(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.

[0008] 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

[0009] The present invention provides *inter alia* novel peptide inhibitors of IL-23R and related methods of use.

[0010] Disclosed is 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 (Xa):

[0011] X1-X2-X3-X4-X5-X6-X7-X8-X9-X10-X11-X12-X13-X14-X15-X16-X17-X18-X19-X20 (Xa),

wherein:

X1, X2 and X3 are any amino acid or absent

X4 is any amino acid or chemical moiety capable of forming a bond with X9;

X5, X6, X7 and X8 are any amino acid;

X9 is any amino acid or chemical moiety capable of forming a bond with X4;

X10, X11, X12, X13, X14 and X15 are any amino acid; and

X16, X17, X18, X19 and X20 are any amino acid or absent;

[0012] wherein the peptide inhibitor is cyclized via a bond between X4 and X9, and

[0013] wherein the peptide inhibitor inhibits the binding of an interleukin-23 (IL-23) to an IL-23 receptor.

[0013a] In one aspect, the present invention 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 (Xa):

X1-X2-X3-X4-X5-X6-X7-X8-X9-X10-X11-X12-X13-X14-X15-X16-X17-X18-X19-X20 (Xa)

wherein

X1 is any amino acid or absent;

X2 is any amino acid or absent;

X3 is any amino acid or absent;

X4 is Cys, Pen, hCys, D-Pen, D-Cys, D-hCys, Met, Glu, Asp, Lys, Orn, Dap, Dab, D-Dap, D-Dab, D-Asp, D-Glu, D-Lys, Sec, 2-chloromethylbenzoic acid, mercapto-propanoic acid, mercapto-butyric acid, 2-chloro-acetic acid, 3-choro-propanoic acid, 4-chloro-butyric acid, 3-chloro-isobutyric acid, Abu, β-azido-Ala-OH, propargylglycine, 2-(3'-butenyl)glycine, 2-allylglycine, 2-(3'-butenyl)glycine, 2-(4'-pentenyl)glycine, 2-(5'-hexenyl)glycine;

X5 is any amino acid;

X6 is any amino acid;

X7 is Trp, Glu, Gly, Ile, Asn, Pro, Arg, Thr or OctGly, or a corresponding α-methyl amino acid form of any of the foregoing;

X8 is any amino acid;

X9 is Cys, Pen, hCys, D-Pen, D-Cys, D-hCys, Glu, Lys, Orn, Dap, Dab, D-Dap, D-Dab, D-Asp, D-Glu, D-Lys, Asp, Leu, Val, Phe, Ser, Sec, Abu, β-azido-Ala-OH, propargylglycine, 2-2-

allylglycine, 2-(3'-butenyl)glycine, 2-(4'-pentenyl)glycine, Ala, hCys, Met, MeCys, (D)Tyr or 2-(5'-hexenyl)glycine;

X10 is Tyr, Phe(4-OMe), 1-Nal, 2-Nal, Aic, α-MePhe, Bip, (D)Cys, Cha, DMT, (D)Tyr, Glu, His, hPhe(3,4-dimethoxy), hTyr, N-Me-Tyr, Trp, Phe(4-$CONH_2$), Phe(4-phenoxy), Thr, Tic, Tyr(3-tBu), Phe(4-tBu), Phe(4-CN), Phe(4-Br), Phe(4-NH_2), Phe(4-F), Phe(3,5-F_2), Phe(4-CH_2CO_2H), Phe(penta-F), Phe(3,4-Cl_2), Phe(4-CF_3), Bip, Cha, 4-PyridylAlanine, βhTyr, OctGly, Phe(4-N_3), Phe(4-Br), Phe[4-(2-aminoethoxy)], Phe, a Phe analog, or a Tyr analog, or a corresponding α-methyl amino acid form of any of the foregoing;

X11 is 2-Nal, 1-Nal, 2,4-dimethylPhe, Bip, Phe(3,4-Cl_2), Phe (3,4-F_2), Phe(4-CO_2H), βhPhe(4-F), α-Me-Trp, 4-phenylcyclohexyl, Phe(4-CF_3), Phe(3,4-OMe_2), α-MePhe, βhNal, βhPhe, βhTyr, βhTrp, Nva(5-phenyl), Phe, His, hPhe, Tic, Trp, Tyr, Phe(4-OMe), Phe(4-Me), Trp(2,5,7-tri-tert-Butyl), Phe(4-Oallyl), Tyr(3-tBu), Phe(4-tBu), Phe(4-guanidino, Phe(4-OBzl), Octgly, Glu(Bzl), 4-Phenylbenzylalanine, Phe[4-(2-aminoethoxy)], 5-Hydroxy-Trp, 6-Chloro-Trp, N-MeTrp, 1,2,3,4-tetrahydro-norharman, Phe(4-$CONH_2$), Phe(3,4-Dimethoxy), Phe(2,3-Cl_2), Phe(2,3-F_2), Phe(4-F), 4-phenylcyclohexylalanine or Bip, or a corresponding α-methyl amino acid form of any of the foregoing;

X12 is His, Phe, Arg, N-Me-His, Val, Cav, Cpa, Leu, Cit, hLeu, 3-Pal, t-butyl-Ala, α-MeLys, D-Ala, (D)Asn, (D)Asp, (D)Leu, (D)Phe, (D)Tyr, Aib, α-MeLeu, α-MeOrn, β-Aib, β-Ala, βhAla, βhArg, βhLeu, βhVal, β-spiro-pip, Glu, hArg, Ile, Lys, N-MeLeu, N-MeArg, Ogl, Orn, Pro, Gln, Ser, Thr, Tle,t-butyl-Gly, 4-amino-4-carboxy-tetrahydropyran (THP), Achc Acpc, Acbc, Acvc, Agp, Aib, α-DiethylGly, α-MeLys(Ac), α-MeOrn, α-MeSer, α-MeVal, Cha, Cit, Cpa, (D)Asn, Glu, hArg, or Lys, or a corresponding α-methyl amino acid form of any of the foregoing;

X13 is Thr, Sarc, Glu, Phe, Arg, Leu, Asn, Cit, Lys, Arg, Orn, Val, βhAla, Lys(Ac), (D)Asn, (D)Leu, (D)Phe, (D)Thr, Ala, α-MeLeu, Aib, β-Ala, β-Glu, βhLeu, βhVal, β-spiro-pip, Cha, Chg, Asp, Dab, Dap, α-DiethylGly, hLeu, Asn, Ogl, Pro, Gln, Ser, β-spiro-pip, Thr, Tle or Aib, or a corresponding α-methyl amino acid form of any of the foregoing;

X14 is Phe, Tyr, Glu, Gly, His, Lys, Leu, Met, Asn, Lys(Ac), Dap(Ac), Dab(Ac), Asp, Pro, Gln, Arg, Ser, Thr, Tic or βhPhe, or a corresponding α-methyl amino acid form of any of the foregoing;

X15 is Gly, Ser, Thr, Gln, Ala, (D)Ala, (D)Asn, (D)Asp, (D)Leu, (D)Phe, (D)Thr, Aea, Asp, Asn, Glu, Phe, Gly, Lys, Leu, Pro, Arg, β-Ala, or Sarc, or a corresponding α-methyl amino acid form of any of the foregoing,

X16 is any amino acid or absent;

X17 is any amino acid or absent;

X18 is any amino acid or absent;

X19 is any amino acid or absent; and

X20 is any amino acid or absent,

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

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

[0014] In certain examples of Xa:

[0015] X1 is absent; X2 is absent; X3 is absent; X4 is Cys, Abu or Pen; X5 is Ala, α-MeOrn, α-MeSer, Cit, Dap, Dab, Dap(Ac), Gly, Lys, Asn, N-MeGln, N-MeArg, Orn, Gln, Arg, Ser or Thr; X6 is Asp or Thr; X7 is Trp or 6-Chloro-Trp; X8 is Glu, Gln or Val; X9 is Cys, Abu or Pen; X10 is 2-Nal, a Phe analog, Tyr, or a Tyr analog; X11 is 1-Nal, 2-Nal, Phe(3,4-dimethoxy), 5-HydroxyTrp, Phe(3,4-Cl_2), Trp or Tyr(3-tBu); X12 is 3-Pal, Acpc, Acbc, Acvc, Achc, Agp, Aib, α-DiethylGly, α-MeLys, α-MeLys(Ac), α-MeLeu, α-MeOrn, α-MeSer, α-MeVal, Cav, Cha, Cit, Cpa, D-Asn, Glu, His, hLeu, hArg, Lys, Leu, Octgly, Orn, 4-amino-4-carboxy-piperidine, Arg, Ser, Thr or THP; X13 is Cit, Asp, Dab, Dap, Phe, His, Dap(Peg2-Ac), Dap(pyroglutaric acid), Glu, HomoArg, Lys, Lys(Ac), Lys(Benzoic acid), Lys(glutaric acid), Lys(IVA), Lys(Peg4-isoGlu-Palm), Lys(pyroglutaric acid), Lys(succinic acid), Asn, Orn, Gln, Arg, Thr or Val; X14 is Asp, Dab(Ac), Dap(Ac), Phe, His, Lys(Ac), Met, Asn(isobutyl), Gln, Arg, Tyr or Asp(1,4-diaminobutane); and X15 is Ala, βAla, Glu, Gly, Asn, Gln, Arg or Ser.

[0016] In certain examples of Xa: X1 is absent; X2 is absent; X3 is absent; X4 is Cys, Abu or Pen; X5 is Ala, α-MeOrn, α-MeSer, Cit, Dap, Dab, Dap(Ac), Gly, Lys, Asn, Orn, Gln, Arg, Ser or Thr; X6 is Asp or Thr; X7 is Trp or 6-Chloro-Trp; X8 is Gln or Val; X9 is Cys, Abu or Pen; X10 is 2-Nal, a Phe analog, Tyr, or a Tyr analog; X11 is 1-Nal, 2-Nal, Phe(3,4-dimethoxy),

5-HydroxyTrp, Phe(3,4-Cl_2), Trp or Tyr(3-tBu); X12 is 3-Pal, Acpc, Acbc, Acvc, Achc, Agp, Aib, α-DiethylGly, α-MeLys, α-MeLys(Ac), α-MeLeu, α-MeOrn, α-MeSer, α-MeVal, Cav, Cha, Cit, Cpa, D-Asn, His, hLeu, hArg, Lys, Leu, Octgly, Orn, 4-amino-4-carboxy-piperidine, or THP; X13 is Cit, Asp, Dab, Dap, Phe, His, Dap(Peg2-Ac), Dap(pyroglutaric acid), Glu, hArg,

Lys, Lys(Ac), Lys(Benzoic acid), Lys(glutaric acid), Lys(IVA), Lys(Peg4-isoGlu-Palm), Lys(pyroglutaric acid), Lys-(succinic acid), Asn, Orn,Gln, Arg, Thr or Val; X14 is Dab(Ac), Dap(Ac), Phe, His, Lys(Ac), Met, Asn, Gln, Arg, or Tyr; and X15 is Ala, betaAla, Gly, Asn, Gln, or Ser.

[0017] In certain examples of Xa: X1 is absent; X2 is absent; X3 is absent; X4 is Cys, Abu or Pen; X5 is Dap, Dap(Ac), Gly, Lys, Gln, Arg, Ser,Thr or Asn; X6 is Thr; X7 is Trp or 6-Chloro-Trp; X8 is Gln; X9 is Cys, Abu or Pen; X10 is 2-Nal, a Phe analog, Tyr, or a Tyr analog; X11 is 1-Nal, 2-Nal, Phe(3,4-dimethoxy), Phe(3,4-Cl_2), or Trp; X12 is Acpc, Acbc, Acvc, Achc, Aib, α-DiethylGly, α-MeLys, α-MeLys(Ac), α-MeLeu, α-MeOrn, α-MeSer, α-MeVal, Cha, Cit, hLeu, Lys, Leu, Arg or THP; X13 is Cit, Asp, Dap, Dap(Peg2-Ac), Dap(pyroglutaric acid), Glu, hArg, Lys, Lys(Ac), Lys(Benzoic acid), Lys(glutaric acid), Lys(IVA), Lys(Peg4-isoGlu-Palm), Lys(pyroglutaric acid), Lys-(succinic acid), Asn, Orn,Gln, Arg, or Val; X14 is Dab(Ac), Dap(Ac), His, Lys(Ac), Asn, Gln, or Tyr; and X15 is Ala, betaAla, Gly, Asn, Gln, or Ser.

[0018] In certain examples of Xa: X1 is absent; X2 is absent; X3 is absent; X4 is Cys, Abu or Pen; X5 is Dap, Dap(Ac), Gln, Ser, Thr or Asn; X6 is Thr; X7 is Trp; X8 is Gln; X9 is Cys, Abu or Pen; X10 is a Phe analog, Tyr, or a Tyr analog; X11 is 2-Nal or Trp; X12 is Acpc, Acbc, Acvc, Achc, Aib, α-DiethylGly, α-MeLys, α-MeLys(Ac), α-MeLeu, α-MeOrn, α-MeSer, α-MeVal, hLeu, Leu, or THP; X13 is Cit, Asp, Glu, Lys, Lys(Ac), Asn, or Gln; X14 is Dab(Ac), Asn, or His; and X15 is Ala, betaAla, Gly, Asn, or Gln.

[0019] In certain examples of Xa: X4 is Cys, Pen, hCys, D-Pen, D-Cys, D-hCys, Met, Glu, Asp, Lys, Orn, Dap, Dab, D-Dap, D-Dab, D-Asp, D-Glu, D-Lys, Sec, 2-chloromethylbenzoic acid, mercapto-propanoic acid, mercapto-butyric acid, 2-chloro-acetic acid, 3-choropropanoic acid, 4-chlorobutyric acid, 3-chloroisobutyric acid, Abu, β-azido-Ala-OH, propargylglycine, 2-(3'-butenyl)glycine, 2-allylglycine, 2-(3'-butenyl)glycine, 2-(4'-pentenyl)glycine, 2-(5'-hexenyl)glycine, or Abu; X7 is Trp, Glu, Gly, Ile, Asn, Pro, Arg, Thr or OctGly, or a corresponding α-methyl amino acid form of any of the foregoing; X9 is Cys, Pen, hCys, D-Pen, D-Cys, D-hCys, Glu, Lys, Orn, Dap, Dab, D-Dap, D-Dab, D-Asp, D-Glu, D-Lys, Asp, Leu, Val, Phe, or Ser, Sec, Abu, β-azido-Ala-OH, propargylglycine, 2-2-allylglycine, 2-(3'-butenyl)glycine, 2-(4'-pentenyl)glycine, Ala, hCys, Abu, Met, MeCys, (D)Tyr or 2-(5'-

form of any of the foregoing; and X17 is Leu, Lys, Arg, Glu, Ser, Gly, Gln or absent, or a corresponding α-methyl amino acid form of any of the foregoing.

[0020] In certain examples of peptide inhibitors of Xa, 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.

[0021] In particular examples of peptide inhibitors of Xa, X4 is Cys and X9 is Cys, and the bond is a disulfide bond. In particular examples, X4 is Pen and X9 is Pen, and the bond is a disulfide bond. In certain examples: X7 is Trp; X10 is Phe, Tyr, a Phe analog, or a Tyr analog; X11 is Trp, 1-Nal or 2-Nal; and X12 is Aib, α-Me-Lys, a-Me-Leu, Achc, Acvc, Acpc, Acbc or THP. In certain examples: X7 is Trp; X10 is Phe, Tyr, a Phe analog, or a Tyr analog; X11 is Trp, 1-Nal or 2-Nal; and X12 is Aib, α-Me-Lys or a-Me-Leu. In particular examples, the peptide inhibitor comprises any of the following the amino acid sequences: Pen-Q-T-W-Q-Pen-[Phe(4-OMe)]-[2-Nal]-[α-Me-Lys]-E-N-G (SEQ ID NO: 254); Pen-N-T-W-Q-[Pen]-[Phe[4-(2-aminoethoxy)]-[2-Nal]-[Aib]-[Lys(Ac)]-N-N (SEQ ID NO: 255); Pen-Q-T-W-Q-[Pen]-[Phe[4-(2-aminoethoxy)]-[2-Nal]-[α-MeLeu]-[Lys(Ac)]-N-N (SEQ ID NO: 256); or Pen-Q-T-W-Q-[Pen]-[Phe(4-$CONH_2$)]-[2-Nal]-[α-MeLys]-[Lys(Ac)]-N-N (SEQ ID NO: 257), wherein the peptide inhibitor comprises a disulfide bond between the two Pen amino acids.

[0022] In particular examples of peptide inhibitors of Xa, X4 is an amino acid, aliphatic acid, alicyclic acid or modified 2- methyl aromatic acid having a carbon side chain capable of forming a thioether bind with X9; X9 is a sulfur-containing amino acid capable of forming a thioether bond with X4, and the bond between X4 and X9 is a thioether bond. In certain examples, X4 is Abu, 2-chloromethylbenzoic acid, mercapto-propanoic acid, mercapto-butyric acid, 2-chloro-acetic acid, 3-chloro-propanoic acid, 4-chloro-butyric acid, 3-chloro-isobutyric acid; and X9 is Abu, Cys, Pen, hCys, D-Pen, D-Cys, or D-hCys.In certain examples, X4 is Abu; and X9 is Cys. In certain examples, X7 is Trp; X10 is Phe, Tyr, a Phe analog, or a Tyr analog; X11 is Trp, 1-Nal or 2-Nal; and X12 is α-Me-Lys, α-Me-Leu, α-Me-Ser, α-Me-Val, Achc, Acvc, Acpc, Acbc, or [4-amino-4-carboxy-tetrahydropyran]. In certain examples, X7 is Trp; X10 is Phe, Tyr, a Phe analog, or a Tyr analog; X11 is Trp, 1-Nal or 2-Nal; and X12 is α-Me-Lys or [4-amino-4-carboxy-tetrahydropyran]. In particular

examples, the peptide inhibitor comprises any of the following amino acid sequences: [Abu]-Q-T-W-Q-C-[Phe(4-OMe)]-[2-Nal]-[α-MeLys]-E-N-G (SEQ ID NO: 258); [Abu]-Q-T-W-Q-C-[Phe(4-(2-aminoethoxy))]-W-[α-MeLys]-E-N-G (SEQ ID NO: 259); or [Abu]-Q-T-W-Q-C-[Phe[4-(2-aminoethoxy)]]-[2-Nal]-[4-amino-4-carboxy-tetrahydropyran]-E-N-N (SEQ ID NO: 260), wherein the peptide inhibitor comprises a thioether bond between the Abu and the C.

[0023] In certain examples of peptide inhibitors of Xa: X4 is Pen, Cys or hCys; X5 is any amino acid; X6 is any amino acid; X7 is Trp, Bip, Gln, His, Glu(Bzl), 4-Phenylbenzylalanine, Tic, Phe[4-(2-aminoethoxy)], Phe(3,4-Cl_2), Phe(4-OMe), 5-Hydroxy-Trp, 6-Chloro-Trp, N-MeTrp, α-Me-Trp, 1,2,3,4 -tetrahydro-norharman, Phe(4-CO_2H), Phe(4-$CONH_2$), Phe(3,4-Dimethoxy), Phe(4-CF_3), Phe(4-tBu), ββ-diPheAla, Glu, Gly, Ile, Asn, Pro, Arg, Thr or Octgly, or a corresponding α-methyl amino acid form of any of the foregoing; X8 is any amino acid; X9 is Pen, Cys or hCys; X10 is 1-Nal, 2-Nal, Aic, Bip, (D)Cys, Cha, DMT, (D)Tyr, Glu, Phe, His, Trp, Thr, Tic, Tyr, 4-pyridylAla, Octgly, a Phe analog or a Tyr analog (optionally, Phe(3,4-F_2), Phe(3,4-Cl_2), F(3-Me), Phe[4-(2-aminoethoxy)], Phe[4-(2-(acetyl-aminoethoxy)], Phe(4-Br), Phe(4-$CONH_2$), Phe(4-Cl), Phe(4-CN), Phe(4-guanidino), Phe(4-Me), Phe(4-NH_2), Phe(4-N_3), Phe(4-OMe), or Phe(4-OBzl)), or a corresponding α-methyl amino acid form of any of the foregoing; X11 is 2-Nal, 1-Nal, 2,4-dimethylPhe, Bip, Phe(3,4-Cl_2), Phe (3,4-F_2), Phe(4-CO_2H), βhPhe(4-F), α-Me-Trp, 4-phenylcyclohexyl, Phe(4-CF_3), α-MePhe, βhNal, βhPhe, βhTyr, βhTrp, Nva(5-phenyl), Phe, His, hPhe, Tic, Tqa, Trp, Tyr, Phe(4-OMe), Phe(4-Me), Trp(2,5,7-tri-tert-Butyl), Phe(4-Oallyl), Tyr(3-tBu), Phe(4-tBu), Phe(4-guanidino, Phe(4-OBzl), Octgly, Glu(Bzl), 4-Phenylbenzylalanine, Phe[4-(2-aminoethoxy)], 5-Hydroxy-Trp, 6-Chloro-Trp, N-MeTrp, 1,2,3,4-tetrahydro-norharman, Phe(4-$CONH_2$), Phe(3,4-OMe_2) Phe(2,3-Cl_2), Phe(2,3-F_2), Phe(4-F), 4-phenylcyclohexylalanine or Bip, or a corresponding α-methyl amino acid form of any of the foregoing; X12 is α-MeLys, α-MeOrn, α-MeLeu, α-MeVal, 4-amino-4-carboxy-tetrahydropyran, Achc, Acpc, Acbc, Acvc, MeLeu, Aib, (D)Ala, (D)Asn, (D)Leu, (D)Asp, (D)Phe, (D)Thr, 3-Pal, Aib, β-Ala, βhGlu, βhAla, βhLeu, βhVal, β-spiro-pip, Cha, Chg, Asp, Dab, Dap, α-DiethylGly, Glu, Phe, hLeu, hArg, hLeu, Ile, Lys, Leu, Asn, N-MeLeu, N-MeArg, Ogl, Orn, Pro, Gln, Arg, Ser, Thr or Tle, or a corresponding α-methyl amino acid form of any of the foregoing; X13 is Lys(Ac), (D)Asn, (D)Leu, (D)Thr, (D)Phe, Ala, Aib, α-MeLeu, β-Ala, βhGlu, βhAla, βhLeu, βhVal, β-spiro-pip, Cha, Chg, Asp, Lys, Arg, Orn, Dab, Dap, α-

DiethylGly, Glu, Phe, hLeu, Lys, Leu, Asn, Ogl, Pro, Gln, Asp, Arg, Ser, spiro-pip, Thr, Tba, Tlc, Val or Tyr, or a corresponding α-methyl amino acid form of any of the foregoing; X14 is Asn, Glu, Phe, Gly, His, Lys, Leu, Met, Asn, Pro, Gln, Arg, Ser, Thr, Tic or Tyr, Lys(Ac), Orn or a corresponding α-methyl amino acid form of any of the foregoing; X15 is Gly, (D)Ala, (D)Asn, (D)Asp, Asn, (D)Leu, (D)Phe, (D)Thr, Ala, AEA, Asp, Glu, Phe, Gly, Lys, Leu, Pro, Gln, Arg or Ser, β-Ala, Arg or a corresponding α-methyl amino acid form of any of the foregoing; X16 is absent, Gly, Ala, Asp, Ser, Pro, Asn or Thr, or a corresponding α-methyl amino acid form of any of the foregoing; X17 is absent, Glu, Ser, Gly or Gln, or a corresponding α-methyl amino acid form of any of the foregoing; X18 is absent or any amino acid; X19 is absent or any amino acid; and X20 is absent or any amino acid. In particular examples, the bond between X4 and X9 is a disulfide bond. In certain examples, X1, X2, and X3 are absent.In certain examples, X17, X19 and X20 are absent. In certain examples, one or both of X4 or X9 is Pen. In certain examples, both X4 and X9 are Pen. In particular examples, X18 is (D)-Lys. In certain examples, the peptide inhibitors comprise one or more, two or more, three or more, or four of the following: X5 is Arg, Asn, Gln, Dap, Orn; X6 is Thr or Ser; X7 is Trp, 2-Nal, 1-Nal, Phe(4-OAllyl), Tyr(3-tBu), Phe(4-tBu), Phe(4-guanidino), Phe(Bzl) or Phe(4-Me), 5-Hydroxy-Trp, 6-Chloro-Trp, N-MeTrp, α-MeTrp or 1,2,3,4 -tetrahydro-norharman; and X8 is Gln, Val, Phe, Glu, Lys. In certain examples, the peptide inhibitors comprise one or more, two or more, three or more, four or more, five or more, six or more, or seven of the following: X10 is Tyr, Phe(4-OBzl), Phe(4-OMe), Phe(4-$CONH_2$), Phe(3,4-Cl_2), Phe(4-tBu), Phe(4-NH_2), Phe(4-Br), Phe(4-CN), Phe(4-CO_2H), Phe(4-(2aminoethoxy)) or Phe(4-guanadino); X11 is Trp, 2-Nal, 1-Nal, Phe(4-OAllyl), Tyr(3-tBu), Phe(4-tBu), Phe(4-guanidino), Phe(Bzl) or Phe(4-Me), 5-Hydroxy-Trp, 6-Chloro-Trp, N-MeTrp, α-MeTrp or 1,2,3,4 -tetrahydro-norharman; X12 is Arg, α-MeLys α-MeLeu, Aib or α-MeOrn; X13 is Lys, Glu or Lys(Ac); X14 is Phe or Asn; X15 is Gly, Sr or Ala; and X16 is absent or AEA. In certain examples, X4 and X9 are Pen; X5 is Gln; X6 is Thr; X7 is Trp; X8 is Gln; X10 is Tyr, Phe(4-OMe) or 2-Nal; X11 is Trp, 2-Nal or 1-Nal; X12 is Arg, αMeLys or α-MeOrn; X13 is Lys, Glu or Lys(Ac); X14 is Phe or Asn; X15 is Gly; and X16 is absent. In certain examples, one or more of X1, X2 and X3 are absent; and one or more, two or more, three or more, or four of X17, X18, X19 and X20 are absent.

[0024] In certain examples of peptide inhibitors of Xa: X4 is Abu, Pen, or Cys; X7 is Trp, Bip, Gln, His, Glu(Bzl), 4-Phenylbenzylalanine, Tic, Phe[4-(2-aminoethoxy)], Phe(3,4-Cl_2), Phe(4-OMe), 5-Hydroxy-Trp, 6-Chloro-Trp, N-MeTrp, α-MeTrp, 1,2,3,4 -tetrahydro-norharman, Phe(4-CO_2H), Phe(4-$CONH_2$), Phe(3,4-Dimethoxy), Phe(4-CF_3), ββ-diPheAla, Phe(4-tBu), Glu, Gly, Ile, Asn, Pro, Arg, Thr or Octgly, or a corresponding α-methyl amino acid form of any of the foregoing; X9 is Abu, Pen, or Cys; X10 is 1-Nal, 2-Nal, Aic, Bip, (D)Cys, Cha, DMT, (D)Tyr, Glu, Phe, His, Trp, Thr, Tic, Tyr, 4-pyridylAla, Octgly a Phe analog or a Tyr analog, or a corresponding α-methyl amino acid form of any of the foregoing; X11 is 2-Nal, 1-Nal, 2,4-dimethylPhe, Bip, 4-phenylcyclohexyl, Glu(Bzl), 4-Phenylbenzylalanine, Tic, Phe[4-(2-aminoethoxy)], Phe(3,4-Cl_2), Phe(3,4-F_2), βhPhe(4-F), Phe(4-OMe), 5-Hydroxy-Trp, 6-Chloro-Trp, N-MeTrp, α-MeTrp, 1,2,3,4 -tetrahydro-norharman, Phe(4-CO_2H), Phe(4-$CONH_2$), Phe(3,4-Dimethoxy), Phe(4-CF_3), Phe(2,3-Cl_2), Phe(2,3-F_2),Phe(4-F), 4-phenylcyclohexylalanine, α-MePhe, βhNal, βhPhe, βhTyr, βhTrp, Bip, Nva(5-phenyl), Phe, His, hPhe, Tqa, Trp, Tyr, Phe(4-Me), Trp(2,5,7-tri-tertButyl), Phe(4-OAllyl), Tyr(3-tBu), Phe(4-tBu), Phe(4-guanidino), Phe(4-OBzl), or Octgly, or a corresponding α-methyl amino acid form of any of the foregoing; X12 is α-MeLys, α-MeOrn, α-MeLeu, MeLeu, Aib, (D)Ala, (D)Asn, (D)Leu, (D)Asp, (D)Phe, (D)Thr, 3-Pal, Aib, β-Ala, βhGlu, βhAla, βhLeu, βhVal, β-spiro-pip, Cha, Chg, Asp, Dab, Dap, α-DiethylGly, Glu, Phe, hLeu, hArg, hLeu, Ile, Lys, Leu, Asn, N-MeLeu, N-MeArg, Ogl, Orn, Pro, Gln, Arg, Ser, Thr or Tle, or a corresponding α-methyl amino acid form of any of the foregoing; X13 is Lys(Ac), (D)Asn, (D)Leu, (D)Thr, (D)Phe, Ala, Aib, α-MeLeu, βAla, βhGlu, βhAla, βhLeu, βhVal, β-spiro-pip, Cha, Chg, Asp, Arg, Orn, Dab, Dap, α-DiethylGly, Glu, Phe, hLeu, Lys, Leu, Asn, Ogl, Pro, Gln, Asp, Arg, Ser, spiro-pip, Thr, Tba, Tlc, Val or Tyr, or a corresponding α-methyl amino acid form of any of the foregoing; X14 is Asn, Glu, Phe, Gly, His, Lys, Leu, Met, Asn, Pro, Gln, Arg, Ser, Thr, Tic or Tyr, or a corresponding α-methyl amino acid form of any of the foregoing; X15 is Gly, (D)Ala, (D)Asn, (D)Asp, Asn, (D)Leu, (D)Phe, (D)Thr, Ala, AEA, Asp, Glu, Phe, Gly, Lys, Leu, Pro, Gln, Arg or Ser, or a corresponding α-methyl amino acid form of any of the foregoing, or X15 is Gly, (D)Ala, (D)Asn, (D)Asp, Asn, (D)Leu, (D)Phe, (D)Thr, Ala, Asn, Ser, AEA, Asp, Glu, Phe, Gly, Lys, Leu, Pro, Gln, Arg or Ser, or a corresponding α-methyl amino acid form of any of the foregoing; X16 is absent, Gly, Ala, Asp, Ser, Pro, Asn or Thr, or a corresponding α-methyl

amino acid form of any of the foregoing; and X17 is absent, Glu, Ser, Gly or Gln, or a corresponding α-methyl amino acid form of any of the foregoing. In particular examples, the peptide inhibitor is cyclized via an intramolecular bond between X4 and X9.In certain examples, one or more of X1, X2, and X3 are absent. In certain examples, one or more of X17, X19 and X20 are absent.In certain examples, one of X4 or X9 is Abu, and the other of X4 or X9 is not Abu.In certain examples, the peptide inhibitors comprise one or more, two or more, three or more, or four of the following: X5 is Arg, Gln, Dap or Orn; X6 is Thr or Ser; X7 is Trp, 2-Nal, 1-Nal, Phe(4-OAllyl), Tyr(3-tBu), Phe(4-tBu), Phe(4-guanidino), Phe(4-OBzl), Phe(4-Me), 5-Hydroxy-Trp, 6-Chloro-Trp, N-MeTrp, or α-MeTrp, 1,2,3,4 -tetrahydro-norharman; and X8 is Gln, Val, Phe, Glu or Lys. In certain examples, the peptide inhibitors comprise one or more, two or more, three or more, four or more, five or more, six or more, or seven of the following: X10 is Tyr, Phe(4-OBzl), Phe(4-OMe), Phe(4-$CONH_2$), Phe(3,4-Cl_2), Phe(4-tBu), Phe(4-NH_2), Phe(4-Br), Phe(4-CN), Phe(4-CO_2H), Phe(4-(2aminoethoxy)) or Phe(4-guanadino); X11 is Trp, 2-Nal, 1-Nal, Phe(4-OAllyl), Tyr(3-tBu), Phe(4-tBu), Phe(4-guanidino), Phe(Bzl) or Phe(4-Me), 5-Hydroxy-Trp, 6-Chloro-Trp, N-MeTrp, α-MeTrp or 1,2,3,4 -tetrahydro-norharman; X12 is Arg, hLeu, (D)Asn, Aib, α-MeLys, α-MeLeu or α-MeOrn; X13 is Lys, Glu or Lys(Ac); X14 is Phe or Asn; X15 is Gly, Ser or Ala, or X15 is Asn, Gly, Ser, βAla or Ala; and X16 is absent or AEA.

[0025] Also disclosed is peptide inhibitors comprising the structure of Formula I:

[0026] R^1-X-R^2 (I)

[0027] or a pharmaceutically acceptable salt or solvate thereof, wherein

[0028] R^1 is a bond, hydrogen, a C1-C6 alkyl, a C6-C12 aryl, a C6-C12 aryl, a C1-C6 alkyl, a C1-C20 alkanoyl, and including PEGylated versions alone or as spacers of any of the foregoing;

[0029] R^2 is a bond, OH or NH_2; and

[0030] X is any of the peptide sequences described herein, e.g., Xa, Ia, Ib, Ic, Id, Ie, .

[0031] Also disclosed is 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 has a sequence or structure set forth herein.In certain examples, one or both peptide monomer subunit is cyclized via an intramolecular bond between X4 and X9. In certain examples, one or both intramolecular bond is a disulfide bond, a thioether bond, a lactam bond, a selenoether, diselenide, or an olefin bond. In certain examples, the linker is any of those shown in Table 2. In certain examples, 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 examples, the N-terminus of each peptide monomer subunit is connected by the linker moiety. In particular examples, the C-terminus of each peptide monomer subunit is connected by the linker moiety. In certain examples, 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.

[0031a] In another aspect, the present invention provides 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 has a sequence or structure set forth as described herein.

[0032] Also disclosed a polynucleotide comprising a sequence encoding a peptide inhibitor of the present disclosure or one or both peptide monomer subunit of a peptide dimer inhibitor of the present disclosure. The present disclosure also included a vector comprising the polynucleotide.

[0032a] In yet another aspect, the present invention provides a polynucleotide comprising a sequence encoding the peptide inhibitor or a peptide monomer subunit of the peptide dimer inhibitor disclosed herein.

[0032b] In yet another aspect, the present invention provides a vector comprising the polynucleotide described herein.

[0033] Also disclosed is a pharmaceutical composition comprising a peptide inhibitor or a peptide dimer inhibitor of the present disclosure, and a pharmaceutically acceptable carrier, excipient, or diluent.In particular examples, the pharmaceutical composition comprises an enteric coating.In certain examples, the enteric coating protects and releases the pharmaceutical composition within a subject's lower gastrointestinal system.

[0033a] In yet another aspect, the present invention provides a pharmaceutical composition comprising the peptide inhibitor or the peptide dimer inhibitor described herein, and a pharmaceutically acceptable carrier, excipient, or diluent.

[0033b] In yet another aspect, the present invention provides use of an effective amount of the pharmaceutical composition of claim 29 or claim 30 in the manufacture of a medicament 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.

Also disclosed a use of an effective amount of the pharmaceutical composition as described herein in the manufacture of a medicament 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. Also is 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 the pharmaceutical composition of the present disclosure. In certain examples, 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 examples, 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 examples, the pharmaceutical composition is provided orally for treating Inflammatory Bowel Disease (IBD), ulcerative colitis, Crohn's disease. In certain examples, the pharmaceutical composition is provided to the subject topically, parenterally, intravenously, subcutaneously, peritonealy, or intravenously for treating psoriasis.

BRIEF DESCRIPTION OF THE DRAWINGS

[0034] Figure 1 provides an example of a rat IL-23 dose-response curve as measured by levels of IL-17A in the rat splenoctye assay.

[0035] Figure 2 is a graph showing IL-12-dependent production of IFNγ from human PBMCs treated with the indicated amounts of Compound A or Compound B.

[0036] Figure 3 shows results for DAI values from Day 7. Statistical analysis for significance was determined using Student's t-test (GraphPad Prism). Differences were noted as signficant *$p<0.05$, **$p<0.01$, ***$p<0.001$, ****$p<0.0001$.

[0037] Figure 4 shows an alignment of the amino acid sequences of human IL23R (SEQ ID NO: 760), mouse IL-23R (SEQ ID NO: 761), rat IL23R (SEQ ID NO: 762), chimp IL-23R (SEQ ID NO: 763), dog IL-23R (SEQ ID NO: 764) and cow IL-23R (SEQ ID NO: 765), with highly conserved amino acid

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 (Xa):

X1-X2-X3-X4-X5-X6-X7-X8-X9-X10-X11-X12-X13-X14-X15-X16-X17-X18-X19-X20 (Xa)

wherein

X1 is any amino acid or absent;

X2 is any amino acid or absent;

X3 is any amino acid or absent;

X4 is Cys, Pen, hCys, D-Pen, D-Cys, D-hCys, Met, Glu, Asp, Lys, Orn, Dap, Dab, D-Dap, D-Dab, D-Asp, D-Glu, D-Lys, Sec, 2-chloromethylbenzoic acid, mercapto-propanoic acid, mercapto-butyric acid, 2-chloro-acetic acid, 3-choro-propanoic acid, 4-chloro-butyric acid, 3-chloro-isobutyric acid, Abu, β-azido-Ala-OH, propargylglycine, 2-(3'-butenyl)glycine, 2-allylglycine, 2-(3'-butenyl)glycine, 2-(4'-pentenyl)glycine, 2-(5'-hexenyl)glycine;

X5 is any amino acid;

X6 is any amino acid;

X7 is Trp, Glu, Gly, Ile, Asn, Pro, Arg, Thr or OctGly, or a corresponding α-methyl amino acid form of any of the foregoing;

X8 is any amino acid;

X9 is Cys, Pen, hCys, D-Pen, D-Cys, D-hCys, Glu, Lys, Orn, Dap, Dab, D-Dap, D-Dab, D-Asp, D-Glu, D-Lys, Asp, Leu, Val, Phe, Ser, Sec, Abu, β-azido-Ala-OH, propargylglycine, 2-2-allylglycine, 2-(3'-butenyl)glycine, 2-(4'-pentenyl)glycine, Ala, hCys, Met, MeCys, (D)Tyr or 2-(5'-hexenyl)glycine;

X10 is Tyr, Phe(4-OMe), 1-Nal, 2-Nal, Aic, α-MePhe, Bip, (D)Cys, Cha, DMT, (D)Tyr, Glu, His, hPhe(3,4-dimethoxy), hTyr, N-Me-Tyr, Trp, Phe(4-$CONH_2$), Phe(4-phenoxy), Thr, Tic, Tyr(3-tBu), Phe(4-tBu), Phe(4-CN), Phe(4-Br), Phe(4-NH_2), Phe(4-F), Phe(3,5-F_2), Phe(4-CH_2CO_2H), Phe(penta-F), Phe(3,4-Cl_2), Phe(4-CF_3), Bip, Cha, 4-PyridylAlanine, βhTyr, OctGly,

Phe(4-N_3), Phe(4-Br), Phe[4-(2-aminoethoxy)], Phe, a Phe analog, or a Tyr analog, or a corresponding α-methyl amino acid form of any of the foregoing;

X11 is 2-Nal, 1-Nal, 2,4-dimethylPhe, Bip, Phe(3,4-Cl_2), Phe (3,4-F_2), Phe(4-CO_2H), βhPhe(4-F), α-Me-Trp, 4-phenylcyclohexyl, Phe(4-CF_3), Phe(3,4-OMe_2), α-MePhe, βhNal, βhPhe, βhTyr, βhTrp, Nva(5-phenyl), Phe, His, hPhe, Tic, Trp, Tyr, Phe(4-OMe), Phe(4-Me), Trp(2,5,7-tri-tert-Butyl), Phe(4-Oallyl), Tyr(3-tBu), Phe(4-tBu), Phe(4-guanidino, Phe(4-OBzl), Octgly, Glu(Bzl), 4-Phenylbenzylalanine, Phe[4-(2-aminoethoxy)], 5-Hydroxy-Trp, 6-Chloro-Trp, N-MeTrp, 1,2,3,4-tetrahydro-norharman, Phe(4-$CONH_2$), Phe(3,4-Dimethoxy), Phe(2,3-Cl_2), Phe(2,3-F_2), Phe(4-F), 4-phenylcyclohexylalanine or Bip, or a corresponding α-methyl amino acid form of any of the foregoing;

X12 is His, Phe, Arg, N-Me-His, Val, Cav, Cpa, Leu, Cit, hLeu, 3-Pal, t-butyl-Ala, α-MeLys, D-Ala, (D)Asn, (D)Asp, (D)Leu, (D)Phe, (D)Tyr, Aib, α-MeLeu, α-MeOrn, β-Aib, β-Ala, βhAla, βhArg, βhLeu, βhVal, β-spiro-pip, Glu, hArg, Ile, Lys, N-MeLeu, N-MeArg, Ogl, Orn, Pro, Gln, Ser, Thr, Tle,t-butyl-Gly, 4-amino-4-carboxy-tetrahydropyran (THP), Achc Acpc, Acbc, Acvc, Agp, Aib, α-DiethylGly, α-MeLys(Ac), α-MeOrn, α-MeSer, α-MeVal, Cha, Cit, Cpa, (D)Asn, Glu, hArg, or Lys, or a corresponding α-methyl amino acid form of any of the foregoing;

X13 is Thr, Sarc, Glu, Phe, Arg, Leu, Asn, Cit, Lys, Arg, Orn, Val, βhAla, Lys(Ac), (D)Asn, (D)Leu, (D)Phe, (D)Thr, Ala, α-MeLeu, Aib, β-Ala, β-Glu, βhLeu, βhVal, β-spiro-pip, Cha, Chg, Asp, Dab, Dap, α-DiethylGly, hLeu, Asn, Ogl, Pro, Gln, Ser, β-spiro-pip, Thr, Tle or Aib, or a corresponding α-methyl amino acid form of any of the foregoing;

X14 is Phe, Tyr, Glu, Gly, His, Lys, Leu, Met, Asn, Lys(Ac), Dap(Ac), Dab(Ac), Asp, Pro, Gln, Arg, Ser, Thr, Tic or βhPhe, or a corresponding α-methyl amino acid form of any of the foregoing;

X15 is Gly, Ser, Thr, Gln, Ala, (D)Ala, (D)Asn, (D)Asp, (D)Leu, (D)Phe, (D)Thr, Aea, Asp, Asn, Glu, Phe, Gly, Lys, Leu, Pro, Arg, β-Ala, or Sarc, or a corresponding α-methyl amino acid form of any of the foregoing,

X16 is any amino acid or absent;

X17 is any amino acid or absent;

X18 is any amino acid or absent;

X19 is any amino acid or absent; and
X20 is any amino acid or absent,
wherein the peptide inhibitor is cyclized via a bond between X4 and X9, and
wherein the peptide inhibitor inhibits the binding of an interleukin-23 (IL-23) to an IL-23 receptor.

2. The peptide inhibitor or pharmaceutically acceptable salt thereof of claim 1, wherein the bond between X4 and X9 is a disulfide bond, a thioether bond, a lactam bond, a triazole ring, or an olefin bond.

3. The peptide inhibitor or pharmaceutically acceptable salt thereof of claim 1 or claim 2, wherein the peptide inhibitor comprises an N-terminal Acetyl group.

4. The peptide inhibitor or pharmaceutically acceptable salt thereof of any one of claims 1-3, wherein the peptide inhibitor comprises a C-terminal NH_2 group.

5. The peptide inhibitor or pharmaceutically acceptable salt thereof of any one of claims 1-4, wherein X4 is Pen and X9 is Pen, and the bond is a disulfide bond.

6. The peptide inhibitor of claim 5, wherein
X7 is Trp;
X10 is Phe, Tyr, a Phe analog, or a Tyr analog;
X11 is Trp, 1-Nal or 2-Nal; and
X12 is Aib, α-Me-Lys, α-Me-Val α-Me-Leu; Achc, Acvc, Acpc, Acpc or THP,.

7. The peptide inhibitor of claim 6, wherein the peptide inhibitor comprises any of the following the amino acid sequences:
Ac-[Pen]-Q-T-W-Q-[Pen]-[Phe(4-OMe)]-[2-Nal]-[α-Me-Lys]-ENG-NH_2 (SEQ ID NO: 282);
Ac-[Pen]-N-T-W-Q-[Pen]-[Phe[4-(2-aminoethoxy)]-[2-Nal]-[Aib]-[Lys(Ac)]-NN-NH_2 (SEQ ID NO: 283);

Ac-[Pen]-Q-T-W-Q-[Pen]-[Phe[4-(2-aminoethoxy)]-[2-Nal]-[α-MeLeu]-[Lys(Ac)]-NN-NH_2 (SEQ ID NO: 285);

Ac-[Pen]-QTWQ-[Pen]-[Phe(4-$CONH_2$)]-[2-Nal]-[α-MeLys]-[Lys(Ac)]-NN-NH_2(SEQ ID NO: 668);

Ac-[Pen]-QTWQ-[Pen]-[Phe[4-(2-aminoethoxy)]-[2-Nal]-[α-MeLeu]-QNN-NH_2 (SEQ ID NO: 603);

Ac-[Pen]-Q-T-W-Q-[Pen]-[Phe(4-$CONH_2$)]-[2-Nal]-[α-MeLys]-[Lys(Ac)]-NN-NH_2 (SEQ ID NO: 286);

Ac-[Pen]-QTWQ-[Pen]-[Phe[4-(2-aminoethoxy)]-[2-Nal]-[α-MeLys]-[Lys(Ac)]-NG-NH_2 (SEQ ID NO: 598);

Ac-[Pen]-QTWQ-[Pen]-[Phe[4-(2-aminoethoxy)]-[2-Nal]-[α-MeLys]-[Lys(Ac)]-NN-NH_2 (SEQ ID NO: 1034);

Ac-[Pen]-QTWQ-[Pen]-[Phe[4-(2-aminoethoxy)]-[2-Nal]-[α-MeLys]-ENA-NH_2 (SEQ ID NO: 601);

Ac-[Pen]-QTWQ-[Pen]-[Phe[4-(2-aminoethoxy)]-[2-Nal]-[α-MeLeu]-[Lys(Ac)]-NN-NH_2 (SEQ ID NO: 602);

Ac-[Pen]-QTWQ-[Pen]-[Phe[4-(2-aminoethoxy)]-[2-Nal]-[α-MeLeu]-QNN-NH_2 (SEQ ID NO: 603);

Ac-[Pen]-QTWQ-[Pen]-[Phe[4-(2-aminoethoxy)]-[2-Nal]-[Aib]-ENN-NH_2 (SEQ ID NO: 604);

Ac-[Pen]-QTWQ-[Pen]-[Phe[4-(2-aminoethoxy)]-[2-Nal]-Aib-[Lys(Ac)]-NN-NH_2 (SEQ ID NO: 605);

Ac-[Pen]-QTWQ-[Pen]-[Phe[4-(2-aminoethoxy)]-[2-Nal]-[Aib]-[Lys(Ac)]-NQ-NH_2 (SEQ ID NO: 606);

Ac-[Pen]-QTWQ-[Pen]-[Phe[4-(2-acetylaminoethoxy)]-[2-Nal]-[α-MeLeu]-[Lys(Ac)]-NN-NH_2 (SEQ ID NO: 613);

Ac-[Pen]-QTWQ-[Pen]-[Phe[4-(2-acetylaminoethoxy)]-[2-Nal]-[α-MeLeu]-QNN-NH_2 (SEQ ID NO: 614);

Ac-[Pen]-NTWQ-[Pen]-[Phe[4-(2-aminoethoxy)]-[2-Nal]-[Aib]-[Lys(Ac)]-N-[βAla]-NH_2 (SEQ ID NO: 639);

Ac-[Pen]-NTWQ-[Pen]-[Phe[4-(2-aminoethoxy)]-[2-Nal]-[hLeu]-[Lys(Ac)]-N-[βAla]-NH_2 (SEQ ID NO: 641);

Ac-[Pen]-QTWQ-[Pen]-[Phe[4-(2-acetylaminoethoxy)]-[2-Nal]-[Aib]-[Lys(Ac)]-NN-NH_2 (SEQ ID NO: 616);

Ac-[Pen]-NTWQ-[Pen]-[Phe[4-(2-aminoethoxy)]-[2-Nal]-[Aib]-[Lys(Ac)]-NN-NH_2 (SEQ ID NO: 632);

Ac-[Pen]-QTWQ-[Pen]-[Phe[4-(2-acetylaminoethoxy)]-[2-Nal]-[Aib]-[Lys(Ac)]-NQ-NH_2 (SEQ ID NO: 617); or

Ac-[Pen]-QTWQ-[Pen]-[Phe(4-OMe)]-[2-Nal]-[Aib]-[Lys(Ac)]-NQ-NH_2 (SEQ ID NO: 623), wherein the peptide inhibitor comprises a disulfide bond between the two Pen amino acids.

8. The peptide inhibitor or pharmaceutically acceptable salt thereof of claim 5, wherein:

X1 is absent;

X2 is absent;

X3 is Glu, (D)Glu, Arg, (D)Arg, Phe, (D)Phe, 2-Nal, Thr, Leu, (D)Gln, or absent;

X4 is Pen;

X5 is Dap, Dap(Ac), Gly, Lys, Gln, Arg, Ser, Thr, or Asn;

X6 is Thr;

X7 is Trp;

X8 is Gln;

X9 is Pen;

X10 is 2-Nal, a Phe analog, Tyr, or a Tyr analog;

X11 is 1-Nal, 2-Nal, Phe(3,4-dimethoxy), or Phe(3,4-Cl_2);

X12 is Acpc, Acbc, Acvc, Achc, Aib, α-DiethylGly, α-MeLys, α-MeLys(Ac), α-MeLeu, α-MeOrn, α-MeSer, α-MeVal, Cha, Cit, hLeu, Lys, Leu, Arg, or 4-amino-4-carboxy-tetrahydropyran;

X13 is Cit, Asp, Glu, Lys, Lys(Ac), Asn, or Gln;

X14 is Dab(Ac), Dap(Ac), His, Lys(Ac), Asn, Gln, or Tyr;

X15 is Ala, betaAla, Gly, Asn, Gln, or Ser;

X16 is any amino acid or absent;

X17 is any amino acid or absent;

X18 is any amino acid or absent;
X19 is any amino acid or absent; and
X20 is any amino acid or absent, wherein the peptide inhibitor is cyclized via a disulfide bond between X4 and X9 of the amino acid sequence, and
wherein 2-Nal is L-2-Napthylalanine, Pen is L-Penicillamine, Dap is L-Diaminopropionic acid, Dap(Ac) is L-Diaminopropionic acid(Ac), 1-Nal is L-1-Napthylalanine,
Acpc is 1-aminocyclopropylcarboxylic acid, Acbc is 1-aminocyclobutanecarboxylic acid, Acvc is 1-aminocyclopentanecarboxylic acid, Achc is 1-aminocyclohexanecarboxylic acid, Aib is 2-aminoisobutyric acid, α-MeLys is alpha-methyl-L-Lysine, α-MeLys(Ac) is alpha-methyl-L-Lysine(Ac), α-MeLeu is alpha-methyl-L-Leucine, α-MeOrn is alpha-methyl-L-Ornathine, α-MeSer is alpha-methyl-L-Serine, α-MeVal is alpha-methyl-L-Valine, Cha is Cyclohexyl-L-alanine, Cit is L-Citrulline, hLeu is L-homoLeucine, Dab(Ac) is L-Diaminobutyric acid(Ac), and betaAla is Beta-alanine.

9. The peptide inhibitor or pharmaceutically acceptable salt thereof of claim 8, wherein X10 is a Phe analog.

10. The peptide inhibitor or pharmaceutically acceptable salt thereof of claim 9, wherein X10 is Phe(4-OMe), Phe(4-$CONH_2$), Phe[4-(2-acetylaminoethoxy) or Phe[4-(2-aminoethoxy)].

11. The peptide inhibitor or pharmaceutically acceptable salt thereof of claim 8, wherein X11 is 2-Nal.

12. The peptide inhibitor or pharmaceutically acceptable salt thereof of claim 8, wherein the peptide inhibitor or pharmaceutically acceptable salt thereof is selected from the group consisting of:
Ac-[Pen]-QTWQ-[Pen]-[Phe[4-(2-aminoethoxy)]-[2-Nal]-[α-MeLeu]-[Lys(Ac)]-NN-NH_2 (SEQ ID NO:602) or a pharmaceutically acceptable salt thereof, wherein the peptide inhibitor is cyclized via a disulfide bond between the Pens;

Ac-[Pen]-NTWQ-[Pen]-[Phe[4-(2-aminoethoxy)]-[2-Nal]-[Aib]-[Lys(Ac)]-NN-NH_2 (SEQ ID NO:632) or a pharmaceutically acceptable salt thereof, wherein the peptide inhibitor is cyclized via a disulfide bond between the Pens;

Ac-[Pen]-NTWQ-[Pen]-[Phe[4-(2-aminoethoxy)]-[2-Nal]-[Aib]-[Lys(Ac)]-N-[betaAla]-NH_2 (SEQ ID NO:639) or a pharmaceutically acceptable salt thereof, wherein the peptide inhibitor is cyclized via a disulfide bond between the Pens;

Ac-[Pen]-QTWQ-[Pen]-[Phe(4-OMe)]-[2-Nal]-[α-MeLys]-[Lys(Ac)]-NN-NH_2 (SEQ ID NO:666) or a pharmaceutically acceptable salt thereof, wherein the peptide inhibitor is cyclized via a disulfide bond between the Pens;

Ac-[Pen]-QTWQ-[Pen]-[Phe(4-$CONH_2$)]-[2-Nal]-[α-MeLys]-[Lys(Ac)]-NN-NH_2 (SEQ ID NO:668) or a pharmaceutically acceptable salt thereof, wherein the peptide inhibitor is cyclized via a disulfide bond between the Pens;

Ac-[Pen]-QTWQ-[Pen]-[Phe(4-$CONH_2$)]-[2-Nal]-[α-MeVal]-[Lys(Ac)]-NN-NH_2 (SEQ ID NO:669) or a pharmaceutically acceptable salt thereof, wherein the peptide inhibitor is cyclized via a disulfide bond between the Pens;

a dimer of two peptide monomers: Ac-[Pen]-QTWQ-[Pen]-[Phe[4-(2-acetylaminoethoxy)]-[2-Nal]-[α-MeVal]-KNN-NH_2 (SEQ ID NO:530), or a pharmaceutically acceptable salt thereof, wherein each of the peptide monomers is cyclized via a disulfide bond between the Pens, and wherein the peptide monomers are linked by a DiGlycolic acid (DIG) linker;

a dimer of two peptide monomers: Ac-[Pen]-QTWQ[Pen]-[Phe[4-(2-acetylaminoethoxy)]-[2-Nal]-K-[Lys(Ac)]-NN-NH_2 (SEQ ID NO:531), or a pharmaceutically acceptable salt thereof, wherein each of the peptide monomers is cyclized via a disulfide bond between the Pens, and wherein the peptide monomers are linked by a DiGlycolic acid (DIG) linker;

a dimer of two peptide monomers: Ac-[Pen]-QTWQ-[Pen]-[Phe(4-OMe)]-[2-Nal]-[α-MeLys]-[Lys(Ac)]-NN-NH_2 (SEQ ID NO:532), or a pharmaceutically acceptable salt thereof, wherein each of the peptide monomers is cyclized via a disulfide bond between the Pens, and wherein the peptide monomers are linked by a DiGlycolic acid (DIG) linker;

a dimer of two peptide monomers: Ac-[Pen]-QTWQ-[Pen]-[Phe(4-$CONH_2$)]-[2-Nal]-[α-MeLys]-[Lys(Ac)]-NN-NH_2 (SEQ ID NO:534), or a pharmaceutically acceptable salt thereof, wherein each of the peptide monomers is cyclized via a disulfide bond between the Pens, and wherein the peptide monomers are linked by a DiGlycolic acid (DIG) linker;

Ac-[(D)Phe]-[Pen]-NTWQ[Pen]-[Phe(4-OMe)]-[2-Nal]-[4-amino-4-carboxy-tetrahydropyran]-[Cit]-NN-NH_2 (SEQ ID NO:1048) or a pharmaceutically acceptable salt thereof, wherein the peptide inhibitor is cyclized via a disulfide bond between the Pens;

Ac-[(D)Phe]-[Pen]-NTWQ[Pen]-[Phe(4-OMe)]-[2-Nal]-[Achc]-ENN-NH_2 (SEQ ID NO:1049) or a pharmaceutically acceptable salt thereof, wherein the peptide inhibitor is cyclized via a disulfide bond between the Pens;

Ac-[Pen]-NTWQ[Pen]-[Phe($CONH_2$)]-[2-Nal]-[Aib]-[Lys(Ac)]-NN-NH_2 (SEQ ID NO:1050) or a pharmaceutically acceptable salt thereof, wherein the peptide inhibitor is cyclized via a disulfide bond between the Pens;

a dimer of two peptide monomers: Ac-[Pen]-NTWQ-[Pen]-[Phe(4-$CONH_2$)]-[2-Nal]-[Aib]-KNN-NH_2 (SEQ ID NO:535), or a pharmaceutically acceptable salt thereof, wherein each of the peptide monomers is cyclized via a disulfide bond between the Pens, and wherein the peptide monomers are linked by a DiGlycolic acid (DIG) linker;

a dimer of two peptide monomers: Ac-[Pen]-QTWQ-[Pen]-[Phe(4-$CONH_2$)]-[2-Nal]-[α-MeLys]-[Lys(Ac)]-NN-NH_2 (SEQ ID NO:534), or a pharmaceutically acceptable salt thereof, wherein each of the peptide monomers is cyclized via a disulfide bond between the Pens, and wherein the peptide monomers are linked by a DiGlycolic acid (DIG) linker;

Ac-[(D)Phe]-[Pen]-NTWQ[Pen]-[Phe(4-OMe)]-[2-Nal]-[4-amino-4-carboxy-tetrahydropyran]-[Cit]-NN-NH_2 (SEQ ID NO:1048) or a pharmaceutically acceptable salt thereof, wherein the peptide inhibitor is cyclized via a disulfide bond between the Pens;

Ac-[(D)Phe]-[Pen]-NTWQ[Pen]-[Phe(4-OMe)]-[2-Nal]-[Achc]-ENN-NH_2 (SEQ ID NO:1049) or a pharmaceutically acceptable salt thereof, wherein the peptide inhibitor is cyclized via a disulfide bond between the Pens;

Ac-[Pen]-NTWQ[Pen]-[Phe($CONH_2$)]-[2-Nal]-[Aib]-[Lys(Ac)]-NN-NH_2 (SEQ ID NO:1050) or a pharmaceutically acceptable salt thereof, wherein the peptide inhibitor is cyclized via a disulfide bond between the Pens; and

a dimer of two peptide monomers: Ac-[Pen]-NTWQ-[Pen]-[Phe(4-$CONH_2$)]-[2-Nal]-[Aib]-KNN-NH_2 (SEQ ID NO:535), or a pharmaceutically acceptable salt thereof, wherein each of the peptide monomers is cyclized via a disulfide bond between the Pens, and wherein the peptide monomers are linked by a DiGlycolic acid (DIG) linker.

13. The peptide inhibitor or pharmaceutically acceptable salt thereof of any one of claims 1-4, wherein

X4 is Abu, 2-chloromethylbenzoic acid, mercapto-propanoic acid, mercapto-butyric acid, 2-chloro-acetic acid, 3-chloro-propanoic acid, 4-chloro-butyric acid, 3-chloro-isobutyric acid; and

X9 is Abu, Cys, Pen, hCys, D-Pen, D-Cys, or D-hCys, and

the bond between X4 and X9 is a thioether bond.

14. The peptide inhibitor or pharmaceutically acceptable salt thereof of claim 13, wherein

(a) X4 is Abu and X9 is Cys; or

(b) X4 is Cys and X9 is Abu.

15. The peptide inhibitor or pharmaceutically acceptable salt thereof of claim 13 or claim 14, wherein

X7 is Trp;

X10 is Phe, Tyr, a Phe analog, or a Tyr analog;

X11 is Trp, 1-Nal or 2-Nal; and

X12 is α-Me-Lys, α-Me-Leu, α-Me-Ser, α-Me-Val, Achc, Acvc, Acpc, Acbc or 4-amino-4-carboxy-tetrahydropyran.

16. The peptide inhibitor of claim 15, wherein the peptide inhibitor comprises any of the following amino acid sequences:

Ac-Cyclo-[[Abu]-QTWQC]]-[Phe(4-OMe)]-[2-Nal]-[α-MeLys]-E-N-G (SEQ ID NO: 430);

Ac-Cyclo-[[Abu]-QTWQC]]-[Phe(4-OMe)]-[2-Nal]-[α-MeOrn]-ENG-NH_2 (SEQ ID NO: 431);

Ac-Cyclo-[[Abu]-QTWQC]]-[Phe(4-CO_2H)]-[2-Nal]-[α-MeLys]-[Lys(Ac)]-NG-NH_2 (SEQ ID NO: 432);

Ac-Cyclo-[[Abu]-QTWQC]]-[Phe(4-OMe)]-[2-Nal]-[α-MeLys]-[Lys(Ac)]-NG-NH_2 (SEQ ID NO: 433);

Ac-Cyclo-[[Abu]-QTWQC]]-[Phe(4-$CONH_2$)]-[2-Nal]-[α-MeLys]-[Lys(Ac)]NG-NH_2 (SEQ ID NO: 434);

Ac-Cyclo-[[Abu]-QTWQC]]-[Phe(4-OMe)]-[2-Nal]-[α-MeLys]-[Lys(Ac)]-NA-NH_2 (SEQ ID NO: 435);

Ac-Cyclo-[[Abu]-QTWQC]]-[Phe(4-OMe)]-[2-Nal]-[α-MeLys]-[Lys(Ac)]-NAE-NH_2 (SEQ ID NO: 436);

Ac-Cyclo-[[Abu]-QTWQC]]-[Phe[4-(2-aminoethoxy)]]-[2-Nal]-[α-MeLys]-ENG-NH_2 (SEQ ID NO: 437);

Ac-Cyclo-[[Abu]-QTWQC]]-[Phe(4-(2-aminoethoxy))]-W-[α-MeLys]-E-N-G (SEQ ID NO: 438);

Ac-Cyclo-[[Abu]-QTWQC]]-[Phe[4-(2-aminoethoxy)]]-[2-Nal]-[α-MeLys]-DNG-NH_2 (SEQ ID NO: 439);

Ac-Cyclo-[[Abu]-QTWQC]]-[Phe[4-(2-aminoethoxy)]]-[2-Nal]-[α-MeLys]-[Lys(succinic acid)]-NG-NH_2 (SEQ ID NO: 440);

Ac-Cyclo-[[Abu]-QTWQC]]-[Phe[4-(2-aminoethoxy)]]-[2-Nal]-[α-MeLys]-[Lys(glutaric acid)]-NG-NH_2 (SEQ ID NO: 441);

Ac-Cyclo-[[Abu]-QTWQC]]-[Phe[4-(2-aminoethoxy)]]-[2-Nal]-[α-MeLys]-[Lys(pyroglutamic acid)]-NG-NH_2 (SEQ ID NO: 442);

Ac-Cyclo-[[Abu]-QTWQC]]-[Phe[4-(2-aminoethoxy)]]-[2-Nal]-[α-MeLys]-[Lys(Ac)]-NG-[(D)Lys]-NH_2 (SEQ ID NO: 444);

Ac-Cyclo-[[Abu]-QTWQC]]-[Phe[4-(2-aminoethoxy)]]-[2-Nal]-[α-MeLys]-[Lys(Ac)]-NG-[AEA]-NH_2 (SEQ ID NO: 445);

Ac-Cyclo-[[Abu]-QTWQC]]-[Phe[4-(2-aminoethoxy)]]-[2-Nal]-[Aib]-QNG-NH_2 (SEQ ID NO: 446);

Ac-Cyclo-[[Abu]-QTWQC]]-[Phe[4-(2-aminoethoxy)]]-[2-Nal]-[Aib]-[Lys(Ac)]-NA-NH_2 (SEQ ID NO: 447);

Ac-Cyclo-[[Abu]-QTWQC]]-[Phe[4-(2-aminoethoxy)]]-[2-Nal]-[Aib]-KNG-NH_2 (SEQ ID NO: 448);

Ac-Cyclo-[[Abu]-QTWQC]]-[Phe[4-(2-aminoethoxy)]]-[2-Nal]-[α-MeLys]-[Lys(Ac)]-NG-NH_2 (SEQ ID NO: 449);

Ac-Cyclo-[[Abu]-QTWQC]]-[Phe[4-(2-(acetyl-aminoethoxy)]]-[2-Nal]-[α-MeLys(Ac)]-[Lys(Ac)]-NG-NH_2 (SEQ ID NO: 656);

Ac-Cyclo-[[Abu]-QTWQC]]-[Phe[4-(2-(acetyl-aminoethoxy)]]-[2-Nal]-[α-MeLys(Ac)]-ENG-NH_2 (SEQ ID NO: 657);

Ac-Cyclo-[[Abu]-QTWQC]]-[Phe[4-(2-aminoethoxy)]]-[2-Nal]-[4-amino-4-carboxy-tetrahydropyran]-ENN-NH_2 (SEQ ID NO: 658);

Ac-Cyclo-[[Abu]-QTWQC]]-[Phe[4-(2-aminoethoxy)]]-[2-Nal]-[α-MeLys]-ENQ-NH_2 (SEQ ID NO: 659);

Ac-Cyclo-[[Abu]-QTWQC]-[Phe[4-(2-aminoethoxy)]]-[2-Nal]-[α-MeLys]-ENN-NH_2 (SEQ ID NO: 912);

Ac-Cyclo-[[Abu]-QTWQC]]-[Phe[4-(2-aminoethoxy)]]-[2-Nal]-[α-MeVal]-[Lys(Ac)]-NG-NH_2 (SEQ ID NO: 660);

Ac-Cyclo-[[Abu]-QTWQC]]-[Phe[4-(2-aminoethoxy)]]-[2-Nal]-[hLeu]-[Lys(Ac)]-N-[βAla]-NH_2 (SEQ ID NO: 661);

Ac-Cyclo-[[Abu]-QTWQC]]-[Phe[4-(2-(acetyl-aminoethoxy)]]-[2-Nal]-[α-MeLys(Ac)]-ENQ-NH_2 (SEQ ID NO: 662);

Ac-Cyclo-[[Abu]-QTWQC]]-[Phe[4-(2-(acetyl-aminoethoxy)]]-[2-Nal]-[α-MeLys(Ac)]-ENN-NH_2 (SEQ ID NO: 663);

Ac-Cyclo-[[Abu]-QTWQC]]-[Phe[4-(2-aminoethoxy)]]-[2-Nal]-[α-MeLeu]-ENN-NH_2 (SEQ ID NO: 664);

Ac-Cyclo-[[Abu]-QTWQC]]-[Phe[4-(2-aminoethoxy)]]-[2-Nal]-[α-MeLeu)-[Cit]-NN-NH_2 (SEQ ID NO: 665);

Ac-Cyclo-[[Abu]-QTWQC]]-[Phe[4-(2-aminoethoxy)]]-[2-Nal]-[α-MeLeu]-[Lys(Ac)]-NN-NH_2 (SEQ ID NO: 766);

Ac-Cyclo-[[Abu]-QTWQC]]-[Phe[4-(2-aminoethoxy)]]-[2-Nal]-[Aib]-[Lys(Ac)]-NG-NH_2 (SEQ ID NO: 767);

Ac-E-Cyclo-[[Abu]-QTWQC]-[Phe[4-(2-aminoethoxy)]]-[2-Nal]-[α-MeLys]-ENN-NH_2 (SEQ ID NO: 965);

Ac-(D)Glu-[Cyclo-[[Abu]-QTWQC]-[Phe[4-(2-aminoethoxy)]]-[2-Nal]-[α-MeLys]-ENN-NH_2 (SEQ ID NO: 966);

Ac-Arg-Cyclo-[[Abu]-QTWQC]-[Phe[4-(2-aminoethoxy)]]-[2-Nal]-[α-MeLys]-ENN-NH_2 (SEQ ID NO: 967);

Ac-[(D)Arg-Cyclo-[[Abu]-QTWQC]-[Phe[4-(2-aminoethoxy)]]-[2-Nal]-[α-MeLys]-ENN-NH_2 (SEQ ID NO: 1041);

Ac-F-Cyclo-[[Abu]-QTWQC]]-[Phe[4-(2-aminoethoxy)]]-[2-Nal]-[α-MeLys]-ENN-NH_2 (SEQ ID NO: 969);

Ac-[(D)Phe]-Cyclo-[[Abu]-QTWQC]-[Phe[4-(2-aminoethoxy)]]-[2-Nal]-[α-MeLys]-ENN-NH_2 (SEQ ID NO: 970);

Ac-[2-Nal]-Cyclo-[[Abu]-QTWQC]-[Phe[4-(2-aminoethoxy)]]-[2-Nal]-[α-MeLys]-ENN-NH_2 (SEQ ID NO: 971);

Ac-Leu-Cyclo-[[Abu]-QTWQC]-[Phe[4-(2-aminoethoxy)]]-[2-Nal]-[α-MeLys]-ENN-NH_2 (SEQ ID NO: 973);

Ac-[(D)Gln]-Cyclo-[[Abu]-QTWQC]-[Phe[4-(2-aminoethoxy)]]-[2-Nal]-[α-MeLys]-ENN-NH_2 (SEQ ID NO: 1042);

Ac-Cyclo-[[Abu]-QTWQC]-[Phe[4-(2-aminoethoxy)]]-[2-Nal]-[α-MeLeu]-ENG-NH_2 (SEQ ID NO: 842);

Ac-T-Cyclo-[[Abu]-QTWQC]-[Phe[4-(2-aminoethoxy)]]-[2-Nal]-[α-MeLys]-ENN-NH_2 (SEQ ID NO: 972);

Ac-Cyclo-[[Abu]-QTWQC]]-[Phe[4-(2-aminoethoxy)]]-[2-Nal]-[α-MeLeu]-QN-[βAla]-NH_2 (SEQ ID NO: 752);

Ac-Cyclo-[[Abu]-QTWQC]]-[Phe[4-(2-aminoethoxy)]]-[2-Nal]-[Acbc]-ENN-NH_2 (SEQ ID NO: 753);

Ac-Cyclo-[[Abu]-QTWQC]]-[Phe[4-(2-aminoethoxy)]]-[2-Nal]-[Achc]- ENN-NH_2 (SEQ ID NO: 754);

Ac-Cyclo-[[Abu]-QTWQC]]-[Phe[4-(2-aminoethoxy)]]-[2-Nal]-[Acvc]-ENN-NH_2 (SEQ ID NO: 755);

Ac-Cyclo-[[Abu]-QTWQC]-[Phe[4-(2-aminoethoxy)]]-[2-Nal]-[4-amino-4-carboxy-piperidine]-ENN-NH_2 (SEQ ID NO: 979);

Ac-Cyclo-[[Abu]-QTWQC]-[Phe[4-(2-aminoethoxy)]]-[2-Nal]-[4-amino-4-carboxy-tetrahydropyran]-ENN-NH_2 (SEQ ID NO: 980);

Ac-Cyclo-[[Abu]-QTWQC]-[Phe[4-(2-aminoethoxy)]]-[2-Nal]-[α-MeLeu]-[Lys(Ac)]-NG-NH_2 (SEQ ID NO: 981);

Ac-Cyclo-[[Abu]-QTWQC]-[Phe[4-(2-aminoethoxy)]]-[2-Nal]-[α-MeLeu]-ENG-NH_2 (SEQ ID NO: 982);

Ac-Cyclo-[[Abu]-QTWQC]-[Phe[4-(2-aminoethoxy)]]-[2-Nal]-[α-MeLeu]-QNG-NH_2 (SEQ ID NO: 983);

Ac-Cyclo-[[Abu]-QTWQC]-[Phe[4-(2-aminoethoxy)]]-[2-Nal]-[α-MeLeu]-QN-[βAla]-NH_2 (SEQ ID NO: 984);

Ac-Cyclo-[[Abu]-QTWQC]-[Phe[4-(2-aminoethoxy)]]-[2-Nal]-[Aib]-QN-[βAla]-NH2 (SEQ ID NO: 987);

Ac-Cyclo-[[Abu]-QTWQC]-[Phe[4-(2-aminoethoxy)]]-[1,2,3,4-tetrahydro–norharman]-[Aib]-QNG-NH2 (SEQ ID NO: 988);

Ac-(D)Phe-Cyclo-[[Abu]-QTWQC]-[Phe[4-(2-aminoethoxy)]]-[2-Nal]-[4-amino-4-carboxy-tetrahydropyran]-ENN-NH2 (SEQ ID NO: 992), or

Ac-[(D)Arg]-Cyclo-[[Abu]-QTWQC]-[Phe[4-(2-aminoethoxy)]]-[2-Nal]-[4-amino-4-carboxy-tetrahydropyran]-ENN-NH2 (SEQ ID NO: 993),

wherein "Cyclo" indicates the peptide inhibitor comprises a thioether bond between the Abu and the C.

17. The peptide inhibitor or pharmaceutically acceptable salt thereof of any one of claims 1-4, wherein

X1 is any amino acid or absent;

X2 is any amino acid or absent;

X3 is any amino acid or absent;

X4 is Abu;

X5 is Gln;

X6 is Thr;

X7 is Trp;

X8 is Gln;

X9 is Cys;

X10 is Phe, Tyr, a Phe analog, or a Tyr analog;

X11 is 1-Nal, 2-Nal, Phe(3,4-dimethoxy), or Phe(3,4-Cl_2);

X12 is α-Me-Lys, α-Me-Leu, α-Me-Ser, α-Me-Val, Achc, Acvc, Acpc, Acbc, Aib, or 4-amino-4-carboxy-tetrahydropyran;
X13 is Thr, Sarc, Glu, Phe, Arg, Leu, Asn, Cit, Lys, Arg, Orn, Val, βhAla, Lys(Ac), (D)Asn, (D)Leu, (D)Phe, (D)Thr, Ala, α-MeLeu, Aib, β-Ala, β-Glu, βhLeu, βhVal, β-spiro-pip, Cha, Chg, Asp, Dab, Dap, α-DiethylGly, hLeu, Asn, Ogl, Pro, Gln, Ser, β-spiro-pip, Thr, Tle or Aib, or a corresponding α-methyl amino acid form of any of the foregoing;
X14 is Phe, Tyr, Glu, Gly, His, Lys, Leu, Met, Asn, Lys(Ac), Dap(Ac), Dab(Ac), Asp, Pro, Gln, Arg, Ser, Thr, Tic or βhPhe, or a corresponding α-methyl amino acid form of any of the foregoing;
X15 is Gly, Ser, Thr, Gln, Ala, (D)Ala, (D)Asn, (D)Asp, (D)Leu, (D)Phe, (D)Thr, Aea, Asp, Asn, Glu, Phe, Gly, Lys, Leu, Pro, Arg, β-Ala, or Sarc, or a corresponding α-methyl amino acid form of any of the foregoing,
X16 is any amino acid or absent;
X17 is any amino acid or absent;
X18 is any amino acid or absent;
X19 is any amino acid or absent; and
X20 is any amino acid or absent,
wherein the peptide inhibitor is cyclized via a thioether bond between X4 and X9, and
wherein 1-Nal is L-1-napthylalanine, 2-Nal is L-2-napthylalanine, Abu is 2-aminobutyric acid, α-Me-Lys is alpha-methyl-L-Lysine, α-Me-Leu is alpha-methyl-L-Leucine, α-Me-Ser is alpha-methyl-L-Serine, α-Me-Val is alpha-methyl-L-Valine, Achc is 1-aminocyclohexanecarboxylic acid, Acvc is 1-aminocyclopentanecarboxylic acid, Acpc is 1-aminocyclopropylcarboxylic acid, Acbc is 1-aminocyclobutanecarboxylic acid, and Aib is 2-aminoisobutyric acid.

18. The peptide inhibitor or pharmaceutically acceptable salt thereof of claim 17, wherein X3 is selected from Glu, (D)Glu, Arg, (D)Arg, Phe, (D)Phe, 2-Nal, Thr, Leu, or (D)Gln.

19. The peptide inhibitor or pharmaceutically acceptable salt thereof of claim 17, wherein X10 is Phe(4-OMe), Phe(4-$CONH_2$), or Phe[4-(2-aminoethoxy)].

20. The peptide inhibitor or pharmaceutically acceptable salt thereof of claim 17, wherein X11 is 2-Nal.

21. The peptide inhibitor or pharmaceutically acceptable salt thereof of claim 17, wherein the peptide inhibitor or pharmaceutically acceptable salt thereof is selected from the group consisting of:

Ac-[Abu]-QTWQCY-[2-Nal]-[α-Me-Lys]-ENG-NH_2 (SEQ ID NO:704) or a pharmaceutically acceptable salt thereof, wherein the peptide inhibitor is cyclized via a thioether bond between Abu and C;

Ac-[Abu]-QTWQC-[Phe(4-OMe)]-[2-Nal]-[α-Me-Lys]-ENG-NH_2 (SEQ ID NO:702) or a pharmaceutically acceptable salt thereof, wherein the peptide inhibitor is cyclized via a thioether bond between Abu and C;

Ac-[Abu]-QTWQC-[Phe[4-(2-aminoethoxy)]-W-[α-Me-Lys]-ENG-NH_2 (SEQ ID NO:782) or a pharmaceutically acceptable salt thereof, wherein the peptide inhibitor is cyclized via a thioether bond between Abu and C;

Ac-[Abu]-QTWQC-[Phe[4-(2-aminoethoxy)]]-[2-Nal]-[α-Me-Lys]-[Lys]-NG-NH_2 (SEQ ID NO:861) or a pharmaceutically acceptable salt thereof, wherein the peptide inhibitor is cyclized via a thioether bond between Abu and C;

Ac-[Abu]-QTWQC-[Phe[4-(2-aminoethoxy)]]-[2-Nal]-[Aib]-QNG-NH_2 (SEQ ID NO:877) or a pharmaceutically acceptable salt thereof, wherein the peptide inhibitor is cyclized via a thioether bond between Abu and C;

Ac-[Abu]-QTWQC-[Phe[4-(2-aminoethoxy)]]-[2-Nal]-[Aib]-[Lys(Ac)]-NA-NH_2 (SEQ ID NO:880) or a pharmaceutically acceptable salt thereof, wherein the peptide inhibitor is cyclized via a thioether bond between Abu and C;

Ac-[Abu]-QTWQC-[Phe[4-(2-(acetyl-aminoethoxy)]]-[2-Nal]-[α-Me-Lys(Ac)]-[Lys(Ac)]-NG-NH_2 (SEQ ID NO:900) or a pharmaceutically acceptable salt thereof, wherein the peptide inhibitor is cyclized via a thioether bond between Abu and C;

Ac-[Abu]-QTWQC-[Phe[4-(2-aminoethoxy)]]-[2-Nal]-[α-Me-Lys]-ENQ-NH_2 (SEQ ID NO:911) or a pharmaceutically acceptable salt thereof, wherein the peptide inhibitor is cyclized via a thioether bond between Abu and C;

Ac-[Abu]-QTWQC-[Phe[4-(2-aminoethoxy)]]-[2-Nal]-[α-Me-Lys]-ENN-NH_2 (SEQ ID NO:912) or a pharmaceutically acceptable salt thereof, wherein the peptide inhibitor is cyclized via a thioether bond between Abu and C;

Ac-[Abu]-QTWQC-[Phe[4-(2-aminoethoxy)]]-[2-Nal]-[α-MeVal]-[Lys(Ac)]-NG-NH_2 (SEQ ID NO:915) or a pharmaceutically acceptable salt thereof, wherein the peptide inhibitor is cyclized via a thioether bond between Abu and C;

Ac-[Abu]-QTWQC-[Phe[4-(2-aminoethoxy)]]-[2-Nal]-[α-Me-Leu)-[Cit]-NN-NH_2 (SEQ ID NO:954) or a pharmaceutically acceptable salt thereof, wherein the peptide inhibitor is cyclized via a thioether bond between Abu and C;

Ac-[(D)Phe]-[Abu]-QTWQC-[Phe[4-(2-aminoethoxy)]]-[2-Nal]-[α-Me-Lys]-ENN-NH_2 (SEQ ID NO:970) or a pharmaceutically acceptable salt thereof, wherein the peptide inhibitor is cyclized via a thioether bond between Abu and C;

Ac-T-[Abu]-QTWQC-[Phe[4-(2-aminoethoxy)]]-[2-Nal]-[α-Me-Lys]-ENN-NH_2 (SEQ ID NO:972) or a pharmaceutically acceptable salt thereof, wherein the peptide inhibitor is cyclized via a thioether bond between Abu and C;

Ac-[Abu]-QTWQC-[Phe[4-(2-aminoethoxy)]]-[2-Nal]-[acbc]-ENN-NH_2 (SEQ ID NO:976) or a pharmaceutically acceptable salt thereof, wherein the peptide inhibitor is cyclized via a thioether bond between Abu and C;

Ac-[Abu]-QTWQC-[Phe[4-(2-aminoethoxy)]]-[2-Nal]-[acpc]- ENN-NH_2 (SEQ ID NO:1043) or a pharmaceutically acceptable salt thereof, wherein the peptide inhibitor is cyclized via a thioether bond between Abu and C;

Ac-[Abu]-QTWQC-[Phe[4-(2-aminoethoxy)]]-[2-Nal]-[achc]-ENN-NH_2 (SEQ ID NO:1047) or a pharmaceutically acceptable salt thereof, wherein the peptide inhibitor is cyclized via a thioether bond between Abu and C;

Ac-[Abu]-QTWQC-[Phe[4-(2-aminoethoxy)]]-[2-Nal]-[4-amino-4-carboxy-tetrahydropyran]-ENN-NH_2 (SEQ ID NO:980) or a pharmaceutically acceptable salt thereof, wherein the peptide inhibitor is cyclized via a thioether bond between Abu and C;

Ac-[Abu]-QTWQC-[Phe[4-(2-aminoethoxy)]]-[2-Nal]-[alpha-methyl-L-Leucine]-QN-[betaAla]-NH_2 (SEQ ID NO:984) or a pharmaceutically acceptable salt thereof, wherein the peptide inhibitor is cyclized via a thioether bond between Abu and C;

Ac-(D)Phe-[Abu]-QTWQC-[Phe[4-(2-aminoethoxy)]]-[2-Nal]-[4-amino-4-carboxy-tetrahydropyran]-ENN-NH_2 (SEQ ID NO:992) or a pharmaceutically acceptable salt thereof, wherein the peptide inhibitor is cyclized via a thioether bond between Abu and C; and Ac-[(D)Arg]-[Abu]-QTWQC-[Phe[4-(2-aminoethoxy)]]-[2-Nal]-[4-amino-4-carboxy-tetrahydropyran]-ENN-NH_2 (SEQ ID NO:993) or a pharmaceutically acceptable salt thereof, wherein the peptide inhibitor is cyclized via a thioether bond between Abu and C.

22. The peptide inhibitor of any one of claims 1-21, wherein the peptide inhibitor comprises the structure of Formula I:

$$R^1\text{-Xa-}R^2 \text{ (I)}$$

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, a C1-C6 alkyl, a C1-C20 alkanoyl, and including PEGylated versions alone or as spacers of any of the foregoing;

Xa is the amino acid sequence of Formula (Xa); and

R^2 is OH or NH_2.

23. 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 has a sequence or structure set forth in any one of claims 1-11 and 13-22.

24. The peptide dimer inhibitor of claim 23, wherein 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.

25. The peptide dimer inhibitor of claim 23 or claim 24, wherein the N-terminus of each peptide monomer subunit is connected by the linker moiety or wherein the C-terminus of each peptide monomer subunit is connected by the linker moiety.

26. The peptide dimer inhibitor of claim 23, wherein the peptide dimer inhibitor comprises one of the following amino acid sequences:
[Ac-Cyclo-[[Abu]-QTWQC]-[Phe(4-OMe)]-[2-Nal]-[α-MeLys]-ENG-NH2]$_2$ DIG (SEQ ID NO: 996);
[Ac-[Pen]-QTWQ-[Pen]-[Phe(4-OMe)]-[2-Nal]-[α-MeVal]-[Lys(Ac)]-NN-[D)Lys]$_2$ DIG (SEQ ID NO: 756);
[Ac-[Pen]-QTWQ-[Pen]-[Phe[4-(2-acetylaminoethoxy)]-[2-Nal]- [α-MeVal]-[Lys(Ac)]-NN-[D)Lys]]$_2$ DIG (SEQ ID NO: 757);
[Ac-[Pen]-QTWQ[Pen]-[Phe[4-(2-acetylaminoethoxy)]]-[2-Nal]-[α-MeVal]-KNN-NH_2]$_2$ DIG (SEQ ID NO: 758);
[Ac-[Pen]-QTWQ[Pen]-[Phe[4-(2-acetylaminoethoxy)]]-[2-Nal]-K-[Lys(Ac)]-NN-NH_2]$_2$ DIG (SEQ ID NO: 759);
[Ac-[Pen]-QTWQ-[Pen]-[Phe(4-OMe)]-[2-Nal]-[α-MeLys]-[Lys(Ac)]-NN-NH_2]$_2$ DIG (SEQ ID NO: 532);
[Ac-[Pen]-QTWQ-[Pen]-[Phe(4-$CONH_2$)]-[2-Nal]-[α-MeLys]-[Lys(Ac)]-NN-NH_2]$_2$ DIG (SEQ ID NO: 534);
[Ac-[(D)Lys]-Cyclo-[[Abu]-QTWQC]-[Phe(4-OMe)]-[2-Nal]-[α-MeLys]-ENG-NH2]$_2$ PEG25 (SEQ ID NO: 997),
[Ac-Cyclo-[[Abu]-QTWQC]-[Phe(4-OBzl)]-W-[α-MeLys]-ENG-NH_2]$_2$ DIG (SEQ ID NO: 998),
[Ac-Cyclo-[[Abu]-QTWQC]-Y(Bzl)-W-[α-MeLys]-ENG-NH_2]$_2$ PEG25 (SEQ ID NO: 999), or
[Ac-[(D)Lys]-Cyclo-[[Abu]-QTWQC]-[Phe(4-OMe)]-[2-Nal]-[α-MeLeu]-ENG-NH_2]$_2$ DIG (SEQ ID NO: 994).

27. A polynucleotide comprising a sequence encoding the peptide inhibitor or a peptide monomer subunit of the peptide dimer inhibitor of any one of claims 1-26.

28. A vector comprising the polynucleotide of claim 27.

29. A pharmaceutical composition comprising the peptide inhibitor or the peptide dimer inhibitor of any one of claims 1-26, and a pharmaceutically acceptable carrier, excipient, or diluent.

30. The pharmaceutical composition of claim 29, further comprising an enteric coating.

31. Use of an effective amount of the pharmaceutical composition of claim 29 or claim 30 in the manufacture of a medicament 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.

32. The use of claim 31, wherein the pharmaceutical composition is to be 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.

33. The use of claim 31 for treating an Inflammatory Bowel Disease (IBD), wherein the pharmaceutical composition is to be provided to the subject orally.

34. The use of claim 33, wherein the IBD is ulcerative colitis, Crohn's disease, or pouchitis after an ileoanal anastomosis.

35. The use of claim 31 for treating psoriasis, wherein the pharmaceutical composition is to be provided to the subject orally, topically, parenterally, intravenously, subcutaneously, peritonealy, or intravenously.

36. The use of any one of claims 31-35, wherein the peptide inhibitor or the peptide dimer inhibitor inhibits binding of an interleukin-23 (IL-23) to the interleukin-23 receptor (IL-23R).