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(54) Title: PEPTIDE INHIBITORS OF INTERLEUKIN-23 RECEPTOR AND THEIR USE TO TREAT INFLAMMATORY DISEASES

(57) Abstract: The present invention provides novel peptide inhibitors of the interleukin-23 receptor, and related compositions and methods of using these peptide inhibitors to treat or prevent a variety of diseases and disorders, including inflammatory bowel diseases.

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PEPTIDE INHIBITORS OF INTERLEUKIN-23 RECEPTOR AND THEIR USE TO TREAT INFLAMMATORY DISEASES

RELATED APPLICATIONS

[0001] This application claims priority to U.S. Provisional Patent Application Serial No. 62/872,477, filed July 10, 2019, which is incorporated herein by reference in its entirety.

SEQUENCE LISTING

[0002] This application is being filed electronically via EFS-Web and includes an electronically submitted sequence listing in .txt format. The .txt file contains a sequence listing entitled PRTH_043_01WO_ST25.txt created on July 2, 2020 and having a size of 171 kilobytes. The sequence listing contained in this .txt file is part of the specification and is incorporated herein by reference in its entirety.

FIELD OF THE INVENTION

[0003] The present invention relates to novel peptide inhibitors of the interleukin-23 receptor (IL-23R), and their use to treat or prevent a variety of diseases and disorders, including inflammatory bowel disease, Crohn's disease and psoriasis.

BACKGROUND

[0004] The interleukin-23 (IL-23) cytokine 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), e.g., ulcerative colitis and Crohn's disease. Studies in acute and chronic mouse models of IBD revealed a primary role of IL-23R and downstream effector cytokines in disease pathogenesis. IL-23R is expressed on various adaptive and innate immune cells including Th17 cells, γδ 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 population that produces IL-6, IL-17, and tumor necrosis factor (TNF).

[0005] 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.

[0006] 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 has 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.

[0007] IL-23 is a heterodimer composed of a unique p19 subunit and the p40 subunit of 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 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, 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-12Rβ1 and IL-23R subunits. Binding of IL-23 to IL-23R activates the Jak-stat signaling molecules, Jak2, Tyk2, and 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.

[0008] Efforts have been made to identify therapeutic moieties that inhibit the IL-23 pathway, for use in treating IL-23-related diseases and disorders. A number of antibodies that bind to IL-23 or IL-23R have been identified, including ustekinumab, a humanized antibody that binds IL-23, which has been approved for the treatment of psoriasis. More recently, polypeptide

inhibitors that bind to IL-23R and inhibit the binding of IL-23 to IL-23R have been identified (see, e.g., US Patent Application Publication No. US2013/0029907). Clinical trials in Crohn's Disease or psoriasis with ustekinumab and briakinumab (which target the common p40 subunit) and tildrakizumab, guselkumab, MEDI2070, and BI-655066 (which target the unique p19 subunit of IL-23) highlight the potential of IL-23 signaling blockade in treatment of human inflammatory diseases. While these findings are promising, challenges remain with respect to identifying stable and selective agents that preferentially target the IL-23 pathway in the intestine, which can be used for the treatment of intestinal inflammation, such as intestinal bowel diseases, including Crohn's disease, ulcerative colitis and related disorders.

[0009] Clearly, there remains a need in the art for new therapeutics targeting the IL-23 pathway, which may be used to treat and prevent IL-23-asociated diseases, including those associated with autoimmune inflammation in the intestinal tract. In addition, compounds and methods for specific targeting of IL-23R from the luminal side of the gut may provide therapeutic benefit to IBD patients suffering from local inflammation of the intestinal tissue. The present invention addresses these needs by providing novel peptide inhibitors that bind IL-23R to inhibit IL-23 binding and signaling and which are suitable for oral administration.

BRIEF SUMMARY OF THE INVENTION

[0010] The present invention provides *inter alia* novel peptide inhibitors of IL-23R and related methods of use.

[0011] In a first aspect, the present invention provides a peptide inhibitor of an interleukin-23 receptor, or a pharmaceutically acceptable salt or solvate thereof, wherein the peptide inhibitor comprises or consists of an amino acid sequence of Formula (I):

X7-X8-X9-X10-X11 (I)

wherein

X7 is unsubstituted Trp, or Trp substituted with cyano, halo, alkyl, haloalkyl, hydroxy, or alkoxy;

X8 is Gln, alpha-Me-Lys, alpha-MeLeu, alpha-MeLys(Ac), beta-homoGln, Cit, Glu, Phe, Asn, Thr, Val, Aib, alpha-MeGln, alpha-MeAsn, Lys(Ac), Dab(Ac), Dap(Ac), homo-Lys(Ac), 1-Nal, 2-Nal, or Trp;

X9 is Abu, Cys, (D)Cys, alpha-MeCys, (D)Pen, or Pen;

X10 is unsubstituted Phe, or Phe substituted with halo, alkyl, haloalkyl, hydroxy, alkoxy, carboxy, carboxamido, 2-aminoethoxy, or 2-acetylaminoethoxy; and

X11 is 2-Nal, unsubstituted Trp, or Trp substituted with cyano, halo, alkyl, haloalkyl, hydroxy, alkoxy, Phe(2-Me), Phe(3-Me), Phe(4-Me), Phe(3,4-dimethoxy), or 1-Nal; and

provided that

i) at least one of X7 and X11 is Trp substituted with cyano, halo, alkyl, haloalkyl, hydroxy, or alkoxy;

ii) when X7 is 5-F substituted Trp, then X11 is other than 2-Nal;

iii) when X7 is 5-OH or 6-Cl substituted Trp, then X9 is other than Cys; and

iv) the compound is other than

Ac-[Pen]-NT-[W(5-Cl)]-Gln-[Pen]-[Phe[4-(2-aminoethoxy)]-[2-Nal]-[α-MeLeu]-[Lys(Ac)]-NN-NH2 (SEQ ID NO:1);

Ac-[Pen]-NT-[W(6-Cl)-Gln-[Pen]-[Phe[4-(2-aminoethoxy)]-[2-Nal]-[α-MeLeu]-[Lys(Ac)]-NN-NH2 (SEQ ID NO: 2);

Ac-[Pen]-NT-[W(6-F)]-Gln-[Pen]-[Phe[4-(2-aminoethoxy)]-[2-Nal]-[α-MeLeu]-[Lys(Ac)]-NN-NH2 (SEQ ID NO: 3);

Ac-[Pen]-NT-[W(4-OMe)]-Gln-[Pen]-[Phe[4-(2-aminoethoxy)]-[2-Nal]-[α-MeLeu]-[Lys(Ac)]-NN-NH2 (SEQ ID NO: 4);

Ac-[Pen]-NT-[W(6-Me)]-Gln-[Pen]-[Phe[4-(2-aminoethoxy)]-[2-Nal]-[α-MeLeu]-[Lys(Ac)]-NN-NH2 (SEQ ID NO: 5);

Ac-[Pen]-NT-[W(7-Me)]-Gln-[Pen]-[Phe[4-(2-aminoethoxy)]-[2-Nal]-[α-MeLeu]-[Lys(Ac)]-NN-NH2 (SEQ ID NO: 6);

Ac-[Pen]-NT-[W(5-F)]-Gln-[Pen]-[Phe[4-(2-aminoethoxy)]-[2-Nal]-[α-MeLeu]-[Lys(Ac)]-NN-NH2 (SEQ ID NO: 7);

Ac-[Pen]-NT-[W(7-F)]-Gln-[Pen]-[Phe[4-(2-aminoethoxy)]-[2-Nal]-[α-MeLeu]-[Lys(Ac)]-NN-NH2 (SEQ ID NO: 8);

Ac-[Pen]-NT-[W(5-OMe)]-Gln-[Pen]-[Phe[4-(2-aminoethoxy)]-[2-Nal]-[α-MeLeu]-[Lys(Ac)]-NN-NH2 (SEQ ID NO: 9);

Ac-[Pen]-NT-[W(5-OH)]-Gln-[Pen]-[Phe[4-(2-aminoethoxy)]-[2-Nal]-[α-MeLeu]-[Lys(Ac)]-NN-NH2 (SEQ ID NO: 10);

Ac-[Pen]-NT-[W(5-Br)]-Gln-[Pen]-[Phe[4-(2-aminoethoxy)]-[2-Nal]-[α-MeLeu]-[Lys(Ac)]-NN-NH2 (SEQ ID NO: 11);

Ac-[Pen]-NTW-Gln-[Pen]-[Phe[4-(2-aminoethoxy)]-W(5-Cl)-[α-MeLeu]-[Lys(Ac)]-NN-NH2 (SEQ ID NO: 12);

Ac-[Pen]-NTW-Gln-[Pen]-[Phe[4-(2-aminoethoxy)]-W(6-Cl)-[α-MeLeu]-[Lys(Ac)]-NN-NH2 (SEQ ID NO: 13);

Ac-[Pen]-NTW-Gln-[Pen]-[Phe[4-(2-aminoethoxy)]-W(6-F)-[α-MeLeu]-[Lys(Ac)]-NN-NH2 (SEQ ID NO: 14);

Ac-[Pen]-NTW-Gln-[Pen]-[Phe[4-(2-aminoethoxy)]-W(4-OMe)-[α-MeLeu]-[Lys(Ac)]-NN-NH2 (SEQ ID NO: 15);

Ac-[Pen]-NTW-Gln-[Pen]-[Phe[4-(2-aminoethoxy)]-W(6-Me)-[α-MeLeu]-[Lys(Ac)]-NN-NH2 (SEQ ID NO: 16);

Ac-[Pen]-NTW-Gln-[Pen]-[Phe[4-(2-aminoethoxy)]-W(7-Me)-[α-MeLeu]-[Lys(Ac)]-NN-NH2 (SEQ ID NO: 17);

Ac-[Pen]-NTW-Gln-[Pen]-[Phe[4-(2-aminoethoxy)]-W(5-F)-[α-MeLeu]-[Lys(Ac)]-NN-NH2 (SEQ ID NO: 18);

Ac-[Pen]-NTW-Gln-[Pen]-[Phe[4-(2-aminoethoxy)]-W(7-F)-[α-MeLeu]-[Lys(Ac)]-NN-NH2 (SEQ ID NO: 19);

Ac-[Pen]-NTW-Gln-[Pen]-[Phe[4-(2-aminoethoxy)]-W(5-OMe)-[α-MeLeu]-[Lys(Ac)]-NN-NH2 (SEQ ID NO: 20);

Ac-[Pen]-NTW-Gln-[Pen]-[Phe[4-(2-aminoethoxy)]-W(5-OH)-[α-MeLeu]-[Lys(Ac)]-NN-NH2 (SEQ ID NO:21);

Ac-[Pen]-NTW-Gln-[Pen]-[Phe[4-(2-aminoethoxy)]-W(5-Br)-[α-MeLeu]-[Lys(Ac)]-NN-NH2 (SEQ ID NO: 22);

Ac-[(D)Arg]-[Abu]-QT-[W(7-Me)]-QC-[Phe[4-(2-aminoethoxy)]-[2-Nal]-[THP]-ENN-NH2 (SEQ ID NO:27);

Ac-[Abu]-QT-[W(7-Me)]-QC-[Phe[4-(2-aminoethoxy)]-[2-Nal]-[THP]-ENN-NH2 (SEQ ID NO: 28);

Ac-[(D)Arg]-[Abu]-QT-[W(7-Me)]-QC-[Phe[4-(2-aminoethoxy)]-[2-Nal]-[THP]-[Lys(Ac)]-NN-NH2 (SEQ ID NO: 29); or

Ac-[Abu]-QT-[W(7-Me)]-QC-[Phe[4-(2-aminoethoxy)]-[2-Nal]-[THP]-[Lys(Ac)]-NN-NH2 (SEQ ID NO: 30);

wherein Pen-Pen form a disulfide bond, or Abu-Cys form a thioether bond;

and

wherein the peptide inhibitor inhibits the binding of an interleukin-23 (IL-23) to an IL-23 receptor.

[0012] In certain embodiments, the present invention excludes compounds listed in Table E1 and/or Table E2.

Table E1. IC_{50}s of Illustrative Peptides Containing the Ac-[Pen]-XXWX-[Pen]-XXXX Motif and Analogues*

SEQ ID No.	Sequence
1	Ac-[Pen]-NT-[W(5-Cl)]-Gln-[Pen]-[Phe[4-(2-aminoethoxy)]-[2-Nal]-[α-MeLeu]-[Lys(Ac)]-NN-NH_2
2	Ac-[Pen]-NT-[W(6-Cl)-Gln-[Pen]-[Phe[4-(2-aminoethoxy)]-[2-Nal]-[α-MeLeu]-[Lys(Ac)]-NN-NH_2
3	Ac-[Pen]-NT-[W(6-F)]-Gln-[Pen]-[Phe[4-(2-aminoethoxy)]-[2-Nal]-[α-MeLeu]-[Lys(Ac)]-NN-NH_2
4	Ac-[Pen]-NT-[W(4-OMe)]-Gln-[Pen]-[Phe[4-(2-aminoethoxy)]-[2-Nal]-[α-MeLeu]-[Lys(Ac)]-NN-NH_2
5	Ac-[Pen]-NT-[W(6-Me)]-Gln-[Pen]-[Phe[4-(2-aminoethoxy)]-[2-Nal]-[α-MeLeu]-[Lys(Ac)]-NN-NH_2
6	Ac-[Pen]-NT-[W(7-Me)]-Gln-[Pen]-[Phe[4-(2-aminoethoxy)]-[2-Nal]-[α-MeLeu]-[Lys(Ac)]-NN-NH_2
7	Ac-[Pen]-NT-[W(5-F)]-Gln-[Pen]-[Phe[4-(2-aminoethoxy)]-[2-Nal]-[α-MeLeu]-[Lys(Ac)]-NN-NH_2
8	Ac-[Pen]-NT-[W(7-F)]-Gln-[Pen]-[Phe[4-(2-aminoethoxy)]-[2-Nal]-[α-MeLeu]-[Lys(Ac)]-NN-NH_2
9	Ac-[Pen]-NT-[W(5-OMe)]-Gln-[Pen]-[Phe[4-(2-aminoethoxy)]-[2-Nal]-[α-MeLeu]-[Lys(Ac)]-NN-NH_2
10	Ac-[Pen]-NT-[W(5-OH)]-Gln-[Pen]-[Phe[4-(2-aminoethoxy)]-[2-Nal]-[α-MeLeu]-[Lys(Ac)]-NN-NH_2
11	Ac-[Pen]-NT-[W(5-Br)]-Gln-[Pen]-[Phe[4-(2-aminoethoxy)]-[2-Nal]-[α-MeLeu]-[Lys(Ac)]-NN-NH_2

SEQ ID No.	Sequence
12	Ac-[Pen]-NTW-Gln-[Pen]-[Phe[4-(2-aminoethoxy)]-W(5-Cl)-[α-MeLeu]-[Lys(Ac)]-NN-NH_2
13	Ac-[Pen]-NTW-Gln-[Pen]-[Phe[4-(2-aminoethoxy)]-W(6-Cl)-[α-MeLeu]-[Lys(Ac)]-NN-NH_2
14	Ac-[Pen]-NTW-Gln-[Pen]-[Phe[4-(2-aminoethoxy)]-W(6-F)-[α-MeLeu]-[Lys(Ac)]-NN-NH_2
15	Ac-[Pen]-NTW-Gln-[Pen]-[Phe[4-(2-aminoethoxy)]-W(4-OMe)-[α-MeLeu]-[Lys(Ac)]-NN-NH_2
16	Ac-[Pen]-NTW-Gln-[Pen]-[Phe[4-(2-aminoethoxy)]-W(6-Me)-[α-MeLeu]-[Lys(Ac)]-NN-NH_2
17	Ac-[Pen]-NTW-Gln-[Pen]-[Phe[4-(2-aminoethoxy)]-W(7-Me)-[α-MeLeu]-[Lys(Ac)]-NN-NH_2
18	Ac-[Pen]-NTW-Gln-[Pen]-[Phe[4-(2-aminoethoxy)]-W(5-F)-[α-MeLeu]-[Lys(Ac)]-NN-NH_2
19	Ac-[Pen]-NTW-Gln-[Pen]-[Phe[4-(2-aminoethoxy)]-W(7-F)-[α-MeLeu]-[Lys(Ac)]-NN-NH_2
20	Ac-[Pen]-NTW-Gln-[Pen]-[Phe[4-(2-aminoethoxy)]-W(5-OMe)-[α-MeLeu]-[Lys(Ac)]-NN-NH_2
21	Ac-[Pen]-NTW-Gln-[Pen]-[Phe[4-(2-aminoethoxy)]-W(5-OH)-[α-MeLeu]-[Lys(Ac)]-NN-NH_2
22	Ac-[Pen]-NTW-Gln-[Pen]-[Phe[4-(2-aminoethoxy)]-W(5-Br)-[α-MeLeu]-[Lys(Ac)]-NN-NH_2

* wherein Pen and Pen form a disulfide bond.

Table E2. IC_{50}s of Illustrative Peptides Containing the Ac-[Abu]-XXWX-[Cys]-XXXX Motif and Analogues*

SEQ ID No.	Sequence
27	Ac-[(D)Arg]-[Abu]-QT-[W(7-Me)]-QC-[Phe[4-(2-aminoethoxy)]-[2-Nal]-[THP]-ENN-NH2
28	Ac-[Abu]-QT-[W(7-Me)]-QC-[Phe[4-(2-aminoethoxy)]-[2-Nal]-[THP]-ENN-NH2

SEQ ID No.	Sequence
29	Ac-[(D)Arg]-[Abu]-QT-[W(7-Me)]-QC-[Phe[4-(2-aminoethoxy)]-[2-Nal]-[THP]-[Lys(Ac)]-NN-NH2
30	Ac-[Abu]-QT-[W(7-Me)]-QC-[Phe[4-(2-aminoethoxy)]-[2-Nal]-[THP]-[Lys(Ac)]-NN-NH2

* wherein Abu and C form a thioether bond.

[0013] In a second aspect, the present invention provides a peptide inhibitor of an interleukin-23 receptor, or a pharmaceutically acceptable salt or solvate thereof, wherein the peptide inhibitor comprises or consists of an amino acid sequence of Formula (II):

X4-X5-X6-X7-X8-X9-X10-X11 (II)

wherein

X4 is Abu, Cys, (D)Cys, alpha-MeCys, (D)Pen, Pen, or Pen(sulfoxide);

X5 is Cit, Glu, Gly, Lys, Asn, Pro, alpha-MeGln, alpha-MeLys, alpha-MeLeu, alpha-MeAsn, Lys(Ac), alpha-MeLys(Ac), Dab(Ac), Dap(Ac), homo-Lys(Ac), Gln, Asp, or Cys;

X6 is Thr, Aib, Asp, Dab, Gly, Pro, Ser, alpha-MeGln, alpha-MeLys, alpha-MeLeu, alpha-MeAsn, alpha-MeThr, alpha-MeSer, or Val;

X7 is unsubstituted Trp, or Trp substituted with cyano, halo, alkyl, haloalkyl, hydroxy, or alkoxy;

X8 is Gln, alpha-Me-Lys, alpha-MeLeu, alpha-MeLys(Ac), beta-homoGln, Cit, Glu, Phe, Asn, Thr, Val, Aib, alpha-MeGln, alpha-MeAsn, Lys(Ac), Dab(Ac), Dap(Ac), homo-Lys(Ac), 1-Nal, 2-Nal, or Trp;

X9 is Abu, Cys, (D)Cys, alpha-MeCys, (D)Pen, Pen, or Pen(sulfoxide); wherein if X4 is Abu then X9 is Cys, (D)Cys, alpha-MeCys, (D)Pen, Pen, or Pen(sulfoxide); and wherein if X9 is Abu, then X4 is Cys, (D)Cys, alpha-MeCys, (D)Pen, Pen, or Pen(sulfoxide);

X10 is unsubstituted Phe, or Phe substituted with halo, alkyl, haloalkyl, hydroxy, alkoxy, carboxy, carboxamido, 2-aminoethoxy, or 2-acetylaminoethoxy; and

X11 is 2-Nal, unsubstituted Trp, or Trp substituted with halo, alkyl, haloalkyl, hydroxy, alkoxy, Phe(2-Me), Phe(3-Me), Phe(4-Me), Phe(3,4-dimethoxy), or 1-Nal;

wherein the peptide inhibitor is cyclized via a bond between X4 and X9, and

provided that:

i) at least one of X7 and X11 is Trp substituted with cyano, halo, alkyl, haloalkyl, hydroxy, or alkoxy;

ii) when X7 is 5-F substituted Trp, then X11 is other than 2-Nal; and

iii) when X7 is 5-OH or 6-Cl substituted Trp, then X9 is other than Cys;

and

wherein the peptide inhibitor inhibits the binding of an interleukin-23 (IL-23) to an IL-23 receptor.

[0014] In one embodiment, X7 is other than 5-F substituted Trp. In another embodiment, when X7 is unsubstituted Trp, or Trp substituted with 1-Me, 5-OH or 6-Cl, then X9 is other than Cys.

[0015] In another aspect, the present invention provides a peptide inhibitor of an interleukin-23 receptor, or a pharmaceutically acceptable salt or solvate thereof, wherein the peptide inhibitor comprises or consists of an amino acid sequence of Formula (I):

X7-X8-X9-X10-X11 (I)

wherein

X7 is unsubstituted Trp, or Trp substituted with cyano, halo, alkyl, haloalkyl, hydroxy, or alkoxy;

X8 is Gln, alpha-Me-Lys, alpha-MeLeu, alpha-MeLys(Ac), beta-homoGln, Cit, Glu, Phe, Asn, Thr, Val, Aib, alpha-MeGln, alpha-MeAsn, Lys(Ac), Dab(Ac), Dap(Ac), homo-Lys(Ac), 1-Nal, 2-Nal, or Trp;

X9 is Abu, Cys, (D)Cys, alpha-MeCys, (D)Pen, or Pen;

X10 is unsubstituted Phe, or Phe substituted with halo, alkyl, haloalkyl, hydroxy, alkoxy, carboxy, carboxamido, 2-aminoethoxy, or 2-acetylaminoethoxy; and

X11 is 2-Nal, unsubstituted Trp, or Trp substituted with cyano, halo, alkyl, haloalkyl, hydroxy, alkoxy, Phe(2-Me), Phe(3-Me), Phe(4-Me), Phe(3,4-dimethoxy), or 1-Nal;

and

provided that

i) at least one of X7 and X11 is Trp substituted with cyano, halo, alkyl, haloalkyl, hydroxy, or alkoxy;

ii) X7 is other than 5-F substituted Trp; and

iii) when X7 is unsubstituted Trp, or Trp substituted with 1-Me, 5-OH or 6-Cl, then X9 is other than Cys;

and

wherein the peptide inhibitor inhibits the binding of an interleukin-23 (IL-23) to an IL-23 receptor.

[0016] In another aspect, the present invention provides a peptide inhibitor of an interleukin-23 receptor, or a pharmaceutically acceptable salt or solvate thereof, wherein the peptide inhibitor comprises or consists of an amino acid sequence of Formula (II):

X4-X5-X6-X7-X8-X9-X10-X11 (II)

wherein

X4 is Abu, Cys, (D)Cys, alpha-MeCys, (D)Pen, Pen, or Pen(sulfoxide);

X5 is Cit, Glu, Gly, Leu, Ile, beta-Ala, Ala, Lys, Asn, Pro, alpha-MeGln, alpha-MeLys, alpha-MeLeu, alpha-MeAsn, Lys(Ac), alpha-MeLys(Ac), Dab(Ac), Dap(Ac), homo-Lys(Ac), Gln, Asp, or Cys;

X6 is Thr, Aib, Asp, Dab, Gly, Pro, Ser, alpha-MeGln, alpha-MeLys, alpha-MeLeu, alpha-MeAsn, alpha-MeThr, alpha-MeSer, or Val;

X7 is unsubstituted Trp, or Trp substituted with cyano, halo, alkyl, haloalkyl, hydroxy, or alkoxy;

X8 is Gln, alpha-Me-Lys, alpha-MeLeu, alpha-MeLys(Ac), beta-homoGln, Cit, Glu, Phe, Asn, Thr, Val, Aib, alpha-MeGln, alpha-MeAsn, Lys(Ac), Dab(Ac), Dap(Ac), homo-Lys(Ac), 1-Nal, 2-Nal, or Trp;

X9 is Abu, Cys, (D)Cys, alpha-MeCys, (D)Pen, Pen, or Pen(sulfoxide); wherein if X4 is Abu then X9 is Cys, (D)Cys, alpha-MeCys, (D)Pen, Pen, or Pen(sulfoxide); and wherein if X9 is Abu, then X4 is Cys, (D)Cys, alpha-MeCys, (D)Pen, Pen, or Pen(sulfoxide);

X10 is unsubstituted Phe, or Phe substituted with halo, alkyl, haloalkyl, hydroxy, alkoxy, carboxy, carboxamido, 2-aminoethoxy, or 2-acetylaminoethoxy; and

X11 is 2-Nal, unsubstituted Trp, or Trp substituted with halo, alkyl, haloalkyl, hydroxy, alkoxy, Phe(2-Me), Phe(3-Me), Phe(4-Me), Phe(3,4-dimethoxy), or 1-Nal;

wherein the peptide inhibitor is cyclized via a bond between X4 and X9, and

provided that:

i) at least one of X7 and X11 is Trp substituted with cyano, halo, alkyl, haloalkyl, hydroxy, or alkoxy;

ii) X7 is other than 5-F substituted Trp; and

iii) when X7 is unsubstituted Trp, or Trp substituted with 1-Me, 5-OH or 6-Cl, then X9 is other than Cys;

and

wherein the peptide inhibitor inhibits the binding of an interleukin-23 (IL-23) to an IL-23 receptor.

[0017] In certain embodiments, X5 is Cit, Glu, Gly, Lys, Asn, Pro, alpha-MeGln, alpha-MeLys, alpha-MeLeu, alpha-MeAsn, Lys(Ac), alpha-MeLys(Ac), Dab(Ac), Dap(Ac), homo-Lys(Ac), Gln, Asp, or Cys. In certain embodiments, X5 is Cit, Glu, Gly, Leu, Ile, beta-Ala, Ala, Lys, Asn, Pro, alpha-MeGln, alpha-MeLys, alpha-MeLeu, alpha-MeAsn, Lys(Ac), alpha-MeLys(Ac), Dab(Ac), Dap(Ac), homo-Lys(Ac), Gln, Asp, or Cys.

[0018] In certain embodiments, X8 is Gln, alpha-Me-Lys, alpha-MeLeu, alpha-MeLys(Ac), beta-homoGln, Cit, Glu, Phe, Asn, Thr, Val, Aib, alpha-MeGln, alpha-MeAsn, Lys(Ac), alpha-MeLys(Ac), Dab(Ac), Dap(Ac), homo-Lys(Ac), 1-Nal, 2-Nal, or Trp. In certain embodiments, X8 is Gln, alpha-Me-Lys, alpha-MeLeu, alpha-MeLys(Ac), beta-homoGln, Cit, Glu, Phe, Asn, Thr, Val, Aib, alpha-MeGln, alpha-MeAsn, Lys(Ac), Dab(Ac), Dap(Ac), homo-Lys(Ac), 1-Nal, 2-Nal, or Trp.

[0019] In certain embodiments, X8 is Gln, alpha-Me-Lys, alpha-MeLeu, alpha-MeLys(Ac), beta-homoGln, Cit, Glu, Phe, Asn, Thr, Val, Aib, alpha-MeGln, alpha-MeAsn, Dab(Ac), Dap(Ac), homo-Lys(Ac), 1-Nal, 2-Nal, Trp, or Lys(R'); and wherein R' is Aib, bAla, IVA, Ala, cyclohexanoic, octanoic, -C(O)CH_2Ph (-C(O)benzyl), trifluorpropionic, Gly, acetyl, valeric, or trifluoroacetyl. In certain embodiments, X8 is Asn, alpha-Me-Lys, alpha-MeLeu, Aib, Cit, or Lys(R'). In certain embodiments, X8 is Lys(R'). In one embodiment, R' is acetyl. In another embodiment R' is Gly, Aib, Ala, or bAla. In another embodiment, R' is Gly, or Aib.

[0020] In one embodiment, X4 is Abu and X9 is Cys, (D)Cys, alpha-MeCys, (D)Pen, or Pen. In another embodiment, X4 is Cys, (D)Cys, alpha-MeCys, (D)Pen, or Pen; and X9 is Abu. In another embodiment, each X4 and X9 is independently Cys, (D)Cys, alpha-MeCys, (D)Pen, or Pen. In another embodiment, each X4 and X9 is Cys, (D)Cys, alpha-MeCys, (D)Pen, or Pen.

[0021] In a particular aspect, the present invention provides a peptide inhibitor of an interleukin-23 receptor, or a pharmaceutically acceptable salt or solvate thereof, wherein the peptide inhibitor comprises or consists of an amino acid sequence of Formula (XIa) or (XIb):

Pen-Asn-Thr-W'-Gln-Pen-[F(4-2ae)]-[2-Nal]-aMeLeu-K(Ac)-Asn-Asn (XIa) or

Pen-Asn-Thr-W-Gln-Pen-[F(4-2ae)]-W'-aMeLeu-K(Ac)-Asn-Asn (XIb)

wherein W' is Trp substituted with cyano, halo, alkyl, haloalkyl, hydroxy, or alkoxy; and the peptide inhibitor is cyclized via a Pen-Pen disulfide bond.

[0022] In another particular aspect, the present invention provides a peptide inhibitor of an interleukin-23 receptor, or a pharmaceutically acceptable salt or solvate thereof, wherein the peptide inhibitor comprises or consists of an amino acid sequence of Formula (XIc) or (XId):

Abu-Asn-Thr-W'-Gln-Cys-[F(4-2ae)]-[2-Nal]-aMeLeu-K(Ac)-Asn-Asn (XIc), or

Abu-Asn-Thr-W-Gln-Cys-[F(4-2ae)]-W'-aMeLeu-K(Ac)-Asn-Asn (XId),

wherein W' is Trp substituted with cyano, halo, alkyl, haloalkyl, hydroxy, or alkoxy; and the peptide inhibitor is cyclized via a Abu-Cys thioether bond.

[0023] In another particular aspect, the present invention provides a peptide inhibitor of an interleukin-23 receptor, or a pharmaceutically acceptable salt or solvate thereof, wherein the peptide inhibitor comprises or consists of an amino acid sequence of Formula (XIe) or (XIf):

Abu-Asn-Thr-W'-Gln-Pen-[F(4-2ae)]-[2-Nal]-aMeLeu-K(Ac)-Asn-Asn (XIe), or

Abu-Asn-Thr-W-Gln-Pen-[F(4-2ae)]-W'-aMeLeu-K(Ac)-Asn-Asn (XIf),

wherein W' is Trp substituted with cyano, halo, alkyl, haloalkyl, hydroxy, or alkoxy; and the peptide inhibitor is cyclized via a Abu-Pen thioether bond.

[0024] In another particular aspect, the present invention provides a peptide inhibitor of an interleukin-23 receptor, or a pharmaceutically acceptable salt or solvate thereof, wherein the peptide inhibitor comprises or consists of an amino acid sequence of Formula (Z):

R^1-X-R^2 (Z)

or a pharmaceutically acceptable salt or solvate thereof, wherein

R^1 is a bond, hydrogen, a C1-C6 alkyl, a C6-C12 aryl, a C6-C12 aryl C1-C6 alkyl, a C1-C20 alkanoyl, and including PEGylated versions alone or as spacers of any of the foregoing; X is the amino acid sequence of Formula (I), Formulas (II)-(XII), Formula (II"), Formula (I'), or an amino acid sequence set forth in Table E3; and R^2 is OH or NH_2.

[0025] In another aspect, the present invention provides a peptide inhibitor of an interleukin-23 receptor, or a pharmaceutically acceptable salt or solvate thereof, wherein the peptide inhibitor comprises or consists of an amino acid sequence of Formula (Z'):

$$R^1\text{-X4-X5-X6-X7-X8-X9-X10-X11-X12-X13-X14-X15-}R^2 \quad (Z')$$

or a pharmaceutically acceptable salt or solvate thereof, wherein

X4 is Abu, Cys, (D)Cys, alpha-MeCys, (D)Pen, Pen, or Pen(sulfoxide);

X5 is Cit, Glu, Gly, Leu, Ile, beta-Ala, Ala, Lys, Asn, Pro, alpha-MeGln, alpha-MeLys, alpha-MeLeu, alpha-MeAsn, Lys(Ac), alpha-MeLys(Ac), Dab(Ac), Dap(Ac), homo-Lys(Ac), Gln, Asp, or Cys; and

X6 is Thr, Aib, Asp, Dab, Gly, Pro, Ser, alpha-MeGln, alpha-MeLys, alpha-MeLeu, alpha-MeAsn, alpha-MeThr, alpha-MeSer, or Val;

X7 is Trp substituted with cyano, halo, alkyl, haloalkyl, hydroxy, or alkoxy;

X8 is Gln, alpha-MeLys, alpha-MeLeu, alpha-MeLys(Ac), beta-homoGln, Cit, Glu, Phe, Asn, Thr, Val, Aib, alpha-MeGln, alpha-MeAsn, Lys(Ac), Dab(Ac), Dap(Ac), homo-Lys(Ac), 1-Nal, 2-Nal, or Trp;

X9 is Abu, Cys, (D)Cys, alpha-MeCys, (D)Pen, Pen or Pen(sulfoxide);

X10 is unsubstituted Phe, or Phe substituted with halo, alkyl, haloalkyl, hydroxy, alkoxy, carboxy, carboxamido, 2-aminoethoxy, or 2-acetylaminoethoxy;

X11 is 2-Nal, Phe(2-Me), Phe(3-Me), Phe(4-Me), Phe(3,4-dimethoxy), 1-Nal, unsubstituted Trp, or Trp substituted with cyano, halo, alkyl, haloalkyl, hydroxy, or alkoxy;

X12 is 4-amino-4-carboxy-tetrahydropyran (THP), alpha-MeLys, alpha-MeLeu, alpha-MeArg, alpha-MePhe, alpha-MeLeu, alpha-MeLys, alpha-MeAsn, alpha-MeTyr, Ala, or cyclohexylAla, Lys, or Aib;

X13 is Aib, Glu, Cit, Gln, Lys(Ac), alpha-MeArg, alpha-MeGlu, alpha-MeLeu, alpha-MeLys, alpha-Me-Asn, alpha-MeLys(Ac), Dab(Ac), Dap(Ac), homo-Lys(Ac), or Lys; or

X13 is Lys, pegylated Lys, b-homoGlu, or Lys(Y2-Ac), wherein Y2 is an amino acid;

X14 is Asn, 2-Nap, Aib, Arg, Cit, Asp, Phe, Gly, Lys, Leu, Ala, (D)Ala, beta-Ala, His, Thr, n-Leu, Gln, Ser, (D)Ser, Tic, Trp, alpha-MeGln, alpha-MeAsn, alpha-MeLys(Ac), Dab(Ac), Dap(Ac), homo-Lys(Ac), or Lys(Ac);

X15 Leu, (D)Leu, beta-Ala, Cit, or (D)Lys;

R^1 is hydrogen, a C1-C6 alkyl, a C6-C12 aryl, a C6-C12aryl-C1-C6alkyl, or a C1-C20 alkanoyl;

R^2 is OH or NH_2;

wherein the peptide inhibitor or pharmaceutically acceptable salt or solvate thereof comprises a disulfide bond between two Pen residues or a thioether bond between Abu and Cys;

and

wherein the peptide inhibitor or pharmaceutically acceptable salt of solvate thereof inhibits the binding of an interleukin-23 (IL-23) to an IL-23 receptor.

[0026] In one embodiment, R^1 is a C_1-C_{20} alkanoyl. In a particular embodiment, R^1 is Ac.

[0027] In another aspect, the disclosure provides a peptide inhibitor of an interleukin-23 receptor, or a pharmaceutically acceptable salt or solvate thereof, wherein the peptide inhibitor comprises or consists of an amino acid sequence of Formula (II"):

X7-X8-X9-X10-X11-X12-X13-X14-X15-R^2 (II")

wherein

X7 is Trp substituted with cyano, halo, alkyl, haloalkyl, hydroxy, or alkoxy;

X8 is Gln, alpha-MeLys, alpha-MeLeu, alpha-MeLys(Ac), beta-homoGln, Cit, Glu, Phe, Asn, Thr, Val, Aib, alpha-MeGln, alpha-MeAsn, Lys(Ac), Dab(Ac), Dap(Ac), homo-Lys(Ac), 1-Nal, 2-Nal, or Trp;

X9 is Abu, Cys, (D)Cys, alpha-MeCys, (D)Pen, Pen or Pen(sulfoxide);

X10 is unsubstituted Phe, or Phe substituted with halo, alkyl, haloalkyl, hydroxy, alkoxy, carboxy, carboxamido, 2-aminoethoxy, or 2-acetylaminoethoxy;

X11 is 2-Nal, Phe(2-Me), Phe(3-Me), Phe(4-Me), Phe(3,4-dimethoxy), 1-Nal, unsubstituted Trp, or Trp substituted with cyano, halo, alkyl, haloalkyl, hydroxy, or alkoxy;

X12 is 4-amino-4-carboxy-tetrahydropyran (THP), alpha-MeLys, alpha-MeLeu, alpha-MeArg, alpha-MePhe, alpha-MeLeu, alpha-MeLys, alpha-MeAsn, alpha-MeTyr, Ala, or cyclohexylAla, Lys, or Aib;

X13 is Aib, Glu, Cit, Gln, Lys(Ac), alpha-MeArg, alpha-MeGlu, alpha-MeLeu, alpha-MeLys, alpha-Me-Asn, alpha-MeLys(Ac), Dab(Ac), Dap(Ac), homo-Lys(Ac), or Lys; or

X13 is Lys, pegylated Lys, b-homoGlu, or Lys(Y2-Ac), wherein Y2 is an amino acid;

X14 is Asn, 2-Nap, Aib, Arg, Cit, Asp, Phe, Gly, Lys, Leu, Ala, (D)Ala, beta-Ala, His, Thr, n-Leu, Gln, Ser, (D)Ser, Tic, Trp, alpha-MeGln, alpha-MeAsn, alpha-MeLys(Ac), Dab(Ac), Dap(Ac), homo-Lys(Ac), or Lys(Ac);

X15 Leu, (D)Leu, beta-Ala, Cit, or (D)Lys;

R^2 is OH or NH_2;

or a pharmaceutically acceptable salt or solvate thereof, wherein the peptide inhibitor or pharmaceutically acceptable salt or solvate thereof comprises a disulfide bond between two Pen residues or a thioether bond between Abu and Cys;

and

wherein the peptide inhibitor or pharmaceutically acceptable salt of solvate thereof inhibits the binding of an interleukin-23 (IL-23) to an IL-23 receptor.

[0028] In certain embodiments the peptide inhibitor comprises an amino acid sequence of Formula (I'):

X4-X5-X6-X7-X8-X9-X10-X11-X12-X13-X14-X15 (I')

wherein

X4 is Abu, Cys, (D)Cys, alpha-MeCys, (D)Pen, Pen, or Pen(sulfoxide);

X5 is Cit, Glu, Gly, Leu, Ile, beta-Ala, Ala, Lys, Asn, Pro, alpha-MeGln, alpha-MeLys, alpha-MeLeu, alpha-MeAsn, Lys(Ac), alpha-MeLys(Ac), Dab(Ac), Dap(Ac), homo-Lys(Ac), Gln, Asp, or Cys; and

[0029] X6 is Thr, Aib, Asp, Dab, Gly, Pro, Ser, alpha-MeGln, alpha-MeLys, alpha-MeLeu, alpha-MeAsn, alpha-MeThr, alpha-MeSer, or Val.In another particular aspect, the present invention provides a peptide inhibitor of an interleukin-23 receptor, or a pharmaceutically acceptable salt or solvate thereof, wherein the peptide inhibitor comprises or is any one of the peptides listed in Table E3, or a pharmaceutically acceptable salt or solvate thereof.

[0030] In particular embodiments of any of the peptide inhibitors disclosed herein, including peptide inhibitors comprising an amino acid sequence of Formula Formula (II)-(XII), X4 is Pen and X9 is Pen, and the bond is a disulfide bond.

[0031] In particular embodiments, any of the peptide inhibitors described herein comprise one or more half-life extension moiety and/or one or more linker moiety conjugated to the peptide inhibitor. In particular embodiments, the half-life extension moiety is conjugated to the peptide inhibitor via one or more linker moieties.

[0032] In certain embodiments, any of the peptide inhibitors described herein further comprises a conjugated chemical substituent. In particular embodiments, the conjugated chemical substituent is a lipophilic substituent or a polymeric moiety, e.g., Ac, Palm, gamaGlu-Palm, isoGlu-Palm, PEG2-Ac, PEG4-isoGlu-Palm, $(PEG)_5$-Palm, succinic acid, glutaric acid, pyroglutaric acid, benzoic acid, IVA, octanoic acid, 1,4 diaminobutane, isobutyl, Alexa488, Alexa647, or biotin. In certain embodiments, the conjugated chemical substituent is a

polyethylene glycol with a molecular mass of 400 Da to 40,000 Da. In particular embodiments, the peptide is conjugated at X8. In another particular embodiment, the peptide is conjugated at X9. In a more particular embodiment, the peptide is conjugated at X10.

[0033] In a related aspect, the present invention includes a peptide dimer inhibitor of an interleukin-23 receptor, wherein the peptide dimer inhibitor comprises two peptide monomer subunits connected via one or more linker moieties, wherein each peptide monomer subunit comprises a sequence of Formula (I), Formula (II)-(XII), or any other sequence or structure set forth herein. In certain embodiments, one or both peptide monomer subunit is cyclized via an intramolecular bond between X4 and X9. In certain embodiments, one or both intramolecular bond is a disulfide bond or a thioether bond. In certain embodiments, the linker is any of those shown in Table 2 or described herein. In certain embodiments, the linker moiety is a diethylene glycol linker, an iminodiacetic acid (IDA) linker, a β-Ala-iminodiaceticacid (β-Ala-IDA) linker, or a PEG linker. In particular embodiments, the N-terminus of each peptide monomer subunit is connected by the linker moiety. In particular embodiments, the C-terminus of each peptide monomer subunit is connected by the linker moiety. In certain embodiments, the linker connects an internal amino acid residue of at least one of the peptide monomer subunits to the N-terminus, C-terminus, or an internal amino acid residue of the other peptide monomer subunit.

[0034] In a further related aspect, the present invention includes a polynucleotide comprising a sequence encoding a peptide inhibitor of the present invention or one or both peptide monomer subunit of a peptide dimer inhibitor of the present invention. The present invention also includes a vector comprising the polynucleotide.

[0035] In another aspect, the present invention includes a pharmaceutical composition comprising a peptide inhibitor or a peptide dimer inhibitor of the present invention, and a pharmaceutically acceptable carrier, excipient, or diluent. In particular embodiments, the pharmaceutical composition comprises an enteric coating. In certain embodiments, the enteric coating protects and releases the pharmaceutical composition within a subject's lower gastrointestinal system.

[0036] In another aspect, the present invention includes a method for treating or preventing a disease associated with IL-23 signalling, including but not limited to an Inflammatory Bowel Disease (IBD), ulcerative colitis, Crohn's disease, Celiac disease (*nontropical Sprue)*, enteropathy associated with seronegative arthropathies, microscopic colitis, collagenous

colitis, eosinophilic gastroenteritis, 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, and Wiskott-Aldrich Syndrome, pouchitis resulting after proctocolectomy and ileoanal anastomosis, gastrointestinal cancer, pancreatitis, insulin-dependent diabetes mellitus, mastitis, cholecystitis, cholangitis, pericholangitis, chronic bronchitis, chronic sinusitis, asthma, psoriasis, or graft versus host disease in a subject, comprising providing to the subject an effective amount of a peptide inhibitor or pharmaceutical composition of the present invention. In certain embodiments, the inflammatory bowel disease is ulcerative colitis or Crohn's disease. In particular embodimnts, the peptide inhibitor or the peptide dimer inhibitor inhibits binding of an interleukin-23 (IL-23) to the interleukin-23 receptor (IL-23R). In certain embodiments, the pharmaceutical composition is provided to the subject by an oral, intravenous, peritoneal, intradermal, subcutaneous, intramuscular, intrathecal, inhalation, vaporization, nebulization, sublingual, buccal, parenteral, rectal, intraocular, inhalation, vaginal, or topical route of administration. In particular embodiments, the pharmaceutical composition is provided orally for treating Inflammatory Bowel Disease (IBD), ulcerative colitis, Crohn's disease. In certain embodiments, the pharmaceutical composition is provided to the subject topically, parenterally, intravenously, subcutaneously, peritonealy, or intravenously for treating psoriasis.

DETAILED DESCRIPTION OF THE INVENTION

[0037] 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. Generally, nomenclature used in connection with, and techniques of, chemistry, molecular biology, cell and cancer biology, immunology, microbiology, pharmacology, and protein and nucleic acid chemistry, described herein, are those well-known and commonly used in the art.

[0038] As used herein, the following terms have the meanings ascribed to them unless specified otherwise.

[0039] Throughout this specification, the word "comprise" or variations such as "comprises" or "comprising" will be understood to imply the inclusion of a stated integer (or components)

or group of integers (or components), but not the exclusion of any other integer (or components) or group of integers (or components).

[0040] The singular forms "a," "an," and "the" include the plurals unless the context clearly dictates otherwise.

[0041] The term "including" is used to mean "including but not limited to." "Including" and "including but not limited to" are used interchangeably.

[0042] The terms "patient," "subject," and "individual" may be used interchangeably and refer to either a human or a non-human animal. These terms include mammals such as humans, primates, livestock animals (e.g., bovines, porcines), companion animals (e.g., canines, felines) and rodents (e.g., mice and rats).

[0043] The term "peptide," as used herein, refers broadly to a sequence of two or more amino acids joined together by peptide bonds. It should be understood that this term does not connote a specific length of a polymer of amino acids, nor is it intended to imply or distinguish whether the polypeptide is produced using recombinant techniques, chemical or enzymatic synthesis, or is naturally occurring.

[0044] The recitations "sequence identity", "percent identity", "percent homology", or, for example, comprising a "sequence 50% identical to," as used herein, refer to the extent that sequences are identical on a nucleotide-by-nucleotide basis or an amino acid-by-amino acid basis over a window of comparison. Thus, a "percentage of sequence identity" may be calculated by comparing two optimally aligned sequences over the window of comparison, determining the number of positions at which the identical nucleic acid base (e.g., A, T, C, G, I) or the identical amino acid residue (e.g., Ala, Pro, Ser, Thr, Gly, Val, Leu, Ile, Phe, Tyr, Trp, Lys, Arg, His, Asp, Glu, Asn, Gln, Cys and Met) occurs in both sequences to yield the number of matched positions, dividing the number of matched positions by the total number of positions in the window of comparison (i.e., the window size), and multiplying the result by 100 to yield the percentage of sequence identity.

[0045] Calculations of sequence similarity or sequence identity between sequences (the terms are used interchangeably herein) can be performed as follows. To determine the percent identity of two amino acid sequences, or of two nucleic acid sequences, the sequences can be aligned for optimal comparison purposes (e.g., gaps can be introduced in one or both of a first and a second amino acid or nucleic acid sequence for optimal alignment and non-homologous sequences can be disregarded for comparison purposes). In certain embodiments, the length of

a reference sequence aligned for comparison purposes is at least 30%, preferably at least 40%, more preferably at least 50%, 60%, and even more preferably at least 70%, 80%, 90%, 100% of the length of the reference sequence. The amino acid residues or nucleotides at corresponding amino acid positions or nucleotide positions are then compared. When a position in the first sequence is occupied by the same amino acid residue or nucleotide as the corresponding position in the second sequence, then the molecules are identical at that position.

[0046] The percent identity between the two sequences is a function of the number of identical positions shared by the sequences, taking into account the number of gaps, and the length of each gap, which need to be introduced for optimal alignment of the two sequences.

[0047] The comparison of sequences and determination of percent identity between two sequences can be accomplished using a mathematical algorithm. In some embodiments, the percent identity between two amino acid sequences is determined using the Needleman and Wunsch, (1970, J. Mol. Biol. 48: 444-453) algorithm which has been incorporated into the GAP program in the GCG software package, using either a Blossum 62 matrix or a PAM250 matrix, and a gap weight of 16, 14, 12, 10, 8, 6, or 4 and a length weight of 1, 2, 3, 4, 5, or 6. In yet another preferred embodiment, the percent identity between two nucleotide sequences is determined using the GAP program in the GCG software package, using an NWSgapdna.CMP matrix and a gap weight of 40, 50, 60, 70, or 80 and a length weight of 1, 2, 3, 4, 5, or 6. Another exemplary set of parameters includes a Blossum 62 scoring matrix with a gap penalty of 12, a gap extend penalty of 4, and a frameshift gap penalty of 5. The percent identity between two amino acid or nucleotide sequences can also be determined using the algorithm of E. Meyers and W. Miller (1989, Cabios, 4: 11-17) which has been incorporated into the ALIGN program (version 2.0), using a PAM120 weight residue table, a gap length penalty of 12 and a gap penalty of 4.

[0048] The peptide sequences described herein can be used as a "query sequence" to perform a search against public databases to, for example, identify other family members or related sequences. Such searches can be performed using the NBLAST and XBLAST programs (version 2.0) of Altschul, et al., (1990, J. Mol. Biol, 215: 403-10). BLAST nucleotide searches can be performed with the NBLAST program, score = 100, wordlength = 12 to obtain nucleotide sequences homologous to nucleic acid molecules of the invention. BLAST protein searches can be performed with the XBLAST program, score = 50, wordlength = 3 to obtain amino acid sequences homologous to protein molecules of the invention. To obtain gapped

alignments for comparison purposes, Gapped BLAST can be utilized as described in Altschul et al. (Nucleic Acids Res. 25:3389-3402, 1997). When utilizing BLAST and Gapped BLAST programs, the default parameters of the respective programs (e.g., XBLAST and NBLAST) can be used.

[0049] The term "conservative substitution" as used herein denotes that one or more amino acids are replaced by another, biologically similar residue. Examples include substitution of amino acid residues with similar characteristics, e.g., small amino acids, acidic amino acids, polar amino acids, basic amino acids, hydrophobic amino acids and aromatic amino acids. See, for example, the table below. In some embodiments of the invention, one or more Met residues are substituted with norleucine (Nle) which is a bioisostere for Met, but which, as opposed to Met, is not readily oxidized. Another example of a conservative substitution with a residue normally not found in endogenous, mammalian peptides and proteins is the conservative substitution of Arg or Lys with, for example, ornithine, canavanine, aminoethylcysteine or another basic amino acid. In some embodiments, one or more cysteines of a peptide analogue of the invention may be substituted with another residue, such as a serine. For further information concerning phenotypically silent substitutions in peptides and proteins, see, for example, Bowie et.al. Science 247, 1306-1310, 1990. In the scheme below, conservative substitutions of amino acids are grouped by physicochemical properties. I: neutral, hydrophilic, II: acids and amides, III: basic, IV: hydrophobic, V: aromatic, bulky amino acids.

I	**II**	**III**	**IV**	**V**
A	N	H	M	F
S	D	R	L	Y
T	E	K	I	W
P	Q		V	
G			C	

[0050] In the scheme below, conservative substitutions of amino acids are grouped by physicochemical properties. VI: neutral or hydrophobic, VII: acidic, VIII: basic, IX: polar, X: aromatic.

VI	VII	VIII	IX	X
A	E	H	M	F
L	D	R	S	Y
I		K	T	W
P			C	
G			N	
V			Q	

[0051] The term "amino acid" or "any amino acid" as used here refers to any and all amino acids, including naturally occurring amino acids (e.g., a-amino acids), unnatural amino acids, modified amino acids, and non-natural amino acids. It includes both D- and L-amino acids. Natural amino acids include those found in nature, such as, e.g., the 23 amino acids that combine into peptide chains to form the building-blocks of a vast array of proteins. These are primarily L stereoisomers, although a few D-amino acids occur in bacterial envelopes and some antibiotics. The 20 "standard," natural amino acids are listed in the above tables. The "non-standard," natural amino acids are pyrrolysine (found in methanogenic organisms and other eukaryotes), selenocysteine (present in many noneukaryotes as well as most eukaryotes), and N-formylmethionine (encoded by the start codon AUG in bacteria, mitochondria and chloroplasts). "Unnatural" or "non-natural" amino acids are non-proteinogenic amino acids (i.e., those not naturally encoded or found in the genetic code) that either occur naturally or are chemically synthesized. Over 140 unnatural amino acids are known and thousands of more combinations are possible. Examples of "unnatural" amino acids include β-amino acids (β^3 and β^2), homo-amino acids, proline and pyruvic acid derivatives, 3-substituted alanine derivatives, glycine derivatives, ring-substituted phenylalanine and tyrosine derivatives, linear core amino acids, diamino acids, D-amino acids, alpha-methyl amino acids and N-methyl amino acids. Unnatural or non-natural amino acids also include modified amino acids. "Modified" amino acids include amino acids (e.g., natural amino acids) that have been chemically modified to include a group, groups, or chemical moiety not naturally present on the amino acid. According to certain embodiments, a peptide inhibitor comprises an intramolecular bond between two amino acid residues present in the peptide inhibitor. It is understood that the amino acid residues that form the bond will be altered somewhat when bonded to each other as compared to when not bonded to each other. Reference to a particular amino acid is meant to encompass

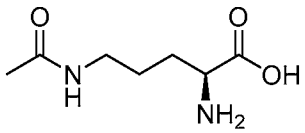
that amino acid in both its unbonded and bonded state. For example, the amino acid residue homoSerine (hSer) or homoSerine(Cl) in its unbonded form may take the form of 2-aminobutyric acid (Abu) when participating in an intramolecular bond according to the present invention. The present invention inclues both peptide inhibitors containing cross-links between X4 and X9, as well as the peptide inhibitors that do not contain cross-links between X4 and X9, e.g., before cross-link formation. As such, the names hSer and Abu are intended to indicate the same amino acids and are used interchangeably.

[0052] For the most part, 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 appended claims differ from those suggestions, they will be made clear to the reader. Some abbreviations useful in describing the invention are defined below in the following Table 1.

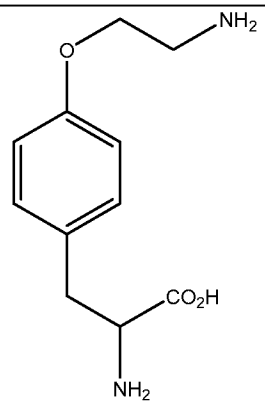
Table 1. Abbreviations of Non-Natural Amino Acids and Chemical Moieties (for amino acid derivatives, all L unless stated)

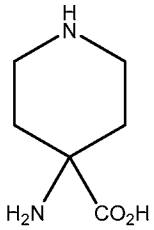
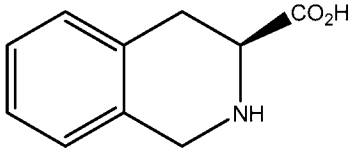
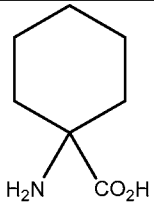
Abbreviation	Definition
Ac-	Acetyl
Hy	Hydrogen (Free N-terminal)
Dap	L-Diaminopropionic acid
Dab	L-Diaminobutyric acid
DabCOMe	N-Acetyl-L-diaminobutyric acid
Orn	L-Ornathine
Pen	L-Penicillamine
Sarc	Sarcosine
Cit	L-Citrulline
Cav	L-Cavanine

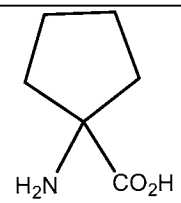
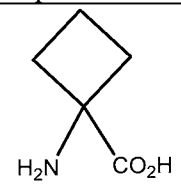
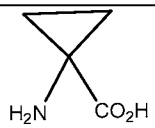
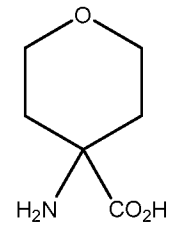
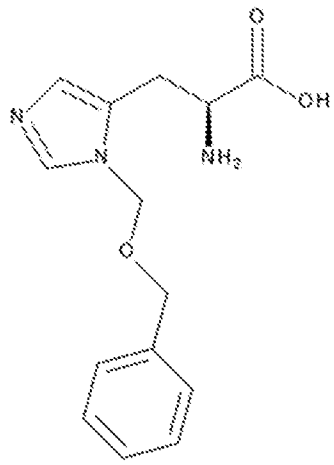
Abbreviation	Definition
Phe-(4-Guanidino)	4-Guanidine-L-Phenylalanine
N-MeArg	N-Methyl-L-Arginine
N-MeTrp	N-Methyl-L-Tryptophan
N-MeGln	N-Methyl-L-Glutamine
N-MeAla	N-Methyl-L-Alanine
N-MeLys	N-Methyl-Lysine
N-MeAsn	N-Methyl-L-Asparagine
6-ChloroTrp	6-Chloro-L-Tryptophan
5-HydroxyTrp	5-Hydroxy-L-Tryptophan
1,2,3,4-tetrahydro-norharman	L-1,2,3,4-tetrahydro-norharman
2-Nal (also referred to as 2-Nap)	L-2-Napthylalanine
1-Nal (also referred to as 1-Nap)	L-1-Napthylalanine
Phe(4-OMe)	4-Methoxy-L-phenylalanine
Abu	2-Aminobutyric acid
Bip	L-4,4'-Biphenylalanine
βAla, beta-Ala, or bA	beta-Alanine
NMeβA or NMebA	N-Me-beta-Alanine
βhTyr	beta homo-L-Tyrosine
βhTrp	beta homo-L-Trptophan
βhAla	beta homo-L-Alanine
βhLeu,	beta homo-L-Leucine
βhVal	beta homo-L-Valine

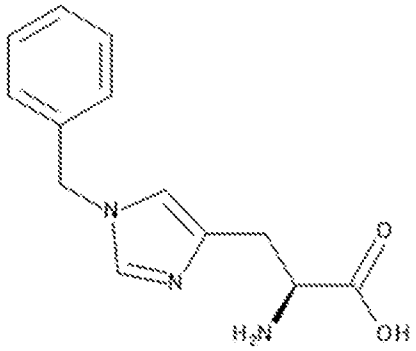
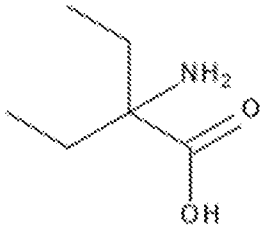
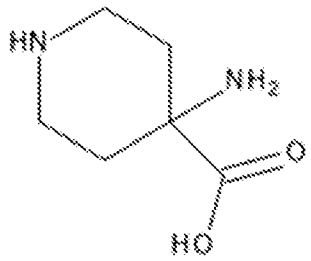
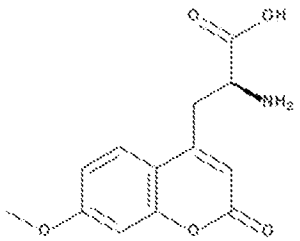
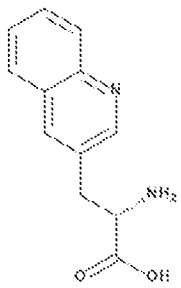
Abbreviation	Definition
Aib	2-aminoisobutyric acid
Azt	L-azetidine-2-carboxylic acid
Tic	(3S)-1,2,3,4-Tetrahydroisoquinoline-7-hydroxy-3-carboxylic Acid
Phe(4-OMe)	4-methoxy-L-phenylalanine
N-Me-Lys	N-Methyl-L-Lysine
N-Me-Lys(Ac)	N-ε-Acetyl-N-Methyl-L-lysine
$CONH_2$	Carboxamide
COOH	Acid
3-Pal	L-3-Pyridylalanine
Phe(4-F)	4-Fluoro-L-Phenylalanine
DMT	2,6-DimethylTyrosine
Phe(4-OMe)	4-Methoxyphenylalanine
hLeu	L-homoLeucine
hArg	L-homoArginine
α-MeCys or a-MeCys	alpha-methyl-L-Cysteine
α-MeLys	alpha-methyl-L-Lysine
α-MeOrn	alpha-methyl-L-Ornathine
OrnCOMe	 N-Acetyl-L-oranthine
α-MeLeu	alpha-methyl-L-Leucine
α-MeTrp	alpha-methyl-L-Tryptophan
α-MePhe or a-MePhe or a-Me-Phe	alpha-methyl-L-Phenylalanine

Abbreviation	Definition
α-MeTyr	alpha-methyl-L-Tyrosine
α–DiethylGly	α-DiethylGlycine
Lys(Ac)	N-ε-acetyl-L-Lysine
Lys(IVA)	(N^{ε}-isovaleric acid)-L-Lysine or (N^{ε}-isovaleroyl)-L-Lysine
Lys($COCF_3$)	(N^{ε}-trifluoroacetyl)-L-Lysine
Lys(COtBu)	[N^{ε}-(C(O)-t-Bu)]-L-Lysine
Lys(R')	[N^{ε}-(R')]-L-Lysine (exemplary R'= Aib, bAla, IVA, Ala, cyclohexanoic, octanoic, -$C(O)CH_2Ph$, trifluorpropionic, Gly, acetyl, trifluoroacetyl, etc)
DTT	Dithiothreotol
Nle	L-Norleucine
βhTrp	L-β-homoTryptophan
βhPhe	L-β-homophenylalanine
βhPro	L-β-homoproline
Phe(4-CF_3)	4-Trifluoromethyl-L-Phenylalanine
β-Glu	L-β-Glutamic acid
βhGlu	L-β-homoglutamic acid
2-2-Indane	2-Aminoindane-2-carboxylic acid
1-1-Indane	1-Aminoindane-1-carboxylic acid
hCha	L-homocyclohexylalanine
Cyclobutyl	L-cyclobutylalanine
βhPhe	L-β-homo-phenylalanine
Gla	Gama-Carboxy-L-Glutamic acid

Abbreviation	Definition
Cpa	Cyclopentyl-L-alanine
Cha	Cyclohexyl-L-alanine
Octgly	L-Octylglycine
t-butyl-Ala	3-(*tert*-butyl)-L-Ala-OH
t-butyl-Gly	*tert*-butyl-glycine
AEP	3-(2-aminoethoxy)propanoic acid
AEA	(2-aminoethoxy)acetic acid
Phe(4-Phenoxy)]	4-Phenoxy-L-phenylalanine
Phe(4-OBzl)	*O-Benzyl*-L-tyrosine
Phe(4-$CONH_2$) or Phe(Cmd)	4-Carbamoyl-L-phenylalanine
Phe(4-CO_2H)	4-Carboxy-L-phenylalanine
Phe(3,4-Cl_2)	3,4 dichloro-L-phenylalanine
Tyr(3-t-Bu)	3-*t*-butyl-L-tyrosine
Phe(t-Bu)	*t*-butyl-L-phenylalanine
Phe[4-(2-aminoethoxy)] or F(4-2ae)	 4-(2-aminoethoxy)-L-phenylalanine
Phe[4-(2-acetylaminoethoxy)]	L-4-[(Ac-NH-CH_2CH_2-O)]-Ph-CH_2-C(H)(NH_2)CO_2H or 4-(2-acetylaminoethoxy)-L-phenylalanine

Abbreviation	Definition
Phe(4-CN)	4-cyano-L-phenylalanine
Phe(4-Br)	4-bromo-L-phenylalanine
Phe(4-NH_2)	4-amino-L-phenylalanine
Phe(4-Me)	4-methyl-L-phenylalanine
4-Pyridylalanine	4-L-Pyridylalanine
4-amino-4-carboxy-piperidine	 4-amino-4-carboxy-piperidine
hPhe(3,4-dimethoxy)	3,4-dimethoxy-L-homophenylalanine
Phe(2,4-Me_2)	2,4-dimethyl-L-phenylalanine
Phe(3,5-F_2)	3,5-difluoro-L-phenylalanine
Phe(penta-F)	pentafluoro-L-phenylalanine
2,5,7-tert butyl Trp	2,5,7-Tris-tert-butyl-L-tryptophan
Tic	 L-1,2,3,4,-tetrahydro-isoquinoline-3-carboxylic acid
Phe(4-OAllyl)	O-*Allyl*-L-Tyrosine
Phe(4-N_3)	4-azidophenylalanine
Achc	 1-aminocyclohexanecarboxylic acid

Abbreviation	Definition
Acvc	 1-aminocyclopentanecarboxylic acid
Acbc	 1-aminocyclobutanecarboxylic acid
Acpc	 1-aminocyclopropylcarboxylic acid
4-amino-4-carboxy-tetrahydropyran or THP	 4-amino-4-carboxy-tetrahydropyran
Ahx	6-aminohexanoic acid
His_3Bom	

Abbreviation	Definition
His_Bzl	
DiethylGly	
Spiral_Pip	
Coumarin	
Quin	

[0053] Throughout the present specification, unless naturally occurring amino acids are referred to by their full name (e.g., alanine, arginine, etc.), they are designated by their conventional three-letter or single-letter abbreviations (e.g., Ala or A for alanine, Arg or R for arginine, etc.). Unless otherwise indicated, three-letter and single-letter abbreviations of amino acids refer to the L-isomeric form of the amino acid in question. The term "L-amino acid," as used herein, refers to the "L" isomeric form of a peptide, and conversely the term "D-amino acid" refers to the "D" isomeric form of a peptide (e.g., Dasp, (D)Asp or D-Asp; Dphe, (D)Phe or D-Phe). Amino acid residues in the D isomeric form can be substituted for any L-amino acid residue, as long as the desired function is retained by the peptide. D-amino acids may be indicated as customary in lower case when referred to using single-letter abbreviations.

[0054] 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 8Ado (8-amino-3,6-dioxaoctanoic acid), Abu (2-amino butyric acid), βhPro (β-homoproline), βhPhe (β-homophenylalanine) and Bip (β,β diphenylalanine), and Ida (Iminodiacetic acid).

[0055] 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 a "Hy-" moiety at the amino terminus (N-terminus) of the sequence, and either an "-OH" moiety or an "-NH_2" moiety at the carboxy terminus (C-terminus) of the sequence. In such cases, and unless otherwise indicated, a "Hy-" moiety at the N-terminus of the sequence in question indicates a hydrogen atom, corresponding to the presence of a free primary or secondary amino group at the N-terminus, while an "-OH" or an "–NH_2" moiety at the C-terminus of the sequence indicates a hydroxy group or an amino group, corresponding to the presence of an amido ($CONH_2$) group at the C-terminus, respectively. In each sequence of the invention, a C-terminal "–OH" moiety may be substituted for a C-terminal "–NH_2" moiety, and vice-versa.

[0056] 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 may be modified when it forms an intramolecular bridge with another amino acid side chain, e.g., one or more hydrogen may be removed or replaced by the bond. Accordingly, as used herein, reference to an amino acid or modified amino acid present in a peptide dimer of the present invention (e.g., at position X4 or position X9) is meant to include the form of such amino acid or modified amino acid present in the peptide both before and after forming the intramolecular bond.

[0057] The term "dimer," as used herein, refers broadly to a peptide comprising two or more monomer subunits. Certain dimers comprise two monomer subunits comprising a sequence of Formula (I) or set forth herein. Dimers of the present invention include homodimers and heterodimers. A monomer subunit of a dimer may be linked at its C- or N-terminus, or it may be linked via internal amino acid residues. Each monomer subunit of a dimer may be linked through the same site, or each may be linked through a different site (e.g., C-terminus, N-terminus, or internal site).

[0058] The term "NH_2," as used herein, can refer to a free amino group present at the amino terminus of a polypeptide. The term "OH," as used herein, can refer to a free carboxy group present at the carboxy terminus of a peptide. Further, the term "Ac," as used herein, refers to Acetyl protection through acylation of the C- or N-terminus of a polypeptide. In certain peptides shown herein, the NH_2 locates at the C-terminus of the peptide indicates an amino group.

[0059] The term "carboxy," as used herein, refers to $–CO_2H$ or -C(O)OH radical.

[0060] The term "isostere replacement," as used herein, refers to any amino acid or other analog moiety having chemical and/or structural properties similar to a specified amino acid. In certain embodiments, an isostere replacement is a conservative substitution or an analog of a specified amino acid.

[0061] The term "cyclized," as used herein, refers to one part of a polypeptide molecule being linked to another part of the polypeptide molecule to form a closed ring, such as by forming a disulfide bridge or thioether bond.

[0062] The term "subunit," as used herein, refers to one of a pair of polypeptide monomers that are joined to form a dimer peptide composition.

[0063] The term "linker moiety," as used herein, refers broadly to a chemical structure that is capable of linking or joining together two peptide monomer subunits to form a dimer.

[0064] The term "pharmaceutically acceptable salt," as used herein, represents salts or zwitterionic forms of the peptides or compounds of the present invention which are water or oil-soluble or dispersible, which are suitable for treatment of diseases without undue toxicity, irritation, and allergic response; which are commensurate with a reasonable benefit/risk ratio, and which are effective for their intended use. The salts can be prepared during the final isolation and purification of the compounds or separately by reacting an amino group with a suitable acid. Representative acid addition salts include acetate, adipate, alginate, citrate, aspartate, benzoate, benzenesulfonate, bisulfate, butyrate, camphorate, camphorsulfonate, digluconate, glycerophosphate, hemisulfate, heptanoate, hexanoate, formate, fumarate, hydrochloride, hydrobromide, hydroiodide, 2-hydroxyethansulfonate (isethionate), lactate, maleate, mesitylenesulfonate, methanesulfonate, naphthylenesulfonate, nicotinate, 2-naphthalenesulfonate, oxalate, pamoate, pectinate, persulfate, 3-phenylproprionate, picrate, pivalate, propionate, succinate, tartrate, trichloroacetate, trifluoroacetate, phosphate, glutamate, bicarbonate, para-toluenesulfonate, and undecanoate. Also, amino groups in the compounds of the present invention can be quaternized with methyl, ethyl, propyl, and butyl chlorides, bromides, and iodides; dimethyl, diethyl, dibutyl, and diamyl sulfates; decyl, lauryl, myristyl, and steryl chlorides, bromides, and iodides; and benzyl and phenethyl bromides. Examples of acids which can be employed to form therapeutically acceptable addition salts include inorganic acids such as hydrochloric, hydrobromic, sulfuric, and phosphoric, and organic acids such as oxalic, maleic, succinic, and citric. A pharmaceutically acceptable salt may suitably be a salt chosen, e.g., among acid addition salts and basic salts. Examples of acid addition salts include chloride salts, citrate salts and acetate salts. Examples of basic salts include salts where the cation is selected among alkali metal cations, such as sodium or potassium ions, alkaline earth metal cations, such as calcium or magnesium ions, as well as substituted ammonium ions, such as ions of the type N(R1)(R2)(R3)(R4)+, where R1, R2, R3 and R4 independently will typically designate hydrogen, optionally substituted C1-6-alkyl or optionally substituted C2-6-alkenyl. Examples of relevant C1-6-alkyl groups include methyl, ethyl, 1-propyl and 2-propyl groups. Examples of C2-6-alkenyl groups of possible relevance include ethenyl, 1-propenyl and 2-propenyl. Other examples of pharmaceutically acceptable salts are described in "Remington's Pharmaceutical Sciences", 17th edition, Alfonso R.

Gennaro (Ed.), Mark Publishing Company, Easton, PA, USA, 1985 (and more recent editions thereof), in the "Encyclopaedia of Pharmaceutical Technology", 3rd edition, James Swarbrick (Ed.), Informa Healthcare USA (Inc.), NY, USA, 2007, and in J. Pharm. Sci. 66: 2 (1977). Also, for a review on suitable salts, see *Handbook of Pharmaceutical Salts: Properties, Selection, and Use* by Stahl and Wermuth (Wiley-VCH, 2002). Other suitable base salts are formed from bases which form non-toxic salts. Representative examples include the aluminum, arginine, benzathine, calcium, choline, diethylamine, diolamine, glycine, lysine, magnesium, meglumine, olamine, potassium, sodium, tromethamine, and zinc salts. Hemisalts of acids and bases may also be formed, e.g., hemisulphate and hemicalcium salts.

[0065] The term "N(alpha)Methylation", as used herein, describes the methylation of the alpha amine of an amino acid, also generally termed as an N-methylation.

[0066] The term "sym methylation" or "Arg-Me-sym", as used herein, describes the symmetrical methylation of the two nitrogens of the guanidine group of arginine. Further, the term "asym methylation" or "Arg-Me-asym" describes the methylation of a single nitrogen of the guanidine group of arginine.

[0067] The term "acylating organic compounds", as used herein refers to various compounds with carboxylic acid functionality that are used to acylate the N-terminus of an amino acid or a monomer or dimer, e.g., a monomer subunit prior to forming a C-terminal dimer. Non-limiting examples of acylating organic compounds include cyclopropylacetic acid, 4-Fluorobenzoic acid, 4-fluorophenylacetic acid, 3-Phenylpropionic acid, Succinic acid, Glutaric acid, Cyclopentane carboxylic acid, 3,3,3-trifluoropropeonic acid, 3-Fluoromethylbutyric acid, Tetrahedro-2H-Pyran-4-carboxylic acid.

[0068] The term "acyl" or "alkanoyl" refers to the univalent group, RCO-, where R is any alkyl attached to one bond of the carbonyl group.

[0069] The term "acetyl" or "Ac" refers to the acyl radical $-C(O)CH_3$.

[0070] The term "alkyl" includes a straight chain or branched, noncyclic or cyclic, saturated aliphatic hydrocarbon containing from 1 to 24 carbon atoms. Representative saturated straight chain alkyls include, but are not limited to, methyl, ethyl, *n*-propyl, *n*-butyl, *n*-pentyl, *n*-hexyl, and the like, while saturated branched alkyls include, without limitation, isopropyl, *sec*-butyl, isobutyl, *tert*-butyl, isopentyl, and the like. Representative saturated cyclic alkyls include, but are not limited to, cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl, and the like, while

unsaturated cyclic alkyls include, without limitation, cyclopentenyl, cyclohexenyl, and the like.

[0071] "Aryl" refers to an aromatic monocyclic or multicyclic hydrocarbon ring system. The aromatic monocyclic or multicyclic hydrocarbon ring system contains only hydrogen and carbon from six to eighteen carbon atoms, where at least one of the rings in the ring system is fully unsaturated, *i.e.*, it contains a cyclic, delocalized (4n+2) π–electron system in accordance with the Hückel theory. Aryl groups include, but are not limited to, groups such as phenyl (Ph), fluorenyl, and naphthyl. Unless stated otherwise specifically in the specification, the term "aryl" or the prefix "ar-" (such as in "aralkyl") is meant to include aryl radicals optionally substituted by one or more substituents independently selected from alkyl, alkenyl, alkynyl, halo, fluoroalkyl, cyano, nitro, optionally substituted aryl, optionally substituted aralkyl, optionally substituted aralkenyl, optionally substituted aralkynyl, optionally substituted carbocyclyl, optionally substituted carbocyclylalkyl, optionally substituted heterocyclyl, optionally substituted heterocyclylalkyl, optionally substituted heteroaryl, optionally substituted

heteroarylalkyl, $-R^b-OR^a$, $-R^b-OC(O)-R^a$, $-R^b-N(R^a)_2$, $-R^b-C(O)R^a$, $-R^b-C(O)OR^a$, $-R^b-C(O)N(R^a)_2$, $-R^b-O-R^c-C(O)N(R^a)_2$, $-R^b-N(R^a)C(O)OR^a$, $-R^b-N(R^a)C(O)R^a$, $-R^b-N(R^a)S(O)_tR^a$ (where t is 1 or 2), $-R^b-S(O)_tOR^a$ (where t is 1 or 2) and $-R^b-S(O)_tN(R^a)_2$ (where t is 1 or 2), where each R^a is independently hydrogen, alkyl, fluoroalkyl, cycloalkyl, cycloalkylalkyl, aryl (optionally substituted with one or more halo groups), aralkyl, heterocyclyl, heterocyclylalkyl, heteroaryl or heteroarylalkyl, each R^b is independently a direct bond or a straight or branched alkylene or alkenylene chain, and R^c is a straight or branched alkylene or alkenylene chain, and where each of the above substituents is unsubstituted unless otherwise indicated.

[0072] "Aralkyl" or "aryl-alkyl" refers to a radical of the formula $-R^c$-aryl where R^c is an alkylene chain as defined above, for example, benzyl, diphenylmethyl and the like. The alkylene chain part of the aralkyl radical is optionally substituted as described above for an alkylene chain. The aryl part of the aralkyl radical is optionally substituted as described above for an aryl group

[0073] "Alkylene" refers to a straight or branched, saturated, aliphatic radical having the number of carbon atoms indicated, and linking at least two other groups, *i.e.*, a divalent hydrocarbon radical. The two moieties linked to the alkylene can be linked to the same atom or different atoms of the alkylene group. For instance, a straight chain alkylene can be the bivalent radical

of -$(CH_2)_n$-, where n is 1, 2, 3, 4, 5 or 6. Representative alkylene groups include, but are not limited to, methylene, ethylene, propylene, isopropylene, butylene, isobutylene, sec-butylene, pentylene and hexylene. Alkylene groups can be substituted or unsubstituted.

[0074] "Halo" or "halogen" refers to bromo (Br), chloro (Cl), fluoro (F) or iodo (I) substituents.

[0075] The terms "haloalkyl" includes alkyl structures in which at least one hydrogen is replaced with a halogen atom. In certain embodiments in which two or more hydrogen atoms are replaced with halogen atoms, the halogen atoms are all the same as one another. In other embodiments in which two or more hydrogen atoms are replaced with halogen atoms, the halogen atoms are not all the same as one another.

[0076] An "alkoxy" group refers to a (alkyl)O- group, where alkyl is as defined herein.

[0077] An "aryloxy" group refers to an (aryl)O- group, where aryl is as defined herein.

[0078] "Aminocarbonyl" or "carboxamido" refers to a -$CONH_2$ radical.

[0079] "2-Aminoethoxy" refers to -OCH_2CH_2-NH_2 radical.

[0080] "2-Acetylaminoethoxy" refers to -OCH_2CH_2-N(H)C(O)Me radical.

[0081] The term "mammal" refers to any mammalian species such as a human, mouse, rat, dog, cat, hamster, guinea pig, rabbit, livestock, and the like.

[0082] As used herein, a "therapeutically effective amount" of the peptide inhibitor of the invention is meant to describe a sufficient amount of the peptide inhibitor to treat an IL-23/IL-23R-related disease, including but not limited to any of the diseases and disorders described herein (for example, to reduce inflammation associated with IBD). In particular embodiments, the therapeutically effective amount will achieve a desired benefit/risk ratio applicable to any medical treatment.

[0083] An "analog" of an amino acid, e.g., a "Phe analog" or a "Tyr analog" means an analog of the referenced amino acid. A variety of amino acid analogs are known and available in the art, including Phe and Tyr analogs. In certain embodiments, an amino acid analog, e.g., a Phe analog or a Tyr analog comprises one, two, three, four or five substitutions as compared to Phe or Tyr, respectively. In certain embodiments, the substitutions are present in the side chains of the amino acids. In certain embodiments, a Phe analog has the structure Phe(R^2), wherein R^2 is a Hy, OH, CH_3, CO_2H, $CONH_2$, $CONH_2OCH_2CH_2NH_2$, *t*-Bu, $OCH_2CH_2NH_2$, phenoxy, OCH_3, OAllyl, Br, Cl, F, NH_2, N3, or guanadino. In certain embodiments, R^2 is $CONH_2OCH_2CH_2NH_2$, OCH_3, $CONH_2$, OCH_3 or CO_2H. Examples of Phe analogs include, but are not limited to: hPhe, Phe(4-OMe), α-Me-Phe, hPhe(3,4-dimethoxy), Phe(4-$CONH_2$),

Phe(4-phenoxy), Phe(4-guanadino), Phe(4-tBu), Phe(4-CN), Phe(4-Br), Phe(4-OBzl), Phe(4-NH_2), BhPhe(4-F), Phe(4-F), Phe(3,5 DiF), Phe(CH_2CO_2H), Phe(penta-F), Phe(3,4-Cl_2), Phe (3,4-F_2), Phe(4-CF_3), ββ-diPheAla, Phe(4-N_3), Phe[4-(2-aminoethoxy)], 4-Phenylbenzylalanine, Phe(4-$CONH_2$), Phe(3,4-Dimethoxy), Phe(4-CF_3), Phe(2,3-Cl_2), and Phe(2,3-F_2). Examples of Tyr analogs include, but are not limited to: hTyr, N-Me-Tyr, Tyr(3-*t*Bu), Tyr(4-N_3) and βhTyr.

Peptide Inhibitors of IL-23R

[0084] Genome-wide association studies (GWAS) have demonstrated significant association of the IL-23 receptor (IL-23R) gene with inflammatory bowel disease (IBD), suggesting that perturbation of IL-23 signaling could be relevant to the pathogenesis of this disease and other inflammatory diseases and disorders. The present invention provides compositions and methods to modulate the IL-23 pathway through antagonism of IL-23R.

[0085] The present invention relates generally to peptides that have IL-23R antagonist activity, including both peptide monomers and peptide dimers. In certain embodiments, this invention demonstrates a new paradigm for treatment of IBD and other diseases and disorders by oral delivery of antagonists of IL-23. IBD represents a local inflammation of the intestinal tissue; therefore, advantageous therapeutic agents act from the luminal side of the intestine, yielding high drug concentrations in diseased tissue, minimizing systemic availability and resulting in improved efficacy and safety when compared to systemic approaches. Oral administration of the compounds of the present invention is expected to maximize drug levels in diseased intestinal tissues while limiting drug concentrations in circulation, thereby providing efficacious, safe, and durable delivery for life-long treatment of IBD and other diseases and disorders.

[0086] In certain embodiments, the present invention relates to various peptides, or peptide dimers comprising hetero- or homo-monomer subunits, that form cyclized structures through disulfide or other bonds. In certain embodiments, the disulfide or other bonds are intramolecular bonds. The cyclized structure of the peptide monomer inhibitors and the monomer subunits of the peptide dimer inhibitors has been shown to increase potency and selectivity of the peptide inhibitors. In certain embodiments, a peptide dimer inhibitor may include one or more intermolecular bonds linking the two monomer peptide subunits within the peptide dimer inhibitor, e.g., an intermolecular bridge between two Pen residues, one in each peptide monomer subunit.

[0087] The present invention provides peptide inhibitors that bind to IL-23R, which may be monomers or dimers. In particular embodiments, the peptide inhibitors inhibit the binding of IL-23 to IL-23R. In certain embodiments, the IL-23R is human IL-23R, and the IL-23 is human IL-23. In certain embodiments, a peptide inhibitor of the present invention reduces IL-23 binding to IL-23R by at least 20%, at least 30%, at least 40%, at least 50%, at least 60%, at least 70%, at least 80%, or at least 90% as compared to a negative control peptide. Methods of determining binding are known in the art and include ELISA assays, as described in the accompanying Examples.

[0088] In certain embodiments, a peptide inhibitor of the present invention has an IC_{50} of > 1 mM, < 1 mM, 500 nM to 1000 nM, < 500 nM, < 250 nM, < 100 nM, < 50 nM, < 25 nM, < 10 nM, < 5 nM, < 2 nM, < 1 nM, or < 5 mM, e.g., for inhibiting binding of IL-23 to IL-23R (e.g., human IL-23 and human IL-23R). Methods of determining activity are known in the art and include any of those described in the accompanying Examples.

[0089] In certain embodiments, a peptide inhibitor of the present invention has increased stability, increased gastrointestinal stability, or increased stability in stimulated intestinal fluid (SIF) or simulated gastric fluid (SGF), and/or under redox conditions (e.g., DTT) as compared to a control peptide. In certain embodiments, a control peptide is an unrelated peptide of the same or similar length. In particular embodiments, a control peptide is a peptide having the identical or a highly related amino acid sequence (e.g., > 90% sequence identity) as the peptide inhibitor. In particular embodiments, a control peptide is a peptide having the identical or a highly related amino acid sequence (e.g., > 90% sequence identity) as the peptide inhibitor, but which does not have a cyclized structure, e.g., through an intramolecular bond between two amino acid residues within the control peptide, or which is not dimerized, or which does not comprise a conjugate for stabilization. In particular embodiments, the only difference between the peptide inhibitor and the control peptide is that the peptide inhibitor comprises one or more amino acid substitutions that introduce one or more amino acid residues into the peptide inhibitor, wherein the introduced amino residue(s) forms an intrasulfide disulfide or thioether bond with another amino acid residue in the peptide inhibitor. One example of a control for a peptide dimer inhibitor is a monomer having the same sequence as one of the monomer subunits present in the peptide dimer inhibitor. One example of a control for a peptide inhibitor comprising a conjugate is a peptide having the same sequence but not

including the conjugated moiety. In certain embodiments, a control peptide is a peptide (e.g., a naturally-occurring peptide) corresponding to a region of IL-23 that binds to IL-23R.

[0090] Methods of determining the stablity of a peptide are known in the art. In certain embodiments, the stability of a peptide inhibitor is determined using an SIF assay, e.g., as described in Example 3. In certain embodiments, the stability of a peptide inhibitor is determined using an SGF assay, e.g., as described in Example 3. In particular embodiments, a peptide inhibitor has a half-life (e.g., in SIF or SGF or DTT) under a given set of conditions (e.g., temperature) of greater than 1 minute, greater than 10 minutes, greater than 20 minutes, greater than 30 minutes, greater than 60 minutes, greater than 90 minutes, greater than 120 minutes, greater than 3 hours, or greater than four hours when exposed to SIF or SGF or DTT. In certain embodiments, the temperature is about 25 °C, about 4 ºC, or about 37 ºC, and the pH is a physiological pH, or a pH about 7.4.

[0091] In some embodiments, the half-life is measured in vitro using any suitable method known in the art, e.g., in some embodiments, the stability of a peptide of the present invention is determined by incubating the peptide with pre-warmed human serum (Sigma) at 37 ° C. Samples are taken at various time points, typically up to 24 hours, and the stability of the sample is analyzed by separating the peptide or peptide dimer from the serum proteins and then analyzing for the presence of the peptide or peptide dimer of interest using LC-MS.

[0092] In some embodiments, a peptide inhibitor of the present invention exhibits improved solubility or improved aggregation characteristics as compared to a control peptide. Solubility may be determined via any suitable method known in the art. In some embodiments, suitable methods known in the art for determining solubility include incubating peptides in various buffers (Acetate pH4.0, Acetate pH5.0, Phos/Citrate pH5.0, Phos Citrate pH6.0, Phos pH 6.0, Phos pH 7.0, Phos pH7.5, Strong PBS pH 7.5, Tris pH7.5, Tris pH 8.0, Glycine pH 9.0, Water, Acetic acid (pH 5.0 and other known in the art) and testing for aggregation or solubility using standard techniques. These include, but are not limited to, visual precipitation, dynamic light scattering, Circular Dichroism and fluorescent dyes to measure surface hydrophobicity, and detect aggregation or fibrillation, for example. In some embodiments, improved solubility means the peptide is more soluble in a given liquid than is a control peptide. In some embodiments, improved aggregation means the peptide has less aggregation in a given liquid under a given set of conditions than a control peptide.

[0093] In certain embodiments advantageous for achieving high compound concentrations in intestinal tissues when delivered orally, peptide inhibitors of the present invention are stable in the gastrointestinal (GI) environment. Proteolytic metabolism in the GI tract is driven by enzymes (including pepsins, trypsin, chymotrypsin, elastase, aminopeptidases, and carboxypeptidase A/B) that are secreted from the pancreas into the lumen or are produced as brush border enzymes. Proteases typically cleave peptides and proteins that are in an extended conformation. In the reducing environment of intestinal fluids, disulfide bonds may be broken, resulting in a linear peptide and rapid proteolysis. This luminal redox environment is largely determined by the Cys/CySS redox cycle. In enterocytes, relevant activities include numerous digestive enzymes such as CYP450 and UDP-glucuronsyl-transferase. Finally, bacteria, present in the large intestine at concentration ranging from 10^{10} to 10^{12} CFU/ml, constitute another metabolic barrier. In certain embodiments, the peptide inhibitors are stable to various pHs that range from strongly acidic in the stomach (pH 1.5-1.9), trending towards basic in the small intestine (pH 6-7.5), and then weakly acidic in the colon (pH 5-7). Such peptide inhibitors are stable during their transit through the various GI compartments, a process that has been estimated to take 3-4 h in the intestine and 6-48 h in the colon.

[0094] In some embodiments, the peptide inhibitors of the present invention have less degradation, e.g., over a period of time (i.e., more degradation stability), e.g., greater than or about 10% less, greater than or about 20% less, greater than or about 30% less, greater than or about 40 less, or greater than or about 50% less degradation than a control peptide. In some embodiments, degradation stability is determined via any suitable method known in the art. In some embodiments, the degradation is enzymatic degradation. For example, in certain embodiments, the peptide inhibitors have reduced susceptibility to degradation by trypsin, chhrmotrypsin or elastase. In some embodiments, suitable methods known in the art for determining degradation stability include the method described in Hawe et al., J Pharm Sci, VOL. 101, No. 3, 2012, p 895-913, incorporated herein in its entirety. Such methods are in some embodiments used to select potent peptide sequences with enhanced shelf lifes. In particular embodiments, peptide stability is determined using a SIF assay or SGF assay, e.g., as described in PCT Publication No. WO 2016/011208.

[0095] In certain embodiments, peptide inhibitors of the present invention inhibit or reduce IL-23-mediated inflammation. In related embodiments, peptide inhibibitors of the present invention inhibit or reduce IL-23-mediated secretion of one or more cytokines, e.g., by binding

to IL-23R on the cell surface, thus inhibiting IL-23 binding to the cell. In particular embodiments, peptide inhibitors of the present invention inhibit or reduce IL-23-mediated activation of Jak2, Tyk2, Stat1, Stat3, Stat4, or Stat5. Methods of determining inhibition of cytokine secretion and inhibition of signaling molecules are known in the art. For example, inhibiton of IL-23/IL-23R signaling may be determined by measuring inhibition of phospho-Stat3 levels in cell lysates, e.g., as described in PCT Publication No. WO 2016/011208.

[0096] In certain embodiments, peptide inhibitors have increased redox stability as compared to a control peptide. A variety of assays that may be used to determine redox stability are known and available in the art. Any of these may be used to determine the redox stability of peptide inhibitors of the present invention.

[0097] In certain embodiments, the present invention provides various peptide inhibitors that bind or associate with the IL-23R, *in vitro* or *in vivo*, to disrupt or block binding between IL-23 and IL-23R. In certain embodiments, the peptide inhibitors bind and/or inhibit human IL-23R. In certain embodiments, the peptide inhibitors bind and/or inhibit both human and rodent IL-23R. In certain embodiments, the peptide inhibitors bind and/or inhibit both human and rat IL-23R. In particular embodiments, the peptide inhibitors inhibit rat IL-23R at least 50%, at least 60%, at least 70%, at least 80%, at least 90%, or at least 95% as well as they bind or inhibit human IL-23R, e.g., as determined by an assay described herein. In certain embodiments, the peptide inhibitors preferentially bind and/or inhibit human and/or rat IL-23R as compared to mouse IL-23R. In particular embodiments, the peptide inhibitors preferentially bind to rat IL-23R as compared to mouse IL-23R. In particular embodiments, the peptide inhibitors preferentially bind to human IL-23R as compared to mouse IL-23R. In certain embodiments, binding of a peptide inhibitor to mouse IL-23R is less than 75%, less than 50%, less than 40%, less than 30%, less than 20%, or less than 10% of binding of the same peptide inhibitor to human IL-23R and/or rat IL-23R. In certain embodiments of peptide inhibitors that preferentially bind and/or inhibit human IL-23R and/or rat IL-23R as compared to mouse IL-23R, the peptide inhibitor binds to a region of IL-23R that is disrupted by the presence of additional amino acids present in mouse IL-23R but not human IL-23R or rat IL-23. In one embodiment, the additional amino acids present in the mouse IL-23R are in the region corresponding to about amino acid residue 315 to about amino acid residue 340 of the mouse IL23R protein, e.g., amino acid region NWQPWSSPFVHQTSQETGKR (SEQ ID NO: 106).

In particular embodiments, the peptide inhibitors bind to a region of human IL-23R from about amino acid 230 to about amino acid residue 370.

[0098] In certain embodiments, peptide inhibitors show GI-restricted localization following oral administration. In particular embodiments, greater than 50%, greater than 60%, greater than 70%, greater than 80%, or greater than 90% of orally administered peptide inhibitor is localized to gastrointestinal organs and tissues. In particular embodiments, blood plasma levels of orally administered peptide inhibitor are less than 20%, less than 10%, less than 5%, less than 2%, less than 1% or less than 0.5% the levels of peptide inhibitor found in the small intestine mucosa, colon mucosa, or proximal colon.

[0099] The various peptide inhibitors of the invention may be constructed solely of natural amino acids. Alternatively, the peptide inhibitors may include non-natural amino acids including, but not limited to, modified amino acids. In certain embodiments, modified amino acids include natural amino acids that have been chemically modified to include a group, groups, or chemical moiety not naturally present on the amino acid. The peptide inhibitors of the invention may additionally include one or more D-amino acids. Still further, the peptide inhibitors of the invention may include amino acid analogs.

[00100] In certain embodiments, peptide inhibitors of the present invention include one or more modified or unnatural amino acids. In some embodiments of the present invention, a peptide inhibitor includes one or more non-natural amino acids shown in Table 1A. In certain embodiments, peptide inhibitors of the present invention include any of those described herein, including but not limited to any of those comprising an amino acid sequence or peptide inhibitor structure shown in any one of the tables herein.

[00101] The present invention also includes any of the peptide inhibitors described herein in either a free or a salt form. Thus, embodiments of any of the peptide inhibitors described herein (and related methods of use thereof) include a pharmaceutically acceptable salt of the peptide inhibitor.

[00102] The present invention also includes variants of any of the peptide inhibitors described herein, including but not limited to any of those comprising a sequence shown in any one of the tables herein, wherein one or more L-amino acid residue is substituted with the D isomeric form of the amino acid residue, e.g., an L-Ala is substituted with a D-Ala.

[00103] Peptide inhibitors described herein include isotopically-labeled peptide inhibitors. In particular embodiments, the present disclosure provides peptide inhibitors identical to any of

those having or recited in the various formulas and structures presented herein, but for the fact that one or more atoms are replaced by an atom having an atomic mass or mass number different from the atomic mass or mass number usually found in nature. Examples of isotopes that can be incorporated into the present compounds include isotopes of hydrogen, carbon, nitrogen, oxygen, fluorine and chlorine, such as ^{2}H, ^{3}H, ^{13}C, ^{14}C, ^{15}N, ^{18}O, ^{17}O, ^{35}S, ^{18}F, ^{36}Cl, respectively. Certain isotopically-labeled compounds described herein, for example those into which radioactive isotopes such as ^{3}H and ^{14}C are incorporated, are useful in drug and/or substrate tissue distribution assays. Furthermore, substitution with isotopes such as deuterium, i.e., ^{2}H, can afford certain therapeutic advantages resulting from greater metabolic stability, for example increased in vivo half-life or reduced dosage requirements.

[00104] The present invention also includes any of the peptide monomer inhibitors described herein linked to a linker moiety, including any of the specific linker moieties described herein. In particular embodiments, a linker is attached to an N-terminal or C-terminal amino acid, while in other embodiments, a linker is attached to an internal amino acid. In particular embodiments, a linker is attached to two internal amino acids, e.g., an internal amino acid in each of two monomer subunits that form a dimer. In some embodiments of the present invention, a peptide inhibitor is attached to one or more linker moieties shown.

[00105] The present invention also includes peptides and peptide dimers comprising a peptide having at least 90%, at least 95%, at least 98%, or at least 99% sequence identity to the peptide sequence of a peptide inhibitor described herein. In particular embodiments, peptide inhibitors of the present invention comprise a core peptide sequence and one or more N-terminal and/or C-terminal modification (e.g., Ac and NH_2) and/or one or more conjugated linker moiety and/or half-life extension moiety. As used herein, the core peptide sequence is the amino acid sequence of the peptide absent such modifications and conjugates.

[00106] In certain embodiments, a peptide inhibitor or a monomer subunit of a peptide inhibitor of the present invention comprises, consists essentially of, or consists of 7 to 35 amino acid residues, 8 to 35 amino acid residues, 9 to 35 amino acid residues, 10 to 35 amino acid residues, 7 to 25 amino acid residues, 8 to 25 amino acid residues, 9 to 25 amino acid residues, 10 to 25 amino acid residues, 7 to 20 amino acid residues, 8 to 20 amino acid residues, 9 to 20 amino acid residues, 10 to 20 amino acid residues, 7 to 18 amino acid residues, 8 to 18 amino acid residues, 9 to 18 amino acid residues, or 10 to 18 amino acid residues, and, optionally, one or more additional non-amino acid moieties, such as a conjugated chemical moiety, e.g., a PEG

or linker moiety. In particular embodiments, a peptide inhibitor of the present invention (or a monomer subunit thereof), including but not limited to those of any embodiments of Formula I, is greater than 10, greater than 12, greater than 15, greater than 20, greater than 25, greater than 30 or greater than 35 amino acids, e.g., 35 to 50 amino acids. In certain embodiments, a peptide inhibitor (or a monomer subunit thereof) is less than 50, less than 35, less than 30, less than 25, less than 20, less than 15, less than 12, or less than 10 amino acids. In particular embodiments, a monomer subunit of a peptide inhibitor (or a peptide monomer inhibitor) comprises or consists of 7, 8, 9, 10, 11, 12, 13, 14, 15, 16, 17, 18, 19, 20, 21, 22, 23, 24, 25, 26, 27, 28, 29, 30, 31, 32, 33, 34, or 35 amino acid residues. In particular embodiments, a monomer subunit of a peptide inhibitor of the present invention comprises or consists of 10 to 23 amino acid residues and, optionally, one or more additional non-amino acid moieties, such as a conjugated chemical moiety, e.g., a PEG or linker moiety. In various embodiments, the monomer subunit comprises or consists of 7 to 35 amino acid residues, 7 to 20 amino acid residues, 8 to 20 amino acid residues, 9 to 20 amino acid residues, 10 to 20 amino acid residues, 8 to 18 amino acid residues, 8 to 19 amino acid residues, 8 to 18 amino acid residues, 9 to 18 amino acid residues, or 10 to 18 amino acid residues. In particular embodiments of any of the various Formulas described herein, X comprises or consists of 7 to 35 amino acid residues, 8 to 35 amino acid residues, 9 to 35 amino acid residues, 10 to 35 amino acid residues, 7 to 25 amino acid residues, 8 to 25 amino acid residues, 9 to 25 amino acid residues, 10 to 25 amino acid residues, 7 to 18 amino acid residues, 8 to 18 amino acid residues, 9 to 18 amino acid residues, or 10 to 18 amino acid residues.

[00107] Certain illustrative peptide inhibitors described herein comprise 12 or more amino acid residues. However, the present invention also includes peptide inhibitors comprising a fragment of any of the peptide sequences described herein, including peptide inhibitors having 7, 8, 9, 10, or 11 amino acid residues. For example, peptide inhibitors of the present invention include peptides comprising or consisting of X4-X9, X4-X10, X4-X11, X4-X12, X4-X13, X4-X14, or X4-X15.

[00108] In particular embodiments of the present invention, the amino acid sequences of the peptide inhibitors are not present within an antibody, or are not present within a V_H or V_L region of an antibody.

Peptide Inhibitors

[00109] Peptide inhibitors of the present invention include peptides comprising or consisting of any of the amino acid sequences described herein, compounds having any of the structures described herein, including compounds comprising any of the peptide sequences described herein, and dimers of any of such peptides and compounds. Peptide inihibitors on the present invention include both peptides not having and those having a bond between X4 and X9, e.g., before and after a cross-link is introduced between X4 and X9. Illustrative peptides of the invention comprise an amino acid sequence or structure described in any of the accompanying tables.

[00110] In certain embodiments, the present invention includes a peptide inhibitor of an interleukin-23 receptor, or a pharmaceutically acceptable salt or solvate thereof, wherein the peptide inhibitor comprises an amino acid sequence of Formula (I):

X7-X8-X9-X10-X11 (I)

wherein

X7 is unsubstituted Trp, or Trp substituted with cyano, halo, alkyl, haloalkyl, hydroxy, or alkoxy;

X8 is Gln, alpha-Me-Lys, alpha-MeLeu, alpha-MeLys(Ac), beta-homoGln, Cit, Glu, Phe, Asn, Thr, Val, Aib, alpha-MeGln, alpha-MeAsn, Lys(Ac), Dab(Ac), Dap(Ac), homo-Lys(Ac), 1-Nal, 2-Nal, or Trp;

X9 is Abu, Cys, (D)Cys, alpha-MeCys, (D)Pen, or Pen;

X10 is unsubstituted Phe, or Phe substituted with halo, alkyl, haloalkyl, hydroxy, alkoxy, carboxy, carboxamido, 2-aminoethoxy, or 2-acetylaminoethoxy; and

X11 is 2-Nal, unsubstituted Trp, or Trp substituted with cyano, halo, alkyl, haloalkyl, hydroxy, alkoxy, Phe(2-Me), Phe(3-Me), Phe(4-Me), Phe(3,4-dimethoxy), or 1-Nal;

and

provided that

i) at least one of X7 and X11 is Trp substituted with cyano, halo, alkyl, haloalkyl, hydroxy, or alkoxy;

ii) when X7 is 5-F substituted Trp, then X11 is other than 2-Nal; and

iii) when X7 is 5-OH or 6-Cl substituted Trp, then X9 is other than Cys; and

wherein the peptide inhibitor inhibits the binding of an interleukin-23 (IL-23) to an IL-23 receptor.

[00111] In certain embodiments, the present invention includes a peptide inhibitor of an interleukin-23 receptor, or a pharmaceutically acceptable salt or solvate thereof, wherein the peptide inhibitor comprises an amino acid sequence of Formula (II'):

X7-X8-X9-X10-X11-X12-X13-X14-X15-R^2 (II")

wherein

X7 is Trp substituted with cyano, halo, alkyl, haloalkyl, hydroxy, or alkoxy;

X8 is Gln, alpha-MeLys, alpha-MeLeu, alpha-MeLys(Ac), beta-homoGln, Cit, Glu, Phe, Asn, Thr, Val, Aib, alpha-MeGln, alpha-MeAsn, Lys(Ac), Dab(Ac), Dap(Ac), homo-Lys(Ac), 1-Nal, 2-Nal, or Trp;

X9 is Abu, Cys, (D)Cys, alpha-MeCys, (D)Pen, Pen or Pen(sulfoxide);

X10 is unsubstituted Phe, or Phe substituted with halo, alkyl, haloalkyl, hydroxy, alkoxy, carboxy, carboxamido, 2-aminoethoxy, or 2-acetylaminoethoxy;

X11 is 2-Nal, Phe(2-Me), Phe(3-Me), Phe(4-Me), Phe(3,4-dimethoxy), 1-Nal, unsubstituted Trp, or Trp substituted with cyano, halo, alkyl, haloalkyl, hydroxy, or alkoxy;

X12 is 4-amino-4-carboxy-tetrahydropyran (THP), alpha-MeLys, alpha-MeLeu, alpha-MeArg, alpha-MePhe, alpha-MeLeu, alpha-MeLys, alpha-MeAsn, alpha-MeTyr, Ala, or cyclohexylAla, Lys, or Aib;

X13 is Aib, Glu, Cit, Gln, Lys(Ac), alpha-MeArg, alpha-MeGlu, alpha-MeLeu, alpha-MeLys, alpha-Me-Asn, alpha-MeLys(Ac), Dab(Ac), Dap(Ac), homo-Lys(Ac), or Lys; or

X13 is Lys, pegylated Lys, b-homoGlu, or Lys(Y2-Ac), wherein Y2 is an amino acid;

X14 is Asn, 2-Nap, Aib, Arg, Cit, Asp, Phe, Gly, Lys, Leu, Ala, (D)Ala, beta-Ala, His, Thr, n-Leu, Gln, Ser, (D)Ser, Tic, Trp, alpha-MeGln, alpha-MeAsn, alpha-MeLys(Ac), Dab(Ac), Dap(Ac), homo-Lys(Ac), or Lys(Ac);

X15 Leu, (D)Leu, beta-Ala, Cit, or (D)Lys;

R^2 is OH or NH_2;

or a pharmaceutically acceptable salt or solvate thereof, wherein the peptide inhibitor or pharmaceutically acceptable salt or solvate thereof comprises a disulfide bond between two Pen residues or a thioether bond between Abu and Cys;

and

wherein the peptide inhibitor or pharmaceutically acceptable salt of solvate thereof inhibits the binding of an interleukin-23 (IL-23) to an IL-23 receptor

[00112] In certain embodiments, the present invention includes a peptide inhibitor of an interleukin-23 receptor, or a pharmaceutically acceptable salt or solvate thereof, wherein the peptide inhibitor comprises an amino acid sequence of Formula (I'):

X4-X5-X6-X7-X8-X9-X10-X11-X12-X13-X14-X15 (I')

wherein

X4 is Abu, Cys, (D)Cys, alpha-MeCys, (D)Pen, Pen, or Pen(sulfoxide);

X5 is Cit, Glu, Gly, Leu, Ile, beta-Ala, Ala, Lys, Asn, Pro, alpha-MeGln, alpha-MeLys, alpha-MeLeu, alpha-MeAsn, Lys(Ac), alpha-MeLys(Ac), Dab(Ac), Dap(Ac), homo-Lys(Ac), Gln, Asp, or Cys; and

X6 is Thr, Aib, Asp, Dab, Gly, Pro, Ser, alpha-MeGln, alpha-MeLys, alpha-MeLeu, alpha-MeAsn, alpha-MeThr, alpha-MeSer, or Val; and X7-X15 are as described for Formula (II").

[00113] In certain embodiments, the present invention includes a peptide inhibitor of an interleukin-23 receptor, or a pharmaceutically acceptable salt or solvate thereof, wherein the peptide inhibitor comprises an amino acid sequence of Formula (Z'):

R^1-X4-X5-X6-X7-X8-X9-X10-X11-X12-X13-X14-X15-R^2 (Z')

or a pharmaceutically acceptable salt or solvate thereof, wherein

X4 is Abu, Cys, (D)Cys, alpha-MeCys, (D)Pen, Pen, or Pen(sulfoxide);

X5 is Cit, Glu, Gly, Leu, Ile, beta-Ala, Ala, Lys, Asn, Pro, alpha-MeGln, alpha-MeLys, alpha-MeLeu, alpha-MeAsn, Lys(Ac), alpha-MeLys(Ac), Dab(Ac), Dap(Ac), homo-Lys(Ac), Gln, Asp, or Cys; and

X6 is Thr, Aib, Asp, Dab, Gly, Pro, Ser, alpha-MeGln, alpha-MeLys, alpha-MeLeu, alpha-MeAsn, alpha-MeThr, alpha-MeSer, or Val;

X7 is Trp substituted with cyano, halo, alkyl, haloalkyl, hydroxy, or alkoxy;

X8 is Gln, alpha-MeLys, alpha-MeLeu, alpha-MeLys(Ac), beta-homoGln, Cit, Glu, Phe, Asn, Thr, Val, Aib, alpha-MeGln, alpha-MeAsn, Lys(Ac), Dab(Ac), Dap(Ac), homo-Lys(Ac), 1-Nal, 2-Nal, or Trp;

X9 is Abu, Cys, (D)Cys, alpha-MeCys, (D)Pen, Pen or Pen(sulfoxide);

X10 is unsubstituted Phe, or Phe substituted with halo, alkyl, haloalkyl, hydroxy, alkoxy, carboxy, carboxamido, 2-aminoethoxy, or 2-acetylaminoethoxy;

X11 is 2-Nal, Phe(2-Me), Phe(3-Me), Phe(4-Me), Phe(3,4-dimethoxy), 1-Nal, unsubstituted Trp, or Trp substituted with cyano, halo, alkyl, haloalkyl, hydroxy, or alkoxy;

X12 is 4-amino-4-carboxy-tetrahydropyran (THP), alpha-MeLys, alpha-MeLeu, alpha-MeArg, alpha-MePhe, alpha-MeLeu, alpha-MeLys, alpha-MeAsn, alpha-MeTyr, Ala, or cyclohexylAla, Lys, or Aib;

X13 is Aib, Glu, Cit, Gln, Lys(Ac), alpha-MeArg, alpha-MeGlu, alpha-MeLeu, alpha-MeLys, alpha-Me-Asn, alpha-MeLys(Ac), Dab(Ac), Dap(Ac), homo-Lys(Ac), or Lys; or

X13 is Lys, pegylated Lys, b-homoGlu, or Lys(Y2-Ac), wherein Y2 is an amino acid;

X14 is Asn, 2-Nap, Aib, Arg, Cit, Asp, Phe, Gly, Lys, Leu, Ala, (D)Ala, beta-Ala, His, Thr, n-Leu, Gln, Ser, (D)Ser, Tic, Trp, alpha-MeGln, alpha-MeAsn, alpha-MeLys(Ac), Dab(Ac), Dap(Ac), homo-Lys(Ac), or Lys(Ac);

X15 Leu, (D)Leu, beta-Ala, Cit, or (D)Lys;

R^1 is hydrogen, a C1-C6 alkyl, a C6-C12 aryl, a C6-C12aryl-C1-C6alkyl, or a C1-C20 alkanoyl;

R^2 is OH or NH_2;

wherein the peptide inhibitor or pharmaceutically acceptable salt or solvate thereof comprises a disulfide bond between two Pen residues or a thioether bond between Abu and Cys;

and

wherein the peptide inhibitor or pharmaceutically acceptable salt of solvate thereof inhibits the binding of an interleukin-23 (IL-23) to an IL-23 receptor.

[00114] In certain embodiments, with respect to Formula (Z'), X4 is Pen, X6 is Thr, X7 is Trp substituted with alkyl at the 1-, 2- or 7-position, and X9 is Pen. In certain embodiments, with respect to Formula (Z'), X4 is Pen, X6 is Thr, X7 is Trp substituted with methl, ethyl, iso-propyl or tert-butyl at the 1-, 2- or 7-position, and X9 is Pen.

[00115] In one embodiment, with respect to Formula (Z'), R^1 is a C_1-C_{20} alkanoyl. In a particular embodiment, R^1 is Ac.

[00116] In a particular aspect, the present invention provides a peptide inhibitor of an interleukin-23 receptor, or a pharmaceutically acceptable salt or solvate thereof, wherein the peptide inhibitor comprises or is any one of the peptides listed in Table E3, or a pharmaceutically acceptable salt or solvate thereof.

[00117] In a more particular aspect, the present invention provides a peptide inhibitor of an interleukin-23 receptor, or a pharmaceutically acceptable salt or solvate thereof, wherein the peptide inhibitor comprises or is any one of the following peptides or amino acid sequences, or a pharmaceutically acceptable salt or solvate thereof:

SEQ ID NO:	Sequence*
201	Ac-[Pen]-NT-[W(7-Me)]-Q-[Pen]-Phe[4-(2-aminoethoxy)]-[2-Nal]-[a-MeLeu]-[Lys(Ac)]-N-[bA]-NH_2;
202	Ac-[Pen]-NT-[W(7-Me)]-Q-[Pen]-Phe[4-(2-aminoethoxy)]-[2-Nal]-[a-MeLys]-[Lys(Ac)]-N-[bA]-NH_2;
203	Ac-[(D)Arg]-Abu-Q-T-[W(7-Me)]-Q-C-Phe[4-(2-aminoethoxy)]-[2-Nal]-[THP]-E-N-[bA]-NH_2;
204	Ac-Abu-Q-T-[W(7-Me)]-Q-C-Phe[4-(2-aminoethoxy)]-[2-Nal]-[THP]-E-N-[bA]-NH_2;
205	Ac-[Pen]-NT-[W(7-Me)]-Q-[Pen]-Phe[4-(2-aminoethoxy)]-[2-Nal]-[a-MeLeu]-[Lys(Ac)]-G-[bA]-NH_2;
206	Ac-[Pen]-NT-[W(7-Me)]-Q-[Pen]-Phe[4-(2-aminoethoxy)]-[2-Nal]-[a-MeLeu]-[Lys(Ac)]-[Cit]-[bA]-NH_2;
207	Ac-[Pen]-NT-[W(7-Me)]-Q-[Pen]-Phe[4-(2-aminoethoxy)]-[2-Nal]-[a-MeLeu]-[Lys(Ac)]-A-[bA]-NH_2;
208	Ac-[Pen]-NT-[W(7-Me)]-Q-[Pen]-Phe[4-(2-aminoethoxy)]-[2-Nal]-[a-MeLeu]-[Lys(Ac)]-L-[bA]-NH_2;
209	Ac-[Pen]-NT-[W(7-Me)]-Q-[Pen]-Phe[4-(2-aminoethoxy)]-[2-Nal]-[a-MeLeu]-[Lys(Ac)]-[(D)Ala]-[bA]-NH_2;
214	Ac-[Pen]-NT-[W(7-Me)]-Q-[Pen]-Phe[4-(2-aminoethoxy)]-[2-Nal]-[a-MeLeu]-[Lys(Ac)]-H-[bA]-NH_2;
217	Ac-[Pen]-NT-[W(7-Me)]-Q-[Pen]-Phe[4-(2-aminoethoxy)]-[2-Nal]-[a-MeLeu]-[Lys(Ac)]-T-[bA]-NH_2;
221	Ac-[Pen]-NT-[W(7-Me)]-Q-[Pen]-Phe[4-(2-aminoethoxy)]-[2-Nal]-[a-MeLeu]-[Lys(Ac)]-S-[bA]-NH_2;
222	Ac-[Pen]-NT-[W(7-Me)]-Q-[Pen]-Phe[4-(2-aminoethoxy)]-[2-Nal]-[a-MeLeu]-[Lys(Ac)]-[(D)Ser]-[bA]-NH_2;
226	Ac-[Pen]-NT-[W(7-Me)]-Q-[Pen]-Phe[4-(2-aminoethoxy)]-[2-Nal]-[a-MeLeu]-[Lys(Ac)]-[bA]-[bA]-NH_2;
227	Ac-[Pen]-NT-[W(7-Me)]-[Cit]-[Pen]-Phe[4-(2-aminoethoxy)]-[2-Nal]-[a-MeLeu]-[Lys(Ac)]-N-[bA]-NH_2;

SEQ ID NO:	Sequence*
228	Ac-[Pen]-NT-[W(6-Cl)]-Q-[Pen]-Phe[4-(2-aminoethoxy)]-[2-Nal]-[a-MeLys]-[Lys(Ac)]-N-[bA]-NH_2;
229	Ac-[Pen]-NT-[W(4-OMe)]-Q-[Pen]-Phe[4-(2-aminoethoxy)]-[2-Nal]-[a-MeLys]-[Lys(Ac)]-N-[bA]-NH_2;
230	Ac-[Pen]-NT-[W(6-Me)]-Q-[Pen]-Phe[4-(2-aminoethoxy)]-[2-Nal]-[a-MeLys]-[Lys(Ac)]-N-[bA]-NH_2;
231	Ac-[Pen]-NT-[W(4-Me)]-Q-[Pen]-Phe[4-(2-aminoethoxy)]-[2-Nal]-[a-MeLys]-[Lys(Ac)]-N-[bA]-NH_2;
232	Ac-[Pen]-NT-[W(1-Me)]-Q-[Pen]-Phe[4-(2-aminoethoxy)]-[2-Nal]-[a-MeLys]-[Lys(Ac)]-N-[bA]-NH_2;
233	Ac-[Pen]-NT-[W(2,5,7-tritBu)]-Q-[Pen]-Phe[4-(2-aminoethoxy)]-[2-Nal]-[a-MeLys]-[Lys(Ac)]-N-[bA]-NH_2;
234	Ac-[Pen]-NT-[W(7-Me)]-[a-MeLys]-[Pen]-Phe[4-(2-aminoethoxy)]-[2-Nal]-[a-MeLeu]-[Lys(Ac)]-N-[bA]-NH_2;
235	Ac-[Pen]-NT-[W(7-Me)]-[a-MeLeu]-[Pen]-Phe[4-(2-aminoethoxy)]-[2-Nal]-[a-MeLys]-[Lys(Ac)]-N-[bA]-NH_2;
236	Ac-[Pen]-NT-[W(7-Me)]-Q-[Pen]-Phe[4-(2-aminoethoxy)]-[2-Nal]-[a-MeLys]-[Aib]-N-[bA]-NH_2;
237	Ac-[Pen]-Q-T-[W(7-Me)]-Q-[Pen]-Phe[4-(2-aminoethoxy)]-[2-Nal]-[a-MeLys]-[Lys(Ac)]-N-[bA]-NH_2;
238	Ac-[Pen]-[Cit]-T-[W(7-Me)]-Q-[Pen]-Phe[4-(2-aminoethoxy)]-[2-Nal]-[a-MeLys]-[Lys(Ac)]-N-[bA]-NH_2;
239	Ac-[Pen]-[Lys(Ac)]-T-[W(7-Me)]-Q-[Pen]-Phe[4-(2-aminoethoxy)]-[2-Nal]-[a-MeLys]-[Lys(Ac)]-N-[bA]-NH_2;
240	Ac-[Pen]-[Aib]-T-[W(7-Me)]-Q-[Pen]-Phe[4-(2-aminoethoxy)]-[2-Nal]-[a-MeLys]-[Lys(Ac)]-N-[bA]-NH_2;
241	Ac-[Pen]-NT-[W(7-Me)]-[Aib]-[Pen]-Phe[4-(2-aminoethoxy)]-[2-Nal]-[a-MeLys]-[Lys(Ac)]-N-[bA]-NH_2;
242	Ac-[Pen]-NT-[W(7-Me)]-[Lys(Ac)]-[Pen]-Phe[4-(2-aminoethoxy)]-[2-Nal]-[a-MeLys]-[Lys(Ac)]-N-[bA]-NH_2;

SEQ ID NO:	Sequence*
244	Ac-[Pen]-NT-[W(7-Me)]-[Lys(Ac)]-[Pen]-Phe[4-(2-aminoethoxy)]-[2-Nal]-[a-MeLys]-[Lys(Ac)]-N-L-NH_2;
245	Ac-[Pen]-NT-[W(7-Me)]-[Lys(Ac)]-[Pen]-Phe[4-(2-aminoethoxy)]-[2-Nal]-[a-MeLys]-[Lys(Ac)]-N-[(D)Leu]-NH_2;
249	Ac-[Pen]-NT-[W(7-Me)]-[Lys(Ac)]-[Pen]-Phe[4-(2-aminoethoxy)]-[2-Nal]-[a-MeLys]-[Lys(Ac)]-N-[Cit]-NH_2;
252	Ac-[Pen]-NT-[W(7-Me)]-[Lys(Ac)]-[Pen]-Phe[4-(2-aminoethoxy)]-[2-Nal]-[a-MeLys]-[Lys(Ac)]-N-[(D)Lys]-NH_2;
267	Ac-[Pen]-NT-[W(7-Me)]-Q-[Pen]-Phe[4-(2-aminoethoxy)]-[2-Nal]-[a-MeLys]-[Lys(Ac)]-N-[bA]-NH_2;
268	Ac-[Pen]-N-T-[W(7-Me)]-[Cit]-[Pen]-Phe[4-(2-aminoethoxy)]-[2-Nal]-[a-MeLys]-[Lys(Ac)]-[bA]-[bA]-NH_2;
269	Ac-[Pen]-N-T-[W(7-Me)]-Q-[Pen]-Phe[4-(2-aminoethoxy)]-[2-Nal]-[a-MeLys]-[Lys(Ac)]-L-[bA]-NH_2;
270	Ac-[Pen]-N-T-[W(7-Me)]-[Lys(Ac)]-[Pen]-Phe[4-(2-aminoethoxy)]-[2-Nal]-[a-MeLys]-[Lys(Ac)]-[bA]-[bA]-NH_2;
271	Ac-[Pen]-N-T-[W(7-Me)]-[Lys(Ac)]-[Pen]-Phe[4-(2-aminoethoxy)]-[2-Nal]-[a-MeLys]-[Lys(Ac)]-S-[bA]-NH_2;
272	Ac-[Pen]-N-T-[W(7-Me)]-[Lys(Ac)]-[Pen]-Phe[4-(2-aminoethoxy)]-[2-Nal]-[a-MeLys]-[Lys(Ac)]-H-[bA]-NH_2;
273	Ac-[Pen]-N-T-[W(7-Me)]-[Lys(Ac)]-[Pen]-Phe[4-(2-aminoethoxy)]-[2-Nal]-[a-MeLys]-E-[bA]-[bA]-NH_2;
279	Ac-[Pen]-N-T-[W(7-Me)]-Q-[Pen]-Phe[4-(2-aminoethoxy)]-[2-Nal]-[a-MeLys]-[Cit]-[bA]-[bA]-NH_2;
280	Ac-[Pen]-N-T-[W(1-Me)]-[Cit]-[Pen]-Phe[4-(2-aminoethoxy)]-[2-Nal]-[a-MeLys]-[Lys(Ac)]-[bA]-[bA]-NH_2;
281	Ac-[Pen]-N-T-[W(7-Me)]-[Cit]-[Pen]-Phe[4-(2-aminoethoxy)]-[2-Nal]-[a-MeLys]-[Cit]-[bA]-[bA]-NH_2;
282	Ac-[Pen]-N-T-[W(7-Me)]-Q-[Pen]-Phe[4-(2-aminoethoxy)]-[2-Nal]-[a-MeLys]-E-N-[bA]-NH_2;

SEQ ID NO:	Sequence*
283	Ac-[Pen]-N-T-[W(7-Me)]-Q-[Pen]-Phe[4-(2-aminoethoxy)]-[W(1-Me)]-[a-MeLys]-[Lys(Ac)]-N-[bA]-NH_2;
284	Ac-[Pen]-N-T-[W(7-Et)]-[Lys(Ac)]-[Pen]-Phe[4-(2-aminoethoxy)]-[2-Nal]-[a-MeLys]-[Lys(Ac)]-N-[(D)Leu]-NH_2;
285	Ac-[Pen]-N-T-[W(7-n-Pr)]-[Lys(Ac)]-[Pen]-Phe[4-(2-aminoethoxy)]-[2-Nal]-[a-MeLys]-[Lys(Ac)]-N-[(D)Leu]-NH_2;
286	Ac-[Pen]-N-T-[W(7-i-Pr)]-[Lys(Ac)]-[Pen]-Phe[4-(2-aminoethoxy)]-[2-Nal]-[a-MeLys]-[Lys(Ac)]-N-[(D)Leu]-NH_2;
288	Ac-[Pen]-N-T-[W(7-OMe)]-[Lys(Ac)]-[Pen]-Phe[4-(2-aminoethoxy)]-[2-Nal]-[a-MeLys]-[Lys(Ac)]-N-[(D)Leu]-NH_2;
296	Ac-[Pen]-N-T-[W(5-CN)]-Q-[Pen]-Phe[4-(2-aminoethoxy)]-[2-Nal]-[a-MeLys]-[Lys(Ac)]-N-[(D)Lys]-NH_2;
297	Ac-[Pen]-N-T-[W(7-OMe)]-Q-[Pen]-Phe[4-(2-aminoethoxy)]-[2-Nal]-[a-MeLys]-[Lys(Ac)]-N-[(D)Lys]-NH_2;
299	Ac-[Pen]-N-T-[W(7-OMe)]-[Lys(Ac)]-[Pen]-Phe[4-(2-aminoethoxy)]-[2-Nal]-[a-MeLys]-[Lys(Ac)]-N-[(D)Lys]-NH_2;
300	Ac-[Pen]-N-T-[W(7-OMe)]-[Cit]-[Pen]-Phe[4-(2-aminoethoxy)]-[2-Nal]-[a-MeLys]-[Lys(Ac)]-N-[(D)Lys]-NH_2;
314	Ac-[Pen]-N-T-[W(7-Me)]-[Lys(Ala)]-[Pen]-Phe[4-(2-aminoethoxy)]-[2-Nal]-[a-MeLys]-[Lys(Ac)]-N-[(D)Leu]-NH_2;
315	Ac-[Pen]-N-T-[W(7-Me)]-[Lys(IVA)]-[Pen]-Phe[4-(2-aminoethoxy)]-[2-Nal]-[a-MeLys]-[Lys(Ac)]-N-[(D)Leu]-NH_2;
316	Ac-[Pen]-N-T-[W(7-Me)]-[Lys(cyclohexanoic)]-[Pen]-Phe[4-(2-aminoethoxy)]-[2-Nal]-[a-MeLys]-[Lys(Ac)]-N-[(D)Leu]-NH_2;
317	Ac-[Pen]-N-T-[W(7-Me)]-[Lys(octanoic)]-[Pen]-Phe[4-(2-aminoethoxy)]-[2-Nal]-[a-MeLys]-[Lys(Ac)]-N-[(D)Leu]-NH_2;
318	Ac-[Pen]-N-T-[W(7-Me)]-[Lys(C(O)CH_2Ph)]-[Pen]-Phe[4-(2-aminoethoxy)]-[2-Nal]-[a-MeLys]-[Lys(Ac)]-N-[(D)Leu]-NH_2;
319	Ac-[Pen]-N-T-[W(7-Me)]-[Lys(trifluoropropionic)]-[Pen]-Phe[4-(2-aminoethoxy)]-[2-Nal]-[a-MeLys]-[Lys(Ac)]-N-[(D)Leu]-NH_2;

SEQ ID NO:	Sequence*
320	Ac-[Pen]-N-T-[W(7-Me)]-[Lys(Gly)]-[Pen]-Phe[4-(2-aminoethoxy)]-[2-Nal]-[a-MeLys]-[Lys(Ac)]-N-[(D)Leu]-NH_2;
321	Ac-[Pen]-N-T-[W(7-Me)]-[Lys(bAla)]-[Pen]-Phe[4-(2-aminoethoxy)]-[2-Nal]-[a-MeLys]-[Lys(Ac)]-N-[(D)Leu]-NH_2;
322	Ac-[Pen]-N-T-[W(7-Me)]-[Lys(Aib)]-[Pen]-Phe[4-(2-aminoethoxy)]-[2-Nal]-[a-MeLys]-[Lys(Ac)]-N-[(D)Leu]-NH_2;
324	Ac-[(D)Arg]-[Abu]-Q-T-[W(7-Me)]-[Lys(Ac)]-[Cys]-Phe[4-(2-aminoethoxy)]-[2-Nal]-[a-MeLys]-[Lys(Ac)]-N-[(D)Lys]-NH_2;
325	Ac-[(D)Arg]-[Abu]-Q-T-[W(7-Me)]-[Lys(Ac)]-[Cys]-Phe[4-(2-aminoethoxy)]-[2-Nal]-[a-MeLys]-[Lys(Ac)]-N-[(D)Leu]-NH_2;
328	Ac-[Pen]-A-T-[W(7-Me)]-[Lys(Ac)]-[Pen]-Phe[4-(2-aminoethoxy)]-[2-Nal]-[a-MeLys]-[Lys(Ac)]-N-[(D)Leu]-NH_2;
329	Ac-[Pen]-G-T-[W(7-Me)]-[Lys(Ac)]-[Pen]-Phe[4-(2-aminoethoxy)]-[2-Nal]-[a-MeLys]-[Lys(Ac)]-N-[(D)Leu]-NH_2;
330	Ac-[Pen]-[Lys(Ac)]-T-[W(7-Me)]-[Lys(Ac)]-[Pen]-Phe[4-(2-aminoethoxy)]-[2-Nal]-[a-MeLys]-[Lys(Ac)]-N-[(D)Leu]-NH_2;
331	Ac-[Pen]-[Cit]-T-[W(7-Me)]-[Lys(Ac)]-[Pen]-Phe[4-(2-aminoethoxy)]-[2-Nal]-[a-MeLys]-[Lys(Ac)]-N-[(D)Leu]-NH_2;
332	Ac-[Pen]-L-T-[W(7-Me)]-[Lys(Ac)]-[Pen]-Phe[4-(2-aminoethoxy)]-[2-Nal]-[a-MeLys]-[Lys(Ac)]-N-[(D)Leu]-NH_2;
333	Ac-[Pen]-P-T-[W(7-Me)]-[Lys(Ac)]-[Pen]-Phe[4-(2-aminoethoxy)]-[2-Nal]-[a-MeLys]-[Lys(Ac)]-N-[(D)Leu]-NH_2;
334	Ac-[Pen]-S-T-[W(7-Me)]-[Lys(Ac)]-[Pen]-Phe[4-(2-aminoethoxy)]-[2-Nal]-[a-MeLys]-[Lys(Ac)]-N-[(D)Leu]-NH_2;
335	Ac-[Pen]-[Dab(Ac)]-T-[W(7-Me)]-[Lys(Ac)]-[Pen]-Phe[4-(2-aminoethoxy)]-[2-Nal]-[a-MeLys]-[Lys(Ac)]-N-[(D)Leu]-NH_2;
336	Ac-[Pen]-R-T-[W(7-Me)]-[Lys(Ac)]-[Pen]-Phe[4-(2-aminoethoxy)]-[2-Nal]-[a-MeLys]-[Lys(Ac)]-N-[(D)Leu]-NH_2;
337	Ac-[Pen]-[hLeu]-T-[W(7-Me)]-[Lys(Ac)]-[Pen]-Phe[4-(2-aminoethoxy)]-[2-Nal]-[a-MeLys]-[Lys(Ac)]-N-[(D)Leu]-NH_2;

SEQ ID NO:	Sequence*
338	Ac-[Pen]-[(D)Asn]-T-[W(7-Me)]-[Lys(Ac)]-[Pen]-Phe[4-(2-aminoethoxy)]-[2-Nal]-[a-MeLys]-[Lys(Ac)]-N-[(D)Leu]-NH_2;
349	Ac-[Pen]-N-T-[W(6-Et)]-[Lys(Ac)]-[Pen]-Phe[4-(2-aminoethoxy)]-[2-Nal]-[a-MeLys]-[Lys(Ac)]-N-[(D)Lys]-NH_2;
351	Ac-[Pen]-N-T-[W(2-Me)]-[Lys(Ac)]-[Pen]-Phe[4-(2-aminoethoxy)]-[2-Nal]-[a-MeLys]-[Lys(Ac)]-N-[(D)Lys]-NH_2;
352	Ac-[Pen]-N-T-[W(7-Me)]-[Lys(Ac)]-[Pen]-Phe[4-(2-aminoethoxy)]-[2-Nal]-[a-MeLys]-[Lys(Ac)]-S-[(D)Lys]-NH_2;
353	Ac-[Pen]-N-T-[W(7-Me)]-[Lys(Ac)]-[Pen]-Phe[4-(2-aminoethoxy)]-[W(2-Me)]-[a-MeLys]-[Lys(Ac)]-N-[(D)Lys]-NH_2;
355	Ac-[Pen]-N-T-[W(7-Me)]-[Lys(Ac)]-[Pen]-Phe[4-(2-aminoethoxy)]-[2-Nal]-[a-MeLys]-[Lys(Ala)]-N-[(D)Leu]-NH_2;
362	Ac-[Pen]-N-T-[W(7-Me)]-[Lys(Ac)]-[Pen]-Phe[4-(2-aminoethoxy)]-[2-Nal]-[a-MeLys]-[Lys(PEG3-OMe)]-N-[(D)Leu]-NH_2; or
363	Ac-[Pen]-N-T-[W(7-Me)]-[Lys(Ac)]-[Pen]-Phe[4-(2-aminoethoxy)]-[2-Nal]-[a-MeLys]-[Lys(PEG11-OMe)]-N-[(D)Leu]-NH_2;

[00118] In related embodiments, the present invention includes a peptide inhibitor of an interleukin-23 receptor, or a pharmaceutically acceptable salt or solvate thereof, wherein the peptide inhibitor comprises an amino acid sequence of Formula (II):

X4-X5-X6-X7-X8-X9-X10-X11 (II)

wherein

X4 is Abu, Cys, (D)Cys, alpha-MeCys, (D)Pen, Pen, or Pen(sulfoxide);

X5 is Cit, Glu, Gly, Leu, Ile, beta-Ala, Ala, Lys, Asn, Pro, alpha-MeGln, alpha-MeLys, alpha-MeLeu, alpha-MeAsn, Lys(Ac), alpha-MeLys(Ac), Dab(Ac), Dap(Ac), homo-Lys(Ac), Gln, Asp, or Cys;

X6 is Thr, Aib, Asp, Dab, Gly, Pro, Ser, alpha-MeGln, alpha-MeLys, alpha-MeLeu, alpha-MeAsn, alpha-MeThr, alpha-MeSer, or Val;

X7 is unsubstituted Trp, or Trp substituted with cyano, halo, alkyl, haloalkyl, hydroxy, or alkoxy;

X8 is Gln, alpha-Me-Lys, alpha-MeLeu, alpha-MeLys(Ac), beta-homoGln, Cit, Glu, Phe, Asn, Thr, Val, Aib, alpha-MeGln, alpha-MeAsn, Lys(Ac), Dab(Ac), Dap(Ac), homo-Lys(Ac), 1-Nal, 2-Nal, or Trp;

X9 is Abu, Cys, (D)Cys, alpha-MeCys, (D)Pen, Pen, or Pen(sulfoxide); wherein if X4 is Abu, then X9 is Cys, (D)Cys, alpha-MeCys, (D)Pen, Pen, or Pen(sulfoxide); and wherein if X9 is Abu, then X4 is Cys, (D)Cys, alpha-MeCys, (D)Pen, Pen or Pen(sulfoxide);

X10 is unsubstituted Phe, or Phe substituted with halo, alkyl, haloalkyl, hydroxy, alkoxy, carboxy, carboxamido, 2-aminoethoxy, or 2-acetylaminoethoxy; and

X11 is 2-Nal, unsubstituted Trp, or Trp substituted with halo, alkyl, haloalkyl, hydroxy, alkoxy, Phe(2-Me), Phe(3-Me), Phe(4-Me), Phe(3,4-dimethoxy), or 1-Nal;

wherein the peptide inhibitor is cyclized via a bond between X4 and X9, and

provided that

i) at least one of X7 and X11 is Trp substituted with cyano, halo, alkyl, haloalkyl, hydroxy, or alkoxy;

ii) when X7 is 5-F substituted Trp, then X11 is other than 2-Nal; and

iii) when X7 is 5-OH or 6-Cl substituted Trp, then X9 is other than Cys;

and

wherein the peptide inhibitor inhibits the binding of an interleukin-23 (IL-23) to an IL-23 receptor.

[00119] In related embodiments, the present invention includes a peptide inhibitor of an interleukin-23 receptor, or a pharmaceutically acceptable salt or solvate thereof, wherein the peptide inhibitor comprises an amino acid sequence of Formula (II):

X4-X5-X6-X7-X8-X9-X10-X11 (II)

wherein X7-X11 are as described for Formula (II"); and

X4 is Abu, Cys, (D)Cys, alpha-MeCys, (D)Pen, Pen, or Pen(sulfoxide);

X5 is Cit, Glu, Gly, Leu, Ile, beta-Ala, Ala, Lys, Asn, Pro, alpha-MeGln, alpha-MeLys, alpha-MeLeu, alpha-MeAsn, Lys(Ac), alpha-MeLys(Ac), Dab(Ac), Dap(Ac), homo-Lys(Ac), Gln, Asp, or Cys;

X6 is Thr, Aib, Asp, Dab, Gly, Pro, Ser, alpha-MeGln, alpha-MeLys, alpha-MeLeu, alpha-MeAsn, alpha-MeThr, alpha-MeSer, or Val.

[00120] In related embodiments, the present invention includes a peptide inhibitor of an interleukin-23 receptor, or a pharmaceutically acceptable salt or solvate thereof, wherein the peptide inhibitor comprises an amino acid sequence of Formula (II):

X4-X5-X6-X7-X8-X9-X10-X11 (II)

wherein X4-X11 are as described for Formula (Z').

[00121] In one embodiment, when X7 is 5-F substituted Trp, then X11 is not 2-Nal.

[00122] In one embodiment, when X7 is 5-F substituted Trp, then X11 is unsubstituted Trp, or Trp substituted with halo, alkyl, haloalkyl, hydroxy, alkoxy, Phe(2-Me), Phe(3-Me), Phe(4-Me), Phe(3,4-dimethoxy), or 1-Nal.

[00123] In certain embodiment, X4 or X9 is Cys, (D)Cys, alpha-MeCys, (D)Pen, or Pen; and the bond between X4 and X9 is a disulfide bond.

[00124] In certain embodiment, X4 is Cys, (D)Cys, or alpha-MeCys.

[00125] In certain embodiment, X4 is (D)Pen, or Pen; or X4 is Pen(sulfoxide).

[00126] In certain embodiment, X4 is Pen.

[00127] In certain embodiment, X9 is Cys, (D)Cys, or alpha-MeCys.

[00128] In certain embodiment, X9 is Pen or (D)Pen.

[00129] In certain embodiment, X9 is Pen.

[00130] In certain embodiment, X4 is Pen and X9 is Pen, and the bond is a disulfide bond.

[00131] In certain embodiment, X4 is Pen and X9 is Cys, and the bond is a disulfide bond.

[00132] In certain embodiment, X4 or X9 is Abu; and the bond between X4 and X9 is a thioether bond.

[00133] In certain embodiment, X4 is Abu, and X9 is Cys, (D)Cys, or alpha-MeCys. In certain embodiment, X9 is Pen or (D)Pen. In a particular embodiment, X9 is Pen. In a more particular embodiment, X9 is Cys. In a most particular embodiment, X4 is Abu, and X9 is Cys.

[00134] In certain embodiment, X4 is Abu and X9 is Cys or Pen, and the bond is a thioether bond.

[00135] In certain embodiment, X4 is Abu and X9 is Cys, and the bond is a thioether bond.

[00136] In certain embodiment, the peptide inhibitor is according to Formula (IIa) (IIb), or (IIc) or comprises a sequence of Formula (IIa) (IIb), or (IIc):

Pen-X5-X6-X7-X8-Pen-X10-X11 (IIa)

Abu-X5-X6-X7-X8-Cys-X10-X11 (IIb), or

Abu-X5-X6-X7-X8-Pen-X10-X11 (IIc)

wherein X5-X8 and X10-X11 are as described for Formula (Z'); and the peptide inhibitor is cyclized via a Pen-Pen disulfide bond; or the peptide inhibitor is cyclized via a Abu-Cys or Abu-Pen thioether bond.

[00137] In certain embodiment, X5 is Asn, Gln, or Glu.

[00138] In certain embodiment, X5 is Asn, or Gln.

[00139] In certain embodiment, X5 is Asn.

[00140] In certain embodiment, the peptide inhibitor is according to Formula (IIIa), (IIIb), (IIIc), or (IIId) or comprises a sequence of Formula (IIIa), (IIIb), (IIIc), or (IIId):

Pen- Asn-X6-X7-X8-Pen-X10-X11 (IIIa),

Pen-Gln-X6-X7-X8-Pen-X10-X11 (IIIb),

Abu- Asn-X6-X7-X8-Cys-X10-X11 (IIIc), or

Abu-Gln-X6-X7-X8-Pen-X10-X11 (IIId)

wherein X6-X8 and X10-X11 are as described for Formula (Z'); and the peptide inhibitor is cyclized via a Pen-Pen disulfide bond; or the peptide inhibitor is cyclized via a Abu-Cys or Abu-Pen thioether bond.

[00141] In certain embodiment, X6 is Thr.

[00142] In certain embodiment, the peptide inhibitor is according to Formula (IVa), (IVb), (IVc), or (IVd) or comprises a sequence of Formula (IVa), (IVb), (IVc), or (IVd):

Pen-Asn-Thr-X7-X8-Pen-X10-X11 (IVa),

Pen-Gln-Thr-X7-X8-Pen-X10-X11 (IVb),

Abu-Asn-Thr-X7-X8-Cys-X10-X11 (IVc), or

Abu-Gln-Thr-X7-X8-Pen-X10-X11 (IVd),

wherein X7-X8 and X10-X11 are as described for Formula (Z'); and the peptide inhibitor is cyclized via a Pen-Pen disulfide bond; or the peptide inhibitor is cyclized via a Abu-Cys or Abu-Pen thioether bond.

[00143] In certain embodiment, X8 is Gln, alpha-Me-Lys, alpha-MeLys(Ac), or Glu. In certain embodiments, X8 is Q, Cit, a-MeLys, a-MeLeu, Aib, Lys(Ac), Lys(Gly), or Lys(Aib).

[00144] In certain embodiment, X8 is Gln. In certain embodiment, X8 is Cit. In certain embodiments, X8 is Lys(Ac).

[00145] In certain embodiment, the peptide inhibitor is according to Formula (Va), (Vb), (Vc), or (Vd) or comprises a sequence of Formula (Va), (Vb), (Vc), or (Vd):

Pen-Asn-Thr-X7-Gln-Pen-X10-X11 (Va),

Pen-Gln-Thr-X7-Gln-Pen-X10-X11 (Vb),

Abu-Asn-Thr-X7-Gln-Cys-X10-X11 (Vc), or

Abu-Gln-Thr-X7-Gln-Pen-X10-X11 (Vd)

wherein X7 and X10-X11 are as described for Formula (Z'); and the peptide inhibitor is cyclized via a Pen-Pen disulfide bond; or the peptide inhibitor is cyclized via a Abu-Cys or Abu-Pen thioether bond.

[00146] In certain embodiment, the peptide inhibitor is according to Formula (Ve), (Vf), (Vg), or (Vh) or comprises a sequence of Formula (Ve), (Vf), (Vg), or (Vh):

Pen-Asn-Thr-X7-Lys(Ac)-Pen-X10-X11 (Ve),

Pen-Gln-Thr-X7-Lys(Ac)-Pen-X10-X11 (Vf),

Abu-Asn-Thr-X7-Lys(Ac)-Cys-X10-X11 (Vg), or

Abu-Gln-Thr-X7-Lys(Ac)-Pen-X10-X11 (Vh)

wherein X7 and X10-X11 are as described for Formula (Z'); and the peptide inhibitor is cyclized via a Pen-Pen disulfide bond; or the peptide inhibitor is cyclized via a Abu-Cys or Abu-Pen thioether bond.

[00147] In certain embodiment, X10 is Phe, Phe[4-(2-aminoethoxy)] [F(4-2ae)], Phe[4-(2-acetylaminoethoxy)], or Phe(4-$CONH_2$).

[00148] In certain embodiment, X10 is Phe[4-(2-aminoethoxy)], or Phe[4-(2-acetylaminoethoxy)]. In certain embodiment, X10 is Phe[4-(2-aminoethoxy)].

[00149] In certain embodiment, the peptide inhibitor is according to Formula (VIa), (VIb), (VIc), or (VId) or comprises a sequence of Formula (VIa), (VIb), (VIc), or (VId):

Pen-Asn-Thr-X7-Gln-Pen-[F(4-2ae)]-X11 (VIa),

Pen-Gln-Thr-X7-Gln-Pen-[F(4-2ae)]-X11 (VIb),

Abu-Asn-Thr-X7-Gln-Cys-[F(4-2ae)]-X11 (VIc), or

Abu-Gln-Thr-X7-Gln-Pen-[F(4-2ae)]-X11 (VId)

wherein X7 and X11 are as described for Formula (Z'); [F(4-2ae)] is Phe[4-(2-aminoethoxy)]; and the peptide inhibitor is cyclized via a Pen-Pen disulfide bond; or the peptide inhibitor is cyclized via a Abu-Cys or Abu-Pen thioether bond.

[00150] In certain embodiment, the peptide inhibitor is according to Formula (VIe), (VIf), (VIg), or (VIh) or comprises a sequence of Formula (VIe), (VIf), (VIg), or (VIh):

Pen-Asn-Thr-X7-Lys(Ac)-Pen-[F(4-2ae)]-X11 (VIe),

Pen-Gln-Thr-X7-Lys(Ac)-Pen-[F(4-2ae)]-X11 (VIf),

Abu-Asn-Thr-X7-Lys(Ac)-Cys-[F(4-2ae)]-X11 (VIg), or

Abu-Gln-Thr-X7-Lys(Ac)-Pen-[F(4-2ae)]-X11 (VIh)

wherein X7 and X11 are as described for Formula (Z'); [F(4-2ae)] is Phe[4-(2-aminoethoxy)]; and the peptide inhibitor is cyclized via a Pen-Pen disulfide bond; or the peptide inhibitor is cyclized via a Abu-Cys or Abu-Pen thioether bond.

[00151] In certain embodiment, the peptide inhibitor comprises an amino acid sequence of Formula (II');

X7-X8-X9-X10-X11-X12-X13-X14-X15 (II')

and wherein

X12 is 4-amino-4-carboxy-tetrahydropyran (THP), alpha-MeLys, alpha-MeLeu, alpha-MeArg, alpha-MePhe, alpha-MeLeu, alpha-MeLys, alpha-MeAsn, alpha-MeTyr, Ala, or cyclohexylAla, Lys, or Aib;

X13 is Aib, Glu, Cit, Gln, Lys(Ac), alpha-MeArg, alpha-MeGlu, alpha-MeLeu, alpha-MeLys, alpha-Me-Asn, alpha-MeLys(Ac), Dab(Ac), Dap(Ac), homo-Lys(Ac), or Lys; or X13 is Lys, pegylated Lys, b-homoGlu, or Lys(Y2-Ac), wherein Y2 is an amino acid;

X14 is Asn, 2-Nap, Aib, Arg, Cit, Asp, Phe, Gly, Lys, Leu, Ala, (D)Ala, beta-Ala, His, Thr, n-Leu, Gln, Ser, (D)Ser, Tic, Trp, alpha-MeGln, alpha-MeAsn, alpha-MeLys(Ac), Dab(Ac), Dap(Ac), homo-Lys(Ac), or Lys(Ac);

X15 is Asn, Leu, Aib, (D)Leu, beta-Ala, Cit, Gln, Asp, alpha-MeGln, alpha-MeAsn, Lys(Ac), (D)Lys, alpha-MeLys(Ac), Dab(Ac), Dap(Ac), homo-Lys(Ac), or absent.

[00152] In certain embodiment, the peptide inhibitor is according to Formula (VIIa), (VIIb), or (VIIc) or comprises a sequence of Formula (VIIa), (VIIb), or (VIIc):

Pen-Asn-Thr-X7-Gln-Pen-[F(4-2ae)]-X11-X12-X13-X14-X15 (VIIa),

Abu-Asn-Thr-X7-Gln-Cys-[F(4-2ae)]-X11-X12-X13-X14-X15 (VIIb), or

Abu-Asn-Thr-X7-Gln-Pen-[F(4-2ae)]-X11-X12-X13-X14-X15 (VIIc)

wherein X7 and X11 are as described for Formula (Z'); X12 is 4-amino-4-carboxy-tetrahydropyran (THP), alpha-MeLys, alpha-MeLeu, alpha-MeArg, alpha-MePhe, alpha-MeLeu, alpha-MeLys, alpha-MeAsn, alpha-MeTyr, Ala, or cyclohexylAla, Lys, or Aib;

X13 is Aib, Glu, Cit, Gln, Lys(Ac), alpha-MeArg, alpha-MeGlu, alpha-MeLeu, alpha-MeLys, alpha-Me-Asn, alpha-MeLys(Ac), Dab(Ac), Dap(Ac), homo-Lys(Ac), or Lys; or X13 is Lys, pegylated Lys, b-homoGlu, or Lys(Y2-Ac), wherein Y2 is an amino acid;

X14 is Asn, 2-Nap, Aib, Arg, Cit, Asp, Phe, Gly, Lys, Leu, Ala, (D)Ala, beta-Ala, His, Thr, n-Leu, Gln, Ser, (D)Ser, Tic, Trp, alpha-MeGln, alpha-MeAsn, alpha-MeLys(Ac), Dab(Ac), Dap(Ac), homo-Lys(Ac), or Lys(Ac);

X15 is Asn, Leu, Aib, (D)Leu, beta-Ala, Cit, Gln, Asp, alpha-MeGln, alpha-MeAsn, Lys(Ac), (D)Lys, alpha-MeLys(Ac), Dab(Ac), Dap(Ac), homo-Lys(Ac), or absent; and the peptide inhibitor is cyclized via a Pen-Pen disulfide bond; or the peptide inhibitor is cyclized via a Abu-Cys or Abu-Pen thioether bond.

[00153] In certain embodiment, the peptide inhibitor is according to Formula (VIId), (VIIe), or (VIIf) or comprises a sequence of Formula (VIId), (VIIe), or (VIIf):

Pen-Asn-Thr-X7-Lys(Ac)-Pen-[F(4-2ae)]-X11-X12-X13-X14-X15 (VIId),

Abu-Asn-Thr-X7-Lys(Ac)-Cys-[F(4-2ae)]-X11-X12-X13-X14-X15 (VIIe), or

Abu-Asn-Thr-X7-Lys(Ac)-Pen-[F(4-2ae)]-X11-X12-X13-X14-X15 (VIIf)

wherein X7 and X11 are as described for Formula (Z'); X12 is 4-amino-4-carboxy-tetrahydropyran (THP), alpha-MeLys, alpha-MeLeu, alpha-MeArg, alpha-MePhe, alpha-MeLeu, alpha-MeLys, alpha-MeAsn, alpha-MeTyr, Ala, or cyclohexylAla, Lys, or Aib;

X13 is Aib, Glu, Cit, Gln, Lys(Ac), alpha-MeArg, alpha-MeGlu, alpha-MeLeu, alpha-MeLys, alpha-Me-Asn, alpha-MeLys(Ac), Dab(Ac), Dap(Ac), homo-Lys(Ac), or Lys; or X13 is Lys, pegylated Lys, b-homoGlu, or Lys(Y2-Ac), wherein Y2 is an amino acid;

X14 is Asn, 2-Nap, Aib, Arg, Cit, Asp, Phe, Gly, Lys, Leu, Ala, (D)Ala, beta-Ala, His, Thr, n-Leu, Gln, Ser, (D)Ser, Tic, Trp, alpha-MeGln, alpha-MeAsn, alpha-MeLys(Ac), Dab(Ac), Dap(Ac), homo-Lys(Ac), or Lys(Ac);

X15 is Asn, Leu, Aib, (D)Leu, beta-Ala, Cit, Gln, Asp, alpha-MeGln, alpha-MeAsn, Lys(Ac), (D)Lys, alpha-MeLys(Ac), Dab(Ac), Dap(Ac), homo-Lys(Ac), or absent; and the peptide inhibitor is cyclized via a Pen-Pen disulfide bond; or the peptide inhibitor is cyclized via a Abu-Cys or Abu-Pen thioether bond.

[00154] In certain embodiment, the peptide inhibitor is according to Formula (VIId) or comprises a sequence of Formula (VIId). In certain embodiment, the peptide inhibitor is according to Formula (VIIe) or comprises a sequence of Formula (VIIe). In certain embodiment, the peptide inhibitor is according to Formula (VIIf) or comprises a sequence of Formula (VIIf).

[00155] In certain embodiments, each X12, X13, X14, or X15 is independently any amino acid. In one embodiment, the amino acid is a natural amino acid. In another embodiment, the amino acid is an unnatural amino acid.

[00156] In certain embodiments, X14 is Asn, 2-Nap, Aib, Arg, Cit, Asp, Phe, Gly, Lys, Leu, Asn, n-Leu, Gln, Ser, Tic, Trp, alpha-MeGln, alpha-MeAsn, alpha-MeLys(Ac), Dab(Ac), Dap(Ac), homo-Lys(Ac), or Lys(Ac). In certain embodiments, X14 is Asn, 2-Nap, Aib, Arg, Cit, Asp, Phe, Gly, Lys, Leu, Ala, (D)Ala, beta-Ala, His, Thr, n-Leu, Gln, Ser, (D)Ser, Tic, Trp, alpha-MeGln, alpha-MeAsn, alpha-MeLys(Ac), Dab(Ac), Dap(Ac), homo-Lys(Ac), or Lys(Ac).

[00157] In certain embodiments, X15 is Asn, Aib,, beta-Ala, Cit, Gln, Asp, alpha-MeGln, alpha-MeAsn, Lys(Ac), alpha-MeLys(Ac), Dab(Ac), Dap(Ac), homo-Lys(Ac), or absent. In certain embodiments, X15 is Asn, Leu, Aib, (D)Leu, beta-Ala, Cit, Gln, Asp, alpha-MeGln, alpha-MeAsn, Lys(Ac), (D)Lys, alpha-MeLys(Ac), Dab(Ac), Dap(Ac), homo-Lys(Ac), or absent.

[00158] In certain embodiments, X13 is Glu, Cit, Gln, Lys(Ac), alpha-MeArg, alpha-MeGlu, alpha-MeLeu, alpha-MeLys, alpha-Me-Asn, alpha-MeLys(Ac), Dab(Ac), Dap(Ac), homo-Lys(Ac), or Lys; or X13 is Lys, pegylated Lys, b-homoGlu, or Lys(Y2-Ac), wherein Y2 is an amino acid. In certain embodiment, X13 is Aib, Glu, Cit, Gln, Lys(Ac), alpha-MeArg, alpha-MeGlu, alpha-MeLeu, alpha-MeLys, alpha-Me-Asn, alpha-MeLys(Ac), Dab(Ac), Dap(Ac), homo-Lys(Ac), or Lys; or X13 is Lys, pegylated Lys, b-homoGlu, or Lys(Y2-Ac), wherein Y2 is an amino acid.

[00159] In certain embodiments, X12 is 4-amino-4-carboxy-tetrahydropyran (THP), alpha-MeLys, alpha-MeLeu, Ala, cyclohexylAla, Lys, or Aib.

[00160] In certain embodiments, X12 is 4-amino-4-carboxy-tetrahydropyran (THP), alpha-MeLys, or alpha-MeLeu.

[00161] In certain embodiments, X12 is alpha-MeLeu. In certain embodiment, X12 is alpha-MeLys. In certain embodiment, X12 is 4-amino-4-carboxy-tetrahydropyran (THP).

[00162] In certain embodiments, X13 is Glu, Gln, Lys(Ac), or Lys.

[00163] In certain embodiments, X13 is Gln, Lys(Ac), or Lys.

[00164] In certain embodiments, X13 is Lys(Ac), or Lys.

[00165] In certain embodiments, X13 is Lys(Ac).

[00166] In certain embodiments, the peptide inhibitor is according to Formula (VIIIa), (VIIIb) or (VIIIc) or comprises a sequence of Formula (VIIIa), (VIIIb) or (VIIIc):

Pen-Asn-Thr-X7-Gln-Pen-[F(4-2ae)]-X11-aMeLeu-K(Ac)-X14-X15 (VIIIa),

Abu-Asn-Thr-X7-Gln-Cys-[F(4-2ae)]-X11-aMeLeu-K(Ac)-X14-X15 (VIIIb), or

Abu-Asn-Thr-X7-Gln-Pen-[F(4-2ae)]-X11-aMeLeu-K(Ac)-X14-X15 (VIIIc)

wherein X7 and X11 are as described for Formula (II); X14, and X15 are as described for Formula (VIIa-c); and the peptide inhibitor is cyclized via a Pen-Pen disulfide bond; or a Abu-Cys or Abu-Pen thioether bond.

[00167] In certain embodiments, the peptide inhibitor is according to Formula (VIIId), (VIIIe) or (VIIIf) or comprises a sequence of Formula (VIIId), (VIIIe) or (VIIIf):

Pen-Asn-Thr-X7-Lys(Ac)-Pen-[F(4-2ae)]-X11-[alpha-MeLys]-K(Ac)-X14-X15 (VIIId),

Abu-Asn-Thr-X7-Lys(Ac)-Cys-[F(4-2ae)]-X11-[alpha-MeLys]-K(Ac)-X14-X15 (VIIIe), or

Abu-Asn-Thr-X7-Lys(Ac)-Pen-[F(4-2ae)]-X11-[alpha-MeLys]-K(Ac)-X14-X15 (VIIIf)

wherein X7 and X11 are as described for Formula (II); X14, and X15 are as described for Formula (VIIa-c); and the peptide inhibitor is cyclized via a Pen-Pen disulfide bond; or a Abu-Cys or Abu-Pen thioether bond.

[00168] In certain embodiments, the peptide inhibitor is according to Formula (VIIId) or comprises a sequence of Formula VIIIf). In certain embodiments, the peptide inhibitor is according to Formula (VIIIe) or comprises a sequence of Formula (VIIIe). In certain embodiments, the peptide inhibitor is according to Formula (VIIIf) or comprises a sequence of Formula (VIIIf).

[00169] In certain embodiments, X14 is Asn. In certain embodiments, X15 is Asn. In certain embodiments, X7, X11, X14, and X15 are as described for Formula (Z').

[00170] In certain embodiments, the peptide inhibitor is according to Formula (IXa), (IXb), or (IXc) or comprises a sequence of Formula (IXa), (IXb), or (IXc):

Pen-Asn-Thr-X7-Gln-Pen-[F(4-2ae)]-X11-[α-MeLeu]-K(Ac)-Asn-Asn (IXa),

Pen-Asn-Thr-X7-Gln-Pen-[F(4-2ae)]-X11-[α-MeLeu]-K(Ac)-Asn-Asn (IXb), or

Pen-Asn-Thr-X7-Gln-Pen-[F(4-2ae)]-X11-[α-MeLeu]-K(Ac)-Asn-Asn (IXc)

wherein X7 and X11 are as described for Formula (II); and the peptide inhibitor is cyclized via a Pen-Pen disulfide bond; or a Abu-Cys or Abu-Pen thioether bond.

[00171] In certain embodiments, the peptide inhibitor is according to Formula (IXd), (IXe), or (IXf) or comprises a sequence of Formula (IXd), (IXe), or (IXf):

Pen-Asn-Thr-X7-Lys(Ac)-Pen-[F(4-2ae)]-X11-[alpha-MeLys]-K(Ac)-Asn-[(D)Leu] (IXd),

Pen-Asn-Thr-X7-Lys(Ac)-Pen-[F(4-2ae)]-X11-[alpha-MeLys]-K(Ac)-Asn-[(D)Leu] (IXe), or

Pen-Asn-Thr-X7-Lys(Ac)-Pen-[F(4-2ae)]-X11-[alpha-MeLys]-K(Ac)-Asn-[(D)Leu] (IXf)

wherein X7 and X11 are as described for Formula (II); and the peptide inhibitor is cyclized via a Pen-Pen disulfide bond; or a Abu-Cys or Abu-Pen thioether bond.

[00172] In certain embodiments, the peptide inhibitor is according to Formula (IXd) or comprises a sequence of Formula (IXd). In certain embodiments, the peptide inhibitor is according to Formula (IXe) or comprises a sequence of Formula (IXe). In certain embodiments, the peptide inhibitor is according to Formula (IXf) or comprises a sequence of Formula (IXf).

[00173] In certain embodiments, X7 is Trp substituted with cyano, halo, alkyl, haloalkyl, hydroxy, or alkoxy; and X11 is as described herein.

[00174] In certain embodiments, X11 is Trp substituted with cyano, halo, alkyl, haloalkyl, hydroxy, or alkoxy; and X7 is as described herein.

[00175] In certain embodiments, the peptide inhibitor is according to Formula (Xa), (Xb), (Xc), (Xd), (Xe), or (Xf) or comprises a sequence of Formula (Xa), (Xb), (Xc), (Xd), (Xe), or (Xf):

Pen-Asn-Thr-W'-Gln-Pen-[F(4-2ae)]-X11-[α-MeLeu]-K(Ac)-Asn-Asn (Xa),

Pen-Asn-Thr-X7-Gln-Pen-[F(4-2ae)]-W'-[α-MeLeu]-K(Ac)-Asn-Asn (Xb),

Abu-Asn-Thr-W'-Gln-Cys-[F(4-2ae)]-X11-[α-MeLeu]-K(Ac)-Asn-Asn (Xc),

Abu-Asn-Thr-X7-Gln-Cys-[F(4-2ae)]-W'-[α-MeLeu]-K(Ac)-Asn-Asn (Xd),

Abu-Asn-Thr-W'-Gln-Pen-[F(4-2ae)]-X11-[α-MeLeu]-K(Ac)-Asn-Asn (Xe), or

Abu-Asn-Thr-X7-Gln-Pen-[F(4-2ae)]-W'-[α-MeLeu]-K(Ac)-Asn-Asn (Xf)

wherein X7 and X11 are as described for Formula (II); W' is Trp substituted with cyano, halo, alkyl, haloalkyl, hydroxy, or alkoxy; and the peptide inhibitor is cyclized via a Pen-Pen disulfide bond; or a Abu-Cys or Abu-Pen thioether bond.

[00176] In certain embodiments, the peptide inhibitor is according to Formula (Xg), (Xh), (Xi), (Xj), (Xk), or (Xl) or comprises a sequence of Formula (Xg), (Xh), (Xi), (Xj), (Xk), or (Xl):

Pen-Asn-Thr-W'-Lys(Ac)-Pen-[F(4-2ae)]-X11-[alpha-MeLys]-K(Ac)-Asn-[(D)Leu] (Xg),

Pen-Asn-Thr-X7-Lys(Ac)-Pen-[F(4-2ae)]-W'-[alpha-MeLys]-K(Ac)-Asn-[(D)Leu] (Xh),

Abu-Asn-Thr-W'-Lys(Ac)-Cys-[F(4-2ae)]-X11-[alpha-MeLys]-K(Ac)-Asn-[(D)Leu] (Xi),

Abu-Asn-Thr-X7-Lys(Ac)-Cys-[F(4-2ae)]-W'-[alpha-MeLys]-K(Ac)-Asn-[(D)Leu] (Xj),

Abu-Asn-Thr-W'-Lys(Ac)-Pen-[F(4-2ae)]-X11-[alpha-MeLys]-K(Ac)-Asn-[(D)Leu] (Xk), or

Abu-Asn-Thr-X7-Lys(Ac)-Pen-[F(4-2ae)]-W'-[alpha-MeLys]-K(Ac)-Asn-[(D)Leu] (Xl)

wherein X7 and X11 are as described for Formula (II); W' is Trp substituted with cyano, halo, alkyl, haloalkyl, hydroxy, or alkoxy; and the peptide inhibitor is cyclized via a Pen-Pen disulfide bond; or a Abu-Cys or Abu-Pen thioether bond.

[00177] In certain embodiments, the peptide inhibitor is according to Formula (Xg) or comprises a sequence of Formula (Xg). In certain embodiments, the peptide inhibitor is according to Formula (Xh) or comprises a sequence of Formula (Xh). In certain embodiments, the peptide inhibitor is according to Formula (Xi) or comprises a sequence of Formula (Xi). In certain embodiments, the peptide inhibitor is according to Formula (Xj) or comprises a sequence of Formula (Xj). In certain embodiments, the peptide inhibitor is according to Formula (Xk) or comprises a sequence of Formula (Xk). In certain embodiments, the peptide inhibitor is according to Formula (Xl) or comprises a sequence of Formula (Xl).

[00178] In certain embodiments, X11 is 2-Nal, Phe(2-Me), Phe(3-Me), Phe(4-Me), Phe(3,4-dimethoxy), or 1-Nal.

[00179] In certain embodiments, X11 is 2-Nal, or 1-Nal.

[00180] In certain embodiments, X11 is 2-Nal.

[00181] In certain embodiments, X7 is unsubstituted Trp. In certain embodiments, X7 is Trp substituted with alkyl. In certain embodiments, X7 is Trp substituted with alkyl at the 1-, 2- or 7-position. In certain embodiments, X7 is Trp substituted with methyl, ethyl, iso-propyl or tert-butyl at the 1-, 2- or 7-position.

[00182] In certain embodiments, the peptide inhibitor is according to Formula (XIa), (XIb), (XIc), (XId), (XIe), or (XIf) or comprises a sequence of Formula (XIa), (XIb), (XIc), (XId), (XIe), or (XIf):

Pen-Asn-Thr-W'-Gln-Pen-[F(4-2ae)]-[2-Nal]-[α-MeLeu]-K(Ac)-Asn-Asn (XIa),

Pen-Asn-Thr-W-Gln-Pen-[F(4-2ae)]-W'-[α-MeLeu]-K(Ac)-Asn-Asn (XIb),

Abu-Asn-Thr-W'-Gln-Cys-[F(4-2ae)]-[2-Nal]-[α-MeLeu]-K(Ac)-Asn-Asn (XIc),

Abu-Asn-Thr-W-Gln-Cys-[F(4-2ae)]-W'-[α-MeLeu]-K(Ac)-Asn-Asn (XId),

Abu-Asn-Thr-W'-Gln-Pen-[F(4-2ae)]-[2-Nal]-[α-MeLeu]-K(Ac)-Asn-Asn (XIe), or

Abu-Asn-Thr-W-Gln-Pen-[F(4-2ae)]-W'-[α-MeLeu]-K(Ac)-Asn-Asn (XIf)

wherein W' is Trp substituted with cyano, halo, alkyl, haloalkyl, hydroxy, or alkoxy; and the peptide inhibitor is cyclized via a Pen-Pen disulfide bond.

[00183] In certain embodiments, X7 is unsubstituted Trp. In certain embodiments, X7 is Trp substituted with alkyl. In certain embodiments, X7 is Trp substituted with alkyl at the 1-, 2- or 7-position. In certain embodiments, X7 is Trp substituted with methyl, ethyl, iso-propyl or tert-butyl at the 1-, 2- or 7-position.

[00184] In certain embodiments, the peptide inhibitor is according to Formula (XIg), (XIh), (XIi), (XIj), (XIk), or (XIl) or comprises a sequence of Formula (XIg), (XIh), (XIi), (XIj), (XIk), or (XIl):

Pen-Asn-Thr-W'-Lys(Ac)-Pen-[F(4-2ae)]-[2-Nal]-[a-MeLys]-K(Ac)-Asn-[(D)Leu] (XIg),

Pen-Asn-Thr-W-Lys(Ac)-Pen-[F(4-2ae)]-W'-[a-MeLys]-K(Ac)-Asn-[(D)Leu] (XIh),

Abu-Asn-Thr-W'-Lys(Ac)-Cys-[F(4-2ae)]-[2-Nal]-[a-MeLys]-K(Ac)-Asn-[(D)Leu] (XIi),

Abu-Asn-Thr-W-Lys(Ac)-Cys-[F(4-2ae)]-W'-[a-MeLys]-K(Ac)-Asn-[(D)Leu] (XIj),

Abu-Asn-Thr-W'-Lys(Ac)-Pen-[F(4-2ae)]-[2-Nal]-[a-MeLys]-K(Ac)-Asn-[(D)Leu] (XIk), or

Abu-Asn-Thr-W-Lys(Ac)-Pen-[F(4-2ae)]-W'-[a-MeLys]-K(Ac)-Asn-[(D)Leu] (XIl)

wherein W' is Trp substituted with cyano, halo, alkyl, haloalkyl, hydroxy, or alkoxy; and the peptide inhibitor is cyclized via a Pen-Pen disulfide bond.

[00185] In certain embodiments, the peptide inhibitor is according to Formula (XIg) or comprises a sequence of Formula (XIg). In certain embodiments, the peptide inhibitor is according to Formula (XIh) or comprises a sequence of Formula (XIh). In certain

embodiments, the peptide inhibitor is according to Formula (XIi) or comprises a sequence of Formula (XIi). In certain embodiments, the peptide inhibitor is according to Formula (XIj) or comprises a sequence of Formula (XIj). In certain embodiments, the peptide inhibitor is according to Formula (XIk) or comprises a sequence of Formula (XIk). In certain embodiments, the peptide inhibitor is according to Formula (XIl) or comprises a sequence of Formula (XIl).

[00186] In certain embodiments, W' is Trp substituted with cyano, halo, alkyl, haloalkyl, hydroxy, or alkoxy. In one embodiment, W' is Trp substituted with alkyl. In certain embodiments, W' is Trp substituted with Me, Et, n-Pr, or i-Pr. In certain embodiments, W' is Trp substituted with Me, Et, i-Pr or t-Bu, at the 1-, 2- or 7-position.

[00187] In certain embodiment, the peptide inhibitor is accoding to Formula (XIg), wherein W' is W' is Trp substituted with cyano, halo, alkyl, haloalkyl, hydroxy, or alkoxy. In certain embodiment, the peptide inhibitor is accoding to Formula (XIg), wherein W' is Trp substituted with alkyl. In certain embodiment, the peptide inhibitor is accoding to Formula (XIg), wherein W' is Trp substituted with Me, Et, n-Pr, i-Pr or t-Bu. In certain embodiment, the peptide inhibitor is accoding to Formula (XIg), wherein W' is Trp substituted with Me, Et, n-Pr, or i-Pr. In certain embodiments, W' is Trp substituted with Me, Et, i-Pr or t-Bu, at the 1-, 2- or 7-position.

[00188] In certain embodiment, the peptide inhibitor is accoding to Formula (XIh), wherein W' is W' is Trp substituted with cyano, halo, alkyl, haloalkyl, hydroxy, or alkoxy. In certain embodiment, the peptide inhibitor is accoding to Formula (XIh), wherein W' is Trp substituted with alkyl. In certain embodiment, the peptide inhibitor is accoding to Formula (XIh), wherein W' is Trp substituted with Me, Et, n-Pr, i-Pr or t-Bu. In certain embodiment, the peptide inhibitor is accoding to Formula (XIh), wherein W' is Trp substituted with Me, Et, n-Pr, or i-Pr. In certain embodiments, W' is Trp substituted with Me, Et, i-Pr or t-Bu, at the 1-, 2- or 7-position.

[00189] In certain embodiment, the peptide inhibitor is accoding to Formula (XIi), wherein W' is W' is Trp substituted with cyano, halo, alkyl, haloalkyl, hydroxy, or alkoxy. In certain embodiment, the peptide inhibitor is accoding to Formula (XIi), wherein W' is Trp substituted with alkyl. In certain embodiment, the peptide inhibitor is accoding to Formula (XIi), wherein W' is Trp substituted with Me, Et, n-Pr, i-Pr or t-Bu. In certain embodiment, the peptide inhibitor is accoding to Formula (XIi), wherein W' is Trp substituted with Me, Et, n-Pr, or i-

Pr. In certain embodiments, W' is Trp substituted with Me, Et, i-Pr or t-Bu, at the 1-, 2- or 7-position.

[00190] In certain embodiment, the peptide inhibitor is accoding to Formula (XIj), wherein W' is W' is Trp substituted with cyano, halo, alkyl, haloalkyl, hydroxy, or alkoxy. In certain embodiment, the peptide inhibitor is accoding to Formula (XIj), wherein W' is Trp substituted with alkyl. In certain embodiment, the peptide inhibitor is accoding to Formula (XIj), wherein W' is Trp substituted with Me, Et, n-Pr, i-Pr or t-Bu. In certain embodiment, the peptide inhibitor is accoding to Formula (XIj), wherein W' is Trp substituted with Me, Et, n-Pr, or i-Pr. In certain embodiments, W' is Trp substituted with Me, Et, i-Pr or t-Bu, at the 1-, 2- or 7-position.

[00191] In certain embodiment, the peptide inhibitor is accoding to Formula (XIk), wherein W' is W' is Trp substituted with cyano, halo, alkyl, haloalkyl, hydroxy, or alkoxy. In certain embodiment, the peptide inhibitor is accoding to Formula (XIk), wherein W' is Trp substituted with alkyl. In certain embodiment, the peptide inhibitor is accoding to Formula (XIk), wherein W' is Trp substituted with Me, Et, n-Pr, i-Pr or t-Bu. In certain embodiment, the peptide inhibitor is accoding to Formula (XIk), wherein W' is Trp substituted with Me, Et, n-Pr, or i-Pr. In certain embodiments, W' is Trp substituted with Me, Et, i-Pr or t-Bu, at the 1-, 2- or 7-position.

[00192] In certain embodiment, the peptide inhibitor is accoding to Formula (XIl), wherein W' is W' is Trp substituted with cyano, halo, alkyl, haloalkyl, hydroxy, or alkoxy. In certain embodiment, the peptide inhibitor is accoding to Formula (XIl), wherein W' is Trp substituted with alkyl. In certain embodiment, the peptide inhibitor is accoding to Formula (XIl), wherein W' is Trp substituted with Me, Et, n-Pr, i-Pr or t-Bu. In certain embodiment, the peptide inhibitor is accoding to Formula (XIl), wherein W' is Trp substituted with Me, Et, n-Pr, or i-Pr. In certain embodiments, W' is Trp substituted with Me, Et, i-Pr or t-Bu, at the 1-, 2- or 7-position.

[00193] In certain embodiments, X7 is Trp substituted with cyano, halo, alkyl, haloalkyl, hydroxy, or alkoxy; and X11 is as described for Formula (Z').

[00194] In certain embodiments, X11 is Trp substituted with cyano, halo, alkyl, haloalkyl, hydroxy, or alkoxy; and X7 is as described for Formula (Z').

[00195] In certain embodiments, X11 is 2-Nal, Phe(2-Me), Phe(3-Me), Phe(4-Me), Phe(3,4-dimethoxy), or 1-Nal. In certain embodiments, X11 is 2-Nal, or 1-Nal. In certain embodiments, X11 is 2-Nal. In certain embodiments, X11 is 1-Nal.

[00196] In certain embodiments, the peptide inhibitor comprises an amino acid sequence of Formula (IVa):

Pen- Asn-Thr-X7-X8-Pen-X10-X11 (IVa),

wherein X8, X10, and X11 are as described for Formula (Z'), and X7 is Trp substituted with alkyl, and the substitution is at 1-, 2, or 7-position. In certain embodiments, X7 is Trp substituted with 1-Me, 2-Me, or 7-Me. In certain embodiments, X8 is Gln, alpha-Me-Lys, alpha-MeLys(Ac), or Glu. In certain embodiments, X8 is Gln. In certain embodiments, X10 is Phe, Phe[4-(2-aminoethoxy)], Phe[4-(2-acetylaminoethoxy)], or Phe(4-$CONH_2$). In certain embodiments, X10 is Phe[4-(2-aminoethoxy)], or Phe[4-(2-acetylaminoethoxy)]. In certain embodiments, X11 is Trp substituted with cyano, halo, alkyl, haloalkyl, hydroxy, or alkoxy. In certain embodiments, X11 is 2-Nal, Phe(2-Me), Phe(3-Me), Phe(4-Me), Phe(3,4-dimethoxy), or 1-Nal. In certain embodiments, X11 is 2-Nal, or 1-Nal. In certain embodiments, X11 is 2-Nal.

[00197] In certain embodiments, the peptide inhibitor comprises the structure of Formula (Z):

R^1-X-R^2 (Z)

or a pharmaceutically acceptable salt or solvate thereof, wherein

R^1 is a bond, hydrogen, a C1-C6 alkyl, a C6-C12 aryl, a C6-C12 aryl-C1-C6 alkyl, a C1-C20 alkanoyl, and including PEGylated versions alone or as spacers of any of the foregoing; X is the amino acid sequence of Formula (I), Formula (II)-(XII), or an amino acid sequence set forth in any of Table E1, E2 or E3; and R^2 is OH or NH_2.

[00198] In certain embodiments, the peptide inhibitor comprises the structure of Formula (Z):

R^1-X-R^2 (Z)

or a pharmaceutically acceptable salt or solvate thereof, wherein

R^1 is a bond, hydrogen, a C1-C6 alkyl, a C6-C12 aryl, a C6-C12 aryl-C1-C6 alkyl, a C1-C20 alkanoyl, and including PEGylated versions alone or as spacers of any of the foregoing; X is the amino acid sequence of Formula (I), Formula (II)-(XII), or an amino acid sequence set forth in any of TableE3; and R^2 is OH or NH_2. In certain embodiments, X of Formula (Z) is the amino acid sequence of Formula (VIIa), (VIIb), (VIIc), (VIId), (VIIe), (VIIf), (VIIIa), (VIIIb), (VIIIc), (VIIId), (VIIIe), (VIIIf), (IXa), (IXb), (IXc), (IXd), (IXe), (IXf), (Xa), (Xb), (Xc),

(Xd), (Xe), (Xf), (Xg), (Xh), (Xi), (Xj), (Xk), (Xl), (XIa), (XIb), (XIc), (XId), (XIe), (XIf), (XIg), (XIh), (XIi), (XIj), (XIk), or (XIl).

[00199] In certain embodiments with respect to Formula (Z), X is the amino acid sequence of Formula (II').

[00200] In certain embodiments with respect to Formula (Z), the peptide comprises X-R^2, and X is the amino acid sequence of Formula (II'), and R^2 is OH or NH_2.

[00201] In certain embodiments with respect to Formula (Z), the peptide comprises an amino acid sequence of Formula (II"):

X7-X8-X9-X10-X11-X12-X13-X14-X15-R^2 (II").

[00202] In certain embodiments, the peptide inhibitor comprises the structure of Formula (Z):

R^1-X-R^2 (Z)

or a pharmaceutically acceptable salt or solvate thereof, wherein

R^1 is a bond, hydrogen, Ac, a C1-C6 alkyl, a C6-C12 aryl, a C6-C12aryl-C1-C6alkyl, or a C1-C20 alkanoyl, and including PEGylated versions alone or as spacers of any of the foregoing;

X is the amino acid sequence of Formula (II'); and

R^2 is OH or NH_2;

or wherein the peptide inhibitor of Formula (Z) is a peptide having an amino acid sequence set forth in Table E3 or a pharmaceutically acceptable salt or solvate thereof.

[00203] In certain embodiments, R^1 is H or C_1-C_{20} alkanoyl.

[00204] In certain embodiments, R^1 is H or Ac.

[00205] In certain embodiments, R^1 is Ac.

[00206] In certain embodiments, W' is Trp substituted with cyano, halo, alkyl, haloalkyl, hydroxy, or alkoxy; and the substitution is at 4-, 5-, 6- or 7- position.

[00207] In certain embodiments, W' is Trp substituted with cyano, F, Cl, Br, I, Me, Et, i-Pr, n-Pr, n-Bu, t-Bu, CF_3, hydroxy, OMe, or OEt; and the substitution is at 4-, 5-, 6- or 7- position. In a particular embodiment, the substitution is at 7- position.

[00208] In certain embodiments, W' is Trp substituted with 5- F, 6-F, 7-F, 5- Cl, 6-Cl, 7-Cl, 5-Me, 6-Me, 7-Me, 7-n-Pr, 7-i-Pr, 5-OH, 6-OH, 7-OH, 5-OMe, 6-OMe, or 7-OMe.

[00209] In a particular embodiment, W' is Trp substituted with 7-Me, 5-F, 7-F, 6-Cl, 6-Me, 4-OMe, 5-OMe, or 5-Br. In a more particular embodiment, W' is Trp substituted with 7-Me, 6-Me, 4-OMe, or 6-Cl. In a most particular embodiment, W' is Trp substituted with 7-Me.

[00210] In one embodiment the peptide inhibitor consists of about or less than 25 amino acids. In another embodiment the peptide inhibitor consists of about or less than 20 amino acids. In another embodiment the peptide inhibitor consists of about or less than 18 amino acids. In another embodiment the peptide inhibitor consists of about or less than 15 amino acids. In another embodiment the peptide inhibitor consists of about or less than 12 amino acids. In another embodiment the peptide inhibitor consists of about or less than 10 amino acids.

[00211] In certain embodiments, the peptide comprises:

-[Pen]-NTW(6-Cl)-Gln-[Pen]-[Phe[4-(2-aminoethoxy)]-[2-Nal]-[α-MeLeu]-[Lys(Ac)]-NN- (SEQ ID NO: 2);

-[Pen]-NTW(6-F)-Gln-[Pen]-[Phe[4-(2-aminoethoxy)]-[2-Nal]-[α-MeLeu]-[Lys(Ac)]-NN- (SEQ ID NO: 3);

-[Pen]-NTW(4-OMe)-Gln-[Pen]-[Phe[4-(2-aminoethoxy)]-[2-Nal]-[α-MeLeu]-[Lys(Ac)]-NN- (SEQ ID NO: 4);

-[Pen]-NTW(6-Me)-Gln-[Pen]-[Phe[4-(2-aminoethoxy)]-[2-Nal]-[α-MeLeu]-[Lys(Ac)]-NN- (SEQ ID NO: 5);

-[Pen]-NTW(7-Me)-Gln-[Pen]-[Phe[4-(2-aminoethoxy)]-[2-Nal]-[α-MeLeu]-[Lys(Ac)]-NN- (SEQ ID NO: 6);

-[Pen]-NTW(5-F)-Gln-[Pen]-[Phe[4-(2-aminoethoxy)]-[2-Nal]-[α-MeLeu]-[Lys(Ac)]-NN- (SEQ ID NO: 7);

-[Pen]-NTW(7-F)-Gln-[Pen]-[Phe[4-(2-aminoethoxy)]-[2-Nal]-[α-MeLeu]-[Lys(Ac)]-NN- (SEQ ID NO: 8);

-[Pen]-NTW(5-OMe)-Gln-[Pen]-[Phe[4-(2-aminoethoxy)]-[2-Nal]-[α-MeLeu]-[Lys(Ac)]-NN- (SEQ ID NO: 9); or

-[Pen]-NTW(5-OH)-Gln-[Pen]-[Phe[4-(2-aminoethoxy)]-[2-Nal]-[α-MeLeu]-[Lys(Ac)]-NN- (SEQ ID NO: 10);

and wherein the peptide inhibitor is cyclized via a Pen-Pen disulfide bond;

or a pharmaceutically acceptable salt or solvate thereof.

[00212] In certain embodiments, the peptide comprises:

-[Pen]-NTW-Gln-[Pen]-[Phe[4-(2-aminoethoxy)]-W(5-Cl)-[α-MeLeu]-[Lys(Ac)]-NN-(SEQ ID NO: 12);

-[Pen]-NTW-Gln-[Pen]-[Phe[4-(2-aminoethoxy)]-W(6-Cl)-[α-MeLeu]-[Lys(Ac)]-NN-(SEQ ID NO: 13);

-[Pen]-NTW-Gln-[Pen]-[Phe[4-(2-aminoethoxy)]-W(6-F)-[α-MeLeu]-[Lys(Ac)]-NN-(SEQ ID NO: 14);

-[Pen]-NTW-Gln-[Pen]-[Phe[4-(2-aminoethoxy)]-W(4-OMe)-[α-MeLeu]-[Lys(Ac)]-NN-(SEQ ID NO: 15);

-[Pen]-NTW-Gln-[Pen]-[Phe[4-(2-aminoethoxy)]-W(6-Me)-[α-MeLeu]-[Lys(Ac)]-NN- (SEQ ID NO: 16);

-[Pen]-NTW-Gln-[Pen]-[Phe[4-(2-aminoethoxy)]-W(7-Me)-[α-MeLeu]-[Lys(Ac)]-NN-(SEQ ID NO: 17);

-[Pen]-NTW-Gln-[Pen]-[Phe[4-(2-aminoethoxy)]-W(5-F)-[α-MeLeu]-[Lys(Ac)]-NN-(SEQ ID NO: 18);

-[Pen]-NTW-Gln-[Pen]-[Phe[4-(2-aminoethoxy)]-W(7-F)-[α-MeLeu]-[Lys(Ac)]-NN-(SEQ ID NO: 19); or

and wherein the peptide inhibitor is cyclized via a Pen-Pen disulfide bond;

or a pharmaceutically acceptable salt or solvate thereof.

[00213] In certain embodiments, the peptide comprises:

-[(D)Arg]-[Abu]-QT-[W(7-Me)]-QC-[Phe[4-(2-aminoethoxy)]-[2-Nal]-[THP]-ENN- (SEQ ID NO: 27);

-[Abu]-QT-[W(7-Me)]-QC-[Phe[4-(2-aminoethoxy)]-[2-Nal]-[THP]-ENN- (SEQ ID NO: 28);

-[(D)Arg]-[Abu]-QT-[W(7-Me)]-QC-[Phe[4-(2-aminoethoxy)]-[2-Nal]-[THP]-[Lys(Ac)]-NN- (SEQ ID NO: 29); or

-[Abu]-QT-[W(7-Me)]-QC-[Phe[4-(2-aminoethoxy)]-[2-Nal]-[THP]-[Lys(Ac)]-NN- (SEQ ID NO: 30);

and wherein the peptide inhibitor is cyclized via a Abu-C thioether bond;

or a pharmaceutically acceptable salt or solvate thereof.

[00214] In certain embodiments, the peptide comprises or is:

-[Abu]-NTW(6-Cl)-Gln-Cys-[Phe[4-(2-aminoethoxy)]-[2-Nal]-[α-MeLeu]-[Lys(Ac)]-NN-(SEQ ID NO: 107);

-[Abu]-NTW(6-F)-Gln-Cys-[Phe[4-(2-aminoethoxy)]-[2-Nal]-[α-MeLeu]-[Lys(Ac)]-NN- (SEQ ID NO: 108);

-[Abu]-NTW(4-OMe)-Gln-Cys-[Phe[4-(2-aminoethoxy)]-[2-Nal]-[α-MeLeu]-[Lys(Ac)]-NN- (SEQ ID NO: 109);

-[Abu]-NTW(6-Me)-Gln-Cys-[Phe[4-(2-aminoethoxy)]-[2-Nal]-[α-MeLeu]-[Lys(Ac)]-NN- (SEQ ID NO: 110);

-[Abu]-NTW(7-Me)-Gln-Cys-[Phe[4-(2-aminoethoxy)]-[2-Nal]-[α-MeLeu]-[Lys(Ac)]-NN- (SEQ ID NO: 111);

-[Abu]-NTW(5-F)-Gln-Cys-[Phe[4-(2-aminoethoxy)]-[2-Nal]-[α-MeLeu]-[Lys(Ac)]-NN- (SEQ ID NO: 112);

-[Abu]-NTW(7-F)-Gln-Cys-[Phe[4-(2-aminoethoxy)]-[2-Nal]-[α-MeLeu]-[Lys(Ac)]-NN- (SEQ ID NO: 113);

-[Abu]-NTW(5-OMe)-Gln-Cys-[Phe[4-(2-aminoethoxy)]-[2-Nal]-[α-MeLeu]-[Lys(Ac)]-NN- (SEQ ID NO: 114); or

-[Abu]-NTW(5-OH)-Gln-Cys-[Phe[4-(2-aminoethoxy)]-[2-Nal]-[α-MeLeu]-[Lys(Ac)]-NN- (SEQ ID NO: 115);

and wherein the peptide inhibitor is cyclized via a Abu-Cys thioether bond;

or a pharmaceutically acceptable salt or solvate thereof.

[00215] In certain embodiments, the peptide comprises:

-[Abu]-NTW-Gln-Cys-[Phe[4-(2-aminoethoxy)]-W(5-Cl)-[α-MeLeu]-[Lys(Ac)]-NN- (SEQ ID NO: 116);

-[Abu]-NTW-Gln-Cys-[Phe[4-(2-aminoethoxy)]-W(6-Cl)-[α-MeLeu]-[Lys(Ac)]-NN- (SEQ ID NO: 117);

-[Abu]-NTW-Gln-Cys-[Phe[4-(2-aminoethoxy)]-W(6-F)-[α-MeLeu]-[Lys(Ac)]-NN- (SEQ ID NO: 118);

-[Abu]-NTW-Gln-Cys-[Phe[4-(2-aminoethoxy)]-W(4-OMe)-[α-MeLeu]-[Lys(Ac)]-NN- (SEQ ID NO: 119);

-[Abu]-NTW-Gln-Cys-[Phe[4-(2-aminoethoxy)]-W(6-Me)-[α-MeLeu]-[Lys(Ac)]-NN- (SEQ ID NO: 120);

-[Abu]-NTW-Gln-Cys-[Phe[4-(2-aminoethoxy)]-W(7-Me)-[α-MeLeu]-[Lys(Ac)]-NN- (SEQ ID NO: 121);

-[Abu]-NTW-Gln-Cys-[Phe[4-(2-aminoethoxy)]-W(5-F)-[α-MeLeu]-[Lys(Ac)]-NN- (SEQ ID NO: 122); or

-[Abu]-NTW-Gln-Cys-[Phe[4-(2-aminoethoxy)]-W(7-F)-[α-MeLeu]-[Lys(Ac)]-NN- (SEQ ID NO: 123);

and wherein the peptide inhibitor is cyclized via a Abu-Cys thioether bond;
or a pharmaceutically acceptable salt or solvate thereof.

[00216] In certain embodiments, the peptide comprises:

-[Abu]-NTW(6-Cl)-Gln-[Pen]-[Phe[4-(2-aminoethoxy)]-[2-Nal]-[α-MeLeu]-[Lys(Ac)]-NN- (SEQ ID NO: 124);

-[Abu]-NTW(6-F)-Gln-[Pen]-[Phe[4-(2-aminoethoxy)]-[2-Nal]-[α-MeLeu]-[Lys(Ac)]-NN- (SEQ ID NO: 125);

-[Abu]-NTW(4-OMe)-Gln-[Pen]-[Phe[4-(2-aminoethoxy)]-[2-Nal]-[α-MeLeu]-[Lys(Ac)]-NN- (SEQ ID NO: 126);

-[Abu]-NTW(6-Me)-Gln-[Pen]-[Phe[4-(2-aminoethoxy)]-[2-Nal]-[α-MeLeu]-[Lys(Ac)]-NN- (SEQ ID NO: 127);

-[Abu]-NTW(7-Me)-Gln-[Pen]-[Phe[4-(2-aminoethoxy)]-[2-Nal]-[α-MeLeu]-[Lys(Ac)]-NN- (SEQ ID NO: 128);

-[Abu]-NTW(5-F)-Gln-[Pen]-[Phe[4-(2-aminoethoxy)]-[2-Nal]-[α-MeLeu]-[Lys(Ac)]-NN- (SEQ ID NO: 129);

-[Abu]-NTW(7-F)-Gln-[Pen]-[Phe[4-(2-aminoethoxy)]-[2-Nal]-[α-MeLeu]-[Lys(Ac)]-NN- (SEQ ID NO: 130);

-[Abu]-NTW(5-OMe)-Gln-[Pen]-[Phe[4-(2-aminoethoxy)]-[2-Nal]-[α-MeLeu]-[Lys(Ac)]-NN- (SEQ ID NO: 131); or

-[Abu]-NTW(5-OH)-Gln-[Pen]-[Phe[4-(2-aminoethoxy)]-[2-Nal]-[α-MeLeu]-[Lys(Ac)]-NN- (SEQ ID NO: 132);

and wherein the peptide inhibitor is cyclized via a Abu-Pen thioether bond;
or a pharmaceutically acceptable salt or solvate thereof.

[00217] In certain embodiments, the peptide comprises:

-[Abu]-NTW-Gln-[Pen]-[Phe[4-(2-aminoethoxy)]-W(5-Cl)-[α-MeLeu]-[Lys(Ac)]-NN- (SEQ ID NO: 133);

-[Abu]-NTW-Gln-[Pen]-[Phe[4-(2-aminoethoxy)]-W(6-Cl)-[α-MeLeu]-[Lys(Ac)]-NN- (SEQ ID NO: 134);

-[Abu]-NTW-Gln-[Pen]-[Phe[4-(2-aminoethoxy)]-W(6-F)-[α-MeLeu]-[Lys(Ac)]-NN- (SEQ ID NO: 135);

-[Abu]-NTW-Gln-[Pen]-[Phe[4-(2-aminoethoxy)]-W(4-OMe)-[α-MeLeu]-[Lys(Ac)]-NN- (SEQ ID NO: 136);

-[Abu]-NTW-Gln-[Pen]-[Phe[4-(2-aminoethoxy)]-W(6-Me)-[α-MeLeu]-[Lys(Ac)]-NN- (SEQ ID NO: 137);

-[Abu]-NTW-Gln-[Pen]-[Phe[4-(2-aminoethoxy)]-W(7-Me)-[α-MeLeu]-[Lys(Ac)]-NN- (SEQ ID NO: 138);

-[Abu]-NTW-Gln-[Pen]-[Phe[4-(2-aminoethoxy)]-W(5-F)-[α-MeLeu]-[Lys(Ac)]-NN- (SEQ ID NO: 139); or

-[Abu]-NTW-Gln-[Pen]-[Phe[4-(2-aminoethoxy)]-W(7-F)-[α-MeLeu]-[Lys(Ac)]-NN- (SEQ ID NO: 140);

and wherein the peptide inhibitor is cyclized via a Abu-Pen thioether bond;

or a pharmaceutically acceptable salt or solvate thereof.

[00218] In certain embodiments, the peptide comprises or is:

Ac-[Pen]-NTW(6-Cl)-Gln-[Pen]-[Phe[4-(2-aminoethoxy)]-[2-Nal]-[α-MeLeu]-[Lys(Ac)]-NN-NH_2 (SEQ ID NO: 2);

Ac-[Pen]-NTW(6-F)-Gln-[Pen]-[Phe[4-(2-aminoethoxy)]-[2-Nal]-[α-MeLeu]-[Lys(Ac)]-NN- NH_2 (SEQ ID NO: 3);

Ac-[Pen]-NTW(4-OMe)-Gln-[Pen]-[Phe[4-(2-aminoethoxy)]-[2-Nal]-[α-MeLeu]-[Lys(Ac)]-NN- NH_2 (SEQ ID NO: 4);

Ac-[Pen]-NTW(6-Me)-Gln-[Pen]-[Phe[4-(2-aminoethoxy)]-[2-Nal]-[α-MeLeu]-[Lys(Ac)]-NN- NH_2 (SEQ ID NO: 5);

Ac-[Pen]-NTW(7-Me)-Gln-[Pen]-[Phe[4-(2-aminoethoxy)]-[2-Nal]-[α-MeLeu]-[Lys(Ac)]-NN- NH_2 (SEQ ID NO: 6);

Ac-[Pen]-NTW(5-F)-Gln-[Pen]-[Phe[4-(2-aminoethoxy)]-[2-Nal]-[α-MeLeu]-[Lys(Ac)]-NN- NH_2 (SEQ ID NO: 7);

Ac-[Pen]-NTW(7-F)-Gln-[Pen]-[Phe[4-(2-aminoethoxy)]-[2-Nal]-[α-MeLeu]-[Lys(Ac)]-NN- NH_2 (SEQ ID NO: 8);

Ac-[Pen]-NTW(5-OMe)-Gln-[Pen]-[Phe[4-(2-aminoethoxy)]-[2-Nal]-[α-MeLeu]-[Lys(Ac)]-NN- NH_2 (SEQ ID NO: 9); or

Ac-[Pen]-NTW(5-OH)-Gln-[Pen]-[Phe[4-(2-aminoethoxy)]-[2-Nal]-[α-MeLeu]-[Lys(Ac)]-NN- NH_2 (SEQ ID NO: 10);

and wherein the peptide inhibitor is cyclized via a Pen-Pen disulfide bond;

or a pharmaceutically acceptable salt or solvate thereof.

[00219] In certain embodiments, the peptide comprises or is:

Ac-[Pen]-NTW-Gln-[Pen]-[Phe[4-(2-aminoethoxy)]-W(5-Cl)-[α-MeLeu]-[Lys(Ac)]-NN-NH_2 (SEQ ID NO: 12);

Ac-[Pen]-NTW-Gln-[Pen]-[Phe[4-(2-aminoethoxy)]-W(6-Cl)-[α-MeLeu]-[Lys(Ac)]-NN-NH_2 (SEQ ID NO: 13);

Ac-[Pen]-NTW-Gln-[Pen]-[Phe[4-(2-aminoethoxy)]-W(6-F)-[α-MeLeu]-[Lys(Ac)]-NN-NH_2 (SEQ ID NO: 14);

Ac-[Pen]-NTW-Gln-[Pen]-[Phe[4-(2-aminoethoxy)]-W(4-OMe)-[α-MeLeu]-[Lys(Ac)]-NN-NH_2 (SEQ ID NO: 15);

Ac-[Pen]-NTW-Gln-[Pen]-[Phe[4-(2-aminoethoxy)]-W(6-Me)-[α-MeLeu]-[Lys(Ac)]-NN-NH_2 (SEQ ID NO: 16);

Ac-[Pen]-NTW-Gln-[Pen]-[Phe[4-(2-aminoethoxy)]-W(7-Me)-[α-MeLeu]-[Lys(Ac)]-NN-NH_2 (SEQ ID NO: 17);

Ac-[Pen]-NTW-Gln-[Pen]-[Phe[4-(2-aminoethoxy)]-W(5-F)-[α-MeLeu]-[Lys(Ac)]-NN-NH_2 (SEQ ID NO: 18); or

Ac-[Pen]-NTW-Gln-[Pen]-[Phe[4-(2-aminoethoxy)]-W(7-F)-[α-MeLeu]-[Lys(Ac)]-NN-NH_2 (SEQ ID NO: 19); or

and wherein the peptide inhibitor is cyclized via a Pen-Pen disulfide bond;

or a pharmaceutically acceptable salt or solvate thereof.

[00220] In certain embodiments, the peptide comprises or is:

Ac-[(D)Arg]-[Abu]-QT-[W(7-Me)]-QC-[Phe[4-(2-aminoethoxy)]-[2-Nal]-[THP]-ENN-NH_2 (SEQ ID NO: 27);

Ac-[Abu]-QT-[W(7-Me)]-QC-[Phe[4-(2-aminoethoxy)]-[2-Nal]-[THP]-ENN-NH_2 (SEQ ID NO: 28);

Ac-[(D)Arg]-[Abu]-QT-[W(7-Me)]-QC-[Phe[4-(2-aminoethoxy)]-[2-Nal]-[THP]-[Lys(Ac)]-NN-NH_2 (SEQ ID NO: 29); or

Ac-[Abu]-QT-[W(7-Me)]-QC-[Phe[4-(2-aminoethoxy)]-[2-Nal]-[THP]-[Lys(Ac)]-NN-NH_2 (SEQ ID NO: 30);

and wherein the peptide inhibitor is cyclized via a Abu-C thioether bond;

or a pharmaceutically acceptable salt or solvate thereof.

[00221] In certain embodiments, the peptide comprises or is:

Ac-[Abu]-NTW(6-Cl)-Gln-Cys-[Phe[4-(2-aminoethoxy)]-[2-Nal]-[α-MeLeu]-[Lys(Ac)]-NN-NH_2 (SEQ ID NO: 107);

Ac-[Abu]-NTW(6-F)-Gln-Cys-[Phe[4-(2-aminoethoxy)]-[2-Nal]-[α-MeLeu]-[Lys(Ac)]-NN-NH_2 (SEQ ID NO: 108);

Ac-[Abu]-NTW(4-OMe)-Gln-Cys-[Phe[4-(2-aminoethoxy)]-[2-Nal]-[α-MeLeu]-[Lys(Ac)]-NN- NH_2 (SEQ ID NO: 109);

Ac-[Abu]-NTW(6-Me)-Gln-Cys-[Phe[4-(2-aminoethoxy)]-[2-Nal]-[α-MeLeu]-[Lys(Ac)]-NN-NH_2 (SEQ ID NO: 110);

Ac-[Abu]-NTW(7-Me)-Gln-Cys-[Phe[4-(2-aminoethoxy)]-[2-Nal]-[α-MeLeu]-[Lys(Ac)]-NN-NH_2 (SEQ ID NO: 111);

Ac-[Abu]-NTW(5-F)-Gln-Cys-[Phe[4-(2-aminoethoxy)]-[2-Nal]-[α-MeLeu]-[Lys(Ac)]-NN-NH_2 (SEQ ID NO: 112);

Ac-[Abu]-NTW(7-F)-Gln-Cys-[Phe[4-(2-aminoethoxy)]-[2-Nal]-[α-MeLeu]-[Lys(Ac)]-NN-NH_2 (SEQ ID NO: 113);

Ac-[Abu]-NTW(5-OMe)-Gln-Cys-[Phe[4-(2-aminoethoxy)]-[2-Nal]-[α-MeLeu]-[Lys(Ac)]-NN- NH_2 (SEQ ID NO: 114); or

Ac-[Abu]-NTW(5-OH)-Gln-Cys-[Phe[4-(2-aminoethoxy)]-[2-Nal]-[α-MeLeu]-[Lys(Ac)]-NN-NH_2 (SEQ ID NO: 115);

and wherein the peptide inhibitor is cyclized via a Abu-Cys thioether bond;

or a pharmaceutically acceptable salt or solvate thereof.

[00222] In certain embodiments, the peptide comprises or is:

Ac-[Abu]-NTW-Gln-Cys-[Phe[4-(2-aminoethoxy)]-W(5-Cl)-[α-MeLeu]-[Lys(Ac)]-NN-NH_2 (SEQ ID NO: 116);

Ac-[Abu]-NTW-Gln-Cys-[Phe[4-(2-aminoethoxy)]-W(6-Cl)-[α-MeLeu]-[Lys(Ac)]-NN-NH_2 (SEQ ID NO: 117);

Ac-[Abu]-NTW-Gln-Cys-[Phe[4-(2-aminoethoxy)]-W(6-F)-[α-MeLeu]-[Lys(Ac)]-NN-NH_2 (SEQ ID NO: 118);

Ac-[Abu]-NTW-Gln-Cys-[Phe[4-(2-aminoethoxy)]-W(4-OMe)-[α-MeLeu]-[Lys(Ac)]-NN-NH_2 (SEQ ID NO: 119);

Ac-[Abu]-NTW-Gln-Cys-[Phe[4-(2-aminoethoxy)]-W(6-Me)-[α-MeLeu]-[Lys(Ac)]-NN-NH_2 (SEQ ID NO: 120);

Ac-[Abu]-NTW-Gln-Cys-[Phe[4-(2-aminoethoxy)]-W(7-Me)-[α-MeLeu]-[Lys(Ac)]-NN-NH_2 (SEQ ID NO: 121);

Ac-[Abu]-NTW-Gln-Cys-[Phe[4-(2-aminoethoxy)]-W(5-F)-[α-MeLeu]-[Lys(Ac)]-NN-NH_2 (SEQ ID NO: 122); or

Ac-[Abu]-NTW-Gln-Cys-[Phe[4-(2-aminoethoxy)]-W(7-F)-[α-MeLeu]-[Lys(Ac)]-NN-NH_2 (SEQ ID NO: 123);

and wherein the peptide inhibitor is cyclized via a Abu-Cys thioether bond;

or a pharmaceutically acceptable salt or solvate thereof.

[00223] In certain embodiments, the peptide comprises or is:

Ac-[Abu]-NT-[W(6-Cl)]-Gln-[Pen]-[Phe[4-(2-aminoethoxy)]-[2-Nal]-[α-MeLeu]-[Lys(Ac)]-NN-NH_2 (SEQ ID NO: 124);

Ac-[Abu]-NT-[W(6-F)]-Gln-[Pen]-[Phe[4-(2-aminoethoxy)]-[2-Nal]-[α-MeLeu]-[Lys(Ac)]-NN- NH_2 (SEQ ID NO: 125);

Ac-[Abu]-NT-[W(4-OMe)]-Gln-[Pen]-[Phe[4-(2-aminoethoxy)]-[2-Nal]-[α-MeLeu]-[Lys(Ac)]-NN- NH_2 (SEQ ID NO: 126);

Ac-[Abu]-NT-[W(6-Me)]-Gln-[Pen]-[Phe[4-(2-aminoethoxy)]-[2-Nal]-[α-MeLeu]-[Lys(Ac)]-NN- NH_2 (SEQ ID NO: 127);

Ac-[Abu]-NT-[W(7-Me)]-Gln-[Pen]-[Phe[4-(2-aminoethoxy)]-[2-Nal]-[α-MeLeu]-[Lys(Ac)]-NN- NH_2 (SEQ ID NO: 128);

Ac-[Abu]-NT-[W(5-F)]-Gln-[Pen]-[Phe[4-(2-aminoethoxy)]-[2-Nal]-[α-MeLeu]-[Lys(Ac)]-NN- NH_2 (SEQ ID NO: 129);

Ac-[Abu]-NT-[W(7-F)]-Gln-[Pen]-[Phe[4-(2-aminoethoxy)]-[2-Nal]-[α-MeLeu]-[Lys(Ac)]-NN- NH_2 (SEQ ID NO: 130);

Ac-[Abu]-NT-[W(5-OMe)]-Gln-[Pen]-[Phe[4-(2-aminoethoxy)]-[2-Nal]-[α-MeLeu]-[Lys(Ac)]-NN- NH_2 (SEQ ID NO: 131); or

Ac-[Abu]-NT-[W(5-OH)]-Gln-[Pen]-[Phe[4-(2-aminoethoxy)]-[2-Nal]-[α-MeLeu]-[Lys(Ac)]-NN- NH_2 (SEQ ID NO: 132);

and wherein the peptide inhibitor is cyclized via a Abu-Pen thioether bond;

or a pharmaceutically acceptable salt or solvate thereof.

[00224] In certain embodiments, the peptide comprises or is:

Ac-[Abu]-NTW-Gln-[Pen]-[Phe[4-(2-aminoethoxy)]-W(5-Cl)-[α-MeLeu]-[Lys(Ac)]-NN-NH_2 (SEQ ID NO: 123);

Ac-[Abu]-NTW-Gln-[Pen]-[Phe[4-(2-aminoethoxy)]-W(6-Cl)-[α-MeLeu]-[Lys(Ac)]-NN-NH_2 (SEQ ID NO: 134);

Ac-[Abu]-NTW-Gln-[Pen]-[Phe[4-(2-aminoethoxy)]-W(6-F)-[α-MeLeu]-[Lys(Ac)]-NN-NH_2 (SEQ ID NO: 135);

Ac-[Abu]-NTW-Gln-[Pen]-[Phe[4-(2-aminoethoxy)]-W(4-OMe)-[α-MeLeu]-[Lys(Ac)]-NN-NH_2 (SEQ ID NO: 136);

Ac-[Abu]-NTW-Gln-[Pen]-[Phe[4-(2-aminoethoxy)]-W(6-Me)-[α-MeLeu]-[Lys(Ac)]-NN-NH_2 (SEQ ID NO: 137);

Ac-[Abu]-NTW-Gln-[Pen]-[Phe[4-(2-aminoethoxy)]-W(7-Me)-[α-MeLeu]-[Lys(Ac)]-NN-NH_2 (SEQ ID NO: 138);

Ac-[Abu]-NTW-Gln-[Pen]-[Phe[4-(2-aminoethoxy)]-W(5-F)-[α-MeLeu]-[Lys(Ac)]-NN-NH_2 (SEQ ID NO: 139); or

Ac-[Abu]-NTW-Gln-[Pen]-[Phe[4-(2-aminoethoxy)]-W(7-F)-[α-MeLeu]-[Lys(Ac)]-NN-NH_2 (SEQ ID NO: 140);

and wherein the peptide inhibitor is cyclized via a Abu-Pen thioether bond;

or a pharmaceutically acceptable salt or solvate thereof.

[00225] In certain embodiments, the peptide comprises or is:

Ac-[Pen]-NT-[W(7-Me)]-[Cit]-[Pen]-Phe[4-(2-aminoethoxy)]-[2-Nal]-[a-MeLys]-[Lys(Ac)]-N-[(D)Arg]-NH_2 (SEQ ID NO: 256);

Ac-[Pen]-NT-[W(7-Me)]-[Cit]-[Pen]-Phe[4-(2-aminoethoxy)]-[2-Nal]-[a-MeLys]-[Lys(Ac)]-N-[(D)Phe]-NH_2 (SEQ ID NO: 257);

Ac-[Pen]-NT-[W(7-Me)]-[Lys(Ac)]-[Pen]-Phe[4-(2-aminoethoxy)]-[2-Nal]-[a-MeLys]-[Lys(Ac)]-N-[(D)Phe]-NH_2 (SEQ ID NO: 258);

Ac-[Pen]-NT-[W(7-Me)]-[Cit]-[Pen]-Phe[4-(2-aminoethoxy)]-[2-Nal]-[a-MeLys]-[Lys(Ac)]-N-[(D)Tyr]-NH_2 (SEQ ID NO: 259);

Ac-[Pen]-NT-[W(7-Me)]-[Cit]-[Pen]-Phe[4-(2-aminoethoxy)]-[2-Nal]-[a-MeLys]-[Lys(Ac)]-N-S-NH_2 (SEQ ID NO: 260);

Ac-[Pen]-NT-[W(7-Me)]-[Cit]-[Pen]-Phe[4-(2-aminoethoxy)]-[2-Nal]-[a-MeLys]-[Lys(Ac)]-N-[(D)Ser]-NH_2 (SEQ ID NO: 261);

Ac-[Pen]-NT-[W(7-Me)]-[Cit]-[Pen]-Phe[4-(2-aminoethoxy)]-[2-Nal]-[a-MeLys]-[Lys(Ac)]-N-[(D)Thr]-NH_2 (SEQ ID NO: 263);

Ac-[Pen]-NT-[W(7-Me)]-[Cit]-[Pen]-Phe[4-(2-aminoethoxy)]-[2-Nal]-[a-MeLys]-[Lys(Ac)]-N-[Aib]-NH_2 (SEQ ID NO: 264);

Ac-[Pen]-NT-[W(7-Me)]-[Cit]-[Pen]-Phe[4-(2-aminoethoxy)]-[2-Nal]-[a-MeLys]-[Lys(Ac)]-[N-MeAla]-NH_2 (SEQ ID NO: 265);

Ac-[Pen]-NT-[W(7-Me)]-Q-[Pen]-Phe[4-(2-aminoethoxy)]-[2-Nal]-[a-MeLys]-[Lys(Ac)]-N-[bA]-NH_2 (SEQ ID NO: 267);

Ac-[Pen]-N-T-[W(7-Me)]-Q-[Pen]-Phe[4-(2-aminoethoxy)]-[2-Nal]-[DiethylGly]-[Lys(Ac)]-N-[bA]-NH_2 (SEQ ID NO: 276);

Ac-[Pen]-N-T-[W(7-Me)]-Q-[Pen]-Phe[4-(2-aminoethoxy)]-[2-Nal]-[Acbc]-[Lys(Ac)]-N-[bA]-NH_2 (SEQ ID NO: 277);

Ac-[Pen]-N-T-[W(7-Me)]-Q-[Pen]-Phe[4-(2-aminoethoxy)]-[2-Nal]-[a-MeOrn]-[Lys(Ac)]-N-[bA]-NH_2 (SEQ ID NO: 278); or

Ac-[Pen]-N-T-[W(7-Me)]-[Lys(Ac)]-[Pen]-Phe[4-(2-aminoethoxy)]-[Quin]-[a-MeLys]-[Lys(Ac)]-N-dL-NH_2 (SEQ ID NO: 141);

and wherein the peptide inhibitor is cyclized via a Pen-Pen disulfide bond;

or a pharmaceutically acceptable salt or solvate thereof.

[00226] In certain embodiments, the peptide comprises or is:

Ac-[Pen]-NT-[W(7-Me)]-Gln-[Pen]-[Phe[4-(2-aminoethoxy)]-[2-Nal]-[α-MeLeu]-[Lys(Ac)]-NN-NH_2 (SEQ ID NO: 6); and wherein the peptide inhibitor is cyclized via a Pen-Pen disulfide bond; or a pharmaceutically acceptable salt or solvate thereof.

[00227] In certain embodiments, the peptide comprises or is:

Ac-[Pen]-NT-[W(4-OMe)]-Gln-[Pen]-[Phe[4-(2-aminoethoxy)]-[2-Nal]-[α-MeLeu]-[Lys(Ac)]-NN-NH_2 (SEQ ID NO: 4);

Ac-[Pen]-NT-[W(6-Me)]-Gln-[Pen]-[Phe[4-(2-aminoethoxy)]-[2-Nal]-[α-MeLeu]-[Lys(Ac)]-NN-NH_2 (SEQ ID NO: 5);

Ac-[Pen]-NTW-Gln-[Pen]-[Phe[4-(2-aminoethoxy)]-W(6-Cl)-[α-MeLeu]-[Lys(Ac)]-NN-NH_2 (SEQ ID NO: 13);

Ac-[Pen]-NTW-Gln-[Pen]-[Phe[4-(2-aminoethoxy)]-W(6-Me)-[α-MeLeu]-[Lys(Ac)]-NN-NH_2 (SEQ ID NO: 16); or

Ac-[Pen]-NTW-Gln-[Pen]-[Phe[4-(2-aminoethoxy)]-W(5-Br)-[α-MeLeu]-[Lys(Ac)]-NN-NH_2 (SEQ ID NO: 22);

and wherein the peptide inhibitor is cyclized via a Pen-Pen disulfide bond;

or a pharmaceutically acceptable salt or solvate thereof.

[00228] In certain embodiments, the peptide comprises or is:

Ac-[(D)Arg]-[Abu]-QT-[W(7-Me)]-QC-[Phe[4-(2-aminoethoxy)]-[2-Nal]-[THP]-ENN-NH_2 (SEQ ID NO: 27);

Ac-[Abu]-QT-[W(7-Me)]-QC-[Phe[4-(2-aminoethoxy)]-[2-Nal]-[THP]-ENN-NH_2 (SEQ ID NO: 28);

Ac-[(D)Arg]-[Abu]-QT-[W(7-Me)]-QC-[Phe[4-(2-aminoethoxy)]-[2-Nal]-[THP]-[Lys(Ac)]-NN-NH_2 (SEQ ID NO: 29); or

Ac-[Abu]-QT-[W(7-Me)]-QC-[Phe[4-(2-aminoethoxy)]-[2-Nal]-[THP]-[Lys(Ac)]-NN-NH_2 (SEQ ID NO: 30);

and wherein the peptide inhibitor is cyclized via a Abu-Cys thioether bond;

or a pharmaceutically acceptable salt or solvate thereof.

[00229] In certain embodiments, the peptide comprises or is:

Ac-[Pen]-NT-[W(7-Me)]-Q-[Pen]-Phe[4-(2-aminoethoxy)]-[2-Nal]-[a-MeLeu]-[Lys(Ac)]-N-[bA]-NH_2 (SEQ ID NO: 201);

Ac-[Pen]-NT-[W(7-Me)]-[Cit]-[Pen]-Phe[4-(2-aminoethoxy)]-[2-Nal]-[a-MeLeu]-[Lys(Ac)]-N-[bA]-NH_2 (SEQ ID NO: 227);

Ac-[Pen]-NT-[W(7-Me)]-[Lys(Ac)]-[Pen]-Phe[4-(2-aminoethoxy)]-[2-Nal]-[a-MeLys]-[Lys(Ac)]-N-[bA]-NH_2 (SEQ ID NO: 242);

Ac-[Pen]-NT-[W(7-Me)]-[Lys(Ac)]-[Pen]-Phe[4-(2-aminoethoxy)]-[2-Nal]-[a-MeLys]-[Lys(Ac)]-N-[(D)Leu]-NH_2 (SEQ ID NO: 245);

Ac-[Pen]-NT-[W(7-Me)]-[Lys(Ac)]-[Pen]-Phe[4-(2-aminoethoxy)]-[2-Nal]-[a-MeLys]-[Lys(Ac)]-N-H-NH_2 (SEQ ID NO: 248);

Ac-[Pen]-NT-[W(7-Me)]-[Lys(Ac)]-[Pen]-Phe[4-(2-aminoethoxy)]-[2-Nal]-[a-MeLys]-[Lys(Ac)]-N-[Cit]-NH_2 (SEQ ID NO: 249);

Ac-[Pen]-NT-[W(7-Me)]-[Lys(Ac)]-[Pen]-Phe[4-(2-aminoethoxy)]-[2-Nal]-[a-MeLys]-[Lys(Ac)]-N-[(D)Val]-NH_2 (SEQ ID NO: 251);

Ac-[Pen]-NT-[W(7-Me)]-[Lys(Ac)]-[Pen]-Phe[4-(2-aminoethoxy)]-[2-Nal]-[a-MeLys]-[Lys(Ac)]-N-[(D)Lys]-NH_2 (SEQ ID NO: 252);

Ac-[Pen]-NT-[W(7-Me)]-[Cit]-[Pen]-Phe[4-(2-aminoethoxy)]-[2-Nal]-[a-MeLys]-[Lys(Ac)]-N-[(D)Arg]-NH_2 (SEQ ID NO: 256);

Ac-[Pen]-NT-[W(7-Me)]-[Lys(Ac)]-[Pen]-Phe[4-(2-aminoethoxy)]-[2-Nal]-[a-MeLys]-[Lys(Ac)]-N-[(D)Phe]-NH_2 (SEQ ID NO: 258);

Ac-[Pen]-NT-[W(7-Me)]-[Cit]-[Pen]-Phe[4-(2-aminoethoxy)]-[2-Nal]-[a-MeLys]-[Lys(Ac)]-N-[(D)Tyr]-NH_2 (SEQ ID NO: 259);

Ac-[Pen]-NT-[W(7-Me)]-[Cit]-[Pen]-Phe[4-(2-aminoethoxy)]-[2-Nal]-[a-MeLys]-[Lys(Ac)]-N-S-NH_2 (SEQ ID NO: 260);

Ac-[Pen]-NT-[W(7-Me)]-[Cit]-[Pen]-Phe[4-(2-aminoethoxy)]-[2-Nal]-[a-MeLys]-[Lys(Ac)]-N-[(D)Ser]-NH_2 (SEQ ID NO: 261);

Ac-[Pen]-NT-[W(7-Me)]-[Cit]-[Pen]-Phe[4-(2-aminoethoxy)]-[2-Nal]-[a-MeLys]-[Lys(Ac)]-N-[(D)Thr]-NH_2 (SEQ ID NO: 263);

Ac-[Pen]-NT-[W(7-Me)]-[Cit]-[Pen]-Phe[4-(2-aminoethoxy)]-[2-Nal]-[a-MeLys]-[Lys(Ac)]-N-[Aib]-NH_2 (SEQ ID NO: 264);

Ac-[Pen]-NT-[W(7-Me)]-[Cit]-[Pen]-Phe[4-(2-aminoethoxy)]-[2-Nal]-[a-MeLys]-[Lys(Ac)]-[N-MeAla]-NH_2 (SEQ ID NO: 265);

Ac-[Pen]-NT-[W(7-Me)]-Q-[Pen]-Phe[4-(2-aminoethoxy)]-[2-Nal]-[a-MeLys]-[Lys(Ac)]-N-[bA]-NH_2 (SEQ ID NO: 267);

Ac-[Pen]-N-T-[W(7-Me)]-Q-[Pen]-Phe[4-(2-aminoethoxy)]-[2-Nal]-[Achc]-[Lys(Ac)]-N-[bA]-NH_2 (SEQ ID NO: 274);

Ac-[Pen]-N-T-[W(7-Me)]-Q-[Pen]-Phe[4-(2-aminoethoxy)]-[2-Nal]-[DiethylGly]-[Lys(Ac)]-N-[bA]-NH_2 (SEQ ID NO: 276);

Ac-[Pen]-N-T-[W(7-Me)]-Q-[Pen]-Phe[4-(2-aminoethoxy)]-[2-Nal]-[Acbc]-[Lys(Ac)]-N-[bA]-NH_2 (SEQ ID NO: 277);

Ac-[Pen]-N-T-[W(7-Me)]-Q-[Pen]-Phe[4-(2-aminoethoxy)]-[2-Nal]-[a-MeOrn]-[Lys(Ac)]-N-[bA]-NH_2 (SEQ ID NO: 278);

Ac-[Pen]-N-T-[W(7-Et)]-[Lys(Ac)]-[Pen]-Phe[4-(2-aminoethoxy)]-[2-Nal]-[a-MeLys]-[Lys(Ac)]-N-[(D)Leu]-NH_2 (SEQ ID NO: 284);

Ac-[Pen]-N-T-[W(7-n-Pr)]-[Lys(Ac)]-[Pen]-Phe[4-(2-aminoethoxy)]-[2-Nal]-[a-MeLys]-[Lys(Ac)]-N-[(D)Leu]-NH_2 (SEQ ID NO: 285);

Ac-[Pen]-N-T-[W(7-Me)]-[Lys(Gly)]-[Pen]-Phe[4-(2-aminoethoxy)]-[2-Nal]-[a-MeLys]-[Lys(Ac)]-N-[(D)Leu]-NH_2; (SEQ ID NO: 320); or

Ac-[Pen]-N-T-[W(7-Me)]-[Lys(Aib)]-[Pen]-Phe[4-(2-aminoethoxy)]-[2-Nal]-[a-MeLys]-[Lys(Ac)]-N-[(D)Leu]-NH_2; (SEQ ID NO: 322);

and wherein the peptide inhibitor is cyclized via a Pen-Pen disulfide bond;

or a pharmaceutically acceptable salt or solvate thereof.

[00230] In certain embodiments, the peptide comprises or is:

Ac-[Pen]-NT-[W(7-Me)]-Q-[Pen]-Phe[4-(2-aminoethoxy)]-[2-Nal]-[a-MeLys]-[Lys(Ac)]-N-[bA]-NH_2 (SEQ ID NO: 202);

Ac-[(D)Arg]-Abu-Q-T-[W(7-Me)]-Q-C-Phe[4-(2-aminoethoxy)]-[2-Nal]-[THP]-E-N-[bA]-NH_2 (SEQ ID NO: 203);

Ac-Abu-Q-T-[W(7-Me)]-Q-C-Phe[4-(2-aminoethoxy)]-[2-Nal]-[THP]-E-N-[bA]-NH_2 (SEQ ID NO: 204);

Ac-[Pen]-NT-[W(7-Me)]-Q-[Pen]-Phe[4-(2-aminoethoxy)]-[2-Nal]-[a-MeLeu]-[Lys(Ac)]-G-[bA]-NH_2 (SEQ ID NO: 205);

Ac-[Pen]-NT-[W(7-Me)]-Q-[Pen]-Phe[4-(2-aminoethoxy)]-[2-Nal]-[a-MeLeu]-[Lys(Ac)]-A-[bA]-NH_2 (SEQ ID NO: 207);

Ac-[Pen]-NT-[W(7-Me)]-Q-[Pen]-Phe[4-(2-aminoethoxy)]-[2-Nal]-[a-MeLeu]-[Lys(Ac)]-L-[bA]-NH_2 (SEQ ID NO: 208);

Ac-[Pen]-NT-[W(7-Me)]-Q-[Pen]-Phe[4-(2-aminoethoxy)]-[2-Nal]-[a-MeLeu]-[Lys(Ac)]-[(D)Ala]-[bA]-NH_2 (SEQ ID NO: 209);

Ac-[Pen]-NT-[W(7-Me)]-Q-[Pen]-Phe[4-(2-aminoethoxy)]-[2-Nal]-[a-MeLeu]-[Lys(Ac)]-H-[bA]-NH_2 (SEQ ID NO: 214);

Ac-[Pen]-NT-[W(7-Me)]-Q-[Pen]-Phe[4-(2-aminoethoxy)]-[2-Nal]-[a-MeLeu]-[Lys(Ac)]-[(D)His]-[bA]-NH_2 (SEQ ID NO: 215);

Ac-[Pen]-NT-[W(7-Me)]-Q-[Pen]-Phe[4-(2-aminoethoxy)]-[2-Nal]-[a-MeLeu]-[Lys(Ac)]-T-[bA]-NH_2 (SEQ ID NO: 217);

Ac-[Pen]-NT-[W(7-Me)]-Q-[Pen]-Phe[4-(2-aminoethoxy)]-[2-Nal]-[a-MeLeu]-[Lys(Ac)]-S-[bA]-NH_2 (SEQ ID NO: 221);

Ac-[Pen]-NT-[W(7-Me)]-Q-[Pen]-Phe[4-(2-aminoethoxy)]-[2-Nal]-[a-MeLeu]-[Lys(Ac)]-[(D)Ser]-[bA]-NH_2 (SEQ ID NO: 222);

Ac-[Pen]-NT-[W(4-Me)]-Q-[Pen]-Phe[4-(2-aminoethoxy)]-[2-Nal]-[a-MeLys]-[Lys(Ac)]-N-[bA]-NH_2 (SEQ ID NO: 231);

Ac-[Pen]-NT-[W(1-Me)]-Q-[Pen]-Phe[4-(2-aminoethoxy)]-[2-Nal]-[a-MeLys]-[Lys(Ac)]-N-[bA]-NH_2 (SEQ ID NO: 232);

Ac-[Pen]-NT-[W(7-Me)]-[a-MeLys]-[Pen]-Phe[4-(2-aminoethoxy)]-[2-Nal]-[a-MeLeu]-[Lys(Ac)]-N-[bA]-NH_2 (SEQ ID NO: 234);

Ac-[Pen]-NT-[W(7-Me)]-[a-MeLeu]-[Pen]-Phe[4-(2-aminoethoxy)]-[2-Nal]-[a-MeLys]-[Lys(Ac)]-N-[bA]-NH_2 (SEQ ID NO: 235);

Ac-[Pen]-NT-[W(7-Me)]-Q-[Pen]-Phe[4-(2-aminoethoxy)]-[2-Nal]-[a-MeLys]-[Aib]-N-[bA]-NH_2 (SEQ ID NO: 236);

Ac-[Pen]-Q-T-[W(7-Me)]-Q-[Pen]-Phe[4-(2-aminoethoxy)]-[2-Nal]-[a-MeLys]-[Lys(Ac)]-N-[bA]-NH_2 (SEQ ID NO: 237);

Ac-[Pen]-[Cit]-T-[W(7-Me)]-Q-[Pen]-Phe[4-(2-aminoethoxy)]-[2-Nal]-[a-MeLys]-[Lys(Ac)]-N-[bA]-NH_2 (SEQ ID NO: 238);

Ac-[Pen]-[Lys(Ac)]-T-[W(7-Me)]-Q-[Pen]-Phe[4-(2-aminoethoxy)]-[2-Nal]-[a-MeLys]-[Lys(Ac)]-N-[bA]-NH_2 (SEQ ID NO: 239);

Ac-[Pen]-NT-[W(7-Me)]-[Lys(Ac)]-[Pen]-Phe[4-(2-aminoethoxy)]-[2-Nal]-[a-MeLys]-[Lys(Ac)]-N-R-NH_2 (SEQ ID NO: 243);

Ac-[Pen]-NT-[W(7-Me)]-[Lys(Ac)]-[Pen]-Phe[4-(2-aminoethoxy)]-[2-Nal]-[a-MeLys]-[Lys(Ac)]-N-L-NH_2 (SEQ ID NO: 244);

Ac-[Pen]-NT-[W(7-Me)]-[Lys(Ac)]-[Pen]-Phe[4-(2-aminoethoxy)]-[2-Nal]-[a-MeLys]-[Lys(Ac)]-N-[NMeArg]-NH_2 (SEQ ID NO: 246);

Ac-[Pen]-NT-[W(7-Me)]-[Lys(Ac)]-[Pen]-Phe[4-(2-aminoethoxy)]-[2-Nal]-[a-MeLys]-[Lys(Ac)]-N-[bhPhe]-NH_2 (SEQ ID NO: 247);

Ac-[Pen]-NT-[W(7-Me)]-[Lys(Ac)]-[Pen]-Phe[4-(2-aminoethoxy)]-[2-Nal]-[a-MeLys]-[Lys(Ac)]-N-V-NH_2 (SEQ ID NO: 250);

Ac-[Pen]-NT-[W(7-Me)]-[Lys(Ac)]-[Pen]-Phe[4-(2-aminoethoxy)]-[2-Nal]-[a-MeLys]-[Lys(Ac)]-N-P-NH_2 (SEQ ID NO: 253);

Ac-[Pen]-NT-[W(7-Me)]-[Lys(Ac)]-[Pen]-Phe[4-(2-aminoethoxy)]-[2-Nal]-[a-MeLys]-[Lys(Ac)]-N-[(D)Pro]-NH_2 (SEQ ID NO: 254);

Ac-[Pen]-NT-[W(7-Me)]-[Lys(Ac)]-[Pen]-Phe[4-(2-aminoethoxy)]-[2-Nal]-[a-MeLys]-[Lys(Ac)]-N-I-NH_2 (SEQ ID NO: 255);

Ac-[Pen]-NT-[W(7-Me)]-[Cit]-[Pen]-Phe[4-(2-aminoethoxy)]-[2-Nal]-[a-MeLys]-[Lys(Ac)]-N-[(D)Phe]-NH_2 (SEQ ID NO: 257);

Ac-[Pen]-N-T-[W(7-Me)]-[Cit]-[Pen]-Phe[4-(2-aminoethoxy)]-[2-Nal]-[a-MeLys]-[Lys(Ac)]-[bA]-[bA]-NH_2 (SEQ ID NO: 268);

Ac-[Pen]-N-T-[W(7-Me)]-Q-[Pen]-Phe[4-(2-aminoethoxy)]-[2-Nal]-[a-MeLys]-[Lys(Ac)]-L-[bA]-NH_2 (SEQ ID NO: 269);

Ac-[Pen]-N-T-[W(7-Me)]-[Lys(Ac)]-[Pen]-Phe[4-(2-aminoethoxy)]-[2-Nal]-[a-MeLys]-[Lys(Ac)]-[bA]-[bA]-NH_2 (SEQ ID NO: 270);

Ac-[Pen]-N-T-[W(7-Me)]-[Lys(Ac)]-[Pen]-Phe[4-(2-aminoethoxy)]-[2-Nal]-[a-MeLys]-[Lys(Ac)]-S-[bA]-NH_2 (SEQ ID NO: 271);

Ac-[Pen]-N-T-[W(7-Me)]-[Lys(Ac)]-[Pen]-Phe[4-(2-aminoethoxy)]-[2-Nal]-[a-MeLys]-[Lys(Ac)]-H-[bA]-NH_2 (SEQ ID NO: 272);

Ac-[Pen]-N-T-[W(7-Me)]-[Lys(Ac)]-[Pen]-Phe[4-(2-aminoethoxy)]-[2-Nal]-[a-MeLys]-E-[bA]-[bA]-NH_2 (SEQ ID NO: 273);

Ac-[Pen]-N-T-[W(7-Me)]-Q-[Pen]-Phe[4-(2-aminoethoxy)]-[2-Nal]-[Spiral_Pip]-[Lys(Ac)]-N-[bA]-NH_2 (SEQ ID NO: 275);

Ac-[Pen]-N-T-[W(7-Me)]-Q-[Pen]-Phe[4-(2-aminoethoxy)]-[2-Nal]-[a-MeLys]-[Cit]-[bA]-[bA]-NH_2 (SEQ ID NO: 279);

Ac-[Pen]-N-T-[W(7-Me)]-Q-[Pen]-Phe[4-(2-aminoethoxy)]-[2-Nal]-[a-MeLys]-E-N-[bA]-NH_2 (SEQ ID NO: 282);

Ac-[Pen]-N-T-[W(7-Me)]-Q-[Pen]-Phe[4-(2-aminoethoxy)]-[W(1-Me)]-[a-MeLys]-[Lys(Ac)]-N-[bA]-NH_2 (SEQ ID NO: 283);

Ac-[Pen]-N-T-[W(7-i-Pr)]-[Lys(Ac)]-[Pen]-Phe[4-(2-aminoethoxy)]-[2-Nal]-[a-MeLys]-[Lys(Ac)]-N-[(D)Leu]-NH_2 (SEQ ID NO: 286);

Ac-[Pen]-N-T-[W(7-OMe)]-[Lys(Ac)]-[Pen]-Phe[4-(2-aminoethoxy)]-[2-Nal]-[a-MeLys]-[Lys(Ac)]-N-[(D)Leu]-NH_2 (SEQ ID NO: 288);

Ac-[Pen]-N-T-[W(7-Me)]-[Lys(Ac)]-[Pen]-[2-Nal]-[2-Nal]-[a-MeLys]-[Lys(Ac)]-N-[(D)Leu]-NH_2 (SEQ ID NO: 289);

Ac-[Pen]-N-T-[W(7-Me)]-[Lys(Ac)]-[Pen]-H-[2-Nal]-[a-MeLys]-[Lys(Ac)]-N-[(D)Leu]-NH_2 (SEQ ID NO: 290);

Ac-[Pen]-N-T-[W(7-OMe)]-Q-[Pen]-Phe[4-(2-aminoethoxy)]-[2-Nal]-[a-MeLys]-[Lys(Ac)]-N-[(D)Lys]-NH_2 (SEQ ID NO: 297);

Ac-[Pen]-N-T-[W(7-OMe)]-[Lys(Ac)]-[Pen]-Phe[4-(2-aminoethoxy)]-[2-Nal]-[a-MeLys]-[Lys(Ac)]-N-[(D)Lys]-NH_2 (SEQ ID NO: 299);

Ac-[Pen]-N-T-[W(7-Me)]-[Lys(Ala)]-[Pen]-Phe[4-(2-aminoethoxy)]-[2-Nal]-[a-MeLys]-[Lys(Ac)]-N-[(D)Leu]-NH_2; (SEQ ID NO: 314);

Ac-[Pen]-N-T-[W(7-Me)]-[Lys(IVA)]-[Pen]-Phe[4-(2-aminoethoxy)]-[2-Nal]-[a-MeLys]-[Lys(Ac)]-N-[(D)Leu]-NH_2; (SEQ ID NO: 315);

Ac-[Pen]-N-T-[W(7-Me)]-[Lys(cyclohexanoic)]-[Pen]-Phe[4-(2-aminoethoxy)]-[2-Nal]-[a-MeLys]-[Lys(Ac)]-N-[(D)Leu]-NH_2; (SEQ ID NO: 316);

Ac-[Pen]-N-T-[W(7-Me)]-[Lys(bAla)]-[Pen]-Phe[4-(2-aminoethoxy)]-[2-Nal]-[a-MeLys]-[Lys(Ac)]-N-[(D)Leu]-NH_2; (SEQ ID NO: 321);

Ac-[(D)Arg]-[Abu]-Q-T-[W(7-Me)]-[Lys(Ac)]-[Cys]-Phe[4-(2-aminoethoxy)]-[2-Nal]-[a-MeLys]-[Lys(Ac)]-N-[(D)Lys]-[Sarc]-NH_2; (SEQ ID NO: 323); or

Ac-[(D)Arg]-[Abu]-Q-T-[W(7-Me)]-[Lys(Ac)]-[Cys]-Phe[4-(2-aminoethoxy)]-[2-Nal]-[a-MeLys]-[Lys(Ac)]-N-[(D)Leu]-NH_2; (SEQ ID NO: 325);

and wherein the peptide inhibitor is cyclized via a Pen-Pen disulfide bond;

or a pharmaceutically acceptable salt or solvate thereof.

[00231] In certain embodiments, the peptide comprises or is:

Ac-[Pen]-N-T-[W(7-Me)]-[Lys(trifluoropropionic)]-[Pen]-Phe[4-(2-aminoethoxy)]-[2-Nal]-[a-MeLys]-[Lys(Ac)]-N-[(D)Leu]-NH_2 (SEQ ID NO: 319);

Ac-[Pen]-N-T-[W(7-Me)]-[Lys(Gly)]-[Pen]-Phe[4-(2-aminoethoxy)]-[2-Nal]-[a-MeLys]-[Lys(Ac)]-N-[(D)Leu]-NH_2 (SEQ ID NO: 320);

Ac-[Pen]-N-T-[W(7-Me)]-[Lys(Aib)]-[Pen]-Phe[4-(2-aminoethoxy)]-[2-Nal]-[a-MeLys]-[Lys(Ac)]-N-[(D)Leu]-NH_2 (SEQ ID NO: 322);

Ac-[Pen]-[Lys(Ac)]-T-[W(7-Me)]-[Lys(Ac)]-[Pen]-Phe[4-(2-aminoethoxy)]-[2-Nal]-[a-MeLys]-[Lys(Ac)]-N-[(D)Leu]-NH_2 (SEQ ID NO: 330);

Ac-[Pen]-[Dab(Ac)]-T-[W(7-Me)]-[Lys(Ac)]-[Pen]-Phe[4-(2-aminoethoxy)]-[2-Nal]-[a-MeLys]-[Lys(Ac)]-N-[(D)Leu]-NH_2 (SEQ ID NO: 335);

Ac-[Pen]-[(D)Asn]-T-[W(7-Me)]-[Lys(Ac)]-[Pen]-Phe[4-(2-aminoethoxy)]-[2-Nal]-[a-MeLys]-[Lys(Ac)]-N-[(D)Leu]-NH_2 (SEQ ID NO: 338);

Ac-[Pen]-N-T-[W(7-Me)]-[Cit]-[Pen]-Phe[4-(2-aminoethoxy)]-[2-Nal]-[a-MeLys]-[Lys(Ac)]-N-[Sarc]-NH_2 (SEQ ID NO: 339);

Ac-[Pen]-N-T-[W(7-Me)]-[Cit]-[Pen]-Phe[4-(2-aminoethoxy)]-[2-Nal]-[a-MeLys]-[Lys(Ac)]-N-[Aib]-[bA]-NH_2 (SEQ ID NO: 340);

Ac-[Pen]-N-T-[W(7-Me)]-[Cit]-[Pen]-Phe[4-(2-aminoethoxy)]-[2-Nal]-[a-MeLys]-[Lys(Ac)]-N-[Aib]-G-NH_2 (SEQ ID NO: 341);

Ac-[Pen]-N-T-[W(7-Me)]-[Cit]-[Pen]-Phe[4-(2-aminoethoxy)]-[2-Nal]-[a-MeLys]-[Lys(Ac)]-N-[Aib]-A-NH_2 (SEQ ID NO: 342);

Ac-[Pen]-N-T-[W(7-Me)]-[Cit]-[Pen]-Phe[4-(2-aminoethoxy)]-[2-Nal]-[a-MeLys]-[Lys(Ac)]-N-[Aib]-[(D)Lys]-NH_2 (SEQ ID NO: 344);

Ac-[Pen]-N-T-[W(7-Me)]-[Cit]-[Pen]-Phe[4-(2-aminoethoxy)]-[2-Nal]-[a-MeLys]-[Lys(Ac)]-N-[Aib]-[(D)Phe]-NH_2 (SEQ ID NO: 346); or

Ac-[Pen]-N-T-[W(7-Me)]-[Cit]-[Pen]-Phe[4-(2-aminoethoxy)]-[2-Nal]-[a-MeLys]-[Lys(Ac)]-N-[Aib]-[(D)Tyr]-NH_2 (SEQ ID NO: 347);

and wherein the peptide inhibitor is cyclized via a Pen-Pen disulfide bond;

or a pharmaceutically acceptable salt or solvate thereof.

[00232] In certain embodiments, the peptide comprises or is Ac-[Pen]-NT-[W(5-F)]-Gln-[Pen]-[Phe[4-(2-aminoethoxy)]-[2-Nal]-[α-MeLeu]-[Lys(Ac)]-NN-NH_2 (SEQ ID NO: 7).

[00233] In certain embodiments, the peptide comprises or is Ac-[Pen]-NTW-Gln-[Pen]-[Phe[4-(2-aminoethoxy)]-W(5-OH)-[α-MeLeu]-[Lys(Ac)]-NN-NH_2 (SEQ ID NO: 21).

[00234] In certain embodiments, the peptide comprises or is:

Ac-[Pen]-NT-[W(7-Me)]-Q-[Pen]-Phe[4-(2-aminoethoxy)]-[2-Nal]-[a-MeLeu]-[Lys(Ac)]-N-[bA]-NH_2 (SEQ ID NO: 201);

Ac-[Pen]-NT-[W(7-Me)]-[Cit]-[Pen]-Phe[4-(2-aminoethoxy)]-[2-Nal]-[a-MeLeu]-[Lys(Ac)]-N-[bA]-NH_2 (SEQ ID NO: 227);

Ac-[Pen]-NT-[W(7-Me)]-[Lys(Ac)]-[Pen]-Phe[4-(2-aminoethoxy)]-[2-Nal]-[a-MeLys]-[Lys(Ac)]-N-[bA]-NH_2 (SEQ ID NO: 242);

Ac-[Pen]-NT-[W(7-Me)]-[Lys(Ac)]-[Pen]-Phe[4-(2-aminoethoxy)]-[2-Nal]-[a-MeLys]-[Lys(Ac)]-N-[(D)Leu]-NH_2 (SEQ ID NO: 245);

Ac-[Pen]-NT-[W(7-Me)]-[Lys(Ac)]-[Pen]-Phe[4-(2-aminoethoxy)]-[2-Nal]-[a-MeLys]-[Lys(Ac)]-N-[Cit]-NH_2 (SEQ ID NO: 249);

Ac-[Pen]-NT-[W(7-Me)]-[Lys(Ac)]-[Pen]-Phe[4-(2-aminoethoxy)]-[2-Nal]-[a-MeLys]-[Lys(Ac)]-N-[(D)Lys]-NH_2 (SEQ ID NO: 252);

Ac-[Pen]-NT-[W(7-Me)]-Q-[Pen]-Phe[4-(2-aminoethoxy)]-[2-Nal]-[a-MeLys]-[Lys(Ac)]-N-[bA]-NH_2 (SEQ ID NO: 267);

Ac-[Pen]-N-T-[W(7-Et)]-[Lys(Ac)]-[Pen]-Phe[4-(2-aminoethoxy)]-[2-Nal]-[a-MeLys]-[Lys(Ac)]-N-[(D)Leu]-NH_2 (SEQ ID NO: 284);

Ac-[Pen]-N-T-[W(7-n-Pr)]-[Lys(Ac)]-[Pen]-Phe[4-(2-aminoethoxy)]-[2-Nal]-[a-MeLys]-[Lys(Ac)]-N-[(D)Leu]-NH_2 (SEQ ID NO: 285);

Ac-[Pen]-N-T-[W(7-Me)]-[Lys(Gly)]-[Pen]-Phe[4-(2-aminoethoxy)]-[2-Nal]-[a-MeLys]-[Lys(Ac)]-N-[(D)Leu]-NH_2; (SEQ ID NO: 320); or

Ac-[Pen]-N-T-[W(7-Me)]-[Lys(Aib)]-[Pen]-Phe[4-(2-aminoethoxy)]-[2-Nal]-[a-MeLys]-[Lys(Ac)]-N-[(D)Leu]-NH_2; (SEQ ID NO: 322);

and wherein the peptide inhibitor is cyclized via a Pen-Pen disulfide bond; or via an Abu-C thioether bond;

or a pharmaceutically acceptable salt or solvate thereof.

[00235] In certain embodiments, the peptide comprises or is:

Ac-[Pen]-NT-[W(7-Me)]-Q-[Pen]-Phe[4-(2-aminoethoxy)]-[2-Nal]-[a-MeLys]-[Lys(Ac)]-N-[bA]-NH_2 (SEQ ID NO: 202);

Ac-[(D)Arg]-Abu-Q-T-[W(7-Me)]-Q-C-Phe[4-(2-aminoethoxy)]-[2-Nal]-[THP]-E-N-[bA]-NH_2 (SEQ ID NO: 203);

Ac-Abu-Q-T-[W(7-Me)]-Q-C-Phe[4-(2-aminoethoxy)]-[2-Nal]-[THP]-E-N-[bA]-NH_2 (SEQ ID NO: 204);

Ac-[Pen]-NT-[W(7-Me)]-Q-[Pen]-Phe[4-(2-aminoethoxy)]-[2-Nal]-[a-MeLeu]-[Lys(Ac)]-G-[bA]-NH_2 (SEQ ID NO: 205);

Ac-[Pen]-NT-[W(7-Me)]-Q-[Pen]-Phe[4-(2-aminoethoxy)]-[2-Nal]-[a-MeLeu]-[Lys(Ac)]-A-[bA]-NH_2 (SEQ ID NO: 207);

Ac-[Pen]-NT-[W(7-Me)]-Q-[Pen]-Phe[4-(2-aminoethoxy)]-[2-Nal]-[a-MeLeu]-[Lys(Ac)]-L-[bA]-NH_2 (SEQ ID NO: 208);

Ac-[Pen]-NT-[W(7-Me)]-Q-[Pen]-Phe[4-(2-aminoethoxy)]-[2-Nal]-[a-MeLeu]-[Lys(Ac)]-[(D)Ala]-[bA]-NH_2 (SEQ ID NO: 209);

Ac-[Pen]-NT-[W(7-Me)]-Q-[Pen]-Phe[4-(2-aminoethoxy)]-[2-Nal]-[a-MeLeu]-[Lys(Ac)]-H-[bA]-NH_2 (SEQ ID NO: 214);

Ac-[Pen]-NT-[W(7-Me)]-Q-[Pen]-Phe[4-(2-aminoethoxy)]-[2-Nal]-[a-MeLeu]-[Lys(Ac)]-T-[bA]-NH_2 (SEQ ID NO: 217);

Ac-[Pen]-NT-[W(7-Me)]-Q-[Pen]-Phe[4-(2-aminoethoxy)]-[2-Nal]-[a-MeLeu]-[Lys(Ac)]-S-[bA]-NH_2 (SEQ ID NO: 221);

Ac-[Pen]-NT-[W(7-Me)]-Q-[Pen]-Phe[4-(2-aminoethoxy)]-[2-Nal]-[a-MeLeu]-[Lys(Ac)]-[(D)Ser]-[bA]-NH_2 (SEQ ID NO: 222);

Ac-[Pen]-NT-[W(4-Me)]-Q-[Pen]-Phe[4-(2-aminoethoxy)]-[2-Nal]-[a-MeLys]-[Lys(Ac)]-N-[bA]-NH_2 (SEQ ID NO: 231);

Ac-[Pen]-NT-[W(1-Me)]-Q-[Pen]-Phe[4-(2-aminoethoxy)]-[2-Nal]-[a-MeLys]-[Lys(Ac)]-N-[bA]-NH_2 (SEQ ID NO: 232);

Ac-[Pen]-NT-[W(7-Me)]-[a-MeLys]-[Pen]-Phe[4-(2-aminoethoxy)]-[2-Nal]-[a-MeLeu]-[Lys(Ac)]-N-[bA]-NH_2 (SEQ ID NO: 234);

Ac-[Pen]-NT-[W(7-Me)]-[a-MeLeu]-[Pen]-Phe[4-(2-aminoethoxy)]-[2-Nal]-[a-MeLys]-[Lys(Ac)]-N-[bA]-NH_2 (SEQ ID NO: 235);

Ac-[Pen]-NT-[W(7-Me)]-Q-[Pen]-Phe[4-(2-aminoethoxy)]-[2-Nal]-[a-MeLys]-[Aib]-N-[bA]-NH_2 (SEQ ID NO: 236);

Ac-[Pen]-Q-T-[W(7-Me)]-Q-[Pen]-Phe[4-(2-aminoethoxy)]-[2-Nal]-[a-MeLys]-[Lys(Ac)]-N-[bA]-NH_2 (SEQ ID NO: 237);

Ac-[Pen]-[Cit]-T-[W(7-Me)]-Q-[Pen]-Phe[4-(2-aminoethoxy)]-[2-Nal]-[a-MeLys]-[Lys(Ac)]-N-[bA]-NH_2 (SEQ ID NO: 238);

Ac-[Pen]-[Lys(Ac)]-T-[W(7-Me)]-Q-[Pen]-Phe[4-(2-aminoethoxy)]-[2-Nal]-[a-MeLys]-[Lys(Ac)]-N-[bA]-NH_2 (SEQ ID NO: 239);

Ac-[Pen]-NT-[W(7-Me)]-[Lys(Ac)]-[Pen]-Phe[4-(2-aminoethoxy)]-[2-Nal]-[a-MeLys]-[Lys(Ac)]-N-L-NH_2 (SEQ ID NO: 244);

Ac-[Pen]-N-T-[W(7-Me)]-[Cit]-[Pen]-Phe[4-(2-aminoethoxy)]-[2-Nal]-[a-MeLys]-[Lys(Ac)]-[bA]-[bA]-NH_2 (SEQ ID NO: 268);

Ac-[Pen]-N-T-[W(7-Me)]-Q-[Pen]-Phe[4-(2-aminoethoxy)]-[2-Nal]-[a-MeLys]-[Lys(Ac)]-L-[bA]-NH_2 (SEQ ID NO: 269);

Ac-[Pen]-N-T-[W(7-Me)]-[Lys(Ac)]-[Pen]-Phe[4-(2-aminoethoxy)]-[2-Nal]-[a-MeLys]-[Lys(Ac)]-[bA]-[bA]-NH_2 (SEQ ID NO: 270);

Ac-[Pen]-N-T-[W(7-Me)]-[Lys(Ac)]-[Pen]-Phe[4-(2-aminoethoxy)]-[2-Nal]-[a-MeLys]-[Lys(Ac)]-S-[bA]-NH_2 (SEQ ID NO: 271);

Ac-[Pen]-N-T-[W(7-Me)]-[Lys(Ac)]-[Pen]-Phe[4-(2-aminoethoxy)]-[2-Nal]-[a-MeLys]-[Lys(Ac)]-H-[bA]-NH_2 (SEQ ID NO: 272);

Ac-[Pen]-N-T-[W(7-Me)]-[Lys(Ac)]-[Pen]-Phe[4-(2-aminoethoxy)]-[2-Nal]-[a-MeLys]-E-[bA]-[bA]-NH_2 (SEQ ID NO: 273);

Ac-[Pen]-N-T-[W(7-Me)]-Q-[Pen]-Phe[4-(2-aminoethoxy)]-[2-Nal]-[a-MeLys]-[Cit]-[bA]-[bA]-NH_2 (SEQ ID NO: 279);

Ac-[Pen]-N-T-[W(7-Me)]-Q-[Pen]-Phe[4-(2-aminoethoxy)]-[2-Nal]-[a-MeLys]-E-N-[bA]-NH_2 (SEQ ID NO: 282);

Ac-[Pen]-N-T-[W(7-Me)]-Q-[Pen]-Phe[4-(2-aminoethoxy)]-[W(1-Me)]-[a-MeLys]-[Lys(Ac)]-N-[bA]-NH_2 (SEQ ID NO: 283);

Ac-[Pen]-N-T-[W(7-i-Pr)]-[Lys(Ac)]-[Pen]-Phe[4-(2-aminoethoxy)]-[2-Nal]-[a-MeLys]-[Lys(Ac)]-N-[(D)Leu]-NH_2 (SEQ ID NO: 286);

Ac-[Pen]-N-T-[W(7-OMe)]-[Lys(Ac)]-[Pen]-Phe[4-(2-aminoethoxy)]-[2-Nal]-[a-MeLys]-[Lys(Ac)]-N-[(D)Leu]-NH_2 (SEQ ID NO: 288);

Ac-[Pen]-N-T-[W(7-OMe)]-Q-[Pen]-Phe[4-(2-aminoethoxy)]-[2-Nal]-[a-MeLys]-[Lys(Ac)]-N-[(D)Lys]-NH_2 (SEQ ID NO: 297);

Ac-[Pen]-N-T-[W(7-OMe)]-[Lys(Ac)]-[Pen]-Phe[4-(2-aminoethoxy)]-[2-Nal]-[a-MeLys]-[Lys(Ac)]-N-[(D)Lys]-NH_2 (SEQ ID NO: 299);

Ac-[Pen]-N-T-[W(7-Me)]-[Lys(Ala)]-[Pen]-Phe[4-(2-aminoethoxy)]-[2-Nal]-[a-MeLys]-[Lys(Ac)]-N-[(D)Leu]-NH_2; (SEQ ID NO: 314);

Ac-[Pen]-N-T-[W(7-Me)]-[Lys(IVA)]-[Pen]-Phe[4-(2-aminoethoxy)]-[2-Nal]-[a-MeLys]-[Lys(Ac)]-N-[(D)Leu]-NH_2; (SEQ ID NO: 315);

Ac-[Pen]-N-T-[W(7-Me)]-[Lys(cyclohexanoic)]-[Pen]-Phe[4-(2-aminoethoxy)]-[2-Nal]-[a-MeLys]-[Lys(Ac)]-N-[(D)Leu]-NH_2; (SEQ ID NO: 316);

Ac-[Pen]-N-T-[W(7-Me)]-[Lys(bAla)]-[Pen]-Phe[4-(2-aminoethoxy)]-[2-Nal]-[a-MeLys]-[Lys(Ac)]-N-[(D)Leu]-NH_2; (SEQ ID NO: 321); or

Ac-[(D)Arg]-[Abu]-Q-T-[W(7-Me)]-[Lys(Ac)]-[Cys]-Phe[4-(2-aminoethoxy)]-[2-Nal]-[a-MeLys]-[Lys(Ac)]-N-[(D)Leu]-NH_2; (SEQ ID NO: 325);

and wherein the peptide inhibitor is cyclized via a Pen-Pen disulfide bond; or via a Abu-C thioether bond;

or a pharmaceutically acceptable salt or solvate thereof.

[00236] In certain embodiments, any of the Phe[4-(2-aminoethoxy)] residues present in a peptide inhibitor described herein may be substituted by Phe[4-(2-acetylaminoethoxy)].

[00237] In additional embodiments, the present invention includes peptide inhibitors that comprise a peptide comprising a variant of any of the sequences of Formulas (I)-(XII), or shown in Table E1, Table E2, or Table E3, which comprises an isostere replacement of one or more amino acid residues of X4-X15. In particular embodiments, the isostere replacement is a conservative amino acid substitution, and in certain embodiments, the isostere replacement is a substitution with an analog of an amino acid.

[00238] In additional embodiments, the present invention includes peptide inhibitors that comprise a peptide comprising a variant of any of the sequences of Formulas (I)-(XII), or shown in Table E1, Table E2, or Table E3, which comprises different amino acid residues (or chemical entities) at one or both of amino acid residues X4 and X9, but wherein the amino acid residues at X4 and X9 are capable of binding each other, e.g., to form an intramolecule bond or triazole ring within the peptide. In particular embodiments, the bond is a disulfide bond, a thioether bond, a lactam bond, a triazole ring, a selenoether bond, a diselenide bond, or an olefin bond

[00239] In a particular embodiment, the peptide inhibitor comprises or consists of: Ac-[Pen]-NT-[W(6-Cl)]-Q-[Pen]-Phe[4-(2-aminoethoxy)]-[2-Nal]-[a-MeLys]-[Lys(Ac)]-N-[bA]-NH_2 (SEQ ID NO: 228).

[00240] In a particular embodiment, the peptide inhibitor comprises or consists of: Ac-[Pen]-NT-[W(1-Me)]-Q-[Pen]-Phe[4-(2-aminoethoxy)]-[2-Nal]-[a-MeLys]-[Lys(Ac)]-N-[bA]-NH_2 (SEQ ID NO: 232).

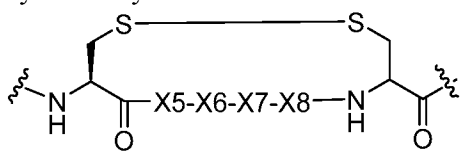
[00241] In a particular embodiment, the peptide inhibitor comprises or consists of:

[00242] Ac-[Pen]-[Cit]-T-[W(7-Me)]-Q-[Pen]-Phe[4-(2-aminoethoxy)]-[2-Nal]-[a-MeLys]-[Lys(Ac)]-N-[bA]-NH_2 (SEQ ID NO: 238)

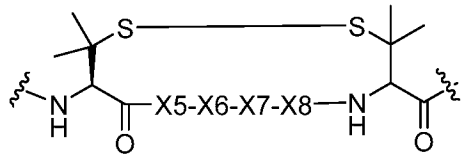
[00243] In a particular embodiment, the peptide inhibitor comprises or consists of: Ac-[Pen]-[Lys(Ac)]-T-[W(7-Me)]-Q-[Pen]-Phe[4-(2-aminoethoxy)]-[2-Nal]-[a-MeLys]-[Lys(Ac)]-N-[bA]-NH_2 (SEQ ID NO: 239)

<u>Representative disulfide and thioether bonds</u>

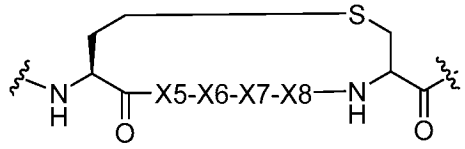
[00244] In one embodiment, the Cys and Cys disulfide bond is as shown below:



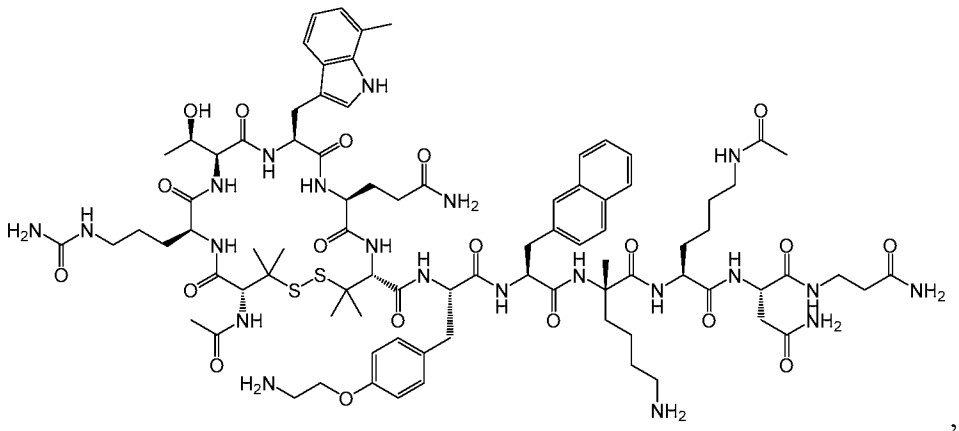
[00245] In one embodiment, the Pen and Pen disulfide bond is as shown below:



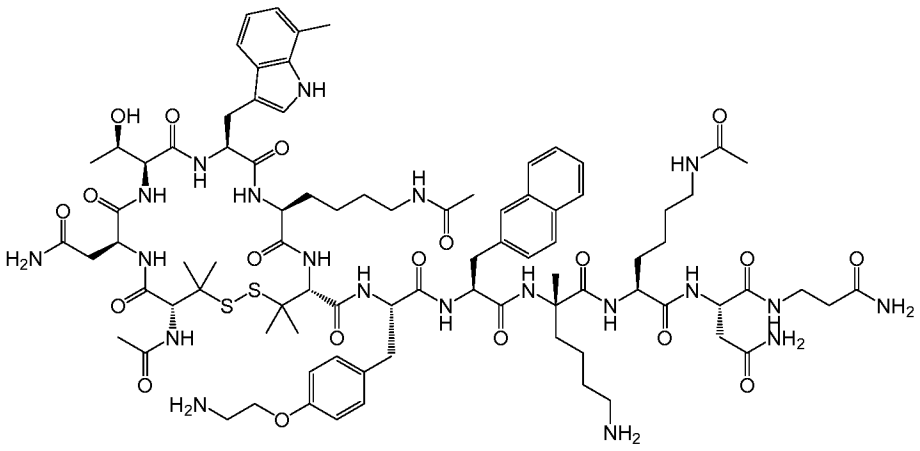
[00246] In one embodiment, the Abu and Cys thioether bond is as shown below:



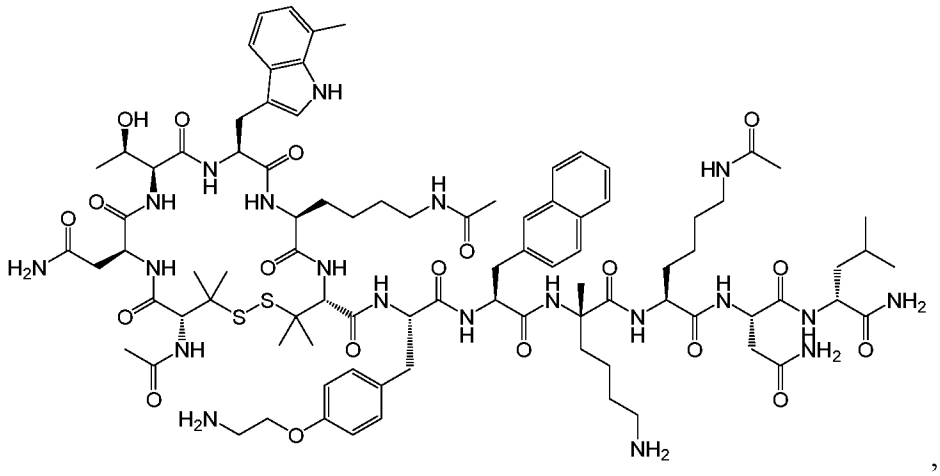
[00247] In a particular embodiment, the peptide inhibitor comprises or consists of: Ac-[Pen]-[Cit]-T-[W(7-Me)]-Q-[Pen]-Phe[4-(2-aminoethoxy)]-[2-Nal]-[a-MeLys]-[Lys(Ac)]-N-[bA]-NH_2 (SEQ ID NO: 238)



Ac-[Pen]-NT-[W(7-Me)]-[Lys(Ac)]-[Pen]-Phe[4-(2-aminoethoxy)]-[2-Nal]-[a-MeLys]-[Lys(Ac)]-N-[bA]-NH_2 (SEQ ID NO: 242)

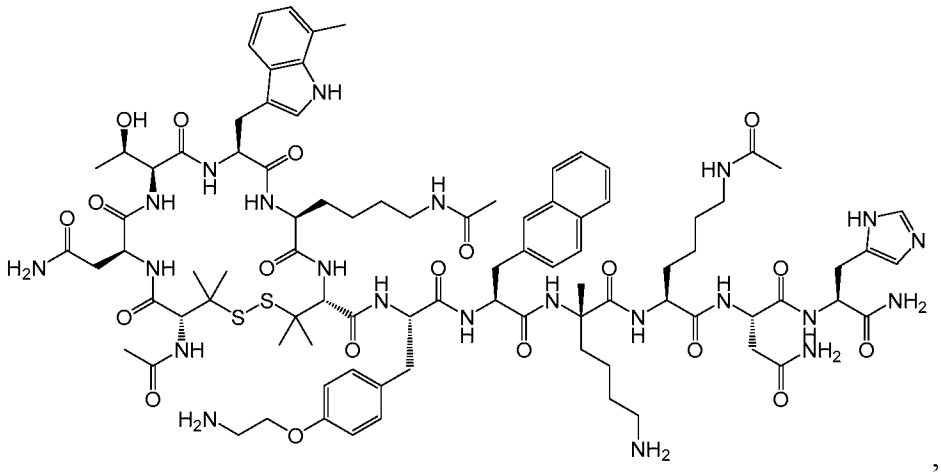


Ac-[Pen]-NT-[W(7-Me)]-[Lys(Ac)]-[Pen]-Phe[4-(2-aminoethoxy)]-[2-Nal]-[a-MeLys]-[Lys(Ac)]-N-[(D)Leu]-NH_2 (SEQ ID NO: 245)



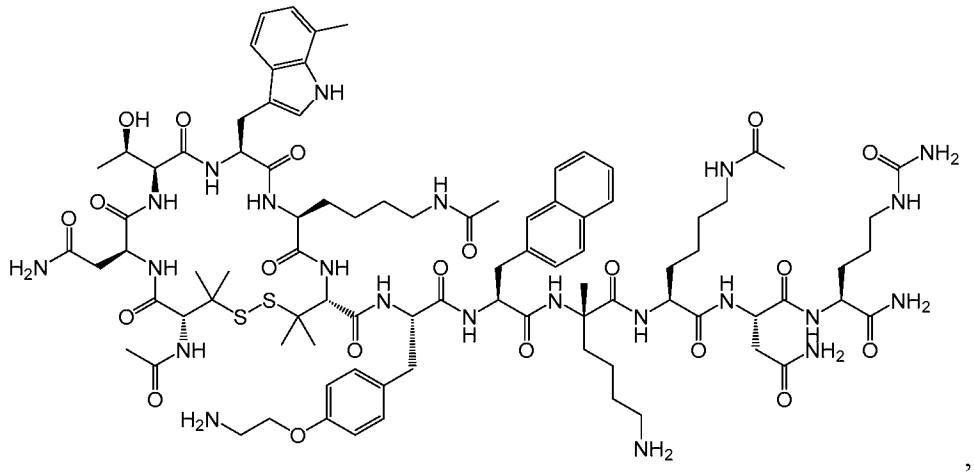
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Ac-[Pen]-NT-[W(7-Me)]-[Lys(Ac)]-[Pen]-Phe[4-(2-aminoethoxy)]-[2-Nal]-[a-MeLys]-[Lys(Ac)]-N-H-NH_2 (SEQ ID NO: 248)

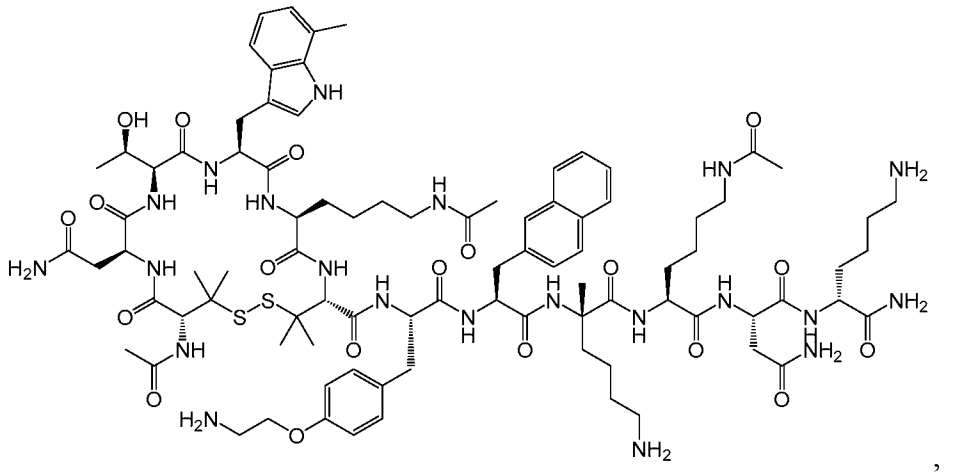


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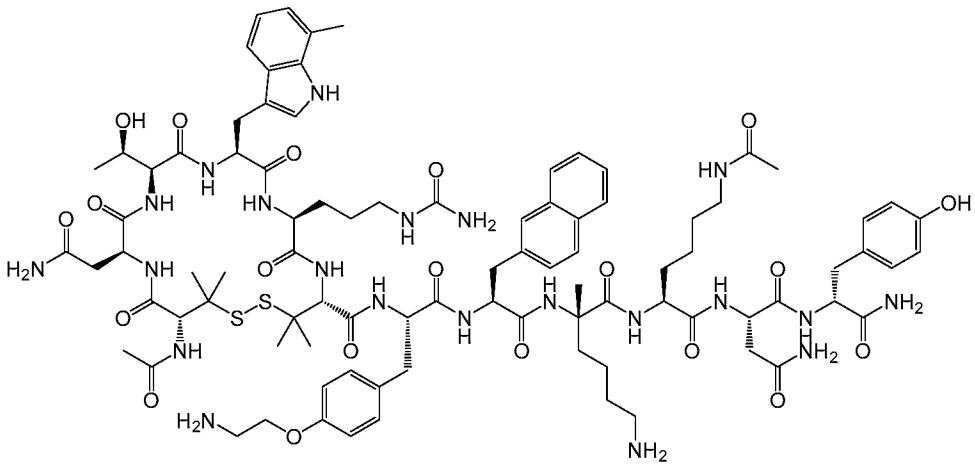
Ac-[Pen]-NT-[W(7-Me)]-[Lys(Ac)]-[Pen]-Phe[4-(2-aminoethoxy)]-[2-Nal]-[a-MeLys]-[Lys(Ac)]-N-[Cit]-NH_2 (SEQ ID NO: 249)



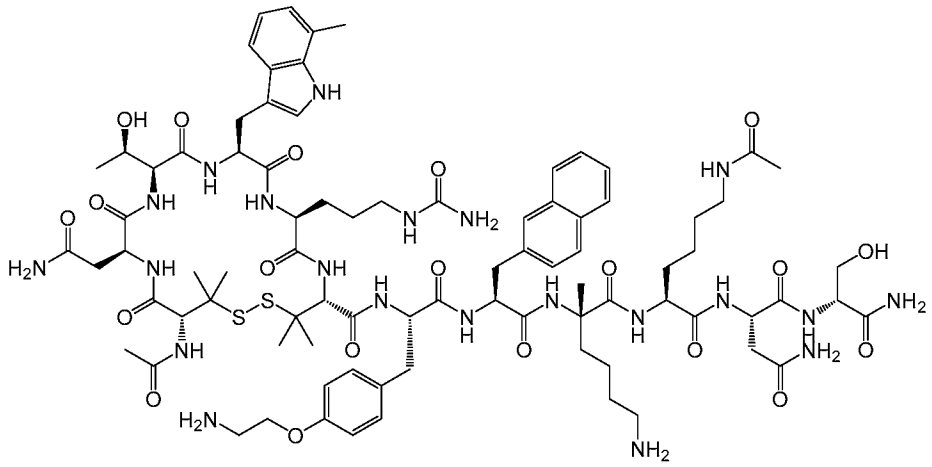
Ac-[Pen]-NT-[W(7-Me)]-[Lys(Ac)]-[Pen]-Phe[4-(2-aminoethoxy)]-[2-Nal]-[a-MeLys]-[Lys(Ac)]-N-[(D)Lys]-NH_2 (SEQ ID NO: 252)



Ac-[Pen]-NT-[W(7-Me)]-[Cit]-[Pen]-Phe[4-(2-aminoethoxy)]-[2-Nal]-[a-MeLys]-[Lys(Ac)]-N-[(D)Tyr]-NH_2 (SEQ ID NO: 259)

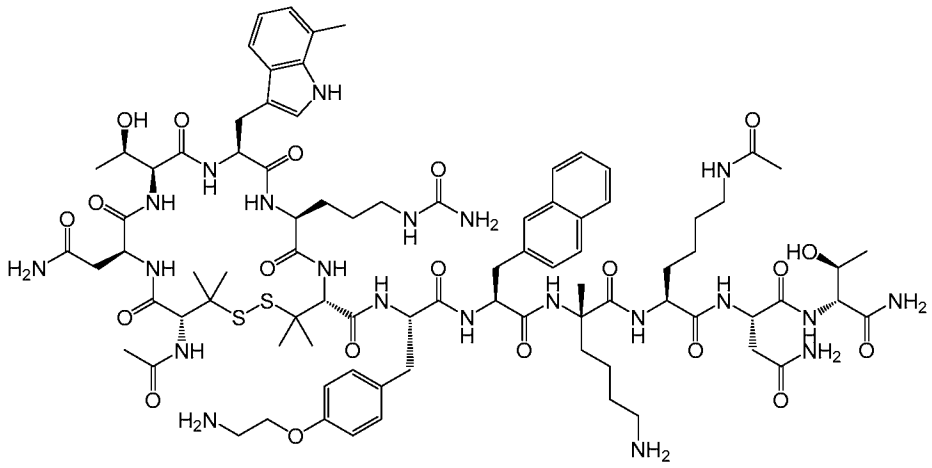


Ac-[Pen]-NT-[W(7-Me)]-[Cit]-[Pen]-Phe[4-(2-aminoethoxy)]-[2-Nal]-[a-MeLys]-[Lys(Ac)]-N-[(D)Ser]-NH_2 (SEQ ID NO: 261)



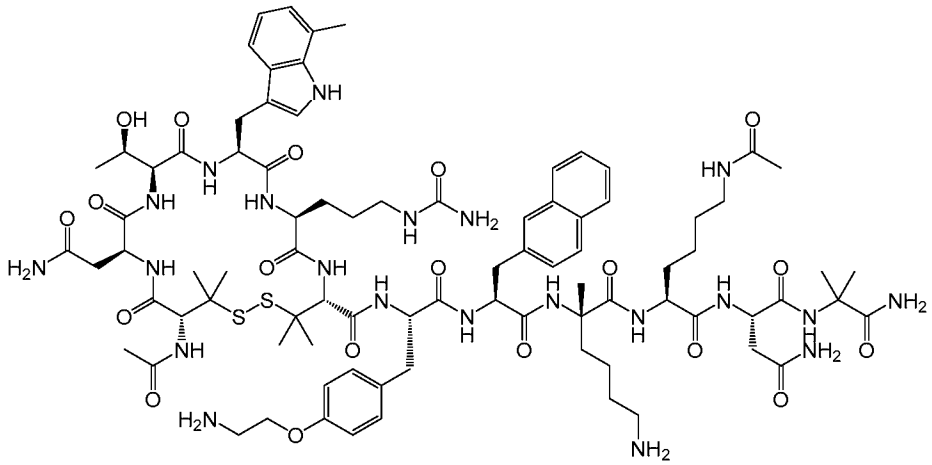
,

Ac-[Pen]-NT-[W(7-Me)]-[Cit]-[Pen]-Phe[4-(2-aminoethoxy)]-[2-Nal]-[a-MeLys]-[Lys(Ac)]-N-[(D)Thr]-NH_2 (SEQ ID NO: 263)



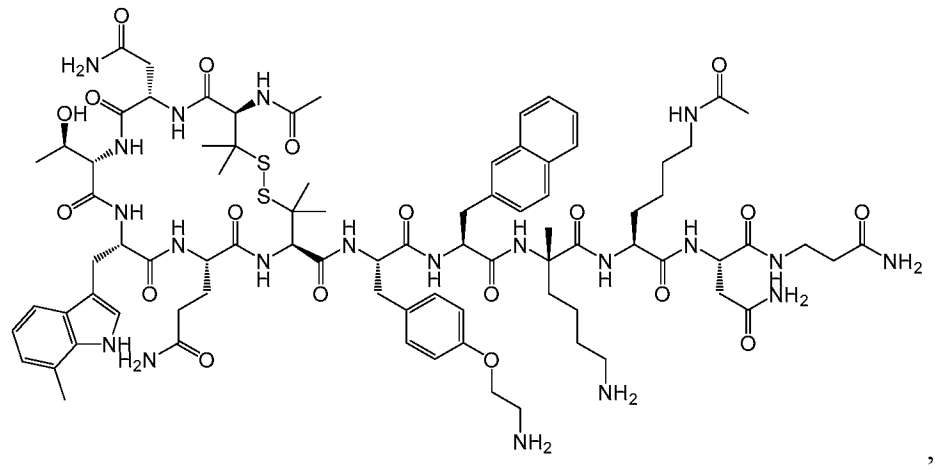
,

Ac-[Pen]-NT-[W(7-Me)]-[Cit]-[Pen]-Phe[4-(2-aminoethoxy)]-[2-Nal]-[a-MeLys]-[Lys(Ac)]-N-[Aib]-NH_2 (SEQ ID NO: 264)



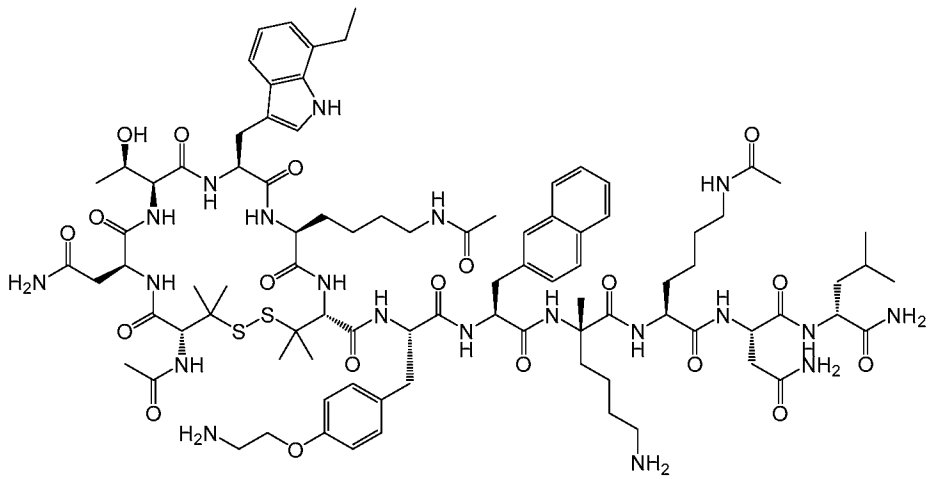
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Ac-[Pen]-NT-[W(7-Me)]-Q-[Pen]-Phe[4-(2-aminoethoxy)]-[2-Nal]-[a-MeLys]-[Lys(Ac)]-N-[bA]-NH_2 (SEQ ID NO: 267)



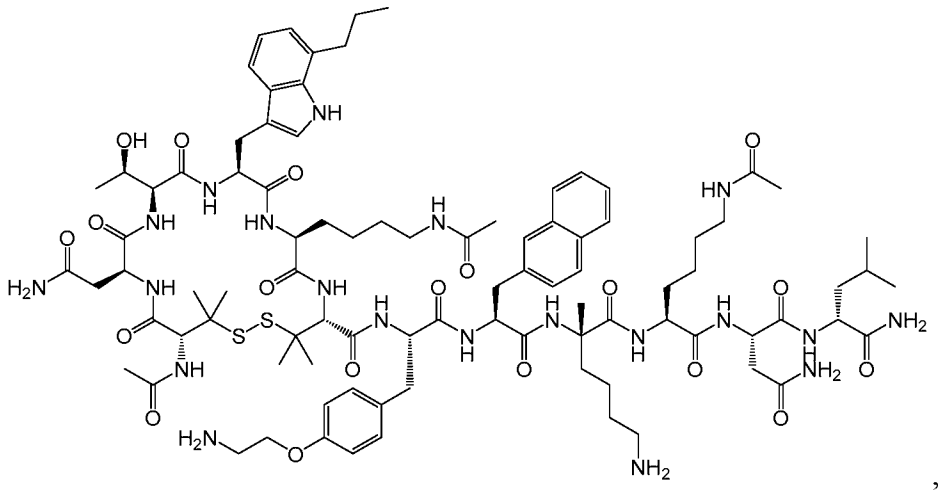
,

Ac-[Pen]-N-T-[W(7-Et)]-[Lys(Ac)]-[Pen]-Phe[4-(2-aminoethoxy)]-[2-Nal]-[a-MeLys]-[Lys(Ac)]-N-[(D)Leu]-NH_2 (SEQ ID NO: 284)



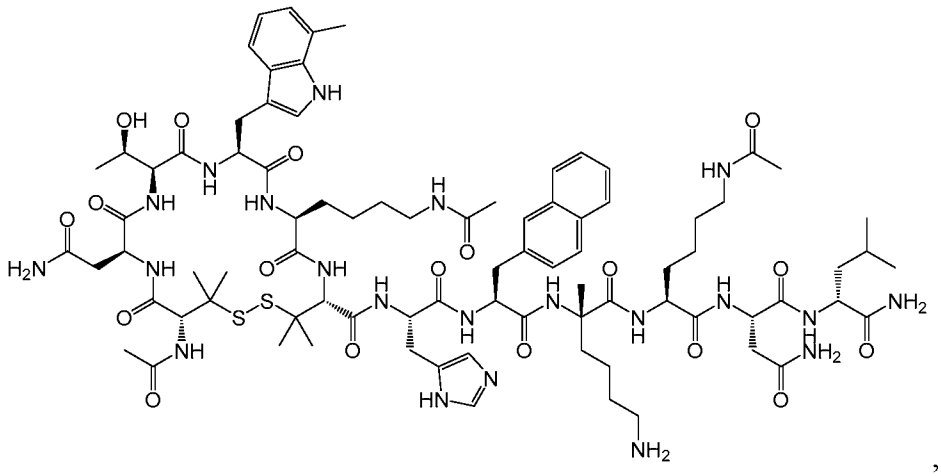
,

Ac-[Pen]-N-T-[W(7-n-Pr)]-[Lys(Ac)]-[Pen]-Phe[4-(2-aminoethoxy)]-[2-Nal]-[a-MeLys]-[Lys(Ac)]-N-[(D)Leu]-NH_2 (SEQ ID NO: 285)



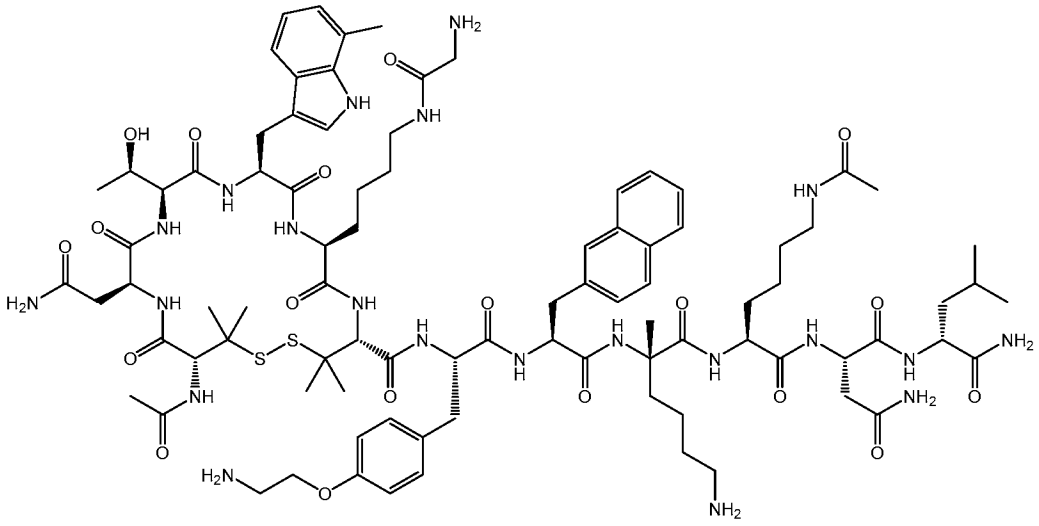
,

Ac-[Pen]-N-T-[W(7-Me)]-[Lys(Ac)]-[Pen]-H-[2-Nal]-[a-MeLys]-[Lys(Ac)]-N-[(D)Leu]-NH_2 (SEQ ID NO: 290)

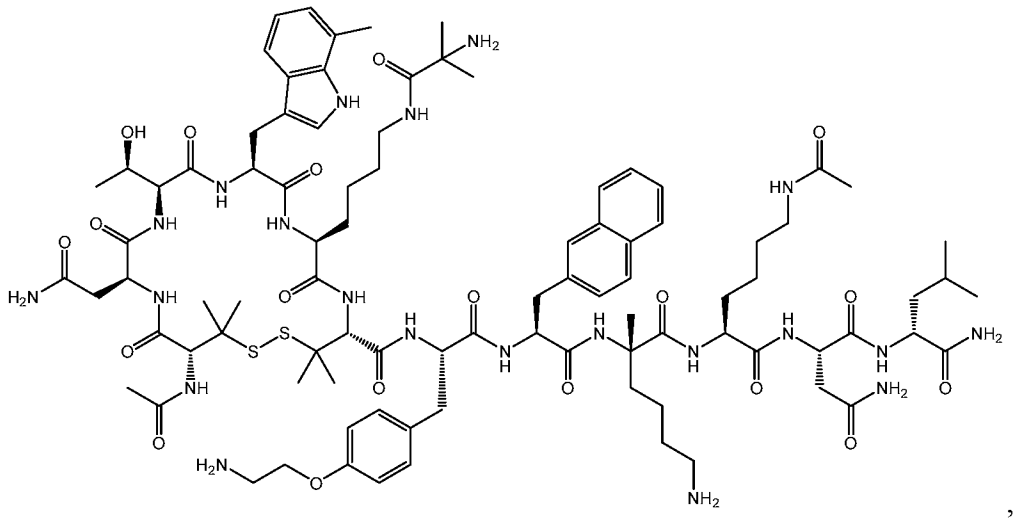


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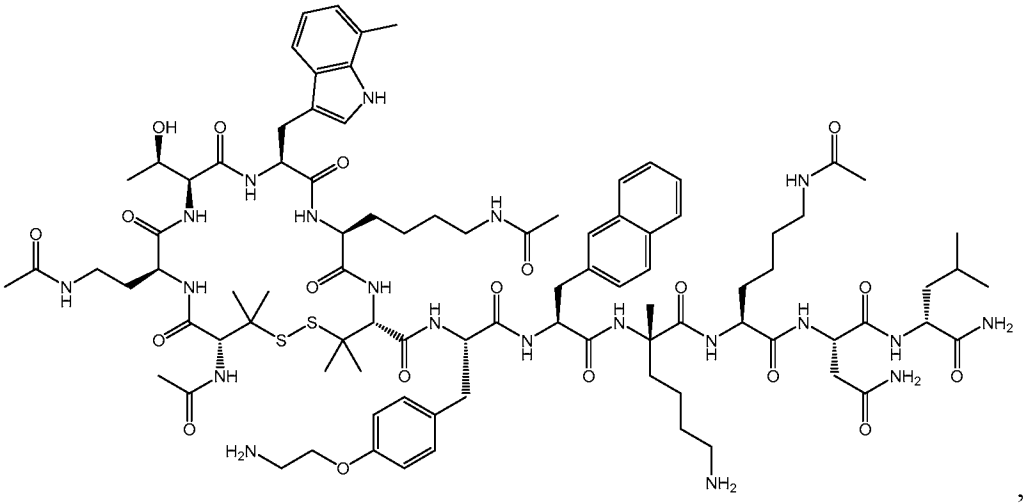
Ac-[Pen]-N-T-[W(7-Me)]-[Lys(Gly)]-[Pen]-Phe[4-(2-aminoethoxy)]-[2-Nal]-[a-MeLys]-[Lys(Ac)]-N-[(D)Leu]-NH_2 (SEQ ID NO: 320)



Ac-[Pen]-N-T-[W(7-Me)]-[Lys(Aib)]-[Pen]-Phe[4-(2-aminoethoxy)]-[2-Nal]-[a-MeLys]-[Lys(Ac)]-N-[(D)Leu]-NH_2 (SEQ ID NO: 322)

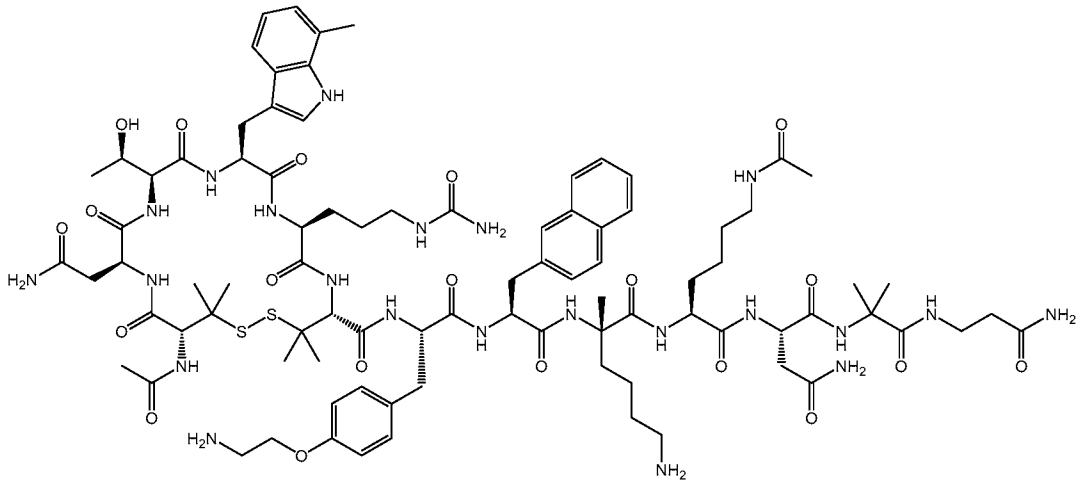


Ac-[Pen]-[Dab(Ac)]-T-[W(7-Me)]-[Lys(Ac)]-[Pen]-Phe[4-(2-aminoethoxy)]-[2-Nal]-[a-MeLys]-[Lys(Ac)]-N-[(D)Leu]-NH_2 (SEQ ID NO: 335)



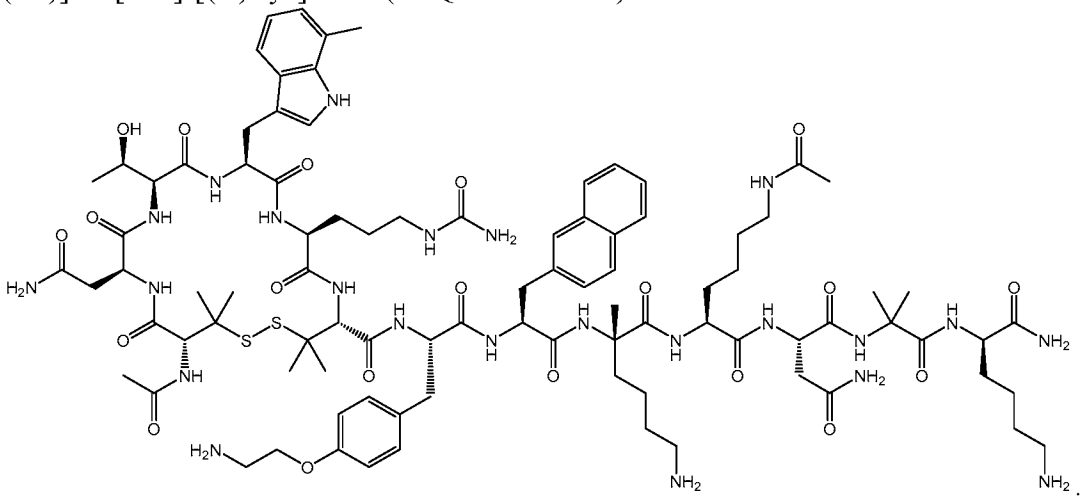
,

Ac-[Pen]-N-T-[W(7-Me)]-[Cit]-[Pen]-Phe[4-(2-aminoethoxy)]-[2-Nal]-[a-MeLys]-[Lys(Ac)]-N-[Aib]-[bA]-NH_2 (SEQ ID NO: 340)



, or

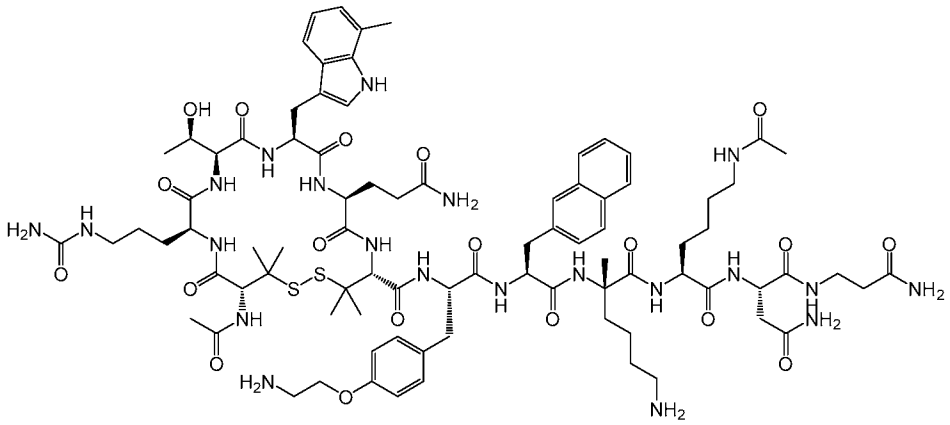
Ac-[Pen]-N-T-[W(7-Me)]-[Cit]-[Pen]-Phe[4-(2-aminoethoxy)]-[2-Nal]-[a-MeLys]-[Lys(Ac)]-N-[Aib]-[(D)Lys]-NH_2 (SEQ ID NO: 344)



.

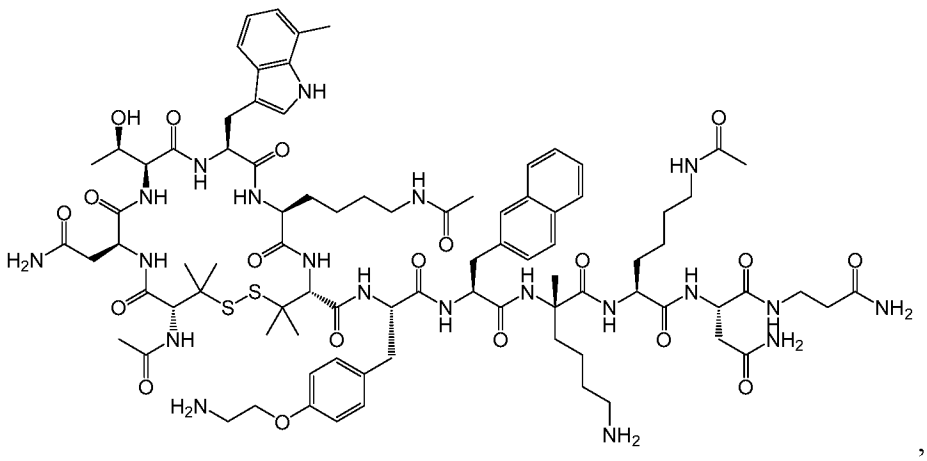
[00248] In certain embodiments, the peptide comprises or is:

Ac-[Pen]-[Cit]-T-[W(7-Me)]-Q-[Pen]-Phe[4-(2-aminoethoxy)]-[2-Nal]-[a-MeLys]-[Lys(Ac)]-N-[bA]-NH_2 (Seq. ID. No. 238)



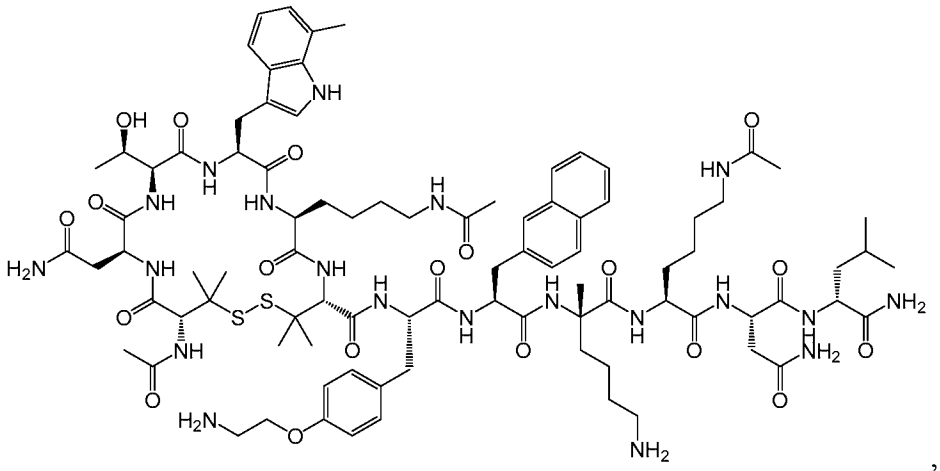
,

Ac-[Pen]-NT-[W(7-Me)]-[Lys(Ac)]-[Pen]-Phe[4-(2-aminoethoxy)]-[2-Nal]-[a-MeLys]-[Lys(Ac)]-N-[bA]-NH_2 (Seq. ID. No. 242)



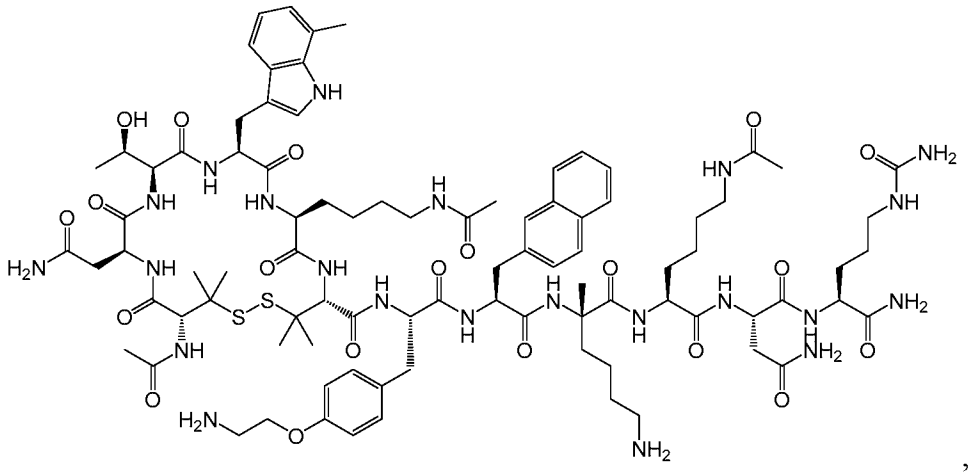
,

Ac-[Pen]-NT-[W(7-Me)]-[Lys(Ac)]-[Pen]-Phe[4-(2-aminoethoxy)]-[2-Nal]-[a-MeLys]-[Lys(Ac)]-N-[(D)Leu]-NH_2 (Seq. ID. No. 245)



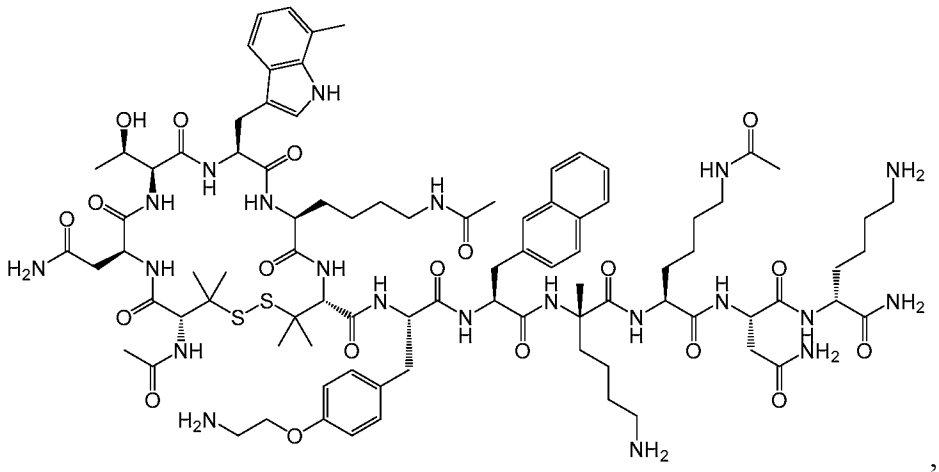
,

Ac-[Pen]-NT-[W(7-Me)]-[Lys(Ac)]-[Pen]-Phe[4-(2-aminoethoxy)]-[2-Nal]-[a-MeLys]-[Lys(Ac)]-N-[Cit]-NH_2 (Seq. ID. No. 249)



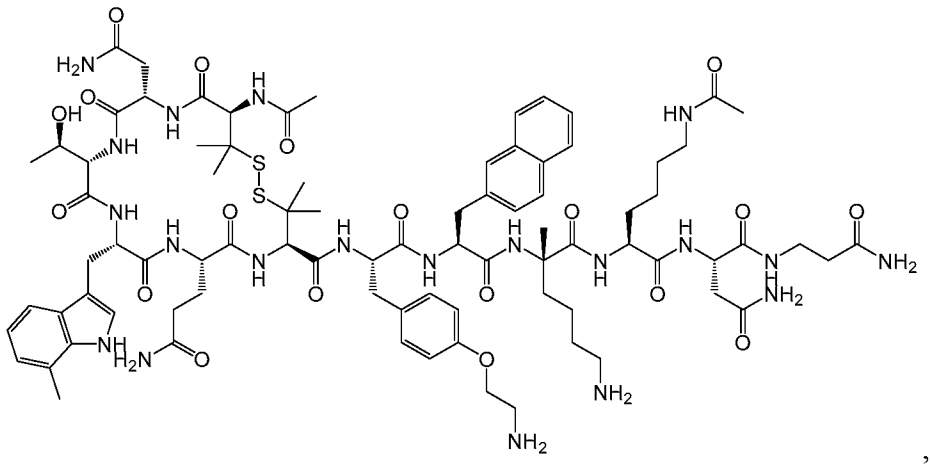
,

Ac-[Pen]-NT-[W(7-Me)]-[Lys(Ac)]-[Pen]-Phe[4-(2-aminoethoxy)]-[2-Nal]-[a-MeLys]-[Lys(Ac)]-N-[(D)Lys]-NH_2 (Seq. ID. No. 252)



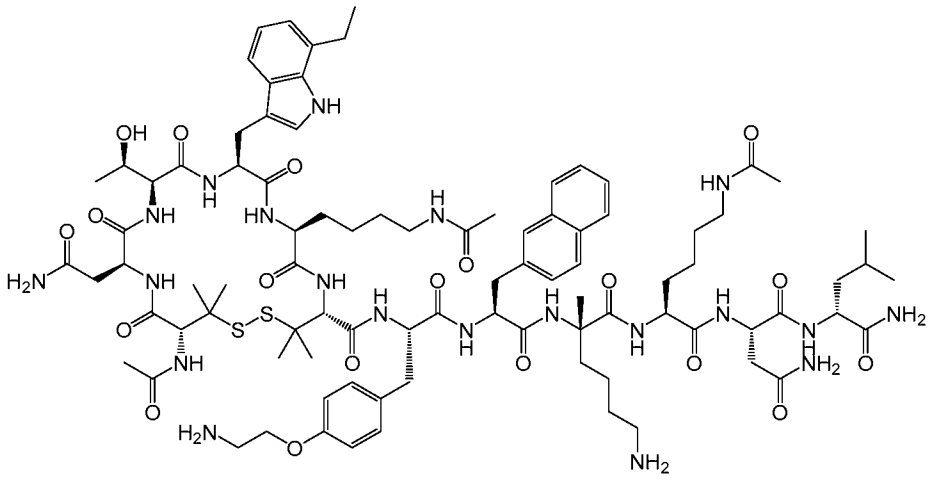
,

Ac-[Pen]-NT-[W(7-Me)]-Q-[Pen]-Phe[4-(2-aminoethoxy)]-[2-Nal]-[a-MeLys]-[Lys(Ac)]-N-[bA]-NH_2 (Seq. ID. No. 267)



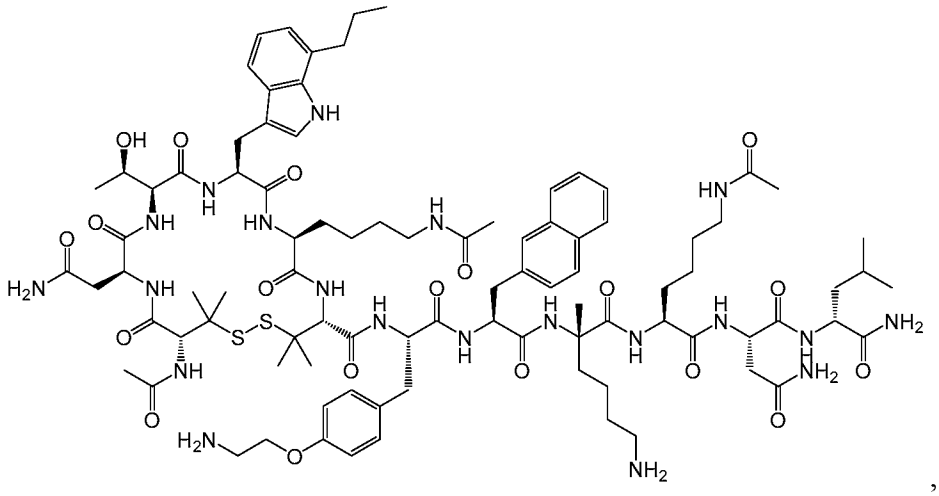
,

Ac-[Pen]-N-T-[W(7-Et)]-[Lys(Ac)]-[Pen]-Phe[4-(2-aminoethoxy)]-[2-Nal]-[a-MeLys]-[Lys(Ac)]-N-[(D)Leu]-NH_2 (Seq. ID. No. 284)

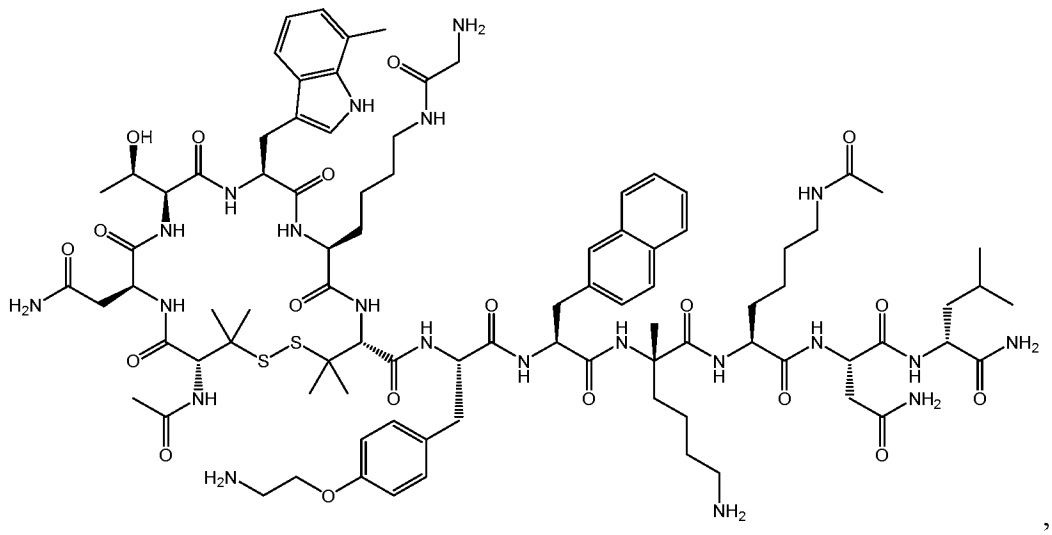


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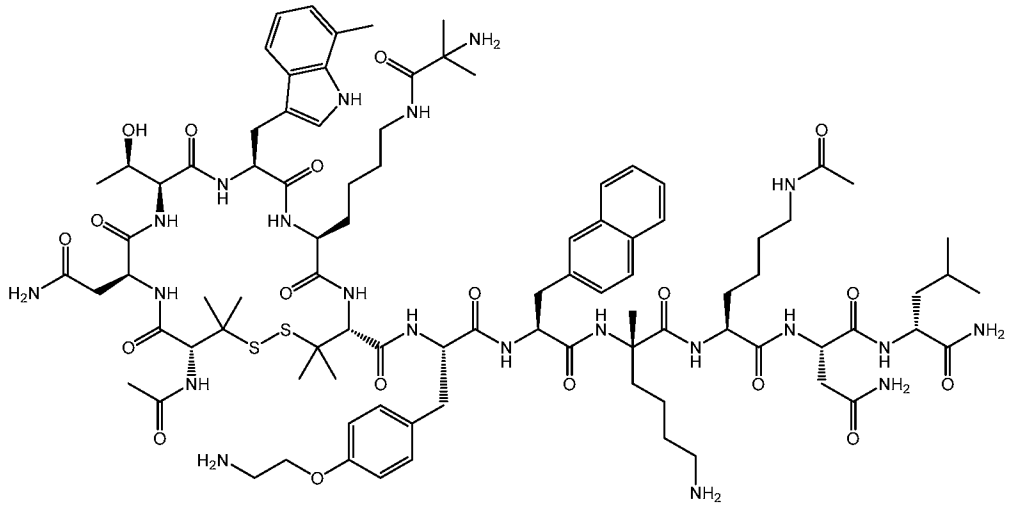
Ac-[Pen]-N-T-[W(7-n-Pr)]-[Lys(Ac)]-[Pen]-Phe[4-(2-aminoethoxy)]-[2-Nal]-[a-MeLys]-[Lys(Ac)]-N-[(D)Leu]-NH_2 (Seq. ID. No. 285)



Ac-[Pen]-N-T-[W(7-Me)]-[Lys(Gly)]-[Pen]-Phe[4-(2-aminoethoxy)]-[2-Nal]-[a-MeLys]-[Lys(Ac)]-N-[(D)Leu]-NH_2 (SEQ ID NO: 320)

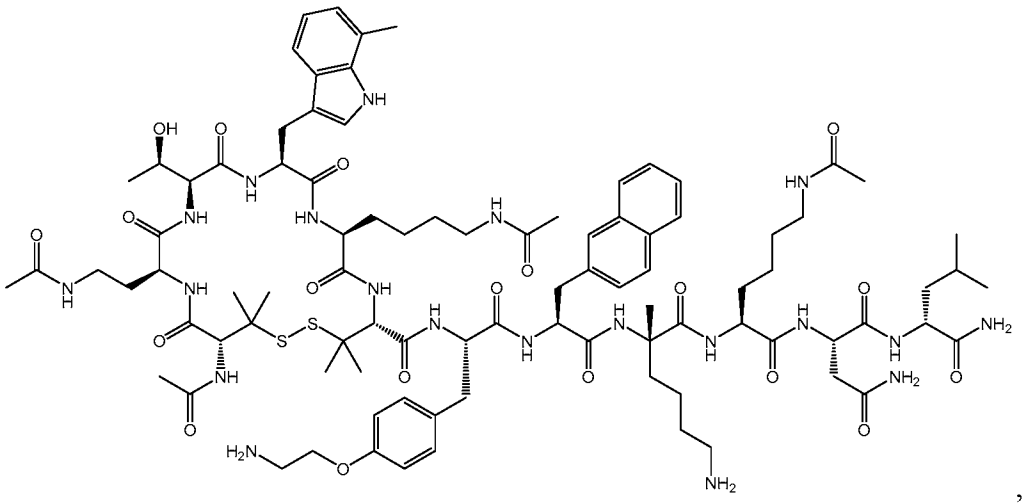


Ac-[Pen]-N-T-[W(7-Me)]-[Lys(Aib)]-[Pen]-Phe[4-(2-aminoethoxy)]-[2-Nal]-[a-MeLys]-[Lys(Ac)]-N-[(D)Leu]-NH_2 (SEQ ID NO: 322)



, or

Ac-[Pen]-[Dab(Ac)]-T-[W(7-Me)]-[Lys(Ac)]-[Pen]-Phe[4-(2-aminoethoxy)]-[2-Nal]-[a-MeLys]-[Lys(Ac)]-N-[(D)Leu]-NH_2 (SEQ ID NO: 335)



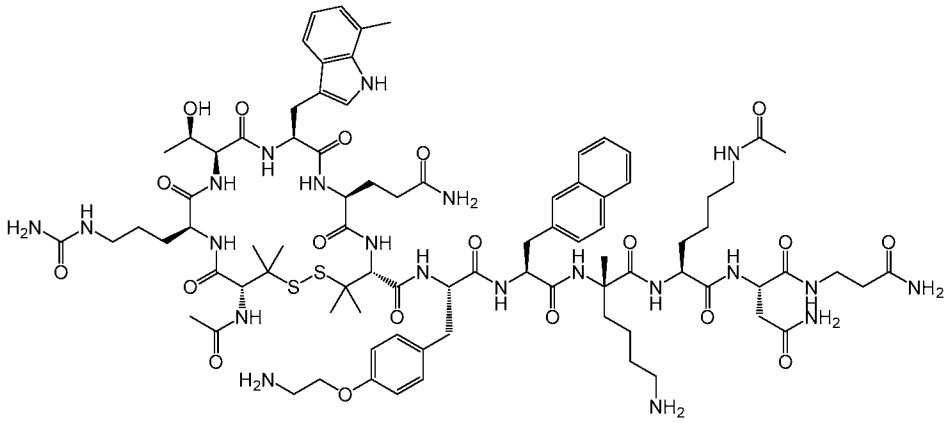
,

and wherein the peptide inhibitor is cyclized via a Pen-Pen disulfide bond;

or a pharmaceutically acceptable salt or solvate thereof.

[00249] In certain embodiments, the peptide comprises or is:

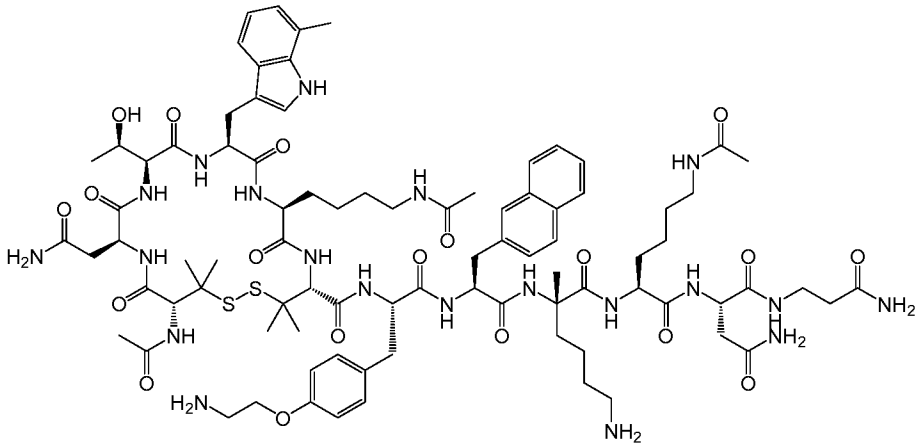
Ac-[Pen]-[Cit]-T-[W(7-Me)]-Q-[Pen]-Phe[4-(2-aminoethoxy)]-[2-Nal]-[a-MeLys]-[Lys(Ac)]-N-[bA]-NH_2 (Seq. ID. No. 238)



wherein the peptide inhibitor is cyclized via a Pen-Pen disulfide bond; or a pharmaceutically acceptable salt or solvate thereof.

[00250] In certain embodiments, the peptide inhibitor comprises or is:

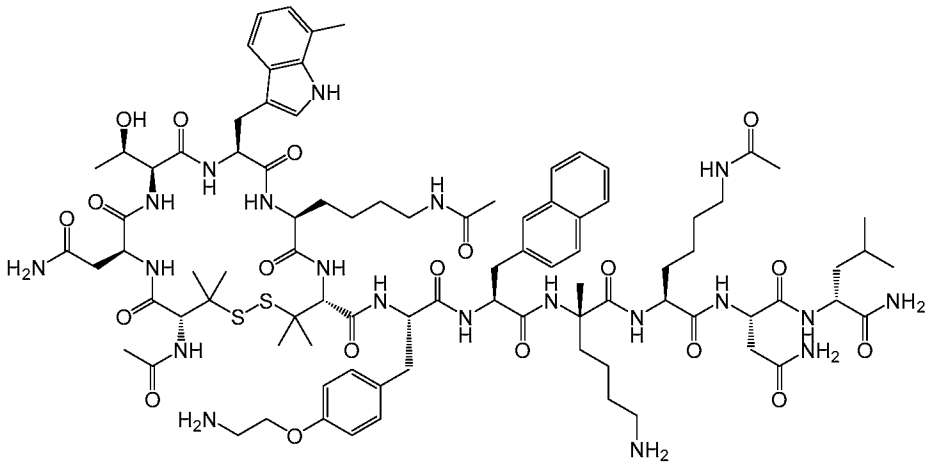
Ac-[Pen]-NT-[W(7-Me)]-[Lys(Ac)]-[Pen]-Phe[4-(2-aminoethoxy)]-[2-Nal]-[a-MeLys]-[Lys(Ac)]-N-[bA]-NH_2 (Seq. ID. No. 242)



wherein the peptide inhibitor is cyclized via a Pen-Pen disulfide bond; or a pharmaceutically acceptable salt or solvate thereof.

[00251] In certain embodiments, the peptide inhibitor comprises or is:

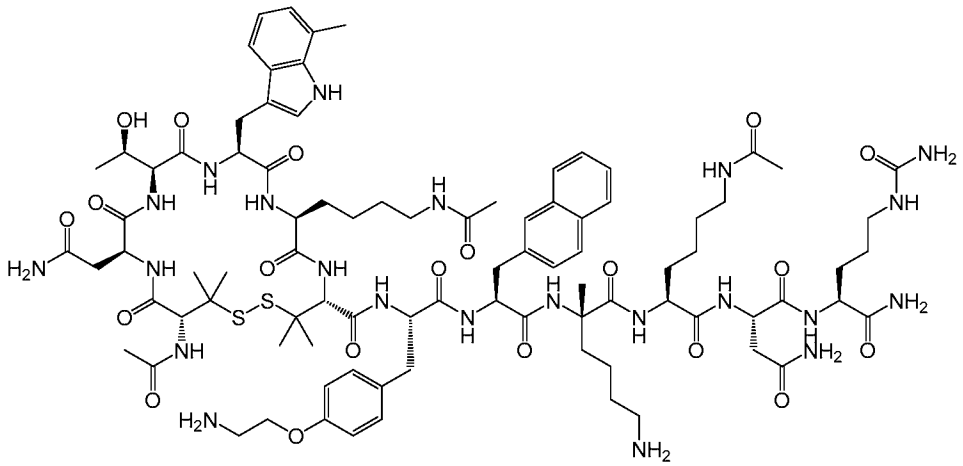
Ac-[Pen]-NT-[W(7-Me)]-[Lys(Ac)]-[Pen]-Phe[4-(2-aminoethoxy)]-[2-Nal]-[a-MeLys]-[Lys(Ac)]-N-[(D)Leu]-NH_2 (Seq. ID. No. 245)



wherein the peptide inhibitor is cyclized via a Pen-Pen disulfide bond; or a pharmaceutically acceptable salt or solvate thereof.

[00252] In certain embodiments, the peptide inhibitor comprises or is:

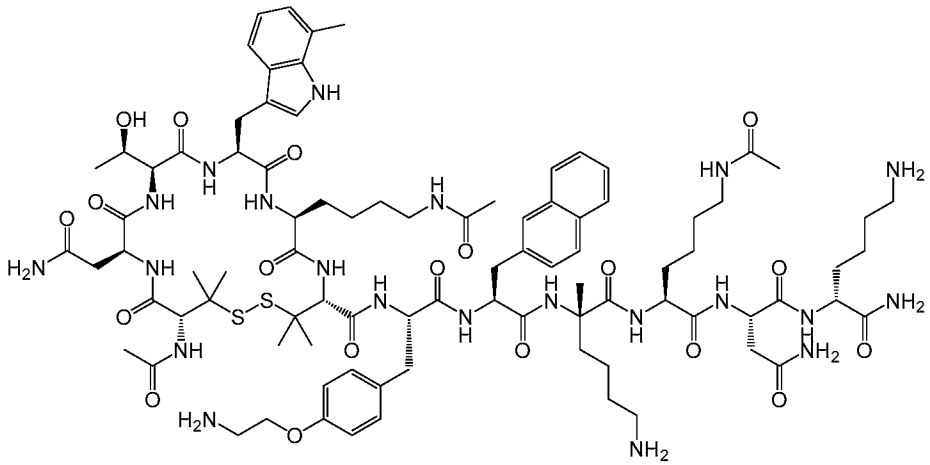
Ac-[Pen]-NT-[W(7-Me)]-[Lys(Ac)]-[Pen]-Phe[4-(2-aminoethoxy)]-[2-Nal]-[a-MeLys]-[Lys(Ac)]-N-[Cit]-NH_2 (Seq. ID. No. 249)



wherein the peptide inhibitor is cyclized via a Pen-Pen disulfide bond; or a pharmaceutically acceptable salt or solvate thereof.

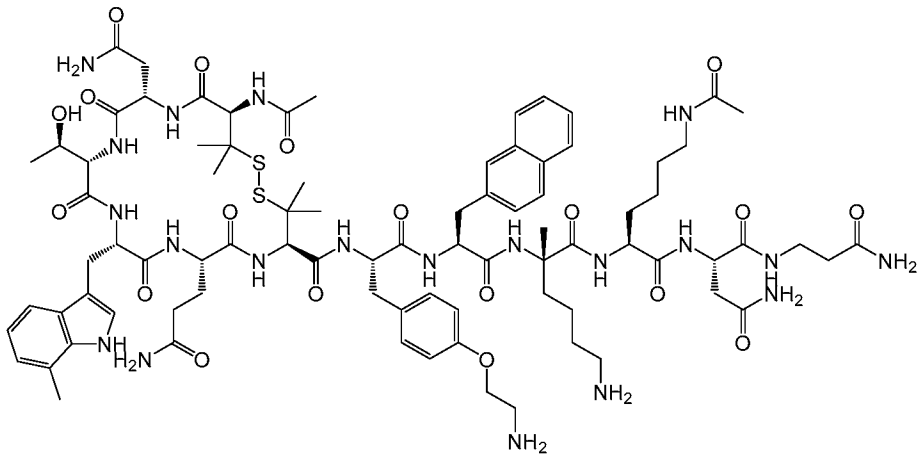
[00253] In certain embodiments, the peptide inhibitor comprises or is:

Ac-[Pen]-NT-[W(7-Me)]-[Lys(Ac)]-[Pen]-Phe[4-(2-aminoethoxy)]-[2-Nal]-[a-MeLys]-[Lys(Ac)]-N-[(D)Lys]-NH_2 (Seq. ID. No. 252)



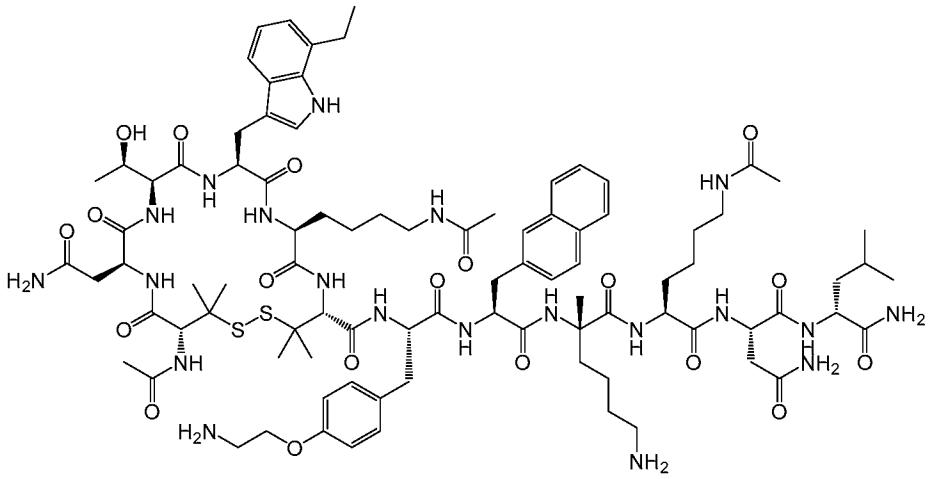
wherein the peptide inhibitor is cyclized via a Pen-Pen disulfide bond; or a pharmaceutically acceptable salt or solvate thereof.

[00254] In certain embodiments, the peptide inhibitor comprises or is: Ac-[Pen]-NT-[W(7-Me)]-Q-[Pen]-Phe[4-(2-aminoethoxy)]-[2-Nal]-[a-MeLys]-[Lys(Ac)]-N-[bA]-NH_2 (Seq. ID. No. 267)



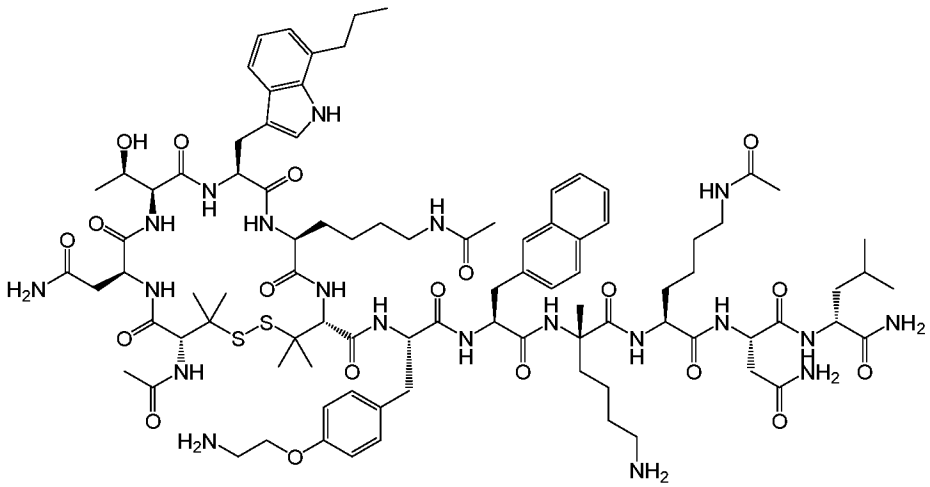
wherein the peptide inhibitor is cyclized via a Pen-Pen disulfide bond; or a pharmaceutically acceptable salt or solvate thereof.

[00255] In certain embodiments, the peptide inhibitor comprises or is: Ac-[Pen]-N-T-[W(7-Et)]-[Lys(Ac)]-[Pen]-Phe[4-(2-aminoethoxy)]-[2-Nal]-[a-MeLys]-[Lys(Ac)]-N-[(D)Leu]-NH_2 (Seq. ID. No. 284)



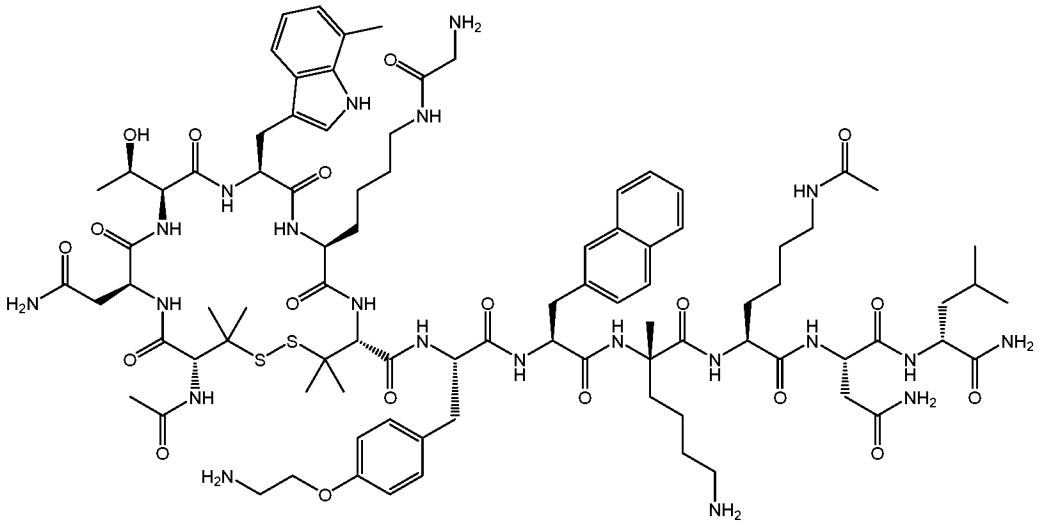
wherein the peptide inhibitor is cyclized via a Pen-Pen disulfide bond; or a pharmaceutically acceptable salt or solvate thereof.

[00256] In certain embodiments, the peptide inhibitor comprises or is: Ac-[Pen]-N-T-[W(7-n-Pr)]-[Lys(Ac)]-[Pen]-Phe[4-(2-aminoethoxy)]-[2-Nal]-[a-MeLys]-[Lys(Ac)]-N-[(D)Leu]-NH_2 (Seq. ID. No. 285)



wherein the peptide inhibitor is cyclized via a Pen-Pen disulfide bond; or a pharmaceutically acceptable salt or solvate thereof.

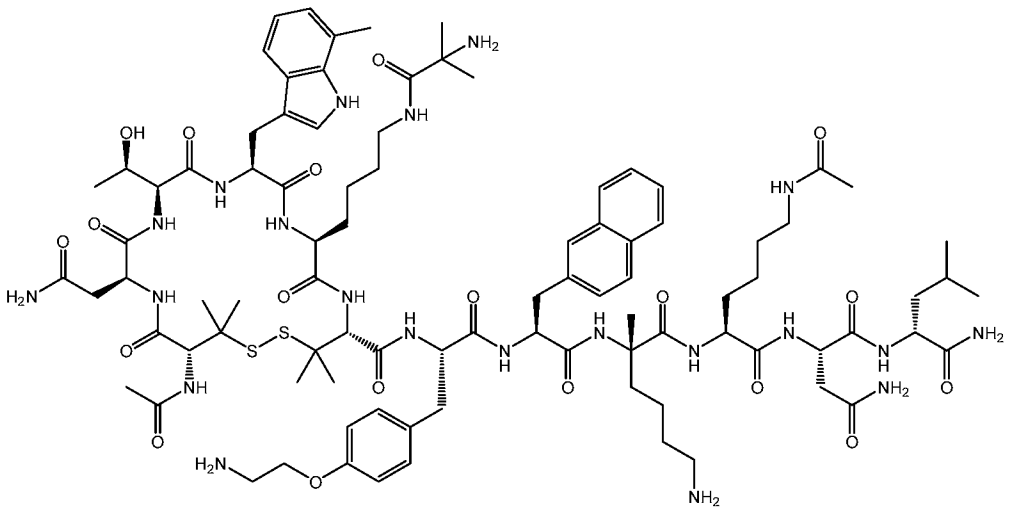
[00257] In certain embodiments, the peptide inhibitor comprises or is: Ac-[Pen]-N-T-[W(7-Me)]-[Lys(Gly)]-[Pen]-Phe[4-(2-aminoethoxy)]-[2-Nal]-[a-MeLys]-[Lys(Ac)]-N-[(D)Leu]-NH_2 (SEQ ID NO: 320)



wherein the peptide inhibitor is cyclized via a Pen-Pen disulfide bond; or a pharmaceutically acceptable salt or solvate thereof.

[00258] In certain embodiments, the peptide inhibitor comprises or is:

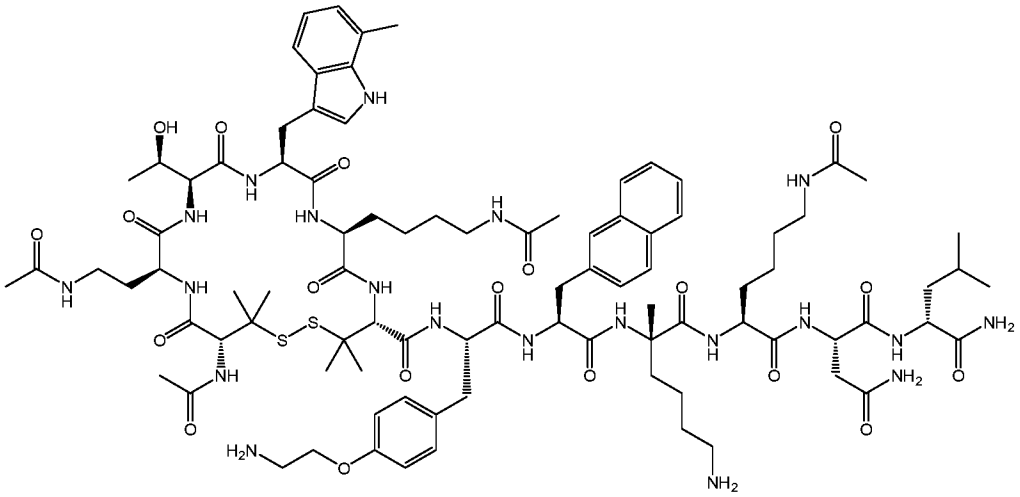
Ac-[Pen]-N-T-[W(7-Me)]-[Lys(Aib)]-[Pen]-Phe[4-(2-aminoethoxy)]-[2-Nal]-[a-MeLys]-[Lys(Ac)]-N-[(D)Leu]-NH_2 (SEQ ID NO: 322)



wherein the peptide inhibitor is cyclized via a Pen-Pen disulfide bond; or a pharmaceutically acceptable salt or solvate thereof.

[00259] In certain embodiments, the peptide inhibitor comprises or is:

Ac-[Pen]-[Dab(Ac)]-T-[W(7-Me)]-[Lys(Ac)]-[Pen]-Phe[4-(2-aminoethoxy)]-[2-Nal]-[a-MeLys]-[Lys(Ac)]-N-[(D)Leu]-NH_2 (SEQ ID NO: 335)



wherein the peptide inhibitor is cyclized via a Pen-Pen disulfide bond; or a pharmaceutically acceptable salt or solvate thereof.

[00260] In certain embodiments, the peptide inhibitor comprises or is: Ac-[(D)Arg]-Abu-Q-T-[W(5-F)]-Q-[Cys]-Phe[4-(2-aminoethoxy)]-[2-Nal]-[THP]-E-N-[bA]-NH_2 (SEQ ID NO: 364).

[00261] In certain embodiments, the peptide comprises or is an amino acid sequence of Formula (II'):

X7-X8-X9-X10-X11-X12-X13-X14-X15 (II')

wherein

X7 is unsubstituted Trp, or Trp substituted with cyano, halo, alkyl, haloalkyl, hydroxy, or alkoxy;

X8 is Gln, alpha-MeLys, alpha-MeLeu, alpha-MeLys(Ac), beta-homoGln, Cit, Glu, Phe, Asn, Thr, Val, Aib, alpha-MeGln, alpha-MeAsn, Lys(Ac), Dab(Ac), Dap(Ac), homo-Lys(Ac), 1-Nal, 2-Nal, or Trp;

X9 is Abu, Cys, (D)Cys, alpha-MeCys, (D)Pen, Pen or Pen(sulfoxide);

X10 is unsubstituted Phe, or Phe substituted with halo, alkyl, haloalkyl, hydroxy, alkoxy, carboxy, carboxamido, 2-aminoethoxy, 2-acetylaminoethoxy, 2-Nal, His, His_3Bom, or His_Bzl;

X11 is 2-Nal, Phe(2-Me), Phe(3-Me), Phe(4-Me), Phe(3,4-dimethoxy), 1-Nal, unsubstituted Trp, or Trp substituted with cyano, halo, alkyl, haloalkyl, hydroxy, or alkoxy;

X12 is 4-amino-4-carboxy-tetrahydropyran (THP), alpha-MeLys, alpha-MeLeu, alpha-MeArg, alpha-MePhe, alpha-MeLeu, alpha-MeLys, alpha-MeAsn, alpha-MeTyr, Ala, or cyclohexylAla, Lys, Aib, Achc, Spiral-Pip, DiethylGly, Acbc, or a-MeOrn;

X13 is Aib, Glu, Cit, Gln, Lys(Ac), alpha-MeArg, alpha-MeGlu, alpha-MeLeu, alpha-MeLys, alpha-Me-Asn, alpha-MeLys(Ac), Dab(Ac), Dap(Ac), homo-Lys(Ac), Lys, or Gly; ; or X13 is Lys, pegylated Lys, b-homoGlu, or Lys(Y2-Ac), wherein Y2 is an amino acid;
X14 is Asn, 2-Nap, Aib, Arg, Cit, Asp, Phe, Gly, Lys, Leu, Ala, (D)Ala, beta-Ala, His, Thr, n-Leu, Gln, Ser, (D)Ser, Tic, Trp, alpha-MeGln, alpha-MeAsn, alpha-MeLys(Ac), Dab(Ac), Dap(Ac), homo-Lys(Ac), Lys(Ac), (D)Leu, Pro, (D)Pro, (D)Phe, (D)His, Ile, (D)Thr, Gly, N-MeAla, Sarc, or aMeLeu;
X15 Leu, (D)Leu, beta-Ala, Cit, (D)Lys Arg, NMeArg, bhPhe, His, Val, (D)Val, (D)Lys, Pro, (D)Pro, Ile, (D)Arg, (D)Phe, (D)Tyr, Ser, (D)Ser, Thr, (D)Thr, N-MeAla, Y, a-MePhe, Sarc, Gly, Ala, (D)Tyr, (D)2-Nal, (D)Asn, or absent;
and
provided that at least one of X7 and X11 is Trp substituted with cyano, halo, alkyl, haloalkyl, hydroxy, or alkoxy; or the peptide inhibitor is

264	Ac-[Pen]-NT-[W(7-Me)]-[Cit]-[Pen]-Phe[4-(2-aminoethoxy)]-[2-Nal]-[a-MeLys]-[Lys(Ac)]-N-[Aib]-NH_2

or

340	Ac-[Pen]-N-T-[W(7-Me)]-[Cit]-[Pen]-Phe[4-(2-aminoethoxy)]-[2-Nal]-[a-MeLys]-[Lys(Ac)]-N-[Aib]-[bA]-NH_2

.

[00262] In certain embodiments, the peptide comprises or is any one of the following peptides or amino acid sequences, or a pharmaceutically acceptable salt or solvate thereof:

SEQ ID NO:	**Sequence***
210	Ac-[Pen]-NT-[W(7-Me)]-Q-[Pen]-Phe[4-(2-aminoethoxy)]-[2-Nal]-[a-MeLeu]-[Lys(Ac)]-[(D)Leu]-[bA]-NH_2
211	Ac-[Pen]-NT-[W(7-Me)]-Q-[Pen]-Phe[4-(2-aminoethoxy)]-[2-Nal]-[a-MeLeu]-[Lys(Ac)]-P-[bA]-NH_2
212	Ac-[Pen]-NT-[W(7-Me)]-Q-[Pen]-Phe[4-(2-aminoethoxy)]-[2-Nal]-[a-MeLeu]-[Lys(Ac)]-[(D)Pro]-[bA]-NH_2

SEQ ID NO:	Sequence*
213	Ac-[Pen]-NT-[W(7-Me)]-Q-[Pen]-Phe[4-(2-aminoethoxy)]-[2-Nal]-[a-MeLeu]-[Lys(Ac)]-[(D)Phe]-[bA]-NH_2
215	Ac-[Pen]-NT-[W(7-Me)]-Q-[Pen]-Phe[4-(2-aminoethoxy)]-[2-Nal]-[a-MeLeu]-[Lys(Ac)]-[(D)His]-[bA]-NH_2
216	Ac-[Pen]-NT-[W(7-Me)]-Q-[Pen]-Phe[4-(2-aminoethoxy)]-[2-Nal]-[a-MeLeu]-[Lys(Ac)]-I-[bA]-NH_2
218	Ac-[Pen]-NT-[W(7-Me)]-Q-[Pen]-Phe[4-(2-aminoethoxy)]-[2-Nal]-[a-MeLeu]-[Lys(Ac)]-[(D)Thr]-[bA]-NH_2
219	Ac-[Pen]-NT-[W(7-Me)]-Q-[Pen]-Phe[4-(2-aminoethoxy)]-[2-Nal]-[a-MeLeu]-G-P-[bA]-NH_2
220	Ac-[Pen]-NT-[W(7-Me)]-Q-[Pen]-Phe[4-(2-aminoethoxy)]-[2-Nal]-[a-MeLeu]-G-[(D)Pro]-[bA]-NH_2
223	Ac-[Pen]-NT-[W(7-Me)]-Q-[Pen]-Phe[4-(2-aminoethoxy)]-[2-Nal]-[a-MeLeu]-[Lys(Ac)]-[N-MeAla]-[bA]-NH_2
224	Ac-[Pen]-NT-[W(7-Me)]-Q-[Pen]-Phe[4-(2-aminoethoxy)]-[2-Nal]-[a-MeLeu]-[Lys(Ac)]-[Sarc]-[bA]-NH_2
225	Ac-[Pen]-NT-[W(7-Me)]-Q-[Pen]-Phe[4-(2-aminoethoxy)]-[2-Nal]-[a-MeLeu]-[Lys(Ac)]-[a-MeLeu]-[bA]-NH_2
243	Ac-[Pen]-NT-[W(7-Me)]-[Lys(Ac)]-[Pen]-Phe[4-(2-aminoethoxy)]-[2-Nal]-[a-MeLys]-[Lys(Ac)]-N-R-NH_2
246	Ac-[Pen]-NT-[W(7-Me)]-[Lys(Ac)]-[Pen]-Phe[4-(2-aminoethoxy)]-[2-Nal]-[a-MeLys]-[Lys(Ac)]-N-[NMeArg]-NH_2
247	Ac-[Pen]-NT-[W(7-Me)]-[Lys(Ac)]-[Pen]-Phe[4-(2-aminoethoxy)]-[2-Nal]-[a-MeLys]-[Lys(Ac)]-N-[bhPhe]-NH_2
248	Ac-[Pen]-NT-[W(7-Me)]-[Lys(Ac)]-[Pen]-Phe[4-(2-aminoethoxy)]-[2-Nal]-[a-MeLys]-[Lys(Ac)]-N-H-NH_2
250	Ac-[Pen]-NT-[W(7-Me)]-[Lys(Ac)]-[Pen]-Phe[4-(2-aminoethoxy)]-[2-Nal]-[a-MeLys]-[Lys(Ac)]-N-V-NH_2
251	Ac-[Pen]-NT-[W(7-Me)]-[Lys(Ac)]-[Pen]-Phe[4-(2-aminoethoxy)]-[2-Nal]-[a-MeLys]-[Lys(Ac)]-N-[(D)Val]-NH_2

SEQ ID NO:	Sequence*
252	Ac-[Pen]-NT-[W(7-Me)]-[Lys(Ac)]-[Pen]-Phe[4-(2-aminoethoxy)]-[2-Nal]-[a-MeLys]-[Lys(Ac)]-N-[(D)Lys]-NH_2
253	Ac-[Pen]-NT-[W(7-Me)]-[Lys(Ac)]-[Pen]-Phe[4-(2-aminoethoxy)]-[2-Nal]-[a-MeLys]-[Lys(Ac)]-N-P-NH_2
254	Ac-[Pen]-NT-[W(7-Me)]-[Lys(Ac)]-[Pen]-Phe[4-(2-aminoethoxy)]-[2-Nal]-[a-MeLys]-[Lys(Ac)]-N-[(D)Pro]-NH_2
255	Ac-[Pen]-NT-[W(7-Me)]-[Lys(Ac)]-[Pen]-Phe[4-(2-aminoethoxy)]-[2-Nal]-[a-MeLys]-[Lys(Ac)]-N-I-NH_2
256	Ac-[Pen]-NT-[W(7-Me)]-[Cit]-[Pen]-Phe[4-(2-aminoethoxy)]-[2-Nal]-[a-MeLys]-[Lys(Ac)]-N-[(D)Arg]-NH_2
257	Ac-[Pen]-NT-[W(7-Me)]-[Cit]-[Pen]-Phe[4-(2-aminoethoxy)]-[2-Nal]-[a-MeLys]-[Lys(Ac)]-N-[(D)Phe]-NH_2
258	Ac-[Pen]-NT-[W(7-Me)]-[Lys(Ac)]-[Pen]-Phe[4-(2-aminoethoxy)]-[2-Nal]-[a-MeLys]-[Lys(Ac)]-N-[(D)Phe]-NH_2
259	Ac-[Pen]-NT-[W(7-Me)]-[Cit]-[Pen]-Phe[4-(2-aminoethoxy)]-[2-Nal]-[a-MeLys]-[Lys(Ac)]-N-[(D)Tyr]-NH_2
260	Ac-[Pen]-NT-[W(7-Me)]-[Cit]-[Pen]-Phe[4-(2-aminoethoxy)]-[2-Nal]-[a-MeLys]-[Lys(Ac)]-N-S-NH_2
261	Ac-[Pen]-NT-[W(7-Me)]-[Cit]-[Pen]-Phe[4-(2-aminoethoxy)]-[2-Nal]-[a-MeLys]-[Lys(Ac)]-N-[(D)Ser]-NH_2
262	Ac-[Pen]-NT-[W(7-Me)]-[Cit]-[Pen]-Phe[4-(2-aminoethoxy)]-[2-Nal]-[a-MeLys]-[Lys(Ac)]-NT-NH_2
263	Ac-[Pen]-NT-[W(7-Me)]-[Cit]-[Pen]-Phe[4-(2-aminoethoxy)]-[2-Nal]-[a-MeLys]-[Lys(Ac)]-N-[(D)Thr]-NH_2
265	Ac-[Pen]-NT-[W(7-Me)]-[Cit]-[Pen]-Phe[4-(2-aminoethoxy)]-[2-Nal]-[a-MeLys]-[Lys(Ac)]-[N-MeAla]-NH_2
266	Ac-[Pen]-NT-[W(7-Me)]-[Cit]-[Pen]-Phe[4-(2-aminoethoxy)]-[2-Nal]-[a-MeLys]-[Lys(Ac)]-N-Y-NH_2
274	Ac-[Pen]-N-T-[W(7-Me)]-Q-[Pen]-Phe[4-(2-aminoethoxy)]-[2-Nal]-[Achc]-[Lys(Ac)]-N-[bA]-NH_2

SEQ ID NO:	Sequence*
275	Ac-[Pen]-N-T-[W(7-Me)]-Q-[Pen]-Phe[4-(2-aminoethoxy)]-[2-Nal]-[Spiral_Pip]-[Lys(Ac)]-N-[bA]-NH_2
276	Ac-[Pen]-N-T-[W(7-Me)]-Q-[Pen]-Phe[4-(2-aminoethoxy)]-[2-Nal]-[DiethylGly]-[Lys(Ac)]-N-[bA]-NH_2
277	Ac-[Pen]-N-T-[W(7-Me)]-Q-[Pen]-Phe[4-(2-aminoethoxy)]-[2-Nal]-[Acbc]-[Lys(Ac)]-N-[bA]-NH_2
278	Ac-[Pen]-N-T-[W(7-Me)]-Q-[Pen]-Phe[4-(2-aminoethoxy)]-[2-Nal]-[a-MeOrn]-[Lys(Ac)]-N-[bA]-NH_2
289	Ac-[Pen]-N-T-[W(7-Me)]-[Lys(Ac)]-[Pen]-[2-Nal]-[2-Nal]-[a-MeLys]-[Lys(Ac)]-N-[(D)Leu]-NH_2
290	Ac-[Pen]-N-T-[W(7-Me)]-[Lys(Ac)]-[Pen]-H-[2-Nal]-[a-MeLys]-[Lys(Ac)]-N-[(D)Leu]-NH_2
291	Ac-[Pen]-N-T-[W(7-Me)]-[Lys(Ac)]-[Pen]-[His_3Bom]-[2-Nal]-[a-MeLys]-[Lys(Ac)]-N-[(D)Leu]-NH_2
292	Ac-[Pen]-N-T-[W(7-Me)]-[Lys(Ac)]-[Pen]-[His_Bzl]-[2-Nal]-[a-MeLys]-[Lys(Ac)]-N-[(D)Leu]-NH_2
293	Ac-[Pen]-N-T-[W(7-Me)]-[Lys(Ac)]-[Pen]-[His_Bzl]-[2-Nal]-[a-MeLys]-[Lys(Ac)]-N-[(D)Leu]-NH_2
323	Ac-[(D)Arg]-[Abu]-Q-T-[W(7-Me)]-[Lys(Ac)]-[Cys]-Phe[4-(2-aminoethoxy)]-[2-Nal]-[a-MeLys]-[Lys(Ac)]-N-[(D)Lys]-[Sarc]-NH_2;
326	Ac-[(D)Arg]-[Abu]-Q-T-[W(7-Me)]-[Lys(Ac)]-[Cys]-Phe[4-(2-aminoethoxy)]-[2-Nal]-[a-MeLys]-[Lys(Ac)]-N-NH_2;
327	Ac-[(D)Arg]-[Abu]-Q-T-[W(7-Me)]-[Lys(Ac)]-[Cys]-Phe[4-(2-aminoethoxy)]-[2-Nal]-[a-MeLys]-[Lys(Ac)]-N-[a-MePhe]-NH_2;
339	Ac-[Pen]-N-T-[W(7-Me)]-[Cit]-[Pen]-Phe[4-(2-aminoethoxy)]-[2-Nal]-[a-MeLys]-[Lys(Ac)]-N-[Sarc]-NH_2;
341	Ac-[Pen]-N-T-[W(7-Me)]-[Cit]-[Pen]-Phe[4-(2-aminoethoxy)]-[2-Nal]-[a-MeLys]-[Lys(Ac)]-N-[Aib]-G-NH_2;

SEQ ID NO:	Sequence*
342	Ac-[Pen]-N-T-[W(7-Me)]-[Cit]-[Pen]-Phe[4-(2-aminoethoxy)]-[2-Nal]-[a-MeLys]-[Lys(Ac)]-N-[Aib]-A-NH_2;
343	Ac-[Pen]-N-T-[W(7-Me)]-[Cit]-[Pen]-Phe[4-(2-aminoethoxy)]-[2-Nal]-[a-MeLys]-[Lys(Ac)]-N-[Aib]-R-NH_2;
344	Ac-[Pen]-N-T-[W(7-Me)]-[Cit]-[Pen]-Phe[4-(2-aminoethoxy)]-[2-Nal]-[a-MeLys]-[Lys(Ac)]-N-[Aib]-[(D)Lys]-NH_2;
345	Ac-[Pen]-N-T-[W(7-Me)]-[Cit]-[Pen]-Phe[4-(2-aminoethoxy)]-[2-Nal]-[a-MeLys]-[Lys(Ac)]-N-[Aib]-[(D)Arg]-NH_2;
346	Ac-[Pen]-N-T-[W(7-Me)]-[Cit]-[Pen]-Phe[4-(2-aminoethoxy)]-[2-Nal]-[a-MeLys]-[Lys(Ac)]-N-[Aib]-[(D)Phe]-NH_2;
347	Ac-[Pen]-N-T-[W(7-Me)]-[Cit]-[Pen]-Phe[4-(2-aminoethoxy)]-[2-Nal]-[a-MeLys]-[Lys(Ac)]-N-[Aib]-[(D)Tyr]-NH_2;
348	Ac-[Pen]-N-T-[W(7-Me)]-[Cit]-[Pen]-Phe[4-(2-aminoethoxy)]-[2-Nal]-[a-MeLys]-[Lys(Ac)]-N-[Aib]- [(D)2-Nal]-NH_2; or
354	Ac-[Pen]-N-T-[W(7-Me)]-[Lys(Ac)]-[Pen]-Phe[4-(2-aminoethoxy)]-[2-Nal]-[a-MeLeu]-[Lys(Ac)]-N-[(D)Asn]-NH_2;
356	Ac-[Pen]-N-T-[W(7-Me)]-[Lys(Ac)]-[Pen]-Phe[4-(2-aminoethoxy)]-[2-Nal]-[a-MeLys]-[Lys(IVA)]-N-[(D)Leu]-NH_2;
357	Ac-[Pen]-N-T-[W(7-Me)]-[Lys(Ac)]-[Pen]-Phe[4-(2-aminoethoxy)]-[2-Nal]-[a-MeLys]-[Lys(cyclohexanoic)]-N-[(D)Leu]-NH_2;
358	Ac-[Pen]-N-T-[W(7-Me)]-[Lys(Ac)]-[Pen]-Phe[4-(2-aminoethoxy)]-[2-Nal]-[a-MeLys]-[Lys(octanoic)]-N-[(D)Leu]-NH_2;
359	Ac-[Pen]-N-T-[W(7-Me)]-[Lys(Ac)]-[Pen]-Phe[4-(2-aminoethoxy)]-[2-Nal]-[a-MeLys]-[Lys(C(O)CH2Ph)]-N-[(D)Leu]-NH_2;
360	Ac-[Pen]-N-T-[W(7-Me)]-[Lys(Ac)]-[Pen]-Phe[4-(2-aminoethoxy)]-[2-Nal]-[a-MeLys]-[Lys(trifluoropropionic)]-N-[(D)Leu]-NH_2; or

SEQ ID NO:	Sequence*
361	Ac-[Pen]-N-T-[W(7-Me)]-[Lys(Ac)]-[Pen]-Phe[4-(2-aminoethoxy)]-[2-Nal]-[a-MeLys]-[Lys(valeric)]-N-[(D)Leu]-NH_2

or a pharmaceutically acceptable salt or solvate thereof, wherein the peptide inhibitor or pharmaceutically acceptable salt or solvate thereof comprises a disulfide bond between two Pen residues or a thioether bond between Abu and Cys;

and

wherein the peptide inhibitor or pharmaceutically acceptable salt of solvate thereof inhibits the binding of an interleukin-23 (IL-23) to an IL-23 receptor.

[00263] In certain embodiments, the peptide comprises or is:

Ac-[(D)Arg]-[Abu]-Q-T-[W(7-Me)]-[Lys(Ac)]-[Cys]-Phe[4-(2-aminoethoxy)]-[2-Nal]-[a-MeLys]-[Lys(Ac)]-N-[(D)Lys]-[Sarc]-NH_2; (SEQ ID NO: 323); or

and wherein the peptide inhibitor is cyclized via a Abu-C thioether bond;

or a pharmaceutically acceptable salt or solvate thereof.

[00264] In certain embodiments, the peptide comprises or is:

Ac-[Pen]-NT-[W(7-Me)]-[Lys(Ac)]-[Pen]-Phe[4-(2-aminoethoxy)]-[2-Nal]-[a-MeLys]-[Lys(Ac)]-N-H-NH_2 (SEQ ID NO: 248);

Ac-[Pen]-NT-[W(7-Me)]-[Lys(Ac)]-[Pen]-Phe[4-(2-aminoethoxy)]-[2-Nal]-[a-MeLys]-[Lys(Ac)]-N-[(D)Val]-NH_2 (SEQ ID NO: 251);

Ac-[Pen]-NT-[W(7-Me)]-[Cit]-[Pen]-Phe[4-(2-aminoethoxy)]-[2-Nal]-[a-MeLys]-[Lys(Ac)]-N-[(D)Arg]-NH_2 (SEQ ID NO: 256);

Ac-[Pen]-NT-[W(7-Me)]-[Lys(Ac)]-[Pen]-Phe[4-(2-aminoethoxy)]-[2-Nal]-[a-MeLys]-[Lys(Ac)]-N-[(D)Phe]-NH_2 (SEQ ID NO: 258);

Ac-[Pen]-NT-[W(7-Me)]-[Cit]-[Pen]-Phe[4-(2-aminoethoxy)]-[2-Nal]-[a-MeLys]-[Lys(Ac)]-N-[(D)Tyr]-NH_2 (SEQ ID NO: 259);

Ac-[Pen]-NT-[W(7-Me)]-[Cit]-[Pen]-Phe[4-(2-aminoethoxy)]-[2-Nal]-[a-MeLys]-[Lys(Ac)]-N-S-NH_2 (SEQ ID NO: 260);

Ac-[Pen]-NT-[W(7-Me)]-[Cit]-[Pen]-Phe[4-(2-aminoethoxy)]-[2-Nal]-[a-MeLys]-[Lys(Ac)]-N-[(D)Ser]-NH_2 (SEQ ID NO: 261);

Ac-[Pen]-NT-[W(7-Me)]-[Cit]-[Pen]-Phe[4-(2-aminoethoxy)]-[2-Nal]-[a-MeLys]-[Lys(Ac)]-N-[(D)Thr]-NH_2 (SEQ ID NO: 263);

Ac-[Pen]-NT-[W(7-Me)]-[Cit]-[Pen]-Phe[4-(2-aminoethoxy)]-[2-Nal]-[a-MeLys]-[Lys(Ac)]-N-[Aib]-NH_2 (SEQ ID NO: 264);

Ac-[Pen]-NT-[W(7-Me)]-[Cit]-[Pen]-Phe[4-(2-aminoethoxy)]-[2-Nal]-[a-MeLys]-[Lys(Ac)]-[N-MeAla]-NH_2 (SEQ ID NO: 265);

Ac-[Pen]-N-T-[W(7-Me)]-Q-[Pen]-Phe[4-(2-aminoethoxy)]-[2-Nal]-[Achc]-[Lys(Ac)]-N-[bA]-NH_2 (SEQ ID NO: 274);

Ac-[Pen]-N-T-[W(7-Me)]-Q-[Pen]-Phe[4-(2-aminoethoxy)]-[2-Nal]-[DiethylGly]-[Lys(Ac)]-N-[bA]-NH_2 (SEQ ID NO: 276);

Ac-[Pen]-N-T-[W(7-Me)]-Q-[Pen]-Phe[4-(2-aminoethoxy)]-[2-Nal]-[Acbc]-[Lys(Ac)]-N-[bA]-NH_2 (SEQ ID NO: 277); or

Ac-[Pen]-N-T-[W(7-Me)]-Q-[Pen]-Phe[4-(2-aminoethoxy)]-[2-Nal]-[a-MeOrn]-[Lys(Ac)]-N-[bA]-NH_2 (SEQ ID NO: 278);

and wherein the peptide inhibitor is cyclized via a Pen-Pen disulfide bond; or via a Abu-C thioether bond;

or a pharmaceutically acceptable salt or solvate thereof.

[00265] In certain embodiments, the peptide comprises or is:

Ac-[Pen]-NT-[W(7-Me)]-Q-[Pen]-Phe[4-(2-aminoethoxy)]-[2-Nal]-[a-MeLeu]-[Lys(Ac)]-[(D)His]-[bA]-NH_2 (SEQ ID NO: 215);

Ac-[Pen]-NT-[W(7-Me)]-[Lys(Ac)]-[Pen]-Phe[4-(2-aminoethoxy)]-[2-Nal]-[a-MeLys]-[Lys(Ac)]-N-R-NH_2 (SEQ ID NO: 243);

Ac-[Pen]-NT-[W(7-Me)]-[Lys(Ac)]-[Pen]-Phe[4-(2-aminoethoxy)]-[2-Nal]-[a-MeLys]-[Lys(Ac)]-N-[NMeArg]-NH_2 (SEQ ID NO: 246);

Ac-[Pen]-NT-[W(7-Me)]-[Lys(Ac)]-[Pen]-Phe[4-(2-aminoethoxy)]-[2-Nal]-[a-MeLys]-[Lys(Ac)]-N-[bhPhe]-NH_2 (SEQ ID NO: 247);

Ac-[Pen]-NT-[W(7-Me)]-[Lys(Ac)]-[Pen]-Phe[4-(2-aminoethoxy)]-[2-Nal]-[a-MeLys]-[Lys(Ac)]-N-V-NH_2 (SEQ ID NO: 250);

Ac-[Pen]-NT-[W(7-Me)]-[Lys(Ac)]-[Pen]-Phe[4-(2-aminoethoxy)]-[2-Nal]-[a-MeLys]-[Lys(Ac)]-N-P-NH_2 (SEQ ID NO: 253);

Ac-[Pen]-NT-[W(7-Me)]-[Lys(Ac)]-[Pen]-Phe[4-(2-aminoethoxy)]-[2-Nal]-[a-MeLys]-[Lys(Ac)]-N-[(D)Pro]-NH_2 (SEQ ID NO: 254);

Ac-[Pen]-NT-[W(7-Me)]-[Lys(Ac)]-[Pen]-Phe[4-(2-aminoethoxy)]-[2-Nal]-[a-MeLys]-[Lys(Ac)]-N-I-NH_2 (SEQ ID NO: 255);

Ac-[Pen]-NT-[W(7-Me)]-[Cit]-[Pen]-Phe[4-(2-aminoethoxy)]-[2-Nal]-[a-MeLys]-[Lys(Ac)]-N-[(D)Phe]-NH_2 (SEQ ID NO: 257);

or

Ac-[(D)Arg]-[Abu]-Q-T-[W(7-Me)]-[Lys(Ac)]-[Cys]-Phe[4-(2-aminoethoxy)]-[2-Nal]-[a-MeLys]-[Lys(Ac)]-N-[(D)Lys]-[Sarc]-NH_2; (SEQ ID NO: 323);

and wherein the peptide inhibitor is cyclized via a Pen-Pen disulfide bond; or via a Abu-C thioether bond;

or a pharmaceutically acceptable salt or solvate thereof.

[00266] T In certain embodiments, the peptide comprises or is:

Ac-[Pen]-N-T-[W(7-Me)]-[Lys(Ac)]-[Pen]-[2-Nal]-[2-Nal]-[a-MeLys]-[Lys(Ac)]-N-[(D)Leu]-NH_2 (SEQ ID NO: 289); or

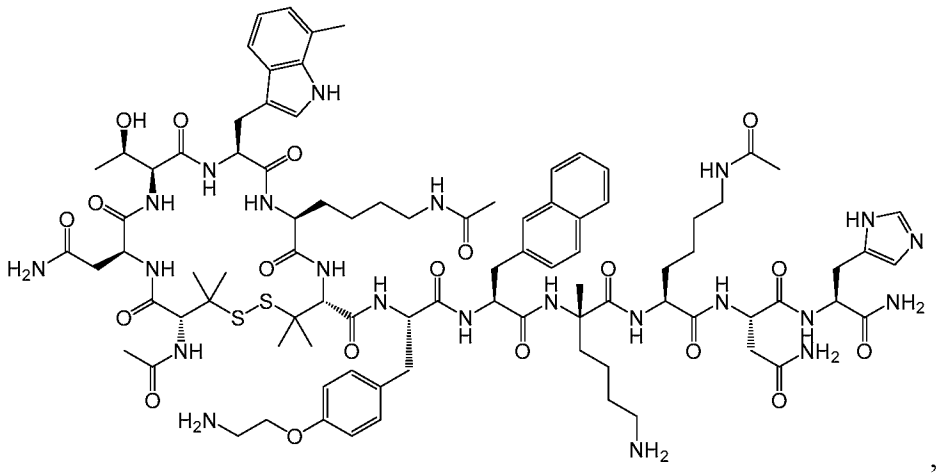
Ac-[Pen]-N-T-[W(7-Me)]-[Lys(Ac)]-[Pen]-H-[2-Nal]-[a-MeLys]-[Lys(Ac)]-N-[(D)Leu]-NH_2 (SEQ ID NO: 290);

and wherein the peptide inhibitor is cyclized via a Pen-Pen disulfide bond; or via a Abu-C thioether bond;

or a pharmaceutically acceptable salt or solvate thereof.

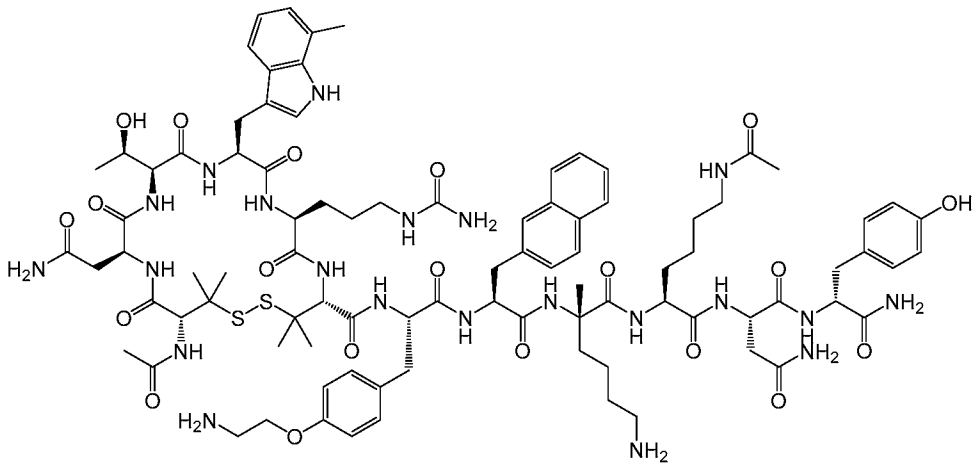
[00267] In certain embodiments, the peptide comprises or is:

Ac-[Pen]-NT-[W(7-Me)]-[Lys(Ac)]-[Pen]-Phe[4-(2-aminoethoxy)]-[2-Nal]-[a-MeLys]-[Lys(Ac)]-N-H-NH_2 (Seq. ID. No. 248)



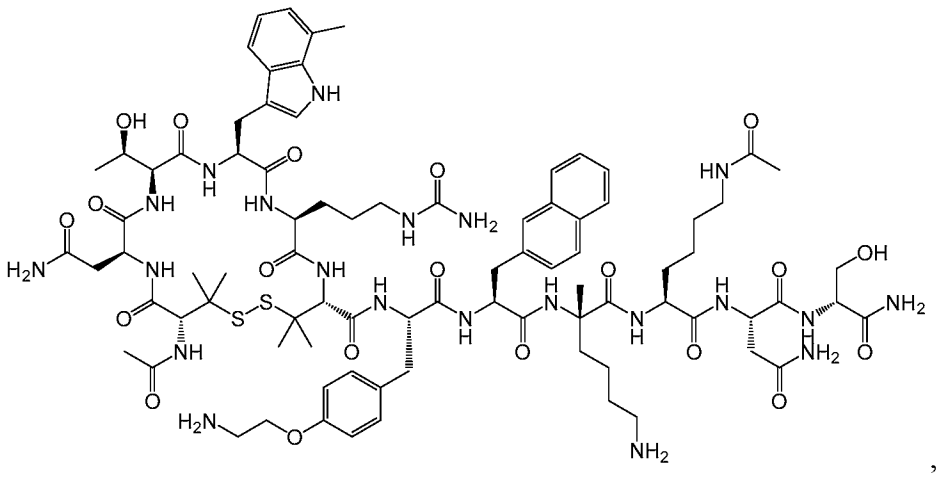
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Ac-[Pen]-NT-[W(7-Me)]-[Cit]-[Pen]-Phe[4-(2-aminoethoxy)]-[2-Nal]-[a-MeLys]-[Lys(Ac)]-N-[(D)Tyr]-NH_2 (Seq. ID. No. 259)



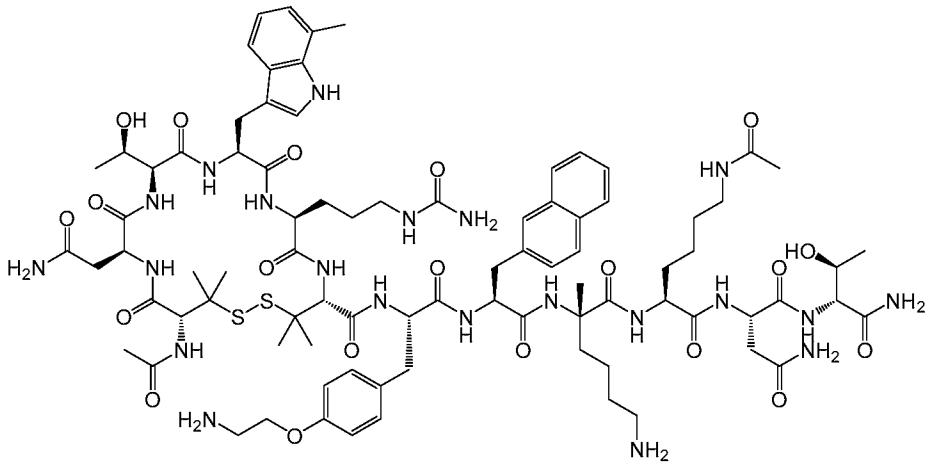
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Ac-[Pen]-NT-[W(7-Me)]-[Cit]-[Pen]-Phe[4-(2-aminoethoxy)]-[2-Nal]-[a-MeLys]-[Lys(Ac)]-N-[(D)Ser]-NH_2 (Seq. ID. No. 261)



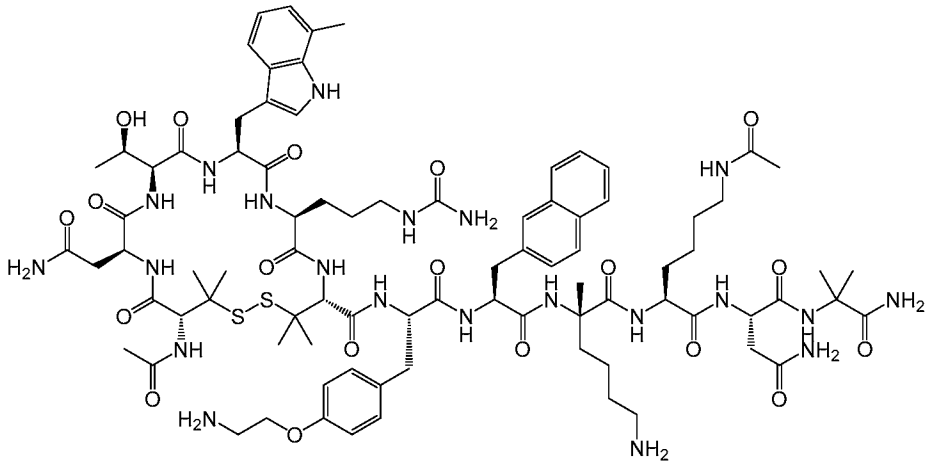
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Ac-[Pen]-NT-[W(7-Me)]-[Cit]-[Pen]-Phe[4-(2-aminoethoxy)]-[2-Nal]-[a-MeLys]-[Lys(Ac)]-N-[(D)Thr]-NH_2 (Seq. ID. No. 263)



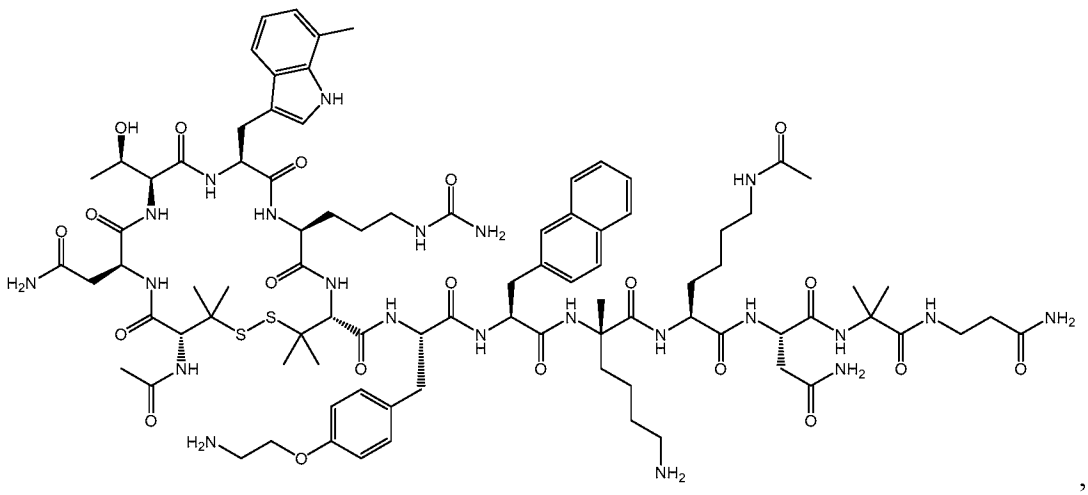
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Ac-[Pen]-NT-[W(7-Me)]-[Cit]-[Pen]-Phe[4-(2-aminoethoxy)]-[2-Nal]-[a-MeLys]-[Lys(Ac)]-N-[Aib]-NH_2 (Seq. ID. No. 264)



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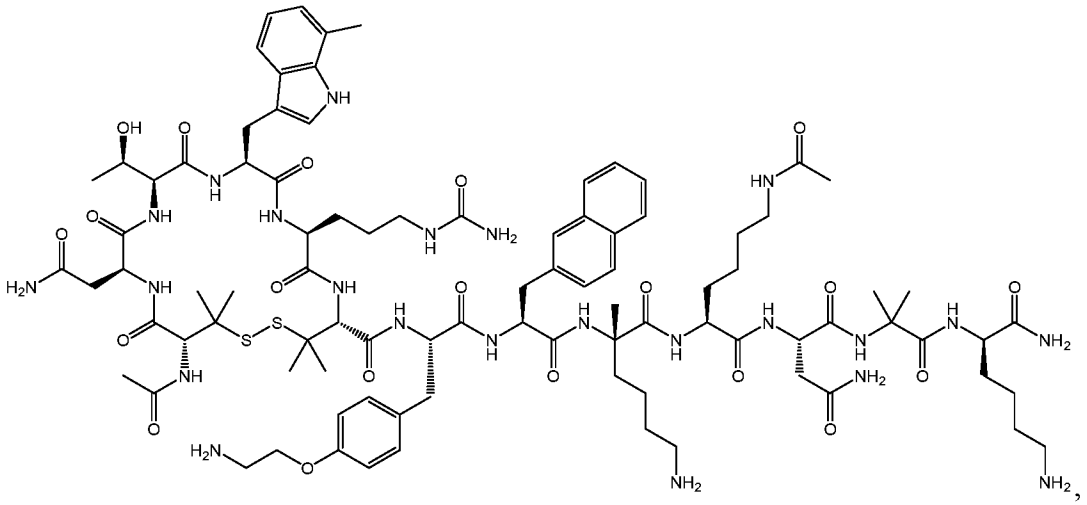
Ac-[Pen]-N-T-[W(7-Me)]-[Cit]-[Pen]-Phe[4-(2-aminoethoxy)]-[2-Nal]-[a-MeLys]-[Lys(Ac)]-N-[Aib]-[bA]-NH_2 (SEQ ID NO: 340)



,

or

Ac-[Pen]-N-T-[W(7-Me)]-[Cit]-[Pen]-Phe[4-(2-aminoethoxy)]-[2-Nal]-[a-MeLys]-[Lys(Ac)]-N-[Aib]-[(D)Lys]-NH_2 (SEQ ID NO: 344)

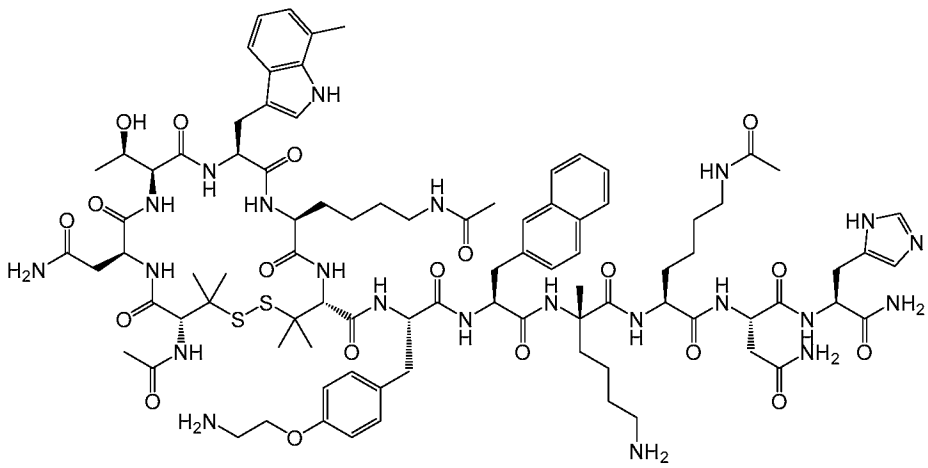


and wherein the peptide inhibitor is cyclized via a Pen-Pen disulfide bond;

or a pharmaceutically acceptable salt or solvate thereof.

[00268] In certain embodiments, the peptide comprises or is:

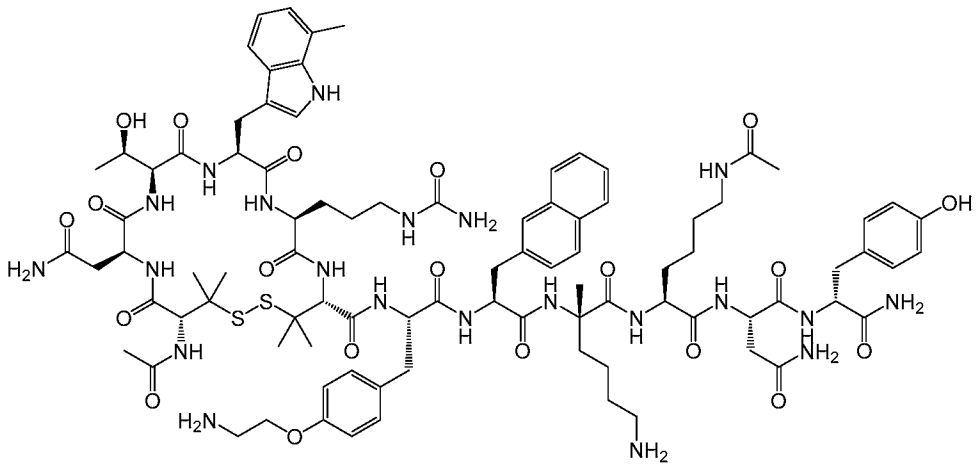
Ac-[Pen]-NT-[W(7-Me)]-[Lys(Ac)]-[Pen]-Phe[4-(2-aminoethoxy)]-[2-Nal]-[a-MeLys]-[Lys(Ac)]-N-H-NH_2 (Seq. ID. No. 248)



wherein the peptide inhibitor is cyclized via a Pen-Pen disulfide bond; or a pharmaceutically acceptable salt or solvate thereof.

[00269] In certain embodiments, the peptide comprises or is:

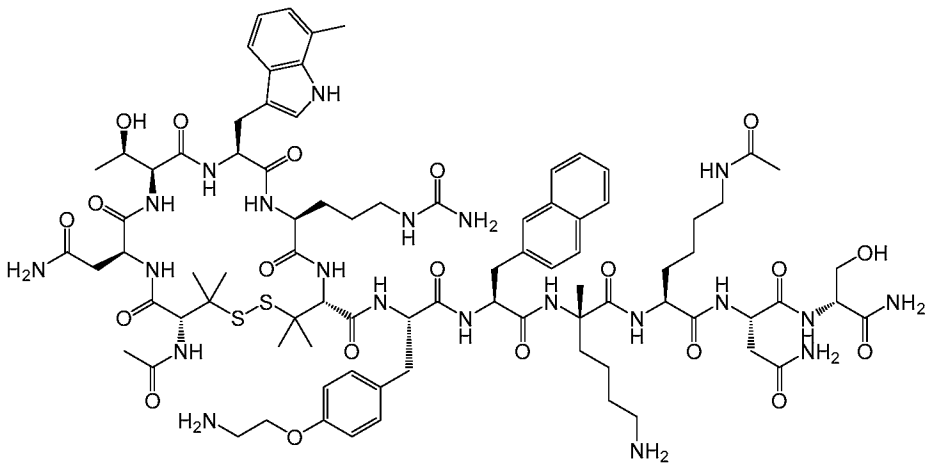
Ac-[Pen]-NT-[W(7-Me)]-[Cit]-[Pen]-Phe[4-(2-aminoethoxy)]-[2-Nal]-[a-MeLys]-[Lys(Ac)]-N-[(D)Tyr]-NH_2 (Seq. ID. No. 259)



wherein the peptide inhibitor is cyclized via a Pen-Pen disulfide bond; or a pharmaceutically acceptable salt or solvate thereof.

[00270] In certain embodiments, the peptide comprises or is:

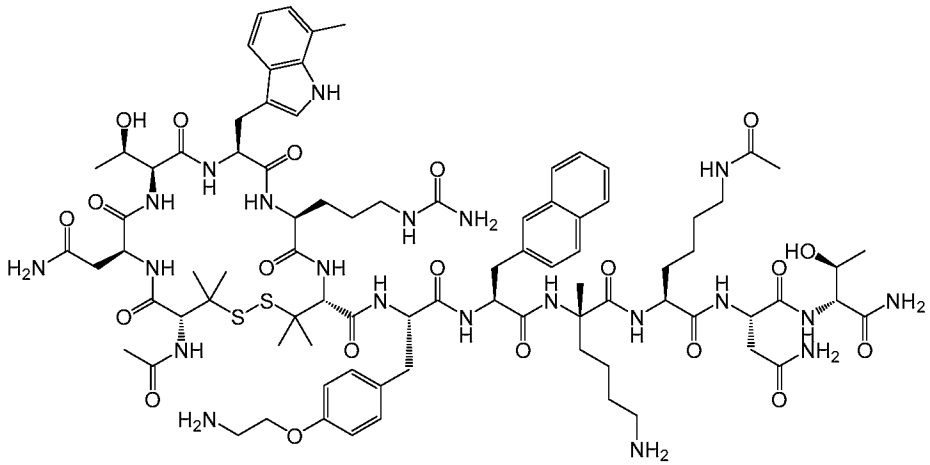
Ac-[Pen]-NT-[W(7-Me)]-[Cit]-[Pen]-Phe[4-(2-aminoethoxy)]-[2-Nal]-[a-MeLys]-[Lys(Ac)]-N-[(D)Ser]-NH_2 (Seq. ID. No. 261)



wherein the peptide inhibitor is cyclized via a Pen-Pen disulfide bond; or a pharmaceutically acceptable salt or solvate thereof.

[00271] In certain embodiments, the peptide comprises or is:

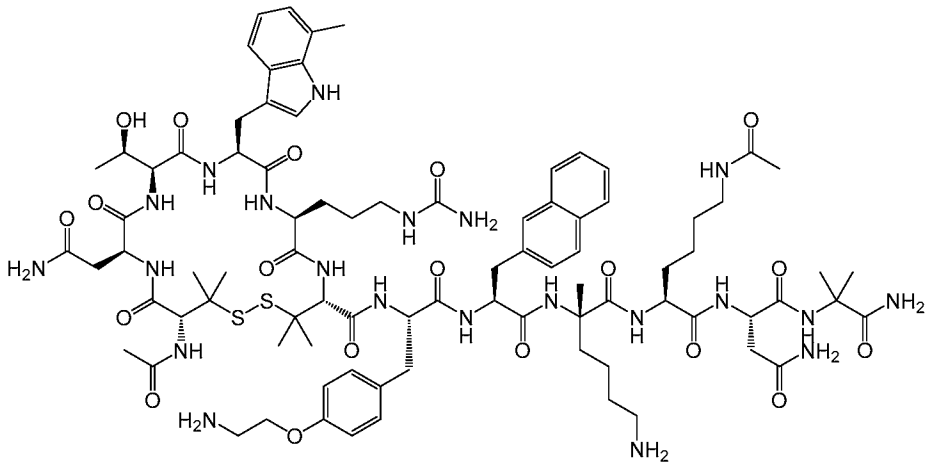
Ac-[Pen]-NT-[W(7-Me)]-[Cit]-[Pen]-Phe[4-(2-aminoethoxy)]-[2-Nal]-[a-MeLys]-[Lys(Ac)]-N-[(D)Thr]-NH_2 (Seq. ID. No. 263)



wherein the peptide inhibitor is cyclized via a Pen-Pen disulfide bond; or a pharmaceutically acceptable salt or solvate thereof.

[00272] In certain embodiments, the peptide comprises or is:

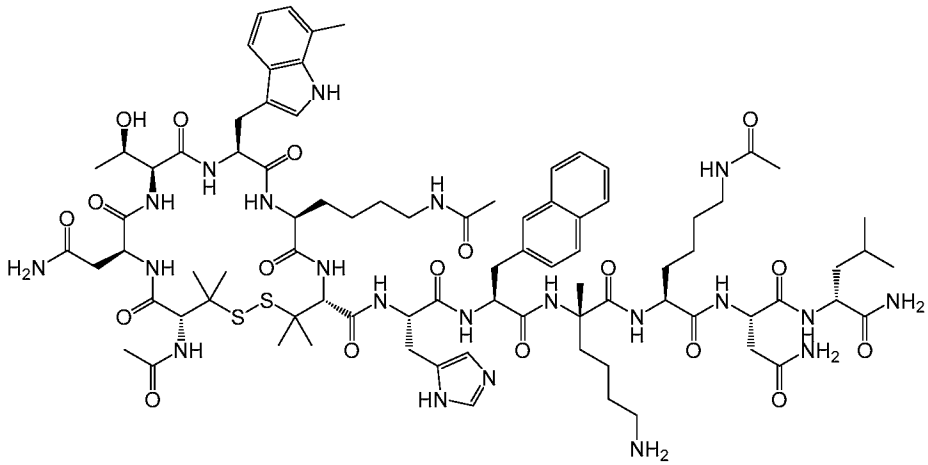
Ac-[Pen]-NT-[W(7-Me)]-[Cit]-[Pen]-Phe[4-(2-aminoethoxy)]-[2-Nal]-[a-MeLys]-[Lys(Ac)]-N-[Aib]-NH_2 (Seq. ID. No. 264)



wherein the peptide inhibitor is cyclized via a Pen-Pen disulfide bond; or a pharmaceutically acceptable salt or solvate thereof.

[00273] In certain embodiments, the peptide comprises or is:

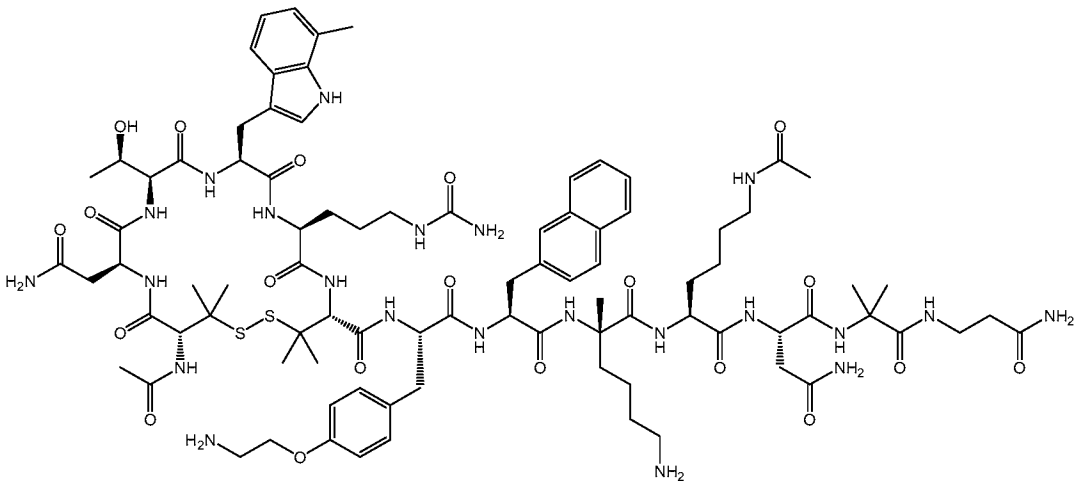
Ac-[Pen]-N-T-[W(7-Me)]-[Lys(Ac)]-[Pen]-H-[2-Nal]-[a-MeLys]-[Lys(Ac)]-N-[(D)Leu]-NH_2 (Seq. ID. No. 290)



wherein the peptide inhibitor is cyclized via a Pen-Pen disulfide bond; or a pharmaceutically acceptable salt or solvate thereof.

[00274] In certain embodiments, the peptide comprises or is:

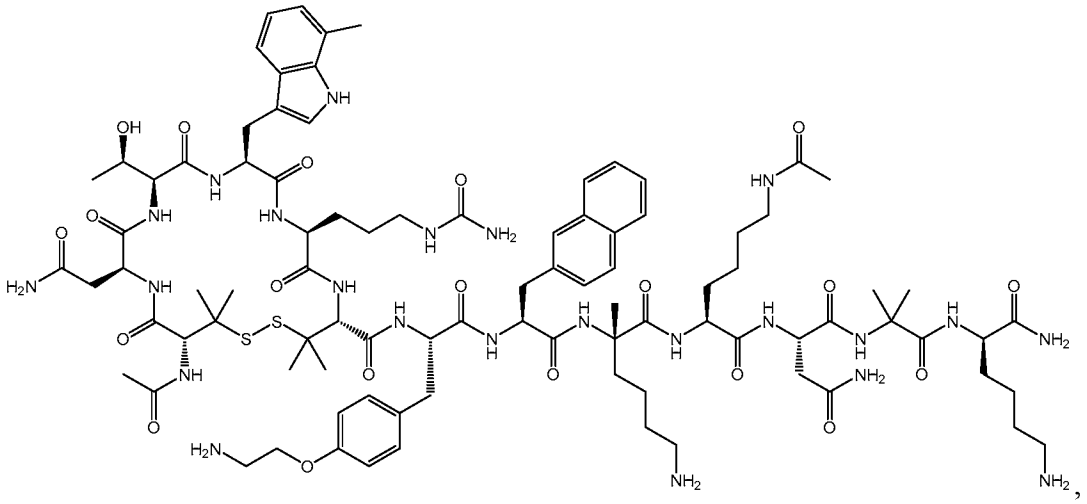
Ac-[Pen]-N-T-[W(7-Me)]-[Cit]-[Pen]-Phe[4-(2-aminoethoxy)]-[2-Nal]-[a-MeLys]-[Lys(Ac)]-N-[Aib]-[bA]-NH_2 (SEQ ID NO: 340)



wherein the peptide inhibitor is cyclized via a Pen-Pen disulfide bond; or a pharmaceutically acceptable salt or solvate thereof.

[00275] In certain embodiments, the peptide comprises or is:

Ac-[Pen]-N-T-[W(7-Me)]-[Cit]-[Pen]-Phe[4-(2-aminoethoxy)]-[2-Nal]-[a-MeLys]-[Lys(Ac)]-N-[Aib]-[(D)Lys]-NH_2 (SEQ ID NO: 344)



wherein the peptide inhibitor is cyclized via a Pen-Pen disulfide bond;

or a pharmaceutically acceptable salt or solvate thereof.

Additional Characteristics of Peptide Inhibitors

[00276] Any of the peptide inhibitors of the present invention may be further defined, e.g., as described below. It is understood that each of the further defining features described herein may be applied to any peptide inhibitors where the amino acids designated at particular positions allow the presence of the further defining feature. In particular embodiments, these features may be present in any of the peptides of Formula (I)-(XII). In more particular embodiments, these features may be present in any of the peptides of Formula Z. In most particular embodiments, these features may be present in any of the peptides of Formula Z'.

[00277] In various embodiments, R^1 is a bond, hydrogen, a C1-C6 alkyl, a C6-C12 aryl, a C6-C12 aryl C1-C6 alkyl, or a C1-C20 alkanoyl, and including PEGylated versions alone or as spacers of any of the foregoing, e.g., acetyl. It is understood that the R^1 may replace or be present in addition to the typical amine group located at the amino terminus of a peptide. It is further understood that R^1 may be absent. In certain embodiments, the peptide inhibitor comprises an N-terminus selected from hydrogen, a C1-C6 alkyl, a C6-C12 aryl, a C6-C12 aryl C1-C6 alkyl, or a C1-C20 alkanoyl, and including PEGylated versions alone or as spacers of any of the foregoing, e.g., acetyl. In particular embodiments of any of the peptide inhibitors described herein, R^1 or the N-terminal moiety is hydrogen. In certain embodiments, R^1 is a bond, e.g., a covalent bond.

[00278] In certain embodiments of any of the peptide inhibitors having any of the various Formulas set forth herein, R^1 or the N-terminal moiety is selected from methyl, acetyl, formyl, benzoyl, trifluoroacetyl, isovaleryl, isobutyryl, octanyl, and the conjugated amides of lauric

acid, hexadecanoic acid, and γ-Glu-hexadecanoic acid. In one embodiment, R^1 or the N-terminal moiety is pGlu. In certain embodiments, R^1 is hydrogen. In particular embodiments, R^1 is acetyl, whereby the peptide inhibitor is acylated at its N-terminus, e.g., to cap or protect an N-terminal amino acid residue, e.g., an N-terminal Pen residue.

[00279] In certain embodiments of any of the peptide inhibitors described herein, R^1 or the N-terminal moiety is an acid. In certain embodiments, R^1 or the N-terminal moiety is an acid selected from acetic acid, formic acid, benzoic acid, trifluoroacetic acid, isovaleric acid, isobutyric acid, octanoic acid, lauric acid, hexadecanoic acid, 4-Biphenylacetic acid, 4-fluorophenylacetic acid, gallic acid, pyroglutamic acid, cyclopentanepropionic acid, glycolic acid, oxalic acid, pyruvic acid, lactic acid, malonic acid, succinic acid, malic acid, maleic acid, fumaric acid, tartaric acid, citric acid, palmitic acid, benzoic acid, 3-(4-hydroxybenzoyl) benzoic acid, cinnamic acid, mandelic acid, 4-methylbicyclo(2.2.2)-oct-2-ene-1-carboxylic acid, glucoheptonic acid, 3-phenylpropionic acid, trimethylacetic acid, tertiary butylacetic acid, lauryl sulfuric acid, gluconic acid, glutamic acid, hydroxynaphthoic acid, salicylic acid, stearic acid, muconic acid, an alkylsulfonic acid and an arylsulfonic acid.

[00280] In particular embodiments, R^1 or the N-terminal moiety is an alkylsulfonic acid selected from methanesulfonic acid, ethanesulfonic acid, 1,2-ethane-disulfonic acid, and 2-hydroxyethanesulfonic acid.

[00281] In particular embodiments, R^1 or the N-terminal moiety is an arylsulfonic acid selected from benzenesulfonic acid, 4- chlorobenzenesulfonic acid, 2-naphthalenesulfonic acid, 4-toluenesulfonic acid, and camphorsulfonic acid.

Peptide Dimers

[00282] In certain embodiments, the present invention includes dimers of the monomer peptide inhibitors described herein, including dimers of any of the monomer peptide inhibitors described herein or in the accompanying tables. These dimers fall within the scope of the general term "peptide inhibitors" as used herein. Illustrative dimers of the present invention are also shown in the accompanying tables, which indicate the dimerized monomer subnits in brackets followed by the linker. Unless otherwise indicated, the subunits are linked via their C-termini. The term "dimer," as in a peptide dimer, refers to compounds in which two peptide monomer subinits are linked. A peptide dimer inhibitor of the present invention may comprise two identical monomer subunits, resulting in a homodimer, or two non-identical monomer subunits, resulting in a heterodimer. A cysteine dimer comprises two peptide monomer

subunits linked through a disulfide bond between a cysteine residue in one monomer subunit and a cysteine residue in the other monomer subunit.

[00283] In some embodiments, the peptide inhibitors of the present invention may be active in a dimer conformation, in particular when free cysteine residues are present in the peptide. In certain embodiments, this occurs either as a synthesized dimer or, in particular, when a free cysteine monomer peptide is present and under oxidizing conditions, dimerizes. In some embodiments, the dimer is a homodimer. In other embodiments, the dimer is a heterodimer.

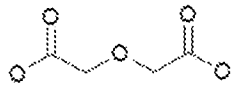
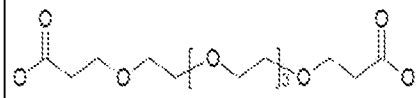
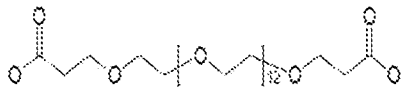
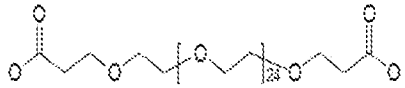
[00284] In certain embodiments, monomer subunits of the present invention may be dimerized by a suitable linking moiety, e.g., a disulphide bridge between two cysteine residues, one in each peptide monomer subunit, or by another suitable linker moiety, including but not limited to those defined herein. Some of the monomer subunits are shown having C- and N-termini that both comprise free amine. Thus, to produce a peptide dimer inhibitor, the monomer subunit may be modified to eliminate either the C- or N-terminal free amine, thereby permitting dimerization at the remaining free amine. Further, in some instances, a terminal end of one or more monomer subunits is acylated with an acylating organic compound selected from the group consisting of: Trifluoropentyl, Acetyl, Octonyl, Butyl, Pentyl, Hexyl, Palmityl, Trifluoromethyl butyric, cyclopentane carboxylic, cyclopropylacetic, 4-fluorobenzoic, 4-fluorophenyl acetic, 3-Phenylpropionic, tetrahedro-2H-pyran-4carboxylic, succinic acid, and glutaric acid. In some instances, monomer subunits comprise both a free carboxy terminal and a free amino terminal, whereby a user may selectively modify the subunit to achieve dimerization at a desired terminus. One having skill in the art therefore, will appreciate that the monomer subunits of the instant invention may be selectively modified to achieve a single, specific amine for a desired dimerization.

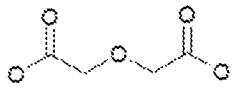
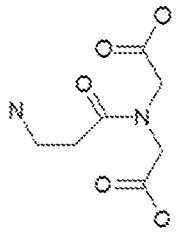
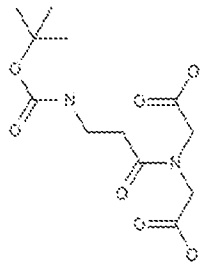
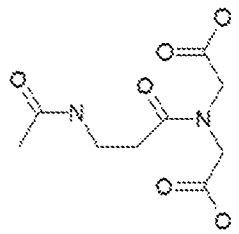
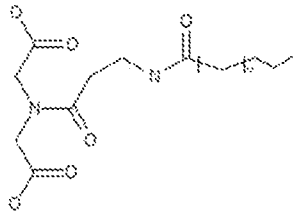
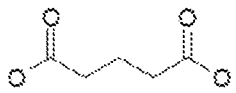
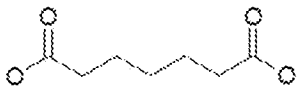
[00285] It is further understood that the C-terminal residues of the monomer subunits disclosed herein are optionally amides. Further, it is understood that, in certain embodiments, dimerization at the C-terminus is facilitated by using a suitable amino acid with a side chain having amine functionality, as is generally understood in the art. Regarding the N-terminal residues, it is generally understood that dimerization may be achieved through the free amine of the terminal residue, or may be achieved by using a suitable amino acid side chain having a free amine, as is generally understood in the art.

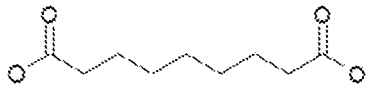
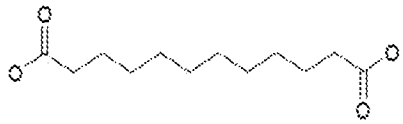
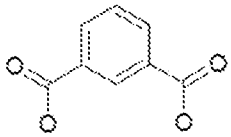
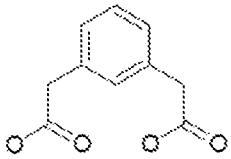
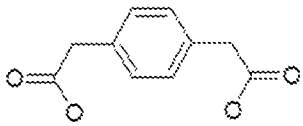
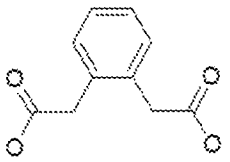
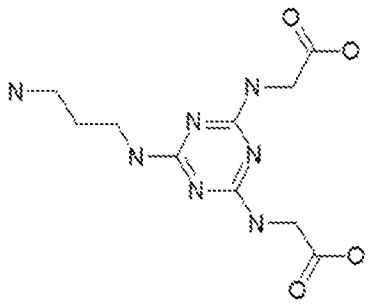
[00286] The linker moieties connecting monomer subunits may include any structure, length, and/or size that is compatible with the teachings herein. In at least one embodiment, a linker

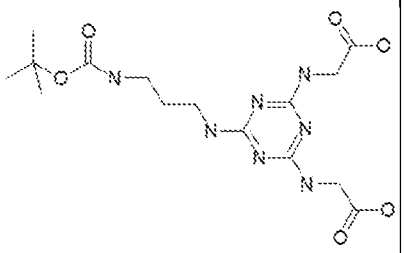
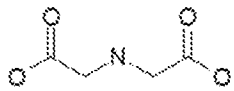
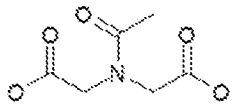
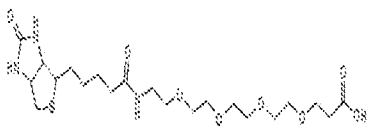
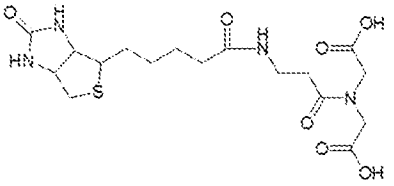
moiety is selected from the non-limiting group consisting of cysteine, lysine, DIG, PEG4, PEG4-biotin, PEG13, PEG25, PEG1K, PEG2K, PEG3.4K, PEG4K, PEG5K, IDA, ADA, Boc-IDA, Glutaric acid, Isophthalic acid, 1,3-phenylenediacetic acid, 1,4-phenylenediacetic acid, 1,2-phenylenediacetic acid, Triazine, Boc-Triazine, IDA-biotin, PEG4-Biotin, AADA, suitable aliphatics, aromatics, heteroaromatics, and polyethylene glycol based linkers having a molecular weight from approximately 400Da to approximately 40,000Da. In certain embodiments, PEG2 is $HO_2CCH_2CH_2OCH_2CH_2OCH_2CH_2CO_2H$. Non-limiting examples of suitable linker moieties are provided in Table 2.

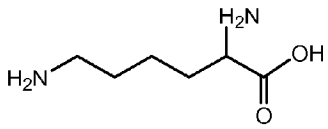
Table 2. Illustrative Linker Moieties

Abbrevation	Description	Structure
DIG	DIGlycolic acid,	
PEG4	Bifunctional PEG linker with 4 PolyEthylene Glycol units	
PEG13	Bifunctional PEG linker with 13 PolyEthylene Glycol units	
PEG25	Bifunctional PEG linker with 25 PolyEthylene Glycol units	
PEG1K	Bifunctional PEG linker with PolyEthylene Glycol Mol wt of 1000Da	
PEG2K	Bifunctional PEG linker with PolyEthylene Glycol Mol wt of 2000Da	
PEG3.4K	Bifunctional PEG linker with PolyEthylene Glycol Mol wt of 3400Da	
PEG5K	Bifunctional PEG linker with PolyEthylene Glycol Mol wt of 5000Da	

Abbrevation	Description	Structure
DIG	DIGlycolic acid	
β-Ala-IDA	β-Ala-Iminodiacetic acid	
Boc-β -Ala-IDA	Boc- β -Ala-Iminodiacetic acid	
Ac-β -Ala -IDA	Ac- β -Ala-Iminodiacetic acid	
IDA-β-Ala-Palm	Palmityl- β -Ala-Iminodiacetic acid	
GTA	Glutaric acid	
PMA	Pemilic acid	

Abbrevation	Description	Structure
AZA	Azelaic acid	
DDA	Dodecanedioic acid	
IPA	Isopthalic aicd	
1,3-PDA	1,3- Phenylenediacetic acid	
1,4-PDA	*1,4*- Phenylenediacetic acid	
1,2-PDA	1,2 - Phenylenediacetic acid	
Triazine	Amino propyl Triazine di-acid	

Abbrevation	Description	Structure
Boc-Triazine	Boc-Triazine di-acid	
ADA	Amino diacetic acid (which may also referred to as Iminodiacetic acid)	
AADA	n-Acetyl amino acetic acid (which may also referred to as N-acetyl Iminodiacetic acid)	
PEG4-Biotin	PEG4-Biotin (Product number 10199, QuantaBioDesign)	
IDA-Biotin	N-Biotin- β -Ala-Iminodiacetic acid	

Abbrevation	Description	Structure
Lys	Lysine	

[00287] In some embodiments, a peptide dimer inhibitor is dimerized via a linker moiety. In some embodiments, a peptide dimer inhibitor is dimerized via an intermolecular disulfide bond formed between two cysteine residues, one in each monomer subunit. In some embodiments, a peptide dimer inhibitor is dimerized via both a linker moiety and an intermolecular disulfide bond formed between two cysteine residues. In some embodiments, the intramolecular bond is a thioether, lactam, triazole, selenoether, diselenide or olefin, instead of the disulfide bond.

[00288] One having skill in the art will appreciate that the linker (e.g., C- and N-terminal linker) moieties disclosed herein are non-limiting examples of suitable linkers, and that the present invention may include any suitable linker moiety. Thus, some embodiments of the present invention comprises a homo- or heterodimer peptide inhibitor comprised of two monomer subunits selected from the peptides shown in any of tables herein or comprising or consisting of a sequence presented in any of tables herein, wherein the C- or N-termini of the respective monomer subunits (or internal amino acid residues) are linked by any suitable linker moiety to provide a dimer peptide inhibitor having IL-23R inhibitory activity. In certain embodiments, a linker binds to the N- or C-terminus of one monomer subunit and an internal amino acid residue of the other monomer subunit making up the dimer. In certain embodiments, a linker binds to an internal amino acid residue of one monomer subunit and an internal amino acid residue of the other monomer subunit making up the dimer. In further embodiments, a linker binds to the N-or C-terminus of both subunits.

[00289] In particular embodiments, one or both of the monomer subunits comprise the sequence or structure of any one of Formula (I)-(XIl), or shown in Table E1, Table E2, or Table E3, or any of the peptides described herein.

[00290] In certain embodiments, a peptide dimer inhibitor has the structure of Formula XII:

$$(R^1\text{-}X\text{-}R^2)_2\text{-}L \quad (XII)$$

[00291] or a pharmaceutically acceptable salt or solvate thereof,

[00292] wherein each R^1 is independently absent, a bond (e.g., a covalent bond), or R1 is selected from hydrogen, a C1-C6 alkyl, a C6-C12 aryl, a C6-C12 aryl C1-C6 alkyl, a C1-C20 alkanoyl, and including PEGylated versions alone or as spacers of any of the foregoing;

[00293] each R^2 is independently absent, a bond (e.g., a covalent bond), or selected from OH or NH_2; L is a linker moiety; andeach X is an independently selected peptide monomer subunit comprising a sequence of Formula (I)-(XII), as described herein. In certain embodiments, one or both peptide monomer subunit of a peptide dimer inhibitor is cyclized, e.g., via an intramolecular bond between X4 and X9. In certain embodiments, one or both peptide monomer subunits is linear or not cyclized.

[00294] In particular embodiments, each R^1 is independently a bond (e.g., a covalent bond), or selected from hydrogen, a C1-C6 alkyl, a C6-C12 aryl, a C6-C12 aryl C1-C6 alkyl, a C1-C20 alkanoyl, and including PEGylated versions alone or as spacers of any of the foregoing. In particular embodimetns, the N-terminus of each subunit includes a moiety selected from hydrogen, a C1-C6 alkyl, a C6-C12 aryl, a C6-C12 aryl C1-C6 alkyl, a C1-C20 alkanoyl, and including PEGylated versions alone or as spacers of any of the foregoing.

[00295] In certain embodiments of any of the peptide inhibitors having any of the various Formulae set forth herein, each R^1 (or N-terminal moiety) is selected from methyl, acetyl, formyl, benzoyl, trifluoroacetyl, isovaleryl, isobutyryl, octanyl, and the conjugated amides of lauric acid, hexadecanoic acid, and γ-Glu-hexadecanoic acid.

[00296] In particular embodiments, each R^2 (or C-terminal moiety) is independently a bond (e.g., a covalent bond), or selected from OH or NH_2.

[00297] In particular embodiments of any of the peptide dimer inhibitors described herein, either or both R^1 is hydrogen.

[00298] In particular embodiments of peptide dimer inhibitors of the present invention, the linker moiety (L) is any of the linkers described herein or shown in Table 1 or 7. In certain embodiments, L is a lysine linker, a diethylene glycol linker, an iminodiacetic acid (IDA) linker, a β-Ala-iminodiaceticacid (β-Ala-IDA) linker, or a PEG linker.

[00299] In various embodiments of any of the peptide dimer inhibitors, each of the peptide monomer subunits is attached to a linker moiety via its N-terminus, C-terminus, or an internal amino acid residue. In certain embodiments of any of the peptide dimer inhibitors, the N-terminus of each peptide monomer subunit is connected by a linker moiety.In certain

embodiments of any of the peptide dimer inhibitors, the C-terminus of each peptide monomer subunit is connected by a linker moiety. In certain embodiments of any of the peptide dimer inhibitors, each peptide monomer subunit is connected by a linker moiety attached to an internal amino acid.

Peptide Inhibitor Conjugates and Biopolymers

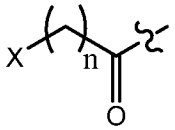
[00300] In certain embodiments, peptide inhibitors of the present invention, including both monomers and dimers, comprise one or more conjugated chemical substituents, such as lipophilic substituents and polymeric moieties, which may be referred to herein as half-life extension moieties. Without wishing to be bound by any particular theory, it is believed that the lipophilic substituent binds to albumin in the bloodstream, thereby shielding the peptide inhibitor from enzymatic degradation, and thus enhancing its half-life. In addition, it is believed that polymeric moieties enhance half-life and reduce clearance in the bloodstream.

[00301] In additional embodiments, any of the peptide inhibitors, e.g. peptides of Formula (I)-(XII) further comprise a linker moiety attached to an amino acid residue present in the inhibitor, e.g., a linker moiety may be bound to a side chain of any amino acid of the peptide inhibitor, to the N-terminal amino acid of the peptide inhibitor, or to the C-terminal amino acid of the peptide inhibitor.

[00302] In additional embodiments, any of the peptide inhibitors e.g. peptides of Formulas (I)-(XII), further comprise half-life extension moiety attached to an amino acid residue present in the inhibitor, e.g., a half-life extension moiety may be bound to a side chain of any amino acid of the peptide inhibitor, to the N-terminal amino acid of the peptide inhibitor, or to the C-terminal amino acid of the peptide inhibitor.

[00303] In additional embodiments, any of the peptide inhibitors e.g. peptides of Formulas (I)-(XII), further comprise half-life extension moiety attached to a linker moiety that is attached to an amino acid residue present in the inhibitor, e.g., a half-life extension moiety may be bound to a linker moiety that is bound to a side chain of any amino acid of the peptide inhibitor, to the N-terminal amino acid of the peptide inhibitor, or to the C-terminal amino acid of the peptide inhibitor.

[00304] In particular embodiments, a peptide inhibitor comprises a half-life extension moiety having the structure shown below, wherein n=0 to 24 or n=14 to 24:

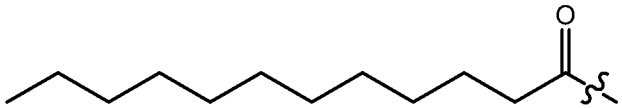
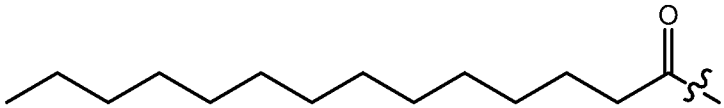
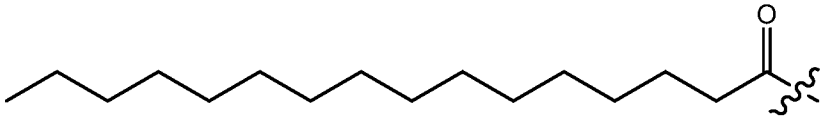
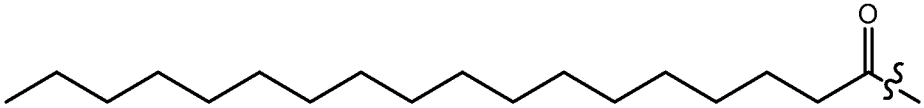
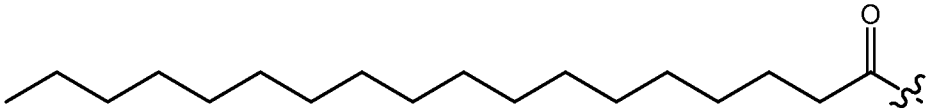
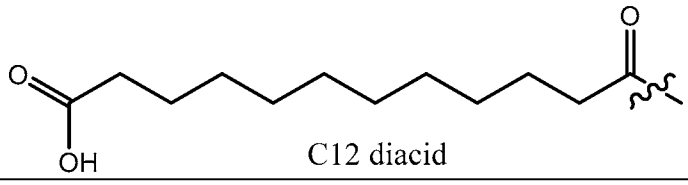
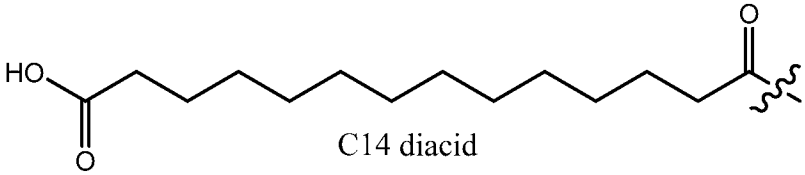
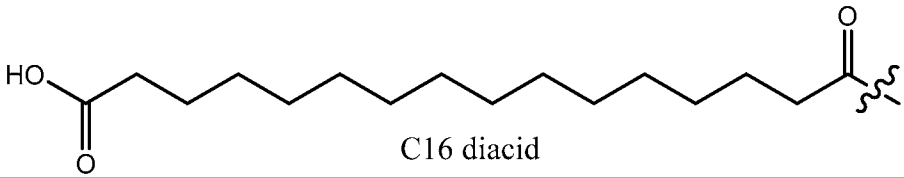


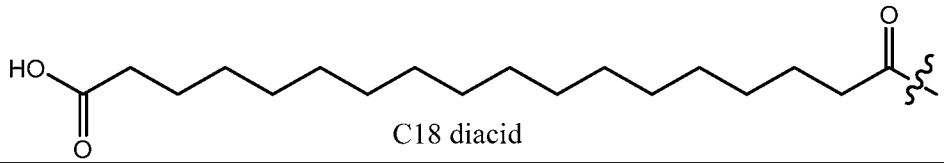
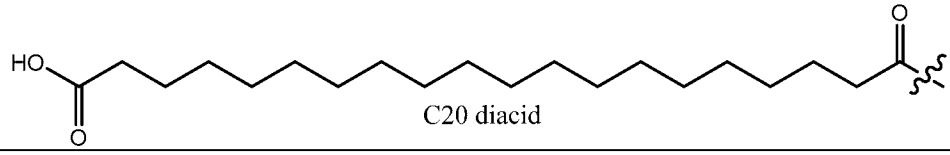
n=0 to 24

X=CH_3, CO_2H, NH_2, OH

[00305] In certain embodiments, a peptide inhibitor of the present invention comprises a half-life extension moiety shown in Table 8.

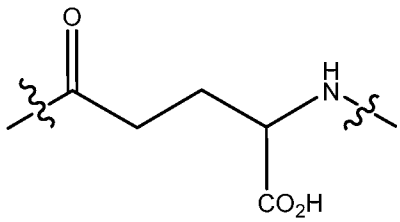
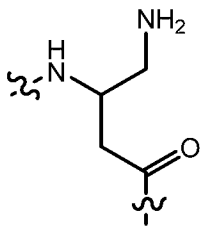
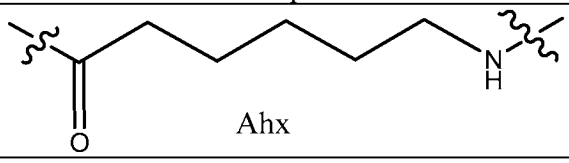
Table 8. Illustrative Half-Life Extension Moieties

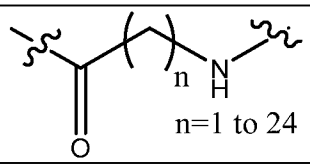
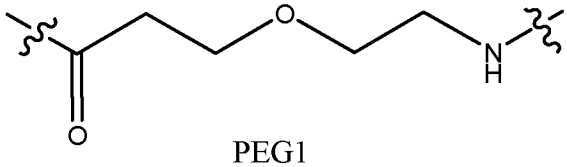
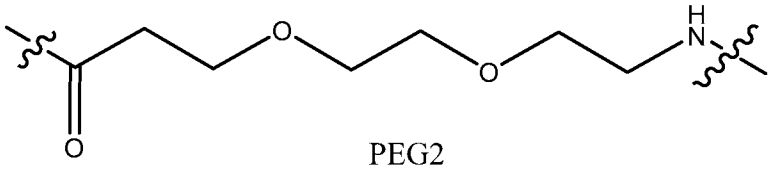
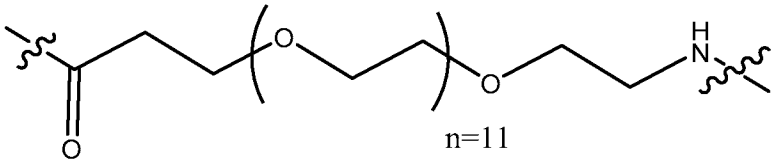
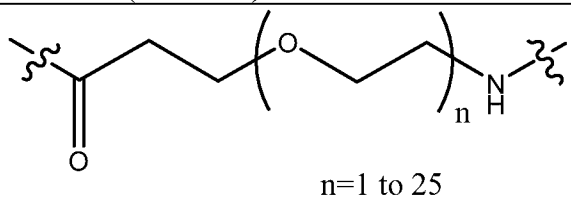
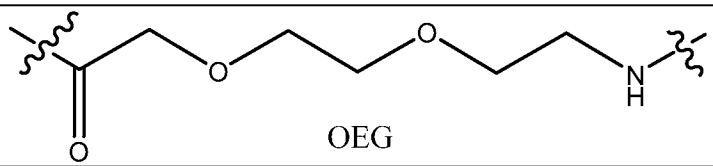
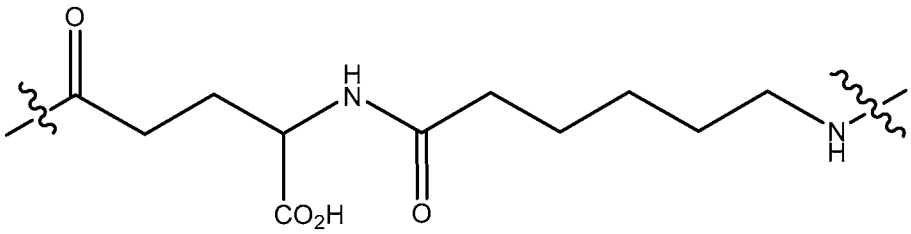
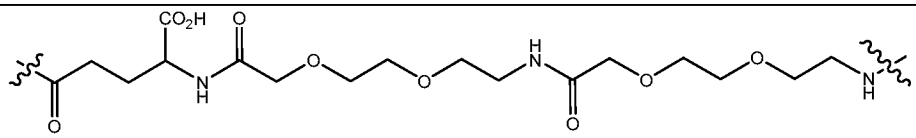
#	Half-Life Extension Moietys
C1	 C12 (Lauric acid)
C2	 C14 (Mysteric acid)
C3	 C16 (Palm or Palmitic acid)
C4	 C18 (Stearic acid)
C5	 C20
C6	 C12 diacid
C7	 C14 diacid
C8	 C16 diacid

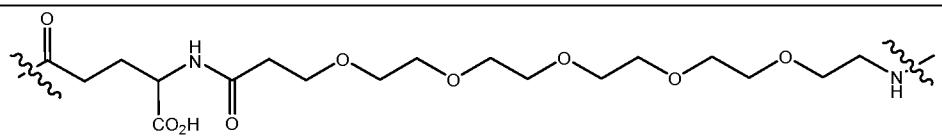
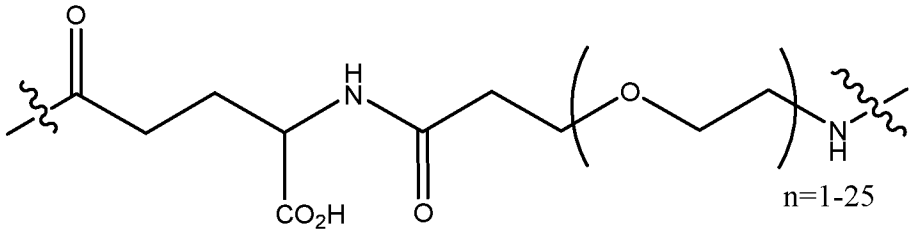
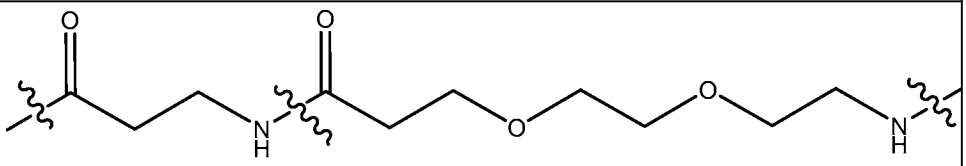
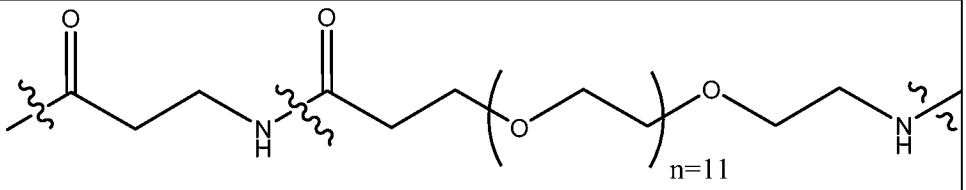
#	Half-Life Extension Moietys
C9	 C18 diacid
C10	 C20 diacid

[00306] In certain embodiments, a half-life extension moiety is bound directly to a peptide inhibitor, while in other embodiments, a half-life extension moiety is bound to the peptide inhibitor via a linker moiety, e.g., any of those depicted in Tables 1, 2 or 4.

Table 4. Illustrative Linker Moieties

#	Linker Moiety
L1	 IsoGlu
L2	 Dapa
L3	 Ahx
L4	Lipidic based linkers:

#	Linker Moiety
	 n=1 to 24
L5	 PEG1
L6	 PEG2
L7	 n=11 PEG11 (40 atoms) also known as PEG12
L8	 n=1 to 25 PEG based linkers
L9	 OEG
L10	 IsoGlu-Ahx
L11	 IsoGlu-OEG-OEG

#	Linker Moiety
L12	 IsoGlu-PEG5
L13	 n=1-25 IsoGlu-PEGn
L14	 βAla-PEG2
L15	 n=11 βAla-PEG11 (40 atoms)

[00307] In particular embodiments, a peptide inhibitor of the present invention comprises any of the linker moieties shown in Tables 2 or 4 and any of the half-life extension moieties shown in Table 3, including any of the following combinations shown in Table 5.

Table 5. Illustrative Combinations of Linkers and Half-Life Extension Moieties in Peptide Inhibitors

Linker	Half-Life Extension Moiety		Linker	Half-Life Extension Moiety		Linker	Half-Life Extension Moiety
L1	C1		L1	C2		L1	C3
L2	C1		L2	C2		L2	C3
L3	C1		L3	C2		L3	C3

L4	C1		L4	C2		L4	C3
L5	C1		L5	C2		L5	C3
L6	C1		L6	C2		L6	C3
L7	C1		L7	C2		L7	C3
L8	C1		L8	C2		L8	C3
L9	C1		L9	C2		L9	C3
L10	C1		L10	C2		L10	C3
L11	C1		L11	C2		L11	C3
L12	C1		L12	C2		L12	C3
L13	C1		L13	C2		L13	C3
L14	C1		L14	C2		L14	C3
L15	C1		L15	C2		L15	C3

Linker	Half-Life Extension Moiety		Linker	Half-Life Extension Moiety		Linker	Half-Life Extension Moiety
L1	C4		L1	C5		L1	C6
L2	C4		L2	C5		L2	C6
L3	C4		L3	C5		L3	C6
L4	C4		L4	C5		L4	C6
L5	C4		L5	C5		L5	C6
L6	C4		L6	C5		L6	C6
L7	C4		L7	C5		L7	C6
L8	C4		L8	C5		L8	C6
L9	C4		L9	C5		L9	C6
L10	C4		L10	C5		L10	C6
L11	C4		L11	C5		L11	C6
L12	C4		L12	C5		L12	C6
L13	C4		L13	C5		L13	C6
L14	C4		L14	C5		L14	C6
L15	C4		L15	C5		L15	C6

Linker	Half-Life Extension Moiety		Linker	Half-Life Extension Moiety		Linker	Half-Life Extension Moiety
L1	C7		L1	C8		L1	C9
L2	C7		L2	C8		L2	C9
L3	C7		L3	C8		L3	C9
L4	C7		L4	C8		L4	C9
L5	C7		L5	C8		L5	C9
L6	C7		L6	C8		L6	C9
L7	C7		L7	C8		L7	C9
L8	C7		L8	C8		L8	C9
L9	C7		L9	C8		L9	C9
L10	C7		L10	C8		L10	C9
L11	C7		L11	C8		L11	C9
L12	C7		L12	C8		L12	C9
L13	C7		L13	C8		L13	C9
L14	C7		L14	C8		L14	C9
L15	C7		L15	C8		L15	C9

Linker	Half-Life Extension Moiety		Linker	Half-Life Extension Moiety		Linker	Half-Life Extension Moiety
L1	C10		L6	C10		L11	C10
L2	C10		L7	C10		L12	C10
L3	C10		L8	C10		L13	C10
L4	C10		L9	C10		L14	C10
L5	C10		L10	C10		L15	C10

[00308] In some embodiments there may be multiple linkers present between the peptide the conjugated moiety, e.g., half-life extension moiety, e.g., as depicted in Table 6.

Table 6. Illustrative Combinations of Linkers and Half-Life Extension Moieties in Peptide Inhibitors

Linker	Half-Life Extension Moiety
L1-L2	C10
L2-L5-L3	C10
L3-L8	C10
L1-L2-L3	C10
L5-L3-L3-L3	C10

Linker	Half-Life Extension Moiety
L1-L2	C8
L2-L5-L3	C8
L3-L8	C8
L1-L2-L3	C8
L5-L3-L3-L3	C8

[00309] In certain embodiments, the half-life of a peptide inhibitor of the invention that includes a conjugated chemical substituent, i.e., a half-life extension moiety, is at least 100%, at least 120%, at least 150%, at least 200%, at least 250%, at least 300%, at least 400%, or at least 500% of the half-life of the same peptide inhibitor but without the conjugated chemical substituent. In certain embodiments, the lipophilic substituents and/or polypermic moieties enhance the permeability of the peptide inhibitor through the epithelium and/or its retention in the lamina propria. In certain embodiments, the permeability through the epithelium and/or the retention in the lamina propria of a peptide inhibitor of the invention that includes a conjugated chemical substituent is at 100%, at least 120%, at least 150%, at least 200%, at least 250%, at least 300%, at least 400%, or at least 500% of the half-life of the same peptide inhibitor but without the conjugated chemical substituent.

[00310] In one embodiment, a side chain of one or more amino acid residues (e.g., Lys residues) in a peptide inhibitor of the invention is conjugated (e.g., covalently attached) to a lipophilic substituent. The lipophilic substituent may be covalently bonded to an atom in the amino acid side chain, or alternatively may be conjugated to the amino acid side chain via one or more spacers. The spacer, when present, may provide spacing between the peptide analogue and the lipophilic substituent. In particular embodiments, the peptide inhibitor comprises any of the conjugated moieties shown in peptides disclosed in Tables 2-6.

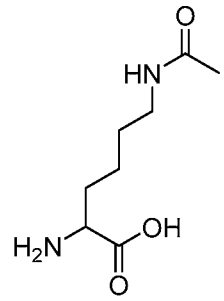
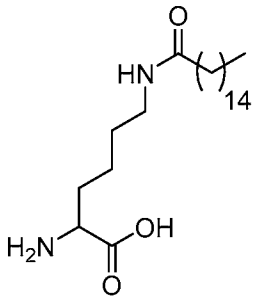
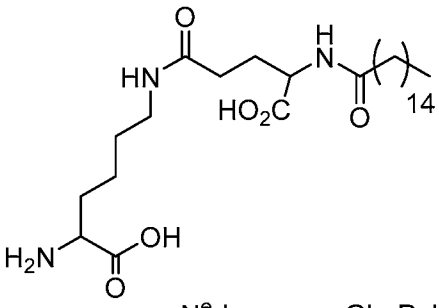
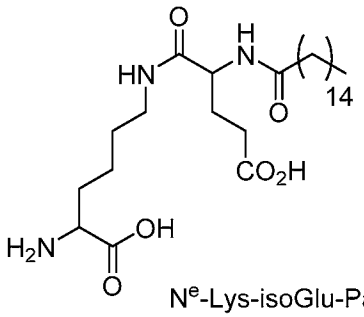
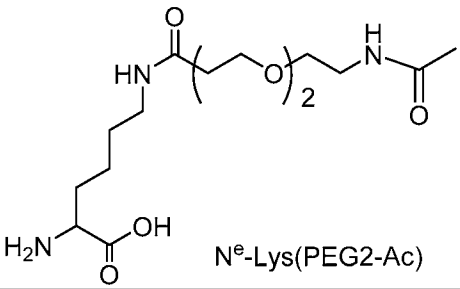
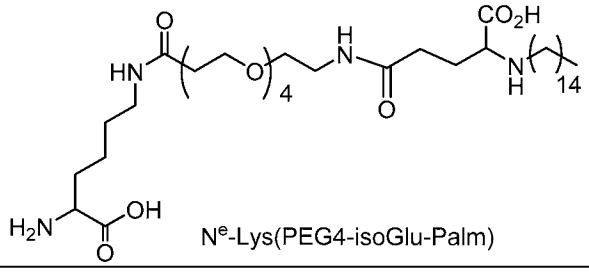
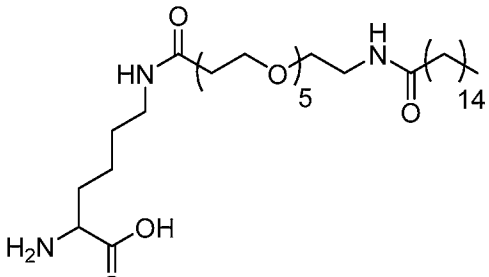
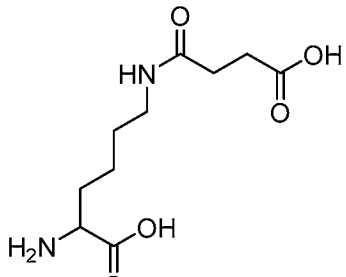
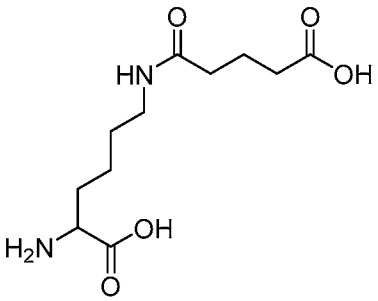
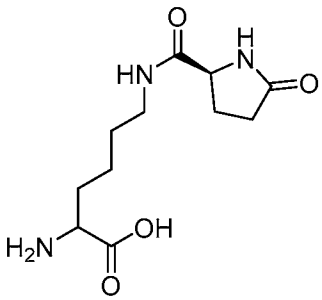
[00311] In certain embodiments, the lipophilic substituent may comprise a hydrocarbon chain having from 4 to 30 C atoms, for example at least 8 or 12 C atoms, and preferably 24 C atoms

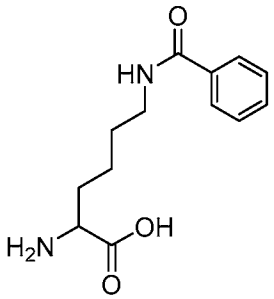
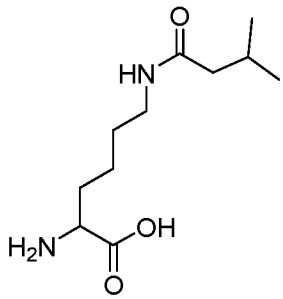
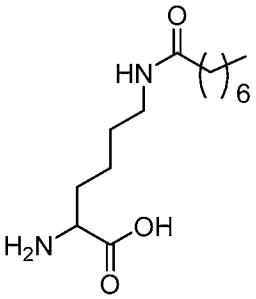
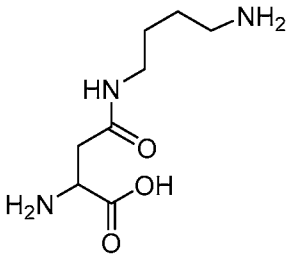
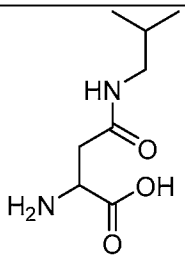
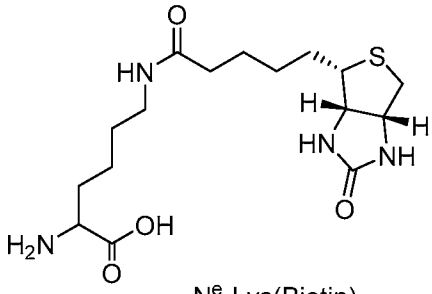
or fewer, or 20 C atoms or fewer. The hydrocarbon chain may be linear or branched and may be saturated or unsaturated. In certain embodiments, the hydrocarbon chain is substituted with a moiety which forms part of the attachment to the amino acid side chain or the spacer, for example an acyl group, a sulfonyl group, an N atom, an O atom or an S atom. In some embodiments, the hydrocarbon chain is substituted with an acyl group, and accordingly the hydrocarbon chain may form part of an alkanoyl group, for example palmitoyl, caproyl, lauroyl, myristoyl or stearoyl.

[00312] A lipophilic substituent may be conjugated to any amino acid side chain in a peptide inhibitor of the invention. In certain embodiment, the amino acid side chain includes a carboxy, hydroxyl, thiol, amide or amine group, for forming an ester, a sulphonyl ester, a thioester, an amide or a sulphonamide with the spacer or lipophilic substituent. For example, the lipophilic substituent may be conjugated to Asn, Asp, Glu, Gln, His, Lys, Arg, Ser, Thr, Tyr, Trp, Cys or Dbu, Dpr or Orn. In certain embodiments, the lipophilic substituent is conjugated to Lys. An amino acid shown as Lys in any of the Formula provided herein may be replaced by, e.g., Dbu, Dpr or Orn where a lipophilic substituent is added.

[00313] In certain embodiments, the peptide inhibitors of the present invention may be modified, e.g., to enhance stability, increase permeability, or enhance drug like characteristics, through conjugation of a chemical moiety to one or more amino acid side chain within the peptide. For example, the N(epsilon) of lysine N(epsilon), the β–carboxyl of aspartic, or the γ–carboxyl of glutamic acid may be appropriately functionalized. Thus, to produce the modified peptide, an amino acid within the peptide may be appropriately modified. Further, in some instances, the side chain is acylated with an acylating organic compound selected from the group consisting of: Trifluoropentyl, Acetyl, Octonyl, Butyl, Pentyl, Hexyl, Palmityl, Trifluoromethyl butyric, cyclopentane carboxylic, cyclopropylacetic, 4-fluorobenzoic, 4-fluorophenyl acetic, 3-Phenylpropionic, tetrahedro-2H-pyran-4carboxylic, succinic acid glutaric acid or bile acids. One having skill is the art will appreciate that a series of conjugates can be linked, e.g., for example PEG4, isoglu and combinations thereof. One having skill is the art will appreciate that an amino acid with the peptide can be isosterically replaced, for example, Lys may be replaced for Dap, Dab, α-MeLys orOrn. Examples of modified residues within a peptide are shown in Table 7.

Table 7. Examples of modified Lysine, Asp and Asn within the peptide

 N^e-Lys(Ac)	 N^e-Lys(Palm)
 N^e-Lys-gamaGlu-Palm	 N^e-Lys-isoGlu-Palm
 N^e-Lys(PEG2-Ac)	 N^e-Lys(PEG4-isoGlu-Palm)
 N^e-Lys$(PEG)_5$-Palm	 N^e-Lys(succinic acid)
 N^e-Lys(glutaric acid)	 N^e-Lys(Pyroglutaric acid)

 N^e-Lys(Benzoic acid)	 N^e-Lys(IVA)
 N^e-Lys(octanoic acid)	 Asp(1,4 diaminobutane)
 Asn(isobutyl)	 N^e-Lys(Biotin)

[00314] In further embodiments of the present invention, alternatively or additionally, a side-chain of one or more amino acid residues in a peptide inhibitor of the invention is conjugated to a polymeric moiety, for example, in order to increase solubility and/or half-life *in vivo* (e.g. in plasma) and/or bioavailability. Such modifications are also known to reduce clearance (e.g. renal clearance) of therapeutic proteins and peptides.

[00315] As used herein, "Polyethylene glycol" or "PEG" is a polyether compound of general Formula H-(O-CH2-CH2)n-OH. PEGs are also known as polyethylene oxides (PEOs) or polyoxyethylenes (POEs), depending on their molecular weight PEO, PEE, or POG, as used herein, refers to an oligomer or polymer of ethylene oxide. The three names are chemically synonymous, but PEG has tended to refer to oligomers and polymers with a molecular mass below 20,000 Da, PEO to polymers with a molecular mass above 20,000 Da, and POE to a polymer of any molecular mass. PEG and PEO are liquids or low-melting solids, depending on their molecular weights. Throughout this disclosure, the 3 names are used indistinguishably.

PEGs are prepared by polymerization of ethylene oxide and are commercially available over a wide range of molecular weights from 300 Da to 10,000,000 Da. While PEG and PEO with different molecular weights find use in different applications, and have different physical properties (e.g. viscosity) due to chain length effects, their chemical properties are nearly identical. The polymeric moiety is preferably water-soluble (amphiphilic or hydrophilic), non-toxic, and pharmaceutically inert. Suitable polymeric moieties include polyethylene glycols (PEG), homo- or co-polymers of PEG, a monomethyl-substituted polymer of PEG (mPEG), or polyoxyethylene glycerol (POG). See, for example, Int. J. Hematology 68:1 (1998); Bioconjugate Chem. 6:150 (1995); and Crit. Rev. Therap. Drug Carrier Sys. 9:249 (1992). Also encompassed are PEGs that are prepared for purpose of half life extension, for example, mono-activated, alkoxy-terminated polyalkylene oxides (POA's) such as mono-methoxy-terminated polyethyelene glycols (mPEG's); bis activated polyethylene oxides (glycols) or other PEG derivatives are also contemplated. Suitable polymers will vary substantially by weights ranging from about 200 Da to about 40,000 Da or from about 200 Da to about 60,000 Da are usually selected for the purposes of the present invention. In certain embodiments, PEGs having molecular weights from 200 to 2,000 or from 200 to 500 are used. Different forms of PEG may also be used, depending on the initiator used for the polymerization process – a common common initiator is a monofunctional methyl ether PEG, or methoxypoly(ethylene glycol), abbreviated mPEG.

[00316] Lower-molecular-weight PEGs are also available as pure oligomers, referred to as monodisperse, uniform, or discrete. These are used in certain embodiments of the present invention.

[00317] PEGs are also available with different geometries: branched PEGs have three to ten PEG chains emanating from a central core group; star PEGs have 10 to 100 PEG chains emanating from a central core group; and comb PEGs have multiple PEG chains normally grafted onto a polymer backbone. PEGs can also be linear. The numbers that are often included in the names of PEGs indicate their average molecular weights (e.g. a PEG with n = 9) would have an average molecular weight of approximately 400 daltons, and would be labeled PEG 400.

[00318] As used herein, "PEGylation" is the act of covalently coupling a PEG structure to the peptide inhibitor of the invention, which is then referred to as a "PEGylated peptide inhibitor". In certain embodiments, the PEG of the PEGylated side chain is a PEG with a molecular weight

from about 200 to about 40,000. In some embodiments, a spacer of a peptide of Formula I, Formula I', or Formula I'' is PEGylated. In certain embodiments, the PEG of a PEGylated spacer is PEG3, PEG4, PEG5, PEG6, PEG7, PEG8, PEG9, PEG10, or PEG11. In certain embodiments, the PEG of a PEGylated spacer is PEG3 or PEG8.

[00319] Other suitable polymeric moieties include poly-amino acids such as poly-lysine, poly-aspartic acid and poly-glutamic acid (see for example Gombotz, et al. (1995), Bioconjugate Chem., vol. 6: 332-351; Hudecz, et al. (1992), Bioconjugate Chem., vol. 3, 49-57 and Tsukada, et al. (1984), J. Natl. Cancer Inst., vol. 73, : 721-729. The polymeric moiety may be straight-chain or branched. In some embodiments, it has a molecular weight of 500-40,000 Da, for example 500-10,000 Da, 1000-5000 Da, 10,000-20,000 Da, or 20,000-40,000 Da.

[00320] In some embodiments, a peptide inhibitor of the invention may comprise two or more such polymeric moieties, in which case the total molecular weight of all such moieties will generally fall within the ranges provided above.

[00321] In some embodiments, the polymeric moiety is coupled (by covalent linkage) to an amino, carboxyl or thiol group of an amino acid side chain. Certain examples are the thiol group of Cys residues and the epsilon amino group of Lys residues, and the carboxyl groups of Asp and Glu residues may also be involved.

[00322] The skilled worker will be well aware of suitable techniques which can be used to perform the coupling reaction. For example, a PEG moiety bearing a methoxy group can be coupled to a Cys thiol group by a maleimido linkage using reagents commercially available from Nektar Therapeutics AL. See also WO 2008/101017, and the references cited above, for details of suitable chemistry. A maleimide-functionalised PEG may also be conjugated to the side-chain sulfhydryl group of a Cys residue.

[00323] As used herein, disulfide bond oxidation can occur within a single step or is a two step process. As used herein, for a single oxidation step, the trityl protecting group is often employed during assembly, allowing deprotection during cleavage, followed by solution oxidation. When a second disulfide bond is required, one has the option of native or selective oxidation. For selective oxidation requiring orthogonal protecting groups, Acm and Trityl is used as the protecting groups for cysteine. Cleavage results in the removal of one protecting pair of cysteine allowing oxidation of this pair. The second oxidative deprotection step of the cysteine protected Acm group is then performed. For native oxidation, the trityl protecting

group is used for all cysteines, allowing for natural folding of the peptide. A skilled worker will be well aware of suitable techniques which can be used to perform the oxidation step.

[00324] Several chemical moieties, including poly(ethylene)glycol, react with functional groups present in the twenty naturally occurring amino acids, such as, for example, the epsilon amino group in lysine amino acid residues, the thiol present in cysteine amino acid residues, or other nucleophilic amino acid side chains. When multiple naturally occurring amino acids react in a peptide inhibitor, these non-specific chemical reactions result in a final peptide inhibitor that contains many isomers of peptides conjugated to one or more poly(ethylene)glycol strands at different locations within the peptide inhibitor.

[00325] One advantage of certain embodiments of the present invention includes the ability to add one or more chemical moiety (such as PEG) by incorporating one or more non-natural amino acid(s) that possess unique functional groups that react with an activated PEG by way of chemistry that is unreactive with the naturally occurring amino acids present in the peptide inhibitor. For example, azide and alkyne groups are unreactive with all naturally occurring functional groups in a protein. Thus, a non-natural amino acid may be incorporated in one or more specific sites in a peptide inhibitor where PEG or another modification is desired without the undesirable non-specific reactions. In certain embodiments, the particular chemistry involved in the reaction results in a stable, covalent link between the PEG strand and the peptide inhibitor. In addition, such reactions may be performed in mild aqueous conditions that are not damaging to most peptides. In certain embodiments, the non-natural amino acid residue is AHA.

[00326] Chemical moieties attached to natural amino acids are limited in number and scope. By contrast, chemical moieties attached to non-natural amino acids can utilize a significantly greater spectrum of useful chemistries by which to attach the chemical moiety to the target molecule. Essentially any target molecule, including any protein (or portion thereof) that includes a non-natural amino acid, e.g., a non-natural amino acid containing a reactive site or side chain where a chemical moiety may attach, such as an aldehyde- or keto-derivatized amino acid, can serve as a substrate for attaching a chemical moiety.

[00327] Numerous chemical moieties may be joined or linked to a particular molecule through various known methods in the art. A variety of such methods are described in U.S. Patent No. 8,568,706. As an illustrative example, azide moieties may be useful in conjugating chemical moieties such as PEG or others described herein. The azide moiety serves as a reactive

functional group, and is absent in most naturally occurring compounds (thus it is unreactive with the native amino acids of naturally occurring compounds). Azides also undergo a selective ligation with a limited number of reaction partners, and azides are small and can be introduced to biological samples without altering the molecular size of significantly. One reaction that allows incorporation or introduction of azides to molecules is the copper-mediated Huisgen [3+2] cycloaddition of an azide. This reaction can be used for the selective PEGylation of peptide inhibitors. (Tornoe et al., J. Org. Chem. 67: 3057, 2002; Rostovtsev et al., Angew. Chem., Int. Ed. 41: 596, 2002; and Wang et al., J. Am. Chem. Soc. 125: 3192, 2003, Speers et al., J. Am. Chem. Soc., 2003, 125, 4686).

Synthesis of Peptide Inhibitors

[00328] The peptide inhibitors of the present invention may be synthesized by many techniques that are known to those skilled in the art. In certain embodiments, monomer subunits are synthesized, purified, and dimerized using the techniques described in the accompanying Examples. In certain embodiments, the present invention provides a method of producing a peptide inhibitor (or monomer subunit thereof) of the present invention, comprising chemically synthesizing a peptide comprising, consisting of, or consisting essentially of a peptide having an amino acid sequence described herein, including but not limited to any of the amino acid sequences set forth in any of Formulas I, II or tables herein. In other embodiments, the peptide is recombinantly synthesized, instead of being chemically synthesized. In certain embodiments, the peptide inhibitor is a dimer, and the method comprises synthezing both monomer subunits of the peptide dimer inhibitor and then dimerizing the two monomer subunits to produce the peptide dimer inhibitor. In various embodiments, dimerization is accomplished via any of the various methods described herein. In particular embodiments, methods of producing a peptide inhibitor (or monomer subunit thereof) further comprise cyclizing the peptide inhibitor (or monomer subunit thereof) after its synthesis. In particular embodiments, cyclization is accomplished via any of the various methods described herein. In certain embodiments, the present invention provides a method of producing a peptide inhibitor (or monomer subunit thereof) of the present invention, comprising introducing an intramolecular bond, e.g., a disulfide, an amide, or a thioether bond between two amino acids residues within a peptide comprising, consisting of, or consisting essentially of a peptide having an amino acid sequence described herein, including but not limited to any of the amino acid sequences set forth in any of Formulas (I) – (IX), the accompanying Examples or Tables.

[00329] In related embodiments, the present invention includes polynucleotides that encode a polypeptide having a sequence set forth in any one of Formulas (I)-(IX), or the accompanying Examples or Table.

[00330] In addition, the present invention includes vectors, e.g., expression vectors, comprising a polynucleotide of the present invention.

Methods of Treatment

[00331] In certain embodiments, the present invention includes methods of inhibiting IL-23 binding to an IL-23R on a cell, comprising contacting the IL-23 with a peptide inhibitor of the present invention. In certain embodiments, the cell is a mammalian cell. In particular embodiments, the method is 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.

[00332] In certain embodiments, the present invention includes methods of inhibiting IL-23 signaling by a cell, comprising contacting the IL-23 with a peptide inhibitor of the present invention. 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 signalling may be determined by measuring changes in phospho-STAT3 levels in the cell.

[00333] In some embodiments, the present invention provides methods for treating a subject afflicted with a condition or indication associated with IL-21 or IL-23R (e.g., activation of the IL-23/IL-23R signaling pathway), wherein the method comprises administering to the subject a peptide inhibitor of the present invention. In one embodiment, a method is provided for treating a subject afflicted with a condition or indication characterized by inappropriate, deregulated, or increased IL-23 or IL-23R activity or signaling, comprising administering to the individual a peptide inhibitor of the present invention in an amount sufficient to inhibit (partially or fully) binding of IL-23 to IL-23R in the subject. In particular embodiments, the inhibition of IL-23 binding to IL-23R occurs in particular organs or 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.

[00334] In some embodiments, methods of the present invention comprise providing a peptide inhibitor of the present invention to a subject in need thereof. In particular embodiments, the subject in need thereof has been diagnosed with or has been determined to be at risk of developing a disease or disorder associated with IL-23/IL-23R. In particular embodiments, the subject is a mammal.

[00335] In certain embodiments, the disease or disorder is autoimmune inflammation and related diseases and disorders, such as multiple sclerosis, asthma, rheumatoid arthritis, inflammatory bowel diseases (IBDs), juvenile IBD, adolescent IBD, Crohn's disease, sarcoidosis, Systemic Lupus Erythematosus, ankylosing spondylitis (axial spondyloarthritis), psoriatic arthritis, or psoriasis. In particular embodiments, the disease or disorder is 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.

[00336] In certain related embodiments, the present invention provides a method of selectively inhibiting IL-23 or IL-23R signaling (or the binding of IL-23 to IL-23R) in a subject in need thereof, comprising providing to the subject a peptide inhibitor of the present invention. In particular embodiments, the present invention includes 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 subject in need thereof, comprising providing to the subject a peptide inhibitor of the present invention by oral administration. In particular embodiments, exposure of the administered peptide inhibitor in GI tissues (e.g., small intestine or colon) is at least 10-fold, at least 20-fold, at least 50-fold, or at least 100-fold greater than the exposure in the blood. In particular embodiments, the present invention includes a method of selectively inhibiting IL23 or IL23R signaling (or the binding of IL23 to IL23R) in the GI tract of 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 invention includes a method of inhibiting GI inflammation and/or neutrophil infiltration to the GI, comprising providing to a subject in need thereof a peptide inhibitor of

the present invention.In some embodiments, methods of the present invention comprise providing a peptide inhibitor of the present invention (i.e., a first therapeutic agent) to 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 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 another embodiment, 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.

[00337] In particular embodiments, the peptide inhibitor, or the pharmaceutical composition comprising a peptide inhibitor, is suspended in a sustained-release matrix. A sustained-release matrix, as used herein, is a matrix made of materials, usually polymers, which are degradable by enzymatic or acid-base hydrolysis or by dissolution. Once inserted into the body, the matrix is acted upon by enzymes and body fluids. A sustained-release matrix desirably is chosen from biocompatible materials such as liposomes, polylactides (polylactic acid), polyglycolide (polymer of glycolic acid), polylactide co-glycolide (copolymers of lactic acid and glycolic acid) polyanhydrides, poly(ortho)esters, polypeptides, hyaluronic acid, collagen, chondroitin sulfate, carboxylic acids, fatty acids, phospholipids, polysaccharides, nucleic acids, polyamino acids, amino acids such as phenylalanine, tyrosine, isoleucine, polynucleotides, polyvinyl propylene, polyvinylpyrrolidone and silicone. One embodiment of a biodegradable matrix is a matrix of one of either polylactide, polyglycolide, or polylactide co-glycolide (co-polymers of lactic acid and glycolic acid).

[00338] In certain embodiments, the present invention includes pharmacetical compositions comprising one or more peptide inhibitors of the present invention and a pharmaceutically acceptable carrier, diluent or excipient. A pharmaceutically acceptable carrier, diluent or excipient refers to a non-toxic 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.

[00339] In certain embodiments, the compositions are 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.

[00340] In certain embodiments, pharmaceutical compositions for parenteral injection comprise pharmaceutically acceptable sterile aqueous or nonaqueous solutions, dispersions, suspensions or emulsions, or sterile powders, for reconstitution into sterile injectable solutions or dispersions just prior to use. Examples of suitable aqueous and nonaqueous carriers, diluents, solvents or vehicles include water, ethanol, polyols (such as glycerol, propylene glycol, polyethylene glycol, and the like), carboxymethylcellulose and suitable mixtures thereof, β-cyclodextrin, vegetable oils (such as olive oil), and injectable organic esters such as ethyl oleate. Proper fluidity may be maintained, for example, by the use of coating materials such as lecithin, by the maintenance of the required particle size in the case of dispersions, and by the use of surfactants. Thes compositions may also contain adjuvants such as preservative, wetting agents, emulsifying agents, and dispersing agents. Prolonged absorption of an injectable pharmaceutical form may be brought about by the inclusion of agents which delay absorption, such as aluminum monostearate and gelatin.

[00341] Injectable depot forms include those made by forming microencapsule matrices of the peptide inhibitor in one or more biodegradable polymers such as polylactide-polyglycolide, poly(orthoesters), poly(anhydrides), and (poly)glycols, such as PEG. Depending upon the ratio of peptide to polymer and the nature of the particular polymer employed, the rate of release of the peptide inhibitor can be controlled. Depot injectable Formulations are also prepared by entrapping the peptide inhibitor in liposomes or microemulsions compatible with body tissues.

[00342] The injectable Formulations may be sterilized, for example, by filtration through a bacterial-retaining filter, or by incorporating sterilizing agents in the form of sterile solid compositions which can be dissolved or dispersed in sterile water or other sterile injectable medium just prior to use.

[00343] Topical administration includes administration to the skin or mucosa, including surfaces of the lung and eye. Compositions for topical lung administration, including those for inhalation and intranasal, may involve solutions and suspensions in aqueous and non-aqueous Formulations and can be prepared as a dry powder which may be pressurized or non-pressurized. In non-pressurized powder compositions, the active ingredientmay be finely divided form may be used in admixture with a larger-sized pharmaceutically acceptable inert carrier comprising particles having a size, for example, of up to 100 micrometers in diameter. Suitable inert carriers include sugars such as lactose.

[00344] Alternatively, the composition may be pressurized and contain a compressed gas, such as nitrogen or a liquefied gas propellant. The liquefied propellant medium and indeed the total composition may bey such that the active ingredient does not dissolve therein to any substantial extent. The pressurized composition may also contain a surface active agent, such as a liquid or solid non-ionic surface active agent or may be a solid anionic surface active agent. It is preferred to use the solid anionic surface active agent in the form of a sodium salt.

[00345] A further form of topical administration is to the eye. A peptide inhibitor of the invention may be delivered in a pharmaceutically acceptable ophthalmic vehicle, such that the peptide inhibitor is maintained in contact with the ocular surface for a sufficient time period to allow the peptide inhibitor to penetrate the corneal and internal regions of the eye, as for example the anterior chamber, posterior chamber, vitreous body, aqueous humor, vitreous humor, cornea, iris/ciliary, lens, choroid/retina and sclera. The pharmaceutically acceptable ophthalmic vehicle may, for example, be an ointment, vegetable oil or an encapsulating material. Alternatively, the peptide inhibitors of the invention may be injected directly into the vitreous and aqueous humour.

[00346] Compositions for rectal or vaginal administration include suppositories which may be prepared by mixing the peptide inhibitorss of this invention with suitable non-irritating excipients or carriers such as cocoa butter, polyethylene glycol or a suppository wax, which are solid at room temperature but liquid at body temperature and, therefore, melt in the rectum or vaginal cavity and release the active compound.

[00347] Peptide inhibitors of the present invention may also be administered in liposomes or other lipid-based carriers. As is known in the art, liposomes are generally derived from phospholipids or other lipid substances. Liposomes are formed by mono- or multi-lamellar hydrated liquid crystals that are dispersed in an aqueous medium. Any non-toxic,

physiologically acceptable and metabolizable lipid capable of forming liposomes can be used. The present compositions in liposome form can contain, in addition to a peptide inhibitor of the present invention, stabilizers, preservatives, excipients, and the like. In certain embodiments, the lipids comprise phospholipids, including the phosphatidyl cholines (lecithins) and serines, both natural and synthetic. Methods to form liposomes are known in the art.

[00348] Pharmaceutical compositions to be used in the invention suitable for parenteral administration may comprise sterile aqueous solutions and/or suspensions of the peptide inhibitos made isotonic with the blood of the recipient, generally using sodium chloride, glycerin, glucose, mannitol, sorbitol, and the like.

[00349] In some aspects, the invention provides a pharmaceutical composition for oral delivery. Compositions and peptide inhibitors of the instant invention may be prepared for oral administration according to any of the methods, techniques, and/or delivery vehicles described herein. Further, one having skill in the art will appreciate that the peptide inhibitors of the instant invention may be modified or integrated into a system or delivery vehicle that is not disclosed herein, yet is well known in the art and compatible for use in oral delivery of peptides.

[00350] In certain embodiments, Formulations for oral administration may comprise adjuvants (e.g. resorcinols and/or nonionic surfactants such as polyoxyethylene oleyl ether and n-hexadecylpolyethylene ether) to artificially increase the permeability of the intestinal walls, and/or enzymatic inhibitors (e.g. pancreatic trypsin inhibitors, diisopropylfluorophosphate (DFF) or trasylol) to inhibit enzymatic degradation. In certain embodiments, the peptide inhibitor of a solid-type dosage form for oral administration can be mixed with at least one additive, such as sucrose, lactose, cellulose, mannitol, trehalose, raffinose, maltitol, dextran, starches, agar, alginates, chitins, chitosans, pectins, gum tragacanth, gum arabic, gelatin, collagen, casein, albumin, synthetic or semisynthetic polymer, or glyceride. These dosage forms can also contain other type(s) of additives, e.g., inactive diluting agent, lubricant such as magnesium stearate, paraben, preserving agent such as sorbic acid, ascorbic acid, alpha-tocopherol, antioxidants such as cysteine, disintegrators, binders, thickeners, buffering agents, pH adjusting agents, sweetening agents, flavoring agents or perfuming agents.

[00351] In particular embodiments, oral dosage forms or unit doses compatible for use with the peptide inhibitors of the present invention may include a mixture of peptide inhibitor and nondrug components or excipients, as well as other non-reusable materials that may be

considered either as an ingredient or packaging. Oral compositions may include at least one of a liquid, a solid, and a semi-solid dosage forms. In some embodiments, an oral dosage form is provided comprising an effective amount of peptide inhibitor, wherein the dosage form comprises at least one of a pill, a tablet, a capsule, a gel, a paste, a drink, a syrup, ointment, and suppository. In some instances, an oral dosage form is provided that is designed and configured to achieve delayed release of the peptide inhibitor in the subject's small intestine and/or colon.

[00352] In one embodiment, an oral pharmaceutical composition comprising a peptide inhibitor of the present invention comprises an enteric coating that is designed to delay release of the peptide inhibitor in the small intestine. In at least some embodiments, a pharmaceutical composition is provided which comprises a peptide inhibitor of the present invention and a protease inhibitor, such as aprotinin, in a delayed release pharmaceutical Formulation. In some instances, pharmaceutical compositions of the instant invention comprise an enteric coat that is soluble in gastric juice at a pH of about 5.0 or higher. In at least one embodiment, a pharmaceutical composition is provided comprising an enteric coating comprising a polymer having dissociable carboxylic groups, such as derivatives of cellulose, including hydroxypropylmethyl cellulose phthalate, cellulose acetate phthalate and cellulose acetate trimellitate and similar derivatives of cellulose and other carbohydrate polymers.

[00353] In one embodiment, a pharmaceutical composition comprising a peptide inhibitor of the present invention is provided in an enteric coating, the enteric coating being designed to protect and release the pharmaceutical composition in a controlled manner within the subject's lower gastrointestinal system, and to avoid systemic side effects. In addition to enteric coatings, the peptide inhibitors of the instant invention may be encapsulated, coated, engaged or otherwise associated within any compatible oral drug delivery system or component. For example, in some embodiments a peptide inhibitor of the present invention is provided in a lipid carrier system comprising at least one of polymeric hydrogels, nanoparticles, microspheres, micelles, and other lipid systems.

[00354] To overcome peptide degradation in the small intestine, some embodiments of the present invention comprise a hydrogel polymer carrier system in which a peptide inhibitor of the present invention is contained, whereby the hydrogel polymer protects the peptide inhibitor from proteolysis in the small intestine and/or colon. The peptide inhibitors of the present invention may further be Formulated for compatible use with a carrier system that is designed

to increase the dissolution kinetics and enhance intestinal absorption of the peptide. These methods include the use of liposomes, micelles and nanoparticles to increase GI tract permeation of peptides.

[00355] Various bioresponsive systems may also be combined with one or more peptide inhibitor of the present invention to provide a pharmaceutical agent for oral delivery. In some embodiments, a peptide inhibitor of the instant invention is used in combination with a bioresponsive system, such as hydrogels and mucoadhesive polymers with hydrogen bonding groups (e.g., PEG, poly(methacrylic) acid [PMAA], cellulose, Eudragit®, chitosan and alginate) to provide a therapeutic agent for oral administration. Other embodiments include a method for optimizing or prolonging drug residence time for a peptide inhibitor disclosed herein, wherein the surface of the peptide inhibitor surface is modified to comprise mucoadhesive properties through hydrogen bonds, polymers with linked mucins or/and hydrophobic interactions. These modified peptide molecules may demonstrate increase drug residence time within the subject, in accordance with a desired feature of the invention. Moreover, targeted mucoadhesive systems may specifically bind to receptors at the enterocytes and M-cell surfaces, thereby further increasing the uptake of particles containing the peptide inhibitor.

[00356] Other embodiments comprise a method for oral delivery of a peptide inhibitor of the present invention, wherein the peptide inhibitor is provided to a subject in combination with permeation enhancers that promote the transport of the peptides across the intestinal mucosa by increasing paracellular or transcellular permeation. Various permeation enhancers and methods for the oral delivery of therapeutic agents is described in Brayden, D.J., Mrsny, R.J., 2011. Oral peptide delivery: prioritizing the leading technologies. Ther. Delivery 2 (12), 1567–1573.

[00357] In certain embodiments, pharmaceutical compositions and Formulations of the present invention comprises a peptide inhibitor of the present invention and one or more permeation enhancer. Examples of absorption enhancers may include Bile salts, fatty acids, surfactants (anionic, cationic, and nonanionic) chelators, Zonular OT, esters, cyclodextrin, dextran sulfate, azone, crown ethers, EDTA, sucrose esters, and phosphotidyl choline, for example. Although absorption enhancers are not typically carriers by themselves, they are also widely associated with other carriers to improve oral bioavailability by transporting of peptides and proteins

across the intestinal mucosa. Such substances can be added to the Formulation as excipients or incorporated to form non specific interactions with the intended peptide inhibitor.

[00358] Dietary components and/or other naturally occurring substances affirmed as enhancing tight junction permeation and as Generally Recognized As Safe (GRAS) include, e.g., asglycerides, acylcarnitines, bile salts, and medium chain fatty acids. Sodium salts of medium chain fatty acids (MCFAS) were also suggested to be permeation enhancers. The most extensively studied MCFAS is sodium caprate, a salt of capric acid, which comprises 2-3% of the fatty acids in the milk fat fraction. To date, sodium caprate is mainly used as an excipient in a suppository Formulation (Doktacillin™) for improving rectal ampicillin absorption. The permeation properties of another dietary MCFAS, sodium caprylate (8-carbon), were shown in vitro to be lower when compared to sodium caprate. Sodium caprylate and a peptidic drug were Formulated in an admixture with other excipients in oil to generate an oily suspension (OS) that enhanced permeability (Tuvia, S. et al., Pharmaceutical Research, Vol. 31, No. 8, pp. 2010-2021 (2014).

[00359] For example, in one embodiment, a permeation enhancer is combined with a peptide inhibitor, wherein the permeation enhancer comprises at least one of a medium-chain fatty acid, a long-chain fatty acid, a bile salt, an amphiphilic surfactant, and a chelating agent. In certain embodiments, medium-chain fatty acid salts promote absorption by increasing paracellular permeability of the intestinal epithelium. In one embodiment, a permeation enhancer comprising sodium N-[hydroxybenzoyl)amino] caprylate is used to form a weak noncovalent association with the peptide inhibitor of the instant invention, wherein the permeation enhancer favors membrane transport and further dissociation once reaching the blood circulation. In another embodiment, a peptide inhibitor of the present invention is conjugated to oligoarginine, thereby increasing cellular penetration of the peptide into various cell types. Further, in at least one embodiment a noncovalent bond is provided between a peptide inhibibitor of the present invention and a permeation enhancer selected from the group consisting of a cyclodextrin (CD) and a dendrimers, wherein the permeation enhancer reduces peptide aggregation and increasing stability and solubility for the peptide inhibitor molecule.

[00360] In certain embodiments, a pharmaceutical composition or Formulation comprises a peptide inhibitor of the present invention and a transient permeability enhancers (TPEs). Permeation enhancers and TPEs may be used to increase orally bioavailability or the peptide inhibitor. One example of a TPE that may be used is an oily suspension Formulation that

disperses a powder containing sodioum caprylate and a therapeutic agent (Tuvia, S. et al., Pharmaceutical Research, Vol. 31, No. 8, pp. 2010-2021 (2014).

[00361] In certain embodiments, pharmaceutical composition and Formulations may include a peptide inhibitor of the present invention and one or more absorption enhancers, enzyme inhibitors, or mucoso adhesive polymers.

[00362] In particular embodiments, peptide inhibors of the present invention are Formulated in a Formulation vehicle, such as, e.g., emulsions, liposomes, microsphere or nanoparticles.

[00363] Other embodiments of the invention provide a method for treating a subject with a peptide inhibitor of the present invention having an increased half-life. In one aspect, the present invention provides a peptide inhibitor having a half-life of at least several hours to one day *in vitro* or *in vivo* (e.g., when administered to a human subject) sufficient for daily (q.d.) or twice daily (b.i.d.) dosing of a therapeutically effective amount. In another embodiment, the peptide inhibitor has a half-life of three days or longer sufficient for weekly (q.w.) dosing of a therapeutically effective amount. Further, in another embodiment, the peptide inhibitor has a half-life of eight days or longer sufficient for bi-weekly (b.i.w.) or monthly dosing of a therapeutically effective amount. In another embodiment, the peptide inhibitor is derivatized or modified such that is has a longer half-life as compared to the underivatized or unmodified peptide inhibitor. In another embodiment, the peptide inhibitor contains one or more chemical modifications to increase serum half-life.

[00364] When used in at least one of the treatments or delivery systems described herein, a peptide inhibitor of the present invention may be employed in pure form or, where such forms exist, in pharmaceutically acceptable salt form.

[00365] The total daily usage of the peptide inhibitors and compositions of the present invention 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.

[00366] In particlar embodiments, the total daily dose of the peptide inhibitors of the invention to be administered to a human or other mammal host in single or divided doses may be in amounts, for example, from 0.0001 to 300 mg/kg body weight daily or 1 to 300 mg/kg body weight daily.

Non-invasive Detection of Intestinal Inflammation

[00367] The peptide inhibitors of the invention 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 a non-invasive diagnostic procedure. In one embodiment, a peptide inhibitor is conjugated with a bifunctional chelator. In another embodiment, a peptide inhibitor is radiolabeled. The labeled peptide inhibitor is then administered to a subject orally or rectally. In one embodiment, the labeled peptide inhibitor is included in drinking water. Following uptake of the peptide inhibitor, microPET imaging may be used to visualize inflammation throughout the subject's bowels and digestive track.

EXAMPLES

SYNTHESIS OF SUBSTITUTED TRYPTOPHANS

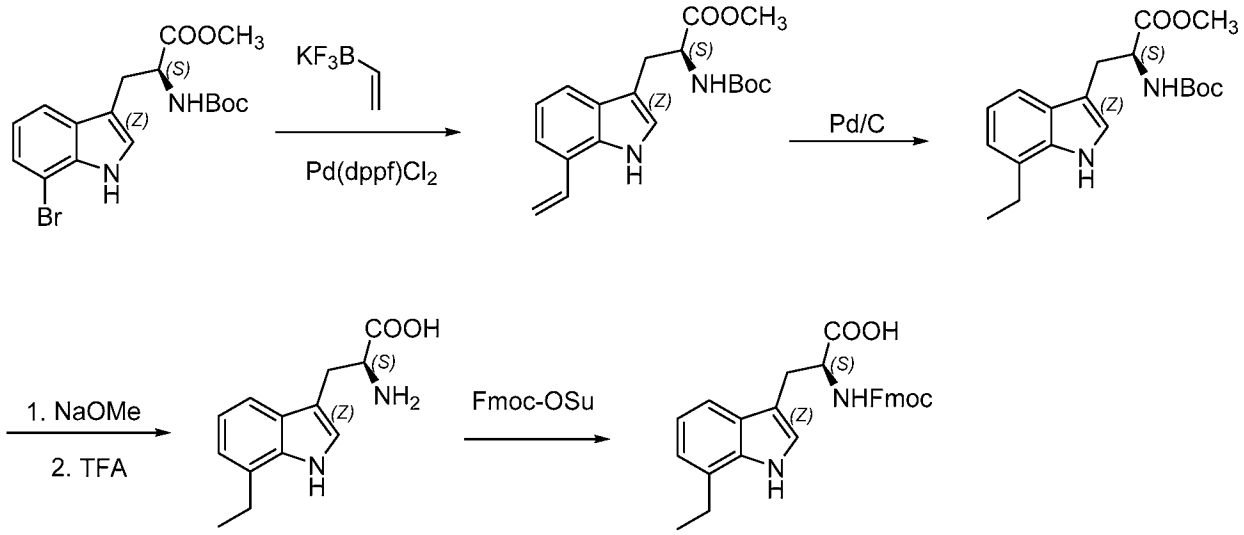
Synthesis of 7-methyl tryptophan

[00368] 7-Methyl tryptophan was purchased from a commercial source. Additiaonally, the compound can be synthesized following one of the methods described below.

Synthesis of 7-ethyl tryptophan

[00369] 7-Ethyl tryptophan was synthesized following the method depicted in Scheme 1:

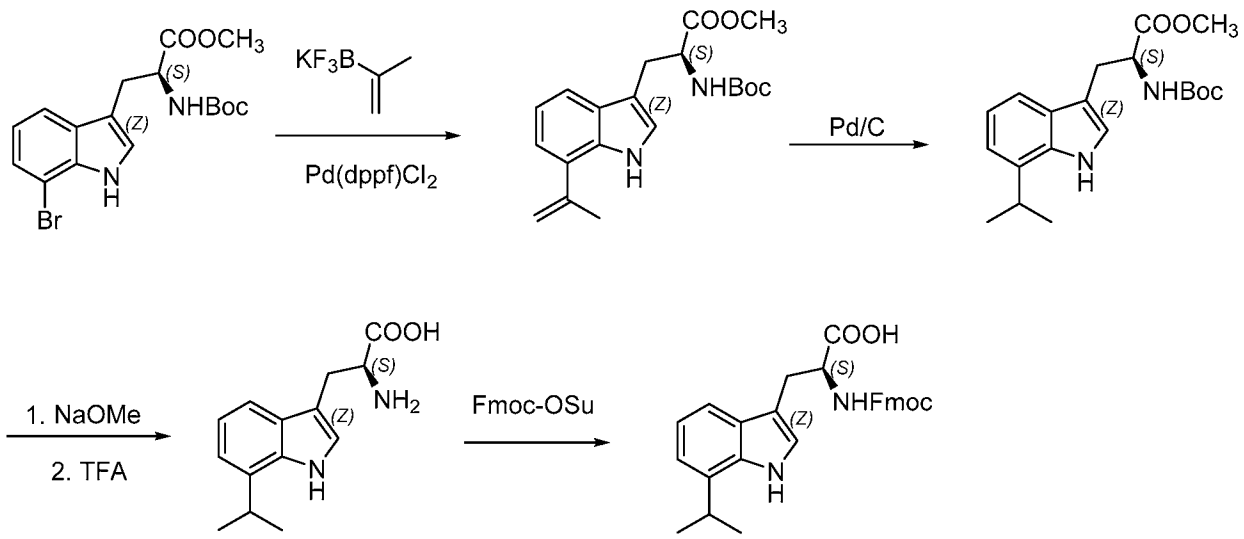
Scheme 1



Synthesis of 7-ispropyl tryptophan

[00370] 7-Isopropyl tryptophan was synthesized following the method depicted in Scheme 2:

Scheme 2



Procedures for 7-isopropyl compound:

Suzuki Coupling:

[00371] To a solution of (S)-methyl 3-(7-bromo-1H-indol-3-yl)-2-((tert-butoxycarbonyl) amino) propanoate (5.0 g, 12.6 mmol) in n-propanol in sealed was added Ptassium isoprenyltrifluoroborate (2.2 g, 15.1 mmol) and was purged with nitrogen. To the above mixture was added triethylamine (3.5 mL, 25.5 mmol) and then the catalyst [1,1'-Bis(diphenylphosphino)ferrocene]dichloropalladium(II), complex with dichloromethane (0.72 g, 0.88 mmol), purged with nitrogen for 10 minutes and heated to 100 °C overnight. The solution was concentrated to residue which was dissolved in ethyl acetate (150 mL) washed with water and brine. The organic layer was concentrated and crude was purified by flash column (3.2 g, 71%) to get thick foamy solid.

Transfer Hydrogenation:

[00372] To a solution of (S)-methyl 2-((tert-butoxycarbonyl) amino)-3-(7-(prop-1-en-2-yl)-1H-indol-3-yl)propanoate (3.1 g, 8.6 mmol) in ethanol (40 mL) was added 10% Pd/C (100 mg, 50% wet catalyst) and then was added ammonium formate (1.6 g, 25.3 mmol) and the resulting mixture was heated to 65- 70 °C, over 2 h. The reaction mixture was concentrated and water was added to the residue and extracted into ethyl acetate (2 x 100 mL). The organic layer was washed with water and brine and concentrated. The product (3.1 g, quantitative) obtained was used as such for the next reaction.

Hydrolysis:

[00373] To a solution of (S)-methyl 2-((tert-butoxycarbonyl) amino)-3-(7-isopropyl-1H-indol-3-yl)propanoate (3.6 g, 10.0 mmol) in THF/MeOH/water (4:1:1) was added lithium hydroxide (1.26 g, 30.0 mmol) and the solution was stirred overnight. The solution was concentrated to remove solvents and diluted with water and was acidified with 10% aqueous citric acid. The water layer containing product was extracted with ethyl acetate (2 x 100 mL). The organic layer was washed with water and brine, dried over Na2SO4 and concentrated to the desired product (2.8 g, 94%) as thick oil. Crude taken into next step without further purification

Boc deprotection:

[00374] To a cold solution of (S)-2-((tert-butoxycarbonyl)amino)-3-(7-isopropyl-1H-indol-3-yl)propanoic acid (2.8 g, 8.0 mmol) in dichloromethane (12 mL) was added Trifluoroacetic acid (6 mL) and the solution was stirred for 5 h at room temperature. The solution was evaporated to dryness re-dissolved in dichloromethane (10 mL) was treated with HCl/ether to and concentrated. The crude hydrochloride salt was suspended in MTBE (25 mL), stirred for 30 minutes and filtered to get S)-2-amino-3-(7-isopropyl-1H-indol-3-yl)propanoic acid hydrochloride (1.3 g, 68%) off white solid (hygroscopic)

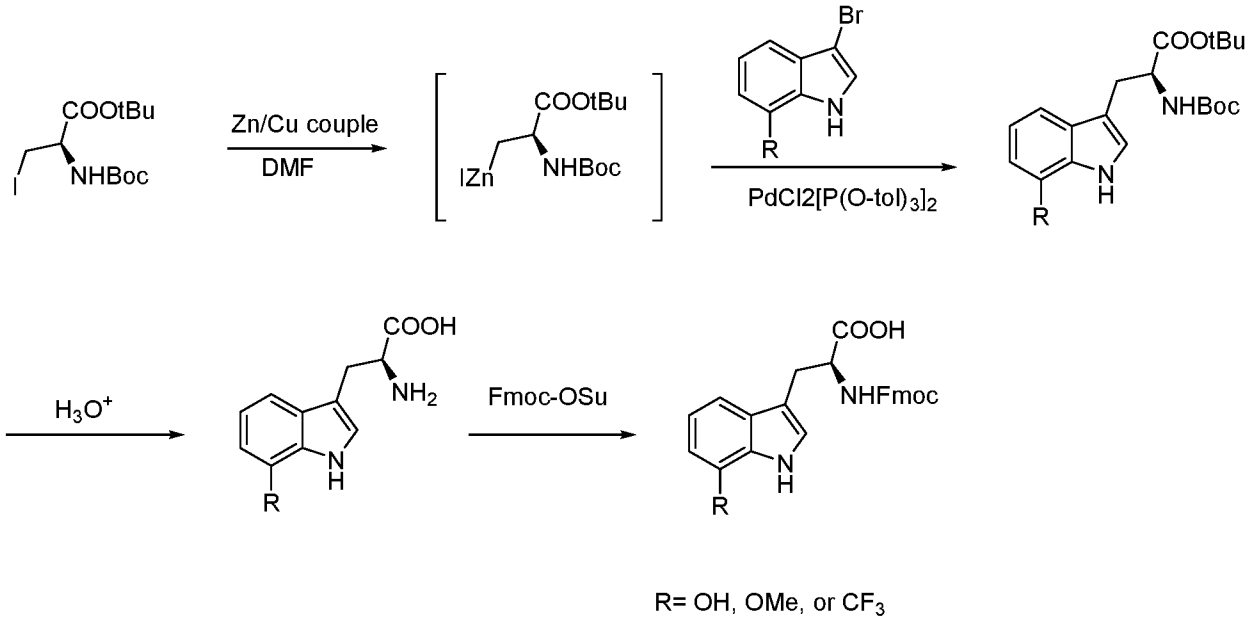
Fmoc protection:

[00375] To a solution of (S)-2-amino-3-(7-isopropyl-1H-indol-3-yl)propanoic acid hydrochloride (1.3 g, 4.6 mmol) in THF/ water (33 mL: 10 mL) was added sodium bicarbonate (1.55 g, 18.4 mmol) and then N-(9-Fluorenylmethoxycarbonyloxy)succinimide (1.55 g, 4.6 mmol) in portions. The resulting mixture was stirred overnight and concentrated to remove THF. The residue was diluted with water and was acidified with 2N HCl and extracted with ethyl acetate (2 x 75 mL). The organic layer was washed with water and brine, dried over Na_2SO_4 and concentrated to get the product as a foamy low melting solid (1.85 g, 86%).

Synthesis of additional 7-substituted tryptophans

[00376] Additional 7-substituted tryptophan were or can be synthesized following the method depicted in Scheme 3:

Additional 7-Substituted Tryptophans



R= OH, OMe, or CF_3

EXAMPLE 1

SYNTHESIS OF PEPTIDE MONOMERS

[00377] Peptide monomers of the present invention were synthesized using the Merrifield solid phase synthesis techniques on Protein Technology's Symphony multiple channel synthesizer. The peptides were assembled using HBTU (O-Benzotriazole-N,N,N',N'-tetramethyl-uronium-hexafluoro-phosphate), Diisopropylethylamine(DIEA) coupling conditions. For some amino acid couplings PyAOP(7-Azabenzotriazol-1-yloxy)tripyrrolidinophosponium hexafluorophosphate) and DIEA conditions were used. Rink Amide MBHA resin (100-200 mesh, 0.57 mmol/g) was used for peptide with C-terminal amides and pre-loaded Wang Resin with N-α-Fmoc protected amino acid was used for peptide with C-terminal acids. The coupling reagents (HBTU and DIEA premixed) were prepared at 100mmol concentration. Similarly amino acids solutions were prepared at 100 mmol concentration. Peptide inhibitors of the present invention were identified based on medical chemistry optimization and/or phage display and screened to identify those having superior binding and/or inhibitory properties.

Assembly

[00378] The peptides were assembled using standard Symphony protocols.The peptide sequences were assembled as follows: Resin (250 mg, 0.14 mmol) in each reaction vial was washed twice with 4ml of DMF followed by treatment with 2.5ml of 20% 4-methyl piperidine (Fmoc de-protection) for 10min. The resin was then filtered and washed two times with DMF

(4ml) and re-treated with N-methyl piperifine for additional 30 minute. The resin was again washed three times with DMF (4 ml) followed by addition 2.5ml of amino acid and 2.5ml of HBTU-DIEA mixture. After 45min of frequent agitations, the resin was filtered and washed three timed with DMF (4 ml each). For a typical peptide of the present invention, double couplings were performed. After completing the coupling reaction, the resin was washed three times with DMF (4 ml each) before proceeding to the next amino acid coupling.

Ring Closing Metathesis to form Olefins

[00379] The resin (100 μmol) was washed with 2 ml of DCM (3 × 1 min) and then with 2 ml of DCE (3 × 1 min) before being treated with a solution of 2 ml of a 6 mM solution of Grubbs' first-generation catalyst in DCE (4.94 mg ml−1; 20 mol% with regard to the resin substitution). The solution was refluxed overnight (12 h) under nitrogenbefore being drained. The resin was washed three times with DMF (4 ml each); DCM (4 ml) before being dried and cleavaed.

Cleavage

[00380] Following completion of the peptide assembly, the peptide was cleaved from the resin by treatment with cleavage reagent, such as reagent K (82.5% trigluoroacetic acid, 5% water, 5% thioanisole, 5% phenol, 2.5% 1,2-ethanedithiol). The cleavage reagent was able to successfully cleave the peptide from the resin, as well as all remaining side chain protecting groups.

[00381] The cleaved peptides were precipitated in cold diethyl ether followed by two washings with ethyl ether. The filtrate was poured off and a second aliquot of cold ether was added, and the procedure repeated. The crude peptide was dissolved in a solution of acetonitrile:water (7:3 with 1% TFA) and filtered. The quality of linear peptide was then verified using electrospray ionization mass spectrometry (ESI-MS) (Micromass/Waters ZQ) before being purified.

Disulfide Bond Formation via Oxidation

[00382] The peptide containing the free thiol (for example diPen) was assembled on a Rink Amide-MBHA resin following general Fmoc-SPPS procedure. The peptide was cleaved from the resin by treatment with cleavage reagent 90% trifluoroacetic acid, 5% water, 2.5% 1,2-ethanedithiol, 2.5% tri-isopropylsilane). The cleaved peptides were precipitated in cold diethyl ether followed by two washings with ethyl ether. The filtrate was poured off and a second aliquot of cold ether was added, and the procedure repeated. The crude peptide was dissolved in a solution of acetonitrile:water (7:3 with 1% TFA) and filtered giving the wanted unoxidized peptide crude peptide.

[00383] The crude, cleaved peptide with X4 and X9 possessing either Cys, Pen, hCys, (D)Pen, (D)Cys or (D)hCys, was dissolved in 20ml of water : acetonitrile. Saturated Iodine in acetic acid was then added drop wise with stirring until yellow color persisted. The solution was stirred for 15 minutes, and the reaction was monitored with analytic HPLC and LCMS. When the reaction was completed, solid ascorbic acid was added until the solution became clear. The solvent mixture was then purified by first being diluted with water and then loaded onto a reverse phase HPLC machine (Luna C18 support, 10u, 100A, Mobile phase A: water containing 0.1% TFA, mobile phase B: Acetonitrile (ACN) containing 0.1% TFA, gradient began with 5% B, and changed to 50% B over 60 minutes at a flow rate of 15ml/min). Fractions containing pure product were then freeze-dried on a lyophilyzer.

Thioether Bond Formation

[00384] The peptide containing the free thiol (e.g., Cys) and hSer(OTBDMS) was assembled on a Rink Amide-MBHA resin following general Fmoc-SPPS procedure. Chlorination was carried out by treating the resin with PPh_3 (10 equiv.) and Cl_3CCN (10 equiv.) in DCM for 2 h. The peptide was cleaved from the resin by treatment with cleavage reagent 90% trifluoroacetic acid, 5% water, 2.5% 1,2-ethanedithiol, 2.5% tri-isopropylsilane). The cleaved peptides were precipitated in cold diethyl ether followed by two washings with ethyl ether. The filtrate was poured off and a second aliquot of cold ether was added, and the procedure repeated. The crude peptide was dissolved in a solution of acetonitrile:water (7:3 with 1% TFA) and filtered giving the wanted uncyclized crude peptide.

[00385] The crude peptide possessing a free thiol (eg Cys, Pen, hCys, (D)Pen, (D)Cys or (D)hCys and the alkyl halide (hSer(Cl)) at either the X4 and X9 position or X9 and X4 position was dissolved in 0.1 M TRIS buffer pH 8.5. Cyclization was allowed to take place overnight at RT. The solvent mixture was then purified by first being diluted two-fold with water and then loaded onto a reverse phase HPLC machine (Luna C18 support, 10u, 100A, Mobile phase A: water containing 0.1% TFA, mobile phase B: Acetonitrile (ACN) containing 0.1% TFA, gradient began with 5% B, and changed to 50% B over 60 minutes at a flow rate of 15ml/min). Fractions containing pure product were then freeze-dried on a lyophilyzer.

Purification

[00386] Analytical reverse-phase, high performance liquid chromatography (HPLC) was performed on a Gemini C18 column (4.6 mm x 250 mm) (Phenomenex). Semi-Preparative reverse phase HPLC was performed on a Gemini 10 μm C18 column (22 mm x 250 mm)

(Phenomenex) or Jupiter 10 μm, 300 A ° C18 column (21.2 mm x 250 mm) (Phenomenex). Separations were achieved using linear gradients of buffer B in A (Mobile phase A: water containing 0.15% TFA, mobile phase B: Acetonitrile (ACN) containing 0.1% TFA), at a flow rate of 1 mL/min (analytical) and 15 mL/min (preparative). Separations were achieved using linear gradients of buffer B in A (Mobile phase A: water containing 0.15% TFA, mobile phase B: Acetonitrile (ACN) containing 0.1% TFA), at a flow rate of 1 mL/min (analytical) and 15mL/min (preparative).

EXAMPLE 1A

ADDITIONAL REPRESENTATIVE SYNTHESIS OF PEPTIDE MONOMERS

[00387] Peptide monomers of the present invention were synthesized using standard Fmoc solid phase synthesis techniques on a CEM Liberty Blue™ microwave peptide synthesizer. The peptides were assembled using Oxyma/DIC (ethyl cyanohydroxyiminoacetate/diisopropylcarbodiimide) with microwave heating. Rink Amide-MBHA resin (100-200 mesh, 0.66 mmol/g) was used for peptides with C-terminal amides and pre-loaded Wang Resin with N-α-Fmoc protected amino acid was used for peptide with C-terminal acids. Oxyma was prepared as a 1M solution in DMF with 0.1M DIEA. DIC was prepared as 0.5M solution in DMF. The Amino acids were prepared at 200mM. Peptide inhibitors of the present invention were identified based on medicinal chemistry optimization and/or phage display and screened to identify those having superior binding and/or inhibitory properties.

Assembly

[00388] The peptides were made using standard CEM Liberty Blue™ protocols. The peptide sequences were assembled as follows: Resin (400 mg, 0.25 mmol) was suspended in 10 ml of 50/50 DMF/DCM. The resin was then transferred to the reaction vessel in the microwave cavity. The peptide was assembled using repeated Fmoc deprotection and Oxyma/DIC coupling cycles. For deprotection, 20% 4-methylpiperidine in DMF was added to the reaction vessel and heated to 90 °C for 65 seconds. The deprotection solution was drained and the resin washed three times with DMF. For most amino acids, 5 equivalents of amino acid, Oxyma and DIC were then added to the reaction vessel and microwave irradiation rapidly heated the mixing reaction to 90 °C for 4 min. For Arginine and Histidine residues, milder conditions

using respective temperatures of 75 and 50 °C for 10 min were used to prevent racemization. Rare and expensive amino acids were often coupled manually overnight at room temperature using only 1.5-2 eq of reagents. Difficult couplings were often double coupled 2 x 4 min at 90 °C. After coupling the resin was washed with DMF and the whole cycle was repeated until the desired peptide assembly was completed.

Ring Closing Metathesis to form Olefins

[00389] The resin (100 μmol) was washed with 2 ml of DCM (3 × 1 min) and then with 2 ml of DCE (3 × 1 min) before being treated with a solution of 2 ml of a 6 mM solution of Grubbs Catalyst® 1st Generation in DCE (4.94 mg ml^{-1}; 20 mol% with regard to the resin substitution). The solution was refluxed overnight (12 h) under nitrogen before being drained. The resin was washed three times with DMF (4 ml each); DCM (4 ml) before being dried and cleaved.

Cleavage

[00390] Following completion of the peptide assembly, the peptide was then cleaved from the resin by treatment with a standard cleavage cocktail of 91:5:2:2 TFA/H_2O/TIPS/DODT for 2 hrs. If more than one Arg(pbf) residue was present the cleavage was allowed to go for an additional hour.

[00391] The cleaved peptides were precipitated in cold diethyl ether. The filtrate was decanted off and a second aliquot of cold ether was added, and the procedure was repeated. The quality of linear peptide was then verified using electrospray ionization mass spectrometry (ESI-MS) (Waters® Micromass® ZQ™) before being purified.

Disulfide Bond Formation via Oxidation

[00392] The peptide containing the free thiol (for example diPen) was assembled on a Rink Amide-MBHA resin following general Fmoc solid phase synthesis, cleavage and isolation as described above.

[00393] The crude, cleaved thiol containing peptide possessing either Cys, Pen, hCys, (D)Pen, (D)Cys or (D)hCys, was dissolved ~2mg/ml in 50/50 acetonitrile/water. Saturated iodine in acetic acid was then added dropwise with stirring until yellow color persisted. The solution was stirred for a few minutes, and the reaction was monitored with analytic HPLC and LCMS. When the reaction was completed, solid ascorbic acid was added until the solution became clear. The solvent mixture was then purified by first being diluted with water and then loaded onto a reverse phase HPLC Column (Luna® C18 support, 10u, 100A, Mobile phase A: water containing 0.1% TFA, mobile phase B: acetonitrile (ACN) containing 0.1% TFA, gradient

began with 15% B, and changed to 50% B over 60 minutes at a flow rate of 15ml/min). Fractions containing pure product were then freeze-dried on a lyophilizer.

Thioether Bond Formation

[00394] The peptide containing the free thiol (e.g., Cys) and hSer(OTBDMS) was assembled on a Rink Amide-MBHA resin following general Fmoc-SPPS procedure. Chlorination was carried out by treating the resin with Dichlorotriphenylphosphorane (5 eq, 0.5M) with Pinene (0.875M) and thioanisole (0.375M) scavengers at room temperature for 2 hours. The chloro-peptides were cleaved from the resin and precipitated as described above.

[00395] The crude peptide possessing a free thiol (e.g. Cys, Pen, hCys, (D)Pen, (D)Cys or (D)hCys and the alkyl halide (hSer(Cl)) were dissolved in 1:1 ACN/water and diluted with one volume of 0.2 M TRIS buffer pH 8.4. Cyclization was performed overnight at room temperature. The reaction mixture was then purified by first being diluted 1x with water and then loaded onto a reverse phase HPLC column (Luna® C18 support, 10u, 100A, Mobile phase A: water containing 0.1% TFA, mobile phase B: Acetonitrile (ACN) containing 0.1% TFA, gradient began at 15% B, and changed to 50% B over 60 minutes at a flow rate of 20 ml/min). Fractions containing pure product as determined by RPHPLC were then freeze-dried on a lyophilizer.

Purification

[00396] Analytical reverse-phase, high performance liquid chromatography (HPLC) was performed on a Gemini® C18 column (4.6 mm x 250 mm) (Phenomenex). Semi-Preparative reverse phase HPLC was performed on a Gemini® 10 μm C18 column (22 mm x 250 mm) (Phenomenex) or Jupiter® 10 μm, 300 A ° C18 column (21.2 mm x 250 mm) (Phenomenex). Separations were achieved using linear gradients of buffer B in A (Mobile phase A: water containing 0.15% TFA, mobile phase B: Acetonitrile (ACN) containing 0.1% TFA), at a flow rate of 1 mL/min (analytical) and 20 mL/min (preparative).

EXAMPLE 1B

ADDITIONAL REPRESENTATIVE SYNTHESIS OF PEPTIDE MONOMERS

SYNTHESIS OF PEPTIDE Ac-[Pen]-NT-[W(7-Me)]-[Lys(Ac)]-[Pen]-Phe[4-(2-aminoethoxy)]-[2-Nal]-[a-MeLys]-[Lys(Ac)]-N-[(D)Lys]-NH_2 (SEQ. ID. NO. 252) (PEPTIDE #252)

[00397] The acetate salt of Peptide #252 was synthesized on a 6.66 mmol scale. Upon completion, 3.24 g of 97% pure Peptide #252 was isolated as a white powder, representing an overall yield of ~25%.

[00398] The Peptide Peptide #252 was constructed on Rink Amide MBHA resin using standard FMOC protection synthesis conditions. The constructed peptide was isolated from the resin and protecting groups by cleavage with strong acid followed by precipitation. The crude precipitate was then purified and counterion exchanged by RP-HPLC. Lyophilization of pure fractions gave the final product Peptide #252.

[00399] Swell Resin: 10 g of Rink Amide MBHA solid phase resin (0.66mmol/g loading) was transferred to a 250 ml peptide vessel with filter frit, ground glass joint and vacuum side arm. The resin was washed 3x with DMF.

[00400] Step 1: Coupling of FMOC-d-Lys(Boc)-OH: Deprotection of the FMOC group was realized by adding 2 resin-bed volumes of 20% 4-methyl piperidine in DMF to the swollen resin and shaking for 3-5 min prior to draining and adding a second, 2-resin-bed volume of the 4-methyl piperidine solution and shaking for an additional 20-30 min. After deprotection the resin was washed 3x DMF with shaking. FMOC-d-Lys(boc)-OH (3 eq, 9.3 g) was dissolved in 100 ml DMF along with Oxyma (4.5 eq, 4.22g). Preactivation of the acid was accomplished by addition of DIC (3.9 eq, 4 ml) and shaking for 15 min prior to addition to the deprotected resin. An additional aliquot of DIC (2.6 eq, 2.65 ml) was added after ~ 15 min of coupling. The progress of the coupling reaction was monitored by the colorimetric Kaiser test. Once the reaction was judged complete the resin was washed 3 x DMF with shaking prior to starting the next deprotection/coupling cycle.

[00401] Step 2: Coupling of FMOC-Asn(Trt)-OH: FMOC Deprotection was again accomplished by adding two sequential, 2-resin-bed volumes of 20% 4-Methyl-Piperidine/DMF, one times 3-5 minutes and one times 20-30 minutes, draining in between treatments. The resin was then washed 3 times prior to coupling protected Asparagine. FMOC-Asn(Trt)-OH (3 eq, 11.8g) was dissolved in DMF along with Oxyma (4.5eq, 4.22g). Preactivation with DIC (3.9 eq, 4 ml) for 15 minutes was done prior to addition to the d-Lys-Rink-Amide resin. After 15 minutes, an additional aliquot of DIC (2.6 eq, 2.65 ml) was added to the reaction. Once the reaction was complete as determined by the Kaiser test the resin was again washed 3x with DMF prior to starting the next deprotection/coupling cycle.

[00402] Step 3: Coupling of FMOC-Lys(Ac)-OH: The FMOC was removed from the N-terminus of the resin bound Asparagine and the resin washed as previously described. FMOC-Lys(Ac)-OH (2eq, 5.42g) was dissolved in 100ml of DMF along with Oxyma (3eq, 2.81g). DIC (2.6 eq, 2.65 ml) was added for preactivation of the acid for ~15 minutes prior to addition to the Asn-dLys-Rink-Amide resin. After ~15 minutes, an additional aliquot of DIC (1.4 eq, 1.43 ml) was added to the reaction. Once the reaction was complete as determined by the Kaiser test the resin was again washed 3x with DMF prior to starting the next deprotection/coupling cycle.

[00403] Step 4: Coupling of FMOC-α-Me-Lys(Boc)-OH: The FMOC was removed from the N-terminus of the resin bound Acetyl Lysine and the resin washed as previously described. FMOC-α-Me-Lys(Boc)-OH (2 eq, 6.27 g) was dissolved in 100ml of DMF along with Oxyma (3eq, 2.81g). DIC (2.6 eq, 2.65 ml) was added for preactivation of the acid ~15 minutes prior to addition to the Lys(Ac)-Asn-dLys-Rink-Amide resin. After ~15 minutes, an additional aliquot of DIC (1.4 eq, 1.43 ml) was added to the reaction. Once the reaction was complete as determined by the Kaiser test the resin was again washed 3x with DMF prior to starting the next deprotection/coupling cycle.

[00404] Step 5: Coupling of FMOC-L-Ala(2-Naphthyl)-OH: The FMOC was removed from the N-terminus of the resin bound peptide and the resin washed as previously described. FMOC-L-Ala(2-Naphthyl)-OH (3 eq, 8.66 g) was dissolved in 100ml of DMF along with Oxyma (4.5 eq, 4.22g). DIC (3.9 eq, 4 ml) was added for preactivation of the acid ~15 minutes prior to addition to the αMeLys- Lys(Ac)-Asn-dLys-Rink-Amide resin. After ~15 minutes, an additional aliquot of DIC (2.6 eq, 2.65 ml) was added to the reaction. Once the reaction was complete as determined by the Kaiser test the resin was again washed 3x with DMF prior to starting the next deprotection/coupling cycle.

[00405] Step 6: Coupling of FMOC-4-[2-(boc-amino-ethoxy)]-L-Phenylalanine : The FMOC was removed from the N-terminus of the resin bound peptide and the resin washed as previously described. FMOC-4-[2-(boc-amino-ethoxy)]-L-Phenylalanine (3 eq, 10.8 g) was dissolved in 100ml of DMF along with Oxyma (4.5 eq, 4.22g). DIC (3.9 eq, 4 ml) was added for preactivation of the acid ~15 minutes prior to addition to the 2Nal-αMeLys-Lys(Ac)-Asn-dLys-Rink-Amide resin. After ~15 minutes, an additional aliquot of DIC (2.6 eq, 2.65 ml) was added to the reaction. Once the reaction was complete as determined by the Kaiser test the resin was again washed 3x with DMF prior to starting the next deprotection/coupling cycle.

[00406] Step 7: Coupling of FMOC-L-Pen(Trt)-OH : The FMOC was removed from the N-terminus of the resin bound peptide and the resin washed as previously described. FMOC-L-Pen(Trt)-OH (3 eq, 12.14 g) was dissolved in 100ml of DMF along with Oxyma (4.5 eq, 4.22g). DIC (3.9 eq, 4 ml) was added for preactivation of the acid ~15 minutes prior to addition to the AEF-2Nal-αMeLys-Lys(Ac)-Asn-dLys-Rink-Amide resin. After ~15 minutes, an additional aliquot of DIC (2.6 eq, 2.65 ml) was added to the reaction. Once the reaction was complete as determined by the Kaiser test the resin was again washed 3x with DMF prior to starting the next deprotection/coupling cycle.

[00407] Step 8: Coupling of FMOC-Lys(Ac)-OH : The FMOC was removed from the N-terminus of the resin bound peptide and the resin washed as previously described. FMOC-Lys(Ac)-OH (2 eq, 5.4 g) was dissolved in 100 ml of DMF along with Oxyma (3 eq, 2.81 g). DIC (2.6 eq, 2.65 ml) was added for preactivation of the acid ~15 minutes prior to addition to the Pen-AEF-2Nal-αMeLys-Lys(Ac)-Asn-dLys-Rink-Amide resin. After ~15 minutes, an additional aliquot of DIC (1.4 eq, 1.43 ml) was added to the reaction. Once the reaction was complete as determined by the Kaiser test the resin was again washed 3x with DMF prior to starting the next deprotection/coupling cycle.

[00408] Step 9: Coupling of FMOC-7-Me-Trp-OH : The FMOC was removed from the N-terminus of the resin bound peptide and the resin washed as previously described. FMOC-7-Me-Trp-OH (2 eq, 5.81 g) was dissolved in 100 ml of DMF along with Oxyma (3 eq, 2.81 g). DIC (2.6 eq, 2.65 ml) was added for preactivation of the acid ~15 minutes prior to addition to the Lys(Ac)-Pen-AEF-2Nal-αMeLys-Lys(Ac)-Asn-dLys-Rink-Amide resin. After ~15 minutes, an additional aliquot of DIC (1.4 eq, 1.43 ml) was added to the reaction. Once the reaction was complete as determined by the Kaiser test the resin was again washed 3x with DMF prior to starting the next deprotection/coupling cycle.

[00409] Step 10: Coupling of FMOC-Thr(tBu)-OH : The FMOC was removed from the N-terminus of the resin bound peptide and the resin washed as previously described. FMOC-Thr(tBu)-OH (4 eq, 10.5g) was dissolved in 100 ml of DMF along with Oxyma (6 eq, 5.62 g). DIC (5.2 eq, 5.3 ml) was added for preactivation of the acid ~15 minutes prior to addition to the 7MeTrp-Lys(Ac)-Pen-AEF-2Nal-αMeLys-Lys(Ac)-Asn-dLys-Rink-Amide resin. After ~15 minutes, an additional aliquot of DIC (2.6 eq, 2.65 ml) was added to the reaction. Once the reaction was complete as determined by the Kaiser test the resin was again washed 3x with DMF prior to starting the next deprotection/coupling cycle.

[00410] Step 11: Coupling of FMOC-Asn(Trt)-OH : The FMOC was removed from the N-terminus of the resin bound peptide and the resin washed as previously described. FMOC-Asn(Trt)-OH (4 eq, 15.8 g) was dissolved in 100 ml of DMF along with Oxyma (6 eq, 5.62 g). DIC (5.2 eq, 5.3 ml) was added for preactivation of the acid ~15 minutes prior to addition to the Thr-7MeTrp-Lys(Ac)-Pen-AEF-2Nal-αMeLys-Lys(Ac)-Asn-dLys-Rink-Amide resin. After ~15 minutes, an additional aliquot of DIC (2.6 eq, 2.65 ml) was added to the reaction. Once the reaction was complete as determined by the Kaiser test the resin was again washed 3x with DMF prior to starting the next deprotection/coupling cycle.

[00411] Step 12: Coupling of FMOC-L-Pen(Trt)-OH : The FMOC was removed from the N-terminus of the resin bound peptide and the resin washed as previously described. FMOC-L-Pen(Trt)-OH (2 eq, 8.1 g) was dissolved in 100ml of DMF along with Oxyma (3 eq, 2.81 g). DIC (2.6 eq, 2.65 ml) was added for preactivation of the acid ~15 minutes prior to addition to the Asn-Thr-7MeTrp-Lys(Ac)-Pen-AEF-2Nal-αMeLys-Lys(Ac)-Asn-dLys-Rink-Amide resin. After ~15 minutes, an additional aliquot of DIC (2.6 eq, 2.65 ml) was added to the reaction. Once the reaction was complete as determined by the Kaiser test the resin was again washed 3x with DMF prior to the final deprotection and acetic acid capping of the constructed peptide.

[00412] Step 13: Acetyl Capping: The FMOC was removed from the N-terminus of the resin bound peptide and the resin washed as previously described. 150 ml of Capping Reagent A (THF/Acetic anhydride/Pyridine, 80:10:10) was added to the constructed Pen-Asn-Thr-7MeTrp-Lys(Ac)-Pen-AEF-2Nal-αMeLys-Lys(Ac)-Asn-dLys-Rink-Amide resin and shaken for 30 min. The resin was washed 3 x with DMF followed by 3x with DCM. The resin was divided into 5 – 50 ml centrifuge tubes and placed under vacuum for 1.5 hrs prior to cleavage with TFA.

[00413] Step 14: TFA Cleavage and Ether precipitation: 200 ml of the TFA cleavage cocktail (90/5/2.5/2.5 TFA/water/Tips/DODT) was prepared. 40 ml of the cleavage cocktail was added to each of the 5 tubes containing the protected resin bound peptide and shaken for two hours. The spent resin was filtered away and the filtrate divided evenly into 18 – 50 ml centrifuge tubes for precipitation. Cold Diethyl Ether was added to each forming a white precipitate that was then centrifuged. The ether was decanted to waste and 2 more ether washes of the precipitate were performed. The resulting white precipitate cake was allowed to dry overnight in the hood to give ~10.4g of crude reduced peptide.

[00414] Step 15: Disulfide Oxidation: The crude peptide was oxidized in four batches. ~ 2.5 g of crude peptide was dissolved in 50 ml of 50/50 acetonitrile/water and diluted to 1L 20% ACN/water. With swirling a saturated solution of Iodine in Acetic acid/Methanol was added dropwise to the 1L peptide solution until the yellow/brown color of the I2 remains and does not fade away. The slightly colored solution was allowed to sit for 5 min prior to quenching the excess I2 with a pinch of Ascorbic acid.

[00415] Step 16: RP-HPLC purification: The RP-HPLC purification was performed in four batches immediately following I2 oxidation. A preparative purification column (Phenomenex, Luna, C18(2), 100A, 250x50mm) was equilibrated at 70ml/min with 5% MPB in MPA (MPA = 0.1% TFA/water, MPB = 0.1% TFA in ACN). The 1 L of quenched oxidized peptide was loaded onto the equilibrated column at 70 ml/min. After the solvent front eluted an elution gradient of 20-38% MPB over 60 min at 70ml/min was run. The desired oxidized peptide eluted at ~26% MPB. Pure fractions were combined from all four purifications and lyophilized to give 3.83g the purified TFA salt ready for counterion exchange.

[00416] Step 17: Counterion Exchange to Acetate: The same preparative RP-HPLC column was equilibrated with 5% MPB in MPA at 70 ml/min (MPA = 0.3% AcOH in Water, MPB = 0.3% AcOH in ACN, MPC = 0.5M NH4OAc in Water.) The entire 3.83 g of purified peptide was dissolved in 50/50 ACN/water and diluted to 15% ACN (~50ml total). The solution was loaded onto the equilibrated column at 70 ml/min and the solvent front eluted. The captured peptide was washed with 5% MPB in MPA for 5 min. The captured peptide was then washed with 5% MPB in MPC for 40 min at 70 ml/min to exchange the counterions from TFA to Acetate. The captured peptide was then washed with 5% MPB in MPA at 70ml/min for 10 min to clear all NH4OAc form system. Finally, the peptide is eluted with a quick gradient of 5-70% MPB in MPA over 60 minutes.

[00417] Step 18: Final Lyophilization and Analysis: The collected fractions were analyzed by analytical RP-HPLC, and all fractions >95% purity were combined. Lyophilization of the combined fractions gave 3.24 g of Peptide #252 as a white powder with a purity of 97 %. Low resolution LC/MS of purified Peptide #252 gave 3 charged states of the peptide, M+3/3 of 621.8, M+2/2 of 932.1 and the molecular ion of 1863.5. The experimental mass agrees with the theoretical mass of 1863.3 da.

EXAMPLE 1C

ADDITIONAL REPRESENTATIVE SYNTHESIS OF PEPTIDE MONOMERS

SYNTHESIS OF PEPTIDE Ac-[Pen]-NT-[W(7-Me)]-[Lys(Ac)]-[Pen]-Phe[4-(2-aminoethoxy)]-[2-Nal]-[a-MeLys]-[Lys(Ac)]-N-[(D)Leu]- NH_2 (SEQ. ID. NO. 245) (PEPTIDE #245)

The acetate salt of Peptide #245 was synthesized on a 6.7 mmol scale.

[00418] The Peptide #245 was constructed on Rink Amide MBHA resin using standard FMOC protection synthesis conditions. The constructed peptide was isolated from the resin and protecting groups by cleavage with strong acid followed by precipitation. The crude precipitate was then oxidized with I2, purified and counterion exchanged by RP-HPLC. Lyophilization of pure fractions gave the final product Peptide #245.

[00419] Swell Resin: 10 g of Rink Amide MBHA solid phase resin (0.66mmol/g loading) was transferred to a 250 ml peptide vessel with filter frit, ground glass joint and vacuum side arm. The resin was washed 3x with DMF.

[00420] Couple FMOC-d-Leucine-OH: Deprotection of the FMOC group was realized by adding 2 resin-bed volumes of 20% 4-Methyl Piperidine in DMF to the swollen resin and shaking for 3-5 min prior to draining and adding a second, 2-resin-bed volume of the 4-Methyl Piperidine solution and shaking for an additional 20-30 min. After deprotection the resin was washed 3x DMF with shaking. FMOC-d-Leucine-OH (3 eq) was dissolved in 100 ml DMF along with Oxyma (4.5 eq). Preactivation of the acid was accomplished by addition of DIC (3.9 eq) and shaking for 15 min prior to addition to the deprotected resin. An additional aliquot of DIC (2.6 eq) was added after ~ 15 min of coupling. The progress of the coupling reaction was monitored by the colorimetric Kaiser test. Once the reaction was judged complete the resin was washed 3 x DMF with shaking prior to starting the next deprotection/coupling cycle.

[00421] Couple FMOC-Asn(Trt)-OH: FMOC Deprotection was again accomplished by adding two sequential, 2-resin-bed volumes of 20% 4-Methyl-Piperidine/DMF, one times 3-5 minutes and one times 20-30 minutes, draining in between treatments. The resin was then washed 3 times prior to coupling protected Asparagine. FMOC-Asn(Trt)-OH (3 eq, 11.8g) was dissolved in DMF along with Oxyma (4.5eq, 4.22g). Preactivation with DIC (3.9 eq, 4 ml) for 15 minutes was done prior to addition to the resin. After 15 minutes, an additional aliquot of DIC (2.6 eq, 2.65 ml) was added to the reaction. Once the reaction was complete as determined by the Kaiser test the resin was again washed 3x with DMF prior to starting the next deprotection/coupling cycle.

[00422] Couple FMOC-Lys(Ac)-OH: The FMOC was removed from the N-terminus of the resin bound Asparagine and the resin washed as previously described. FMOC-Lys(Ac)-OH (2eq, 5.42g) was dissolved in 100ml of DMF along with Oxyma (3eq, 2.81g). DIC (2.6 eq, 2.65 ml) was added for preactivation of the acid for ~15 minutes prior to addition to the Asn-dLeu-Rink-Amide resin. After ~15 minutes, an additional aliquot of DIC (1.4 eq, 1.43 ml) was added to the reaction. Once the reaction was complete as determined by the Kaiser test the resin was again washed 3x with DMF prior to starting the next deprotection/coupling cycle.

[00423] Couple FMOC-α-Me-Lys(Boc)-OH: The FMOC was removed from the N-terminus of the resin bound Acetyl Lysine and the resin washed as previously described. FMOC-α-Me-Lys(Boc)-OH (2 eq, 6.27 g) was dissolved in 100ml of DMF along with Oxyma (3eq, 2.81g). DIC (2.6 eq, 2.65 ml) was added for preactivation of the acid ~15 minutes prior to addition to the resin. After ~15 minutes, an additional aliquot of DIC (1.4 eq, 1.43 ml) was added to the reaction. Once the reaction was complete as determined by the Kaiser test the resin was again washed 3x with DMF prior to starting the next deprotection/coupling cycle.

[00424] Couple FMOC-L-Ala(2-Naphthyl)-OH: The FMOC was removed from the N-terminus of the resin bound peptide and the resin washed as previously described. FMOC-L-Ala(2-Naphthyl)-OH (3 eq, 8.66 g) was dissolved in 100ml of DMF along with Oxyma (4.5 eq, 4.22g). DIC (3.9 eq, 4 ml) was added for preactivation of the acid ~15 minutes prior to addition to the resin. After ~15 minutes, an additional aliquot of DIC (2.6 eq, 2.65 ml) was added to the reaction. Once the reaction was complete as determined by the Kaiser test the resin was again washed 3x with DMF prior to starting the next deprotection/coupling cycle.

[00425] Couple FMOC-4-[2-(boc-amino-ethoxy)]-L-Phenylalanine : The FMOC was removed from the N-terminus of the resin bound peptide and the resin washed as previously described. FMOC-4-[2-(boc-amino-ethoxy)]-L-Phenylalanine (3 eq, 10.8 g) was dissolved in 100ml of DMF along with Oxyma (4.5 eq, 4.22g). DIC (3.9 eq, 4 ml) was added for preactivation of the acid ~15 minutes prior to addition to the resin. After ~15 minutes, an additional aliquot of DIC (2.6 eq, 2.65 ml) was added to the reaction. Once the reaction was complete as determined by the Kaiser test the resin was again washed 3x with DMF prior to starting the next deprotection/coupling cycle.

[00426] Couple FMOC-L-Pen(Trt)-OH : The FMOC was removed from the N-terminus of the resin bound peptide and the resin washed as previously described. FMOC-L-Pen(Trt)-OH (3 eq, 12.14 g) was dissolved in 100ml of DMF along with Oxyma (4.5 eq, 4.22g). DIC (3.9 eq, 4 ml) was added for preactivation of the acid ~15 minutes prior to addition to the resin. After ~15

minutes, an additional aliquot of DIC (2.6 eq, 2.65 ml) was added to the reaction. Once the reaction was complete as determined by the Kaiser test the resin was again washed 3x with DMF prior to starting the next deprotection/coupling cycle.

[00427] Couple FMOC-Lys(Ac)-OH : The FMOC was removed from the N-terminus of the resin bound peptide and the resin washed as previously described. FMOC-Lys(Ac)-OH (2 eq, 5.4 g) was dissolved in 100 ml of DMF along with Oxyma (3 eq, 2.81 g). DIC (2.6 eq, 2.65 ml) was added for preactivation of the acid ~15 minutes prior to addition to the resin. After ~15 minutes, an additional aliquot of DIC (1.4 eq, 1.43 ml) was added to the reaction. Once the reaction was complete as determined by the Kaiser test the resin was again washed 3x with DMF prior to starting the next deprotection/coupling cycle.

[00428] Couple FMOC-7-Me-Trp-OH : The FMOC was removed from the N-terminus of the resin bound peptide and the resin washed as previously described. FMOC-7-Me-Trp-OH (2 eq, 5.81 g) was dissolved in 100 ml of DMF along with Oxyma (3 eq, 2.81 g). DIC (2.6 eq, 2.65 ml) was added for preactivation of the acid ~15 minutes prior to addition to the resin. After ~15 minutes, an additional aliquot of DIC (1.4 eq, 1.43 ml) was added to the reaction. Once the reaction was complete as determined by the Kaiser test the resin was again washed 3x with DMF prior to starting the next deprotection/coupling cycle.

[00429] Couple FMOC-Thr(tBu)-OH : The FMOC was removed from the N-terminus of the resin bound peptide and the resin washed as previously described. FMOC-Thr(tBu)-OH (4 eq, 10.5g) was dissolved in 100 ml of DMF along with Oxyma (6 eq, 5.62 g). DIC (5.2 eq, 5.3 ml) was added for preactivation of the acid ~15 minutes prior to addition to the resin. After ~15 minutes, an additional aliquot of DIC (2.6 eq, 2.65 ml) was added to the reaction. Once the reaction was complete as determined by the Kaiser test the resin was again washed 3x with DMF prior to starting the next deprotection/coupling cycle.

[00430] Couple FMOC-Asn(Trt)-OH : The FMOC was removed from the N-terminus of the resin bound peptide and the resin washed as previously described. FMOC-Asn(Trt)-OH (4 eq, 15.8 g) was dissolved in 100 ml of DMF along with Oxyma (6 eq, 5.62 g). DIC (5.2 eq, 5.3 ml) was added for preactivation of the acid ~15 minutes prior to addition to the resin. After ~15 minutes, an additional aliquot of DIC (2.6 eq, 2.65 ml) was added to the reaction. Once the reaction was complete as determined by the Kaiser test the resin was again washed 3x with DMF prior to starting the next deprotection/coupling cycle.

[00431] Couple FMOC-L-Pen(Trt)-OH : The FMOC was removed from the N-terminus of the resin bound peptide and the resin washed as previously described. FMOC-L-Pen(Trt)-OH (2 eq, 8.1 g) was dissolved in 100ml of DMF along with Oxyma (3 eq, 2.81 g). DIC (2.6 eq, 2.65 ml) was added for preactivation of the acid ~15 minutes prior to addition to the resin. After ~15 minutes, an additional aliquot of DIC (2.6 eq, 2.65 ml) was added to the reaction. Once the reaction was complete as determined by the Kaiser test the resin was again washed 3x with DMF prior to the final deprotection and acetic acid capping of the constructed peptide.

[00432] Acetyl Capping: The FMOC was removed from the N-terminus of the resin bound peptide and the resin washed as previously described. 150 ml of Capping Reagent A (THF/Acetic anhydride/Pyridine, 80:10:10) was added to the constructed peptide amide resin and shaken for 30 min. The resin was washed 3 x with DMF followed by 3x with DCM. The resin was divided into 5 – 50 ml centrifuge tubes and placed under vacuum for 1.5 hrs prior to cleavage with TFA.

[00433] TFA Cleavage and Ether precipitation: 200 ml of the TFA cleavage cocktail (90/5/2.5/2.5 TFA/water/Tips/DODT) was prepared. 40 ml of the cleavage cocktail was added to each of the 5 tubes containing the protected resin bound peptide and shaken for two hours. The spent resin was filtered away and the filtrate divided evenly into 18 – 50 ml centrifuge tubes for precipitation. Cold Diethyl Ether was added to each forming a white precipitate that was then centrifuged. The ether was decanted to waste and 2 more ether washes of the precipitate were performed. The resulting white precipitate cakes were allowed to dry overnight in the hood to give the crude reduced peptide.

[00434] Disulfide Oxidation**:** The crude peptide was oxidized in four batches. ~ 2.5 g of crude peptide was dissolved in 50 ml of 50/50 acetonitrile/water and diluted to 1L 20% ACN/water. With swirling a saturated solution of Iodine in Acetic acid/Methanol was added dropwise to the 1L peptide solution until the yellow/brown color of the I2 remains and does not fade away. The slightly colored solution was allowed to sit for 5 min prior to quenching the excess I2 with a pinch of Ascorbic acid.

[00435] RP-HPLC purification: The RP-HPLC purification was performed in four batches immediately following I2 oxidation. A preparative purification column (Phenomenex, Luna, C18(2), 100A, 250x50mm) was equilibrated at 70ml/min with 5% MPB in MPA (MPA = 0.1% TFA/water, MPB = 0.1% TFA in ACN). The 1 L of quenched oxidized peptide was loaded onto the equilibrated column at 70 ml/min. After the solvent front eluted an elution gradient of 20-40% MPB over 60 min at 70ml/min was run. The desired oxidized peptide eluted near 30% buffer B.

Pure fractions were combined from all four purifications and lyophilized to give the purified TFA salt ready for counterion exchange.

[00436] Counterion Exchange to Acetate: The same preparative RP-HPLC column was equilibrated with 5% MPB in MPA at 70 ml/min (MPA = 0.3% AcOH in Water, MPB = 0.3% AcOH in ACN, MPC = 0.5M NH4OAc in Water.) The entirety of purified peptide was dissolved in 50/50 ACN/water and diluted to 15% ACN (~50ml total). The solution was loaded onto the equilibrated column at 70 ml/min and the solvent front eluted. The captured peptide was washed with 5% MPB in MPA for 5 min. The captured peptide was then washed with 5% MPB in MPC for 40 min at 70 ml/min to exchange the counterions from TFA to Acetate. The captured peptide was then washed with 5% MPB in MPA at 70ml/min for 10 min to clear all NH4OAc from the system. Finally, the peptide is eluted with a quick gradient of 5-70% MPB in MPA over 60 minutes.

[00437] Final Lyophilization and Analysis**:** The collected fractions were analyzed by analytical RP-HPLC, and all fractions >95% purity were combined. Lyophilization of the combined fractions gave Peptide #245 as a white powder with a purity of 97 %. Experimental LC/MS of the purified Peptide #245 agrees with the theoretical mass of 1848.26 amu.

EXAMPLE 1D

ADDITIONAL REPRESENTATIVE SYNTHESIS OF PEPTIDE MONOMERS

SYNTHESIS OF PEPTIDE Ac-[Pen]-NT-[W(7-Me)]-[Lys(Ac)]-[Pen]-Phe[4-(2-aminoethoxy)]-[2-Nal]-[a-MeLys]-[Lys(Ac)]-N-H-NH_2 (SEQ. ID. NO. 248) (PEPTIDE #248)

[00438] The acetate salt of Peptide #248 was synthesized on a 6.7 mmol scale.

[00439] The Peptide #248 was constructed on Rink Amide MBHA resin using standard FMOC protection synthesis conditions. The constructed peptide was isolated from the resin and protecting groups by cleavage with strong acid followed by precipitation. The crude precipitate was then oxidized with I2, purified and counterion exchanged to Acetate by RP-HPLC. Lyophilization of pure fractions gave the final product Peptide #252.

[00440] Swell Resin: 10 g of Rink Amide MBHA solid phase resin (0.66mmol/g loading) was transferred to a 250 ml peptide vessel with filter frit, ground glass joint and vacuum side arm. The resin was washed 3x with DMF.

[00441] Step 1: Coupling of FMOC-His(trt)-OH: Deprotection of the FMOC group was realized by adding 2 resin-bed volumes of 20% 4-methyl piperidine in DMF to the swollen resin and shaking for 3-5 min prior to draining and adding a second, 2-resin-bed volume of the 4-methyl piperidine solution and shaking for an additional 20-30 min. After deprotection the resin was washed 3x DMF with shaking. FMOC-His(trt)-OH (3 eq) was dissolved in 100 ml DMF along with Oxyma (4.5 eq, 4.22g). Preactivation of the acid was accomplished by addition of DIC (3.9 eq, 4 ml) and shaking for 15 min prior to addition to the deprotected resin. An additional aliquot of DIC (2.6 eq, 2.65 ml) was added after ~ 15 min of coupling. The progress of the coupling reaction was monitored by the colorimetric Kaiser test. Once the reaction was judged complete the resin was washed 3 x DMF with shaking prior to starting the next deprotection/coupling cycle.

[00442] Step 2: Coupling of FMOC-Asn(Trt)-OH: FMOC Deprotection was again accomplished by adding two sequential, 2-resin-bed volumes of 20% 4-Methyl-Piperidine/DMF, one times 3-5 minutes and one times 20-30 minutes, draining in between treatments. The resin was then washed 3 times prior to coupling protected Asparagine. FMOC-Asn(Trt)-OH (3 eq, 11.8g) was dissolved in DMF along with Oxyma (4.5eq, 4.22g). Preactivation with DIC (3.9 eq, 4 ml) for 15 minutes was done prior to addition to the resin. After 15 minutes, an additional aliquot of DIC (2.6 eq, 2.65 ml) was added to the reaction. Once the reaction was complete as determined by the Kaiser test the resin was again washed 3x with DMF prior to starting the next deprotection/coupling cycle.

[00443] Step 3: Coupling of FMOC-Lys(Ac)-OH: The FMOC was removed from the N-terminus of the resin bound Asparagine and the resin washed as previously described. FMOC-Lys(Ac)-OH (2eq, 5.42g) was dissolved in 100ml of DMF along with Oxyma (3eq, 2.81g). DIC (2.6 eq, 2.65 ml) was added for preactivation of the acid for ~15 minutes prior to addition to the resin. After ~15 minutes, an additional aliquot of DIC (1.4 eq, 1.43 ml) was added to the reaction. Once the reaction was complete as determined by the Kaiser test the resin was again washed 3x with DMF prior to starting the next deprotection/coupling cycle.

[00444] Step 4: Coupling of FMOC-α-Me-Lys(Boc)-OH: The FMOC was removed from the N-terminus of the resin bound Acetyl Lysine and the resin washed as previously described. FMOC-α-Me-Lys(Boc)-OH (2 eq, 6.27 g) was dissolved in 100ml of DMF along with Oxyma (3eq, 2.81g). DIC (2.6 eq, 2.65 ml) was added for preactivation of the acid ~15 minutes prior to addition to resin. After ~15 minutes, an additional aliquot of DIC (1.4 eq, 1.43 ml) was

added to the reaction. Once the reaction was complete as determined by the Kaiser test the resin was again washed 3x with DMF prior to starting the next deprotection/coupling cycle.

[00445] Step 5: Coupling of FMOC-L-Ala(2-Naphthyl)-OH: The FMOC was removed from the N-terminus of the resin bound peptide and the resin washed as previously described. FMOC-L-Ala(2-Naphthyl)-OH (3 eq, 8.66 g) was dissolved in 100ml of DMF along with Oxyma (4.5 eq, 4.22g). DIC (3.9 eq, 4 ml) was added for preactivation of the acid ~15 minutes prior to addition to the resin. After ~15 minutes, an additional aliquot of DIC (2.6 eq, 2.65 ml) was added to the reaction. Once the reaction was complete as determined by the Kaiser test the resin was again washed 3x with DMF prior to starting the next deprotection/coupling cycle.

[00446] Step 6: Coupling of FMOC-4-[2-(boc-amino-ethoxy)]-L-Phenylalanine : The FMOC was removed from the N-terminus of the resin bound peptide and the resin washed as previously described. FMOC-4-[2-(boc-amino-ethoxy)]-L-Phenylalanine (3 eq, 10.8 g) was dissolved in 100ml of DMF along with Oxyma (4.5 eq, 4.22g). DIC (3.9 eq, 4 ml) was added for preactivation of the acid ~15 minutes prior to addition to the resin. After ~15 minutes, an additional aliquot of DIC (2.6 eq, 2.65 ml) was added to the reaction. Once the reaction was complete as determined by the Kaiser test the resin was again washed 3x with DMF prior to starting the next deprotection/coupling cycle.

[00447] Step 7: Coupling of FMOC-L-Pen(Trt)-OH : The FMOC was removed from the N-terminus of the resin bound peptide and the resin washed as previously described. FMOC-L-Pen(Trt)-OH (3 eq, 12.14 g) was dissolved in 100ml of DMF along with Oxyma (4.5 eq, 4.22g). DIC (3.9 eq, 4 ml) was added for preactivation of the acid ~15 minutes prior to addition to the resin. After ~15 minutes, an additional aliquot of DIC (2.6 eq, 2.65 ml) was added to the reaction. Once the reaction was complete as determined by the Kaiser test the resin was again washed 3x with DMF prior to starting the next deprotection/coupling cycle.

[00448] Step 8: Coupling of FMOC-Lys(Ac)-OH : The FMOC was removed from the N-terminus of the resin bound peptide and the resin washed as previously described. FMOC-Lys(Ac)-OH (2 eq, 5.4 g) was dissolved in 100 ml of DMF along with Oxyma (3 eq, 2.81 g). DIC (2.6 eq, 2.65 ml) was added for preactivation of the acid ~15 minutes prior to addition to the resin. After ~15 minutes, an additional aliquot of DIC (1.4 eq, 1.43 ml) was added to the reaction. Once the reaction was complete as determined by the Kaiser test the resin was again washed 3x with DMF prior to starting the next deprotection/coupling cycle.

[00449] Step 9: Coupling of FMOC-7-Me-Trp-OH : The FMOC was removed from the N-terminus of the resin bound peptide and the resin washed as previously described. FMOC-7-Me-Trp-OH (2 eq, 5.81 g) was dissolved in 100 ml of DMF along with Oxyma (3 eq, 2.81 g). DIC (2.6 eq, 2.65 ml) was added for preactivation of the acid ~15 minutes prior to addition to the resin. After ~15 minutes, an additional aliquot of DIC (1.4 eq, 1.43 ml) was added to the reaction. Once the reaction was complete as determined by the Kaiser test the resin was again washed 3x with DMF prior to starting the next deprotection/coupling cycle.

[00450] Step 10: Coupling of FMOC-Thr(tBu)-OH : The FMOC was removed from the N-terminus of the resin bound peptide and the resin washed as previously described. FMOC-Thr(tBu)-OH (4 eq, 10.5g) was dissolved in 100 ml of DMF along with Oxyma (6 eq, 5.62 g). DIC (5.2 eq, 5.3 ml) was added for preactivation of the acid ~15 minutes prior to addition to the resin. After ~15 minutes, an additional aliquot of DIC (2.6 eq, 2.65 ml) was added to the reaction. Once the reaction was complete as determined by the Kaiser test the resin was again washed 3x with DMF prior to starting the next deprotection/coupling cycle.

[00451] Step 11: Coupling of FMOC-Asn(Trt)-OH : The FMOC was removed from the N-terminus of the resin bound peptide and the resin washed as previously described. FMOC-Asn(Trt)-OH (4 eq, 15.8 g) was dissolved in 100 ml of DMF along with Oxyma (6 eq, 5.62 g). DIC (5.2 eq, 5.3 ml) was added for preactivation of the acid ~15 minutes prior to addition to the resin. After ~15 minutes, an additional aliquot of DIC (2.6 eq, 2.65 ml) was added to the reaction. Once the reaction was complete as determined by the Kaiser test the resin was again washed 3x with DMF prior to starting the next deprotection/coupling cycle.

[00452] Step 12: Coupling of FMOC-L-Pen(Trt)-OH : The FMOC was removed from the N-terminus of the resin bound peptide and the resin washed as previously described. FMOC-L-Pen(Trt)-OH (2 eq, 8.1 g) was dissolved in 100ml of DMF along with Oxyma (3 eq, 2.81 g). DIC (2.6 eq, 2.65 ml) was added for preactivation of the acid ~15 minutes prior to addition to the resin. After ~15 minutes, an additional aliquot of DIC (2.6 eq, 2.65 ml) was added to the reaction. Once the reaction was complete as determined by the Kaiser test the resin was again washed 3x with DMF prior to the final deprotection and acetic acid capping of the constructed peptide.

[00453] Step 13: Acetyl Capping: The FMOC was removed from the N-terminus of the resin bound peptide and the resin washed as previously described. 150 ml of Capping Reagent A (THF/Acetic anhydride/Pyridine, 80:10:10) was added to the resin and shaken for 30 min. The

resin was washed 3 x with DMF followed by 3x with DCM. The resin was divided into 5 – 50 ml centrifuge tubes and placed under vacuum for 1.5 hrs prior to cleavage with TFA.

[00454] Step 14: TFA Cleavage and Ether precipitation: 200 ml of the TFA cleavage cocktail (90/5/2.5/2.5 TFA/water/Tips/DODT) was prepared. 40 ml of the cleavage cocktail was added to each of the 5 tubes containing the protected resin bound peptide and shaken for two hours. The spent resin was filtered away and the filtrate divided evenly into 18 – 50 ml centrifuge tubes for precipitation. Cold Diethyl Ether was added to each forming a white precipitate that was then centrifuged. The ether was decanted to waste and 2 more ether washes of the precipitate were performed. The resulting white precipitate cake was allowed to dry overnight in the hood to give the crude reduced peptide.

[00455] Step 15: Disulfide Oxidation: The crude peptide was oxidized in four batches. ~ 2.5 g of crude peptide was dissolved in 50 ml of 50/50 acetonitrile/water and diluted to 1L 20% ACN/water. With swirling a saturated solution of Iodine in Acetic acid/Methanol was added dropwise to the 1L peptide solution until the yellow/brown color of the I2 remains and does not fade away. The slightly colored solution was allowed to sit for 5 min prior to quenching the excess I2 with a pinch of Ascorbic acid.

[00456] Step 16: RP-HPLC purification: The RP-HPLC purification was performed in four batches immediately following I2 oxidation and quenching. A preparative purification column (Phenomenex, Luna, C18(2), 100A, 250x50mm) was equilibrated at 70ml/min with 5% MPB in MPA (MPA = 0.1% TFA/water, MPB = 0.1% TFA in ACN). The 1 L of quenched oxidized peptide was loaded onto the equilibrated column at 70 ml/min. After the solvent front eluted an elution gradient of 20-38% MPB over 60 min at 70ml/min was run. The desired oxidized peptide eluted at ~26% MPB. Pure fractions were combined from all four purifications and lyophilized to give the purified TFA salt ready for counterion exchange.

[00457] Step 17: Counterion Exchange to Acetate: The same preparative RP-HPLC column was equilibrated with 5% MPB in MPA at 70 ml/min (MPA = 0.3% AcOH in Water, MPB = 0.3% AcOH in ACN, MPC = 0.5M NH4OAc in Water.) The entire 3.83 g of purified peptide was dissolved in 50/50 ACN/water and diluted to 15% ACN (~50ml total). The solution was loaded onto the equilibrated column at 70 ml/min and the solvent front eluted. The captured peptide was washed with 5% MPB in MPA for 5 min. The captured peptide was then washed with 5% MPB in MPC for 40 min at 70 ml/min to exchange the counterions from TFA to Acetate. The captured peptide was then washed with 5% MPB in MPA at 70ml/min for 10

min to clear all NH4OAc form system. Finally, the peptide is eluted with a quick gradient of 5-70% MPB in MPA over 60 minutes.

[00458] Step 18: Final Lyophilization and Analysis: The collected fractions were analyzed by analytical RP-HPLC, and all fractions >95% purity were combined. Lyophilization of the combined fractions gave Peptide #248 as a white powder with a purity of >97%. LC/MS of purified Peptide #248 agreed with the theoretical molecular weight of 1872.24.

EXAMPLE 1E

ADDITIONAL REPRESENTATIVE SYNTHESIS OF PEPTIDE MONOMERS

SYNTHESIS OF PEPTIDE Ac-[Pen]-NT-[W(7-Me)]-[Cit]-[Pen]-Phe[4-(2-aminoethoxy)]-[2-Nal]-[a-MeLys]-[Lys(Ac)]-[N-MeAla]-NH_2 (SEQ. ID. NO. 265) (PEPTIDE #265)

[00459] The acetate salt of Peptide #265 was synthesized on a 6.7 mmol scale.

[00460] The Peptide #265 was constructed on Rink Amide MBHA resin using standard FMOC protection synthesis conditions. The constructed peptide was isolated from the resin and protecting groups by cleavage with strong acid followed by precipitation. The crude precipitate was then oxidized with I2, purified and counterion exchanged to Acetate by RP-HPLC. Lyophilization of pure fractions gave the final product Peptide #265.

[00461] Swell Resin: 10 g of Rink Amide MBHA solid phase resin (0.66mmol/g loading) was transferred to a 250 ml peptide vessel with filter frit, ground glass joint and vacuum side arm. The resin was washed 3x with DMF.

[00462] Step 1: Coupling of FMOC-N-MeAla-OH: Deprotection of the FMOC group was realized by adding 2 resin-bed volumes of 20% 4-methyl piperidine in DMF to the swollen resin and shaking for 3-5 min prior to draining and adding a second, 2-resin-bed volume of the 4-methyl piperidine solution and shaking for an additional 20-30 min. After deprotection the resin was washed 3x DMF with shaking. FMOC-N-MeAla-OH (3 eq) was dissolved in 100 ml DMF along with Oxyma (4.5 eq, 4.22g). Preactivation of the acid was accomplished by addition of DIC (3.9 eq, 4 ml) and shaking for 15 min prior to addition to the deprotected resin. An additional aliquot of DIC (2.6 eq, 2.65 ml) was added after ~ 15 min of coupling. The progress of the coupling reaction was monitored by the colorimetric Kaiser test. Once the reaction was judged complete the resin was washed 3 x DMF with shaking prior to starting the next deprotection/coupling cycle.

[00463] Step 2: Coupling of FMOC-Lys(Ac)-OH: The FMOC was removed from the N-terminus of the resin bound Asparagine and the resin washed as previously described. FMOC-Lys(Ac)-OH (2eq, 5.42g) was dissolved in 100ml of DMF along with Oxyma (3eq, 2.81g). DIC (2.6 eq, 2.65 ml) was added for preactivation of the acid for ~15 minutes prior to addition to the resin. After ~15 minutes, an additional aliquot of DIC (1.4 eq, 1.43 ml) was added to the reaction. Once the reaction was complete as determined by the Kaiser test the resin was again washed 3x with DMF prior to starting the next deprotection/coupling cycle.

[00464] Step 3: Coupling of FMOC-α-Me-Lys(Boc)-OH: The FMOC was removed from the N-terminus of the resin bound Acetyl Lysine and the resin washed as previously described. FMOC-α-Me-Lys(Boc)-OH (2 eq, 6.27 g) was dissolved in 100ml of DMF along with Oxyma (3eq, 2.81g). DIC (2.6 eq, 2.65 ml) was added for preactivation of the acid ~15 minutes prior to addition to resin. After ~15 minutes, an additional aliquot of DIC (1.4 eq, 1.43 ml) was added to the reaction. Once the reaction was complete as determined by the Kaiser test the resin was again washed 3x with DMF prior to starting the next deprotection/coupling cycle.

[00465] Step 4: Coupling of FMOC-L-Ala(2-Naphthyl)-OH: The FMOC was removed from the N-terminus of the resin bound peptide and the resin washed as previously described. FMOC-L-Ala(2-Naphthyl)-OH (3 eq, 8.66 g) was dissolved in 100ml of DMF along with Oxyma (4.5 eq, 4.22g). DIC (3.9 eq, 4 ml) was added for preactivation of the acid ~15 minutes prior to addition to the resin. After ~15 minutes, an additional aliquot of DIC (2.6 eq, 2.65 ml) was added to the reaction. Once the reaction was complete as determined by the Kaiser test the resin was again washed 3x with DMF prior to starting the next deprotection/coupling cycle.

[00466] Step 5: Coupling of FMOC-4-[2-(boc-amino-ethoxy)]-L-Phenylalanine : The FMOC was removed from the N-terminus of the resin bound peptide and the resin washed as previously described. FMOC-4-[2-(boc-amino-ethoxy)]-L-Phenylalanine (3 eq, 10.8 g) was dissolved in 100ml of DMF along with Oxyma (4.5 eq, 4.22g). DIC (3.9 eq, 4 ml) was added for preactivation of the acid ~15 minutes prior to addition to the resin. After ~15 minutes, an additional aliquot of DIC (2.6 eq, 2.65 ml) was added to the reaction. Once the reaction was complete as determined by the Kaiser test the resin was again washed 3x with DMF prior to starting the next deprotection/coupling cycle.

[00467] Step 6: Coupling of FMOC-L-Pen(Trt)-OH : The FMOC was removed from the N-terminus of the resin bound peptide and the resin washed as previously described. FMOC-L-Pen(Trt)-OH (3 eq, 12.14 g) was dissolved in 100ml of DMF along with Oxyma (4.5 eq, 4.22g).

DIC (3.9 eq, 4 ml) was added for preactivation of the acid ~15 minutes prior to addition to the resin. After ~15 minutes, an additional aliquot of DIC (2.6 eq, 2.65 ml) was added to the reaction. Once the reaction was complete as determined by the Kaiser test the resin was again washed 3x with DMF prior to starting the next deprotection/coupling cycle.

[00468] Step 7: Coupling of FMOC-Cit-OH : The FMOC was removed from the N-terminus of the resin bound peptide and the resin washed as previously described. FMOC-Cit-OH (2 eq) was dissolved in 100 ml of DMF along with Oxyma (3 eq, 2.81 g). DIC (2.6 eq, 2.65 ml) was added for preactivation of the acid ~15 minutes prior to addition to the resin. After ~15 minutes, an additional aliquot of DIC (1.4 eq, 1.43 ml) was added to the reaction. Once the reaction was complete as determined by the Kaiser test the resin was again washed 3x with DMF prior to starting the next deprotection/coupling cycle.

[00469] Step 8: Coupling of FMOC-7-Me-Trp-OH : The FMOC was removed from the N-terminus of the resin bound peptide and the resin washed as previously described. FMOC-7-Me-Trp-OH (2 eq, 5.81 g) was dissolved in 100 ml of DMF along with Oxyma (3 eq, 2.81 g). DIC (2.6 eq, 2.65 ml) was added for preactivation of the acid ~15 minutes prior to addition to the resin. After ~15 minutes, an additional aliquot of DIC (1.4 eq, 1.43 ml) was added to the reaction. Once the reaction was complete as determined by the Kaiser test the resin was again washed 3x with DMF prior to starting the next deprotection/coupling cycle.

[00470] Step 9: Coupling of FMOC-Thr(tBu)-OH : The FMOC was removed from the N-terminus of the resin bound peptide and the resin washed as previously described. FMOC-Thr(tBu)-OH (4 eq, 10.5g) was dissolved in 100 ml of DMF along with Oxyma (6 eq, 5.62 g). DIC (5.2 eq, 5.3 ml) was added for preactivation of the acid ~15 minutes prior to addition to the resin. After ~15 minutes, an additional aliquot of DIC (2.6 eq, 2.65 ml) was added to the reaction. Once the reaction was complete as determined by the Kaiser test the resin was again washed 3x with DMF prior to starting the next deprotection/coupling cycle.

[00471] Step 10: Coupling of FMOC-Asn(Trt)-OH : The FMOC was removed from the N-terminus of the resin bound peptide and the resin washed as previously described. FMOC-Asn(Trt)-OH (4 eq, 15.8 g) was dissolved in 100 ml of DMF along with Oxyma (6 eq, 5.62 g). DIC (5.2 eq, 5.3 ml) was added for preactivation of the acid ~15 minutes prior to addition to the resin. After ~15 minutes, an additional aliquot of DIC (2.6 eq, 2.65 ml) was added to the reaction. Once the reaction was complete as determined by the Kaiser test the resin was again washed 3x with DMF prior to starting the next deprotection/coupling cycle.

[00472] Step 11: Coupling of FMOC-L-Pen(Trt)-OH : The FMOC was removed from the N-terminus of the resin bound peptide and the resin washed as previously described. FMOC-L-Pen(Trt)-OH (2 eq, 8.1 g) was dissolved in 100ml of DMF along with Oxyma (3 eq, 2.81 g). DIC (2.6 eq, 2.65 ml) was added for preactivation of the acid ~15 minutes prior to addition to the resin. After ~15 minutes, an additional aliquot of DIC (2.6 eq, 2.65 ml) was added to the reaction. Once the reaction was complete as determined by the Kaiser test the resin was again washed 3x with DMF prior to the final deprotection and acetic acid capping of the constructed peptide.

[00473] Step 12: Acetyl Capping: The FMOC was removed from the N-terminus of the resin bound peptide and the resin washed as previously described. 150 ml of Capping Reagent A (THF/Acetic anhydride/Pyridine, 80:10:10) was added to the resin and shaken for 30 min. The resin was washed 3 x with DMF followed by 3x with DCM. The resin was divided into 5 – 50 ml centrifuge tubes and placed under vacuum for 1.5 hrs prior to cleavage with TFA.

[00474] Step 13: TFA Cleavage and Ether precipitation: 200 ml of the TFA cleavage cocktail (90/5/2.5/2.5 TFA/water/Tips/DODT) was prepared. 40 ml of the cleavage cocktail was added to each of the 5 tubes containing the protected resin bound peptide and shaken for two hours. The spent resin was filtered away and the filtrate divided evenly into 18 – 50 ml centrifuge tubes for precipitation. Cold Diethyl Ether was added to each forming a white precipitate that was then centrifuged. The ether was decanted to waste and 2 more ether washes of the precipitate were performed. The resulting white precipitate cake was allowed to dry overnight in the hood to give the crude reduced peptide.

[00475] Step 14: Disulfide Oxidation: The crude peptide was oxidized in four batches. ~ 2.5 g of crude peptide was dissolved in 50 ml of 50/50 acetonitrile/water and diluted to 1L 20% ACN/water. With swirling a saturated solution of Iodine in Acetic acid/Methanol was added dropwise to the 1L peptide solution until the yellow/brown color of the I2 remains and does not fade away. The slightly colored solution was allowed to sit for 5 min prior to quenching the excess I2 with a pinch of Ascorbic acid.

[00476] Step 15: RP-HPLC purification: The RP-HPLC purification was performed in four batches immediately following I2 oxidation and quenching. A preparative purification column (Phenomenex, Luna, C18(2), 100A, 250x50mm) was equilibrated at 70ml/min with 5% MPB in MPA (MPA = 0.1% TFA/water, MPB = 0.1% TFA in ACN). The 1 L of quenched oxidized peptide was loaded onto the equilibrated column at 70 ml/min. After the solvent front eluted

an elution gradient of 20-38% MPB over 60 min at 70ml/min was run. The desired oxidized peptide eluted at ~28% MPB. Pure fractions were combined from all four purifications and lyophilized to give the purified TFA salt ready for counterion exchange.

[00477] Step 16: Counterion Exchange to Acetate: The same preparative RP-HPLC column was equilibrated with 5% MPB in MPA at 70 ml/min (MPA = 0.3% AcOH in Water, MPB = 0.3% AcOH in ACN, MPC = 0.5M NH4OAc in Water.) The entire 3.83 g of purified peptide was dissolved in 50/50 ACN/water and diluted to 15% ACN (~50ml total). The solution was loaded onto the equilibrated column at 70 ml/min and the solvent front eluted. The captured peptide was washed with 5% MPB in MPA for 5 min. The captured peptide was then washed with 5% MPB in MPC for 40 min at 70 ml/min to exchange the counterions from TFA to Acetate. The captured peptide was then washed with 5% MPB in MPA at 70ml/min for 10 min to clear all NH4OAc form system. Finally, the peptide is eluted with a quick gradient of 5-70% MPB in MPA over 60 minutes.

[00478] Step 17: Final Lyophilization and Analysis: The collected fractions were analyzed by analytical RP-HPLC, and all fractions >95% purity were combined. Lyophilization of the combined fractions gave Peptide #265 as a white powder with a purity of >97%. LC/MS of purified Peptide #265 agreed with the theoretical molecular weight of 1807.17.

EXAMPLE 2

PEPTIDE INHIBITION OF BINDING OF INTERLEUKIN-23 TO THE INTERLEUKIN-23 RECEPTOR

[00479] Peptide optimization was performed to identify peptide inhibitors of IL-23 signalling that were active at low concentrations (e.g., IC_{50} <10 nM). Peptides were tested to identify peptides that inhibit the binding of IL-23 to human IL-23R and inhibit IL-23/IL-23R functional activity, as described below.

[00480] Assays were performed to determine peptide activity as described below, and the results of these assays are provided in Tables E1-E3. Human ELISA indicates the IL23-IL23R competitive binding assay described below, Rat ELISA indicates the rat IL-23R competitive binding ELISA assay described below, and pStat3HTRF indicates the DB cells IL-23R pSTAT3 cell assay described below. The peptides depicted in Table E1 are cyclized via a disulfide bridge formed between two Pen residues in these peptides. The peptides depicted in Table E2 are cyclized via a thioether bond between the indicated amino acid residues. Table E2 provides an illustrative structure depicting thioether cyclization, which is indicated in the

table by the term "cyclo," with the cyclic region bracketed immediately following the term "cyclo." For certain peptides, the residue Abu is present where indicated, whereas in other embodiments, e.g., those related to the non-cyclized form, the Abu may be referred to as a hSer(Cl) or homoSer residue. The petpides depicted in Table E3 are cyclized via a disulfide bridge formed between two Pen residues or a thioether bond between Abu and Cys.

IL23-IL23R Competitive Binding ELISA

[00481] An Immulon® 4HBX plate was coated with 50 ng/well of IL23R_huFC and incubated overnight at 4°C. The wells were washed four times with PBST, blocked with PBS containing 3% Skim Milk for 1 hour at room temperature, and washed again four times with PBST. Serial dilutions of test peptides and IL-23 at a final concentration of 2 nM diluted in Assay Buffer (PBS containing 1% Skim Milk) were added to each well, and incubated for 2 hours at room temperature. After the wells were washed, bound IL-23 was detected by incubation with 50 ng/well of goat anti-p40 polyclonal antibodies (R&D Systems #AF309) diluted in Assay Buffer for 1 hour at room temperature. The wells were again washed four times with PBST. The secondary antibodies, HRP conjugated donkey anti-goat IgG (Jackson ImmunoResearch Laboratories #705-035-147) diluted 1:5000 in Assay Buffer was then added, and incubated for 30 minutes at room temperature. The plate was finally washed as above. Signals were visualized with TMB One Component HRP Membrane Substrate, quenched with 2 M sulfuric acid and read spectrophotometrically at 450 nm. IC_{50} values for various test peptides determined from these data are shown in Tables E1-E3.

Rat IL-23R Competitive Binding ELISA

[00482] An assay plate was coated with 300 ng/well of Rat IL-23R_huFC and incubated overnight at 4°C. The wells were washed, blocked, and washed again. Serial dilutions of test peptides and IL-23 at a final concentration of 7 nM were added to each well, and incubated for 2 hours at room temperature. After the wells were washed, bound IL-23 was detected with goat anti-p40 polyclonal antibodies, followed by an HRP conjugated donkey anti-goat IgG. Signals were visualized with TMB One Component HRP Membrane Substrate and quenched with 2 M sulfuric acid. IC_{50} values for various test peptides determined from these data are shown in Tables E1-E3.

DB Cells IL23R pSTAT3 Cell Assay

[00483] IL-23 plays a central role in supporting and maintaining Th17 differentiation *in vivo*. This process is thought to be mediated primarily through the Signal Transducer and Activator

of Transcription 3 (STAT3), with phosphorylation of STAT3 (to yield pSTAT3) leading to upregulation of RORC and pro-inflammatory IL-17. This cell assay examines the levels of pSTAT3 in IL-23R-expressing DB cells when stimulated with IL-23 in the presence of test compounds. Serial dilutions of test peptides and IL-23 (Humanzyme #HZ-1261) at a final concentration of 0.5 nM, were added to each well in a 96 well tissue culture plate (Corning #CLS3894). DB cells (ATCC #CRL-2289), cultured in RPMI-1640 medium (Thermo Scientific #11875093) supplemented with 10% FBS, were added at 5 X 10E5 cells/well and incubated for 30 minutes at 37°C in a 5% CO_2 humidified incubator. Changes in phospho-STAT3 levels in the cell lysates were detected using the Cisbio HTRF pSTAT3 (Tyr705) Cellular Assay Kit (Cisbio #62AT3PEH), according to manufacturer's Two Plate Assay protocol. IC_{50} values determined from these data are shown in Table E3. Where not shown, data was not yet determined.

Table E3. IC_{50}s of Additional Illustrative Peptides Comprising the -X7-X8-X9-X10-X11- Motif and Analogues

SEQ ID No.	Sequence*	pStat3 HTRF (nM)
201	Ac-[Pen]-NT-[W(7-Me)]-Q-[Pen]-Phe[4-(2-aminoethoxy)]-[2-Nal]-[a-MeLeu]-[Lys(Ac)]-N-[bA]-NH_2	1.05
202	Ac-[Pen]-NT-[W(7-Me)]-Q-[Pen]-Phe[4-(2-aminoethoxy)]-[2-Nal]-[a-MeLys]-[Lys(Ac)]-N-[bA]-NH_2	1.1
203	Ac-[(D)Arg]-Abu-Q-T-[W(7-Me)]-Q-C-Phe[4-(2-aminoethoxy)]-[2-Nal]-[THP]-E-N-[bA]-NH_2	1.84
204	Ac-Abu-Q-T-[W(7-Me)]-Q-C-Phe[4-(2-aminoethoxy)]-[2-Nal]-[THP]-E-N-[bA]-NH_2	1.75
205	Ac-[Pen]-NT-[W(7-Me)]-Q-[Pen]-Phe[4-(2-aminoethoxy)]-[2-Nal]-[a-MeLeu]-[Lys(Ac)]-G-[bA]-NH_2	4.46
206	Ac-[Pen]-NT-[W(7-Me)]-Q-[Pen]-Phe[4-(2-aminoethoxy)]-[2-Nal]-[a-MeLeu]-[Lys(Ac)]-[Cit]-[bA]-NH_2	12
207	Ac-[Pen]-NT-[W(7-Me)]-Q-[Pen]-Phe[4-(2-aminoethoxy)]-[2-Nal]-[a-MeLeu]-[Lys(Ac)]-A-[bA]-NH_2	1.46
208	Ac-[Pen]-NT-[W(7-Me)]-Q-[Pen]-Phe[4-(2-aminoethoxy)]-[2-Nal]-[a-MeLeu]-[Lys(Ac)]-L-[bA]-NH_2	5.39
209	Ac-[Pen]-NT-[W(7-Me)]-Q-[Pen]-Phe[4-(2-aminoethoxy)]-[2-Nal]-[a-MeLeu]-[Lys(Ac)]-[(D)Ala]-[bA]-NH_2	9.84
210	Ac-[Pen]-NT-[W(7-Me)]-Q-[Pen]-Phe[4-(2-aminoethoxy)]-[2-Nal]-[a-MeLeu]-[Lys(Ac)]-[(D)Leu]-[bA]-NH_2	66.1
211	Ac-[Pen]-NT-[W(7-Me)]-Q-[Pen]-Phe[4-(2-aminoethoxy)]-[2-Nal]-[a-MeLeu]-[Lys(Ac)]-P-[bA]-NH_2	178
212	Ac-[Pen]-NT-[W(7-Me)]-Q-[Pen]-Phe[4-(2-aminoethoxy)]-[2-Nal]-[a-MeLeu]-[Lys(Ac)]-[(D)Pro]-[bA]-NH_2	36.5

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213	Ac-[Pen]-NT-[W(7-Me)]-Q-[Pen]-Phe[4-(2-aminoethoxy)]-[2-Nal]-[a-MeLeu]-[Lys(Ac)]-[(D)Phe]-[bA]-NH_2	35.5
214	Ac-[Pen]-NT-[W(7-Me)]-Q-[Pen]-Phe[4-(2-aminoethoxy)]-[2-Nal]-[a-MeLeu]-[Lys(Ac)]-H-[bA]-NH_2	1.53
215	Ac-[Pen]-NT-[W(7-Me)]-Q-[Pen]-Phe[4-(2-aminoethoxy)]-[2-Nal]-[a-MeLeu]-[Lys(Ac)]-[(D)His]-[bA]-NH_2	4.94
216	Ac-[Pen]-NT-[W(7-Me)]-Q-[Pen]-Phe[4-(2-aminoethoxy)]-[2-Nal]-[a-MeLeu]-[Lys(Ac)]-I-[bA]-NH_2	13.5
217	Ac-[Pen]-NT-[W(7-Me)]-Q-[Pen]-Phe[4-(2-aminoethoxy)]-[2-Nal]-[a-MeLeu]-[Lys(Ac)]-T-[bA]-NH_2	1.61
218	Ac-[Pen]-NT-[W(7-Me)]-Q-[Pen]-Phe[4-(2-aminoethoxy)]-[2-Nal]-[a-MeLeu]-[Lys(Ac)]-[(D)Thr]-[bA]-NH_2	11
219	Ac-[Pen]-NT-[W(7-Me)]-Q-[Pen]-Phe[4-(2-aminoethoxy)]-[2-Nal]-[a-MeLeu]-G-P-[bA]-NH_2	93.7
220	Ac-[Pen]-NT-[W(7-Me)]-Q-[Pen]-Phe[4-(2-aminoethoxy)]-[2-Nal]-[a-MeLeu]-G-[(D)Pro]-[bA]-NH_2	195
221	Ac-[Pen]-NT-[W(7-Me)]-Q-[Pen]-Phe[4-(2-aminoethoxy)]-[2-Nal]-[a-MeLeu]-[Lys(Ac)]-S-[bA]-NH_2	1.27
222	Ac-[Pen]-NT-[W(7-Me)]-Q-[Pen]-Phe[4-(2-aminoethoxy)]-[2-Nal]-[a-MeLeu]-[Lys(Ac)]-[(D)Ser]-[bA]-NH_2	5.02
223	Ac-[Pen]-NT-[W(7-Me)]-Q-[Pen]-Phe[4-(2-aminoethoxy)]-[2-Nal]-[a-MeLeu]-[Lys(Ac)]-[N-MeAla]-[bA]-NH_2	134
224	Ac-[Pen]-NT-[W(7-Me)]-Q-[Pen]-Phe[4-(2-aminoethoxy)]-[2-Nal]-[a-MeLeu]-[Lys(Ac)]-[Sarc]-[bA]-NH_2	124
225	Ac-[Pen]-NT-[W(7-Me)]-Q-[Pen]-Phe[4-(2-aminoethoxy)]-[2-Nal]-[a-MeLeu]-[Lys(Ac)]-[a-MeLeu]-[bA]-NH_2	56.7
226	Ac-[Pen]-NT-[W(7-Me)]-Q-[Pen]-Phe[4-(2-aminoethoxy)]-[2-Nal]-[a-MeLeu]-[Lys(Ac)]-[bA]-[bA]-NH_2	25.7
227	Ac-[Pen]-NT-[W(7-Me)]-[Cit]-[Pen]-Phe[4-(2-aminoethoxy)]-[2-Nal]-[a-MeLeu]-[Lys(Ac)]-N-[bA]-NH_2	0.702
228	Ac-[Pen]-NT-[W(6-Cl)]-Q-[Pen]-Phe[4-(2-aminoethoxy)]-[2-Nal]-[a-MeLys]-[Lys(Ac)]-N-[bA]-NH_2	25.7
229	Ac-[Pen]-NT-[W(4-OMe)]-Q-[Pen]-Phe[4-(2-aminoethoxy)]-[2-Nal]-[a-MeLys]-[Lys(Ac)]-N-[bA]-NH_2	23.1
230	Ac-[Pen]-NT-[W(6-Me)]-Q-[Pen]-Phe[4-(2-aminoethoxy)]-[2-Nal]-[a-MeLys]-[Lys(Ac)]-N-[bA]-NH_2	25
231	Ac-[Pen]-NT-[W(4-Me)]-Q-[Pen]-Phe[4-(2-aminoethoxy)]-[2-Nal]-[a-MeLys]-[Lys(Ac)]-N-[bA]-NH_2	5.85
232	Ac-[Pen]-NT-[W(1-Me)]-Q-[Pen]-Phe[4-(2-aminoethoxy)]-[2-Nal]-[a-MeLys]-[Lys(Ac)]-N-[bA]-NH_2	4.5
233	Ac-[Pen]-NT-[W(2,5,7-tritBu)]-Q-[Pen]-Phe[4-(2-aminoethoxy)]-[2-Nal]-[a-MeLys]-[Lys(Ac)]-N-[bA]-NH_2	>1000
234	Ac-[Pen]-NT-[W(7-Me)]-[a-MeLys]-[Pen]-Phe[4-(2-aminoethoxy)]-[2-Nal]-[a-MeLeu]-[Lys(Ac)]-N-[bA]-NH_2	3.48

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235	Ac-[Pen]-NT-[W(7-Me)]-[a-MeLeu]-[Pen]-Phe[4-(2-aminoethoxy)]-[2-Nal]-[a-MeLys]-[Lys(Ac)]-N-[bA]-NH_2	3.21
236	Ac-[Pen]-NT-[W(7-Me)]-Q-[Pen]-Phe[4-(2-aminoethoxy)]-[2-Nal]-[a-MeLys]-[Aib]-N-[bA]-NH_2	5.21
237	Ac-[Pen]-Q-T-[W(7-Me)]-Q-[Pen]-Phe[4-(2-aminoethoxy)]-[2-Nal]-[a-MeLys]-[Lys(Ac)]-N-[bA]-NH_2	3.39
238	Ac-[Pen]-[Cit]-T-[W(7-Me)]-Q-[Pen]-Phe[4-(2-aminoethoxy)]-[2-Nal]-[a-MeLys]-[Lys(Ac)]-N-[bA]-NH_2	1.06
239	Ac-[Pen]-[Lys(Ac)]-T-[W(7-Me)]-Q-[Pen]-Phe[4-(2-aminoethoxy)]-[2-Nal]-[a-MeLys]-[Lys(Ac)]-N-[bA]-NH_2	1.66
240	Ac-[Pen]-[Aib]-T-[W(7-Me)]-Q-[Pen]-Phe[4-(2-aminoethoxy)]-[2-Nal]-[a-MeLys]-[Lys(Ac)]-N-[bA]-NH_2	17.7
241	Ac-[Pen]-NT-[W(7-Me)]-[Aib]-[Pen]-Phe[4-(2-aminoethoxy)]-[2-Nal]-[a-MeLys]-[Lys(Ac)]-N-[bA]-NH_2	12.5
242	Ac-[Pen]-NT-[W(7-Me)]-[Lys(Ac)]-[Pen]-Phe[4-(2-aminoethoxy)]-[2-Nal]-[a-MeLys]-[Lys(Ac)]-N-[bA]-NH_2	0.641
243	Ac-[Pen]-NT-[W(7-Me)]-[Lys(Ac)]-[Pen]-Phe[4-(2-aminoethoxy)]-[2-Nal]-[a-MeLys]-[Lys(Ac)]-N-R-NH_2	1.87
244	Ac-[Pen]-NT-[W(7-Me)]-[Lys(Ac)]-[Pen]-Phe[4-(2-aminoethoxy)]-[2-Nal]-[a-MeLys]-[Lys(Ac)]-N-L-NH_2	1.45
245	Ac-[Pen]-NT-[W(7-Me)]-[Lys(Ac)]-[Pen]-Phe[4-(2-aminoethoxy)]-[2-Nal]-[a-MeLys]-[Lys(Ac)]-N-[(D)Leu]-NH_2	0.51
246	Ac-[Pen]-NT-[W(7-Me)]-[Lys(Ac)]-[Pen]-Phe[4-(2-aminoethoxy)]-[2-Nal]-[a-MeLys]-[Lys(Ac)]-N-[NMeArg]-NH_2	4.83
247	Ac-[Pen]-NT-[W(7-Me)]-[Lys(Ac)]-[Pen]-Phe[4-(2-aminoethoxy)]-[2-Nal]-[a-MeLys]-[Lys(Ac)]-N-[bhPhe]-NH_2	
248	Ac-[Pen]-NT-[W(7-Me)]-[Lys(Ac)]-[Pen]-Phe[4-(2-aminoethoxy)]-[2-Nal]-[a-MeLys]-[Lys(Ac)]-N-H-NH_2	0.127
249	Ac-[Pen]-NT-[W(7-Me)]-[Lys(Ac)]-[Pen]-Phe[4-(2-aminoethoxy)]-[2-Nal]-[a-MeLys]-[Lys(Ac)]-N-[Cit]-NH_2	0.639
250	Ac-[Pen]-NT-[W(7-Me)]-[Lys(Ac)]-[Pen]-Phe[4-(2-aminoethoxy)]-[2-Nal]-[a-MeLys]-[Lys(Ac)]-N-V-NH_2	1.82
251	Ac-[Pen]-NT-[W(7-Me)]-[Lys(Ac)]-[Pen]-Phe[4-(2-aminoethoxy)]-[2-Nal]-[a-MeLys]-[Lys(Ac)]-N-[(D)Val]-NH_2	0.986
252	Ac-[Pen]-NT-[W(7-Me)]-[Lys(Ac)]-[Pen]-Phe[4-(2-aminoethoxy)]-[2-Nal]-[a-MeLys]-[Lys(Ac)]-N-[(D)Lys]-NH_2	0.338
253	Ac-[Pen]-NT-[W(7-Me)]-[Lys(Ac)]-[Pen]-Phe[4-(2-aminoethoxy)]-[2-Nal]-[a-MeLys]-[Lys(Ac)]-N-P-NH_2	1.44
254	Ac-[Pen]-NT-[W(7-Me)]-[Lys(Ac)]-[Pen]-Phe[4-(2-aminoethoxy)]-[2-Nal]-[a-MeLys]-[Lys(Ac)]-N-[(D)Pro]-NH_2	3.65
255	Ac-[Pen]-NT-[W(7-Me)]-[Lys(Ac)]-[Pen]-Phe[4-(2-aminoethoxy)]-[2-Nal]-[a-MeLys]-[Lys(Ac)]-N-I-NH_2	2.5
256	Ac-[Pen]-NT-[W(7-Me)]-[Cit]-[Pen]-Phe[4-(2-aminoethoxy)]-[2-Nal]-[a-MeLys]-[Lys(Ac)]-N-[(D)Arg]-NH_2	0.754

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257	Ac-[Pen]-NT-[W(7-Me)]-[Cit]-[Pen]-Phe[4-(2-aminoethoxy)]-[2-Nal]-[a-MeLys]-[Lys(Ac)]-N-[(D)Phe]-NH_2	3.88
258	Ac-[Pen]-NT-[W(7-Me)]-[Lys(Ac)]-[Pen]-Phe[4-(2-aminoethoxy)]-[2-Nal]-[a-MeLys]-[Lys(Ac)]-N-[(D)Phe]-NH_2	0.92
259	Ac-[Pen]-NT-[W(7-Me)]-[Cit]-[Pen]-Phe[4-(2-aminoethoxy)]-[2-Nal]-[a-MeLys]-[Lys(Ac)]-N-[(D)Tyr]-NH_2	0.607
260	Ac-[Pen]-NT-[W(7-Me)]-[Cit]-[Pen]-Phe[4-(2-aminoethoxy)]-[2-Nal]-[a-MeLys]-[Lys(Ac)]-N-S-NH_2	0.699
261	Ac-[Pen]-NT-[W(7-Me)]-[Cit]-[Pen]-Phe[4-(2-aminoethoxy)]-[2-Nal]-[a-MeLys]-[Lys(Ac)]-N-[(D)Ser]-NH_2	0.522
262	Ac-[Pen]-NT-[W(7-Me)]-[Cit]-[Pen]-Phe[4-(2-aminoethoxy)]-[2-Nal]-[a-MeLys]-[Lys(Ac)]-NT-NH_2	0.996
263	Ac-[Pen]-NT-[W(7-Me)]-[Cit]-[Pen]-Phe[4-(2-aminoethoxy)]-[2-Nal]-[a-MeLys]-[Lys(Ac)]-N-[(D)Thr]-NH_2	0.603
264	Ac-[Pen]-NT-[W(7-Me)]-[Cit]-[Pen]-Phe[4-(2-aminoethoxy)]-[2-Nal]-[a-MeLys]-[Lys(Ac)]-N-[Aib]-NH_2	0.596
265	Ac-[Pen]-NT-[W(7-Me)]-[Cit]-[Pen]-Phe[4-(2-aminoethoxy)]-[2-Nal]-[a-MeLys]-[Lys(Ac)]-[N-MeAla]-NH_2	1.15
266	Ac-[Pen]-NT-[W(7-Me)]-[Cit]-[Pen]-Phe[4-(2-aminoethoxy)]-[2-Nal]-[a-MeLys]-[Lys(Ac)]-N-Y-NH_2	2.78
267	Ac-[Pen]-NT-[W(7-Me)]-Q-[Pen]-Phe[4-(2-aminoethoxy)]-[2-Nal]-[a-MeLys]-[Lys(Ac)]-N-[bA]-NH_2	0.506
268	Ac-[Pen]-N-T-[W(7-Me)]-[Cit]-[Pen]-Phe[4-(2-aminoethoxy)]-[2-Nal]-[a-MeLys]-[Lys(Ac)]-[bA]-[bA]-NH_2	3.24
269	Ac-[Pen]-N-T-[W(7-Me)]-Q-[Pen]-Phe[4-(2-aminoethoxy)]-[2-Nal]-[a-MeLys]-[Lys(Ac)]-L-[bA]-NH_2	10.1
270	Ac-[Pen]-N-T-[W(7-Me)]-[Lys(Ac)]-[Pen]-Phe[4-(2-aminoethoxy)]-[2-Nal]-[a-MeLys]-[Lys(Ac)]-[bA]-[bA]-NH_2	4.43
271	Ac-[Pen]-N-T-[W(7-Me)]-[Lys(Ac)]-[Pen]-Phe[4-(2-aminoethoxy)]-[2-Nal]-[a-MeLys]-[Lys(Ac)]-S-[bA]-NH_2	1.91
272	Ac-[Pen]-N-T-[W(7-Me)]-[Lys(Ac)]-[Pen]-Phe[4-(2-aminoethoxy)]-[2-Nal]-[a-MeLys]-[Lys(Ac)]-H-[bA]-NH_2	7.13
273	Ac-[Pen]-N-T-[W(7-Me)]-[Lys(Ac)]-[Pen]-Phe[4-(2-aminoethoxy)]-[2-Nal]-[a-MeLys]-E-[bA]-[bA]-NH_2	2.69
274	Ac-[Pen]-N-T-[W(7-Me)]-Q-[Pen]-Phe[4-(2-aminoethoxy)]-[2-Nal]-[Achc]-[Lys(Ac)]-N-[bA]-NH_2	0.484
275	Ac-[Pen]-N-T-[W(7-Me)]-Q-[Pen]-Phe[4-(2-aminoethoxy)]-[2-Nal]-[Spiral_Pip]-[Lys(Ac)]-N-[bA]-NH_2	2.17
276	Ac-[Pen]-N-T-[W(7-Me)]-Q-[Pen]-Phe[4-(2-aminoethoxy)]-[2-Nal]-[DiethylGly]-[Lys(Ac)]-N-[bA]-NH_2	0.564
277	Ac-[Pen]-N-T-[W(7-Me)]-Q-[Pen]-Phe[4-(2-aminoethoxy)]-[2-Nal]-[Acbc]-[Lys(Ac)]-N-[bA]-NH_2	0.639
278	Ac-[Pen]-N-T-[W(7-Me)]-Q-[Pen]-Phe[4-(2-aminoethoxy)]-[2-Nal]-[a-MeOrn]-[Lys(Ac)]-N-[bA]-NH_2	0.849

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279	Ac-[Pen]-N-T-[W(7-Me)]-Q-[Pen]-Phe[4-(2-aminoethoxy)]-[2-Nal]-[a-MeLys]-[Cit]-[bA]-[bA]-NH_2	5.97
280	Ac-[Pen]-N-T-[W(1-Me)]-[Cit]-[Pen]-Phe[4-(2-aminoethoxy)]-[2-Nal]-[a-MeLys]-[Lys(Ac)]-[bA]-[bA]-NH_2	17.1
281	Ac-[Pen]-N-T-[W(7-Me)]-[Cit]-[Pen]-Phe[4-(2-aminoethoxy)]-[2-Nal]-[a-MeLys]-[Cit]-[bA]-[bA]-NH_2	17.7
282	Ac-[Pen]-N-T-[W(7-Me)]-Q-[Pen]-Phe[4-(2-aminoethoxy)]-[2-Nal]-[a-MeLys]-E-N-[bA]-NH_2	1.37
283	Ac-[Pen]-N-T-[W(7-Me)]-Q-[Pen]-Phe[4-(2-aminoethoxy)]-[W(1-Me)]-[a-MeLys]-[Lys(Ac)]-N-[bA]-NH_2	4.52
284	Ac-[Pen]-N-T-[W(7-Et)]-[Lys(Ac)]-[Pen]-Phe[4-(2-aminoethoxy)]-[2-Nal]-[a-MeLys]-[Lys(Ac)]-N-[(D)Leu]-NH_2	0.34
285	Ac-[Pen]-N-T-[W(7-Pr)]-[Lys(Ac)]-[Pen]-Phe[4-(2-aminoethoxy)]-[2-Nal]-[a-MeLys]-[Lys(Ac)]-N-[(D)Leu]-NH_2	0.849
286	Ac-[Pen]-N-T-[W(7-i-Pr)]-[Lys(Ac)]-[Pen]-Phe[4-(2-aminoethoxy)]-[2-Nal]-[a-MeLys]-[Lys(Ac)]-N-[(D)Leu]-NH_2	1.61
288	Ac-[Pen]-N-T-[W(7-OMe)]-[Lys(Ac)]-[Pen]-Phe[4-(2-aminoethoxy)]-[2-Nal]-[a-MeLys]-[Lys(Ac)]-N-[(D)Leu]-NH_2	1.48
289	Ac-[Pen]-N-T-[W(7-Me)]-[Lys(Ac)]-[Pen]-[2-Nal]-[2-Nal]-[a-MeLys]-[Lys(Ac)]-N-[(D)Leu]-NH_2	1.91
290	Ac-[Pen]-N-T-[W(7-Me)]-[Lys(Ac)]-[Pen]-H-[2-Nal]-[a-MeLys]-[Lys(Ac)]-N-[(D)Leu]-NH_2	2.45
291	Ac-[Pen]-N-T-[W(7-Me)]-[Lys(Ac)]-[Pen]-[His_3Bom]-[2-Nal]-[a-MeLys]-[Lys(Ac)]-N-[(D)Leu]-NH_2	>1000
292	Ac-[Pen]-N-T-[W(7-Me)]-[Lys(Ac)]-[Pen]-[His_Bzl]-[2-Nal]-[a-MeLys]-[Lys(Ac)]-N-[(D)Leu]-NH_2	128
293	Ac-[Pen]-N-T-[W(7-Me)]-[Lys(Ac)]-[Pen]-[His_Bzl]-[2-Nal]-[a-MeLys]-[Lys(Ac)]-N-[(D)Leu]-NH_2	224
296	Ac-[Pen]-N-T-[W(5-CN)]-Q-[Pen]-Phe[4-(2-aminoethoxy)]-[2-Nal]-[a-MeLys]-[Lys(Ac)]-N-[(D)Lys]-NH_2	6.29
297	Ac-[Pen]-N-T-[W(7-OMe)]-Q-[Pen]-Phe[4-(2-aminoethoxy)]-[2-Nal]-[a-MeLys]-[Lys(Ac)]-N-[(D)Lys]-NH_2	1.04
299	Ac-[Pen]-N-T-[W(7-OMe)]-[Lys(Ac)]-[Pen]-Phe[4-(2-aminoethoxy)]-[2-Nal]-[a-MeLys]-[Lys(Ac)]-N-[(D)Lys]-NH_2	2.86
300	Ac-[Pen]-N-T-[W(7-OMe)]-[Cit]-[Pen]-Phe[4-(2-aminoethoxy)]-[2-Nal]-[a-MeLys]-[Lys(Ac)]-N-[(D)Lys]-NH_2	>1000
314	Ac-[Pen]-N-T-[W(7-Me)]-[Lys(Ala)]-[Pen]-Phe[4-(2-aminoethoxy)]-[2-Nal]-[a-MeLys]-[Lys(Ac)]-N-[(D)Leu]-NH_2;	1.15
315	Ac-[Pen]-N-T-[W(7-Me)]-[Lys(IVA)]-[Pen]-Phe[4-(2-aminoethoxy)]-[2-Nal]-[a-MeLys]-[Lys(Ac)]-N-[(D)Leu]-NH_2;	1.41
316	Ac-[Pen]-N-T-[W(7-Me)]-[Lys(cyclohexyl)]-[Pen]-Phe[4-(2-aminoethoxy)]-[2-Nal]-[a-MeLys]-[Lys(Ac)]-N-[(D)Leu]-NH_2;	5.6
317	Ac-[Pen]-N-T-[W(7-Me)]-[Lys(octanoic)]-[Pen]-Phe[4-(2-aminoethoxy)]-[2-Nal]-[a-MeLys]-[Lys(Ac)]-N-[(D)Leu]-NH_2;	13

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318	Ac-[Pen]-N-T-[W(7-Me)]-[Lys(benzyl)]-[Pen]-Phe[4-(2-aminoethoxy)]-[2-Nal]-[a-MeLys]-[Lys(Ac)]-N-[(D)Leu]-NH_2;	1.9
319	Ac-[Pen]-N-T-[W(7-Me)]-[Lys(trifluoropropionic)]-[Pen]-Phe[4-(2-aminoethoxy)]-[2-Nal]-[a-MeLys]-[Lys(Ac)]-N-[(D)Leu]-NH_2;	0.714
320	Ac-[Pen]-N-T-[W(7-Me)]-[Lys(Gly)]-[Pen]-Phe[4-(2-aminoethoxy)]-[2-Nal]-[a-MeLys]-[Lys(Ac)]-N-[(D)Leu]-NH_2;	0.632
321	Ac-[Pen]-N-T-[W(7-Me)]-[Lys(bAla)]-[Pen]-Phe[4-(2-aminoethoxy)]-[2-Nal]-[a-MeLys]-[Lys(Ac)]-N-[(D)Leu]-NH_2;	1.04
322	Ac-[Pen]-N-T-[W(7-Me)]-[Lys(Aib)]-[Pen]-Phe[4-(2-aminoethoxy)]-[2-Nal]-[a-MeLys]-[Lys(Ac)]-N-[(D)Leu]-NH_2;	0.648
323	Ac-[(D)Arg]-[Abu]-Q-T-[W(7-Me)]-[Lys(Ac)]-[Cys]-Phe[4-(2-aminoethoxy)]-[2-Nal]-[a-MeLys]-[Lys(Ac)]-N-[(D)Lys]-[Sarc]-NH_2;	5.33
324	Ac-[(D)Arg]-[Abu]-Q-T-[W(7-Me)]-[Lys(Ac)]-[Cys]-Phe[4-(2-aminoethoxy)]-[2-Nal]-[a-MeLys]-[Lys(Ac)]-N-[(D)Lys]-NH_2;	27
325	Ac-[(D)Arg]-[Abu]-Q-T-[W(7-Me)]-[Lys(Ac)]-[Cys]-Phe[4-(2-aminoethoxy)]-[2-Nal]-[a-MeLys]-[Lys(Ac)]-N-[(D)Leu]-NH_2;	4.45
326	Ac-[(D)Arg]-[Abu]-Q-T-[W(7-Me)]-[Lys(Ac)]-[Cys]-Phe[4-(2-aminoethoxy)]-[2-Nal]-[a-MeLys]-[Lys(Ac)]-N-NH_2;	18.4
327	Ac-[(D)Arg]-[Abu]-Q-T-[W(7-Me)]-[Lys(Ac)]-[Cys]-Phe[4-(2-aminoethoxy)]-[2-Nal]-[a-MeLys]-[Lys(Ac)]-N-[a-MePhe]-NH_2;	12.7
328	Ac-[Pen]-A-T-[W(7-Me)]-[Lys(Ac)]-[Pen]-Phe[4-(2-aminoethoxy)]-[2-Nal]-[a-MeLys]-[Lys(Ac)]-N-[(D)Leu]-NH_2;	0.78
329	Ac-[Pen]-G-T-[W(7-Me)]-[Lys(Ac)]-[Pen]-Phe[4-(2-aminoethoxy)]-[2-Nal]-[a-MeLys]-[Lys(Ac)]-N-[(D)Leu]-NH_2;	0.77
330	Ac-[Pen]-[Lys(Ac)]-T-[W(7-Me)]-[Lys(Ac)]-[Pen]-Phe[4-(2-aminoethoxy)]-[2-Nal]-[a-MeLys]-[Lys(Ac)]-N-[(D)Leu]-NH_2;	1.38
331	Ac-[Pen]-[Cit]-T-[W(7-Me)]-[Lys(Ac)]-[Pen]-Phe[4-(2-aminoethoxy)]-[2-Nal]-[a-MeLys]-[Lys(Ac)]-N-[(D)Leu]-NH_2;	0.834
332	Ac-[Pen]-L-T-[W(7-Me)]-[Lys(Ac)]-[Pen]-Phe[4-(2-aminoethoxy)]-[2-Nal]-[a-MeLys]-[Lys(Ac)]-N-[(D)Leu]-NH_2;	1.06
333	Ac-[Pen]-P-T-[W(7-Me)]-[Lys(Ac)]-[Pen]-Phe[4-(2-aminoethoxy)]-[2-Nal]-[a-MeLys]-[Lys(Ac)]-N-[(D)Leu]-NH_2;	9.3
334	Ac-[Pen]-S-T-[W(7-Me)]-[Lys(Ac)]-[Pen]-Phe[4-(2-aminoethoxy)]-[2-Nal]-[a-MeLys]-[Lys(Ac)]-N-[(D)Leu]-NH_2;	0.55
335	Ac-[Pen]-[Dab(Ac)]-T-[W(7-Me)]-[Lys(Ac)]-[Pen]-Phe[4-(2-aminoethoxy)]-[2-Nal]-[a-MeLys]-[Lys(Ac)]-N-[(D)Leu]-NH_2;	0.567
336	Ac-[Pen]-R-T-[W(7-Me)]-[Lys(Ac)]-[Pen]-Phe[4-(2-aminoethoxy)]-[2-Nal]-[a-MeLys]-[Lys(Ac)]-N-[(D)Leu]-NH_2;	1.49
337	Ac-[Pen]-[hLeu]-T-[W(7-Me)]-[Lys(Ac)]-[Pen]-Phe[4-(2-aminoethoxy)]-[2-Nal]-[a-MeLys]-[Lys(Ac)]-N-[(D)Leu]-NH_2;	0.779
338	Ac-[Pen]-[(D)Asn]-T-[W(7-Me)]-[Lys(Ac)]-[Pen]-Phe[4-(2-aminoethoxy)]-[2-Nal]-[a-MeLys]-[Lys(Ac)]-N-[(D)Leu]-NH_2;	41.8
339	Ac-[Pen]-N-T-[W(7-Me)]-[Cit]-[Pen]-Phe[4-(2-aminoethoxy)]-[2-Nal]-[a-MeLys]-[Lys(Ac)]-N-[Sarc]-NH_2;	6.3

SEQ ID No.	Sequence*	pStat3 HTRF (nM)
340	Ac-[Pen]-N-T-[W(7-Me)]-[Cit]-[Pen]-Phe[4-(2-aminoethoxy)]-[2-Nal]-[a-MeLys]-[Lys(Ac)]-N-[Aib]-[bA]-NH_2;	0.322
341	Ac-[Pen]-N-T-[W(7-Me)]-[Cit]-[Pen]-Phe[4-(2-aminoethoxy)]-[2-Nal]-[a-MeLys]-[Lys(Ac)]-N-[Aib]-G-NH_2;	0.934
342	Ac-[Pen]-N-T-[W(7-Me)]-[Cit]-[Pen]-Phe[4-(2-aminoethoxy)]-[2-Nal]-[a-MeLys]-[Lys(Ac)]-N-[Aib]-A-NH_2;	0.664
343	Ac-[Pen]-N-T-[W(7-Me)]-[Cit]-[Pen]-Phe[4-(2-aminoethoxy)]-[2-Nal]-[a-MeLys]-[Lys(Ac)]-N-[Aib]-R-NH_2;	1.43
344	Ac-[Pen]-N-T-[W(7-Me)]-[Cit]-[Pen]-Phe[4-(2-aminoethoxy)]-[2-Nal]-[a-MeLys]-[Lys(Ac)]-N-[Aib]-[(D)Lys]-NH_2;	0.724
345	Ac-[Pen]-N-T-[W(7-Me)]-[Cit]-[Pen]-Phe[4-(2-aminoethoxy)]-[2-Nal]-[a-MeLys]-[Lys(Ac)]-N-[Aib]-[(D)Arg]-NH_2;	0.639
346	Ac-[Pen]-N-T-[W(7-Me)]-[Cit]-[Pen]-Phe[4-(2-aminoethoxy)]-[2-Nal]-[a-MeLys]-[Lys(Ac)]-N-[Aib]-[(D)Phe]-NH_2;	0.784
347	Ac-[Pen]-N-T-[W(7-Me)]-[Cit]-[Pen]-Phe[4-(2-aminoethoxy)]-[2-Nal]-[a-MeLys]-[Lys(Ac)]-N-[Aib]-[(D)Tyr]-NH_2;	0.637
348	Ac-[Pen]-N-T-[W(7-Me)]-[Cit]-[Pen]-Phe[4-(2-aminoethoxy)]-[2-Nal]-[a-MeLys]-[Lys(Ac)]-N-[Aib]- [(D)2-Nal]-NH_2;	5.02
349	Ac-[Pen]-N-T-[W(6-Et)]-[Lys(Ac)]-[Pen]-Phe[4-(2-aminoethoxy)]-[2-Nal]-[a-MeLys]-[Lys(Ac)]-N-[(D)Lys]-NH_2;	12.7
351	Ac-[Pen]-N-T-[W(2-Me)]-[Lys(Ac)]-[Pen]-Phe[4-(2-aminoethoxy)]-[2-Nal]-[a-MeLys]-[Lys(Ac)]-N-[(D)Lys]-NH_2;	11.3
352	Ac-[Pen]-N-T-[W(7-Me)]-[Lys(Ac)]-[Pen]-Phe[4-(2-aminoethoxy)]-[2-Nal]-[a-MeLys]-[Lys(Ac)]-S-[(D)Lys]-NH_2;	0.927
353	Ac-[Pen]-N-T-[W(7-Me)]-[Lys(Ac)]-[Pen]-Phe[4-(2-aminoethoxy)]-[W(2-Me)]-[a-MeLys]-[Lys(Ac)]-N-[(D)Lys]-NH_2;	0.715
354	Ac-[Pen]-N-T-[W(7-Me)]-[Lys(Ac)]-[Pen]-Phe[4-(2-aminoethoxy)]-[2-Nal]-[a-MeLeu]-[Lys(Ac)]-N-[(D)Asn]-NH_2;	0.283
355	Ac-[Pen]-N-T-[W(7-Me)]-[Lys(Ac)]-[Pen]-Phe[4-(2-aminoethoxy)]-[2-Nal]-[a-MeLys]-[Lys(Ala)]-N-[(D)Leu]-NH_2;	0.456
356	Ac-[Pen]-N-T-[W(7-Me)]-[Lys(Ac)]-[Pen]-Phe[4-(2-aminoethoxy)]-[2-Nal]-[a-MeLys]-[Lys(IVA)]-N-[(D)Leu]-NH_2;	0.193
357	Ac-[Pen]-N-T-[W(7-Me)]-[Lys(Ac)]-[Pen]-Phe[4-(2-aminoethoxy)]-[2-Nal]-[a-MeLys]-[Lys(cyclohexyl)]-N-[(D)Leu]-NH_2;	0.331
358	Ac-[Pen]-N-T-[W(7-Me)]-[Lys(Ac)]-[Pen]-Phe[4-(2-aminoethoxy)]-[2-Nal]-[a-MeLys]-[Lys(octanoic)]-N-[(D)Leu]-NH_2;	3.03
359	Ac-[Pen]-N-T-[W(7-Me)]-[Lys(Ac)]-[Pen]-Phe[4-(2-aminoethoxy)]-[2-Nal]-[a-MeLys]-[Lys(benzyl)]-N-[(D)Leu]-NH_2;	0.725
360	Ac-[Pen]-N-T-[W(7-Me)]-[Lys(Ac)]-[Pen]-Phe[4-(2-aminoethoxy)]-[2-Nal]-[a-MeLys]-[Lys(trifluoropropionic)]-N-[(D)Leu]-NH_2;	0.568
361	Ac-[Pen]-N-T-[W(7-Me)]-[Lys(Ac)]-[Pen]-Phe[4-(2-aminoethoxy)]-[2-Nal]-[a-MeLys]-[Lys(valeric)]-N-[(D)Leu]-NH_2;	0.596
362	Ac-[Pen]-N-T-[W(7-Me)]-[Lys(Ac)]-[Pen]-Phe[4-(2-aminoethoxy)]-[2-Nal]-[a-MeLys]-[Lys(PEG3-OMe)]-N-[(D)Leu]-NH_2;	0.107

SEQ ID No.	Sequence*	pStat3 HTRF (nM)
363	Ac-[Pen]-N-T-[W(7-Me)]-[Lys(Ac)]-[Pen]-Phe[4-(2-aminoethoxy)]-[2-Nal]-[a-MeLys]-[Lys(PEG11-OMe)]-N-[(D)Leu]-NH_2;	0.446
364	Ac-[(D)Arg]-Abu-Q-T-[W(5-F)]-Q-[Cys]-Phe[4-(2-aminoethoxy)]-[2-Nal]-[THP]-E-N-[bA]-NH_2	

* wherein Cys and Cys, or Pen and Pen form a disulfide bond; and Abu and Cys or Abu and Pen form a thioether bond.

EXAMPLE 3

NK CELL BASED ASSAY

[00484] Natural killer (NK) cells, purified from human peripheral blood of healthy donors by negative selection (Miltenyi Biotech, Cat # 130-092-657), were cultured in complete media (RPMI 1640 containing 10% FBS, L-glutamine and penicillin-streptomycin) in the presence of IL-2 (RnD, Cat # 202-IL-010/CF) at 25 ng/mL. After 7 days, cells were centrifuged, and resuspended in complete media at 1E6 cells/mL. Recombinant IL-23 at predetermined EC_{50} to EC_{75} and IL-18 (RnD, Cat # B003-5) at 10 ng/mL were mixed with varying concentrations of peptides, and added to NK cells seeded at 1E5 cells per well. After 20 to 24 hours, IFNγ in the supernatant was quantified using Quantikine ELISA (RnD, Cat # DIF50).

Table E4. IC_{50} of Illustrative Peptide Inhibitors in Primary Cell Line (NK Cell Assay)

SEQ ID No.	NK Cell Assay IC_{50} (nM)
201	3.06
202	3.49
203	2.3
205	16.6
206	21.4
207	8.4
208	7.8
209	30.1
210	>500
212	157
213	60
214	6.3
215	20
216	>500
217	13.3
218	50.2
221	5.5
223	8.3

224	>500
225	114
226	9.55
227	2.95
232	9
234	7.7
235	10.2
236	5.82
238	2.99
239	4.1
242	2.37
245	2.7
251	8.19
252	3.32
258	9.7
259	7.6
261	4.87
264	5.15
284	3.16
289	5.12

290	11
320	3.35
324	9.35
325	12.7
334	4.52
337	11.1
340	2.1
349	45.5
352	3.5
353	7.1
354	1.62
355	5.34
356	4.01
357	3.8
358	6.3
359	4.97
360	1.1
361	1.47
362	3.81
363	4.36

EXAMPLE 4

STABILITY OF PEPTIDE INHIBITORS IN SIMULATED INTESTINAL FLUID (SIF), SIMULATED GASTRIC FLUID (SGF) AND REDOX CONDITIONS

[00485] Studies were carried out in simulated intestinal fluid (SIF) and simulated gastric fluid (SGF) to evaluate gastric stability of the peptide inhibitors of the present invention. In addition, studies were carried out to assess redox stability of the peptide inhibiotrs of the present invention.

[00486] SIF was prepared by adding 6.8 g of monobasic potassium phosphate and 10.0 g of pancreatin to 1.0 L of water. After dissolution, the pH was adjusted to 6.8 using NaOH. DMSO stocks (2 mM) were first prepared for the test compounds. Aliquots of the DMSO solutions were dosed into 6 individual tubes, each containing 0.5 mL of SIF, which is pre-warmed to 37°C. The final test compound concentration was 20 μM. The vials were kept in a benchtop Thermomixer® for the duration of the experiment. At each timepoint (0, 5, 10, 20, 40, 60, or 360 minutes or 24 hours), 1.0 mL of acetonitrile containing 1% formic acid was added to one vial to terminate the reaction. Samples were stored at 4°C until the end of the experiment. After the final timepoint is sampled, the tubes were mixed and then centrifuged at 3,000 rpm for 10 minutes. Aliquots of the supernatant were removed, diluted 1:1 into distilled water containing internal standard, and analyzed by LCMS/MS. Percent remaining at each timepoint was calculated based on the peak area response ratio of test to compound to internal standard. Time 0 was set to 100%, and all later timepoints were calculated relative to time 0. Half-lives were calculated by fitting to a first-order exponential decay equation using Graphpad. Stablity in SIF assays is shown in Tables E9 and E10.

[00487] SGF was prepared by adding 20 mg NaCl, 32 mg porcine pepsin (MP Biochemicals, catalog 02102599), and 70μl HCl to 10ml water (final pH=2). Aliquots of SGF (0.5ml each) were pre-warmed at 37°C. To start the reaction, 1μl of peptide stock solution (10mM in DMSO) was added to 0.5ml SGF and thoroughly mixed such that the final peptide concentration was 20μM. The reactions were incubated at 37°C with gentle shaking. At each time point (0, 15, 30, 60 min) 50μl aliquots were removed and added to 200 ul acetonitrile containing 0.1% formic acid to quench the reaction. Samples are stored at 4°C until the end of the experiment and centrifuged at 10,000 rpm for 5 minutes. Aliquots of the supernatant were removed, diluted 1:1 into distilled water containing internal standard, and analyzed by LCMS/MS. Percent remaining at each timepoint was calculated based on the peak area response ratio of test to compound to internal standard. Time 0 was set to 100%, and all later

timepoints were calculated relative to time 0. Half-lives were calculated by fitting to a first-order exponential decay equation using GraphPad. Stability in SGF assays in shown in Table E5.

Table E5. Stability of Illustrative Peptides Inhibitors in Simulated Intestinal Fluid (SIF) and Simulated Gastric Fluid (SGF)

SEQ ID No.	SGF t1/2 (hr) §	SIF t1/2 (hr) §
201	14	24
202	24	24
203		24
204		19
205		24
206		24
209		15
214	24	24
217	24	24
221	9	24
222		19
227	24	24
233	24	24
234	24	24
235	24	24
236	24	24
238		24
239		24
240		7
242		24
243	24	<1
244	24	1
245	24	24

SEQ ID No.	SGF t1/2 (hr) §	SIF t1/2 (hr) §
246	24	24
247	24	24
248	24	32
249	24	3
250	24	11
251	24	20
252	24	24
253	24	10
254	24	16
255	24	19
256		24
257		5
258		14
259		12
261		18
263		14
264	24	18
267		24
268		15
269		24
270		24
271		22
272		24

SEQ ID No.	SGF t1/2 (hr) §	SIF t1/2 (hr) §
273		8
274		5
275		24
276		13
278		19
279		7
280		8
281		14
282		24
283		24
284		2
285		9
286		24
288		12
289		12
290		16
291		24
292		20
293		8
296		24
297		24
299		24
300		24
314		24
315		24
316		24
317		24
318		24

SEQ ID No.	SGF t1/2 (hr) §	SIF t1/2 (hr) §
319		24
320		21
321		24
322		24
323		20
324		13
325		14
326		4
327		24
328		23
329		12
330		24
331		15
332		24
333		22
334		24
335		20
336		10
337		24
338		10
339		24
340		17
341		17
342		16
343		13
344		9
345		12
346		19

SEQ ID No.	SGF t1/2 (hr) §	SIF t1/2 (hr) §
347		12
348		13
349		24
351		12
352		7
353		24
354		11
355		8

SEQ ID No.	SGF t1/2 (hr) §	SIF t1/2 (hr) §
356		10
357		14
358		24
359		11
360		24
361		24
362		24
363		24

§ the matrix used is 100 fold dilution of standard SIF concentration

EXAMPLE 5

STABILITY OF PEPTIDE INHIBITORS IN HUMAN AND CYNOMLOGUS (MONKEY) FECES

[00488] Studies were carried out in human or cynomlogus monkey fecal homogenate to evaluate gastrointestinal stability of the peptide inhibitors of the present invention.

[00489] Fecal homogenate (20%) was prepared by adding 4 mL of growth medium (1 liter contains 2 g peptone water powder, 2 g yeast extract, 0.1 g NaCl, 0.04 g KH_2PO_4, 0.01 g $CaCl_2 \cdot 6H_2O$, 0.01 g $MgSO_4 \cdot 7H_2O$, 2 mL Tween 80, 0.5 g bile salts, 0.5 g L-cysteine HCl, 2 g $NaHCO_3$, and 10 µL Vitamin K, pH adjusted to 6.8, and sterilized by filtration through a 0.22 µm filter) to every gram of feces (pooled freshly collected human or cynomolgus monkey feces). The suspension was vortexed to break up large clumps, and homogenized using a bead mill homogenizer. Centrifuged the homogenate at 2800 x g for 15 min. The supernatant is taken out and used for incubations. DMSO stocks (10 mM) were first prepared for the test compounds. Incubations were performed in an anaerobic chamber conditioned at 37°C. Aliquots of the DMSO solutions were dosed into 1.0 mL aliquots of 20% fecal homogenate, which are pre-warmed to 37°C. The final test compound concentration was 20 µM. At each timepoint (0, 20 min, 1, 3, 6, or 24 hours), 100 µL aliquot of each incubation mixture is taken out and added to separate tubes containing 300 µL of 50% acetonitrile/50% methanol and an internal standard to terminate the reaction. Samples were taken out of the anaerobic chamber and stored at 4°C until the end of the experiment. After the final timepoint is sampled, the tubes

were mixed and then centrifuged at 3,000 rpm for 10 minutes. Aliquots of the supernatant were removed, diluted 1:1 into distilled water containing 0.1% formic acid, and analyzed by LC/MS/MS. Percent remaining at each timepoint was calculated based on the peak area response ratio of test to compound to internal standard. Time 0 was set to 100%, and all later timepoints were calculated relative to time 0. Half-lives were calculated by fitting to a first-order exponential decay equation using Graphpad or Excel. Stablity in fecal homogenate assays is shown in Tables.

EXAMPLE 6

STABILITY OF PEPTIDE INHIBITORS IN RAT PLASMA

[00490] Peptides of interest (20 μM) were incubated with pre-warmed rat plasma (SD rat, mixed gender pooled, EDTA, filtered through 0.22 μm, BioreclamationIVT) at 37°C. Aliquots were taken at various time points up to 24 hours (e.g. 0, 0.25, 1, 3, 6 and 24 hr), and immediately quenched with 4 volumes of organic solvent (acetonitrile/methanol (1:1) and 0.1% formic acid, containing 1 μM internal standard). Quenched samples were stored at 4 °C until the end of the experiment and centrifuged at 4,000 rpm for 10 minutes. The supernatant were diluted 1:1 with deionized water and analyzed using LC-MS. Percentage remaining at each time point was calculated based on the peak area ratio (analyte over internal standard) relative to the initial level at time zero. Half-lives were calculated by fitting to a first-order exponential decay equation using GraphPad.

Table E6. Stability of Illustrative Peptides Inhibitors in Human Feces, Monkey Feces, and Rat Plasma

SEQ ID No.	t1/2:Human Feces anaerobic (hr)	t1/2: Monkey Feces anaerobic (hr)	t1/2: Rat Plasma EDTA (hr)
201	>24	19	<0.3
202	>24	10	>24
203	0	4	
204	1	5	
205	>24	>24	1
206	20	>24	
207	>24	>24	2
208	>24	>24	2
209	>24	>24	1

SEQ ID No.	t1/2:Human Feces anaerobic (hr)	t1/2: Monkey Feces anaerobic (hr)	t1/2: Rat Plasma EDTA (hr)
210	>24	>24	<0.3
211	10	>24	7
212	>24	>24	0
213	>24	>24	<0.3
214	>24	>24	1
215	>24	>24	2
216	>24	>24	13
217	>24	>24	2
218	>24	>24	1
219	16	24	3
220	>24	21	1
221	>24	>24	2
222	>24	>24	4
223	>24	>24	9
224	>24	>24	
225	>24	>24	0
226	>24	>24	8
227	>24	>24	0
228	>24	13	>24
229	>24	7	
230	>24	10	
231	>24	15	
232	>24	10	>24
233	>24	>24	>24
234	>24	>24	7
235	>24	>24	5
236	>24	>24	>19.8
237	>24	6	>24
238	>24	7	>24
239	>24	7	>24
240	4	3	8
241	>24	15	>24
242	>24	8	>24
243	1	0	21
244	15	10	>24
245	>24	>24	>24
246	>24	>24	>24
247	>24	>24	>24
248	>22.3	6	>24
249	>17	5	>24

SEQ ID No.	t1/2:Human Feces anaerobic (hr)	t1/2: Monkey Feces anaerobic (hr)	t1/2: Rat Plasma EDTA (hr)
250	>19.5	12	>24
251	>24	>24	>24
252	>24	>24	>24
253	1	3	>24
254	>24	>24	12
255	>24	15	>24
256	>24	>24	>24
257	>24	23	>24
258	>24	>24	>24
259	>24	16	>24
260	15	3	>24
261	>24	4	>24
262	15	3	>24
263	>24	9	>24
264	>24	>24	>24
265	2	4	>24
266	16	7	>24
267	>24	4	>24
268	>24	>24	>24
269	>24	>24	>24
270	>24	>24	>24
271	>24	>24	>24
272	>24	>24	>24
273	>24	12	>24
274	>24	4	5
275	>24	8	>24
276	>24	13	5
277	0	5	6
278	>24	15	>24
279	>24	>24	>24
280	>24	>24	>24
281	>24	>24	>24
282	>24	22	>24
283	>24	17	>24
284	>24	>24	>24
285	>24	>24	>24
286	>24	>24	>24
288	>24	>24	>24
289	>24	>24	>24
290	>24	>24	>24

SEQ ID No.	t1/2:Human Feces anaerobic (hr)	t1/2: Monkey Feces anaerobic (hr)	t1/2: Rat Plasma EDTA (hr)
291	>24	>24	>24
292	>24	>24	>24
293	>24	>24	>24
296	>24	>24	>24
297	>24	>24	>24
299	>24	>24	>24
300	>24	>24	>24
314	>24	>24	>24
315	>24	>24	>24
316	>24	>24	>24
317	>24	>24	>24
319	>24	>24	>24
320	>24	15	>24
321	>24	>24	>24
322	>24	>24	>24
323	>24	13	>24
324	>24	13	>24
325	>24	22	>24
326	11	11	>24
327	>24	24	>24
328	>24	>24	>24
329	>24	>24	>24
330	>24	>24	>24
331	>24	>24	>24
332	>24	>24	>24
333	>24	24	>24
334	>24	>24	>24
335	>24	>24	>24
336	>24	>24	>24
337	>24	>24	>24
338	>24	>24	>24
339	>24	18	>24
340	>24	>24	>24
341	>24	>24	>24
342	12	15	>24
343	12	0	>24
344	>24	>24	>24
345	>24	>24	>24
346	>24	>24	24
347	>24	>24	>24

SEQ ID No.	t1/2:Human Feces anaerobic (hr)	t1/2: Monkey Feces anaerobic (hr)	t1/2: Rat Plasma EDTA (hr)
348	>24	>24	>24
349	>24	>24	>24
351	>24	>24	>24
352	>24	>24	>24
353	>24	>24	>24
354	>24	>24	7
355	12	>24	>24
356	>24	>24	>24
357	>24	>24	>24
358	>24	>24	>24
359	>24	>24	>24
360	>24	>24	>24
361	>24	>24	>24
362	>24	>24	>24
363	>24	>24	>24

[00491] All of the above U.S. patents, U.S. patent application publications, U.S. patent applications, foreign patents, foreign patent applications and non-patent publications referred to in this specification and/or listed in the Application Data Sheet, are incorporated herein by reference, in their entirety.

[00493] From the foregoing it will be appreciated that, although specific embodiments of the invention have been described herein for purposes of illustration, various modifications may be made without deviating from the spirit and scope of the invention. Accordingly, the invention is not limited except as by the appended claims.

CLAIMS

What is claimed is:

1. A peptide inhibitor of an interleukin-23 receptor, or a pharmaceutically acceptable salt or solvate thereof, wherein the peptide inhibitor comprises an amino acid sequence of Formula (II"):

X7-X8-X9-X10-X11-X12-X13-X14-X15-R^2 (II")

wherein

X7 is Trp substituted with cyano, halo, alkyl, haloalkyl, hydroxy, or alkoxy;

X8 is Gln, alpha-MeLys, alpha-MeLeu, alpha-MeLys(Ac), beta-homoGln, Cit, Glu, Phe, Asn, Thr, Val, Aib, alpha-MeGln, alpha-MeAsn, Lys(Ac), Dab(Ac), Dap(Ac), homo-Lys(Ac), 1-Nal, 2-Nal, or Trp;

X9 is Abu, Cys, (D)Cys, alpha-MeCys, (D)Pen, Pen or Pen(sulfoxide);

X10 is unsubstituted Phe, or Phe substituted with halo, alkyl, haloalkyl, hydroxy, alkoxy, carboxy, carboxamido, 2-aminoethoxy, or 2-acetylaminoethoxy;

X11 is 2-Nal, Phe(2-Me), Phe(3-Me), Phe(4-Me), Phe(3,4-dimethoxy), 1-Nal, unsubstituted Trp, or Trp substituted with cyano, halo, alkyl, haloalkyl, hydroxy, or alkoxy;

X12 is 4-amino-4-carboxy-tetrahydropyran (THP), alpha-MeLys, alpha-MeLeu, alpha-MeArg, alpha-MePhe, alpha-MeLeu, alpha-MeLys, alpha-MeAsn, alpha-MeTyr, Ala, or cyclohexylAla, Lys, or Aib;

X13 is Aib, Glu, Cit, Gln, Lys(Ac), alpha-MeArg, alpha-MeGlu, alpha-MeLeu, alpha-MeLys, alpha-Me-Asn, alpha-MeLys(Ac), Dab(Ac), Dap(Ac), homo-Lys(Ac), or Lys; or

X13 is Lys, pegylated Lys, b-homoGlu, or Lys(Y2-Ac), wherein Y2 is an amino acid;

X14 is Asn, 2-Nap, Aib, Arg, Cit, Asp, Phe, Gly, Lys, Leu, Ala, (D)Ala, beta-Ala, His, Thr, n-Leu, Gln, Ser, (D)Ser, Tic, Trp, alpha-MeGln, alpha-MeAsn, alpha-MeLys(Ac), Dab(Ac), Dap(Ac), homo-Lys(Ac), or Lys(Ac);

X15 Leu, (D)Leu, beta-Ala, Cit, or (D)Lys;

R^2 is OH or NH_2;

or a pharmaceutically acceptable salt or solvate thereof, wherein the peptide inhibitor or pharmaceutically acceptable salt or solvate thereof comprises a disulfide bond between two Pen residues or a thioether bond between Abu and Cys;

and

wherein the peptide inhibitor or pharmaceutically acceptable salt of solvate thereof inhibits the binding of an interleukin-23 (IL-23) to an IL-23 receptor.

2. The peptide inhibitor or pharmaceutically acceptable salt or solvate thereof of claim 1, wherein the peptide inhibitor comprises an amino acid sequence of Formula (I'):

X4-X5-X6-X7-X8-X9-X10-X11-X12-X13-X14-X15 (I')

wherein

X4 is Abu, Cys, (D)Cys, alpha-MeCys, (D)Pen, Pen, or Pen(sulfoxide);

X5 is Cit, Glu, Gly, Leu, Ile, beta-Ala, Ala, Lys, Asn, Pro, alpha-MeGln, alpha-MeLys, alpha-MeLeu, alpha-MeAsn, Lys(Ac), alpha-MeLys(Ac), Dab(Ac), Dap(Ac), homo-Lys(Ac), Gln, Asp, or Cys; and

X6 is Thr, Aib, Asp, Dab, Gly, Pro, Ser, alpha-MeGln, alpha-MeLys, alpha-MeLeu, alpha-MeAsn, alpha-MeThr, alpha-MeSer, or Val.

3. The peptide inhibitor or pharmaceutically acceptable salt or solvate thereof of claim 1, wherein the peptide inhibitor is according to Formula (Z'):

R^1-X4-X5-X6-X7-X8-X9-X10-X11-X12-X13-X14-X15-R^2 (Z')

or a pharmaceutically acceptable salt or solvate thereof, wherein

X4 is Abu, Cys, (D)Cys, alpha-MeCys, (D)Pen, Pen, or Pen(sulfoxide);

X5 is Cit, Glu, Gly, Leu, Ile, beta-Ala, Ala, Lys, Asn, Pro, alpha-MeGln, alpha-MeLys, alpha-MeLeu, alpha-MeAsn, Lys(Ac), alpha-MeLys(Ac), Dab(Ac), Dap(Ac), homo-Lys(Ac), Gln, Asp, or Cys; and

X6 is Thr, Aib, Asp, Dab, Gly, Pro, Ser, alpha-MeGln, alpha-MeLys, alpha-MeLeu, alpha-MeAsn, alpha-MeThr, alpha-MeSer, or Val;

X7 is Trp substituted with cyano, halo, alkyl, haloalkyl, hydroxy, or alkoxy;

X8 is Gln, alpha-MeLys, alpha-MeLeu, alpha-MeLys(Ac), beta-homoGln, Cit, Glu, Phe, Asn, Thr, Val, Aib, alpha-MeGln, alpha-MeAsn, Lys(Ac), Dab(Ac), Dap(Ac), homo-Lys(Ac), 1-Nal, 2-Nal, or Trp;

X9 is Abu, Cys, (D)Cys, alpha-MeCys, (D)Pen, Pen or Pen(sulfoxide);

X10 is unsubstituted Phe, or Phe substituted with halo, alkyl, haloalkyl, hydroxy, alkoxy, carboxy, carboxamido, 2-aminoethoxy, or 2-acetylaminoethoxy;
X11 is 2-Nal, Phe(2-Me), Phe(3-Me), Phe(4-Me), Phe(3,4-dimethoxy), 1-Nal, unsubstituted Trp, or Trp substituted with cyano, halo, alkyl, haloalkyl, hydroxy, or alkoxy;
X12 is 4-amino-4-carboxy-tetrahydropyran (THP), alpha-MeLys, alpha-MeLeu, alpha-MeArg, alpha-MePhe, alpha-MeLeu, alpha-MeLys, alpha-MeAsn, alpha-MeTyr, Ala, or cyclohexylAla, Lys, or Aib;
X13 is Aib, Glu, Cit, Gln, Lys(Ac), alpha-MeArg, alpha-MeGlu, alpha-MeLeu, alpha-MeLys, alpha-Me-Asn, alpha-MeLys(Ac), Dab(Ac), Dap(Ac), homo-Lys(Ac), or Lys; or
X13 is Lys, pegylated Lys, b-homoGlu, or Lys(Y2-Ac), wherein Y2 is an amino acid;
X14 is Asn, 2-Nap, Aib, Arg, Cit, Asp, Phe, Gly, Lys, Leu, Ala, (D)Ala, beta-Ala, His, Thr, n-Leu, Gln, Ser, (D)Ser, Tic, Trp, alpha-MeGln, alpha-MeAsn, alpha-MeLys(Ac), Dab(Ac), Dap(Ac), homo-Lys(Ac), or Lys(Ac);
X15 Leu, (D)Leu, beta-Ala, Cit, or (D)Lys;
R^1 is hydrogen, a C1-C6 alkyl, a C6-C12 aryl, a C6-C12aryl-C1-C6alkyl, or a C1-C20 alkanoyl;
R^2 is OH or NH_2;
wherein the peptide inhibitor or pharmaceutically acceptable salt or solvate thereof comprises a disulfide bond between two Pen residues or a thioether bond between Abu and Cys;
and
wherein the peptide inhibitor or pharmaceutically acceptable salt of solvate thereof inhibits the binding of an interleukin-23 (IL-23) to an IL-23 receptor.

4. The peptide inhibitor or pharmaceutically acceptable salt or solvate thereof of claim 1, wherein the peptide inhibitor comprises or is any one of the following, or a pharmaceutically acceptable salt or solvate thereof:

SEQ ID NO:	**Sequence**
201	Ac-[Pen]-NT-[W(7-Me)]-Q-[Pen]-Phe[4-(2-aminoethoxy)]-[2-Nal]-[a-MeLeu]-[Lys(Ac)]-N-[bA]-NH_2

SEQ ID NO:	Sequence
202	Ac-[Pen]-NT-[W(7-Me)]-Q-[Pen]-Phe[4-(2-aminoethoxy)]-[2-Nal]-[a-MeLys]-[Lys(Ac)]-N-[bA]-NH_2
203	Ac-[(D)Arg]-Abu-Q-T-[W(7-Me)]-Q-C-Phe[4-(2-aminoethoxy)]-[2-Nal]-[THP]-E-N-[bA]-NH_2
204	Ac-Abu-Q-T-[W(7-Me)]-Q-C-Phe[4-(2-aminoethoxy)]-[2-Nal]-[THP]-E-N-[bA]-NH_2
205	Ac-[Pen]-NT-[W(7-Me)]-Q-[Pen]-Phe[4-(2-aminoethoxy)]-[2-Nal]-[a-MeLeu]-[Lys(Ac)]-G-[bA]-NH_2
206	Ac-[Pen]-NT-[W(7-Me)]-Q-[Pen]-Phe[4-(2-aminoethoxy)]-[2-Nal]-[a-MeLeu]-[Lys(Ac)]-[Cit]-[bA]-NH_2
207	Ac-[Pen]-NT-[W(7-Me)]-Q-[Pen]-Phe[4-(2-aminoethoxy)]-[2-Nal]-[a-MeLeu]-[Lys(Ac)]-A-[bA]-NH_2
208	Ac-[Pen]-NT-[W(7-Me)]-Q-[Pen]-Phe[4-(2-aminoethoxy)]-[2-Nal]-[a-MeLeu]-[Lys(Ac)]-L-[bA]-NH_2
209	Ac-[Pen]-NT-[W(7-Me)]-Q-[Pen]-Phe[4-(2-aminoethoxy)]-[2-Nal]-[a-MeLeu]-[Lys(Ac)]-[(D)Ala]-[bA]-NH_2
214	Ac-[Pen]-NT-[W(7-Me)]-Q-[Pen]-Phe[4-(2-aminoethoxy)]-[2-Nal]-[a-MeLeu]-[Lys(Ac)]-H-[bA]-NH_2
217	Ac-[Pen]-NT-[W(7-Me)]-Q-[Pen]-Phe[4-(2-aminoethoxy)]-[2-Nal]-[a-MeLeu]-[Lys(Ac)]-T-[bA]-NH_2
221	Ac-[Pen]-NT-[W(7-Me)]-Q-[Pen]-Phe[4-(2-aminoethoxy)]-[2-Nal]-[a-MeLeu]-[Lys(Ac)]-S-[bA]-NH_2
222	Ac-[Pen]-NT-[W(7-Me)]-Q-[Pen]-Phe[4-(2-aminoethoxy)]-[2-Nal]-[a-MeLeu]-[Lys(Ac)]-[(D)Ser]-[bA]-NH_2
226	Ac-[Pen]-NT-[W(7-Me)]-Q-[Pen]-Phe[4-(2-aminoethoxy)]-[2-Nal]-[a-MeLeu]-[Lys(Ac)]-[bA]-[bA]-NH_2
227	Ac-[Pen]-NT-[W(7-Me)]-[Cit]-[Pen]-Phe[4-(2-aminoethoxy)]-[2-Nal]-[a-MeLeu]-[Lys(Ac)]-N-[bA]-NH_2
228	Ac-[Pen]-NT-[W(6-Cl)]-Q-[Pen]-Phe[4-(2-aminoethoxy)]-[2-Nal]-[a-MeLys]-[Lys(Ac)]-N-[bA]-NH_2

SEQ ID NO:	Sequence
229	Ac-[Pen]-NT-[W(4-OMe)]-Q-[Pen]-Phe[4-(2-aminoethoxy)]-[2-Nal]-[a-MeLys]-[Lys(Ac)]-N-[bA]-NH_2
230	Ac-[Pen]-NT-[W(6-Me)]-Q-[Pen]-Phe[4-(2-aminoethoxy)]-[2-Nal]-[a-MeLys]-[Lys(Ac)]-N-[bA]-NH_2
231	Ac-[Pen]-NT-[W(4-Me)]-Q-[Pen]-Phe[4-(2-aminoethoxy)]-[2-Nal]-[a-MeLys]-[Lys(Ac)]-N-[bA]-NH_2
232	Ac-[Pen]-NT-[W(1-Me)]-Q-[Pen]-Phe[4-(2-aminoethoxy)]-[2-Nal]-[a-MeLys]-[Lys(Ac)]-N-[bA]-NH_2
233	Ac-[Pen]-NT-[W(2,5,7-tritBu)]-Q-[Pen]-Phe[4-(2-aminoethoxy)]-[2-Nal]-[a-MeLys]-[Lys(Ac)]-N-[bA]-NH_2
234	Ac-[Pen]-NT-[W(7-Me)]-[a-MeLys]-[Pen]-Phe[4-(2-aminoethoxy)]-[2-Nal]-[a-MeLeu]-[Lys(Ac)]-N-[bA]-NH_2
235	Ac-[Pen]-NT-[W(7-Me)]-[a-MeLeu]-[Pen]-Phe[4-(2-aminoethoxy)]-[2-Nal]-[a-MeLys]-[Lys(Ac)]-N-[bA]-NH_2
236	Ac-[Pen]-NT-[W(7-Me)]-Q-[Pen]-Phe[4-(2-aminoethoxy)]-[2-Nal]-[a-MeLys]-[Aib]-N-[bA]-NH_2
237	Ac-[Pen]-Q-T-[W(7-Me)]-Q-[Pen]-Phe[4-(2-aminoethoxy)]-[2-Nal]-[a-MeLys]-[Lys(Ac)]-N-[bA]-NH_2
238	Ac-[Pen]-[Cit]-T-[W(7-Me)]-Q-[Pen]-Phe[4-(2-aminoethoxy)]-[2-Nal]-[a-MeLys]-[Lys(Ac)]-N-[bA]-NH_2
239	Ac-[Pen]-[Lys(Ac)]-T-[W(7-Me)]-Q-[Pen]-Phe[4-(2-aminoethoxy)]-[2-Nal]-[a-MeLys]-[Lys(Ac)]-N-[bA]-NH_2
240	Ac-[Pen]-[Aib]-T-[W(7-Me)]-Q-[Pen]-Phe[4-(2-aminoethoxy)]-[2-Nal]-[a-MeLys]-[Lys(Ac)]-N-[bA]-NH_2
241	Ac-[Pen]-NT-[W(7-Me)]-[Aib]-[Pen]-Phe[4-(2-aminoethoxy)]-[2-Nal]-[a-MeLys]-[Lys(Ac)]-N-[bA]-NH_2
242	Ac-[Pen]-NT-[W(7-Me)]-[Lys(Ac)]-[Pen]-Phe[4-(2-aminoethoxy)]-[2-Nal]-[a-MeLys]-[Lys(Ac)]-N-[bA]-NH_2
244	Ac-[Pen]-NT-[W(7-Me)]-[Lys(Ac)]-[Pen]-Phe[4-(2-aminoethoxy)]-[2-Nal]-[a-MeLys]-[Lys(Ac)]-N-L-NH_2

SEQ ID NO:	Sequence
245	Ac-[Pen]-NT-[W(7-Me)]-[Lys(Ac)]-[Pen]-Phe[4-(2-aminoethoxy)]-[2-Nal]-[a-MeLys]-[Lys(Ac)]-N-[(D)Leu]-NH_2
249	Ac-[Pen]-NT-[W(7-Me)]-[Lys(Ac)]-[Pen]-Phe[4-(2-aminoethoxy)]-[2-Nal]-[a-MeLys]-[Lys(Ac)]-N-[Cit]-NH_2
252	Ac-[Pen]-NT-[W(7-Me)]-[Lys(Ac)]-[Pen]-Phe[4-(2-aminoethoxy)]-[2-Nal]-[a-MeLys]-[Lys(Ac)]-N-[(D)Lys]-NH_2
267	Ac-[Pen]-NT-[W(7-Me)]-Q-[Pen]-Phe[4-(2-aminoethoxy)]-[2-Nal]-[a-MeLys]-[Lys(Ac)]-N-[bA]-NH_2
268	Ac-[Pen]-N-T-[W(7-Me)]-[Cit]-[Pen]-Phe[4-(2-aminoethoxy)]-[2-Nal]-[a-MeLys]-[Lys(Ac)]-[bA]-[bA]-NH_2
269	Ac-[Pen]-N-T-[W(7-Me)]-Q-[Pen]-Phe[4-(2-aminoethoxy)]-[2-Nal]-[a-MeLys]-[Lys(Ac)]-L-[bA]-NH_2
270	Ac-[Pen]-N-T-[W(7-Me)]-[Lys(Ac)]-[Pen]-Phe[4-(2-aminoethoxy)]-[2-Nal]-[a-MeLys]-[Lys(Ac)]-[bA]-[bA]-NH_2
271	Ac-[Pen]-N-T-[W(7-Me)]-[Lys(Ac)]-[Pen]-Phe[4-(2-aminoethoxy)]-[2-Nal]-[a-MeLys]-[Lys(Ac)]-S-[bA]-NH_2
272	Ac-[Pen]-N-T-[W(7-Me)]-[Lys(Ac)]-[Pen]-Phe[4-(2-aminoethoxy)]-[2-Nal]-[a-MeLys]-[Lys(Ac)]-H-[bA]-NH_2
273	Ac-[Pen]-N-T-[W(7-Me)]-[Lys(Ac)]-[Pen]-Phe[4-(2-aminoethoxy)]-[2-Nal]-[a-MeLys]-E-[bA]-[bA]-NH_2
279	Ac-[Pen]-N-T-[W(7-Me)]-Q-[Pen]-Phe[4-(2-aminoethoxy)]-[2-Nal]-[a-MeLys]-[Cit]-[bA]-[bA]-NH_2
280	Ac-[Pen]-N-T-[W(1-Me)]-[Cit]-[Pen]-Phe[4-(2-aminoethoxy)]-[2-Nal]-[a-MeLys]-[Lys(Ac)]-[bA]-[bA]-NH_2
281	Ac-[Pen]-N-T-[W(7-Me)]-[Cit]-[Pen]-Phe[4-(2-aminoethoxy)]-[2-Nal]-[a-MeLys]-[Cit]-[bA]-[bA]-NH_2
282	Ac-[Pen]-N-T-[W(7-Me)]-Q-[Pen]-Phe[4-(2-aminoethoxy)]-[2-Nal]-[a-MeLys]-E-N-[bA]-NH_2
283	Ac-[Pen]-N-T-[W(7-Me)]-Q-[Pen]-Phe[4-(2-aminoethoxy)]-[W(1-Me)]-[a-MeLys]-[Lys(Ac)]-N-[bA]-NH_2

SEQ ID NO:	Sequence
284	Ac-[Pen]-N-T-[W(7-Et)]-[Lys(Ac)]-[Pen]-Phe[4-(2-aminoethoxy)]-[2-Nal]-[a-MeLys]-[Lys(Ac)]-N-[(D)Leu]-NH_2
285	Ac-[Pen]-N-T-[W(7-n-Pr)]-[Lys(Ac)]-[Pen]-Phe[4-(2-aminoethoxy)]-[2-Nal]-[a-MeLys]-[Lys(Ac)]-N-[(D)Leu]-NH_2
286	Ac-[Pen]-N-T-[W(7-i-Pr)]-[Lys(Ac)]-[Pen]-Phe[4-(2-aminoethoxy)]-[2-Nal]-[a-MeLys]-[Lys(Ac)]-N-[(D)Leu]-NH_2
288	Ac-[Pen]-N-T-[W(7-OMe)]-[Lys(Ac)]-[Pen]-Phe[4-(2-aminoethoxy)]-[2-Nal]-[a-MeLys]-[Lys(Ac)]-N-[(D)Leu]-NH_2
296	Ac-[Pen]-N-T-[W(5-CN)]-Q-[Pen]-Phe[4-(2-aminoethoxy)]-[2-Nal]-[a-MeLys]-[Lys(Ac)]-N-[(D)Lys]-NH_2
297	Ac-[Pen]-N-T-[W(7-OMe)]-Q-[Pen]-Phe[4-(2-aminoethoxy)]-[2-Nal]-[a-MeLys]-[Lys(Ac)]-N-[(D)Lys]-NH_2
299	Ac-[Pen]-N-T-[W(7-OMe)]-[Lys(Ac)]-[Pen]-Phe[4-(2-aminoethoxy)]-[2-Nal]-[a-MeLys]-[Lys(Ac)]-N-[(D)Lys]-NH_2
300	Ac-[Pen]-N-T-[W(7-OMe)]-[Cit]-[Pen]-Phe[4-(2-aminoethoxy)]-[2-Nal]-[a-MeLys]-[Lys(Ac)]-N-[(D)Lys]-NH_2
314	Ac-[Pen]-N-T-[W(7-Me)]-[Lys(Ala)]-[Pen]-Phe[4-(2-aminoethoxy)]-[2-Nal]-[a-MeLys]-[Lys(Ac)]-N-[(D)Leu]-NH_2;
315	Ac-[Pen]-N-T-[W(7-Me)]-[Lys(IVA)]-[Pen]-Phe[4-(2-aminoethoxy)]-[2-Nal]-[a-MeLys]-[Lys(Ac)]-N-[(D)Leu]-NH_2;
316	Ac-[Pen]-N-T-[W(7-Me)]-[Lys(cyclohexanoic)]-[Pen]-Phe[4-(2-aminoethoxy)]-[2-Nal]-[a-MeLys]-[Lys(Ac)]-N-[(D)Leu]-NH_2;
317	Ac-[Pen]-N-T-[W(7-Me)]-[Lys(octanoic)]-[Pen]-Phe[4-(2-aminoethoxy)]-[2-Nal]-[a-MeLys]-[Lys(Ac)]-N-[(D)Leu]-NH_2;
318	Ac-[Pen]-N-T-[W(7-Me)]-[Lys(C(O)CH_2Ph)]-[Pen]-Phe[4-(2-aminoethoxy)]-[2-Nal]-[a-MeLys]-[Lys(Ac)]-N-[(D)Leu]-NH_2;
319	Ac-[Pen]-N-T-[W(7-Me)]-[Lys(trifluoropropionic)]-[Pen]-Phe[4-(2-aminoethoxy)]-[2-Nal]-[a-MeLys]-[Lys(Ac)]-N-[(D)Leu]-NH_2;
320	Ac-[Pen]-N-T-[W(7-Me)]-[Lys(Gly)]-[Pen]-Phe[4-(2-aminoethoxy)]-[2-Nal]-[a-MeLys]-[Lys(Ac)]-N-[(D)Leu]-NH_2;

SEQ ID NO:	Sequence
321	Ac-[Pen]-N-T-[W(7-Me)]-[Lys(bAla)]-[Pen]-Phe[4-(2-aminoethoxy)]-[2-Nal]-[a-MeLys]-[Lys(Ac)]-N-[(D)Leu]-NH_2;
322	Ac-[Pen]-N-T-[W(7-Me)]-[Lys(Aib)]-[Pen]-Phe[4-(2-aminoethoxy)]-[2-Nal]-[a-MeLys]-[Lys(Ac)]-N-[(D)Leu]-NH_2;
324	Ac-[(D)Arg]-[Abu]-Q-T-[W(7-Me)]-[Lys(Ac)]-[Cys]-Phe[4-(2-aminoethoxy)]-[2-Nal]-[a-MeLys]-[Lys(Ac)]-N-[(D)Lys]-NH_2;
325	Ac-[(D)Arg]-[Abu]-Q-T-[W(7-Me)]-[Lys(Ac)]-[Cys]-Phe[4-(2-aminoethoxy)]-[2-Nal]-[a-MeLys]-[Lys(Ac)]-N-[(D)Leu]-NH_2;
328	Ac-[Pen]-A-T-[W(7-Me)]-[Lys(Ac)]-[Pen]-Phe[4-(2-aminoethoxy)]-[2-Nal]-[a-MeLys]-[Lys(Ac)]-N-[(D)Leu]-NH_2;
329	Ac-[Pen]-G-T-[W(7-Me)]-[Lys(Ac)]-[Pen]-Phe[4-(2-aminoethoxy)]-[2-Nal]-[a-MeLys]-[Lys(Ac)]-N-[(D)Leu]-NH_2;
330	Ac-[Pen]-[Lys(Ac)]-T-[W(7-Me)]-[Lys(Ac)]-[Pen]-Phe[4-(2-aminoethoxy)]-[2-Nal]-[a-MeLys]-[Lys(Ac)]-N-[(D)Leu]-NH_2;
331	Ac-[Pen]-[Cit]-T-[W(7-Me)]-[Lys(Ac)]-[Pen]-Phe[4-(2-aminoethoxy)]-[2-Nal]-[a-MeLys]-[Lys(Ac)]-N-[(D)Leu]-NH_2;
332	Ac-[Pen]-L-T-[W(7-Me)]-[Lys(Ac)]-[Pen]-Phe[4-(2-aminoethoxy)]-[2-Nal]-[a-MeLys]-[Lys(Ac)]-N-[(D)Leu]-NH_2;
333	Ac-[Pen]-P-T-[W(7-Me)]-[Lys(Ac)]-[Pen]-Phe[4-(2-aminoethoxy)]-[2-Nal]-[a-MeLys]-[Lys(Ac)]-N-[(D)Leu]-NH_2;
334	Ac-[Pen]-S-T-[W(7-Me)]-[Lys(Ac)]-[Pen]-Phe[4-(2-aminoethoxy)]-[2-Nal]-[a-MeLys]-[Lys(Ac)]-N-[(D)Leu]-NH_2;
335	Ac-[Pen]-[Dab(Ac)]-T-[W(7-Me)]-[Lys(Ac)]-[Pen]-Phe[4-(2-aminoethoxy)]-[2-Nal]-[a-MeLys]-[Lys(Ac)]-N-[(D)Leu]-NH_2;
336	Ac-[Pen]-R-T-[W(7-Me)]-[Lys(Ac)]-[Pen]-Phe[4-(2-aminoethoxy)]-[2-Nal]-[a-MeLys]-[Lys(Ac)]-N-[(D)Leu]-NH_2;
337	Ac-[Pen]-[hLeu]-T-[W(7-Me)]-[Lys(Ac)]-[Pen]-Phe[4-(2-aminoethoxy)]-[2-Nal]-[a-MeLys]-[Lys(Ac)]-N-[(D)Leu]-NH_2;
338	Ac-[Pen]-[(D)Asn]-T-[W(7-Me)]-[Lys(Ac)]-[Pen]-Phe[4-(2-aminoethoxy)]-[2-Nal]-[a-MeLys]-[Lys(Ac)]-N-[(D)Leu]-NH_2;

SEQ ID NO:	Sequence
349	Ac-[Pen]-N-T-[W(6-Et)]-[Lys(Ac)]-[Pen]-Phe[4-(2-aminoethoxy)]-[2-Nal]-[a-MeLys]-[Lys(Ac)]-N-[(D)Lys]-NH_2;
351	Ac-[Pen]-N-T-[W(2-Me)]-[Lys(Ac)]-[Pen]-Phe[4-(2-aminoethoxy)]-[2-Nal]-[a-MeLys]-[Lys(Ac)]-N-[(D)Lys]-NH_2;
352	Ac-[Pen]-N-T-[W(7-Me)]-[Lys(Ac)]-[Pen]-Phe[4-(2-aminoethoxy)]-[2-Nal]-[a-MeLys]-[Lys(Ac)]-S-[(D)Lys]-NH_2;
353	Ac-[Pen]-N-T-[W(7-Me)]-[Lys(Ac)]-[Pen]-Phe[4-(2-aminoethoxy)]-[W(2-Me)]-[a-MeLys]-[Lys(Ac)]-N-[(D)Lys]-NH_2;
355	Ac-[Pen]-N-T-[W(7-Me)]-[Lys(Ac)]-[Pen]-Phe[4-(2-aminoethoxy)]-[2-Nal]-[a-MeLys]-[Lys(Ala)]-N-[(D)Leu]-NH_2;
362	Ac-[Pen]-N-T-[W(7-Me)]-[Lys(Ac)]-[Pen]-Phe[4-(2-aminoethoxy)]-[2-Nal]-[a-MeLys]-[Lys(PEG3-OMe)]-N-[(D)Leu]-NH_2; or
363	Ac-[Pen]-N-T-[W(7-Me)]-[Lys(Ac)]-[Pen]-Phe[4-(2-aminoethoxy)]-[2-Nal]-[a-MeLys]-[Lys(PEG11-OMe)]-N-[(D)Leu]-NH_2

5. The peptide inhibitor or pharmaceutically acceptable salt or solvate thereof of claim 1, wherein the peptide inhibitor comprises an amino acid sequence of Formula (II):

X4-X5-X6-X7-X8-X9-X10-X11 (II)

wherein

X4 is Abu, Cys, (D)Cys, alpha-MeCys, (D)Pen, Pen, or Pen(sulfoxide);

X5 is Cit, Glu, Gly, Leu, Ile, beta-Ala, Ala, Lys, Asn, Pro, alpha-MeGln, alpha-MeLys, alpha-MeLeu, alpha-MeAsn, Lys(Ac), alpha-MeLys(Ac), Dab(Ac), Dap(Ac), homo-Lys(Ac), Gln, Asp, or Cys; and

X6 is Thr, Aib, Asp, Dab, Gly, Pro, Ser, alpha-MeGln, alpha-MeLys, alpha-MeLeu, alpha-MeAsn, alpha-MeThr, alpha-MeSer, or Val.

6. The peptide inhibitor or pharmaceutically acceptable salt or solvate thereof of claim 1, wherein X4 or X9 is Cys, (D)Cys, alpha-MeCys, (D)Pen, or Pen; and the bond between X4 and X9 is a disulfide bond.

7. The peptide inhibitor or pharmaceutically acceptable salt or solvate thereof of claim 1, wherein X4 is (D)Pen, or Pen; or X4 is Pen(sulfoxide).

8. The peptide inhibitor or pharmaceutically acceptable salt or solvate thereof of claim 1, wherein X4 is Pen.

9. The peptide inhibitor or pharmaceutically acceptable salt or solvate thereof of any one of claims 1-8, wherein X9 is Cys, (D)Cys, or alpha-MeCys.

10. The peptide inhibitor or pharmaceutically acceptable salt or solvate thereof of any one of claims 1-8, wherein X9 is Pen or (D)Pen.

11. The peptide inhibitor or pharmaceutically acceptable salt or solvate thereof of any one of claims 1-8, wherein X9 is Pen.

12. The peptide inhibitor or pharmaceutically acceptable salt or solvate thereof of claim 1, wherein X4 is Pen and X9 is Pen, and the bond is a disulfide bond.

13. The peptide inhibitor or pharmaceutically acceptable salt or solvate thereof of claim 1, wherein X4 or X9 is Abu; and the bond between X4 and X9 is a thioether bond.

14. The peptide inhibitor or pharmaceutically acceptable salt or solvate thereof of claim 1, wherein the peptide inhibitor comprises an amino acid sequence of Formula (IIa) (IIb), or (IIc):

Pen-X5-X6-X7-X8-Pen-X10-X11 (IIa),

Abu-X5-X6-X7-X8-Cys-X10-X11 (IIb), or

Abu-X5-X6-X7-X8-Pen-X10-X11 (IIc),

wherein X5-X8 and X10-X11 are as described in claim 1; and the peptide inhibitor is cyclized via a Pen-Pen disulfide bond; or the peptide inhibitor is cyclized via a Abu-Cys or Abu-Pen thioether bond.

15. The peptide inhibitor or pharmaceutically acceptable salt or solvate thereof of any one of claims 1-14, wherein X5 is Asn, Gln, or Glu.

16. The peptide inhibitor or pharmaceutically acceptable salt or solvate thereof of any one of claims 1-14, wherein X5 is Asn, or Gln.

17. The peptide inhibitor or pharmaceutically acceptable salt or solvate thereof of any one of claims 1-14, wherein X5 is Asn.

18. The peptide inhibitor or pharmaceutically acceptable salt or solvate thereof of claim 1, wherein the peptide inhibitor comprises an amino acid sequence of Formula (IIIa), (IIIb), (IIIc), or (IIId):

Pen- Asn-X6-X7-X8-Pen-X10-X11 (IIIa),

Pen-Gln-X6-X7-X8-Pen-X10-X11 (IIIb),

Abu- Asn-X6-X7-X8-Cys-X10-X11 (IIIc), or

Abu-Gln-X6-X7-X8-Pen-X10-X11 (IIId),

wherein X6-X8 and X10-X11 are as described in claim 1; and the peptide inhibitor is cyclized via a Pen-Pen disulfide bond; or a Abu-Cys or Abu-Pen thioether bond.

19. The peptide inhibitor or pharmaceutically acceptable salt or solvate thereof of any one of claims 1-18, wherein X6 is Thr.

20. The peptide inhibitor or pharmaceutically acceptable salt or solvate thereof of claim 1, wherein the peptide inhibitor comprises an amino acid sequence of Formula (IVa), (IVb), (IVc), or (IVd):

Pen- Asn-Thr-X7-X8-Pen-X10-X11 (IVa),

Pen-Gln-Thr-X7-X8-Pen-X10-X11 (IVb),

Abu- Asn-Thr-X7-X8-Cys-X10-X11 (IVc), or

Abu-Gln-Thr-X7-X8-Pen-X10-X11 (IVd),

wherein X7-X8 and X10-X11 are as described in claim 1; and the peptide inhibitor is cyclized via a Pen-Pen disulfide bond; or a Abu-Cys or Abu-Pen thioether bond.

21. The peptide inhibitor or pharmaceutically acceptable salt or solvate thereof of any one of claims 1-20, wherein X8 is Gln, alpha-Me-Lys, alpha-MeLys(Ac), or Glu.

22. The peptide inhibitor or pharmaceutically acceptable salt or solvate thereof of any one of claims 1-20, wherein X8 is Gln.

23. The peptide inhibitor or pharmaceutically acceptable salt or solvate thereof of claim 1, wherein the peptide inhibitor comprises an amino acid sequence of Formula (Va), (Vb), (Vc), or (Vd):

Pen- Asn-Thr-X7-Gln-Pen-X10-X11 (Va),

Pen-Gln-Thr-X7-Gln-Pen-X10-X11 (Vb),

Abu-Asn-Thr-X7-Gln-Cys-X10-X11 (Vc), or

Abu-Gln-Thr-X7-Gln-Pen-X10-X11 (Vd)

wherein X7 and X10-X11 are as described in claim 1; and the peptide inhibitor is cyclized via a Pen-Pen disulfide bond; or a Abu-Cys or Abu-Pen thioether bond.

24. The peptide inhibitor or pharmaceutically acceptable salt or solvate thereof of claim 1, wherein the peptide inhibitor comprises an amino acid sequence of Formula (Ve), (Vf), (Vg), or (Vh):

Pen-Asn-Thr-X7-Lys(Ac)-Pen-X10-X11 (Ve),

Pen-Gln-Thr-X7-Lys(Ac)-Pen-X10-X11 (Vf),

Abu-Asn-Thr-X7-Lys(Ac)-Cys-X10-X11 (Vg), or

Abu-Gln-Thr-X7-Lys(Ac)-Pen-X10-X11 (Vh)

wherein X7 and X10-X11 are as described in claim 1; and the peptide inhibitor is cyclized via a Pen-Pen disulfide bond; or a Abu-Cys or Abu-Pen thioether bond.

25. The peptide inhibitor or pharmaceutically acceptable salt or solvate thereof of any one of claims 1-24, wherein X10 is Phe, Phe[4-(2-aminoethoxy)], Phe[4-(2-acetylaminoethoxy)], or Phe(4-$CONH_2$).

26. The peptide inhibitor or pharmaceutically acceptable salt or solvate thereof of any one of claims 1-24, wherein X10 is Phe[4-(2-aminoethoxy)], or Phe[4-(2-acetylaminoethoxy)].

27. The peptide inhibitor or pharmaceutically acceptable salt or solvate thereof of claim 1, wherein the peptide inhibitor comprises an amino acid sequence of Formula(VIa), (VIb), (VIc), or (VId):

Pen- Asn-Thr-X7-Gln-Pen-[F(4-2ae)]-X11 (VIa),

Pen-Gln-Thr-X7-Gln-Pen-[F(4-2ae)]-X11 (VIb),

Abu-Asn-Thr-X7-Gln-Cys-[F(4-2ae)]-X11 (VIc), or

Abu-Gln-Thr-X7-Gln-Pen-[F(4-2ae)]-X11 (VId)

wherein X7 and X11 are as described in claim 1; [F(4-2ae)] is Phe[4-(2-aminoethoxy)].

28. The peptide inhibitor or pharmaceutically acceptable salt or solvate thereof of claim 1, wherein the peptide inhibitor comprises an amino acid sequence of Formula (VIe), (VIf), (VIg), or (VIh):

Pen-Asn-Thr-X7-Lys(Ac)-Pen-[F(4-2ae)]-X11 (VIe),

Pen-Gln-Thr-X7-Lys(Ac)-Pen-[F(4-2ae)]-X11 (VIf),

Abu-Asn-Thr-X7-Lys(Ac)-Cys-[F(4-2ae)]-X11 (VIg), or

Abu-Gln-Thr-X7-Lys(Ac)-Pen-[F(4-2ae)]-X11 (VIh)

wherein X7 and X11 are as described in claim 1; [F(4-2ae)] is Phe[4-(2-aminoethoxy)].

29. The peptide inhibitor or pharmaceutically acceptable salt or solvate thereof of claim 1, wherein the peptide inhibitor comprises an amino acid sequence of Formula (VIIa), (VIIb), or (VIIc):

Pen- Asn-Thr-X7-Gln-Pen-[F(4-2ae)]-X11-X12-X13-X14-X15 (VIIa),

Abu- Asn-Thr-X7-Gln-Cys-[F(4-2ae)]-X11-X12-X13-X14-X15 (VIIb), or

Abu- Asn-Thr-X7-Gln-Pen-[F(4-2ae)]-X11-X12-X13-X14-X15 (VIIc)

wherein X7 and X11-X15 are as described in claim 1.

30. The peptide inhibitor or pharmaceutically acceptable salt or solvate thereof of claim 1, wherein the peptide inhibitor comprises an amino acid sequence of Formula (VIId), (VIIe), or (VIIf) or comprises a sequence of Formula (VIId), (VIIe), or (VIIf):

Pen-Asn-Thr-X7-Lys(Ac)-Pen-[F(4-2ae)]-X11-X12-X13-X14-X15 (VIId),

Abu-Asn-Thr-X7-Lys(Ac)-Cys-[F(4-2ae)]-X11-X12-X13-X14-X15 (VIIe), or

Abu-Asn-Thr-X7-Lys(Ac)-Pen-[F(4-2ae)]-X11-X12-X13-X14-X15 (VIIf)

wherein X7 and X11-X15 are as described in claim 1.

31. The peptide inhibitor or pharmaceutically acceptable salt or solvate thereof of any one of claims 1-30, wherein X12 is 4-amino-4-carboxy-tetrahydropyran (THP), alpha-MeLys, alpha-MeLeu, Ala, cyclohexylAla, Lys, or Aib.

32. The peptide inhibitor or pharmaceutically acceptable salt or solvate thereof of any one of claims 1-30, wherein X12 is 4-amino-4-carboxy-tetrahydropyran (THP), alpha-MeLys, or alpha-MeLeu.

33. The peptide inhibitor or pharmaceutically acceptable salt or solvate thereof of any one of claims 1-30, wherein X12 is alpha-MeLeu.

34. The peptide inhibitor or pharmaceutically acceptable salt or solvate thereof of any one of claims 1-31, wherein X13 is Glu, Gln, Lys(Ac), or Lys.

35. The peptide inhibitor or pharmaceutically acceptable salt or solvate thereof of any one of claims 1-31, wherein X13 is Gln, Lys(Ac), or Lys.

36. The peptide inhibitor or pharmaceutically acceptable salt or solvate thereof of any one of claims 1-31, wherein X13 is Lys(Ac), or Lys.

37. The peptide inhibitor or pharmaceutically acceptable salt or solvate thereof of any one of claims 1-31, wherein X13 is Lys(Ac).

38. The peptide inhibitor or pharmaceutically acceptable salt or solvate thereof of claim 1, wherein the peptide inhibitor comprises an amino acid sequence of Formula (VIIIa), (VIIIb) or (VIIIc):

Pen-Asn-Thr-X7-Gln-Pen-[F(4-2ae)]-X11-aMeLeu-K(Ac)-X14-X15 (VIIIa),

Abu-Asn-Thr-X7-Gln-Cys-[F(4-2ae)]-X11-aMeLeu-K(Ac)-X14-X15 (VIIIb), or

Abu-Asn-Thr-X7-Gln-Pen-[F(4-2ae)]-X11-aMeLeu-K(Ac)-X14-X15 (VIIIc)

wherein X7, X11, X14, and X15 are as described in claim 1.

39. The peptide inhibitor or pharmaceutically acceptable salt or solvate thereof of claim 1, wherein the peptide inhibitor comprises an amino acid sequence of Formula (VIIId), (VIIIe) or (VIIIf) or comprises a sequence of Formula (VIIId), (VIIIe) or (VIIIf):

Pen-Asn-Thr-X7-Lys(Ac)-Pen-[F(4-2ae)]-X11-[alpha-MeLys]-K(Ac)-X14-X15 (VIIId),

Abu-Asn-Thr-X7-Lys(Ac)-Cys-[F(4-2ae)]-X11-[alpha-MeLys]-K(Ac)-X14-X15 (VIIIe), or

Abu-Asn-Thr-X7-Lys(Ac)-Pen-[F(4-2ae)]-X11-[alpha-MeLys]-K(Ac)-X14-X15 (VIIIf)

wherein X7, X11, X14, and X15 are as described in claim 1.

40. The peptide inhibitor or pharmaceutically acceptable salt or solvate thereof of any one of claims 1-39, wherein X7 is Trp substituted with cyano, halo, alkyl, haloalkyl, hydroxy, or alkoxy; and X11 is as described in claim 1.

41. The peptide inhibitor or pharmaceutically acceptable salt or solvate thereof of any one of claims 1-40, wherein X11 is Trp substituted with cyano, halo, alkyl, haloalkyl, hydroxy, or alkoxy; and X7 is as described in claim 1.

42. The peptide inhibitor or pharmaceutically acceptable salt or solvate thereof of any one of claims 1-40, wherein X11 is 2-Nal, Phe(2-Me), Phe(3-Me), Phe(4-Me), Phe(3,4-dimethoxy), or 1-Nal.

43. The peptide inhibitor or pharmaceutically acceptable salt or solvate thereof of any one of claims 1-40, wherein X11 is 2-Nal, or 1-Nal.

44. The peptide inhibitor or pharmaceutically acceptable salt or solvate thereof of any one of claims 1-40, wherein X11 is 2-Nal.

45. The peptide inhibitor or pharmaceutically acceptable salt or solvate thereof of any one of claims 1-40, wherein X11 is 1-Nal.

46. The peptide inhibitor or pharmaceutically acceptable salt or solvate thereof of claim 1, wherein the peptide inhibitor comprises an amino acid sequence of Formula (IVa):

Pen-Asn-Thr-X7-X8-Pen-X10-X11 (IVa),

wherein X8, X10, and X11 are as in claim 1, and X7 is Trp substituted with alkyl, and the substitution is at 1-, 2, or 7-position.

47. The peptide inhibitor or pharmaceutically acceptable salt or solvate thereof of claim 46, wherein X7 is Trp substituted with 1-Me, 2-Me, or 7-Me.

48. The peptide inhibitor or pharmaceutically acceptable salt or solvate thereof of any one of claims 46-47, wherein X8 is Gln, alpha-Me-Lys, alpha-MeLys(Ac), or Glu.

49. The peptide inhibitor or pharmaceutically acceptable salt or solvate thereof of any one of claims 46-47, wherein X8 is Gln.

50. The peptide inhibitor or pharmaceutically acceptable salt or solvate thereof of any one of claims 46-47, wherein X8 is Q, Cit, a-MeLys, a-MeLeu, Aib, Lys(Ac), Lys(Gly), or Lys(Aib).

51. The peptide inhibitor or pharmaceutically acceptable salt or solvate thereof of any one of claims 46-47, wherein X8 is Lys(Ac).

52. The peptide inhibitor or pharmaceutically acceptable salt or solvate thereof of any one of claims 46-51, wherein X10 is Phe, Phe[4-(2-aminoethoxy)], Phe[4-(2-acetylaminoethoxy)], or Phe(4-$CONH_2$).

53. The peptide inhibitor or pharmaceutically acceptable salt or solvate thereof of any one of claims 46-51, wherein X10 is Phe[4-(2-aminoethoxy)], or Phe[4-(2-acetylaminoethoxy)].

54. The peptide inhibitor or pharmaceutically acceptable salt or solvate thereof of any one of claims 46-53, wherein X11 is Trp substituted with cyano, halo, alkyl, haloalkyl, hydroxy, or alkoxy.

55. The peptide inhibitor or pharmaceutically acceptable salt or solvate thereof of any one of claims 46-53, wherein X11 is 2-Nal, Phe(2-Me), Phe(3-Me), Phe(4-Me), Phe(3,4-dimethoxy), or 1-Nal.

56. The peptide inhibitor or pharmaceutically acceptable salt or solvate thereof of any one of claims 46-53, wherein X11 is 2-Nal, or 1-Nal.

57. The peptide inhibitor or pharmaceutically acceptable salt or solvate thereof of any one of claims 46-53, wherein X11 is 2-Nal.

58. The peptide inhibitor or pharmaceutically acceptable salt or solvate thereof of any one of claims 1-57, wherein the peptide inhibitor comprises the structure of Formula (Z):

$$R^1\text{-}X\text{-}R^2 \quad (Z)$$

or a pharmaceutically acceptable salt or solvate thereof, wherein

R^1 is hydrogen, a C1-C6 alkyl, a C6-C12 aryl, a C6-C12aryl-C1-C6alkyl, or a C1-C20 alkanoyl, and including PEGylated versions alone or as spacers of any of the foregoing;

X is the amino acid sequence of Formula (I), any of Formula (II)-(XII), or an amino acid sequence set forth in Table E3; and

R^2 is OH or NH_2.

59. The peptide inhibitor or pharmaceutically acceptable salt or solvate thereof of claim 58, wherein X is the amino acid sequence of Formula (II').

60. The peptide inhibitor or pharmaceutically acceptable salt or solvate thereof of claim 58, wherein the peptide comprises X-R^2, and X is the amino acid sequence of Formula (II'), and R^2 is OH or NH_2.

61. The peptide inhibitor or pharmaceutically acceptable salt or solvate thereof of claim 58, wherein the peptide comprises an amino acid sequence of Formula (II"):

X7-X8-X9-X10-X11-X12-X13-X14-X15-R^2 (II").

62. The peptide inhibitor or pharmaceutically acceptable salt or solvate thereof of any one of claims 1-61, wherein the peptide inhibitor comprises the structure of Formula (Z):

R^1-X-R^2 (Z)

or a pharmaceutically acceptable salt or solvate thereof, wherein

R^1 is a bond, hydrogen, Ac, a C1-C6 alkyl, a C6-C12 aryl, a C6-C12aryl-C1-C6alkyl, or a C1-C20 alkanoyl, and including PEGylated versions alone or as spacers of any of the foregoing;

X is the amino acid sequence of Formula (II'); and

R^2 is OH or NH_2;

or wherein the peptide inhibitor of Formula (Z) is a peptide having an amino acid sequence set forth in Table E3 or a pharmaceutically acceptable salt or solvate thereof.

63. The peptide inhibitor or pharmaceutically acceptable salt or solvate thereof of any one of claims 58-62, wherein R^1 is H or C1-C20 alkanoyl.

64. The peptide inhibitor or pharmaceutically acceptable salt or solvate thereof of any one of claims 58-62, wherein R^1 is H or Ac.

65. The peptide inhibitor or pharmaceutically acceptable salt or solvate thereof any one of claims 58-62, wherein R^1 is Ac.

66. The peptide inhibitor of claim 1, wherein the peptide inhibitor comprises or is:

Ac-[Pen]-NT-[W(7-Me)]-Q-[Pen]-Phe[4-(2-aminoethoxy)]-[2-Nal]-[a-MeLeu]-[Lys(Ac)]-N-[bA]-NH_2 (SEQ ID NO: 201);
Ac-[Pen]-NT-[W(7-Me)]-[Cit]-[Pen]-Phe[4-(2-aminoethoxy)]-[2-Nal]-[a-MeLeu]-[Lys(Ac)]-N-[bA]-NH_2 (SEQ ID NO: 227);
Ac-[Pen]-NT-[W(7-Me)]-[Lys(Ac)]-[Pen]-Phe[4-(2-aminoethoxy)]-[2-Nal]-[a-MeLys]-[Lys(Ac)]-N-[bA]-NH_2 (SEQ ID NO: 242);
Ac-[Pen]-NT-[W(7-Me)]-[Lys(Ac)]-[Pen]-Phe[4-(2-aminoethoxy)]-[2-Nal]-[a-MeLys]-[Lys(Ac)]-N-[(D)Leu]-NH_2 (SEQ ID NO: 245);
Ac-[Pen]-NT-[W(7-Me)]-[Lys(Ac)]-[Pen]-Phe[4-(2-aminoethoxy)]-[2-Nal]-[a-MeLys]-[Lys(Ac)]-N-[Cit]-NH_2 (SEQ ID NO: 249);
Ac-[Pen]-NT-[W(7-Me)]-[Lys(Ac)]-[Pen]-Phe[4-(2-aminoethoxy)]-[2-Nal]-[a-MeLys]-[Lys(Ac)]-N-[(D)Lys]-NH_2 (SEQ ID NO: 252);
Ac-[Pen]-NT-[W(7-Me)]-Q-[Pen]-Phe[4-(2-aminoethoxy)]-[2-Nal]-[a-MeLys]-[Lys(Ac)]-N-[bA]-NH_2 (SEQ ID NO: 267);
Ac-[Pen]-N-T-[W(7-Et)]-[Lys(Ac)]-[Pen]-Phe[4-(2-aminoethoxy)]-[2-Nal]-[a-MeLys]-[Lys(Ac)]-N-[(D)Leu]-NH_2 (SEQ ID NO: 284);
Ac-[Pen]-N-T-[W(7-n-Pr)]-[Lys(Ac)]-[Pen]-Phe[4-(2-aminoethoxy)]-[2-Nal]-[a-MeLys]-[Lys(Ac)]-N-[(D)Leu]-NH_2 (SEQ ID NO: 285);
Ac-[Pen]-N-T-[W(7-Me)]-[Lys(Gly)]-[Pen]-Phe[4-(2-aminoethoxy)]-[2-Nal]-[a-MeLys]-[Lys(Ac)]-N-[(D)Leu]-NH_2; (SEQ ID NO: 320); or
Ac-[Pen]-N-T-[W(7-Me)]-[Lys(Aib)]-[Pen]-Phe[4-(2-aminoethoxy)]-[2-Nal]-[a-MeLys]-[Lys(Ac)]-N-[(D)Leu]-NH_2; (SEQ ID NO: 322);
and wherein the peptide inhibitor is cyclized via a Pen-Pen disulfide bond; or via an Abu-C thioether bond;
or a pharmaceutically acceptable salt or solvate thereof.

67. The peptide inhibitor of claim 1, wherein the peptide inhibitor comprises or is:
Ac-[Pen]-NT-[W(7-Me)]-Q-[Pen]-Phe[4-(2-aminoethoxy)]-[2-Nal]-[a-MeLys]-[Lys(Ac)]-N-[bA]-NH_2 (SEQ ID NO: 202);
Ac-[(D)Arg]-Abu-Q-T-[W(7-Me)]-Q-C-Phe[4-(2-aminoethoxy)]-[2-Nal]-[THP]-E-N-[bA]-NH_2 (SEQ ID NO: 203);

Ac-Abu-Q-T-[W(7-Me)]-Q-C-Phe[4-(2-aminoethoxy)]-[2-Nal]-[THP]-E-N-[bA]-NH_2 (SEQ ID NO: 204);

Ac-[Pen]-NT-[W(7-Me)]-Q-[Pen]-Phe[4-(2-aminoethoxy)]-[2-Nal]-[a-MeLeu]-[Lys(Ac)]-G-[bA]-NH_2 (SEQ ID NO: 205);

Ac-[Pen]-NT-[W(7-Me)]-Q-[Pen]-Phe[4-(2-aminoethoxy)]-[2-Nal]-[a-MeLeu]-[Lys(Ac)]-A-[bA]-NH_2 (SEQ ID NO: 207);

Ac-[Pen]-NT-[W(7-Me)]-Q-[Pen]-Phe[4-(2-aminoethoxy)]-[2-Nal]-[a-MeLeu]-[Lys(Ac)]-L-[bA]-NH_2 (SEQ ID NO: 208);

Ac-[Pen]-NT-[W(7-Me)]-Q-[Pen]-Phe[4-(2-aminoethoxy)]-[2-Nal]-[a-MeLeu]-[Lys(Ac)]-[(D)Ala]-[bA]-NH_2 (SEQ ID NO: 209);

Ac-[Pen]-NT-[W(7-Me)]-Q-[Pen]-Phe[4-(2-aminoethoxy)]-[2-Nal]-[a-MeLeu]-[Lys(Ac)]-H-[bA]-NH_2 (SEQ ID NO: 214);

Ac-[Pen]-NT-[W(7-Me)]-Q-[Pen]-Phe[4-(2-aminoethoxy)]-[2-Nal]-[a-MeLeu]-[Lys(Ac)]-T-[bA]-NH_2 (SEQ ID NO: 217);

Ac-[Pen]-NT-[W(7-Me)]-Q-[Pen]-Phe[4-(2-aminoethoxy)]-[2-Nal]-[a-MeLeu]-[Lys(Ac)]-S-[bA]-NH_2 (SEQ ID NO: 221);

Ac-[Pen]-NT-[W(7-Me)]-Q-[Pen]-Phe[4-(2-aminoethoxy)]-[2-Nal]-[a-MeLeu]-[Lys(Ac)]-[(D)Ser]-[bA]-NH_2 (SEQ ID NO: 222);

Ac-[Pen]-NT-[W(4-Me)]-Q-[Pen]-Phe[4-(2-aminoethoxy)]-[2-Nal]-[a-MeLys]-[Lys(Ac)]-N-[bA]-NH_2 (SEQ ID NO: 231);

Ac-[Pen]-NT-[W(1-Me)]-Q-[Pen]-Phe[4-(2-aminoethoxy)]-[2-Nal]-[a-MeLys]-[Lys(Ac)]-N-[bA]-NH_2 (SEQ ID NO: 232);

Ac-[Pen]-NT-[W(7-Me)]-[a-MeLys]-[Pen]-Phe[4-(2-aminoethoxy)]-[2-Nal]-[a-MeLeu]-[Lys(Ac)]-N-[bA]-NH_2 (SEQ ID NO: 234);

Ac-[Pen]-NT-[W(7-Me)]-[a-MeLeu]-[Pen]-Phe[4-(2-aminoethoxy)]-[2-Nal]-[a-MeLys]-[Lys(Ac)]-N-[bA]-NH_2 (SEQ ID NO: 235);

Ac-[Pen]-NT-[W(7-Me)]-Q-[Pen]-Phe[4-(2-aminoethoxy)]-[2-Nal]-[a-MeLys]-[Aib]-N-[bA]-NH_2 (SEQ ID NO: 236);

Ac-[Pen]-Q-T-[W(7-Me)]-Q-[Pen]-Phe[4-(2-aminoethoxy)]-[2-Nal]-[a-MeLys]-[Lys(Ac)]-N-[bA]-NH_2 (SEQ ID NO: 237);

Ac-[Pen]-[Cit]-T-[W(7-Me)]-Q-[Pen]-Phe[4-(2-aminoethoxy)]-[2-Nal]-[a-MeLys]-[Lys(Ac)]-N-[bA]-NH_2 (SEQ ID NO: 238);

Ac-[Pen]-[Lys(Ac)]-T-[W(7-Me)]-Q-[Pen]-Phe[4-(2-aminoethoxy)]-[2-Nal]-[a-MeLys]-[Lys(Ac)]-N-[bA]-NH_2 (SEQ ID NO: 239);

Ac-[Pen]-NT-[W(7-Me)]-[Lys(Ac)]-[Pen]-Phe[4-(2-aminoethoxy)]-[2-Nal]-[a-MeLys]-[Lys(Ac)]-N-L-NH_2 (SEQ ID NO: 244);

Ac-[Pen]-N-T-[W(7-Me)]-[Cit]-[Pen]-Phe[4-(2-aminoethoxy)]-[2-Nal]-[a-MeLys]-[Lys(Ac)]-[bA]-[bA]-NH_2 (SEQ ID NO: 268);

Ac-[Pen]-N-T-[W(7-Me)]-Q-[Pen]-Phe[4-(2-aminoethoxy)]-[2-Nal]-[a-MeLys]-[Lys(Ac)]-L-[bA]-NH_2 (SEQ ID NO: 269);

Ac-[Pen]-N-T-[W(7-Me)]-[Lys(Ac)]-[Pen]-Phe[4-(2-aminoethoxy)]-[2-Nal]-[a-MeLys]-[Lys(Ac)]-[bA]-[bA]-NH_2 (SEQ ID NO: 270);

Ac-[Pen]-N-T-[W(7-Me)]-[Lys(Ac)]-[Pen]-Phe[4-(2-aminoethoxy)]-[2-Nal]-[a-MeLys]-[Lys(Ac)]-S-[bA]-NH_2 (SEQ ID NO: 271);

Ac-[Pen]-N-T-[W(7-Me)]-[Lys(Ac)]-[Pen]-Phe[4-(2-aminoethoxy)]-[2-Nal]-[a-MeLys]-[Lys(Ac)]-H-[bA]-NH_2 (SEQ ID NO: 272);

Ac-[Pen]-N-T-[W(7-Me)]-[Lys(Ac)]-[Pen]-Phe[4-(2-aminoethoxy)]-[2-Nal]-[a-MeLys]-E-[bA]-[bA]-NH_2 (SEQ ID NO: 273);

Ac-[Pen]-N-T-[W(7-Me)]-Q-[Pen]-Phe[4-(2-aminoethoxy)]-[2-Nal]-[a-MeLys]-[Cit]-[bA]-[bA]-NH_2 (SEQ ID NO: 279);

Ac-[Pen]-N-T-[W(7-Me)]-Q-[Pen]-Phe[4-(2-aminoethoxy)]-[2-Nal]-[a-MeLys]-E-N-[bA]-NH_2 (SEQ ID NO: 282);

Ac-[Pen]-N-T-[W(7-Me)]-Q-[Pen]-Phe[4-(2-aminoethoxy)]-[W(1-Me)]-[a-MeLys]-[Lys(Ac)]-N-[bA]-NH_2 (SEQ ID NO: 283);

Ac-[Pen]-N-T-[W(7-i-Pr)]-[Lys(Ac)]-[Pen]-Phe[4-(2-aminoethoxy)]-[2-Nal]-[a-MeLys]-[Lys(Ac)]-N-[(D)Leu]-NH_2 (SEQ ID NO: 286);

Ac-[Pen]-N-T-[W(7-OMe)]-[Lys(Ac)]-[Pen]-Phe[4-(2-aminoethoxy)]-[2-Nal]-[a-MeLys]-[Lys(Ac)]-N-[(D)Leu]-NH_2 (SEQ ID NO: 288);

Ac-[Pen]-N-T-[W(7-OMe)]-Q-[Pen]-Phe[4-(2-aminoethoxy)]-[2-Nal]-[a-MeLys]-[Lys(Ac)]-N-[(D)Lys]-NH_2 (SEQ ID NO: 297);

Ac-[Pen]-N-T-[W(7-OMe)]-[Lys(Ac)]-[Pen]-Phe[4-(2-aminoethoxy)]-[2-Nal]-[a-MeLys]-[Lys(Ac)]-N-[(D)Lys]-NH_2 (SEQ ID NO: 299);

Ac-[Pen]-N-T-[W(7-Me)]-[Lys(Ala)]-[Pen]-Phe[4-(2-aminoethoxy)]-[2-Nal]-[a-MeLys]-[Lys(Ac)]-N-[(D)Leu]-NH_2; (SEQ ID NO: 314);

Ac-[Pen]-N-T-[W(7-Me)]-[Lys(IVA)]-[Pen]-Phe[4-(2-aminoethoxy)]-[2-Nal]-[a-MeLys]-[Lys(Ac)]-N-[(D)Leu]-NH_2; (SEQ ID NO: 315);

Ac-[Pen]-N-T-[W(7-Me)]-[Lys(cyclohexanoic)]-[Pen]-Phe[4-(2-aminoethoxy)]-[2-Nal]-[a-MeLys]-[Lys(Ac)]-N-[(D)Leu]-NH_2; (SEQ ID NO: 316);

Ac-[Pen]-N-T-[W(7-Me)]-[Lys(bAla)]-[Pen]-Phe[4-(2-aminoethoxy)]-[2-Nal]-[a-MeLys]-[Lys(Ac)]-N-[(D)Leu]-NH_2; (SEQ ID NO: 321); or

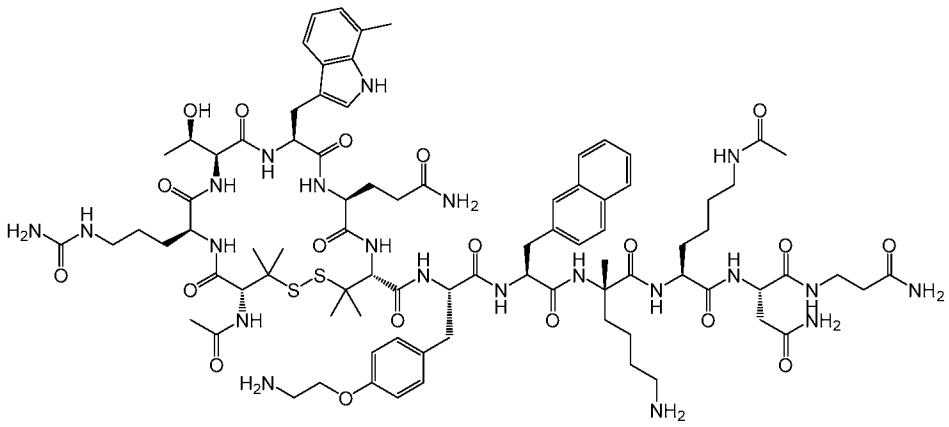
Ac-[(D)Arg]-[Abu]-Q-T-[W(7-Me)]-[Lys(Ac)]-[Cys]-Phe[4-(2-aminoethoxy)]-[2-Nal]-[a-MeLys]-[Lys(Ac)]-N-[(D)Leu]-NH_2; (SEQ ID NO: 325);

and wherein the peptide inhibitor is cyclized via a Pen-Pen disulfide bond; or via a Abu-C thioether bond;

or a pharmaceutically acceptable salt or solvate thereof.

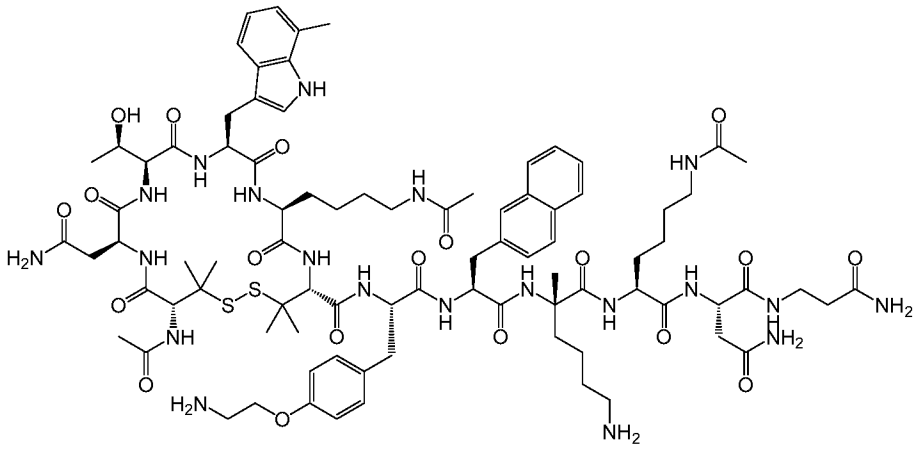
68. The peptide inhibitor of claim 1, wherein the peptide inhibitor comprises or is:

Ac-[Pen]-[Cit]-T-[W(7-Me)]-Q-[Pen]-Phe[4-(2-aminoethoxy)]-[2-Nal]-[a-MeLys]-[Lys(Ac)]-N-[bA]-NH_2 (Seq. ID. No. 238)



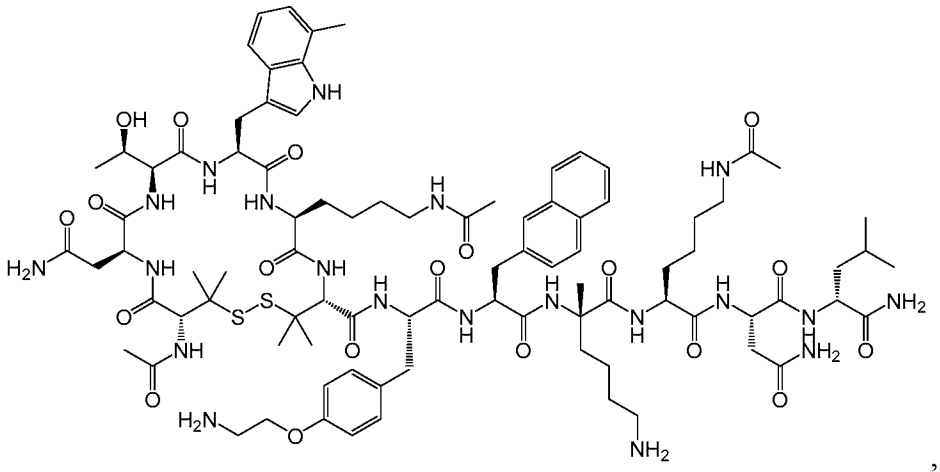
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Ac-[Pen]-NT-[W(7-Me)]-[Lys(Ac)]-[Pen]-Phe[4-(2-aminoethoxy)]-[2-Nal]-[a-MeLys]-[Lys(Ac)]-N-[bA]-NH_2 (Seq. ID. No. 242)



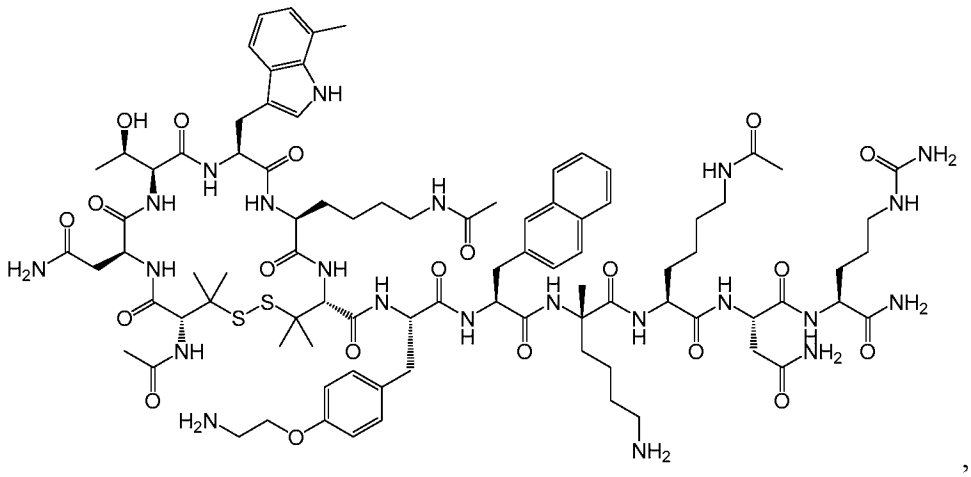
,

Ac-[Pen]-NT-[W(7-Me)]-[Lys(Ac)]-[Pen]-Phe[4-(2-aminoethoxy)]-[2-Nal]-[a-MeLys]-[Lys(Ac)]-N-[(D)Leu]-NH_2 (Seq. ID. No. 245)



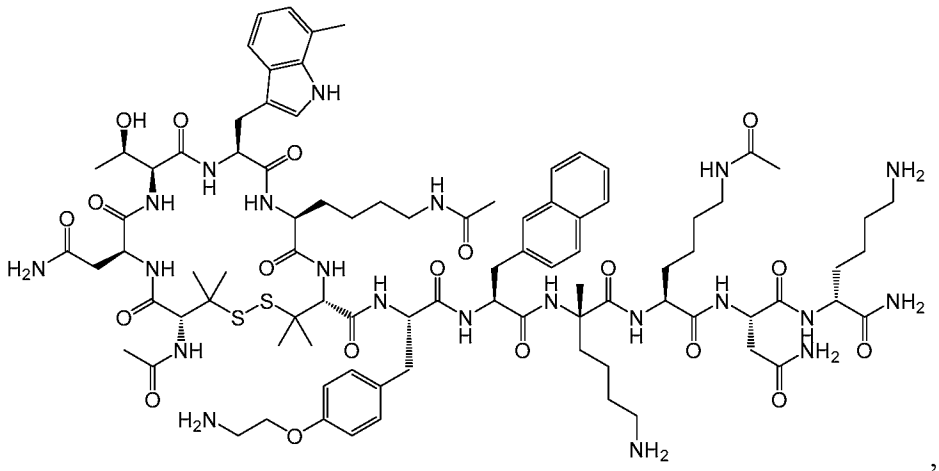
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Ac-[Pen]-NT-[W(7-Me)]-[Lys(Ac)]-[Pen]-Phe[4-(2-aminoethoxy)]-[2-Nal]-[a-MeLys]-[Lys(Ac)]-N-[Cit]-NH_2 (Seq. ID. No. 249)



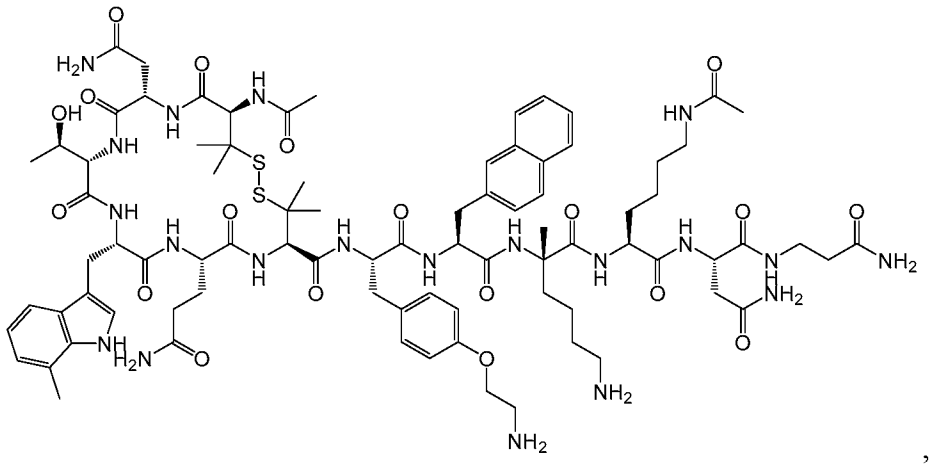
,

Ac-[Pen]-NT-[W(7-Me)]-[Lys(Ac)]-[Pen]-Phe[4-(2-aminoethoxy)]-[2-Nal]-[a-MeLys]-[Lys(Ac)]-N-[(D)Lys]-NH_2 (Seq. ID. No. 252)



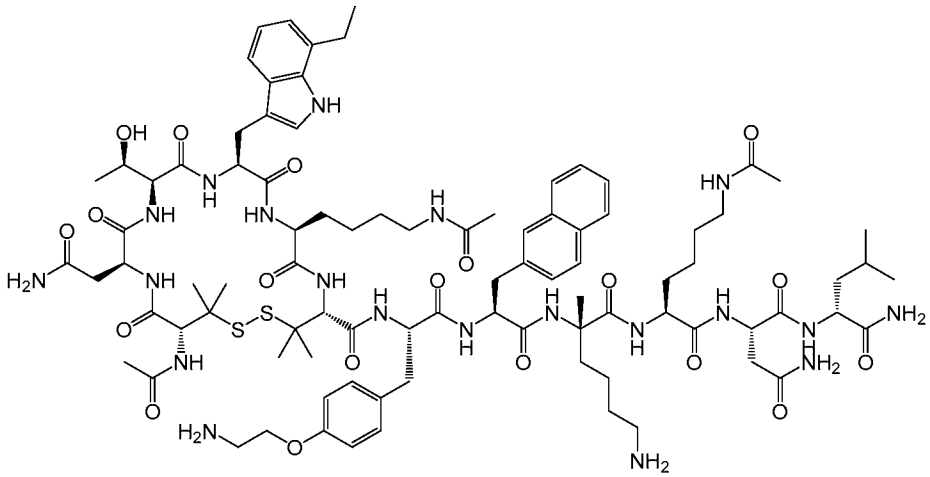
,

Ac-[Pen]-NT-[W(7-Me)]-Q-[Pen]-Phe[4-(2-aminoethoxy)]-[2-Nal]-[a-MeLys]-[Lys(Ac)]-N-[bA]-NH_2 (Seq. ID. No. 267)

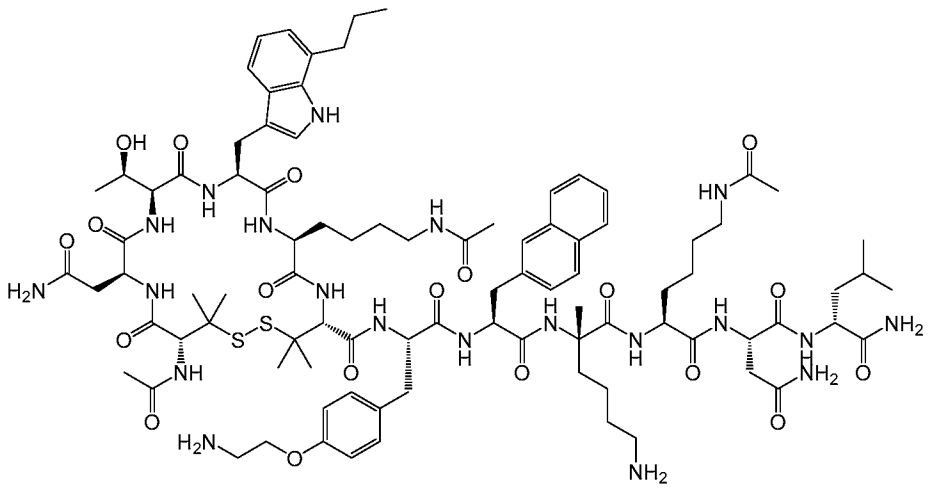


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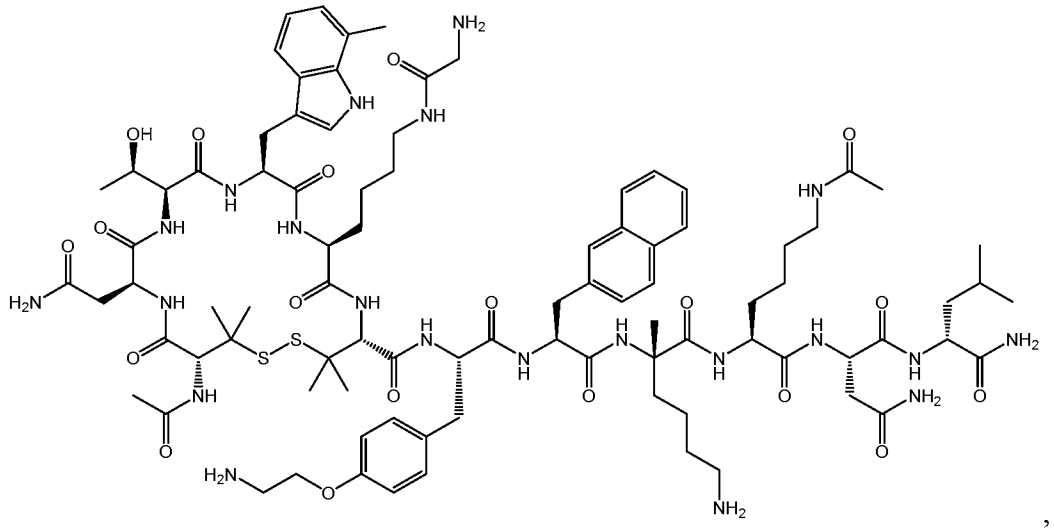
Ac-[Pen]-N-T-[W(7-Et)]-[Lys(Ac)]-[Pen]-Phe[4-(2-aminoethoxy)]-[2-Nal]-[a-MeLys]-[Lys(Ac)]-N-[(D)Leu]-NH_2 (Seq. ID. No. 284)



Ac-[Pen]-N-T-[W(7-n-Pr)]-[Lys(Ac)]-[Pen]-Phe[4-(2-aminoethoxy)]-[2-Nal]-[a-MeLys]-[Lys(Ac)]-N-[(D)Leu]-NH_2 (Seq. ID. No. 285)

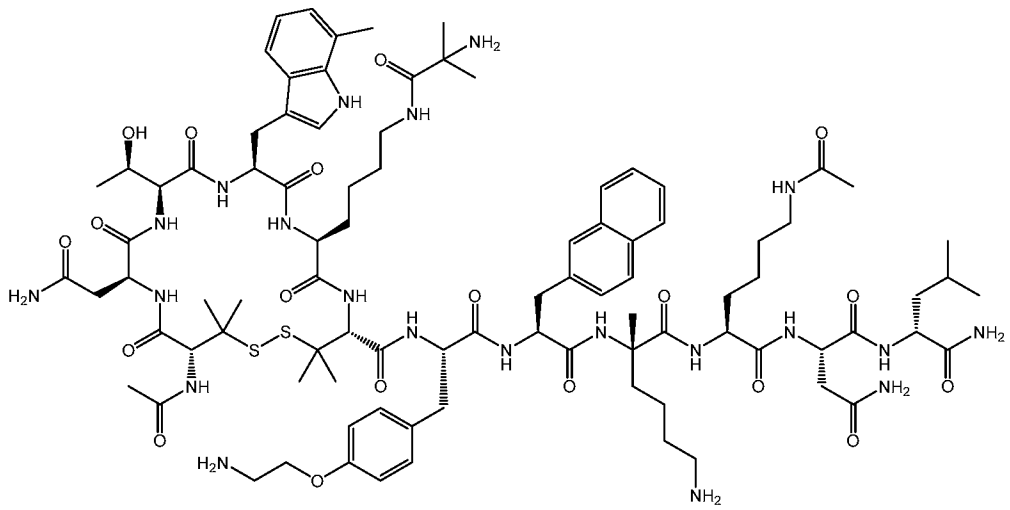


Ac-[Pen]-N-T-[W(7-Me)]-[Lys(Gly)]-[Pen]-Phe[4-(2-aminoethoxy)]-[2-Nal]-[a-MeLys]-[Lys(Ac)]-N-[(D)Leu]-NH_2 (SEQ ID NO: 320)



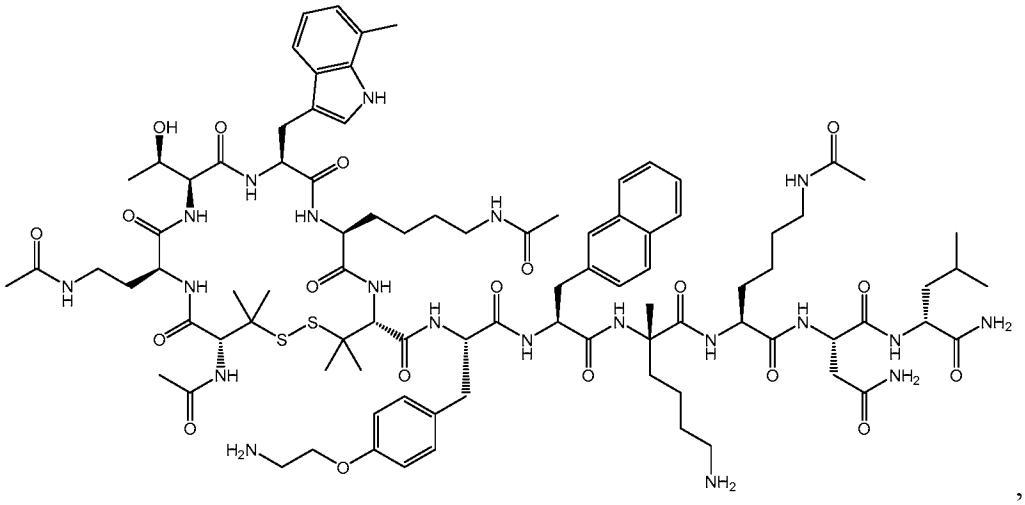
,

Ac-[Pen]-N-T-[W(7-Me)]-[Lys(Aib)]-[Pen]-Phe[4-(2-aminoethoxy)]-[2-Nal]-[a-MeLys]-[Lys(Ac)]-N-[(D)Leu]-NH_2 (SEQ ID NO: 322)



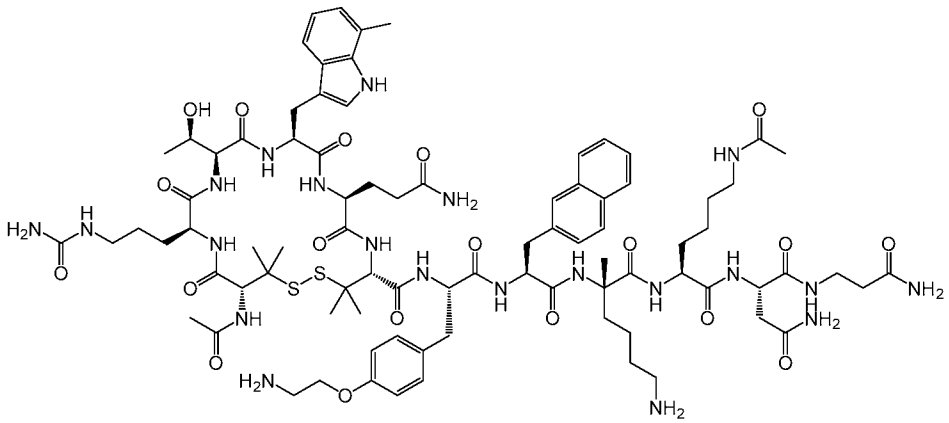
, or

Ac-[Pen]-[Dab(Ac)]-T-[W(7-Me)]-[Lys(Ac)]-[Pen]-Phe[4-(2-aminoethoxy)]-[2-Nal]-[a-MeLys]-[Lys(Ac)]-N-[(D)Leu]-NH_2 (SEQ ID NO: 335)



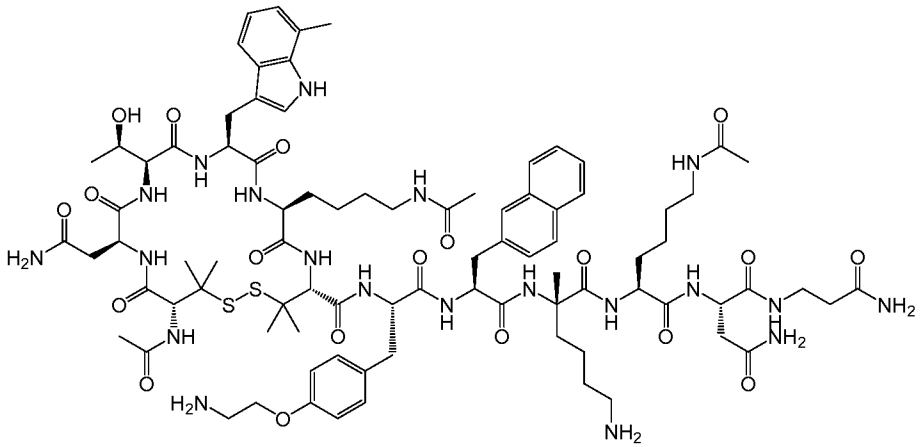
and wherein the peptide inhibitor is cyclized via a Pen-Pen disulfide bond;
or a pharmaceutically acceptable salt or solvate thereof.

69. The peptide inhibitor of claim 1, wherein the peptide inhibitor comprises or is: Ac-[Pen]-[Cit]-T-[W(7-Me)]-Q-[Pen]-Phe[4-(2-aminoethoxy)]-[2-Nal]-[a-MeLys]-[Lys(Ac)]-N-[bA]-NH_2 (Seq. ID. No. 238)



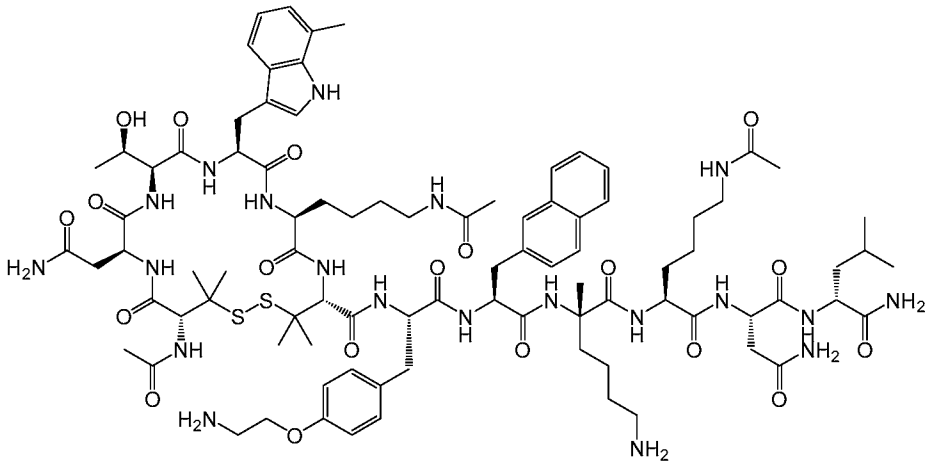
wherein the peptide inhibitor is cyclized via a Pen-Pen disulfide bond; or a pharmaceutically acceptable salt or solvate thereof.

70. The peptide inhibitor of claim 1, wherein the peptide inhibitor comprises or is: Ac-[Pen]-NT-[W(7-Me)]-[Lys(Ac)]-[Pen]-Phe[4-(2-aminoethoxy)]-[2-Nal]-[a-MeLys]-[Lys(Ac)]-N-[bA]-NH_2 (Seq. ID. No. 242)



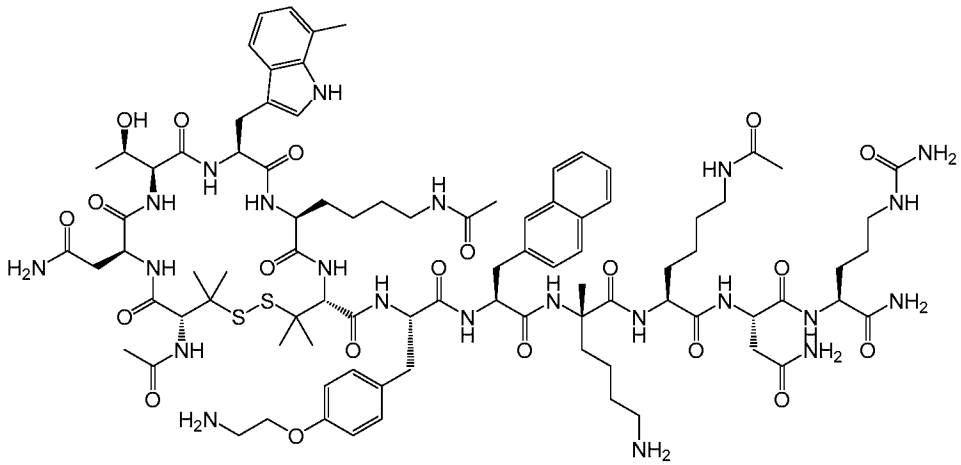
wherein the peptide inhibitor is cyclized via a Pen-Pen disulfide bond; or a pharmaceutically acceptable salt or solvate thereof.

71. The peptide inhibitor of claim 1, wherein the peptide inhibitor comprises or is: Ac-[Pen]-NT-[W(7-Me)]-[Lys(Ac)]-[Pen]-Phe[4-(2-aminoethoxy)]-[2-Nal]-[a-MeLys]-[Lys(Ac)]-N-[(D)Leu]-NH_2 (Seq. ID. No. 245)



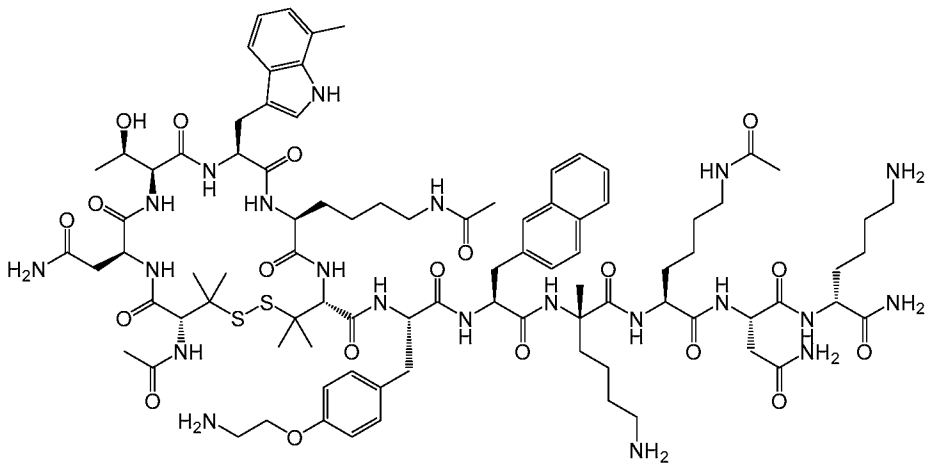
wherein the peptide inhibitor is cyclized via a Pen-Pen disulfide bond; or a pharmaceutically acceptable salt or solvate thereof.

72. The peptide inhibitor of claim 1, wherein the peptide inhibitor comprises or is: Ac-[Pen]-NT-[W(7-Me)]-[Lys(Ac)]-[Pen]-Phe[4-(2-aminoethoxy)]-[2-Nal]-[a-MeLys]-[Lys(Ac)]-N-[Cit]-NH_2 (Seq. ID. No. 249)



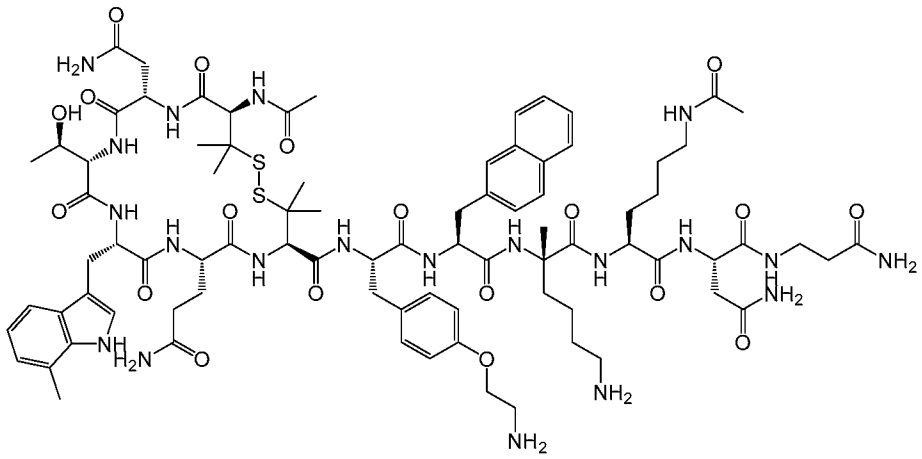
wherein the peptide inhibitor is cyclized via a Pen-Pen disulfide bond; or a pharmaceutically acceptable salt or solvate thereof.

73. The peptide inhibitor of claim 1, wherein the peptide inhibitor comprises or is Ac-[Pen]-NT-[W(7-Me)]-[Lys(Ac)]-[Pen]-Phe[4-(2-aminoethoxy)]-[2-Nal]-[a-MeLys]-[Lys(Ac)]-N-[(D)Lys]-NH_2 (Seq. ID. No. 252)



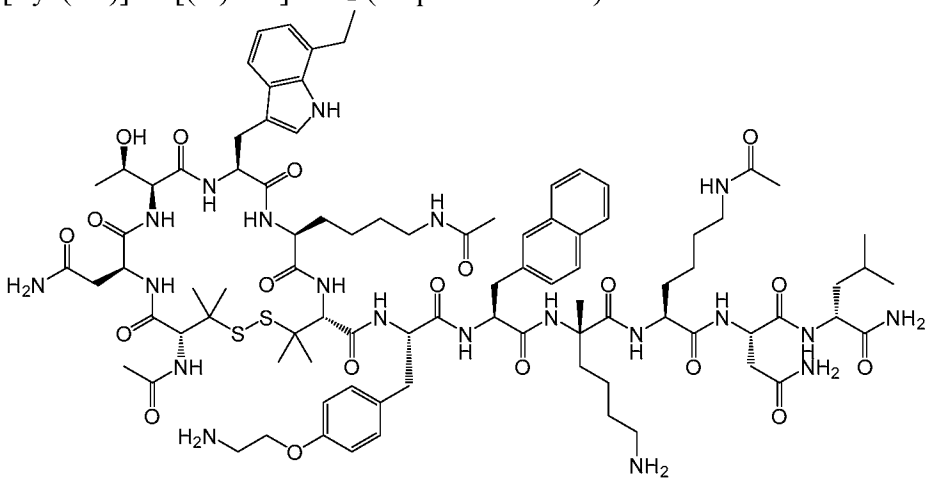
wherein the peptide inhibitor is cyclized via a Pen-Pen disulfide bond; or a pharmaceutically acceptable salt or solvate thereof.

74. The peptide inhibitor of claim 1, wherein the peptide inhibitor comprises or is: Ac-[Pen]-NT-[W(7-Me)]-Q-[Pen]-Phe[4-(2-aminoethoxy)]-[2-Nal]-[a-MeLys]-[Lys(Ac)]-N-[bA]-NH_2 (Seq. ID. No. 267)



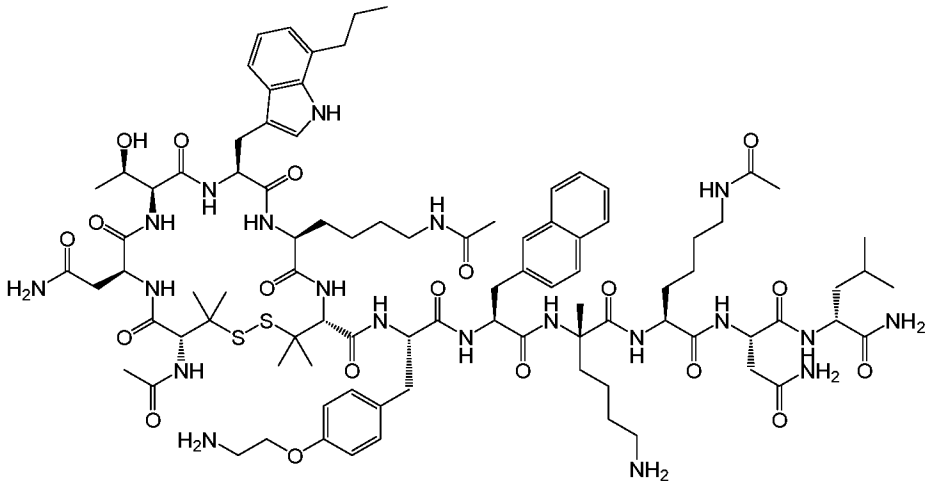
wherein the peptide inhibitor is cyclized via a Pen-Pen disulfide bond; or a pharmaceutically acceptable salt or solvate thereof.

75. The peptide inhibitor of claim 1, wherein the peptide inhibitor comprises or is: Ac-[Pen]-N-T-[W(7-Et)]-[Lys(Ac)]-[Pen]-Phe[4-(2-aminoethoxy)]-[2-Nal]-[a-MeLys]-[Lys(Ac)]-N-[(D)Leu]-NH_2 (Seq. ID. No. 284)



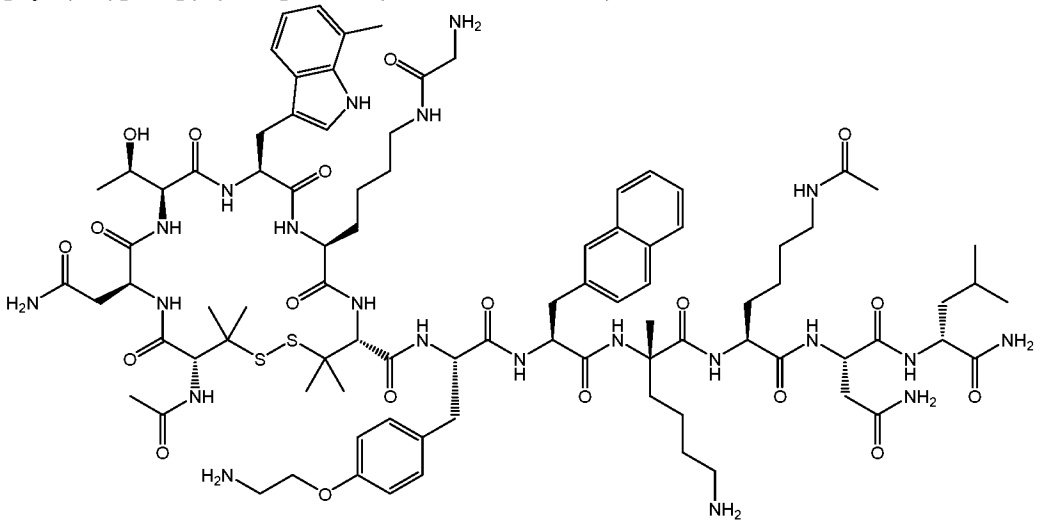
wherein the peptide inhibitor is cyclized via a Pen-Pen disulfide bond; or a pharmaceutically acceptable salt or solvate thereof.

76. The peptide inhibitor of claim 1, wherein the peptide inhibitor comprises or is: Ac-[Pen]-N-T-[W(7-n-Pr)]-[Lys(Ac)]-[Pen]-Phe[4-(2-aminoethoxy)]-[2-Nal]-[a-MeLys]-[Lys(Ac)]-N-[(D)Leu]-NH_2 (Seq. ID. No. 285)



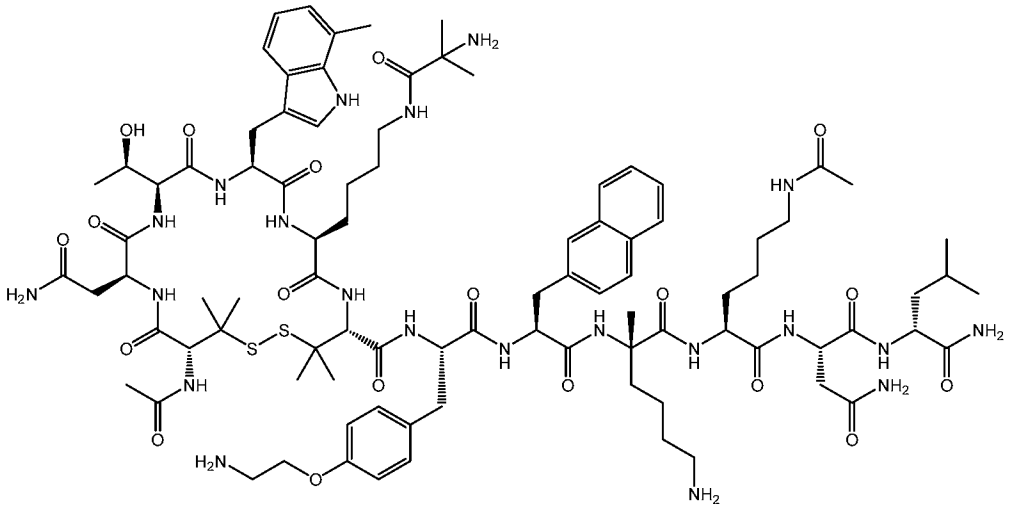
wherein the peptide inhibitor is cyclized via a Pen-Pen disulfide bond; or a pharmaceutically acceptable salt or solvate thereof.

77. The peptide inhibitor of claim 1, wherein the peptide inhibitor comprises or is: Ac-[Pen]-N-T-[W(7-Me)]-[Lys(Gly)]-[Pen]-Phe[4-(2-aminoethoxy)]-[2-Nal]-[a-MeLys]-[Lys(Ac)]-N-[(D)Leu]-NH_2 (SEQ ID NO: 320)



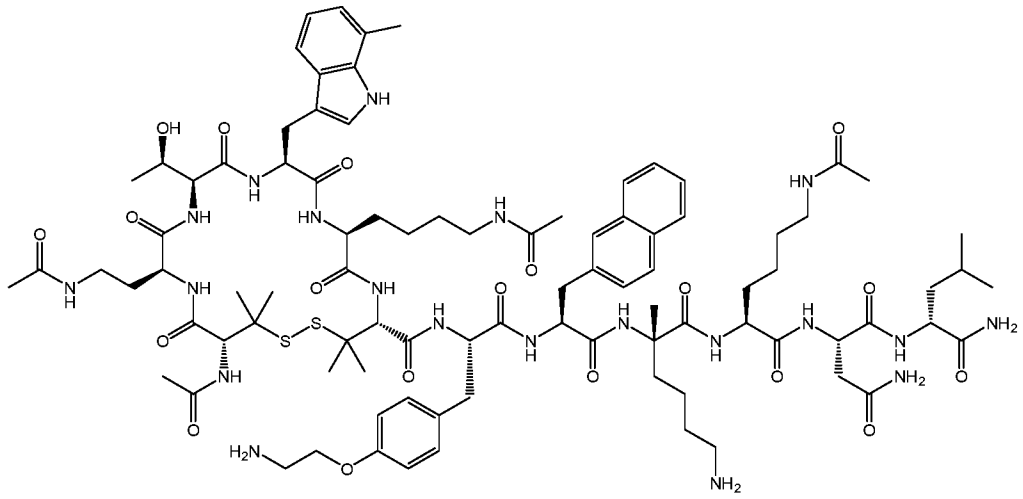
wherein the peptide inhibitor is cyclized via a Pen-Pen disulfide bond; or a pharmaceutically acceptable salt or solvate thereof.

78. The peptide inhibitor of claim 1, wherein the peptide inhibitor comprises or is: Ac-[Pen]-N-T-[W(7-Me)]-[Lys(Aib)]-[Pen]-Phe[4-(2-aminoethoxy)]-[2-Nal]-[a-MeLys]-[Lys(Ac)]-N-[(D)Leu]-NH_2 (SEQ ID NO: 322)



wherein the peptide inhibitor is cyclized via a Pen-Pen disulfide bond; or a pharmaceutically acceptable salt or solvate thereof.

79. The peptide inhibitor of claim 1, wherein the peptide inhibitor comprises or is: Ac-[Pen]-[Dab(Ac)]-T-[W(7-Me)]-[Lys(Ac)]-[Pen]-Phe[4-(2-aminoethoxy)]-[2-Nal]-[a-MeLys]-[Lys(Ac)]-N-[(D)Leu]-NH_2 (SEQ ID NO: 335)



wherein the peptide inhibitor is cyclized via a Pen-Pen disulfide bond; or a pharmaceutically acceptable salt or solvate thereof.

80. The peptide inhibitor of claim 1, wherein the peptide inhibitor comprises or is: Ac-[(D)Arg]-Abu-Q-T-[W(5-F)]-Q-[Cys]-Phe[4-(2-aminoethoxy)]-[2-Nal]-[THP]-E-N-[bA]-NH_2
(SEQ ID NO: 364).

81. A peptide inhibitor of an interleukin-23 receptor, or a pharmaceutically acceptable salt or solvate thereof, wherein the peptide inhibitor comprises an amino acid sequence of Formula (I):

X7-X8-X9-X10-X11 (I)

wherein

X7 is unsubstituted Trp, or Trp substituted with cyano, halo, alkyl, haloalkyl, hydroxy, or alkoxy;

X8 is Gln, alpha-MeLys, alpha-MeLeu, alpha-MeLys(Ac), beta-homoGln, Cit, Glu, Phe, Asn, Thr, Val, Aib, alpha-MeGln, alpha-MeAsn, Lys(Ac), Dab(Ac), Dap(Ac), homo-Lys(Ac), 1-Nal, 2-Nal, or Trp;

X9 is Abu, Cys, (D)Cys, alpha-MeCys, (D)Pen, Pen or Pen(sulfoxide);

X10 is unsubstituted Phe, or Phe substituted with halo, alkyl, haloalkyl, hydroxy, alkoxy, carboxy, carboxamido, 2-aminoethoxy, or 2-acetylaminoethoxy; and

X11 is 2-Nal, Phe(2-Me), Phe(3-Me), Phe(4-Me), Phe(3,4-dimethoxy), 1-Nal, unsubstituted Trp, or Trp substituted with cyano, halo, alkyl, haloalkyl, hydroxy, or alkoxy;

and

provided that

i) at least one of X7 and X11 is Trp substituted with cyano, halo, alkyl, haloalkyl, hydroxy, or alkoxy;

ii) X7 is other than 5-F substituted Trp;

iii) when X7 is unsubstituted Trp, or Trp substituted with 1-Me, 5-OH or 6-Cl; then X9 is other than Cys; and

iv) the compound is other than

Ac-[Pen]-NT-[W(5-Cl)]-Gln-[Pen]-[Phe[4-(2-aminoethoxy)]-[2-Nal]-[α-MeLeu]-[Lys(Ac)]-NN-NH_2 (SEQ ID NO: 1);

Ac-[Pen]-NT-[W(6-Cl)-Gln-[Pen]-[Phe[4-(2-aminoethoxy)]-[2-Nal]-[α-MeLeu]-[Lys(Ac)]-NN-NH_2 (SEQ ID NO: 2);

Ac-[Pen]-NT-[W(6-F)]-Gln-[Pen]-[Phe[4-(2-aminoethoxy)]-[2-Nal]-[α-MeLeu]-[Lys(Ac)]-NN-NH_2 (SEQ ID NO: 3);

Ac-[Pen]-NT-[W(4-OMe)]-Gln-[Pen]-[Phe[4-(2-aminoethoxy)]-[2-Nal]-[α-MeLeu]-[Lys(Ac)]-NN-NH_2 (SEQ ID NO: 4);

Ac-[Pen]-NT-[W(6-Me)]-Gln-[Pen]-[Phe[4-(2-aminoethoxy)]-[2-Nal]-[α-MeLeu]-[Lys(Ac)]-NN-NH_2 (SEQ ID NO: 5);

Ac-[Pen]-NT-[W(7-Me)]-Gln-[Pen]-[Phe[4-(2-aminoethoxy)]-[2-Nal]-[α-MeLeu]-[Lys(Ac)]-NN-NH_2 (SEQ ID NO: 6);

Ac-[Pen]-NT-[W(5-F)]-Gln-[Pen]-[Phe[4-(2-aminoethoxy)]-[2-Nal]-[α-MeLeu]-[Lys(Ac)]-NN-NH_2 (SEQ ID NO: 7);

Ac-[Pen]-NT-[W(7-F)]-Gln-[Pen]-[Phe[4-(2-aminoethoxy)]-[2-Nal]-[α-MeLeu]-[Lys(Ac)]-NN-NH_2 (SEQ ID NO: 8);

Ac-[Pen]-NT-[W(5-OMe)]-Gln-[Pen]-[Phe[4-(2-aminoethoxy)]-[2-Nal]-[α-MeLeu]-[Lys(Ac)]-NN-NH_2 (SEQ ID NO: 9);

Ac-[Pen]-NT-[W(5-OH)]-Gln-[Pen]-[Phe[4-(2-aminoethoxy)]-[2-Nal]-[α-MeLeu]-[Lys(Ac)]-NN-NH_2 (SEQ ID NO: 10);

Ac-[Pen]-NT-[W(5-Br)]-Gln-[Pen]-[Phe[4-(2-aminoethoxy)]-[2-Nal]-[α-MeLeu]-[Lys(Ac)]-NN-NH_2 (SEQ ID NO: 11);

Ac-[Pen]-NTW-Gln-[Pen]-[Phe[4-(2-aminoethoxy)]-W(5-Cl)-[α-MeLeu]-[Lys(Ac)]-NN-NH_2 (SEQ ID NO: 12);

Ac-[Pen]-NTW-Gln-[Pen]-[Phe[4-(2-aminoethoxy)]-W(6-Cl)-[α-MeLeu]-[Lys(Ac)]-NN-NH_2 (SEQ ID NO: 13);

Ac-[Pen]-NTW-Gln-[Pen]-[Phe[4-(2-aminoethoxy)]-W(6-F)-[α-MeLeu]-[Lys(Ac)]-NN-NH_2 (SEQ ID NO: 14);

Ac-[Pen]-NTW-Gln-[Pen]-[Phe[4-(2-aminoethoxy)]-W(4-OMe)-[α-MeLeu]-[Lys(Ac)]-NN-NH_2 (SEQ ID NO: 15);

Ac-[Pen]-NTW-Gln-[Pen]-[Phe[4-(2-aminoethoxy)]-W(6-Me)-[α-MeLeu]-[Lys(Ac)]-NN-NH_2 (SEQ ID NO: 16);

Ac-[Pen]-NTW-Gln-[Pen]-[Phe[4-(2-aminoethoxy)]-W(7-Me)-[α-MeLeu]-[Lys(Ac)]-NN-NH_2 (SEQ ID NO: 17);

Ac-[Pen]-NTW-Gln-[Pen]-[Phe[4-(2-aminoethoxy)]-W(5-F)-[α-MeLeu]-[Lys(Ac)]-NN-NH_2 (SEQ ID NO: 18);

Ac-[Pen]-NTW-Gln-[Pen]-[Phe[4-(2-aminoethoxy)]-W(7-F)-[α-MeLeu]-[Lys(Ac)]-NN-NH_2 (SEQ ID NO: 19);

Ac-[Pen]-NTW-Gln-[Pen]-[Phe[4-(2-aminoethoxy)]-W(5-OMe)-[α-MeLeu]-[Lys(Ac)]-NN-NH_2 (SEQ ID NO: 20);

Ac-[Pen]-NTW-Gln-[Pen]-[Phe[4-(2-aminoethoxy)]-W(5-OH)-[α-MeLeu]-[Lys(Ac)]-NN-NH_2 (SEQ ID NO: 21);

Ac-[Pen]-NTW-Gln-[Pen]-[Phe[4-(2-aminoethoxy)]-W(5-Br)-[α-MeLeu]-[Lys(Ac)]-NN-NH_2 (SEQ ID NO: 22);

Ac-[(D)Arg]-[Abu]-QT-[W(7-Me)]-QC-[Phe[4-(2-aminoethoxy)]-[2-Nal]-[THP]-ENN-NH_2 (SEQ ID NO: 27);

Ac-[Abu]-QT-[W(7-Me)]-QC-[Phe[4-(2-aminoethoxy)]-[2-Nal]-[THP]-ENN-NH_2 (SEQ ID NO: 28);

Ac-[(D)Arg]-[Abu]-QT-[W(7-Me)]-QC-[Phe[4-(2-aminoethoxy)]-[2-Nal]-[THP]-[Lys(Ac)]-NN-NH_2 (SEQ ID NO: 29); or

Ac-[Abu]-QT-[W(7-Me)]-QC-[Phe[4-(2-aminoethoxy)]-[2-Nal]-[THP]-[Lys(Ac)]-NN-NH_2 (SEQ ID NO: 30);

wherein Pen-Pen form a disulfide bond, or Abu-Cys form a thioether bond;

and

wherein the peptide inhibitor inhibits the binding of an interleukin-23 (IL-23) to an IL-23 receptor.

82. The peptide inhibitor or pharmaceutically acceptable salt or solvate thereof of claim 81, wherein the peptide inhibitor comprises an amino acid sequence of Formula (II'):

X7-X8-X9-X10-X11-X12-X13-X14-X15 (II')

and wherein

X12 is 4-amino-4-carboxy-tetrahydropyran (THP), alpha-MeLys, alpha-MeLeu, alpha-MeArg, alpha-MePhe, alpha-MeLeu, alpha-MeLys, alpha-MeAsn, alpha-MeTyr, Ala, or cyclohexylAla, Lys, or Aib;

X13 is Aib, Glu, Cit, Gln, Lys(Ac), alpha-MeArg, alpha-MeGlu, alpha-MeLeu, alpha-MeLys, alpha-Me-Asn, alpha-MeLys(Ac), Dab(Ac), Dap(Ac), homo-Lys(Ac), or Lys; or

X13 is Lys, pegylated Lys, b-homoGlu, or Lys(Y2-Ac), wherein Y2 is an amino acid;

X14 is Asn, 2-Nap, Aib, Arg, Cit, Asp, Phe, Gly, Lys, Leu, Ala, (D)Ala, beta-Ala, His, Thr, n-Leu, Gln, Ser, (D)Ser, Tic, Trp, alpha-MeGln, alpha-MeAsn, alpha-MeLys(Ac), Dab(Ac), Dap(Ac), homo-Lys(Ac), or Lys(Ac);

X15 is Asn, Leu, Aib, (D)Leu, beta-Ala, Cit, Gln, Asp, alpha-MeGln, alpha-MeAsn, Lys(Ac), (D)Lys, alpha-MeLys(Ac), Dab(Ac), Dap(Ac), homo-Lys(Ac), or absent.

83. A peptide inhibitor of an interleukin-23 receptor, or a pharmaceutically acceptable salt or solvate thereof, wherein the peptide inhibitor comprises an amino acid sequence of Formula (II'):

X7-X8-X9-X10-X11-X12-X13-X14-X15 (II')

wherein

X7 is unsubstituted Trp, or Trp substituted with cyano, halo, alkyl, haloalkyl, hydroxy, or alkoxy;

X8 is Gln, alpha-MeLys, alpha-MeLeu, alpha-MeLys(Ac), beta-homoGln, Cit, Glu, Phe, Asn, Thr, Val, Aib, alpha-MeGln, alpha-MeAsn, Lys(Ac), Dab(Ac), Dap(Ac), homo-Lys(Ac), 1-Nal, 2-Nal, or Trp;

X9 is Abu, Cys, (D)Cys, alpha-MeCys, (D)Pen, Pen or Pen(sulfoxide);

X10 is unsubstituted Phe, or Phe substituted with halo, alkyl, haloalkyl, hydroxy, alkoxy, carboxy, carboxamido, 2-aminoethoxy, 2-acetylaminoethoxy, 2-Nal, His, His_3Bom, or His_Bzl;

X11 is 2-Nal, Phe(2-Me), Phe(3-Me), Phe(4-Me), Phe(3,4-dimethoxy), 1-Nal, unsubstituted Trp, or Trp substituted with cyano, halo, alkyl, haloalkyl, hydroxy, or alkoxy;

X12 is 4-amino-4-carboxy-tetrahydropyran (THP), alpha-MeLys, alpha-MeLeu, alpha-MeArg, alpha-MePhe, alpha-MeLeu, alpha-MeLys, alpha-MeAsn, alpha-MeTyr, Ala, or cyclohexylAla, Lys, Aib, Achc, Spiral-Pip, DiethylGly, Acbc, or a-MeOrn;

X13 is Aib, Glu, Cit, Gln, Lys(Ac), alpha-MeArg, alpha-MeGlu, alpha-MeLeu, alpha-MeLys, alpha-Me-Asn, alpha-MeLys(Ac), Dab(Ac), Dap(Ac), homo-Lys(Ac), Lys, or Gly; or X13 is Lys, pegylated Lys, b-homoGlu, or Lys(Y2-Ac), wherein Y2 is an amino acid;

X14 is Asn, 2-Nap, Aib, Arg, Cit, Asp, Phe, Gly, Lys, Leu, Ala, (D)Ala, beta-Ala, His, Thr, n-Leu, Gln, Ser, (D)Ser, Tic, Trp, alpha-MeGln, alpha-MeAsn, alpha-MeLys(Ac), Dab(Ac), Dap(Ac), homo-Lys(Ac), Lys(Ac), (D)Leu, Pro, (D)Pro, (D)Phe, (D)His, Ile, (D)Thr, Gly, N-MeAla, Sarc, or aMeLeu;

X15 Leu, (D)Leu, beta-Ala, Cit, (D)Lys Arg, NMeArg, bhPhe, His, Val, (D)Val, (D)Lys, Pro, (D)Pro, Ile, (D)Arg, (D)Phe, (D)Tyr, Ser, (D)Ser, Thr, (D)Thr, N-MeAla, Y, a-MePhe, Sarc, Gly, Ala, (D)Tyr, (D)2-Nal, (D)Asn, or absent;

and

provided that at least one of X7 and X11 is Trp substituted with cyano, halo, alkyl, haloalkyl, hydroxy, or alkoxy; or the peptide inhibitor is

SEQ ID NO: 264	Ac-[Pen]-NT-[W(7-Me)]-[Cit]-[Pen]-Phe[4-(2-aminoethoxy)]-[2-Nal]-[a-MeLys]-[Lys(Ac)]-N-[Aib]-NH_2

or

SEQ ID NO: 340	Ac-[Pen]-N-T-[W(7-Me)]-[Cit]-[Pen]-Phe[4-(2-aminoethoxy)]-[2-Nal]-[a-MeLys]-[Lys(Ac)]-N-[Aib]-[bA]-NH_2

.

84. The peptide inhibitor or pharmaceutically acceptable salt or solvate thereof of claim 83, wherein the peptide inhibitor comprises or is any one of the following or a pharmaceutically acceptable salt or solvate thereof:

SEQ ID NO:	**Sequence***
210	Ac-[Pen]-NT-[W(7-Me)]-Q-[Pen]-Phe[4-(2-aminoethoxy)]-[2-Nal]-[a-MeLeu]-[Lys(Ac)]-[(D)Leu]-[bA]-NH_2
211	Ac-[Pen]-NT-[W(7-Me)]-Q-[Pen]-Phe[4-(2-aminoethoxy)]-[2-Nal]-[a-MeLeu]-[Lys(Ac)]-P-[bA]-NH_2
212	Ac-[Pen]-NT-[W(7-Me)]-Q-[Pen]-Phe[4-(2-aminoethoxy)]-[2-Nal]-[a-MeLeu]-[Lys(Ac)]-[(D)Pro]-[bA]-NH_2
213	Ac-[Pen]-NT-[W(7-Me)]-Q-[Pen]-Phe[4-(2-aminoethoxy)]-[2-Nal]-[a-MeLeu]-[Lys(Ac)]-[(D)Phe]-[bA]-NH_2
215	Ac-[Pen]-NT-[W(7-Me)]-Q-[Pen]-Phe[4-(2-aminoethoxy)]-[2-Nal]-[a-MeLeu]-[Lys(Ac)]-[(D)His]-[bA]-NH_2
216	Ac-[Pen]-NT-[W(7-Me)]-Q-[Pen]-Phe[4-(2-aminoethoxy)]-[2-Nal]-[a-MeLeu]-[Lys(Ac)]-I-[bA]-NH_2
218	Ac-[Pen]-NT-[W(7-Me)]-Q-[Pen]-Phe[4-(2-aminoethoxy)]-[2-Nal]-[a-MeLeu]-[Lys(Ac)]-[(D)Thr]-[bA]-NH_2
219	Ac-[Pen]-NT-[W(7-Me)]-Q-[Pen]-Phe[4-(2-aminoethoxy)]-[2-Nal]-[a-MeLeu]-G-P-[bA]-NH_2

SEQ ID NO:	Sequence*
220	Ac-[Pen]-NT-[W(7-Me)]-Q-[Pen]-Phe[4-(2-aminoethoxy)]-[2-Nal]-[a-MeLeu]-G-[(D)Pro]-[bA]-NH_2
223	Ac-[Pen]-NT-[W(7-Me)]-Q-[Pen]-Phe[4-(2-aminoethoxy)]-[2-Nal]-[a-MeLeu]-[Lys(Ac)]-[N-MeAla]-[bA]-NH_2
224	Ac-[Pen]-NT-[W(7-Me)]-Q-[Pen]-Phe[4-(2-aminoethoxy)]-[2-Nal]-[a-MeLeu]-[Lys(Ac)]-[Sarc]-[bA]-NH_2
225	Ac-[Pen]-NT-[W(7-Me)]-Q-[Pen]-Phe[4-(2-aminoethoxy)]-[2-Nal]-[a-MeLeu]-[Lys(Ac)]-[a-MeLeu]-[bA]-NH_2
243	Ac-[Pen]-NT-[W(7-Me)]-[Lys(Ac)]-[Pen]-Phe[4-(2-aminoethoxy)]-[2-Nal]-[a-MeLys]-[Lys(Ac)]-N-R-NH_2
246	Ac-[Pen]-NT-[W(7-Me)]-[Lys(Ac)]-[Pen]-Phe[4-(2-aminoethoxy)]-[2-Nal]-[a-MeLys]-[Lys(Ac)]-N-[NMeArg]-NH_2
247	Ac-[Pen]-NT-[W(7-Me)]-[Lys(Ac)]-[Pen]-Phe[4-(2-aminoethoxy)]-[2-Nal]-[a-MeLys]-[Lys(Ac)]-N-[bhPhe]-NH_2
248	Ac-[Pen]-NT-[W(7-Me)]-[Lys(Ac)]-[Pen]-Phe[4-(2-aminoethoxy)]-[2-Nal]-[a-MeLys]-[Lys(Ac)]-N-H-NH_2
250	Ac-[Pen]-NT-[W(7-Me)]-[Lys(Ac)]-[Pen]-Phe[4-(2-aminoethoxy)]-[2-Nal]-[a-MeLys]-[Lys(Ac)]-N-V-NH_2
251	Ac-[Pen]-NT-[W(7-Me)]-[Lys(Ac)]-[Pen]-Phe[4-(2-aminoethoxy)]-[2-Nal]-[a-MeLys]-[Lys(Ac)]-N-[(D)Val]-NH_2
252	Ac-[Pen]-NT-[W(7-Me)]-[Lys(Ac)]-[Pen]-Phe[4-(2-aminoethoxy)]-[2-Nal]-[a-MeLys]-[Lys(Ac)]-N-[(D)Lys]-NH_2
253	Ac-[Pen]-NT-[W(7-Me)]-[Lys(Ac)]-[Pen]-Phe[4-(2-aminoethoxy)]-[2-Nal]-[a-MeLys]-[Lys(Ac)]-N-P-NH_2
254	Ac-[Pen]-NT-[W(7-Me)]-[Lys(Ac)]-[Pen]-Phe[4-(2-aminoethoxy)]-[2-Nal]-[a-MeLys]-[Lys(Ac)]-N-[(D)Pro]-NH_2
255	Ac-[Pen]-NT-[W(7-Me)]-[Lys(Ac)]-[Pen]-Phe[4-(2-aminoethoxy)]-[2-Nal]-[a-MeLys]-[Lys(Ac)]-N-I-NH_2
256	Ac-[Pen]-NT-[W(7-Me)]-[Cit]-[Pen]-Phe[4-(2-aminoethoxy)]-[2-Nal]-[a-MeLys]-[Lys(Ac)]-N-[(D)Arg]-NH_2

SEQ ID NO:	Sequence*
257	Ac-[Pen]-NT-[W(7-Me)]-[Cit]-[Pen]-Phe[4-(2-aminoethoxy)]-[2-Nal]-[a-MeLys]-[Lys(Ac)]-N-[(D)Phe]-NH_2
258	Ac-[Pen]-NT-[W(7-Me)]-[Lys(Ac)]-[Pen]-Phe[4-(2-aminoethoxy)]-[2-Nal]-[a-MeLys]-[Lys(Ac)]-N-[(D)Phe]-NH_2
259	Ac-[Pen]-NT-[W(7-Me)]-[Cit]-[Pen]-Phe[4-(2-aminoethoxy)]-[2-Nal]-[a-MeLys]-[Lys(Ac)]-N-[(D)Tyr]-NH_2
260	Ac-[Pen]-NT-[W(7-Me)]-[Cit]-[Pen]-Phe[4-(2-aminoethoxy)]-[2-Nal]-[a-MeLys]-[Lys(Ac)]-N-S-NH_2
261	Ac-[Pen]-NT-[W(7-Me)]-[Cit]-[Pen]-Phe[4-(2-aminoethoxy)]-[2-Nal]-[a-MeLys]-[Lys(Ac)]-N-[(D)Ser]-NH_2
262	Ac-[Pen]-NT-[W(7-Me)]-[Cit]-[Pen]-Phe[4-(2-aminoethoxy)]-[2-Nal]-[a-MeLys]-[Lys(Ac)]-NT-NH_2
263	Ac-[Pen]-NT-[W(7-Me)]-[Cit]-[Pen]-Phe[4-(2-aminoethoxy)]-[2-Nal]-[a-MeLys]-[Lys(Ac)]-N-[(D)Thr]-NH_2
265	Ac-[Pen]-NT-[W(7-Me)]-[Cit]-[Pen]-Phe[4-(2-aminoethoxy)]-[2-Nal]-[a-MeLys]-[Lys(Ac)]-[N-MeAla]-NH_2
266	Ac-[Pen]-NT-[W(7-Me)]-[Cit]-[Pen]-Phe[4-(2-aminoethoxy)]-[2-Nal]-[a-MeLys]-[Lys(Ac)]-N-Y-NH_2
274	Ac-[Pen]-N-T-[W(7-Me)]-Q-[Pen]-Phe[4-(2-aminoethoxy)]-[2-Nal]-[Achc]-[Lys(Ac)]-N-[bA]-NH_2
275	Ac-[Pen]-N-T-[W(7-Me)]-Q-[Pen]-Phe[4-(2-aminoethoxy)]-[2-Nal]-[Spiral_Pip]-[Lys(Ac)]-N-[bA]-NH_2
276	Ac-[Pen]-N-T-[W(7-Me)]-Q-[Pen]-Phe[4-(2-aminoethoxy)]-[2-Nal]-[DiethylGly]-[Lys(Ac)]-N-[bA]-NH_2
277	Ac-[Pen]-N-T-[W(7-Me)]-Q-[Pen]-Phe[4-(2-aminoethoxy)]-[2-Nal]-[Acbc]-[Lys(Ac)]-N-[bA]-NH_2
278	Ac-[Pen]-N-T-[W(7-Me)]-Q-[Pen]-Phe[4-(2-aminoethoxy)]-[2-Nal]-[a-MeOrn]-[Lys(Ac)]-N-[bA]-NH_2
289	Ac-[Pen]-N-T-[W(7-Me)]-[Lys(Ac)]-[Pen]-[2-Nal]-[2-Nal]-[a-MeLys]-[Lys(Ac)]-N-[(D)Leu]-NH_2

SEQ ID NO:	Sequence*
290	Ac-[Pen]-N-T-[W(7-Me)]-[Lys(Ac)]-[Pen]-H-[2-Nal]-[a-MeLys]-[Lys(Ac)]-N-[(D)Leu]-NH_2
291	Ac-[Pen]-N-T-[W(7-Me)]-[Lys(Ac)]-[Pen]-[His_3Bom]-[2-Nal]-[a-MeLys]-[Lys(Ac)]-N-[(D)Leu]-NH_2
292	Ac-[Pen]-N-T-[W(7-Me)]-[Lys(Ac)]-[Pen]-[His_Bzl]-[2-Nal]-[a-MeLys]-[Lys(Ac)]-N-[(D)Leu]-NH_2
293	Ac-[Pen]-N-T-[W(7-Me)]-[Lys(Ac)]-[Pen]-[His_Bzl]-[2-Nal]-[a-MeLys]-[Lys(Ac)]-N-[(D)Leu]-NH_2
323	Ac-[(D)Arg]-[Abu]-Q-T-[W(7-Me)]-[Lys(Ac)]-[Cys]-Phe[4-(2-aminoethoxy)]-[2-Nal]-[a-MeLys]-[Lys(Ac)]-N-[(D)Lys]-[Sarc]-NH_2;
326	Ac-[(D)Arg]-[Abu]-Q-T-[W(7-Me)]-[Lys(Ac)]-[Cys]-Phe[4-(2-aminoethoxy)]-[2-Nal]-[a-MeLys]-[Lys(Ac)]-N-NH_2;
327	Ac-[(D)Arg]-[Abu]-Q-T-[W(7-Me)]-[Lys(Ac)]-[Cys]-Phe[4-(2-aminoethoxy)]-[2-Nal]-[a-MeLys]-[Lys(Ac)]-N-[a-MePhe]-NH_2;
339	Ac-[Pen]-N-T-[W(7-Me)]-[Cit]-[Pen]-Phe[4-(2-aminoethoxy)]-[2-Nal]-[a-MeLys]-[Lys(Ac)]-N-[Sarc]-NH_2;
341	Ac-[Pen]-N-T-[W(7-Me)]-[Cit]-[Pen]-Phe[4-(2-aminoethoxy)]-[2-Nal]-[a-MeLys]-[Lys(Ac)]-N-[Aib]-G-NH_2;
342	Ac-[Pen]-N-T-[W(7-Me)]-[Cit]-[Pen]-Phe[4-(2-aminoethoxy)]-[2-Nal]-[a-MeLys]-[Lys(Ac)]-N-[Aib]-A-NH_2;
343	Ac-[Pen]-N-T-[W(7-Me)]-[Cit]-[Pen]-Phe[4-(2-aminoethoxy)]-[2-Nal]-[a-MeLys]-[Lys(Ac)]-N-[Aib]-R-NH_2;
344	Ac-[Pen]-N-T-[W(7-Me)]-[Cit]-[Pen]-Phe[4-(2-aminoethoxy)]-[2-Nal]-[a-MeLys]-[Lys(Ac)]-N-[Aib]-[(D)Lys]-NH_2;
345	Ac-[Pen]-N-T-[W(7-Me)]-[Cit]-[Pen]-Phe[4-(2-aminoethoxy)]-[2-Nal]-[a-MeLys]-[Lys(Ac)]-N-[Aib]-[(D)Arg]-NH_2;
346	Ac-[Pen]-N-T-[W(7-Me)]-[Cit]-[Pen]-Phe[4-(2-aminoethoxy)]-[2-Nal]-[a-MeLys]-[Lys(Ac)]-N-[Aib]-[(D)Phe]-NH_2;

SEQ ID NO:	Sequence*
347	Ac-[Pen]-N-T-[W(7-Me)]-[Cit]-[Pen]-Phe[4-(2-aminoethoxy)]-[2-Nal]-[a-MeLys]-[Lys(Ac)]-N-[Aib]-[(D)Tyr]-NH_2;
348	Ac-[Pen]-N-T-[W(7-Me)]-[Cit]-[Pen]-Phe[4-(2-aminoethoxy)]-[2-Nal]-[a-MeLys]-[Lys(Ac)]-N-[Aib]- [(D)2-Nal]-NH_2; or
354	Ac-[Pen]-N-T-[W(7-Me)]-[Lys(Ac)]-[Pen]-Phe[4-(2-aminoethoxy)]-[2-Nal]-[a-MeLeu]-[Lys(Ac)]-N-[(D)Asn]-NH_2;
356	Ac-[Pen]-N-T-[W(7-Me)]-[Lys(Ac)]-[Pen]-Phe[4-(2-aminoethoxy)]-[2-Nal]-[a-MeLys]-[Lys(IVA)]-N-[(D)Leu]-NH_2;
357	Ac-[Pen]-N-T-[W(7-Me)]-[Lys(Ac)]-[Pen]-Phe[4-(2-aminoethoxy)]-[2-Nal]-[a-MeLys]-[Lys(cyclohexanoic)]-N-[(D)Leu]-NH_2;
358	Ac-[Pen]-N-T-[W(7-Me)]-[Lys(Ac)]-[Pen]-Phe[4-(2-aminoethoxy)]-[2-Nal]-[a-MeLys]-[Lys(octanoic)]-N-[(D)Leu]-NH_2;
359	Ac-[Pen]-N-T-[W(7-Me)]-[Lys(Ac)]-[Pen]-Phe[4-(2-aminoethoxy)]-[2-Nal]-[a-MeLys]-[Lys(C(O)CH2Ph)]-N-[(D)Leu]-NH_2;
360	Ac-[Pen]-N-T-[W(7-Me)]-[Lys(Ac)]-[Pen]-Phe[4-(2-aminoethoxy)]-[2-Nal]-[a-MeLys]-[Lys(trifluoropropionic)]-N-[(D)Leu]-NH_2; or
361	Ac-[Pen]-N-T-[W(7-Me)]-[Lys(Ac)]-[Pen]-Phe[4-(2-aminoethoxy)]-[2-Nal]-[a-MeLys]-[Lys(valeric)]-N-[(D)Leu]-NH_2

or a pharmaceutically acceptable salt or solvate thereof, wherein the peptide inhibitor or pharmaceutically acceptable salt or solvate thereof comprises a disulfide bond between two Pen residues or a thioether bond between Abu and Cys;

and

wherein the peptide inhibitor or pharmaceutically acceptable salt of solvate thereof inhibits the binding of an interleukin-23 (IL-23) to an IL-23 receptor.

85. The peptide inhibitor of claim 81, wherein the peptide inhibitor comprises or is: Ac-[(D)Arg]-[Abu]-Q-T-[W(7-Me)]-[Lys(Ac)]-[Cys]-Phe[4-(2-aminoethoxy)]-[2-Nal]-[a-MeLys]-[Lys(Ac)]-N-[(D)Lys]-[Sarc]-NH_2; (SEQ ID NO: 323); or
and wherein the peptide inhibitor is cyclized via a Abu-C thioether bond;
or a pharmaceutically acceptable salt or solvate thereof.

86. The peptide inhibitor of claim 81, wherein the peptide inhibitor comprises or is: Ac-[Pen]-NT-[W(7-Me)]-[Lys(Ac)]-[Pen]-Phe[4-(2-aminoethoxy)]-[2-Nal]-[a-MeLys]-[Lys(Ac)]-N-H-NH_2 (SEQ ID NO: 248);
Ac-[Pen]-NT-[W(7-Me)]-[Lys(Ac)]-[Pen]-Phe[4-(2-aminoethoxy)]-[2-Nal]-[a-MeLys]-[Lys(Ac)]-N-[(D)Val]-NH_2 (SEQ ID NO: 251);
Ac-[Pen]-NT-[W(7-Me)]-[Cit]-[Pen]-Phe[4-(2-aminoethoxy)]-[2-Nal]-[a-MeLys]-[Lys(Ac)]-N-[(D)Arg]-NH_2 (SEQ ID NO: 256);
Ac-[Pen]-NT-[W(7-Me)]-[Lys(Ac)]-[Pen]-Phe[4-(2-aminoethoxy)]-[2-Nal]-[a-MeLys]-[Lys(Ac)]-N-[(D)Phe]-NH_2 (SEQ ID NO: 258);
Ac-[Pen]-NT-[W(7-Me)]-[Cit]-[Pen]-Phe[4-(2-aminoethoxy)]-[2-Nal]-[a-MeLys]-[Lys(Ac)]-N-[(D)Tyr]-NH_2 (SEQ ID NO: 259);
Ac-[Pen]-NT-[W(7-Me)]-[Cit]-[Pen]-Phe[4-(2-aminoethoxy)]-[2-Nal]-[a-MeLys]-[Lys(Ac)]-N-S-NH_2 (SEQ ID NO: 260);
Ac-[Pen]-NT-[W(7-Me)]-[Cit]-[Pen]-Phe[4-(2-aminoethoxy)]-[2-Nal]-[a-MeLys]-[Lys(Ac)]-N-[(D)Ser]-NH_2 (SEQ ID NO: 261);
Ac-[Pen]-NT-[W(7-Me)]-[Cit]-[Pen]-Phe[4-(2-aminoethoxy)]-[2-Nal]-[a-MeLys]-[Lys(Ac)]-N-[(D)Thr]-NH_2 (SEQ ID NO: 263);
Ac-[Pen]-NT-[W(7-Me)]-[Cit]-[Pen]-Phe[4-(2-aminoethoxy)]-[2-Nal]-[a-MeLys]-[Lys(Ac)]-N-[Aib]-NH_2 (SEQ ID NO: 264);
Ac-[Pen]-NT-[W(7-Me)]-[Cit]-[Pen]-Phe[4-(2-aminoethoxy)]-[2-Nal]-[a-MeLys]-[Lys(Ac)]-[N-MeAla]-NH_2 (SEQ ID NO: 265);
Ac-[Pen]-N-T-[W(7-Me)]-Q-[Pen]-Phe[4-(2-aminoethoxy)]-[2-Nal]-[Achc]-[Lys(Ac)]-N-[bA]-NH_2 (SEQ ID NO: 274);
Ac-[Pen]-N-T-[W(7-Me)]-Q-[Pen]-Phe[4-(2-aminoethoxy)]-[2-Nal]-[DiethylGly]-[Lys(Ac)]-N-[bA]-NH_2 (SEQ ID NO: 276);

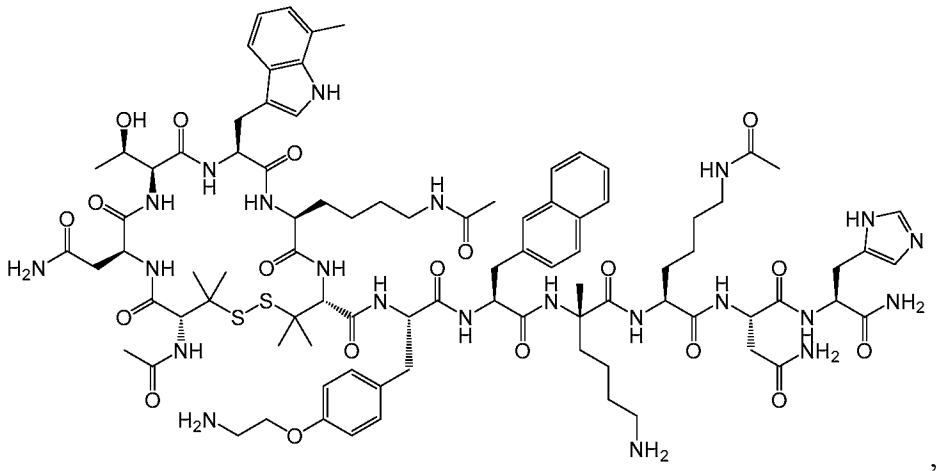
Ac-[Pen]-N-T-[W(7-Me)]-Q-[Pen]-Phe[4-(2-aminoethoxy)]-[2-Nal]-[Acbc]-[Lys(Ac)]-N-[bA]-NH_2 (SEQ ID NO: 277); or
Ac-[Pen]-N-T-[W(7-Me)]-Q-[Pen]-Phe[4-(2-aminoethoxy)]-[2-Nal]-[a-MeOrn]-[Lys(Ac)]-N-[bA]-NH_2 (SEQ ID NO: 278);
and wherein the peptide inhibitor is cyclized via a Pen-Pen disulfide bond; or via a Abu-C thioether bond;
or a pharmaceutically acceptable salt or solvate thereof.

87. The peptide inhibitor of claim 81, wherein the peptide inhibitor comprises or is:
Ac-[Pen]-NT-[W(7-Me)]-Q-[Pen]-Phe[4-(2-aminoethoxy)]-[2-Nal]-[a-MeLeu]-[Lys(Ac)]-[(D)His]-[bA]-NH_2 (SEQ ID NO: 215);
Ac-[Pen]-NT-[W(7-Me)]-[Lys(Ac)]-[Pen]-Phe[4-(2-aminoethoxy)]-[2-Nal]-[a-MeLys]-[Lys(Ac)]-N-R-NH_2 (SEQ ID NO: 243);
Ac-[Pen]-NT-[W(7-Me)]-[Lys(Ac)]-[Pen]-Phe[4-(2-aminoethoxy)]-[2-Nal]-[a-MeLys]-[Lys(Ac)]-N-[NMeArg]-NH_2 (SEQ ID NO: 246);
Ac-[Pen]-NT-[W(7-Me)]-[Lys(Ac)]-[Pen]-Phe[4-(2-aminoethoxy)]-[2-Nal]-[a-MeLys]-[Lys(Ac)]-N-[bhPhe]-NH_2 (SEQ ID NO: 247);
Ac-[Pen]-NT-[W(7-Me)]-[Lys(Ac)]-[Pen]-Phe[4-(2-aminoethoxy)]-[2-Nal]-[a-MeLys]-[Lys(Ac)]-N-V-NH_2 (SEQ ID NO: 250);
Ac-[Pen]-NT-[W(7-Me)]-[Lys(Ac)]-[Pen]-Phe[4-(2-aminoethoxy)]-[2-Nal]-[a-MeLys]-[Lys(Ac)]-N-P-NH_2 (SEQ ID NO: 253);
Ac-[Pen]-NT-[W(7-Me)]-[Lys(Ac)]-[Pen]-Phe[4-(2-aminoethoxy)]-[2-Nal]-[a-MeLys]-[Lys(Ac)]-N-[(D)Pro]-NH_2 (SEQ ID NO: 254);
Ac-[Pen]-NT-[W(7-Me)]-[Lys(Ac)]-[Pen]-Phe[4-(2-aminoethoxy)]-[2-Nal]-[a-MeLys]-[Lys(Ac)]-N-I-NH_2 (SEQ ID NO: 255);
Ac-[Pen]-NT-[W(7-Me)]-[Cit]-[Pen]-Phe[4-(2-aminoethoxy)]-[2-Nal]-[a-MeLys]-[Lys(Ac)]-N-[(D)Phe]-NH_2 (SEQ ID NO: 257);
or
Ac-[(D)Arg]-[Abu]-Q-T-[W(7-Me)]-[Lys(Ac)]-[Cys]-Phe[4-(2-aminoethoxy)]-[2-Nal]-[a-MeLys]-[Lys(Ac)]-N-[(D)Lys]-[Sarc]-NH_2; (SEQ ID NO: 323);
and wherein the peptide inhibitor is cyclized via a Pen-Pen disulfide bond; or via a Abu-C thioether bond;

or a pharmaceutically acceptable salt or solvate thereof.

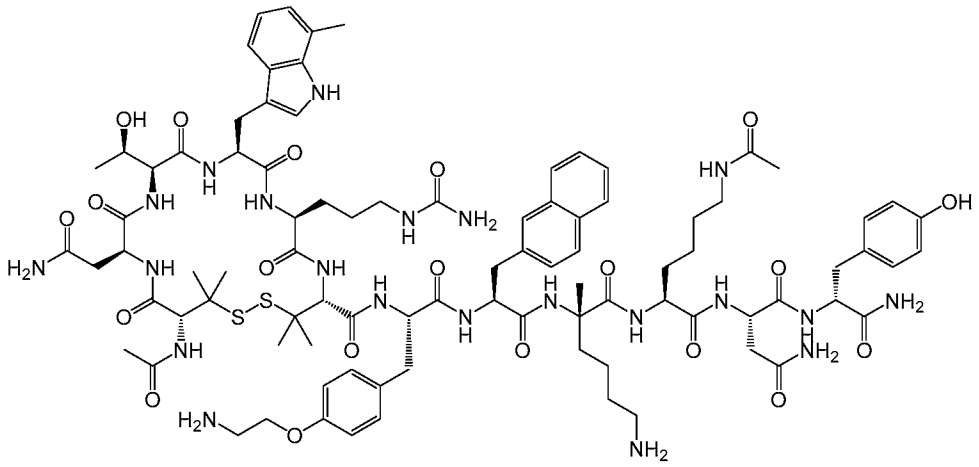
88. The peptide inhibitor of claim 83, wherein the peptide inhibitor comprises or is: Ac-[Pen]-N-T-[W(7-Me)]-[Lys(Ac)]-[Pen]-[2-Nal]-[2-Nal]-[a-MeLys]-[Lys(Ac)]-N-[(D)Leu]-NH_2 (SEQ ID NO: 289); or Ac-[Pen]-N-T-[W(7-Me)]-[Lys(Ac)]-[Pen]-H-[2-Nal]-[a-MeLys]-[Lys(Ac)]-N-[(D)Leu]-NH_2 (SEQ ID NO: 290);
and wherein the peptide inhibitor is cyclized via a Pen-Pen disulfide bond; or via a Abu-C thioether bond;
or a pharmaceutically acceptable salt or solvate thereof.

89. The peptide inhibitor of claim 81, wherein the peptide inhibitor comprises or is: Ac-[Pen]-NT-[W(7-Me)]-[Lys(Ac)]-[Pen]-Phe[4-(2-aminoethoxy)]-[2-Nal]-[a-MeLys]-[Lys(Ac)]-N-H-NH_2 (Seq. ID. No. 248)

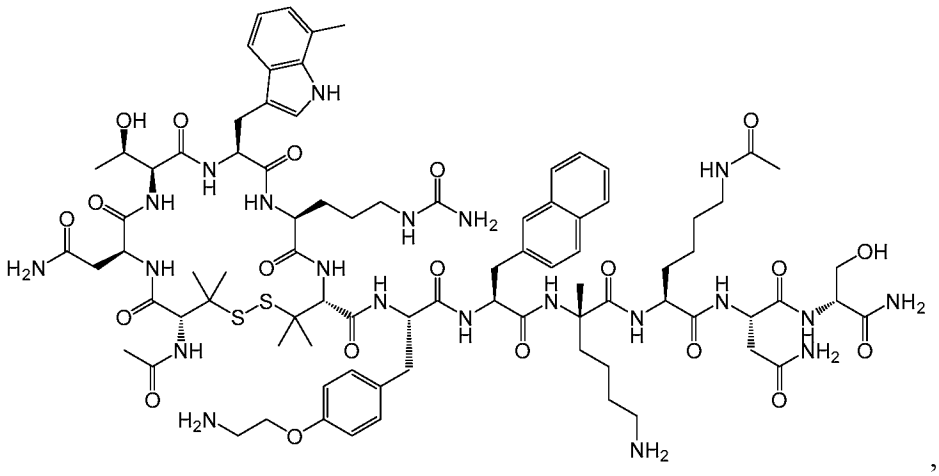


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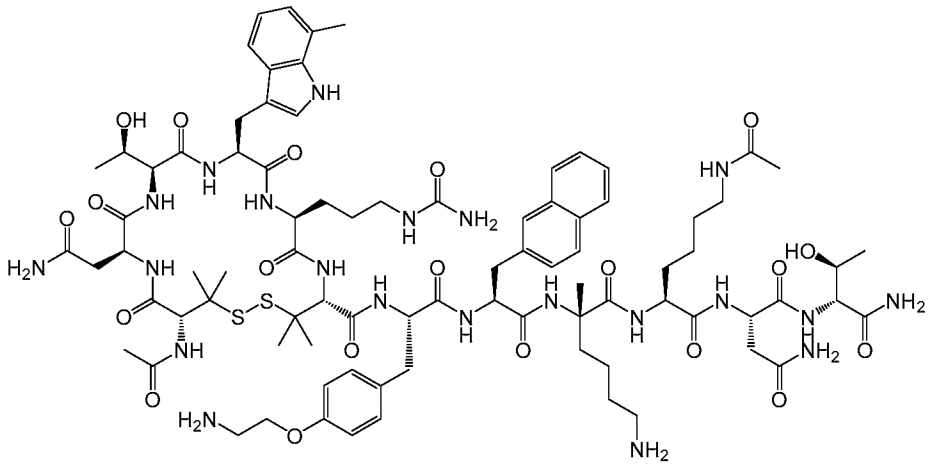
Ac-[Pen]-NT-[W(7-Me)]-[Cit]-[Pen]-Phe[4-(2-aminoethoxy)]-[2-Nal]-[a-MeLys]-[Lys(Ac)]-N-[(D)Tyr]-NH_2 (Seq. ID. No. 259)



Ac-[Pen]-NT-[W(7-Me)]-[Cit]-[Pen]-Phe[4-(2-aminoethoxy)]-[2-Nal]-[a-MeLys]-[Lys(Ac)]-N-[(D)Ser]-NH_2 (Seq. ID. No. 261)

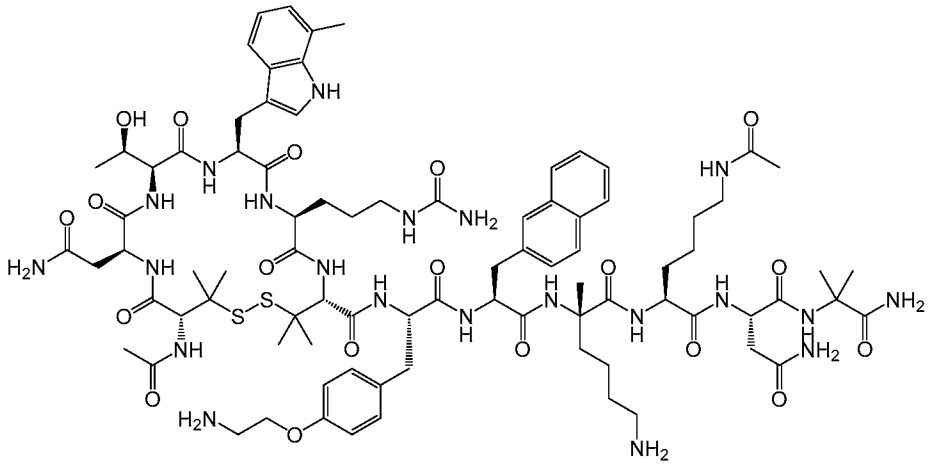


Ac-[Pen]-NT-[W(7-Me)]-[Cit]-[Pen]-Phe[4-(2-aminoethoxy)]-[2-Nal]-[a-MeLys]-[Lys(Ac)]-N-[(D)Thr]-NH_2 (Seq. ID. No. 263)



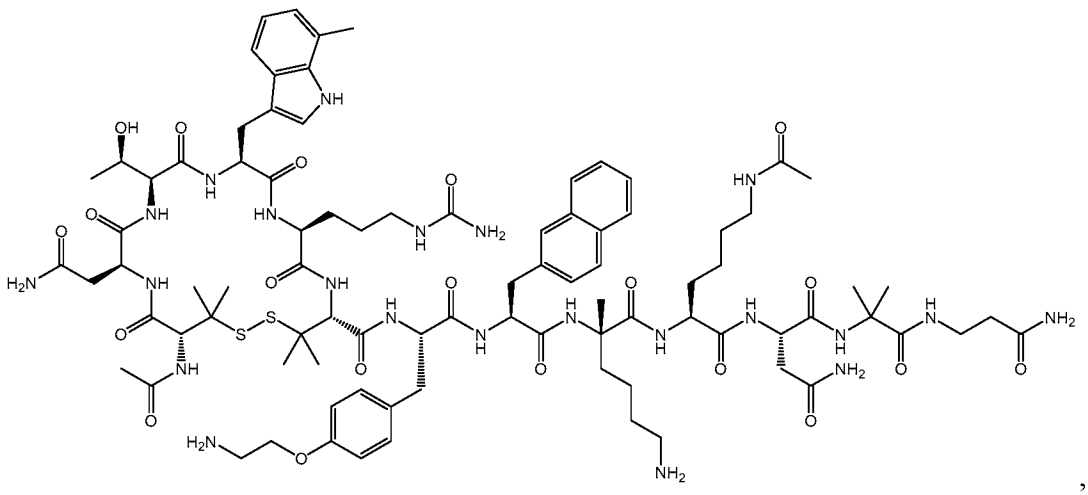
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Ac-[Pen]-NT-[W(7-Me)]-[Cit]-[Pen]-Phe[4-(2-aminoethoxy)]-[2-Nal]-[a-MeLys]-[Lys(Ac)]-N-[Aib]-NH_2 (Seq. ID. No. 264)



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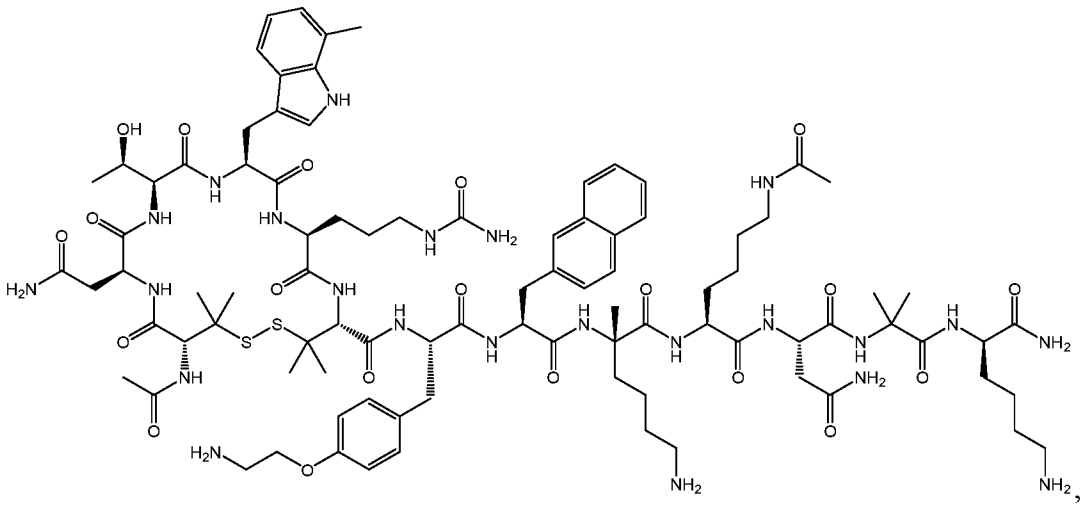
Ac-[Pen]-N-T-[W(7-Me)]-[Cit]-[Pen]-Phe[4-(2-aminoethoxy)]-[2-Nal]-[a-MeLys]-[Lys(Ac)]-N-[Aib]-[bA]-NH_2 (SEQ ID NO: 340)



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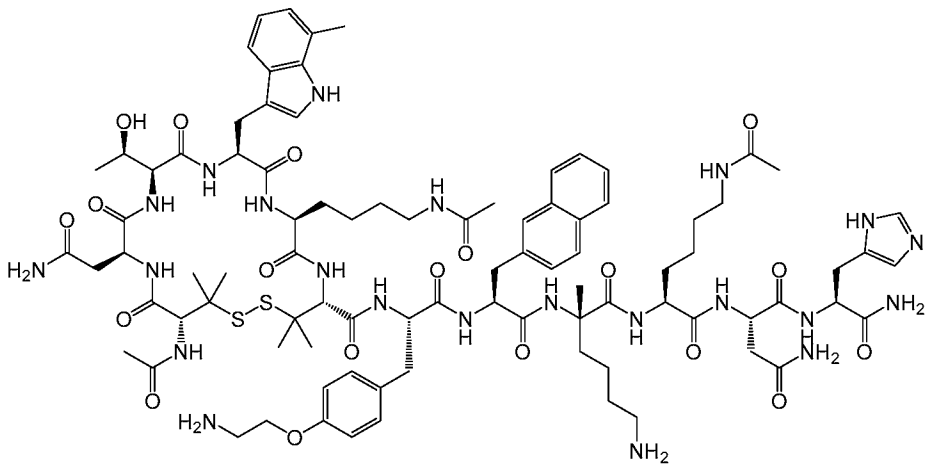
or

Ac-[Pen]-N-T-[W(7-Me)]-[Cit]-[Pen]-Phe[4-(2-aminoethoxy)]-[2-Nal]-[a-MeLys]-[Lys(Ac)]-N-[Aib]-[(D)Lys]-NH_2 (SEQ ID NO: 344)



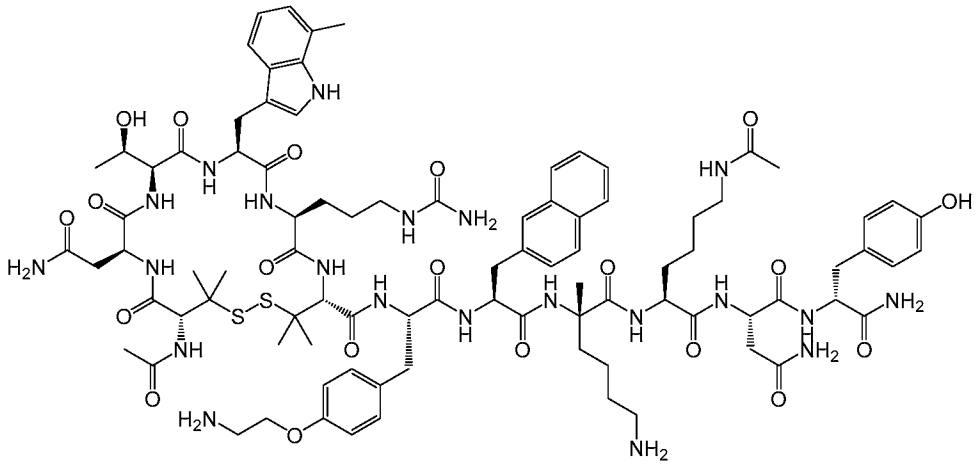
and wherein the peptide inhibitor is cyclized via a Pen-Pen disulfide bond;
or a pharmaceutically acceptable salt or solvate thereof.

90. The peptide inhibitor of claim 81, wherein the peptide inhibitor comprises or is: Ac-[Pen]-NT-[W(7-Me)]-[Lys(Ac)]-[Pen]-Phe[4-(2-aminoethoxy)]-[2-Nal]-[a-MeLys]-[Lys(Ac)]-N-H-NH_2 (Seq. ID. No. 248)



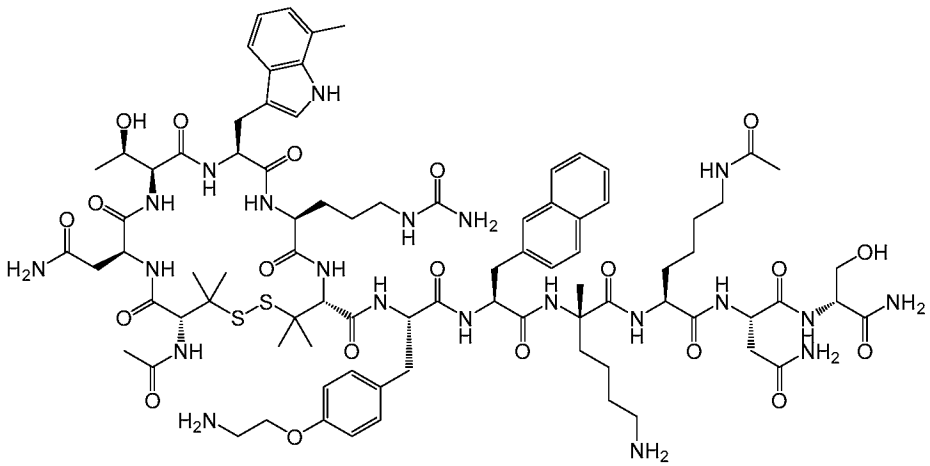
wherein the peptide inhibitor is cyclized via a Pen-Pen disulfide bond; or a pharmaceutically acceptable salt or solvate thereof.

91. The peptide inhibitor of claim 81, wherein the peptide inhibitor comprises or is: Ac-[Pen]-NT-[W(7-Me)]-[Cit]-[Pen]-Phe[4-(2-aminoethoxy)]-[2-Nal]-[a-MeLys]-[Lys(Ac)]-N-[(D)Tyr]-NH_2 (Seq. ID. No. 259)



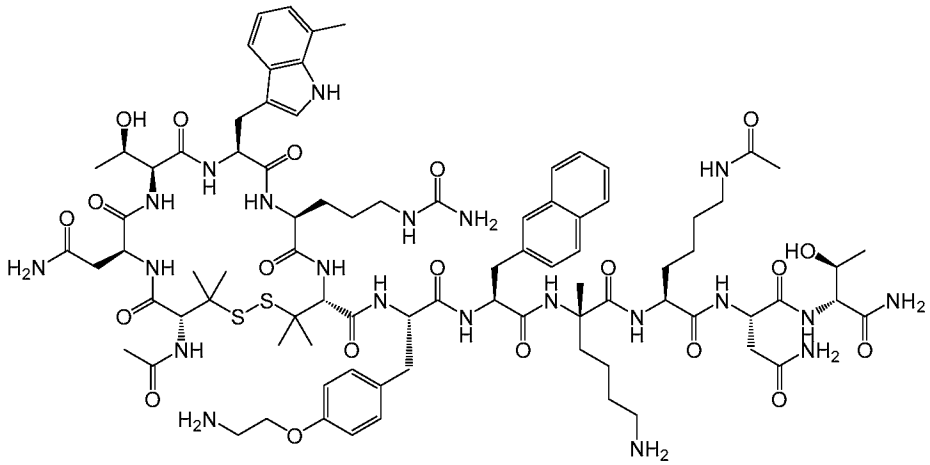
wherein the peptide inhibitor is cyclized via a Pen-Pen disulfide bond; or a pharmaceutically acceptable salt or solvate thereof.

92. The peptide inhibitor of claim 81, wherein the peptide inhibitor comprises or is: Ac-[Pen]-NT-[W(7-Me)]-[Cit]-[Pen]-Phe[4-(2-aminoethoxy)]-[2-Nal]-[a-MeLys]-[Lys(Ac)]-N-[(D)Ser]-NH_2 (Seq. ID. No. 261)



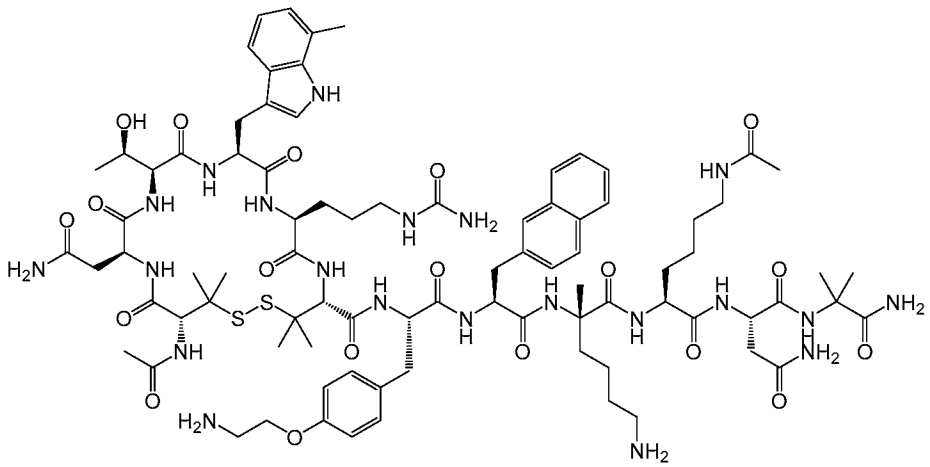
wherein the peptide inhibitor is cyclized via a Pen-Pen disulfide bond; or a pharmaceutically acceptable salt or solvate thereof.

93. The peptide inhibitor of claim 81, wherein the peptide inhibitor comprises or is: Ac-[Pen]-NT-[W(7-Me)]-[Cit]-[Pen]-Phe[4-(2-aminoethoxy)]-[2-Nal]-[a-MeLys]-[Lys(Ac)]-N-[(D)Thr]-NH_2 (Seq. ID. No. 263)



wherein the peptide inhibitor is cyclized via a Pen-Pen disulfide bond; or a pharmaceutically acceptable salt or solvate thereof.

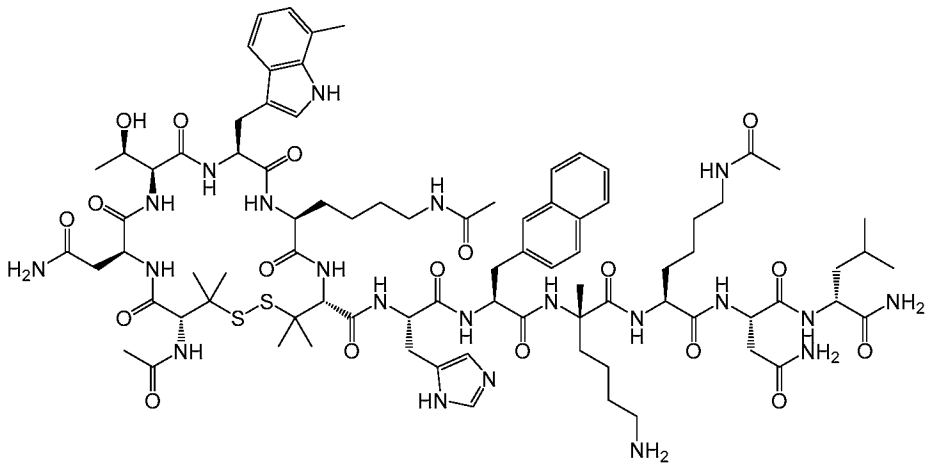
94. The peptide inhibitor of claim 81, wherein the peptide inhibitor comprises or is: Ac-[Pen]-NT-[W(7-Me)]-[Cit]-[Pen]-Phe[4-(2-aminoethoxy)]-[2-Nal]-[a-MeLys]-[Lys(Ac)]-N-[Aib]-NH_2 (Seq. ID. No. 264)



wherein the peptide inhibitor is cyclized via a Pen-Pen disulfide bond; or a pharmaceutically acceptable salt or solvate thereof.

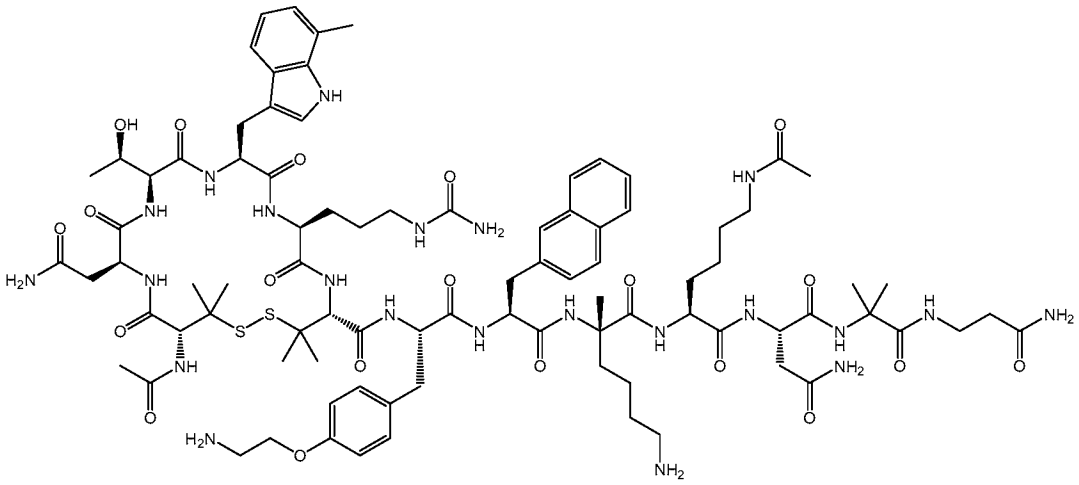
95. The peptide inhibitor of claim 83, wherein the peptide inhibitor comprises or is:

Ac-[Pen]-N-T-[W(7-Me)]-[Lys(Ac)]-[Pen]-H-[2-Nal]-[a-MeLys]-[Lys(Ac)]-N-[(D)Leu]-NH_2 (Seq. ID. No. 290)



wherein the peptide inhibitor is cyclized via a Pen-Pen disulfide bond; or a pharmaceutically acceptable salt or solvate thereof.

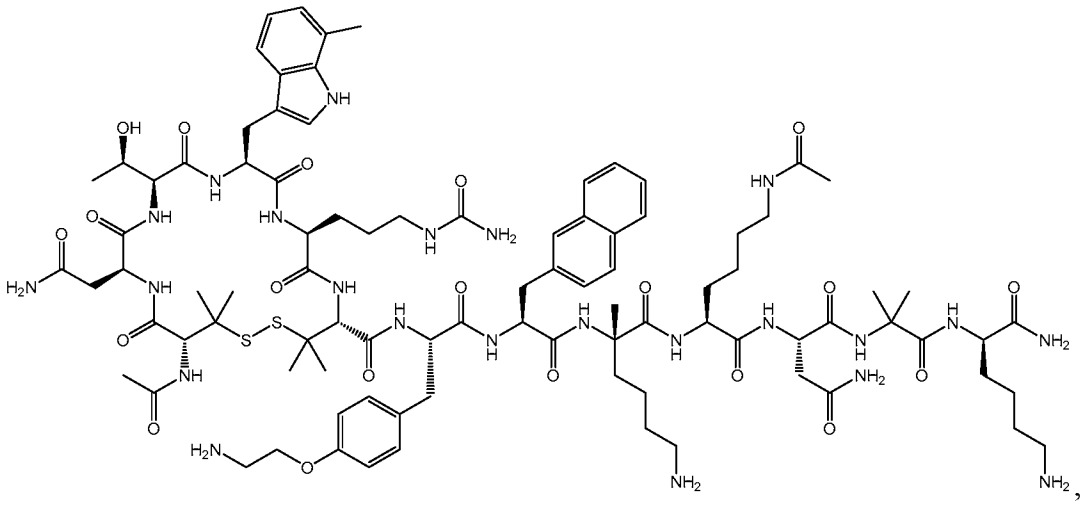
96. The peptide inhibitor of claim 81, wherein the peptide inhibitor comprises or is: Ac-[Pen]-N-T-[W(7-Me)]-[Cit]-[Pen]-Phe[4-(2-aminoethoxy)]-[2-Nal]-[a-MeLys]-[Lys(Ac)]-N-[Aib]-[bA]-NH_2 (SEQ ID NO: 340)



wherein the peptide inhibitor is cyclized via a Pen-Pen disulfide bond; or a pharmaceutically acceptable salt or solvate thereof.

97. The peptide inhibitor of claim 81, wherein the peptide inhibitor comprises or is:

Ac-[Pen]-N-T-[W(7-Me)]-[Cit]-[Pen]-Phe[4-(2-aminoethoxy)]-[2-Nal]-[a-MeLys]-[Lys(Ac)]-N-[Aib]-[(D)Lys]-NH_2 (SEQ ID NO: 344)



wherein the peptide inhibitor is cyclized via a Pen-Pen disulfide bond;
or a pharmaceutically acceptable salt or solvate thereof.

98. A polynucleotide comprising a sequence encoding the peptide inhibitor of any one of claims 1-97.

99. A vector comprising the polynucleotide of claim 98.

100. A pharmaceutical composition comprising the peptide inhibitor or pharmaceutically acceptable salt or solvate thereof of any one of claims 1-97, and a pharmaceutically acceptable carrier, excipient, or diluent.

101. The pharmaceutical composition of claim 100, further comprising an enteric coating.

102. The pharmaceutical composition of claim 101, wherein the enteric coating protects and releases the pharmaceutical composition within a subject's lower gastrointestinal system.

103. A method for treating an Inflammatory Bowel Disease (IBD), ulcerative colitis, Crohn's disease, Celiac disease (*nontropical Sprue)*, enteropathy associated with

seronegative arthropathies, microscopic colitis, collagenous colitis, eosinophilic gastroenteritis, 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, and Wiskott-Aldrich Syndrome, pouchitis resulting after proctocolectomy and ileoanal anastomosis, gastrointestinal cancer, pancreatitis, insulin-dependent diabetes mellitus, mastitis, cholecystitis, cholangitis, pericholangitis, chronic bronchitis, chronic sinusitis, asthma, psoriasis, psoriatic arthritis, or graft versus host disease in a subject, comprising providing to the subject an effective amount of the peptide inhibitor or peptide inhibitor or pharmaceutically acceptable salt or solvate thereof of any one of claims 1-98, or the pharmaceutical composition of any one of claims 101-103.

104. The method of claim 103, wherein the peptide inhibitor or pharmaceutically acceptable salt or solvate thereof or the pharmaceutical composition is provided to the subject by an oral, parenteral, intravenous, peritoneal, intradermal, subcutaneous, intramuscular, intrathecal, inhalation, vaporization, nebulization, sublingual, buccal, parenteral, rectal, intraocular, inhalation, topically, vaginal, or topical route of administration.

105. The method of claim 103 for treating an Inflammatory Bowel Disease (IBD), wherein the peptide inhibitor or pharmaceutically acceptable salt or solvate thereof or the pharmaceutical composition is provided to the subject orally.

106. The method of claim 105, wherein the IBD is ulcerative colitis.

107. The method of claim 105, wherein the IBD is Crohn's disease.

108. The method of claim 103 for treating psoriasis, wherein the peptide inhibitor or pharmaceutically acceptable salt or solvate thereof or the pharmaceutical composition is provided to the subject orally, topically, parenterally, intravenously, subcutaneously, peritonealy, or intravenously.

INTERNATIONAL SEARCH REPORT

International application No.
PCT/US 20/41409

A. CLASSIFICATION OF SUBJECT MATTER

IPC - C07K 7/56, C07K 7/08, C07K 14/54, C07K 7/02, C07K 7/00, A61P 1/00, C12N 15/11 (2020.01)

CPC - C07K 7/08, C07K 7/02, A61K 38/00, C07K 7/56, A61P 1/00, A61P 1/04, A61P 1/16, A61P 1/18, A61P 11/00, A61P 11/02, A61P 11/06, A61P 15/14, A61P 17/06, A61P 19/02, A61P 3/10, A61P 35/00, A61P 37/06, A61P 43/00, A61P 5/48, C07K 14/54, C07K 7/02, C07K 7/50, C07K 7/64, A61K 38/00, G01N 2800/065

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
See Search History document

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched
See Search History document

Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)
See Search History document

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	WO 2018/136646 A1 (PROTAGONIST THERAPEUTICS INC [US]) 26 July 2018 (26.07.2018) pg 134, SEQ ID NO: 188	1, 2, 3, 5, 81, 82, 83
A	US 10,196,424 B2 (PROTAGONIST THERAPEUTICS INC [US]) 05 February 2019 (05.02.2019) claim 1	1, 2, 3, 5, 81, 82, 83

☐ Further documents are listed in the continuation of Box C. ☐ See patent family annex.

* Special categories of cited documents:
"A" document defining the general state of the art which is not considered to be of particular relevance
"D" document cited by the applicant in the international application
"E" earlier application or patent but published on or after the international filing date
"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)
"O" document referring to an oral disclosure, use, exhibition or other means
"P" document published prior to the international filing date but later than the priority date claimed
"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention
"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone
"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art
"&" document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
03 November 2020	03DEC 2020
Name and mailing address of the ISA/US Mail Stop PCT, Attn: ISA/US, Commissioner for Patents P.O. Box 1450, Alexandria, Virginia 22313-1450 Facsimile No. 571-273-8300	Authorized officer Lee Young Telephone No. PCT Helpdesk: 571-272-4300

INTERNATIONAL SEARCH REPORT

International application No.
PCT/US 20/41409

Box No. II Observations where certain claims were found unsearchable (Continuation of item 2 of first sheet)

This international search report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. ☐ Claims Nos.:
because they relate to subject matter not required to be searched by this Authority, namely:

2. ☐ Claims Nos.:
because they relate to parts of the international application that do not comply with the prescribed requirements to such an extent that no meaningful international search can be carried out, specifically:

3. ☒ Claims Nos.: 15-17, 19, 21, 22, 25, 26, 31-37, 40-45, 52-65, 98-108
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

Box No. III Observations where unity of invention is lacking (Continuation of item 3 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows:

This application contains the following inventions or groups of inventions which are not so linked as to form a single general inventive concept under PCT Rule 13.1.

********** See Supplemental Sheet to continue **********

1. ☐ As all required additional search fees were timely paid by the applicant, this international search report covers all searchable claims.

2. ☐ As all searchable claims could be searched without effort justifying additional fees, this Authority did not invite payment of additional fees.

3. ☐ As only some of the required additional search fees were timely paid by the applicant, this international search report covers only those claims for which fees were paid, specifically claims Nos.:

4. ☒ No required additional search fees were timely paid by the applicant. Consequently, this international search report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:
1, 2, 3, 5, 81, 82, 83, restricted to X7 is cyano-Trp; X8 is Gln; X9 is Abu; X10 is Phe; X11 is 2-Nal, X12 is THP, X13 is Aib, X14 is Asn, X15 is Leu; X4 is Abu; X5 is Cit, X6 is Thr

Remark on Protest

☐ The additional search fees were accompanied by the applicant's protest and, where applicable, the payment of a protest fee.

☐ The additional search fees were accompanied by the applicant's protest but the applicable protest fee was not paid within the time limit specified in the invitation.

☐ No protest accompanied the payment of additional search fees.

In Continuation of
Box III. Observations where unity of invention is lacking:

Group I+, claims 1-14, 18, 20, 23, 24, 27-30, 38, 39, 46-51, 66-97 directed to a peptide inhibitor of IL-23. The peptide inhibitor will be searched to the extent that X7 is Trp substituted with cyano; X8 is Gln; X9 is Abu; X10 is unsubstituted Phe; X11 is 2-Nal, X12 is THP, X13 is Aib, X14 is Asn, X15 is Leu; X4 is Abu; X5 is Cit, X6 is Thr. It is believed that claims 1, 2, 3, 5, 81, 82, 83 encompass this first named invention, and thus these claims will be searched without fee to the extent that the peptide inhibitor will be searched to the extent that X7 is Trp substituted with cyano; X8 is Gln; X9 is Abu; X10 is unsubstituted Phe; X11 is 2-Nal, X12 is THP, X13 is Aib, X14 is Asn, X15 is Leu; X4 is Abu; X5 is Cit, X6 is Thr. Additional peptide inhibitor(s) will be searched upon the payment of additional fees. Applicants must specify the claims that encompass any additionally elected peptide inhibitor(s). Applicants must further indicate, if applicable, the claims which encompass the first named invention, if different than what was indicated above for this group. Failure to clearly identify how any paid additional invention fees are to be applied to the "+" group(s) will result in only the first claimed invention to be searched. An exemplary election would be a peptide inhibitor
SEQ ID NO: 340 (Ac-[Pen]-N-T-[W(7-Me)]-[Cit]-[Pen]-Phe[4-(2-aminoethoxy)]-[2-Nal]-[a-MeLys]-[Lys(Ac)]-N-[Aib]-[bA]-NH2) or
SEQ ID NO: 264 (Ac-[Pen]-N-T-[W(7-Me)]-[Cit]-[Pen]-Phe[4-(2-aminoethoxy)]-[2-Nal]-[a-MeLys]-[Lys(Ac)]-N-[Aib]-NH2), i.e. claims 1, (10,11)/1, 20, 46, 47, 50, 81-83, 86, 89, 94, 96.

The inventions listed as Group I+ do not relate to a single special technical feature under PCT Rule 13.1 because, under PCT Rule 13.2, they lack the same or corresponding special technical features for the following reasons:

The special technical feature of each invention of Group I+ is a specific peptide inhibitor of IL23R recited therein.

The special technical feature of some inventions of Group I+ is a specific definition of X7 and/or X15 amino acids in Formula (II') recited therein.

Some inventions of Group I+ share the technical features of a peptide inhibitor of an IL23R comprising amino acid sequence of Formula (I) (claim 81). However, this shared technical feature does not represent an improvement over prior art as being anticipated by WO2018/136646 A1 to PROTAGONIST THERAPEUTICS INC [US] (hereinafter "PROTAGONIST").

PROTAGONIST discloses a peptide inhibitor of IL23R comprising Formula (I) (pg 134, SEQ ID NO: 188 (Ac-[Pen]-NTWQ-[Pen]-[Phe[4-(2-aminoethoxy)]-[2-Nal]-[a-MeLeu]- Lys(Ac)-[Cit]-N-NH2) as follows:
X7 is unsubstituted Trp,
X8 is Gln,
X9 is [Pen],
X10 is [Phe[4-(2-aminoethoxy)],
X11 is [2-Nal].
As the technical feature was known in the art at the time of the invention, this cannot be considered a special technical feature that would otherwise unify the inventions.

Some inventions of Group I+ share the technical features of a peptide inhibitor of an IL23R comprising amino acid sequence X8-X14 of Formula (II') (claim 1) or amino acids X7-X14 of Formula (II') (claim 83). However, these shared technical features do not represent an improvement over prior art as being anticipated by PROTAGONIST, as above.
PROTAGONIST discloses a peptide inhibitor of IL23R comprising amino acid sequence X8-X14 of Formula (II') (as defined in claim 1) or amino acids X7-X14 of Formula (II') (as defined in claim 83) (pg 134, SEQ ID NO: 188 (Ac-[Pen]-NTWQ-[Pen]-[Phe[4-(2-aminoethoxy)]-[2-Nal]-[a-MeLeu]- Lys(Ac)-[Cit]-N-NH2) as follows:
X7 is unsubstituted Trp,
X8 is Gln,
X9 is [Pen],
X10 is [Phe[4-(2-aminoethoxy)],
X11 is [2-Nal],
X12 is [a-MeLeu],
X13 is Lys(Ac),
X14 is [Cit].
As the technical feature/common structural core of X8-X14 of Formula (II') (as defined in claim 1) or amino acids X7-X14 of Formula (II') (as defined in claim 83) was known in the art at the time of the invention, this cannot be considered a special technical feature that would otherwise unify the inventions.

Therefore, inventions of Group I+ lack unity under PCT Rule 13 because they do not share the same or corresponding special technical feature.

INTERNATIONAL SEARCH REPORT

International application No.

PCT/US 20/41409

Continuation of:
A. CLASSIFICATION OF SUBJECT MATTER

IPC - C12N 15/24, C12Q 1/00, C07K 14/715