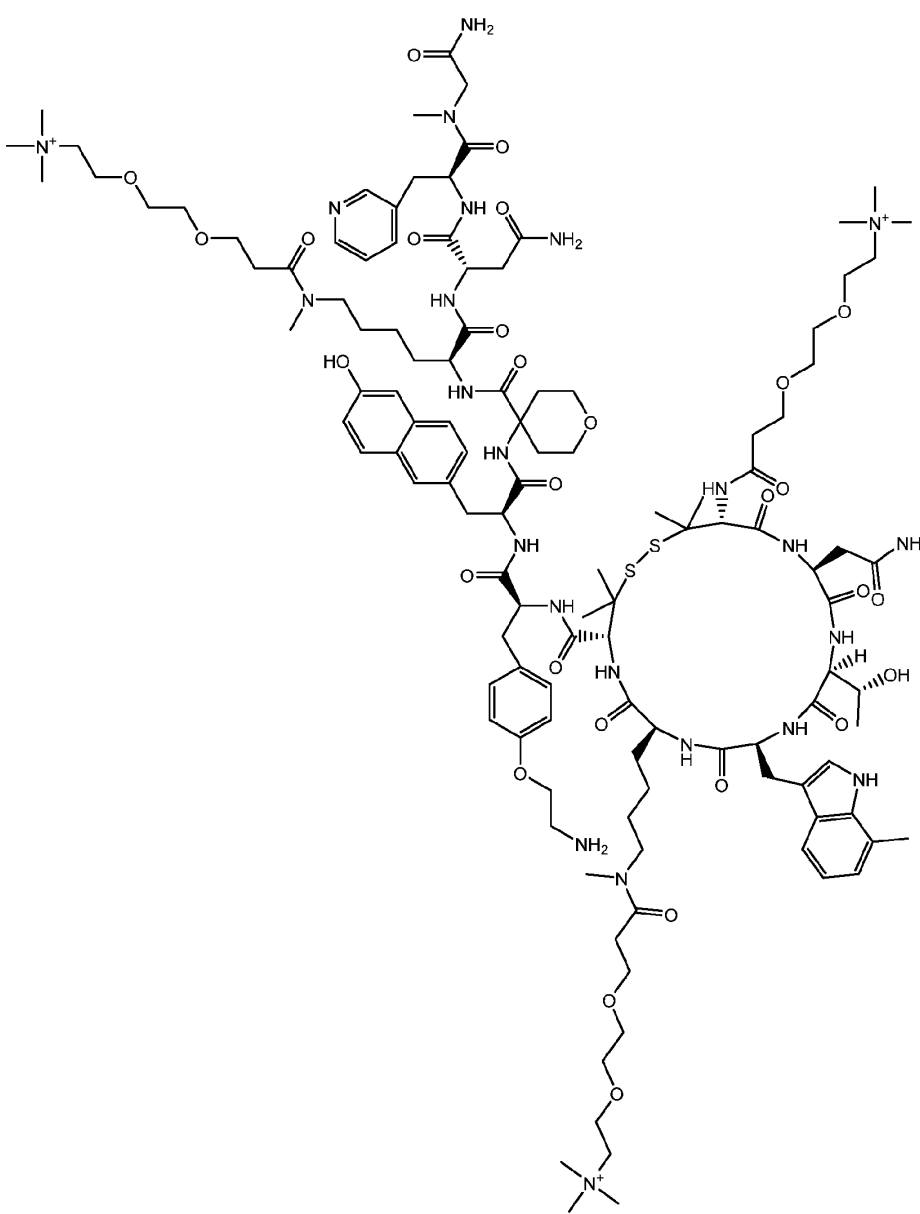
CN(C)C(=O)CCN1C(=O)C[C@H](C1C(=O)N[C@@H](C(=O)NCC(=O)N)C(=O)NCC(=O)O)C[C@H](N2C(=O)CC[C@H](C2)C(=O)NCC(=O)O)C(=O)NCC(=O)O

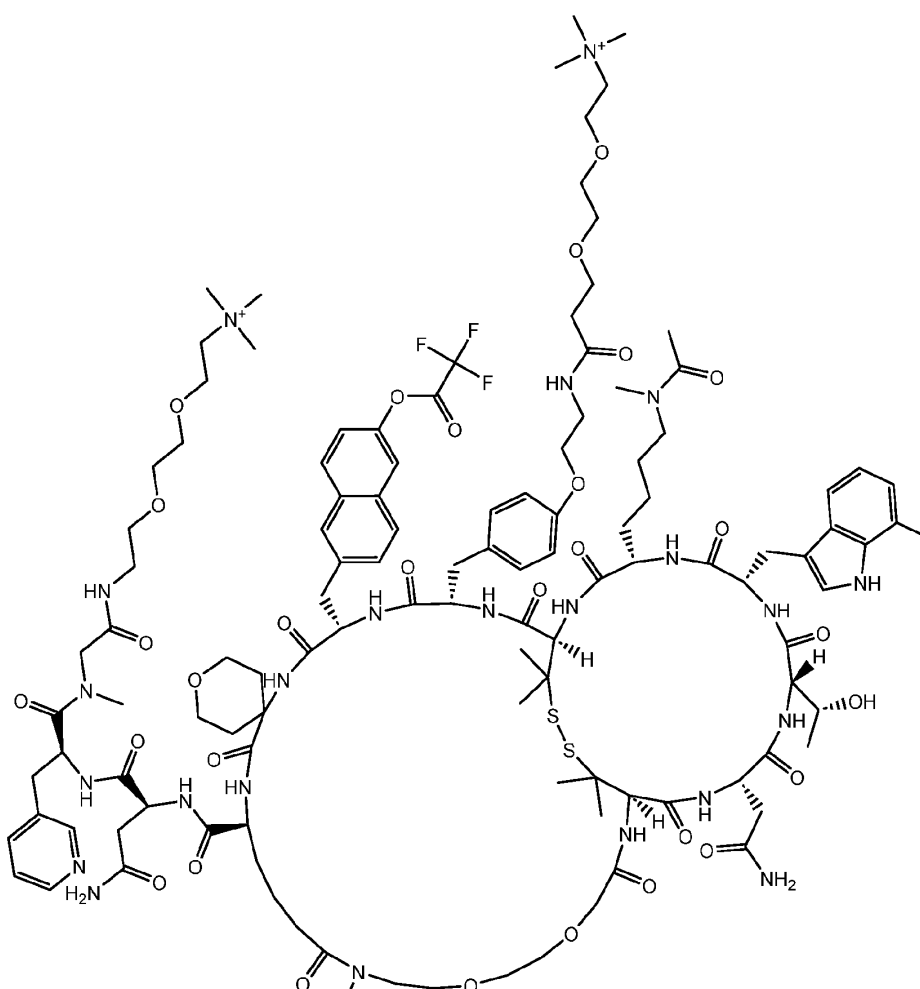
mPEG3CO-SP6-Pen(3)-N(NMe)₂-T-7MeW-Dab(NMecPEG3a)-Pen(3)-AEF-6OH2NaI-THP-E-N-3PyA-Sar-CON(Me)₂

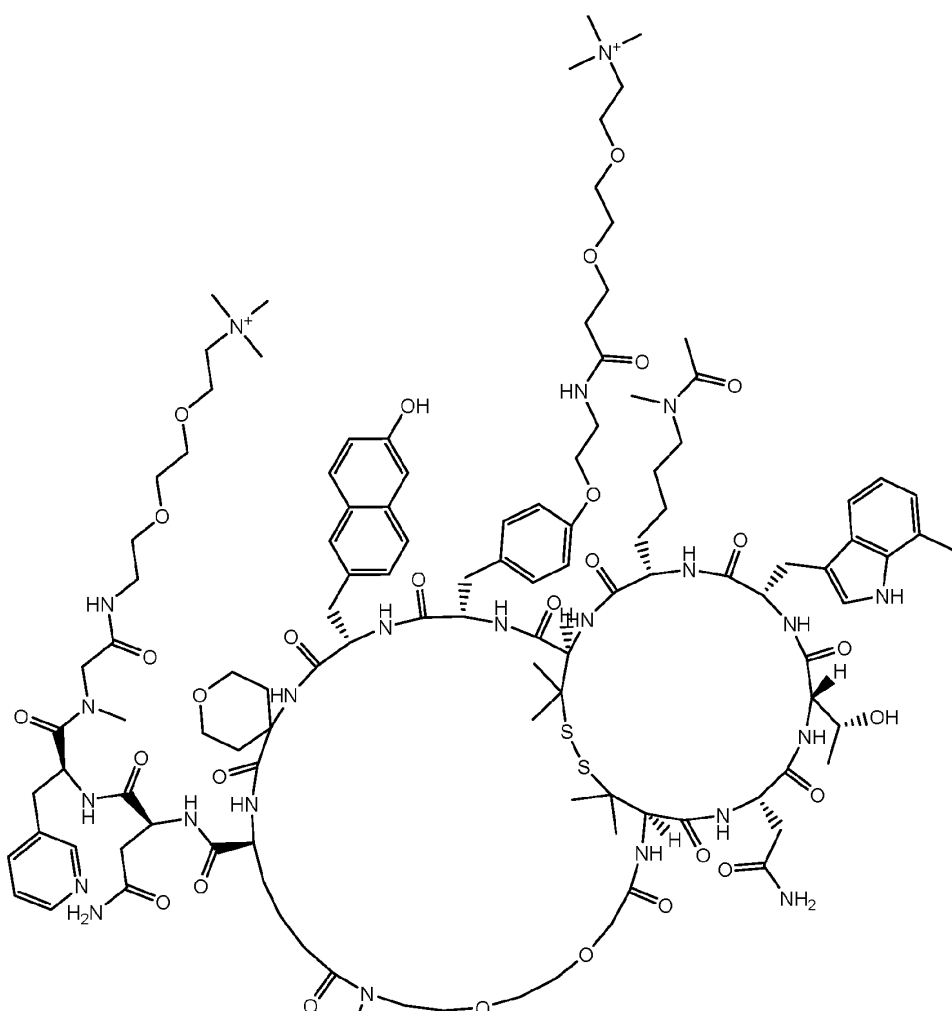
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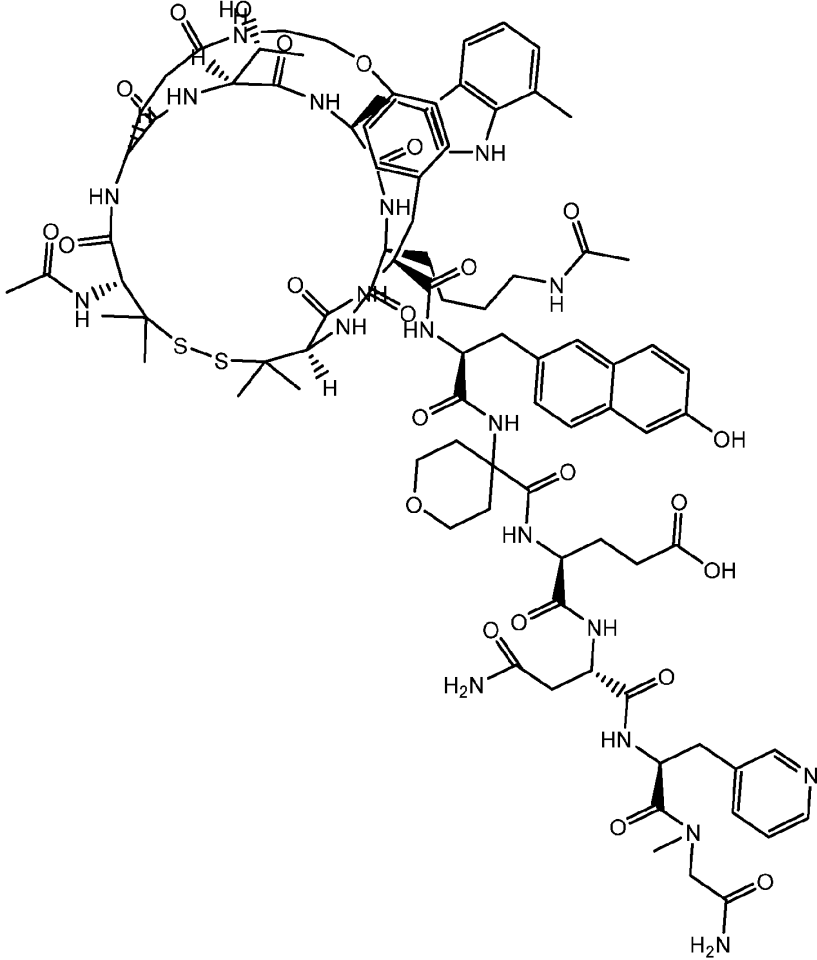
SEQ ID NO	Structure
326	 cPEG3aCO-Pen(3)-E(2)-T-7MeW-K(NMecPEG3a)-Pen(3)-AEF(2)-6OH2NaI-THP-E-N-3Pya-Sar-CONH2

SEQ ID NO	Structure
327	 MeCO-Pen(3)-N-T-7MeW-K(NMecPEG3a)-Pen(3)-AEF-6OH2NaI-THP-K(NMecPEG3a)-N-3PyA-Sar-CONH2

SEQ ID NO	Structure
328	 cPEG3aCO-Pen(3)-N-T-7MeW-K(NMecPEG3a)-Pen(3)-AEF-6OH2Nal-THP-K(NMecPEG3a)-N-3Py-Sar-CONH2

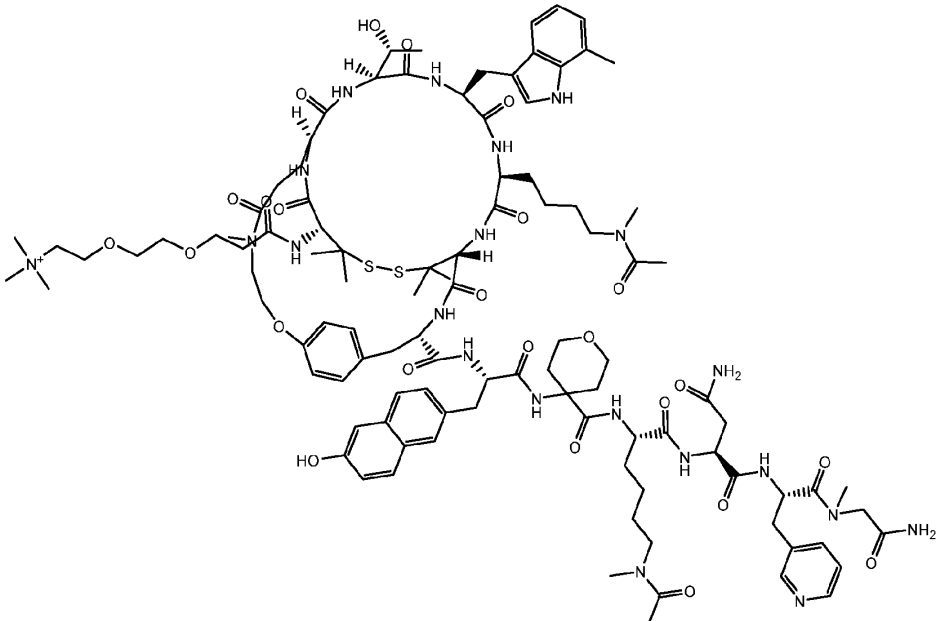
SEQ ID NO	Structure
329	 PEG2NMe(2)-Pen(3)-N-T-7MeW-K(NMeAc)-Pen(3)-AEF(NHPEG3a)-6O(COCF3)2NaI-THP-hE(2)-N-3Py-Sar-CONH(PEG3a)

SEQ ID NO	Structure
330	 Chemical structure of a large macrocyclic peptide (SEQ ID NO 330). The structure features a large central ring with various side chains attached, including PEG chains, penicillins, and aromatic residues. The structure is highly complex, showing multiple amide bonds, ester linkages, and various functional groups. PEG2NMe(2)-Pen(3)-N-T-7MeW-K(NMeAc)-Pen(3)-AEF(NHPEG3a)-6OH2NaI-THP-hE(2)-N-3Py-Sar-CONH(PEG3a)

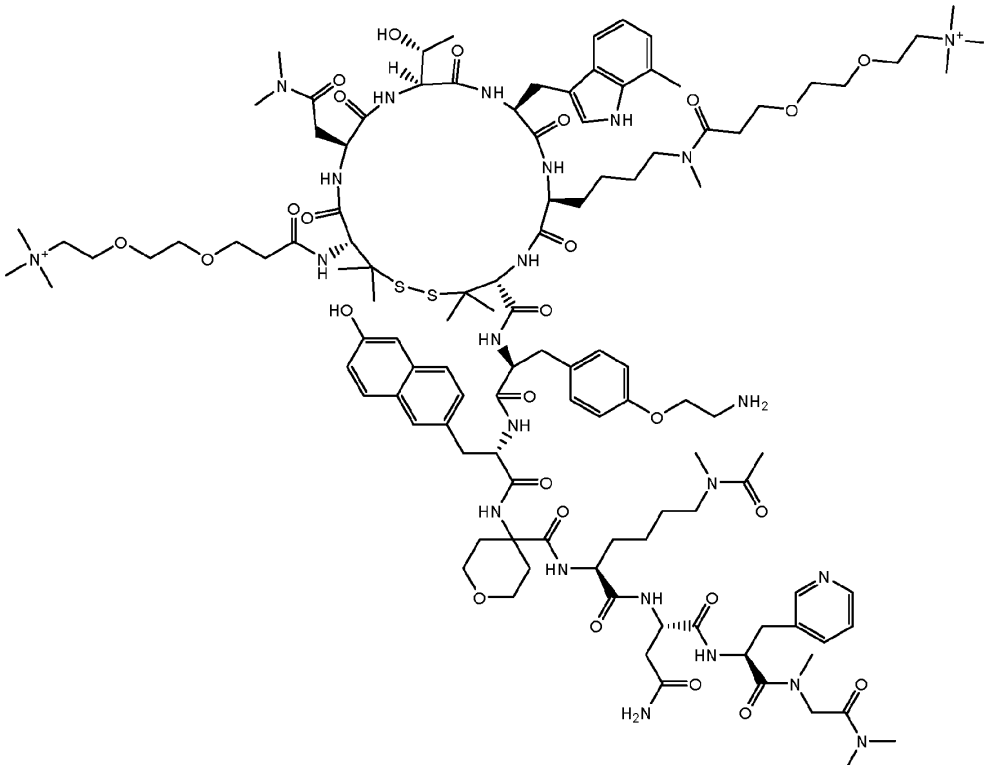
SEQ ID NO	Structure
331	 MeCO-Pen(3)-E(2)-T-7MeW-K(Ac)-Pen(3)-AEF(2)-6OH2Nal-THP-E-N-3PyA-Sar-CONH2

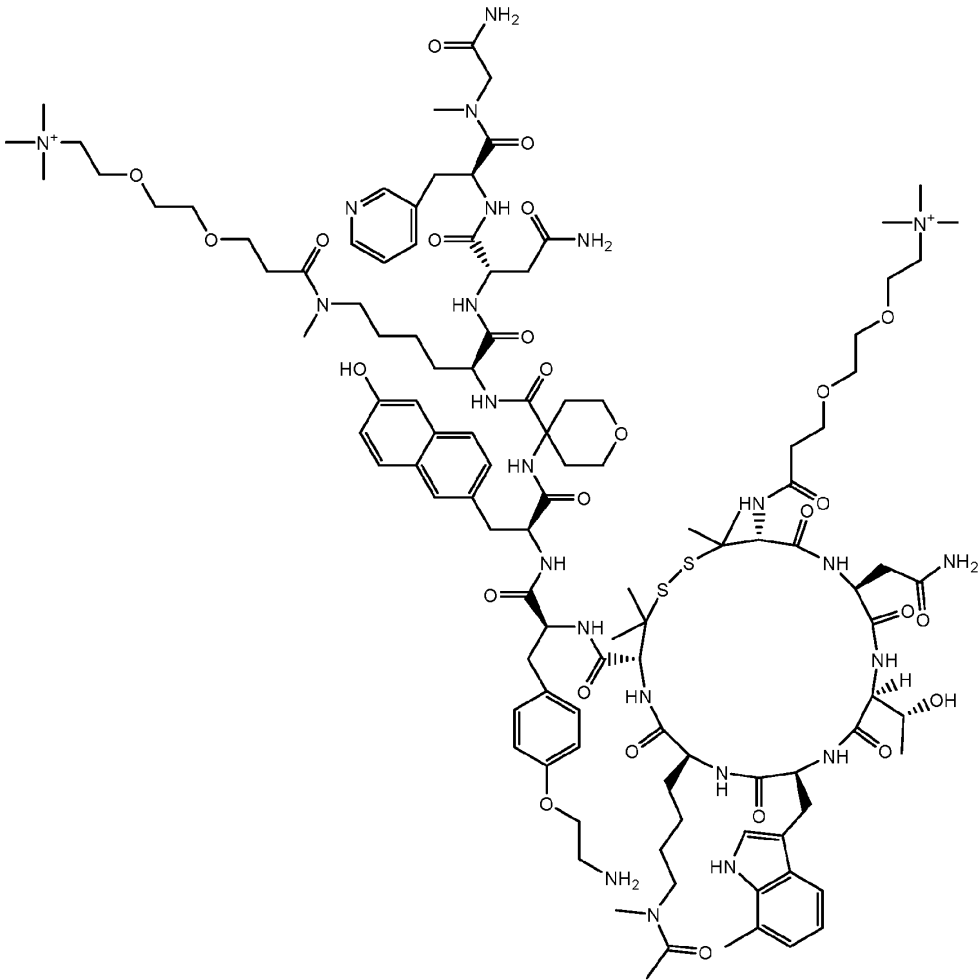
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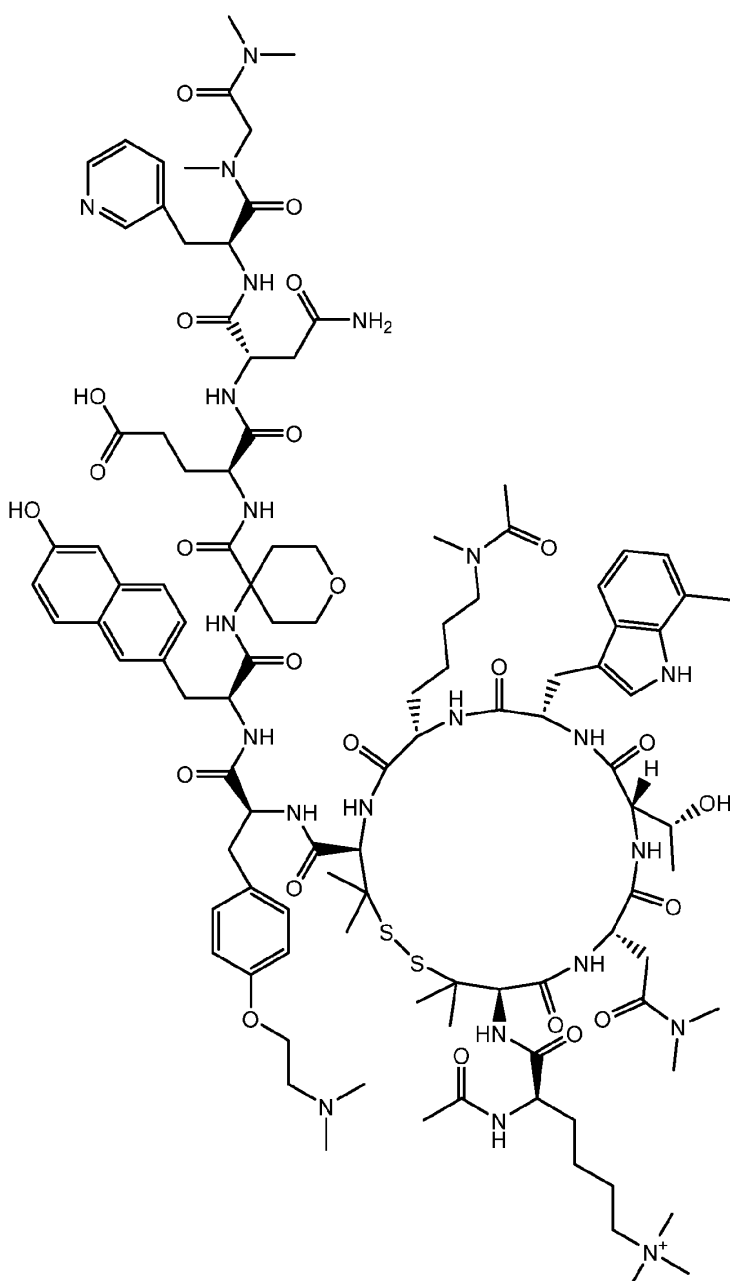
cPEG3aCO-Pen(3)-E(6)-T-7MeW-K(NMeAc)-Pen(3)-AEF(6)-6OH2NaI-THP-E-N-3Pya-Sar-CONH(PEG3a)

SEQ ID NO	Structure
333	 cPEG3aCO-Pen(3)-E(2)-T-7MeW-K(NMeAc)-Pen(3)-AEF(NMe)(2)-6OH2NaI-THP-K(NMeAc)-N-3Pya-Sar-CONH2

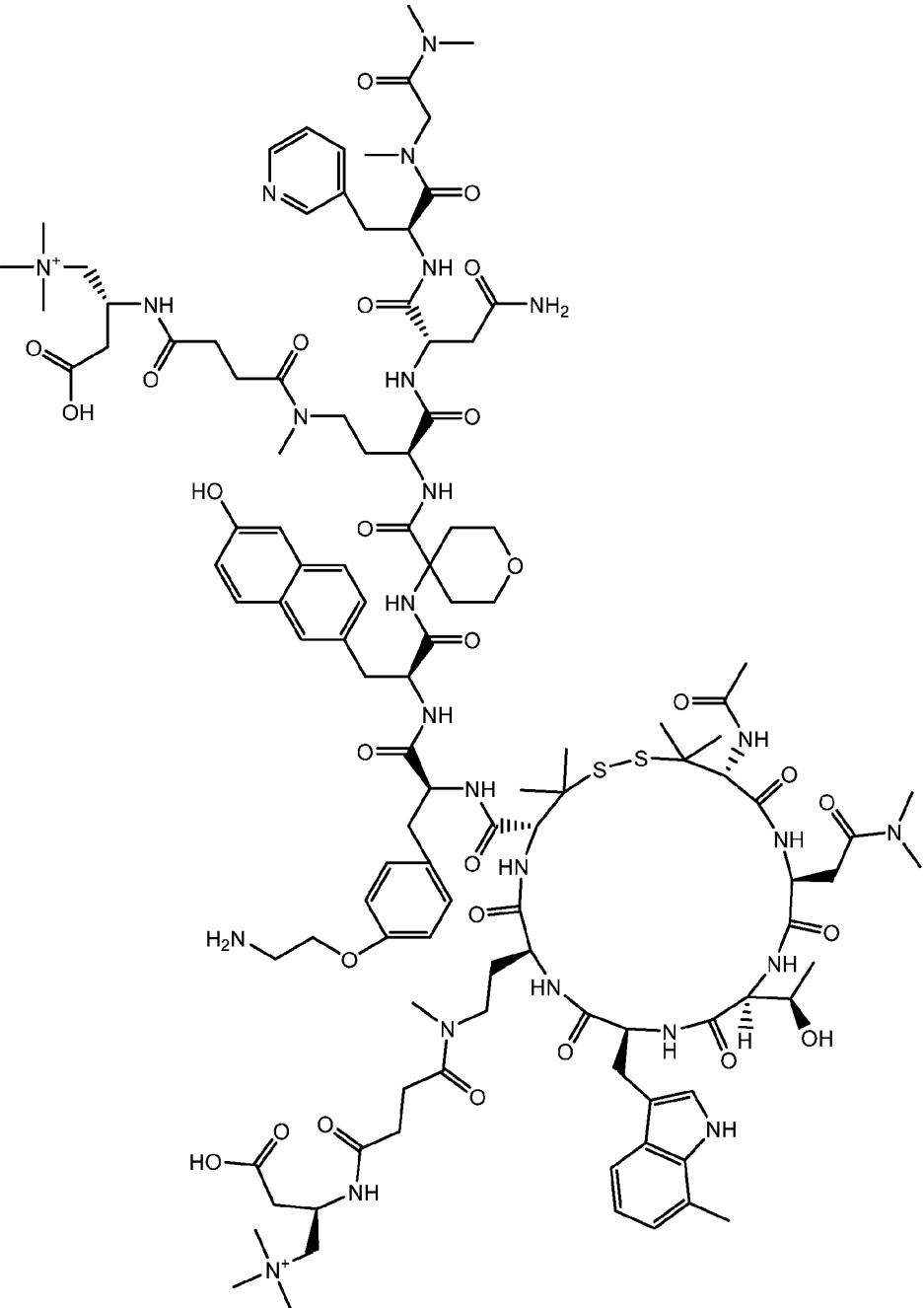
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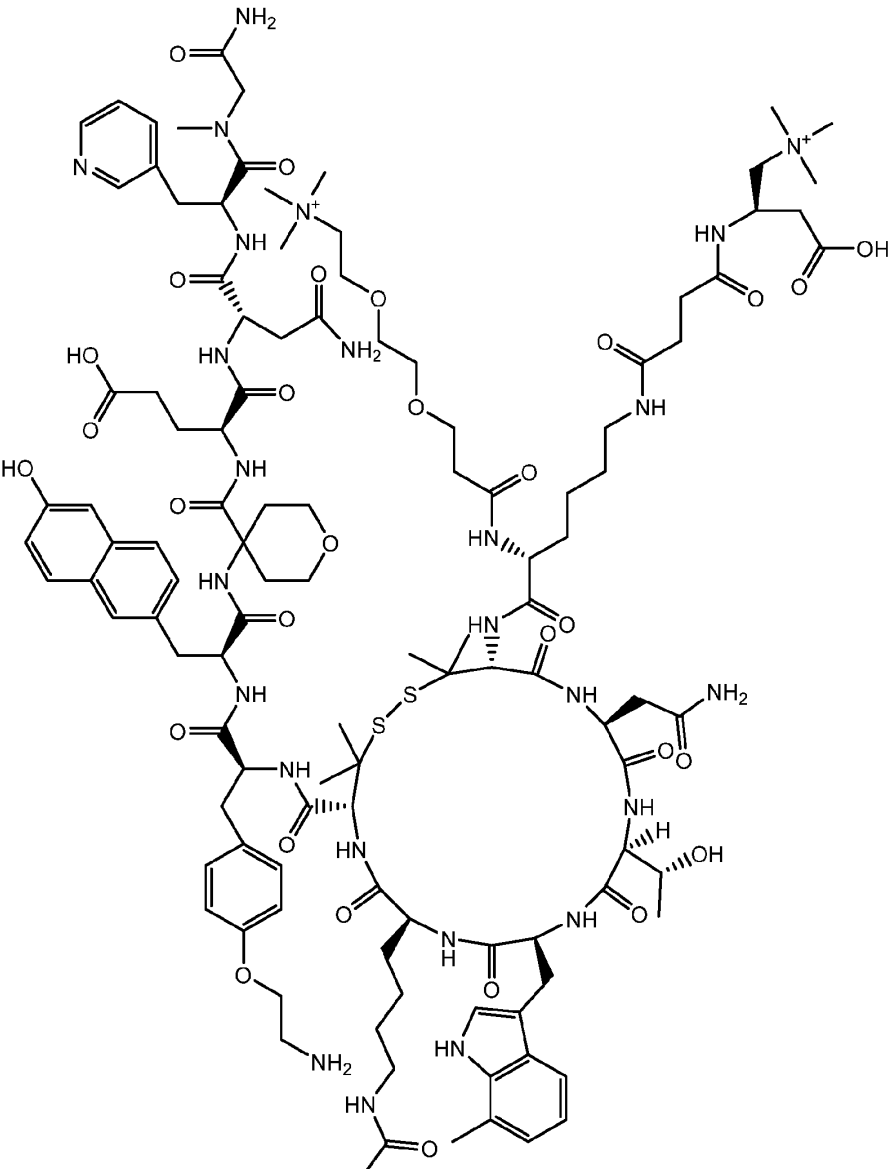
SEQ ID NO	Structure
335	 cPEG3aCO-Pen(3)-N(N(Me)₂)-T-7MeW-K(NMecPEG3a)-Pen(3)-AEF-6OH2Nal-THP-K(NMeAc)-N-3Pya-Sar-CON(Me)₂

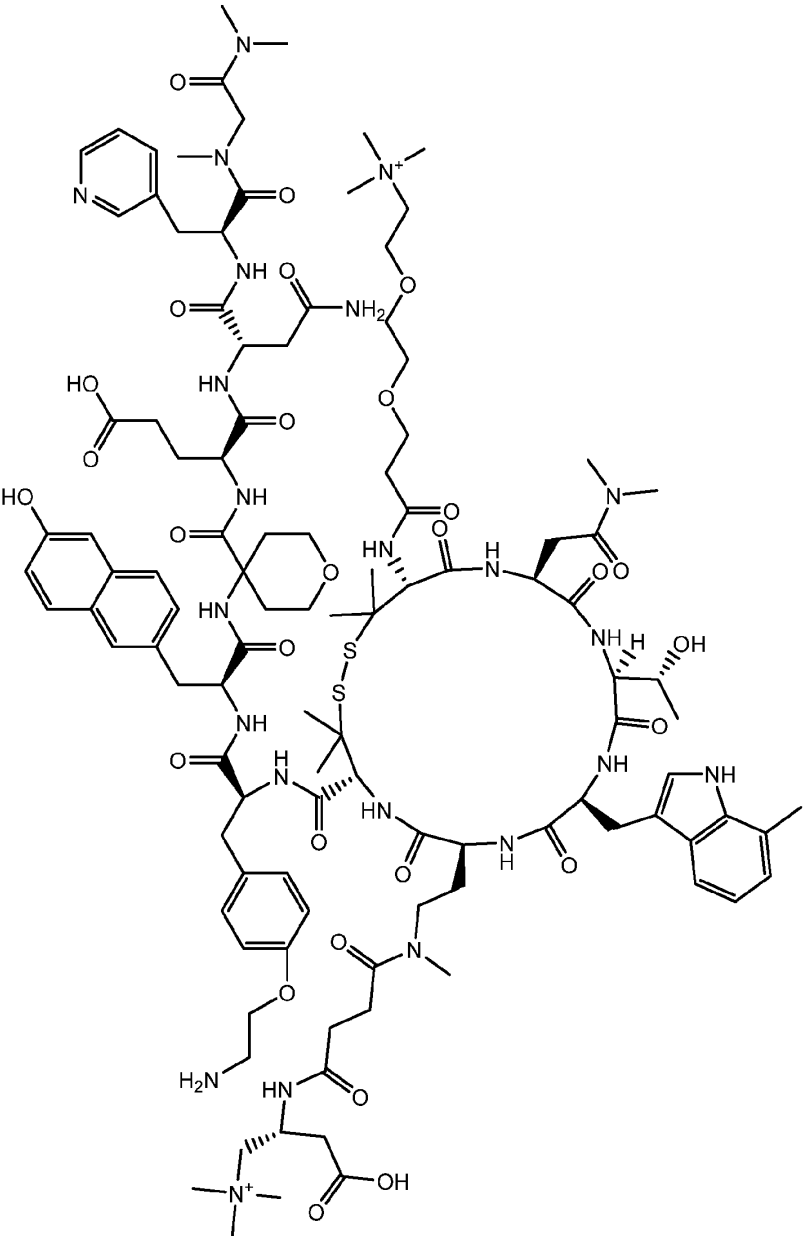
SEQ ID NO	Structure
336	 cPEG3aCO-Pen(3)-N-T-7MeW-K(NMeAc)-Pen(3)-AEF-6OH2Nal-THP-K(NMecPEG3a)-N-3Pya-Sar-CONH2

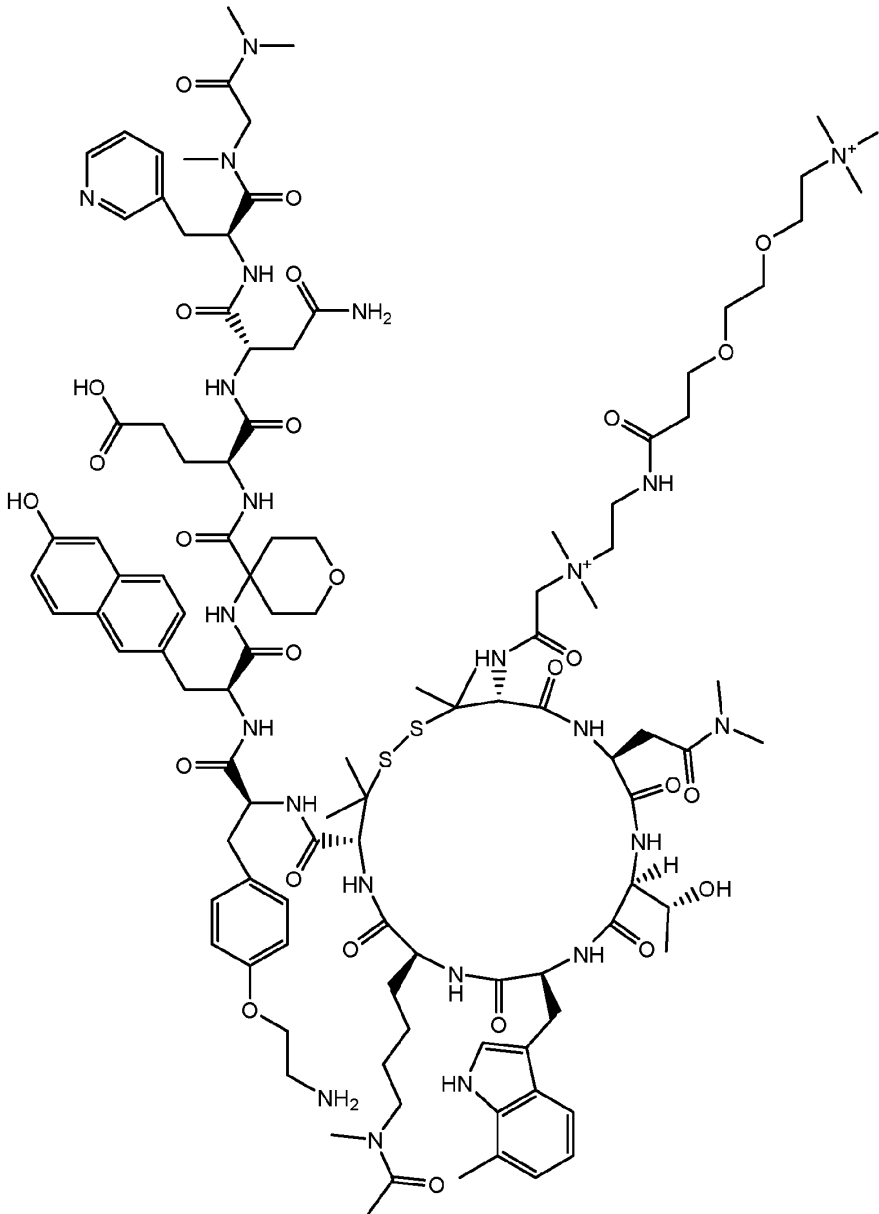
SEQ ID NO	Structure
337	 MeCO-k(Me)₃-Pen(3)-N(N(Me)₂)-T-7MeW-K(NMeAc)-Pen(3)-AEF(N(Me)₂)-6OH₂Nal-THP-E-N-3Py_a-Sar-CON(Me)₂

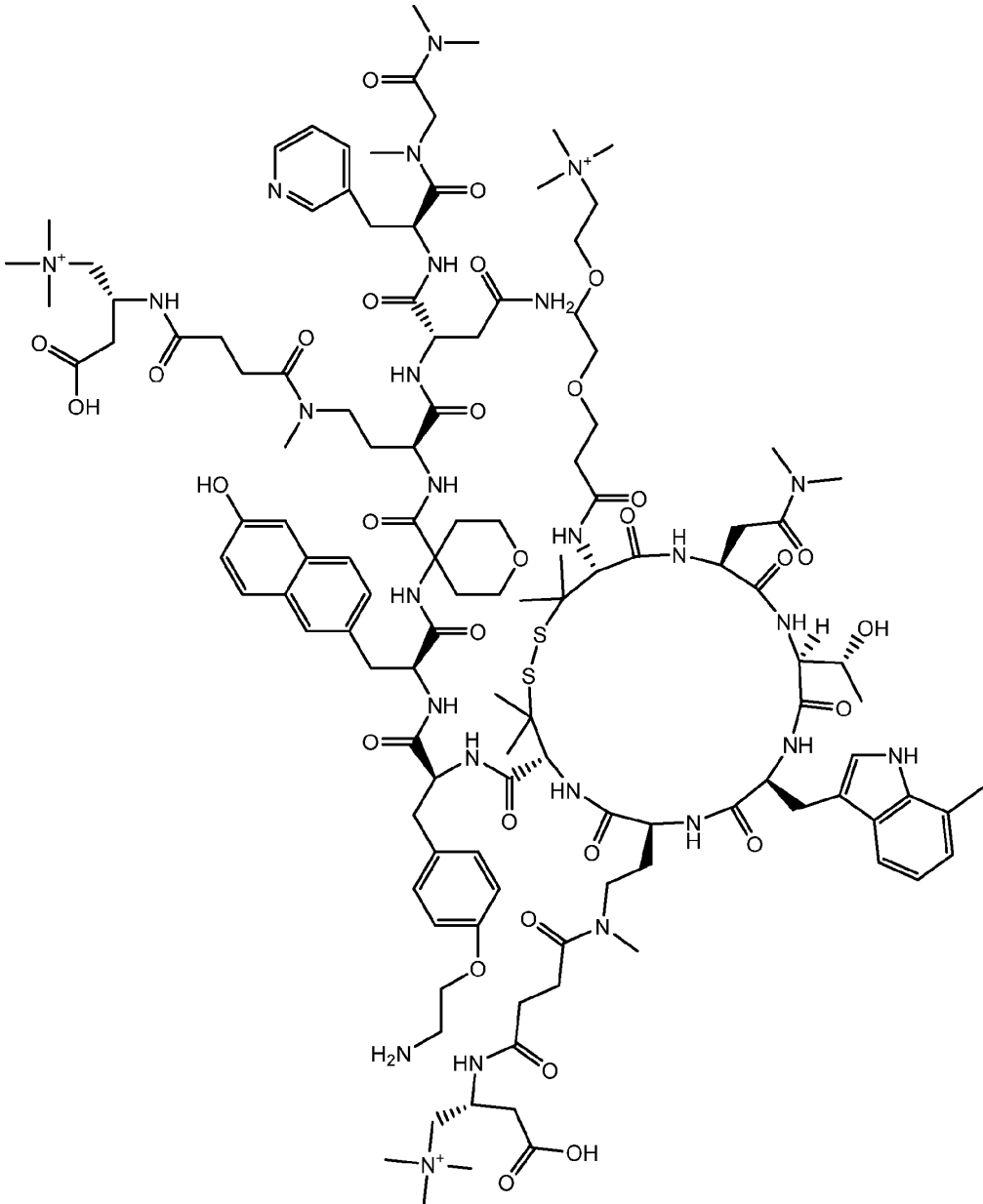
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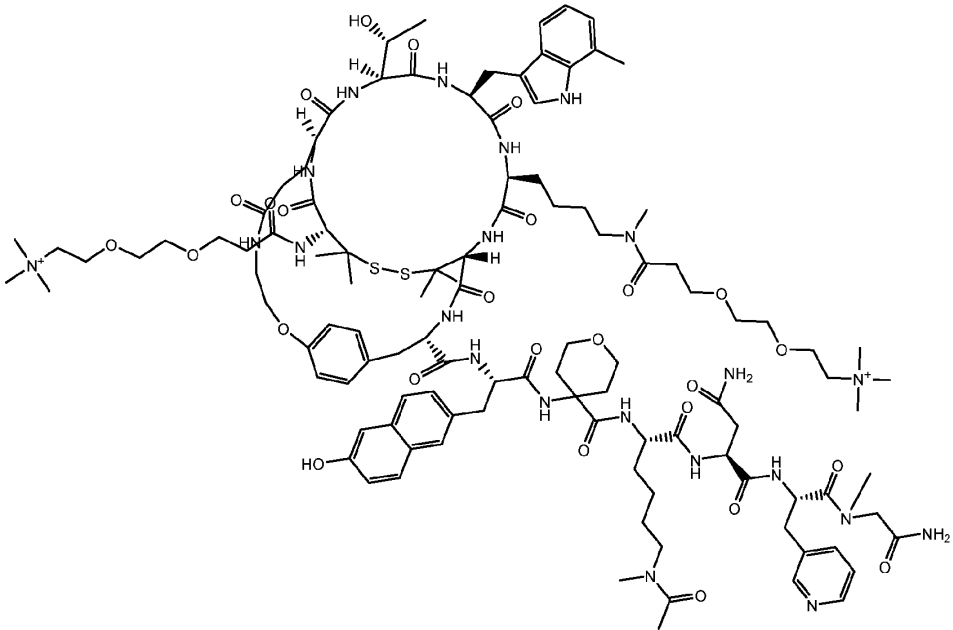
SEQ ID NO	Structure
339	 MeCO-Pen(3)-N(N(Me)₂)-T-7MeW-Dab(NMecarn)-Pen(3)-AEF-6OH₂Nal-THP-Dab(NMecarn)-N-3Pya-Sar-CON(Me)₂

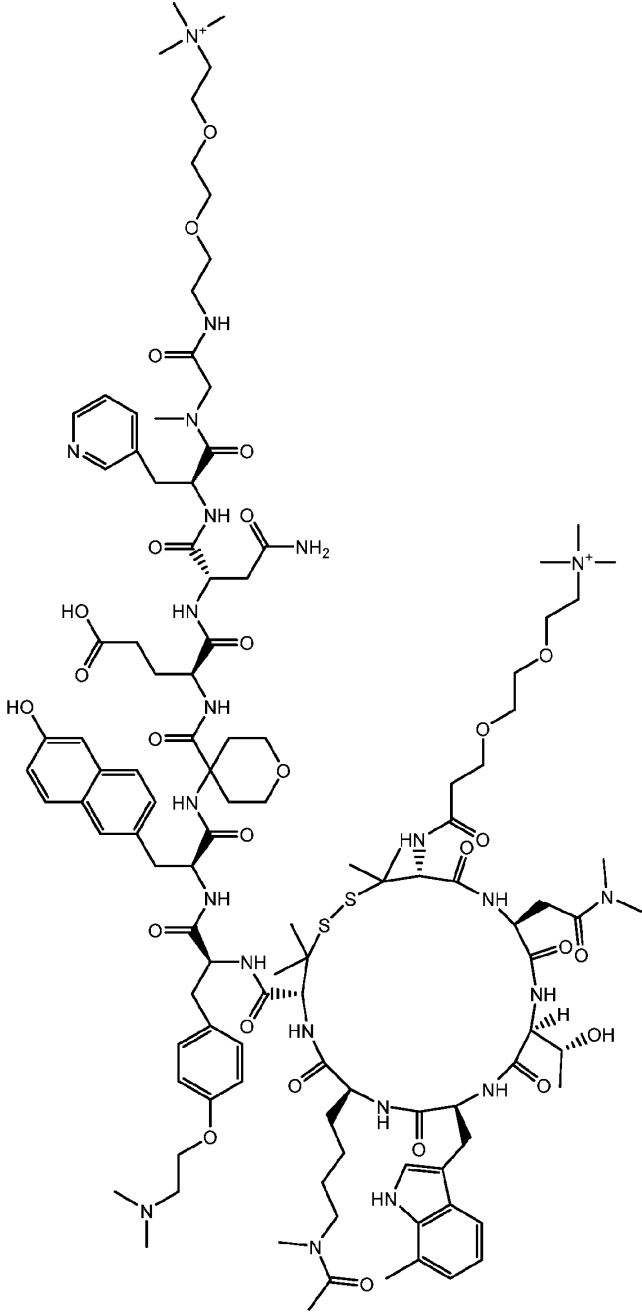
SEQ ID NO	Structure
340	 cPEG3aCO-k(d)-Pen(3)-N-T-7MeW-K(Ac)-Pen(3)-AEF-6OH2Nal-THP-E-N-3PyA-Sar-CONH2

SEQ ID NO	Structure
341	 cPEG3aCO-Pen(3)-N(N(Me)₂)-T-7MeW-Dab(NMecarn)-Pen(3)-AEF-6OH2Nal-THP-E-N-3Pya-Sar-CON(Me)₂

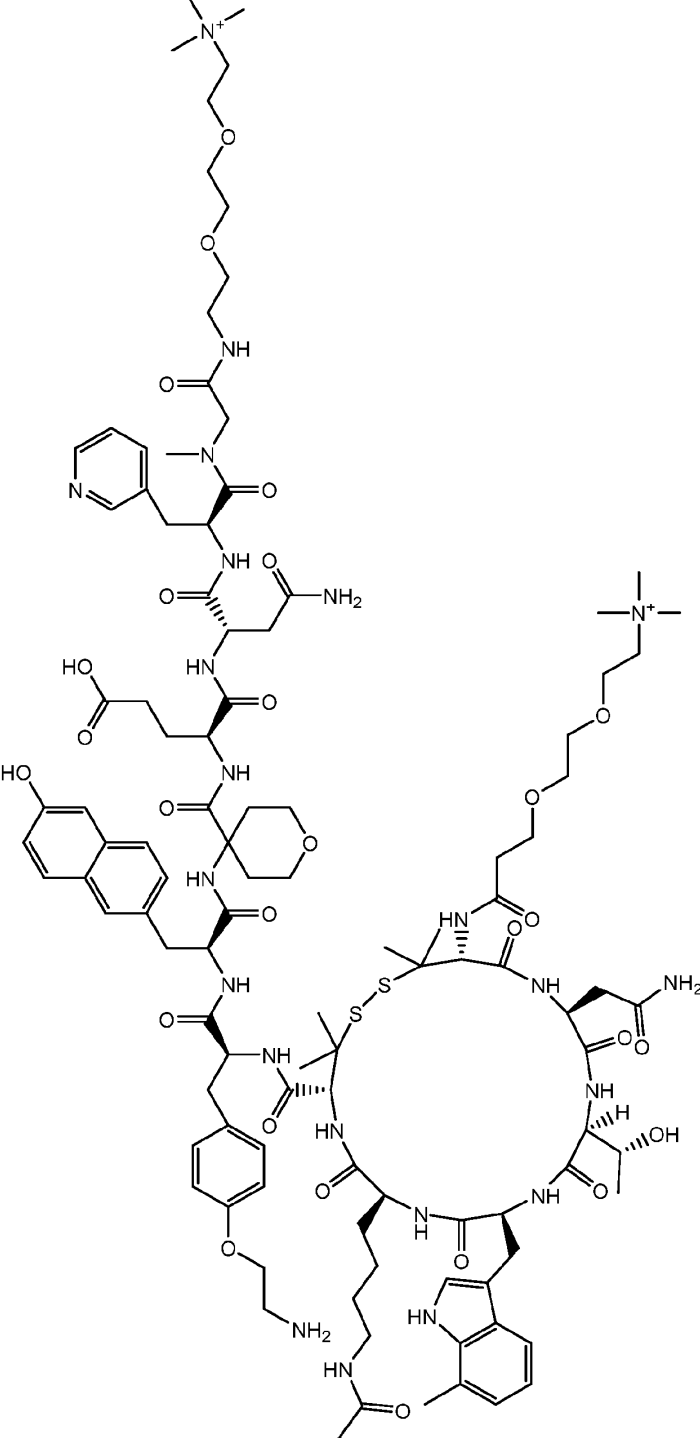
SEQ ID NO	Structure
342	 cPEG3aCO-SP6-Pen(3)-N(N(Me)2)-T-7MeW-K(NMeAc)-Pen(3)-AEF-6OH2NaI-THP-E-N-3Py-Sar-CON(Me)2

SEQ ID NO	Structure
343	 cPEG3aCO-Pen(3)-N(NMe)2-T-7MeW-Dab(NMecarn)-Pen(3)-AEF-6OH2Nal-THP-Dab(NMecarn)-N-3PyA-Sar-CON(Me)2

SEQ ID NO	Structure
344	 cPEG3aCO-Pen(3)-E(2)-T-7MeW-K(NMecPEG3a)-Pen(3)-AEF(2)-6OH2Nal-THP-K(NMeAc)-N-3Py-Sar-CONH2

SEQ ID NO	Structure
345	 cPEG3aCO-Pen(3)-N(NMe)₂-T-7MeW-K(NMeAc)-Pen(3)-AEF(NMe)₂-6OH2Nal-THP-E-N-3Py-Sar-CONH(PEG3a)

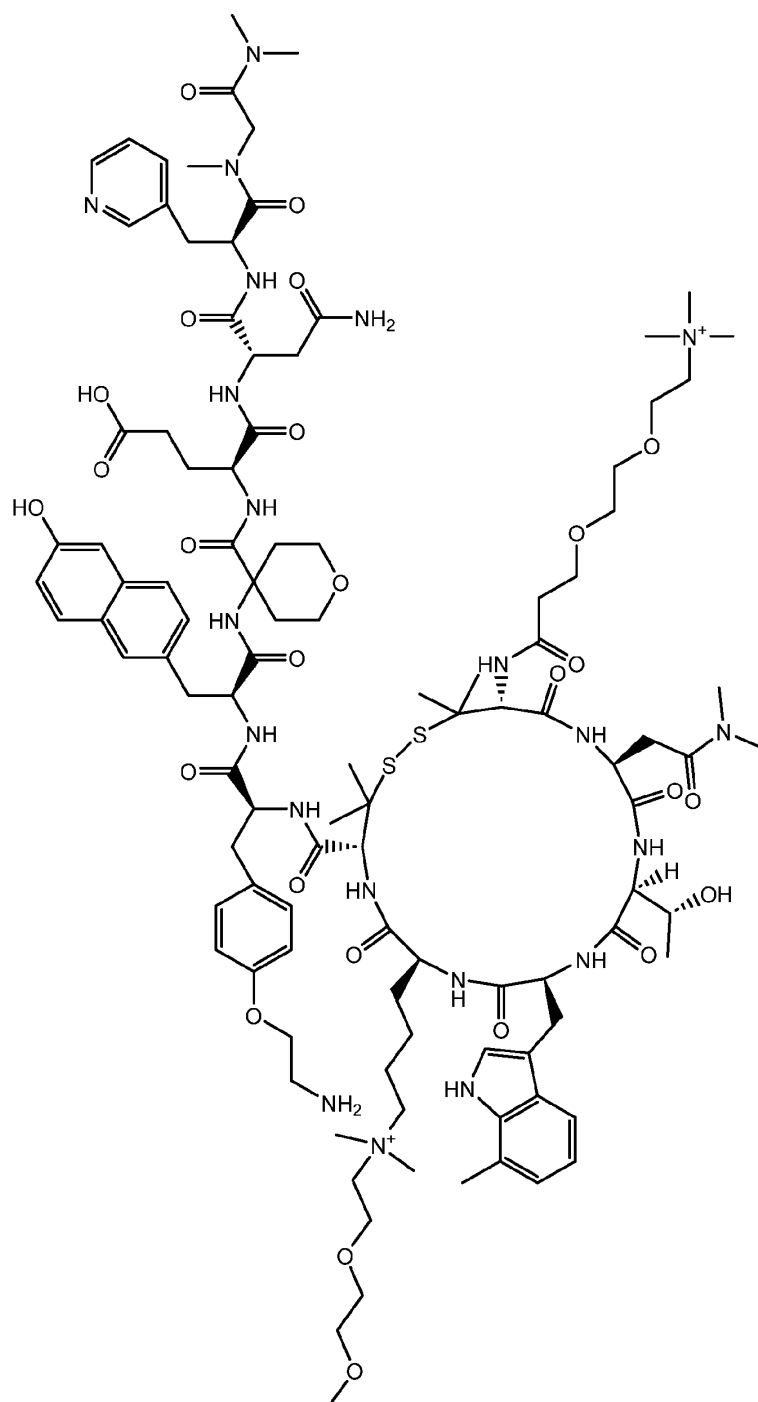
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SEQ ID NO	Structure
347	 cPEG3aCO-Pen(3)-N-T-7MeW-K(Ac)-Pen(3)-AEF-6OH2Nal-THP-E-N-3Pya-Sar-CONH(PEG3a)

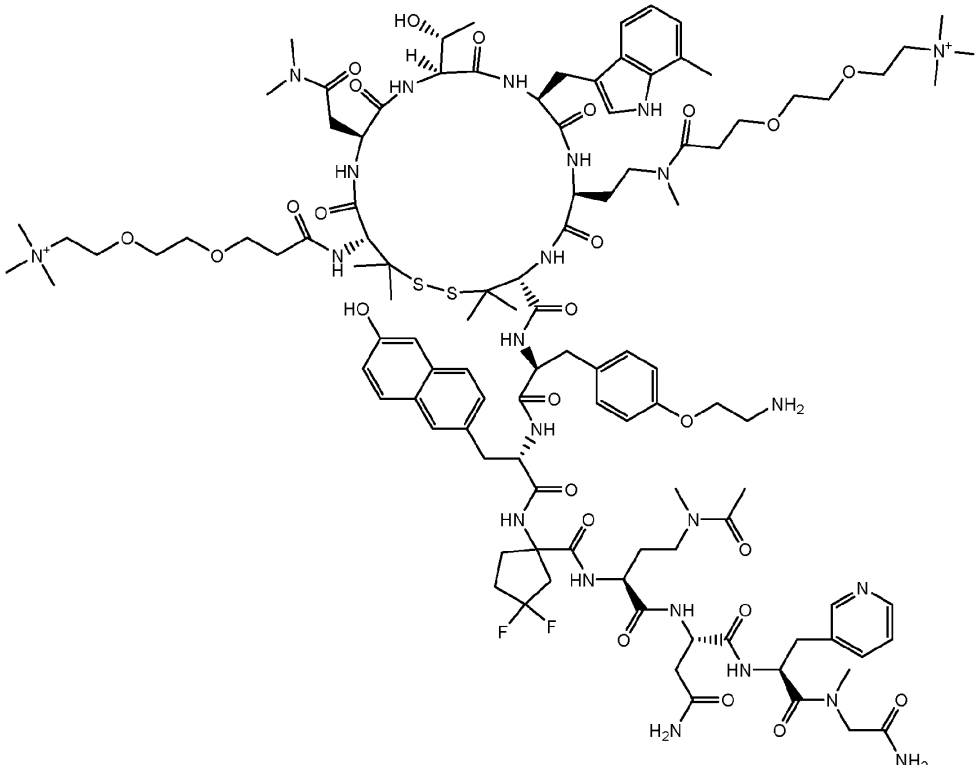
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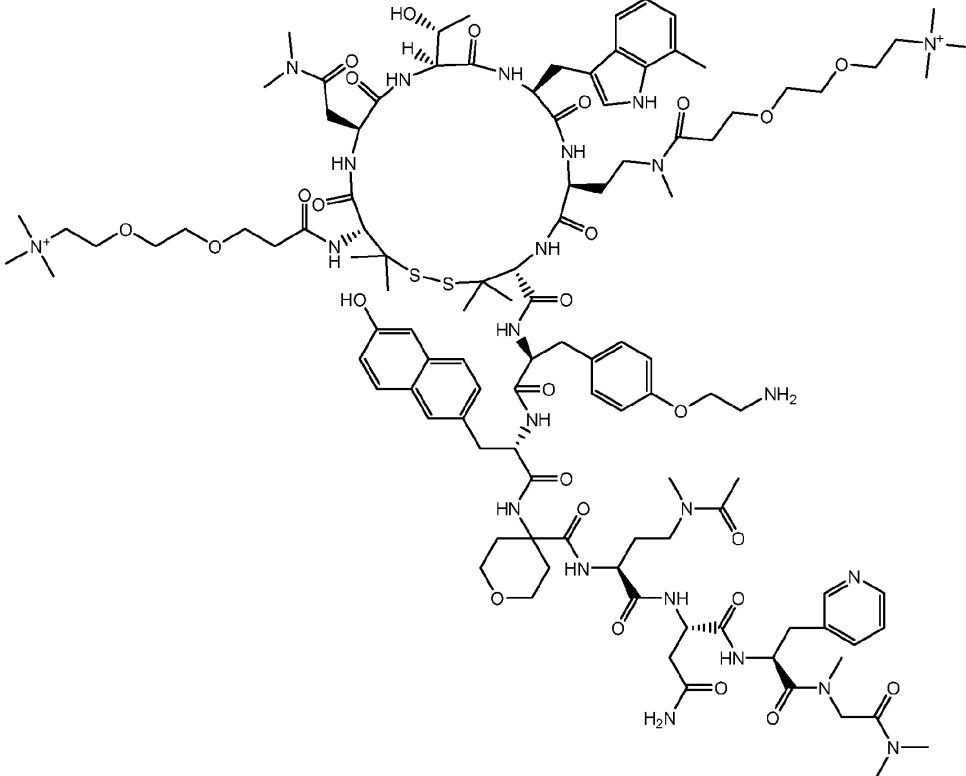
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350



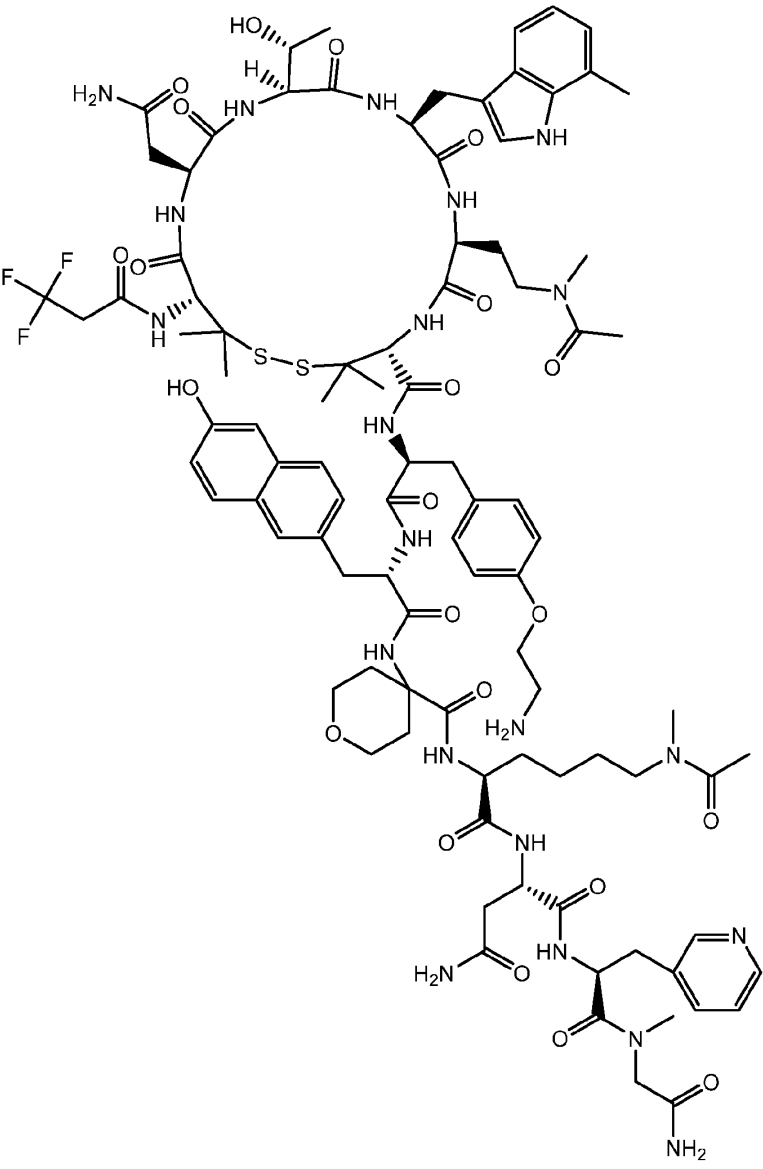
cPEG3aCO-Pen(3)-N(N(Me)₂)-T-7MeW-Lys(N+Me2mPEG3)-Pen(3)-AEF-6OH2Nal-THP-E-N-3Py-Sar-CON(Me)₂

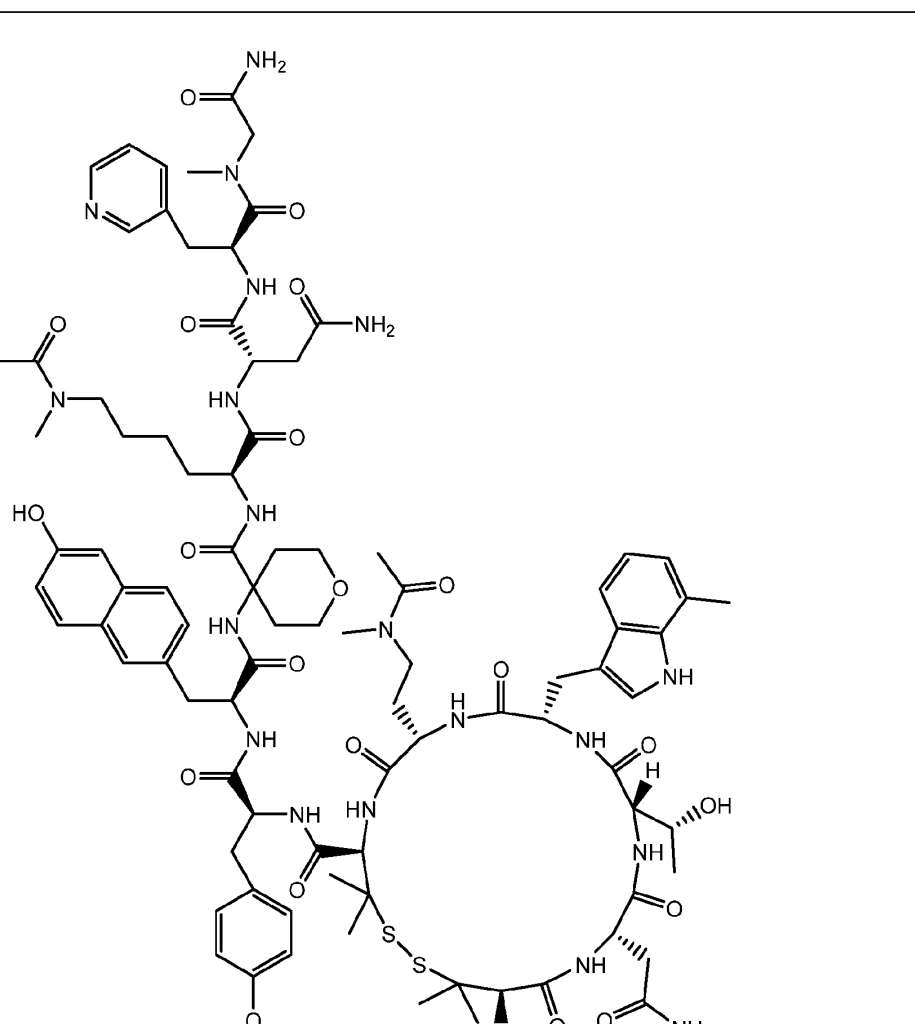
SEQ ID NO	Structure
351	 cPEG3aCO-Pen(3)-N(N(Me)2)-T-7MeW-Dab(NMecPEG3a)-Pen(3)-AEF-6OH2Nal-diFCpx-Dab(NMeAc)-N-3Pya-Sar-CONH2

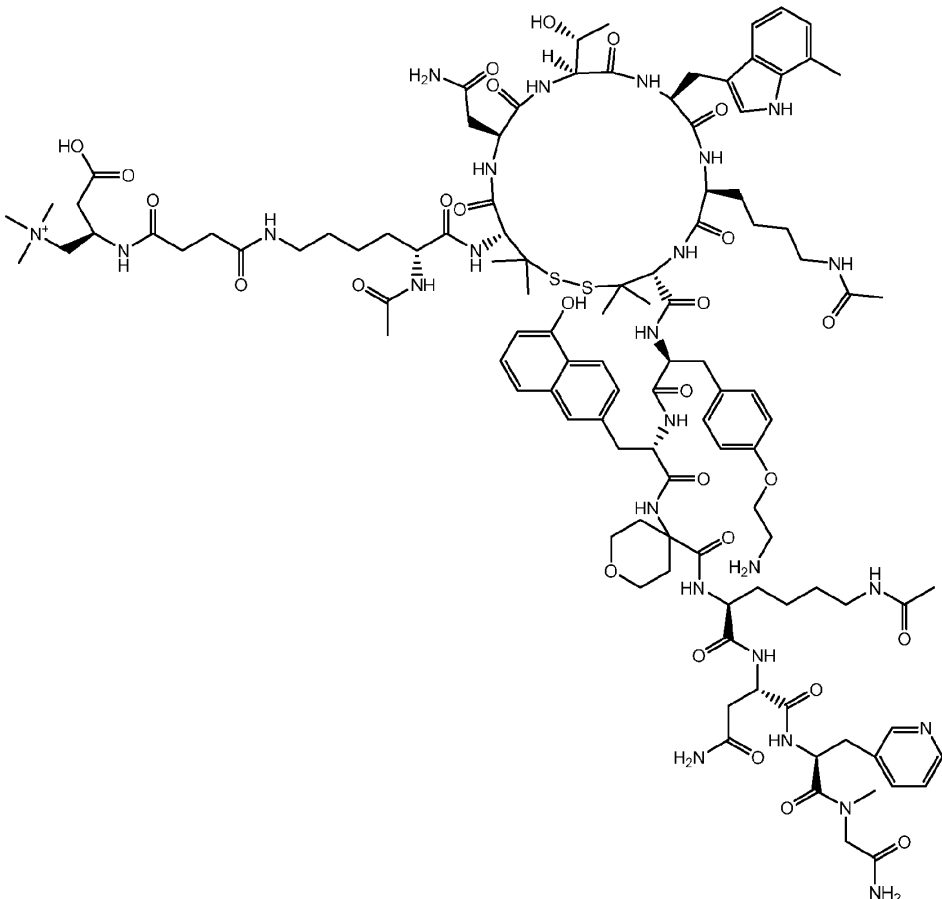
SEQ ID NO	Structure
352	 cPEG3aCO-Pen(3)-N(NMe)2-T-7MeW-Dab(NMecPEG3a)-Pen(3)-AEF-6OH2NaI-THP-Dab(NMeAc)-N-3Pva-Sar-CON(Me)2

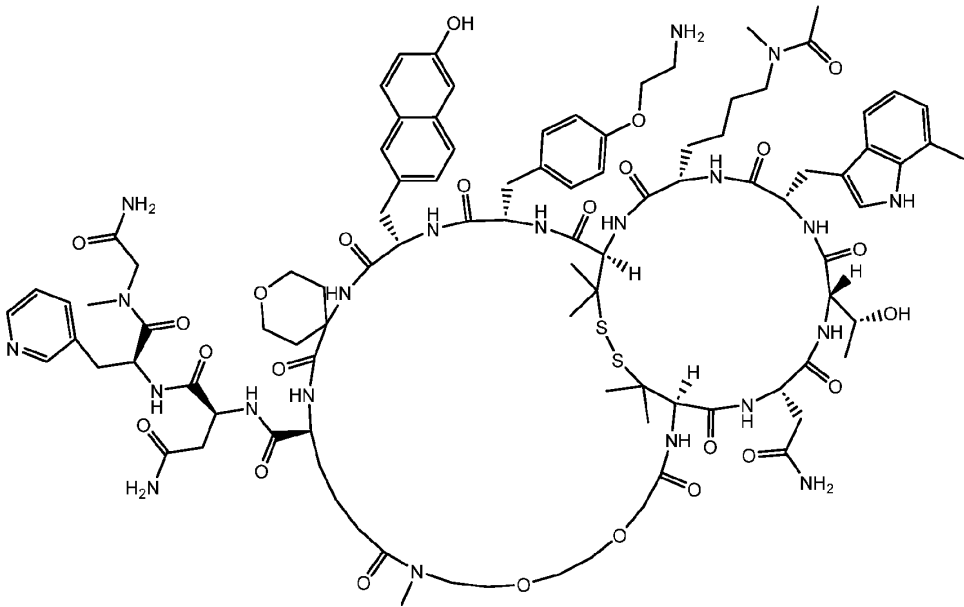
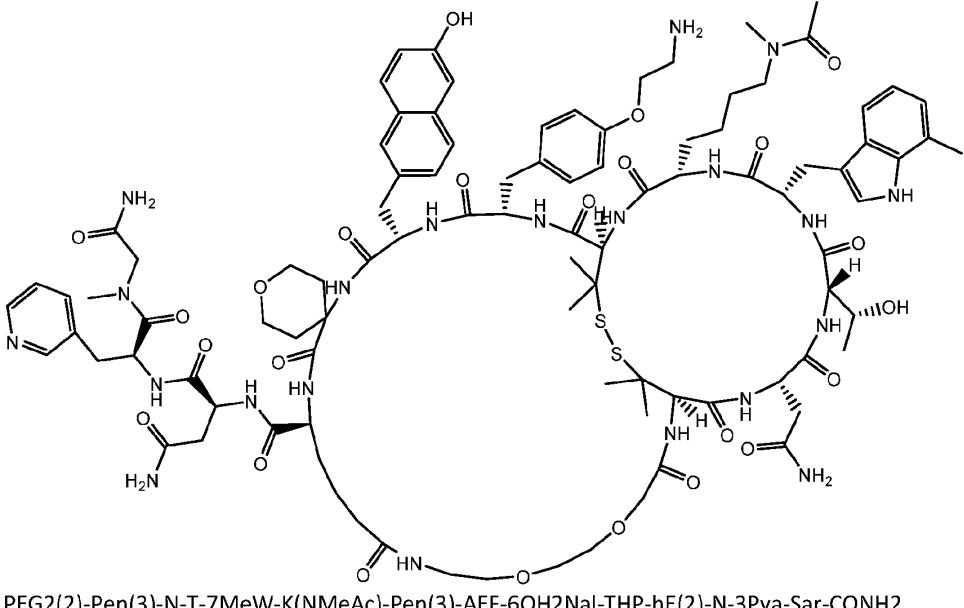
SEQ ID NO	Structure
353	cPEG3aCO-Pen(3)-N(N(Me)2)-T-7MeW-Dab(NMecPEG3a)-Pen(3)-AEF-6OH₂Nal-(diFcpx(R)) -E-N-3PyA-Sar-CONH₂

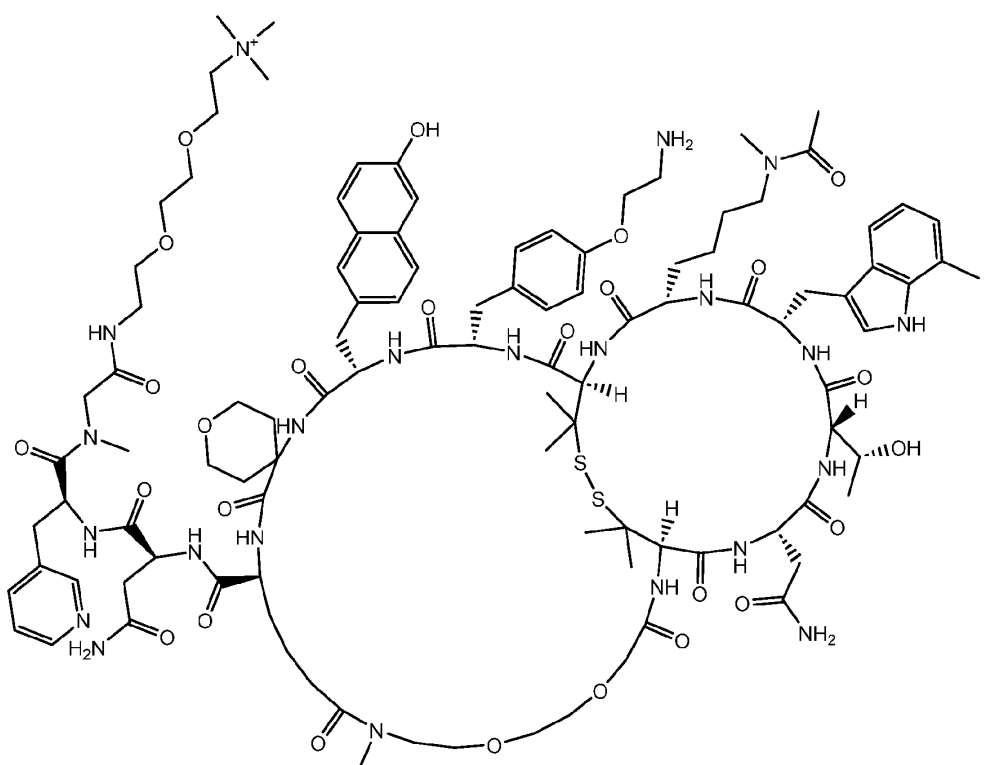
SEQ ID NO	Structure
354	cPEG3aCO-Pen(3)-N(N(Me)₂)-T-7MeW-Dab(NMecPEG3a)-Pen(3)-AEF-6OH₂NaI--diFCpx(S)-E-N-3Pva-Sar-CONH₂

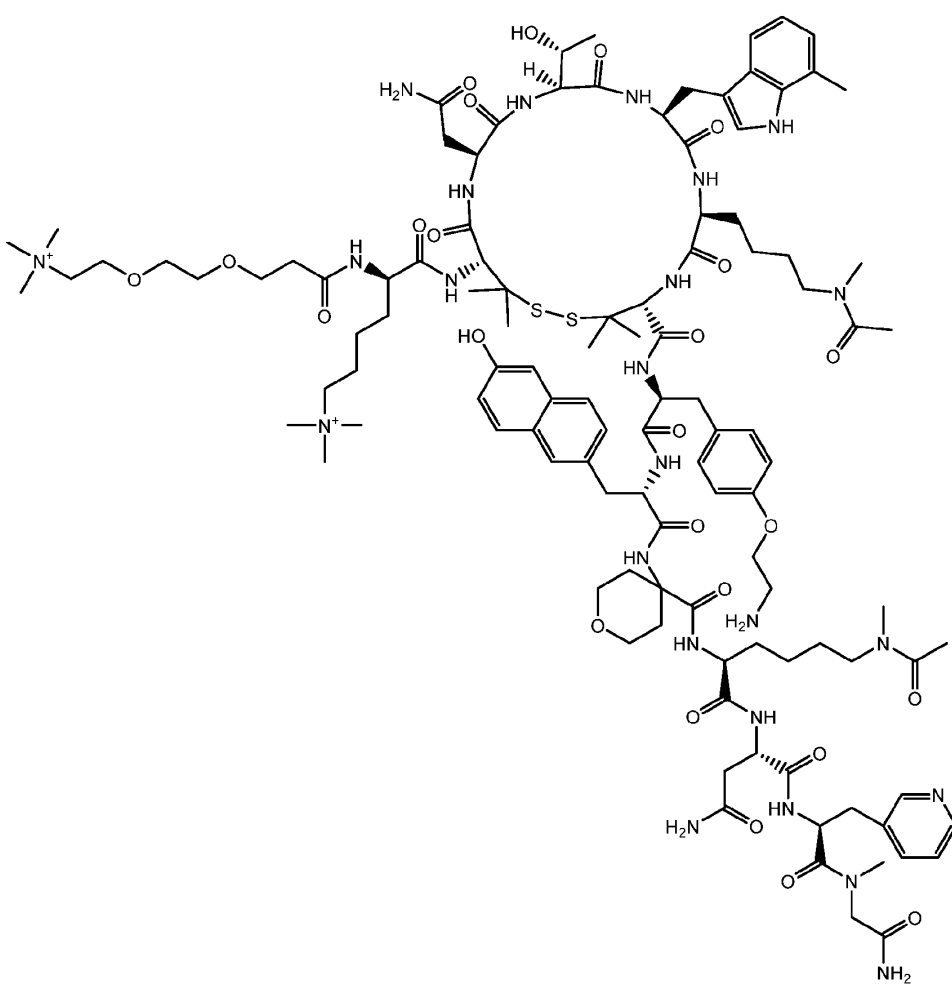
SEQ ID NO	Structure
355	 CF3Propylamide-Pen(3)-N-T-7MeW-Dab(NMeAc)-Pen(3)-AEF-6OH2Nal-THP-K(NMeAc)-N-3Py-Sar-CONH2

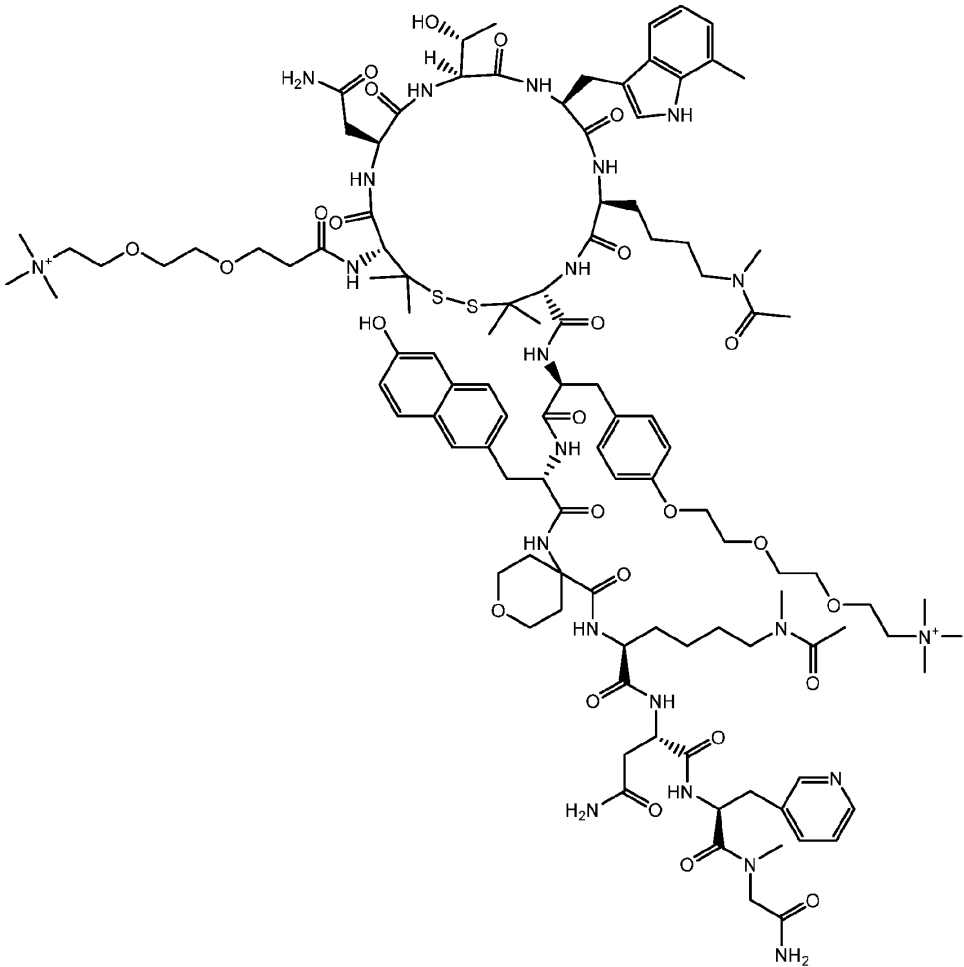
SEQ ID NO	Structure
356	 MeCO-Pen(3)-N-T-7MeW-Dab(NMeAc)-Pen(3)-AEF-6OH2NaI-THP-K(NMeAc)-N-3Pya-Sar-CONH2

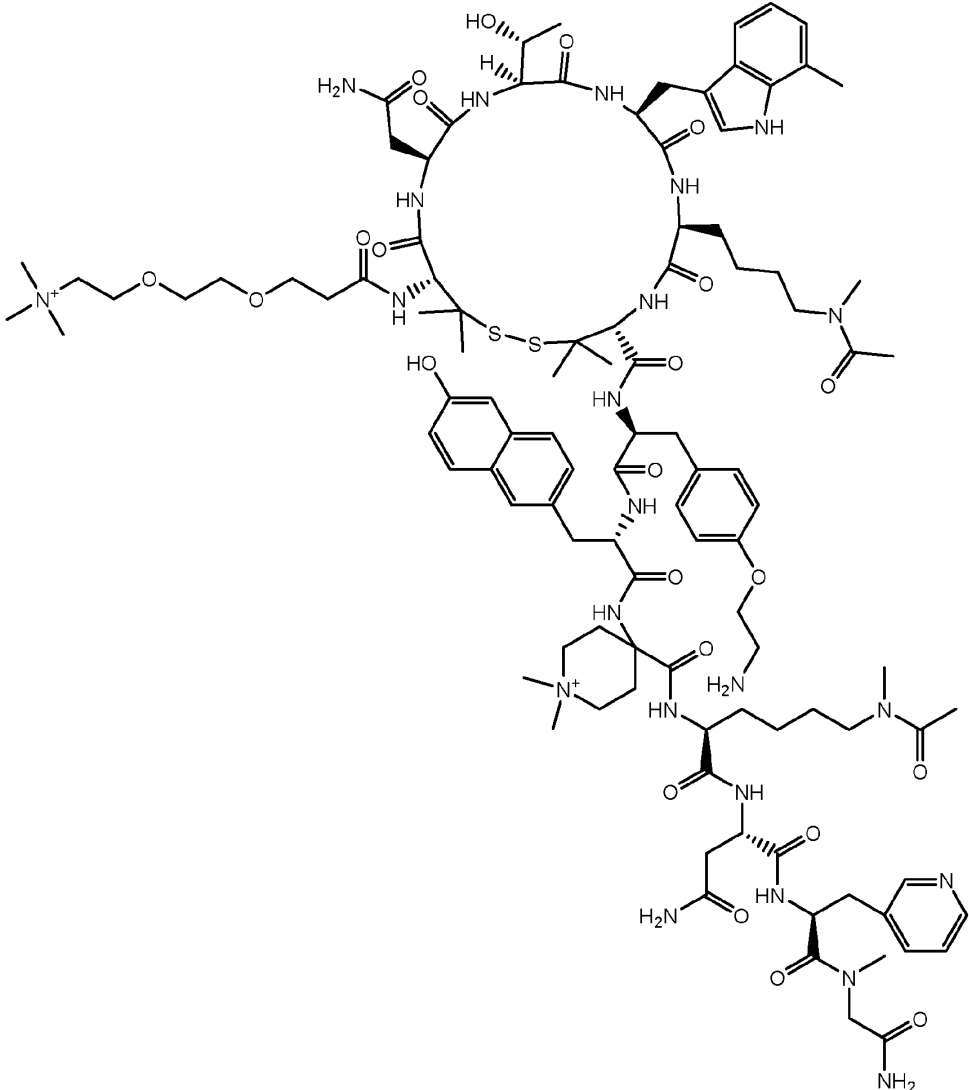
SEQ ID NO	Structure
357	 MeCO-k(d)-Pen(3)-N-T-7MeW-K(Ac)-Pen(3)-AEF-6OH2Nal-THP-K(Ac)-N-3Pya-Sar-CONH2

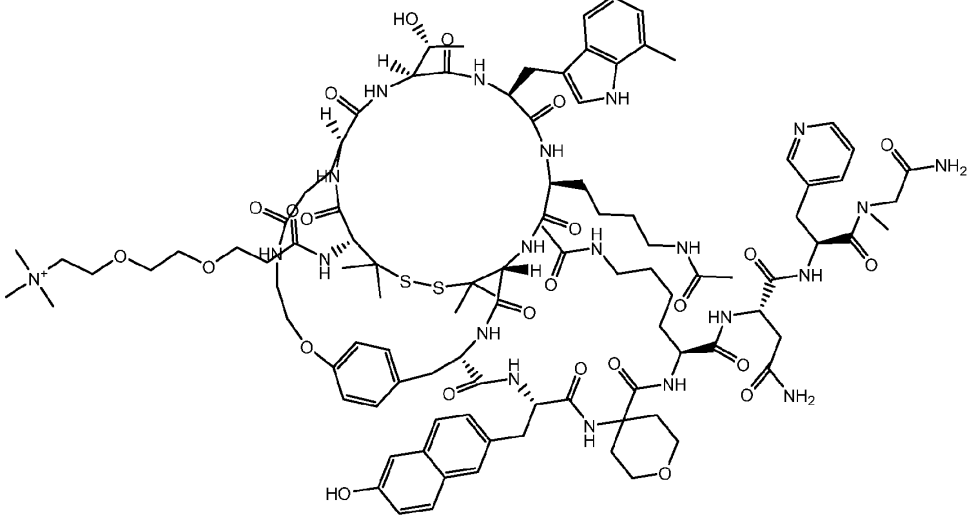
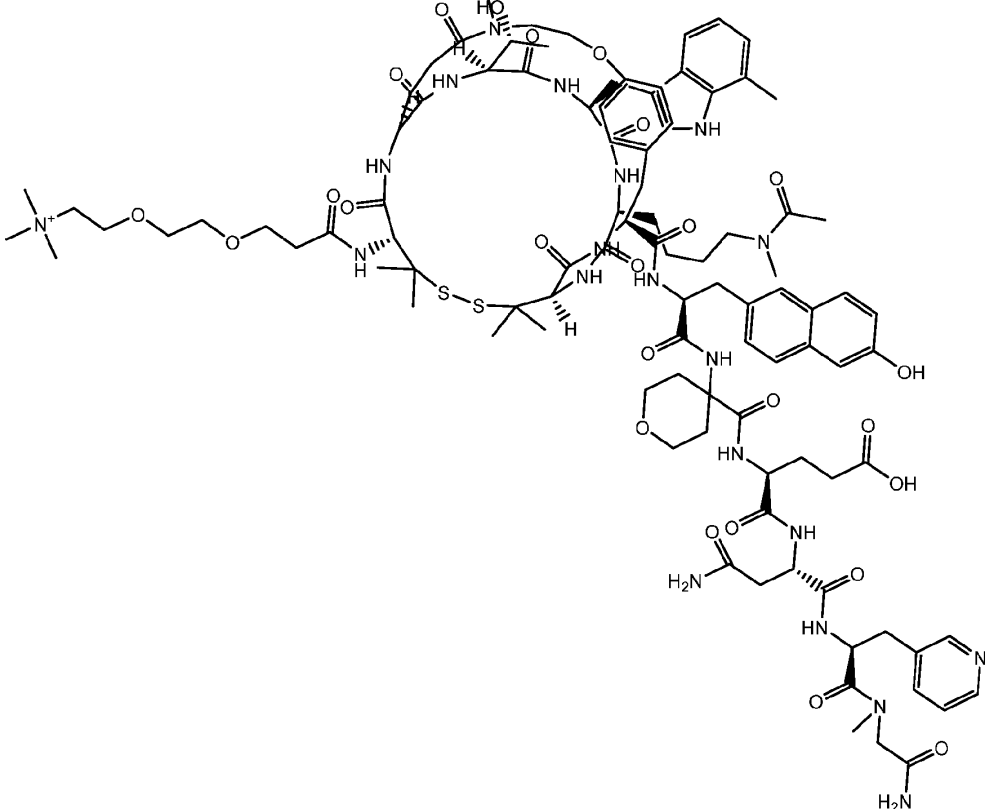
SEQ ID NO	Structure
358	 Chemical structure of a cyclic peptide (SEQ ID NO 358). The structure features a large macrocyclic ring with a PEG2 linker (polyethylene glycol) and various side chains. The side chains include a 7MeW residue (7-methyl-tryptophan), a K(NMeAc) residue (lysine with an N-methylacetyl group), and a 6OH2Nal-THP-hE(2)-N-3PyA-Sar-CONH2 sequence. The structure is highly complex, showing multiple amide bonds, hydroxyl groups, and a variety of aromatic and aliphatic side chains. PEG2NMe(2)-Pen(3)-N-T-7MeW-K(NMeAc)-Pen(3)-AEF-6OH2Nal-THP-hE(2)-N-3PyA-Sar-CONH2
359	 Chemical structure of a cyclic peptide (SEQ ID NO 359). The structure features a large macrocyclic ring with a PEG2 linker (polyethylene glycol) and various side chains. The side chains include a 7MeW residue (7-methyl-tryptophan), a K(NMeAc) residue (lysine with an N-methylacetyl group), and a 6OH2Nal-THP-hE(2)-N-3PyA-Sar-CONH2 sequence. The structure is highly complex, showing multiple amide bonds, hydroxyl groups, and a variety of aromatic and aliphatic side chains. PEG2(2)-Pen(3)-N-T-7MeW-K(NMeAc)-Pen(3)-AEF-6OH2Nal-THP-hE(2)-N-3PyA-Sar-CONH2

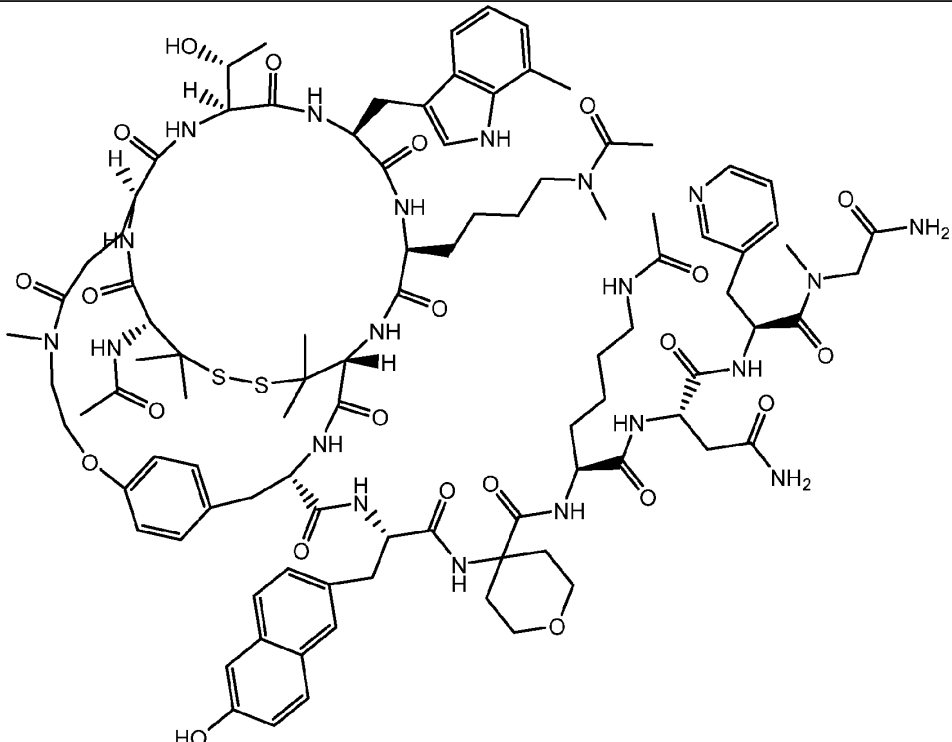
SEQ ID NO	Structure
360	 Chemical structure of a large cyclic peptide (SEQ ID NO 360). The structure is a macrocycle with a backbone consisting of amide bonds. The side chains include: - PEG2NMe(2)-Pen(3)-N-T-7MeW-K(NMeAc)-Pen(3)-AEF-6OH2Nal-THP-hE(2)-N-3Pyra-Sar-CONH(PEG3a) 6OH2Nal (6-hydroxy-2-nalanyl) - THP (tetrahydropyran) - hE(2) (2-hydroxyethyl) - N-3Pyra (3-pyridyl) - Sar (sarcosine) - CONH(PEG3a) (carboxamide-linked PEG3a)

SEQ ID NO	Structure
361	 cPEG3aCO-k(Me)3-Pen(3)-N-T-7MeW-K(NMeAc)-Pen(3)-AEF-6OH2Nal-THP-K(NMeAc)-N-3Pya-Sar-CONH2

SEQ ID NO	Structure
362	 cPEG3aCO-Pen(3)-N-T-7MeW-K(NMeAc)-Pen(3)-APEG3F-6OH2Nal-THP-K(NMeAc)-N-3PyA-Sar-CONH2

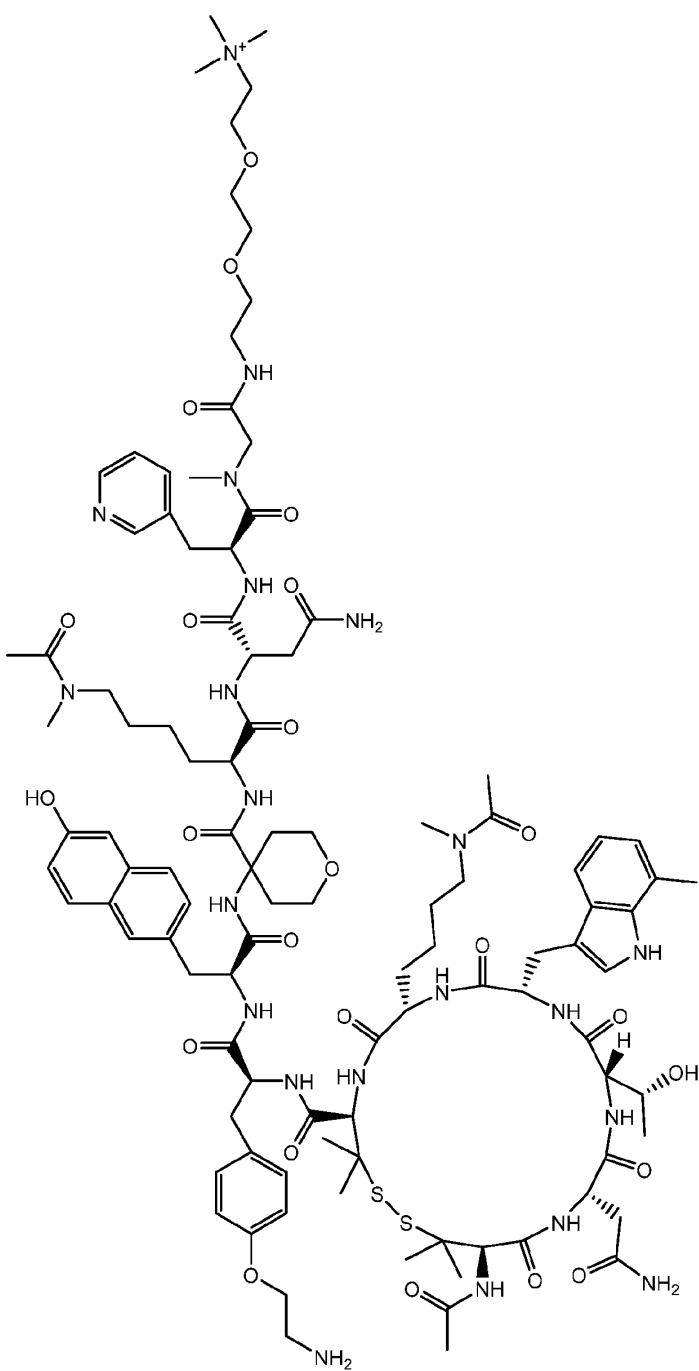
SEQ ID NO	Structure
363	 The chemical structure depicts a large cyclic peptide with a central macrocyclic ring. The ring is substituted with several side chains, including a PEG chain, a 6-hydroxy-2-naphthyl group, a 3-pyridyl group, and a 3-aminopropyl group. The structure also features a disulfide bridge and a quaternary ammonium group. The side chains are connected to the main ring via amide bonds. cPEG3aCO-Pen(3)-N-T-7MeW-K(NMeAc)-Pen(3)-AEF-6OH2Nal-Pip(NMe2)-K(NMeAc)-N-3Py-Sar-CONH2

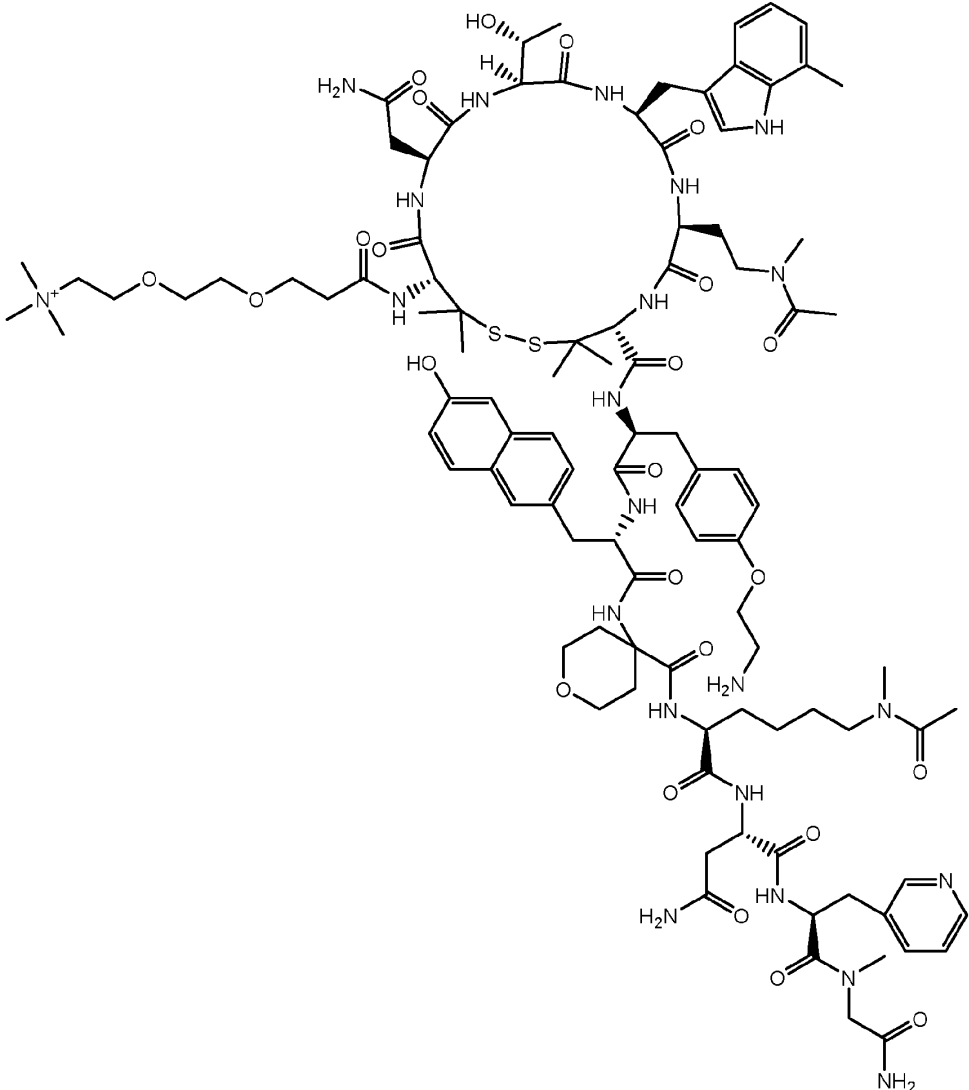
SEQ ID NO	Structure
364	 cPEG3aCO-Pen(3)-E(2)-T-7MeW-K(Ac)-Pen(3)-AEF(2)-6OH2Nal-THP-K(Ac)-N-3Pyra-Sar-CONH2
365	 cPEG3aCO-Pen(3)-E(2)-T-7MeW-K(NMeAc)-Pen(3)-AEF(NMe)(2)-6OH2Nal-THP-E-N-3Pyra-Sar-CONH2

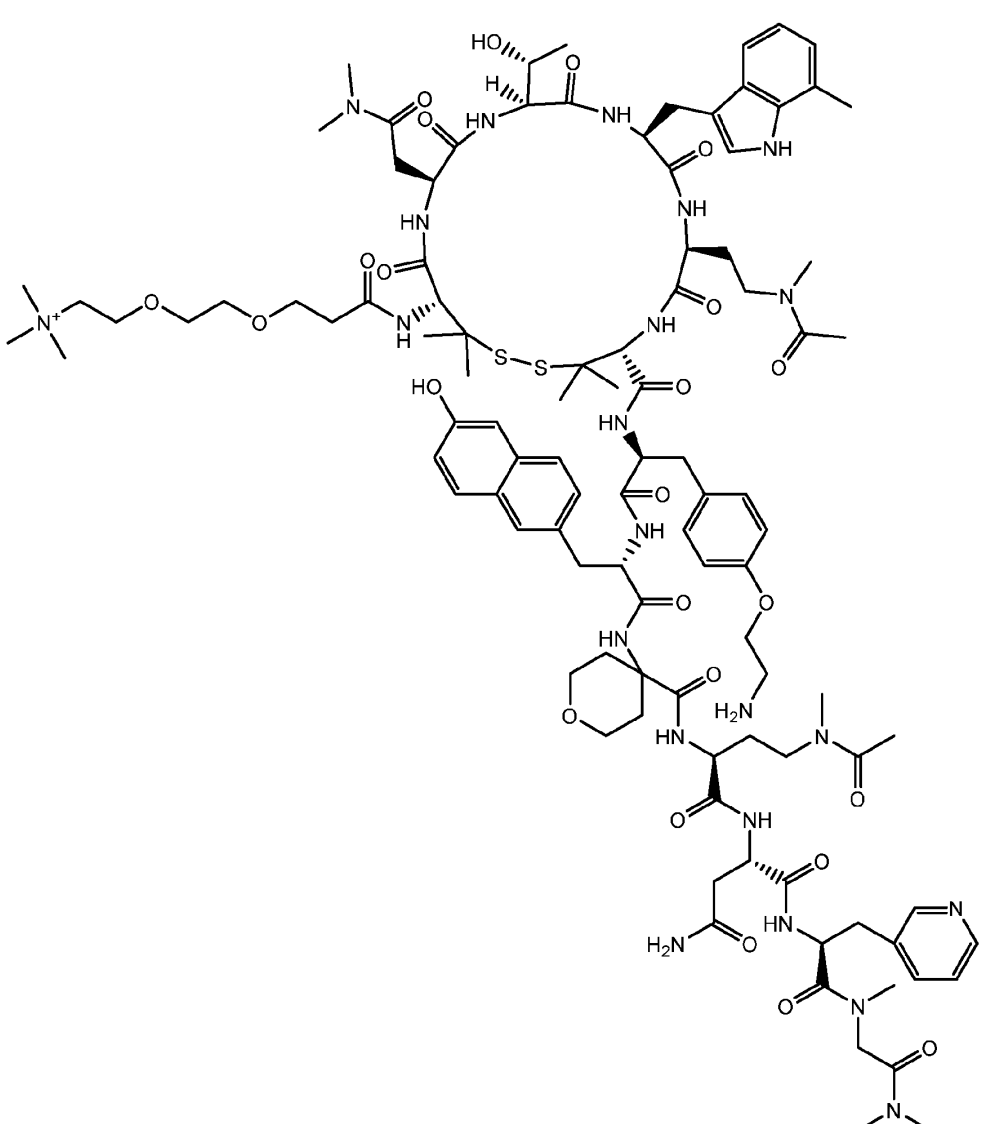
SEQ ID NO	Structure
366	 The chemical structure is a large, complex cyclic peptide. It features a central macrocyclic ring with several side chains. Notable features include a disulfide bridge (S-S) connecting two parts of the ring, a penicillin moiety, a thiazolidine ring, and various aromatic and aliphatic side chains. The structure is highly detailed, showing stereochemistry and specific functional groups like amide bonds, hydroxyl groups, and a carboxamide group. MeCO-Pen(3)-E(2)-T-7MeW-K(NMeAc)-Pen(3)-AEF(NMe)(2)-6OH2Nal-THP-K(Ac)-N-3Pyra-Sar-CONH2

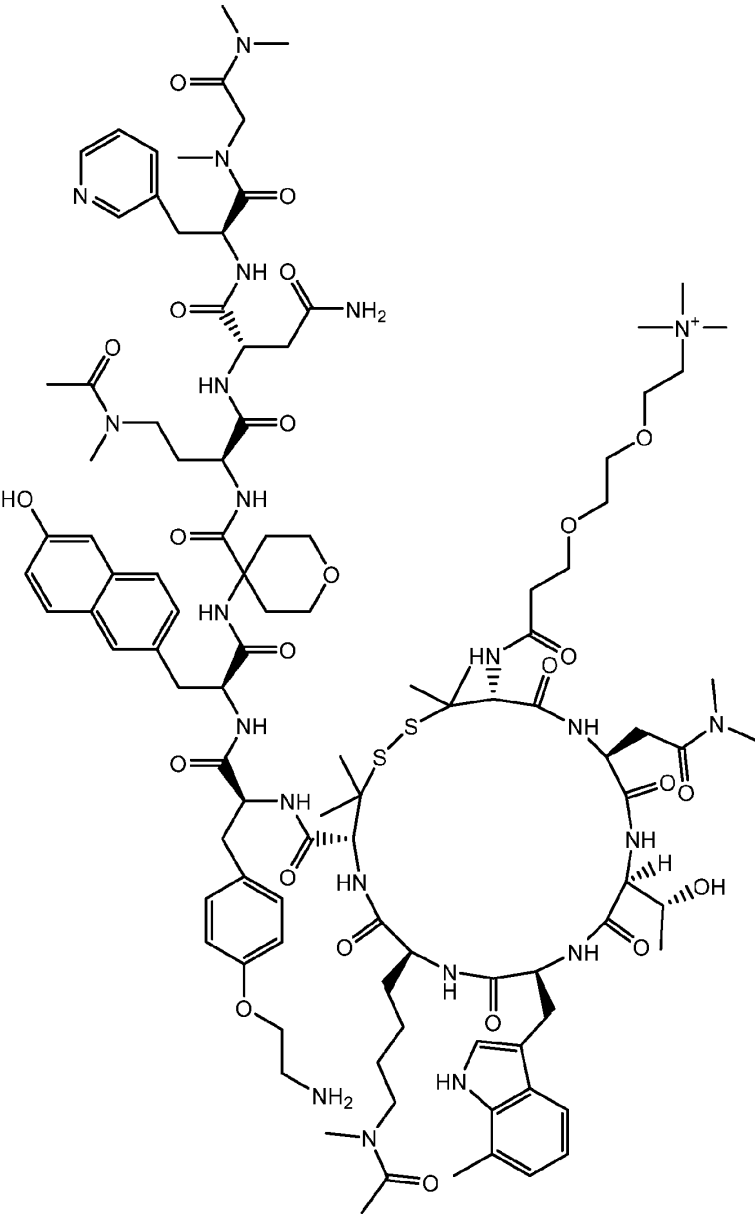
CN(C)CCOCCOCCOCCNC(=O)C[C@H](C(=O)N[C@@H](Cc1cccnc1)C(=O)N[C@@H](C(=O)NCC(=O)N)C(=O)N[C@@H](Cc2ccc(O)cc2)C(=O)N[C@@H](Cc3ccc(OCCN)cc3)C(=O)N[C@@H](Cc4ccccc4)C(=O)N[C@@H](Cc5ccccc5)C(=O)N[C@@H](Cc6ccccc6)C(=O)N[C@@H](Cc7ccccc7)C(=O)N[C@@H](Cc8ccccc8)C(=O)N[C@@H](Cc9ccccc9)C(=O)N[C@@H](Cc10ccccc10)C(=O)N[C@@H](Cc11ccccc11)C(=O)N[C@@H](Cc12ccccc12)C(=O)N[C@@H](Cc13ccccc13)C(=O)N[C@@H](Cc14ccccc14)C(=O)N[C@@H](Cc15ccccc15)C(=O)N[C@@H](Cc16ccccc16)C(=O)N[C@@H](Cc17ccccc17)C(=O)N[C@@H](Cc18ccccc18)C(=O)N[C@@H](Cc19ccccc19)C(=O)N[C@@H](Cc20ccccc20)C(=O)N[C@@H](Cc21ccccc21)C(=O)N[C@@H](Cc22ccccc22)C(=O)N[C@@H](Cc23ccccc23)C(=O)N[C@@H](Cc24ccccc24)C(=O)N[C@@H](Cc25ccccc25)C(=O)N[C@@H](Cc26ccccc26)C(=O)N[C@@H](Cc27ccccc27)C(=O)N[C@@H](Cc28ccccc28)C(=O)N[C@@H](Cc29ccccc29)C(=O)N[C@@H](Cc30ccccc30)C(=O)N[C@@H](Cc31ccccc31)C(=O)N[C@@H](Cc32ccccc32)C(=O)N[C@@H](Cc33ccccc33)C(=O)N[C@@H](Cc34ccccc34)C(=O)N[C@@H](Cc35ccccc35)C(=O)N[C@@H](Cc36ccccc36)C(=O)N[C@@H](Cc37ccccc37)C(=O)N[C@@H](Cc38ccccc38)C(=O)N[C@@H](Cc39ccccc39)C(=O)N[C@@H](Cc40ccccc40)C(=O)N[C@@H](Cc41ccccc41)C(=O)N[C@@H](Cc42ccccc42)C(=O)N[C@@H](Cc43ccccc43)C(=O)N[C@@H](Cc44ccccc44)C(=O)N[C@@H](Cc45ccccc45)C(=O)N[C@@H](Cc46ccccc46)C(=O)N[C@@H](Cc47ccccc47)C(=O)N[C@@H](Cc48ccccc48)C(=O)N[C@@H](Cc49ccccc49)C(=O)N[C@@H](Cc50ccccc50)C(=O)N[C@@H](Cc51ccccc51)C(=O)N[C@@H](Cc52ccccc52)C(=O)N[C@@H](Cc53ccccc53)C(=O)N[C@@H](Cc54ccccc54)C(=O)N[C@@H](Cc55ccccc55)C(=O)N[C@@H](Cc56ccccc56)C(=O)N[C@@H](Cc57ccccc57)C(=O)N[C@@H](Cc58ccccc58)C(=O)N[C@@H](Cc59ccccc59)C(=O)N[C@@H](Cc60ccccc60)C(=O)N[C@@H](Cc61ccccc61)C(=O)N[C@@H](Cc62ccccc62)C(=O)N[C@@H](Cc63ccccc63)C(=O)N[C@@H](Cc64ccccc64)C(=O)N[C@@H](Cc65ccccc65)C(=O)N[C@@H](Cc66ccccc66)C(=O)N[C@@H](Cc67ccccc67)C(=O)N[C@@H](Cc68ccccc68)C(=O)N[C@@H](Cc69ccccc69)C(=O)N[C@@H](Cc70ccccc70)C(=O)N[C@@H](Cc71ccccc71)C(=O)N[C@@H](Cc72ccccc72)C(=O)N[C@@H](Cc73ccccc73)C(=O)N[C@@H](Cc74ccccc74)C(=O)N[C@@H](Cc75ccccc75)C(=O)N[C@@H](Cc76ccccc76)C(=O)N[C@@H](Cc77ccccc77)C(=O)N[C@@H](Cc78ccccc78)C(=O)N[C@@H](Cc79ccccc79)C(=O)N[C@@H](Cc80ccccc80)C(=O)N[C@@H](Cc81ccccc81)C(=O)N[C@@H](Cc82ccccc82)C(=O)N[C@@H](Cc83ccccc83)C(=O)N[C@@H](Cc84ccccc84)C(=O)N[C@@H](Cc85ccccc85)C(=O)N[C@@H](Cc86ccccc86)C(=O)N[C@@H](Cc87ccccc87)C(=O)N[C@@H](Cc88ccccc88)C(=O)N[C@@H](Cc89ccccc89)C(=O)N[C@@H](Cc90ccccc90)C(=O)N[C@@H](Cc91ccccc91)C(=O)N[C@@H](Cc92ccccc92)C(=O)N[C@@H](Cc93ccccc93)C(=O)N[C@@H](Cc94ccccc94)C(=O)N[C@@H](Cc95ccccc95)C(=O)N[C@@H](Cc96ccccc96)C(=O)N[C@@H](Cc97ccccc97)C(=O)N[C@@H](Cc98ccccc98)C(=O)N[C@@H](Cc99ccccc99)C(=O)N[C@@H](Cc100ccccc100)C(=O)N[C@@H](Cc101ccccc101)C(=O)N[C@@H](Cc102ccccc102)C(=O)N[C@@H](Cc103ccccc103)C(=O)N[C@@H](Cc104ccccc104)C(=O)N[C@@H](Cc105ccccc105)C(=O)N[C@@H](Cc106ccccc106)C(=O)N[C@@H](Cc107ccccc107)C(=O)N[C@@H](Cc108ccccc108)C(=O)N[C@@H](Cc109ccccc109)C(=O)N[C@@H](Cc110ccccc110)C(=O)N[C@@H](Cc111ccccc111)C(=O)N[C@@H](Cc112ccccc112)C(=O)N[C@@H](Cc113ccccc113)C(=O)N[C@@H](Cc114ccccc114)C(=O)N[C@@H](Cc115ccccc115)C(=O)N[C@@H](Cc116ccccc116)C(=O)N[C@@H](Cc117ccccc117)C(=O)N[C@@H](Cc118ccccc118)C(=O)N[C@@H](Cc119ccccc119)C(=O)N[C@@H](Cc120ccccc120)C(=O)N[C@@H](Cc121ccccc121)C(=O)N[C@@H](Cc122ccccc122)C(=O)N[C@@H](Cc123ccccc123)C(=O)N[C@@H](Cc124ccccc124)C(=O)N[C@@H](Cc125ccccc125)C(=O)N[C@@H](Cc126ccccc126)C(=O)N[C@@H](Cc127ccccc127)C(=O)N[C@@H](Cc128ccccc128)C(=O)N[C@@H](Cc129ccccc129)C(=O)N[C@@H](Cc130ccccc130)C(=O)N[C@@H](Cc131ccccc131)C(=O)N[C@@H](Cc132ccccc132)C(=O)N[C@@H](Cc133ccccc133)C(=O)N[C@@H](Cc134ccccc134)C(=O)N[C@@H](Cc135ccccc135)C(=O)N[C@@H](Cc136ccccc136)C(=O)N[C@@H](Cc137ccccc137)C(=O)N[C@@H](Cc138ccccc138)C(=O)N[C@@H](Cc139ccccc139)C(=O)N[C@@H](Cc140ccccc140)C(=O)N[C@@H](Cc141ccccc141)C(=O)N[C@@H](Cc142ccccc142)C(=O)N[C@@H](Cc143ccccc143)C(=O)N[C@@H](Cc144ccccc144)C(=O)N[C@@H](Cc145ccccc145)C(=O)N[C@@H](Cc146ccccc146)C(=O)N[C@@H](Cc147ccccc147)C(=O)N[C@@H](Cc148ccccc148)C(=O)N[C@@H](Cc149ccccc149)C(=O)N[C@@H](Cc150ccccc150)C(=O)N[C@@H](Cc151ccccc151)C(=O)N[C@@H](Cc152ccccc152)C(=O)N[C@@H](Cc153ccccc153)C(=O)N[C@@H](Cc154ccccc154)C(=O)N[C@@H](Cc155ccccc155)C(=O)N[C@@H](Cc156ccccc156)C(=O)N[C@@H](Cc157ccccc157)C(=O)N[C@@H](Cc158ccccc158)C(=O)N[C@@H](Cc159ccccc159)C(=O)N[C@@H](Cc160ccccc160)C(=O)N[C@@H](Cc161ccccc161)C(=O)N[C@@H](Cc162ccccc162)C(=O)N[C@@H](Cc163ccccc163)C(=O)N[C@@H](Cc164ccccc164)C(=O)N[C@@H](Cc165ccccc165)C(=O)N[C@@H](Cc166ccccc166)C(=O)N[C@@H](Cc167ccccc167)C(=O)N[C@@H](Cc168ccccc168)C(=O)N[C@@H](Cc169ccccc169)C(=O)N[C@@H](Cc170ccccc170)C(=O)N[C@@H](Cc171ccccc171)C(=O)N[C@@H](Cc172ccccc172)C(=O)N[C@@H](Cc173ccccc173)C(=O)N[C@@H](Cc174ccccc174)C(=O)N[C@@H](Cc175ccccc175)C(=O)N[C@@H](Cc176ccccc176)C(=O)N[C@@H](Cc177ccccc177)C(=O)N[C@@H](Cc178ccccc178)C(=O)N[C@@H](Cc179ccccc179)C(=O)N[C@@H](Cc180ccccc180)C(=O)N[C@@H](Cc181ccccc181)C(=O)N[C@@H](Cc182ccccc182)C(=O)N[C@@H](Cc183ccccc183)C(=O)N[C@@H](Cc184ccccc184)C(=O)N[C@@H](Cc185ccccc185)C(=O)N[C@@H](Cc186ccccc186)C(=O)N[C@@H](Cc187ccccc187)C(=O)N[C@@H](Cc188ccccc188)C(=O)N[C@@H](Cc189ccccc189)C(=O)N[C@@H](Cc190ccccc190)C(=O)N[C@@H](Cc191ccccc191)C(=O)N[C@@H](Cc192ccccc192)C(=O)N[C@@H](Cc193ccccc193)C(=O)N[C@@H](Cc194ccccc194)C(=O)N[C@@H](Cc195ccccc195)C(=O)N[C@@H](Cc196ccccc196)C(=O)N[C@@H](Cc197ccccc197)C(=O)N[C@@H](Cc198ccccc198)C(=O)N[C@@H](Cc199ccccc199)C(=O)N[C@@H](Cc200ccccc200)C(=O)N[C@@H](Cc201ccccc201)C(=O)N[C@@H](Cc202ccccc202)C(=O)N[C@@H](Cc203ccccc203)C(=O)N[C@@H](Cc204ccccc204)C(=O)N[C@@H](Cc205ccccc205)C(=O)N[C@@H](Cc206ccccc206)C(=O)N[C@@H](Cc207ccccc207)C(=O)N[C@@H](Cc208ccccc208)C(=O)N[C@@H](Cc209ccccc209)C(=O)N[C@@H](Cc210ccccc210)C(=O)N[C@@H](Cc211ccccc211)C(=O)N[C@@H](Cc212ccccc212)C(=O)N[C@@H](Cc213ccccc213)

468

SEQ ID NO	Structure
368	 MeCO-Pen(3)-N-T-7MeW-K(NMeAc)-Pen(3)-AEF-6OH2NaI-THP-K(NMeAc)-N-3Py-Sar-CONH(PEG3a)

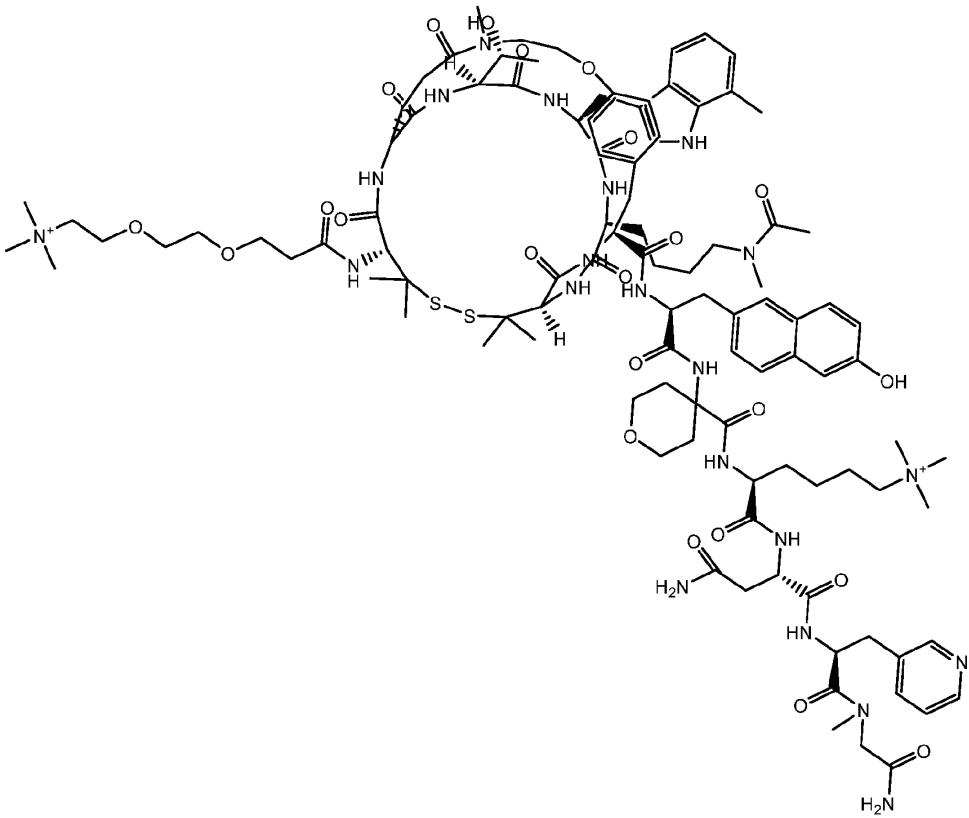
SEQ ID NO	Structure
369	 The chemical structure depicts a large cyclic peptide with a central ring. The ring is substituted with several side chains, including a PEG chain, a thiol group, a hydroxyl group, a phenyl group, a thiazole ring, a pyridine ring, and a morpholine ring. The side chains are connected to the ring via amide bonds. The structure is highly complex and contains many functional groups. cPEG3aCO-Pen(3)-N-T-7MeW-Dab(NMeAc)-Pen(3)-AEF-6OH2NaI-THP-K(NMeAc)-N-3Pya-Sar-CONH2

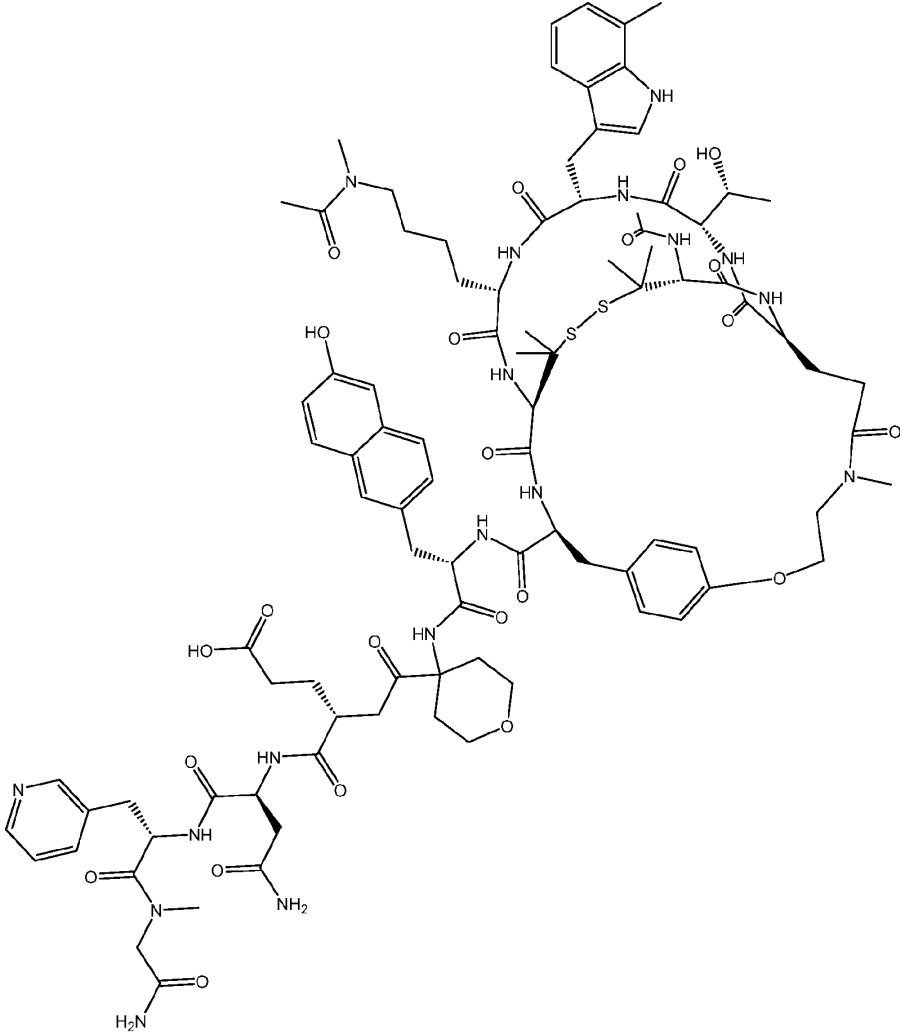
SEQ ID NO	Structure
370	 cPEG3aCO-Pen(3)-N(N(Me)2)-T-7MeW-Dab(NMeAc)-Pen(3)-AEF-6OH2Nal-THP-Dab(NMeAc)-N-3Py-Sar-CON(Me)2

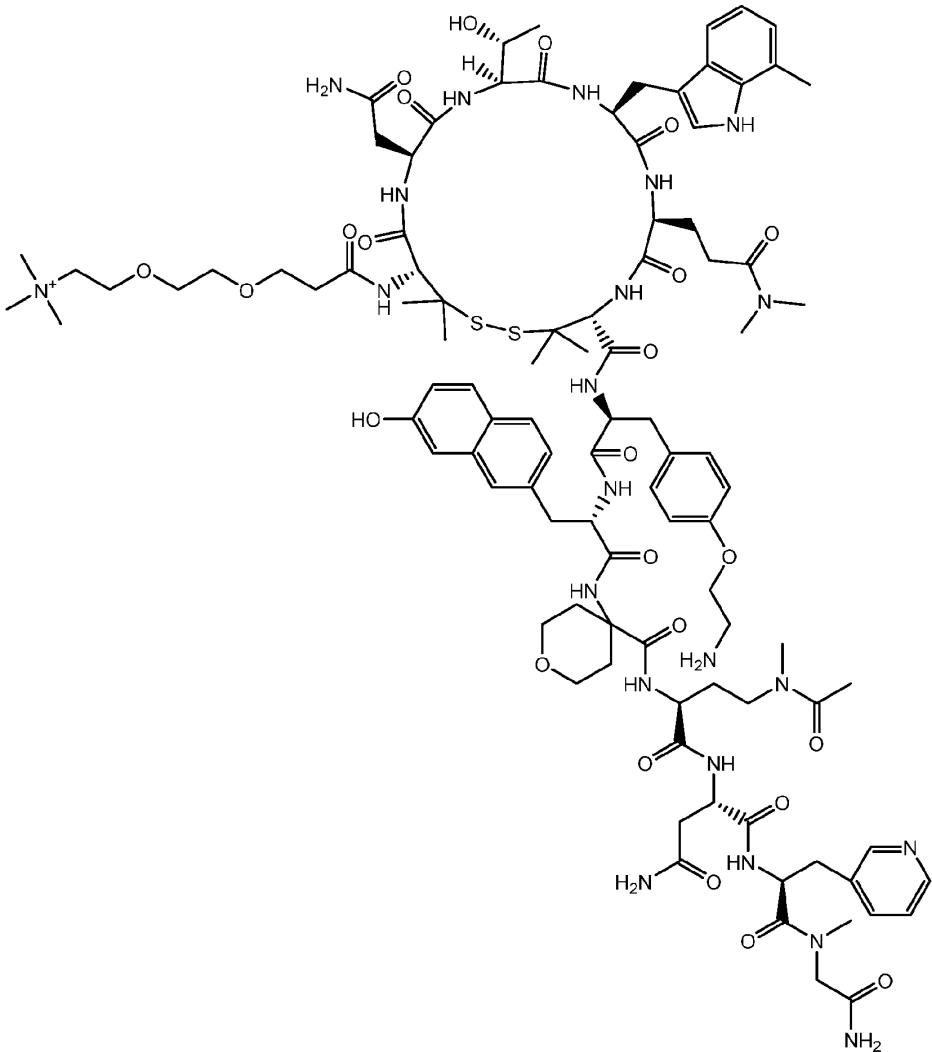
SEQ ID NO	Structure
371	 The chemical structure of compound 371 is a large, complex peptide molecule. It features a central cyclic core, likely a macrocycle, with various side chains attached. The side chains include aromatic groups (e.g., pyridine, naphthalene, phenol), aliphatic groups (e.g., methyl, ethyl, propyl), and charged groups (e.g., quaternary ammonium, carboxylate). The structure is highly branched and contains multiple amide bonds, suggesting a complex folding or conformation. The molecule is labeled with the sequence: cPEG3aCO-Pen(3)-N(N(Me)2)-T-7MeW-K(NMeAc)-Pen(3)-AEF-6OH2Nal-THP-Dab(NMeAc)-N-3Py-Sar-CON(Me)2.

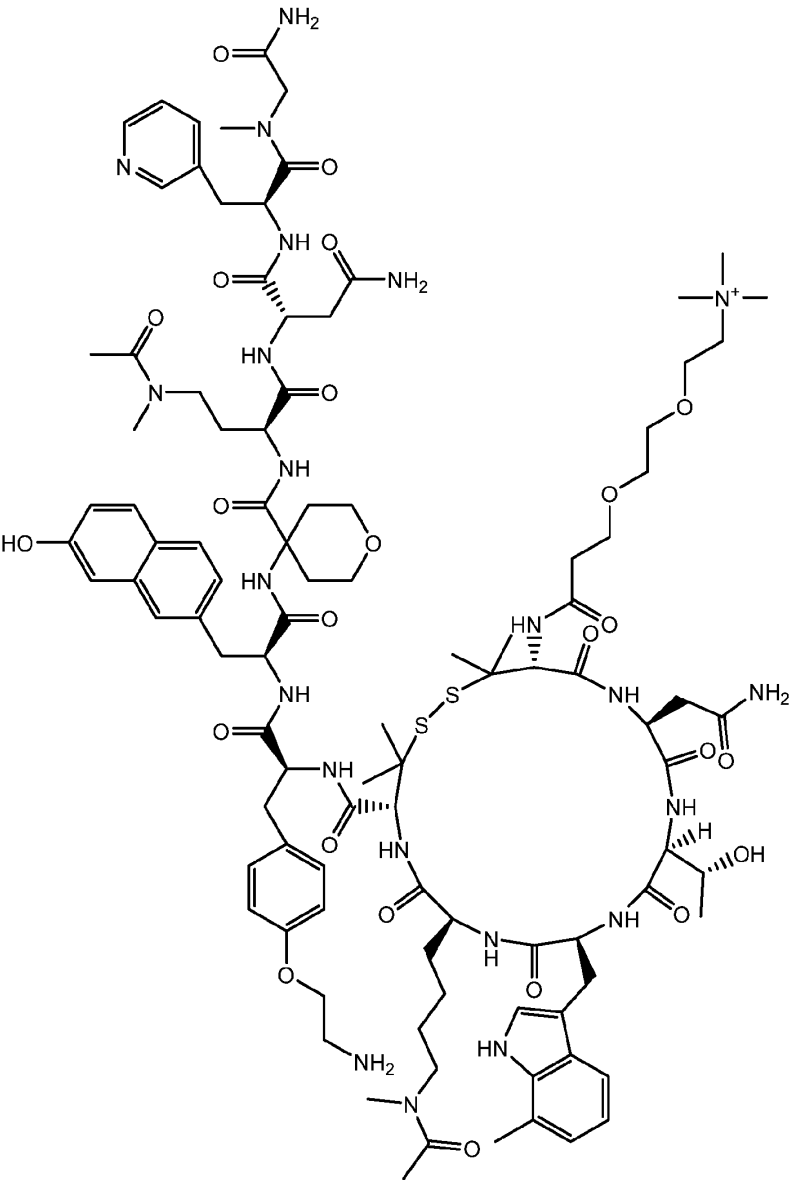
SEQ ID NO	Structure
372	cPEG3aCO-Pen(3)-E(2)-T-7MeW-K(Ac)-Pen(3)-AEF(2)-6OH2NaI-THP-E-N-3Py-Sar-CONH2

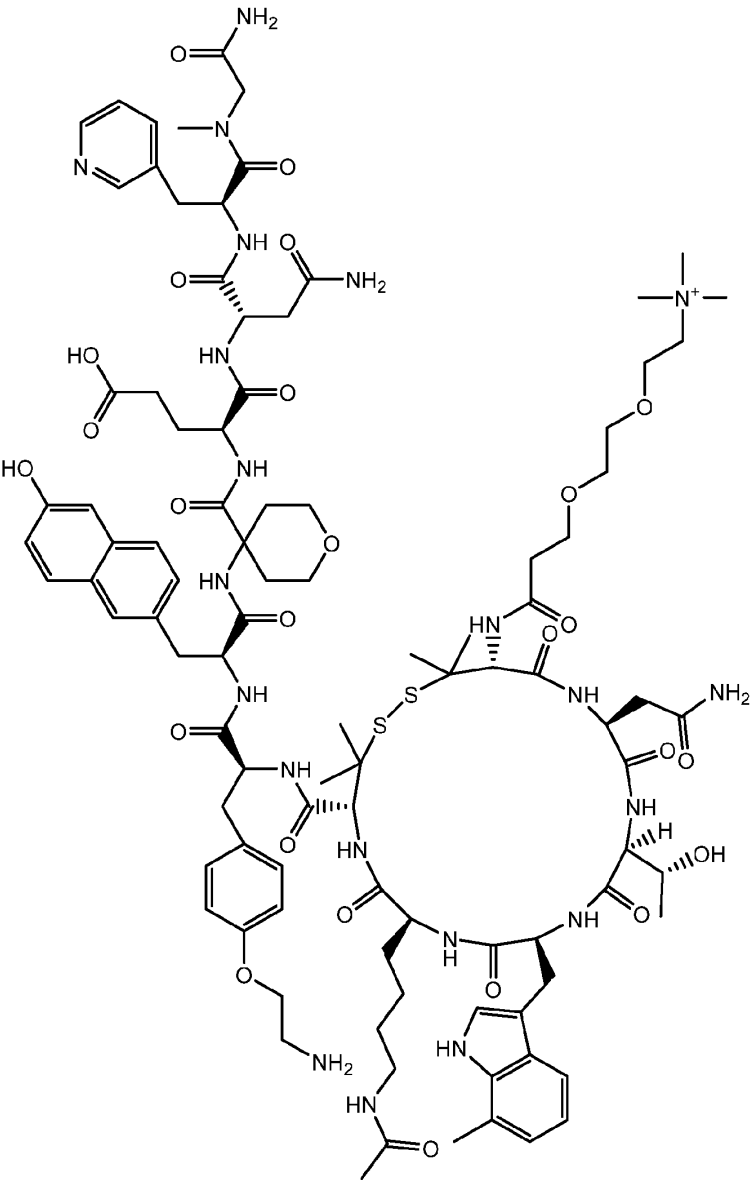
[illegible]

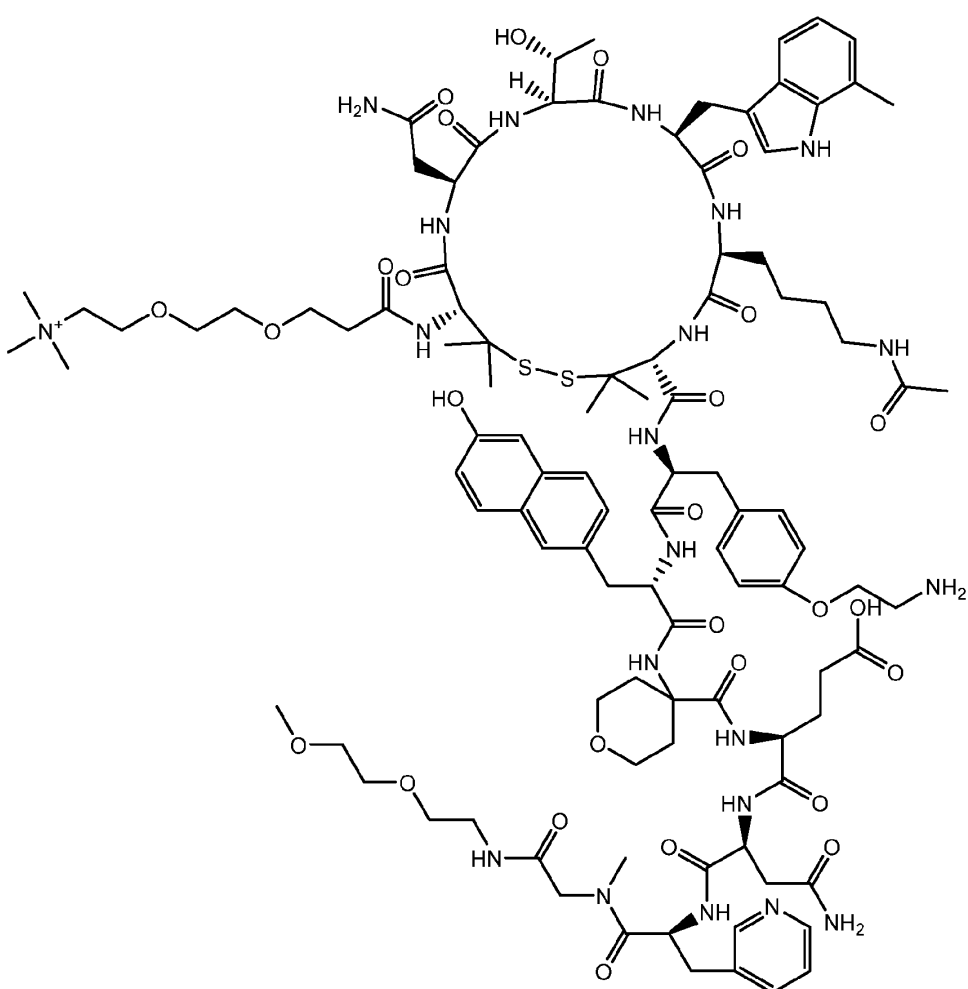
SEQ ID NO	Structure
374	 cPEG3aCO-Pen(3)-E(2)-T-7MeW-K(NMeAc)-Pen(3)-AEF(NMe)(2)-6OH2Nal-THP-K(Me)3-N-3Py-Sar-CONH2

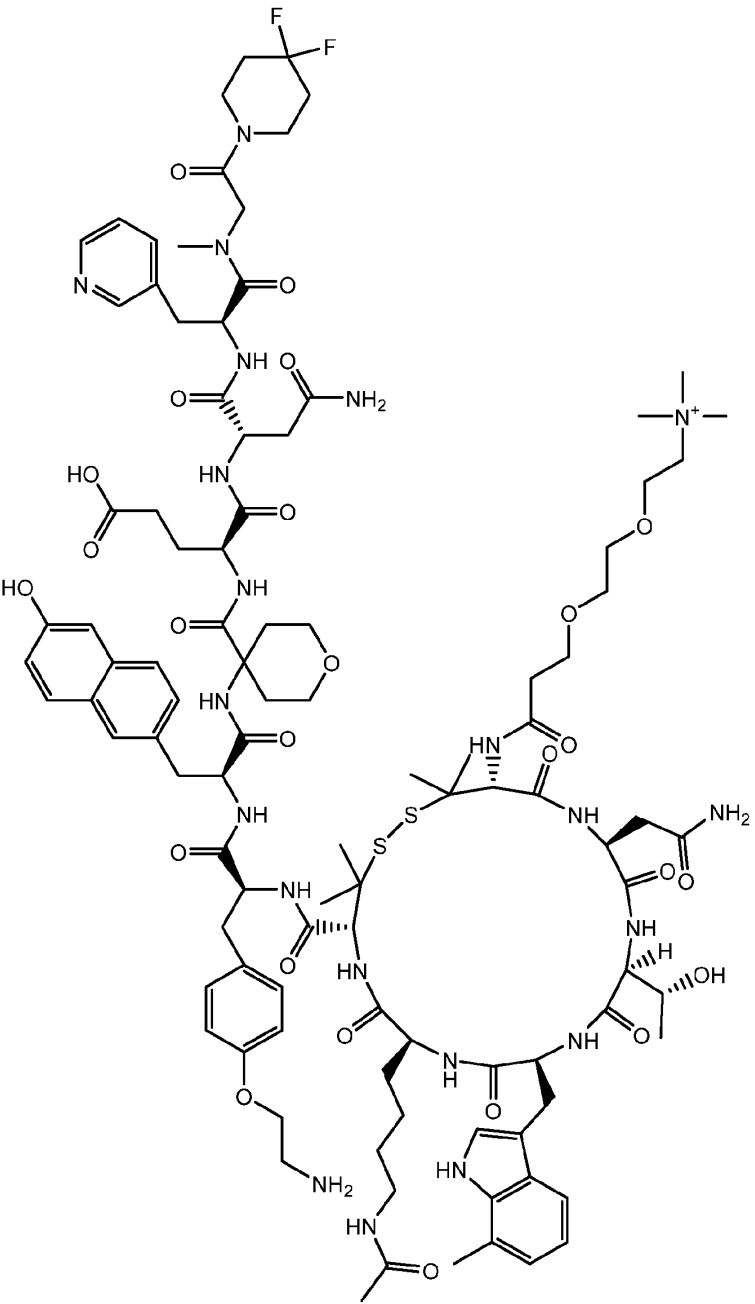
SEQ ID NO	Structure
375	 MeCO-Pen(3)-E(2)-T-7MeW-K(NMeAc)-Pen(3)-AEF(NMe)(2)-6OH2Nal-THP-E-N-3Pya-Sar-CONH2

SEQ ID NO	Structure
376	 cPEG3aCO-Pen(3)-N-T-7MeW-Q(N(Me)2)-Pen(3)-AEF-6OH2NaI-THP-Dab(NMeAc)-N-3Py-Sar-CONH2

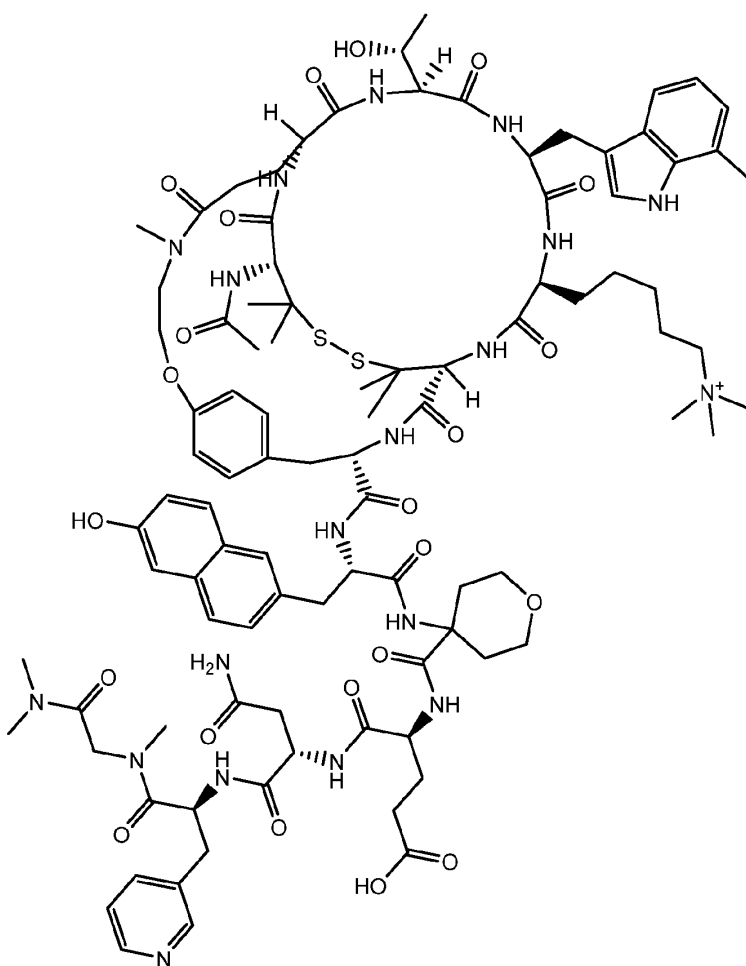
SEQ ID NO	Structure
377	 The chemical structure depicts a large, complex molecule, likely a peptide derivative. It features a central cyclic core, possibly a macrocycle, with various side chains and modifications. Key features include: - A central cyclic structure with a disulfide bridge (S-S) and a carbonyl group (C=O). - Side chains including a pyridine ring, a hydroxyl group (HO-), a methyl group (CH₃), a hydroxyl group (OH), and a quaternary ammonium group (N⁺). - Amide bonds (NH-C=O) connecting various residues. - A long, flexible chain extending from the central structure, containing a hydroxyl group (HO-) and a quaternary ammonium group (N⁺). cPEG3aCO-Pen(3)-N-T-7MeW-K(NMeAc)-Pen(3)-AEF-6OH2Nal-THP-Dab(NMeAc)-N-3Py-Sar-CONH₂

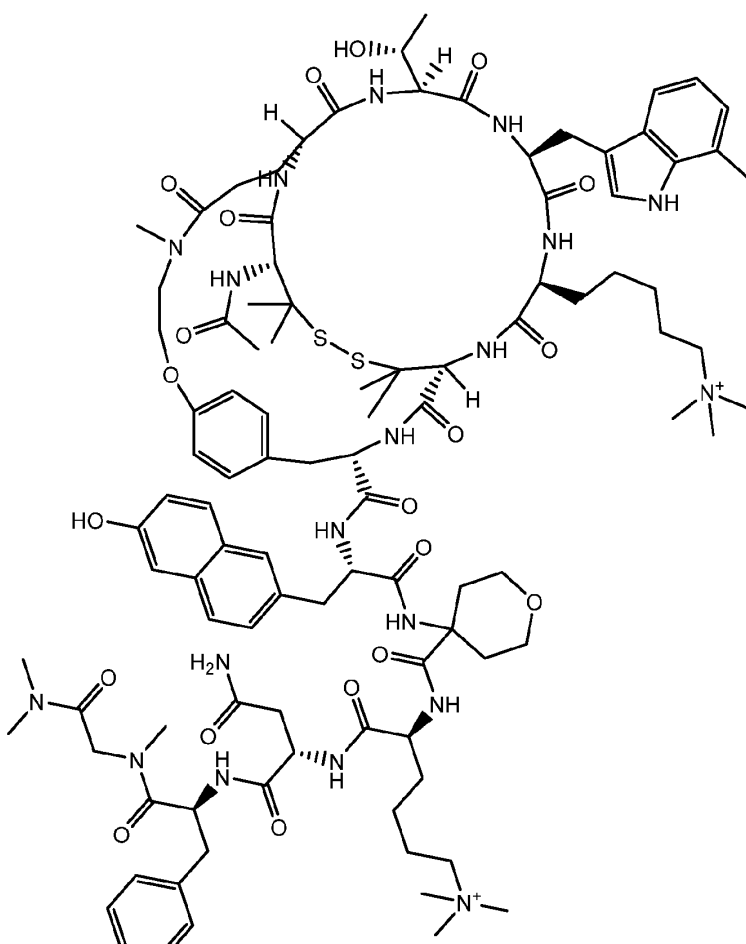
SEQ ID NO	Structure
378	 The chemical structure is a complex peptide derivative, specifically a cyclic peptide. It features a central cyclic backbone with various side chains. Key features include a pyridine ring, a hydroxyl group, a carboxylic acid, a thiol, and a quaternary ammonium group. The structure is highly branched and contains multiple amide bonds. The side chains are connected to the backbone via amide bonds, and the backbone is a cyclic peptide with a thiol group. The structure is highly branched and contains multiple amide bonds. The side chains are connected to the backbone via amide bonds, and the backbone is a cyclic peptide with a thiol group. cPEG3aCO-Pen(3)-N-T-7MeW-K(Ac)-Pen(3)-AEF-6OH2NaI-THP-E-N-3Pya-Sar-CONH2

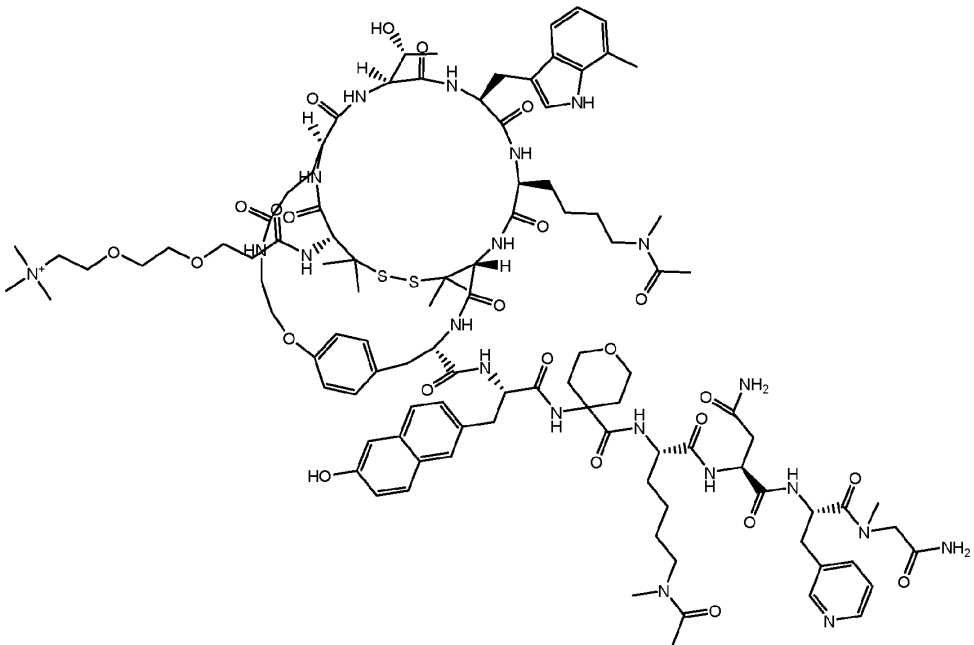
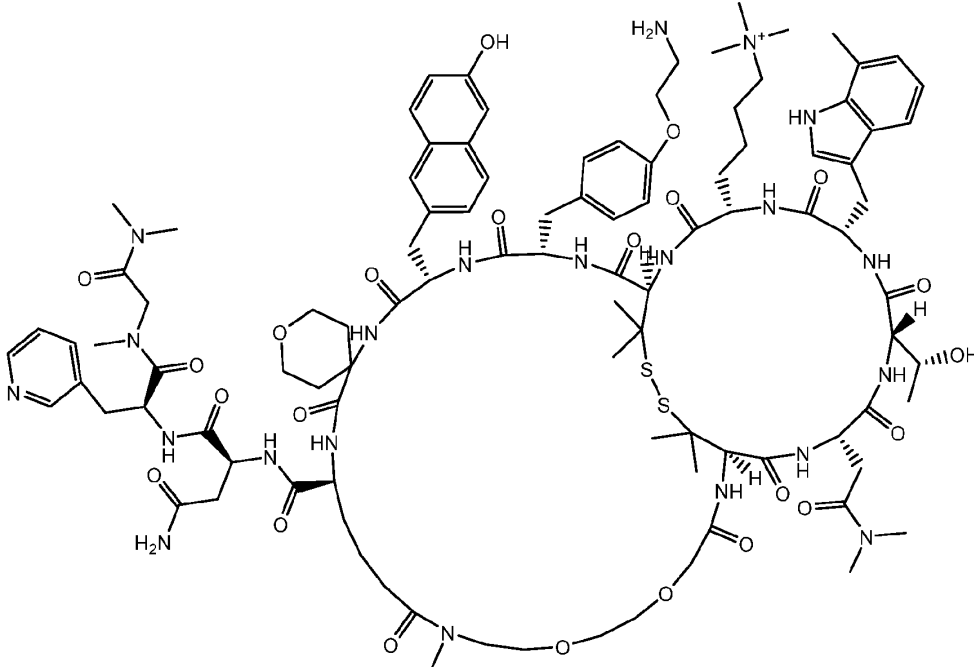
SEQ ID NO	Structure
379	 cPEG3aCO-Pen(3)-N-T-7MeW-K(Ac)-Pen(3)-AEF-6OH2Nal-THP-E-N-3Pya-Sar-CONH(mPEG2)

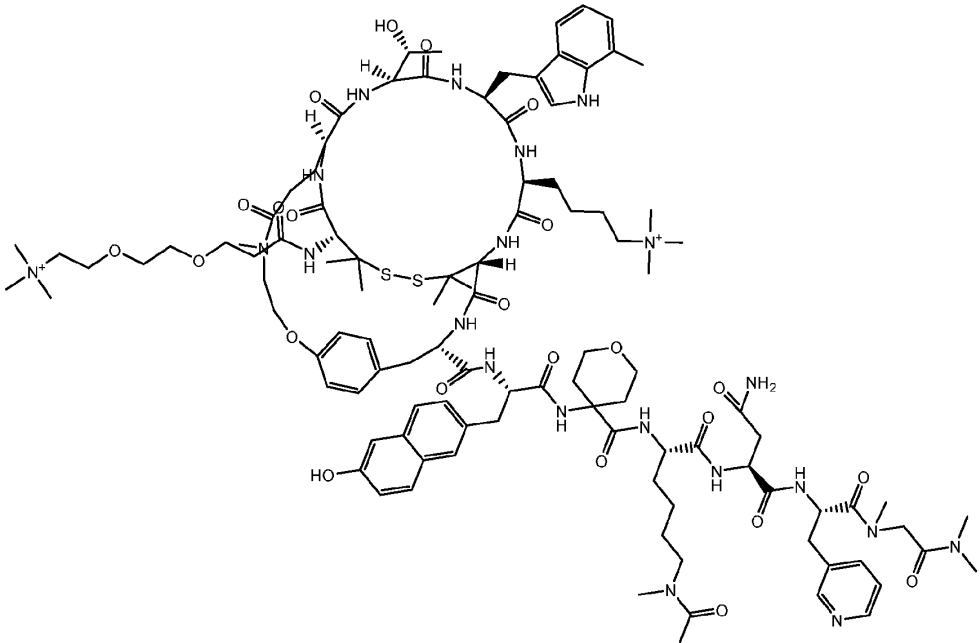
SEQ ID NO	Structure
380	 cPEG3aCO-Pen(3)-N-T-7MeW-K(Ac)-Pen(3)-AEF-6OH2Nal-THP-E-N-3Pya-Sar-CO(DiFPip)

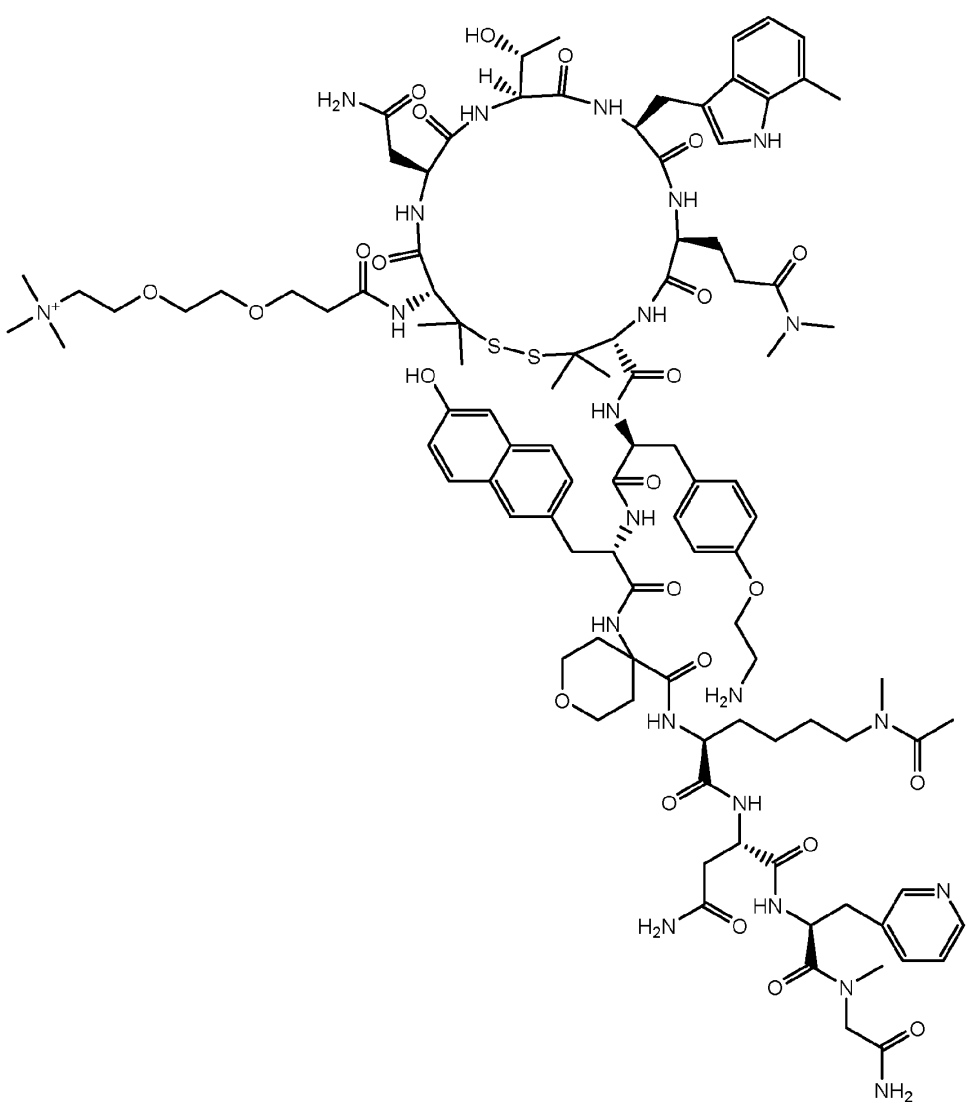
SEQ ID NO	Structure
381	cPEG3aCO-Pen(3)-N-T-7MeW-K(Ac)-Pen(3)-AEF-6OH₂NaI-THP-K(Ac)-N-3PyA-Sar-CONH(PEG3a)

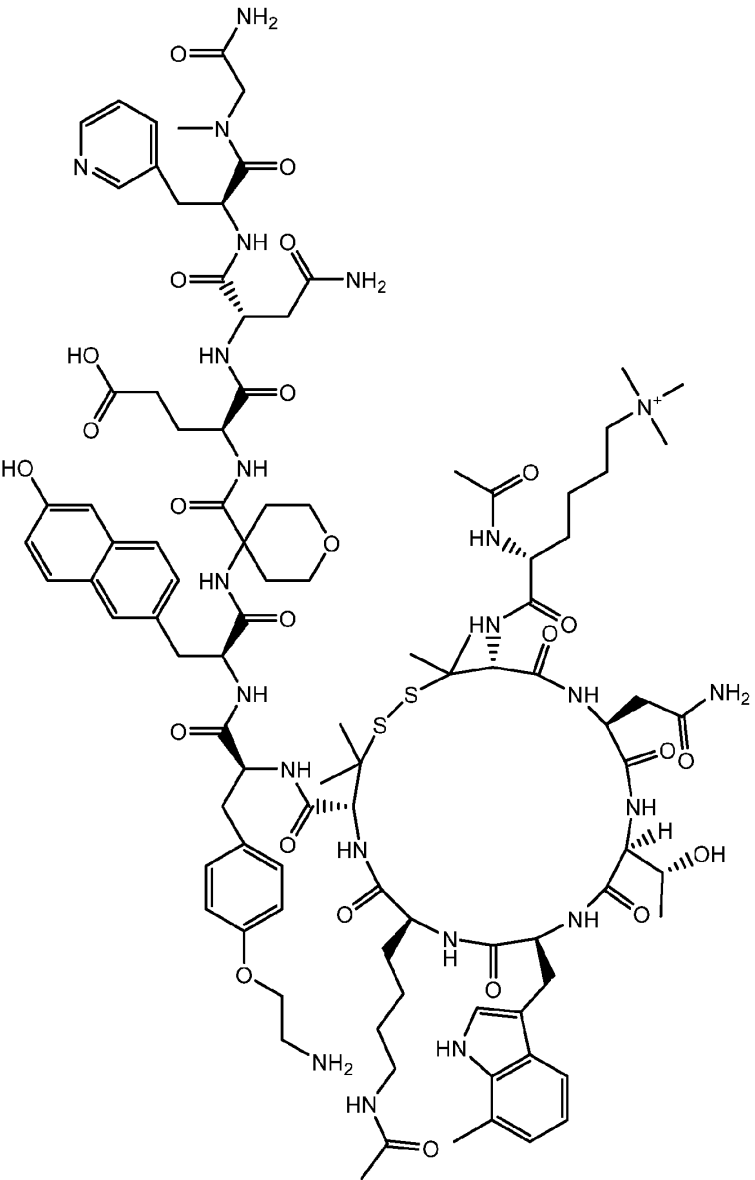
SEQ ID NO	Structure
382	 MeCO-Pen(3)-E(2)-T-7MeW-hK(Me)3-Pen(3)-AEF(NMe)(2)-6OH2NaI-THP-E-N-3PyA-Sar-CON(Me)2

SEQ ID NO	Structure
383	 MeCO-Pen(3)-E(2)-T-7MeW-hK(Me)3-Pen(3)-AEF(NMe)(2)-6OH2NaI-THP-K(Me)3-N-3PyA-Sar-CON(Me)2

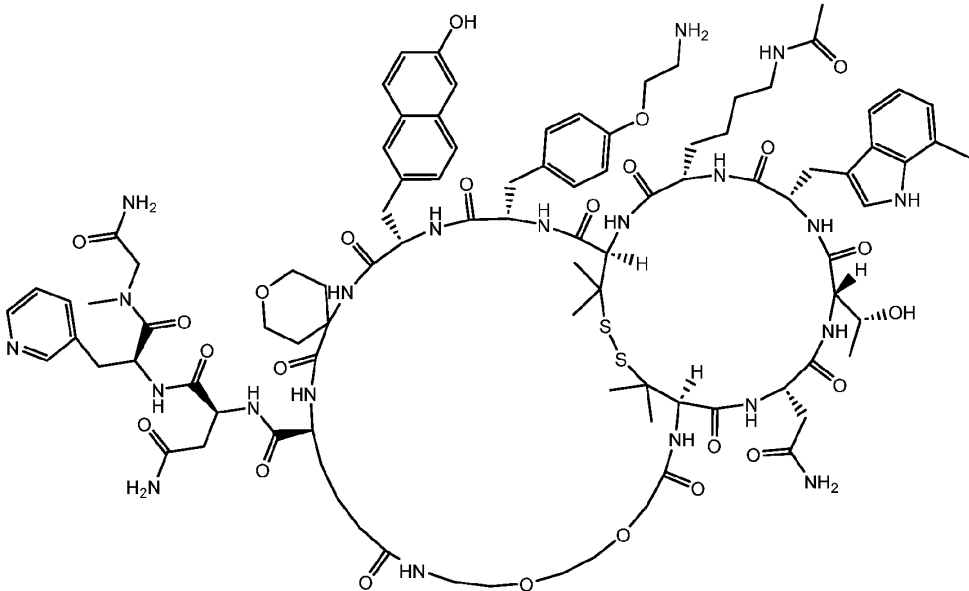
SEQ ID NO	Structure
384	 cPEG3aCO-Pen(3)-E(2)-T-7MeW-K(NMeAc)-Pen(3)-AEF(2)-6OH2Nal-THP-K(NMeAc)-N-3Pyra-Sar-CONH2
385	 PEG2NMe(2)-Pen(3)-N(N(Me)2)-T-7MeW-K(Me)3-Pen(3)-AEF-6OH2Nal-THP-hE(2)-N-3Pyra-Sar-CON(Me)2

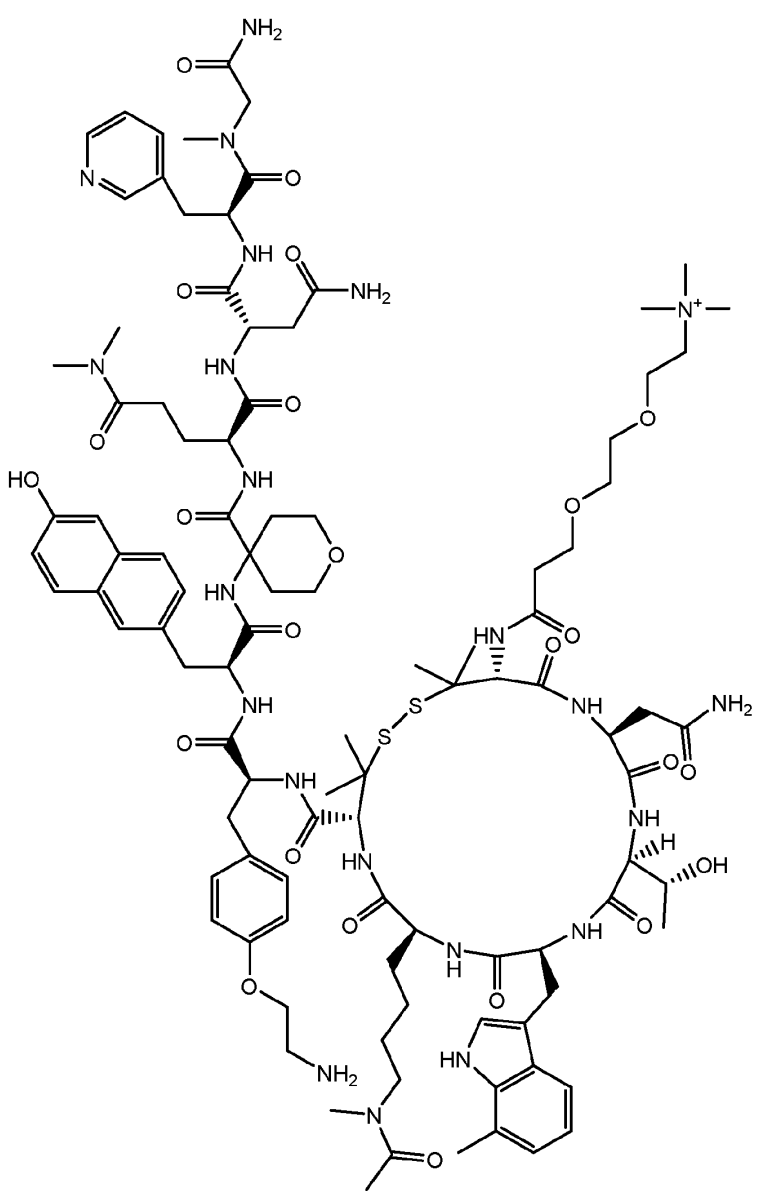
SEQ ID NO	Structure
386	 cPEG3aCO-Pen(3)-E(2)-T-7MeW-K(Me)3-Pen(3)-AEF(NMe)(2)-6OH2Nal-THP-K(NMeAc)-N-3Pya-Sar-CON(Me)2

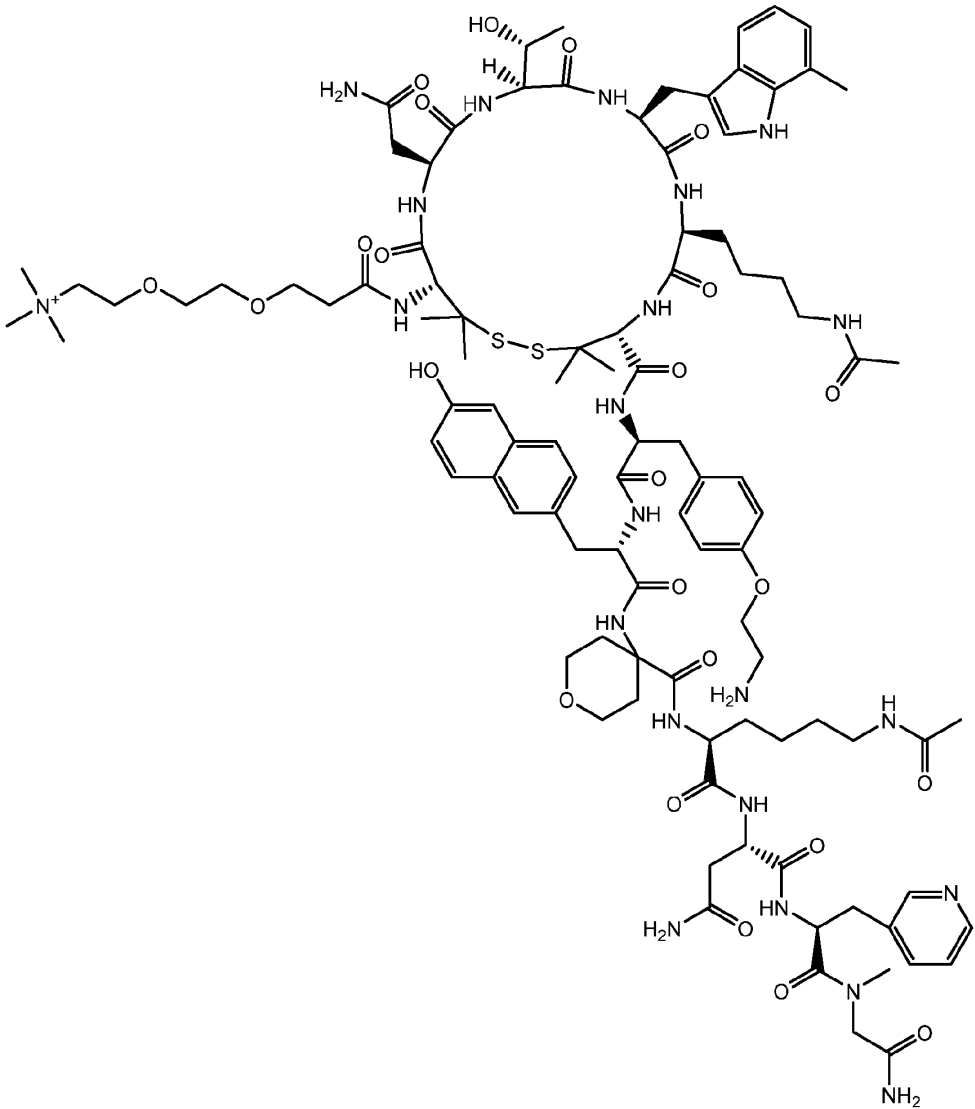
SEQ ID NO	Structure
387	 The chemical structure shows a large cyclic peptide backbone with several side chains. The side chains include a PEG chain with a quaternary ammonium group, a thiol group, a naphthyl group, a morpholine ring, a pyridine ring, and a tryptophan derivative. The structure is highly complex and contains many functional groups. cPEG3aCO-Pen(3)-N-T-7MeW-Q(N(Me)2)-Pen(3)-AEF-6OH2Nal-THP-K(NMeAc)-N-3Pya-Sar-CONH2

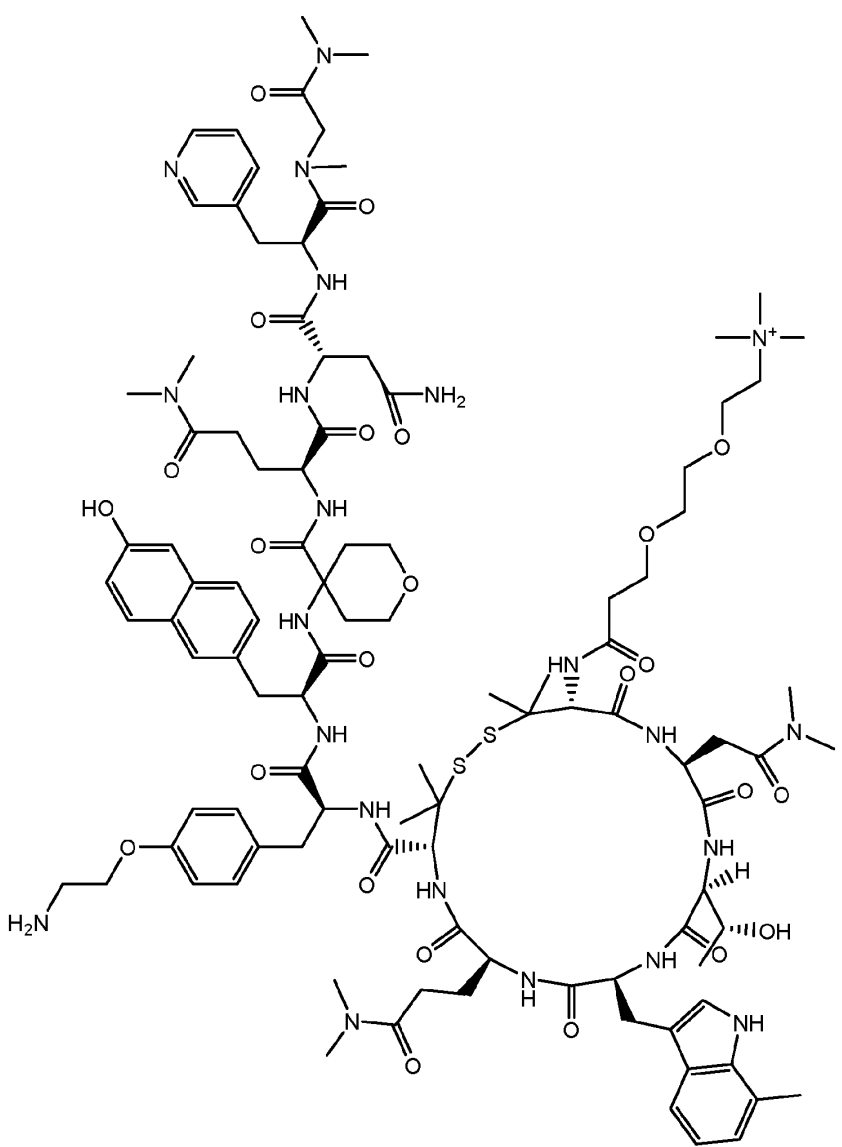
SEQ ID NO	Structure
388	 MeCO-k(Me)3-Pen(3)-N-T-7MeW-K(Ac)-Pen(3)-AEF-6OH2Nal-THP-E-N-3Pya-Sar-CONH2

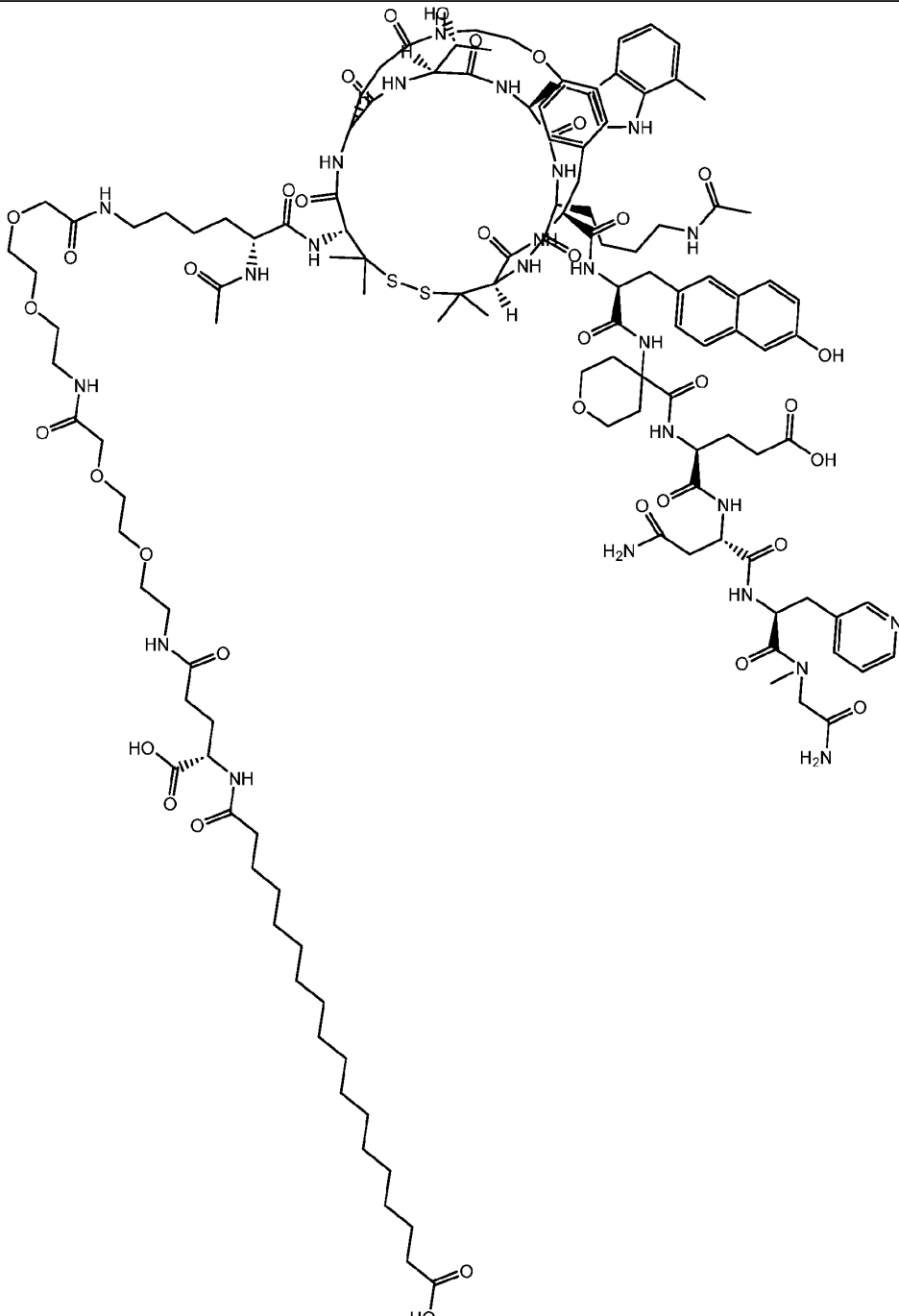
[illegible]

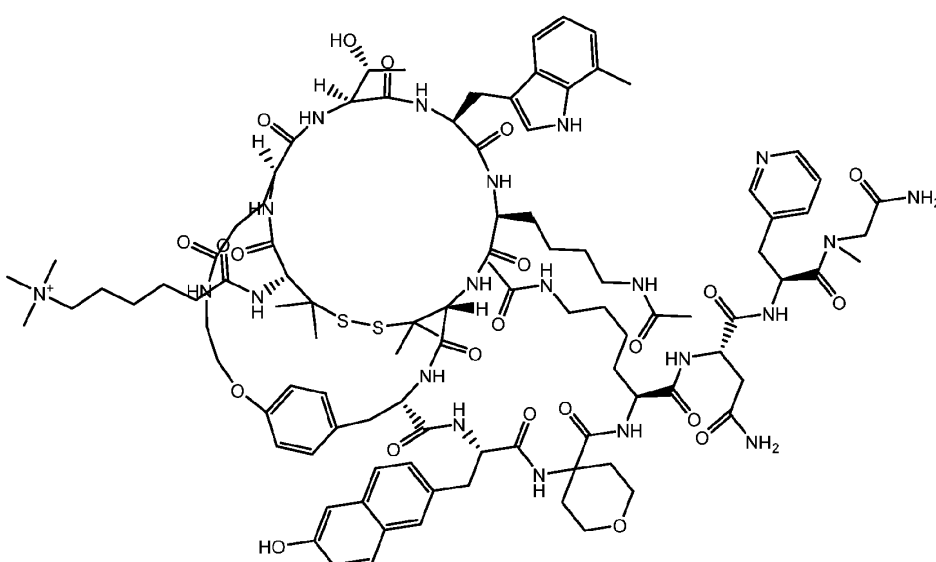
SEQ ID NO	Structure
391	 Chemical structure of a large cyclic peptide, specifically a 391-residue macrocycle. The structure is highly complex, featuring a large central ring with numerous side chains. Key features include: - A PEG (polyethylene glycol) chain attached to the ring. - Penicillin (Pen) side chains, which are fused bicyclic systems. - Aromatic side chains, including a 7-methoxytryptophan (7MeW) residue and a 6-hydroxytryptophan (6OH2NaI) residue. - A thioether bridge (S-S) connecting two parts of the ring. - Various other functional groups, including amide bonds, hydroxyl groups, and a terminal amine group. PEG2(2)-Pen(3)-N-T-7MeW-K(Ac)-Pen(3)-AEF-6OH2NaI-THP-hE(2)-N-3Pya-Sar-CONH2

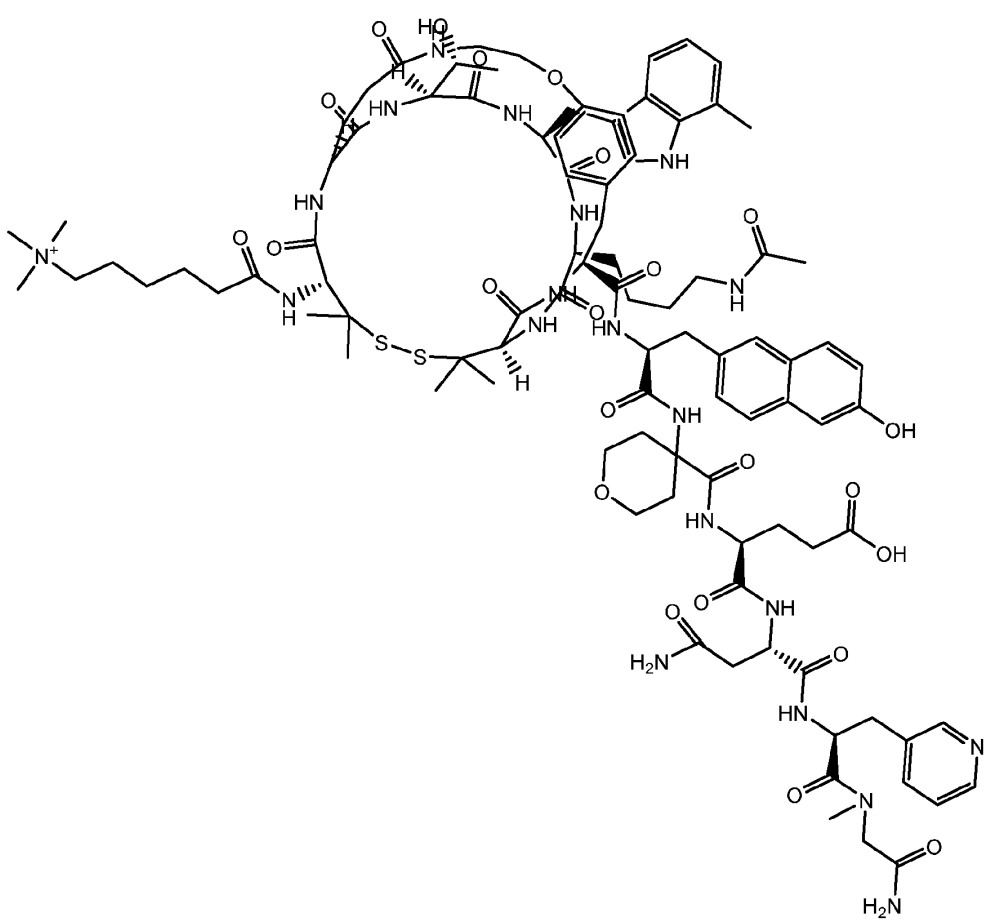
SEQ ID NO	Structure
392	 cPEG3aCO-Pen(3)-N-T-7MeW-K(NMeAc)-Pen(3)-AEF-6OH2Nal-THP-Q(N(Me)2)-N-3Py-Sar-CONH2

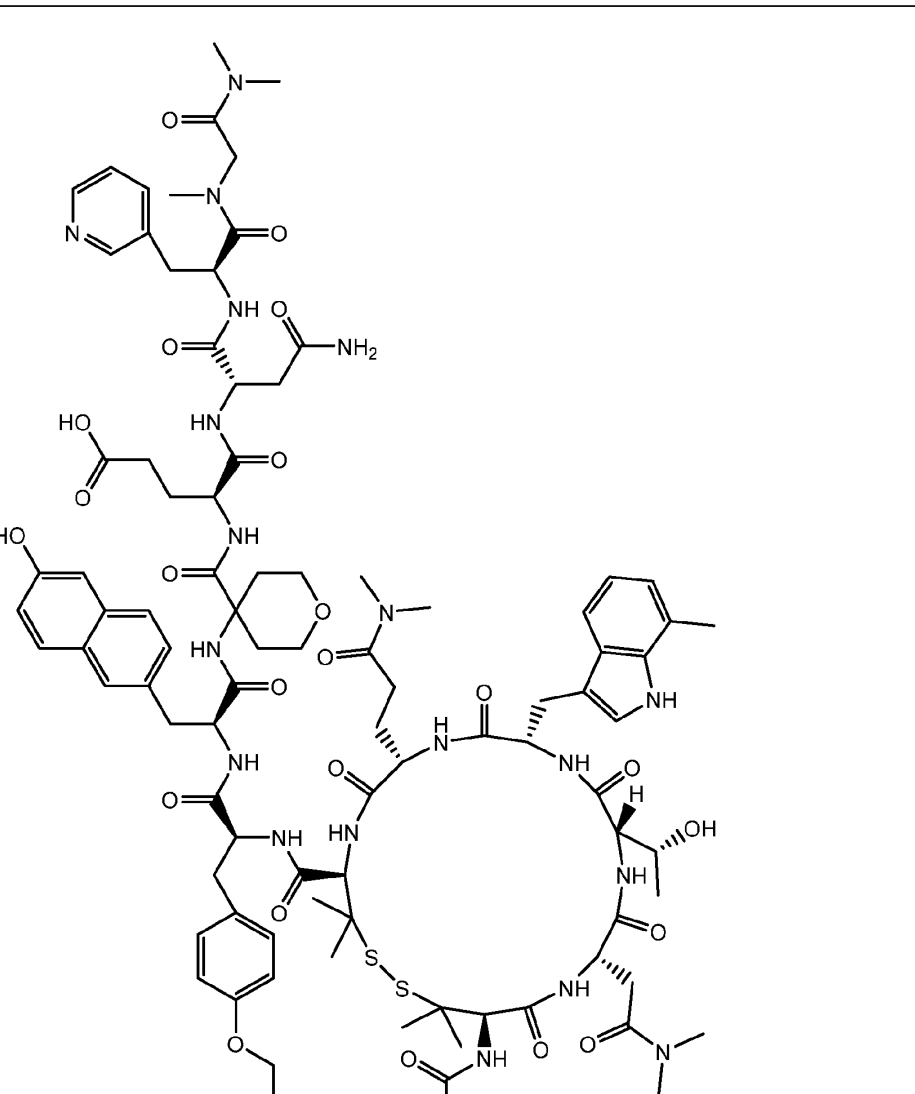
SEQ ID NO	Structure
393	 The chemical structure is a large cyclic peptide with a 24-residue backbone. The side chains include a PEG chain (cPEG3aCO), a thiol (S-S), a naphthyl group (6OH2Nal), a thiomorpholine (THP), a pyridine (3Py), and a tryptophan derivative (Sar-CONH2). The structure is shown in a 2D representation with stereochemistry indicated by wedges and dashes. cPEG3aCO-Pen(3)-N-T-7MeW-K(Ac)-Pen(3)-AEF-6OH2Nal-THP-K(Ac)-N-3Py-Sar-CONH2

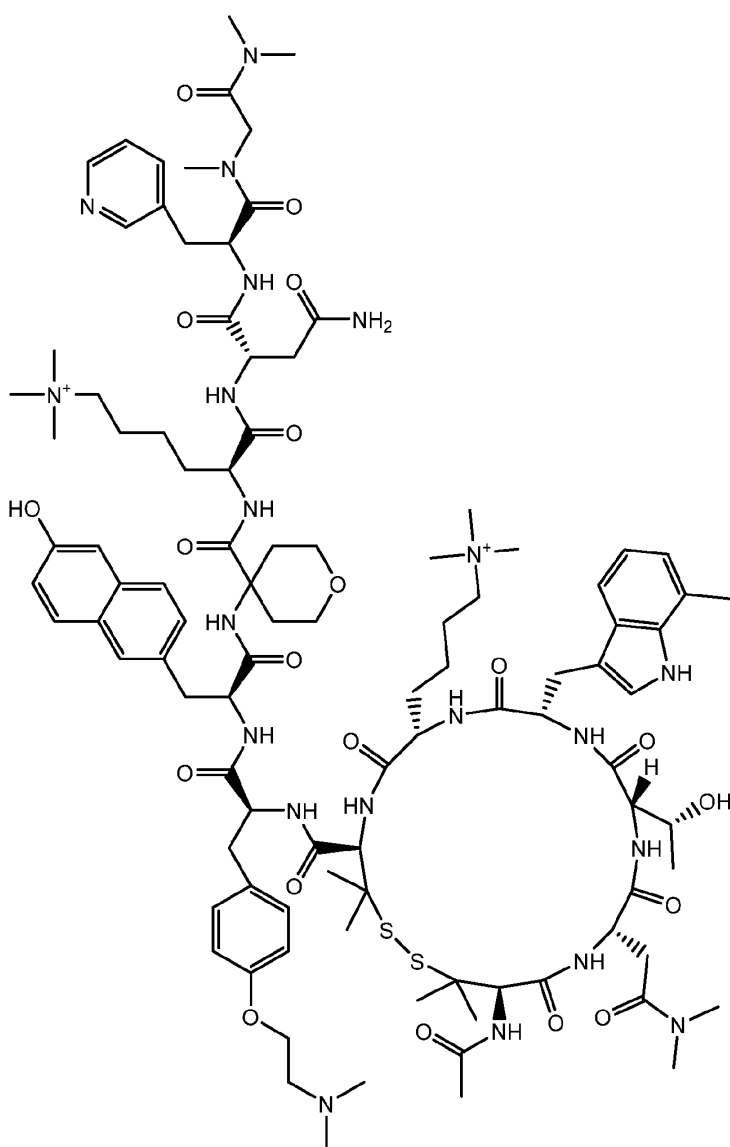
SEQ ID NO	Structure
394	 cPEG3aCO-Pen(3)-N(N(Me)2)-T-7MeW-Q(N(Me)2)-Pen(3)-AEF-6OH2Nal-THP-Q(N(Me)2)-N-3Pya-Sar-CON(Me)2

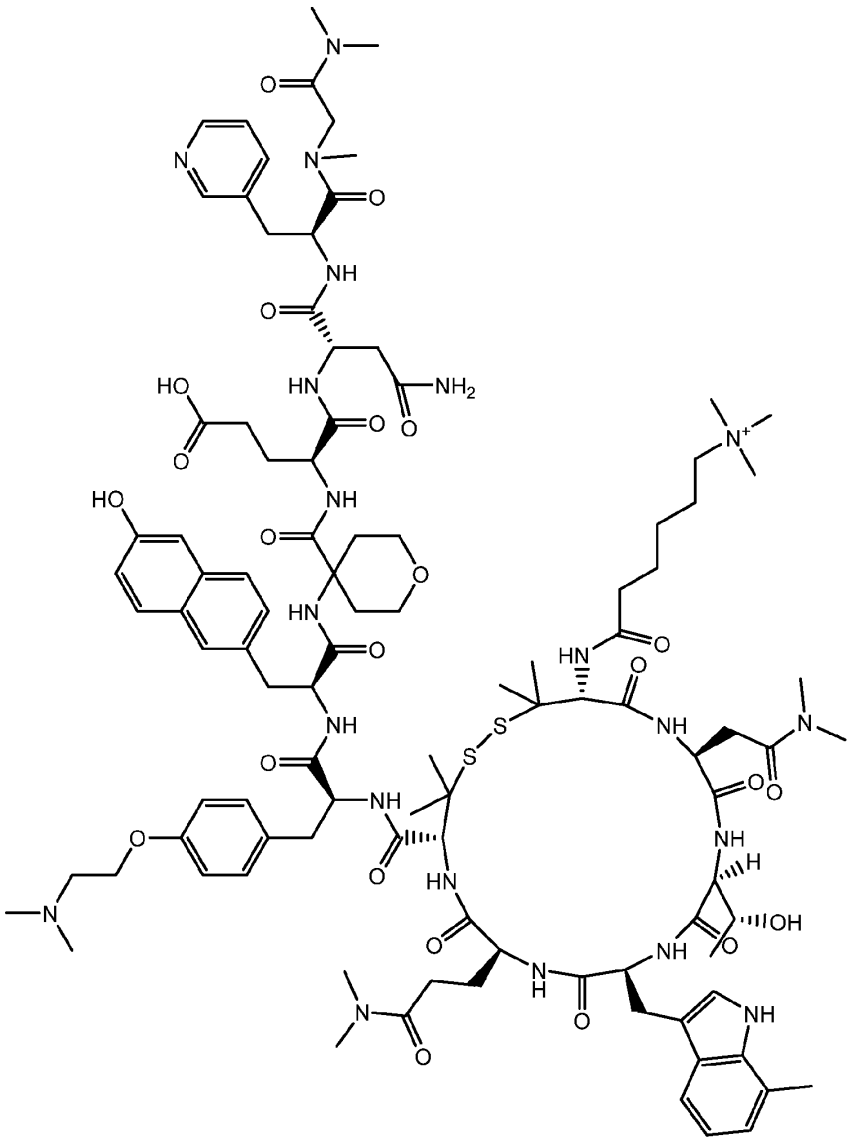
SEQ ID NO	Structure
395	 The chemical structure shows a large cyclic peptide backbone with a disulfide bridge. The side chains include a long PEG chain, a penicillin derivative, a 7-methyl-2-(2-oxo-2-phenylacetyl)-7-oxo-7,8-dihydro-2H-pyridine-6-carboxamide, a 6-hydroxy-2-nal, a thiazolidine, and a 3-pyridyl-L-sar. The structure is highly complex with multiple amide bonds and various functional groups. MeCO-k(PEG2PEG2gEC18OH)-Pen(3)-E(2)-T-7MeW-K(Ac)-Pen(3)-AEF(2)-6OH2Nal-THP-E-N-3Pya-Sar-CONH2

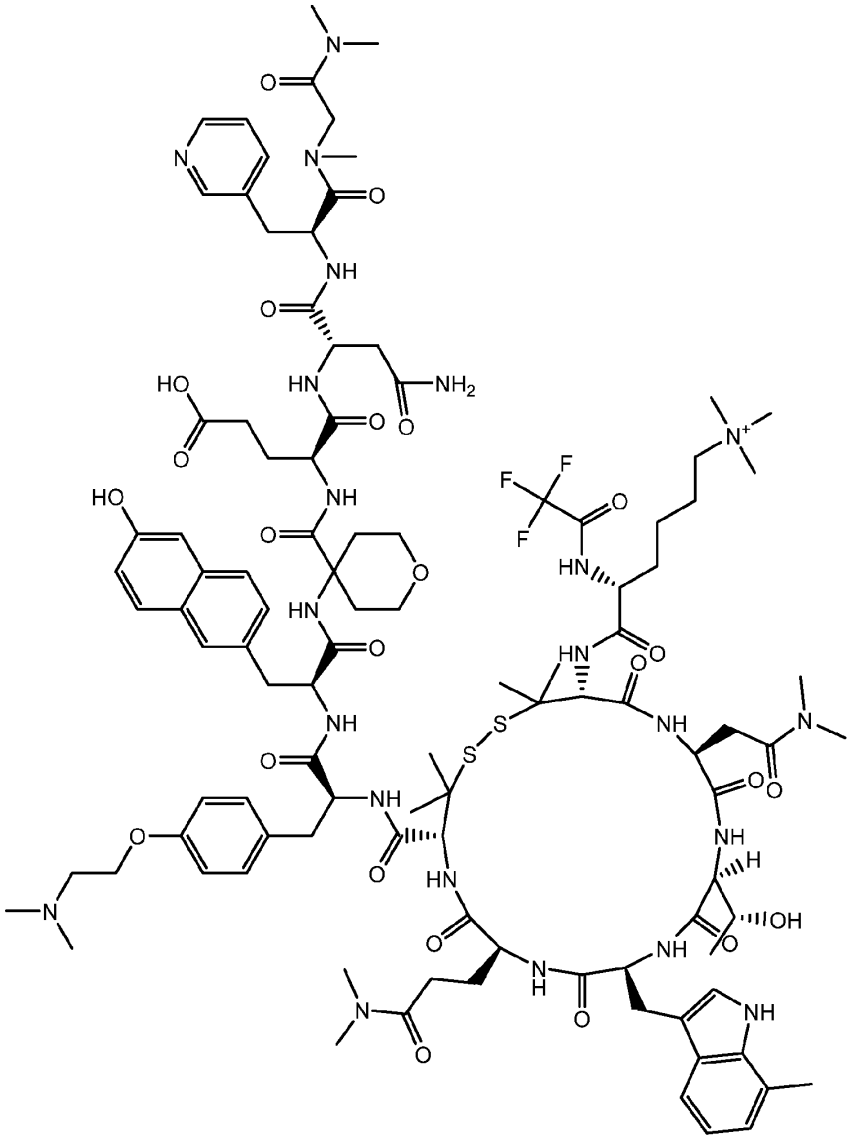
SEQ ID NO	Structure
396	 5cpaCO-Pen(3)-E(2)-T-7MeW-K(Ac)-Pen(3)-AEF(2)-6OH2NaI-THP-K(Ac)-N-3Pya-Sar-CONH2

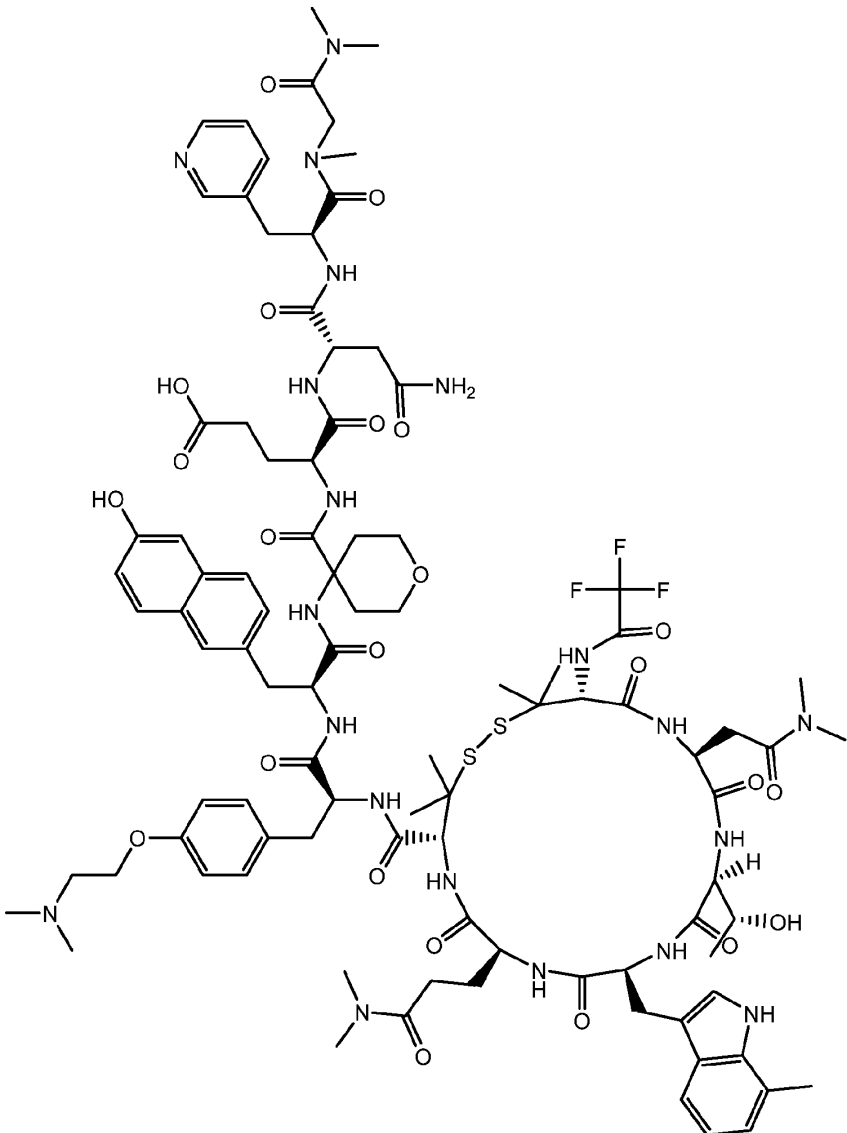
SEQ ID NO	Structure
397	 5cpaCO-Pen(3)-E(2)-T-7MeW-K(Ac)-Pen(3)-AEF(2)-6OH2NaI-THP-E-N-3Pya-Sar-CONH2

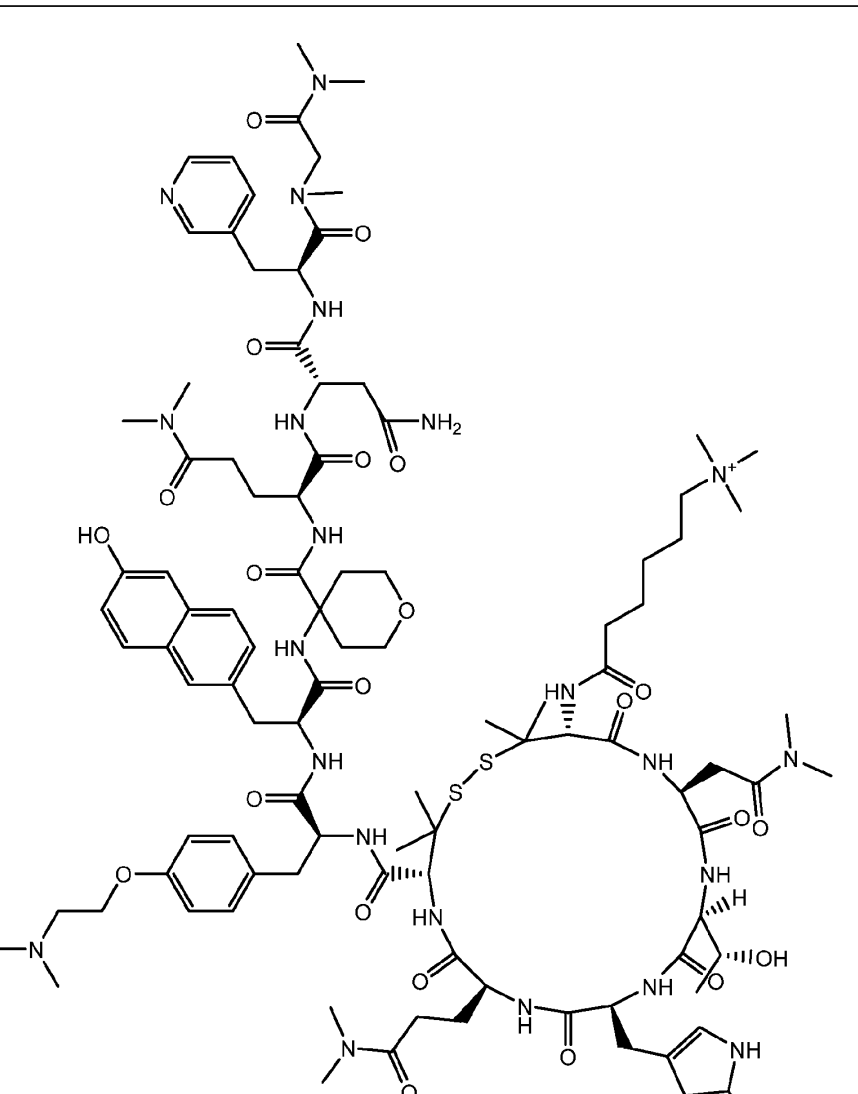
SEQ ID NO	Structure
398	 MeCO-Pen(3)-N(N(Me)2)-T-7MeW-Q(N(Me)2)-Pen(3)-AEF(N(Me)2)-6OH2Nal-THP-E-N-3PyA-Sar-CON(Me)2

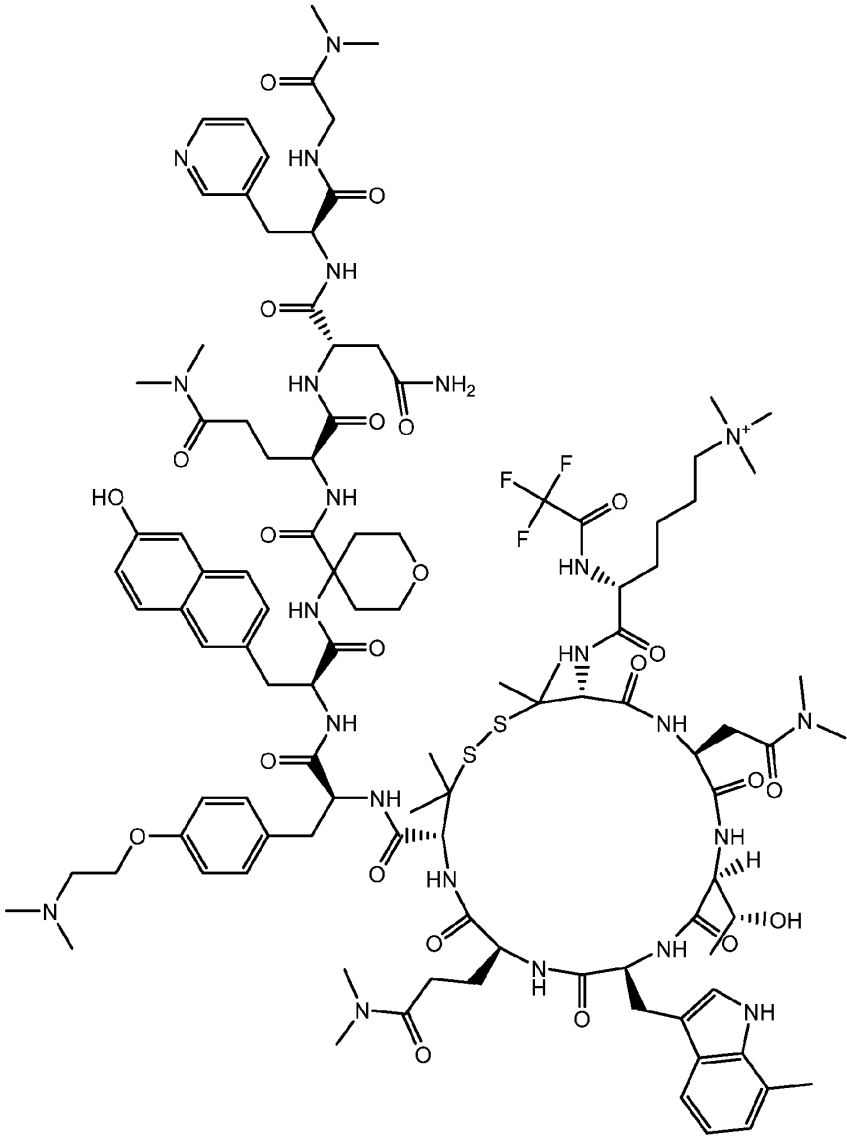
SEQ ID NO	Structure
399	 The chemical structure shows a large cyclic peptide with a 20-residue backbone. The residues are: MeCO-Pen(3)-N(N(Me)2)-T-7MeW-K(Me)3-Pen(3)-AEF(N(Me)2)-6OH2Nal-THP-K(Me)3-N-3Py-Sar-CON(Me)2. The structure is highly complex with various side chains including a pyridine ring, a thiazolidine ring, a hydroxyl group, and a dimethylamino group. The backbone is a cyclic peptide with a disulfide bridge between two cysteine residues. MeCO-Pen(3)-N(N(Me)2)-T-7MeW-K(Me)3-Pen(3)-AEF(N(Me)2)-6OH2Nal-THP-K(Me)3-N-3Py-Sar-CON(Me)2

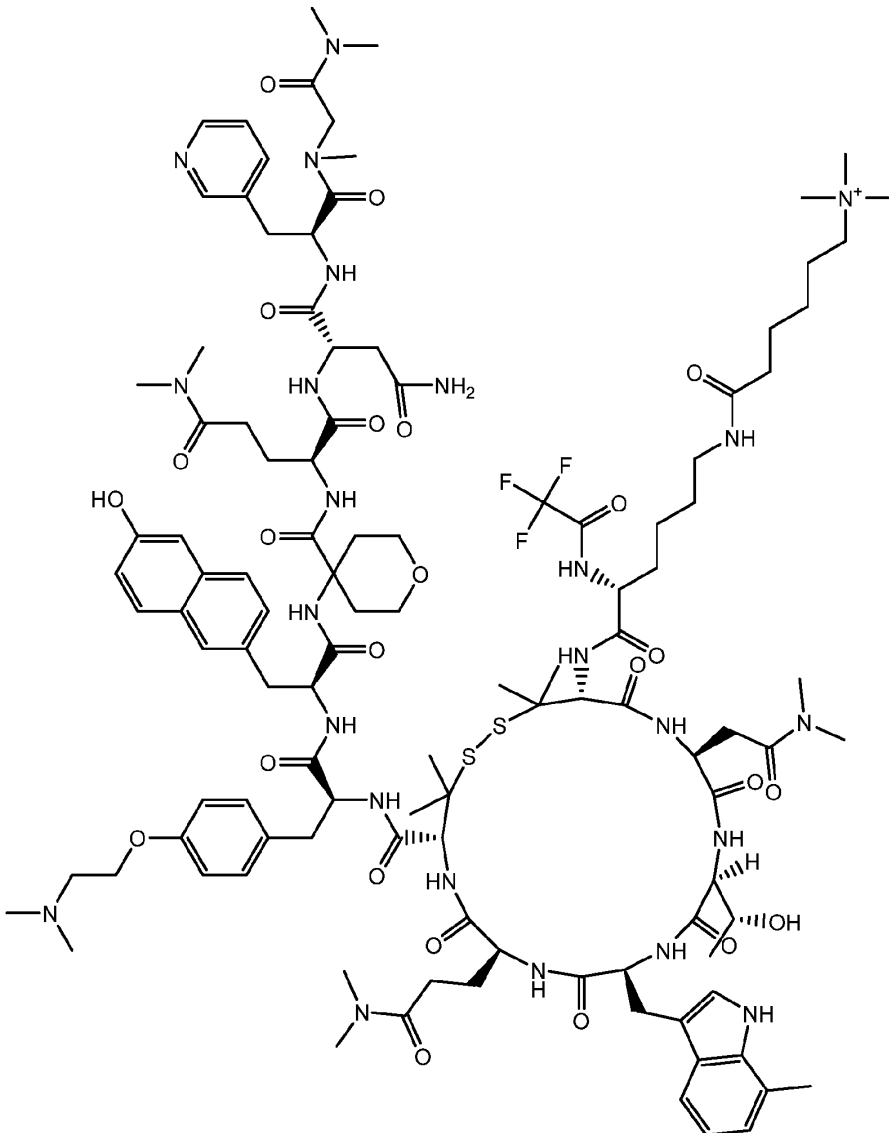
SEQ ID NO	Structure
400	 5cpaCO-Pen(3)-N(N(Me)2)-T-7MeW-Q(N(Me)2)-Pen(3)-AEF(N(Me)2)-6OH2Nal-THP-E-N-3Py-Sar-CON(Me)2

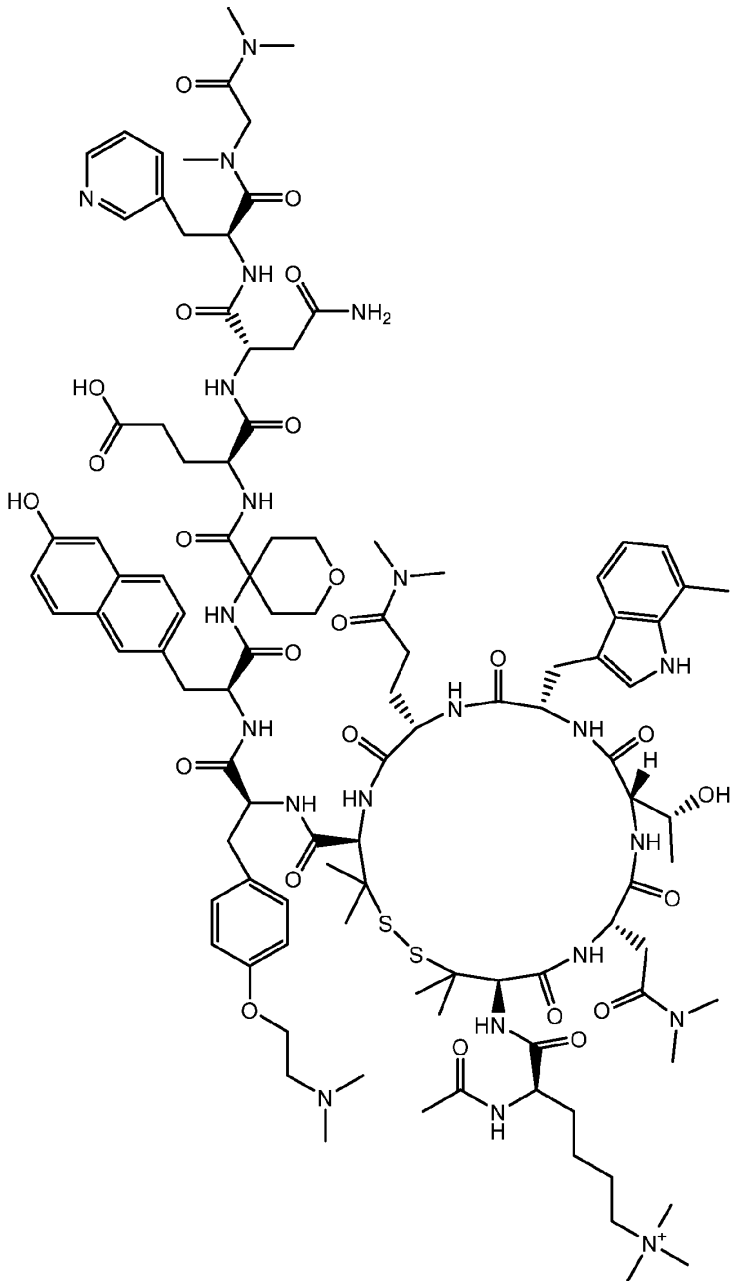
SEQ ID NO	Structure
401	 CF3CO-k(Me)3-Pen(3)-N(N(Me)2)-T-7MeW-Q(N(Me)2)-Pen(3)-AEF(N(Me)2)-6OH2NaI-THP-E-N-3Pya-Sar-CON(Me)2

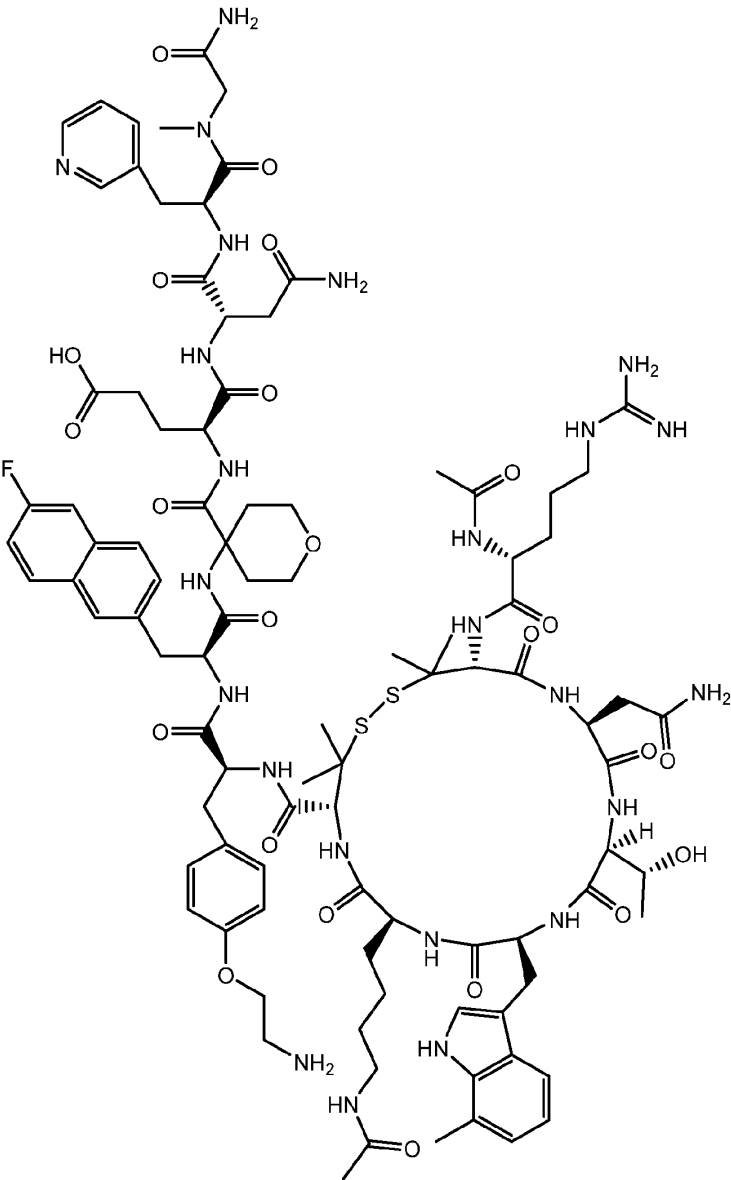
SEQ ID NO	Structure
402	 CF3CO-Pen(3)-N(N(Me)2)-T-7MeW-Q(N(Me)2)-Pen(3)-AEF(N(Me)2)-6OH2Nal-THP-E-N-3Py-Sar-CON(Me)2

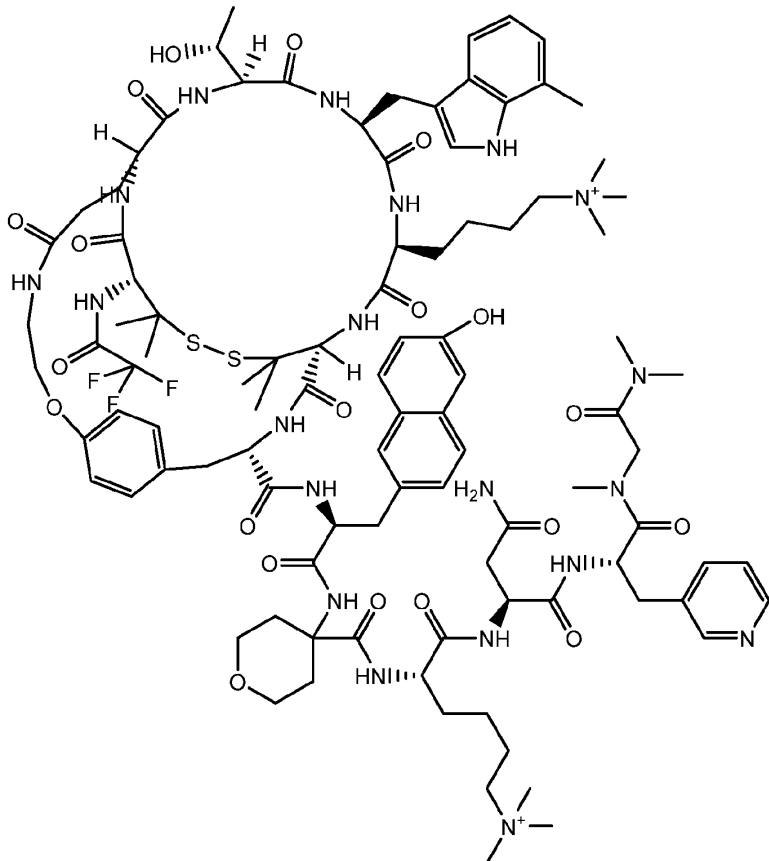
SEQ ID NO	Structure
403	 5cpaCO-Pen(3)-N(NMe)₂-T-7MeW-Q(NMe)₂-Pen(3)-AEF(NMe)₂-6OH₂Nal-THP-Q(NMe)₂-N-3Py-Sar-CON(Me)₂

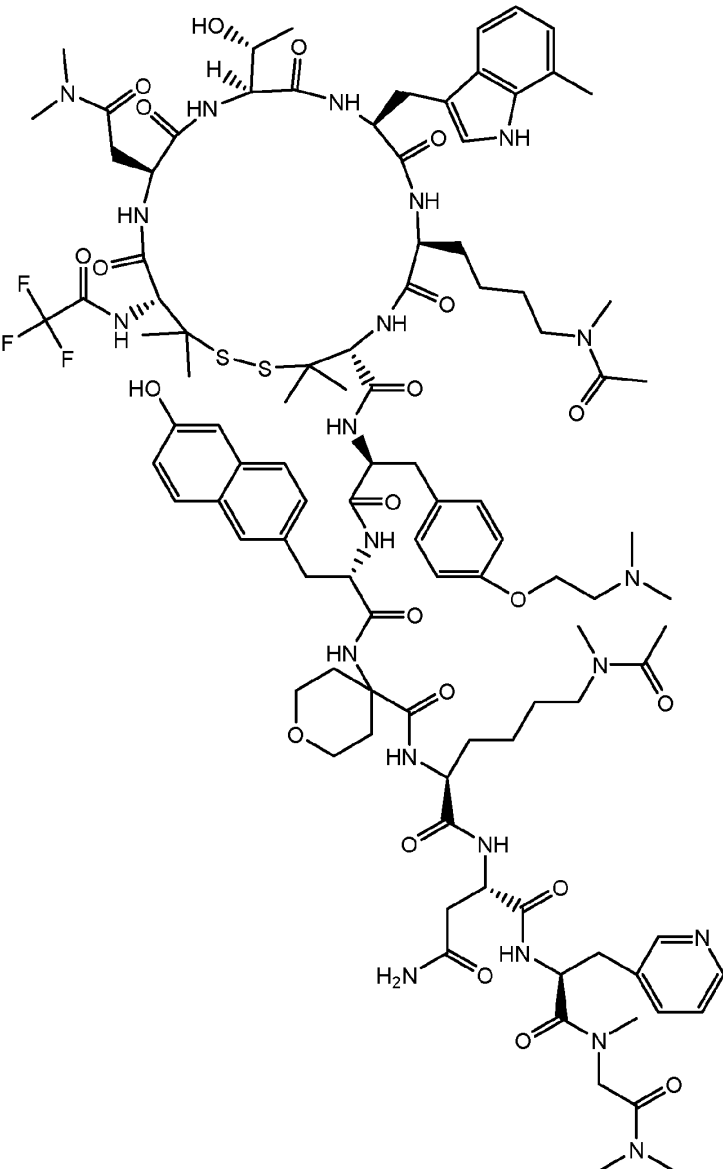
SEQ ID NO	Structure
404	 CF3CO-k(Me)3-Pen(3)-N(N(Me)2)-T-7MeW-Q(N(Me)2)-Pen(3)-AEF(N(Me)2)-6OH2NaI-THP-Q(N(Me)2)-N-3Pya-Sar-CON(Me)2

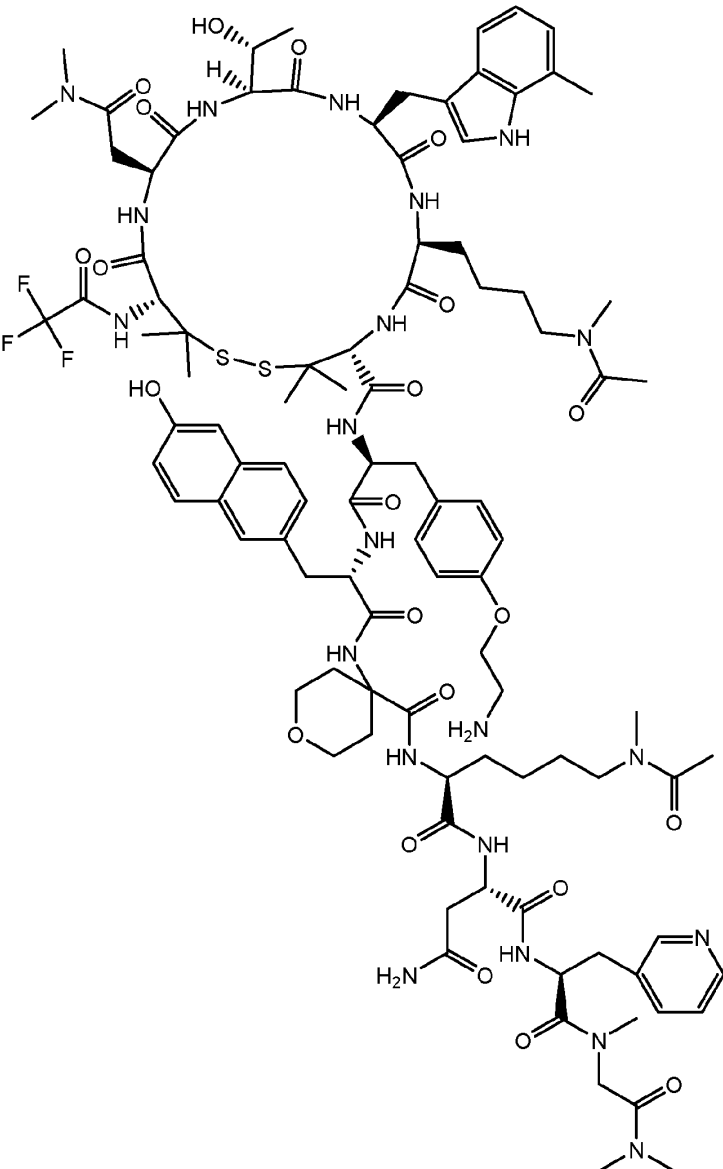
SEQ ID NO	Structure
405	 CF3CO-k(5cpa)-Pen(3)-N(N(Me)2)-T-7MeW-Q(N(Me)2)-Pen(3)-AEF(N(Me)2)-6OH2Nal-THP-Q(N(Me)2)-N-3Pya-Sar-CON(Me)2

SEQ ID NO	Structure
406	 MeCO-k(Me)₃-Pen(3)-N(N(Me)₂)-T-7MeW-Q(N(Me)₂)-Pen(3)-AEF(N(Me)₂)-6OH₂NaI-THP-E-N-3Py-Sar-CON(Me)₂

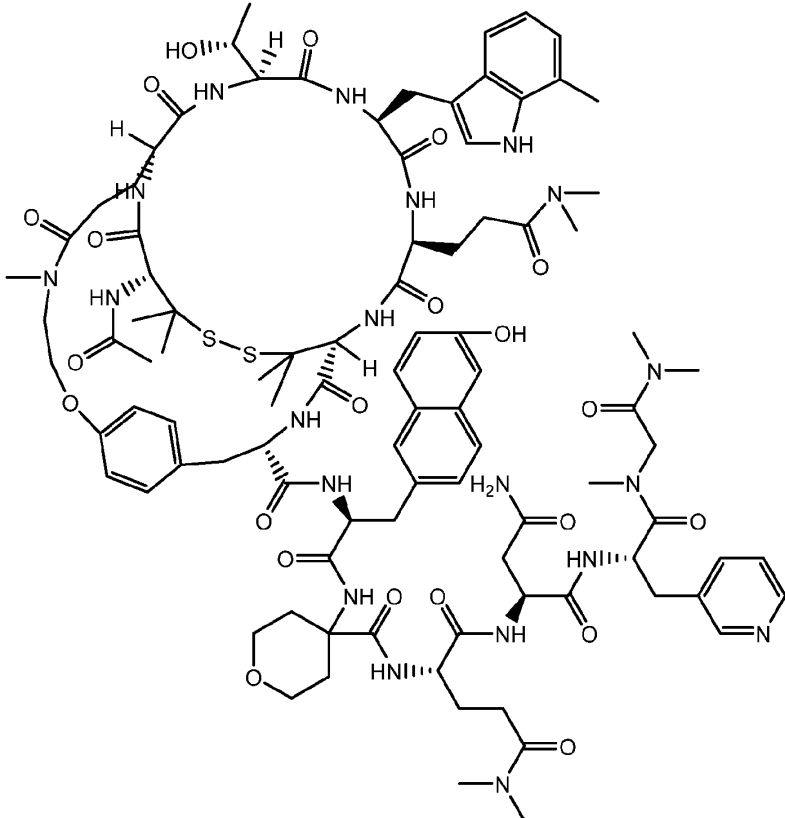
SEQ ID NO	Structure
407	 The chemical structure represents a complex cyclic peptide. The backbone is a 16-membered ring with a disulfide bridge (S-S) between two cysteine residues. The side chains are diverse, including a pyridine ring, a fluorophenyl group, a thiazolidine ring, a guanidino group, and a hydroxymethyl group. The structure is shown in a 2D representation with stereochemistry indicated by wedges and dashes. MeCO-r-Pen(3)-N-T-7MeW-K(Ac)-Pen(3)-AEF-6F2Nal-THP-E-N-3Py-Sar-CONH2

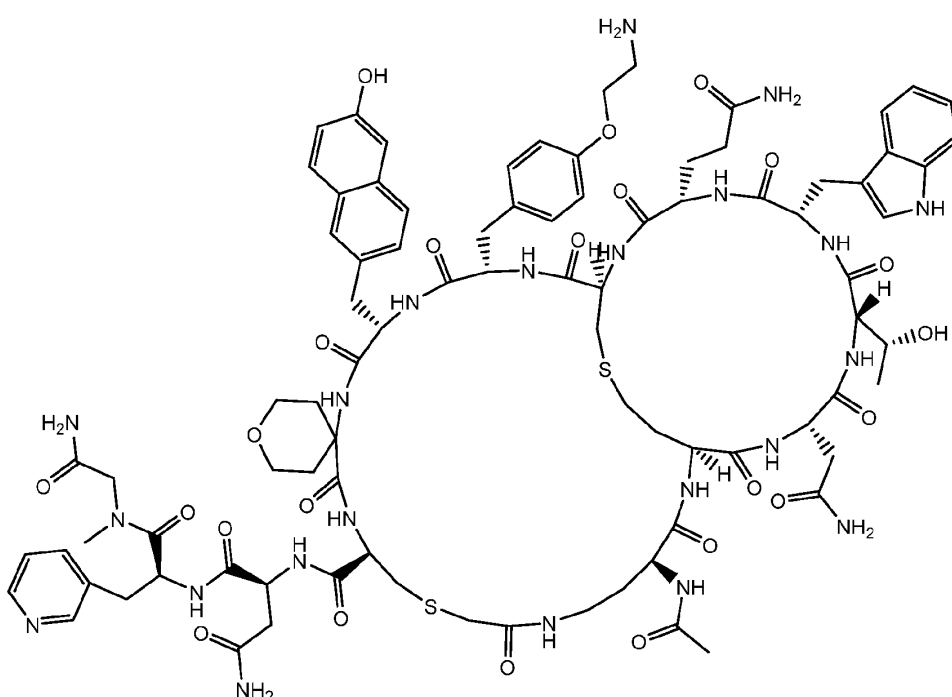
SEQ ID NO	Structure
408	 CF3CO-Pen(3)-E(2)-T-7MeW-K(Me)3-Pen(3)-AEF(2)-6OH2NaI-THP-K(Me)3-N-3Py-Sar-CON(Me)2

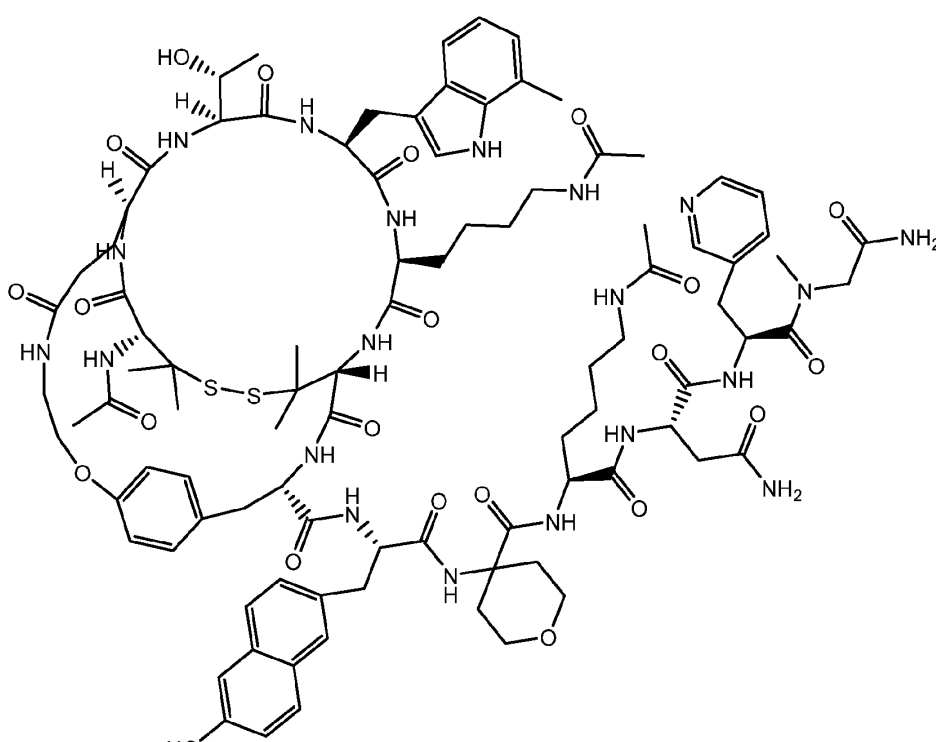
SEQ ID NO	Structure
409	 CF3CO-Pen(3)-N(N(Me)2)-T-7MeW-K(NMeAc)-Pen(3)-AEF(N(Me)2)-6OH2NaI-THP-K(NMeAc)-N-3Py-Sar-CON(Me)2

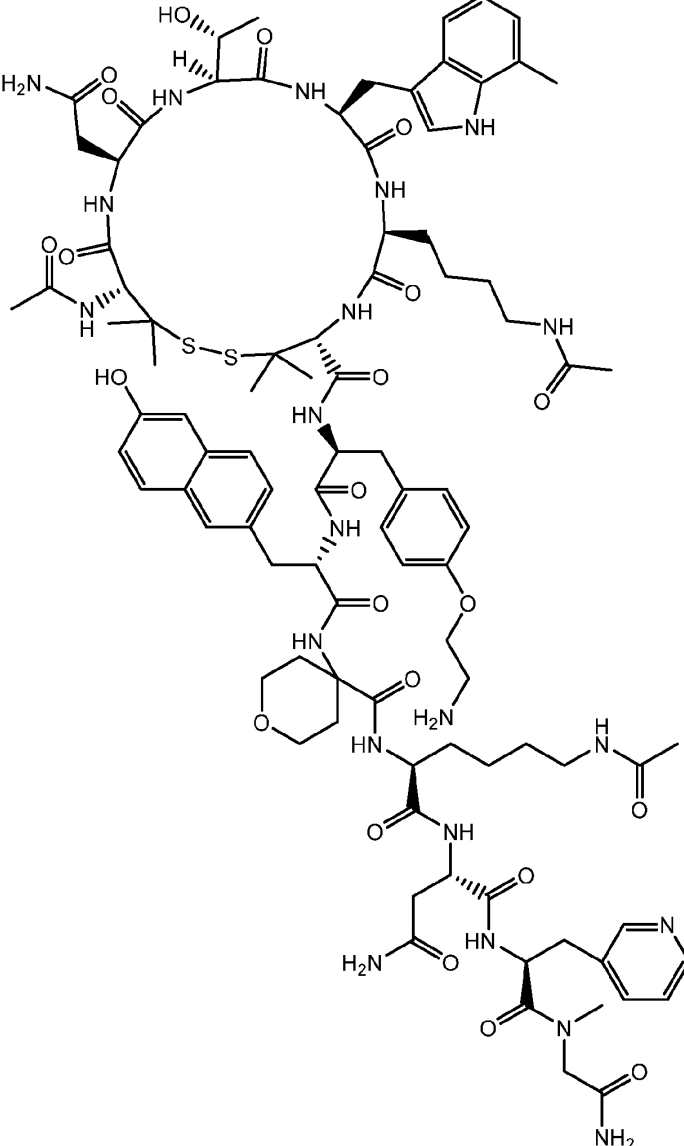
SEQ ID NO	Structure
410	 CF3CO-Pen(3)-N(N(Me)2)-T-7MeW-K(NMeAc)-Pen(3)-AEF-6OH2Nal-THP-K(NMeAc)-N-3Pya-Sar-CON(Me)2

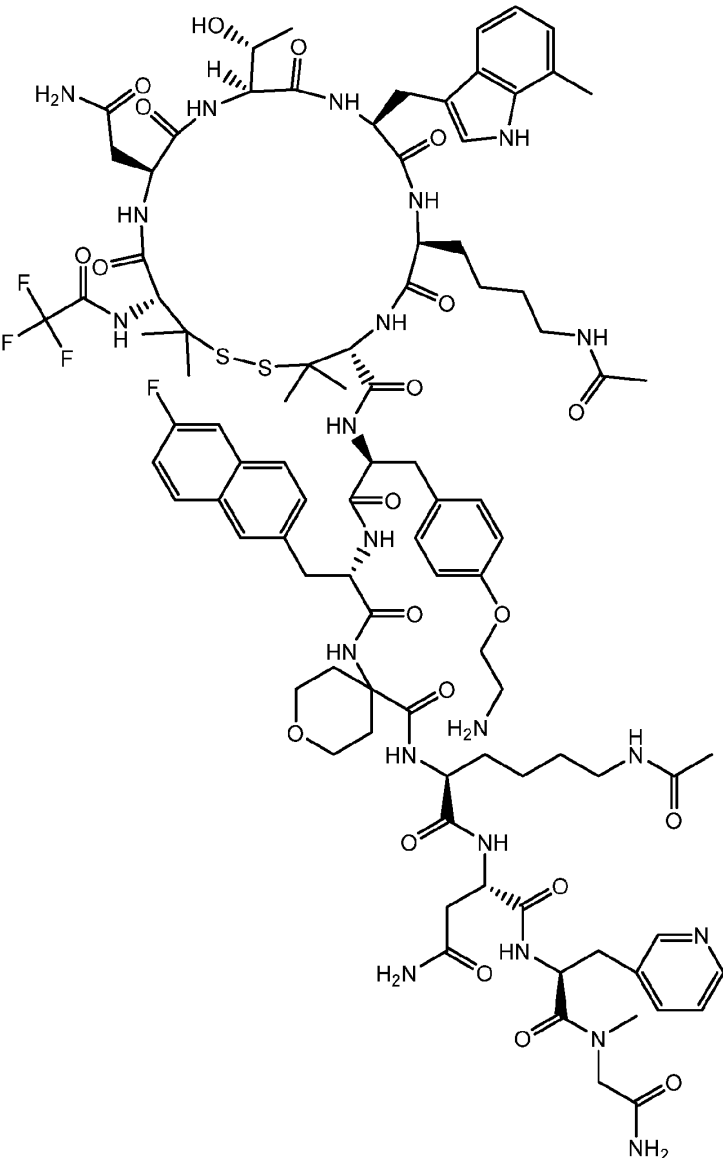
SEQ ID NO	Structure
411	MeCO-Pen(3)-N-T-7MeW-K(Ac)-Pen(3)-AEF-6F2Nal-THP-K(Ac)-N-3Pya-Sar-CONH2

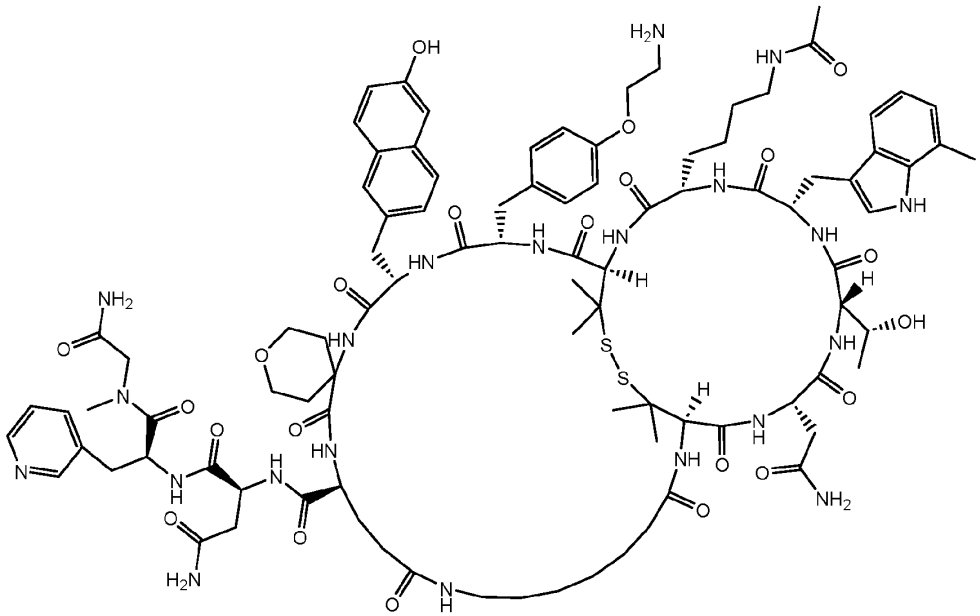
SEQ ID NO	Structure
412	 MeCO-Pen(3)-E(2)-T-7MeW-Q(N(Me)2)-Pen(3)-AEF(NMe)(2)-6OH2Nal-THP-Q(N(Me)2)-N-3Py-Sar-CON(Me)2

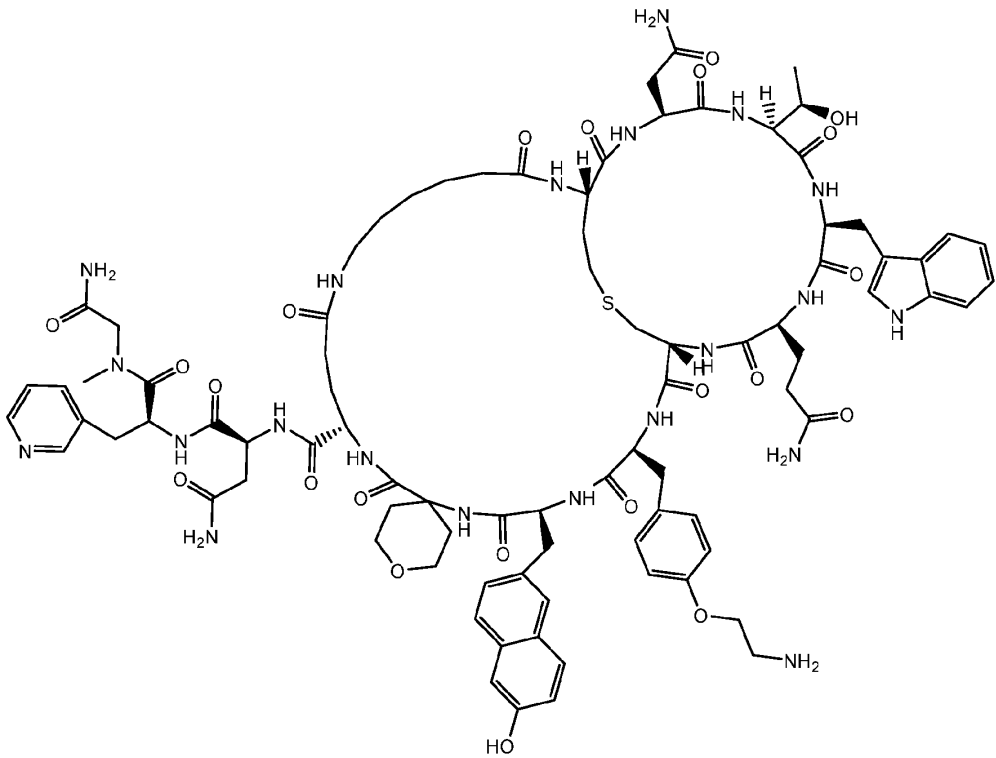
SEQ ID NO	Structure
413	 MeCO-dab(COCH₂)(1*)-Abu(1)-N-T-W-Q-C(1)-AEF-6OH₂Nal-THP-C(1*)-N-3Py-Sar-CONH₂

SEQ ID NO	Structure
414	 MeCO-Pen(3)-E(2)-T-7MeW-K(Ac)-Pen(3)-AEF(2)-6OH2NaI-THP-K(Ac)-N-3PyA-Sar-CONH2

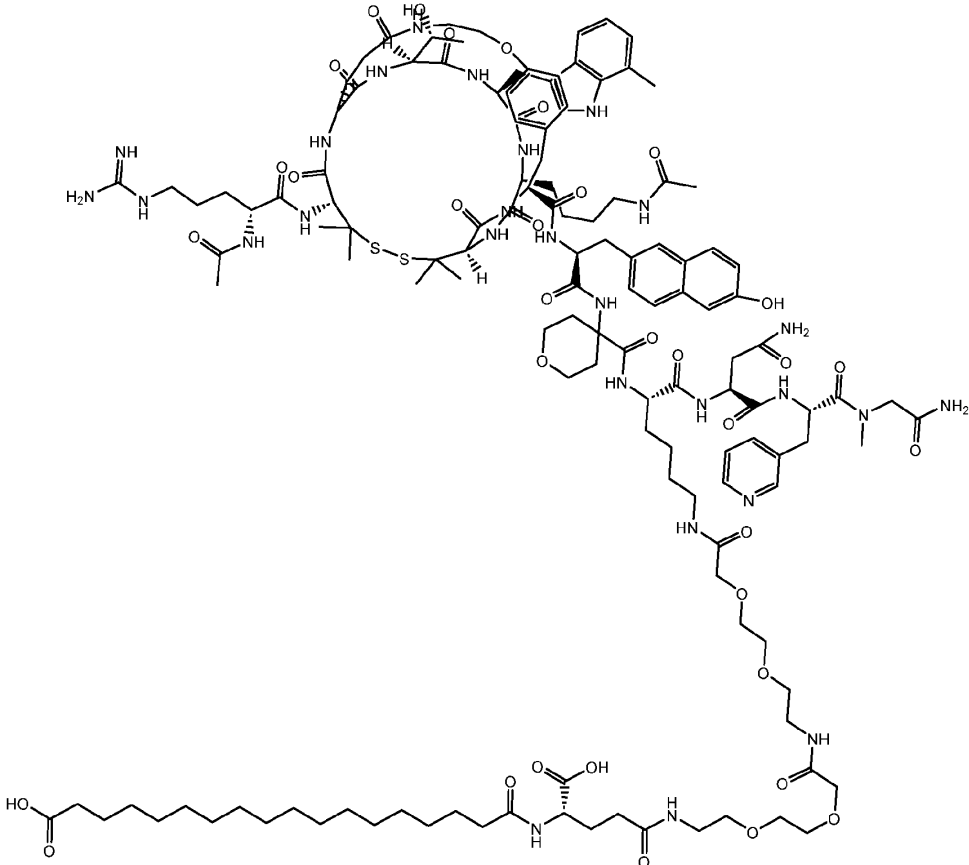
SEQ ID NO	Structure
415	 The chemical structure depicts a large cyclic peptide with a 20-residue backbone. The side chains are diverse, featuring aromatic rings (phenyl, naphthyl, indole, pyridine), aliphatic chains, and functional groups such as hydroxyl, amine, and amide. A disulfide bridge is present between two cysteine residues. The structure is shown in a 2D representation with stereochemistry indicated by wedges and dashes. MeCO-Pen(3)-N-T-7MeW-K(Ac)-Pen(3)-AEF-6OH2Nal-THP-K(Ac)-N-3Pyra-Sar-CONH2

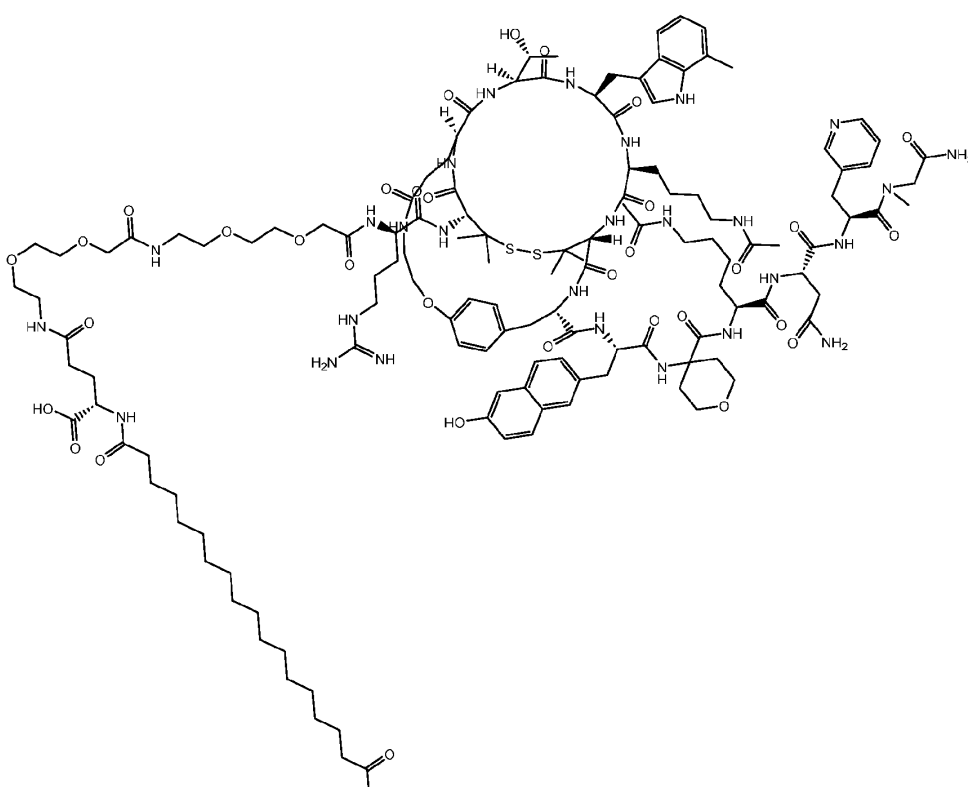
SEQ ID NO	Structure
416	 CF3CO-Pen(3)-N-T-7MeW-K(Ac)-Pen(3)-AEF-6F2Nal-THP-K(Ac)-N-3Pya-Sar-CONH2

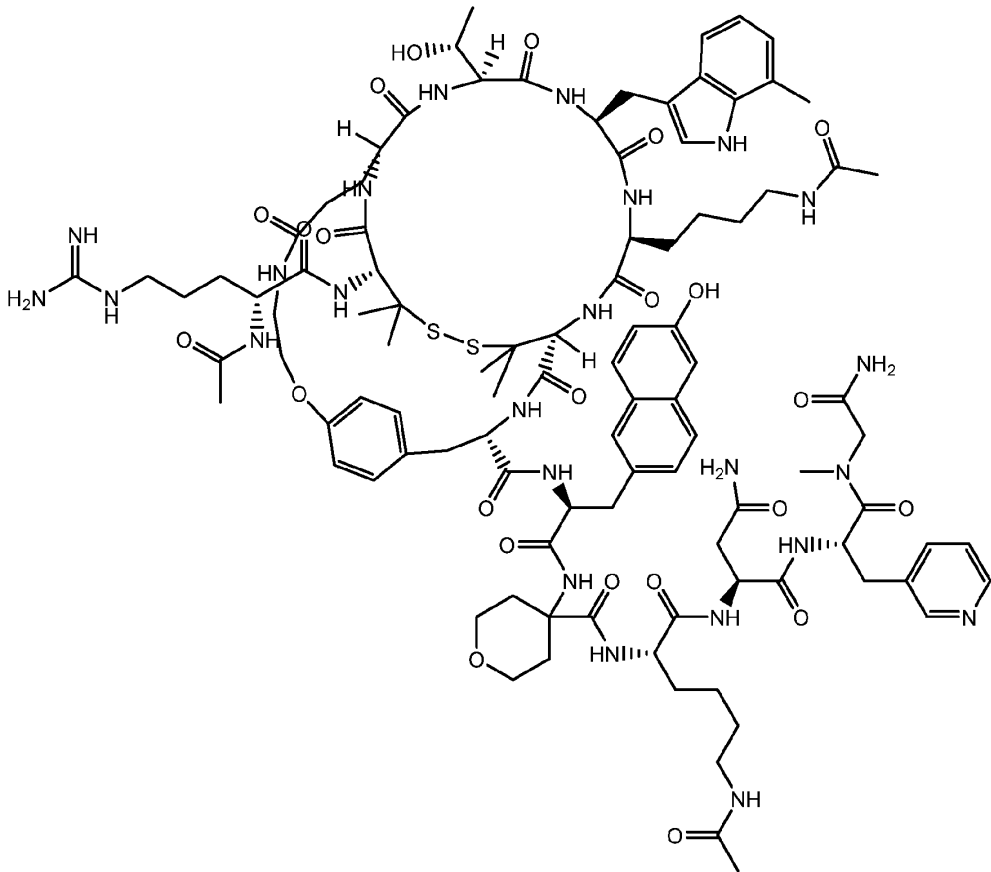
SEQ ID NO	Structure
417	 7Ahp(2)-Pen(3)-N-T-7MeW-K(Ac)-Pen(3)-AEF-6OH2Nal-THP-E(2)-N-3Pya-Sar-CONH2

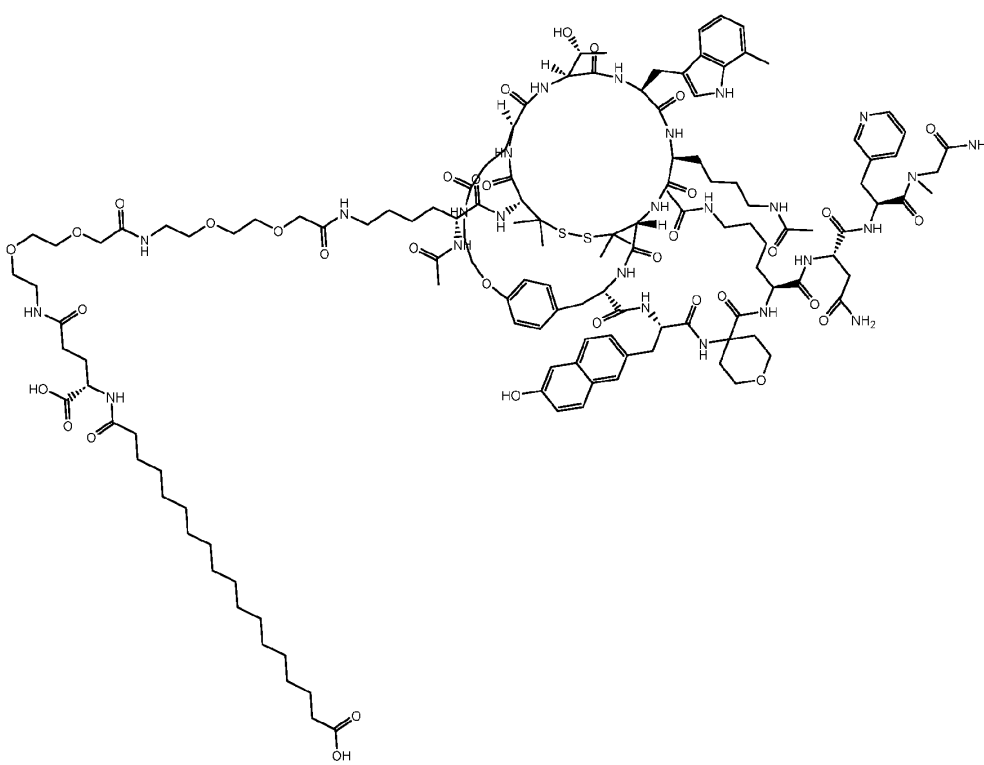
SEQ ID NO	Structure
418	 6Ahx(2)-Abu(1)-N-T-W-Q-C(1)-AEF-6OH2NaI-THP-E(2)-N-3Pya-Sar-CONH2

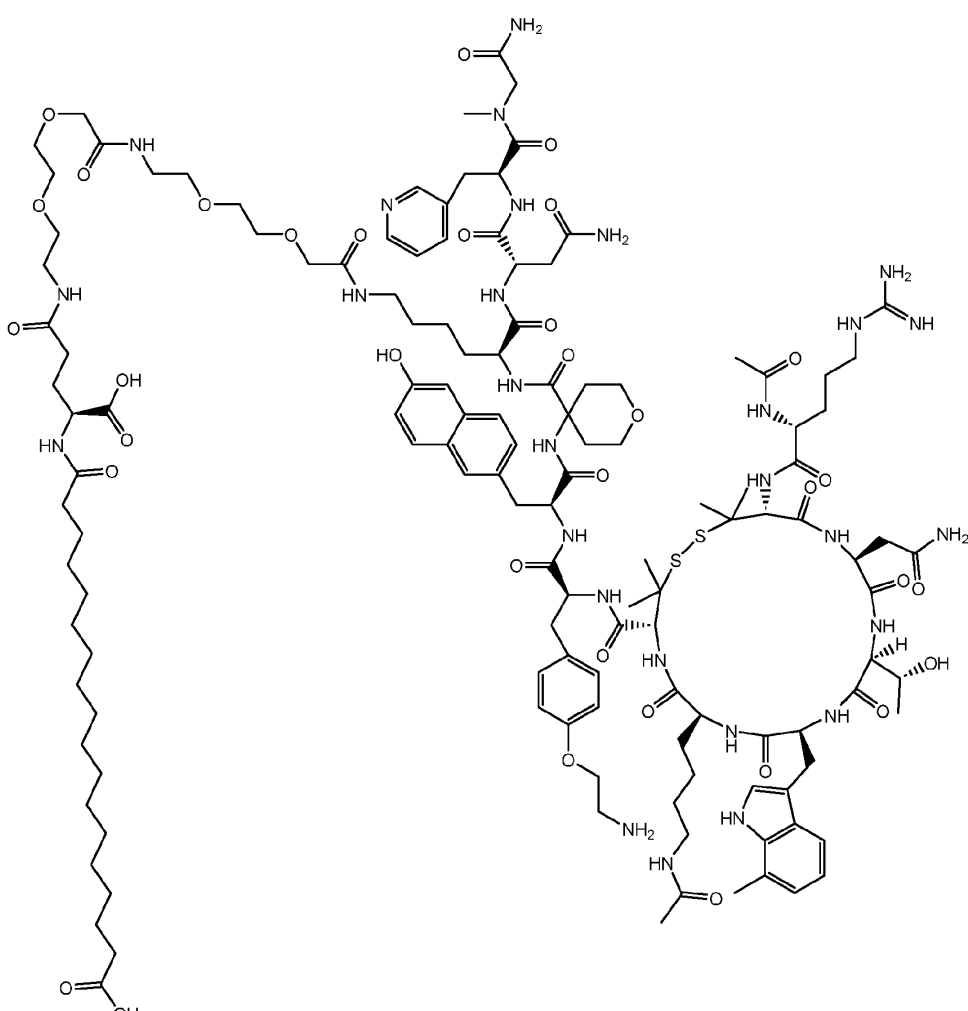
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SEQ ID NO	Structure
420	 MeCO-r-Pen(3)-E(2)-T-7MeW-K(Ac)-Pen(3)-AEF(2)-6OH2Nal-THP-K(PEG2PEG2gEC18OH)-N-3Pyra-Sar-CONH2

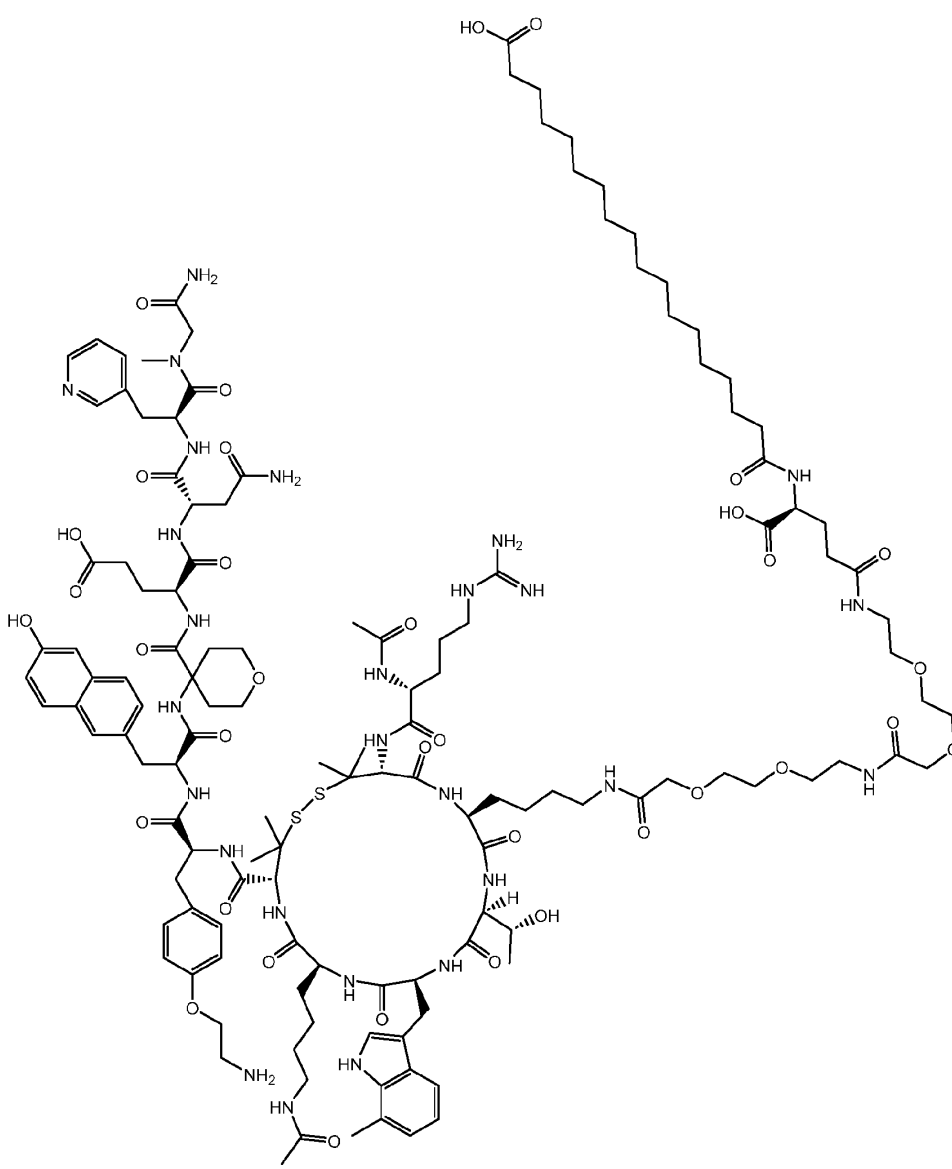
SEQ ID NO	Structure
421	 HOC18gEPEG2PEG2CO-r-Pen(3)-E(2)-T-7MeW-K(Ac)-Pen(3)-AEF(2)-6OH2Nal-THP-K(Ac)-N-3Py-Sar-CONH2

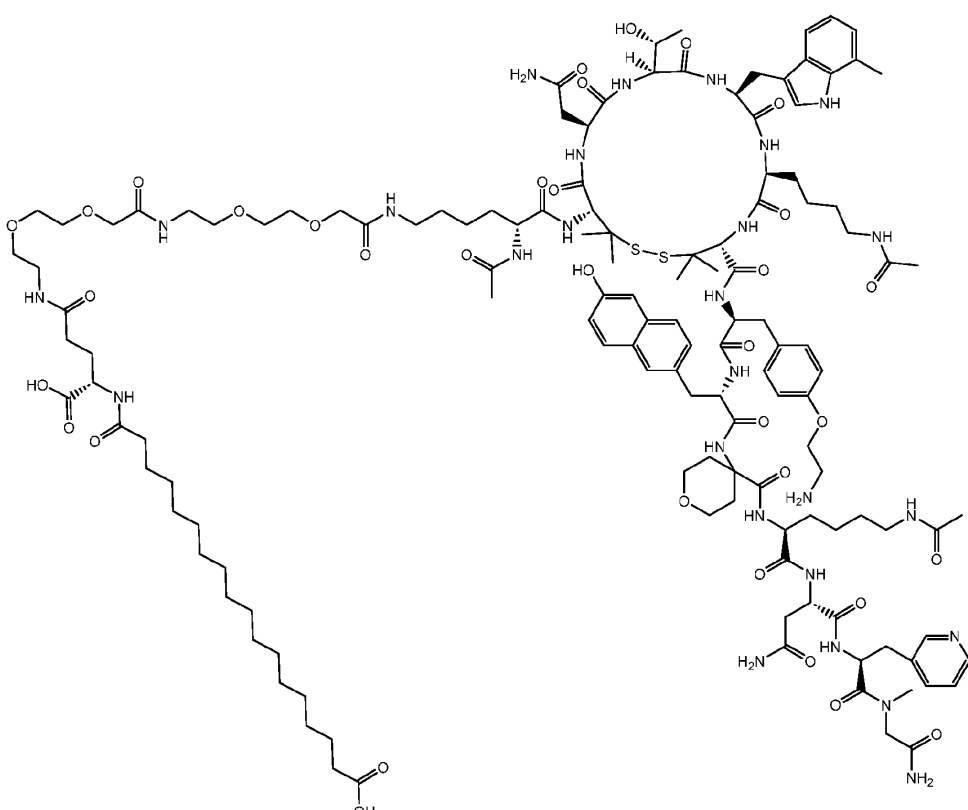
SEQ ID NO	Structure
422	 MeCO-r-Pen(3)-E(2)-T-7MeW-K(Ac)-Pen(3)-AEF(2)-6OH2Nal-THP-K(Ac)-N-3Pya-Sar-CONH2

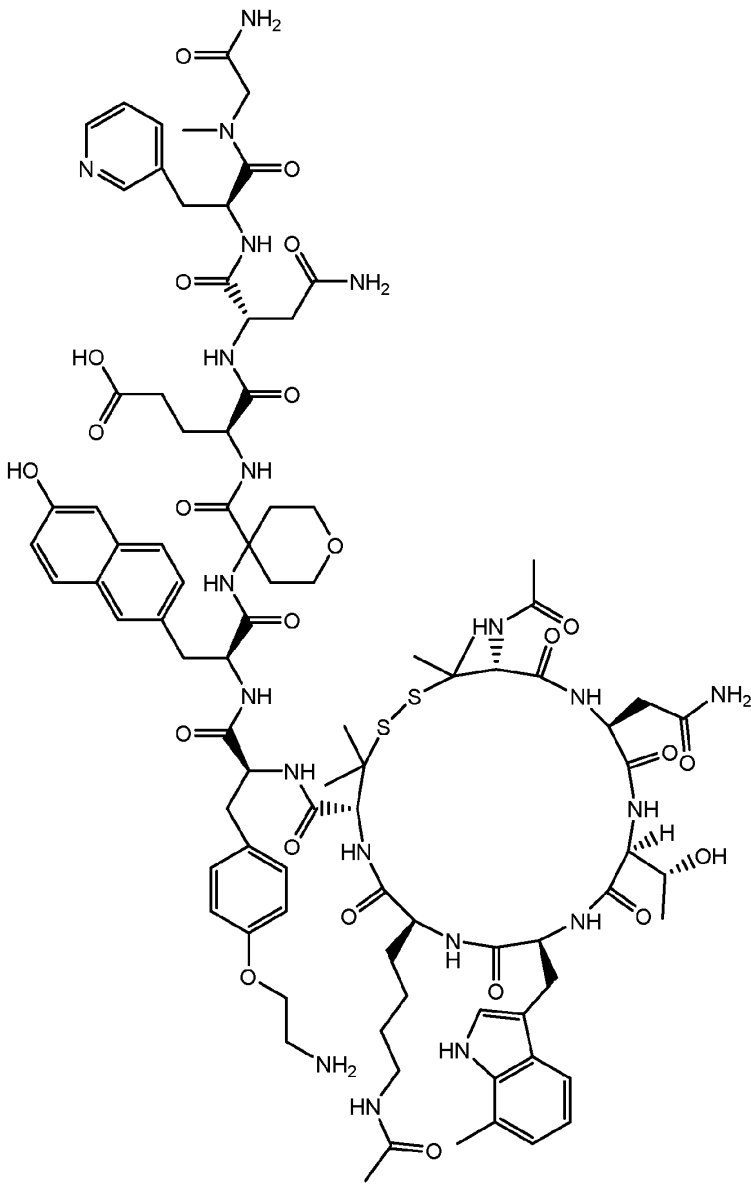
SEQ ID NO	Structure
423	 MeCO-k(PEG2PEG2gEC18OH)-Pen(3)-E(2)-T-7MeW-K(Ac)-Pen(3)-AEF(2)-6OH2Nal-THP-K(Ac)-N-3Pyra-Sar-CONH2

SEQ ID NO	Structure
424	 MeCO-r-Pen(3)-N-T-7MeW-K(Ac)-Pen(3)-AEF-6OH2Nal-THP-K(PEG2PEG2gEC18OH)-N-3Pya-Sar-CONH2

SEQ ID NO	Structure
425	MeCO-r-Pen(3)-K(PEG2PEG2gEC18OH)-T-7MeW-K(Ac)-Pen(3)-AEF-6OH2Nal-THP-E-N-3Pyra-Sar-CONH2

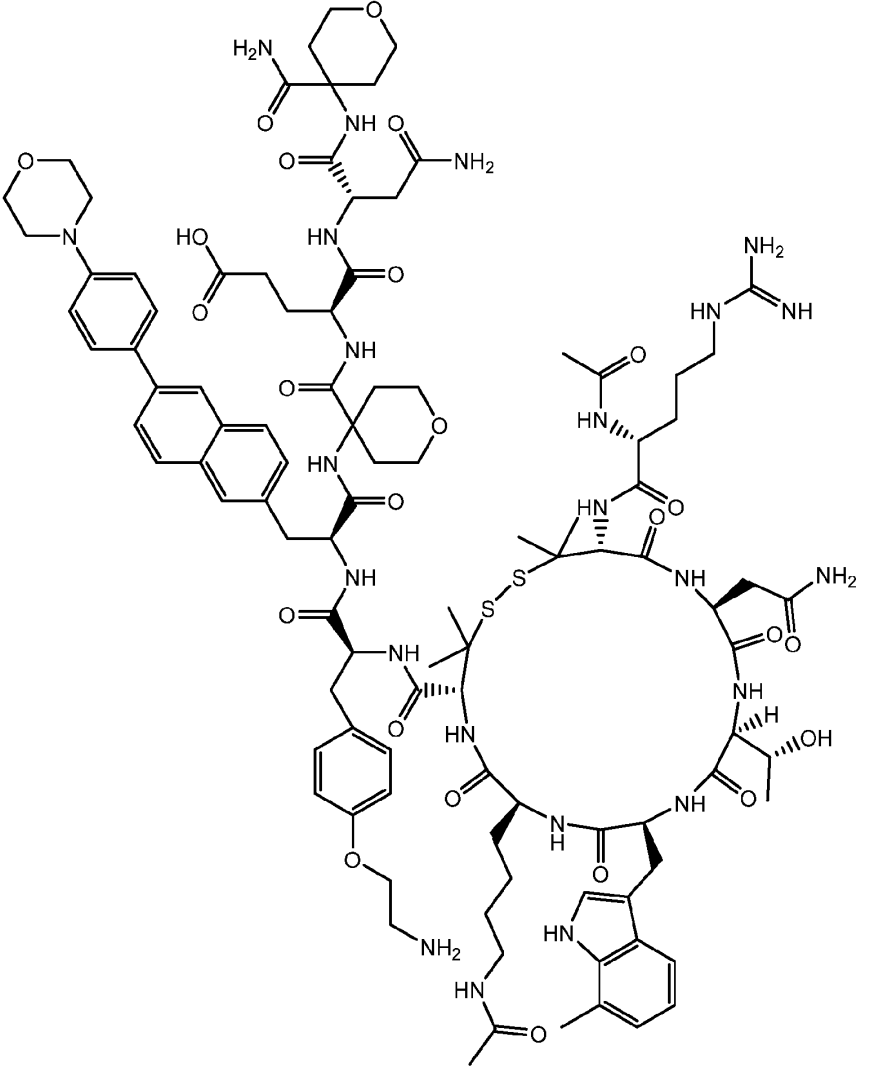
SEQ ID NO	Structure
426	 MeCO-k(PEG2PEG2gEC18OH)-Pen(3)-N-T-7MeW-K(Ac)-Pen(3)-AEF-6OH2Nal-THP-E-N-3Pya-Sar-CONH2

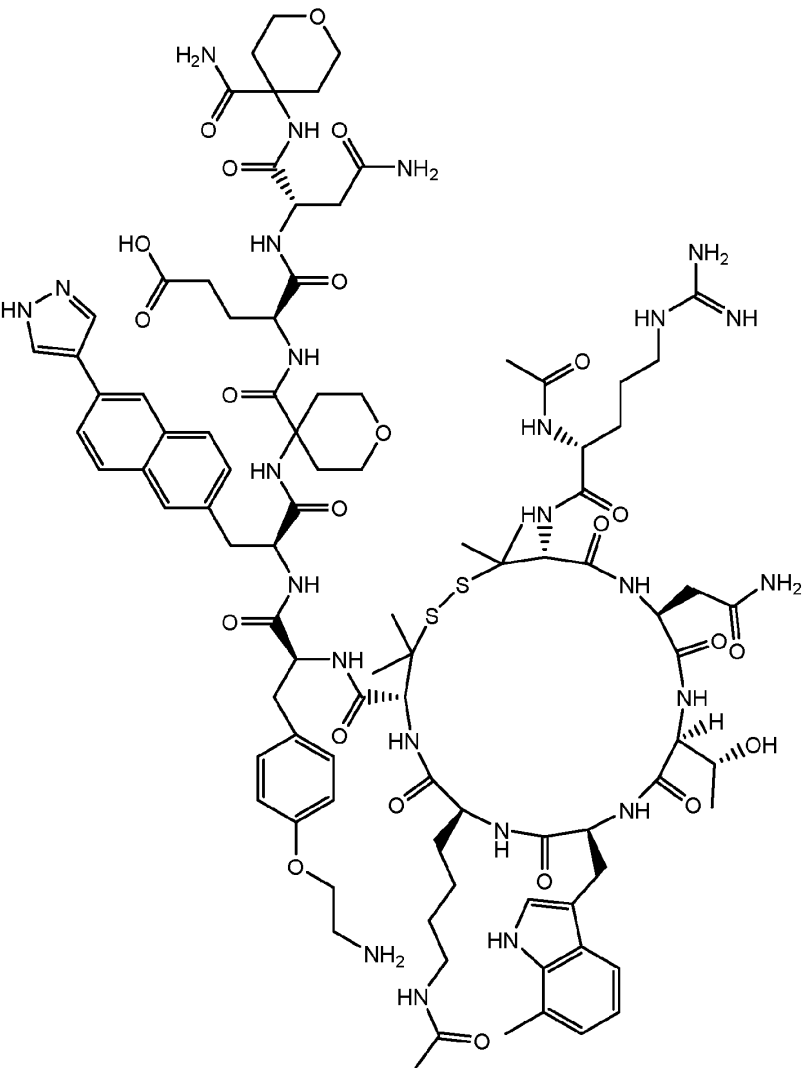
SEQ ID NO	Structure
427	 MeCO-k(PEG2PEG2gEC18OH)-Pen(3)-N-T-7MeW-K(Ac)-Pen(3)-AEF-6OH2Nal-THP-K(Ac)-N-3Pyra-Sar-CONH2

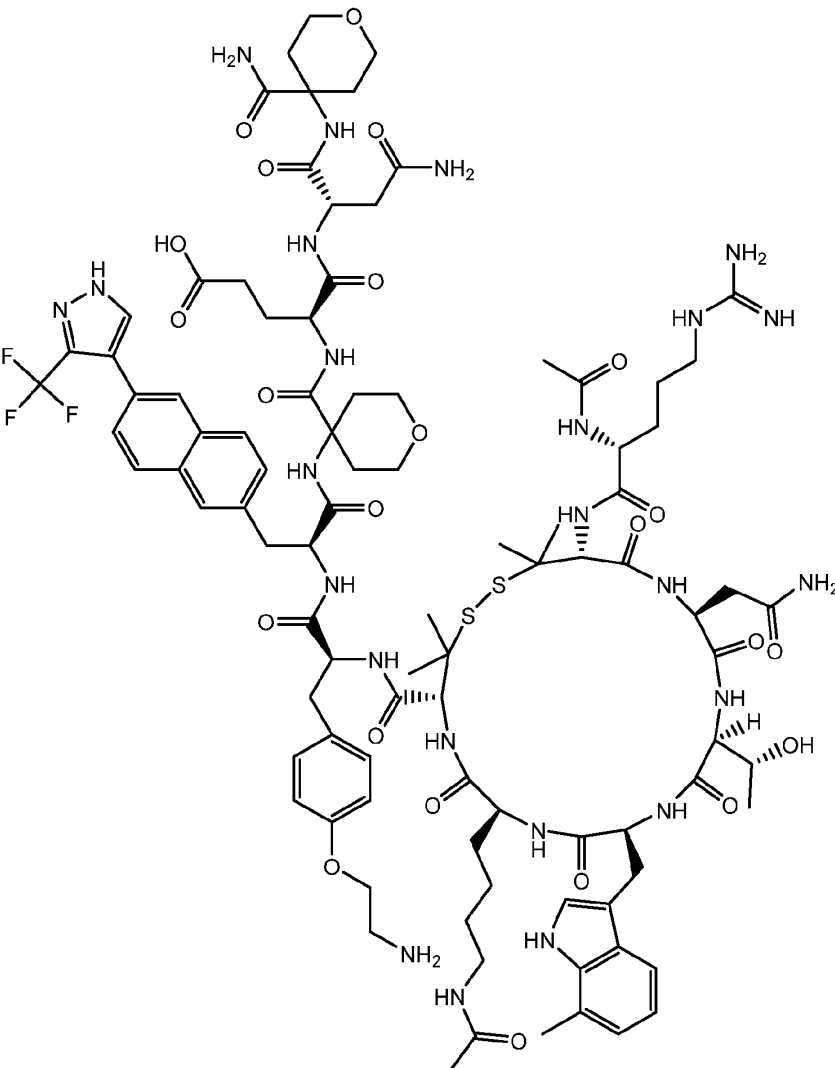
SEQ ID NO	Structure
428	 The chemical structure depicts a large cyclic peptide. The backbone is a 16-membered ring with a disulfide bridge (S-S) between two cysteine residues. The side chains are diverse: a 3-pyridylmethyl group, a 4-hydroxybenzyl group, a 2-methyl-5-oxo-1,3-dioxol-4-ylmethyl group, a 4-aminophenyl group, a 2-aminopropyl group, a 2-amino-3-hydroxypropyl group, a 2-amino-3-oxopropyl group, a 2-amino-3-oxobutyl group, a 2-amino-3-oxopentyl group, a 2-amino-3-oxohexyl group, a 2-amino-3-oxoheptyl group, a 2-amino-3-oxooctyl group, a 2-amino-3-oxononyl group, a 2-amino-3-oxodecyl group, a 2-amino-3-oxoundecyl group, and a 2-amino-3-oxododecyl group. The structure is labeled with the sequence: MeCO-Pen(3)-N-T-7MeW-K(Ac)-Pen(3)-AEF-6OH2Nal-THP-E-N-3Py-Sar-CONH2.

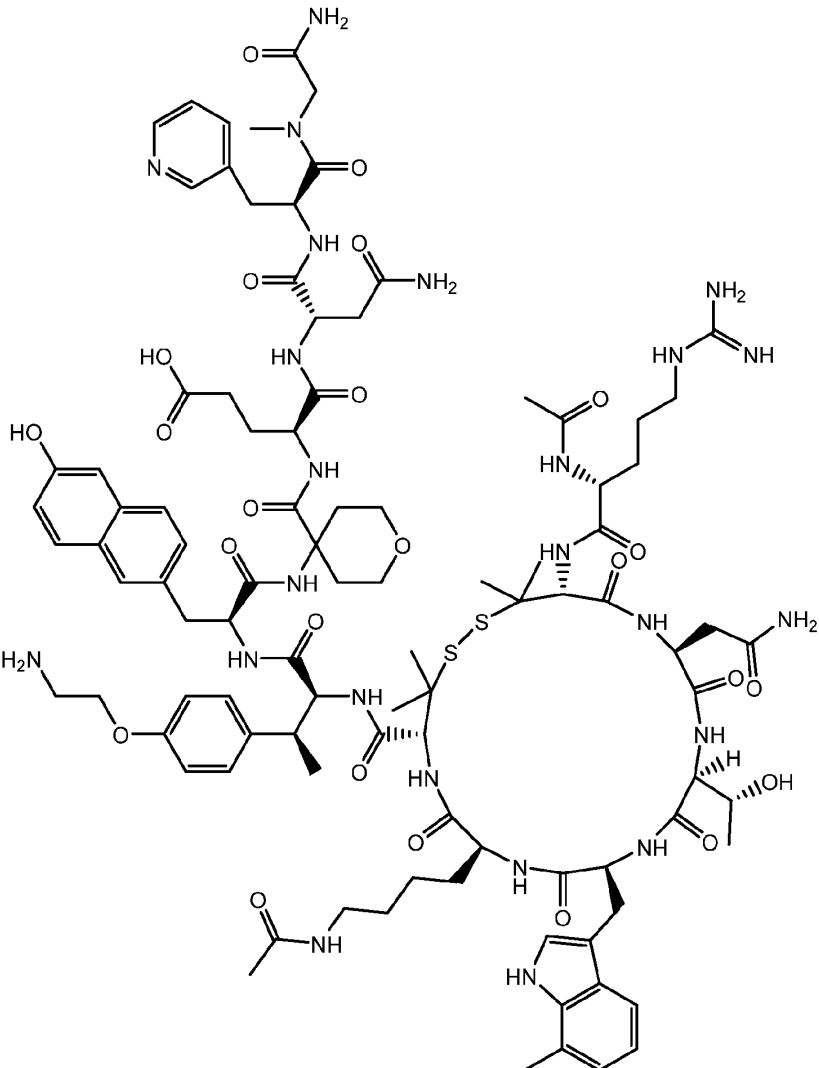
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[illegible]

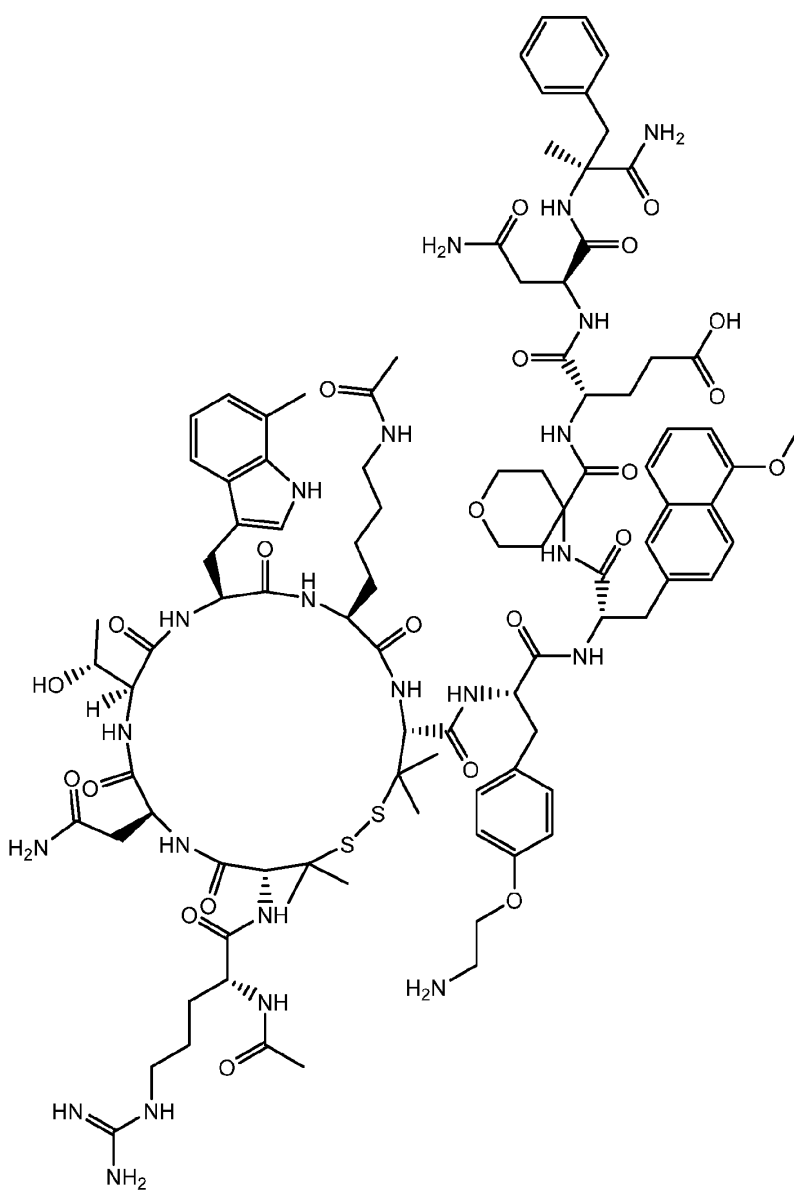
SEQ ID NO	Structure
432	 MeCO-r-Pen(3)-N-T-7MeW-K(Ac)-Pen(3)-AEF-2Nal6(Ph4(NMorph))-THP-E-N-THP-CONH2

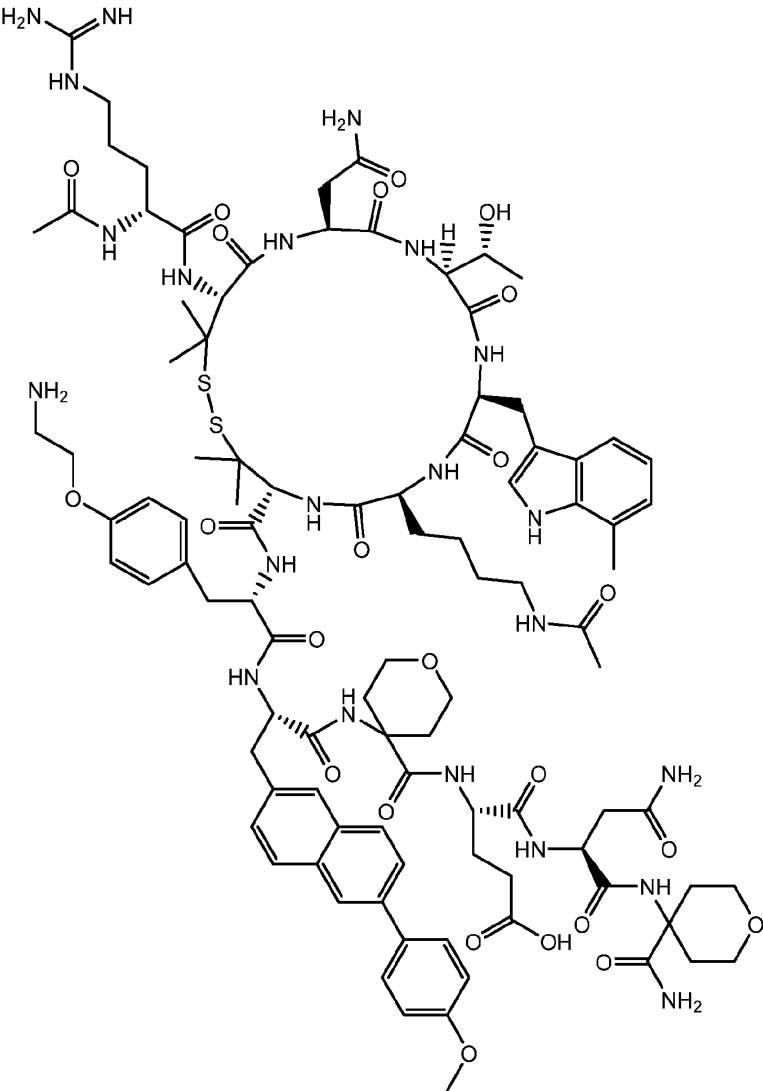
SEQ ID NO	Structure
433	 The chemical structure depicts a large cyclic peptide with a 16-residue backbone. The side chains are diverse, including a morpholine-containing group, a pyrazole ring, a thiazole ring, a hydroxyl group, and a guanidino group. The structure is shown in a 2D representation with stereochemistry indicated by wedges and dashes. MeCO-r-Pen(3)-N-T-7MeW-K(Ac)-Pen(3)-AEF-2Nal6(3Pyrazole)-THP-E-N-THP-CONH₂

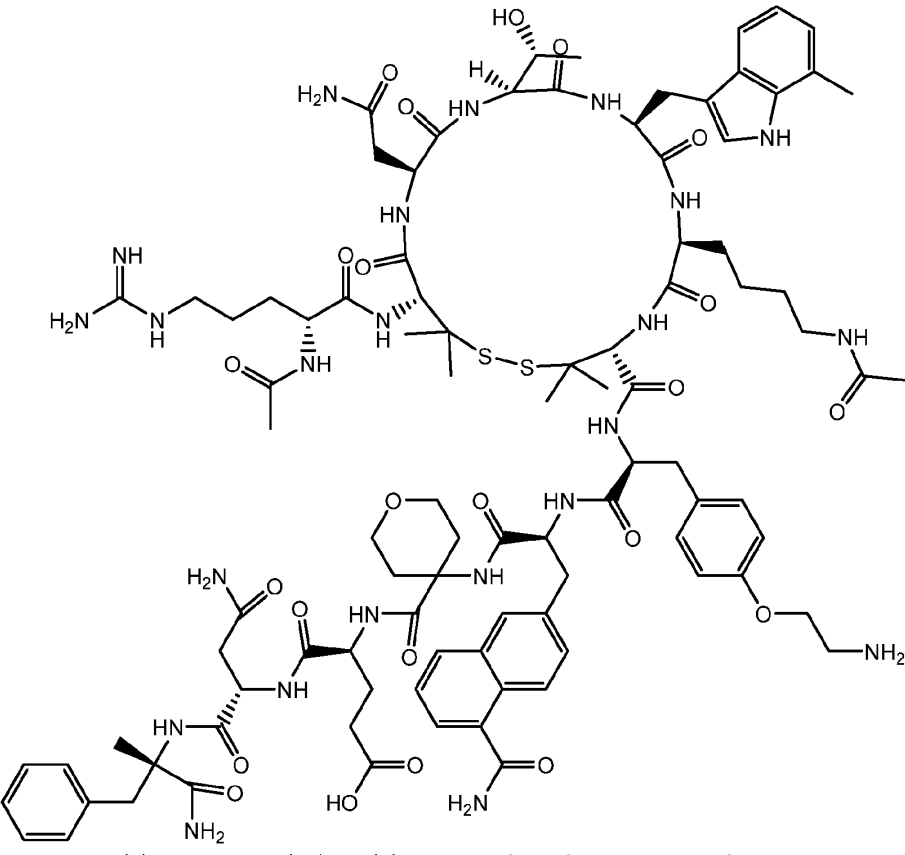
SEQ ID NO	Structure
434	 MeCO-r-Pen(3)-N-T-7MeW-K(Ac)-Pen(3)-AEF-2Nal6((5CF3)3Pyrazole)-THP-E-N-THP-CONH2

SEQ ID NO	Structure
435	 MeCO-r-Pen(3)-N-T-7MeW-K(Ac)-Pen(3)-bMeAEF(3S)-6OH2Nal-THP-E-N-3Pya-Sar-CONH2

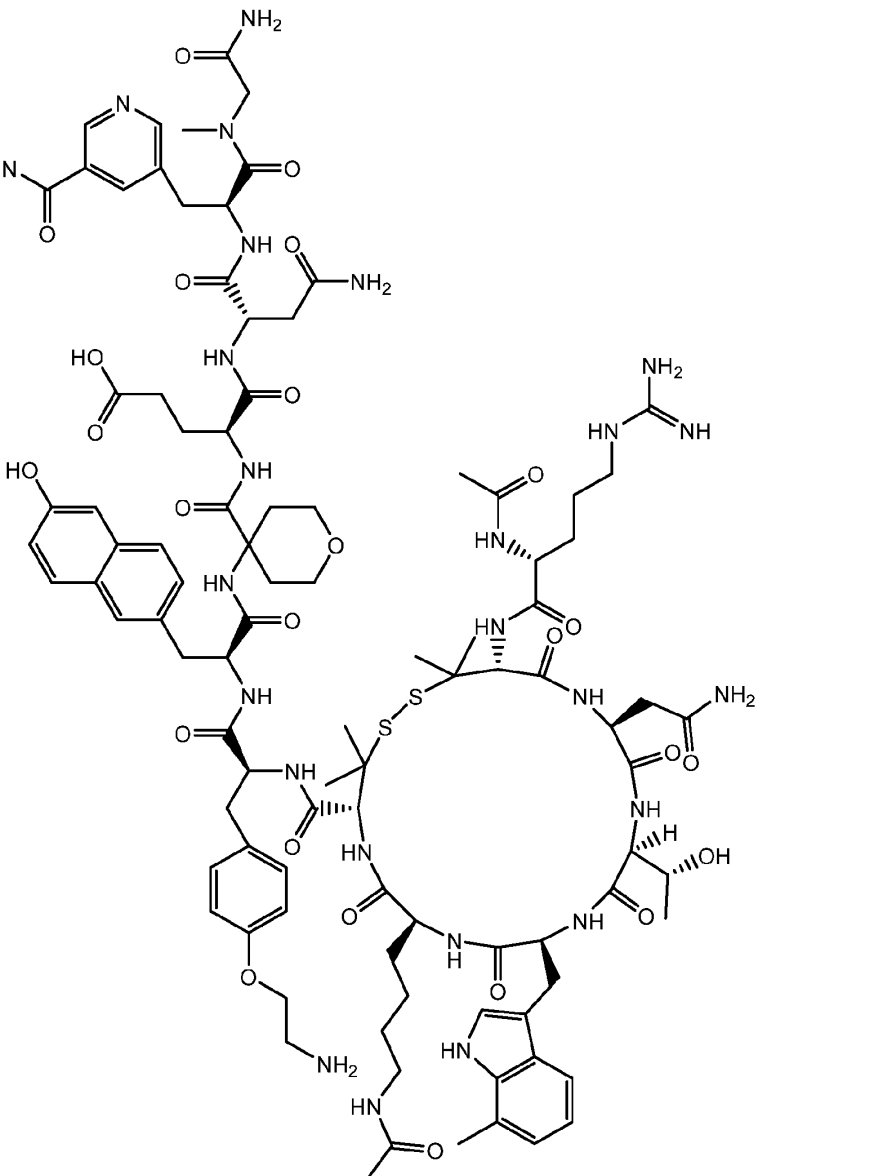
SEQ ID NO	Structure
436	MeCO-r-Pen(3)-N-T-7MeW-K(Ac)-Pen(3)-bMeAEF(3R)-6OH2NaI-THP-E-N-3Pyra-Sar-CONH2

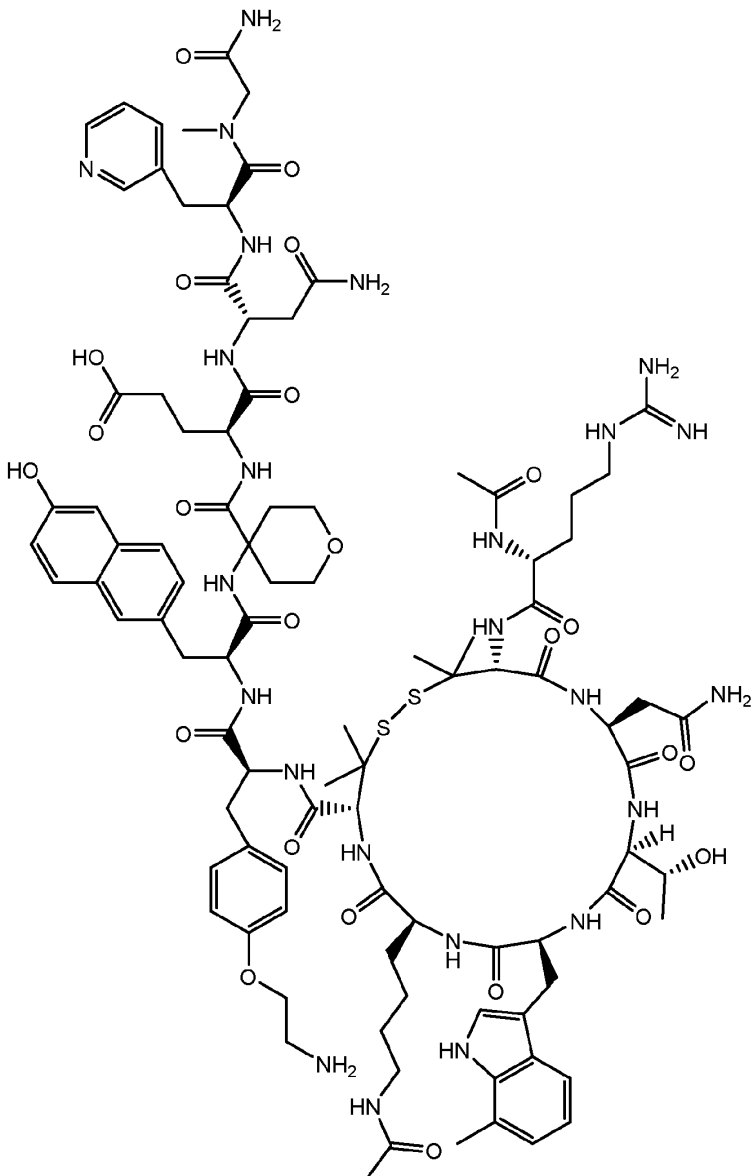
SEQ ID NO	Structure
437	 MeCO-r-Pen(3)-N-T-7MeW-K(Ac)-Pen(3)-AEF-5OMe2Nal-THP-E-N-aMePhe-CONH2

SEQ ID NO	Structure
438	 MeCO-r-Pen(3)-N-T-7MeW-K(Ac)-Pen(3)-AEF-2Nal6(4OMePh)-THP-E-N-THP-CONH2

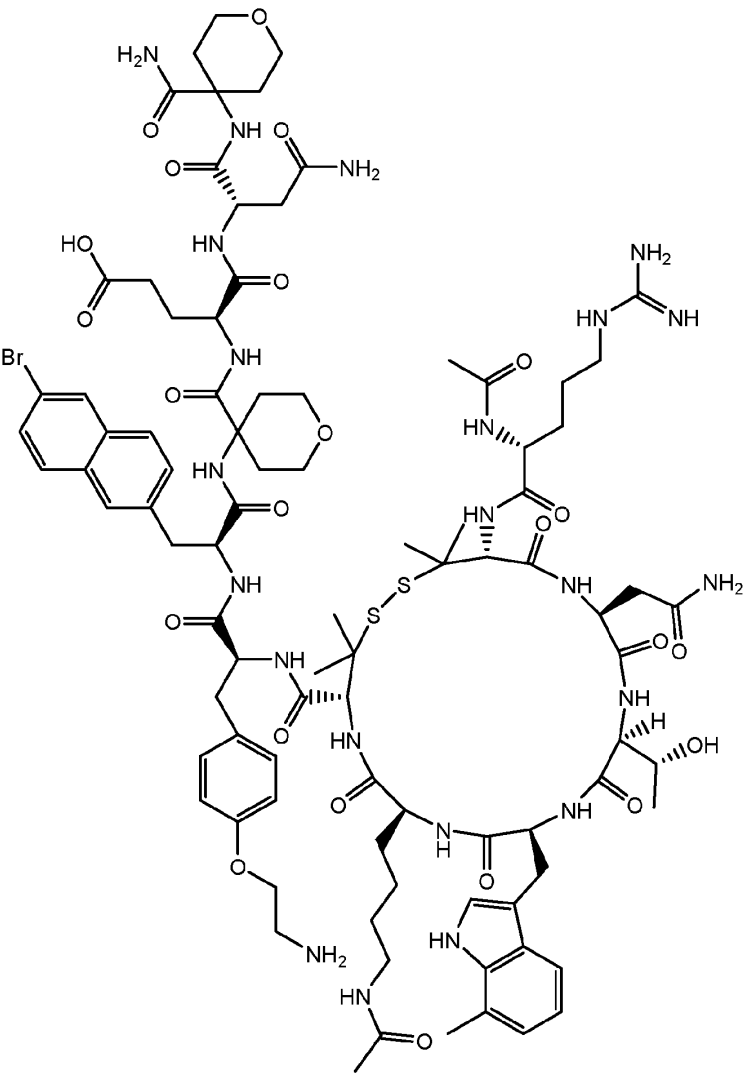
SEQ ID NO	Structure
439	 The chemical structure depicts a large cyclic peptide, specifically a 50-residue macrocycle. The backbone is a continuous chain of amide bonds forming a large ring. The side chains are diverse, including: a 3-aminopropyl group, a 4-aminobutyl group, a 5-aminopentyl group, a 6-aminohexyl group, a 7-aminoseptyl group, an 8-aminooctyl group, a 9-aminononyl group, a 10-aminodecyl group, a 11-aminoundecyl group, a 12-aminododecyl group, a 13-aminotridecyl group, a 14-aminotetradecyl group, a 15-aminopentadecyl group, a 16-aminohexadecyl group, a 17-aminoseptadecyl group, a 18-aminooctadecyl group, a 19-aminononadecyl group, a 20-aminobioctadecyl group, a 21-aminobioheptadecyl group, a 22-aminobiohexadecyl group, a 23-aminobioquintadecyl group, a 24-aminobiotetradecyl group, a 25-aminobiotridecyl group, a 26-aminobiotridecyl group, a 27-aminobiooctadecyl group, a 28-aminobioheptadecyl group, a 29-aminobiohexadecyl group, a 30-aminobioquintadecyl group, a 31-aminobiotetradecyl group, a 32-aminobiotridecyl group, a 33-aminobiotridecyl group, a 34-aminobiooctadecyl group, a 35-aminobioheptadecyl group, a 36-aminobiohexadecyl group, a 37-aminobioquintadecyl group, a 38-aminobiotetradecyl group, a 39-aminobiotridecyl group, a 40-aminobiotridecyl group, a 41-aminobiooctadecyl group, a 42-aminobioheptadecyl group, a 43-aminobiohexadecyl group, a 44-aminobioquintadecyl group, a 45-aminobiotetradecyl group, a 46-aminobiotridecyl group, a 47-aminobiotridecyl group, a 48-aminobiooctadecyl group, a 49-aminobioheptadecyl group, and a 50-aminobiohexadecyl group. The structure also features a disulfide bridge (S-S) and a hydroxyl group (OH) on the backbone. The side chains are attached to the backbone via amide bonds, with some showing stereochemistry (wedges and dashes). MeCO-r-Pen(3)-N-T-7MeW-K(Ac)-Pen(3)-AEF-5amido2Nal-THP-E-N-aMePhe-CONH2

[illegible]

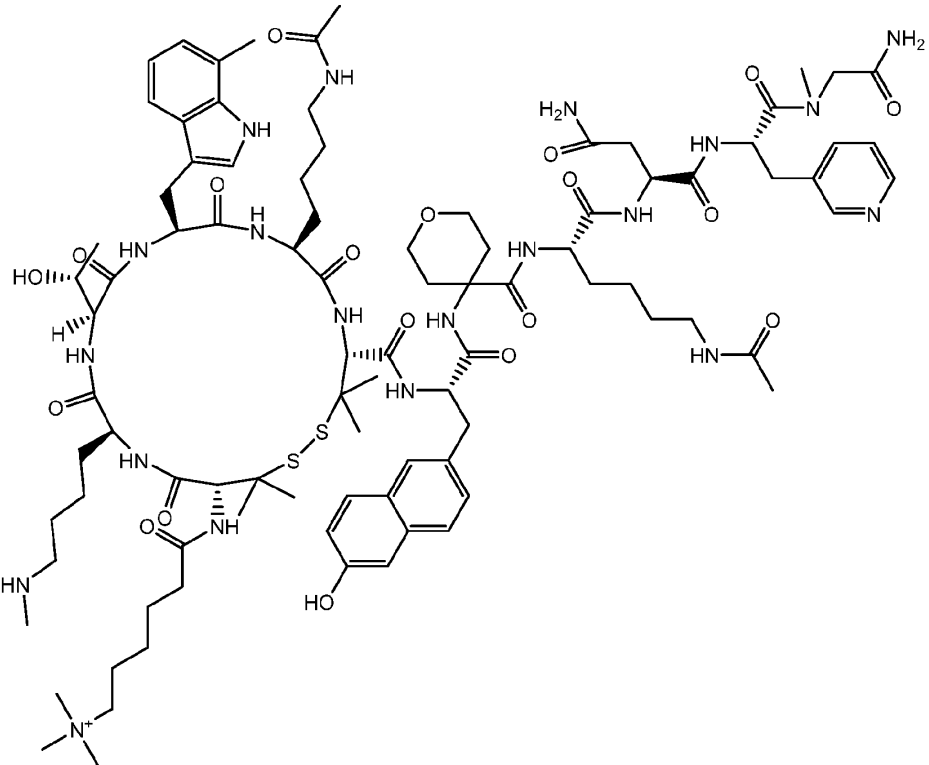
SEQ ID NO	Structure
441	 MeCO-r-Pen(3)-N-T-7MeW-K(Ac)-Pen(3)-AEF-6OH2Nal-THP-E-N-5AmPyridinAla-Sar-CONH2

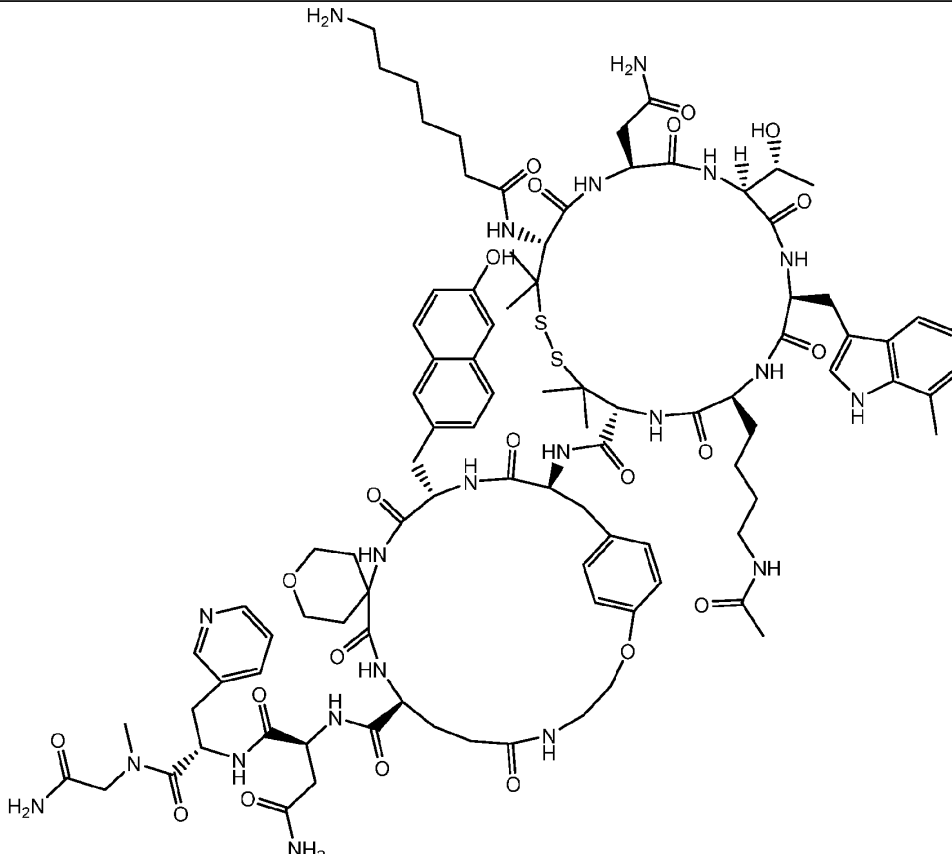
SEQ ID NO	Structure
442	 MeCO-r-Pen(3)-N-T-7MeW-K(Ac)-Pen(3)-AEF-6OH2Nal-THP-E-N-3Pva-Sar-CONH2

[illegible]

SEQ ID NO	Structure
444	 The chemical structure depicts a large cyclic peptide with a 24-residue backbone. The backbone is a 24-membered ring containing four amide bonds and a disulfide bridge between two cysteine residues. The side chains are diverse, including a thiazolidine ring, a 4-bromophenyl group, a 4-hydroxyphenyl group, a 4-aminophenyl group, a 4-hydroxyphenyl group, a 4-aminophenyl group, a 4-hydroxyphenyl group, a 4-aminophenyl group, a 4-hydroxyphenyl group, a 4-aminophenyl group, a 4-hydroxyphenyl group, a 4-aminophenyl group, a 4-hydroxyphenyl group, a 4-aminophenyl group, a 4-hydroxyphenyl group, a 4-aminophenyl group, a 4-hydroxyphenyl group, a 4-aminophenyl group, a 4-hydroxyphenyl group, a 4-aminophenyl group, a 4-hydroxyphenyl group, a 4-aminophenyl group, a 4-hydroxyphenyl group, and a 4-aminophenyl group. The structure is highly complex and represents a large cyclic peptide. MeCO-r-Pen(3)-N-T-7MeW-K(Ac)-Pen(3)-AEF-6Br2NaI-THP-E-N-THP-CONH2

[illegible]

SEQ ID NO	Structure
446	 5cpaCO-Pen(3)-K(NMe)-T-7MeW-K(Ac)-Pen(3)-6OH2Nal-THP-K(Ac)-N-3Pya-Sar-CONH2

SEQ ID NO	Structure
447	 7Ahp-Pen(3)-N-T-7MeW-K(Ac)-Pen(3)-AEF(2)-6OH2Nal-THP-E(2)-N-3Pyra-Sar-CONH2

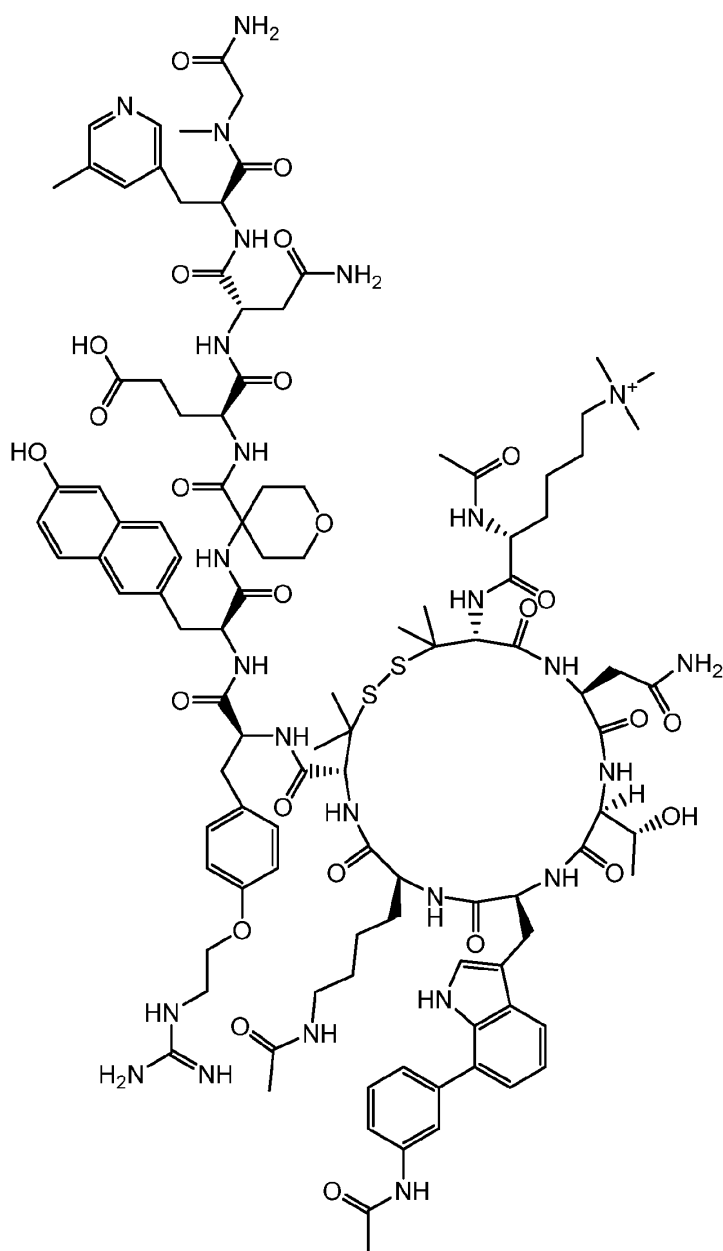
In the peptide sequences shown above, where a number in parenthesis follows a particular residue, that residue is linked to another residue in the sequence that is denoted with the same number. For example, in the sequence MeCO-k(d)-Pen(3)-E(2)-T-7MeW-K(Ac)-Pen(3)-AEF(2)-6OH2Nal-THP-K(Ac)-N-3Pyra-Sar-CONH2 (SEQ ID NO: 133), the two Pen(3) residues are linked to one another, and the E(2) residue is linked to the AEF(2) residue.

In some embodiments, the present disclosure provides a peptide selected from the group consisting of:

- MeCO-k(Me)3-Pen(3)-N-T-7(3NAcPh)W-K(Ac)-Pen(3)-AEF(G)-6OH2Nal-THP-E-N-5MePyridinAla-Sar-CONH2 (SEQ ID NO: 11),
- MeCO-r-Pen(3)-N-T-7(3NAcPh)W-K(Ac)-Pen(3)-AEF(G)-6OH2Nal-THP-E-N-5MePyridinAla-Sar-CONH2 (SEQ ID NO: 15),
- cPEG3aCO-Pen(3)-N-T-7(3NAcPh)W-K(Ac)-Pen(3)-AEF(G)-6OH2Nal-THP-K(NMeAc)-N-3Pyra-Sar-CONH2 (SEQ ID NO: 34),

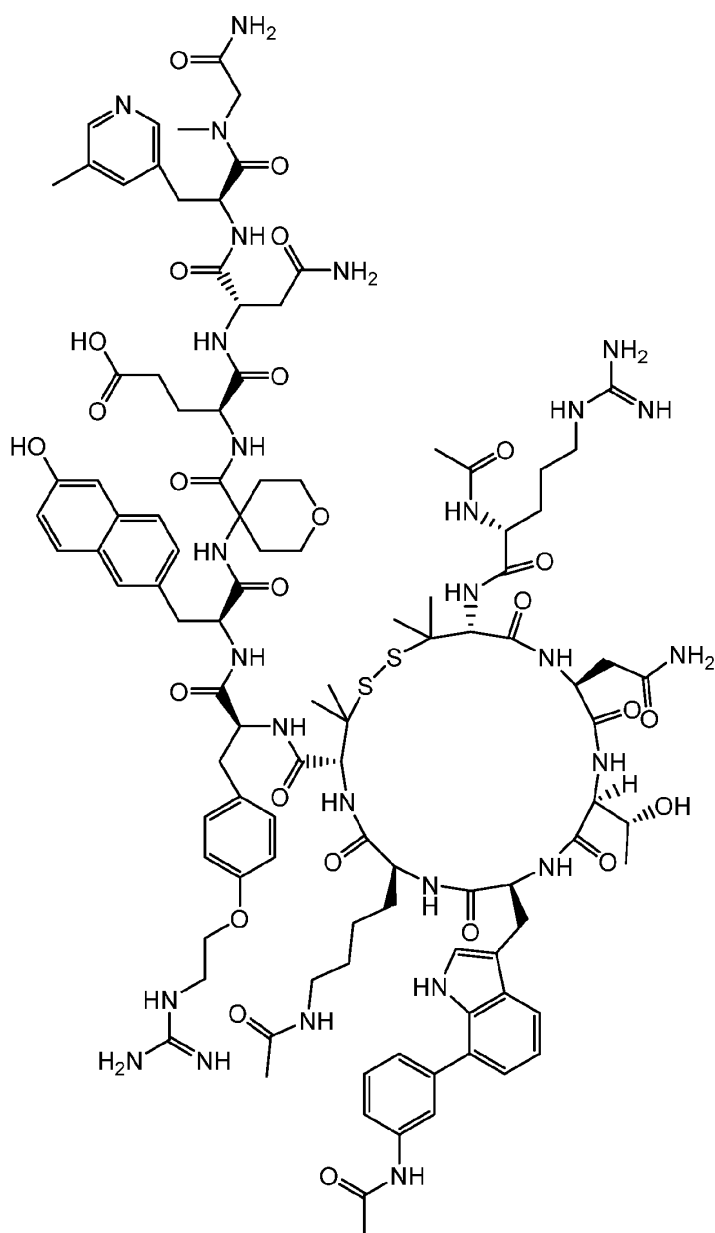
- MeCO-r-Pen(3)-N-T-7MeW-K(Ac)-Pen(3)-TMAPF-6OH2Nal-THP-E-N-3Pyra-Sar-CONH2 (SEQ ID NO: 59),
- MeCO-k(Me)3-Pen(3)-N-T-7(3NAcPh)W-K(Ac)-Pen(3)-AEF-6OH2Nal-THP-E-N-3Pyra-Sar-CONH2 (SEQ ID NO: 68),
- 5 5cpaCO-Pen(3)-K(5)-T-7MeW-K(Ac)-Pen(3)-AEF(5)-6OH2Nal-THP-K(Ac)-N-3Pyra-Sar-CONH2 (SEQ ID NO: 112)
- MeCO-r-Pen(3)-N-T-7(3NAcPh)W-K(Ac)-Pen(3)-AEF-6OH2Nal-THP-E-N-3Pyra-Sar-CONH2 (SEQ ID NO: 287),
- 10 MeCO-Pen(3)-N(NMe2)-T-7MeW-K(NMeAc)-Pen(3)-AEF(NMePEG3a)-6OH2Nal-THP-K(NMeAc)-N-3Pyra-Sar-CONH(PEG3a) (SEQ ID NO: 315),
- cPEG3aCO-Pen(3)-N-T-7MeW-K(NMePEG3a)-Pen(3)-AEF-6OH2Nal-THP-E-N-3Pyra-Sar-CONH2 (SEQ ID NO: 319),
- PEG2NMe(2)-Pen(3)-N-T-7MeW-K(NMeAc)-Pen(3)-AEF-6OH2Nal-THP-hE(2)-N-3Pyra-Sar-CONH2 (SEQ ID NO: 358),
- 15 cPEG3aCO-Pen(3)-E(2)-T-7MeW-K(Ac)-Pen(3)-AEF(2)-6OH2Nal-THP-K(Ac)-N-3Pyra-Sar-CONH2 (SEQ ID NO: 364),
- cPEG3aCO-Pen(3)-N(N(Me)2)-T-7MeW-K(NMeAc)-Pen(3)-AEF-6OH2Nal-THP-Dab(NMeAc)-N-3Pyra-Sar-CON(Me)2 (SEQ ID NO: 371),
- cPEG3aCO-k(2)-Pen(3)-N(N(Me)2)-T-7MeW-K(NMeAc)-Pen(3)-AEF-6OH2Nal-THP-hE(2)-N-3Pyra-Sar-CON(Me)2 (SEQ ID NO: 373), and
- 20 cPEG3aCO-Pen(3)-N-T-7MeW-K(NMeAc)-Pen(3)-AEF-6OH2Nal-THP-Q(N(Me)2)-N-3Pyra-Sar-CONH2 (SEQ ID NO: 392),
- or a pharmaceutically acceptable salt thereof.

In some embodiments, the present disclosure provides a peptide having the following structure:



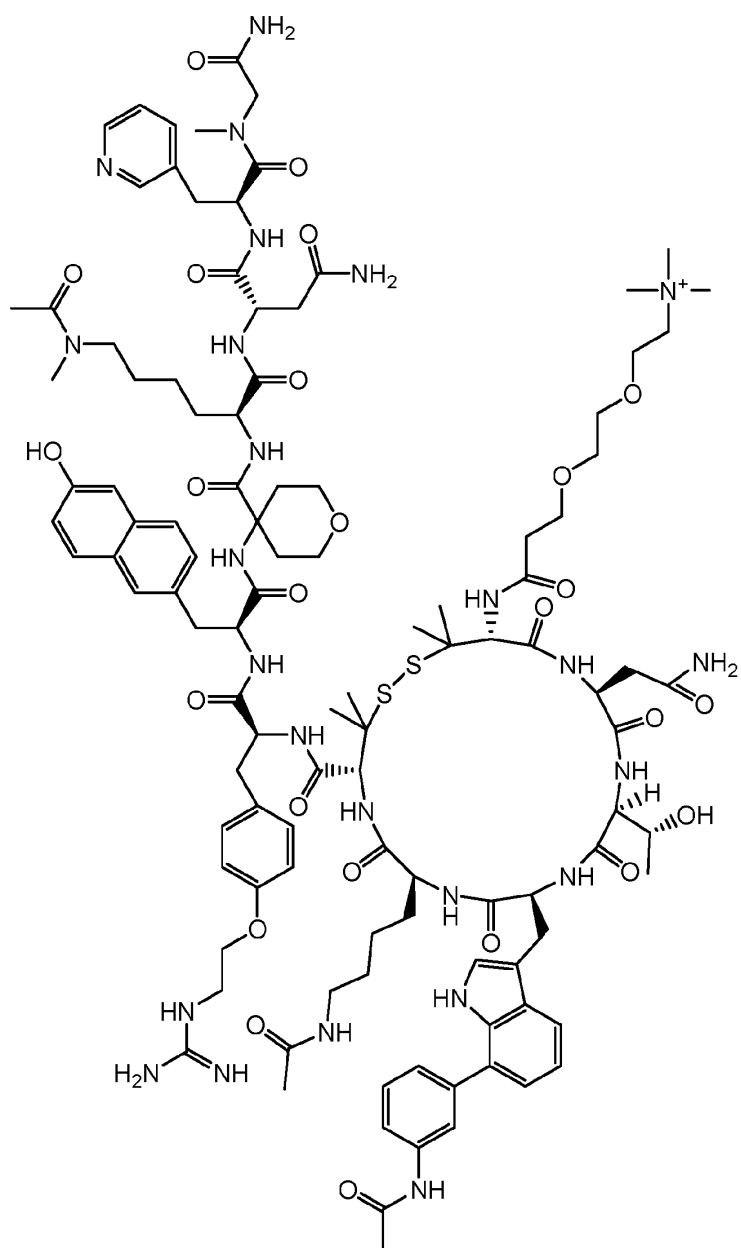
or a pharmaceutically acceptable salt thereof.

In some embodiments, the present disclosure provides a peptide having the following structure:



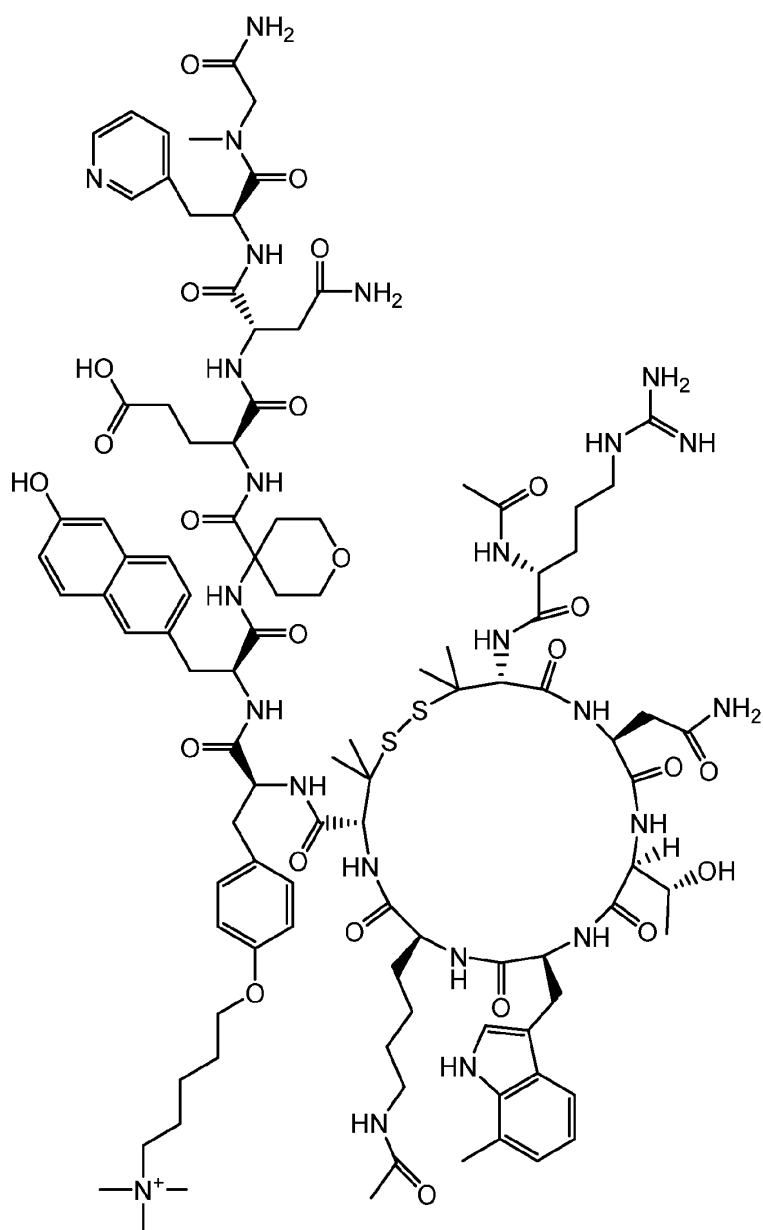
or a pharmaceutically acceptable salt thereof.

In some embodiments, the present disclosure provides a peptide having the following structure:



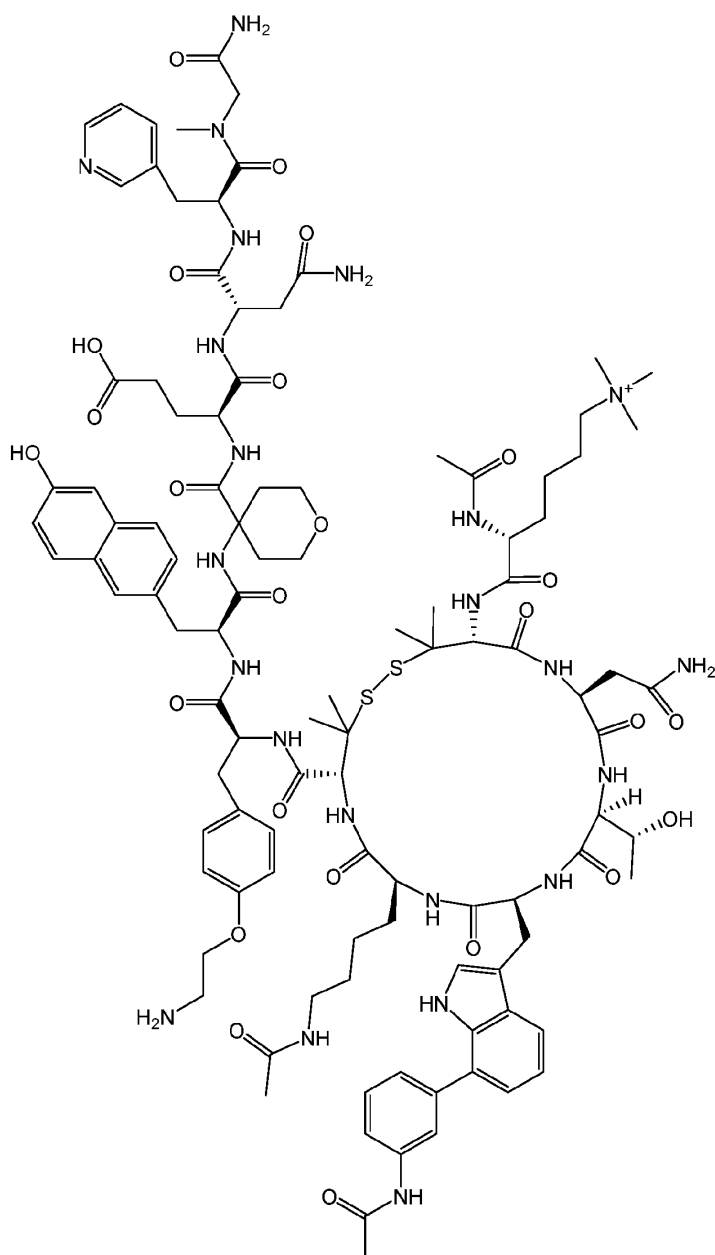
or a pharmaceutically acceptable salt thereof.

In some embodiments, the present disclosure provides a peptide having the following structure:



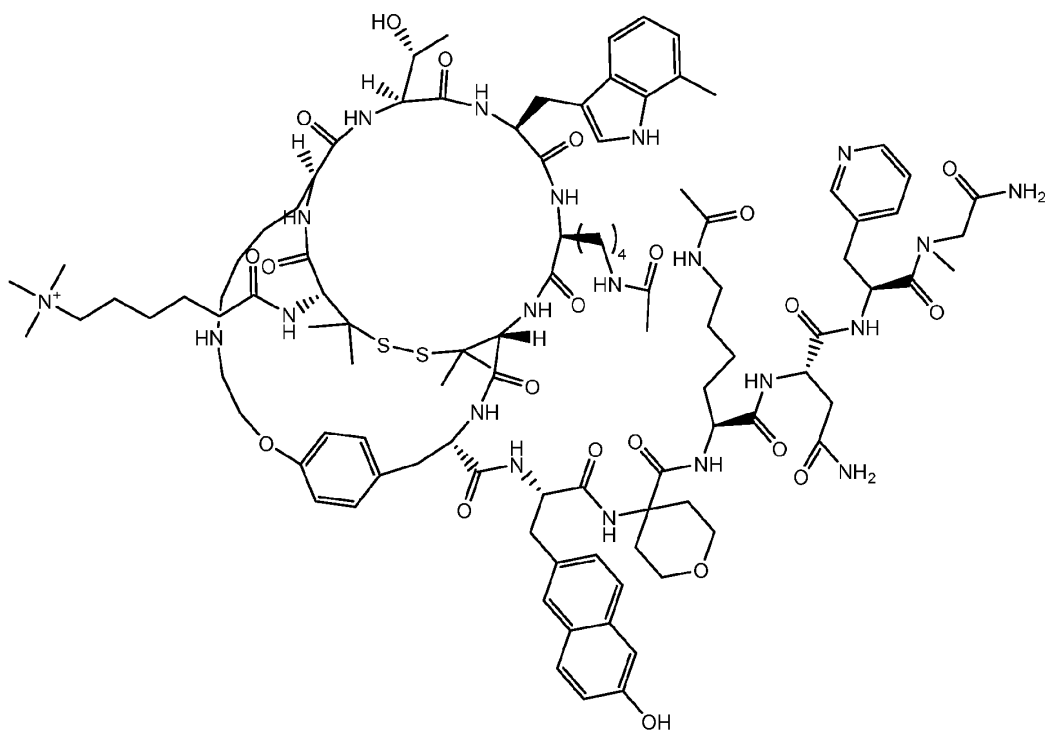
or a pharmaceutically acceptable salt thereof.

In some embodiments, the present disclosure provides a peptide having the following structure:



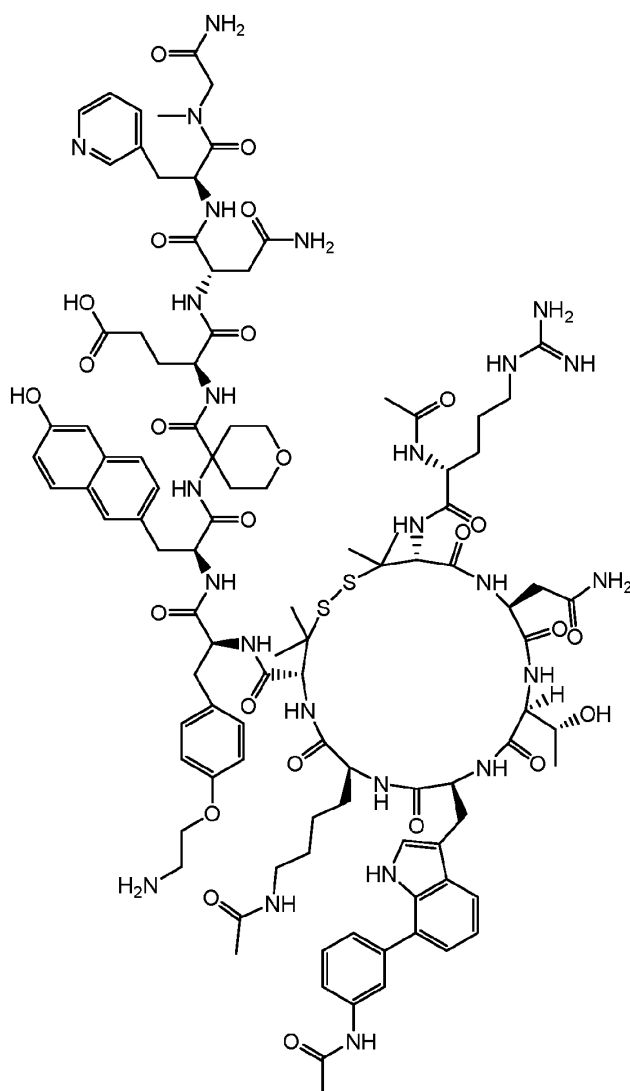
or a pharmaceutically acceptable salt thereof.

In some embodiments, the present disclosure provides a peptide having the following structure:



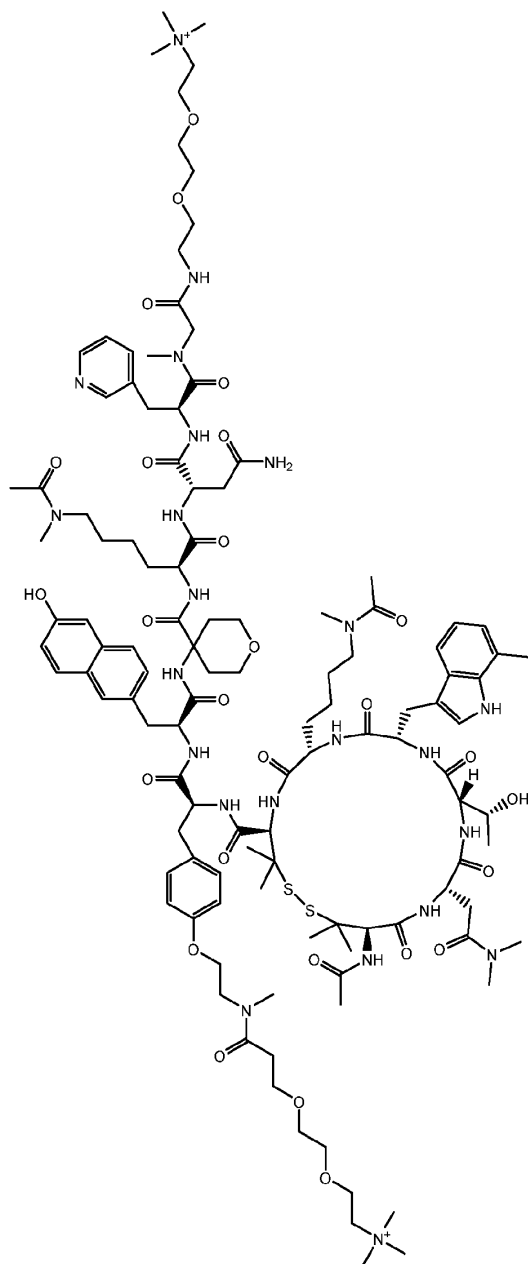
or a pharmaceutically acceptable salt thereof.

In some embodiments, the present disclosure provides a peptide having the following structure:



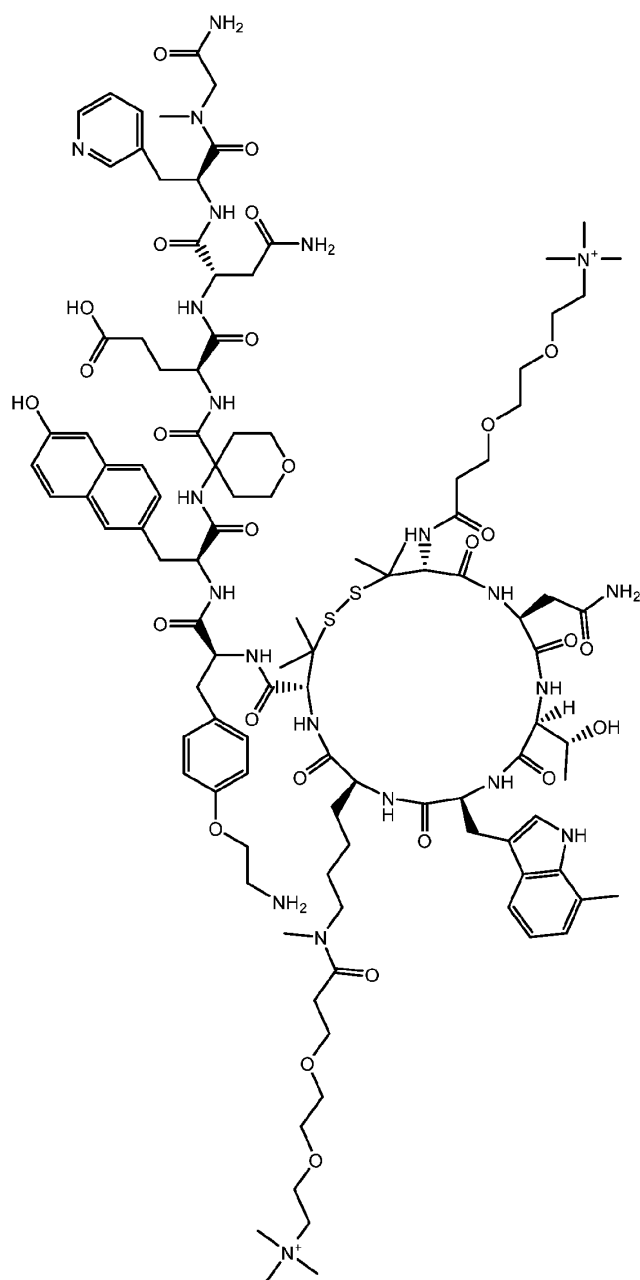
or a pharmaceutically acceptable salt thereof.

In some embodiments, the present disclosure provides a peptide having the following structure:



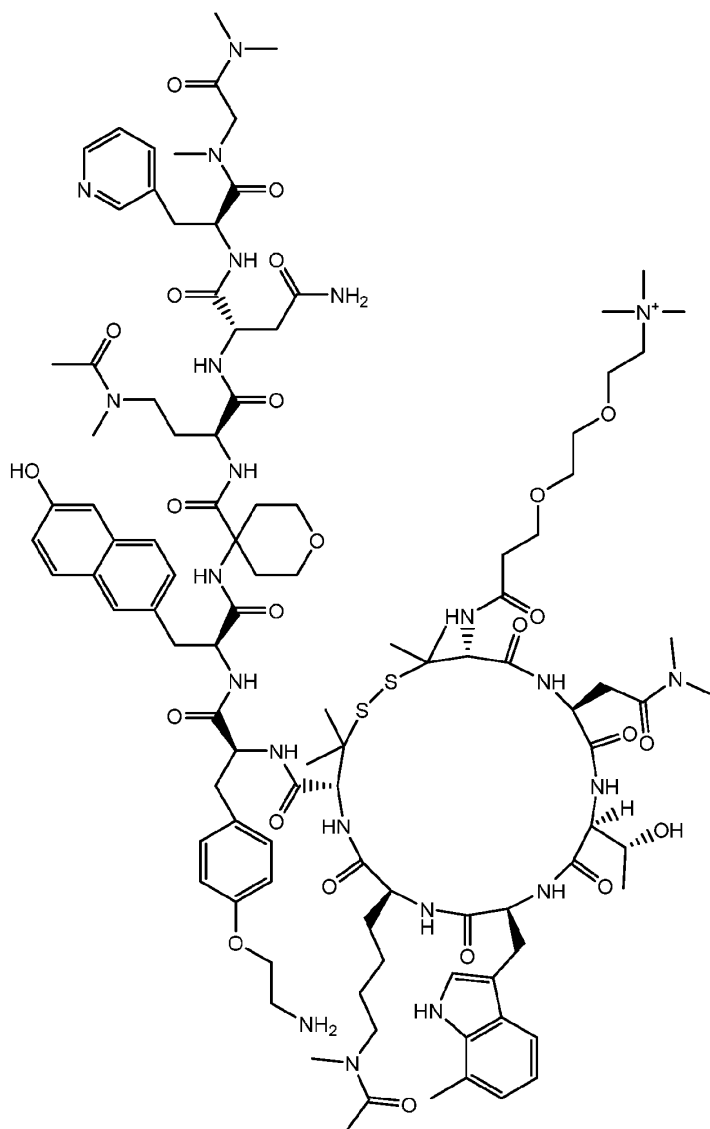
or a pharmaceutically acceptable salt thereof.

In some embodiments, the present disclosure provides a peptide having the following structure:



or a pharmaceutically acceptable salt thereof.

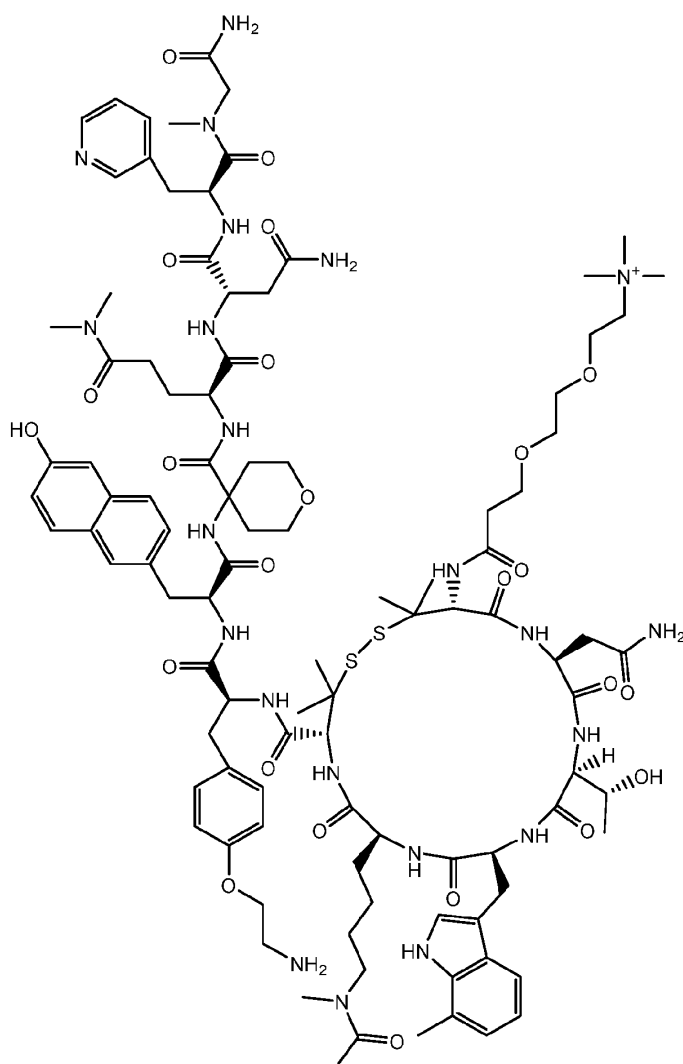
In some embodiments, the present disclosure provides a peptide having the following structure:



or a pharmaceutically acceptable salt thereof.

560

In some embodiments, the present disclosure provides a peptide having the following structure:



or a pharmaceutically acceptable salt thereof.

5

Methods of Synthesis

The compounds described herein may be synthesized by many techniques that are known to those skilled in the art. In some aspects, the present disclosure provides a method of chemically synthesizing a peptide of the present disclosure. In some embodiments, a portion of the peptide is recombinantly synthesized, instead of being chemically synthesized. In some aspects, methods of producing a peptide further include cyclizing the peptide precursor after the constituent subunits have been attached. In particular aspects, cyclization is accomplished via

10

any of the various methods described herein.

The present disclosure further describes synthesis of compounds described herein. In some aspects, one or more of the amino acid residues or amino acid monomers are lipidated and then covalently attached to one another to form a peptide of the disclosure. In some aspects, one or more of the amino acid residues or amino acid monomers are covalently attached to one another and lipidated at an intermediate oligomer stage before attaching additional amino acids and cyclization to form a peptide of the disclosure. In some aspects, a cyclic peptide is synthesized and then lipidated to form a compound of the disclosure. Illustrative synthetic methods are described in the Examples.

10 Pharmaceutical Compositions

The present disclosure further relates to a pharmaceutical composition comprising an IL-23R inhibitor described herein. In particular, the present disclosure includes pharmaceutical compositions comprising one or more peptides of the present disclosure and a pharmaceutically acceptable carrier, diluent or excipient. The pharmaceutically acceptable carrier, diluent or excipient may be a solid, semi-solid or liquid filler, diluent, encapsulating material or formulation auxiliary of any type. Prevention of the action of microorganisms may be ensured by the inclusion of various antibacterial and antifungal agents, for example, paraben, chlorobutanol, phenol sorbic acid, and the like. It may also be desirable to include isotonic agents such as sugars, sodium chloride, and the like.

20 The pharmaceutical compositions may be administered orally, parenterally, intracisternally, intravaginally, intraperitoneally, intrarectally, topically (as by powders, ointments, drops, suppository, or transdermal patch), by inhalation (such as intranasal spray), ocularly (such as intraocularly) or buccally. The term "parenteral" as used herein refers to modes of administration which include intravenous, intramuscular, intraperitoneal, intrasternal, subcutaneous, intradermal and intraarticular injection and infusion. Accordingly, in certain embodiments, the compositions are formulated for delivery by any of these routes of administration. A pharmaceutical composition may be formulated for and administered orally. A pharmaceutical composition may be formulated for and administered parenterally. In some embodiments, the pharmaceutical composition is administered orally.

30 The IL-23R inhibitors of the present disclosure may be prepared and/or formulated as pharmaceutically acceptable salts and/or other forms thereof or when appropriate in neutral form. Pharmaceutically acceptable salts are non-toxic salts of a neutral form of a compound that possess the desired pharmacological activity of the neutral form. These salts may be derived from inorganic or organic acids or bases. For example, a compound that contains a basic nitrogen may be prepared as a pharmaceutically acceptable salt by contacting the compound

with an inorganic or organic acid. Non-limiting examples of pharmaceutically acceptable salts can be found in Remington: The Science and Practice of Pharmacy, 21st Edition, Lippincott Williams and Wilkins, Philadelphia, Pa., 2006.

The present disclosure relates to pharmaceutical compositions comprising an IL-23R inhibitor described herein or pharmaceutically acceptable salts, isomers, or a mixture thereof, in which one or more hydrogen atoms attached to a carbon atom may be replaced by a deuterium atom or D. As known in the art, the deuterium atom is a non-radioactive isotope of the hydrogen atom. Such compounds may increase resistance to metabolism, and thus may be useful for increasing the half-life of the compounds described herein or pharmaceutically acceptable salts, isomer, or a mixture thereof when administered to a mammal. *See, e.g., Foster, "Deuterium Isotope Effects in Studies of Drug Metabolism," Trends Pharmacol. Sci., 5(12):524-527 (1984).* Such compounds are synthesized by means well known in the art, for example by employing starting materials in which one or more hydrogen atoms have been replaced by deuterium.

Examples of isotopes that can be incorporated into the disclosed compounds also include isotopes of hydrogen, carbon, nitrogen, oxygen, phosphorous, fluorine, chlorine, and iodine, such as ²H, ³H, ¹¹C, ¹³C, ¹⁴C, ¹³N, ¹⁵N, ¹⁵O, ¹⁷O, ¹⁸O, ³¹P, ³²P, ³⁵S, ¹⁸F, ³⁶Cl, ¹²³I, and ¹²⁵I, respectively. Substitution with positron emitting isotopes, such as ¹¹C, ¹⁸F, ¹⁵O and ¹³N, can be useful in Positron Emission Topography (PET) studies for examining substrate receptor occupancy. Isotopically-labeled peptides of the present disclosure can generally be prepared by conventional techniques known to those skilled in the art or by processes analogous to those described in the Examples as set out below using an appropriate isotopically-labeled reagent in place of the non-labeled reagent previously employed.

When used in at least one of the treatments or delivery systems described herein, a peptide inhibitor of the present disclosure may be employed in pure form or, where such forms exist, in pharmaceutically acceptable salt form.

The total daily usage of the IL-23R inhibitor and compositions of the present disclosure can be decided by the attending physician within the scope of sound medical judgment. The specific therapeutically effective dose level for any particular subject will depend upon a variety of factors including: a) the disorder being treated and the severity of the disorder; b) activity of the specific compound employed; c) the specific composition employed, the age, body weight, general health, sex and diet of the patient; d) the time of administration, route of administration, and rate of excretion of the specific peptide inhibitor employed; e) the duration of the treatment; f) drugs used in combination or coincidental with the specific peptide inhibitor employed, and like factors well known in the medical arts.

The compositions may conveniently be presented in unit dosage form and can be prepared by any of the methods well known in the art of pharmacy. Techniques and compositions generally are found in Remington's Pharmaceutical Sciences (Mack Publishing Co., Easton, PA). Such methods include the step of bringing into association the active
5 ingredient with the carrier which constitutes one or more accessory ingredients. In general the compositions are prepared by uniformly and intimately bringing into association the active ingredient with liquid carriers or finely divided solid carriers or both, and then, if necessary, shaping the product.

10 *Non-Invasive Detection of Intestinal Inflammation*

The IL-23R inhibitors of the present disclosure may be used for detection, assessment and diagnosis of intestinal inflammation by microPET imaging, wherein the peptide inhibitor is labeled with a chelating group or a detectable label, as part of a non-invasive diagnostic procedure. In certain embodiments, an IL-23R inhibitor of the present disclosure is conjugated
15 with a bifunctional chelator. In certain embodiments, an IL-23R inhibitor of the present disclosure is radiolabeled. The labeled IL-23R inhibitor is then administered to a subject orally or rectally. In certain embodiments, the IL-23R inhibitor is included in drinking water. Following uptake of the IL-23R inhibitor, microPET imaging may be used to visualize inflammation throughout the subject's bowels and digestive track.

20

Methods of Treatment and Uses

The present disclosure relates to methods for treating a subject afflicted with a condition or indication associated with IL-23 or IL-23R activity (e.g., activation of the IL-23/IL-23R signaling pathway), wherein the method comprises administering to the subject an IL-23R
25 inhibitor disclosed herein. In one aspect, the present disclosure provides a method for treating a subject afflicted with a condition or indication characterized by aberrant or dysregulated IL-23 or IL-23R activity or signaling, comprising administering to the subject a peptide inhibitor of the present disclosure in an amount sufficient to inhibit (partially or fully) binding of IL-23 to an IL-23R in the subject. The inhibition of IL-23 binding to IL-23R may occur in particular organs or
30 tissues of the subject, e.g., the stomach, small intestine, large intestine/colon, intestinal mucosa, lamina propria, Peyer's Patches, mesenteric lymph nodes, or lymphatic ducts.

The present disclosure relates to methods comprising providing a peptide inhibitor described herein to a subject in need thereof. The subject in need thereof may be a subject that has been diagnosed with or has been determined to be at risk of developing a disease or disorder

associated with IL-23/IL-23R. The subject may be a mammal. The subject may be, in particular, a human.

The disease or disorder to be treated by treatment with an IL-23R inhibitor of the present disclosure may be an inflammatory disease or disorder, an autoimmune inflammation diseases or disorder, and/or related disorders, including multiple sclerosis, asthma, rheumatoid arthritis, inflammation of the gut, inflammatory bowel diseases (IBDs), juvenile IBD, adolescent IBD, Crohn's disease, ulcerative colitis, sarcoidosis, Systemic Lupus Erythematosus, ankylosing spondylitis (axial spondyloarthritis), psoriatic arthritis, or psoriasis. In particular, the disease or disorder may be psoriasis (e.g., plaque psoriasis, guttate psoriasis, inverse psoriasis, pustular psoriasis, Palmo-Plantar Pustulosis, psoriasis vulgaris, or erythrodermic psoriasis), atopic dermatitis, acne ectopica, ulcerative colitis, Crohn's disease, Celiac disease (nontropical Sprue), enteropathy associated with seronegative arthropathies, microscopic colitis, collagenous colitis, eosinophilic gastroenteritis/esophagitis, colitis associated with radio- or chemo-therapy, colitis associated with disorders of innate immunity as in leukocyte adhesion deficiency-1, chronic granulomatous disease, glycogen storage disease type 1b, Hermansky-Pudlak syndrome, Chediak-Higashi syndrome, Wiskott-Aldrich Syndrome, pouchitis, pouchitis resulting after proctocolectomy and ileoanal anastomosis, gastrointestinal cancer, pancreatitis, insulin-dependent diabetes mellitus, mastitis, cholecystitis, cholangitis, primary biliary cirrhosis, viral-associated enteropathy, pericholangitis, chronic bronchitis, chronic sinusitis, asthma, uveitis, or graft versus host disease.

The present disclosure provides a method or use of an IL-23R inhibitor for treating an inflammatory disease or disorder in a subject in need thereof that includes administering to the subject a therapeutically effective amount of an IL-23R inhibitor of the present disclosure, a pharmaceutically acceptable salt thereof, or a composition disclosed herein comprising an IL-23 inhibitor of the present disclosure.

The present disclosure provides a method or use of an IL-23R inhibitor for treating an autoimmune disease or disorder in a subject in need thereof that includes administering to the subject a therapeutically effective amount of an IL-23R inhibitor of the present disclosure, a pharmaceutically acceptable salt thereof, or a composition disclosed herein comprising an IL-23 inhibitor of the present disclosure.

The present disclosure provides a method or use of an IL-23R inhibitor for treating an autoimmune inflammation disease or disorder in a subject in need thereof that includes administering to the subject a therapeutically effective amount of an IL-23R inhibitor of the present disclosure, a pharmaceutically acceptable salt thereof, or a composition disclosed herein comprising an IL-23 inhibitor of the present disclosure.

Suitable inflammatory diseases, autoimmune inflammation diseases, and/or related disorders for treatment with a compound or pharmaceutically acceptable salt thereof, or a composition of the present disclosure, may include, but are not limited to inflammatory bowel disease (IBD), Crohn's disease (CD), ulcerative colitis (UC), psoriasis (PsO), or psoriatic arthritis (PsA) and the like. The inflammatory disease to be treated may be inflammatory bowel disease (IBD), Crohn's disease, or ulcerative colitis. The inflammatory disease to be treated may be selected from psoriasis or psoriatic arthritis. The inflammatory disease to be treated may be psoriasis. The inflammatory disease to be treated may be psoriatic arthritis. The inflammatory disease to be treated may be IBD. The inflammatory disease to be treated may be Crohn's disease. The inflammatory disease to be treated may be ulcerative colitis.

Production of IL-23 is enriched in the intestine, where it is believed to play a key role in regulating the balance between tolerance and immunity through T-cell-dependent and T-cell-independent pathways of intestinal inflammation through effects on T-helper 1 (Th1) and Th17-associated cytokines, as well as restraining regulatory T-cell responses in the gut, favoring inflammation. In addition, polymorphisms in the IL-23 receptor (IL-23R) have been associated with susceptibility to inflammatory bowel diseases (IBDs), further establishing the critical role of the IL-23 pathway in intestinal homeostasis. Peptides and methods for specific targeting of the IL-23R from the luminal side of the gut may provide therapeutic benefit to IBD patients suffering from local inflammation of the intestinal tissue.

Accordingly, the present disclosure also provides a method of treating or preventing inflammatory bowel disease (IBD), Crohn's disease (CD), or ulcerative colitis (UC), in a subject in need thereof, said method comprising administering to the subject a therapeutically effective amount of a peptide of the present disclosure, a pharmaceutically acceptable salt thereof, or a pharmaceutical composition described herein comprising an IL-23 inhibitor. In some embodiments, the method is for treating or preventing inflammatory bowel disease (IBD). In some embodiments, the method is for treating or preventing Crohn's disease (CD). In some embodiments, the method is for treating or preventing ulcerative colitis (UC).

Psoriasis, a chronic skin disease affecting about 2%-3% of the general population has been shown to be mediated by the body's T cell inflammatory response mechanisms. IL-23 is one of several interleukins implicated as a key player in the pathogenesis of psoriasis, purportedly by maintaining chronic autoimmune inflammation via the induction of interleukin-17, regulation of T memory cells, and activation of macrophages. Expression of IL-23 and IL-23R has been shown to be increased in tissues of patients with psoriasis, and antibodies that neutralize IL-23 showed IL-23-dependent inhibition of psoriasis development in animal models of psoriasis. Orally bioavailable peptide inhibitors of IL-23 may provide both a non-steroidal

treatment option for patients with mild to moderate psoriasis and treatment for moderate to severe psoriasis that does not require delivery by infusion.

Accordingly, the present disclosure also provides a method of treating or preventing psoriasis (PsO) or psoriatic arthritis (PsA) in a subject in need thereof, said method comprising
5 administering to the subject a therapeutically effective amount of a peptide of the present disclosure, a pharmaceutically acceptable salt thereof, or a pharmaceutical composition described herein comprising an IL-23 inhibitor. In some embodiments, the method is for treating or preventing psoriasis (PsO). In some embodiments, the method is for treating or preventing psoriatic arthritis (PsA).

10 The present disclosure further relates to a method of selectively inhibiting IL-23 or IL-23R signaling (or the binding of IL-23 to IL-23R) in a subject (e.g., in a subject in need thereof), comprising administering to the subject a peptide inhibitor of the IL-23R described herein. In some embodiments, the present disclosure includes and provides a method of selectively inhibiting IL-23 or IL-23R signaling (or the binding of IL-23 to IL-23R) in the GI tract of a
15 subject (e.g., a subject in need thereof), comprising providing to the subject a peptide inhibitor of the IL-23R of the present disclosure by oral administration. The exposure of GI tissues (e.g., small intestine or colon) to the administered peptide inhibitor may be at least 10-fold, at least 20-fold, at least 50-fold, or at least 100-fold greater than the exposure (level) in the blood. In particular embodiments, the present disclosure includes a method of selectively inhibiting IL23
20 or IL23R signaling (or the binding of IL23 to IL23R) in the GI tract of a subject (e.g., a subject in need thereof), comprising providing to the subject a peptide inhibitor, wherein the peptide inhibitor does not block the interaction between IL-6 and IL-6R or antagonize the IL-12 signaling pathway. In a further related embodiment, the present disclosure provides a method of inhibiting GI inflammation and/or neutrophil infiltration to the GI, comprising providing to a
25 subject in need thereof a peptide inhibitor of the present disclosure. In some embodiments, methods of the present disclosure comprise providing a peptide inhibitor of the present disclosure (i.e., a first therapeutic agent) to a subject (e.g., a subject in need thereof) in combination with a second therapeutic agent. In certain embodiments, the second therapeutic agent is provided to the subject before and/or simultaneously with and/or after the peptide
30 inhibitor is administered to the subject. In particular embodiments, the second therapeutic agent is an anti-inflammatory agent. In certain embodiments, the second therapeutic agent is a non-steroidal anti-inflammatory drug, steroid, or immune modulating agent. In certain embodiments, the method comprises administering to the subject a third therapeutic agent. In certain embodiments, the second therapeutic agent is an antibody that binds IL-23 or IL-23R.

The present disclosure also relates to methods of inhibiting IL-23 binding to an IL-23R on a cell, comprising contacting the IL-23R with a peptide inhibitor of the receptor disclosed herein. The cell may be a mammalian cell. The method may be performed in vitro or in vivo. Inhibition of binding may be determined by a variety of routine experimental methods and assays known in the art.

The present disclosure relates to methods of inhibiting IL-23 signaling by a cell, comprising contacting the IL-23R with a peptide inhibitor described herein. In certain embodiments, the cell is a mammalian cell. In particular embodiments, the method is performed in vitro or in vivo. In particular embodiments, the inhibition of IL-23 signaling may be determined by measuring changes in phospho-STAT3 levels in the cell.

In any of the foregoing methods, IL-23R inhibitor administration to the subject may be conducted orally, but other routes of administration are not excluded. Other routes of administration include, but are not limited to, parenteral, subcutaneous, intravenous, intramuscular, intraperitoneal, transdermal, topical, buccal or ocular routes. Dosages of a peptide inhibitor of IL-23R described herein, or salt thereof to be administered to a subject may be determined by a person of skill in the art taking into account the disease or condition being treated, including its severity, and factors including age, weight, sex, and the like.

Examples

The following examples are not intended to limit the scope of the present disclosure, but rather to provide guidance to the skilled artisan to prepare and use the peptides, compositions, and methods of the present disclosure. While particular aspects of the present disclosure are described, the skilled artisan will appreciate that various changes and modifications can be made without departing from the spirit and scope of the disclosure.

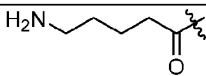
Some abbreviations useful in describing the disclosure are defined below in the following tables.

Herein and throughout the application, the following abbreviations may be used.

Abbreviation	Definition
ACN	acetonitrile
Boc	tert-butoxy-carbonyl
carnitine-succinate, carn	(R)-4-(tert-butoxy)-2-(3-(hydroxy-12-methoxy)propanamido)- N,N,N-trimethyl-4-oxobutan-1-aminium
DCM	dichloromethane
Dde	N-(1-(4,4-dimethyl-2,6-dioxocyclohexylidene)ethyl
DIC	N,N'-diisopropylcarbodiimide

Abbreviation	Definition
DIPEA	N, N-diisopropylethylamine
DMF	N,N-dimethylformamide
DMSO	dimethyl sulfoxide
DTT	dithiothreitol
ESI	electrospray ionization
Et ₂ O	diethyl ether
Fmoc or Fmoc	((9H-fluoren-9-yl)methoxy)carbonyl
h	hour
HATU	1-[bis(dimethylamino)methylene]-1H-1,2,3-triazolo[4,5-b]pyridinium 3-oxide hexafluorophosphate
HOAT or HOAt	1-hydroxy-7-azabenzotriazole
HPLC	high-performance liquid chromatography
MeOH	methanol
min	minute
MS	mass spectrometry
MTBE	methyl tert-butyl ether
MW	microwave
NDMBA	1,3-dimethylbarbituric acid
Oxyma	ethyl cyanohydroxyiminoacetate
RT	room temperature
SPPS	solid-phase peptide synthesis
TBAF	tetrabutylammonium fluoride
TEA	triethylamine
TFA	trifluoroacetic acid
TFE	tetrafluoroethylene
THF	tetrahydrofuran
TIPS	triisopropyl silane
TIS	triisopropyl silane
UPLC	ultra performance liquid chromatography

Table 5. N-Terminal Modification Abbreviations

Abbreviation	Structure
5Ava	

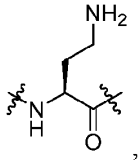
Abbreviation	Structure
5cpaCO	
6Ahx	
7Ahp	
CF3CO	
CF3Propylamide	
EtCO	
MeCO	
PEG2	
PEG2NMe	
cPEG3aCO	
cPEG5aCO	
mPEG12CO	
C12gEPEG2PEG2CO	
C14gEPEG2PEG2CO	
HOC18gEPEG2PEG2CO	
HOC20gEPEG2PEG2CO	

Abbreviation	Structure
HOC18gEPEG6CO	
HOC18gEPEG12CO	
HOC18gEPEG2SP6PEG2CO	
(d)gEPEG2PEG2CO	

Table 6. C-Terminal Modification Abbreviations

Abbreviation	Structure
CONH2	
CO(DiFPip)	
CON(Me)2	
CONH(PEG3a)	
CONH(PEG3a)	

The amino acid structures provided in Table 7, below, are presented without stereochemical indicators at the alpha carbon; however, it is to be understood that these amino acids occur as either the L-amino acid or the D-amino acid. Unless an amino acid residue of Table 7 is represented with a lower-case abbreviation or with the letter D before it, all amino acids abbreviations described in the table refer to the L-amino acid configuration. For example, “Dab” refers to the L-stereoisomer:



and the corresponding D-stereoisomer is represented as “dab,” “dDab,” or “D-Dab”:

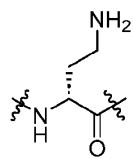
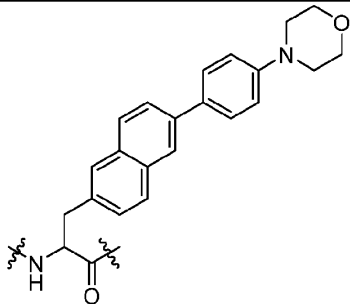
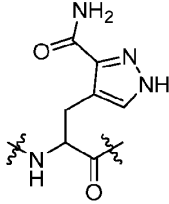
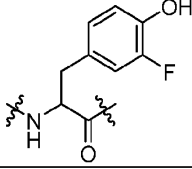
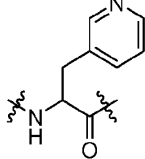
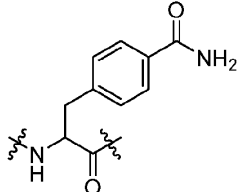
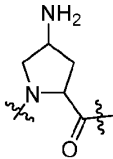
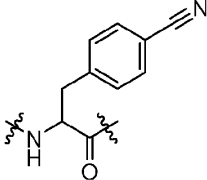
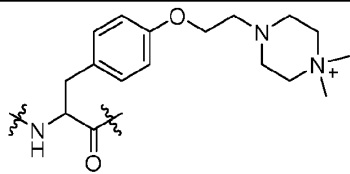
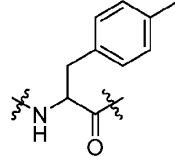
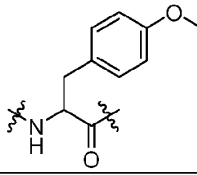
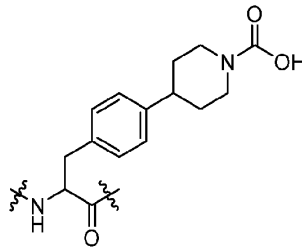
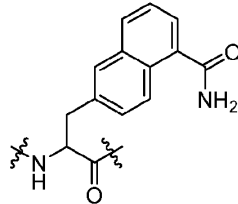
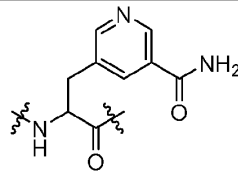
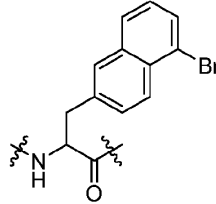
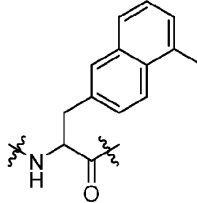


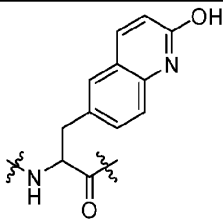
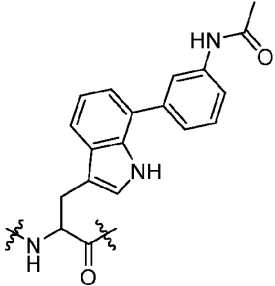
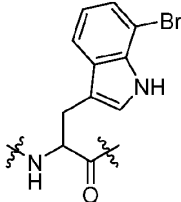
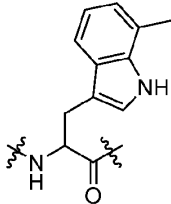
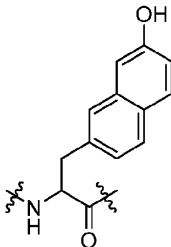
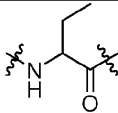
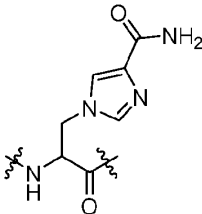
Table 7. Monomer Abbreviations

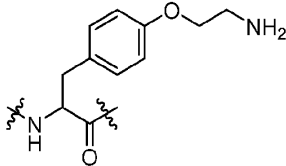
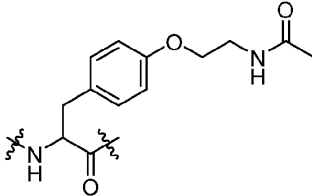
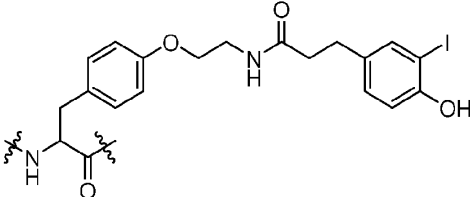
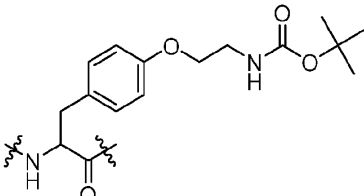
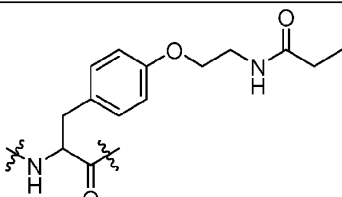
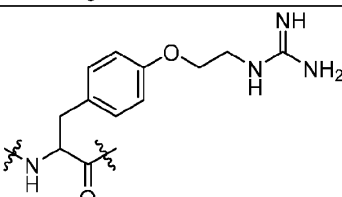
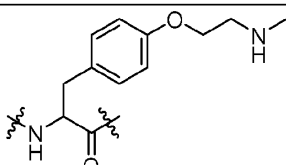
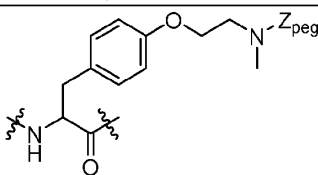
Abbreviation	Structure
2Nal6((5CF3)3Pyrazole)	The structure shows a polymer repeat unit with a backbone consisting of an amide group and a carbonyl group. A side chain is attached to the backbone, consisting of a methylene group and a terminal group that is a 5-(trifluoromethyl)pyrazol-2-yl group.
2Nal6(3Pyrazole)	The structure shows a polymer repeat unit with a backbone consisting of an amide group and a carbonyl group. A side chain is attached to the backbone, consisting of a methylene group and a terminal group that is a 3-pyrazolyl group.
2Nal6(4OMePh)	The structure shows a polymer repeat unit with a backbone consisting of an amide group and a carbonyl group. A side chain is attached to the backbone, consisting of a methylene group and a terminal group that is a 4-methoxyphenyl group.
2Nal6(Ph2OH)	The structure shows a polymer repeat unit with a backbone consisting of an amide group and a carbonyl group. A side chain is attached to the backbone, consisting of a methylene group and a terminal group that is a 2-phenylphenyl group.

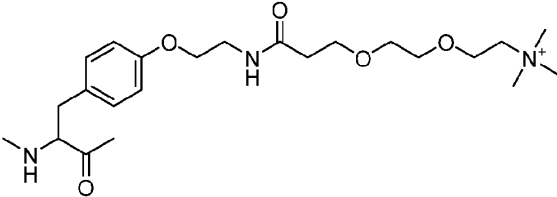
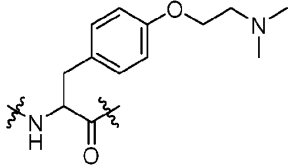
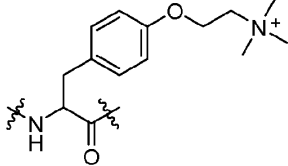
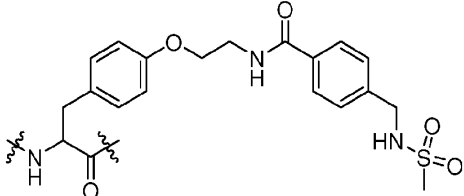
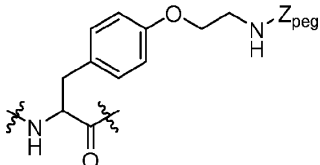
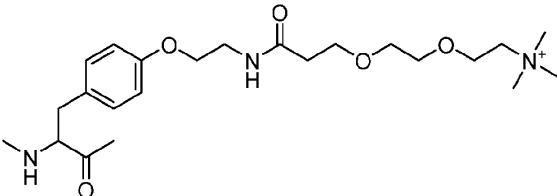
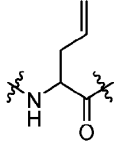
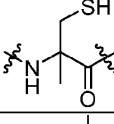
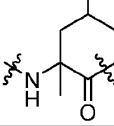
Abbreviation	Structure
2Nal6(Ph4(NMorph))	 Chemical structure of 2Nal6(Ph4(NMorph)). It features a central naphthalene ring system. At the 2-position, there is a side chain consisting of a methylene group attached to a chiral center (represented by a carbon with a wavy bond), which is also bonded to an amide group (NH) and a carbonyl group (C=O). At the 6-position, there is a side chain consisting of a methylene group attached to a chiral center (represented by a carbon with a wavy bond), which is also bonded to an amide group (NH) and a carbonyl group (C=O). The naphthalene ring is substituted at the 1-position with a 4-(morpholin-4-yl)phenyl group.
3AmPyrazolAla	 Chemical structure of 3AmPyrazolAla. It features a central naphthalene ring system. At the 2-position, there is a side chain consisting of a methylene group attached to a chiral center (represented by a carbon with a wavy bond), which is also bonded to an amide group (NH) and a carbonyl group (C=O). At the 3-position, there is a side chain consisting of a methylene group attached to a chiral center (represented by a carbon with a wavy bond), which is also bonded to an amide group (NH) and a carbonyl group (C=O). The naphthalene ring is substituted at the 1-position with a 4-(morpholin-4-yl)phenyl group.
3FTyr	 Chemical structure of 3FTyr. It features a central naphthalene ring system. At the 2-position, there is a side chain consisting of a methylene group attached to a chiral center (represented by a carbon with a wavy bond), which is also bonded to an amide group (NH) and a carbonyl group (C=O). At the 3-position, there is a side chain consisting of a methylene group attached to a chiral center (represented by a carbon with a wavy bond), which is also bonded to an amide group (NH) and a carbonyl group (C=O). The naphthalene ring is substituted at the 1-position with a 4-(morpholin-4-yl)phenyl group.
3Pya	 Chemical structure of 3Pya. It features a central naphthalene ring system. At the 2-position, there is a side chain consisting of a methylene group attached to a chiral center (represented by a carbon with a wavy bond), which is also bonded to an amide group (NH) and a carbonyl group (C=O). At the 3-position, there is a side chain consisting of a methylene group attached to a chiral center (represented by a carbon with a wavy bond), which is also bonded to an amide group (NH) and a carbonyl group (C=O). The naphthalene ring is substituted at the 1-position with a 4-(morpholin-4-yl)phenyl group.
4AmF	 Chemical structure of 4AmF. It features a central naphthalene ring system. At the 2-position, there is a side chain consisting of a methylene group attached to a chiral center (represented by a carbon with a wavy bond), which is also bonded to an amide group (NH) and a carbonyl group (C=O). At the 4-position, there is a side chain consisting of a methylene group attached to a chiral center (represented by a carbon with a wavy bond), which is also bonded to an amide group (NH) and a carbonyl group (C=O). The naphthalene ring is substituted at the 1-position with a 4-(morpholin-4-yl)phenyl group.
4AminoPro	 Chemical structure of 4AminoPro. It features a central naphthalene ring system. At the 2-position, there is a side chain consisting of a methylene group attached to a chiral center (represented by a carbon with a wavy bond), which is also bonded to an amide group (NH) and a carbonyl group (C=O). At the 4-position, there is a side chain consisting of a methylene group attached to a chiral center (represented by a carbon with a wavy bond), which is also bonded to an amide group (NH) and a carbonyl group (C=O). The naphthalene ring is substituted at the 1-position with a 4-(morpholin-4-yl)phenyl group.
4CNF	 Chemical structure of 4CNF. It features a central naphthalene ring system. At the 2-position, there is a side chain consisting of a methylene group attached to a chiral center (represented by a carbon with a wavy bond), which is also bonded to an amide group (NH) and a carbonyl group (C=O). At the 4-position, there is a side chain consisting of a methylene group attached to a chiral center (represented by a carbon with a wavy bond), which is also bonded to an amide group (NH) and a carbonyl group (C=O). The naphthalene ring is substituted at the 1-position with a 4-(morpholin-4-yl)phenyl group.

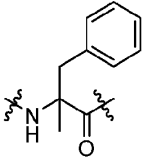
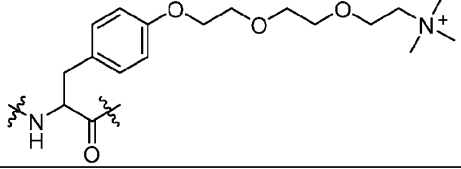
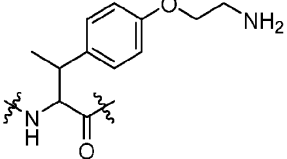
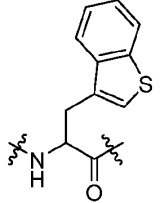
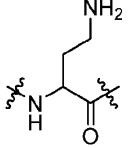
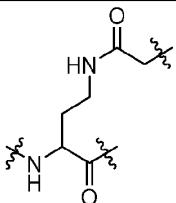
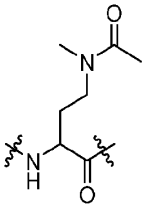
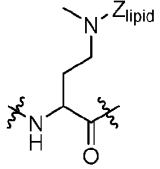
Abbreviation	Structure
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4MeF	
4OMeF	
4PipPhe	
5amido2Nal	
5AmPyridinAla	
5Br2Nal	
5Me2Nal	

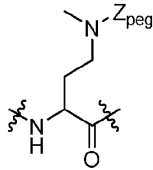
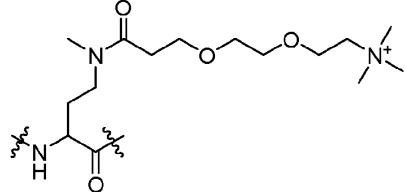
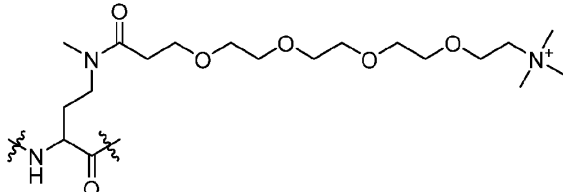
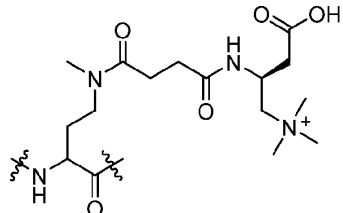
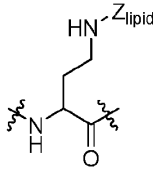
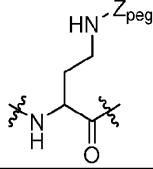
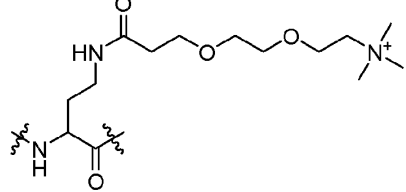
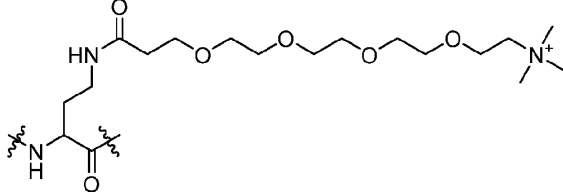
Abbreviation	Structure
5MePyridinAla	
5OMe2Nal	
6Br2Nal	
6F2Nal	
6MeQui	
6O(COCF3)2Nal	
6OH2Nal	

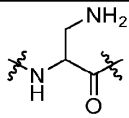
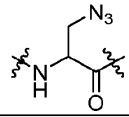
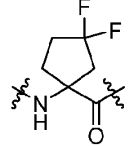
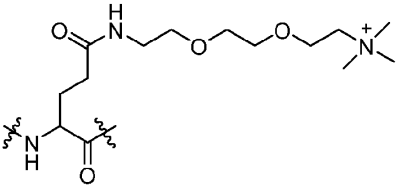
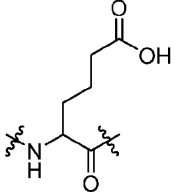
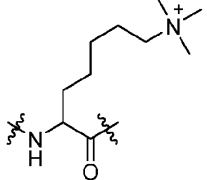
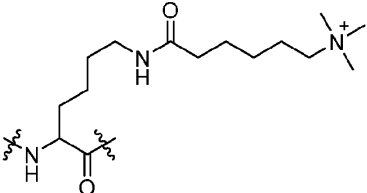
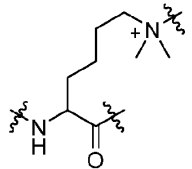
Abbreviation	Structure
6OHQui	
7(3NacPh)W	
7BrW	
7MeW	
7OH2Nal	
Abu	 2-aminobutyric acid
ACIPA	

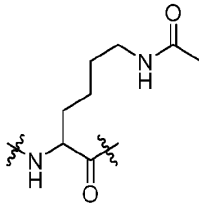
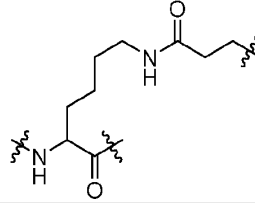
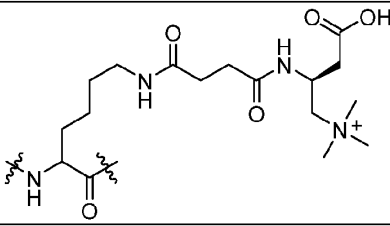
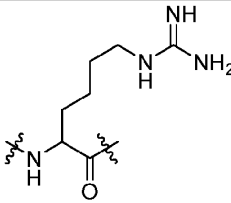
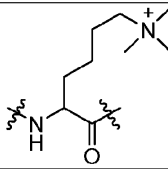
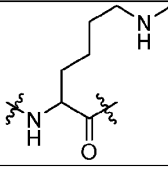
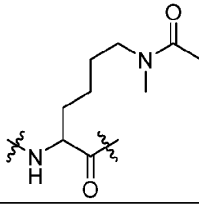
Abbreviation	Structure
AEF	
AEF(Ac)	
AEF(BH)	
AEF(Boc)	
AEF(EtCO)	
AEF(G)	
AEF(NMe)	
AEF(NMe)-Z _{peg}	

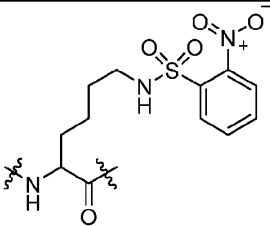
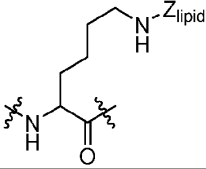
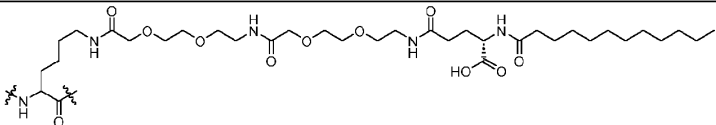
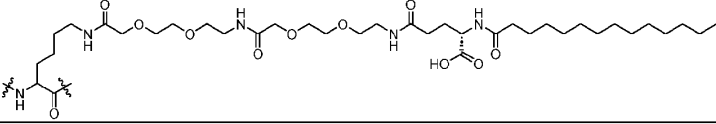
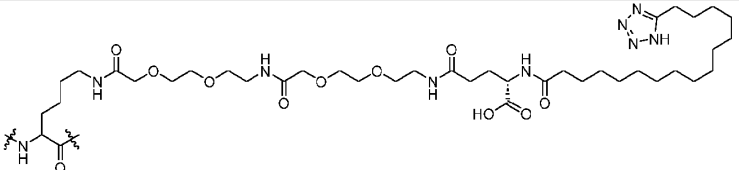
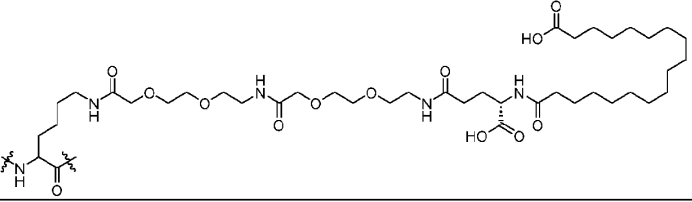
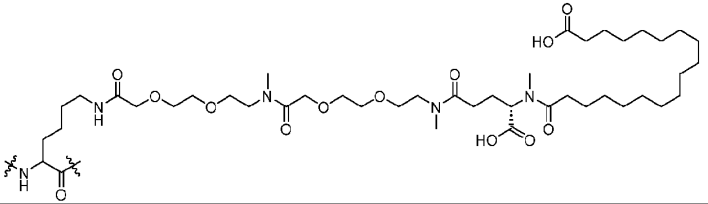
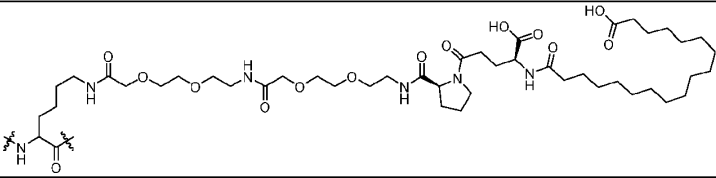
Abbreviation	Structure
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AEF(NMe2)	
AEF(NMe3)	
AEF(SMSB)	
AEF-Z _{peg}	
AEF(NHPEG3a)	
aG	
aMeC	
aMeL	

Abbreviation	Structure
aMePhe	
APEG3F	
bMeAEF	
BT	
Dab	 2,4-diaminobutyric acid
Dab(COCH2)	
Dab(NMeAc)	
Dab(NMe)-Z _{lipid}	

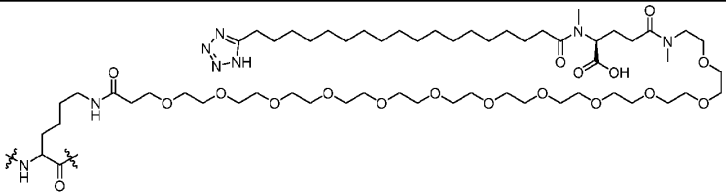
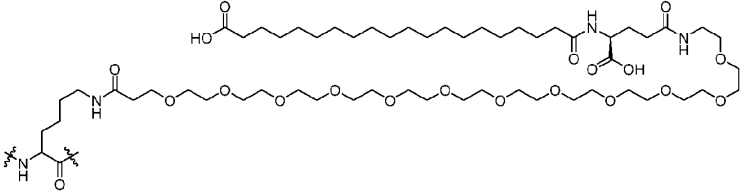
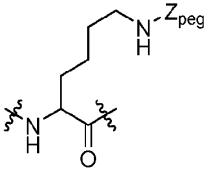
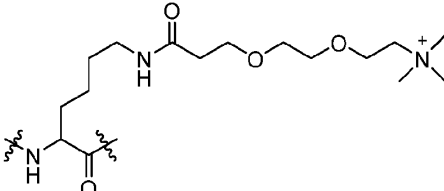
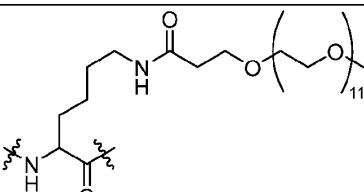
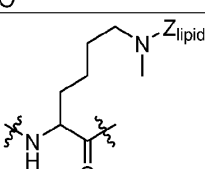
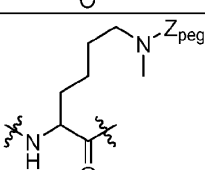
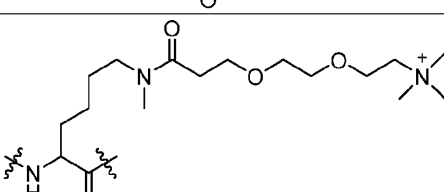
Abbreviation	Structure
Dab(NMe)-Z _{peg}	
Dab(NMecPEG3a)	
Dab(NMecPEG5a)	
Dab(NMecarn)	
Dab-Z _{lipid}	
Dab-Z _{peg}	
Dab(cPEG3a)	
Dab(cPEG5a)	

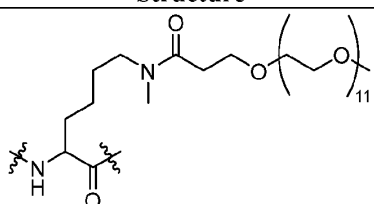
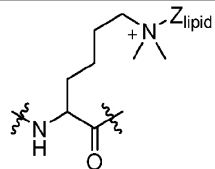
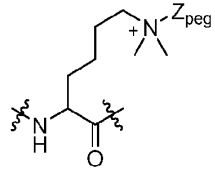
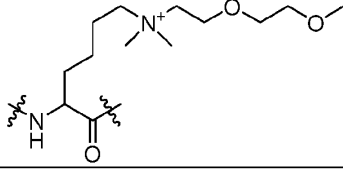
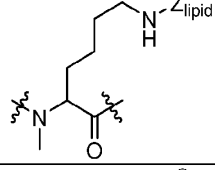
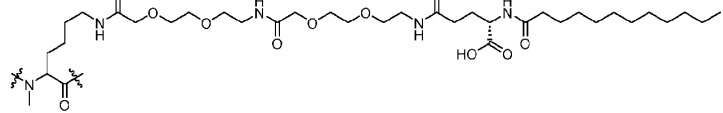
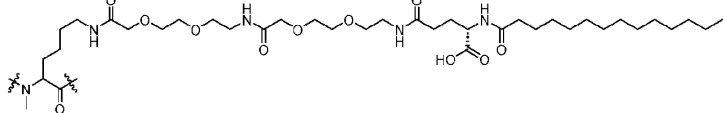
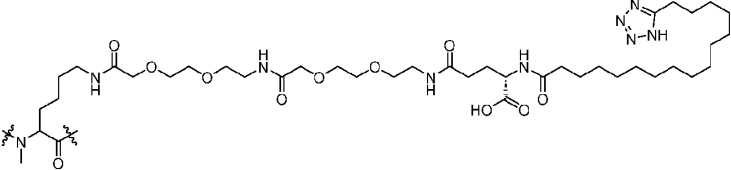
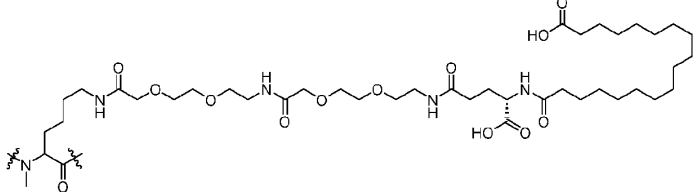
Abbreviation	Structure
Dap	 2,3-diaminopropionic acid
Dap(N3)	
diFCpx	
E(COcPEG3a)	
hE	
hK(Me)3 or hK(Me)3	
K(5cpa)	
K(a)	

Abbreviation	Structure
K(Ac)	
K(COCH2CH2)	
K(d)	
K(G)	
K(Me)3	
K(NMe)	
K(NMeAc)	

Abbreviation	Structure
K(NNs)	
K-Z _{lipid}	
K(PEG2PEG2gEC12)	
K(PEG2PEG2gEC14)	
K(PEG2PEG2gEC16tetrazole)	
K(PEG2PEG2gEC18OH)	
K(PEG2NMcPEG2NMegENMc C18OH)	
K(PEG2PEG2PgEC18OH)	

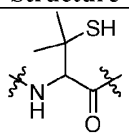
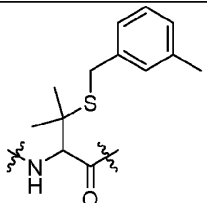
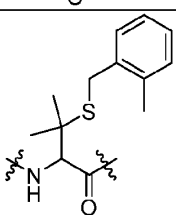
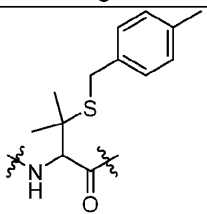
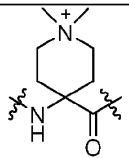
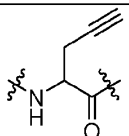
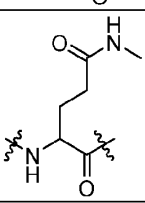
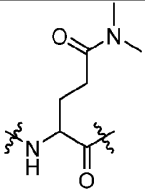
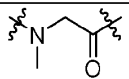
Abbreviation	Structure
K(PEG2PEG2gEC18tetrazole)	
K(PEG2NMcPEG2NMegENMcC18Tetrazole)	
K(PEG2PEG2gEC20OH)	
K(SP6PEG2gEC18OH)	
K(PEG2gEgEPEG24SBC16Tetrazole)	
K(PEG6gEC18OH)	
K(PEG12gEC18OH)	
K(PEG12NMegENMcC18OH)	

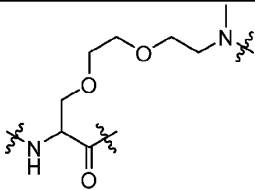
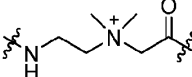
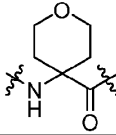
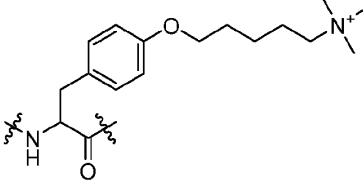
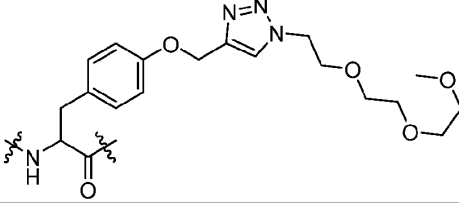
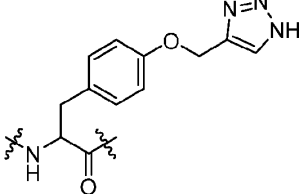
Abbreviation	Structure
K(PEG12NMe _g ENMe C18Tetrazole)	
K(PEG12gEC20OH)	
K-Z _{peg}	
K(cPEG3a)	
K(mPEG12)	
K(NMe)-Z _{lipid}	
K(NMe)-Z _{peg}	
K(NMecPEG3a)	

Abbreviation	Structure
K(NMePEG12)	
Lys(N+Me2)-Z _{lipid}	
Lys(N+Me2)-Z _{peg}	
Lys(N+Me2mPEG3)	
NMeK-Z _{lipid}	
NMeK(PEG2PEG2gEC12)	
NMeK(PEG2PEG2gEC14)	
NMeK(PEG2PEG2gEC16tetrazole)	
NMeK(PEG2PEG2gEC18OH)	

Abbreviation	Structure
NMeK(PEG2NMePEG2NMe gENMeC18OH)	
NMeK(PEG2PEG2PgEC18OH)	
NMeK(PEG2PEG2gE C18tetrazole)	
NMeK(PEG2NMePEG2NMe gENMeC18Tetrazole)	
NMeK(PEG2PEG2gEC20OH)	
NMeK(SP6PEG2gEC18OH)	
NMeK(PEG2gEgEPEG24SB C16Tetrazole)	
NMeK(PEG6gEC18OH)	

Abbreviation	Structure
NMeK(PEG12gEC18OH)	
NMeK(PEG12NMegENMe C18OH)	
NMeK(PEG12NMegENMe C18Tetrazole)	
NMeK(PEG12gEC20OH)	
NMeK-Z _{peg}	
MMoEF	
N(NMe)	
N(NMe2)	

Abbreviation	Structure
Pen	
Pen(mXyl)	
Pen(oXyl)	
Pen(pXyl)	
Pip(NMe2)	
Pra	
Q(NMe)	
Q(NMe2)	
Sar	

Abbreviation	Structure
Ser(MePEG2)	
SP6	
THP	
TMAPF	
Y(OTzl(mPEG3))	
Y(OTzl)	

Example 1: General Procedure for Solid-Phase Synthesis of Peptides

Peptides were chemically synthesized using optimized 9-fluorenylmethoxy carbonyl (Fmoc) solid phase peptide synthesis protocols. For C-terminal amides, Rink-amide MBHA resin or CTC resin which was then coupled to an amide after cleavage was used. The side chain protecting groups were as follows: D-Arg: Pbf; Thr, 6OH2Nal: O-tButyl; E: O-tButyl or OAll; Asn, Pen: Trityl; AEF: Boc; D-Lys: Fmoc; Lys(NMe): Alloc; Lys(Dde): Dde. For coupling, a two to five-fold excess of a solution containing Fmoc amino acid, HATU and DIEA (1:0.95:2) in DMF was added to swelled resin for 1 to 16 hours. Double coupling was employed when coupling 6OH2Nal, 6F2Nal, or other sterically hindered amino acids (i.e., the resin was treated with the amino acid and coupling reagents a second time to promote reaction completion). Fmoc

protecting group removal was achieved by treatment with a DMF, piperidine (4:1) solution for 30 min. The cycles were repeated until the full-length peptide is obtained.

- 5 Dde protecting group removal was achieved by treatment with a 3% hydrazine hydrate in DMF for 20 min (this process was repeated 3 times). Alloc and OAll protecting group removal was achieved by treatment with a mixture of PdTetrakis/NDMBA (1,3-Dimethylbarbituric acid)/phenylsilane (0.3:10:50 eq) in dry DCM under N₂ atmosphere for 30 min or in a mixture of PdTetrakis/ phenylsilane (0.1:10) in dry DCM under N₂ atmosphere for 15 min. The resin was then washed with DCM and cycle repeated 2 times.

Certain materials and reagents are listed below.

#	Materials	Coupling reagents	Reaction time	Note
1	Fmoc-Asp-OAll (2.0 eq.)	HATU (1.90 eq) and DIEA (4.0 eq)	1 h	
2	NH ₂ -3Pyra-Sar-CON(Me) ₂ (2 eq)	HATU (1.90 eq) and DIEA (4.0 eq)	2 h	
3	Fmoc-Lys(Dde)-OH (2.0 eq)	HATU (1.90 eq) and DIEA (4.0 eq)	2h	
4	Fmoc-Sar-OH (3.0 eq)	HATU (2.85 eq) and DIEA (6.0 eq)	1-2 h	
5	Fmoc-3Pyra-OH (2.0-3.0 eq)	HATU (1.90-2.85 eq) and DIEA (4.0-6.0 eq)	1-3 h	
6	Fmoc-Asn(Trt)-OH (3.0-5.0 eq)	HATU (2.85-4.75 eq) and DIEA (6.0-10 eq)	1-2 h	

7	Fmoc-Glu(OtBu)-OH (3.0-5.0 eq)	HATU (2.85-4.75 eq) and DIEA (6.0-10.0 eq)	1-2 h	
8	Fmoc-Q(N(Me) ₂)-OH (2.0 eq)	HATU (1.90 eq) and DIEA (4.0 eq)	1-2 h	
9	Fmoc-K(NMeAlloc)-OH (2.0 eq)	HATU (1.90 eq) and DIEA (4.0 eq)	1-3 h	
10	Fmoc-K(NMeAc)-OH (2.0-3.0 eq)	HATU (1.90-2.85 eq) and DIEA (4.0-6.0 eq)	1-2 h	
11	Fmoc-THP-OH (2.0-3.0 eq)	HATU (1.90-2.85 eq) and DIEA (4.0-6.0 eq)	2 h	
12	Fmoc-6OH ₂ Nal-OH (2.0-3.0 eq)	HATU (1.90-2.85 eq) and DIEA (4.0-6 eq)	2 h*2	Double coupling
13	Fmoc-6F ₂ Nal-OH (2.0 eq)	HATU (1.9 eq) and DIEA (4.0 eq)	2 h*2	Double coupling
13	Fmoc-6Br ₂ Nal-OH (2.0 eq)	HATU (1.9 eq) and DIEA (4.0 eq)	2 h*2	Double coupling
14	Fmoc-AEF(Boc)-OH (2.0-3.0 eq)	HATU (1.90-2.85 eq) and DIEA (4.0-6.0 eq)	1-2 h	
15	Fmoc-AEF(N(Me) ₂)-OH (2.0 eq)	HATU (1.90 eq) and DIEA (4.0 eq)	1-2 h	

16	Fmoc-AEF(Alloc)-OH (3.0 eq)	HATU (2.85 eq) and DIEA (6.0 eq)	1h	
17	Fmoc-Pen(Trt)-OH (2.0-3.0 eq)	HATU (1.90-2.85 eq) and DIEA (4.0-6.0 eq)	2 h	
18	Fmoc- K(Ac)-OH (2.0-3.0 eq)	HATU (1.90-2.85 eq) and DIEA (4.0-6 eq)	1-2 h	
19	Fmoc-7MeTrp-OH (2.0-3.0 eq)	HATU (1.90-2.85 eq) and DIEA (4.0-6.0 eq)	1-2 h	
20	Fmoc-7(3NAcPh)Trp-OH (2.0 eq)	HATU (1.90-2.85 eq) and DIEA (4.0-6 eq)	2h	
21	Fmoc-Thr(tBu)-OH (3.0-5.0 eq)	HATU (2.85-4.75 eq) and DIEA (6.0-10 eq)	1-2 h	
22	Fmoc-Asn(Trt)-OH (3.0 eq)	HATU (2.85 eq) and DIEA (6.0 eq)	2h	
23	Fmoc-N(N(Me)2)-OH (2.0 eq)	HATU (1.90 eq) and DIEA (4.0 eq)	1-2 h	
24	Fmoc-Glu(OAll)-OH (2.0 eq)	HATU (1.9 eq) and DIEA (4.0 eq)	2h	
25	Pd(PPh ₃) ₄ (0.1 eq), PhSiH ₃ (10 eq)	DCM	15min*3 times	De-OAll and De-Alloc

26	HATU (2.0 eq) and DIEA (4.0 eq)	DMF	1h	Cyclization resin
27	Fmoc-Pen(Trt)-OH (3.0 eq)	HATU (2.85 eq) and DIEA (6.0 eq)	2h	
28	Fmoc-d-Arg(Pbf)-OH (3.0 eq)	HATU (2.85 eq) and DIEA (6.0 eq)	2 h	
29	Dde-d-Lys(Fmoc)-OH (2.0 eq)	HATU (1.90 eq) and DIEA (4.0 eq)	1 h	
30	5cpa (2.0 eq)	HATU (1.90 eq) and DIEA (4.0 eq)	2 h	
31	cPEG3a (2.0 eq)	HATU (1.90 eq) and DIEA (4.0 eq)	2-3 h	
32	Fmoc-hk(Me) ₃ -OH (2.0 eq)	HATU (1.90 eq) and DIEA (4.0 eq)	2 h	
33	PEG2NMePEG2N MegENMeC18Tetraazole(2.0 eq)	HATU (1.9 eq) and DIEA (4.0 eq)	16 h	
34	PEG2PEG2gEC18 OH(2.0 eq)	DIC (2.0 eq) and HOAT (2.0 eq)	16 h	
35	10%Ac ₂ O /5%NMM /85%DMF	N/A	1 h	
36	ETFA(10 eq +10 eq)	DBU (15 eq) DMF	1 h*4 times and overnight	

37	3% hydrazine hydrate in DMF	N/A	20 min	3 times
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General procedure for cleavage of peptides off resin

Side chain deprotection and cleavage of the peptides was achieved by stirring the dry resin in a solution of trifluoroacetic acid, water, DTT and tri-isopropylsilane (90:2.5:5:2.5) for 3 hours. The mixture was then filtered and cold methyl tert-butyl ether (MTBE) was added to the combined filtrate to precipitate the peptide. The resulting mixture was centrifuged (3000 rpm, 3 min) and decanted. The pellet was washed with MTBE and centrifuged. The pellet was lyophilized to provide the linear peptide.

10 General procedure for cyclization

To effect cyclization of thiol-containing residues, iodine solution in MeOH (0.1M) was added to a solution of the linear peptide (20% MeCN/H₂O (1mmol/L)) drop-wise until a yellow color persisted. After about 2h, analysis by LCMS showed that the linear peptide was no longer present. The excess iodine was quenched by the addition of 1M Na₂S₂O₃ in water (turned colorless instantly).

General procedure for purification of peptides

Purification of the peptides was achieved using reverse-phase high performance liquid chromatography (RP-HPLC). Purification of the cyclized peptides was achieved using preparative RP-HPLC with a C18 column with a flow rate of 20-250 mL/min. Separation was achieved using gradients of buffer B in A (Buffer A: 0.075% TFA in water; Buffer B: ACN). (Note 1). Analysis was performed using a C18 column with a flow rate of 1 mL/min (Note 2).

Note 1: Preparative HPLC Methods

25 Prep. HPLC Method A: Description: Mobile Phase: 0.075% TFA in water (solvent A) and acetonitrile (solvent B) Column: Phenomenex Luna® C18, 250*100 mm, 10 µm, 120Å column; Flow Rate: 250 mL/min; Wavelength: UV 220nm&254nm; Oven Temp. Room temperature

30 Prep. HPLC Method B: Description: Mobile Phase: 0.5% AcOH in water (solvent A) and acetonitrile (solvent B) Column: Phenomenex Luna® C18, 250*100 mm, 10 µm, 120Å column; Flow Rate: 250 mL/min; Wavelength: UV 220nm&254nm; Oven Temp. Room temperature

Prep. HPLC Method C: Description: Mobile Phase: 0.075% TFA in water (solvent A) and acetonitrile (solvent B) Column: Luna 100*25 mm, C18, 10 μ m, 100Å + Gemini® 150*30 mm, C18, 5 μ m, 110Å column; Flow Rate: 20 mL/min; Wavelength: UV 220nm&254nm; Oven Temp. Room temperature

- 5 Prep. HPLC Method D: Description: Mobile Phase: 0.5% AcOH in water (solvent A) and acetonitrile (solvent B) Column: Luna 100*25 mm, C18, 10 μ m, 100Å + Gemini® 150*30 mm, C18, 5 μ m, 110Å column; Flow Rate: 20 mL/min; Wavelength: UV 220nm&254nm; Oven Temp. Room temperature

- 10 Prep. HPLC Method E: Description: Mobile Phase: 0.075% TFA in water (solvent A) and acetonitrile (solvent B) Column: Welch Ultimate XB-C18, 250*50 mm, 7 μ m, 120Å + Welch Xtimate C18, 250*50 mm, 10 μ m, 120Å column; Flow Rate: 80 mL/min; Wavelength: UV 220nm&254nm; Oven Temp. Room temperature

- 15 Prep. HPLC Method F: Description: Mobile Phase: 0.5% AcOH in water (solvent A) and acetonitrile (solvent B) Column: Welch Ultimate® XB-C18, 250*50 mm, 10 μ m, 120Å + Welch Xtimate® C18, 250*50 mm, 10 μ m, 120Å column; Flow Rate: 80 mL/min; Wavelength: UV 220nm&254nm; Oven Temp. Room temperature

- 20 Prep. HPLC Method G: Description: Mobile Phase: 0.075% TFA in water (solvent A) and acetonitrile (solvent B) Column: Luna C18, 200*25 mm, 10 μ m, 100Å + Gemini C18, 150*30 mm, 5 μ m, 110Å column; Flow Rate: 20 mL/min; Wavelength: UV 220nm&254nm; Oven Temp. Room temperature

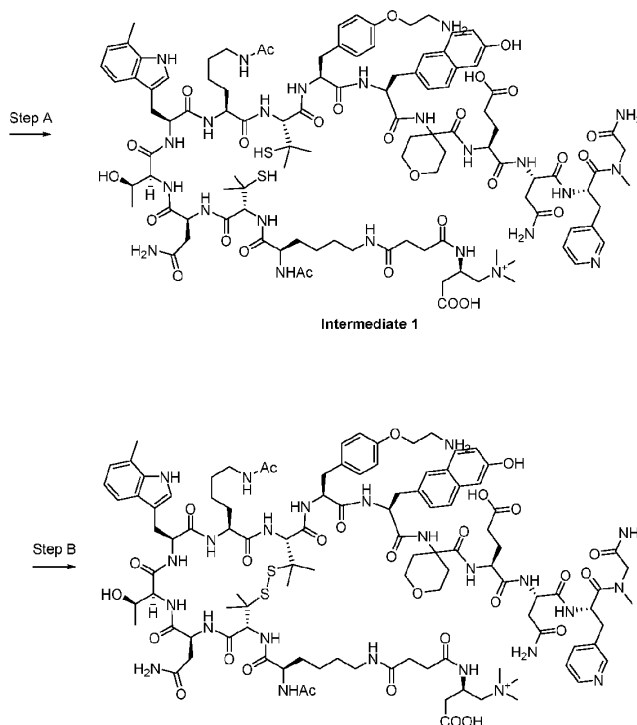
Prep. HPLC Method H: Description: Mobile Phase: 0.075% TFA in water (solvent A) and acetonitrile (solvent B) Column: YMC-Actus Triart C18, 250*30 mm, 5 μ m, 120Å column; Flow Rate: 20 mL/min; Wavelength: UV 220nm&254nm; Oven Temp. Room temperature

- 25 Prep. HPLC Method I: Description: Mobile Phase: 0.075% TFA in water (solvent A) and acetonitrile (solvent B) Column: Luna 8 cm*250 mm, C18, 5 μ m, 100Å column; Flow Rate: 150 mL/min; Wavelength: UV 220nm&254nm; Oven Temp. Room temperature

Note 2: Analytical HPLC Method:

- 30 Mobile Phase: 0.1% TFA in water (solvent A) and 0.1%TFA in acetonitrile (solvent B), using the elution gradient 10%-80% (solvent B) over 0.9 minutes and using the elution gradient 80%-90% for 0.6 minutes at a flow rate of 1.0 ml/min; Column: Xbridge C18,3.5 μ m,2.1*30mm; Wavelength: UV 220nm&254nm; Column temperature: 30°C; MS ionization: ESI

Example 2: Synthesis of SEQ ID NO: 349 – MeCO-k(d)-Pen(3)-N-T-7MeW-K(Ac)-Pen(3)-AEF-6OH2Nal-THP-E-N-3Pya-Sar-CONH2



5 MeCO-k(d)-Pen(3)-N-T-7MeW-K(Ac)-Pen(3)-AEF-6OH2Nal-THP-E-N-3Pya-Sar-CONH2
SEQ ID NO: 349

Step A – Synthesis of Intermediate 1: The peptide was synthesized by Solid-phase Peptide Synthesis (SPPS) using Fmoc/t-Bu chemistry. The assembly was performed on a Rink-amide AM resin (220 μmol , 100-200 Mesh; loading 0.35 mmol/g) on the CEM Liberty Blue microwave peptide synthesizer (CEM Inc.). During peptide assembly on solid phase, the side chain protecting groups were: tert-butyl for Thr and Glu; trityl for Pen and Asn; tert-butoxycarbonyl for AEF. The D-Lys at position X₃ was protected by the orthogonal Dde protecting group.

All the amino acids were dissolved at a 0.4 M concentration in DMF. The acylation reactions were performed for 3 min at 90°C under MW irradiation with 5 fold excess of activated amino acids over the resin free amino groups. The amino acids were activated with equimolar amounts of 0.5 M solution of DIC in DMF and Oxyma solution 1 M in DMF. Double acylation reactions were performed for 3Pya at X₁₅. Manual coupling was performed for 6OH2Nal at X₁₁ using DIC-HOAT (3eq, 1:1:1) at room temperature. Fmoc deprotections were

performed using 20% (V/V) piperidine in DMF. Capping of the free amino group was performed manually using 10 eq of acetic anhydride in DMF.

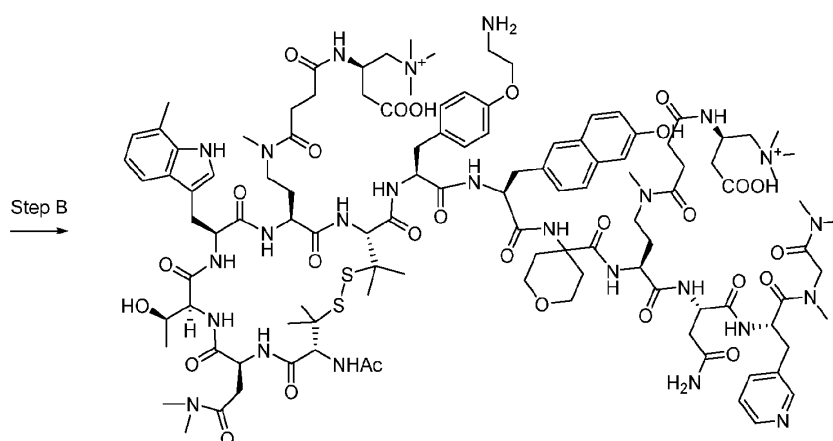
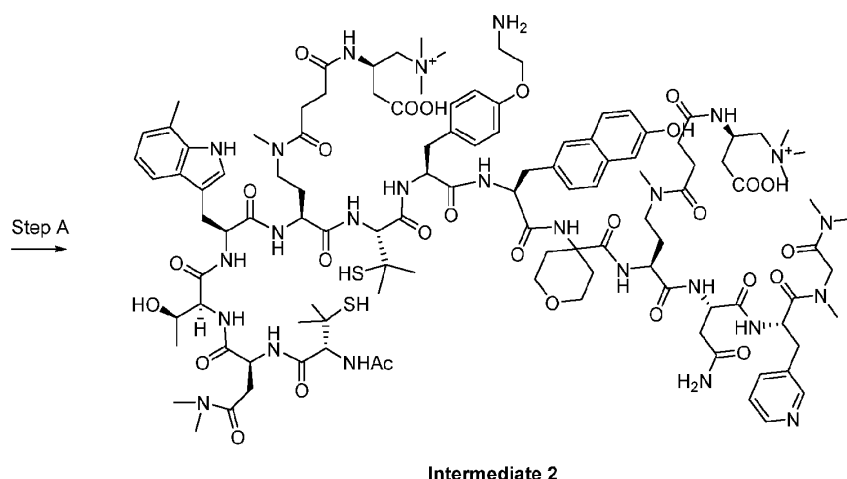
At the end of the peptide assembly on solid phase, the resin was treated with 100 ml of 3% hydrazine solution in DMF. The solution was drained, and the resin washed with DCM (3 × 5 mL) and DMF (5 × 5 mL). Carnitine-succinate ((3eq, d) was coupled to the lysine residue at the X₃ position using HATU/DIPEA (1:1:2) at room temperature.

At the end of the assembly the resin was washed with DMF, MeOH, DCM, Et₂O. The peptide was cleaved from solid support using 30 ml of TFA solution (v/v) (87.5% TFA, 5% H₂O, 2.5% TIPS, 5%Phenol) for approximately 1.5 hours, at room temperature. The resin was then filtered and the filtrate was triturated in cold MTBE (135mL). After centrifugation, the peptide pellets were washed with fresh cold diethyl ether. The process was repeated twice. Final pellets were dried, resuspended in H₂O and acetonitrile 1:1 + 0.1% TFA and stirred overnight. The suspension was then lyophilized to afford intermediate 1 (Yield = 88%). LCMS anal. calc. For C₁₀₇H₁₅₃N₂₄O₂₈S²⁺: 2287.66Da; found; 1144.6 (M+2)²⁺

Step B – Synthesis of SEQ ID NO: 349: MeCO-k(d)-Pen(3)-N-T-7MeW-K(Ac)-Pen(3)-AEF-6OH2Nal-THP-E-N-3Pyra-Sar-CONH2:

Intermediate 1 was dissolved in ACN/H₂O (5mg/ml). Saturated iodine in acetic acid was then added dropwise to the solution while stirring until yellow color persisted. The reaction was completed in 20 min (as monitored by UPLC-MS). Solid ascorbic acid was added until the solution became clear. After lyophilization the cyclized peptide was purified by reverse-phase HPLC using preparative Waters DeltaPak C4 (200x40mm, 300Å, 15µm). Mobile phase A: + 0.1% TFA, mobile phase B: Acetonitrile (ACN) + 0.1% TFA. The following gradient of eluent B was used: 10%B to 10%B over 5min, to 25%B over 25min, flow rate 80 mL/min, wavelength 214 nm. The collected fractions were lyophilized to afford SEQ ID NO: 349: MeCO-k(d)-Pen(3)-N-T-7MeW-K(Ac)-Pen(3)-AEF-6OH2Nal-THP-E-N-3Pyra-Sar-CONH2 (Yield= 31%) LCMS anal. calc. For C₁₀₇H₁₅₁N₂₄O₂₈S₂⁺: 2285.64Da; found; 1143.3 (M+2)²⁺

Example 3: Synthesis of SEQ ID NO: 339 – MeCO-Pen(3)-N(N(Me)₂)-T-7MeW-Dab(NMecarn)-Pen(3)-AEF-6OH2Nal-THP- Dab(NMecarn)-N-3Pyra-Sar-CON(Me)₂



MeCO-Pen(3)-N(N(Me)₂)-T-7MeW-Dab(NMecarn)-Pen(3)-AEF-6OH₂Nal-THP-Dab(NMecarn)-N-3Pya-Sar-CON(Me)₂

SEQ ID NO: 339

- 5 Step A – Synthesis of Intermediate 2: The peptide was synthesized by Solid-phase Peptide Synthesis (SPPS) using Fmoc/t-Bu chemistry. The assembly was performed on a Rink-amide AM resin (220 μmol, 100-200 Mesh; loading 0.35 mmol/g). The first amino acid was loaded manually using an equimolar solution of Fmoc-Asp-OAll, HOAt and DIC in DMF, at room temperature. Complete acylation was monitored by ninhydrin test. The resin was then
- 10 treated with 0.25 eq of Pd Tetrakis, 24 eq of phenylsilane in 5ml of dry DCM under N₂ atmosphere for 30 min (process repeated 2 times); washed with DCM, DMF, and a solution of 0.5% sodium dimethyldithiocarbamate (0.5%) and DIPEA (0.5%) in DMF. Fmoc-OSu and DIPEA (1:1, 2 eq) in DCM were added and stirred at room temperature for 30 minutes. Further peptide elongation was performed by manually pre-activating the resin with HATU (1.2 eq),

DIPEA (2.2 eq) and then adding a solution of DIPEA (2.2 eq) and 3PyA-Sar-CON(Me)₂ dimer (2.2 eq in DMF. The reaction mixture was stirred for 1 h at room temperature. Complete acylation was monitored by test cleavage. The resin was then placed in a microwave reaction vessel and the assembly was continued on the CEM Liberty Blue microwave peptide synthesizer (CEM Inc.). During peptide assembly on solid phase, the side chain protecting groups were: tert-butyl for Thr and Glu; trityl for Pen and Asn. All the amino acids were dissolved at a 0.4 M concentration in DMF. The acylation reactions were performed for 3 min at 90°C under MW irradiation with 5 folds excess of activated amino acids over the resin free amino groups. The amino acids were activated with equimolar amounts of 0.5 M solution of DIC in DMF and Oxyma solution 1M in DMF. Double acylation reactions were performed for 3PyA at X₁₅. 6OH2Nal at X₁₁, DabNMeAlloc at X₈ and DabNMeAlloc at X₁₃ were coupled manually using DIC-HOAT (3 eq, 1:1:1) at room temperature and complete acylation was monitored by ninhydrin test. Fmoc deprotections were performed using 20% (V/V) piperidine in DMF. Capping of the free amino group was performed manually using 10eq of acetic anhydride in DMF.

The resin was then treated with 0.3 eq of Pd Tetrakis, 50 eq of phenylsilane and 10 eq of barbituric acid in 5 ml of dry DCM under N₂ atmosphere for 20 min (process repeated 2 times); washed with DCM, DMF, and a solution of sodium dimethyldithiocarbamate (0.5%) and DIPEA (0.5%) in DMF. Further side chain derivatization was performed manually using HATU (4 eq), DIPEA (8 eq) and then adding 4 eq of carnitine-succinate. The reaction was complete after 1 h.

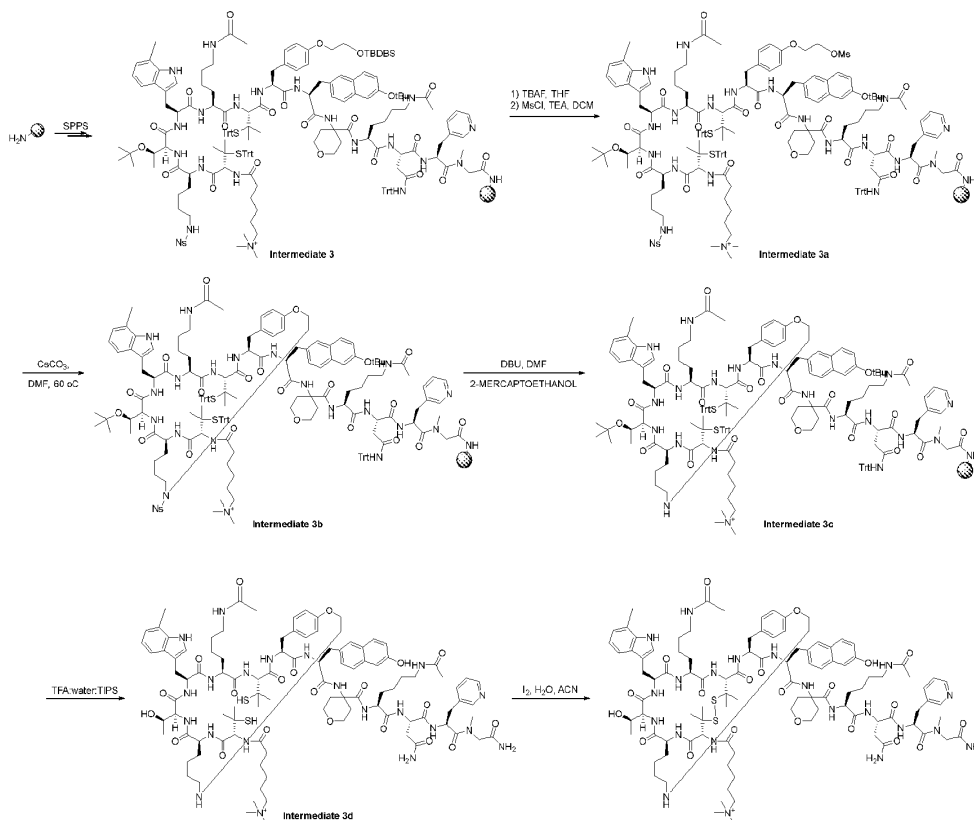
At the end of the assembly, the resin was washed with DMF, MeOH, DCM, and Et₂O. The peptide was cleaved from solid support using 30 ml of TFA solution (v/v) (87.5% TFA, 5% H₂O, 2.5% TIPS, 5% phenol) for approximately 1.5 hours, at room temperature. The resin was then filtered and the filtrate was triturated in cold MTBE (135mL). After centrifugation, the peptide pellets were washed with cold diethyl ether. The process was repeated twice. Final pellets were dried, resuspended in H₂O and acetonitrile 1:1 + 0.1% TFA and stirred overnight. The suspension was then lyophilized to afford the desired linear Intermediate 2 (Yield= 78%). LCMS anal. calc. For C₁₁₃H₁₆₇N₂₅O₂₈S₂⁺: 2387.84Da; found; 1193.7 (M+2)²⁺

Step B – Synthesis of MeCO-Pen(3)-N(N(Me)₂)-T-7MeW-Dab(NMecarn)-Pen(3)-AEF-6OH2Nal-THP- Dab(NMecarn)-N-3PyA-Sar-CON(Me)₂ SEQ ID NO: 339: The peptide (Intermediate 2) was dissolved in ACN\H₂O (5mg\ml). Saturated iodine in acetic acid was then added dropwise to the solution while stirring until yellow color persisted. The reaction was complete in 30 min (monitored by UPLC-MS). Solid ascorbic acid was added until the solution became clear. After lyophilization, the cyclized peptide was purified by reverse-phase HPLC using preparative Waters DeltaPak C4 (200x40mm, 300Å, 15µm). Mobile phase A: + 0.1%

TFA, mobile phase B: Acetonitrile (ACN) + 0.1% TFA. The following gradient of eluent B was used: 10%B to 10%B over 5min, to 25%B over 25min, flow rate 80 mL/min, wavelength 214 nm. Collected fractions were lyophilized to afford SEQ ID NO: 339 (Yield= 23%) LCMS anal. calc. For $C_{113}H_{165}N_{25}O_{28}S_2^+$: 2384.17; found; 1192.5 (M+2)²⁺

5

Example 4: Synthesis of SEQ ID NO: 112 – 5cpaCO-Pen(3)-K(5)-T-7MeW-K(Ac)-Pen(3)-AEF(5)-6OH2Nal-THP-K(Ac)-N-3Pya-Sar-CONH2



5cpaCO-Pen(3)-K(5)-T-7MeW-K(Ac)-Pen(3)-AEF(5)-6OH2Nal-THP-K(Ac)-N-3Pya-Sar-CONH2

10

SEQ ID NO: 112

Step A – Synthesis of Intermediate 3: The synthesis was performed using Fmoc-protected amino acids on a solid-phase Rink amide MBHA resin (Novabiochem, 0.42 mmol/g, 100-200 mesh) with a CEM Liberty Blue automated microwave peptide synthesizer. The peptide was synthesized on a 0.25 mmol scale. Typical reaction conditions were as follows:

15

Deprotection Conditions: Fmoc deprotection was carried out using 20% piperidine in DMF (10 mL) under microwave conditions (90 °C, 1 min).

Residue Coupling Conditions: Fmoc-protected amino acid (5 mL of a 0.2 M amino acid stock solution in DMF, 1 mmol) was delivered to the resin, followed by DIC (2.041 mL, 0.5 M, 1 mmol) and ethyl (hydroxyimino)cyanoacetate (1 mL, 1 M, 1 mmol) at 90 °C for 3.5 min. Double couplings were used for 3PyA, THP and Thr and for residues incorporated after THP and Thr (6OH2Nal and K(NNs)). Residue Y(OEtOTBDMS) and 5cpa were coupled using manual coupling conditions: the mixture of Fmoc-protected amino acid (0.75 mmol), HATU (0.75 mmol) and 4-methylmorpholine (1.5 mmol) in DMF (8 mL) was added to the resin (0.25 mmol) and then mixed for 2 hours at room temperature. At the end of the assembly, the peptide resin intermediate 3 was washed with DCM.

10 Step B –Synthesis of Intermediate 3a: Intermediate 3 (0.25 mmol) was swelled in THF (8 mL) for 15 min, then TBAF (2.5 mL, 1 M in THF, 2.5 mmol) was added. The reaction was mixed at room temperature for 1 hr. The resin was then drained, washed with DMF (8 mL, 3 times) and DCM (8 mL, 3 times). To the resulting resin in DCM (20 mL) was added TEA (0.523 mL, 0.728 g/mL, 3.75 mmol) in DCM (5 mL) and then followed by the slow addition of solution
15 of methanesulfonyl chloride (0.195 mL, 1.48 g/mL, 2.5 mmol) in DCM (5 mL). The reaction was mixed at room temperature for 1 hr, then drained and washed with DCM (3 x). Microcleavage of the resin with TFA showed the desired product. LCMS anal. calc. for $C_{109}H_{155}N_{22}O_{28}S_4$ 2349.824; found: 784 (M+3)²⁺

20 Step C –Synthesis of Intermediate 3b: Intermediate 3a (0.25 mmol) was swelled in DMF (10 mL) for 15 min, then was added to a saturated solution of Cs₂CO₃ in DMF (200 mL). The reaction mixture was heated at 68 °C for 1 hr. The resin was then cooled to room temperature, drained, washed with water (3 x), DMF (3 x) and DCM (3 x). Microcleavage of the resin with TFA showed the desired product. LCMS anal. calc. for $C_{108}H_{151}N_{22}O_{25}S_3^+$ 2252.03, found: 752 (M+3)³⁺

25 Step D –Synthesis of Intermediate 3c: To intermediate 3b (0.5 mmol) in DMF (20 mL) was added a solution of 1,8-diazabicyclo[5.4.0]undec-7-ene (373.5 µL, 1.019 g/mL, 2.5 mmol) in DMF (3 mL), followed by 2-mercaptoethanol (350.7 µL, 1.114 g/mL, 5 mmol) in DMF (3 mL). The reaction mixture was mixed for 20 min. The resin was washed with DCM and DMF. The procedure was repeated once more. Microcleavage of the resin with TFA showed the
30 desired product. The resin was washed with DMF, MeOH, and DCM. LCMS anal. calc. for $C_{102}H_{148}N_{21}O_{21}S_2^+$ 2067.06, found: 689.9 (M+3)³⁺

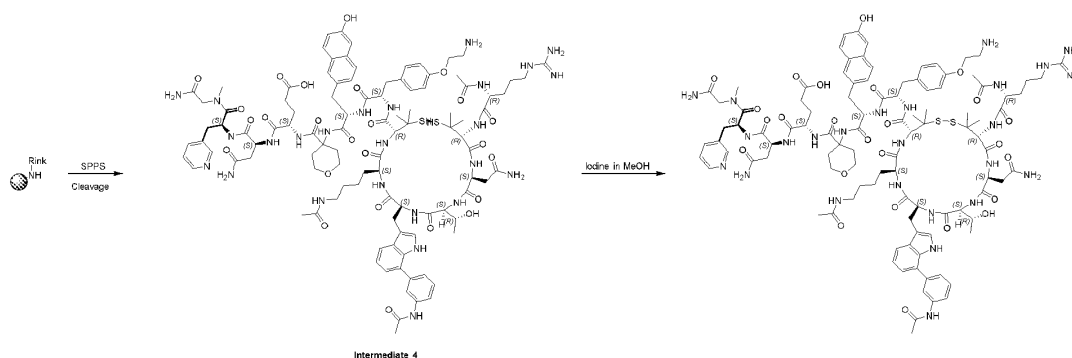
Step E –Synthesis of Intermediate 3d: Intermediate 3c (0.15 mmol) was treated with a solution of TFA/H₂O/TIPS 92.5/5/2.5 for 30 mins at 42 °C on a CEM Razor cleavage station. The mixture was then concentrated and added to cold methyl-*t*-butyl ether in order to precipitate
35 the peptide. After centrifugation, the peptide pellets were washed with fresh cold methyl-*t*-butyl

ether. This process was repeated twice. Final pellets were dried, resuspended in H₂O and acetonitrile, then lyophilized to afford the desired protected intermediate 3d as a light yellow solid. LCMS anal. calc. for C₁₀₂H₁₄₈N₂₁O₂₁S₂⁺: 2067.06; found: 1034.3 (M+2)²⁺

Step E – Synthesis of SEQ ID NO: 112: Intermediate 3d was dissolved in 40%

- 5 ACN/water (50 mL). Iodine in methanol (0.1 M) was then added drop wise with stirring until a yellow color persisted. The reaction was monitored with UPLC-MS. When the reaction was complete, solid ascorbic acid was added until the solution became clear. The solvent mixture was then lyophilized, and the resulting material was then dissolved in DMSO and was purified by C18 reverse-phase HPLC (Waters XBridge OBD C18, 50x150 mm, 5 μm, 130Å), using as
10 eluents (A) 0.1% TFA in water and (B) 0.1% TFA in acetonitrile, gradient began with 15% B, and changed to 30% B over 25 minutes at a flow rate of 80ml/min). Fractions containing pure product were collected and then freeze-dried to afford the desired product as a white powder. LCMS anal. Calcd. C₁₀₂H₁₄₆N₂₁O₂₁S₂⁺: 2065.04 found: 1033.3 (M+2)²⁺

15 **Example 5: Synthesis of SEQ ID NO: 287 – MeCO-r-Pen(3)-N-T-7(3NAcPh)W-K(Ac)-Pen(3)-AEF-6OH2Nal-THP-E-N-3Pya-Sar-CONH2**



MeCO-r-Pen(3)-N-T-7(3NAcPh)W-K(Ac)-Pen(3)-AEF-6OH2Nal-THP-E-N-3Pya-Sar-CONH2

20

SEQ ID NO: 287

- Step A – Synthesis of Intermediate 4: The peptide was synthesized by solid-phase peptide synthesis using Fmoc chemistry. DMF was added to a vessel containing Rink Amide MBHA Resin (2.0 mmol, 6.0 g, sub: 0.33 mmol/g), and the resin was allowed to swell for 2 hours. Then, 20% piperidine/DMF was added to the resin and mixed for 30 minutes. The
25 mixture was drained and washed five times with DMF (for 30 seconds each). Fmoc-amino acid solution was then added to the resin and mixed for 30 seconds before the addition of activation buffer. The amino acid was allowed to react with the resin for 1-4 hours under N₂. Then, 20% piperidine/DMF was added and mixed for 30 min. The procedure was repeated for subsequent

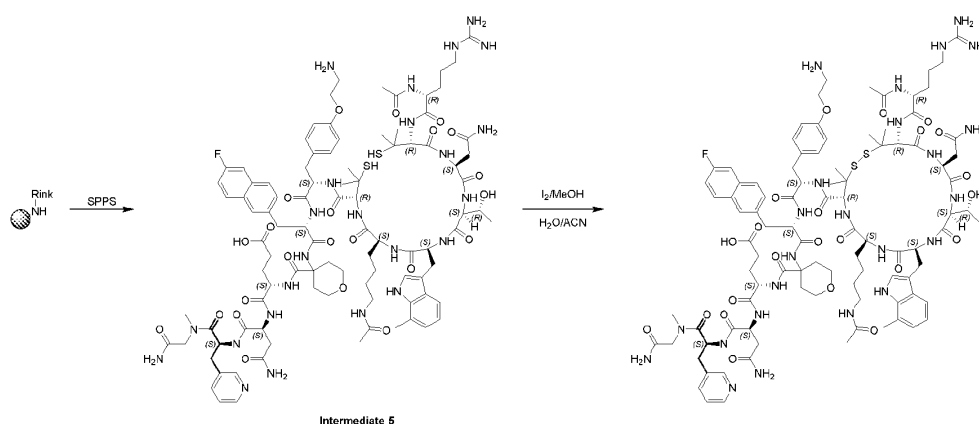
amino acid coupling(s). Coupling reactions were monitored by ninhydrin (A: 5% ninhydrin /EtOH; B: 80% phenol /EtOH; C: pyridine) or tetrachlor (A: 2% tetrachlor/ DMF; B: 2% aldehyde/ DMF 110°C for 3min) color test. Subsequently, the resin was washed with DMF 5 times, and then with MeOH 3 times before drying under vacuum.

- 5 To cleave the peptide from the resin, 120 mL of cleavage buffer (5.0% DTT /2.5% H₂O /2.5% TIS /90%TFA) was added to the flask containing the side chain protected peptide on resin at room temperature, and the solution was stirred for 3 hrs. The mixture was then filtered and washed with 5 mL TFA. The combined filtrate was triturated with cold methyl tertbutyl ether (MTBE). The mixture was centrifuged (3000 rpm, 3 min) and decanted. The pellet was washed
10 with MTBE and centrifuged. The residue was lyophilized to give Intermediate 4 (3.6 g).

- Step B – Peptide cyclization and purification: Intermediate 4 (3.6 g, 1.6 mmol) was dissolved in 20% MeCN /H₂O (2000 mL). To a stirred solution of the peptide was added iodine in MeOH (0.1M, 12.0 mL) drop-wise until the color of the solution remained yellow. After ~2h, LCMS showed the reaction was complete. Excess iodine was quenched by the addition of 1M
15 Na₂S₂O₃ in water (15 uL) (turned colorless instantly). MeCN (10-20 mL) was then added to reduce turbidity. The solution was purified by Prep-HPLC (A: 0.075% TFA in H₂O, B: ACN) (Note 1: Method A) and Prep-HPLC (A: 0.5% AcOH in H₂O, B: ACN) (Note 1: Method B) to give SEQ ID NO: 287 (1117.4 mg, 90.8% purity, 26.0% yield for this step; over all yield: 21.4%) obtained as white solid. Analysis was performed using a C18 column with a flow rate of
20 1 mL/min (Note 2).

LCMS Summary: calculated MW: 2189.47, observed MW: 1095.5 (M+2H)²⁺.

- Example 6: Synthesis of SEQ ID NO: 407 – MeCO-r-Pen(3)-N-T-7MeW-K(Ac)-Pen(3)-**
25 **AEF-6F2NaI-THP-E-N-3Pyra-Sar-CONH₂**



MeCO-r-Pen(3)-N-T-7MeW-K(Ac)-Pen(3)-AEF-6F2Nal-THP-E-N-3Pya-Sar-CONH₂

SEQ ID NO: 407

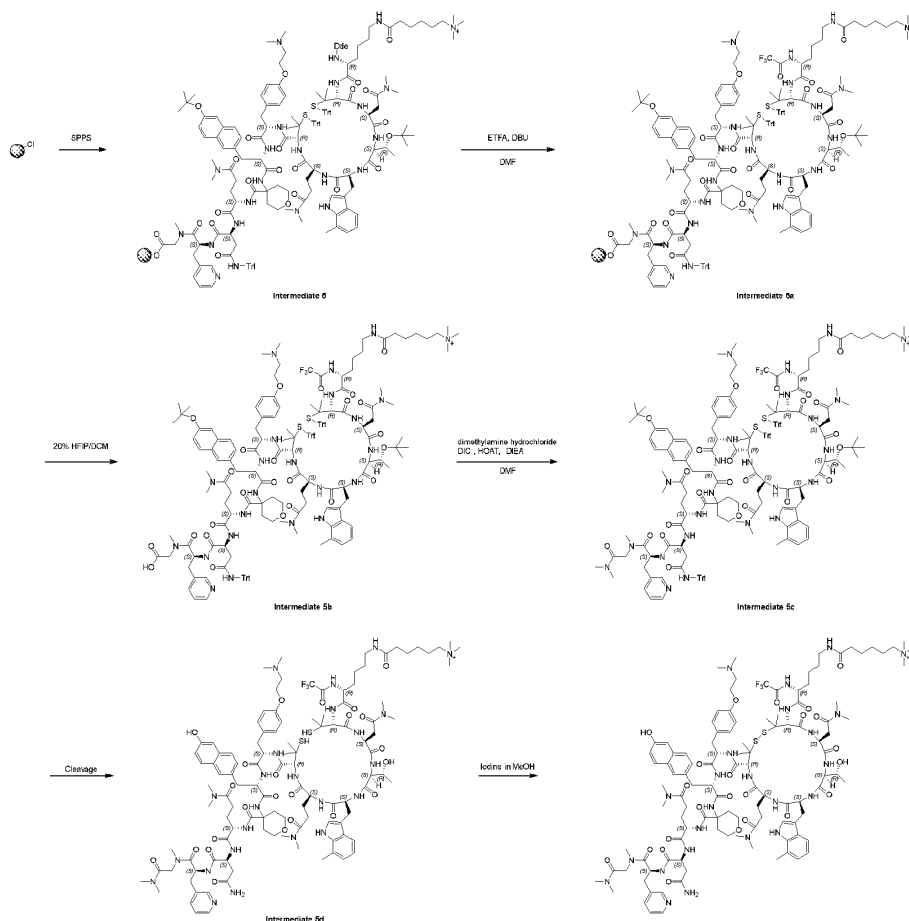
Step A – Synthesis of Intermediate 5: The peptide was synthesized by solid-phase peptide synthesis using Fmoc chemistry. DMF was added to a vessel containing MBHA Resin (0.20 mmol, 0.64 g, sub: 0.31 mmol/g), and the resin was allowed to swell for 2 hours. Then, 20% piperidine/DMF was added to the resin and mixed for 30 minutes. The mixture was drained and washed five times with DMF (for 30 seconds each). Fmoc-amino acid solution was then added to the resin and mixed for 30 seconds before the addition of activation buffer. The amino acid was allowed to react with the resin for 1-4 hours under N₂. Then, 20% piperidine/DMF was added and mixed for 30 min. The procedure was repeated for subsequent amino acid coupling(s). Coupling reactions were monitored by ninhydrin (A: 5% ninhydrin /EtOH; B: 80% phenol /EtOH; C: pyridine) or tetrachlor (A: 2% tetrachlor/ DMF; B: 2% aldehyde/ DMF 110°C for 3min) color test. Subsequently, the resin was washed with DMF 5 times, and then with MeOH 3 times before drying under vacuum.

To cleave the peptide from the resin, 12 mL of cleavage buffer (5.0% DTT /2.5% H₂O /2.5% TIS /90%TFA) was added to the flask containing the side chain protected peptide on resin at room temperature, and the solution was stirred for 3 hrs. The mixture was then filtered and washed with 5 mL TFA. The combined filtrate was triturated with cold methyl tertbutyl ether (MTBE). The mixture was centrifuged (3000 rpm, 3 min) and decanted. The pellet was washed with MTBE and centrifuged. The residue was lyophilized to give Intermediate 5 (350 mg).

Step B – Peptide cyclization and purification: Intermediate 5 (350 mg, 0.17 mmol) was dissolved in 20% MeCN /H₂O (200 mL). To a stirred solution of the peptide was added iodine in MeOH (0.1M, 0.8 mL) drop-wise until the color of the solution remained yellow. After ~2h LCMS showed the reaction was complete. Excess iodine was quenched by the addition of 1M Na₂S₂O₃ in water (15 uL) (turned colorless instantly). MeCN (10-20 mL) was then added to reduce turbidity. The solution was purified by Prep-HPLC (A: 0.075% TFA in H₂O, B: ACN) (Note 1: Method C) and repurified by Prep-HPLC (A: 0.5% AcOH in H₂O, B: ACN) (Note 1: Method D), then the product was lyophilized with 0.1% TFA mobile phase to give SEQ ID NO: 407 (92.8 mg, 97.0% purity, 22.1% yield for this step; over all yield: 18.6%) obtained as white solid.

Analysis was performed using a C18 column with a flow rate of 1 mL/min (Note 2).
LCMS Summary: calculated MW: 2072.3, observed MW: 1036.9 (M+2H)²⁺, 691.8 (M+3H)³⁺

Example 7: Synthesis of SEQ ID NO: 405 – CF₃CO-k(5cpa)-Pen(3)-N(N(Me)₂)-T-7MeW-Q(N(Me)₂)-Pen(3)-AEF(N(Me)₂)-6OH₂Nal-THP-Q(N(Me)₂)-N-3Pya-Sar-CON(Me)₂



5 CF₃CO-k(5cpa)-Pen(3)-N(N(Me)₂)-T-7MeW-Q(N(Me)₂)-Pen(3)-AEF(N(Me)₂)-6OH₂Nal-THP-Q(N(Me)₂)-N-3Pya-Sar-CON(Me)₂
SEQ ID NO: 405

Step A – Synthesis of Intermediate 6: The peptide was synthesized by solid-phase peptide synthesis using Fmoc chemistry. DMF was added to a vessel containing Sar-CTC Resin (0.50 mmol, 1.6 g, sub: 0.31 mmol/g), and the resin was allowed to swell for 2 hours. Then, 20% piperidine/DMF was added to the resin and mixed for 30 minutes. The mixture was drained and washed five times with DMF (for 30 seconds each). Fmoc-amino acid solution was then added to the resin and mixed for 30 seconds before the addition of activation buffer. The amino acid was allowed to react with the resin for 1-4 hours under N₂. Then, 20% piperidine/DMF was added and mixed for 30 min. The procedure was repeated for subsequent amino acid coupling(s). Coupling reactions were monitored by ninhydrin (A: 5% ninhydrin /EtOH; B: 80% phenol

/EtOH; C: pyridine) or tetrachlor (A: 2% tetrachlor/ DMF; B: 2% aldehyde/ DMF 110°C for 3min) color test. Subsequently, the resin was washed with DMF 5 times, and then with MeOH 3 times before drying under vacuum.

To cleave the peptide from the resin, 80 mL of cleavage buffer (20% HFIP /DCM) was added to the resin and stirred for 30 minutes. The mixture was then concentrated under reduced pressure. The peptide was dissolved in ACN/water and lyophilized overnight to give Intermediate 5b (1.2 g).

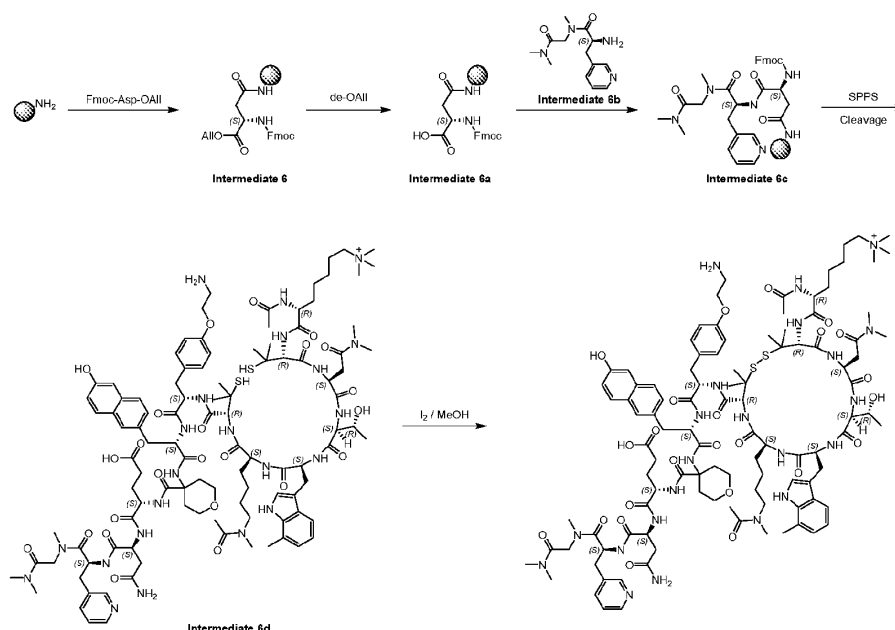
Step B – Preparation of Intermediate 6c: To a solution of Intermediate 6b (1.2 g, 0.40 mmol) in DMF (10.0 mL) was added dimethylamine hydrochloride (65.2 mg, 2.00 eq), DIC (123 uL, 2.00 eq), HOAT (108 mg, 2.00 eq) and DIEA (136 uL, 2.00 eq). The mixture was stirred at 25 °C for 1 h. The reaction was monitored by LCMS. Because LCMS showed the starting material didn't react completely, one additional equivalent of each of dimethylamine hydrochloride, DIC, HOAT and DIEA was added, and the reaction allowed to continue for 16 h. Afterward, LCMS showed the starting material was consumed. The filtrate was triturated with cold methyl tertbutyl ether (MTBE) (50 mL) and centrifuged (3000 rpm, 3 min) to give an oily liquid. The ether was dried with nitrogen to afford Intermediate 5c.

Step C – Preparation of Intermediate 6d: To a flask containing the side chain-protected peptide at room temperature was added 35 mL cleavage buffer (5.0% DTT/ 2.5% H₂O/ 2.5% TIS/ 90% TFA) at room temperature. The mixture was stirred for 3 hours. The mixture was then filtered and washed with 5 mL TFA. The combined filtrate was triturated with cold methyl tertbutyl ether (MTBE). The mixture was centrifuged (3000 rpm, 3 min) and decanted. The pellet was washed with MTBE and centrifuged. The residue was lyophilized to give Intermediate 5d (600 mg).

Step D – Synthesis of SEQ ID NO: 405: Intermediate 6d (600 mg, 0.255 mmol) was dissolved in 20% MeCN/H₂O (500 mL). To a stirred solution of the peptide was added iodine in MeOH (0.1M, 3.5 mL) drop-wise until the color of the solution remained yellow. After ~2h LCMS showed the reaction was complete. Excess iodine was quenched by the addition of 1M Na₂S₂O₃ in water (15 uL) (turned colorless instantly). MeCN (10-20 mL) was added to reduce turbidity. The solution was purified by Prep-HPLC (A: 0.075% TFA in H₂O, B: ACN) (Note 1: Method C) to give SEQ ID NO: 405 (99 mg, 93.43% purity, 13.4% yield for this step; over all yield: 6.87%) obtained as white solid.

Analysis was performed using a C18 column with a flow rate of 1 mL/min (Note 2). LCMS Summary: calculated MW: 2349.76, observed MW: 784.0 [(M+3H)/3].

Example 8: Synthesis of SEQ ID NO: 389 – MeCO-hk(Me)₃-Pen(3)-N(N(Me)₂)-T-7MeW-K(NMeAc)-Pen(3)-AEF-6OH₂Nal-THP-E-N-3Pyra-Sar-CON(Me)₂



MeCO-hk(Me)₃-Pen(3)-N(N(Me)₂)-T-7MeW-K(NMeAc)-Pen(3)-AEF-6OH₂Nal-THP-E-N-

5

3Pyra-Sar-CON(Me)₂

SEQ ID NO: 389

Step A – Synthesis of Intermediate 6d: The peptide was synthesized by solid-phase peptide synthesis using Fmoc chemistry. DMF was added to a vessel containing Rink Amide MBHA resin (1.0 mmol, 3.33 g, sub: 0.3 mmol/g), and the resin was allowed to swell for 2 hours. Then, 20% piperidine/DMF was added to the resin and mixed for 30 minutes. The mixture was drained and washed five times with DMF (for 30 seconds each). Fmoc-amino acid solution was then added to the resin and mixed for 30 seconds before the addition of activation buffer. The amino acid was allowed to react with the resin for 1-4 hours under N₂. Then, 20% piperidine/DMF was added and mixed for 30 min. The procedure was repeated for subsequent amino acid coupling(s). Coupling reactions were monitored by ninhydrin (A: 5% ninhydrin /EtOH; B: 80% phenol /EtOH; C: pyridine) or tetrachlor (A: 2% tetrachlor/ DMF; B: 2% aldehyde/ DMF 110°C for 3min) color test. Subsequently, the resin was washed with DMF 5 times, and then with MeOH 3 times before drying under vacuum.

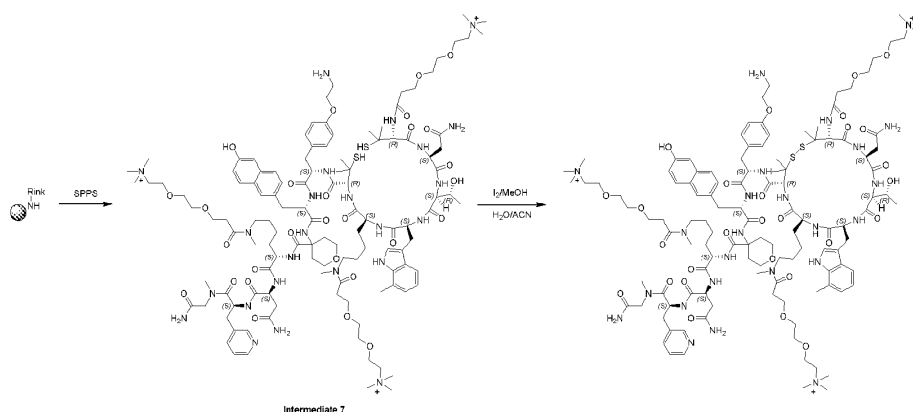
To cleave the peptide from the resin, 60 mL of cleavage buffer (5.0% DTT /2.5% H₂O /2.5% TIS /90%TFA) was added to the flask containing the side chain protected peptide on resin at room temperature, and the solution was stirred for 3 hrs. The mixture was then filtered and washed with 15 mL TFA. The combined filtrate was triturated with cold methyl tertbutyl ether

(MTBE). The mixture was centrifuged (3000 rpm, 3 min) and decanted. The pellet was washed with MTBE and centrifuged. The residue was lyophilized to give Intermediate 6d (2.0 g).

Step B – Peptide Cyclization and Purification: Intermediate 6d (2.0 g, 0.92 mmol) was dissolved in 20% MeCN/H₂O (1000 mL). To a stirred solution of the peptide was added iodine in MeOH (0.1M, 2.5 mL) drop-wise until the color of the solution remained yellow. After ~2h LCMS showed the reaction was complete. Excess iodine was quenched by the addition of 1M Na₂S₂O₃ in water (15 uL) (turned colorless instantly). MeCN (10-20 mL) was added to reduce turbidity. The solution was purified by Prep-HPLC (A: 0.075% TFA in H₂O, B: ACN) (Note 1: Method E) to give SEQ ID NO: 389 (270.4 mg, 94.6% purity, 11.0% yield for this step; over all yield: 10.1%) obtained as white solid. Analysis was performed using a C18 column with a flow rate of 1 mL/min (Note 2).

LCMS Summary: calculated MW: 2169.5, observed MW: 1085.1 (M+2H)²⁺, 724.1 (M+3H)³⁺.

Example 9: Synthesis of SEQ ID NO: 328 – cPEG3aCO-Pen(3)-N-T-7MeW-K(NMecPEG3a)-Pen(3)-AEF-6OH2Nal-THP-K(NMecPEG3a)-N-3Pya-Sar-CONH2



cPEG3aCO-Pen(3)-N-T-7MeW-K(NMecPEG3a)-Pen(3)-AEF-6OH2Nal-THP-K(NMecPEG3a)-N-3Pya-Sar-CONH2
SEQ ID NO: 328

Step A – Synthesis of Intermediate 7: The peptide was synthesized by solid-phase peptide synthesis using Fmoc chemistry. DMF was added to a vessel containing MBHA Resin (0.30 mmol, 1.15 g, sub: 0.26 mmol/g), and the resin was allowed to swell for 2 hours. Then, 20% piperidine/DMF was added to the resin and mixed for 30 minutes. The mixture was drained and washed five times with DMF (for 30 seconds each). Fmoc-amino acid solution was then added to the resin and mixed for 30 seconds before the addition of activation buffer. The amino

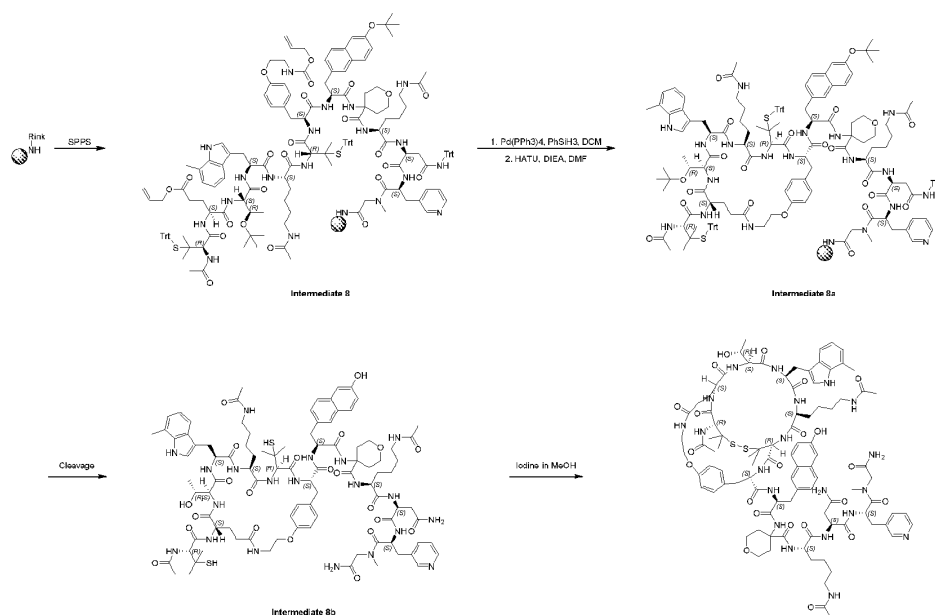
acid was allowed to react with the resin for 1-4 hours under N₂. Then, 20% piperidine/DMF was added and mixed for 30 min. The procedure was repeated for subsequent amino acid coupling(s). Coupling reactions were monitored by ninhydrin (A: 5% ninhydrin /EtOH; B: 80% phenol /EtOH; C: pyridine) or tetrachlor (A: 2% tetrachlor/ DMF; B: 2% aldehyde/ DMF 110°C for 3min) color test. Subsequently, the resin was washed with DMF 5 times, and then with MeOH 3 times before drying under vacuum.

To cleave the peptide from the resin, 25 mL of cleavage buffer (5.0% DTT /2.5% H₂O /2.5% TIS /90%TFA) was added to the flask containing the side chain protected peptide on resin at room temperature, and the solution was stirred for 3 hrs. The mixture was then filtered and washed with 5 mL TFA. The combined filtrate was triturated with cold methyl tertbutyl ether (MTBE). The mixture was centrifuged (3000 rpm, 3 min) and decanted. The pellet was washed with MTBE and centrifuged. The residue was lyophilized to give Intermediate 7 (600 mg).

Step B – Peptide Cyclization and Purification: Intermediate 7 (600 mg, 0.24 mmol) was dissolved in 20% MeCN/H₂O (400 mL). To a stirred solution of the peptide was added iodine in MeOH (0.1M, 3.0 mL) drop-wise until the color of the solution remained yellow. After ~2h LCMS showed the reaction was complete. Excess iodine was quenched by the addition of 1M Na₂S₂O₃ in water (turned colorless instantly). MeCN (10-20 mL) was added to reduce turbidity. The solution was purified by Prep-HPLC (A: 0.075% TFA in H₂O, B: ACN) (Note 1: Method C) to give SEQ ID NO: 328 (89.6 mg, 96.9% purity, 11.7 % yield for this step, over all yield: 9.54% yield) obtained as white solid. Analysis was performed using a C18 column with a flow rate of 1 mL/min (Note 2).

LCMS Summary: calculated MW: 2464.0, observed MW: 821.0 [(M+3H)/3].

Example 10: Synthesis of SEQ ID NO: 414 – MeCO-Pen(3)-E(2)-T-7MeW-K(Ac)-Pen(3)-AEF(2)-6OH2Nal-THP-K(Ac)-N-3Pya-Sar-CONH₂



MeCO-Pen(3)-E(2)-T-7MeW-K(Ac)-Pen(3)-AEF(2)-6OH2Nal-THP-K(Ac)-N-3Pya-Sar-
CONH2

SEQ ID NO: 414

- 5 Step A – Synthesis of Intermediate 8b: The peptide was synthesized by solid-phase peptide synthesis using Fmoc chemistry. DMF was added to a vessel containing MBHA Resin (0.2 mmol, 0.65 g, sub: 0.31 mmol/g), and the resin was allowed to swell for 2 hours. Then, 20% piperidine/DMF was added to the resin and mixed for 30 minutes. The mixture was drained and washed five times with DMF (for 30 seconds each). Fmoc-amino acid solution was then added
- 10 to the resin and mixed for 30 seconds before the addition of activation buffer. The amino acid was allowed to react with the resin for 1-4 hours under N₂. Then, 20% piperidine/DMF was added and mixed for 30 min. The procedure was repeated for subsequent amino acid coupling(s). Coupling reactions were monitored by ninhydrin (A: 5% ninhydrin /EtOH; B: 80% phenol /EtOH; C: pyridine) or tetrachlor (A: 2% tetrachlor/ DMF; B: 2% aldehyde/ DMF 110°C for
- 15 3min) color test. Subsequently, the resin was washed with DMF 5 times, and then with MeOH 3 times before drying under vacuum.

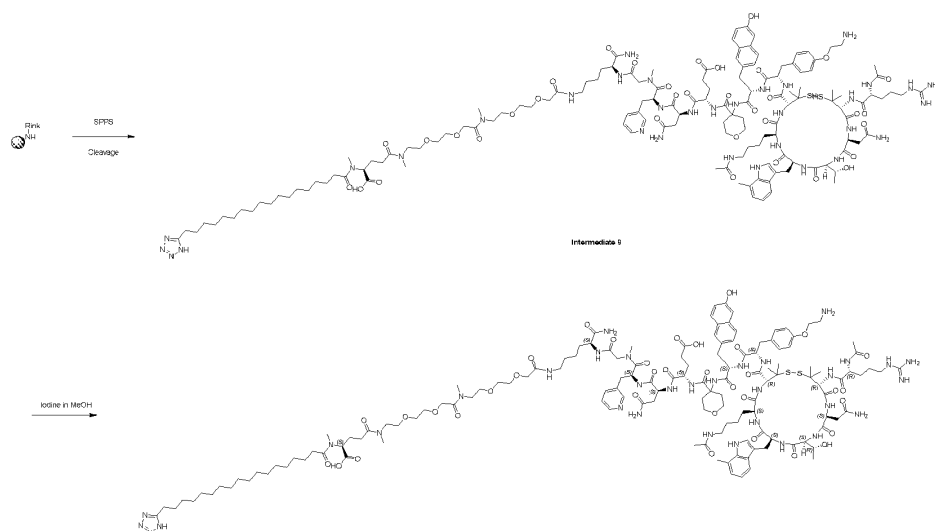
To cleave the peptide from the resin, 12 mL of cleavage buffer (5.0% DTT /2.5% H₂O /2.5% TIS /90%TFA) was added to the flask containing the side chain protected peptide on resin at room temperature, and the solution was stirred for 3 hrs. The mixture was then filtered and

20 washed with 5 mL TFA. The combined filtrate was triturated with cold methyl tertbutyl ether (MTBE). The mixture was centrifuged (3000 rpm, 3 min) and decanted. The pellet was washed with MTBE and centrifuged. The residue was lyophilized to give Intermediate 8b (350 mg).

Step B – Peptide Cyclization and Purification: Intermediate 8b (350 mg, 0.17 mmol) was dissolved in 20% MeCN /H₂O (200 mL). To a stirred solution of the peptide was added iodine in MeOH (0.1M, 0.8 mL) drop-wise until the color of the solution remained yellow. After ~2h LCMS showed the reaction was complete. Excess iodine was quenched by the addition of 1M Na₂S₂O₃ in water (15 uL) (turned colorless instantly). MeCN (10-20 mL) was added to reduce turbidity. The solution was purified by Prep-HPLC (A: 0.075% TFA in H₂O, B: ACN) (Note 1: Method G) to give SEQ ID NO: 414(31.2 mg, 98.2% purity, 8.28% yield for this step; over all yield: 7.41%) obtained as white solid. Analysis was performed using a C18 column with a flow rate of 1 mL/min (Note 2).

LCMS Summary: calculated MW: 1952.2, observed MW: 976.9 (M+2H)²⁺.

Example 11: Synthesis of SEQ ID NO: 115 – MeCO-r-Pen(3)-N-T-7MeW-K(Ac)-Pen(3)-AEF-6OH₂Nal-THP-E-N-3Pya-Sar-K(PEG₂NMePEG₂NMeG₂ENMeC₁₈Tetrazole)-CONH₂



MeCO-r-Pen(3)-N-T-7MeW-K(Ac)-Pen(3)-AEF-6OH₂Nal-THP-E-N-3Pya-Sar-K(PEG₂NMePEG₂NMeG₂ENMeC₁₈Tetrazole)-CONH₂

SEQ ID NO: 115

Step A – Synthesis of Intermediate 9: The peptide was synthesized by solid-phase peptide synthesis using Fmoc chemistry. DMF was added to a vessel containing MBHA Resin (0.2 mmol, 0.65 g, sub: 0.31 mmol/g), and the resin was allowed to swell for 2 hours. Then, 20% piperidine/DMF was added to the resin and mixed for 30 minutes. The mixture was drained and washed five times with DMF (for 30 seconds each). Fmoc-amino acid solution was then added

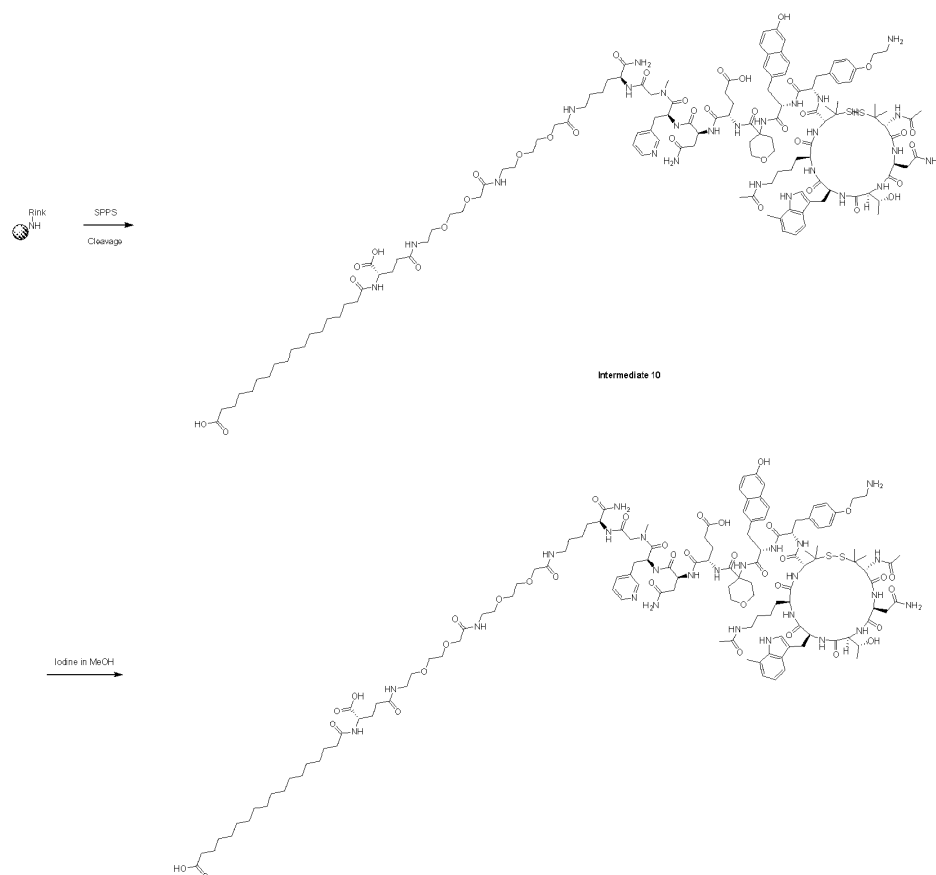
to the resin and mixed for 30 seconds before the addition of activation buffer. The amino acid was allowed to react with the resin for 1-4 hours under N₂. Then, 20% piperidine/DMF was added and mixed for 30 min. The procedure was repeated for subsequent amino acid coupling(s). Coupling reactions were monitored by ninhydrin (A: 5% ninhydrin /EtOH; B: 80% phenol /EtOH; C: pyridine) or tetrachlor (A: 2% tetrachlor/ DMF; B: 2% aldehyde/ DMF 110°C for 3min) color test. Subsequently, the resin was washed with DMF 5 times, and then with MeOH 3 times before drying under vacuum.

To cleave the peptide from the resin, 20 mL of cleavage buffer (5.0% DTT /2.5% H₂O /2.5% TIS /90%TFA) was added to the flask containing the side chain protected peptide on resin at room temperature, and the solution was stirred for 3 hrs. The mixture was then filtered and washed with 5 mL TFA. The combined filtrate was triturated with cold methyl tertbutyl ether (MTBE). The mixture was centrifuged (3000 rpm, 3 min) and decanted. The pellet was washed with MTBE and centrifuged. The residue was lyophilized to give Intermediate 9 (451 mg).

Step B – Peptide Cyclization and Purification: Intermediate 9 (451 mg, 0.151 mmol) was dissolved in 20% MeCN /H₂O (300 mL). To a stirred solution of the peptide was added iodine in MeOH (0.1M, 1.0 mL) drop-wise until the color of the solution remained yellow. After ~2h LCMS showed the reaction was complete. Excess iodine was quenched by the addition of 1M Na₂S₂O₃ in water (15 uL) (turned colorless instantly). MeCN (10-20 mL) was added to reduce turbidity. The solution was purified by Prep-HPLC (A: 0.075% TFA in H₂O, B: ACN) (Note 1: Method H) to give SEQ ID NO: 115 (43.7 mg, 96.1% purity, 8.08% yield for this step; over all yield: 6.08%) obtained as white solid. Analysis was performed using a C18 column with a flow rate of 1 mL/min (Note 2).

LCMS Summary: calculated MW: 2994.53, observed MW: 998.89[(M+3H)/3].

Example 12: Synthesis of SEQ ID NO: 283 – MeCO-Pen(3)-N-T-7MeW-K(Ac)-Pen(3)-AEF-6OH2NaI-THP-E-N-3Pyra-Sar-K(PEG2PEG2gEC18OH)-CONH2



MeCO-Pen(3)-N-T-7MeW-K(Ac)-Pen(3)-AEF-6OH2Nal-THP-E-N-3Py-Sar-
K(PEG2PEG2gEC18OH)-CONH2

SEQ ID NO: 283

- 5 Step A – Synthesis of Intermediate 10: The peptide was synthesized by solid-phase peptide synthesis using Fmoc chemistry. DMF was added to a vessel containing MBHA Resin (0.3 mmol, 1.0 g, sub: 0.28 mmol/g), and the resin was allowed to swell for 2 hours. Then, 20% piperidine/DMF was added to the resin and mixed for 30 minutes. The mixture was drained and washed five times with DMF (for 30 seconds each). Fmoc-amino acid solution was then added
- 10 to the resin and mixed for 30 seconds before the addition of activation buffer. The amino acid was allowed to react with the resin for 1-16 hours under N₂. Then, 20% piperidine/DMF was added and mixed for 30 min. The procedure was repeated for subsequent amino acid coupling(s). Coupling reactions were monitored by ninhydrin (A: 5% ninhydrin /EtOH; B: 80% phenol /EtOH; C: pyridine) or tetrachlor (A: 2% tetrachlor/ DMF; B: 2% aldehyde/ DMF 110°C for
- 15 3min) color test. Subsequently, the resin was washed with DMF 5 times, and then with MeOH 3 times before drying under vacuum.

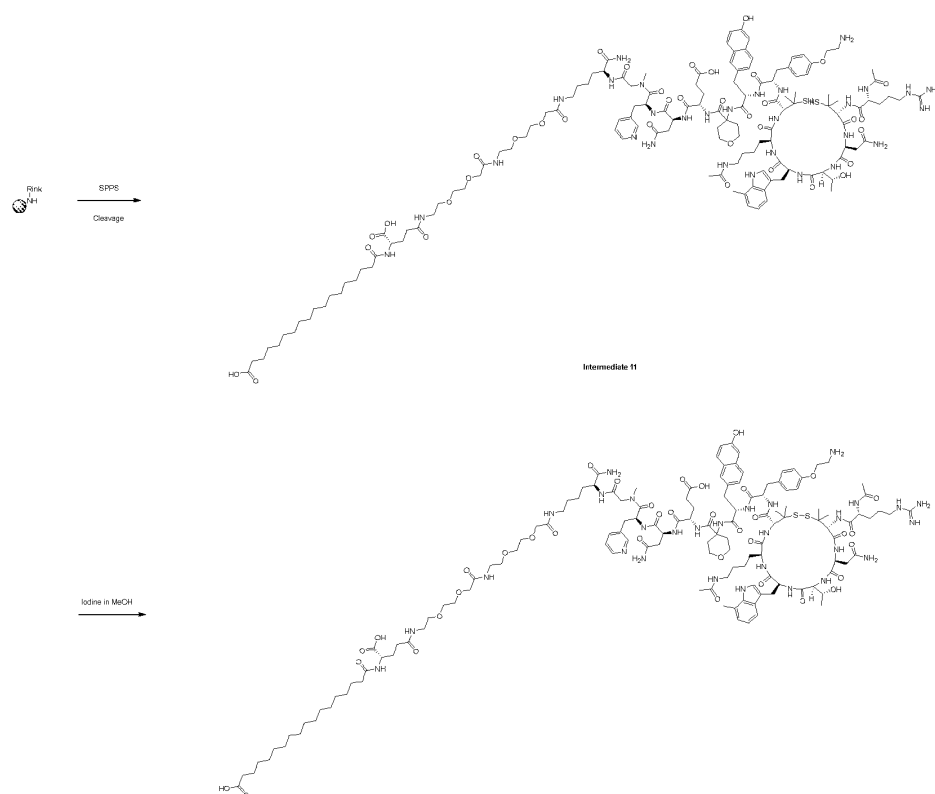
To cleave the peptide from the resin, 75 mL of cleavage buffer (5.0% DTT /2.5% H₂O /2.5% TIS /90%TFA) was added to the flask containing the side chain protected peptide on resin at room temperature, and the solution was stirred for 3 hrs. The mixture was then filtered and washed with 5 mL TFA. The combined filtrate was triturated with cold methyl tertbutyl ether (MTBE). The mixture was centrifuged (3000 rpm, 3 min) and decanted. The pellet was washed with MTBE and centrifuged. The residue was lyophilized to give Intermediate 10 (680 mg).

Step B – Peptide Cyclization and Purification: Intermediate 10 (680 mg, 0.246 mmol) was dissolved in 20% MeCN /H₂O (300 mL). To a stirred solution of the peptide was added iodine in MeOH (0.1M, 1.5 mL) drop-wise until the color of the solution remained yellow. After ~2h LCMS showed the reaction was complete. Excess iodine was quenched by the addition of 1M Na₂S₂O₃ in water (15 uL) (turned colorless instantly). MeCN (10-20 mL) was added to reduce turbidity. The solution was purified by Prep-HPLC (A: 0.075% TFA in H₂O, B: ACN) (Note 1: Method H) to give SEQ ID NO: 283 (99.4 mg, 96.1% purity, 12.9% yield for this step; over all yield: 10.6%) obtained as white solid. Analysis was performed using a C18 column with a flow rate of 1 mL/min (Note 2).

LCMS Summary: calculated MW: 2758.21, observed MW: 1380.2 (M+2H)²⁺.

Example 13: Synthesis of SEQ ID NO: 282 – MeCO-r-Pen(3)-N-T-7MeW-K(Ac)-Pen(3)-AEF-6OH2NaI-THP-E-N-3Pyra-Sar-K(PEG2PEG2gEC18OH)-CONH2

20



MeCO-r-Pen(3)-N-T-7MeW-K(Ac)-Pen(3)-AEF-6OH2Nal-THP-E-N-3Pyra-Sar-
K(PEG2PEG2gEC18OH)-CONH2

SEQ ID NO: 282

- 5 Step A – Synthesis of Intermediate 11: The peptide was synthesized by solid-phase peptide synthesis using Fmoc chemistry. DMF was added to a vessel containing MBHA Resin (0.3 mmol, 1.0 g, sub: 0.28 mmol/g), and the resin was allowed to swell for 2 hours. Then, 20% piperidine/DMF was added to the resin and mixed for 30 minutes. The mixture was drained and washed five times with DMF (for 30 seconds each). Fmoc-amino acid solution was then added
- 10 to the resin and mixed for 30 seconds before the addition of activation buffer. The amino acid was allowed to react with the resin for 1-16 hours under N₂. Then, 20% piperidine/DMF was added and mixed for 30 min. The procedure was repeated for subsequent amino acid coupling(s). Coupling reactions were monitored by ninhydrin (A: 5% ninhydrin /EtOH; B: 80% phenol /EtOH; C: pyridine) or tetrachlor (A: 2% tetrachlor/ DMF; B: 2% aldehyde/ DMF 110°C for
- 15 3min) color test. Subsequently, the resin was washed with DMF 5 times, and then with MeOH 3 times before drying under vacuum.

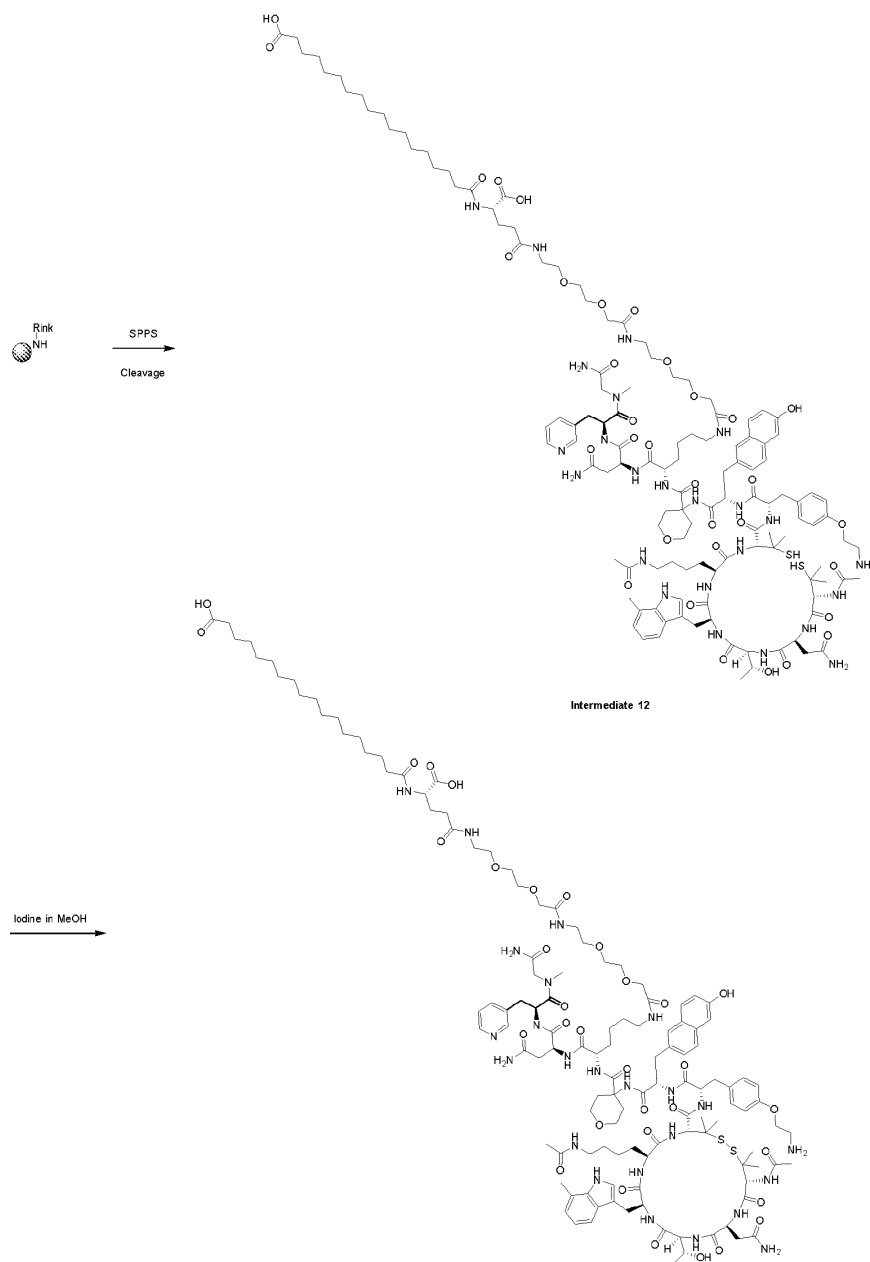
To cleave the peptide from the resin, 25 mL of cleavage buffer (5.0% DTT /2.5% H₂O /2.5% TIS /90%TFA) was added to the flask containing the side chain protected peptide on resin at room temperature, and the solution was stirred for 3 hrs. The mixture was then filtered and

washed with 5 mL TFA. The combined filtrate was triturated with cold methyl tertbutyl ether (MTBE). The mixture was centrifuged (3000 rpm, 3 min) and decanted. The pellet was washed with MTBE and centrifuged. The residue was lyophilized to give Intermediate 11 (750 mg).

- Step B – Peptide Cyclization and Purification: Intermediate 11 (750 mg, 0.257 mmol)
- 5 was dissolved in 20% MeCN /H₂O (300 mL). To a stirred solution of the peptide was added iodine in MeOH (0.1M, 1.5 mL) drop-wise until the color of the solution remained yellow. After ~2h LCMS showed the reaction was complete. Excess iodine was quenched by the addition of 1M Na₂S₂O₃ in water (15 uL) (turned colorless instantly). MeCN (10-20 mL) was added to reduce turbidity. The solution was purified by Prep-HPLC (A: 0.075% TFA in H₂O, B:
- 10 ACN) (Note 1: Method H) to give SEQ ID NO: 282 (109.2 mg, 93.2% purity, 12.1% yield for this step; over all yield: 10.4%) obtained as white solid. Analysis was performed using a C18 column with a flow rate of 1 mL/min (Note 2).

LCMS Summary: calculated MW: 2914.4, observed MW: 1458.3 (M+2H)²⁺.

Example 14: Synthesis of SEQ ID NO: 273 – MeCO-Pen(3)-N-T-7MeW-K(Ac)-Pen(3)-AEF-6OH2NaI-THP-K(PEG2PEG2gEC18OH)-N-3PyA-Sar-CONH2



MeCO-Pen(3)-N-T-7MeW-K(Ac)-Pen(3)-AEF-6OH2NaI-THP-K(PEG2PEG2gEC18OH)-N-

5

3PyA-Sar-CONH2

SEQ ID NO: 273

Step A – Synthesis of Intermediate 12: The peptide was synthesized by solid-phase peptide synthesis using Fmoc chemistry. DMF was added to a vessel containing MBHA Resin

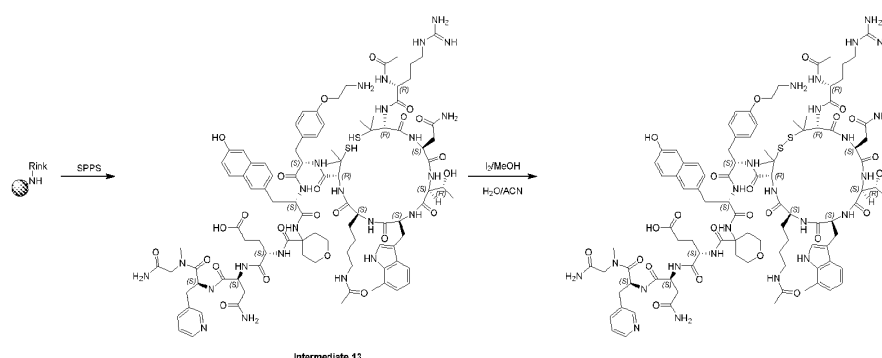
(1.0 mmol, 2.9 g, sub: 0.35 mmol/g), and the resin was allowed to swell for 2 hours. Then, 20% piperidine/DMF was added to the resin and mixed for 30 minutes. The mixture was drained and washed five times with DMF (for 30 seconds each). Fmoc-amino acid solution was then added to the resin and mixed for 30 seconds before the addition of activation buffer. The amino acid
5 was allowed to react with the resin for 1-16 hours under N₂. Then, 20% piperidine/DMF was added and mixed for 30 min. The procedure was repeated for subsequent amino acid coupling(s). Coupling reactions were monitored by ninhydrin (A: 5% ninhydrin /EtOH; B: 80% phenol /EtOH; C: pyridine) or tetrachlor (A: 2% tetrachlor/ DMF; B: 2% aldehyde/ DMF 110°C for 3min) color test. Subsequently, the resin was washed with DMF 5 times, and then with MeOH 3
10 times before drying under vacuum.

To cleave the peptide from the resin, 90 mL of cleavage buffer (5.0% DTT /2.5% H₂O /2.5% TIS /90%TFA) was added to the flask containing the side chain protected peptide on resin at room temperature, and the solution was stirred for 3 hrs. The mixture was then filtered and washed with 5 mL TFA. The combined filtrate was triturated with cold methyl tertbutyl ether
15 (MTBE). The mixture was centrifuged (3000 rpm, 3 min) and decanted. The pellet was washed with MTBE and centrifuged. The residue was lyophilized to give Intermediate 12 (2.0 g).

Step B – Peptide Cyclization and Purification: Intermediate 12 (2.0 g, 0.76 mmol) was dissolved in 20% MeCN /H₂O (1000 mL). To a stirred solution of the peptide was added iodine in MeOH (0.1M, 5.0 mL) drop-wise until the color of the solution remained yellow. After ~2h
20 LCMS showed the reaction was complete. Excess iodine was quenched by the addition of 1M Na₂S₂O₃ in water (15 uL) (turned colorless instantly). MeCN (10-20 mL) was added to reduce turbidity. The solution was purified by Prep-HPLC (A: 0.075% TFA in H₂O, B: ACN) (Note 1: Method F) to give SEQ ID NO: 273 (434.5 mg, 97.6% purity, 19.5% yield for this step; over all yield: 14.8%) obtained as white solid. Analysis was performed using a C18 column with a flow
25 rate of 1 mL/min (Note 2).

LCMS Summary: calculated MW: 2629.1, observed MW: 1314.8 (M+2H)²⁺.

**Example 15: Synthesis of SEQ ID NO: 442 – MeCO-r-Pen(3)-N-T-7MeW-K(Ac)-Pen(3)-
30 AEF-6OH2Nal-THP-E-N-3Pya-Sar-CONH₂**



MeCO-r-Pen(3)-N-T-7MeW-K(Ac)-Pen(3)-AEF-6OH2Nal-THP-E-N-3Pya-Sar-CONH2

SEQ ID NO: 442

Step A – Synthesis of Intermediate 13: The peptide was synthesized by solid-phase peptide synthesis using Fmoc chemistry. DMF was added to a vessel containing MBHA Resin (0.20 mmol, 0.64 g, sub: 0.31 mmol/g), and the resin was allowed to swell for 2 hours. Then, 20% piperidine/DMF was added to the resin and mixed for 30 minutes. The mixture was drained and washed five times with DMF (for 30 seconds each). Fmoc-amino acid solution was then added to the resin and mixed for 30 seconds before the addition of activation buffer. The amino acid was allowed to react with the resin for 1-4 hours under N₂. Then, 20% piperidine/DMF was added and mixed for 30 min. The procedure was repeated for subsequent amino acid coupling(s). Coupling reactions were monitored by ninhydrin (A: 5% ninhydrin /EtOH; B: 80% phenol /EtOH; C: pyridine) or tetrachlor (A: 2% tetrachlor/ DMF; B: 2% aldehyde/ DMF 110°C for 3min) color test. Subsequently, the resin was washed with DMF 5 times, and then with MeOH 3 times before drying under vacuum.

To cleave the peptide from the resin, 12 mL of cleavage buffer (5.0% DTT /2.5% H₂O /2.5% TIS /90%TFA) was added to the flask containing the side chain protected peptide on resin at room temperature, and the solution was stirred for 3 hrs. The mixture was then filtered and washed with 5 mL TFA. The combined filtrate was triturated with cold methyl tertbutyl ether (MTBE). The mixture was centrifuged (3000 rpm, 3 min) and decanted. The pellet was washed with MTBE and centrifuged. The residue was lyophilized to give Intermediate 13 (400 mg).

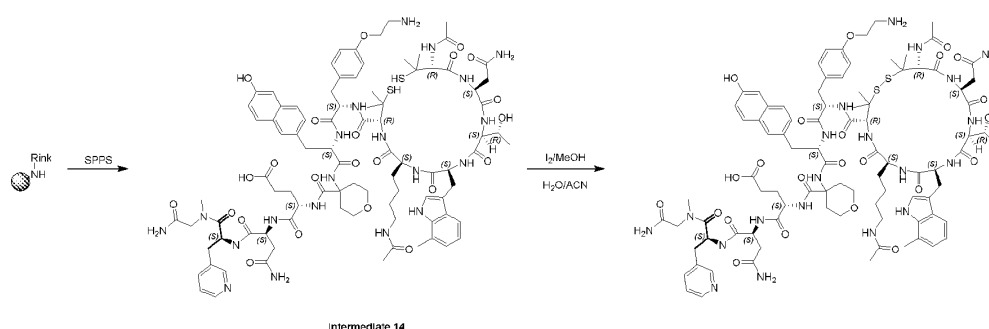
Step B – Peptide Cyclization and Purification: Intermediate 13 (400 mg, 0.193 mmol) was dissolved in 20% MeCN /H₂O (200 mL). To a stirred solution of the peptide was added iodine in MeOH (0.1M, 1.0 mL) drop-wise until the color of the solution remained yellow. After ~2h LCMS showed the reaction was complete. Excess iodine was quenched by the addition of 1M Na₂S₂O₃ in water (15 uL) (turned colorless instantly). MeCN (10-20 mL) was added to reduce turbidity. The solution was purified by Prep-HPLC (A: 0.075% TFA in H₂O, B: ACN) (Note 1: Method C) to give SEQ ID NO: 442 (50.8 mg, 94.2% purity, 10.3% yield for this

step; over all yield: 9.9%) obtained as white solid. Analysis was performed using a C18 column with a flow rate of 1 mL/min (Note 2).

LCMS Summary: calculated MW: 2070.3, observed MW: 1036.2 (M+2H)²⁺, 691.1 (M+3H)³⁺.

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Example 16: Synthesis of SEQ ID NO: 428 – MeCO-Pen(3)-N-T-7MeW-K(Ac)-Pen(3)-AEF-6OH2Nal-THP-E-N-3Pya-Sar-CONH2



MeCO-Pen(3)-N-T-7MeW-K(Ac)-Pen(3)-AEF-6OH2Nal-THP-E-N-3Pya-Sar-CONH2
SEQ ID NO: 428

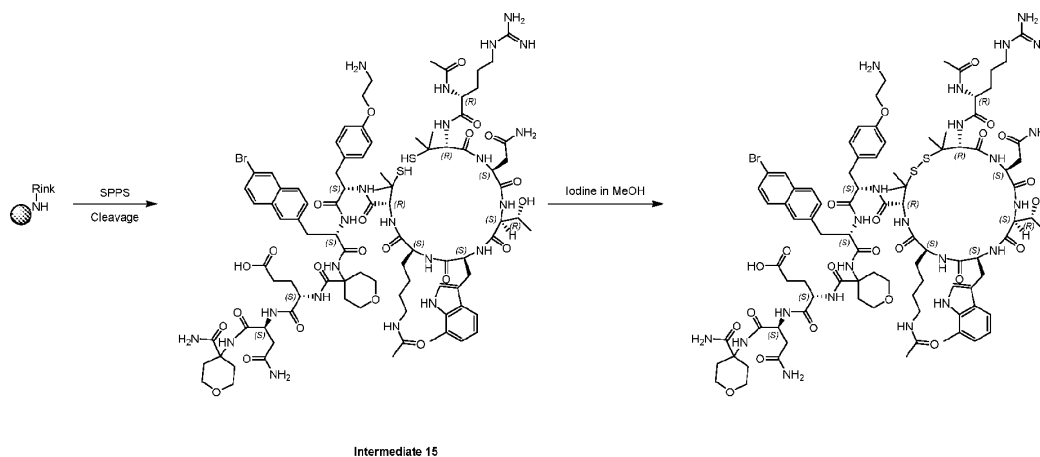
Step A – Synthesis of Intermediate 14: The peptide was synthesized by solid-phase peptide synthesis using Fmoc chemistry. DMF was added to a vessel containing MBHA Resin (0.10 mmol, 0.32 g, sub: 0.31 mmol/g), and the resin was allowed to swell for 2 hours. Then, 20% piperidine/DMF was added to the resin and mixed for 30 minutes. The mixture was drained and washed five times with DMF (for 30 seconds each). Fmoc-amino acid solution was then added to the resin and mixed for 30 seconds before the addition of activation buffer. The amino acid was allowed to react with the resin for 1-4 hours under N₂. Then, 20% piperidine/DMF was added and mixed for 30 min. The procedure was repeated for subsequent amino acid coupling(s). Coupling reactions were monitored by ninhydrin (A: 5% ninhydrin /EtOH; B: 80% phenol /EtOH; C: pyridine) or tetrachlor (A: 2% tetrachlor/ DMF; B: 2% aldehyde/ DMF 110°C for 3min) color test. Subsequently, the resin was washed with DMF 5 times, and then with MeOH 3 times before drying under vacuum.

To cleave the peptide from the resin, 8 mL of cleavage buffer (5.0% DTT /2.5% H₂O /2.5% TIS /90%TFA) was added to the flask containing the side chain protected peptide on resin at room temperature, and the solution was stirred for 3 hrs. The mixture was then filtered and washed with 5 mL TFA. The combined filtrate was triturated with cold methyl tertbutyl ether (MTBE). The mixture was centrifuged (3000 rpm, 3 min) and decanted. The pellet was washed with MTBE and centrifuged. The residue was lyophilized to give Intermediate 14 (195 mg).

Step B – Peptide Cyclization and Purification: Intermediate 14 (195 mg, 0.10 mmol) was dissolved in 20% MeCN /H₂O (100 mL). To a stirred solution of this peptide was added iodine in MeOH (0.1M, 0.5 mL) drop-wise until the color of the solution remained yellow. After about 2h LCMS analysis showed that Intermediate 14 was no longer present. The excess iodine was quenched by the addition of 1M Na₂S₂O₃ in water (15 µL). MeCN (10-20 mL) was added to reduce the turbidity of the solution. The peptide was purified by Prep-HPLC (A: 0.075% TFA in H₂O, B: ACN) (Note 1: Method C) to provide SEQ ID NO: 428 (18.9 mg, 99.3% purity, 8.61% yield for this step; over all yield: 8.6%) obtained as white solid. Analysis was performed using a C18 column with a flow rate of 1 mL/min (Note 2).

LCMS Summary: calculated MW: 1914.17, observed MW: 958.0 (M+2H)²⁺.

Example 17: Synthesis of SEQ ID NO: 444 – MeCO-r-Pen(3)-N-T-7MeW-K(Ac)-Pen(3)-AEF-6Br2Nal-THP-E-N-THP-CONH₂



MeCO-r-Pen(3)-N-T-7MeW-K(Ac)-Pen(3)-AEF-6Br2Nal-THP-E-N-THP-CONH₂
SEQ ID NO: 444

Step A – Synthesis of Intermediate 15: The peptide was synthesized by solid-phase peptide synthesis using Fmoc chemistry. DMF was added to a vessel containing MBHA Resin (3 mmol, 9.6 g, sub: 0.31 mmol/g), and the resin was allowed to swell for 2 hours. Then, 20% piperidine/DMF was added to the resin and mixed for 30 minutes. The mixture was drained and washed five times with DMF (for 30 seconds each). Fmoc-amino acid solution was then added to the resin and mixed for 30 seconds before the addition of activation buffer. The amino acid was allowed to react with the resin for 1-16 hours under N₂. Then, 20% piperidine/DMF was added and mixed for 30 min. The procedure was repeated for subsequent amino acid coupling(s). Coupling reactions were monitored by ninhydrin (A: 5% ninhydrin /EtOH; B: 80% phenol /EtOH; C: pyridine) or tetrachlor (A: 2% tetrachlor/ DMF; B: 2% aldehyde/ DMF 110°C for

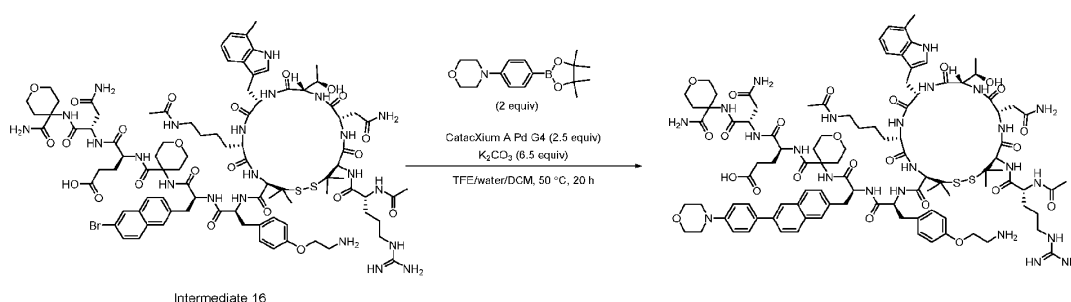
3min) color test. Subsequently, the resin was washed with DMF 5 times, and then with MeOH 3 times before drying under vacuum.

To cleave the peptide from the resin, 200 mL of cleavage buffer (5.0% DTT /2.5% H₂O /2.5% TIS /90%TFA) was added to the flask containing the side chain protected peptide on resin
5 at room temperature, and the solution was stirred for 3 hrs. The mixture was then filtered and washed with 20 mL TFA. The combined filtrate was triturated with cold methyl tertbutyl ether (MTBE). The mixture was centrifuged (3000 rpm, 3 min) and decanted. The pellet was washed with MTBE and centrifuged. The residue was lyophilized to give Intermediate 15 (6.0 g).

Step B – Peptide Cyclization and Purification: Intermediate 15 (6.0 g, 2.93 mmol) was
10 dissolved in 20% MeCN /H₂O (3.0 L). To a stirred solution of the peptide was added iodine in MeOH (0.1M, 15 mL) drop-wise until the color of the solution remained yellow. After ~2h LCMS showed the reaction was complete. Excess iodine was quenched by the addition of 1M Na₂S₂O₃ in water (15 uL) (turned colorless instantly). MeCN (150-200 mL) was added to reduce turbidity. The solution was purified by Prep-HPLC (A: 0.075% TFA in H₂O, B: ACN)
15 (Note 1: Method I) to give SEQ ID NO: 444 (2.35g, 96.7% purity, 34.1% yield for this step; over all yield: 33.4%) obtained as white solid. Analysis was performed using a C18 column with a flow rate of 1 mL/min (Note 2).

LCMS Summary: calculated MW: 2041.1, observed MW: 1021.3 (M+2H)²⁺.

20 **Example 18: Synthesis of SEQ ID NO: 432 – MeCO-r-Pen(3)-N-T-7MeW-K(Ac)-Pen(3)-AEF-2Nal6(Ph4(NMorph))-THP-E-N-THP-CONH₂**



MeCO-r-Pen(3)-N-T-7MeW-K(Ac)-Pen(3)-AEF-2Nal6(Ph4(NMorph))-THP-E-N-THP-CONH₂

25 SEQ ID NO: 432

In a glovebox, a 1 dram vial was charged with Intermediate 16 (15 mg, 7.4 μmol), 4-[4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)phenyl]morpholine (4.3 mg, 15 μmol, 2 equiv), CataCXium A Pd G4 (13.6 mg, 18.4 μmol, 2.5 equiv), and K₂CO₃ (6.6 mg, 48 μmol, 6.5 equiv) before adding TFE (0.37 mL), water (0.37 mL), and DCM (75 μL). The reaction vial was sealed,

brought out of the glovebox and heated at 50 °C with stirring for 20 h before cooling to room temperature, adding SiliaMet DMT scavenger (15 mg) and DMF (0.5 mL) and stirring for an additional 3 h. The resulting mixture was acidified by the addition of a MeCN/water (9:1, 1% TFA) mixture and filtered, rinsed with minimal DMF, and concentrated to a volume of approx. 1 mL by rotary evaporation. Purification by mass-directed liquid chromatography (HPLC (Waters XSelect CSH C18, 5u, 19x100 mm) using a gradient of 20-28% B over 25 minutes at a flow rate of 25 mL/min (mobile phase A: water + 0.16% Formic Acid, mobile phase B: acetonitrile + 0.16% Formic Acid)) afforded SEQ ID NO: 432 as a white solid 2 (4.5 mg, 27% yield). LCMS calc'd for C₁₀₁H₁₃₉N₂₃O₂₄S₂: 2123.49, obsvd (m/z): 1062.2 [M+2H]²⁺.

Example 19: IL23R Reporter Assay

Compounds were serially diluted in 100% (v/v) DMSO) and plated using an Echo acoustic dispenser (Labcyte) into 1536-well non-treated black assay plates (Corning # 9146). 3 µL of HEK293 cells containing IL-23R, IL-12Rβ1 and a firefly luciferase reporter gene driven by a STAT-inducible promoter (Promega) were added to the plates (4000 cells/well), followed by 3 µL of 10 ng/mL IL-23 (equivalent to EC₉₀ concentration). After 5h at 37°C, 5% CO₂, 95% relative humidity, cells were placed at 20°C and treated with BioGlo reagent (Promega) according to the Manufacturer's instructions. Luminescence was measured on a Pherastar FSX (BMG LabTech). Data were normalized to IL-23 treatment (0% inhibition) and 30 µM of control inhibitor (100% inhibition), and IC₅₀ values were determined using a 4-parameter Hill equation. Data for exemplary compounds are shown below.

A: IC₅₀ < 0.01 µM;

B: 0.01 µM ≤ IC₅₀ < 0.1 µM;

C: 0.1 µM ≤ IC₅₀

ND: Not determined

Table 8. IL-23 Binding Data

SEQ ID NO	IC ₅₀
1	A
2	A
3	A
4	A
5	A
6	A
7	A
8	A
9	A

SEQ ID NO	IC ₅₀
10	A
11	A
12	A
13	A
14	A
15	A
16	A
17	A
18	A

SEQ ID NO	IC ₅₀
19	A
20	A
21	A
22	A
23	A
24	A
25	A
26	A
27	A
28	A
29	A
30	A
31	A
32	A
33	A
34	A
35	A
36	A
37	A
38	A
39	A
40	A
41	A
42	A
43	B
44	A
45	B
46	B
47	B
48	A
49	A
50	A
51	A
52	A
53	A
54	B
55	B
56	A
57	B
58	A
59	A
60	A
61	A
62	A
63	A
64	B
65	A

SEQ ID NO	IC ₅₀
66	A
67	A
68	A
69	A
70	B
71	A
72	A
73	A
74	A
75	A
76	A
77	A
78	A
79	A
80	A
81	A
82	A
83	B
84	A
85	A
86	A
87	A
88	B
89	A
90	A
91	A
92	A
93	A
94	A
95	A
96	B
97	B
98	A
99	A
100	A
101	A
102	A
103	A
104	A
105	B
106	A
107	B
108	A
109	A
110	B
111	A
112	A

SEQ ID NO	IC ₅₀
113	A
114	A
115	B
116	B
117	B
118	B
119	B
120	C
121	B
122	B
123	B
124	B
125	B
126	B
127	B
128	B
129	B
130	C
131	ND
132	A
133	A
134	B
135	B
136	A
137	A
138	B
139	B
140	B
141	B
142	B
143	A
144	B
145	B
146	A
147	B
148	B
149	A
150	B
151	B
152	C
153	B
154	C
155	B
156	B
157	A
158	A
159	A

SEQ ID NO	IC ₅₀
160	A
161	ND
162	ND
163	ND
164	B
165	ND
166	B
167	C
168	C
169	B
170	B
171	A
172	A
173	B
174	B
175	C
176	C
177	C
178	C
179	C
180	C
181	B
182	B
183	C
184	B
185	B
186	B
187	C
188	C
189	C
190	B
191	B
192	B
193	B
194	B
195	B
196	B
197	B
198	ND
199	ND
200	C
201	B
202	B
203	B
204	B
205	B
206	B

SEQ ID NO	IC ₅₀
207	B
208	B
209	B
210	B
211	C
212	B
213	B
214	B
215	B
216	B
217	B
218	B
219	A
220	B
221	B
222	C
223	B
224	B
225	B
226	A
227	B
228	B
229	B
230	A
231	B
232	B
233	B
234	B
235	B
236	B
237	B
238	B
239	B
240	B
241	B
242	B
243	B
244	B
245	B
246	B
247	ND
248	ND
249	B
250	B
251	B
252	B
253	B

SEQ ID NO	IC ₅₀
254	B
255	B
256	B
257	B
258	B
259	B
260	B
261	B
262	B
263	B
264	B
265	B
266	B
267	B
268	B
269	B
270	B
271	B
272	C
273	B
274	C
275	C
276	C
277	B
278	C
279	C
280	B
281	A
282	B
283	B
284	B
285	B
286	B
287	A
288	C
289	C
290	A
291	A
292	A
293	A
294	A
295	A
296	A
297	A
298	B
299	A
300	A

SEQ ID NO	IC ₅₀
301	A
302	A
303	A
304	A
305	A
306	A
307	A
308	A
309	A
310	A
311	A
312	A
313	A
314	B
315	A
316	A
317	ND
318	A
319	A
320	A
321	A
322	A
323	A
324	A
325	A
326	A
327	A
328	A
329	B
330	A
331	A
332	A
333	A
334	A
335	A
336	A
337	A
338	A
339	A
340	A
341	B
342	A
343	A
344	A
345	A
346	A
347	A

SEQ ID NO	IC ₅₀
348	A
349	A
350	A
351	A
352	A
353	A
354	A
355	A
356	A
357	A
358	A
359	A
360	A
361	A
362	A
363	A
364	A
365	A
366	A
367	ND
368	A
369	A
370	A
371	A
372	A
373	A
374	A
375	A
376	A
377	A
378	A
379	A
380	A
381	A
382	A
383	A
384	A
385	A
386	A
387	A
388	A
389	A
390	A
391	A
392	A
393	A
394	A

SEQ ID NO	IC ₅₀
395	B
396	A
397	A
398	A
399	A
400	A
401	A
402	A
403	A
404	A
405	A
406	A
407	A
408	A
409	A
410	A
411	A
412	A
413	A
414	A
415	A
416	A
417	A
418	ND
419	B
420	B
421	B

SEQ ID NO	IC ₅₀
422	A
423	B
424	C
425	B
426	B
427	B
428	A
429	C
430	C
431	C
432	C
433	ND
434	ND
435	B
436	B
437	C
438	ND
439	C
440	B
441	A
442	A
443	B
444	C
445	C
446	C
447	C

Example 19: PBMC pSTAT3 Assay

Cryopreserved peripheral blood mononuclear cells (PBMCs) from healthy donors were thawed and washed twice in ImmunoCult-XF T cell expansion medium (XF-TCEM) supplemented with CTL anti-aggregate wash. The cells were counted, resuspended at 2-6x10⁵ cells per mL XF-TCEM supplemented with penicillin/streptomycin and 100 ng/mL IL-1β (BioLegend, 579404), and cultured in tissue culture flasks coated with anti-CD3 (eBioscience, 16-0037-85 or BD Pharmingen, 555329) at 37oC in 5% CO2. On day 4 of culture, PBMCs were collected, washed twice in RPMI-1640 supplemented with 0.1% BSA (RPMI-BSA), and incubated in RPMI-BSA in upright tissue culture flasks for ~4 hours at 37oC in 5% CO2. Following this ‘starvation,’ a total of 6x10⁴ cells in 30 μL RPMI-BSA was transferred into each well of a 384-well plate pre-spotted with peptide or DMSO. The cells were incubated for 30 minutes prior to the addition of IL-23 at a final concentration of 5 ng/mL. The cells were stimulated with cytokine for 30 minutes at 37oC in 5% CO2, transferred onto ice for 10 minutes, and lysed. Cell lysates were stored at -80°C until phosphorylated STAT3 was measured using the phospho-STAT panel kit (Meso Scale Discovery, K15202D). Results are provided below.

- A: IC₅₀ < 0.01 nM;
- B: 0.01 nM ≤ IC₅₀ < 0.1 nM;
- C: 0.1 nM ≤ IC₅₀ < 1 nM;
- D: 1 nM ≤ IC₅₀;
- ND: Not determined

Table 9. PBMC pSTAT3 Assay Results

SEQ ID NO	PBMC pSTAT3 IC ₅₀	SEQ ID NO	PBMC pSTAT3 IC ₅₀
1	ND	14	A
2	ND	15	A
3	ND	16	A
4	ND	17	A
5	A	18	A
6	B	19	B
7	B	20	B
8	A	21	A
9	D	22	A
10	A	23	B
11	A	24	B
12	A	25	B
13	A	26	B

SEQ ID NO	PBMC pSTAT3 IC ₅₀
27	A
28	ND
29	B
30	B
31	B
32	A
33	A
34	B
35	B
36	ND
37	ND
38	ND
39	ND
40	A
41	ND
42	D
43	ND
44	ND
45	ND
46	ND
47	ND
48	ND
49	ND
50	ND
51	ND
52	ND
53	ND
54	ND
55	ND
56	A
57	C
58	B
59	B
60	B
61	B
62	C
63	B
64	C
65	C
66	B
67	B
68	B
69	A
70	ND
71	ND

SEQ ID NO	PBMC pSTAT3 IC ₅₀
72	ND
73	ND
74	B
75	ND
76	ND
77	A
78	A
79	A
80	ND
81	ND
82	ND
83	ND
84	ND
85	ND
86	ND
87	ND
88	ND
89	B
90	B
91	B
92	B
93	B
94	C
95	B
96	B
97	C
98	A
99	A
100	A
101	A
102	A
103	A
104	B
105	C
106	B
107	B
108	A
109	A
110	C
111	B
112	A
113	B
114	A
115	C
116	C

SEQ ID NO	PBMC pSTAT3 IC ₅₀
117	ND
118	C
119	C
120	C
121	ND
122	C
123	ND
124	C
125	ND
126	C
127	C
128	C
129	C
130	C
131	C
132	A
133	A
134	C
135	C
136	A
137	A
138	ND
139	B
140	C
141	B
142	B
143	A
144	C
145	B
146	A
147	C
148	B
149	B
150	C
151	C
152	C
153	B
154	C
155	ND
156	C
157	A
158	A
159	A
160	A
161	A

SEQ ID NO	PBMC pSTAT3 IC ₅₀
162	A
163	A
164	C
165	D
166	C
167	C
168	C
169	C
170	C
171	A
172	A
173	ND
174	C
175	ND
176	D
177	D
178	D
179	D
180	D
181	C
182	C
183	C
184	C
185	C
186	C
187	C
188	C
189	C
190	C
191	C
192	C
193	C
194	B
195	B
196	C
197	C
198	C
199	ND
200	C
201	C
202	C
203	C
204	C
205	B
206	C

SEQ ID NO	PBMC pSTAT3 IC ₅₀
207	C
208	C
209	B
210	C
211	C
212	C
213	C
214	C
215	B
216	B
217	B
218	D
219	B
220	C
221	D
222	D
223	C
224	C
225	C
226	C
227	C
228	C
229	C
230	A
231	C
232	C
233	C
234	C
235	C
236	C
237	C
238	C
239	C
240	C
241	C
242	C
243	B
244	C
245	C
246	C
247	C
248	C
249	C
250	C
251	C

SEQ ID NO	PBMC pSTAT3 IC ₅₀
252	B
253	C
254	C
255	C
256	C
257	B
258	C
259	C
260	C
261	A
262	C
263	C
264	A
265	C
266	B
267	C
268	C
269	C
270	C
271	C
272	C
273	B
274	C
275	C
276	C
277	C
278	C
279	C
280	ND
281	ND
282	C
283	C
284	C
285	C
286	C
287	B
288	ND
289	ND
290	B
291	ND
292	B
293	ND
294	B
295	B
296	ND

SEQ ID NO	PBMC pSTAT3 IC ₅₀
297	ND
298	ND
299	B
300	B
301	B
302	B
303	ND
304	ND
305	ND
306	ND
307	ND
308	ND
309	B
310	B
311	ND
312	ND
313	ND
314	D
315	B
316	ND
317	ND
318	B
319	B
320	B
321	B
322	B
323	ND
324	B
325	ND
326	ND
327	ND
328	ND
329	ND
330	ND
331	ND
332	ND
333	ND
334	ND
335	A
336	B
337	A
338	ND
339	B
340	A
341	ND

SEQ ID NO	PBMC pSTAT3 IC ₅₀
342	B
343	B
344	B
345	B
346	B
347	B
348	ND
349	A
350	B
351	ND
352	B
353	ND
354	ND
355	B
356	A
357	ND
358	A
359	ND
360	B
361	B
362	ND
363	B
364	A
365	A
366	A
367	ND
368	A
369	B
370	A
371	A
372	A
373	A
374	ND
375	ND
376	ND
377	A
378	A
379	ND
380	ND
381	A
382	A
383	A
384	A
385	B
386	A

SEQ ID NO	PBMC pSTAT3 IC ₅₀
387	A
388	A
389	A
390	A
391	A
392	A
393	A
394	A
395	C
396	A
397	A
398	B
399	C
400	B
401	B
402	A
403	B
404	B
405	B
406	B
407	B
408	B
409	B
410	B
411	A
412	B
413	B
414	A
415	B
416	A
417	A

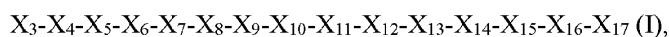
SEQ ID NO	PBMC pSTAT3 IC ₅₀
418	ND
419	B
420	B
421	C
422	A
423	C
424	C
425	C
426	ND
427	C
428	A
429	D
430	D
431	D
432	ND
433	D
434	D
435	B
436	C
437	D
438	D
439	C
440	D
441	B
442	A
443	D
444	D
445	D
446	D
447	C

While the foregoing specification teaches the principles of the present invention, with
5 examples provided for the purpose of illustration, it will be understood that the practice of the
invention encompasses all of the usual variations, adaptations and/or modifications as come within
the scope of the following claims and their equivalents.

CLAIMS

What is claimed is:

1. A peptide of Formula (I), comprising the amino acid sequence:



or a pharmaceutically acceptable salt thereof, wherein:

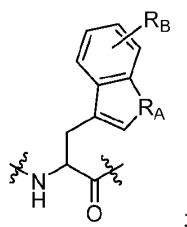
X_3 is any amino acid or absent;

X_4 is any amino acid;

X_5 is any amino acid;

X_6 is any amino acid;

X_7 is:



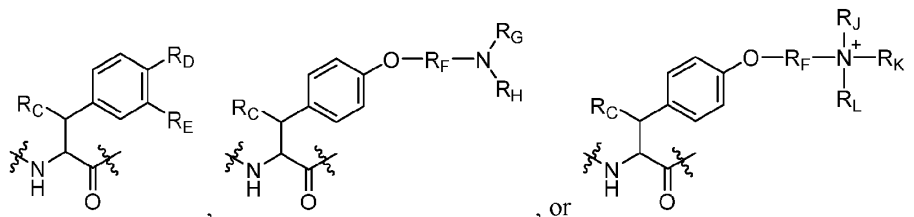
R_A is O, NH, N- $C_{(1-5)}$ alkyl, or S;

R_B is -H, halo, $C_{(1-3)}$ alkyl, or phenyl, wherein the phenyl is optionally substituted with one -N(H)C(O) $C_{(1-3)}$ alkyl group;

X_8 is any amino acid;

X_9 is any amino acid;

X_{10} is:



R_C is -H or - $C_{(1-3)}$ alkyl;

R_D is -H, -OH, -CN, - $C_{(1-3)}$ alkyl, - $OC_{(1-3)}$ alkyl, - $OC_{(1-3)}$ alkyl-(5-membered heteroaryl), -C(O)NH₂, or heterocyclyl, wherein the - $OC_{(1-3)}$ alkyl-(5-membered heteroaryl) is optionally substituted with a polyethylene glycol chain, and wherein the heterocyclyl is optionally substituted with one -C(O)NH₂ group;

R_E is -H or halo;

R_F is - $C_{(1-6)}$ alkylene or a bivalent polyethylene glycol chain;

R_G is $-H$, $-C_{(1-3)}\text{alkyl}$, or a bond to the amino acid at X_5 or X_{13} ;

R_H is $-H$, $-C_{(1-3)}\text{alkyl}$, $-C(NH)NH_2$, $-C(O)-R_{H1}$;

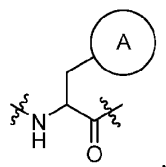
or R_G and R_H taken together with the nitrogen atom to which they are attached form a 5- to 8-membered heterocyclyl group;

5 R_{H1} is $-C_{(1-5)}\text{alkyl}$, $-OC_{(1-5)}\text{alkyl}$, $-C_{(1-3)}\text{alkyl-phenyl}$, $-\text{phenyl-}C_{(1-3)}\text{alkyl-N(H)-S(O)}_2-C_{(1-3)}\text{alkyl}$, or a polyethylene glycol chain, wherein the $-C_{(1-3)}\text{alkyl-phenyl}$ is optionally substituted with one to three groups selected from halo and $-OH$;

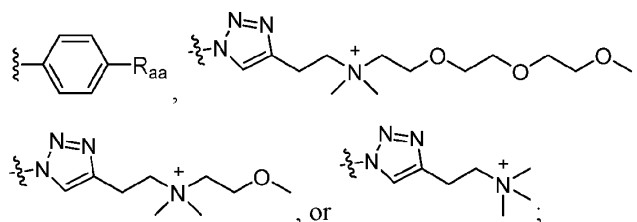
R_J , R_K , and R_L are each, independently, $C_{(1-3)}\text{alkyl}$;

or R_J and R_K taken together with the nitrogen atom to which they are attached form a 5- to 8-membered heterocyclyl group;

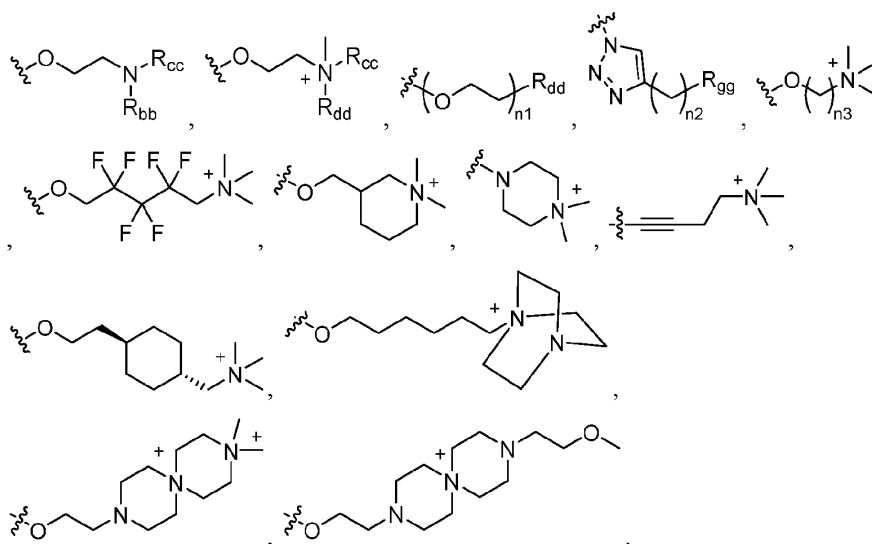
or X_{10} is:

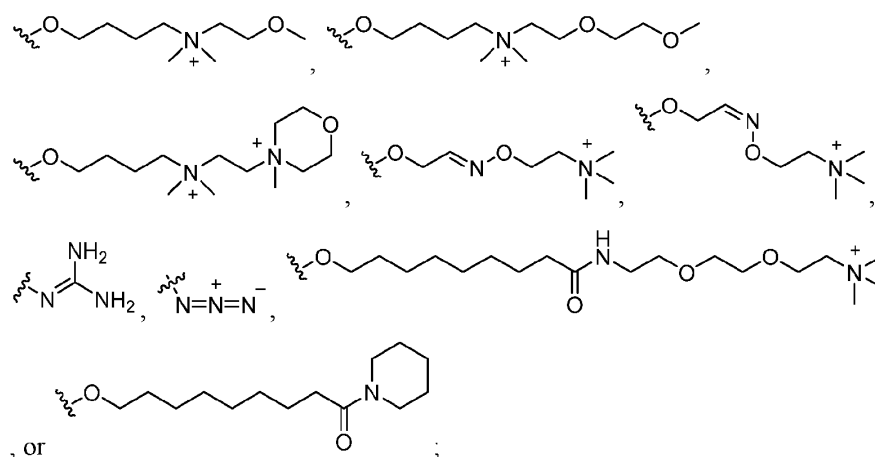


A is

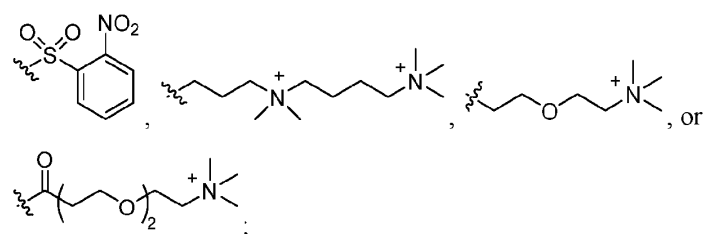


R_{aa} is $-OCHF_2$, $-O(CH_2)_9CO_2H$,

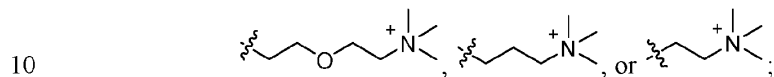




5 R_{bb} is -H, -CH₃, -C(O)CH₃, -C(NH)NH₂, -(CH₂)₃O(CH₂)₂OCH₃, -CH₂CH₂OCH₃, -
(CH₂CH₂O)₃CH₃, -(CH₂CH₂O)₆CH₃,

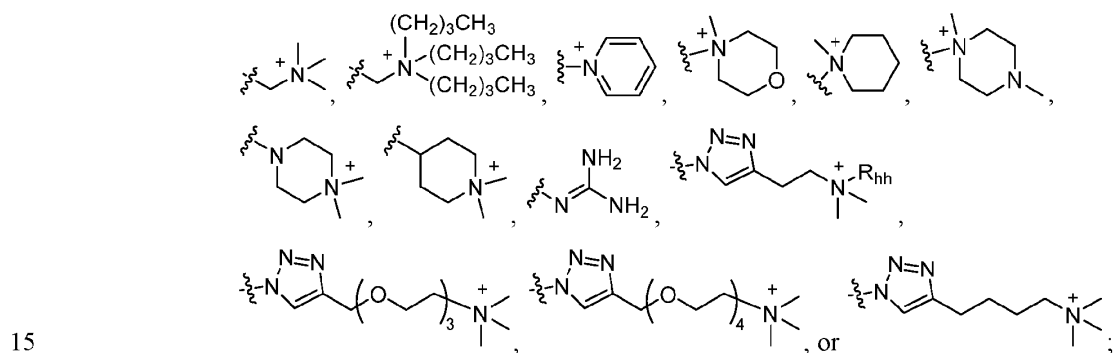


R_{cc} is -H, -CH₃, -(CH₂)₃O(CH₂)₂OCH₃,



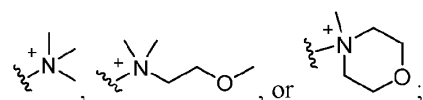
n_1 is 1, 2, or 3;

R_{dd} is



n2 is 1, 2, 3, 4, or 5;

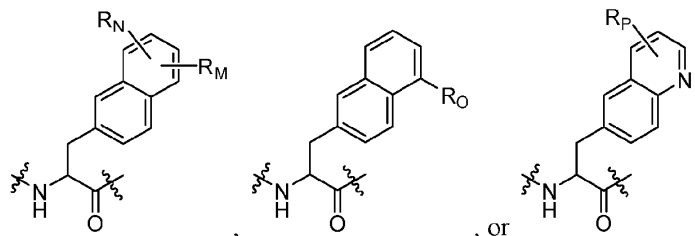
R_{gg} is -OCH₃,



n_3 is 3, 4, 5, 6, or 8;

R_{hh} is -H, $-(CH_2)_7CH_3$, $-(CH_2)_{15}CH_3$, $-(CH_2)_2OCH_3$, or $-(CH_2CH_2O)_3CH_3$;

X_{11} is:



- 5 R_M is halo, -OH, $-C_{(1-3)}alkyl$, $-OC(O)C_{(1-3)}haloalkyl$, phenyl, or 5- to 6-membered heteroaryl, wherein the phenyl and 5- to 6-membered heteroaryl are each optionally substituted with one to three groups selected from -OH, $-OC_{(1-3)}alkyl$, $-C_{(1-3)}haloalkyl$, and 3- to 6-membered heterocyclyl;

R_N is -H or -OH;

- 10 R_O is $-OC_{(1-3)}alkyl$ or $-C(O)NH_2$;

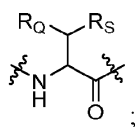
R_P is halo, -OH, $-C_{(1-3)}alkyl$, $-OC_{(1-3)}alkyl$, $-C(O)NH_2$, $-OC(O)C_{(1-3)}haloalkyl$, phenyl, or 5- to 6-membered heteroaryl, wherein the phenyl and 5- to 6-membered heteroaryl are each optionally substituted with one to three groups selected from -OH, $-OC_{(1-3)}alkyl$, $-C_{(1-3)}haloalkyl$, and 3- to 6-membered heterocyclyl;

- 15 X_{12} is any amino acid;

X_{13} is any amino acid;

X_{14} is any amino acid;

X_{15} is Ala, THP, or



- 20 R_Q is -H or $-C_{(1-3)}alkyl$;

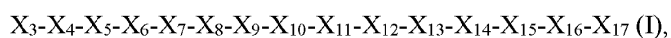
R_S is phenyl or 5- to 6-membered heteroaryl, each of which is optionally substituted with one $-C(O)NH_2$ group;

X_{16} is any amino acid or absent; and

X_{17} is any amino acid or absent;

- 25 wherein the peptide is cyclized to form a first ring, wherein the first ring comprises 4 to 14 amino acids.

2. The peptide of claim 1, comprising the amino acid sequence:



or a pharmaceutically acceptable salt thereof, wherein:

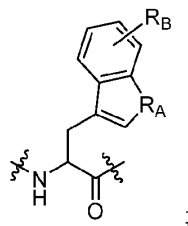
X₃ is any amino acid or absent;

X₄ is an amino acid that is linked to the amino acid at X₉;

X₅ is any amino acid;

5 X₆ is any amino acid;

X₇ is:



R_A is O, NH, N-C₍₁₋₅₎alkyl, or S;

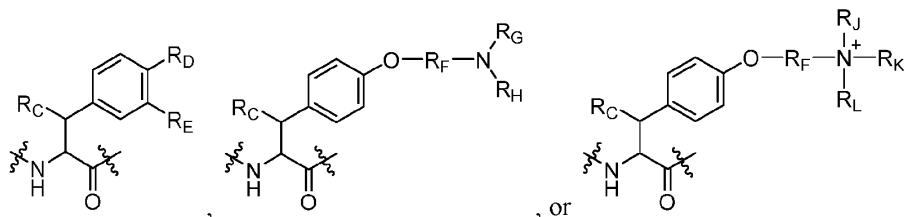
R_B is -H, halo, C₍₁₋₃₎alkyl, or phenyl, wherein the phenyl is optionally substituted with

10 one -N(H)C(O)C₍₁₋₃₎alkyl group;

X₈ is any amino acid;

X₉ is an amino acid that is linked to the amino acid at X₄;

X₁₀ is:



15 R_C is -H or -C₍₁₋₃₎alkyl;

R_D is -H, -OH, -CN, -C₍₁₋₃₎alkyl, -OC₍₁₋₃₎alkyl, -OC₍₁₋₃₎alkyl-(5-membered heteroaryl), -C(O)NH₂, or heterocyclyl, wherein the -OC₍₁₋₃₎alkyl-(5-membered heteroaryl) is optionally substituted with a polyethylene glycol chain, and wherein the heterocyclyl is optionally substituted with one -C(O)NH₂ group;

20 R_E is -H or halo;

R_F is -C₍₁₋₆₎alkylene or a bivalent polyethylene glycol chain;

R_G is -H, -C₍₁₋₃₎alkyl, or a bond to the amino acid at X₅ or X₁₃;

R_H is -H, -C₍₁₋₃₎alkyl, -C(NH)NH₂, -C(O)-R_{H1};

or R_G and R_H taken together with the nitrogen atom to which they are attached form a 5-

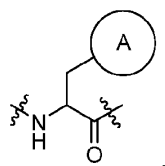
25 to 8-membered heterocyclyl group;

R_{H1} is -C₍₁₋₅₎alkyl, -OC₍₁₋₅₎alkyl, -C₍₁₋₃₎alkyl-phenyl, -phenyl-C₍₁₋₃₎alkyl-N(H)-S(O)₂-C₍₁₋₃₎alkyl, or a polyethylene glycol chain, wherein the -C₍₁₋₃₎alkyl-phenyl is optionally substituted with one to three groups selected from halo and -OH;

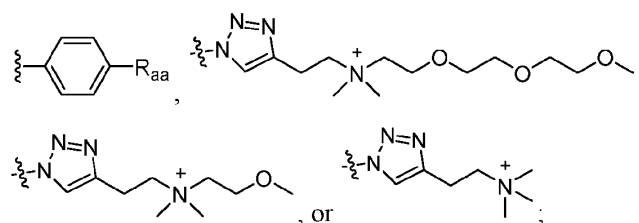
R_J, R_K, and R_L are each, independently, C₍₁₋₃₎alkyl;

5 or R_J and R_K taken together with the nitrogen atom to which they are attached form a 5- to 8-membered heterocyclcyl group;

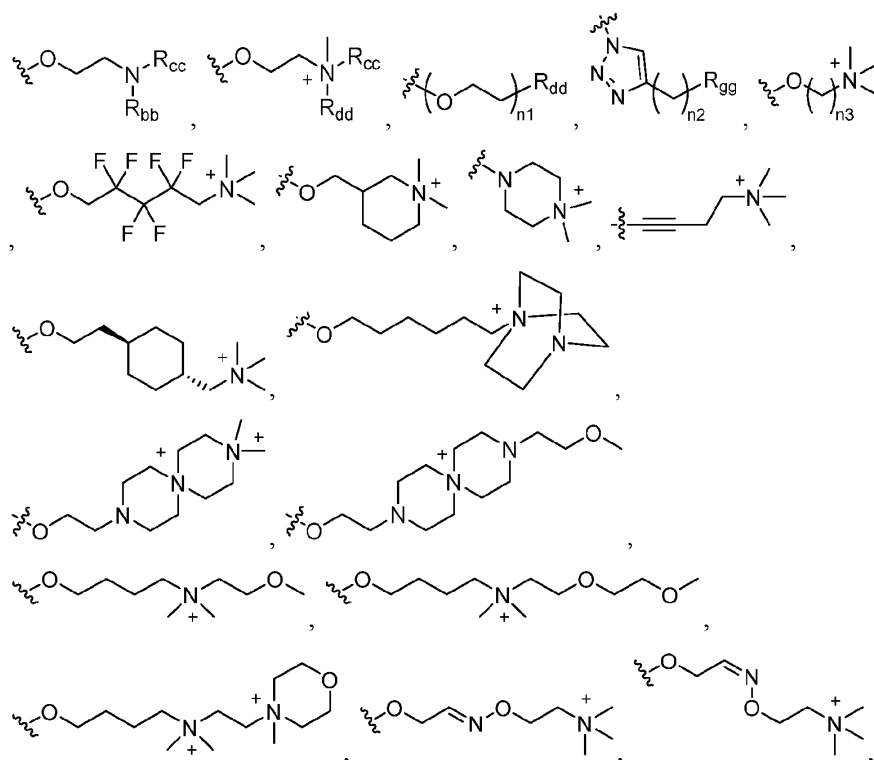
or X_{10} is:

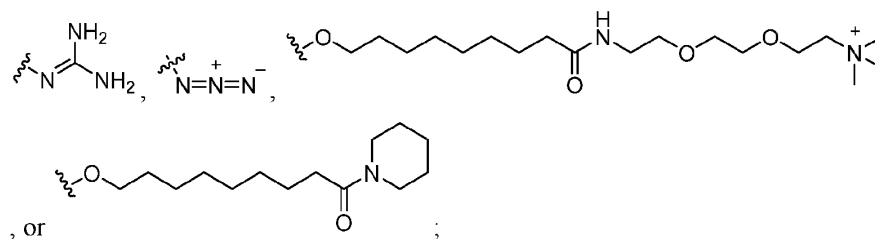


A is

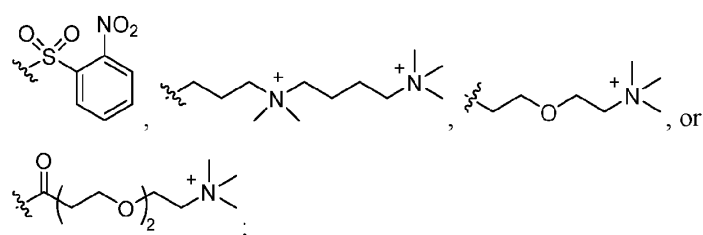


R_{aa} is -OCHF₂, -O(CH₂)₉CO₂H,

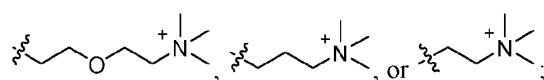




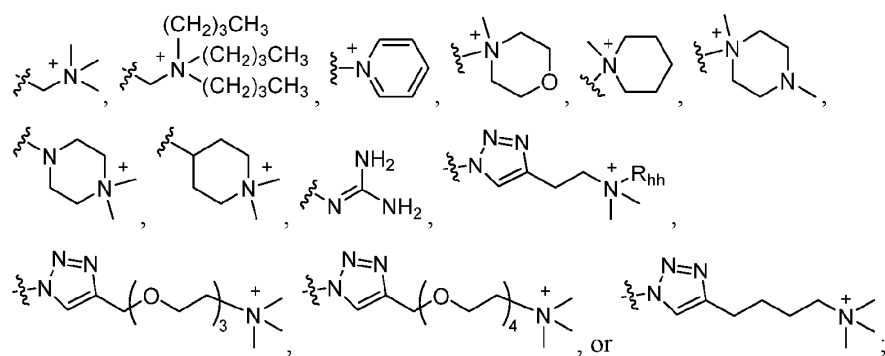
R_{bb} is -H, -CH₃, -C(O)CH₃, -C(NH)NH₂, -(CH₂)₃O(CH₂)₂OCH₃, -CH₂CH₂OCH₃, -H₂O)₃CH₃, -(CH₂CH₂O)₆CH₃,



R_{cc} is -H, -CH₃, -(CH₂)₃O(CH₂)₂OCH₃,

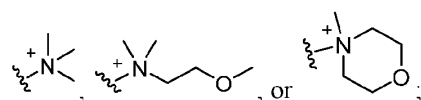


n_1 is 1, 2, or 3;

 R_{dd} is

n_2 is 1, 2, 3, 4, or 5;

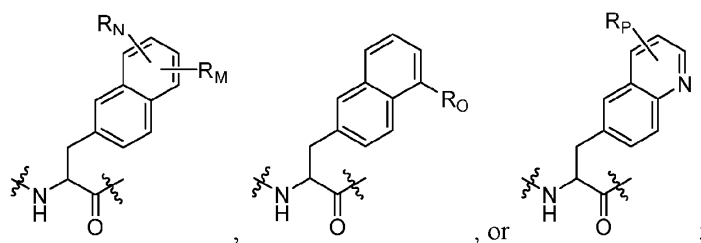
R_{gg} is -OCH₃,



n_3 is 3, 4, 5, 6, or 8;

R_{hh} is -H, -(CH₂)₇CH₃, -(CH₂)₁₅CH₃, -(CH₂)₂OCH₃, or -(CH₂CH₂O)₃CH₃;

X_{11} is:



R_M is halo, -OH, $-C_{(1-3)}\text{alkyl}$, $-\text{OC(O)}C_{(1-3)}\text{haloalkyl}$, phenyl, or 5- to 6-membered heteroaryl, wherein the phenyl and 5- to 6-membered heteroaryl are each optionally substituted with one to three groups selected from -OH, $-\text{OC}_{(1-3)}\text{alkyl}$, $-C_{(1-3)}\text{haloalkyl}$, and 3- to 6-membered heterocyclyl;

R_N is -H or -OH;

R_O is $-\text{OC}_{(1-3)}\text{alkyl}$ or $-\text{C(O)NH}_2$;

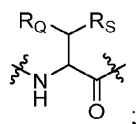
R_P is halo, -OH, $-C_{(1-3)}\text{alkyl}$, $-\text{OC}_{(1-3)}\text{alkyl}$, $-\text{C(O)NH}_2$, $-\text{OC(O)}C_{(1-3)}\text{haloalkyl}$, phenyl, or 5- to 6-membered heteroaryl, wherein the phenyl and 5- to 6-membered heteroaryl are each optionally substituted with one to three groups selected from -OH, $-\text{OC}_{(1-3)}\text{alkyl}$, $-C_{(1-3)}\text{haloalkyl}$, and 3- to 6-membered heterocyclyl;

X_{12} is any amino acid;

X_{13} is any amino acid;

X_{14} is any amino acid;

X_{15} is Ala, THP, or



R_Q is -H or $-C_{(1-3)}\text{alkyl}$;

R_S is phenyl or 5- to 6-membered heteroaryl, each of which is optionally substituted with one $-\text{C(O)NH}_2$ group;

X_{16} is any amino acid or absent; and

X_{17} is any amino acid or absent.

3. The peptide of claim 1, comprising the amino acid sequence:

$X_3\text{-}X_4\text{-}X_5\text{-}X_6\text{-}X_7\text{-}X_8\text{-}X_9\text{-}X_{10}\text{-}X_{11}\text{-}X_{12}\text{-}X_{13}\text{-}X_{14}\text{-}X_{15}\text{-}X_{16}\text{-}X_{17}$ (I),

or a pharmaceutically acceptable salt thereof, wherein:

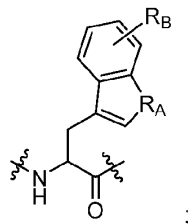
X_3 is any amino acid or absent;

X_4 is any amino acid;

X_5 is any amino acid;

X_6 is any amino acid;

X₇ is:



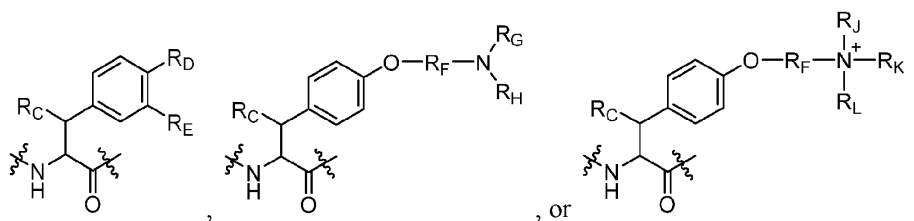
RA is O, NH, N-C₍₁₋₅₎alkyl, or S;

RB is -H, halo, C₍₁₋₃₎alkyl, or phenyl, wherein the phenyl is optionally substituted with one -N(H)C(O)C₍₁₋₃₎alkyl group;

X₈ is any amino acid;

X₉ is any amino acid;

X₁₀ is:



RC is -H or -C₍₁₋₃₎alkyl;

RD is -H, -OH, -CN, -C₍₁₋₃₎alkyl, -OC₍₁₋₃₎alkyl, -OC₍₁₋₃₎alkyl-(5-membered heteroaryl), -C(O)NH₂, or heterocyclyl, wherein the -OC₍₁₋₃₎alkyl-(5-membered heteroaryl) is optionally substituted with a polyethylene glycol chain, and wherein the heterocyclyl is optionally substituted with one -C(O)NH₂ group;

RE is -H or halo;

RF is -C₍₁₋₆₎alkylene or a bivalent polyethylene glycol chain;

RG is -H, -C₍₁₋₃₎alkyl, or a bond to the amino acid at X₅ or X₁₃;

RH is -H, -C₍₁₋₃₎alkyl, -C(NH)NH₂, -C(O)-R_{H1};

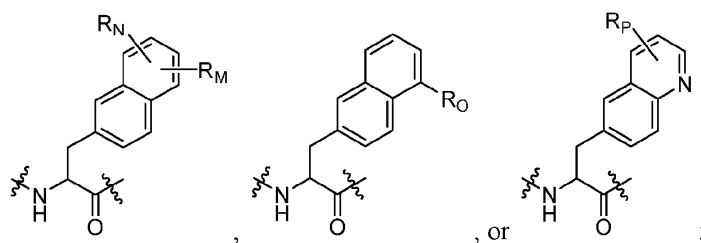
or RG and RH taken together with the nitrogen atom to which they are attached form a 5- to 8-membered heterocyclyl group;

R_{H1} is -C₍₁₋₅₎alkyl, -OC₍₁₋₅₎alkyl, -C₍₁₋₃₎alkyl-phenyl, -phenyl-C₍₁₋₃₎alkyl-N(H)-S(O)₂-C₍₁₋₃₎alkyl, or a polyethylene glycol chain, wherein the -C₍₁₋₃₎alkyl-phenyl is optionally substituted with one to three groups selected from halo and -OH;

R_J, R_K, and R_L are each, independently, C₍₁₋₃₎alkyl;

or R_J and R_K taken together with the nitrogen atom to which they are attached form a 5- to 8-membered heterocyclyl group;

X₁₁ is:



R_M is halo, -OH, $-C_{(1-3)}\text{alkyl}$, $-\text{OC(O)}C_{(1-3)}\text{haloalkyl}$, phenyl, or 5- to 6-membered heteroaryl, wherein the phenyl and 5- to 6-membered heteroaryl are each optionally substituted with one to three groups selected from -OH, $-\text{OC}_{(1-3)}\text{alkyl}$, $-C_{(1-3)}\text{haloalkyl}$, and 3- to 6-membered heterocyclyl;

R_N is -H or -OH;

R_O is $-\text{OC}_{(1-3)}\text{alkyl}$ or $-\text{C(O)NH}_2$;

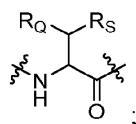
R_P is halo, -OH, $-C_{(1-3)}\text{alkyl}$, $-\text{OC}_{(1-3)}\text{alkyl}$, $-\text{C(O)NH}_2$, $-\text{OC(O)}C_{(1-3)}\text{haloalkyl}$, phenyl, or 5- to 6-membered heteroaryl, wherein the phenyl and 5- to 6-membered heteroaryl are each optionally substituted with one to three groups selected from -OH, $-\text{OC}_{(1-3)}\text{alkyl}$, $-C_{(1-3)}\text{haloalkyl}$, and 3- to 6-membered heterocyclyl;

X_{12} is any amino acid;

X_{13} is any amino acid;

X_{14} is any amino acid;

X_{15} is Ala, THP, or



R_Q is -H or $-C_{(1-3)}\text{alkyl}$;

R_S is phenyl or 5- to 6-membered heteroaryl, each of which is optionally substituted with one $-\text{C(O)NH}_2$ group;

X_{16} is any amino acid or absent; and

X_{17} is any amino acid or absent;

X_{17} is any amino acid or absent;

wherein the peptide is cyclized to form a first ring, wherein the first ring comprises 4 to 14 amino acids.

25

4. The peptide of any one of claims 1-3, comprising the amino acid sequence:



or a pharmaceutically acceptable salt thereof, wherein:

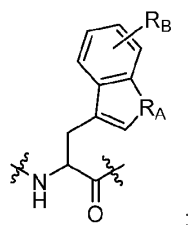
X_3 is any amino acid or absent;

X₄ is an amino acid that is linked to the amino acid at X₉;

X₅ is any amino acid;

X₆ is any amino acid;

X₇ is:



5

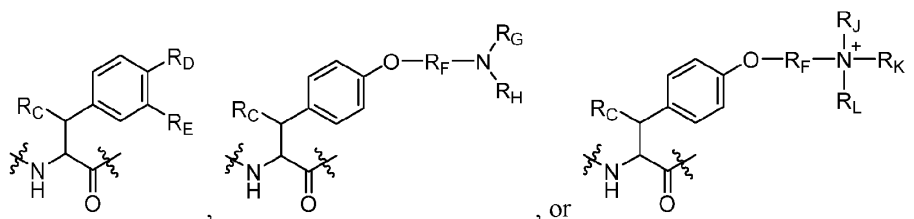
R_A is O, NH, N-C₍₁₋₅₎alkyl, or S;

R_B is -H, halo, C₍₁₋₃₎alkyl, or phenyl, wherein the phenyl is optionally substituted with one -N(H)C(O)C₍₁₋₃₎alkyl group;

X₈ is any amino acid;

10 X₉ is an amino acid that is linked to the amino acid at X₄;

X₁₀ is:



R_C is -H or -C₍₁₋₃₎alkyl;

15 R_D is -H, -OH, -CN, -C₍₁₋₃₎alkyl, -OC₍₁₋₃₎alkyl, -OC₍₁₋₃₎alkyl-(5-membered heteroaryl), -C(O)NH₂, or heterocyclyl, wherein the -OC₍₁₋₃₎alkyl-(5-membered heteroaryl) is optionally substituted with a polyethylene glycol chain, and wherein the heterocyclyl is optionally substituted with one -C(O)NH₂ group;

R_E is -H or halo;

R_F is -C₍₁₋₆₎alkylene or a bivalent polyethylene glycol chain;

20 R_G is -H, -C₍₁₋₃₎alkyl, or a bond to the amino acid at X₅ or X₁₃;

R_H is -H, -C₍₁₋₃₎alkyl, -C(NH)NH₂, -C(O)-R_{H1};

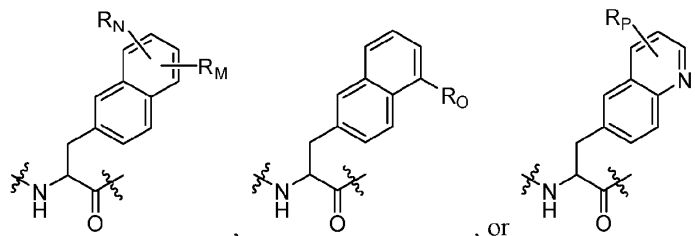
or R_G and R_H taken together with the nitrogen atom to which they are attached form a 5- to 8-membered heterocyclyl group;

25 R_{H1} is -C₍₁₋₅₎alkyl, -OC₍₁₋₅₎alkyl, -C₍₁₋₃₎alkyl-phenyl, -phenyl-C₍₁₋₃₎alkyl-N(H)-S(O)₂-C₍₁₋₃₎alkyl, or a polyethylene glycol chain, wherein the -C₍₁₋₃₎alkyl-phenyl is optionally substituted with one to three groups selected from halo and -OH;

R_J, R_K, and R_L are each, independently, C₍₁₋₃₎alkyl;

or R_J and R_K taken together with the nitrogen atom to which they are attached form a 5- to 8-membered heterocyclyl group;

X_{11} is:



- 5 R_M is halo, -OH, $-C_{(1-3)}\text{alkyl}$, $-\text{OC(O)}C_{(1-3)}\text{haloalkyl}$, phenyl, or 5- to 6-membered heteroaryl, wherein the phenyl and 5- to 6-membered heteroaryl are each optionally substituted with one to three groups selected from -OH, $-\text{OC}_{(1-3)}\text{alkyl}$, $-C_{(1-3)}\text{haloalkyl}$, and 3- to 6-membered heterocyclyl;

R_N is -H or -OH;

- 10 R_O is $-\text{OC}_{(1-3)}\text{alkyl}$ or $-\text{C(O)NH}_2$;

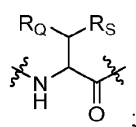
R_P is halo, -OH, $-C_{(1-3)}\text{alkyl}$, $-\text{OC}_{(1-3)}\text{alkyl}$, $-\text{C(O)NH}_2$, $-\text{OC(O)}C_{(1-3)}\text{haloalkyl}$, phenyl, or 5- to 6-membered heteroaryl, wherein the phenyl and 5- to 6-membered heteroaryl are each optionally substituted with one to three groups selected from -OH, $-\text{OC}_{(1-3)}\text{alkyl}$, $-C_{(1-3)}\text{haloalkyl}$, and 3- to 6-membered heterocyclyl;

- 15 X_{12} is any amino acid;

X_{13} is any amino acid;

X_{14} is any amino acid;

X_{15} is Ala, THP, or



- 20 R_Q is -H or $-C_{(1-3)}\text{alkyl}$;

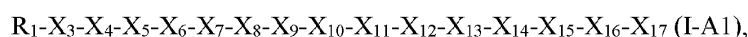
R_S is phenyl or 5- to 6-membered heteroaryl, each of which is optionally substituted with one $-\text{C(O)NH}_2$ group;

X_{16} is any amino acid or absent; and

X_{17} is any amino acid or absent.

25

5. The peptide of any one of claims 1-4, comprising the amino acid sequence of Formula (I-A1):

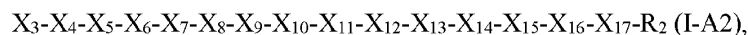


or a pharmaceutically acceptable salt thereof, wherein:

R₁ is 5Ava, 5cpaCO, 6Ahx, 7Ahp, CF₃CO, CF₃Propylamide, EtCO, MeCO, PEG₂, PEG₂NMe, a polyethylene glycol chain, or a lipophilic substituent, wherein the 5Ava, 6Ahx, 7Ahp, PEG₂, and PEG₂NMe are linked to the amino acid at X₁₃.

5

6. The peptide of any one of claims 1-5, comprising the amino acid sequence of Formula (I-A2):



or a pharmaceutically acceptable salt thereof, wherein:

10 R₂ is CONH₂, CO(DiFPip), CON(Me)₂, a polyethylene glycol chain, or a lipophilic substituent.

7. The peptide of any one of claims 1-6, comprising the amino acid sequence of Formula (I-A3):

15 R₁-X₃-X₄-X₅-X₆-X₇-X₈-X₉-X₁₀-X₁₁-X₁₂-X₁₃-X₁₄-X₁₅-X₁₆-X₁₇-R₂ (I-A3),

or a pharmaceutically acceptable salt thereof, wherein:

R₁ is 5Ava, 5cpaCO, 6Ahx, 7Ahp, CF₃CO, CF₃Propylamide, EtCO, MeCO, PEG₂, PEG₂NMe, a polyethylene glycol chain, or a lipophilic substituent, wherein the 5Ava, 6Ahx, 7Ahp, PEG₂, and PEG₂NMe are linked to the amino acid at X₁₃; and

20 R₂ is CONH₂, CO(DiFPip), CON(Me)₂, a polyethylene glycol chain, or a lipophilic substituent.

8. The peptide of any one of claims 1-7, or a pharmaceutically acceptable salt thereof, wherein the amino acid at X₃ is linked to the amino acid at X₁₃.

25

9. The peptide of any one of claims 1-7, or a pharmaceutically acceptable salt thereof, wherein the amino acid at X₅ is linked to the amino acid at X₁₀.

10. The peptide of any one of claims 1-7, or a pharmaceutically acceptable salt thereof, wherein the amino acid at X₁₀ is linked to the amino acid at X₁₃.

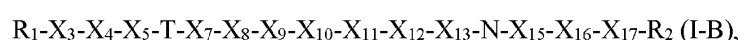
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11. The peptide of any one of claims 1-5 or 7, or a pharmaceutically acceptable salt thereof, wherein R₁ is linked to the amino acid at X₁₃.

12. The peptide of any one of claims 1-11, or a pharmaceutically acceptable salt thereof, wherein the amino acid at X₃, X₅, X₆, X₈, X₁₂, X₁₃, X₁₄, X₁₆, or X₁₇ is conjugated to a polyethylene glycol chain.

5 13. The peptide of any one of claims 1-112, or a pharmaceutically acceptable salt thereof, wherein the amino acid at X₃, X₅, X₆, X₈, X₁₂, X₁₃, X₁₄, X₁₆, or X₁₇ is conjugated to a lipophilic substituent.

14. The peptide of any one of claims 1-13, or a pharmaceutically acceptable salt thereof, comprising an amino acid sequence of Formula (I-B), comprising the amino acid sequence:



wherein:

R₁ is 5Ava, 5cpaCO, 6Ahx, 7Ahp, CF₃CO, CF₃Propylamide, EtCO, MeCO, PEG₂, PEG₂NMe, Z_{peg}, or Z_{lipid};

15 X₃ is Dab(COCH₂), K(COCH₂CH₂), hK(Me)₃, K, K(5cpa), K-Z_{peg}, K-Z_{lipid}, K(d), K(Me)₃, Ser(MePEG₂), R, SP6, or absent;

X₄ is 4AminoPro, Abu, aG, aMeC, C, Dap, Pen, Pen(oXyl), Pen(mXyl), Pen(pXyl), or Pra;

20 X₅ is D, E, hE, K, K(a), K(Ac), K(d), K(G), K(NMe), K(NNs), K-Z_{peg}, K-Z_{lipid}, L, N, N(NMe), N(NMe₂), Q, Q(NMe), or Q(NMe₂);

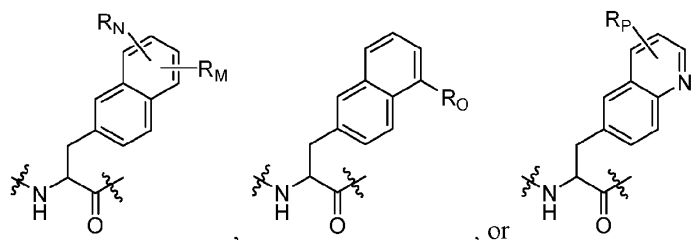
X₇ is 7(3NacPh)W, 7BrW, 7MeW, BT, or W;

X₈ is Dab(NMeAc), Dab(NMecarn), Dab-Z_{peg}, hK(Me)₃, K(Ac), K(Me)₃, K(NMeAc), NMeK-Z_{peg}, K-Z_{peg}, K-Z_{lipid}, Lys(N⁺Me₂)-Z_{peg}, Q, or Q(NMe₂);

X₉ is aMeC, aG, C, D, E, hE, Pen, or Dap(N₃);

25 X₁₀ is 4DMPzEF, 4OMeF, AEF, AEF(G), AEF(NMe), AEF(NMe₂), AEF-Z_{peg}, AEF(NMe)-Z_{peg}, APEG3F, bMeAEF, F, MMoEF, TMAPF, or Y;

X₁₁ is:



30 R_M is halo, -OH, -C₍₁₋₃₎alkyl, -OC(O)C₍₁₋₃₎haloalkyl, phenyl, or 5- to 6-membered heteroaryl, wherein the phenyl and 5- to 6-membered heteroaryl are each optionally substituted

with one to three groups selected from -OH, -OC₍₁₋₃₎alkyl, -C₍₁₋₃₎haloalkyl, and 3- to 6-membered heterocyclyl;

R_N is -H or -OH;

R_O is -OC₍₁₋₃₎alkyl or -C(O)NH₂;

5 R_P is halo, -OH, -C₍₁₋₃₎alkyl, -OC₍₁₋₃₎alkyl, -C(O)NH₂, -OC(O)C₍₁₋₃₎haloalkyl, phenyl, or 5- to 6-membered heteroaryl, wherein the phenyl and 5- to 6-membered heteroaryl are each optionally substituted with one to three groups selected from -OH, -OC₍₁₋₃₎alkyl, -C₍₁₋₃₎haloalkyl, and 3- to 6-membered heterocyclyl;

X₁₂ is THP, aMeL, diFCpx, or Pip(NMe₂);

10 X₁₃ is C, D, Dab(NMeAc), Dab(NMecarn), E, E(COcPEG3a), hE, K(Ac), K(Me)₃, K(NMeAc), K-Z_{peg}, K-Z_{lipid}, L, or Q(NMe₂);

X₁₅ is 3AmPyrazolAla, 3Pya, 5AmPyridinAla, 5MePyridinAla, Ala, ACIPA, aMePhe, H, or THP;

X₁₆ is Sar, NMeK-Z_{lipid}, or absent;

15 X₁₇ is K-Z_{lipid}, NMeK-Z_{lipid}, or absent;

R₂ is CONH₂, CO(DiFPip), CON(Me)₂, or Z_{peg};

Z_{peg}, independently for each occurrence, is a polyethylene glycol chain;

Z_{lipid}, independently for each occurrence, is a lipophilic substituent;

wherein the peptide is cyclized via a linkage between the residues at X₄ and X₉;

20 wherein:

(a) when R₁ is 5Ava, 6Ahx, 7Ahp, PEG₂, or PEG₂NMe, then the peptide further comprises a linkage between the residue at R₁ and a residue selected from E or hE at X₁₃;

(b) when X₃ is Dab(COCH₂), k(COCH₂CH₂), or Ser(MePEG₂), and optionally when X₃ is k, then the peptide further comprises a linkage between the residue at X₃ and a
25 residue selected from C, D, or hE at X₁₃;

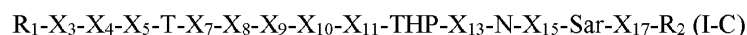
(c) when X₅ is D, E, hE, K, K(a), K(Ac), K(d), K(G), K(NMe), or K(NNs), and optionally when X₅ is K-Z_{peg} or K-Z_{lipid}, then the peptide further comprises a linkage between the residue at X₅ and a residue selected from AEF or AEF(NMe) at X₁₀;

(d) when X₁₀ is AEF or AEF(NMe), the peptide optionally further comprises a
30 linkage between the residue at X₁₀ and a residue selected from D, E, hE, K, K(a), K(Ac), K(d), K(G), K(NMe), K(NNs), K-Z_{peg}, and K-Z_{lipid} at X₅ or an E residue at X₁₃;

(e) when X₁₃ is C, D, or hE, and optionally when X₁₃ is E, then the peptide further comprises a linkage between the residue at X₁₃ and a residue selected from 5Ava, 6Ahx, 7Ahp, PEG₂, and PEG₂NMe at R₁ or a residue selected from Dab(COCH₂), k(COCH₂CH₂), k, and
35 Ser(MePEG₂) at X₃ or an AEF residue at X₁₀;

provided that the peptide comprises no more than one linkage between any one of R₁ and X₁₃, X₃ and X₁₃, X₅ and X₁₀, and X₁₀ and X₁₃.

15. The peptide of any one of claims 1-13, or a pharmaceutically acceptable salt thereof,
5 comprising an amino acid sequence of Formula (I-C):



wherein:

- R₁ is 5cpaCO, CF₃CO, MeCO, Z_{peg}, or Z_{lipid};
X₃ is hk(Me)₃, k, k-Z_{peg}, k-Z_{lipid}, k(d), k(Me)₃, K-Z_{peg}, K-Z_{lipid}, r, R, SP6, or absent
10 X₄ is 4AminoPro, Abu, aG, aMeC, C, Dap, Pen, Pen(oXyl), Pen(mXyl), Pen(pXyl), or Pra;
X₅ is D, E, hE, K, K(a), K(Ac), K(d), K(G), K(NMe), K(NNs), K-Z_{peg}, K-Z_{lipid}, N, N(NMe₂), Q, or Q(NMe₂);
X₇ is 7(3NAcPh)W, 7MeW, or W;
15 X₈ is Dab(NMeAc), Dab(NMecarn), Dab-Z_{peg}, K(Ac), K(NMeAc), NMeK-Z_{peg}, K-Z_{peg}, K-Z_{lipid}, Q, or Q(NMe₂);
X₉ is aMeC, aG, C, D, E, hE, Pen, or Dap(N₃);
X₁₀ is AEF, AEF(G), AEF(NMe), AEF(NMe₂), AEF-Z_{peg}, AEF(NMe)-Z_{peg}, bMeAEF, MMoEF, or TMAPF;
20 X₁₁ is 2Nal6((5CF₃)₃Pyrazole), 6OH₂Nal, 2Nal6(Ph₂OH), 2Nal6(Ph₄(NMorph)), 2Nal6(3Pyrazole), 2Nal6(4OMePh), 5OMe₂Nal, 5amido₂Nal, 5Br₂Nal, 5Me₂Nal, 6MeQui, 6O(COCF₃)₂Nal, 6F₂Nal, 6Br₂Nal, or 7OH₂Nal;
X₁₃ is Dab(NMeAc), Dab(NMecarn), E, K(Ac), K(NMeAc), K-Z_{peg}, or K-Z_{lipid};
X₁₅ is 3Pya, 5MePyridinAla, or THP;
25 X₁₇ is K-Z_{lipid}, NMeK-Z_{lipid}, or absent;
R₂ is CONH₂, CON(Me)₂, or Z_{peg};
Z_{peg}, independently for each occurrence, is a polyethylene glycol chain;
Z_{lipid}, independently for each occurrence, is a lipophilic substituent;
wherein the peptide is cyclized via a linkage between the residues at X₄ and X₉; and
30 wherein when X₅ is D, E, hE, K, K(a), K(Ac), K(d), K(G), K(NMe), or K(NNs), and optionally when X₅ is K-Z_{peg} or K-Z_{lipid}, then the peptide further comprises a linkage between the residue at X₅ and a residue selected from AEF or AEF(NMe) at X₁₀.

16. The peptide of any one of claims 1-13 or 15, or a pharmaceutically acceptable salt
35 thereof, comprising an amino acid sequence of Formula (I-D):

R_1 -X₃-Pen-X₅-T-X₇-X₈-Pen-X₁₀-6OH₂Nal-THP-X₁₃-N-3Py_a-Sar-X₁₇-R₂ (I-D)

wherein:

- R₁ is MeCO, Z_{peg}, or Z_{lipid};
- X₃ is k-Z_{peg}, k-Z_{lipid}, k(Me)₃, r, or absent
- 5 X₅ is D, E, hE, N, N(NMe₂), Q, or Q(NMe₂);
- X₇ is 7(3NAcPh)W, 7MeW, or W;
- X₈ is K(Ac), K(NMeAc), NMeK-Z_{peg}, K-Z_{peg}, or K-Z_{lipid};
- X₁₀ is AEF or TMAPF;
- X₁₃ is E, K(Ac), K(NMeAc), K-Z_{peg}, or K-Z_{lipid};
- 10 X₁₇ is K-Z_{lipid}, NMeK-Z_{lipid}, or absent;
- R₂ is CONH₂, CON(Me)₂, or Z_{peg};
- Z_{peg}, independently for each occurrence, is a polyethylene glycol chain;
- Z_{lipid}, independently for each occurrence, is a lipophilic substituent;
- wherein the peptide is cyclized via a linkage between the Pen residues at X₄ and X₉; and
- 15 wherein when X₅ is D, E, or hE, then the peptide further comprises a linkage between the residue at X₅ and the AEF residue at X₁₀.

17. The peptide of any one of claims 1-13, 15, or 16, or a pharmaceutically acceptable salt thereof, comprising an amino acid sequence of Formula (I-E):

20 R_1 -X₃-Pen-X₅-T-7(3NAcPh)W-X₈-Pen-X₁₀-6OH₂Nal-THP-X₁₃-N-3Py_a-Sar-X₁₇-R₂ (I-E)

wherein:

- R₁ is MeCO or Z_{peg};
- X₃ is r or absent
- X₅ is E, N, or N(NMe₂);
- 25 X₈ is K(Ac) or K(NMeAc);
- X₁₀ is AEF or TMAPF;
- X₁₃ is E, K(Ac), or K(NMeAc);
- X₁₇ is K-Z_{lipid} or absent;
- R₂ is CONH₂ or CON(Me)₂;
- 30 Z_{peg}, independently for each occurrence, is a polyethylene glycol chain;
- Z_{lipid}, independently for each occurrence, is a lipophilic substituent;
- wherein the peptide is cyclized via a linkage between the Pen residues at X₄ and X₉; and
- wherein when X₅ is E then the peptide further comprises a linkage between the E residue at X₅ and the AEF residue at X₁₀.

35

18. The peptide of claim 1-7, 12, or 13, or a pharmaceutically acceptable salt thereof, wherein:

R₁ is 5cpaCO, CF₃CO, CF₃Propylamide, EtCO, MeCO, Z_{peg}, or Z_{lipid};

X₃ is hk(Me)₃, k, k(5cpa), k-Z_{peg}, k-Z_{lipid}, k(d), k(Me)₃, K-Z_{peg}, K-Z_{lipid}, r, R, SP6, or

5 absent

X₄ is 4AminoPro, Abu, aG, aMeC, C, Dap, Pen, Pen(oXyl), Pen(mXyl), Pen(pXyl), or Pra;

X₅ is K-Z_{peg}, K-Z_{lipid}, L, N, N(NMe₂), Q, or Q(NMe₂);

X₇ is 7(3NAcPh)W, 7BrW, 7MeW, BT, or W;

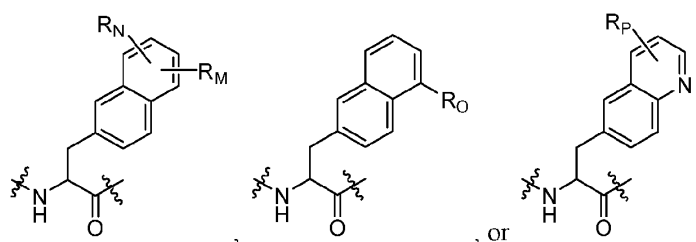
10 X₈ is Dab(NMeAc), Dab(NMecarn), Dab-Z_{peg}, hK(Me)₃, K(Ac), K(Me)₃, K(NMeAc), NMeK-Z_{peg}, K-Z_{peg}, K-Z_{lipid}, Lys(N+Me₂)-Z_{peg}, Q, or Q(NMe₂);

X₉ is aMeC, aG, C, D, E, hE, Pen, or Dap(N₃);

X₁₀ is 4DMPzEF, 4OMeF, AEF, AEF(G), AEF(NMe), AEF(NMe₂), AEF-Z_{peg},

AEF(NMe)-Z_{peg}, APEG3F, bMeAEF, F, MMoEF, TMAPF, or Y;

15 X₁₁ is:



R_M is halo, -OH, -C₍₁₋₃₎alkyl, -OC(O)C₍₁₋₃₎haloalkyl, phenyl, or 5- to 6-membered heteroaryl, wherein the phenyl and 5- to 6-membered heteroaryl are each optionally substituted with one to three groups selected from -OH, -OC₍₁₋₃₎alkyl, -C₍₁₋₃₎haloalkyl, and 3- to 6-membered heterocycle;

R_N is -H or -OH;

R_O is -OC₍₁₋₃₎alkyl or -C(O)NH₂;

20 R_P is halo, -OH, -C₍₁₋₃₎alkyl, -OC₍₁₋₃₎alkyl, -C(O)NH₂, -OC(O)C₍₁₋₃₎haloalkyl, phenyl, or 5- to 6-membered heteroaryl, wherein the phenyl and 5- to 6-membered heteroaryl are each optionally substituted with one to three groups selected from -OH, -OC₍₁₋₃₎alkyl, -C₍₁₋₃₎haloalkyl, and 3- to 6-membered heterocycle;

25 X₁₂ is THP, aMeL, diFCpx, or Pip(NMe₂);

X₁₃ is Dab(NMeAc), Dab(NMecarn), E, E(COcPEG3a), K(Ac), K(Me)₃, K(NMeAc), K-Z_{peg}, K-Z_{lipid}, L, or Q(NMe₂);

X₁₅ is 3AmPyrazolAla, 3Pya, 5AmPyridinAla, 5MePyridinAla, Ala, ACIPA, aMePhe, H, or THP;

X₁₆ is Sar, NMeK-Z_{lipid}, or absent;

X₁₇ is K-Z_{lipid}, NMeK-Z_{lipid}, or absent;

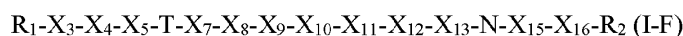
5 R₂ is CONH₂, CO(DiFPip), CON(Me)₂, or Z_{peg};

Z_{peg}, independently for each occurrence, is a polyethylene glycol chain;

Z_{lipid}, independently for each occurrence, is a lipophilic substituent;

wherein the peptide is cyclized via a linkage between the residues at X₄ and X₉.

10 19. The peptide of any one of claims 1-11, or a pharmaceutically acceptable salt thereof, comprising an amino acid sequence of Formula (I-F):



wherein:

R₁ is 5Ava, 5cpaCO, 6Ahx, 7Ahp, CF₃CO, CF₃Propylamide, EtCO, MeCO, PEG₂,

15 PEG₂NMe, or Z_{peg};

X₃ is Dab(COCH₂), k(COCH₂CH₂), hk(Me)₃, k, k(5cpa), k(d), k(Me)₃, Ser(MePEG₂), r, R, SP₆, or absent;

X₄ is 4AminoPro, Abu, aG, aMeC, C, Dap, Pen, Pen(oXyl), Pen(mXyl), Pen(pXyl), or Pra;

20 X₅ is D, E, hE, K, K(a), K(Ac), K(d), K(G), K(NMe), K(NNs), K-Z_{peg}, L, N, N(NMe), N(NMe₂), Q, Q(NMe), or Q(NMe₂);

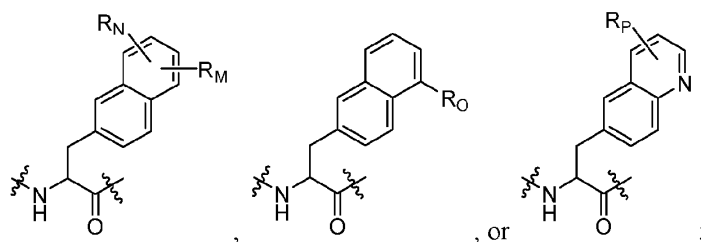
X₇ is 7(3NAcPh)W, 7BrW, 7MeW, BT, or W;

X₈ is Dab(NMeAc), Dab(NMecarn), Dab-Z_{peg}, hK(Me)₃, K(Ac), K(Me)₃, K(NMeAc), NMeK-Z_{peg}, K-Z_{peg}, Lys(N+Me₂)-Z_{peg}, Q, or Q(NMe₂);

25 X₉ is aMeC, aG, C, D, E, hE, Pen, or Dap(N₃);

X₁₀ is 4DMPzEF, 4OMeF, AEF, AEF(G), AEF(NMe), AEF(NMe₂), AEF-Z_{peg}, AEF(NMe)-Z_{peg}, APEG₃F, bMeAEF, F, MMoEF, TMAPF, or Y;

X₁₁ is:



R_M is halo, -OH, -C₍₁₋₃₎alkyl, -OC(O)C₍₁₋₃₎haloalkyl, phenyl, or 5- to 6-membered heteroaryl, wherein the phenyl and 5- to 6-membered heteroaryl are each optionally substituted with one to three groups selected from -OH, -OC₍₁₋₃₎alkyl, -C₍₁₋₃₎haloalkyl, and 3- to 6-membered heterocyclyl;

5 R_N is -H or -OH;

R_O is -OC₍₁₋₃₎alkyl or -C(O)NH₂;

R_P is halo, -OH, -C₍₁₋₃₎alkyl, -OC₍₁₋₃₎alkyl, -C(O)NH₂, -OC(O)C₍₁₋₃₎haloalkyl, phenyl, or 5- to 6-membered heteroaryl, wherein the phenyl and 5- to 6-membered heteroaryl are each optionally substituted with one to three groups selected from -OH, -OC₍₁₋₃₎alkyl, -C₍₁₋₃₎haloalkyl, 10 and 3- to 6-membered heterocyclyl;

X₁₂ is THP, aMeL, diFCpx, or Pip(NMe₂);

X₁₃ is C, D, Dab(NMeAc), Dab(NMecarn), E, E(COcPEG3a), hE, K(Ac), K(Me)₃, K(NMeAc), K-Z_{peg}, L, or Q(NMe₂);

X₁₅ is 3AmPyrazolAla, 3PyA, 5AmPyridinAla, 5MePyridinAla, Ala, ACIPA, aMePhe, H, 15 or THP;

X₁₆ is Sar or absent;

R₂ is CONH₂, CO(DiFPip), CON(Me)₂, or Z_{peg};

Z_{peg}, independently for each occurrence, is a polyethylene glycol;

wherein the peptide is cyclized via a linkage between the residues at X₄ and X₉;

20 wherein:

(a) when R₁ is 5Ava, 6Ahx, 7Ahp, PEG₂, or PEG₂NMe, then the peptide further comprises a linkage between the residue at R₁ and a residue selected from E or hE at X₁₃;

(b) when X₃ is Dab(COCH₂), k(COCH₂CH₂), or Ser(MePEG₂), and optionally when X₃ is k, then the peptide further comprises a linkage between the residue at X₃ and a 25 residue selected from C, D, or hE at X₁₃;

(c) when X₅ is D, E, hE, K, K(a), K(Ac), K(d), K(G), K(NMe), or K(NNs), and optionally when X₅ is K-Z_{peg}, then the peptide further comprises a linkage between the residue at X₅ and a residue selected from AEF or AEF(NMe) at X₁₀;

(d) when X₁₀ is AEF or AEF(NMe), the peptide optionally further comprises a 30 linkage between the residue at X₁₀ and a residue selected from D, E, hE, K, K(a), K(Ac), K(d), K(G), K(NMe), K(NNs), and K-Z_{peg} at X₅ or an E residue at X₁₃;

(e) when X₁₃ is C, D, or hE, and optionally when X₁₃ is E, then the peptide further comprises a linkage between the residue at X₁₃ and a residue selected from 5Ava, 6Ahx, 7Ahp, PEG₂, and PEG₂NMe at R₁ or a residue selected from Dab(COCH₂), k(COCH₂CH₂), k, and 35 Ser(MePEG₂) at X₃ or an AEF residue at X₁₀;

provided that the peptide comprises no more than one linkage between any one of R₁ and X₁₃, X₃ and X₁₃, X₅ and X₁₀, and X₁₀ and X₁₃.

20. The peptide of any one of claims 1-14, 18, or 19, or a pharmaceutically acceptable salt thereof, wherein the peptide is not MeCO-Pen-N-T-7MeW-K(Ac)-Pen-AEF-6OHQui-THP-E-N-3Pyra-Sar-CONH₂.

21. The peptide of any one of claims 5 or 7-16, or 18-20, or a pharmaceutically acceptable salt thereof, wherein R₁ is MeCO or Z_{peg}.

10

22. The peptide of any one of claims 5, 7-20, or a pharmaceutically acceptable salt thereof, wherein R₁ is MeCO.

23. The peptide of any one of claims 1-13 or 20-22, or a pharmaceutically acceptable salt thereof, wherein X₃ is Dab(COCH₂), Dab(NMeAc), Dab(NMecarn), Dab-Z_{peg}, Dab-Z_{lipid}, K(COCH₂CH₂), hK(Me)₃, K, K(5cpa), K(Ac), K(d), K(G), K(Me)₃, K(NMe), K(NMeAc), K(NNs), K-Z_{peg}, K-Z_{lipid}, NMeK-Z_{peg}, NMeK-Z_{lipid}, Ser(MePEG₂), R, SP₆, or absent; wherein the Dab(COCH₂), K(COCH₂CH₂), and Ser(MePEG₂) are linked to the amino acid at X₁₃.

20

24. The peptide of claim 1-13 or 20-22, or a pharmaceutically acceptable salt thereof, wherein X₃ is dDab(COCH₂), dDab(NMeAc), dDab(Nmecarn), dDab-Z_{peg}, dDab-Z_{lipid}, k(COCH₂CH₂), hk(Me)₃, k, k(5cpa), k(Ac), k(d), k(G), k(Me)₃, k(NMe), k(NMeAc), k(NNs), k-Z_{peg}, k-Z_{lipid}, NMek-Z_{peg}, NMek-Z_{lipid}, dSer(MePEG₂), r, SP₆, or absent; wherein the dDab(COCH₂), k(COCH₂CH₂), and dSer(MePEG₂) are linked to the amino acid at X₁₃.

25

25. The peptide of any one of claims 1-13 or 20-22, or a pharmaceutically acceptable salt thereof, wherein X₃ is Dab(COCH₂), k(COCH₂CH₂), hk(Me)₃, k, k(5cpa), k-Z_{peg}, k-Z_{lipid}, k(d), k(Me)₃, K-Z_{peg}, K-Z_{lipid}, Ser(MePEG₂), r, R, SP₆, or absent; wherein the Dab(COCH₂), k(COCH₂CH₂), and Ser(MePEG₂) are linked to the amino acid at X₁₃.

30

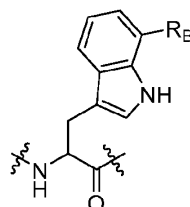
26. The peptide of any one of claims 1-13, 15, 16, 18, 20-22, 24, or 25, or a pharmaceutically acceptable salt thereof, wherein X₃ is k-Z_{peg}, k-Z_{lipid}, k(Me)₃, r, or absent.

35

27. The peptide of any one of claims 1-13, 15, 16, 18-22, or 24-26, or a pharmaceutically acceptable salt thereof, wherein X₃ is r.
- 5 28. The peptide of any one of claims 1-16 or 18-27, or a pharmaceutically acceptable salt thereof, wherein X₃ is absent.
29. The peptide of any one of claims 1-13 or 20-28, or a pharmaceutically acceptable salt thereof, wherein X₄ is Abu, C, or Pen.
- 10 30. The peptide of any one of claims 1-13 or 20-29, or a pharmaceutically acceptable salt thereof, wherein X₅ is D, E, hE, K, K(5cpa), K(a), K(Ac), K(d), K(G), K(Me)₃, K(NMe), K(NMeAc), K(NNs), K-Z_{peg}, K-Z_{lipid}, NMeK-Z_{peg}, NMeK-Z_{lipid}, L, N, N(NMe), N(NMe₂), Q, Q(NMe), or Q(NMe₂);
- 15 wherein the D, E, hE, K, K(a), K(Ac), K(d), K(G), K(NMe), and K(NNs) are linked to the amino acid at X₁₀, and optionally wherein the K-Z_{peg} or K-Z_{lipid} are linked to the amino acid at X₁₀.
31. The peptide of any one of claims 1-13 or 20-30, or a pharmaceutically acceptable salt thereof, wherein X₅ is D, E, hE, K, K(a), K(Ac), K(d), K(G), K(Nme), K(NNs), K-Z_{peg}, K-Z_{lipid}, L, N, N(NMe₂), Q, or Q(NMe₂);
- 20 wherein the D, E, hE, K, K(a), K(Ac), K(d), K(G), K(NMe), and K(NNs) are linked to the amino acid at X₁₀, and optionally wherein the K-Z_{peg} or K-Z_{lipid} are linked to the amino acid at X₁₀.
- 25 32. The peptide of any one of claims 1-15 or 19-31, or a pharmaceutically acceptable salt thereof, wherein X₅ is E, N, or N(NMe₂), wherein the E is linked to the amino acid at X₁₀.
33. The peptide of any one of claims 1-15 or 19-32, or a pharmaceutically acceptable salt thereof, wherein X₅ is E linked to an AEF residue at X₁₀.
- 30 34. The peptide of any one of claims 1-15 or 19-32, or a pharmaceutically acceptable salt thereof, wherein X₅ is N.

35. The peptide of any one of claims 1-13 or 20-34, or a pharmaceutically acceptable salt thereof, wherein X₆ is T.

36. The peptide of any one of claims 1-13 or 20-35, or a pharmaceutically acceptable salt thereof, wherein X₇ is:



37. The peptide of any one of claims 1-13 or 20-35, or a pharmaceutically acceptable salt thereof, wherein X₇ is 7(3NacPh)W, 7BrW, 7MeW, BT, or W.

10

38. The peptide of any one of claims 1-16 or 18-37, or a pharmaceutically acceptable salt thereof, wherein X₇ is 7(3NacPh)W or 7MeW.

39. The peptide of any one of claims 1-13 or 20-38, or a pharmaceutically acceptable salt thereof, wherein X₈ is Dab(NMeAc), Dab(NMecarn), Dab-Z_{peg}, Dab-Z_{lipid}, hK(Me)₃, K, K(5cpa), K(Ac), K(d), K(G), K(Me)₃, K(NMe), K(NMeAc), K(NNs), K-Z_{peg}, K-Z_{lipid}, NMeK-Z_{peg}, NMeK-Z_{lipid}, Lys(N+Me₂)-Z_{peg}, Lys(N+Me₂)-Z_{lipid}, Q, or Q(NMe₂).

40. The peptide of any one of claims 1-13 or 20-39, or a pharmaceutically acceptable salt thereof, wherein X₈ is Dab(NMeAc), Dab(NMecarn), Dab-Z_{peg}, hK(Me)₃, K(Ac), K(Me)₃, K(NMeAc), NMeK-Z_{peg}, K-Z_{peg}, K-Z_{lipid}, Lys(N+Me₂)-Z_{peg}, Q, or Q(NMe₂).

41. The peptide of any one of claims 1-15, 18, or 20-40, or a pharmaceutically acceptable salt thereof, wherein X₈ is K(Ac), K(NMeAc), NMeK-Z_{peg}, K-Z_{peg}, or K-Z_{lipid}.

25

42. The peptide of any one of claims 1-15 or 18-41, or a pharmaceutically acceptable salt thereof, wherein X₈ is K(Ac) or K(NMeAc).

43. The peptide of any one of claims 1-13 or 20-42, or a pharmaceutically acceptable salt thereof, wherein X₉ is aMeC, C, or Pen.

30

44. The peptide of any one of claims 1-15 or 18-43, or a pharmaceutically acceptable salt thereof, wherein:

X₄ is Abu and X₉ is aMeC;

X₄ is Abu and X₉ is C;

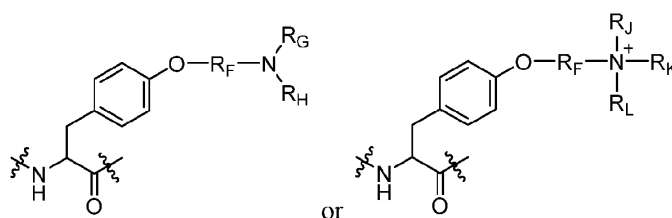
5 X₄ is C and X₉ is aMeC; or

X₄ is Pen and X₉ is Pen.

45. The peptide of any one of claims 1-15 or 18-44, or a pharmaceutically acceptable salt thereof, wherein X₄ is Pen and X₉ is Pen.

10

46. The peptide of any one of claims 1-13 or 20-45, or a pharmaceutically acceptable salt thereof, wherein X₁₀ is:



15 47. The peptide of any one of claims 1-13 or 20-45, or a pharmaceutically acceptable salt thereof, wherein X₁₀ is 4DMPzEF, 4OMeF, AEF, AEF(G), AEF(NMe), AEF(NMe₂), AEF-Z_{peg}, AEF(NMe)-Z_{peg}, APEG3F, bMeAEF, F, MMoEF, TMAPF, or Y.;

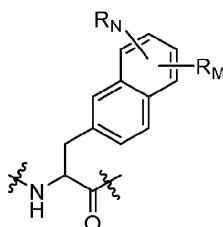
optionally wherein the AEF or AEF(NMe) is linked to the amino acid at X₅ or the amino acid at X₁₃.

20

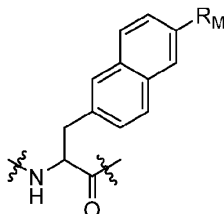
48. The peptide of any one of claims 1-47, or a pharmaceutically acceptable salt thereof, wherein X₁₀ is AEF.

49. The peptide of any one of claims 1-13 or 20-48, or a pharmaceutically acceptable salt thereof, wherein X₁₁ is:

25



50. The peptide of any one of claims 1-13 or 20-49, or a pharmaceutically acceptable salt thereof, wherein X_{11} is:



5

51. The peptide of any one of claims 1-14 or 18-48, or a pharmaceutically acceptable salt thereof, wherein X_{11} is 2Nal6((5CF₃)3Pyrazole), 6OH₂Nal, 2Nal6(Ph₂OH), 2Nal6(Ph₄(NMorph)), 2Nal6(3Pyrazole), 2Nal6(4OMePh), 5OMe₂Nal, 5amido₂Nal, 5Br₂Nal, 5Me₂Nal, 6MeQui, 6O(COCF₃)₂Nal, 6F₂Nal, 6Br₂Nal, or 7OH₂Nal.

10

52. The peptide of any one of claims 1-15 or 18-49, or a pharmaceutically acceptable salt thereof, wherein X_{11} is 2Nal6((5CF₃)3Pyrazole), 6OH₂Nal, 2Nal6(Ph₂OH), 2Nal6(Ph₄(NMorph)), 2Nal6(3Pyrazole), 2Nal6(4OMePh), 5Br₂Nal, 5Me₂Nal, 6O(COCF₃)₂Nal, 6F₂Nal, 6Br₂Nal, or 7OH₂Nal.

15

53. The peptide of any one of claims 1-15 or 18-52, or a pharmaceutically acceptable salt thereof, wherein X_{11} is 6OH₂Nal.

54. The peptide of any one of claims 1-13 or 20-53, or a pharmaceutically acceptable salt thereof, wherein X_{12} is THP, aMeL, diFCpx, or Pip(Nme₂).

20

55. The peptide of any one of claims 1-14 or 18-54, or a pharmaceutically acceptable salt thereof, wherein X_{12} is THP.

25 56. The peptide of any one of claims 1-13 or 20-55, or a pharmaceutically acceptable salt thereof, wherein X_{13} is C, D, Dab(NMeAc), Dab(NMecarn), Dab-Z_{peg}, Dab-Z_{lipid}, E, E(COcPEG3a), hE, K, K(5cpa), K(Ac), K(d), K(G), K(Me)₃, K(NMe), K(NMeAc), K(NNs), K-Z_{peg}, K-Z_{lipid}, NMeK-Z_{peg}, NMeK-Z_{lipid}, L, or Q(NMe₂);

30 wherein the C, D, and hE are linked to R₁, the amino acid at X₃, or the amino acid at X₁₀, and optionally wherein the E is linked to R₁, the amino acid at X₃, or the amino acid at X₁₀.

57. The peptide of any one of claims 1-13 or 20-56, or a pharmaceutically acceptable salt thereof, wherein X_{13} is Dab(NMeAc), Dab(NMecarn), E, K(Ac), K(NMeAc), K-Z_{peg}, or K-Z_{lipid}.

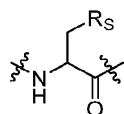
58. The peptide of any one of claims 1-16 or 18-57, or a pharmaceutically acceptable salt thereof, wherein X_{13} is E, K(Ac), or K(NMeAc).

59. The peptide of any one of claims 1-58, or a pharmaceutically acceptable salt thereof, wherein X_{13} is E.

60. The peptide of any one of claims 1-58, or a pharmaceutically acceptable salt thereof, wherein X_{13} is K(Ac).

61. The peptide of any one of claims 1-13 or 20-60, or a pharmaceutically acceptable salt thereof, wherein X_{14} is N.

62. The peptide of any one of claims 1-13 or 20-61, or a pharmaceutically acceptable salt thereof, wherein X_{15} is:



63. The peptide of any one of claims 1-13 or 20-61, or a pharmaceutically acceptable salt thereof, wherein X_{15} is 3AmPyrazolAla, 3Py, 5AmPyridinAla, 5MePyridinAla, Ala, ACIPA, aMePhe, H, or THP.

64. The peptide of any one of claims 1-15 or 18-63, or a pharmaceutically acceptable salt thereof, wherein X_{15} is 3Py.

65. The peptide of any one of claims 1-13 or 20-64, or a pharmaceutically acceptable salt thereof, wherein X_{16} is Sar, Dab-Z_{peg}, Dab-Z_{lipid}, K-Z_{peg}, K-Z_{lipid}, NMeK-Z_{peg}, NMeK-Z_{lipid}, or absent.

66. The peptide of any one of claims 1-13 or 20-65, or a pharmaceutically acceptable salt thereof, wherein X_{16} is Sar, NMeK-Z_{lipid}, or absent.

67. The peptide of any one of claims 1-14 or 18-66, or a pharmaceutically acceptable salt thereof, wherein X₁₆ is Sar.
68. The peptide of any one of claims 1-13 or 20-67, or a pharmaceutically acceptable salt thereof, wherein X₁₇ is Dab-Z_{peg}, Dab-Z_{lipid}, K-Z_{peg}, K-Z_{lipid}, NMeK-Z_{peg}, NMeK-Z_{lipid}, or absent.
69. The peptide of any one of claims 1-13 or 20-68, or a pharmaceutically acceptable salt thereof, wherein X₁₇ is K-Z_{lipid}, NMeK-Z_{lipid}, or absent.
70. The peptide of any one of claims 1-18 or 20-69, or a pharmaceutically acceptable salt thereof, wherein X₁₇ is K-Z_{lipid}.
71. The peptide of any one of claims 1-18 or 20-70, or a pharmaceutically acceptable salt thereof, wherein X₁₇ is absent.
72. The peptide of any one of claims 6-71, or a pharmaceutically acceptable salt thereof, wherein R₂ is CONH₂.
73. The peptide of any one of claims 1-13, or a pharmaceutically acceptable salt thereof, comprising a sequence according to any one of the following Formulas:
- X₃-X₄-X₅-X₆-7MeW-X₈-X₉-X₁₀-X₁₁-X₁₂-X₁₃-X₁₄-X₁₅-X₁₆-X₁₇ (I-G1a),
X₃-X₄-X₅-X₆-7(3NAcPh)W-X₈-X₉-X₁₀-X₁₁-X₁₂-X₁₃-X₁₄-X₁₅-X₁₆-X₁₇ (I-G1b),
X₃-X₄-X₅-X₆-X₇-X₈-X₉-AEF-X₁₁-X₁₂-X₁₃-X₁₄-X₁₅-X₁₆-X₁₇ (I-H1),
X₃-X₄-X₅-X₆-X₇-X₈-X₉-X₁₀-6OH2Nal-X₁₂-X₁₃-X₁₄-X₁₅-X₁₆-X₁₇ (I-I1),
X₃-X₄-X₅-X₆-X₇-X₈-X₉-X₁₀-X₁₁-X₁₂-X₁₃-X₁₄-3Pya-X₁₆-X₁₇ (I-J1),
X₃-X₄-X₅-X₆-7MeW-X₈-X₉-AEF-6OH2Nal-X₁₂-X₁₃-X₁₄-3Pya-X₁₆-X₁₇ (I-K1a),
X₃-X₄-X₅-X₆-7(3NAcPh)W-X₈-X₉-AEF-6OH2Nal-X₁₂-X₁₃-X₁₄-3Pya-X₁₆-X₁₇ (I-K1b),
r-X₄-X₅-X₆-7MeW-X₈-X₉-AEF-6OH2Nal-X₁₂-X₁₃-X₁₄-3Pya-X₁₆-X₁₇ (I-L1a),
r-X₄-X₅-X₆-7(3NAcPh)W-X₈-X₉-AEF-6OH2Nal-X₁₂-X₁₃-X₁₄-3Pya-X₁₆-X₁₇ (I-L1b),
X₃-Pen-X₅-X₆-7MeW-X₈-Pen-AEF-6OH2Nal-X₁₂-X₁₃-X₁₄-3Pya-X₁₆-X₁₇ (I-M1a),
X₃-Pen-X₅-X₆-7(3NAcPh)W-X₈-Pen-AEF-6OH2Nal-X₁₂-X₁₃-X₁₄-3Pya-X₁₆-X₁₇ (I-M1b),
X₃-X₄-X₅-X₆-7MeW-X₈-X₉-AEF-6OH2Nal-X₁₂-X₁₃-X₁₄-3Pya-Sar-X₁₇ (I-N1a),
X₃-X₄-X₅-X₆-7(3NAcPh)W-X₈-X₉-AEF-6OH2Nal-X₁₂-X₁₃-X₁₄-3Pya-Sar-X₁₇ (I-N1b),
X₃-X₄-X₅-X₆-7MeW-X₈-X₉-AEF-6OH2Nal-X₁₂-X₁₃-X₁₄-3Pya-X₁₆ (I-O1a), or

X₃-X₄-X₅-X₆-7(3NAcPh)W-X₈-X₉-AEF-6OH₂Nal-X₁₂-X₁₃-X₁₄-3Py_a-X₁₆ (I-O1b).

74. The peptide of any one of claims 1-4, or a pharmaceutically acceptable salt thereof, comprising a sequence according to any one of the following Formulas:
- 5 R₁-X₃-X₄-X₅-T-7MeW-X₈-X₉-X₁₀-X₁₁-X₁₂-X₁₃-N-X₁₅-X₁₆-X₁₇-R₂ (I-G2a),
 R₁-X₃-X₄-X₅-T-7(3NAcPh)W-X₈-X₉-X₁₀-X₁₁-X₁₂-X₁₃-N-X₁₅-X₁₆-X₁₇-R₂ (I-G2b),
 R₁-X₃-X₄-X₅-T-X₇-X₈-X₉-AEF-X₁₁-X₁₂-X₁₃-N-X₁₅-X₁₆-X₁₇-R₂ (I-H2),
 R₁-X₃-X₄-X₅-T-X₇-X₈-X₉-X₁₀-6OH₂Nal-X₁₂-X₁₃-N-X₁₅-X₁₆-X₁₇-R₂ (I-I2),
 R₁-X₃-X₄-X₅-T-X₇-X₈-X₉-X₁₀-X₁₁-X₁₂-X₁₃-N-3Py_a-X₁₆-X₁₇-R₂ (I-J2),
 10 R₁-X₃-X₄-X₅-T-7MeW-X₈-X₉-AEF-6OH₂Nal-X₁₂-X₁₃-N-3Py_a-X₁₆-X₁₇-R₂ (I-K2a),
 R₁-X₃-X₄-X₅-T-7(3NAcPh)W-X₈-X₉-AEF-6OH₂Nal-X₁₂-X₁₃-N-3Py_a-X₁₆-X₁₇-R₂ (I-K2b),
 R₁-r-X₄-X₅-T-7MeW-X₈-X₉-AEF-6OH₂Nal-X₁₂-X₁₃-N-3Py_a-X₁₆-X₁₇-R₂ (I-L2a),
 R₁-r-X₄-X₅-T-7(3NAcPh)W-X₈-X₉-AEF-6OH₂Nal-X₁₂-X₁₃-N-3Py_a-X₁₆-X₁₇-R₂ (I-L2b),
 15 R₁-X₃-Pen-X₅-T-7MeW-X₈-Pen-AEF-6OH₂Nal-X₁₂-X₁₃-N-3Py_a-X₁₆-X₁₇-R₂ (I-M2a),
 R₁-X₃-Pen-X₅-T-7(3NAcPh)W-X₈-Pen-AEF-6OH₂Nal-X₁₂-X₁₃-N-3Py_a-X₁₆-X₁₇-R₂ (I-M2b),
 R₁-X₃-X₄-X₅-T-7MeW-X₈-X₉-AEF-6OH₂Nal-X₁₂-X₁₃-N-3Py_a-Sar-X₁₇-R₂ (I-N2a),
 R₁-X₃-X₄-X₅-T-7(3NAcPh)W-X₈-X₉-AEF-6OH₂Nal-X₁₂-X₁₃-N-3Py_a-Sar-X₁₇-R₂ (I-N2b),
 20 N2b),
 R₁-X₃-X₄-X₅-T-7MeW-X₈-X₉-AEF-6OH₂Nal-X₁₂-X₁₃-N-3Py_a-X₁₆-R₂ (I-O2a), or
 R₁-X₃-X₄-X₅-T-7(3NAcPh)W-X₈-X₉-AEF-6OH₂Nal-X₁₂-X₁₃-N-3Py_a-X₁₆-R₂ (I-O2b).

75. The peptide of any one of claims 1, 3, 5-7, 12, 13, or 21-74, wherein the first ring comprises 4-9 or 11 amino acids.

76. The peptide of any one of claims 1, 3, 5-7, 12, 13, or 21-74, wherein the first ring is formed between X₄ and X₉, X₄ and X₁₃, X₅ and X₁₀, X₃ and X₁₃, or X₆ and X₉.

- 30 77. The peptide of claim 76, wherein the first ring is formed between X₄ and X₉, X₄ and X₁₃, or X₆ and X₉.

78. The peptide of claim 77, wherein the first ring is formed between X₄ and X₉ via a linker having one or more groups selected from the group consisting of a disulfide, thioether, amide, olefin, ether, alkylene, and triazole.

79. The peptide of claim 77, wherein the first ring is formed between X₄ and X₁₃ via a linker having one or more groups selected from the group consisting of a disulfide, thioether, amide, olefin, ether, alkylene, and triazole.
- 5
80. The peptide of claim 77, wherein the first ring is formed between X₆ and X₉ via a linker having one or more groups selected from the group consisting of a disulfide, thioether, amide, olefin, ether, alkylene, and triazole.
- 10
81. The peptide of any one of claims 1, 3, 5-7, 12, 13, or 21-80, wherein the peptide is further cyclized to form a second ring comprising 4-11 or 14 amino acids.
82. The peptide of claim 81, wherein the peptide is further cyclized to form a second ring comprising 4, 6, 10, or 11 amino acids.
- 15
83. The peptide of claim 78, wherein the peptide is further cyclized to form a second ring, wherein:
- the second ring is formed between X₃ and X₁₃ via a linker having one or more groups selected from the group consisting of a disulfide, thioether, amide, olefin, ether, alkylene, and
- 20 triazole;
- the second ring is formed between X₅ and X₁₀ via a linker having one or more groups selected from the group consisting of a disulfide, thioether, amide, olefin, ether, alkylene, and triazole;
- the second ring is formed between X₁₀ and X₁₃ via a linker having one or more groups
- 25 selected from the group consisting of a disulfide, thioether, amide, olefin, ether, alkylene, and triazole; or
- the second ring is formed between X₁₃ and the N-terminus of the peptide via a linker having one or more groups selected from the group consisting of a disulfide, thioether, amide, olefin, ether, alkylene, and triazole.
- 30
84. The peptide of claim 79, wherein the peptide is further cyclized to form a second ring, wherein:
- the second ring is formed between X₅ and X₁₀ via a linker having one or more groups selected from the group consisting of a disulfide, thioether, amide, olefin, ether, alkylene, and
- 35 triazole; or

the second ring is formed between X₆ and X₉ via a linker having one or more groups selected from the group consisting of a disulfide, thioether, amide, olefin, ether, alkylene, and triazole.

- 5 85. The peptide of claim 80, wherein the peptide is further cyclized to form a second ring, wherein:

the second ring is formed between X₃ and X₁₃ via a linker having one or more groups selected from the group consisting of a disulfide, thioether, amide, olefin, ether, alkylene, and triazole;

- 10 the second ring is formed between X₄ and X₁₃ via a linker having one or more groups selected from the group consisting of a disulfide, thioether, amide, olefin, ether, alkylene, and triazole;

the second ring is formed between X₅ and X₁₀ via a linker having one or more groups selected from the group consisting of a disulfide, thioether, amide, olefin, ether, alkylene, and

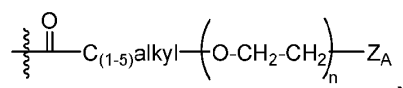
- 15 triazole;

the second ring is formed between X₁₀ and X₁₃ via a linker having one or more groups selected from the group consisting of a disulfide, thioether, amide, olefin, ether, alkylene, and triazole; or

- the second ring is formed between X₁₃ and the N-terminus of the peptide via a linker
20 having one or more groups selected from the group consisting of a disulfide, thioether, amide, olefin, ether, alkylene, and triazole.

86. The peptide of any one of claims 1-85, or a pharmaceutically acceptable salt thereof, wherein each polyethylene glycol chain, independently, terminates in an ammonium group or a
25 methyl group.

87. The peptide of any one of claims 1-86, or a pharmaceutically acceptable salt thereof, wherein each polyethylene glycol chain, independently for each occurrence, is:



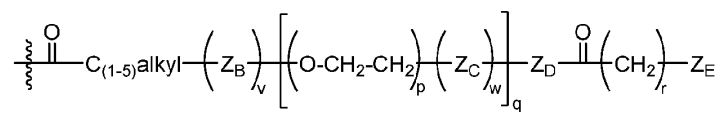
- 30 wherein:

Z_A is -OCH₃ or -N⁺(CH₃)₃; and

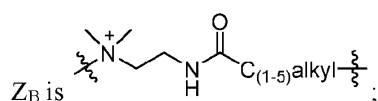
n is an integer from 2 to 15.

88. The peptide of any one of claims 1-87, or a pharmaceutically acceptable salt thereof, wherein R₁, R₂ or any amino acid in the amino acid sequence is conjugated to a polyethylene glycol chain.

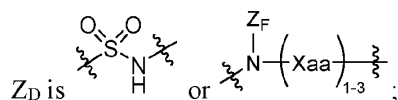
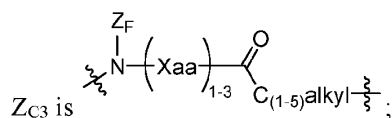
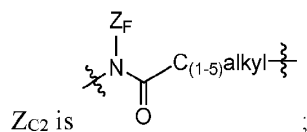
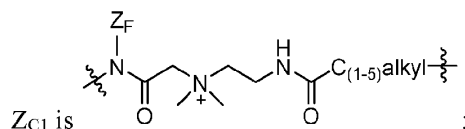
- 5 89. The peptide of any one of claims 5-7, 13-18 or 20-88, or a pharmaceutically acceptable salt thereof, wherein each lipophilic substituent, independently for each occurrence, is:



wherein:



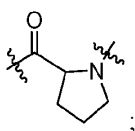
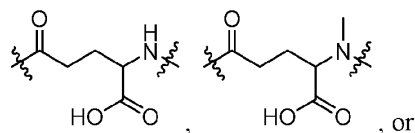
Z_C is $\text{Z}_{\text{C}1}$, $\text{Z}_{\text{C}2}$, or $\text{Z}_{\text{C}3}$;



15 Z_E is -H, -COOH, or tetrazolyl;

Z_F is -H or -CH₃;

Xaa is, independently for each occurrence,



p , independently for each occurrence, is 1, 2, 3, 4, 5, or 6;

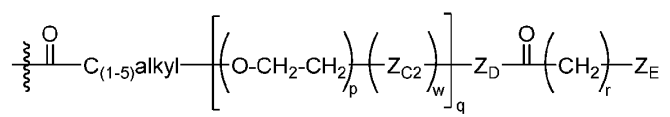
20 q is 1, 2, 3, 4, 5, or 6;

r is an integer from 6 to 24;

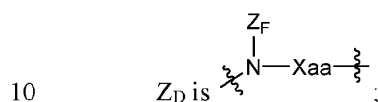
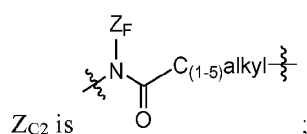
v is 0 or 1; and

w, independently for each occurrence, is 0 or 1.

90. The peptide of any one of claims 12-18 or 20-89, or a pharmaceutically acceptable salt thereof, wherein each lipophilic substituent, independently for each occurrence, is

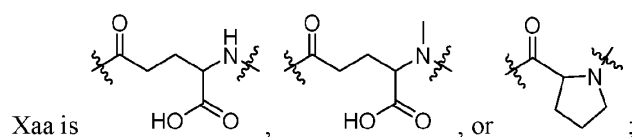


wherein:



Z_E is -H, -COOH, or tetrazolyl;

Z_F is -H or -CH₃;



p, independently for each occurrence, is 1, 2, 3, 4, 5, or 6;

q is 1, 2, 3, 4, 5, or 6;

r is an integer from 6 to 24; and

w, independently for each occurrence, is 0 or 1.

91. The peptide of any one of claims 1-18 or 20-88, or a pharmaceutically acceptable salt thereof, wherein R₁, R₂ or any amino acid in the amino acid sequence is conjugated to a lipophilic substituent.

92. The peptide of any one of claims 12-18 or 20-91, wherein the peptide comprises no more than one lipophilic substituent.

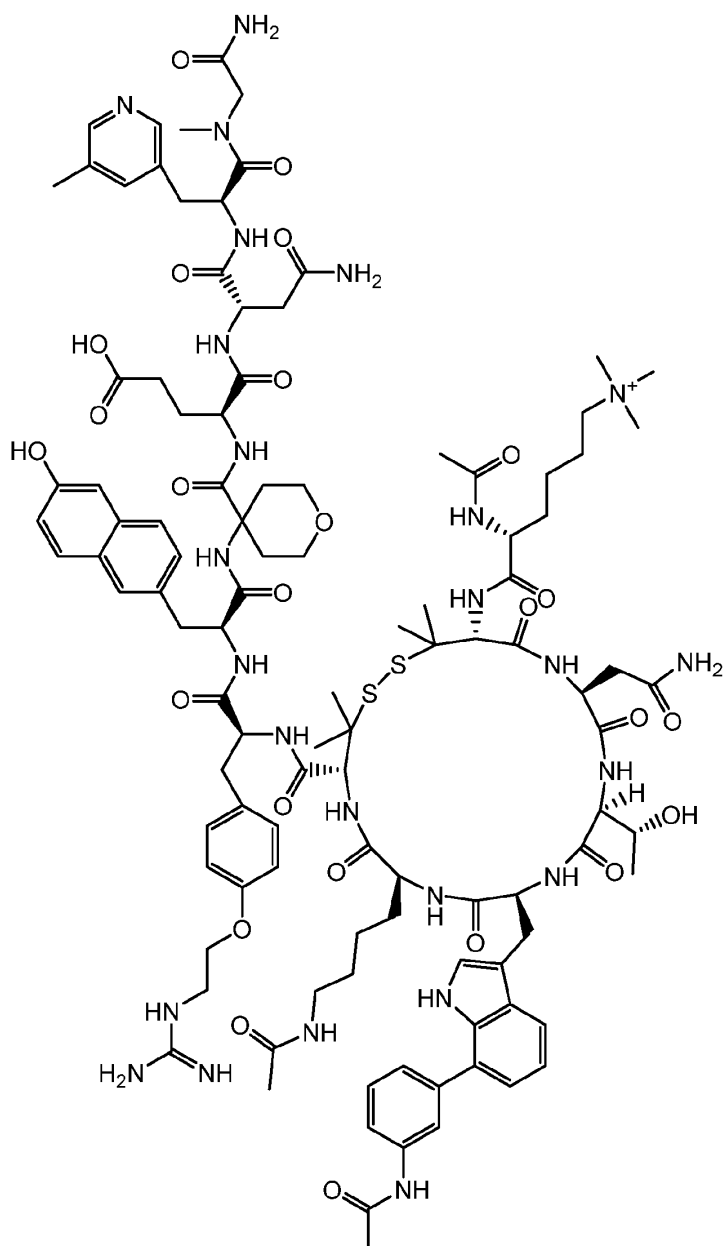
25

93. A peptide having the amino acid sequence of any one of SEQ ID NOS: 1-447, or a pharmaceutically acceptable salt thereof.

94. The peptide of claim 93 having an amino acid sequence selected from the group consisting of:

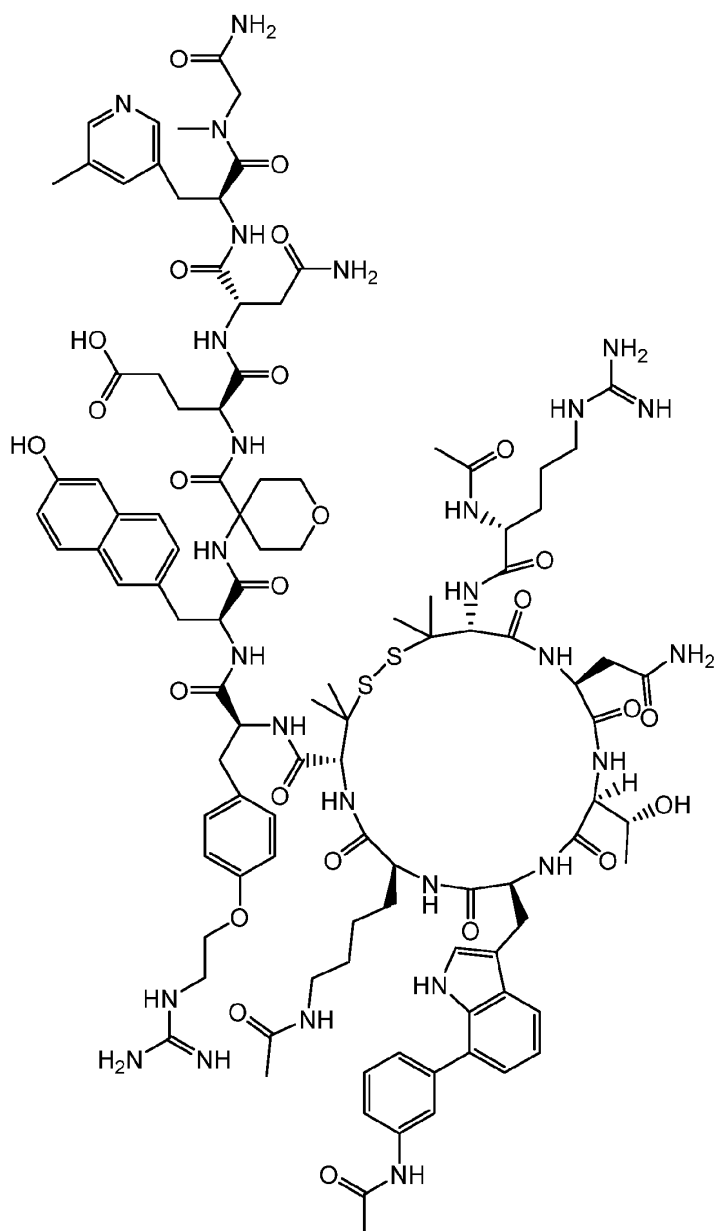
- MeCO-k(Me)₃-Pen(3)-N-T-7(3NAcPh)W-K(Ac)-Pen(3)-AEF(G)-6OH₂Nal-THP-E-N-
 5 5MePyridinAla-Sar-CONH₂ (SEQ ID NO: 11),
 MeCO-r-Pen(3)-N-T-7(3NAcPh)W-K(Ac)-Pen(3)-AEF(G)-6OH₂Nal-THP-E-N-
 5MePyridinAla-Sar-CONH₂ (SEQ ID NO: 15),
 cPEG3aCO-Pen(3)-N-T-7(3NAcPh)W-K(Ac)-Pen(3)-AEF(G)-6OH₂Nal-THP-
 K(NMeAc)-N-3Pyra-Sar-CONH₂ (SEQ ID NO: 34),
 10 MeCO-r-Pen(3)-N-T-7MeW-K(Ac)-Pen(3)-TMAPF-6OH₂Nal-THP-E-N-3Pyra-Sar-
 CONH₂ (SEQ ID NO: 59),
 MeCO-k(Me)₃-Pen(3)-N-T-7(3NAcPh)W-K(Ac)-Pen(3)-AEF-6OH₂Nal-THP-E-N-
 3Pyra-Sar-CONH₂ (SEQ ID NO: 68),
 5cpaCO-Pen(3)-K(5)-T-7MeW-K(Ac)-Pen(3)-AEF(5)-6OH₂Nal-THP-K(Ac)-N-3Pyra-
 15 Sar-CONH₂ (SEQ ID NO: 112)
 MeCO-r-Pen(3)-N-T-7(3NAcPh)W-K(Ac)-Pen(3)-AEF-6OH₂Nal-THP-E-N-3Pyra-Sar-
 CONH₂ (SEQ ID NO: 287),
 MeCO-Pen(3)-N(NMe₂)-T-7MeW-K(NMeAc)-Pen(3)-AEF(NMePEG3a)-6OH₂Nal-
 THP-K(NMeAc)-N-3Pyra-Sar-CONH(PEG3a) (SEQ ID NO: 315),
 20 cPEG3aCO-Pen(3)-N-T-7MeW-K(NMePEG3a)-Pen(3)-AEF-6OH₂Nal-THP-E-N-
 3Pyra-Sar-CONH₂ (SEQ ID NO: 319),
 PEG2NMe(2)-Pen(3)-N-T-7MeW-K(NMeAc)-Pen(3)-AEF-6OH₂Nal-THP-hE(2)-N-
 3Pyra-Sar-CONH₂ (SEQ ID NO: 358),
 cPEG3aCO-Pen(3)-E(2)-T-7MeW-K(Ac)-Pen(3)-AEF(2)-6OH₂Nal-THP-K(Ac)-N-
 25 3Pyra-Sar-CONH₂ (SEQ ID NO: 364),
 cPEG3aCO-Pen(3)-N(NMe₂)-T-7MeW-K(NMeAc)-Pen(3)-AEF-6OH₂Nal-THP-
 Dab(NMeAc)-N-3Pyra-Sar-CON(Me)₂ (SEQ ID NO: 371),
 cPEG3aCO-k(2)-Pen(3)-N(NMe₂)-T-7MeW-K(NMeAc)-Pen(3)-AEF-6OH₂Nal-THP-
 hE(2)-N-3Pyra-Sar-CON(Me)₂ (SEQ ID NO: 373), and
 30 cPEG3aCO-Pen(3)-N-T-7MeW-K(NMeAc)-Pen(3)-AEF-6OH₂Nal-THP-Q(NMe₂)-N-
 3Pyra-Sar-CONH₂ (SEQ ID NO: 392),
 or a pharmaceutically acceptable salt thereof.

95. A peptide having the following structure:



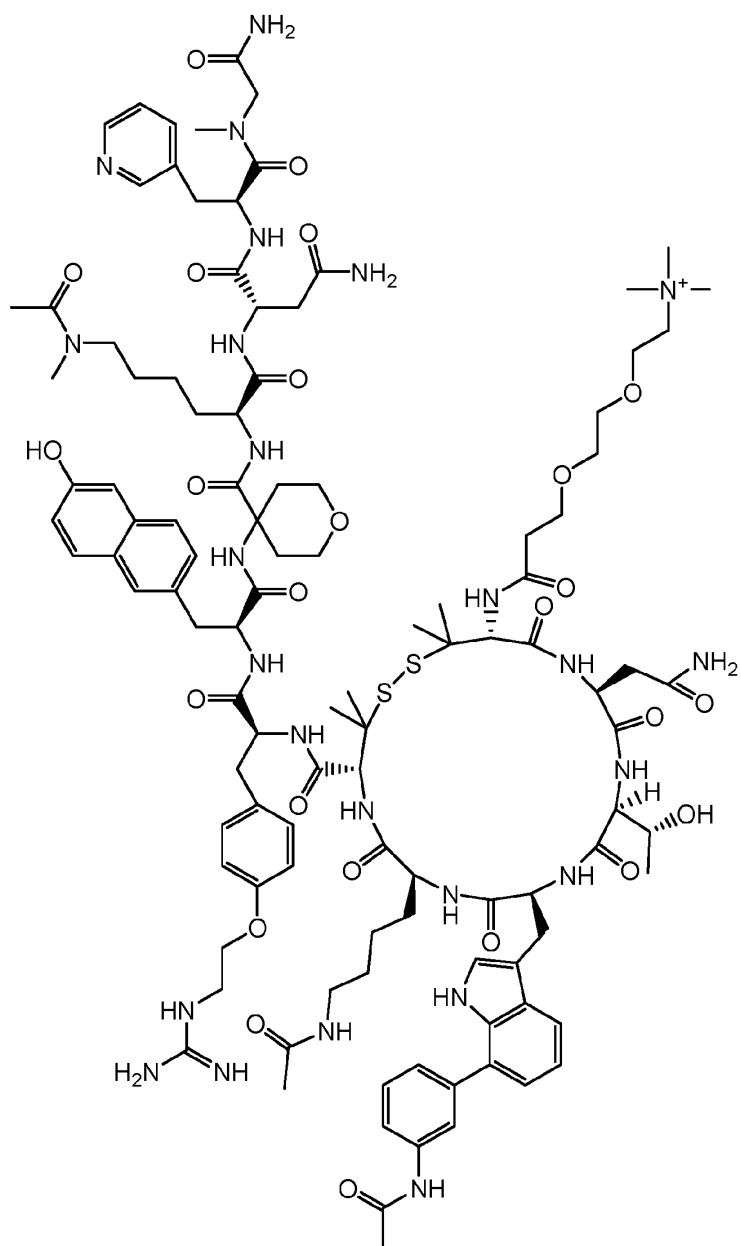
or a pharmaceutically acceptable salt thereof.

96. A peptide having the following structure:



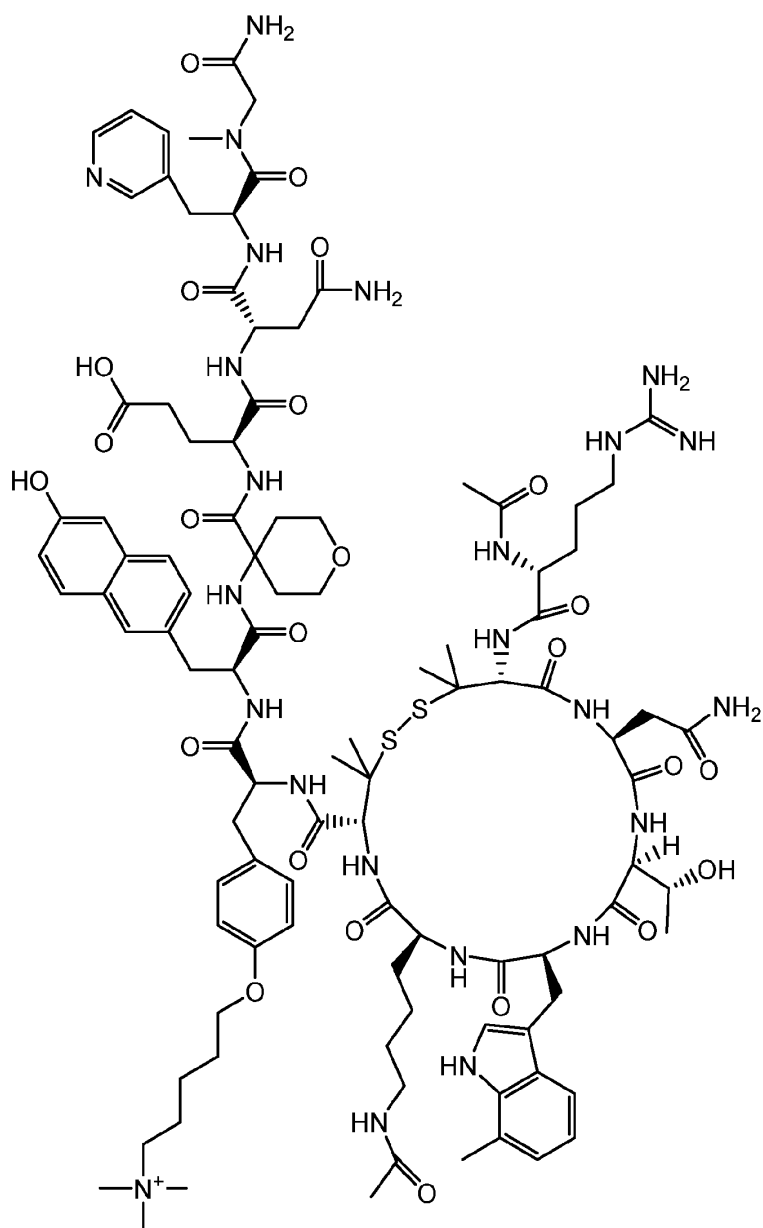
or a pharmaceutically acceptable salt thereof.

97. A peptide having the following structure:



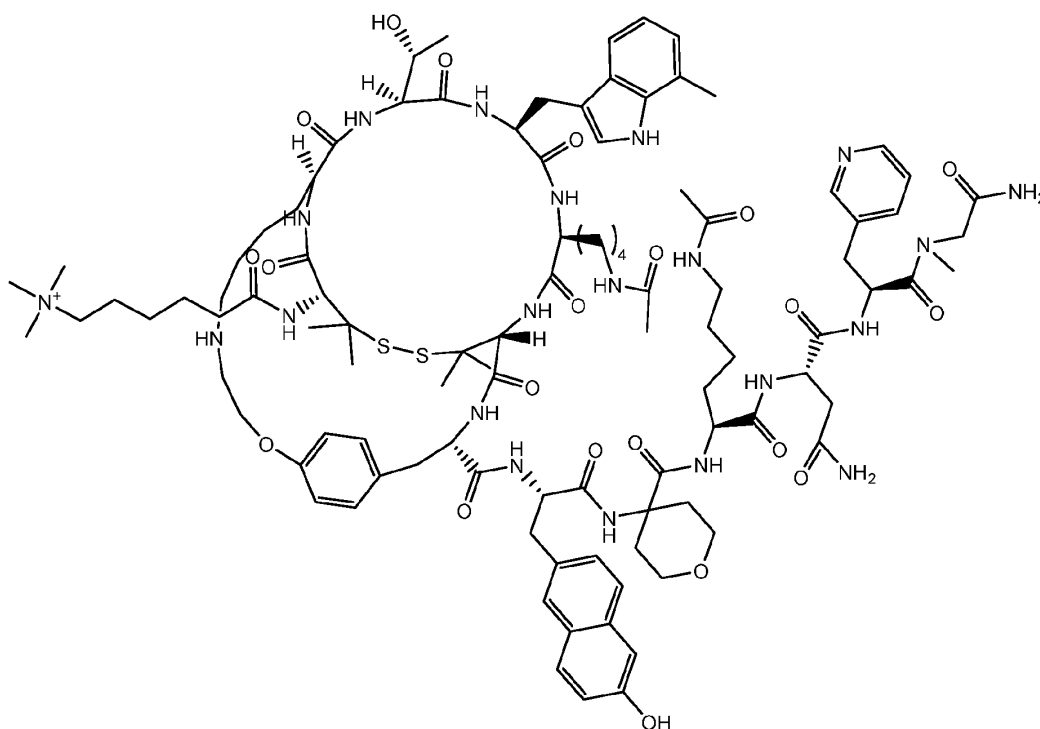
or a pharmaceutically acceptable salt thereof.

98. A peptide having the following structure:



or a pharmaceutically acceptable salt thereof.

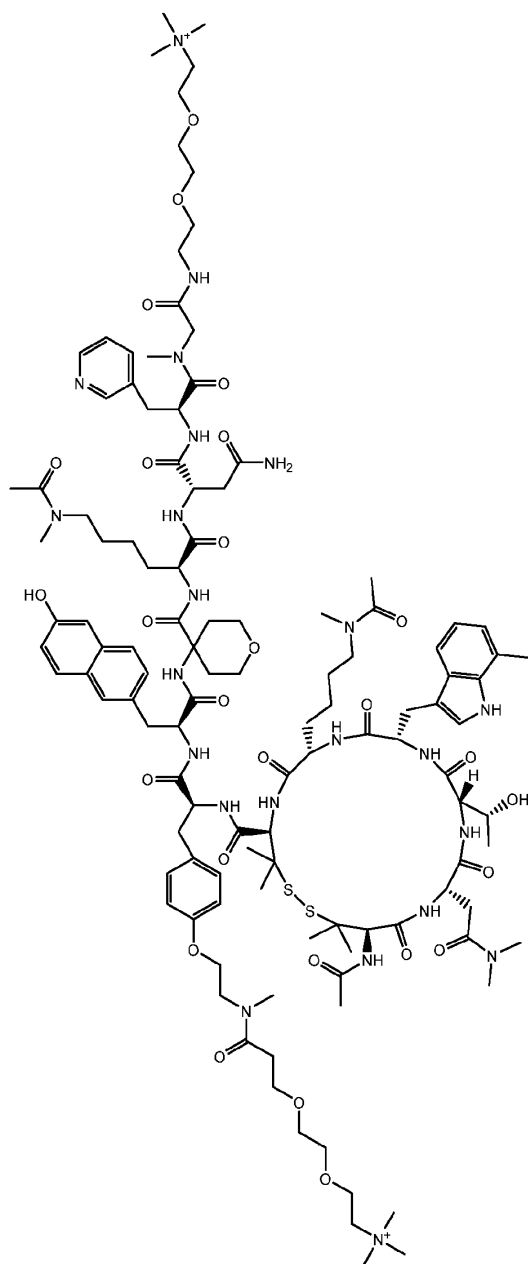
100. A peptide having the following structure:



or a pharmaceutically acceptable salt thereof.

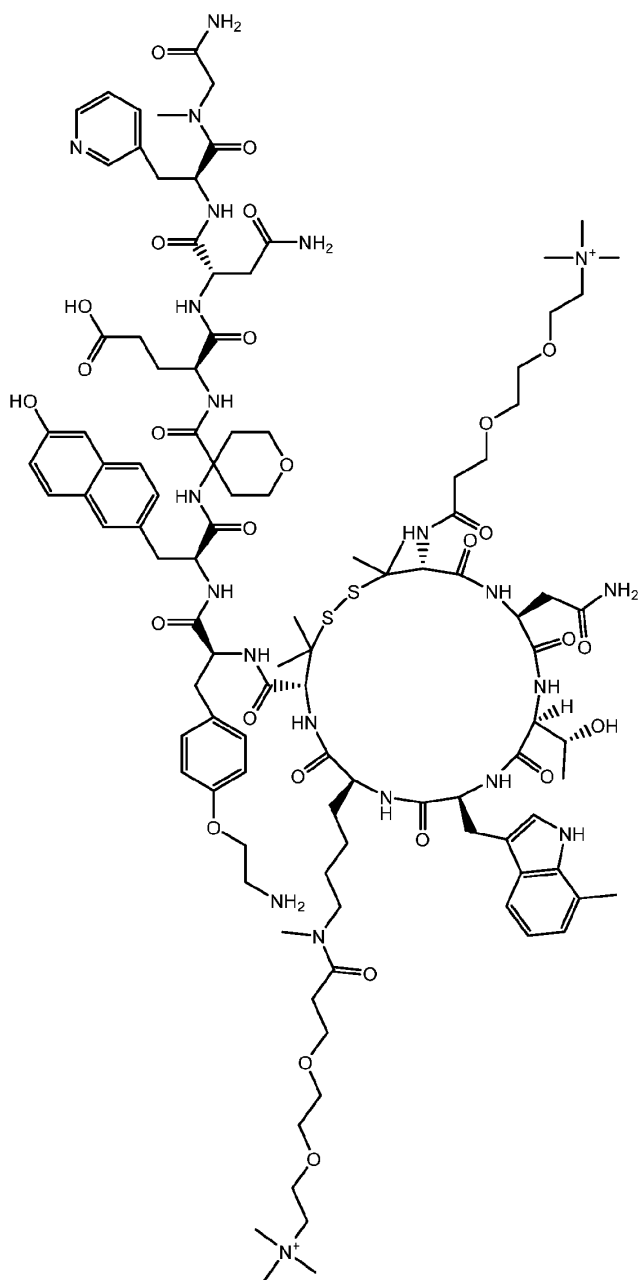
675

102. A peptide having the following structure:



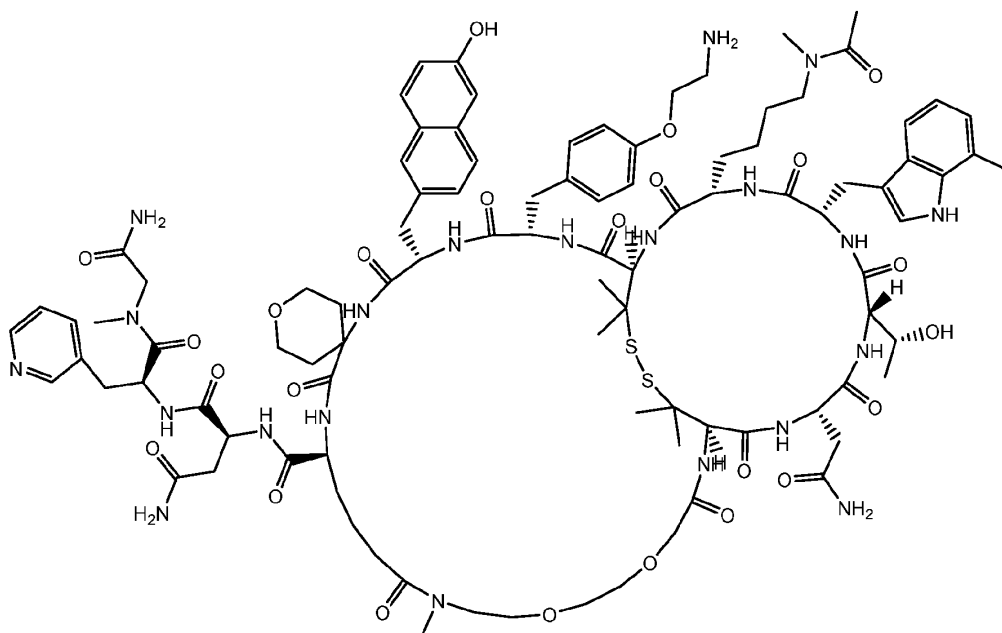
or a pharmaceutically acceptable salt thereof.

103. A peptide having the following structure:



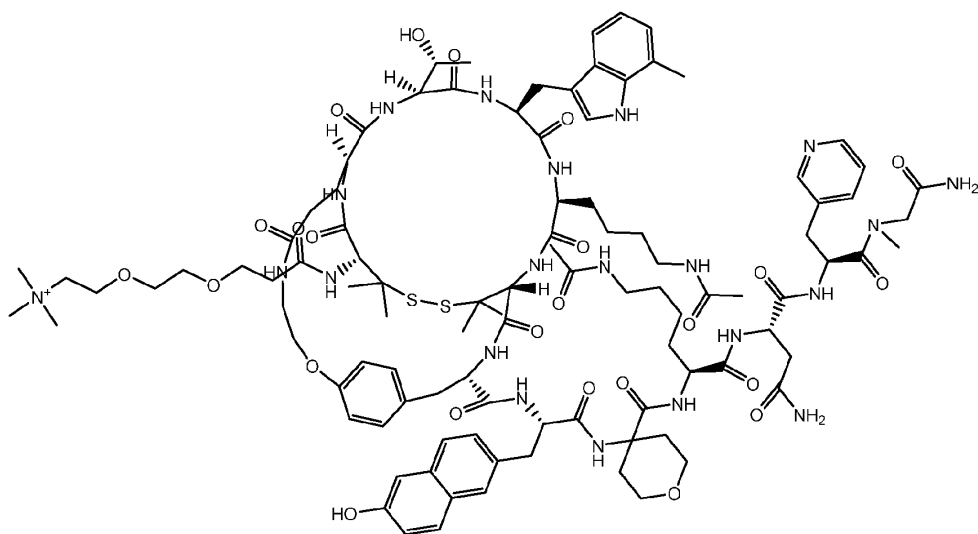
or a pharmaceutically acceptable salt thereof.

104. A peptide having the following structure:



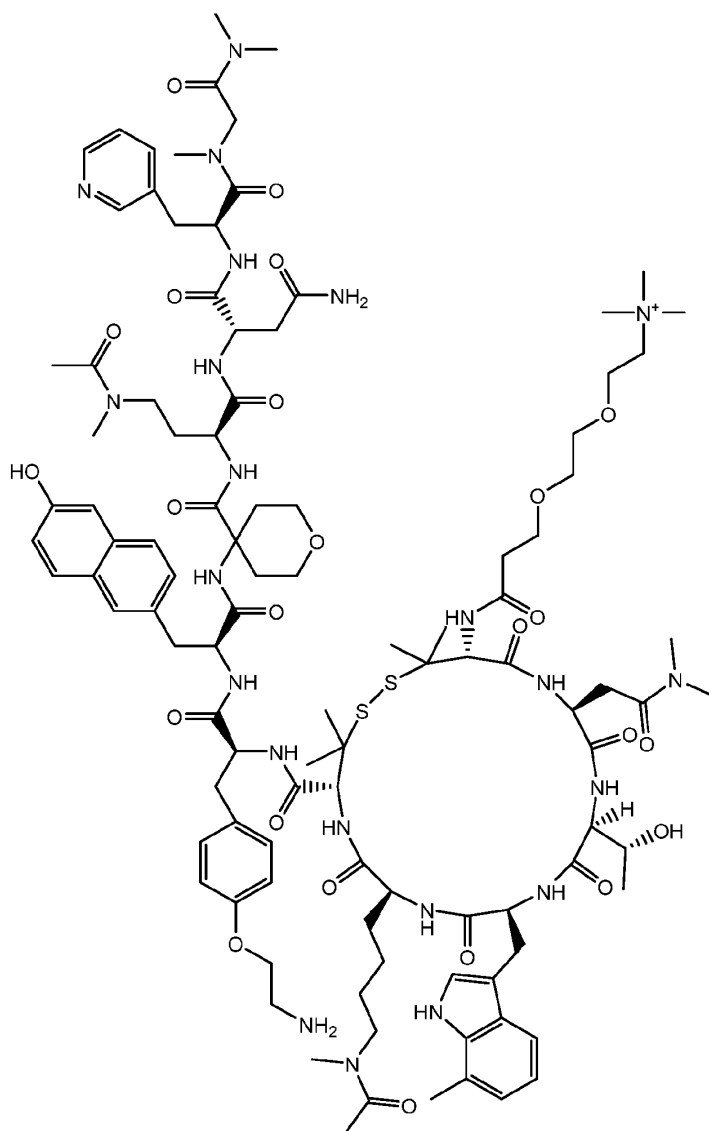
or a pharmaceutically acceptable salt thereof.

5 105. A peptide having the following structure:



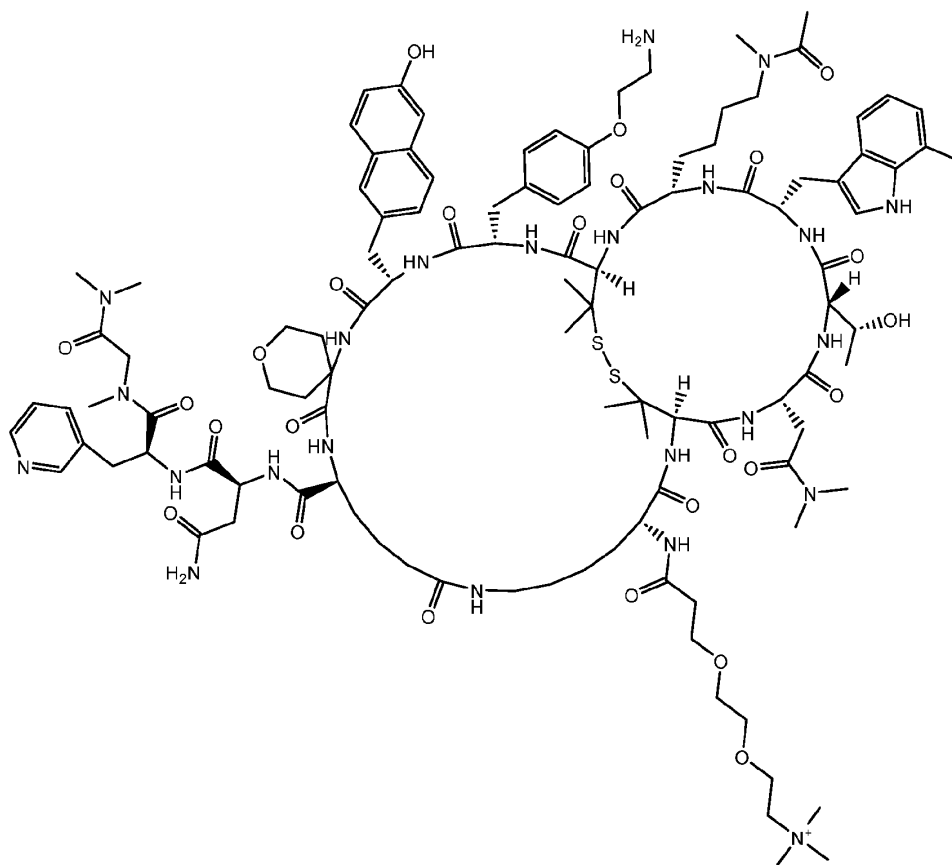
or a pharmaceutically acceptable salt thereof.

106. A peptide having the following structure:



or a pharmaceutically acceptable salt thereof.

107. A peptide having the following structure:



or a pharmaceutically acceptable salt thereof.

111. The method of claim 110, wherein the disease or disorder is selected from multiple sclerosis, asthma, rheumatoid arthritis, inflammation of the gut, inflammatory bowel diseases (IBDs), juvenile IBD, adolescent IBD, Crohn's disease, ulcerative colitis, Celiac disease (nontropical Sprue), microscopic colitis, collagenous colitis, eosinophilic
- 5 gastroenteritis/esophagitis, colitis associated with radio- or chemo-therapy, colitis associated with disorders of innate immunity as in leukocyte adhesion deficiency-1, sarcoidosis, Systemic Lupus Erythematosus, ankylosing spondylitis (axial spondyloarthritis), psoriatic arthritis, psoriasis (e.g., plaque psoriasis, guttate psoriasis, inverse psoriasis, pustular psoriasis, Palmo-Plantar Pustulosis, psoriasis vulgaris, or erythrodermic psoriasis), atopic dermatitis, acne
- 10 ectopica, enteropathy associated with seronegative arthropathies, chronic granulomatous disease, glycogen storage disease type 1b, Hermansky-Pudlak syndrome, Chediak-Higashi syndrome, Wiskott-Aldrich Syndrome, pouchitis, pouchitis resulting after proctocolectomy and ileoanal anastomosis, gastrointestinal cancer, pancreatitis, insulin-dependent diabetes mellitus, mastitis, cholecystitis, cholangitis, primary biliary cirrhosis, viral-associated enteropathy, pericholangitis,
- 15 chronic bronchitis, chronic sinusitis, asthma, uveitis, or graft versus host disease.

112. The method of claim 110, wherein the disease or disorder is selected from ulcerative colitis (UC), Crohn's disease (CD), psoriasis (PsO), or psoriatic arthritis (PsA).