

HUMAN INTERLEUKIN (IL)-17 CYTOKINE BINDING PEPTIDES**CROSS-REFERENCE TO RELATED APPLICATIONS**

[0001] This application claims the benefit of priority to U.S. Provisional Application Nos. 63/614,421, filed December 22, 2023; 63/634,353, filed April 15, 2024; 63/664,097, filed June 25, 2024; 63/679,506, filed August 5, 2024; 63/684,260, filed August 16, 2024; 63/713,993, filed October 30, 2024; and 63/722,927, filed November 20, 2024, the disclosures of each of which are incorporated herein by reference in their entireties.

**INCORPORATION-BY-REFERENCE OF MATERIAL ELECTRONICALLY
SUBMITTED**

[0002] A Sequence Listing is provided herewith as a Sequence Listing XML, "PTGX-008WO_SEQ_LIST_12_24" created on December 17, 2024, and having a size of 2,770,896 bytes. The contents of the Sequence Listing XML are incorporated by reference herein in their entirety.

FIELD OF THE INVENTION

[0003] The present disclosure relates to peptide compounds which are human IL-17 cytokine inhibitors or antagonists. The peptide compounds bind to a human IL-17 cytokine in order to prevent or reduce the ability of the IL-17 cytokine to bind to its cognate IL-17 receptor(s). In this sense, the peptide compounds of the invention can also be considered to be neutralizing agents of human IL-17 or (upstream) antagonists of human IL-17 receptor activation. The present disclosure also relates to pharmaceutical compositions comprising the inhibitors, and methods of treating or preventing diseases, conditions or disorders mediated or associated with IL-17.

BACKGROUND

[0004] The interleukin-17 (IL-17) cytokine family consists of 6 members or isoforms, IL-17A–F. These isoforms have the ability to form active cytokine dimers through disulfide bridges. (Aggarwal, S. et al., *J. Leukoc. Biol.* 2002, 71 (1), 1–8; Pappu, R. et al., *Immunology* 2011, 134 (1), 8–16). Among the IL-17 family, IL-17A is the most extensively studied member in terms of its biological activity. IL-17A and IL-17F are closely related isoforms and often co-expressed in cells. Besides for homodimers, they can also form a heterodimeric cytokine called IL-17A/F (IL-17AF). (Goepfert, A. et al., *Sci. Rep.* 2017, 7 (1), 8906). In

this regard, IL-17AA (homodimer) can be used to refer to IL-17A, and IL-17FF (homodimer) can be used for IL-17F.

[0005] IL-17s are secreted by hematopoietic cells, including Th17 (CD4⁺ T cells), Tc17 (cytotoxic CD8⁺ T cells), other T cells such as $\gamma\delta$ T cells, NK cells, ILC3 (group 3 innate lymphoid cells), and “natural” Th17 cells (CD4⁺ ROR γ T⁺ thymocytes). (Brembilla, N. C. et al., *Immunol.* 2018, 9, 1682), and myeloid cells. These IL-17s play a role in host defense and various immune functional responses. (Jin, W. et al., *Emerg. Microbes Infect.* 2013, 2 (9), 1–5). They induce the production of pro-inflammatory cytokines such as IL-1, IL-6, and IL-21, as well as chemokines such as CXCL1. This leads to the recruitment of innate immune cells to the site of infection and facilitates the elimination of the pathogen. (Valeri, M. et al., *Pathog. Dis.* 2016, 74, ftw111).

[0006] While IL-17A is crucial for host defense, its deregulation can result in overproduction of pro-inflammatory cytokines, leading to tissue damage and chronic inflammation. Studies have demonstrated that IL-17AA is implicated in autoimmune diseases such as psoriasis, psoriatic arthritis, rheumatoid arthritis, ankylosing spondylitis, and nonradiographic axial spondyloarthritis. (Majumder, S. et al., *Annu. Rev. Immunol.* 2021, 39, 537–556). IL-17A levels are elevated in various inflammatory conditions, including sepsis, pneumonia, systemic lupus erythematosus, rheumatoid arthritis, allograft rejection, and cancer.

[0007] IL-17 cytokines mediate their biological functions by binding to specific surface receptors on target cells. The first identified IL-17 receptor (IL-17R) was IL-17RA, which was later followed by the discovery of four additional members of the IL-17R family (IL-17R B-E). IL-17 receptors are expressed in a variety of cell populations, including keratinocytes, fibroblasts, mesothelial cells, epithelial cells, and leukocytes. These receptors are mostly heterodimeric, composed of 2 subunits: IL-17RA through IL-17RE with IL-17RA serving as a common subunit. (Kirkham, B. W. et al. *Immunology* 2014, 141, 133–142).

[0008] IL-17RA is expressed in all cell types, especially on epithelial cells, fibroblasts, and innate immune cells like macrophages and neutrophils. (Ho, A. W. et al., *Immunopathol.* 2010, 32, 33–42). Each subunit of the IL-17 receptor has distinct regions, including an extracellular cytokine binding region, a transmembrane domain, and an intracellular signaling domain. Heterodimeric IL-17RA/IL-17RC complex serves as the primary receptor for IL-17AA, IL-17FF, and IL-17AF. Binding of these cytokines to the receptor leads to receptor dimerization. IL-17AA can also signal through the IL-17RA/IL-17RD heterodimer, while IL-17FF may bind to a homodimer of IL-17RC. The receptor dimer interacts via

SEFIR domains and mediates signaling via an Act1-dependent pathway, promoting the activation of pro-inflammatory factors such as NF- κ B. (Velichko, S. et al., *PLoS One* 2016, 11).

[0009] Injectable monoclonal antibodies (mAb), such as the anti-IL-17A mAb secukinumab and ixekizumab, the dual anti-IL-17A and anti-IL-17F mAb bimekizumab and the anti-IL-17RA mAb brodalumab, are recognized as effective treatments with acceptable safety profiles for moderate to severe psoriasis and other inflammatory diseases such as psoriatic arthritis and axial spondyloarthritis. (Hawkes, J. E. et al., *Immunol.* 2018, 201 (6), 1605–1613). Secukinumab and ixekizumab specifically target IL-17A, while bimekizumab binds to both IL-17A and IL-17F, thereby, blocking the activation of IL-17 receptors (composed of IL-17RA/IL-17RC), reducing the inflammatory drive to alleviate inflammation. Brodalumab, on the other hand, binds to the receptor, IL-17RA, which inhibits the activation of all receptors using IL-17RA as a subunit, including IL-17AA, AF, and FF, as well as IL-17C and IL-17E. (Tollenaere, M. A. X. et al., *Br. J. Dermatol.* 2021, 185 (3), 585–594).

[0010] However, monoclonal antibodies have disadvantages. They are typically expensive, administered non-orally, and have limited tissue penetration (Arkin, M. R. et al., *Chem. Biol.* 2014, 21, 1102–1114). The challenge of modulating a large protein–protein interaction (PPI) using small molecules is well known, primarily due to their smaller size and low specificity. In contrast, peptide drugs have unique properties such as sufficient size combined with structural-backbone flexibility, enabling them to act as potent and specific inhibitors of PPIs (Wang L. et al., *Signal Transduction and Targeted Therapy* (2022) 7:48). Therefore, there is a need to develop novel peptide compounds that target IL-17 cytokines for the treatment of various diseases. The present invention meets this and other needs.

BRIEF SUMMARY OF THE INVENTION

[0011] As used herein, the “X” notation for residue positions is equivalent to the three-letter “Xaa” notation, and both “X” and “Xaa” mean that any amino acid, natural or unnatural, can be at that position, unless specified otherwise.

[0012] In one aspect, the invention provides a peptide comprising or consisting of a sequence of Formula (I): R¹-X00-X0-X1-X2-X3-X4-X5-X6-X7-X8-X9-X10-X11-X12-X13-X14-X15-X16-R², wherein:

R¹ is R^a-C(O)- or hydrogen, wherein R^a is C₁₋₂₀ alkyl or C₃₋₈ cycloalkyl; or R¹ is acetyl, 1Pip_AceticAcid, 3-hydroxypropionic acid, C6_diacid, cyclopropanecarboxylic acid, cyclohexanecarboxylic acid, glutaric acid, isovaleric acid, methanesulfonyl acetic acid,

Mor_propanoic_acid, PVA (pivalic acid), 1PEG2_1PEG2_IsoGlu_C12,
 1PEG2_1PEG2_IsoGlu_C12_Diacid, 1PEG2_1PEG2_IsoGlu_C18_diacid,
 1PEG2_1PEG2_IsoGlu_Palm, 1PEG2_1PEG2_Ahx_C18_Diacid,
 1PEG2_PEG2_Ahx_Palm, or absent;
 R^2 is NH_2 or OH or absent;
 X00 is Cha, dH, dK, Ogl, Tle or absent;
 X0 is 2Pal, 3Pal, Aib, Asn, d2Pal, d3Pal, dA, dE, dF, dH, dK, dL, dQ, dS, Gln, Glu,
 Glu_OMe, His, Ile, Lys, Lys_1PEG2_1PEG2_IsoGlu_C12,
 Lys_1PEG2_1PEG2_IsoGlu_C18_diacid, Lys_1PEG2_1PEG2_IsoGlu_Palm, Lys_Me3,
 NMe_His, Orn, Pro, Sar, Thr, Tle, or absent;
 X1 is 1Nal, Bip, Cha, Chg, Cyclopropyl_Al原因, Dgl, DIP, dI, hCha, hF, hhF, Ile, Lys,
 Lys_1PEG2_1PEG2_IsoGlu_C18_diacid, Lys_1PEG2_1PEG2_IsoGlu_C12,
 Lys_1PEG2_1PEG2_IsoGlu_Palm, Ogl, Phe_4Me, Tba, Tle, Val, or absent;
 X2 is 2Pal, 3Pal, aMe_Arg, Agb, Agp, bhF, Cit, Dab, Dab_Ac, Dab_2HyAc, Dab_Ms,
 Dab_Ts, dDab2HyAc, dH, dT, Glu, Gln, His, hR, Hse, Lys, Lys_1PEG2_Ac,
 Lys_1PEG2_1PEG2_C18_diacid, Lys_1PEG2_1PEG2_IsoGlu_C12, Lys_Ac,
 Lys_Dimethyl, Lys_Me3, Lys_PEG2_Me3, Lys_1PEG2Ac, Lys_2HyAc, LysMPA, Lys_Ms,
 Lys_Ns, Lys_Ts, NMe_Thr, Orn, Orn_Ac, Orn_Ms, OrnPVA, Orn_Ts, Phe_2Ad, Phe_3Ad,
 Phe_4Ad, Phe_4_2ae, Phe_4ad, Phe_4_COOH, Phe_4_Cl, Phe_4guan, Phe_4OMe,
 Phe_4_Morph, Phe_pentaF, Q_NHMe, Q_NMe2, Q_Pyro, Q_EtOMe, Q_MecPro, Tet1, Thr,
 or Thi;
 X3 is Ala_cycBu, AlaCF3, AlaCHF2, Aoc, bhV, Cha, Chg, Cprg, Cpg, cyclopentyl_Al原因,
 cyclopropyl_Al原因, Cys, Dgl, DiethylGly, dL, dV, H_Cha, Hcy, hL, Hph, Igl, Nle, NMe_Leu,
 nVF3, O4S, O5S, Ogl, Phe_4tBu, Phe_4Cl, Phe_4_OMe, Phe_4_Me, Phe_3_4_Cl2
 [Phe_34diCl], Phe_4_CF3, Peptoid_CH2_V, Pra, Tba, Tle, or Val;
 X4 is Asn, dT, Dab, Gln, Glu, Glu_OMe, hE, His, hR, Lys_Me3, Orn, Phe4_COOH,
 Phe_4_Morph, Tet1, Thr, or Thr_Me;
 X5 is Abu, aMe_Lys_Ac, Cha, Cys, Chg, Dab_Acetyl, dI, dLys_Ac, Glu, Hcy, hE, Hhc,
 HhPen, Ile, Lys, Lys_Ac, LysN3, LysPhAc, NMe_Lys_Ac, O2S, O3S, O3S_Reduced,
 O4S_Reduced, O5S, O5S_Reduced, Orn_Acetyl, or Pen;

X6 is 4R_BenzyloxyPro, 4RPhePro, 4S_Amp, 4S_Amp_Cyclhex, 4S_Amp_Hex, 4S_Amp_IVA, 4S_Amp_tBu, 4SCF3Pro, 4ScyclohexPro, 5RPhePro, Azetidinone, Dfp, dP, Hpr, Oic, or Pro;

X7 is Acvc, Aib, Ala, aMe_Phe, Arg, Aze, Cys, Dab, dC, Gln, Glu, His, Hpr, hR, Lys_1PEG2_1PEG2_Ahx_C18_Diacid, Lys_1PEG2_1PEG2_IsoGlu_C12, Lys_1PEG2_1PEG2_IsoGlu_C18_diacid, Lys_1PEG2_1PEG2_IsoGlu_Palm, Lys_Ac, O3S, O3S_Me, O4S, Pro, Ser, Tba, or Tic;

X8 is aMe_Asp, aMe_Glu, Asp, dD, Gla, Gln, Glu, Phe_3COOH, Phe_4COOH, Tet1, or Tet2;

X9 is Aoc, Cha, Cys, Dgl, hCha, Hcy, Leu, Nle, O3S, O3S_Reduced, O6S, Ogl, Phe_34diF, Phe_4CF3, or Tba;

X10 is 1Nal, 2Nal, Aib, aMe_Phe, aMe_Trp, Aoc, Cys, DIP, dW, hCha, Gln, Hph, Lys_1PEG2_1PEG2_IsoGlu_C12, Phe, Phe_34diCl, Phe_3Ad, Phe_4ad, Phe4_COOH, Phe_4OMe, Phg, Tba, Tle, Trp_4Cl, Trp_4Me, Trp_5Cl, Trp_5CONH2, Trp_5Et, Trp_5Me, Trp_6CF3, Trp_6Cl, Trp_6CONH2, Trp_6Me, Trp_7Cl, Trp_7Me, Trp_7Phe, or Trp;

X11 is Aib, aMe_Asp, aMe_Leu, aMe_Phe, Asn, Asp, Cys, Chg, dA, dS, Gln, Glu, Hcy, Leu, Lys_1PEG2_1PEG2_IsoGlu_C12, Lys_Ac, Lys_Me3, O3S, O3S_Me, O4S, Phe_4Ad, Phe_4tBu, Ser, Tba, or Tle;

X12 is 1Nal, aMe_Trp, Hph_34diCl, Orn_Bz, Trp, Trp_4Cl, Trp_5Br, Trp_5Cl, Trp_5Et, Trp_5Me, Trp_56diCl, Trp_56diMe, Trp_6Cl, Trp_6CF3, Trp_6Me, or Trp_7Cl;

X13 is Abu, aMe_Cys, aMe_Lys_Ac, Cys, Cha, Dab_Acetyl, Glu, Hcy, hE, Hhc, HhPen, Ile, Lys, Lys_Ac, LysN3, O2S, O3S, O3S_Me, O3S_Me_Reduced, O3S_Reduced, O4S_Reduced, Orn_Acetyl, or Pen;

X14 is Aib, Arg, Asn, Cys, dE, dF, dH, dK, dL, dN, dQ, dR, Gln, Glu, Lys, Lys_1PEG2_1PEG2_IsoGlu_C12, Lys_Ac, Lys_Hexy, Lys_PEG12_NH, Lys_PEG4_1PEG2_NH2, Lys_PEG4_PEG4_NH2, Lys_PEG8_NH2, O3S, O3S_Me, Orn_Acetyl, PEG12, Tba, or absent;

X15 is dE, dK, dR, Glu, Lys, Lys_PEG4_PEG4_NH2, Lys_Dimethyl, Pro, or absent; and

X16 is dE, dF, dH, dK, dL, dR, dQ, Lys, Lys_1PEG2_1PEG2_IsoGlu_C12, Lys_1PEG2_1PEG2_IsoGlu_Palm, Lys_PEG4_PEG4_NH2, Lys_Ac, or absent;

wherein:

- (i) the peptide optionally comprises a cyclic structure wherein at least two amino acid residues in the peptide (monomer) are either: (a) directly covalently linked, or (b) indirectly covalently linked through a cyclization linker;
- (ii) the peptide is optionally a monomer in a homodimer or heterodimer complex, wherein each monomer is directly covalently linked to each other, or indirectly covalently linked to each other through a dimerization linker; and/or
- (iii) the peptide is optionally conjugated with a half-life extension moiety.

Formula (I).

[0013] In other aspects, to the extent a peptide Formula, including any of the SEQ ID NO formulas herein, does not include residue(s) at an X0 and/or an X00 position, the peptide may further comprise a residue(s) at X0 and/or X00 between R¹ and X1, wherein the residue options for X0 and X00 are specified above in Formula (I).

[0014] In one aspect, a peptide of the invention comprises a cyclic structure characterized by an intramolecular cross-link between residues X5 and X13 (X5-X13), X7 and X11 (X7-X11), X9 and X13 (X9-X13), or X10 and X14 (X10-X14). The intramolecular cross-link can comprise a covalent bond directly or indirectly between the cross-linked residues, wherein the covalent bond comprises an amide bond (lactam bond), a disulfide bond, a thioether bond, a carbon-carbon single bond, or a carbon-carbon double bond (an olefin).

[0015] Furthermore, in other aspects, any Formula of the invention can be modified such that the residue options for one position of a cross-link can be swapped with the residue options for the other position of a cross-link. For example, if a Formula specifies certain residues at position X5 and other residues at position X13, the invention contemplates that the residue options at position X13 can instead be for X5, and the residue options at position X5 can instead be those for X13. This also applies for X7-X11, X9-X13, and X10-X14, whether the cross-links are direct or indirect (via a cyclization linker) between the side chains of the residues.

[0016] In one aspect, a peptide of the invention comprises an intramolecular cross-link that is a direct covalent bond between the cross-linked residues. The two cross-linked amino acid residues can be, for example, at X5 and X13 or X9 and X13, and the two amino acids are directly covalently linked through a disulfide bond. The two amino acid residues cross-linked through a disulfide bond can be, for example, both, or individually, Hhc, Hcy, Pen, hhPen, or Cys, their respective D-amino acid configuration, and their α -methyl variant.

[0017] In another aspect, a peptide of the invention comprises direct thioether cross-links between two amino acid side-chains, between a side-chain and an N-terminal (R1) moiety, or between a side-chain and a C-terminal (R2) moiety. The two amino acid residues (or an amino acid and an R group) directly cross-linked through a thioether bond can be, for example, a residue with a free thiol in its side chain such as Cys, Hhc, Hcy, Pen, or HhPen, with a residue with a free alkyl in its side chain such as aMe_Lys_Ac, Dab_Acetyl, Dap_Ac, dLys_Ac, NMe_Lys_Ac, Lys_Ac, Lys_PEG12_Ac, LysPhAc, and Orn_Acetyl. In some aspects, their *D*-form or *a*-methyl variant can be used. With respect to N-terminal or C-terminal to side-chain cyclization, the N- or C-terminal can be a moiety with a free alkyl group such as an acetyl moiety, and the side chain can be a residue with a free thiol; vice-versa. Generally, for direct or indirect thioether cyclization, one residue or moiety has a free thiol group and the other residue or moiety has a free alkyl group such that cross-linking of these free groups results in a thioether bond.

[0018] In one aspect, a peptide of the invention comprises two directly cross-linked amino acid residues at X5 and X13, X7 and X11, X9 and X13, or X10 and X14, and wherein these two amino acids are directly covalently linked through a thioether bond. The two amino acid residues directly cross-linked through a thioether bond can be, for example: aMe_Cys, Cys, dC, Hhc, Hcy, or Pen (*i.e.*, an amino acid with a free thiol group in its side-chain), for one residue of the pair; and aMe_Lys_Ac, Dab_Acetyl, dLys_Ac, Lys_Ac, LysPhAc, NMe_Lys_Ac, Orn_Acetyl, O2S_Reduced, O3S_Reduced, O4S_Reduced, or O5S_Reduced for the other residue of the pair (*i.e.*, an amino acid with a free acetyl group in its side-chain), in either order.

[0019] In another aspect, a peptide of the invention comprises two directly cross-linked amino acid residues are at X5 and X13, or X9 and X13, and the two amino acids are directly covalently linked through a carbon-carbon double bond. The two amino acid residues cross-linked through a carbon-carbon double bond can be, for example, both, or individually, O2S, O3S, O4S, O5S, O6S, or O3S_Me.

[0020] In another aspect, a peptide of the invention comprises two directly cross-linked amino acid residues are at X5 and X13, or at X9 and X13, and the two amino acids are directly covalently linked through a carbon-carbon single bond. The two amino acid residues cross-linked through a carbon-carbon single bond can be, for example, both, or individually, reduced version of the amino acids suitable for carbon-carbon double bond cross-links, *i.e.*, reduced

forms of O2S, O3S, O4S, O5S, O6S, or O3S_Me. In one aspect, the two amino acid residues cross-linked through a carbon-carbon single bond are individually or both O3S_Me_Reduced, O3S_Reduced, or O4S_Reduced.

[0021] In another aspect, a peptide of the invention comprises two directly cross-linked amino acid residues at X5 and X13, and the two amino acids are directly covalently linked through an amide bond (lactam). The two amino acid residues are suitable for cyclic amide bond cross-linking if one has a side chain with a free amine and the other with a free carboxylic acid, such as Lys paired with Glu, hE, or Asp. Hence, in one aspect, one of X5 and X13 is Lys and the other is Glu, hE, or Asp.

[0022] In another aspect, a peptide of the invention comprises two directly cross-linked amino acid residues at X5LysN3 and X13Abu, or X5Abu and X13 LysN3. The side chains of these two amino acids are directly covalently linked. Specifically, a hydrogen from theazole ring of LysN3 reacts with a free hydroxyl from Abu to form the cross-link as shown in paragraph [00324].

[0023] In one aspect, a peptide of the invention comprises an intramolecular cross-link that is an indirect covalent bond between the cross-linked residues, wherein each of the cross-linked residues form a direct covalent bond with a cyclization linker. The cyclization linker can be, for example, a linear or cyclic alkane or an alkene with two free alkyl groups, a Butane_Link, a Carbonyl_Link, a Dimethylcyclopropane_Link, an Ebutene_Link, a Hexane_Link, a Methylene_Link, an Oxetane_Link, a Pentane_Link, a Propane_Link, an mXylene_Link, a pXylene_Link, or an oXylene_Link.

[0024] In another aspect, for residues that include a free thiol group in their side chains (which includes, but are not limited to, Cys, Hcy, Hhc, Pen, HHpen, their respective D-amino acid configuration, and their α -methyl variants), a Cyclization linker may be used to mediate a thioether (or a "bis-thioether") intramolecular cross-link between each the two side chains. The free thiol group at each side chain forms a thioether bond with a free alkyl moiety of a Cyclization linker, and the Cyclization linker needs to have two free alkyl moieties. Representative Cyclization linkers include, but are not limited to, a Butane_Link, a Carbonyl_Link, a Dimethylcyclopropane_Link, a Ebutene_Link, a Hexane_Link, a Methylene_Link, an Oxetane_Link, a Pentane_Link, a Propane_Link, a Trimethylbenzene_Link, an mXylene_Link, a pXylene_Link, or an oXylene_Link. See

Table 1 for abbreviations and corresponding structures for Cyclization linkers and unnatural amino acids. Herein, intramolecular cross-links formed with a Cyclization linker can be referred to as an “indirect” cross-link, and cross-linked formed without a Cyclization linker can be referred to as a “direct” cross-link.

[0025] In one aspect, a peptide of the invention comprises an intramolecular cross-link that is an indirect covalent bond between the cross-linked residues, the cyclization linker comprises one of the Xylene_Linkers, and the two amino acid residues cross-linked through a thioether bond with the cyclization linker are at X5 and X13, X7 and X11, X9 and X13, or X10 and X14, wherein the residues are, for example, both, or individually, Cys or dC.

[0026] In one aspect, a peptide of the invention comprises an intramolecular cross-link that is an indirect covalent bond between the cross-linked residues, the cyclization linker comprises a Butane_Linkers, a Carbonyl_Linkers, a Dimethylcyclopropane_Linkers, an Ebutene_Linkers, a Hexane_Linkers, a Methylene_Linkers, an Oxetane_Linkers, a Pentane_Linkers, or a Propane_Linkers, and the two amino acid residues cross-linked through a (bis- or di-)thioether bond with the cyclization linker can be, for example, both, or individually, Cys, dC, Hcy, Hhc, HhPen, or Pen (or a residue with a free thiol group), at for example, X5-X13, X9-X13, X10-X14, or X7-X11. These linkers are representative, and other alkane or alkene linkers are suitable if they have terminal ends or two suitable free chemical groups that can each react with a free thiol at each cyclization position to form thioether bonds (relative to the cyclization linker – a bis- or di-thioether bond) ((e.g., free alkyl groups of the cyclization linker can be modified to alkyl halides for reaction with deprotonated thiols to form thioether bonds).

[0027] In some aspects, a peptide of the invention can be a monomer (i.e., a monomeric subunit) of a homodimer or heterodimer peptide molecule. Each monomer of the dimer can have a direct covalent attachment to a dimerization linker, regardless of whether the monomer comprises a cyclic structure or a linear structure. Often, especially for cyclic monomers, each monomer of a dimer compound comprises Lys or dK at X14, X15, or X16 that is directly covalently linked to a PEG linker.

[0028] In one aspect, a PEG linker comprises $-(OCH_2CH_2)_n-$, wherein n is between 5 and 25.

[0029] In one aspect for the dimers of the invention, each monomer is directly covalently linked to a PEG linker through an amide bond, wherein one monomer is linked to one terminal end of the PEG linker and the other monomer is linked to the other terminal end of the PEG

linker. The PEG linker can be, for example, a molecule with repeating PEG units with an acidic moiety at the terminal ends of the molecule, such as PEG5DA, PEG9DA, PEG13DA, PEG21DA, or PEG25DA.

[0030] In another aspect for the dimers of the invention, each monomer can comprise a residue with a free amine in its side chain such that the free amine can react with a free hydroxyl of a dimerization linker to form an amide bond. For example, X14 can be Lys_PEG4_PEG4_NH2, which has a free amine in its side chain, and the free amine can react with a free hydroxyl at one of the terminal ends of the DIG_Linkers. If each monomer has X14Lys_PEG4_PEG4_NH2, then each monomer will form an amide bond with the DIG_Linkers, thereby forming a dimer. The ordinary artisan understands that other amino acids are suitable, including other variants of lysine with PEG side chains having a free amine, including but not limited to, Lys_PEG8_NH2 and Lys_PEG4_1PEG2_NH2.

[0031] In some aspects, a dimer of the instant invention with a PEG dimerization linker (e.g., PEG21DA) attached to a lysine can be modified such that the lysine is substituted with Lys_PEG4_PEG4_NH2, Lys_PEG8_NH2, or Lys_PEG4_1PEG2_NH2, and the PEG linker is substituted with a DIG_Linkers.

[0032] In another aspect for the dimers of the invention, each monomer is directly covalently linked to a pBiphenyl_Linkers, as a dimerization linker, through a thioether bond. For example, a free thiol group in a side chain of an amino acid residue (e.g., Cys, Hcy, Hhc, Pen, etc.) can be directly covalently linked to a pBiphenyl_Linkers to form a (bis- or di-)thioether bond.

[0033] In one aspect, a peptide of the invention, whether linear or cyclic, and whether in monomeric or dimer form, exhibits an IC₅₀ value of less than about 20 nM in a human IL-17 HEK Blue assay. All of the exemplary peptide compounds of Figure 1 have an IC₅₀ less than 20 nM in a human IL-17 HEK Blue assay.

[0034] In related aspects, the peptide exhibits an IC₅₀ value of less than about 10 nM, 5 nM, or 1 nM, in a human IL-17 HEK Blue assay. The human IL-17 HEK Blue assay can be, for example, a human IL-17AA HEK Blue assay, a human IL-17AF HEK Blue assay, or a human IL-17FF HEK Blue assay.

[0035] In one aspect, a peptide of the invention exhibits an IC₅₀ value of less than about 1 nM in a human IL-17AA HEK Blue assay, less than about 1 nM in a human IL-17AF HEK Blue assay, and less than about 1, 5, 10, or 20 nM in a human IL-17FF HEK Blue assay.

[0036] In another aspect, a peptide of the invention exhibits an IC₅₀ value of less than about 1 nM in a human IL-17AA HEK Blue assay and less than about 1, 5, or 10 nM in a human IL-17FF HEK Blue assay.

[0037] In another aspect, a peptide of the invention exhibits an IC₅₀ value of less than about 1 nM in a human IL-17AA HEK Blue assay, less than about 1 nM in a human IL-17AF HEK Blue assay, and less than about 1, 5, or 10 nM in a human IL-17FF HEK Blue assay.

[0038] In one aspect, a peptide of the invention, whether linear or cyclic, and whether in monomeric or dimer form, exhibits a half-life greater than about 0.5 hours in an SGF and/or SIF stability assay. In related aspects, the peptide exhibits a half-life greater than about 1.0 hours, 1.5 hours, or 2.0 hours in an SGF and/or SIF stability assay.

[0039] In other aspects, a peptide of the invention exhibits an IC₅₀ less than about 1 nM in a human IL-17AA HEK Blue assay and less than about 5 nM in a human IL-17FF HEK Blue assay, a half-life greater than about 0.5, 1.0, 1.5, or 2.0 hours in an SGF assay, and a half-life greater than about 2.0 hours in an SIF assay. In a related aspect, a peptide of the invention exhibits an IC₅₀ less than about 1 nM in both a human IL-17AA HEK Blue assay and a human IL-17AF HEK Blue assay, less than about 5 nM in a human IL-17FF HEK Blue assay, a half-life greater than about 0.5, 1.0, 1.5, or 2.0 hours in an SGF assay, and a half-life greater than about 2.0 hours in an SIF assay. In a related aspect, when a peptide of the invention exhibits a half-life greater than 2.0 hours in an SGF assay and in an SIF assay, the peptide is suitable for formulation in solid or liquid form for oral administration, and without excipients or coating(s) to protect the peptide from the acidic conditions of the gastric environment. In another related aspect, when a peptide of the invention exhibits a half-life that does not exceed 0.5, 1.0, or 1.5 hours in an SGF assay, the peptide can be formulated in a solid form with an enteric coating.

[0040] In another aspect, a peptide of the invention that exhibits an IC₅₀ less than about 20 nM, 10 nM, 5 nM, or 1 nM in a human IL-17 AA, AF, or FF HEK Blue assay can be administered to a subject subcutaneously, irrespective of the peptide's half-life in an SGF or SIF assay.

[0041] In another aspect, a homodimer peptide compound of the invention exhibits at least a 2-fold improvement in its IC₅₀ value in a human IL-17 HEK Blue assay as compared to its monomeric form. In related aspects, said peptide compound exhibits at least a 5-fold, 10-fold, 20-fold, 25-fold, 50-fold, or 100-fold fold improvement (*i.e.*, lower IC₅₀) in its IC₅₀ value in a human IL-17 HEK Blue assay as compared to its monomeric form.

[0042] In another aspect, a homodimer peptide compound of the invention exhibits at least a 2-fold improvement in its half-life in an SGF and/or an SIF stability assay as compared to its monomeric form. In related aspects, said peptide compound exhibits at least a 3-fold, 4-fold, 5-fold, or 10-fold improvement (*i.e.*, longer time) in its half-life in an SGF and/or an SIF stability assay.

[0043] In one aspect, for any one of the peptides comprising a monomer sequence of SEQ ID NO:1-720, any of the amino acids, natural or unnatural, can be substituted with its corresponding D-amino acid, or vice versa. In related aspects, up to all, 15, 14, 13, 12, 11, 10, 9, 8, 7, 6, 5, 4, 3, 2, or 1 amino acid(s) can be substituted with its corresponding D-amino acid, or vice versa.

[0044] In another aspect, for any one of the peptides comprising a monomer sequence of SEQ ID NO:1-720, up to 10, 9, 8, 7, 6, 5, 4, 3, 2, or 1 amino acid(s) can be replaced with a conservative substitution and/or a corresponding analog (e.g., if the peptide has a lysine analog at a particular position, then other lysine analogs can provide the corresponding analog substitution, see Table 1). In one aspect, a peptide comprising a lysine analog can be substituted with a different lysine analog with a side-chain comprising one or more of: a palmitoyl moiety (Palm), a PEG moiety, an isoglutamine moiety (IsoGlu), an aminocaproic acid moiety (Ahx), a C1-20 alkyl moiety, and a C1-30 alkyl-C(O)- moiety.

[0045] In another aspect, if a peptide has a lysine analog at a particular position, the lysine analog can be substituted with another lysine analog that comprises a side-chain with one of the different combinations of linkers and half-life extension moieties listed in Table 4.

[0046] In another aspect, for any one of the peptides comprising a monomer sequence of SEQ ID NO:1-720, up to 10, 9, 8, 7, 6, 5, 4, 3, 2, or 1 unnatural amino acid(s) can be replaced with its corresponding natural amino acid (e.g., if the peptide has a lysine analog at a particular position, then it can be substituted with lysine, see Table 1 for analog information).

[0047] For any of the Formulas herein, R1 and R2 can be the moieties specified for Formula (I) above. Herein, a “Formula” includes not only Formula (I) et al., but also SEQ ID NO formulas.

[0048] In one aspect, for a peptide according to any of the Formulas herein, R1 is, or can be changed to, acetyl, glutaric acid, or isovaleric acid, and R2 is amine.

[0049] In one aspect, for a peptide according to any of the Formulas herein, R1 is, or can be changed to, isovaleric acid, and R2 is amine.

[0050] In one aspect, for a peptide according to any of the Formulas herein, X0 is, or can be changed to, dE, E, His, dH, or absent. In one aspect, X0 can be changed to dE or E.

[0051] In another aspect, for a peptide according to any of the Formulas herein, X00 is, or can be changed to, dH.

[0052] In one aspect, for a peptide according to any of the Formulas herein, R1 is (or can be changed to) isovaleric acid, X0 is (or can be changed to) dH, and R2 is amine.

[0053] In one aspect, for a peptide according to any of the Formulas herein, X1 is, or can be changed to, Ile or Val.

[0054] In one aspect, for a peptide according to any of the Formulas herein, X2 is, or can be changed to, Lys_Me3.

[0055] In one aspect, for a peptide according to any of the Formulas herein, X3 is, or can be changed to, Tle or Val.

[0056] In one aspect, for a peptide according to any of the Formulas herein, X4 is, or can be changed to, Glu.

[0057] In one aspect, for a peptide according to any of the Formulas herein X6 is, or can be changed to, Oic or an Oic analog.

[0058] In one aspect, for a peptide according to any of the Formulas herein, X7 is, or can be changed to, Ala.

[0059] In one aspect, for a peptide according to any of the Formulas herein, X8 is, or can be changed to, Asp.

[0060] In one aspect, for a peptide according to any of the Formulas herein, X9 is, or can be changed to, Ogl or an Ogl analog.

[0061] In one aspect, for a peptide according to any of the Formulas herein, X10 is, or can be changed to, Trp, 1Nal, or a Trp analog.

[0062] In one aspect, for a peptide according to any of the Formulas herein, X11 is, or can be changed to, Asp or Glu.

[0063] In one aspect, for a peptide according to any of the Formulas herein, X12 is, or can be changed to, Trp or a Trp analog.

[0064] In one aspect for a peptide according to any of the Formulas herein, X14 is, or can be changed to, Lys, Lys_PEG8_NH2, Lys_PEG4_1PEG2_NH2, or Lys_PEG4_PEG4_NH2.

[0065] In one aspect for a peptide according to any of the Formulas herein, X15 is, or can be changed to, dR.

[0066] In one aspect, for a peptide that is a monomer comprising X14Lys in a homodimer compound according to any of the Formulas herein, the dimerization linker is PEG21DA.

[0067] In one aspect, for a peptide that is a monomer in a homodimer compound according to any of the Formulas herein, a dimerization linker comprises a linear structure, a COOH group at both terminal ends, and between 15-25 PEG units.

[0068] In another aspect, for a peptide that is a monomer in a homodimer compound according to any of the Formulas herein, an X14 lysine residue can be modified such that the lysine side chain comprises between 4-25 PEG units, between 6-20 PEG units, or between 8-15 PEG units, and a free amine. In this aspect, the dimerization linker can comprise two free hydroxyls, such that each free hydroxyl can form an amide bond with the free amine present in the side chain of the modified lysine residue comprising said PEG units. As stated, the DIG linker can serve as a dimerization linker in this aspect, as the DIG linker has two carboxylic acid moieties (each comprising a free hydroxyl).

[0069] In one aspect, any one of the peptides of the invention may be in the form of a pharmaceutically acceptable salt.

[0070] In one aspect, the invention provides a homodimer peptide compound that exhibits an IC₅₀ equal to or less than 10 nM in a HEK Blue human IL-17 assay, wherein the compound has two monomer cyclic peptides both comprising or consisting of the same amino acid sequence from Formula (II):

R¹-X00-X0-X1-X2-X3-X4-X5-X6-X7-X8-X9-X10-X11-X12-X13-X14-X15-X16-R²,

wherein:

R1 is acetyl (Ac), 3-hydroxypropionic acid, C6_diacid, cyclopropanecarboxylic acid, glutaric acid, isovaleric acid, methanesulfonyl acetic acid, 1PEG2_1PEG2_IsoGlu_Palm, 1PEG2_1PEG2_IsoGlu_C18_Diacid, 1PEG2_1PEG2_IsoGlu_C12, or absent;

R2 is NH₂, OH, or absent;

X00 is dH or absent;

X0 is dE, dH, Gln, Glu, Glu_OMe, His, Ile, Lys_Me3, Sar, Tle, or absent;

X1 is Cha, Chg, Cyclopropyl_Ala, DIP, Ile, Lys_1PEG2_1PEG2_IsoGlu_C12, Ogl, Tba, or Val;

X2 is 2Pal, 3Pal, Agb, Agp, Cit, Dab_Ac, Dab2HyAc, DabMs, DabTs, dDab2HyAc, Gln, Glu, His, hR, Hse, Lys, Lys_1PEG2_1PEG2_C18_diacid, Lys_1PEG2_1PEG2_IsoGlu_C12, Lys_Ac, Lys_Dimethyl, Lys_Me3, Lys_PEG2_Me3, Lys1PEG2Ac, Lys2HyAc, LysMPA, LysMs, LysNs, LysTs, OrnAc, Orn2HyAc, OrnMs, OrnPVA, OrnTs, Phe_2Ad, Phe_3Ad, Phe_4_Morph, Phe_4Ad, Phe_4COOH, Phe_4Guan, Phe_4OMe, Phe_pentaF, Q_NHMe, Q_NMe2, Q_Pyro, Q_EtOMe, Tet1, Thi, or Thr;

X3 is AlaCF3, AlaCHF2, Ala_cycBu, Aoc, Cha, Chg, Cpg, cyclopentyl_Ala, cyclopropyl_Ala, Cys, dV, H_Cha, Hcy, Hph, Igl, nVF3, Ogl, Phe_34diCl, Phe_4CF3, Phe_4Cl, Phe_4Me, Phe_4OMe, Phe_4tBu, Tba, Tle, or Val;

X4 is Asn, Gln, Glu, Glu_OMe, His, hE, hR, Lys_Me3, Phe4_COOH, Thr, or Thr_Me;

X5 is Abu, Cys, Cha, Chg, Dab_Acetyl, Glu, Hcy, hE, Hhc, Ile, Lys, Lys_Ac, LysN3, LysPhAc, O2S, O3S, O3S_Reduced, O4S, O4S_Reduced, Orn_Acetyl, or Pen;

X6 is 4RBenzyloxyPro, 4RPhePro, 4S_Amp_Cyclohex, 4S_Amp_Hex, 4S_Amp_IVA, 4S_Amp_tBu, 4SCF3Pro, 4SCyclohexPro, 5RPhePro, Azetidinone, Hpr, Oic, or Pro;

X7 is Ala, Acvc, Aib, aMe_Phe, Arg, Cys, Gln, Glu, His, hR,

Lys_1PEG2_1PEG2_Ahx_C18_diacid, Lys_1PEG2_1PEG2_IsoGlu_C12,

Lys_1PEG2_1PEG2_IsoGlu_C18_diacid, Lys_1PEG2_1PEG2_IsoGlu_Palm, Lys_Ac,

O3S_Me, Oic, Pro, Ser, or Tba

X8 is aMe_Glu, Asp, dD, Gla, Glu, Phe_3COOH, Phe_4COOH, Tet1, or Tet2;

X9 is Aoc, Dgl, Hcy, Leu, O3S, O3S_Reduced, or Ogl;

X10 is 1Nal, 2Nal, aMe_Phe, aMe_Trp, Cys, Hph, Lys_1PEG2_1PEG2_IsoGlu_C12, Phe_4COOH, Trp_4Cl, Trp_4Me, Trp_5Cl, Trp_5CONH2, Trp_5Et, Trp_5Me, Trp_6CF3, Trp_6Cl, Trp_6CONH2, Trp_6Me, Trp_7Cl, Trp_7Me, Trp_7Phe, or Trp;

X11 is Aib, Ala, aMe_Asp, aMe_Leu, aMe_Phe, Asn, Asp, Cys, Chg, Gln, Glu, Leu, Lys_1PEG2_1PEG2_IsoGlu_C12, Lys_Ac, Lys_Me3, O3S_Me, Phe_4Ad, Phe_4tBu, Ser, Tba, or Tle;

X12 is 1Nal, aMe_Trp, Orn_Bz, Trp, Trp_56diCl, Trp_56diMe, Trp_5Br, Trp_5Cl, Trp_5Et, Trp_5Me, Trp_6CF3, Trp_6Cl, or Trp6Me;

X13 is Abu, aMe_Cys, aMe_Lys_Ac, Cys, Cha, Dab_Acetyl, Glu, Hcy, hE, Hhc, Ile, Lys, Lys_Ac, LysN3, O2S, O3S, O3S_Me, O3S_Me_Reduced, O3S_Reduced, O4S, O4S_Reduced, Orn_Acetyl, or Pen;

X14 is Asn, dK, dR, Lys, Lys_Ac, Lys_PEG4_1PEG2_NH2, Lys_PEG4_PEG4_NH2, Lys_PEG8_NH2, Orn_Acetyl, or PEG12;

X15 is dR, dK, Lys, Lys_PEG4_PEG4_NH2, or Lys_Dimethyl, or absent;

X16 is dK, Lys, Lys_Ac, Lys_1PEG2_1PEG2_IsoGlu_C12, Lys_1PEG2_1PEG2_IsoGlu_Palm, Lys_PEG4_PEG4_NH2, or absent;

wherein:

(i) the monomer comprises a cyclic structure wherein two amino acid residues in the peptide monomer are directly covalently linked or indirectly covalently linked through a through an amide bond, a disulfide bond, a thioether bond, a carbon-carbon single bond, or a carbon-carbon double bond, wherein the two amino acid residues are at X5 and X13, X7 and X11, X9 and X13, or X10 and X14; and

(ii.a) each monomer is directly covalently linked to a polyethylene glycol (PEG) linker at X14, X15, or X16 through an amide bond, wherein the PEG linker comprises $-(OCH_2CH_2)_n-$, wherein n is between 5 and 25, and wherein one monomer is linked to one terminal end of the PEG linker and the other monomer is linked to the other terminal end of the PEG linker, or
 (ii.b) each monomer is directly covalently linked to a DIG_linker (diglycolic acid linker) at X14, X15, or X16 through an amide bond, where X14, X15, or X16 is Lys_PEG4_PEG4_NH2, Lys_PEG4_1PEG2_NH2, or Lys_PEG8_NH2.

(Formula (II).)

[0071] In another aspect, the invention provides a Formula (II) monomer that is not part of a homodimer compound. In this aspect, because X14Lys (or X15Lys or X16Lys) is often a residue that mediates dimerization, it can be substituted with another amino acid, for example, any of the residues listed at X14 in Formula (I). In some aspects, for a Formula (II) monomer that is not part of a homodimer compound, X14 is Asn or Lys_Ac.

[0072] In others aspects of Formula (II), the HEK Blue human IL-17 assay is a human IL-17AA, human IL-17AF, or human IL-17FF assay.

[0073] For the following Formula (II) sub-formulas, i.e., Formula (II.A) et al., R1 and R2 are the moieties specified for Formula (II) above.

[0074] In another aspect, for a Formula (II) homodimer, the cyclic structure of each monomer comprises two amino acid residues directly covalently linked through a disulfide bond at: (a) X5 and X13, wherein X5 is Hhc and X13 is Hhc; or (b) X9 and X13, wherein X9 is Hcy and X13 is Hhc.

[0075] In one aspect, for a Formula (II) homodimer, a monomer peptide of the homodimer compound comprises or consists of an amino acid sequence of Formula (II.A):

R1-X00-X0-X1-X2-X3-X4-X5-X6-X7-X8-X9-X10-X11-X12-X13-X14-X15-X16-R2,

wherein:

R1 is acetyl, 3-hydroxypropionic acid, C6_diacid, cyclopropanecarboxylic acid, glutaric acid, isovaleric acid, methanesulfonyl acetic acid, or absent; R2 is NH₂, OH, or absent;

X00 is dH or absent,

X0 is dE, dH, Gln, Glu, Glu_OMe, His, Ile, Lys_Me3, Sar, Tle, or absent;

X1 is Chg, Ile, Lys_1PEG2_1PEG2_IsoGlu_C12, Ogl, or Val;

X2 is 2Pal, 3Pal, Agb, Agp, Dab_Acetyl, Dab_2HyAc, Dab_Ms, Dab_Ts, dDab_2HyAc, Gln, Glu, His, hR, Hse, Lys, Lys_1PEG2_1PEG2_C18_Diacid, Lys_1PEG2_1PEG2_IsoGlu_C12, Lys_Ac, Lys_Dimethyl, Lys_Me3, Lys1PEG2Ac, Lys2HyAc, LysMs, LysTs, OrnAc, OrnMs, OrnTs, Phe_2Ad, Phe_3Ad, Phe_4Ad, Phe_4Guan, Q_NHMe, Q_NMe2, Q_Pyro, Tet1, or Thr;;

X3 is Ala_cycBu, Aoc, Cha, Chg, Cpg, cyclopropyl_Al原因, dV, H_Cha, Hph, Igl, Ogl, Phe_34diCl, Phe_4CF3, Phe_4Cl, Phe_4Me, Phe_4OMe, Phe_4tBu, Tba, Tle, or Val;

X4 is Glu, hR, or Thr;

X5 is Hhc;

X6 is Oic or Pro;

X7 is Ala, Acvc, aMe_Phe, Gln, Glu, His, hR, Lys_Ac, Pro, Ser, or Tba;

X8 is aMe_Glu, Asp, dD, Gla, Glu, Tet1, or Tet2;

X9 is Leu or Ogl;

X10 is 1Nal, aMe_Trp, Trp_7Phe, or Trp;

X11 is aMe_Phe, Asp, or Glu;

X12 is aMe_Trp, Trp_5Br, Trp_5Cl, Trp_5Me, Trp_6Cl, Trp_6Me, or Trp;

X13 is Hhc;

X14 is Asn, dR, dK, Lys, Lys_PEG4_1PEG2_NH2, Lys_PEG8_NH2, or Lys_PEG4_PEG4_NH2;

X15 is dR, Lys, or absent;

X16 is absent;

wherein: (a) X5 and X13 are directly covalently linked through a disulfide bond; wherein each monomer is directly covalently linked to a PEG linker at X14 or X15 through an amide bond, and (b) X14 or X15 is dK or Lys, and wherein one monomer is linked to one terminal end of the PEG linker and the other monomer is linked to the other terminal end of the PEG linker, or X2 is dK or Lys and wherein one monomer is linked to one terminal end of the PEG linker and the other monomer is linked to the other terminal end of the PEG linker, or X14 is Lys_PEG4_PEG4_NH2, Lys_PEG8_NH2, or Lys_PEG4_1PEG2_NH2, and wherein one monomer is linked to one terminal end of a DIG_Linker and the other monomer is linked to the other terminal end of the DIG_Linker. (Formula (II.A)).

[0076] In related aspects of Formula (II.A), Hhc at X5 and/or X13 can be substituted with another amino acid having a free thiol in its side-chain, such as Cys, Hcy, Pen, HhPen, their D-forms, and their α -methyl variants.

[0077] In one aspect, for a Formula (II) homodimer, a monomer peptide of the homodimer compound comprises or consists of an amino acid sequence of Formula (II.B):

R^1 -X00-X0-X1-X2-X3-X4-X5-X6-X7-X8-X9-X10-X11-X12-X13-X14-X15-X16- R^2 ,

wherein: R1 is acetyl, 3-hydroxypropionic acid, C6_diacid, cyclopropanecarboxylic acid, glutaric acid, isovaleric acid, methanesulfonyl acetic acid, or absent; R2 is amine, hydroxyl, or

absent; X00 is dH or absent, X0 is dE, dH, Gln, Glu, Glu_OMe, His, Ile, Lys_Me3, Sar, Tle, or absent; X1 is Ile or Val; X2 is His or Lys_Me3; X3 is Tba or Val; X4 is Thr; X5 is Chg, Ile, or Tle; X6 is Azetidinone, Oic, or Pro; X7 is Ala; X8 is Asp or Gla; X9 is Hcy; X10 is Trp; X11 is Asp or Glu; X12 is Trp; X13 is Hhc; X14 is Lys, Lys_PEG4_1PEG2_NH2, Lys_PEG8_NH2, or Lys_PEG4_PEG4_NH2; X15 is dR; X16 is absent; wherein: (i) the cyclic structure of each monomer comprises X9 and X13 that are directly covalently linked through a disulfide bond; and (ii) each monomer is directly covalently linked to a PEG linker at X14Lys through an amide bond, wherein one monomer is linked to one terminal end of the PEG linker and the other monomer is linked to the other terminal end of the PEG linker; or each monomer is directly covalently linked to a DIG linker at X14Lys_PEG4_PEG4_NH2, X14Lys_PEG4_1PEG2_NH2, or X14Lys_PEG8_NH2, through an amide bond, wherein one monomer is linked to one terminal end of the DIG linker and the other monomer is linked to the other terminal end. (Formula (II.B)).

[0078] In related aspects of Formula (II.B), Hcy at X9 and/or Hhc at X13 can be substituted with another amino acid having a free thiol in its side-chain, such as Cys, Hcy, Pen, HhPen, their D-forms, and their α -methyl variants.

[0079] In another aspect, for a Formula (II) homodimer, the cyclic structure of each monomer comprises two amino acid residues directly covalently linked through a thioether bond at: (a) X5 and X13, wherein X5 is Cys, Dab_Acetyl, Hcy, Hhc, Lys_Ac, LysPhAc, Orn_Acetyl, or Pen, and X13 is aMe_Cys, aMe_Lys_Ac, Cys, Dab_Acetyl, Hcy, Hhc, Lys_Ac, Orn_Acetyl, or Pen; (b) X7 and X11, wherein X7 is Cys or Lys_Ac and X11 is Cys or Lys_Ac; or (c) X10 and X14, wherein X10 is Cys and X14 is Lys_Ac or Orn_Acetyl; and wherein aMe_Cys, Cys, Hcy, Hhc, or Pen is paired with aMe_Lys_Ac, Dab_Acetyl, Lys_Ac, LysPhAc, or Orn_Acetyl, and vice versa.

[0080] In one aspect, for a Formula (II) homodimer, a monomer peptide of the homodimer compound comprises or consists of an amino acid sequence of Formula (II.C):

R^1 -X00-X0-X1-X2-X3-X4-X5-X6-X7-X8-X9-X10-X11-X12-X13-X14-X15-X16- R^2 ,

wherein:

R1 is acetyl, 3-hydroxypropionic acid, C6_diacid, cyclopropanecarboxylic acid, glutaric acid, isovaleric acid, methanesulfonyl acetic acid, or absent; R2 is amine, hydroxyl, or absent; X00 is dH or absent, X0 is dE, dH, Gln, Glu, Glu_OMe, His, Ile, Lys_Me3, Sar, Tle, or absent; X1 is Chg, Ile, Lys_1PEG2_1PEG2_C18_diacid, Lys_1PEG2_1PEG2_IsoGlu_Palm, Lys_1PEG2_1PEG2_IsoGlu_C12, Lys_1PEG2_1PEG2_IsoGlu_C18_Diacid, Ogl, or Val; X2 is 2Pal, 3Pal, Agb, Agp, aMe_Arg, Cit, Dab_Ac, Dab2HyAc, DabMs, DabTs, dDab2HyAc, Gln, Glu, His, hR, Hse, Lys, Lys_1PEG2_1PEG2_C18_diacid, Lys_1PEG2_1PEG2_IsoGlu_C12, Lys_1PEG2_1PEG2_IsoGlu_C18_Diacid, Lys_Ac, Lys_Dimethyl, Lys_Me3, Lys1PEG2Ac, Phe_4_Morph, Phe_4COOH, Phe_4OMe, Phe_pentaF, Thr, or Thi; or Thr; X3 is Cha, H_Cha, Ogl, Phe_4tBu, Tba, or Tle, or Val; X4 is Asn, Gln, Glu, His, Phe_4COOH, Thr, or Thr_Me; X5 is Cys, Dab_Acetyl, Hcy, Lys_Ac, LysPhAc, Orn_Acetyl, or Pen; X6 is Oic, or Pro; X7 is Aib, Ala, Arg, His, Lys_1PEG2_1PEG2_Ahx_C18_Diacid, Lys_1PEG2_1PEG2_IsoGlu_C18_Diacid, Lys_1PEG2_1PEG2_IsoGlu_Palm; X8 is aMe_Glu, Asp, Gla, Glu, or Tet1; X9 is Ogl; X10 is 1Nal, Trp, Trp_4Cl, Trp_4Me, Trp_5Cl, Trp_5CONH2, Trp_5Et, Trp_5Me, Trp_6CF3, Trp_6Cl, Trp_6CONH2, Trp_6Me, Trp_7Cl, Trp_7Me, or Trp_7Phe; X11 is aMe_Asp, Asp, Gln, or Glu; X12 is Trp, Trp_56diCl, Trp_56diMe, Trp_5Et, Trp_5Me, Trp_6CF3, Trp_6Cl, or Trp_6Me; X13 is aMe_Cys, aMe_Lys_Ac, Cys, Dab_Acetyl, Hcy, Hhc, Lys_Ac, Orn_Acetyl, or Pen; X14 is Lys, Lys_PEG4_1PEG2_NH2, Lys_PEG8_NH2, or Lys_PEG4_PEG4_NH2; X15 is dR; X16 is absent;

wherein: (i) the cyclic structure of each monomer comprises X5 and X13 that are directly covalently linked through a thioether bond; wherein aMe_Cys, Cys, Hcy, Hhc, or Pen is paired with aMe_Lys_Ac, Dab_Acetyl, Lys_Ac, LysPhAc, or Orn_Acetyl, and vice versa;

and (ii) each monomer is directly covalently linked to a PEG linker at X14Lys through an amide bond, wherein one monomer is linked to one terminal end of the PEG linker and the other monomer is linked to the other terminal end of the PEG linker or each monomer is directly covalently linked to a PEG linker at X14Lys through an amide bond, wherein one monomer is linked to one terminal end of the PEG linker and the other monomer is linked to the other terminal end of the PEG linker; or each monomer is directly covalently linked to a DIG linker at X14Lys_PEG4_PEG4_NH2, X14Lys_PEG8_NH2, or X14Lys_PEG4_1PEG2_NH2, through an amide bond, wherein one monomer is linked to one terminal end of the DIG linker and the other monomer is linked to the other terminal end.

(Formula (II.C)).

[0081] In one aspect, for a Formula (II) homodimer, a monomer peptide of the homodimer compound comprises or consists of an amino acid sequence of Formula (II.D):

R^1 -X00-X0-X1-X2-X3-X4-X5-X6-X7-X8-X9-X10-X11-X12-X13-X14-X15-X16- R^2 ,

wherein: R1 is acetyl, 3-hydroxypropionic acid, C6_diacid, cyclopropanecarboxylic acid, glutaric acid, isovaleric acid, methanesulfonyl acetic acid, or absent; R2 is amine, hydroxyl, or absent; X00 is dH or absent; X0 is dE, dH, Gln, Glu, Glu_OMe, His, Ile, Lys_Me3, Sar, Tle, or absent; X1 is Ile or Val; X2 is His, Lys_Me3, or Thr; X3 is Tba, Tle, or Val; X4 is Thr or Glu; X5 is Ile; X6 is Oic or Pro; X7 is Cys or Lys_Ac; X8 is Asp; X9 is Leu or Ogl; X10 is Trp or 1Nal; X11 is Cys or Lys_Ac; X12 is aMe_Trp or Trp; X13 is Ile; X14 is Lys, Lys_PEG4_1PEG2_NH2, Lys_PEG8_NH2, or Lys_PEG4_PEG4_NH2; X15 is dR; X16 is absent; wherein X7 and X11 are not both Cys or Lys_Ac; and wherein: (i) the cyclic structure of each monomer comprises X7 and X11 that are directly covalently linked through a thioether bond; and (ii) each monomer is directly covalently linked to a PEG linker at X14Lys through an amide bond, wherein one monomer is linked to one terminal end of the PEG linker and the other monomer is linked to the other terminal end of the PEG linker or each monomer is directly covalently linked to a PEG linker at X14Lys through an amide bond, wherein one monomer is linked to one terminal end of the PEG linker and the other monomer is linked to the other terminal end of the PEG linker; or each monomer is directly covalently linked to a DIG linker at X14Lys_PEG4_PEG4_NH2, X14Lys_PEG4_1PEG2_NH2, X14Lys_PEG8_NH2, through

an amide bond, wherein one monomer is linked to one terminal end of the DIG linker and the other monomer is linked to the other terminal end.

(Formula (II.D).)

[0082] In one aspect, for a Formula (II) homodimer, a monomer peptide of the homodimer compound comprises or consists of an amino acid sequence of Formula (II.E):

$R^1\text{-X00-X0-X1-X2-X3-X4-X5-X6-X7-X8-X9-X10-X11-X12-X13-X14-X15-X16-R}^2$,

wherein: R1 is acetyl, 3-hydroxypropionic acid, C6_diacid, cyclopropanecarboxylic acid, glutaric acid, isovaleric acid, methanesulfonyl acetic acid, or absent; R2 is amine, hydroxyl, or absent; X00 is dH or absent, X0 is dE, dH, Gln, Glu, Glu_OMe, His, Ile, Lys_Me3, Sar, Tle, or absent; X1 is Ile or Val; X2 is Thr or Lys_Me3; X3 is Tba or Tle; X4 is Thr or Glu; X5 is Chg or Ile; X6 is Oic or Pro; X7 is Ala; X8 is Asp; X9 is Ogl; X10 is Cys; X11 is Asp or Glu; X12 is Trp; X13 is Ile; X14 is Lys or Orn_Ac; X15 is dR; X16 is Lys, Lys_PEG4_1PEG2_NH2, Lys_PEG8_NH2, or Lys_PEG4_PEG4_NH2; wherein: (i) the cyclic structure of each monomer comprises X10 and X14 that are directly covalently linked through a thioether bond; and (ii) each monomer is directly covalently linked to a PEG linker at X16Lys through an amide bond, wherein one monomer is linked to one terminal end of the PEG linker and the other monomer is linked to the other terminal end of the PEG linker; or each monomer is directly covalently linked to a DIG linker at X16Lys_PEG4_PEG4_NH2, X16Lys_PEG4_1PEG2_NH2, or X14Lys_PEG8_NH2, through an amide bond, wherein one monomer is linked to one terminal end of the DIG linker and the other monomer is linked to the other terminal end. (Formula (II.E)).

[0083] In other aspects, the cyclic structure of a monomer of Formula (II) comprises the two amino acid residues directly covalently linked through: (a) a carbon-carbon single bond (-C-C-) at X5 and X13, X9-X13, X7-X11, or X10-X14, wherein the residues of these pairs are individually or both O3S_Reduced, O3S_Methyl_Reduced, or O4S_Reduced; or (b) a carbon-carbon double bond (-C=C-) at X5 and X13, X9-X13, X7-X11, or X10-X14, wherein the residues of these pairs are individually or both O2S, O3S, O4S, O3S_methyl, or O4S_Methyl.

[0084] In one aspect, for a Formula (II) homodimer, a monomer peptide of the homodimer compound comprises or consists of an amino acid sequence of Formula (II.F):

R^1 -X00-X0-X1-X2-X3-X4-X5-X6-X7-X8-X9-X10-X11-X12-X13-X14-X15-X16- R^2 ,

wherein:

R1 is acetyl, 3-hydroxypropionic acid, C6_diacid, cyclopropanecarboxylic acid, glutaric acid, isovaleric acid, methanesulfonyl acetic acid, or absent; R2 is amine, hydroxyl, or absent; X00 is dH or absent, X0 is dE, dH, Gln, Glu, Glu_OMe, His, Ile, Lys_Me3, Sar, Tle, or absent; X1 is Ile, Val, or Tba; X2 is Gln, His, Hse, Lys_Me3, or Thr; X3 is cyclopropyl-Ala, Tba, Tle, or Val; X4 is Glu or Thr; X5 is O3S_Reduced or O4S_Reduced; X6 is Pro or Oic; X7 is Ala; X8 is Asp or Gla; X9 is Ogl; X10 is 1Nal or Trp; X11 is Asp or Glu; X12 is Trp or Trp5Me; X13 is O3S_Reduced, O3S_Methyl_Reduced, O4S_Reduced; X14 is Lys, Lys_PEG4_1PEG2_NH2, Lys_PEG8_NH2, or Lys_PEG4_PEG4_NH2; X15 is dR; and X16 is absent; wherein: (i) the cyclic structure of each monomer comprises X5 and X13 that are directly covalently linked through a carbon-carbon single bond (-C-C-); and (ii) each monomer is directly covalently linked to a PEG linker at X14Lys through an amide bond, wherein one monomer is linked to one terminal end of the PEG linker and the other monomer is linked to the other terminal end of the PEG linker; or each monomer is directly covalently linked to a DIG linker at X14Lys_PEG4_PEG4_NH2, X14Lys_PEG4_1PEG2_NH2, or X14Lys_PEG8_NH2, through an amide bond, wherein one monomer is linked to one terminal end of the DIG linker and the other monomer is linked to the other terminal end. (Formula (II.F)).

[0085] In one aspect, for a Formula (II) homodimer, a monomer peptide of the homodimer compound comprises or consists of an amino acid sequence of Formula (II.G):

R^1 -X00-X0-X1-X2-X3-X4-X5-X6-X7-X8-X9-X10-X11-X12-X13-X14-X15-X16- R^2 ,

wherein R1 is acetyl, 3-hydroxypropionic acid, C6_diacid, cyclopropanecarboxylic acid, glutaric acid, isovaleric acid, methanesulfonyl acetic acid, or absent; R2 is amine, hydroxyl, or absent; X00 is dH or absent, X0 is dE, dH, Gln, Glu, Glu_OMe, His, Ile, Lys_Me3, Sar, Tle, or absent; X1 is Chg, Val, or Ile; X2 is His, Lys_Me3, or Thr; X3 is Ogl, Val, Tba, or Tle; X4 is Thr or Glu; X5 is Ile or Chg; X6 is Oic or Pro; X7 is O3S_Me; X8 is Asp or Gla; X9 is Ogl; X10 is 1Nal or Trp; X11 is O3S_Me; X12 is Trp; X13 is Ile; X14 is Asn; X15 is dR; and X16 is Lys, Lys_PEG4_1PEG2_NH2, Lys_PEG8_NH2, or Lys_PEG4_PEG4_NH2; wherein: (i) the cyclic structure of each monomer comprises X7 and X11 that are directly covalently linked

through a carbon-carbon double bond ($-C=C-$); and (ii) each monomer is directly covalently linked to a PEG linker at X16Lys through an amide bond, wherein one monomer is linked to one terminal end of the PEG linker and the other monomer is linked to the other terminal end of the PEG linker; or each monomer is directly covalently linked to a DIG linker at X16Lys_PEG4_PEG4_NH2, X16Lys_PEG4_1PEG2_NH2, X16Lys_PEG8_NH2, through an amide bond, wherein one monomer is linked to one terminal end of the DIG linker and the other monomer is linked to the other terminal end.

(Formula (II.G)).

[0086] In one aspect, for a Formula (II) homodimer, a monomer peptide of the homodimer compound comprises or consists of an amino acid sequence of Formula (II.H):

$R^1-X00-X0-X1-X2-X3-X4-X5-X6-X7-X8-X9-X10-X11-X12-X13-X14-X15-X16-R^2$,

wherein R1 is acetyl, 3-hydroxypropionic acid, C6_diacid, cyclopropanecarboxylic acid, glutaric acid, isovaleric acid, methanesulfonyl acetic acid, or absent; R2 is amine, hydroxyl, or absent; X00 is dH or absent, X0 is dE, dH, Gln, Glu, Glu_OMe, His, Ile, Lys_Me3, Sar, Tle, or absent; X1 is Chg, Val, or Ile; X2 is His, Lys_Me3, or Thr; X3 is Ogl, Tba, Tle, or Val; X4 is Thr or Glu; X5 is Chg or Ile; X6 is Oic or Pro; X7 is Ala or Cys; X8 is Asp or Gla; X9 is O3S; X10 is Trp or 1Nal; X11 is Asp, Glu, or Lys_Ac; X12 is Trp; X13 is O3S; X14 is Lys, Lys_PEG4_1PEG2_NH2, Lys_PEG4_PEG4_NH2, Lys_PEG8_NH2; X15 is dR; and X16 is absent; wherein: (i) the cyclic structure of each monomer comprises X9 and X13 that are directly covalently linked through a carbon-carbon double bond ($-C=C-$); and (ii) each monomer is directly covalently linked to a PEG linker at X14Lys through an amide bond, wherein one monomer is linked to one terminal end of the PEG linker and the other monomer is linked to the other terminal end of the PEG linker; or each monomer is directly covalently linked to a DIG linker at X14Lys_PEG4_PEG4_NH2, X14Lys_PEG4_1PEG2_NH2, or X14Lys_PEG8_NH2, through an amide bond, wherein one monomer is linked to one terminal end of the DIG linker and the other monomer is linked to the other terminal end.

(Formula (II.H)).

[0087] In another aspect of Formula (II), each monomer of the dimer has a cyclic structure comprising two amino acid residues with a side-chain comprising a free thiol that are indirectly covalently linked through: a thioether bond with a Butane_Linkers, a Carbonyl_Linkers, a

Dimethylcyclopropane_Linker, an Ebutene_Linker, a Hexane_Linker, a Methylene_Linker, an Oxetane_Linker, a Pentane_Linker, a Propane_Linker, an mXylene_Linker, a pXylene_Linker, or an oXylene_Linker. at: (a) X5 and X13, wherein the residues are individually or both, Cys, Hcy, Hhc, or Pen, and with any of the linkers listed above or with any alkane or alkene linker with suitable ends or two suitable free chemical groups that can each react with a free thiol to form a thioether bond (or relative to the linker – a bis- or di-thioether bond); (b) X7 and X11, wherein both X7 and X11 are Cys, and with the a Xylene linker, or (c) X7 and X11, wherein X7 and X11 are individually or both Cys or Hcy and with the Propane_Linker.

[0088] In one aspect, for a Formula (II) homodimer, a monomer peptide of the homodimer compound comprises or consists of an amino acid sequence of Formula (II.I):

$R^1\text{-X00-X0-X1-X2-X3-X4-X5-X6-X7-X8-X9-X10-X11-X12-X13-X14-X15-X16-R}^2$,

wherein:

wherein: R1 is acetyl, 3-hydroxypropionic acid, C6_diacid, cyclopropanecarboxylic acid, glutaric acid, isovaleric acid, methanesulfonyl acetic acid, or absent; R2 is amine, hydroxyl, or absent; X00 is dH or absent, X0 is dE, dH, Gln, Glu, Glu_OMe, His, Ile, Lys_Me3, Sar, Tle, or absent; X1 is Cha, Cyclopropyl_Al原因, DIP, Ile, Tba, or Val; X2 is Gln, His, Hse, Lys_Me3, Lys_Dimethyl, Lys_PEG2_Me3, Lys2HyAc, LysMPA, LysNs, Orn_Ac, Orn2HyAc, OrnPVA, Phe_2Ad, Phe_3Ad, Q_NHMe, Q_NMe2, Q_Pyro, Q_EtOMe, or Tet1; X3 is AlaCF3, AlaCHF2, cyclopentyl_Al原因, cyclopropyl_Al原因, nVF3, Tba, Tle, or Val; X4 is Asn, Glu, Glu_OMe, hE, Lys_Me3, Phe_4COOH, or Thr; X5 is Cys, Hcy, or Pen; X6 is 4RBenzyloxyPro, 4RPhePro, 4S_Amp_Cyclohex, 4S_Amp_Hex, 4S_Amp_IVA, 4S_Amp_tBu, 4SCF3Pro, 4SCyclohexPro, 5RPhePro, Oic, or Pro; X7 is Ala, Gln, His, Lys_1PEG2_1PEG2_IsoGlu_C18_diacid, Lys_Ac, Oic, or Pro; X8 is Asp, Gla, Glu, Phe_3COOH, or Phe_4COOH; X9 is Aoc, Dgl, or Ogl; X10 is 1Nal, 2Nal, aMe_Phe, aMe_Trp, Hph, Phe_4COOH, or Trp; X11 is Aib, Ala, Asn, Asp, aMe_Leu, aMe_Phe, Chg, Glu, Leu, Lys_Me3, Phe_4Ad, Phe_4tBu, Ser, Tba, or Tle; X12 is 1Nal, aMe_Trp, Orn_Bz, Trp_6Cl, or Trp; X13 is Cys, Hcy, or Pen; X14 is dK, Lys, Lys_PEG4_1PEG2_NH2, Lys_PEG8_NH2, or Lys_PEG4_PEG4_NH2; X15 is dR; and X16 is absent; wherein: (i) the cyclic structure of each monomer comprises X5 and X13 that are indirectly covalently linked through a thioether bond

with a Butane_Link, a Carbonyl_Link, a Dimethylcyclopropane_Link, an EButene linker, a Hexane_Link, an Oxetane_Link, a Pentane_Link, a Propane linker, an oXylene linker, an mXylene linker, or a pXylene linker; and (ii) each monomer is directly covalently linked to a PEG linker at X14 through an amide bond, wherein one monomer is linked to one terminal end of the PEG linker and the other monomer is linked to the other terminal end of the PEG linker; or each monomer is directly covalently linked to a DIG linker at X14Lys_PEG4_PEG4_NH2, X14Lys_PEG4_1PEG2_NH2, X14Lys_PEG8_NH2, through an amide bond, wherein one monomer is linked to one terminal end of the DIG linker and the other monomer is linked to the other terminal end. (Formula (II.I)).

[0089] In one aspect, for a Formula (II) homodimer, a monomer peptide of the homodimer compound comprises or consists of an amino acid sequence of Formula (II.J):

R^1 -X00-X0-X1-X2-X3-X4-X5-X6-X7-X8-X9-X10-X11-X12-X13-X14-X15-X16- R^2 ,
 wherein R1 is acetyl, 3-hydroxypropionic acid, C6_diacid, cyclopropanecarboxylic acid, glutaric acid, isovaleric acid, methanesulfonyl acetic acid, or absent; R2 is amine, hydroxyl, or absent; X00 is dH or absent, X0 is dE, dH, Gln, Glu, Glu_OMe, His, Ile, Lys_Me3, Sar, Tle, or absent; X1 is Ile or Val; X2 is His, Lys_Me3, or Thr; X3 is Tle or Val; X4 is Glu or Thr; X5 is Ile; X6 is Pro or Oic; X7 is Cys; X8 is Asp or Gla; X9 is Leu or Ogl; X10 is 1Nal or Trp; X11 is Cys or Hcy; X12 is Trp; X13 is Ile; X14 is Asn, Lys, Lys_PEG4_1PEG2_NH2, Lys_PEG8_NH2, or Lys_PEG4_PEG4_NH2; X15 is dR; and X16 is Lys, Lys_PEG4_PEG4_NH2, Lys_PEG4_1PEG2_NH2, Lys_PEG8_NH2, or absent; wherein: (i) the cyclic structure of each monomer comprises X7 and X11 that are indirectly covalently linked through a bis-thioether bond with the a Xylene linker (m-, o-, or p-) or a Propane_Link; and
 (ii) each monomer is directly covalently linked to a PEG linker at X14 or X16 through an amide bond when X14 or X16 is Lys, wherein one monomer is linked to one terminal end of the PEG linker and the other monomer is linked to the other terminal end of the PEG linker; or each monomer is directly covalently linked to a DIG linker at X14 or X16, through an amide bond, wherein X14 or X16 is Lys_PEG4_PEG4_NH2, Lys_PEG4_1PEG2_NH2, or Lys_PEG8_NH2, wherein one monomer is linked to one terminal end of the DIG linker and the other monomer is linked to the other terminal end. (Formula (II.J)).

[0090] In some aspects, a homodimer compound of the invention lacks an amino acid at X00 and X0 positions.

[0091] In some aspects, a homodimer compound of the invention lacks an amino acid at X00. In another aspect, a homodimer compound of the invention can have, or can be modified to have, isovaleric acid at R1, dH at X00 and dE at X0.

[0092] In other aspects, a homodimer compound of the invention has a dimerization linker that is a PEG linker, which can be, for example, PEG5DA, PEG9DA, PEG13DA, PEG21DA, PEG25DA, or a PEG linker comprising greater than 25 PEG units.

[0093] In other aspects, a homodimer compound of the invention exhibits an IC₅₀ value of less than about 20 nM, less than about 10 nM, less than about 5 nM, or less than about 1 nM, in a human IL-17 HEK Blue assay.

[0094] In other aspects a homodimer compound of the invention exhibits a half-life greater than about 0.5 hours, 1.0 hours, 1.5 hours, or 2.0 hours in an SGF and/or SIF stability assay.

[0095] In other aspects, for any of the homodimers of Formula (II), which includes Formula (II.A et al.), R¹ and R² are the same as for Formula (I).

[0096] In one aspect, the invention provides a peptide compound that has an IC₅₀ less than 10 nM for each of hIL-17AA, hIL-17AF, and hIL-17FF, or at least for each of hIL-17AA and hIL-17FF, in a human IL-17 AA, AF, and/or FF HEK Blue assay, wherein the peptide compound comprises a monomer peptide comprising or consisting of the sequence of Formula (III):

R¹- X00-X0-X1-X2-X3-X4-X5-X6-X7-X8-X9-X10-X11-X12-X13-X14-X15-X16-R²,

wherein:

R¹ is 1Pip_AceticAcid, acetyl, 3-hydroxypropionic acid, C6_diacid, cyclopropanecarboxylic acid, glutaric acid, isovaleric acid, methanesulfonyl acetic acid, Mor_propanoic_acid, or absent; R² is NH₂ or OH or absent;

X00 is Cha, dH, Tle, or absent;

X0 is 2Pal, Asn, d2Pal, dE, dH, dQ, Gln, Glu, Glu_OMe, His, Ile, Lys, Lys_Me3, NMe_His, Orn, Sar, Tle, or absent;

X1 is 1Nal, Cha, Cyclopropyl_Ala, Dgl, DIP, hCha, hF, hhF, Ile, Ogl, Phe_4Me, Tba, Tle, or Val;

X2 is 2Pal, 3Pal, Dab_Ac, Dab2HyAc, DabMs, DabTs, Gln, Glu, His, Hse, Lys_Ac, Lys_Dimethyl, Lys_Me3, Lys_PEG2_Me3, Lys1PEG2Ac, Lys2HyAc, LysMPA, LysMs, Orn_Ac, Orn2HyAc, OrnAc, OrnMs, OrnPVA, Phe_2Ad, Phe_3Ad, Phe_4Ad, Q_NHMe, Q_NMe2, Q_Pyro, Q_EtOMe, Tet1, or Thr;

X3 is Ala_cycBu, AlaCF3, AlaCHF2, Aoc, Cha, Chg, Cyclopentyl_Ala, Cyclopropyl_Ala, hCha, nVF3, Ogl, Phe_4tBu, Tba, Tle, or Val;

X4 is Asn, Gln, Glu, Glu_OMe, hE, His, LysMe3, Phe_4COOH, or Thr;

X5 is Cys, Hcy, Hhc, Lys_Ac, LysN3, O2S, O3S, O3S_Reduced, O3S_Me, O3S_Me_Reduced, O4S, O4S_Reduced, O5S, O5S_Reduced, or Pen;

X6 is 4SCF3Pro, 4SCyclohexPro, Oic, or Pro;

X7 is Acvc, Ala, Dab, Gln, Glu, His, Hpr, hR, Lys_Ac, Oic, Pro, Ser, or Tba;

X8 is aMe_Glu, Asp, Gla, Glu, or Tet1;

X9 is Aoc, Dgl, or Ogl;

X10 is 1Nal, 2Nal, aMe_Phe, aMe_Trp, Aoc, Cys, hCha, Hph, Phe_4COOH, Trp, Trp_4Cl, Trp_4Me, Trp_5Cl, Trp_5CONH2, Trp_5Et, Trp_5Me, Trp_6Cl, Trp_6CONH2, Trp_6Me, Trp_7Cl, Trp_7Me, or Trp_7Phe;

X11 is Aib, Ala, aMe_Asp, aMe_Leu, aMe_Phe, Asn, Asp, Chg, Glu, Leu, Lys_Me3, O3S, Phe_4Ad, Phe_4tBu, Ser, Tba, or Tle;

X12 is aMe_Trp, Trp, Trp_56diCl, Trp_5Cl, Trp_5Me, or Trp_6Cl;

X13 is Abu, Cys, Dab_Acetyl, Hcy, Hhc, O2S, O3S, O3S_Reduced, O3S_Me, O3S_Me_Reduced, O4S, O4S_Reduced, O5S, O5S_Reduced, or Pen;

X14 is Aib, Asn, Cys, dK, dL, dN, dQ, dR, Gln, Lys, Lys_1PEG2_1PEG2_IsoGlu_C12, Lys_Ac, Lys_PEG4_PEG4_NH2, Lys_PEG4_1PEG2_NH2, Lys_PEG8_NH2, Tba, or absent;

X15 is dR, dE, or absent;

X16 is dE, dQ, or absent;

wherein the peptide comprises a cyclic structure wherein X5 and X13 are either: (a) directly covalently linked or (b) indirectly covalently linked through a cyclization linker; and

wherein: (i) the peptide is optionally a monomer in a homodimer or heterodimer complex, wherein each monomer is directly covalently linked to each other or indirectly covalently

linked to each other through a dimerization linker; and/or (ii) the peptide is optionally conjugated with a half-life extension moiety.

(Formula (III)).

[0097] In one aspect of Formula (III), both X5 and X13 are Hhc, and these two residues are directly covalently linked through a disulfide bond.

[0098] In another aspect of Formula (III), X5 is Lys_Ac and X13 is Cys, or X5 is Hhc and X13 is Dab_Acetyl, and these two residues are directly covalently linked through a thioether bond.

[0099] In another aspect of Formula (III), X5 is Lys_Ac and X13 is Hhc, and these two residues are directly covalently linked through a thioether bond.

[00100] In another aspect of Formula (III), X5 is Lys and X13 is hE (or vice versa), and these two residues are directly covalently linked through an amide bond (lactam).

[00101] In another aspect of Formula (III), X5 is LysN3 and X13 is Abu (or vice versa), and these two residue are directly covalently linked as shown in paragraph [00324].

[00102] In another aspect of Formula (III), X5 and X13 are individually or both O2S, O3S, O3S_Methyl, or O4S, and these two residues are directly covalently linked through a carbon-carbon double bond.

[00103] In another aspect of Formula (III), X5 and X13 are individually or both O3S_Reduced, O3S_Me_Reduced, O4S_Reduced, or O5S_Reduced, and these two residues are directly covalently linked through a carbon-carbon single bond.

[00104] In another aspect of Formula (III), X5 and X13 are both, or individually, Hcy, Cys, Hhc, or Pen, wherein X5 and X13 are indirectly covalently linked through a thioether bond, wherein these two residues are indirectly covalently linked through a thioether bond with a terminal end of a Butane_Linkers, a Carbonyl_Linkers, a Dimethylcyclopropane_Linkers, an EButene_Linkers, a Methylene_Linkers, an Oxetane_Linkers, a Pentane_Linkers, or a Propane_Linkers.

[00105] In another aspect of Formula (III), X5 and X13 are both, or individually, Hcy, Cys, Hhc, or Pen, wherein X5 and X13 are indirectly covalently linked through a thioether bond, wherein these two residues are indirectly covalently linked through a thioether bond with a Xylene_Linkers.

[00106] In other aspects of Formula (III), the peptide is a monomer in a homodimer compound, and wherein each monomer is directly covalently linked to a PEG linker at X14 through an amide bond, wherein one monomer is linked to one terminal end of the PEG linker and the other monomer is linked to the other terminal end of the PEG linker, and wherein X14 is Lys or dK. The PEG linker can be, for example, PEG5DA, PEG9DA, PEG13DA, PEG21DA, or PEG25DA. In another aspect, the PEG linker can comprise a linear structure with a COOH group at each terminal end and between 15-25 PEG units.

[00107] In other aspects of Formula (III), the peptide is a monomer in a homodimer compound, and wherein each monomer is directly covalently linked to a DIG_linker at X14 through an amide bond, wherein one monomer is linked to one terminal end of the DIG_linker and the other monomer is linked to the other terminal end, and wherein X14 is Lys_PEG4_PEG4_NH2, Lys_PEG4_1PEG2_NH2, or Lys_PEG8_NH2.

[00108] In one aspect of Formula (III), the compound exhibits an IC₅₀ value of less than about 5 nM, or 1 nM, in a human IL-17 HEK Blue assay.

[00109] In other aspects of Formula (III), the compound exhibits a half-life greater than about 0.5 hours, 1.0 hours, 1.5 hours, or 2.0 hours, in an SGF and/or SIF stability assay.

[00110] In another aspect of Formula (III), R¹ is acetyl, glutaric acid, or isovaleric acid, and R² is an amine.

[00111] In one aspect, the invention provides a peptide compound that has an IC₅₀ for hIL-17AA that is less than about 1nM and for hIL-17FF that is less than about 10 nM in a human IL-17 HEK Blue assay, wherein the peptide compound comprises a monomer peptide comprises or consists of the sequence of Formula (IV):

R¹-X00-X0-X1-X2-X3-X4-X5-X6-X7-X8-X9-X10-X11-X12-X13-X14-X15-X16-R²,

wherein:

R¹ is acetyl, 3-hydroxypropionic acid, C6_diacid, cyclopropanecarboxylic acid, glutaric acid, isovaleric acid, methanesulfonyl acetic acid, or absent; R² is NH₂, OH, or absent;

X00 is dH, Tle, or absent;

X0 is 2Pal, d2Pal, Asn, dE, dH, dQ, Gln, Glu, Glu_OMe, His, Ile, Lys, Lys_Me3, NMe_His, Orn, Sar, Thr, Tle, or absent;

X1 is 1Nal, Cha, Cyclopropyl_Ala, Dgl, DIP, hCha, hF, hhF, Ile, Ogl, Phe_4Me, Tba, Tle, or Val;

X2 is 2Pal, 3Pal, Dab_Ac, Dab2HyAc, DabMs, DabTs, E, Gln, His, Hse, Lys_Ac, Lys_Dimethyl, Lys_Me3, Lys_PEG2_Me3, Lys1PEG2Ac, Lys2HyAc, LysMPA, LysMs, OrnAc, Orn2HyAc, OrnMs, OrnPVA, Phe_2Ad, Phe_3Ad, Phe_4Ad, Q_NHMe, Q_NMe2, Q_Pyro, Q_EtOMe, Tet1, or Thr;

X3 is Ala_cycBu, AlaCF3, AlaCHF2, Aoc, Cha, Chg, Cyclopentyl_Ala, Cyclopropyl_Ala, hCha, nVF3, Ogl, Phe_4tBu, Tba, Tle, or Val;

X4 is Asn, Gln, Glu, Glu_OMe, hE, His, LysMe3, Phe_4COOH, or Thr;

X5 is Cys, Hcy, Hhc, Lys_Ac, LysN3, O2S, O3S, O3S_Reduced, O3S_Me, O3S_Me_Reduced, O4S, O4S_Reduced, O5S, O5S_Reduced, or Pen;

X6 is 4SCF3Pro, 4SCyclohexPro, Oic, or Pro;

X7 is Acvc, Ala, Dab, Gln, Glu, His, hR, Lys_Ac, Oic, Pro, Ser, or Tba;

X8 is aMe_Glu, Asp, Gla, Glu, or Tet1;

X9 is Aoc, Dgl, or Ogl;

X10 is 1Nal, 2Nal, aMe_Phe, aMe_Trp, Aoc, Cys, hCha, Hph, Phe_4COOH, Trp, Trp_4Cl, Trp_4COOH, Trp_4Me, Trp_5CONH2, Trp_6CONH2, Trp_6Me, Trp_7Me, or Trp_7Phe;

X11 is Aib, Ala, aMe_Asp, aMe_Leu, aMe_Phe, Asn, Asp, Chg, Glu, Leu, Lys_Me3, Phe_4Ad, Ser, Tba, or Tle;

X12 is aMe_Trp, Trp, Trp_56diCl, Trp_5Cl, Trp_5Me, or Trp_6Cl;

X13 is Abu, Cys, Dab_Acetyl, Hcy, Hhc, O2S, O3S, O3S_Reduced, O3S_Me, O3S_Me_Reduced, O4S, O4S_Reduced, O5S, O5S, or Pen;

X14 is Aib, Asn, Cys, dK, dN, dQ, dR, Gln, Lys, Lys_Ac, Lys_PEG4_PEG4_NH2, Lys_PEG4_1PEG2_NH2, Lys_PEG8_NH2, Tba, or absent;

X15 is dE, dR, or absent; and

X16 is dE, dQ, or absent;

wherein the peptide comprises a cyclic structure wherein X5 and X13 are either: (a) directly covalently linked or (b) indirectly covalently linked through a cyclization linker; and

wherein: (i) the peptide is optionally a monomer in a homodimer or heterodimer complex, wherein each monomer is directly covalently linked to each other or indirectly covalently

linked to each other through a dimerization linker; and/or (ii) the peptide is optionally conjugated with a half-life extension moiety.

(Formula (IV)).

[00112] In one aspect of Formula (IV), both X5 and X13 are both Hhc, and these two residues are directly covalently linked through a disulfide bond.

[00113] In another aspect of Formula (IV), X5 is Lys_Ac and X13 is Cys, and these two residues are directly covalently linked through a thioether bond.

[00114] In another aspect of Formula (IV), X5 is Hhc and X13 is Dab_Acetyl, and these two residues are directly covalently linked through a thioether bond.

[00115] In another aspect of Formula (IV), X5 is O5S_Reduced and X13 is Dab_Acetyl, and these two residues are directly covalently linked through a thioether bond.

[00116] In another aspect of Formula (IV), X5 is O5S_Reduced and X13 is Hhc, and these two residues are directly covalently linked through a thioether bond.

[00117] In another aspect of Formula (IV), X5 is Lys and X13 is hE, or vice versa, and these two residues are directly covalently linked through an amide bond (lactam).

[00118] In another aspect of Formula (IV), X5 is LysN3 or Lys and X13 is Abu or hE, and these two residues are directly covalently linked as shown in paragraph [00324].

[00119] In another aspect of Formula (IV), both X5 and X13 are individually, or both, O3S_Reduced, O3S_Methyl_Reduced, or O4S_Reduced, and these two residues are directly covalently linked through a carbon-carbon single bond.

[00120] In another aspect of Formula (IV), X5 and X13 are individually, or both, O2S, O3S, O3S_Me, or O4S, and these two residues are directly covalently linked through a carbon-carbon double bond.

[00121] In another aspect of Formula (IV), X5 and X13 are individually, or both, Cys, Hcy, Hhc, or Pen, wherein X5 and X13 are indirectly covalently linked through a thioether bond, wherein these two residues are indirectly covalently linked through a thioether bond with a terminal end of a Carbonyl_Linkers, a Dimethylcyclopropane_Linkers, an EButene_Linkers, a Methylene_Linkers, an Oxetane_Linkers, a Pentane_Linkers, a Propane_Linkers, or a pXylene_Linkers.

[00122] In other aspects of Formula (IV), the peptide is a monomer in a homodimer compound, and wherein each monomer is directly covalently linked to a PEG linker at X14Lys through an amide bond, wherein one monomer is linked to one terminal end of the PEG linker and the other monomer is linked to the other terminal end of the PEG linker. The PEG linker can be, for example, PEG5DA, PEG9DA, PEG13DA, PEG21DA, or PEG25DA.

[00123] In another aspect of Formula (IV), the peptide is a monomer in a homodimer compound, and wherein each monomer is directly covalently linked to a DIG_linker at X14Lys_PEG4_PEG4_NH2, X14Lys_PEG4_1PEG2_NH2, or X14Lys_PEG8_NH2, through an amide bond, wherein one monomer is linked to one terminal end of this linker and the other monomer is linked to the other terminal end.

[00124] In other aspects of Formula (IV), the compound exhibits a half-life greater than about 0.5 hours, 1.0 hours, 1.5 hours, or 2.0 hours, in an SGF and/or SIF stability assay.

[00125] In one aspect, the invention provides a peptide compound that has an IC₅₀ for hIL-17AA that is less than about 1nM and for hIL-17FF that is less than about 5 nM in a human IL-17 HEK Blue assay, wherein the peptide compound comprises a monomer peptide that comprises or consists of the sequence of Formula (V):

R¹-X00-X0-X1-X2-X3-X4-X5-X6-X7-X8-X9-X10-X11-X12-X13-X14-X15-X16-R²,

wherein:

R¹ is acetyl, 3-hydroxypropionic acid, C6_diacid, cyclopropanecarboxylic acid, glutaric acid, isovaleric acid, methanesulfonyl acetic acid, or absent; R² is NH₂, OH, or absent;

X00 is dH, Tle or absent;

X0 is dE, dH, dQ, Gln, Glu, Glu_OMe, His, Ile, Lys, Lys_Me3, Orn, Sar, Thr, Tle, or absent;

X1 is Cha, Cyclopropyl_Alal, Dgl, DIP, hhF, Ile, Tba, Tle, or Val;

X2 is 2Pal, 3Pal, Dab_Ac, Dab2HyAc, DabMs, DabTs, Gln, Glu, His, Hse, Lys_Ac, Lys_Dimethyl, Lys_Me3, Lys_PEG2_Me3, Lys1PEG2Ac, Lys2HyAc, LysMPA, LysMs, OrnAc, Orn2HyAc, OrnMs, OrnPVA, Phe_3Ad, Phe_4Ad, Q_NHMe, Q_NMe2, Q_Pyro, Q_EtOMe, Tet1, or Thr;

X3 is Ala_cycBu, AlaCF3, AlaCHF2, Cha, Chg, Cyclopentyl_Alal, Cyclopropyl_Alal, hCha, nVF3, Ogl, Tba, Tle, or Val;

X4 is Asn, Gln, Glu, Glu_OMe, hE, His, Phe_4COOH, or Thr;

X5 is Cys, Hcy, Hhc, Lys_Ac, LysN3, O2S, O3S, O3S_Reduced, O3S_Me, O3S_Me_Reduced, O4S, O4S_Reduced, O5S_Reduced, or Pen;

X6 is 4SCF3Pro or Oic;

X7 is Acvc, Ala, Gln, Glu, Lys_Ac, Oic, Pro, Ser, or Tba;

X8 is aMe_Glu, Asp, Gla, Glu, or Tet1;

X9 is Aoc, Dgl, or Ogl;

X10 is 1Nal, 2Nal, Aoc, Hph, Phe_4COOH, Trp, Trp_4Cl, Trp_4COOH, Trp_6CONH2, Trp_6Me, Trp_7Me, or Trp_7Phe;

X11 is Aib, Ala, aMe_Leu, aMe_Phe, Asn, Asp, Chg, Glu, Leu, Lys_Me3, Phe_4Ad, Ser, Tba, or Tle;

X12 is aMe_Trp, Trp, Trp_56diCl, or Trp_6Cl;

X13 is Abu, Cys, Dab_Acetyl, Hcy, Hhc, O2S, O3S, O3S_Reduced, O3S_Me, O3S_Me_Reduced, O4S, O4S_Reduced, or Pen;

X14 Asn, dK, Gln, Lys, Lys_PEG4_PEG4_NH2, Lys_PEG4_1PEG2_NH2, Lys_PEG8_NH2, or absent;

X15 is dE, dR, or absent; and

X16 is dE or absent;

wherein the peptide comprises a cyclic structure wherein X5 and X13 are either: (a) directly covalently linked or (b) indirectly covalently linked through a cyclization linker; and

wherein: (i) the peptide is optionally a monomer in a homodimer or heterodimer complex, wherein each monomer is directly covalently linked to each other or indirectly covalently linked to each other through a dimerization linker; and/or (ii) the peptide is optionally conjugated with a half-life extension moiety.

(Formula (V)).

[00126] In one aspect of Formula (V), both X5 and X13 are Hhc, and these two residues are directly covalently linked through a disulfide bond.

[00127] In another aspect of Formula (V), X5 is Lys_Ac and X13 is Cys, and these two residues are directly covalently linked through a thioether bond.

[00128] In another aspect of Formula (V), X5 is Hhc and X13 is Dab_Acetyl, and these two residues are directly covalently linked through a thioether bond.

[00129] In another aspect of Formula (V), X5 is O5S_Reduced and X13 is Hhc, and these two residues are directly covalently linked through a thioether bond.

[00130] In another aspect of Formula (V), X5 is LysN3 and X13 is Abu, and these two residues are directly covalently linked as shown in paragraph [00324].

[00131] In another aspect of Formula (V), X5 is O2S, O3S, or O4S, and X13 is O2S, O3S, O4S, or O3S_Me, and these two residues are directly covalently linked through a carbon-carbon double bond.

[00132] In another aspect of Formula (V), X5 is O3S_Reduced and X13 is O3S_Reduced or O3S_Me_Reduced, and these two residues are directly covalently linked through a carbon-carbon single bond.

[00133] In another aspect of Formula (V), X5 is Cys or Hcy, and X13 is Cys or Hcy, wherein X5 and X13 are indirectly covalently linked through a thioether bond, wherein these two residues are indirectly covalently linked through a thioether bond with a terminal end of a Butane_Linkers, a Carbonyl_Linkers, a Dimethylcyclopropane_Linkers, an EButene_Linkers, an Oxetane_Linkers, a Pentane_Linkers, Propane_Linkers, or a pXylene_Linkers.

[00134] In other aspects of Formula (V), the peptide is a monomer in a homodimer compound, and wherein each monomer is directly covalently linked to a PEG linker at X14Lys through an amide bond, wherein one monomer is linked to one terminal end of the PEG linker and the other monomer is linked to the other terminal end of the PEG linker. The PEG linker can be, for example, PEG5DA, PEG9DA, PEG13DA, PEG21DA, or PEG25DA.

[00135] In another aspect of Formula (V), the peptide is a monomer in a homodimer compound, and wherein each monomer is directly covalently linked to a DIG_linker at X14Lys_PEG4_PEG4_NH2, X14Lys_PEG4_1PEG2_NH2, or X14Lys_PEG8_NH2, through an amide bond, wherein one monomer is linked to one terminal end of this linker and the other monomer is linked to the other terminal end.

[00136] In other aspects of Formula (V), the compound exhibits a half-life greater than about 0.5 hours, 1.0 hours, 1.5 hours, or 2.0 hours, in an SGF and/or SIF stability assay.

[00137] In one aspect, the invention provides a peptide compound that has an IC₅₀ for hIL-17AA that is less than about 1nM and for hIL-17FF that is less than about 1 nM in a human

IL-17 HEK Blue assay, wherein the peptide compound comprises a monomer peptide comprising or consisting of the sequence of Formula (VI):

R^1 -X00-X0-X1-X2-X3-X4-X5-X6-X7-X8-X9-X10-X11-X12-X13-X14-X15-X16- R^2 ,

wherein:

R^1 is acetyl, 3-hydroxypropionic acid, C6_diacid, cyclopropanecarboxylic acid, glutaric acid, isovaleric acid, methanesulfonyl acetic acid, or absent; R^2 is NH_2 , OH, or absent;

X00 is dH or absent;

X0 is dE, dH, Gln, Glu, Glu_OMe, His, Ile, Lys_Me3, Sar, Tle, or absent;

X1 is Cyclopropyl_Alal, Ile, Tba, or Val;

X2 is Dab_Ac, Gln, Glu, His, Hse, Lys_Ac, Lys_Me3, Lys1PEG2Ac, Lys2HyAc, LysMs, Orn2HyAc, OrnAc, Q_NHMe, Q_NMe2, Q_EtOMe, or Thr;

X3 is Cyclopropyl_Alal, Ogl, Tba, Tle, or Val;

X4 is Asn, Glu, Glu_OMe, hE, Phe_4COOH, or Thr;

X5 is Cys, Hcy, Hhc, O2S, O3S, O3S_Reduced, or O4S;

X6 is Oic;

X7 is Acvc, Ala, Gln, Glu, Lys_Ac, Pro, Ser, or Tba;

X8 is Asp or Gla;

X9 is Dgl, or Ogl;

X10 is 1Nal, 2Nal, or Trp;

X11 is Aib, Asp, or Glu;

X12 is aMe_Trp or Trp;

X13 is Cys, Hcy, Hhc, O2S, O3S, O3S_Me, O3S_Me_Reduced, O3S_Reduced, or O4S;

X14 Asn, Lys, Lys_PEG4_1PEG2_NH2, Lys_PEG8_NH2, or Lys_PEG4_PEG4_NH2;

X15 is dR; and

X16 is dE or absent;

wherein the peptide comprises a cyclic structure wherein X5 and X13 are either: (a) directly covalently linked or (b) indirectly covalently linked through a cyclization linker; and

wherein: (i) the peptide is optionally a monomer in a homodimer or heterodimer complex, wherein each monomer is directly covalently linked to each other or indirectly covalently

linked to each other through a dimerization linker; and/or (ii) the peptide is optionally conjugated with a half-life extension moiety.

(Formula (VI)).

[00138] In one aspect of Formula (VI), both X5 and X13 are Hhc, and these two residues are directly covalently linked through a disulfide bond.

[00139] In another aspect of Formula (VI), X5 is O2S, O3S, or O4S, and X13 is O2S, O3S, O4S, or O3S_Me, and these two residues are directly covalently linked through a carbon-carbon double bond.

[00140] In another aspect of Formula (VI), X5 is O3S_Reduced and X13 is O3S_Reduced or O3S_Me_Reduced, and these two residues are directly covalently linked through a carbon-carbon single bond.

[00141] In another aspect of Formula (VI), X5 is Cys or Hcy, and X13 is Cys or Hcy, wherein X5 and X13 are indirectly covalently linked through a thioether bond, wherein these two residues are indirectly covalently linked through a thioether bond with a terminal end of a Butane_Linkers, a Carbonyl_Linkers, a Dimethylcyclopropane_Linkers, an EButene_Linkers, an Oxetane_Linkers, a Pentane_Linkers, or a Propane_Linkers.

[00142] In other aspects of Formula (VI), the peptide is a monomer in a homodimer compound, and wherein each monomer is directly covalently linked to a PEG linker at X14Lys through an amide bond, wherein one monomer is linked to one terminal end of the PEG linker and the other monomer is linked to the other terminal end of the PEG linker. The PEG linker can be, for example, PEG5DA, PEG9DA, PEG13DA, PEG21DA, or PEG25DA.

[00143] In another aspect of Formula (VI), the peptide is a monomer in a homodimer compound, and wherein each monomer is directly covalently linked to a DIG_linker at X14Lys_PEG4_PEG4_NH2, X14Lys_PEG4_1PEG2_NH2, or X14Lys_PEG8_NH2, through an amide bond, wherein one monomer is linked to one terminal end of this linker and the other monomer is linked to the other terminal end.

[00144] In other aspects of Formula (VI), the compound exhibits a half-life greater than about 0.5 hours, 1.0 hours, 1.5 hours, or 2.0 hours, in an SGF and/or SIF stability assay.

[00145] In one aspect, the invention provides a peptide compound that has an IC₅₀ for hIL-17AA that is less than about 1nM, wherein the peptide compound comprises a monomer peptide comprising or consisting of the sequence of Formula (VII):

R¹-X00-X0-X1-X2-X3-X4-X5-X6-X7-X8-X9-X10-X11-X12-X13-X14-X15-X16-X17-X18-X19-X20-X21-X22-X23-X24-R²,

wherein:

R¹ is acetyl, 3-hydroxypropionic acid, C6_diacid, cyclopropanecarboxylic acid, glycolic acid, glutaric acid, isovaleric acid, methanesulfonyl acetic acid, or absent; R² is NH₂ or OH or absent;

X00 is bA, dH, dK, Tle or absent;

X0 is 2Pal, Aib, Asn, d2Pal, d3Pal, dA, dE, dH, dL, dQ, dS, Gla, Gln, Glu, Glu_OMe, His, Ile, Lys, Lys_Me3, NMe_His, Orn, Pro, Sar, Thr, Tle, or absent;

X1 is 1Nal, Aph, Dgl, hCha, hF, hhF, Ile, Lys_1PEG2_1PEG2_IsoGluC12, Ogl, Phe_4Me, Tba, Tle, or Val;

X2 is 2Pal, 3Pal, Gln, His, Hse, Lys_1PEG2_1PEG2_IsoGluC12, Lys_Me3, Orn, Phe_3Ad, Phe_4_2ae, or Phe_4ad;

X3 is Cpg, Cyclopropyl_Ala, Dgl, Ogl, Phe_4tBu, Tba, Tle, or Val;

X4 is Asn, Glu, or Thr;

X5 is Cys, Hcy, Hhc, Ile, Lys_Ac, O3S, O3S_Reduced, or O5S_Reduced;

X6 is Oic or Pro;

X7 is Ala, Aze, Dab, His, Lys_Ac, O3S_Me, or Tic;

X8 is Asp or Gla;

X9 is Dgl, Ogl, or O3S;

X10 is 1Nal, 2Nal, aMe_Phe, aMe_Trp, Aoc, Cys, Gln, hCha, Hph, O3S, Phe_4Ad, Phe_4COOH, Tba, Tle, Trp, Trp_4Cl, Trp_4Me, Trp_5Cl, Trp_5Me, Trp_6Cl, Trp_6Me, Trp_7Cl, Trp_7Me, or Trp_7Phe;

X11 is Asp, dA, Glu, or O3S_Me;

X12 is aMe_Trp, Trp, Trp_5Cl, Trp_5Me, or Trp_6Cl;

X13 is Cys, Hcy, Hhc, Ile, O3S, O3S_Me, O3S_Reduced, or O4S;

X14 Aib, Arg, Asn, Asp, Cys, dE, dK, dN, dQ, dR, Glu, Gln, Gly, Lys, Lys_1PEG2_1PEG2_IsoGlu_C12, Lys_Ac, O3S_Me, Tba, or absent;

X15 is Ala, Asn, dE, dR, dQ, Gln, Gly, Leu, Pro, Ser, or absent;

X16 is Aad, dE, dH, dQ, PEG4, PEG6, PEG8, Ser, Thr, Val, or absent;

X17 is Asp, Gly, Glu, His, Ile, Pro, or absent;

X18 is His, Ile, Ser, Tle, Val, or absent;

X19 is His, Ile, Val, or absent;

X20 is His, Thr, Val, or absent;

X21 is Ile, Thr, Val, or absent;

X22 is Ile, Thr, or absent;

X23 is Ile or absent;

X24 is Oic, Pro, or absent;

wherein the peptide comprises a cyclic structure wherein X5 and X13, X9 and X13, or X7 and X11, are either: (a) directly covalently linked or (b) indirectly covalently linked through a cyclization linker.

(Formula (VII)).

[00146] In one aspect of Formula (VII), the peptide compound consists of a monomer (i.e., not a multimer).

[00147] In one aspect of Formula (VII), both X5 and X13 are Hhc, and these two residues are directly covalently linked through a disulfide bond.

[00148] In one aspect of Formula (VII), X5 is Lys_Ac and X13 is Cys, and these two residues are directly covalently linked through a thioether bond.

[00149] In one aspect of Formula (VII), X5 is O5S_Reduced and X13 is Hhc, and these two residues are directly covalently linked through a thioether bond.

[00150] In another aspect of Formula (VII), both X5 and X13 are O3S, or X5 and X13 are individually or both O3S, O4S, or O3S_Methyl, and these two residues are directly covalently linked through a carbon-carbon double bond.

[00151] In another aspect of Formula (VII), both X5 and X13 are O3S_Reduced, and these two residues are directly covalently linked through a carbon-carbon single bond.

[00152] In another aspect of Formula (VII), X5 is Cys or Hcy, and X13 is Cys or Hcy, wherein X5 and X13 are indirectly covalently linked through a thioether bond, wherein these two residues are indirectly covalently linked through a thioether bond with a terminal end of a

Butane_Linkers, Dimethylcyclopropane_Linkers, an EButene_Linkers, a Hexane_Linkers, a Methylene_Linkers, an Oxetane_Linkers, a Pentane_Linkers, a Propane_Linkers, or a Xylene_Linkers.

[00153] In another aspect of Formula (VII), X9 and X13 are both O3S, which are directly covalently linked through a carbon-carbon single bond.

[00154] In another aspect of Formula (VII), X7 and X11 are both O3S_Me, which are directly covalently linked through a carbon-carbon double bond.

[00155] In other aspects, a peptide of Formula (VII) can be a monomer in a homodimer compound. As described herein, the monomer can be dimerized in multiple ways, such as having a lysine at a residue at X14-X16, which can be covalently attached to a PEG linker through an amide bond, or having a lysine with a modified side-chain that comprises PEG units and a free amine, such that the amine can form an amide bond with a linker having free COOH groups, such as the DIG_Linkers.

[00156] In other aspects of Formula (VII), the compound exhibits a half-life greater than about 0.5 hours, 1.0 hours, 1.5 hours, or 2.0 hours, in an SGF and/or SIF stability assay.

[00157] In another aspect of Formula (VII), the compound has an IC₅₀ for hIL-17AA that is less than about 1nM and an IC₅₀ for hIL-17FF that is less than about 10 nM, wherein the peptide comprises the following:

R¹ is acetyl, glutaric acid, glycolic acid, or isovaleric acid; R² is NH₂;

X00 is bA or absent;

X0 is 2Pal, d2Pal, dE, dH, Gla, Glu, His, NMe_His, Tle, or absent;

X1 is 1Nal, Aph, Dgl, hF, hhF, Ile, Tle, or Val;

X2 is 2Pal, 3Pal, or His;

X3 is Tba or Tle;

X4 is Thr;

X5 is Cys, Hcy, Hhc, or O3S;

X6 is Oic;

X7 is Ala or Lys_Ac;

X8 is Asp;

X9 is Dgl or Ogl;

X10 is Cys, Trp, Trp_7Me, or Trp_7Phe;

X11 is Asp or Glu;

X12 is aMe_Trp or Trp;

X13 is Hcy, Hhc, O3S, O3S_Me, or O4S;

X14 Aib, Asn, Asp, Cys, Gln, Gly, Lys_1PEG2_1PEG2_IsoGlu_C12, or Lys_Ac;

X15 is Ala, Asn, dQ, dR, Gln, Gly, Leu, Ser, or absent;

X16 is Aad, dE, Ser, Thr, Val, or absent;

X17 is Asp, His, or absent; and

X18 is Ser, Val, or absent;

wherein the peptide comprises a cyclic structure wherein X5 and X13 are either: (a) directly covalently linked or (b) indirectly covalently linked through a cyclization linker.

[00158] In another aspect of Formula (VII), the compound has an IC₅₀ for hIL-17AA that is less than about 1nM and an IC₅₀ for hIL-17FF that is less than about 10 nM, and the compound exhibits a half-life in both an SGF and an SIF assay greater than about 2 hours, wherein the peptide comprises the following:

R¹ is acetyl, glutaric acid, glycolic acid, or isovaleric acid; R² is NH₂;

X00 is bA or absent;

X0 is 2Pal, d2Pal, dE, dH, Glu, His, NMe_His, Tle, or absent;

X1 is 1Nal, Aph, Dgl, hF, hhF, Ile, Tle, or Val;

X2 is 2Pal, 3Pal, or His;

X3 is Tba or Tle;

X4 is Thr;

X5 is Cys, Hcy, Hhc, or O3S;

X6 is Oic;

X7 is Ala or Lys_Ac;

X8 is Asp;

X9 is Dgl or Ogl;

X10 is Cys, Trp, Trp_7Me, or Trp_7Phe;

X11 is Asp or Glu;

X12 is aMe_Trp or Trp;

X13 is Hcy, Hhc, O3S, O3S_Me, or O4S;

X14 Aib, Asn, Cys, Gln, Lys_1PEG2_1PEG2_IsoGlu_C12, or Lys_Ac;

X15 is Ala, dQ, dR, Gln, or absent;

X16 is Aad, dE, or absent;

wherein the peptide comprises a cyclic structure wherein X5 and X13 are either: (a) directly covalently linked or (b) indirectly covalently linked through a cyclization linker.

[00159] In one embodiment of Formula (VII), X17-X24 are absent.

[00160] In one embodiment of Formula (VII), X19-X24 are absent.

[00161] In one aspect, the invention provides a peptide compound that has an IC₅₀ for hIL-17AA and FF that is less than about 1nM, wherein the peptide compound exhibits a half-life in an SIF assay greater than about 2 hours, wherein the peptide compound comprises a monomer peptide comprising or consisting of the sequence of Formula (VIII):

R¹-X00-X0-X1-X2-X3-X4-X5-X6-X7-X8-X9-X10-X11-X12-X13-X14-X15-X16-R²,

wherein:

R¹ is acetyl, 3-hydroxypropionic acid, C6_diacid, cyclopropanecarboxylic acid, glutaric acid, isovaleric acid, methanesulfonyl acetic acid, or absent; R² is NH₂, OH, or absent;

X00 is dH or absent;

X0 is dE, dH, Gln, Glu, His, Ile, Lys_Me3, Sar, Tle, or absent;

X1 is Cyclopropyl_Alal, Ile, Tba, or Val;

X2 is Dab_Ac, Gln, His, Lys_Ac, Lys_Me3, Lys1PEG2Ac, Lys2HyAc, Orn2HyAc, OrnAc, or Thr;

X3 is Cyclopropyl_Alal, Ogl, Tba, Tle, or Val;

X4 is Asn, Glu, Glu_OMe, hE, or Thr;

X5 is Cys, Hcy, Hhc, O2S, O3S, O3S_Reduced, or O4S;

X6 is Oic;

X7 is Acvc, Ala, Gln, Glu, Lys_Ac, Pro, Ser, or Tba;

X8 is Asp or Gla;

X9 is Dgl, or Ogl;

X10 is 1Nal, 2Nal, or Trp;

X11 is Aib, Asp, or Glu;

X12 is aMe_Trp or Trp;

X13 is Cys, Hcy, Hhc, O2S, O3S, O3S_Me, O3S_Reduced, or O4S;

X14 is Asn, Lys, Lys_PEG4_1PEG2_NH2, Lys_PEG8_NH2, or Lys_PEG4_PEG4_NH2;

X15 is dR; and

X16 is absent;

wherein the peptide comprises a cyclic structure wherein X5 and X13 are either: (a) directly covalently linked or (b) indirectly covalently linked through a cyclization linker; and

wherein the peptide is optionally a monomer in a homodimer complex, wherein each monomer is directly covalently linked to each other or indirectly covalently linked to each other through a dimerization linker.

(Formula (VIII)).

[00162] In one aspect of Formula (VIII), both X5 and X13 are Hhc, and these two residues are directly covalently linked through a disulfide bond.

[00163] In another aspect of Formula (VIII), X5 and X13 are individually, or both, O2S, O3S, O3S_Me, or O4S, and these two residues are directly covalently linked through a carbon-carbon double bond.

[00164] In another aspect of Formula (VIII), X5 is O3S_Reduced and X13 is O3S_Reduced, and these two residues are directly covalently linked through a carbon-carbon single bond.

[00165] In another aspect of Formula (VIII), X5 is Cys or Hcy, and X13 is Cys or Hcy, wherein X5 and X13 are indirectly covalently linked through a thioether bond, wherein these two residues are indirectly covalently linked through a thioether bond with a terminal end of a Dimethylcyclopropane_Linker, an Oxetane_Linker, a Pentane_Linker, or a Propane_Linker.

[00166] In other aspects of Formula (VIII), the peptide is a monomer in a homodimer compound, and wherein each monomer is directly covalently linked to a PEG linker at X14Lys through an amide bond, wherein one monomer is linked to one terminal end of the PEG linker and the other monomer is linked to the other terminal end of the PEG linker. The PEG linker can be, for example, PEG5DA, PEG9DA, PEG13DA, PEG21DA, or PEG25DA.

[00167] In another aspect of Formula (VIII), the peptide is a monomer in a homodimer compound, and wherein each monomer is directly covalently linked to a DIG_linker at

X14Lys_PEG4_PEG4_NH2, X14Lys_PEG4_1PEG2_NH2, or X14Lys_PEG8_NH2, through an amide bond, wherein one monomer is linked to one terminal end of this linker and the other monomer is linked to the other terminal end.

[00168] In other aspects of Formula (VIII), the compound exhibits a half-life greater than about 0.5 hours, 1.0 hours, 1.5 hours, or 2.0 hours, in an SGF stability assay.

[00169] In one aspect, the invention provides a peptide compound that has an IC₅₀ for hIL-17AA that is less than about 1 nM and for IL-17FF that is less than about 5nM, wherein the peptide compound exhibits a half-life in both an SGF and an SIF assay greater than about 2 hours, wherein the peptide compound comprises a monomer peptide comprising or consisting of the sequence of Formula (IX):

R¹-X00-X0-X1-X2-X3-X4-X5-X6-X7-X8-X9-X10-X11-X12-X13-X14-X15-X16-R²,

wherein:

R¹ is acetyl, 3-hydroxypropionic acid, C6_diacid, cyclopropanecarboxylic acid, glutaric acid, isovaleric acid, methanesulfonyl acetic acid, or absent; R² is NH₂ or OH or absent;

X00 is dH or absent;

X0 is dE, dH, Glu, His, Ile, Lys_Me3, Sar, Tle, or absent;

X1 is Ile or Val;

X2 is His, Lys_Me3, or Gln;

X3 is Tba, Tle, or Val;

X4 is Asn, Glu, Glu_OMe, hE, or Thr;

X5 is Cys, Hcy, Hhc, O3S, or O3S_Reduced;

X6 is Oic;

X7 is Acvc, Ala, Gln, Glu, Lys_Ac, Pro, Ser, or Tba;

X8 is Asp or Gla;

X9 is Dgl or Ogl;

X10 is 1Nal, 2Nal, or Trp;

X11 is Aib, Asp, or Glu;

X12 is aMe_Trp or Trp;

X13 is Cys, Hcy, Hhc, O3S, O3S_Me, or O3S_Reduced;

X14 is Lys, Lys_PEG4_1PEG2_NH2, Lys_PEG8_NH2, or Lys_PEG4_PEG4_NH2;

X15 is dR; and

X16 is absent;

wherein the peptide comprises a cyclic structure wherein X5 and X13 are either: (a) directly covalently linked or (b) indirectly covalently linked through a cyclization linker; and

wherein: (i) the peptide is a monomer in a homodimer complex, wherein each monomer is covalently linked to a dimerization linker; and/or (ii) the peptide is optionally conjugated with a half-life extension moiety.

(Formula (IX)).

[00170] In one aspect of Formula (IX), both X5 and X13 are Hhc, and these two residues are directly covalently linked through a disulfide bond.

[00171] In another aspect of Formula (IX), X5 is O3S, and X13 is O3S or O3S_Me, and these two residues are directly covalently linked through a carbon-carbon double bond.

[00172] In another aspect of Formula (IX), X5 is O3S_Reduced and X13 is O3S_Reduced, and these two residues are directly covalently linked through a carbon-carbon single bond.

[00173] In another aspect of Formula (IX), X5 is O5S_Reduced and X13 is Hhc, and these two residues are directly covalently linked through a thioether bond.

[00174] In another aspect of Formula (IX), X5 is Cys or Hcy, and X13 is Cys or Hcy, wherein X5 and X13 are indirectly covalently linked through a thioether bond, wherein these two residues are indirectly covalently linked through a thioether bond with a terminal end of a Dimethylcyclopropane_Linkers, a Pentane_Linkers, or a Propane_Linkers.

[00175] In other aspects of Formula (IX), the peptide is a monomer in a homodimer compound, and wherein each monomer is directly covalently linked to a PEG linker at X14Lys or X14dK through an amide bond, wherein one monomer is linked to one terminal end of the PEG linker and the other monomer is linked to the other terminal end of the PEG linker. The PEG linker can be, for example, PEG5DA, PEG9DA, PEG13DA, PEG21DA, or PEG25DA.

[00176] In another aspect of Formula (IX), the peptide is a monomer in a homodimer compound, and wherein each monomer is directly covalently linked to a DIG_linker at X14Lys_PEG4_PEG4_NH2, X14Lys_PEG4_1PEG2_NH2, or X14Lys_PEG8_NH2 (or its D-form, i.e., dK_PEG4_PEG4_NH2 et al.) through an amide bond, wherein one monomer is

linked to one terminal end of this linker and the other monomer is linked to the other terminal end.

[00177] In another aspect of Formula (IX), the peptide has an IC₅₀ less than 1 nM in a HEK Blue human IL-17FF assay.

[00178] In other aspects of the invention, a peptide can be a monomer in a homotrimer compound, and wherein the monomer has a modified lysine with a side-chain comprising at least one PEG unit and a free amine, such as Lys_PEG4_PEG4_NH₂, Lys_PEG4_1NH₂, Lys_PEG8_NH₂, Lys_PEG10_NH₂, or Lys_PEG12_NH, at X14, X15, or X16. The modified lysine residue in each monomer is covalently linked to the same multimerization linker (e.g., TAEP linker) with at least three free COOH groups, such that the COOH groups and the free amine in the modified lysine side-chains can form an amide bond. The PEG12 portion can be modified to increase or decrease the number of PEG units.

[00179] In other aspects of the invention, a peptide can be a monomer in a homotetramer compound with Lys_Hexy at X14, X15, or X16, and wherein the methyl at the terminal end of the side chain of Lys_Hexy residue in each monomer is covalently linked to the same multimerization linker, TetN3, through a carbon-carbon single bond.

[00180] In other aspects, the invention provides a peptide compound comprising a sequence of any one of SEQ ID NO:1-720 and/or having the two-dimensional chemical structure as encoded by a SMILES formula as listed in Figure 1.

[00181] In one aspect, the invention provides a pharmaceutical composition comprising a peptide of any one of the Formulas herein (including SEQ ID NO formulas), any of the peptide compounds of Figure 1 (i.e., compounds 1-897) or a pharmaceutically acceptable salt thereof and a pharmaceutically acceptable carrier or excipient.

[00182] In another aspect, the invention provides a method of inhibiting the binding of a human IL-17 cytokine to a human IL-17 receptor, the method comprising contacting the human IL-17 cytokine with a peptide of any one of the Formulas herein (including SEQ ID NO formulas), or any one of the compounds of Figure 1 (i.e., compounds 1-897), or a pharmaceutically acceptable salt or solvate thereof.

[00183] In one aspect, the invention provides a method for treating an IL-17 related inflammatory disease or an autoimmune disease in a subject, the method comprising: administering to the subject an effective amount of a peptide of any one of the Formulas herein

(including SEQ ID NO formulas). The inflammatory disease or autoimmune disease can be, for example, psoriasis, plaque psoriasis, generalized pustular psoriasis, psoriatic erythroderma, psoriatic arthritis (including moderate to severe psoriatic arthritis), rheumatoid arthritis, ulcerative colitis, hidradentis suppurativa, spondyloarthritis (SpA), SpA types including ankylosing spondylitis, axial spondyloarthritis, enteropathic spondyloarthritis, peripheral spondyloarthritis, psoriatic arthritis, reactive arthritis, , or nonradiographic axial spondyloarthritis.

[00184] In one aspect, the present disclosure provides a peptide comprising the sequence set forth in one of the SEQ ID NO sequence formulas listed in Figure 1.

[00185] In another aspect, the present disclosure provides a peptide compound as described by its SMILES formula as listed in Figure 1.

[00186] In another aspect, the present disclosure provides a peptide compound having the two-dimensional chemical structure encoded by its SMILES formula as listed in Figure 1.

[00187] In another aspect, the present disclosure provides a peptide compound having the two-dimensional chemical structure as shown in Figure 6.

[00188] In one aspect, the present disclosure provides a method for treating a human IL-17 related disease or disorder in a subject by administering a peptide compound comprising the two-dimensional chemical structure as shown in Figure 6.

[00189] In one aspect, the present disclosure provides a method for treating a human IL-17 related disease or disorder in a subject by administering a peptide compound comprising a sequence set for in one of the SEQ ID NO sequence formulas listed in Figure 1 or as described by its SMILES formula as listed in Figure 1.

BRIEF DESCRIPTION OF THE FIGURES

[00190] **Figure 1.** Figure 1.1-1.245 provides a summary table for over 800 different peptide based compounds of the invention. These are representative compounds that exhibit potency in inhibiting human IL-17 cytokine biological activity. All of the peptide compounds described in Figure 1 have an IC₅₀ less than or equal to 20 nM in a human IL-17 HEK Blue Assay.

[00191] Figure 1 provides three rows of information for each peptide compound. Each peptide compound is given a Compound number (C#). The first row provides information per the columns of the Tables. The second row provides the peptide string sequence of the peptide compound, which string sequence includes terminal chemical moieties (i.e., R1 at the N-terminus and R2 at the C-terminus of the peptide string sequence). The third row provides the SMILES string sequence of the peptide compound. SMILES stands for Simplified Molecular Input Line Entry System, which is an ASCII string line notation that represents a chemical

structure. The SMILES strings for the compounds disclosed herein can be translated to a two-dimensional chemical structure through numerous publicly available sites, including the Smi2Depict tool from the ChemDB Portal: <https://re.edugen.wiley.com/cgi-bin/Smi2DepictWeb.py>

[00192] The first column provides information as to whether the compound is a Monomer (M) or a Dimer (D) and its molecular weight (MW) in Daltons. If a compound is a dimer, the default is that the compound is a homodimer. It will be explicitly stated if a dimer compound is a heterodimer. In the broadest sense, the invention contemplates that any monomer disclosed herein can be used to form homodimers, heterodimers (i.e., different monomer peptides dimerized together), homotrimers, homotetramers, or other multimers, and Figure 1 includes many non-limiting examples between monomers and their respective homodimer complexes.

[00193] First row information also includes three columns relating to cyclization. If a peptide compound comprises a monomer that is cyclized, the "Cyclization Positions" column will indicate a pair of residues that are cross-linked. For example, the notation "X7C-X11C" indicates that a cysteine at position 7 and a cysteine at position 11 are cross-linked. The table includes some bicyclic compounds where two pairs of residues are cross-linked, e.g., "X7C-X11Lys_Ac" and "X9O3S and X13O3S." The next column, "Cyclization Chemical Bond," indicates the type of covalent bond that is formed between the pair or pairs of cross-linked residues. The third column relating to cyclization is "Cyclization Linker." If a Cyclization Linker is present, this indicates that the residues at the Cyclization Positions are indirectly linked, as each Cyclization Position residue makes a direct linkage with the Cyclization Linker. Furthermore, for homodimers, by definition, both monomers are identical, and both will include the Cyclization Linker. If a Cyclization Linker is not present, but Cyclization Positions are indicated, this means that the residues at the Cyclization Positions make a direct linkage with each other. The resultant chemical bonds formed between the Cyclization Position residues and the Cyclization Linker or between the Cyclization Position residues directly is indicated under the Cyclization Chemical Bond column. The Cyclization Positions in this Table are not necessarily meant to be limiting, and some compounds might comprise an additional cyclic structure besides those formed at position pairs X5-X13, X7-X11, X9-X13, and X10-X14. The chemical structure encoded by the SMILES strings will indicate whether the compounds have a monomer with one cyclic structure or multiple cyclic structures. Further, the Cyclization Positions can inform whether the first amino acid residue in a string sequence starts at X1, X0, X-1, etc., with respect to the Formulas herein. For example, Compound 601 has a peptide monomer sequence of ac-I-Lys_Me3-V-E-Hcy-Oic-A-D-Ogl-W-E-W-Hcy-K-dR-am (SEQ ID NO:438). The first moiety "ac" (acetyl) is R1, as acetyl is not an amino acid.

The first amino acid, “I” or isoleucine is at position X0 as Figure 1 states that the Cyclization Positions for SEQ ID NO:438 are X5Hcy and X13Hcy.

[00194] The column “Dimerization; Linker, Position, Chemical Bond” relates to compounds that are dimers. If a Dimerization Linker is present, this indicates that each monomer of the dimer makes an indirect linkage with each other as each monomer makes a direct linkage with the Dimerization Linker. If a Dimerization Linker is not present, but the compound is a dimer, this means that the residue at the Dimerization Position of each monomer makes a direct linkage with each other. The resultant chemical bonds formed between the Dimerization Position residues and the Dimerization Linker or directly between the Dimerization Position residues is indicated.

[00195] The next column is titled “Stability Assays (SGF; SIF).” As described in more detail herein (e.g., Example 7), SGF and SIF are assays that can be used to assess the stability of peptides in conditions that simulate gastric (SGF) and intestinal (SIF) conditions. For compounds that have been tested in one or both of these assays, time of stability data is presented, where : >2 hours of stability is indicated by +++, 1.5-2 hours is ++, 1-1.5 (not including 1.5) is +, and <1 hour is +.

[00196] The final column presents potency data, i.e., whether the compound exhibits inhibitory or neutralizing characteristics against human IL-17 cytokine biological activity or function. The column provides human IL-17 HEK Blue assay (e.g., Example 5) IC₅₀ data, where each compound has at least been tested with respect to its potency against the human IL-17 “AA” isoform. If the compound has also been tested against the human IL-17AF or FF isoforms and showed sufficient potency, then the “AF” and/or the “FF” data has also been included. The legend for the IC₅₀ data is: <1 nM is +++, from 1 nM to 5 nM (including 5 nM) is ++, > 5 nM to 10 nM (including 10 nM) is +, and greater than 10 nM to 20 nM is +.

[00197] **Figure 2** shows a schematic of the human IL-17 HEK Blue assay (Invivogen). In the top panel, when either human IL-17AA, AF, or FF is contacted with HEK Blue cells, the binding of these cytokines with the shown IL-17 receptor (IL-17RA-IL-17RC heterodimer receptor) leads to activation of downstream intracellular signaling such that the AP-1 and NF- κ B transcription factors are activated to upregulate expression of the SEAP reporter gene (which allows for colorimetric analysis of SEAP reporter gene expression). The bottom panel shows the activity of the human IL-17AA and human IL-17FF in the assay, with the murine IL-17AA isoform being a negative control. The inhibitory (or neutralizing / antagonist) potency of the compounds of the invention can be tested by determining the amount of the compound needed to reduce the activity of the human cytokine by half, i.e., the IC₅₀ of the compound.

[00198] **Figure 3** presents an in vivo model and data for evaluating pharmacodynamic and pharmacokinetic properties of the peptide-based compounds of the invention. (See Example 6.) The in vivo model is a murine inflammation/psoriasis model with human IL-17. Recombinant human IL-17A (rhIL-17A) is administered subcutaneously to the mice. The rhIL-17A upregulates the expression of CXCL1, which is a chemokine produced by keratinocytes. By monitoring CXCL1 levels in the ear and serum, one can assess the pharmacodynamic properties of the peptide-based compounds of the invention by determining the levels needed to reduce the rhIL-17A-triggered upregulation of CXCL1 levels. Furthermore, repeated administration of rhIL-17A triggers a psoriasis-like cutaneous phenotype characterized by erythema and ear thickness.

[00199] The top panel of **Figure 3** shows the design of the initial experiments conducted with the in vivo model. (Example 6.) There are three treatment groups for each experiment, where mice were treated with either: (a) vehicle (no active ingredient – otherwise same formulation solution as with PO or SC), (b) Compound 82 through oral administration (“PO”), and (c) Compound 82 by subcutaneous injection (“SC” or “sc”). After 0.5 hours, mice in each treatment group were given 0.2 µg/animal of rhIL-17A subcutaneously. At least two hours after rhIL-17A, ear and serum samples are collected and analyzed for CXCL1 levels (ear and/or serum) and for Compound levels (ear and/or serum). The data in the bottom left panel shows that there is a significant reduction of rhIL-17 induced CXCL-1 secretion after a single PO dose of Compound 82.

[00200] **Figure 4** and **Figure 5** show data from in vivo model experiments conducted with Compound 285 and Compound 288, respectively. See Example 6. These experiments show that the in vitro potency and stability profiles of the peptide compounds can be consistent with in vivo potency and stability.

[00201] **Figure 6** provides two-dimensional chemical structures for several peptide compounds of the invention. **Figure 6A** provides the structure for C599, which is an example of alkane or alkene linker-mediated cyclization with residues having a free thiol group in their side chains, and shows (di)thioether cyclization of X5Hcy and X13Hcy via a Propane_linker. **Figure 6B** provides the structure for C600, which is another example of (di)thioether cyclization. **Figure 6C** provides the structure for C601, which is another example of (di)thioether cyclization. **Figure 6D** provides the structure for C581, which is another example of (di)thioether cyclization. **Figure 6E** provides the structure for C587, which is an example of a hydrocarbon cyclization from the direct covalent linkage of O3S side-chains. **Figure 6F** provides the structure for C314, which is an example of disulfide cyclization between the free thiol groups

of X5Hhc and X13Hhc. **Figure 6G** provides the structure for C533, which is an example of a hydrocarbon cyclization from the direct covalent linkage of O3S_Reduced side-chains. **Figure 6H** provides the structure for C517, which is another example of (di)thioether cyclization. **Figure 6I** provides the structure for C537, which is yet another example of alkane or alkene linker-mediated cyclization with residues having a free thiol group in their side chains, and shows (di)thioether cyclization of X5Cys and X13Cys via a Pentane_linker. **Figure 6J** provides the structure for C535, which is another example of O3S-O3S cyclization. **Figure 6K** provides the structure for C764, which shows thioether cyclization of X5Hcy and X13 Hcy via a Propane_Linker. **Figure 6L** provides the structure for C792, which shows thioether cyclization of X5Hcy and X13 Hcy via a Propane_Linker. **Figure 6M** provides the structure for C609, which shows thioether cyclization of X5Hcy and X13 Hcy via a Propane_Linker. **Figure 6N** provides the structure for C677, which shows thioether cyclization of X5Hcy and X13 Hcy via a Propane_Linker. **Figure 6O** provides the structure for C796, which shows thioether cyclization of X5Hcy and X13 Hcy via a Propane_Linker. **Figure 6P** provides the structure for C808, which shows thioether cyclization of X5Hcy and X13 Hcy via a Propane_Linker. **Figure 6Q** provides the structure for C665, which shows thioether cyclization of X5Hcy and X13 Hcy via a Propane_Linker. **Figure 6R** top image provides the structure for C815; the bottom image provides the structure for a DKP-type prodrug form of C815, wherein instead of dK at position X0, the tripeptide dK-Sar-isoDLys_1PEG2_1PEG2_isoGlu_C18_Diacid is present. **Figure 6S** provides the structure for C813, which shows carbon-carbon single bond cyclization of X5O3S_Reduced and X13O3S_Reduced. **Figure 6T** provides the structure for C824, which shows thioether cyclization of X5Hcy and X13 Hcy via a Propane_Linker. **Figure 6U** provides the structure for C825, which shows thioether cyclization of X5Hcy and X13 Hcy via a Propane_Linker. **Figure 6V** provides the structure for C829, which shows thioether cyclization of X5Hcy and X13 Hcy via a Propane_Linker. **Figure 6W** provides the structure for C833, which shows thioether cyclization of X5Hcy and X13 Hcy via a Propane_Linker. **Figure 6X** provides the structure for C834, which shows thioether cyclization of X5Hcy and X13 Hcy via a Propane_Linker. **Figure 6Y** provides the structure for C836, which shows carbon-carbon single bond cyclization of X5O3S_Reduced and X13O3S_Me_Reduced. **Figure 6Z** provides the structure for C847, which shows thioether cyclization of X5Hcy and X13 Hcy via a Propane_Linker.

[00202] **Figures 7A-7C** provide the serum and skin CXCL-1 levels after oral administration with Compounds 829, 834 (serum only), and 836 and rhIL-17, respectively. (See Example 6;

modified Figure 3 model.). These orally administrated compounds reduced serum and skin CXCL-1 levels as compared to levels with rhIL-17 administration alone.

[00203] **Figure 8** presents data with Compounds 829, 834, and 836 in a rat 5-day IL-23-induced skin inflammation efficacy model. In this model, ear inflammation is induced by repeated intradermal injections of IL-23, and ear thickness is measured over time. (See Examples.) Repeated injections with IL-23 resulted in an increase in ear thickness by day 5. IL-23-induced ear thickness was significantly lower by day 5 in rats receiving oral Compound 829 and 836.

DETAILED DESCRIPTION OF THE INVENTION

[00204] In general, the present disclosure relates to synthetic or recombinant peptides exhibiting IL-17 inhibitory activities and methods of using the same. In some embodiments, the peptides exhibit inhibitory activity against a human IL-17 cytokine by preventing or reducing the ability of a human IL-17 cytokine to bind to its cognate receptor, thereby preventing or reducing IL-17 receptor activation and downstream signal transduction. In some embodiments, the peptides disclosed herein have a cyclic structure, which herein, is also referred to as an intramolecular cross-link between two amino acids (i.e., a direct covalent bond between the side-chains of the two amino acids or an indirect covalent bond between the side-chains of the two amino acids mediated by a cyclization linker), between two terminal chemical groups (e.g., R1 and R2 for a head-to-tail cyclization), or between an amino acid side chain and an R1 or R2 group.

[00205] As stated, side-chain to side-chain cyclic ring structures are formed either by direct covalent linkage between two peptide residues or by indirect covalent linkage between two peptide residues, wherein each residue makes a direct covalent linkage with a linker, often at the terminal ends of the linker. Four major cyclization structures are described for peptides: X5-X13, X9-X13, X7-X11, and X10-X14, where these X pairing indicate the positions of two residues that are covalently cross-linked together, whether directly or indirectly through a linker. It should be noted that these cyclization positions do not necessarily correspond to positional length, i.e., some peptides have amino acids at X00 and/or X0, which are located N-terminal to position X1. In yet other embodiments, the peptides disclosed herein have a dimeric structure, wherein two monomeric peptides or peptide fragments are covalently linked together either directly or through a linker or linking moiety. In other embodiments, the peptides disclosed herein have a non-cyclic or linear structure. Herein, when a linker is used to mediate cyclization, it is referred to as a cyclization linker; and when a linker is used to mediate dimerization, it is referred to as a dimerization linker.

[00206] The invention provides a large representative set of compounds that are potent inhibitors of human IL-17 cytokines, which is exhibited by their nanomolar potency in IL-17 functional assays. Further, the invention contemplates peptide compounds that are suitable for oral administration, which is reflected by compound stability in assays that simulate gastric and intestinal conditions. Indeed, the invention provides murine in vivo data showing the peptide compounds can inhibit human IL-17 cytokine function, whether by subcutaneous injection or oral administration.

1. Definitions and Nomenclature

[00207] Unless otherwise defined herein, scientific and technical terms used in this application shall have 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.

[00208] As used herein, the following terms have the meanings ascribed to them in the art unless specified otherwise.

[00209] 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).

[00210] The singular forms “a,” “an,” and “the” include the plurals unless the context clearly dictates otherwise.

[00211] The term “including” is used to mean “including but not limited to.” “Including” and “including but not limited to” are used interchangeably.

[00212] 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). The term “mammal” refers to any mammalian species such as a human, mouse, rat, dog, cat, hamster, guinea pig, rabbit, livestock, and the like.

[00213] The term “peptide,” as used herein, refers broadly to a sequence of two or more amino acids joined together by peptide bonds, where such amino acids can be natural or unnatural amino acid residues. Further, 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.

[00214] “About” when referring to a value includes the stated value +/- 10% of the stated value. For example, about 50% includes a range of from 45% to 55%, while about 20 molar equivalents includes a range of from 18 to 22 molar equivalents. Accordingly, when referring to a range, “about” refers to each of the stated values +/- 10% of the stated value of each end of the range. For instance, a ratio of from about 1 to about 3 (weight/weight) includes a range of from 0.9 to 3.3.

[00215] 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.

[00216] 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.

[00217] 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.

[00218] 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.

[00219] 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, word length = 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, word length = 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.

[00220] 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.

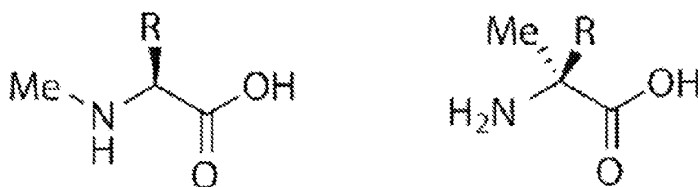
I	II	III	IV	V
A	N	H	M	F
S	D	R	L	Y
T	E	K	I	W
P	Q		V	
G			C	

[00221] 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	

[00222] 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., α -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 non eukaryotes 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 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, α -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. Numerous examples of unnatural amino acids are described in Table 1.

[00223] All amino acids have a central carbon atom surrounded by a hydrogen atom, a carboxyl group (COOH), an amino group (NH₂) and an R-group (also referred to as the side-chain). Amino acids are often modified by attaching chemical moieties to the central carbon atom (also referred to as the α -carbon), side-chain, amino group, or the carboxyl group. For example, α -methyl variants of an amino acids have a methyl group attached to the central carbon, replacing the hydrogen that is normally attached. N-methyl variants have a methyl group attached to the nitrogen of the amino group, replacing a hydrogen. N-methylation (left) vs. α -methylation (right) is shown below.



[00224] 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.

[00225] 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., (D)Asp or D-Asp or dAsp or dD; (D)Phe or D-Phe or dPhe or dF). Amino acid residues in the D isomeric form can be substituted for any L-amino acid residue, whether natural or unnatural, as long as the desired function is retained by the peptide. D-amino acids may be indicated as customary in lower case prefix letter “d.” For example, L-arginine can be represented as “Arg” or “R,” while D-arginine can be represented as “dArg” or “dR.” Similarly, L-lysine can be represented as “Lys” or “K,” while D-lysine can be represented as “dLys” or “dK.” The D-amino acid nomenclature can also be used with unnatural amino acids, e.g., see Table 1.

[00226] The term “linker moiety” or “linker” or “linking moiety” as used herein, refers broadly to a doubly functionalized chemical structure that is capable of linking or joining together at least two chemical groups.

[00227] The term “disulfide bond” or “disulfide linkage” has its conventional meaning, e.g., a $R_1-S-S-R_2$ bond. The linkage is also called a disulfide bridge and is usually derived by the coupling of two thiol groups. Amino acids with free thiol groups include Cys, Hcy, Hhc, Pen, HhPen, dCys, dPen, dHcy, dHhc, dHhPen, and the like.

[00228] The term “thioether bond” or “thioether linkage” has its conventional meaning, e.g., a R_1-S-R_2 bond. Thioethers are also called sulfides, and thioethers are typically prepared by alkylation of thiols.

[00229] The term “amide bond” or “amide linkage” has its conventional meaning, e.g., an -NH-C(O)- or a -C(O)-NH- bond. A common preparation is to couple a carboxylic acid with an amine.

[00230] The term “solvate” in the context of the present invention refers to a complex of defined stoichiometry formed between a solute (e.g., an IL-17 cytokine inhibitor or pharmaceutically acceptable salt thereof according to the invention) and a solvent. The solvent in this connection may, for example, be water, ethanol or another pharmaceutically acceptable, typically small-molecular organic species, such as, but not limited to, acetic acid or lactic acid. When the solvent in question is water, such a solvate is normally referred to as a hydrate.

[00231] 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.

[00232] The term “C_{n-m}” indicates a range which includes the endpoints, wherein *n* and *m* are integers and indicate the number of carbons. Examples include C₁₋₄, C₁₋₆, C₁₋₂₀ and the like.

[00233] The term “alkyl” includes a straight chain or branched, noncyclic or cyclic, saturated aliphatic hydrocarbon containing from 1 to 24 carbon atoms. The term “C_{n-m} alkyl,” refers to an alkyl group having *n* to *m* carbon atoms. For example, “C₁₋₆ alkyl” refers to a hydrocarbon radical straight or branched, containing from 1 to 6 carbon atoms that is derived by the removal of one hydrogen atom from a single carbon atom of a parent alkane. 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.

[00234] The term “alkylene” refers to a divalent alkyl group, particularly having from 1 to 24 carbon atoms. The term is exemplified by groups such as methylene (-CH₂-), ethylene (-CH₂CH₂-), the propylene isomers (e.g., -CH₂CH₂CH₂- and -CH(CH₃)CH₂-) and the like.

[00235] The term “alkoxy” refers to the group “alkyl-O-”. Examples of alkoxy groups include, e.g., methoxy, ethoxy, *n*-propoxy, iso-propoxy, *n*-butoxy, *tert*-butoxy, *sec*-butoxy, *n*-pentoxy, *n*-hexoxy and 1,2-dimethylbutoxy.

[00236] The term “alkenyl” alone or in combination with other terms, means a straight-chain or branched hydrocarbon group corresponding to an alkyl group having one or more double carbon-carbon bonds. An alkenyl group formally corresponds to an alkene with one C-H bond replaced by the point of attachment of the alkenyl group to the remainder of the compound. The term “C_{n-m} alkenyl” refers to an alkenyl group having *n* to *m* carbons. In some embodiments, the alkenyl moiety contains 2 to 16, 2 to 14, or 2 to 8 carbon atoms. Example

alkenyl groups include, but are not limited to, ethenyl, *n*-propenyl, isopropenyl, *n*-butenyl, *sec*-butenyl, 5-pentenyl, 8-octenyl, and the like.

[00237] The term “alkenylene” means a straight or branched bivalent hydrocarbon chain containing at least one carbon-carbon double bond. Representative alkenylene include –CH=CH–, –CH₂CH=CH–, –C(CH₃)=CH–, –CH₂CH=CHCH₂–, and the like

[00238] The term “cycloalkyl” or “carbocycle” by themselves or in combination with other terms means cyclic versions of “alkyl” in which all ring atoms are carbon. “Cycloalkyl” or “carbocycle” refers to a mono- or polycyclic group. When used in connection with cycloalkyl substituents, the term “polycyclic” refers herein to fused and non-fused alkyl cyclic structures. “Cycloalkyl” or “carbocycle” may form a bridged ring or a spiro ring. In some embodiments, the cycloalkyl group may have one or more double or triple bond(s) in the cycloalkyl ring. Examples of cycloalkyl include cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl, and the like.

[00239] The term “halo” or “halogen” refers to atoms occupying group VIIA of the periodic table, such as fluoro, chloro, bromo or iodo.

[00240] The term “haloalkyl” refers to an unbranched or branched alkyl group as defined above, wherein one or more (e.g., 1 to 6 or 1 to 3) hydrogen atoms are replaced by a halogen. For example, where a residue is substituted with more than one halogen, it may be referred to by using a prefix corresponding to the number of halogen moieties attached. Dihaloalkyl and trihaloalkyl refer to alkyl substituted with two (“di”) or three (“tri”) halo groups, which may be, but are not necessarily, the same halogen. Examples of haloalkyl include, e.g., trifluoromethyl, difluoromethyl, fluoromethyl, trichloromethyl, 2,2,2-trifluoroethyl, 1,2-difluoroethyl, 3-bromo-2-fluoropropyl, 1,2-dibromoethyl and the like.

[00241] The term “alkanoyl” means an alkyl-C(O)- group, wherein the alkyl group is as defined herein. Representative alkanoyl groups include methanoyl, ethanoyl, 3-methylbutanoyl, and the like.

[00242] “Benzyl” means a phenyl-CH₂ - group. Representative benzyl include 4-bromobenzyl, 4-methoxybenzyl, 4-aminobenzyl, and the like.

[00243] “Carbamoyl” means a group of formula R^xR^yNCO- wherein R^x and R^y are independently hydrogen or alkyl. Representative carbamoyl groups include carbamoyl (H₂NCO-), methylcarbamoyl (MeNHCO-), and the like.

[00244] “Thiol”, “mercapto” or “sulfanyl” means an -SH group.

[00245] The term “alkylthio” means an alkyl-S- group, wherein the alkyl group is defined herein. Representative alkylthio groups include methylthio, ethylthio, propylthio, isopropylthio, and the like.

[00246] As used herein, “functional group” on the side chain of an amino acid means -COOH, -NH₂, -NH-, -SH, -SCH₃, -OH, -C(O)NH₂, guanidiny, imidazolyl, pyrrolidinyl, phenyl, indolyl, and the like.

[00247] The term “NH₂,” as used herein, refers to the free amino group that is often present at the amino terminus of a peptide. The term “OH,” as used herein, refers to a free carboxy group, often present at the carboxy terminus of a peptide. Further, the term “Ac,” as used herein, refers to acetyl group, wherein acetyl protection of a NH₂ terminus of a peptide can be achieved through acylation.

[00248] The term “carboxy,” as used herein, refers to -CO₂H.

[00249] 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), Daba (2,4-diaminobutanoic acid), Dapa (2,3-diaminopropanoic acid), γ -Glu (γ -glutamic acid), pGlu (pyroglutamic acid), Gaba (γ -aminobutanoic acid), β -Pro (pyrrolidine-3-carboxylic acid), 8Ado (8-amino-3,6-dioxaoctanoic acid), Abu (2-aminobutyric acid), bhPro (β -homo-proline), bhPhe (β -homo-L-phenylalanine), bhAsp (β -homo-aspartic acid), Dpa (β,β diphenylalanine), Ida (Iminodiacetic acid), hCys (homocysteine), bhDpa (β -homo- β,β -diphenylalanine). Additional unnatural amino acids are listed in Table 1.

[00250] 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. In many embodiments, peptide sequences disclosed herein comprise an “Ac” (acetyl) moiety at the amino terminus (N-terminus) and an “Am” moiety (amine; see Table 1, “am” = H₂N-R₁) (which covers amide moieties when R₁ of H₂N-R₁ comprises a carbonyl) as well at the carboxy terminus (C-terminus) of the sequence. In some cases, a “H” moiety at the N-terminus 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 “-NH₂” moiety at the C-terminus of the sequence indicates a hydroxy group or an amino group, corresponding to the presence of an amido (CONH₂) group at the C-terminus, respectively. In each sequence of the invention, a C-terminal “-OH” moiety may be substituted for a C-terminal “-NH₂” moiety, and vice-versa. Peptide Formulas of the invention refer to N-terminal moieties as an “R1” (or R₁) group and C-terminal moieties as an “R2” (or R₂) group.

[00251] As used herein, the term “cycle” or “cyclic” and the like, refers to a molecule having a chemical structure that includes a ring or cycle formed by at least eight covalently bonded

ring atoms. In some embodiments, a cyclic peptide means the peptide comprises a ring or cycle formed by at least 9 covalently bonded ring atoms. The term “cyclized” or “cyclization,” as used herein, refers to a reaction in which one part of a peptide molecule becomes linked to another part of the peptide molecule to form a closed ring, such as by forming a disulfide bridge or other similar bond. Herein, a “cyclic peptide,” is a peptide that has been cyclized or “cross-linked” (an intramolecular cross-link) by covalently bonding two amino acids together, whether directly or indirectly through a cyclization linker.

[00252] 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. As conventionally understood, each amino acid has a specific side chain, known as an R group, that is attached to the α carbon. Unnatural amino acids often differ from natural amino acids by side chain substitution. Amino acid side chains, natural or unnatural, can comprise “reactive” or “free” substituent chemical moieties that can form chemical bonds with other molecules. For example, the side-chain of cysteine comprises a free thiol (sulfhydryl) group that can react with another free thiol group to form a disulfide bond or with a free alkyl group to form a thioether bond.

[00253] “Pharmaceutically effective amount” refers to an amount of a compound of the invention in a composition or combination thereof that provides the desired therapeutic or pharmaceutical result.

[00254] “Pharmaceutically acceptable excipient” includes without limitation any adjuvant, carrier, excipient, glidant, sweetening agent, diluent, preservative, dye/colorant, flavor enhancer, surfactant, wetting agent, dispersing agent, suspending agent, stabilizer, isotonic agent, solvent, or emulsifier which has been approved by the United States Food and Drug Administration as being acceptable for use in humans or domestic animals.

[00255] Provided are also pharmaceutically acceptable salts and tautomeric forms of the compounds described herein. “Pharmaceutically acceptable” or “physiologically acceptable” refer to compounds, salts, compositions, dosage forms and other materials which are useful in preparing a pharmaceutical composition that is suitable for veterinary or human pharmaceutical use.

[00256] 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-phenylpropionate, 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, but are not limited to, 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 NX_4^+ (wherein X is C_1-C_6 alkyl). Also included are base addition salts, such as sodium or potassium salts. 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.

[00257] Compounds described herein may include isotopically labeled compounds, which are identical to those 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 ^2H , ^3H , ^{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 ^3H and ^{14}C are incorporated, are useful in drug and/or substrate tissue distribution assays. Further, substitution with isotopes such as deuterium, i.e., ^2H , can afford certain therapeutic advantages resulting from greater metabolic stability, for example increased in vivo half-life or reduced dosage requirements. In particular embodiments, the compounds disclosed herein are isotopically substituted with deuterium. In more particular embodiments, one or more hydrogen atoms in the compounds disclosed herein can be replaced by a deuterium atom or D.

[00258] The compounds of the invention, or their pharmaceutically acceptable salts may contain one or more asymmetric centers and may thus give rise to enantiomers, diastereomers, and other stereoisomeric forms that may be defined, in terms of absolute stereochemistry, as (*R*)- or (*S*)- or, as (*D*)- or (*L*)- for amino acids. The present invention is meant to include all such possible isomers, as well as their racemic and optically pure forms. Optically active (+) and (-), (*R*)- and (*S*)-, or (*D*)- and (*L*)- isomers may be prepared using chiral synthons or chiral reagents, or resolved using conventional techniques, for example, chromatography and fractional crystallization. Conventional techniques for the preparation/isolation of individual enantiomers include chiral synthesis from a suitable optically pure precursor or resolution of the racemate (or the racemate of a salt or derivative) using, for example, chiral high pressure liquid chromatography (HPLC). When the compounds described herein contain olefinic double bonds or other centers of geometric asymmetry, and unless specified otherwise, it is intended that the compounds include both *E* and *Z* geometric isomers. Likewise, all tautomeric forms are also intended to be included. Where compounds are represented in their chiral form, it is understood that the aspect encompasses, but is not limited to, the specific diastereomerically or enantiomerically enriched form. Where chirality is not specified but is present, it is understood that the aspect is directed to either the specific diastereomerically or enantiomerically enriched form; or a racemic or scalemic mixture of such compound(s). As used herein, "scalemic mixture" is a mixture of stereoisomers at a ratio other than 1:1.

[00259] "Stereoisomer" and "stereoisomers" refer to compounds that differ in the chirality of one or more stereocenters. Stereoisomers include enantiomers and diastereomers. The compounds may exist in stereoisomeric form if they possess one or more asymmetric centers or a double bond with asymmetric substitution and, therefore, can be produced as individual stereoisomers or as mixtures. Unless otherwise indicated, the description is intended to include

individual stereoisomers as well as mixtures. The methods for the determination of stereochemistry and the separation of stereoisomers are well-known in the art (see, e.g., Chapter 4 of Advanced Organic Chemistry, 4th ed., J. March, John Wiley and Sons, New York, 1992).

[00260] “Tautomer” refers to alternate forms of a compound that differ in the position of a proton, such as enol-keto and imine-enamine tautomers, or the tautomeric forms of heteroaryl groups containing a ring atom attached to both a ring -NH- and a ring =N- such as pyrazoles, imidazoles, benzimidazoles, triazoles, and tetrazoles.

[00261] “Therapeutically effective amount” or “effective amount” as used herein refers to an amount that is effective to elicit the desired biological or medical response, including the amount of a compound that, when administered to a subject for treating a disease, is sufficient to affect such treatment for the disease. The effective amount will vary depending on the compound, the disease, and its severity and the age, weight, etc., of the subject to be treated. The effective amount can include a range of amounts. As is understood in the art, an effective amount may be in one or more doses, i.e., a single dose or multiple doses may be required to achieve the desired treatment endpoint. An effective amount may be considered in the context of administering one or more therapeutic agents, and a single agent may be considered to be given in an effective amount if, in conjunction with one or more other agents, a desirable or beneficial result may be or is achieved. Suitable doses of any co-administered compounds may optionally be lowered due to the combined action (e.g., additive or synergistic effects) of the compounds.

[00262] “Treatment” or “treat” or “treating” as used herein refers to an approach for obtaining beneficial or desired results. For purposes of the present invention, beneficial or desired results include, but are not limited to, alleviation of a symptom and/or diminishment of the extent of a symptom and/or preventing a worsening of a symptom associated with a disease or condition. In one aspect, “treatment” or “treating” includes one or more of the following: (a) inhibiting the disease or condition (e.g., decreasing one or more symptoms resulting from the disease or condition, and/or diminishing the extent of the disease or condition); (b) slowing or arresting the development of one or more symptoms associated with the disease or condition (e.g., stabilizing the disease or condition, delaying the worsening or progression of the disease or condition); (c) relieving the disease or condition, e.g., causing the regression of clinical symptoms, ameliorating the disease state, delaying the progression of the disease, increasing the quality of life, and/or prolonging survival; and (d) preventing the disease, condition or disorder in a subject who may be predisposed to the disease, condition or disorder but does not

yet experience or display the pathology or symptomatology of the disease. In some embodiments, treating refers to inhibiting or ameliorating the disease. In some embodiments, treating is preventing the disease.

[00263] “Co-administration” as used herein refers to administration of unit dosages of the compounds disclosed herein before or after administration of unit dosages of one or more additional therapeutic agents, for example, administration of the compound disclosed herein within seconds, minutes, or hours of the administration of one or more additional therapeutic agents. For example, in some aspects, a unit dose of a compound of the invention is administered first, followed within seconds or minutes by administration of a unit dose of one or more additional therapeutic agents. Alternatively, in other aspects, a unit dose of one or more additional therapeutic agents is administered first, followed by administration of a unit dose of a compound of the invention within seconds or minutes. In some aspects, a unit dose of a compound of the invention is administered first, followed, after a period of hours (e.g., 1-12 hours), by administration of a unit dose of one or more additional therapeutic agents. In other aspects, a unit dose of one or more additional therapeutic agents is administered first, followed, after a period of hours (e.g., 1-12 hours), by administration of a unit dose of a compound of the invention. Co-administration of a compound disclosed herein with one or more additional therapeutic agents generally refers to simultaneous or sequential administration of a compound disclosed herein and one or more additional therapeutic agents, such that therapeutically effective amounts of each agent are present in the body of the patient.

[00264] With respect to the IL-17 cytokine binding peptides of the invention, the terms “antagonizing” or “inhibiting” or “neutralizing” are used synonymously, and mean the peptides can reduce or prevent IL-17 cytokine binding with its cognate IL-17 receptor(s). The inhibitory activity of a peptide compound of the invention can be assessed, for example, by assaying the activity of the IL-17 receptor signaling pathway. Because an inhibitor of an IL-17 cytokine may prevent or inhibit or decrease the ability of an IL-17 cytokine to bind to its cognate IL-17 receptor(s), inhibition of IL-17 cytokine binding to its receptor(s) should therefore decrease or prevent downstream signaling events of an activated IL-17 receptor complex. For example, the inhibitory peptides can decrease the expression level of genes that are upregulated from IL-17 receptor activation. Downstream signaling events of IL-17AA, AF, and FF can lead to overexpression of IL-6, TNF α , COX2, G-CSF, GM-CSF, CXCL10, CXCL1, CCL2, CXCL2, CCL7, CXCL5, CCL20, and/or CXCL8, which can contribute to autoimmunity and inflammatory diseases or disorders.

[00265] The term “Polyethylene glycol” or “PEG” is a polyether compound of general formula $H-(O-CH_2-CH_2)_n-OH$. 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 g/mol, PEO to polymers with a molecular mass above 20,000 g/mol, 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 three names may be used indistinguishably. PEGs are prepared by polymerization of ethylene oxide and are commercially available over a wide range of molecular weights from 300 g/mol to 10,000,000 g/mol. 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 polyethylene 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 to about 40,000 are usually selected for the purposes of the present invention. In certain embodiments, PEGs having molecular weights from 200 to 2,000 daltons or from 200 to 500 daltons are used. Different forms of PEG may also be used, depending on the initiator used for the polymerization process, e.g., a common initiator is a monofunctional methyl ether PEG, or methoxypoly(ethylene glycol), abbreviated mPEG. Other suitable initiators are known in the art and are suitable for use in the present invention.

[00266] 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.

[00267] 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.

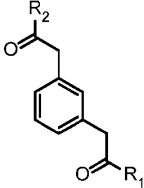
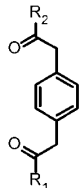
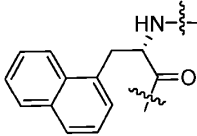
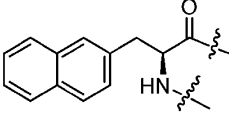
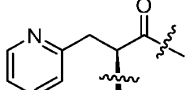
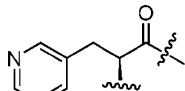
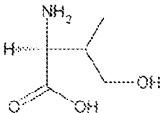
[00268] As used herein, “PEGylation” is the act of coupling (e.g., covalently) a PEG structure to a desired molecule forming a PEGylated molecule. Herein, in some embodiments, a linker molecule comprising a PEG structure connects two peptides of the invention thereby forming a dimeric molecule (e.g., a homodimer comprising two identical peptide monomers or a heterodimer comprising two different peptide monomers). Herein, PEG comprising linkers can be used as dimerization linkers and/or to improve the in vivo half-life of the peptide compounds of the invention.

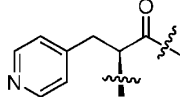
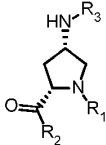
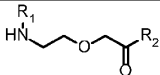
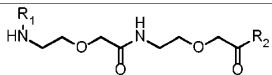
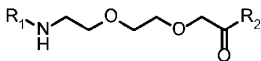
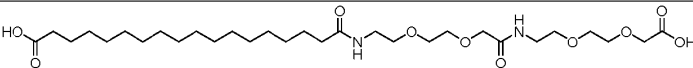
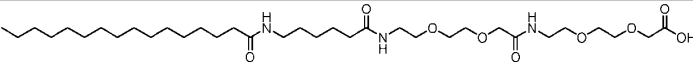
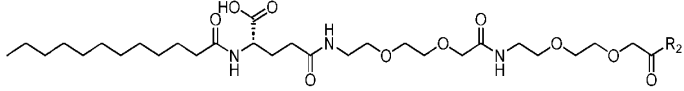
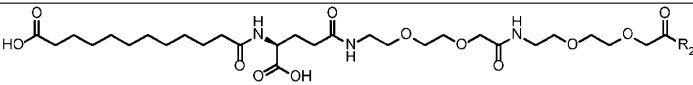
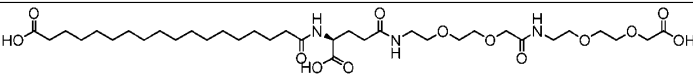
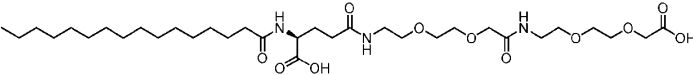
[00269] The skilled worker will be well aware of suitable techniques which can be used to perform the coupling reaction. As discussed herein, PEG linkers can comprise one or more reactive groups (and for dimerization, at least two separate functional groups), including an amine, carboxylic acid, and acrylate groups. Further, 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.

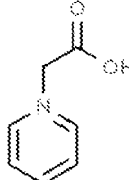
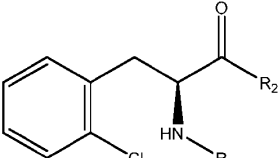
[00270] For the most part, the names of naturally occurring and non-naturally occurring aminoacyl residues used herein follow the naming conventions suggested by the IUPAC Commission on the Nomenclature of Organic Chemistry and the IUPAC-IUB Commission on Biochemical Nomenclature as set out in “Nomenclature 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 does not usually include D-forms of amino acids (natural or unnatural) – the POSA understands that the stereogenic carbon alpha to the amino group simply has the D-configuration rather than the L-configuration.

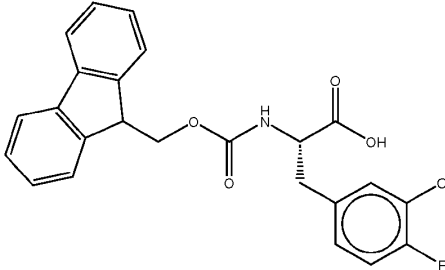
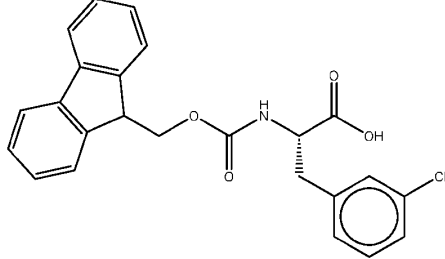
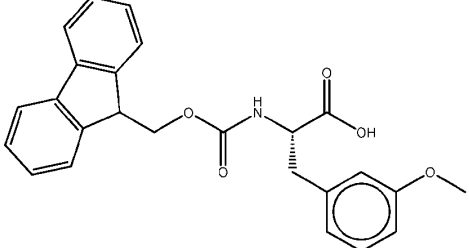
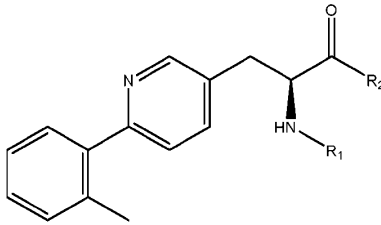
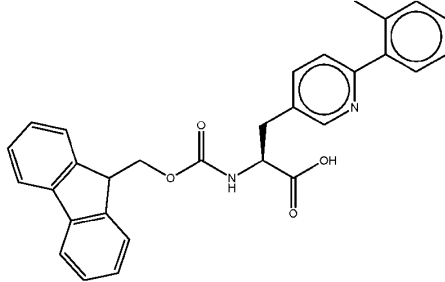
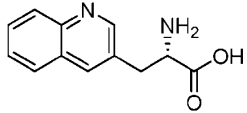
[00271] **Table 1. Abbreviations of Non-Natural Amino Acids and Chemical Moieties**

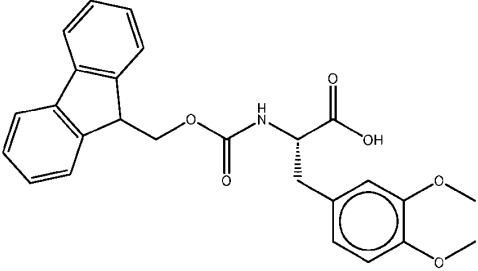
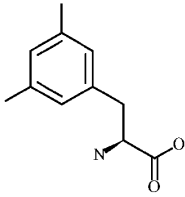
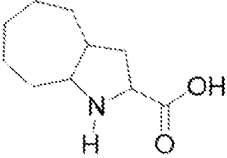
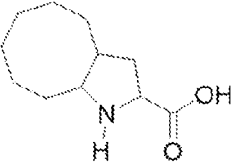
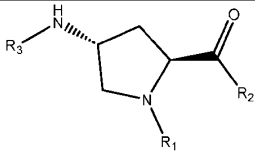
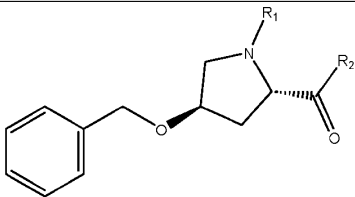
Abbreviation & Analog Info	Definition
1-1-Indane	1-Aminoindane-1-carboxylic acid
1,3 - Phenylenediacetic acid or 13_Phenyl_diAceticAcid	meta-Phenylenediacetic acid

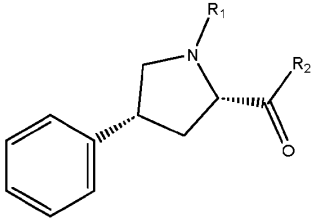
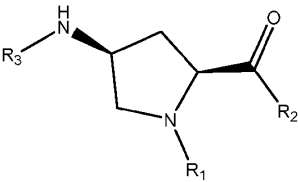
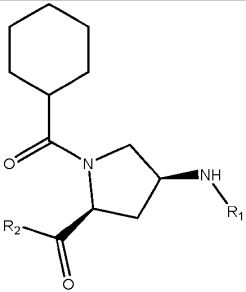
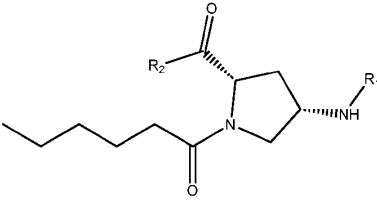
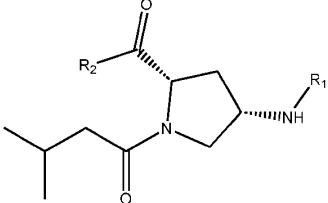
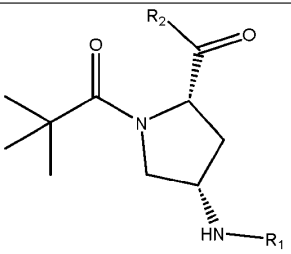
	 R1 is OH, R2 is OH
1,4- Phenylenediacetic acid or 14_Phenyl_diAceticAcid	para-Phenylenediacetic acid  R1 is OH, R2 is OH
2-2-Indane	2-Aminoindane-2-carboxylic acid
2-Methyltrifluorobutyric acid	2-methyl-4,4,4-Butyric acid
1Nal (Analog of Trp)	(S)-2-amino-3-(naphthalen-1-yl)propanoic acid 
2Nal (Analog of Trp)	(S)-2-amino-3-(naphthalen-2-yl)propanoic acid 
2Pal (Analog of Phe)	(S)-2-amino-3-(pyridin-2-yl)propanoic acid 
3Pal (Analog of Tyr)	(S)-2-amino-3-(pyridin-3-yl)propanoic acid 
4OH_Val	4-hydroxy-valine 

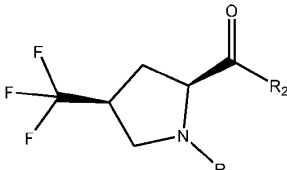
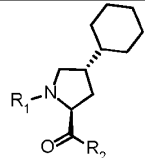
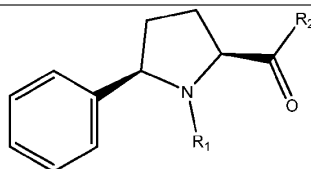
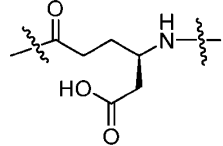
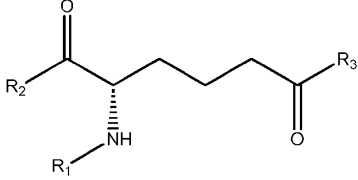
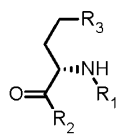
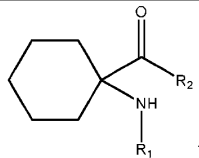
4Pal (Analog of Tyr)	(S)-2-amino-3-(pyridin-4-yl)propanoic acid 
4S_Amp (Analog of Pro)	 R1 is H; R2 is OH; R3 is H
1Peg1 or 1PEG1 (Analog of Gly)	 R1 is H; R2 is OH
1Peg1_1Peg1 (Analog of Gly)	 R1 is H; R2 is OH
1Peg2 or 1PEG2 (Analog of Gly)	–[C(O)-CH2-(Peg)2-NH]– or –[C(O)-CH2-(OCH2CH2)2-NH]–  R1 is H, R2 is OH
1Peg2-1Peg2 or 1PEG2-1PEG2 (Analog of Gly)	–[(C(O)-CH2-(OCH2CH2)2-NH-C(O)-CH2-(OCH2CH2)2-NH]–
1PEG2_1PEG2_Ahx_C18_D iacid,	
1PEG2_PEG2_Ahx_Palm	
1PEG2_1PEG2_IsoGlu_C12 (Analog of Lys)	 R2 is OH
1PEG2_1PEG2_IsoGlu_C12 _Diacid (Analog of Lys)	 R2 is OH
1PEG2_1PEG2_IsoGlu_C18 _Diacid	
1PEG2_1PEG2_IsoGlu_Palm (Analog of Gly)	
1Peg8 or 1PEG8	–[C(O)-CH2-(Peg)8-NH]– or –[C(O)-CH2-(OCH2CH2)8-NH]–

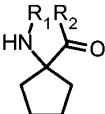
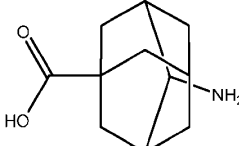
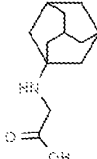
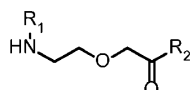
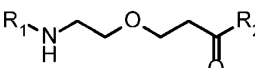
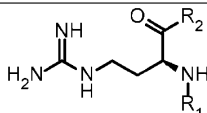
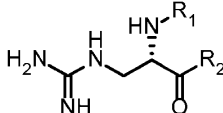
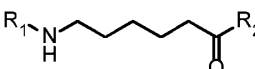
(Analog of Gly)	
1Peg11 or 1PEG11 (Analog of Gly)	$-\text{[C(O)-CH}_2\text{-(Peg)11-NH]}-$ or $-\text{[C(O)-CH}_2\text{-(OCH}_2\text{CH}_2\text{)11-NH]}-$
1Pip_AceticAcid (or 1Pip_Acetic_Acid)	2-(1-pyridyl)acetic acid 
2Chlorophenyl	 R1 is H; R2 is OH
2Peg2 or PEG2	$-\text{[C(O)-CH}_2\text{-CH}_2\text{-(Peg)2-NH]}-$ or $-\text{[C(O)-CH}_2\text{-CH}_2\text{-(OCH}_2\text{CH}_2\text{)2-NH]}-$
2Peg4 or PEG4	$-\text{[C(O)-CH}_2\text{-CH}_2\text{-(Peg)4-NH]}-$ or $-\text{[C(O)-CH}_2\text{-CH}_2\text{-(OCH}_2\text{CH}_2\text{)4-NH]}-$
2Peg8 or PEG8	$-\text{[C(O)-CH}_2\text{-CH}_2\text{-(Peg)8-NH]}-$ PEG
2Peg11 or PEG11	$-\text{[C(O)-CH}_2\text{-CH}_2\text{-(Peg)11-NH]}-$ or $-\text{[C(O)-CH}_2\text{-CH}_2\text{-(OCH}_2\text{CH}_2\text{)11-NH]}-$
2Peg11' or 2Peg12 or PEG12	$-\text{[C(O)-CH}_2\text{-CH}_2\text{-(Peg)12-NH]}-$ or $-\text{[C(O)-CH}_2\text{-CH}_2\text{-(OCH}_2\text{CH}_2\text{)12-NH]}-$
2Peg11'_Ahx_Palm or 2Peg12_Ahx_Palm or PEG12_Ahx_Palm	$-\text{[C(O)-CH}_2\text{-CH}_2\text{-(Peg)12-NH]}-\text{C(O)-(CH}_2\text{)5-N(H)-C(O)-(CH}_2\text{)14CH}_3$ or $-\text{[C(O)-CH}_2\text{-CH}_2\text{-(OCH}_2\text{CH}_2\text{)12-NH]}-\text{C(O)-(CH}_2\text{)5-N(H)-C(O)-(CH}_2\text{)14CH}_3$
2Peg11'_Palm or 2Peg12_Palm or PEG12_Palm	$-\text{[C(O)-CH}_2\text{-CH}_2\text{-(Peg)12-NH]}-\text{C(O)-(CH}_2\text{)14CH}_3$ or $-\text{[C(O)-CH}_2\text{-CH}_2\text{-(OCH}_2\text{CH}_2\text{)12-NH]}-\text{C(O)-(CH}_2\text{)14CH}_3$
2Peg11'_C18_Diacid or 2Peg12_C18_Diacid or PEG12_C18_Diacid	$-\text{[C(O)-CH}_2\text{-CH}_2\text{-(Peg)12-NH]}-\text{C(O)-(CH}_2\text{)16C(O)OH}$ or $-\text{[C(O)-CH}_2\text{-CH}_2\text{-(OCH}_2\text{CH}_2\text{)12-NH]}-\text{C(O)-(CH}_2\text{)16C(O)OH}$

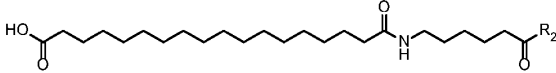
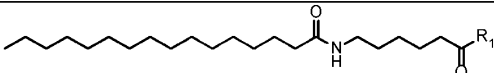
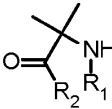
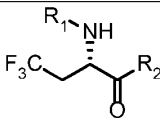
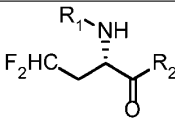
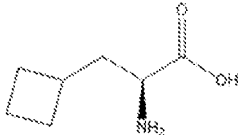
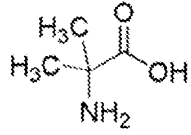
3chloro4fluorophenyl	
3chlorophenyl	
3Methoxyphenyl	
3-pyridylalanine-4	 R1 is H; R2 is OH
3-pyridylalanine-4_2_methylphenyl	
3Quin or 3-Quin or Quin_3	 3-(quinolin-3-yl)-alanine

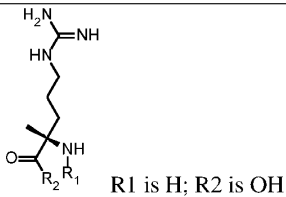
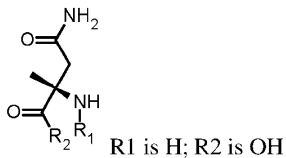
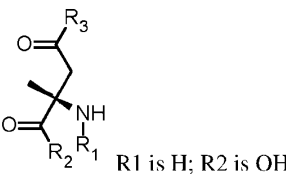
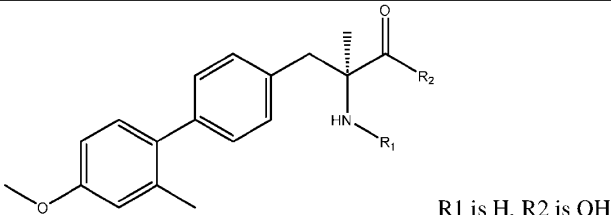
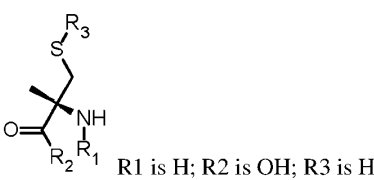
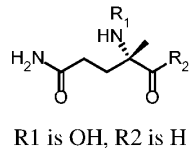
34Dimethoxyphenyl	
35_DimethylPhenyl	
45cHept_Pro (Analog of Pro or Oic)	
45cOct_Pro (Analog of Pro or Oic)	
4R_Amp (Analog of Pro)	 R1 is H, R2 is OH, R3 is H
4R_BenzyloxyPro or 4RBenzyloxyPro (Analog of Pro)	 R1 is H, R2 is OH

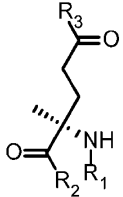
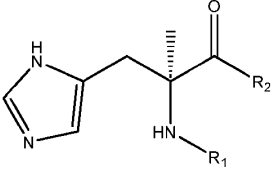
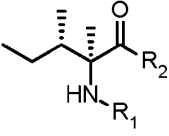
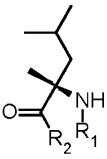
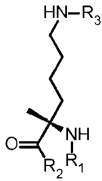
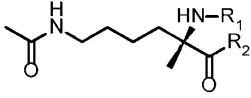
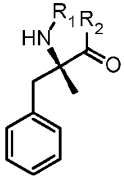
4RPhePro (Analog of Pro)	 R1 is H, R2 is H
4S_Amp (Analog of Pro)	 R1 is H, R2 is OH, R3 is H
4S_Amp_Cyclhex 4S_Amp_Cyclohex (Analog of Pro)	or  R1 is H, R2 is OH
4S_Amp_Hex (Analog of Pro)	 R1 is H, R2 is OH
4S_Amp_IVA (Analog of Pro)	 R1 is H, R2 is OH
4S_Amp_tBu (Analog of Pro)	 R1 is H, R2 is OH

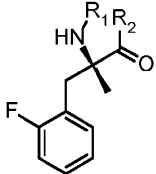
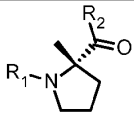
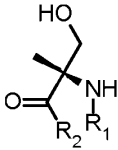
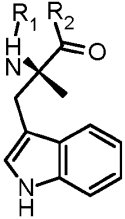
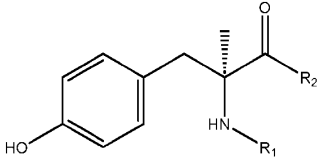
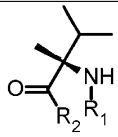
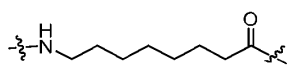
4SCF3Pro (Analog of Pro)	 R1 is H, R2 is H
4ScyclohexPro (Analog of Pro)	 R1 is H, R2 is OH
5RPhePro (Analog of Pro)	 R1 is H, R2 is OH
Aaa	
Aad	 R1 is H; R2 is OH; R3 is OH
Abu (Analog of Cys)	2-aminobutyric acid  R1 is H; R2 is OH; R3 is H
Ac	Acetyl
Achc (Analog of Ala)	 R1 is H, R2 is OH

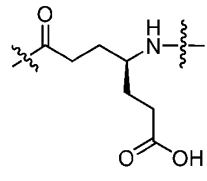
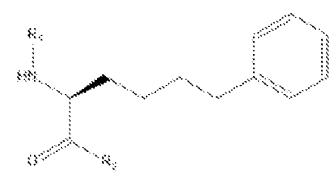
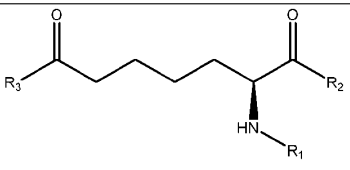
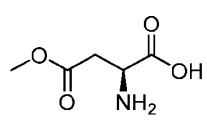
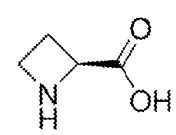
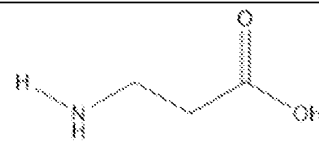
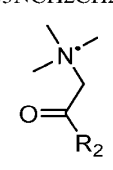
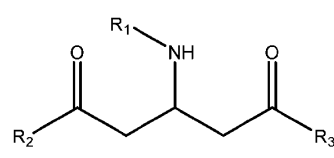
Acvc (Analog of Ala)	 R1 is H, R2 is OH
Adamantane (Analog of Gly)	
Adamantyl_Gly	
Adc	10-aminodecanoic acid; -NH-(CH2)9-C(O)-
Ado	12-aminododecanoic acid; -NH-(CH2)11C(O)-
Aea (Analog of Gly)	(2-aminoethoxy)acetic acid  R1 is H, R2 is OH
Aep (Analog of Gly)	3-(2-aminoethoxy)propanoic acid  R1 is H, R2 is OH
Agb (Analog of Arg)	 R1 is H, R2 is OH
Agp (Analog of Arg)	 R1 is H, R2 is OH
Ahx (Analog of Gly)	Aminohexanoic acid or 6-aminohexanoic acid  R1 is H; R2 is OH

Ahx_C18_Diacid (Analog of Leu or Ile)	 R2 is OH
Ahx_Palm (Analog of Gly)	 R1 is OH
Aib (Analog of Ala)	2-aminoisobutyric acid  R1 is H; R2 is OH
AlaCF3 (Analog of Ala)	 R1 is H; R2 is OH
AlaCHF2 (Analog of Ala)	 R1 is H; R2 is H
Ala_cycBu (Analog of Leu)	
alkanoyl	-C(O)-alkanyl
alkenoyl	-C(O)-alkenyl
Amc	4-(aminomethyl)cyclohexane carboxylic acid
aMe_Alal, a-MeAlal, aMeAlal, or (a-Me)Alal (Analog of Ala)	α-methylalanine 
aMe_Arg, a-MeArg, aMeArg, or (a-Me)Arg (Analog of Arg)	α -methylarginine

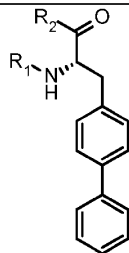
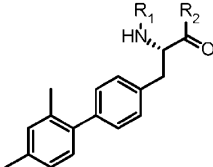
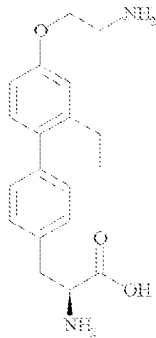
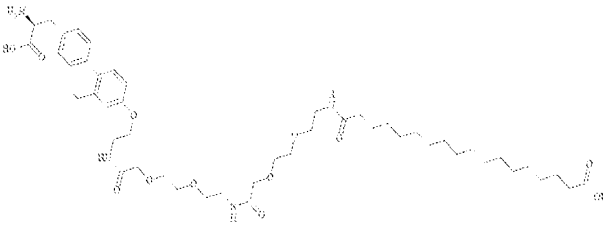
	 R1 is H; R2 is OH
aMe_Asn (Analog of Asn)	α-methyl asparagine  R1 is H; R2 is OH
aMe_Asp (Analog of Asp)	α-methyl aspartic acid  R1 is H; R2 is OH
aMeBip2pMe4pOMe	 R1 is H, R2 is OH
aMe_Cys, a-MeCys, aMeCys, or α -MeCys (Analog of Cys)	α-methyl cysteine  R1 is H; R2 is OH; R3 is H
aMe_Gln (Analog of Gln)	α-methyl glutamine  R1 is OH, R2 is H
aMe_Glu (Analog of Glu)	α-methyl glutamic acid

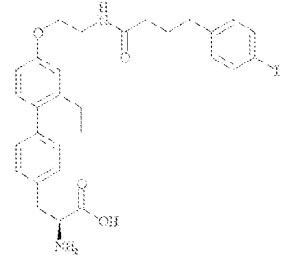
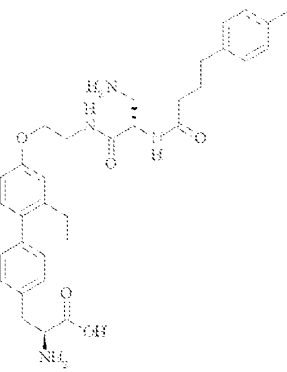
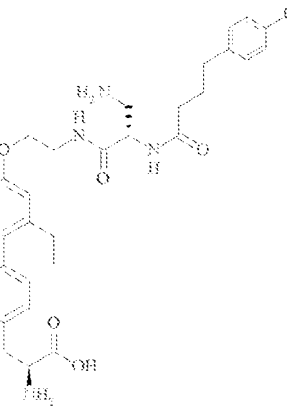
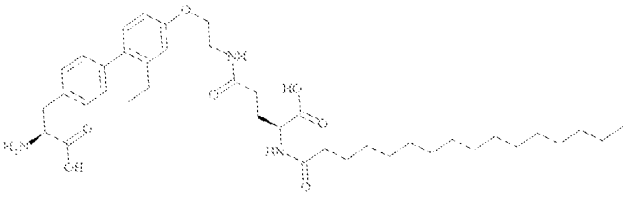
	 R1 is H; R2 is OH; R3 is OH
aMe_His (Analog of His)	 R1 is H; R2 is OH
aMe_Ile (Analog of Ile)	α-methyl isoleucine  R1 is OH; R2 is H
aMe_Leu (Analog of Leu)	α-methyl leucine  R1 is H; R2 is OH
aMe_Lys (Analog of Lys)	α-methyl lysine  R1 is H; R2 is OH; R3 is H
aMe_Lys_Ac (Analog of Lys)	 R1 is H; R2 is OH
aMc_Phe or aMc_F (Analog of Phe)	 R1 is H; R2 is OH

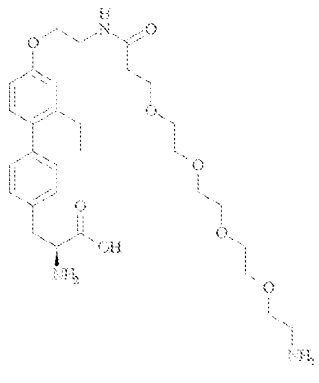
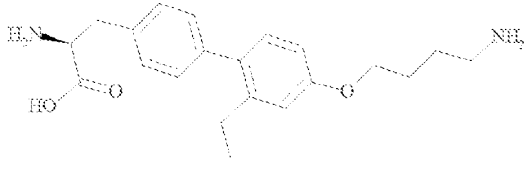
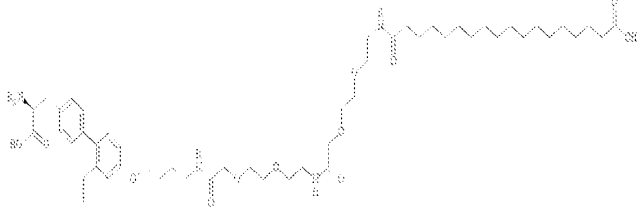
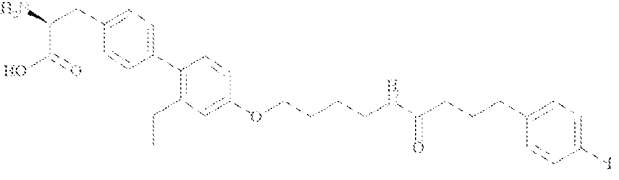
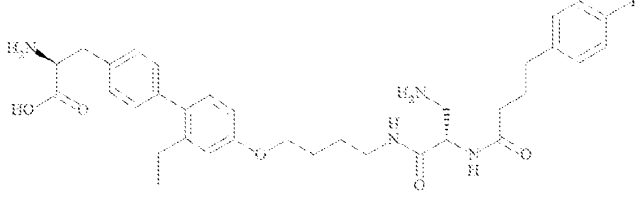
aMe_Phe_2F or aMe_2F_Phe (Analog of Phe)	 R1 is H, R2 is OH
aMe_Pro (Analog of Pro)	 R1 is H, R2 is OH
aMe_Ser (Analog of Ser)	 R1 is H, R2 is OH
aMe_Trp (Analog of Trp)	 R1 is H; R2 is OH
aMe_Tyr (Analog of Tyr)	 R1 is H; R2 is OH
aMe_Val (Analog of Val)	 R1 is H, R2 is OH
Aoc (Analog of Ile)	8-aminooctanoic acid 
Apa	4-aminoheptanedioic acid

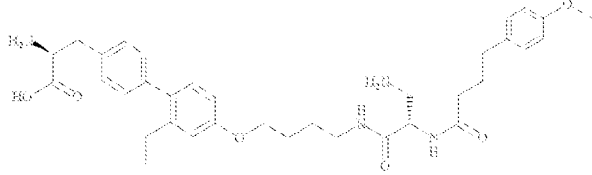
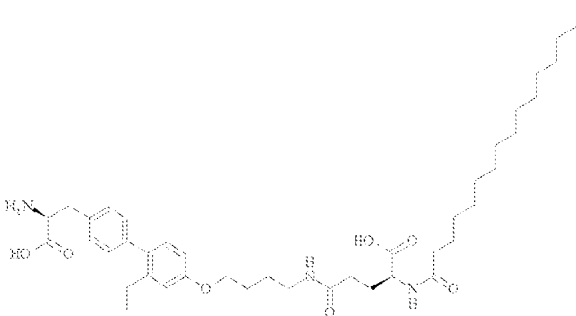
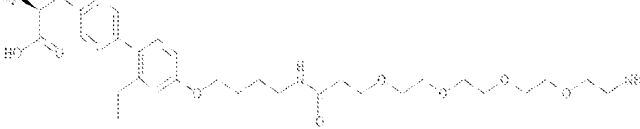
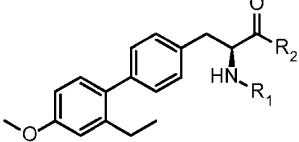
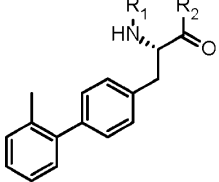
	
Aph (Analog of Phe)	 R1 is H, R2 is OH
Api (Analog of Glu)	 R1 is H, R2 is OH, R3 is OH
Asp_OMe or (OMe)Asp (Analog of Asp)	L-Aspartic acid β -methyl ester 
Aze or Azetidinone (Analog of Pro)	Azetidine-2-carboxylic acid 
bA	
Betaine	(CH ₃) ₃ NCH ₂ CH ₂ CO ₂ H  R2 is OH
β Glu or bGlu or bE (Analog of Glu)	β -Glutamic acid  R1 is H; R2 is OH, R3 is OH

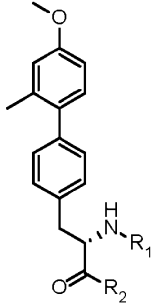
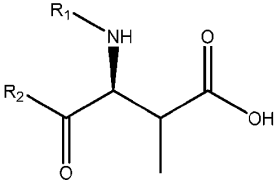
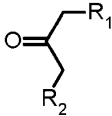
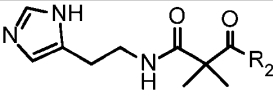
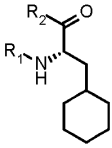
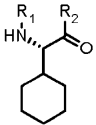
bh, b-h, bhomo, or b-homo	β -homo
bhQ or bhGln (Analog of Gln)	β -homoglutamine R1 is H; R2 is OH
bhF or β hPhe or bhPhe (Analog of Phe)	β -homophenylalanine R1 is H, R2 is OH
bhGlu or β hGlu or bhE (Analog of Glu)	β -homoglutamic acid
bhP or bhPro (Analog of Pro)	β -homoproline R1 is H, R2 is OH
bhV or bhVal (Analog of Val)	β -homovaline R1 is H, R2 is OH
bhW or β hTrp or bhTrp (Analog of Trp)	β -homotryptophan R1 is H, R2 is OH
bhY or β hTyr or bhTyr (Analog of Tyr)	β -homotyrosine R1 is H, R2 is OH
Bip (Analog of Phe)	3-(biphenyl-4-yl)alanine

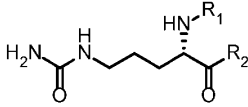
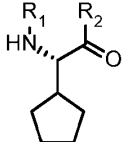
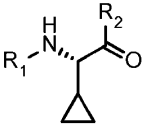
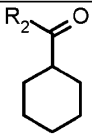
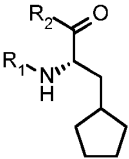
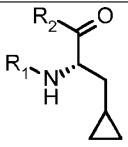
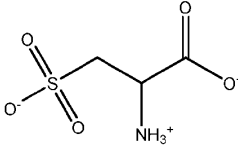
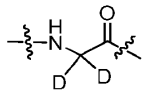
	 R1 is H, R2 is OH
Bip24Me or Bip24_Me (Analog of Phe)	 R1 is H, R2 is OH
Bip_2pEt4pOC2N	
Bip_2pEt4pOC2N_1PEG2_1 PEG2_C18_Diacid	 CCc1cc(OCCNC(=O)COCCOCCNC(=O)COCCOCCNC(=O)CCCCC CCCCCCCCCCCC(=O)O)ccc1c2ccc(C[C@H](N)C(=O)O)cc2

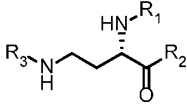
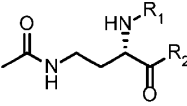
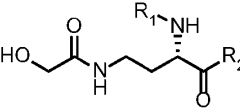
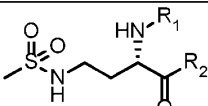
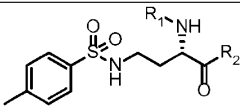
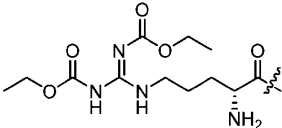
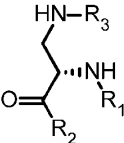
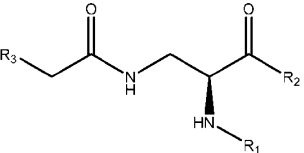
Bip_2pEt4pOC2N_Albutag	 Chemical structure of Bip_2pEt4pOC2N_Albutag. It features a biphenyl core with a 4-ethoxyphenyl group at position 2 of one ring and a 4-((2S,3S)-3-((4-iodophenyl)amino)-2-hydroxypropyl)phenyl group at position 4 of the other ring. The biphenyl system is connected via an ether linkage to a 4-((2S,3S)-3-((4-iodophenyl)amino)-2-hydroxypropyl)phenyl group.
Bip_2pEt4pOC2N_Dap_Alb utag	 Chemical structure of Bip_2pEt4pOC2N_Dap_Alb utag. It features a biphenyl core with a 4-ethoxyphenyl group at position 2 of one ring and a 4-((2S,3S)-3-((4-iodophenyl)amino)-2-hydroxypropyl)phenyl group at position 4 of the other ring. The biphenyl system is connected via an ether linkage to a 4-((2S,3S)-3-((4-iodophenyl)amino)-2-hydroxypropyl)phenyl group.
Bip_2pEt4pOC2N_Dap_Me OPheTag,	 Chemical structure of Bip_2pEt4pOC2N_Dap_Me OPheTag,. It features a biphenyl core with a 4-ethoxyphenyl group at position 2 of one ring and a 4-((2S,3S)-3-((4-methoxyphenyl)amino)-2-hydroxypropyl)phenyl group at position 4 of the other ring. The biphenyl system is connected via an ether linkage to a 4-((2S,3S)-3-((4-methoxyphenyl)amino)-2-hydroxypropyl)phenyl group.
Bip_2pEt4pOC2N_IsoGlu_P alm	 Chemical structure of Bip_2pEt4pOC2N_IsoGlu_P alm. It features a biphenyl core with a 4-ethoxyphenyl group at position 2 of one ring and a 4-((2S,3S)-3-((4-iodophenyl)amino)-2-hydroxypropyl)phenyl group at position 4 of the other ring. The biphenyl system is connected via an ether linkage to a 4-((2S,3S)-3-((4-iodophenyl)amino)-2-hydroxypropyl)phenyl group.

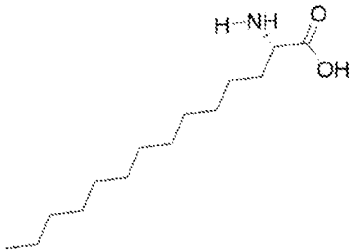
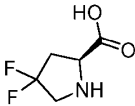
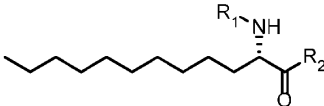
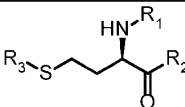
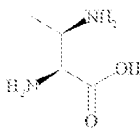
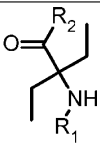
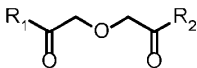
Bip_2pEt4pOC2N_PEG4_am	
Bip_2pEt4pOC4N	
Bip_2pEt4pOC4N_1PEG2_1 PEG2_C18_Diacid	 <chem>CCc1cc(OCCCCNC(=O)COCCOCCNC(=O)COCCOCCNC(=O)CCCCCCCCCCCCCCCC(=O)O)ccc1c2ccc(C[C@H](N)C(=O)O)cc2</chem>
Bip_2pEt4pOC4N_Albutag	
Bip_2pEt4pOC4N_Dap_Albutag	

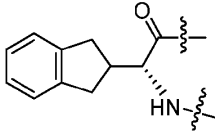
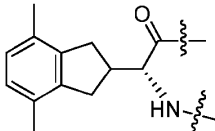
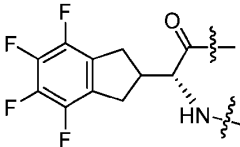
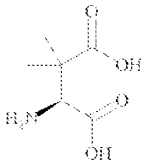
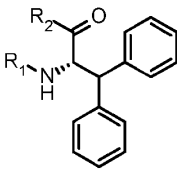
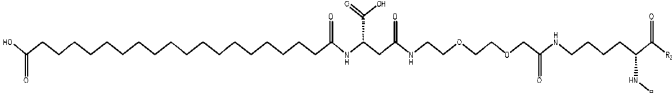
Bip_2pEt4pOC4N_Dap_Me OPheTag	
Bip_2pEt4pOC4N_IsoGlu_P alm	
Bip_2pEt4pOC4N_PEG4_am	 <chem>CCc1cc(OCCCCNC(=O)CCOCCOCCOCCOCCN)ccc1c2ccc(C[C@H](N)C(=O)O)cc2</chem>
Bip_2pEt4pOMe (Analog of Phe)	 R1 is H, R2 is OH
Bip_2pMe (Analog of Phe)	 R1 is H, R2 is OH

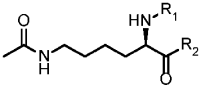
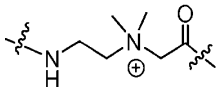
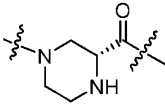
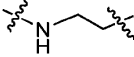
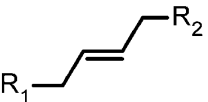
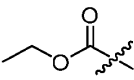
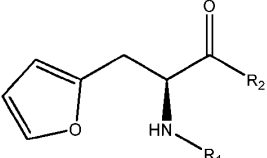
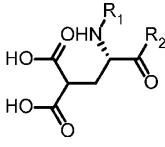
Bip_2pMe4pOMe (Analog of Phe)	 R1 is H, R2 is OH
bMeAsp	 R1 is H, R2 is OH
Boc-Triazine	Boc-Triazine di-acid
Butane_Linker	 R1 is H, R2 is OH
Carbonyl_Linker	 R1 is H, R2 is H
Cap (Analog of His)	 R2 is H
Cav	Cavanine or Canavanine
Cha (Analog of Leu)	Cyclohexylalanine  R1 is H, R2 is OH
Chg (Analog of Ile)	α-cyclohexylglycine  R1 is H, R2 is OH
Cit	Citrulline

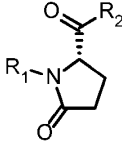
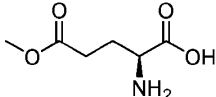
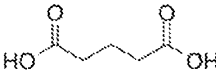
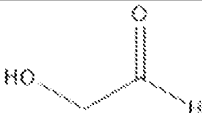
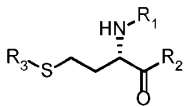
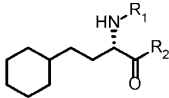
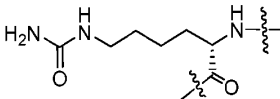
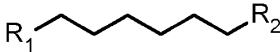
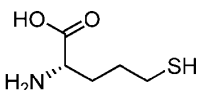
(Analog of Arg)	 R1 is H, R2 is OH
Cpg (Analog of Val)	 R1 is H; R2 is OH
Cprg (Analog of Gly)	 R1 is H; R2 is OH
C-StBu	S-tert-butylthio-cysteine
C-tBu	S-tert-butyl-cysteine
Cyclohexanecarboxylic_Acid or Cyclohexanoic_Acid or cyclohexanecarboxylic acid	 R2 is OH
Cyclopentyl_Ala (Analog of Leu)	 R1 is H; R2 is OH
Cyclopropyl_Ala (Analog of Leu)	 R1 is H; R2 is OH
Cysteate or Cysteic acid (Analog of Cys)	
d2Gly or d2G (Analog of Gly)	Glycine-2,2-d2 
Daba or Dab (Analog of Lys)	2,4-diaminobutyric acid

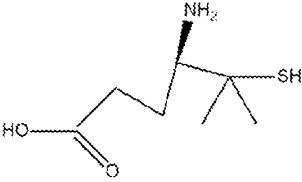
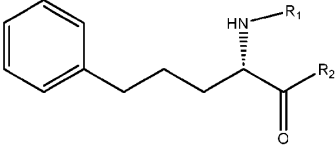
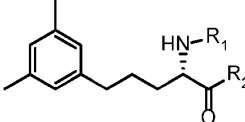
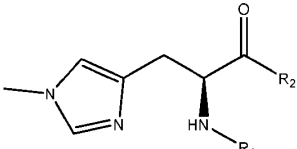
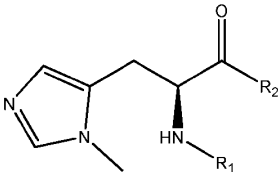
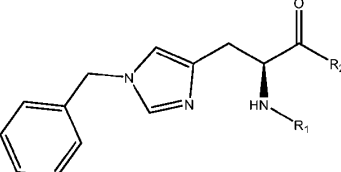
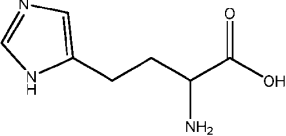
	 R1 is H; R2 is OH; R3 is H
Dab_Ac or Dab_Acetyl (Analog of Gln)	 R1 is H; R2 is OH
Dab_2HyAc (Analog of Lys)	 R1 is H; R2 is OH
Dab_Ms (Analog of Lys)	 R1 is H; R2 is OH
Dab_Ts (Analog of Lys)	 R1 is H; R2 is H
dArg_Eoc (Analog of Arg)	
Dapa or Dap (Analog of Lys)	L-Diaminopropionic acid  R1 is H, R2 is OH, R3 is H
Dap_Ac	 R1 is H, R2 is OH, R3 is H
Dapa(AcBr)	NY-(bromoacetyl)-2,3- diaminopropionic acid
Dapa(Palm)	Hexadecanoyl-β-Diaminopropionic acid

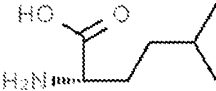
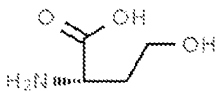
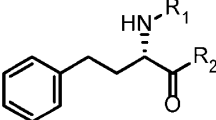
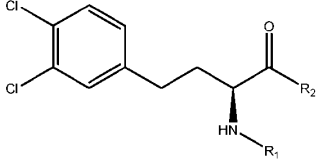
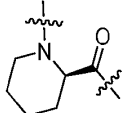
dDap (D)Dap or dDapa	D-Diaminopropionic acid
Ddgl (Analog of Dgl or Ogl)	
dCit or (D)Cit	D-Citrulline
Dfp (Analog of Pro)	(S)-4,4-difluoropyrrolidine-2-carboxylic acid 
Dgl (Analog of Ala)	 R1 is H, R2 is OH
dHey or dhCys	 R1 is H, R2 is OH, R3 is H
Diaminobutanoic_Acid	
DiethylGly (Analog of Ile)	 R1 is H, R2 is OH
DIG	Diglycolic acid  R1 is OH, R2 is OH
DIG-OH	Glycolic monoacid

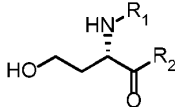
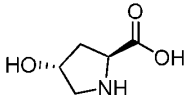
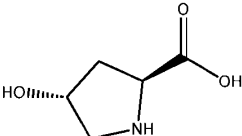
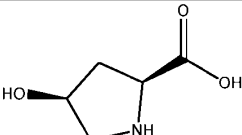
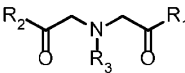
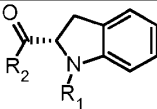
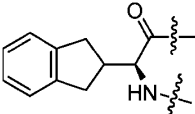
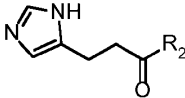
dIgl or (D)Igl (Analog of Phe)	(2R)-2-amino-2-(2,3-dihydro-1H-inden-2-yl)acetic acid 
dIgl_4_7_Dimethyl or dIgl(4_7_Dimethyl)	(R)-2-amino-2-(4,7-dimethyl-2,3-dihydro-1H-inden-2-yl)acetic acid 
dIgl_Tetrafluoro	(R)-2-amino-2-(4,5,6,7-tetrafluoro-2,3-dihydro-1H-inden-2-yl)acetic acid 
diMe_Asp	
Dimethylcyclopropane_Linker	 R1 is H, R2 is OH
DIP or DPA (Analog of Phe)	Diphenylalanine  R1 is H; R2 is OH
dIsoLys_1PEG2_IsoGlu_C20_Diacid	 R1 is H; R2 is OH SMILES: <chem>O=C([R2])[C@@H](CCCCNC(COCCOCCNC(C[C@@H](C(O)=O)NC(CCCCCCCCCCCCCCCCCC(O)=O)=O)=O)N[R1])</chem>

dLys_Ac (Analog of Lys)	(D)-Lys_Ac  R1 is H; R2 is OH
D-Npc or D-NPC	(D)-nipecotic acid
dOrn or (D)Orn	D-Ornithine
DMG_N_2ae	
dPiperazine	(R)-piperazine-2-carboxylic acid 
DTT	Dithiothreitol
EA (Analog of Gly)	
EButene_Linker	 R1 is H; R2 is H
EOC	Ethoxycarbonyl 
Fur	 R1 is H; R2 is OH
Gaba or GABA	γ -aminobutyric acid (NH ₂ CH ₂ CH ₂ CH ₂ CO ₂ H)
Gla (Analog of Glu)	γ -Carboxy-glutamic acid  R1 is H; R2 is OH
Glp (Analog of Pro)	Pyroglutamic acid

	 R1 is H; R2 is OH
Glu_OMe or (OMe)Glu (Analog of Glu)	L-Glutamic acid gamma-methyl ester 
Glutaric acid	C5 dicarboxylic acid 
Glycolic acid	
hC or hCys or Hcy (Analog of Cys)	Homocysteine  R1 is H, R2 is OH, R3 is H
hCha or H_Cha	Homocyclohexylalanine  R1 is H; R2 is OH
hCit (Analog of Arg)	Homo-citrulline 
Hexane_Linker	 R1 is H, R2 is OH
Hhc, hhCys, or HhCys (Analog of Cys)	(S)-2-amino-5-mercaptopentanoic acid or homo-homocysteine 

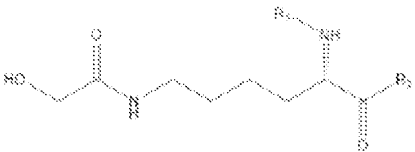
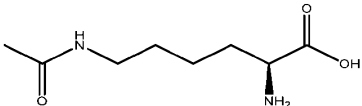
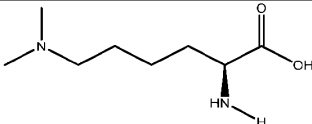
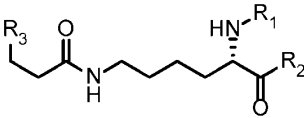
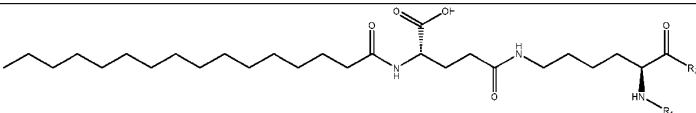
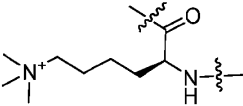
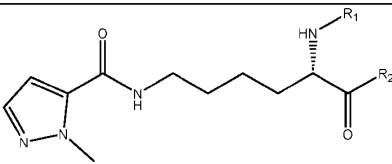
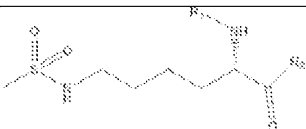
hhPen (Analog of Cys)	
hhF or HhPhe	Homohomophenylalanine  R1 is OH, R2 is OH
HHPhe_35Me (Analog of Phe)	 R1 is OH, R2 is OH
His_1Me	 R1 is OH, R2 is OH
His_3Me	 R1 is OH, R2 is OH
His_Bzl	 R1 is OH, R2 is OH
hHis or hH	Homohistidine 
hL or hLeu (Analog of Leu)	Homoleucine

	
hR or hArg (Analog of Arg)	Homoarginine 
hS or Homoserine or hSer (Analog of Ser)	Homoserine 
Hph or hPh or hF (Analog of Phe)	Homophenylalanine  R1 is H, R2 is OH
Hph_34diCl	 R1 is H, R2 is OH
Hpr or HoPro or hP (Analog of Pro)	Homoproline; (R)-piperidine-2-carboxylic acid 
Hse or hSer or hS	Homoserine

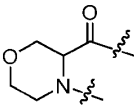
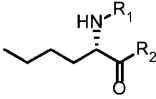
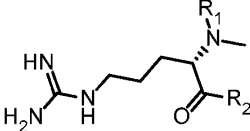
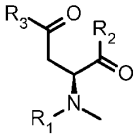
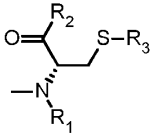
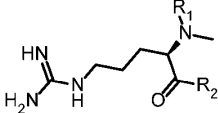
(Analog of Ser)	 R1 is H; R2 is OH
Hyp (Analog of Pro)	Hydroxyproline 
Hyp_4R or 4R_Hyp (Analog of Pro)	
Hyp_4S or 4S_Hyp (Analog of Pro)	
IDA or Ida	Iminodiacetic acid  R1 is OH, R2 is OH, R3 is H
IDA-Palm	(Palmitoyl)-Iminodiacetic acid
Idc (Analog of Pro)	 R1 is H, R2 is OH
Igl (Analog of Phe)	(2S)-2-amino-2-(2,3-dihydro-1H-inden-2-yl)acetic acid 
Imidazole_PropanoicAcid or Imidazole_Propanoic_Acid (Analog of His)	 R2 is OH
Inp (Analog of Gln or Glu)	isonipecotic acid

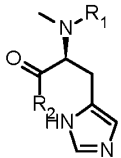
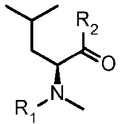
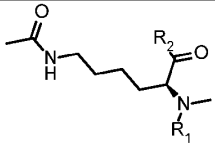
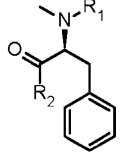
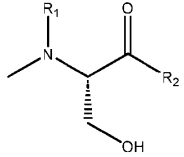
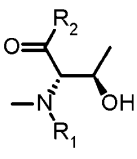
isoAsp (Analog of Asp)	
IsoGlu-octanoic acid	Octanoyl-γ-Glu
IsoGlu_Palm	 Hexadecanoyl-γ-Glu
Isoindole (Analog of Pro)	 R1 is H, R2 is H
Isovaleric acid (IVA)	 R2 is OH
K-octanoic acid	Octanoyl-ε-Lys
Lys_1PEG2_Ac (Analog of Lys)	 R1 is H; R2 is OH
Lys_1PEG2_IsoGlu_C20diacid id or Lys_1PEG2_IsoGlu_C20_Diacid	 R1 is H, R2 is OH <chem>OC(CCCCCCCCCCCCCCCCCCCCN[C@@H](C(=O)=O)CCC(NCCOCCOCC(=O)N[C@@H](CCCCNC(=O)[C@H]([R2])=O)N[R1])=O)=O=O=O</chem>

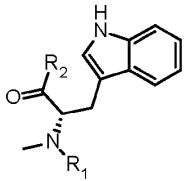
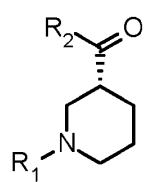
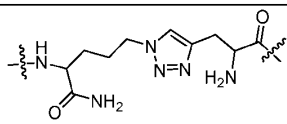
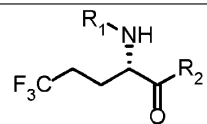
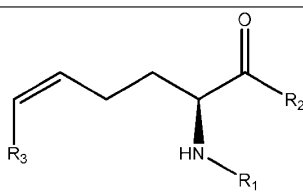
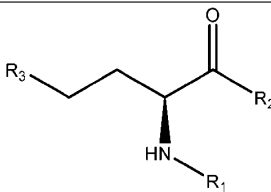
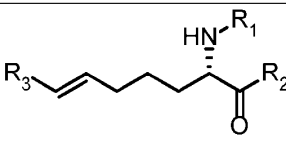
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Lys_2HyAc (Analog of Lys)	 R1 is H, R2 is OH
Lys_Ac (Analog of Lys)	
Lys_Dimethyl (Analog of Lys)	
Lys_Hexy (Analog of Lys)	 R1 is H, R2 is OH, R3 is H
Lys_IsoGlu_Palm (Analog of Lys)	 R1 is H; R2 is OH
Lys_Me3 (Analog of Lys)	
LysMPA (Analog of Lys)	 R1 is H, R2 is H
Lys_Ms (Analog of Lys)	 R1 is H; R2 is OH

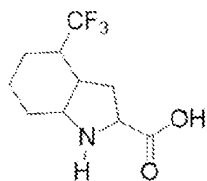
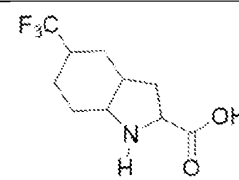
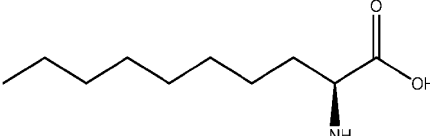
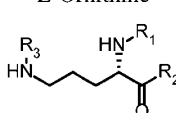
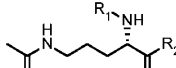
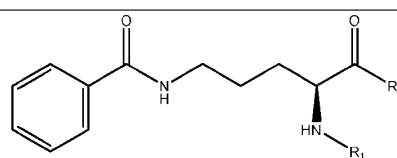
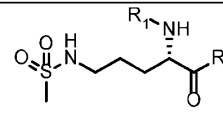
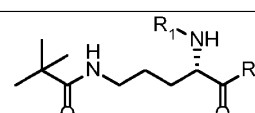
LysN3 (Analog of Lys)	R1 is H, R2 is OH, R3 is H, R4 is H
Lys_Ns (Analog of Lys)	R1 is H; R2 is OH
Lys_PEG12_NH (Analog of Lys)	R1 is H, R2 is OH, R3 is H
Lys_PEG2_IsoGlu_Palm	R1 is H, R2 is OH
Lys_PEG2_Me3 (Analog of Lys)	R1 is H; R2 is OH
Lys_PEG4_PEG4_NH2	R1 is H, R2 is OH, R3 is H
LysPhAc or Lys_AcPhe (Analog of Lys)	R1 is H; R2 is OH
Lys_Ts (Analog of Lys)	R1 is H; R2 is OH
Methylene_Linker	R1 is H; R2 is OH
Mor_propanoic acid	R1 is H, R2 is OH

Morph (Analog of Pro)	Morpholine-3-carboxylic acid 
Morpholino	
NH2	Free Amine
nL or Nleu or Nle (Analog of Leu)	Norleucine  R1 is H; R2 is OH
NMe_Arg (Analog of Arg)	N-methyl-arginine  R1 is H; R2 is OH
NMe_Asp (Analog of Asp)	N-methyl-aspartic acid  R1 is H; R2 is OH; R3 is OH
NMe_Cys, or (NMe)Cys (Analog of Cys)	N-methyl-cysteine  R1 is H, R2 is OH, R3 is H
NMe_dR or (NMe)dR (Analog of Arg)	N-methyl-D-arginine  R1 is H, R2 is OH

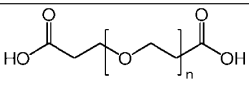
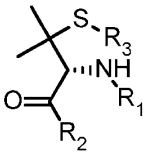
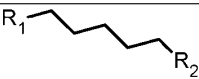
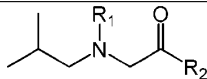
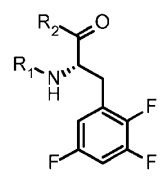
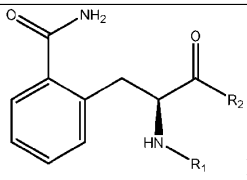
NMe_His (Analog of His)	 R1 is H, R2 is OH
NMe_Leu (Analog of Leu)	N-methyl-leucine  R1 is H, R2 is OH
NMe_Lys_Ac (Analog of Lys)	 R1 is H; R2 is OH
NMe_Phe or (NMe)Phe (Analog of Phe)	N-methyl-phenylalanine  R1 is H; R2 is OH
NMe_Ser (Analog of Ser)	 R1 is H, R2 is OH
NMe_Thr or (NMe)Thr (Analog of Thr)	N-methyl-threonine  R1 is H; R2 is OH
NMe_Trp or (NMe)Trp (Analog of Trp)	N-methyl-tryptophan

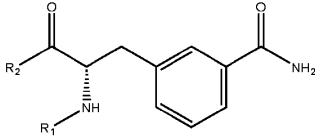
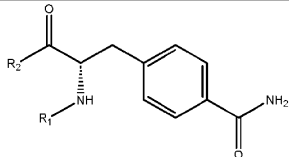
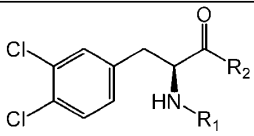
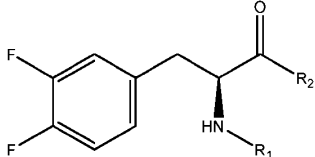
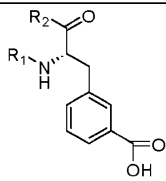
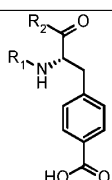
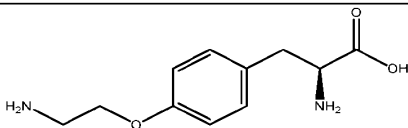
	 R1 is H; R2 is OH
Npc or NPC (Analog of Pro)	Nipecotic acid  R1 is H, R2 is OH
Nvam_Triazole_MA	
nVF3 (Analog of Val)	 R1 is H, R2 is OH
O2S (Analog of Cys)	 R1 is H, R2 is OH, R3 is H
O2S_Reduced (Analog of Cys)	 R1 is H, R2 is OH, R3 is H
O3S (Analog of Cys)	 R1 is H, R2 is OH, and R3 is H

O3S_Me (Analog of Cys)	R1 is H, R2 is OH, and R3 is H
O3S_Reduced (Analog of Cys)	R1 is H, R2 is OH, and R3 is H
O4S (Analog of Cys)	R1 is H, R2 is OH, and R3 is H
O4S_Reduced (Analog of Cys)	R1 is H, R2 is OH, and R3 is H
O5S (Analog of Cys)	R1 is H, R2 is OH, and R3 is H
O5S_Reduced (Analog of Cys)	R1 is H, R2 is OH, and R3 is H
O6S (Analog of Cys)	R1 is H, R2 is OH, and R3 is H
O6R_Me (Analog of Cys)	
Oic (Analog of Pro)	Octahydroindole-2-carboxylic acid or (2S,3aS,7aS)-octahydro-1H-indole-2-carboxylic acid

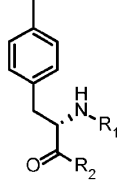
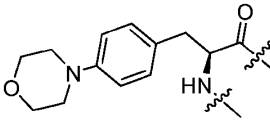
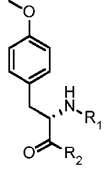
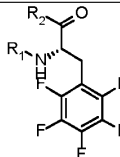
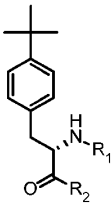
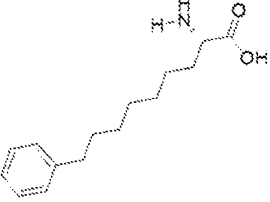
Oic_4CF3 (Analog of Pro or Oic)	
Oic_5CF3 (Analog of Pro or Oic)	
Ogl (Analog of Leu)	
Orn (Analog of Lys)	L-Ornithine  R1 is H; R2 is OH; R3 is H
Orn_Ac or OrnAc or Orn_Acetyl (Analog of Lys)	 R1 is H; R2 is OH
OrnBz or Orn_Bz	 R1 is H; R2 is OH
Orn_Ms or OrnMs (Analog of Lys)	 R1 is H; R2 is OH
OrnPVA (Analog of Lys)	 R1 is H, R2 is H

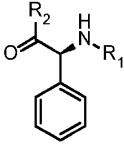
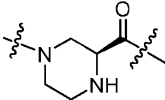
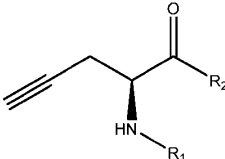
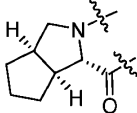
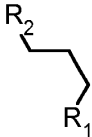
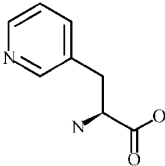
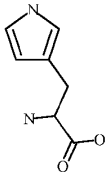
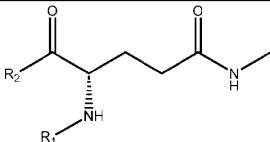
Orn_Ts (Analog of Lys)	R1 is H; R2 is OH
Orn_5_Morpholino or Orn(5_Morpholino)	
Oxetane_Linker	R1 is H, R2 is OH
Palm	Palmitic or Palmitoyl or C(O)-(CH2)14CH3
pBiphenyl_Linker	
PEG or (PEG)n or -(OCH2CH2)n-	-(OCH2CH2)n- n is 1, 2, 3, 4, etc; the dashes at either end indicate that the PEG molecule can be functionalized at the terminal ends of the molecule; the (OCH2CH2) unit is an individual PEG “unit” or “subunit”
Peg1K	(PEG)n, Mol wt of 1000Da
Peg3.4K	PEG Mol wt of 3400Da
Peg5K	PEG wt of 5000Da
PEG4	R1 is H, R2 is OH
PEG6	R1 is H, R2 is OH
PEG8	R1 is H, R2 is OH
PEG3_Mal_ME	

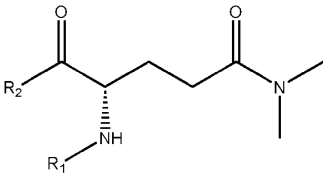
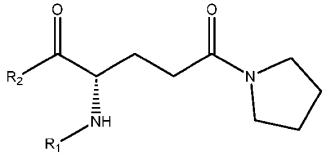
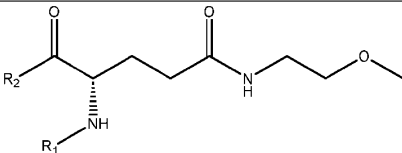
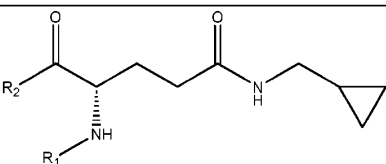
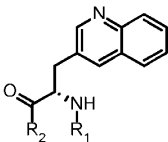
PEGDA (PEG diacid)	 or, $C_3H_5O_2(OCH_2CH_2)_nCHO_2$ where n is at least 1. "DA" of PEGDA indicates the molecule is functionalized with a carboxylic acid at both ends.
PEG13DA	See PEGDA, where n=13 for the number of PEG units, i.e., - (OCH ₂ CH ₂) _n - n is 13
PEG21DA	See PEGDA, where n=21
PEG25DA	See PEGDA, where n=25
Pen (Analog of Cys)	Penicillamine  R₁ is H; R₂ is OH; R₃ is H
Pentane_Linker	 R₁ is H, R₂ is OH
Peptoid_CH2_V (Analog of Val)	 R₁ is H; R₂ is OH
Phe(2,3,5-triF), or (2,3,5-triF)Phe or Phe_235F (Analog of Phe)	(2,3,5-Trifluoro)-L-Phenylalanine  R₁ is H, R₂ is OH
Phe_2_ad or Phe_2Ad (Analog of Phe)	 R₁ is H, R₂ is OH

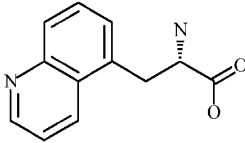
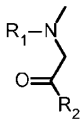
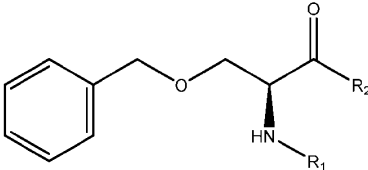
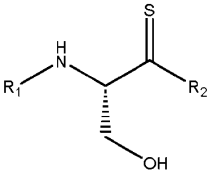
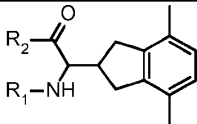
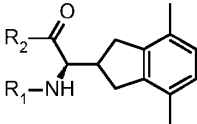
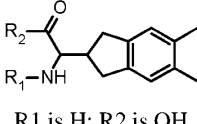
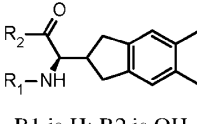
Phe_3_ad or Phe_3Ad (Analog of Phe)	 R1 is H, R2 is OH
Phe_4_ad or Phe_4Ad (Analog of Phe)	 R1 is H, R2 is OH
Phe_3_4_Cl2 , or Phe_34diCl (Analog of Tyr)	 R1 is H; R2 is OH
Phe_34diF (Analog of Tyr)	 R1 is H; R2 is OH
Phe_3COOH (Analog of Tyr)	 R1 is H, R2 is OH
Phe_4COOH (Analog of Tyr)	 R1 is H, R2 is OH
Phe_4_2ae (Analog of Tyr)	

Phe_4Ad (Analog of Tyr)	R1 is H, R2 is OH
Phe_4_CF3, Phe_4CF3, Phe(4-CF3), Phe(4 CF3), (4- CF3)Phe or (4CF3)Phe (Analog of Phe)	(4-Trifluoromethyl)-L-Phenylalanine R1 is H; R2 is OH
Phe_4_Cl or Phe_4Cl (Analog of Tyr)	R1 is H, R2 is OH
Phe_4_COOH or Phe_4COOH (Analog of Tyr)	R1 is H, R2 is OH
Phe_4F, Phe(4-F), Phe(4F), (4-F)Phe or (4F)Phe (Analog of Tyr)	4-Fluoro-L-Phenylalanine R1 is H, R2 is OH
Phe_4guan (Analog of Arg)	R1 is H, R2 is OH

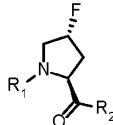
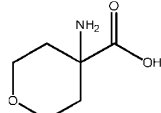
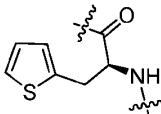
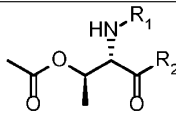
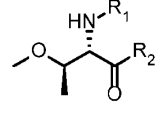
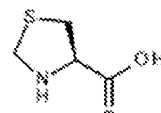
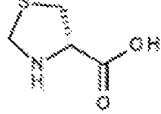
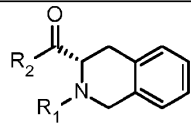
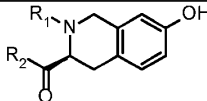
Phe_4Me, Phe_4_Me, or Phe_4Me (Analog of Phe)	 R1 is H; R2 is OH
Phe_4_Morph, Phe_4Morph or Phe(4_Morpholino) (Analog of Tyr)	
Phe_4_OMe or Phe_4OMe (Analog of Tyr)	 R1 is H; R2 is OH
Phe_pentaF (Analog of Phe)	 R1 is H; R2 is OH
Phe_4tBu (Analog of Phe)	4-t-butylphenylalanine  R1 is H; R2 is OH
Phenyl_Hgl (Analog of Leu or Ogl)	
Phg (Analog of Phe)	Phenylglycine

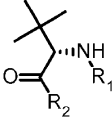
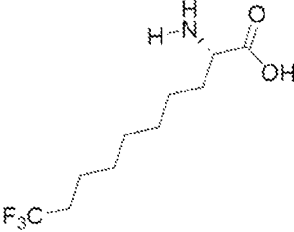
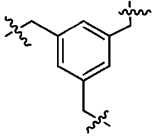
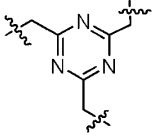
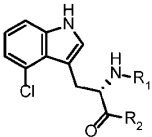
	 R1 is H, R2 is OH
Piperazine (Analog of Pro)	(S)-piperazine-2-carboxylic acid 
Pra	 R1 is H, R2 is OH
Pro_Cpn or Pro(Cpn) (Analog of Pro)	(1S,3aR,6aS)-octahydroR-Ocyclopenta[c]pyrrole-1-carboxylic acid 
Propane_Linker	 R1 is H; R2 is H
Pyridin3yl	
Pyrrole_PA	
Q_NHMe (Analog of Gln)	

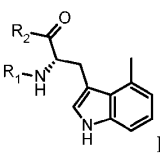
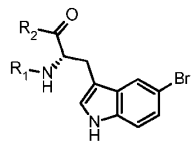
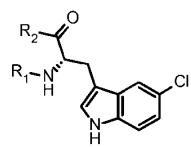
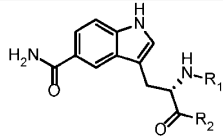
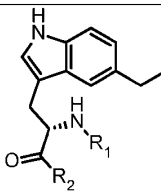
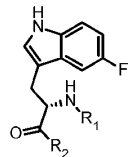
	R1 is H; R2 is OH
Q_NMe2 (Analog of Gln)	
	R1 is H; R2 is OH
Q_Pyro (Analog of Gln)	
	R1 is H; R2 is OH
Q_EtOMe (Analog of Gln)	
	R1 is H; R2 is OH
Q_MecPro (Analog of Gln)	
	R1 is H; R2 is OH
Quin_3 (Analog of Phe)	3-(quinolin-3-yl)-alanine 
	R1 is H; R2 is OH
Quin_4 (Analog of Phe)	3-(quinolin-4-yl)-alanine
Quin_5 (Analog of Phe)	3-(quinolin-5-yl)-alanine
Quin_6 (Analog of Phe)	3-(quinolin-6-yl)-alanine
Quin_7 (Analog of Phe)	3-(quinolin-7-yl)-alanine
Quin_8 (Analog of Phe)	3-(quinolin-8-yl)-alanine

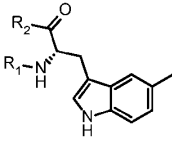
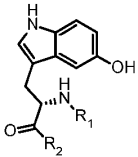
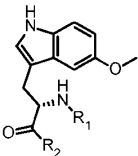
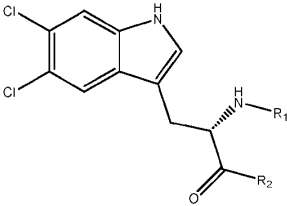
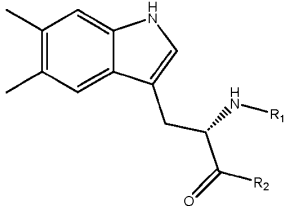
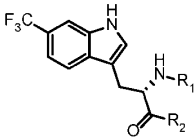
Quinolin_5_yl	
Sarc or Sar (Analog of Gly)	Sarcosine  R₁ is H; R₂ is OH
Ser_Bz (Analog of Ser)	 R₁ is H; R₂ is OH
SThioamide	 R₁ is H, R₂ is H; SMILES: S=C([R2])[C@@H](N[R1])CO
T1 (Analog of Pro)	 R₁ is H; R₂ is OH
T2 (Analog of Pro)	 R₁ is H; R₂ is OH
T3 (Analog of Pro)	 R₁ is H; R₂ is OH
T4 (Analog of Pro)	 R₁ is H; R₂ is OH

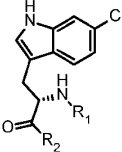
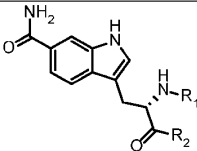
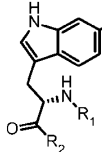
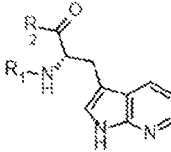
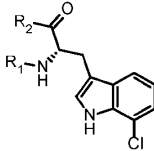
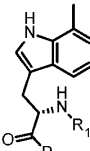
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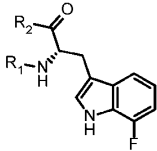
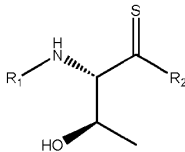
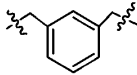
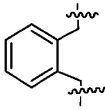
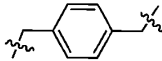
Tfp	 R1 is H; R2 is OH
THP or Thp (Analog of Ser)	
Thi (Analog of Tyr)	(S)-2-amino-3-(thiophen-2-yl)propanoic acid 
Thr_Ac (Analog of Thr)	 R1 is H; R2 is OH
Thr_Me (Analog of Thr)	 R1 is H; R2 is OH
Thz	(4R)-Thiazolidine-4-carboxylic acid 
dThz	(4S)-Thiazolidine-4-carboxylic acid 
Tic (Analog of Pro)	 R1 is H; R2 is OH
Tic_7OH (Analog of Pro)	

	R1 is H; R2 is OH
Tle (Analog of Ile)	tert-Leucine  R1 is H; R2 is OH
Trifluorobutyric acid	4,4,4-Trifluorobutyric acid
Trifluoro_Ogl (Analog of Leu or Ogl)	
Trifluoropentanoic acid	5,5,5-Trifluoropentanoic acid
Trimethylbenzene or Trimethylbenzene_Linkers (Analog of Gly)	
TrimethylTriazine	
Triazine	Amino propyl Triazine di-acid
Trp_4Cl (Analog of Trp)	4-chloro-tryptophan  R1 is H, R2 is OH

Trp_4Me (Analog of Trp)	4-methyl-tryptophan  R1 is H, R2 is OH
Trp_5Br (Analog of Trp)	5-bromo-tryptophan  R1 is H, R2 is OH
Trp_5Cl (Analog of Trp)	5-chloro-tryptophan  R1 is H, R2 is OH
Trp_5CONH2 (Analog of Trp)	 R1 is H, R2 is OH
Trp_5Et (Analog of Trp)	 R1 is H, R2 is OH
Trp_5F (Analog of Trp)	5-fluoro-tryptophan  R1 is H, R2 is OH

Trp_5Me (Analog of Trp)	5-methyl-tryptophan  R1 is H, R2 is OH
Trp_5OH (Analog of Trp)	5-hydroxy-tryptophan  R1 is H, R2 is OH
Trp_5OMe (Analog of Trp)	5-methoxy-tryptophan  R1 is H, R2 is OH
Trp_56diCl (Analog of Trp)	 R1 is H, R2 is OH
Trp_56diMe (Analog of Trp)	 R1 is H, R2 is OH
Trp_6CF3 (Analog of Trp)	6-trifluoromethyl-tryptophan  R1 is H, R2 is OH
Trp_6Cl	6-chloro-tryptophan

(Analog of Trp)	 R1 is H, R2 is OH
Trp_6CONH2 (Analog of Trp)	 R1 is H, R2 is OH
Trp_6Me (Analog of Trp)	6-methyl-tryptophan  R1 is H; R2 is OH
Trp_7Aza (Analog of Trp)	 R1 is H; R2 is OH
Trp_7Cl (Analog of Trp)	7-chloro-tryptophan  R1 is H, R2 is OH
Trp_7Me (Analog of Trp)	7-methyl-tryptophan  R1 is H, R2 is OH

Trp_7Phe or Trp_7F (Analog of Trp)	7-phenyl-tryptophan  R1 is H, R2 is OH
TThioamide	 R1 is H, R2 is H; SMILES is <chem>S=C([C@@H](N[R1])[C@H](O)C)[R2]</chem>
mXylene_Linker	
oXylene_Linker	
pXylene_Linker	

[00272] 2. Peptide-Based Compounds That Bind to Human IL-17 Cytokines

[00273] The peptide compounds of the invention are synthetic or recombinant peptide-based compounds that bind to one or more human IL-17 cytokine isoforms. In most embodiments, the peptide compounds of the invention are potent inhibitors of human IL-17 cytokines, which is reflected by nanomolar and sub-nanomolar IC₅₀ values for the peptides in inhibiting/reducing IL-17 dependent secreted embryonic alkaline phosphatase (SEAP) reporter gene expression in the human IL-17 HEK-Blue™ assay. (InvivoGen IL-17 Reporter HEK 293 Cells; see Figure 1 and Example 5.) In other embodiments, the peptide compounds exhibit stability in a simulated gastrointestinal degradation assays (SGF and SIF assays). In certain instances, the peptide compounds will have both nanomolar (or less) potency and stability. In

some embodiments, the peptide compounds have a cyclic (an intramolecular cross-link between at least two positions of the peptide) or linear structure. In some embodiments, the peptide compounds are monomeric or dimeric compounds. As explained hereinbelow, the peptide compounds of the invention can be categorized into various groupings based on one or more structural or functional features.

[00274] In most embodiments, the main subunit of the peptide compounds of the invention is a string of natural and/or unnatural amino acids mostly having a length of 14-16 amino acids. This main subunit can be referred to as a monomer, monomer peptide, a monomeric unit or subunit, a monomeric peptide, and the like. Sometimes the monomer includes a chemical moiety, that is not a natural or unnatural amino acid, interspersed within the carbon backbone of the string of amino acids (natural and/or unnatural. In other words – a chemical moiety that is not an amino acid will only be given an X position within a sequence formula if is not at the terminal ends of the peptide string (as such non-amino acid moieties present at a terminal end of a peptide string are identified as R1 or R2 within a sequence formula). A monomer of the invention can have a linear structure or comprise a cyclic structure. See Section 2A below regarding cyclic structures. A monomer of the invention can also be part of a multimeric molecule, whether a homodimeric molecule, a heterodimeric molecule, or other multimers such as homotrimers and homotetramers. Multimeric molecules can be formed by joining monomer subunits by any conventional means. In some embodiments, dimeric molecules are formed by covalently linking monomers directly, or indirectly through a dimerization linker molecule. See Section 2B below regarding dimers. For trimers and tetramers, multimerization linkers with multiple equivalent reactive ends (see, e.g., TAEP (for trimerization) or TetN3 (for tetramerization) in Table 1) are used. It is desired that the peptide compounds of the invention demonstrate significant potency in inhibiting or neutralizing human IL-17 function. See Section 2C. Additionally, the peptide compounds may exhibit potential for oral administration as reflected by time of stability in assays that simulate gastric and intestinal conditions. See Section 2C. However, peptide compounds that do not exhibit stability in such assays are still suitable for other modes of administration, *e.g.*, subcutaneous injection or intravenous injection.

[00275] For all Formulas (including SEQ ID NOs) of the invention, the sequence can comprise natural and unnatural amino acids, as well as chemical moieties that are not natural or unnatural amino acids. Abbreviations for unnatural amino acids and chemical moieties are provided in Table 1. The sequences reflect a linear monomer peptide sequence and do not necessarily reflect the secondary structure of the peptide compound. Table 1 provides information for when the linear monomer peptide sequence underlies a cyclic peptide structure and/or a dimeric (or other multimeric) structure. When the peptide-based compounds comprise a cyclic structure, at least two positions in the linear peptide sequence will be connected or cross-linked, whether through a direct covalent linkage or through an indirect covalent linkage (where at least two positions in the peptide sequence each make an independent covalent linkage with a cyclization linker). Further, when the peptide monomers are part of a dimeric (or other multimeric) peptide complex, Table 1 provides the dimerization (or other multimerization) information. At least one position from each monomer will be covalently connected to each other directly, or more often, indirectly through a covalent linkage with a dimerization/multimerization linker. The peptide compositions of the invention can comprise linear peptide monomers, linear peptide dimers, cyclic peptide monomers, cyclic peptide dimers, and other linear or cyclic multimers.

[00276] For the Formulas, including the SEQ ID NO formulas, the R¹ (or R₁) and R² (or R₂) positions represent non-amino acid (natural or unnatural) chemical moieties that are present on the terminal ends of the linear amino acid sequence. In most embodiments, R¹ represents a chemical moiety present at the N-terminus (or left terminus) of a monomeric peptide string, wherein R¹ is R^a-C(O)- or hydrogen, wherein R^a is C₁₋₂₀ alkyl or C₃₋₈ cycloalkyl. A common R¹ group is an acetyl (Ac) or isovaleric acid (IVA) group. Sometimes R¹ is absent. In most embodiments, R² represents a chemical moiety present at the C-terminus (or right terminus) of a monomeric peptide string, wherein R² is NH₂ or OH. Sometimes R² is absent. In some embodiments, the R₁ and R₂ options presented in Formula (I) can be applied for any peptide of the invention.

[00277] A generic formula for the peptide monomers of the invention is a peptide sequence of Formula (I):

R¹-X00-X0-X1-X2-X3-X4-X5-X6-X7-X8-X9-X10-X11-X12-X13-X14-X15-X16-R²,

wherein:

R^1 is R^a -C(O)- or hydrogen, wherein R^a is C_{1-20} alkyl or C_{3-8} cycloalkyl; or R^1 is acetyl,
 1Pip_AceticAcid, cyclohexanecarboxylic acid, glutaric_Acid, isovaleric acid,
 Mor_propanoic_acid, 1PEG2_1PEG2_IsoGlu_C12, 1PEG2_1PEG2_IsoGlu_C12_Diacid,
 1PEG2_1PEG2_IsoGlu_C18_diacid, 1PEG2_1PEG2_IsoGlu_Palm,
 1PEG2_1PEG2_Ahx_C18_Diacid, 1PEG2_PEG2_Ahx_Palm, or absent;
 R^2 is NH_2 or OH or absent;
 X_{00} is Cha, dK, Ogl, Tle or absent;
 X_0 is 2Pal, 3Pal, Aib, Asn, d2Pal, d3Pal, dA, dE, dF, dH, dK, dL, dQ, dS, Gln, Glu, Glu_OMe,
 His, Ile, Lys, Lys_1PEG2_1PEG2_IsoGlu_C12, Lys_1PEG2_1PEG2_IsoGlu_C18_diacid,
 Lys_1PEG2_1PEG2_IsoGlu_Palm, Lys_Me3, NMe_His, Orn, Pro, Sar, Thr, Tle, or absent;
 X_1 is 1Nal, Bip, Cha, Chg, Cyclopropyl_Ala, Dgl, DIP, dI, hCha, hF, hhF, Ile, Lys,
 Lys_1PEG2_1PEG2_IsoGlu_C18_diacid, Lys_1PEG2_1PEG2_IsoGlu_C12,
 Lys_1PEG2_1PEG2_IsoGlu_Palm, Ogl, Phe_4Me, Tba, Tle, Val, or absent;
 X_2 is 2Pal, 3Pal, aMe_Arg, Agb, Agp, bhF, Cit, Dab, Dab_Ac, Dab_2HyAc, Dab_Ms,
 Dab_Ts, dDab2HyAc, dH, dT, Glu, Gln, His, hR, Hse, Lys, Lys_1PEG2_Ac,
 Lys_1PEG2_1PEG2_C18_diacid, Lys_1PEG2_1PEG2_IsoGlu_C12, Lys_Ac, Lys_Dimethyl,
 Lys_Me3, Lys_PEG2_Me3, Lys_1PEG2Ac, Lys_2HyAc, LysMPA, Lys_Ms, Lys_Ns,
 Lys_Ts, NMe_Thr, Orn, Orn_Ac, Orn_Ms, OrnPVA, Orn_Ts, Phe_2Ad, Phe_3Ad, Phe_4Ad,
 Phe_4_2ae, Phe_4ad, Phe_4-COOH, Phe_4-Cl, Phe_4guan, Phe_4OMe, Phe_4_Morph,
 Phe_pentaF, Q_NHMe, Q_NMe2, Q_Pyro, Q_EtOMe, Q_MecPro, Tet1, Thr, or Thi;
 X_3 is Ala_cycBu, AlaCF3, AlaCHF2, Aoc, bhV, Cha, Chg, Cprg, Cpg, cyclopentyl_Ala,
 cyclopropyl_Ala, Cys, Dgl, DiethylGly, dL, dV, H_Cha, Hcy, hL, Hph, Igl, Nle, NMe_Leu,
 nVF3, O4S, O5S, Ogl, Phe_4tBu, Phe_4Cl, Phe_4-OMe, Phe_4-Me, Phe_3_4-Cl2
 [Phe_34diCl], Phe_4-CF3, Peptoid_CH2_V, Pra, Tba, Tle, or Val;
 X_4 is Asn, dT, Dab, Gln, Glu, Glu_OMe, hE, His, hR, Lys_Me3, Orn, Phe4-COOH,
 Phe_4_Morph, Tet1, Thr, or Thr_Me;
 X_5 is Abu, aMe_Lys_Ac, Cha, Cys, Chg, Dab_Acetyl, dI, dLys_Ac, Glu, Hcy, hE, Hhc,
 HhPen, Ile, Lys, Lys_Ac, LysN3, LysPhAc, NMe_Lys_Ac, O2S, O3S, O3S_Reduced,
 O4S_Reduced, O5S, O5S_Reduced, Orn_Acetyl, or Pen;

X6 is 4R_BenzyloxyPro, 4RPhePro, 4S_Amp, 4S_Amp_Cyclhex, 4S_Amp_Hex, 4S_Amp_IVA, 4S_Amp_tBu, 4SCF3Pro, 4ScyclohexPro, 5RPhePro, Azetidinone, Dfp, dP, Hpr, Oic, or Pro;

X7 is Acvc, Aib, Ala, aMe_Phe, Arg, Aze, Cys, Dab, dC, Gln, Glu, His, Hpr, hR, Lys_1PEG2_1PEG2_Ahx_C18_Diacid, Lys_1PEG2_1PEG2_IsoGlu_C12, Lys_1PEG2_1PEG2_IsoGlu_C18_diacid, Lys_1PEG2_1PEG2_IsoGlu_Palm, Lys_Ac, O3S, O3S_Me, O4S, Pro, Ser, Tba, or Tic;

X8 is aMe_Asp, aMe_Glu, Asp, dD, Gla, Gln, Glu, Phe_3COOH, Phe_4COOH, Tet1, or Tet2;

X9 is Aoc, Cha, Cys, Dgl, hCha, Hcy, Leu, Nle, O3S, O3S_Reduced, O6S, Ogl, Phe_34diF, Phe_4CF3, or Tba;

X10 is 1Nal, 2Nal, Aib, aMe_Phe, aMe_Trp, Aoc, Cys, DIP, dW, hCha, Gln, Hph, Lys_1PEG2_1PEG2_IsoGlu_C12, Phe, Phe_34diCl, Phe_3Ad, Phe_4ad, Phe4_COOH, Phe_4OMe, Phg, Tba, Tle, Trp_4Cl, Trp_4Me, Trp_5Cl, Trp_5CONH2, Trp_5Et, Trp_5Me, Trp_6CF3, Trp_6Cl, Trp_6CONH2, Trp_6Me, Trp_7Cl, Trp_7Me, Trp_7Phe, or Trp;

X11 is Aib, aMe_Asp, aMe_Leu, aMe_Phe, Asn, Asp, Cys, Chg, dA, dS, Gln, Glu, Hcy, Leu, Lys_1PEG2_1PEG2_IsoGlu_C12, Lys_Ac, Lys_Me3, O3S, O3S_Me, O4S, Phe_4Ad, Phe_4tBu, Ser, Tba, or Tle;

X12 is 1Nal, aMe_Trp, Hph_34diCl, Orn_Bz, Trp, Trp_4Cl, Trp_5Br, Trp_5Cl, Trp_5Et, Trp_5Me, Trp_56diCl, Trp_56diMe, Trp_6Cl, Trp_6CF3, Trp_6Me, or Trp_7Cl;

X13 is Abu, aMe_Cys, aMe_Lys_Ac, Cys, Cha, Dab_Acetyl, Glu, Hcy, hE,,Hhc, HhPen, Ile, Lys, Lys_Ac, LysN3, O2S, O3S, O3S_Me, O3S_Me_Reduced, O3S_Reduced, O4S_Reduced, Orn_Acetyl, or Pen;

X14 is Aib, Arg, Asn, Cys, dE, dF, dH, dK, dL, dN, dQ, dR, Gln, Glu, Lys,

Lys_1PEG2_1PEG2_IsoGlu_C12, Lys_Ac, Lys_Hexy, Lys_PEG12_NH,

Lys_PEG4_PEG4_NH2, O3S, O3S_Me, Orn_Acetyl, PEG12, Tba, or absent;

X15 is dE, dK, dR, Glu, Lys, Lys_PEG4_PEG4_NH2, Lys_Dimethyl, Pro, or absent; and

X16 is dE, dF, dH, dK, dL, dR, dQ, Lys, Lys_1PEG2_1PEG2_IsoGlu_C12, Lys_1PEG2_1PEG2_IsoGlu_Palm, Lys_PEG4_PEG4_NH2, Lys_Ac, or absent;

wherein:

(i) the peptide optionally comprises a cyclic structure wherein at least two amino acid residues in the peptide (monomer) are either: (a) directly covalently linked, or (b) indirectly covalently linked through a cyclization linker;

(ii) the peptide is optionally a monomer in a homodimer or heterodimer complex, wherein each monomer is directly covalently linked to each other, or indirectly covalently linked to each other through a dimerization linker; and/or

(iii) the peptide is optionally conjugated with a half-life extension moiety.

(Formula (I).)

[00278] To the extent that a Formula is described differently between different parts of the application, the Formulas should be reconciled by over-inclusion. For example, if a Formula in one part of the application states that a particular X position can have a residue not described for the same Formula in another part of the application, then the Formula should include the residue.

[00279] To provide a representative scope of the invention, Figure 1 (i.e., Figure 1.1 et al.) presents biochemical and functional information for over 800 different peptide-based compounds that are all potent (at least nanomolar) inhibitors of human IL-17 cytokines. These compounds include monomeric linear peptide compounds, dimeric linear peptide compounds, monomeric cyclic peptide compounds, dimeric cyclic peptide compounds, trimeric cyclic peptide compounds, and tetrameric cyclic peptide compounds, all of which have an IC₅₀ of 20 nM or less in at least the human IL-17AA HEK Blue Assay. Accordingly, all of the peptide compounds described in Figure 1 are potent inhibitors of human IL-17 and have therapeutic potential as injectable compounds. A large subset of these potent compounds also show potential for oral administration and oral formulation given their stability as measured by half-life time (T_{1/2}) in SGF and/or SIF assays.

[00280] In some embodiments, the invention also provides specific selections (or substitutions) that can be applied to the Formulas herein and to the peptides described in Figure 1:

[00281] In some embodiments, R1 is acetyl, 3-hydroxypropionic acid, C6_diacid, cyclopropanecarboxylic acid, glutaric acid, isovaleric acid, or methanesulfonyl acetic acid.

[00282] In some embodiments, R1 is substituted for Hexafluoro_Isovaleric acid.

[00283] In some embodiments, X00 is dH.

[00284] In some embodiments, X0 is dE, dH, Glu, His, Ile, Tle, or Sar.

[00285] In some embodiments, X1 is Ile or Val.

[00286] In some embodiments, X1 is Tle.

[00287] In some embodiments, X0 is His or dH, and X1 is 1Nal, hF, hhF, or Phe_4Me.

[00288] In some embodiments, X2 is Gln, His, or Lys_Me3.

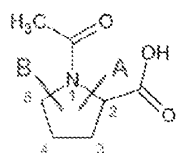
[00289] In some embodiments, X3 is Tba, Tle, or Val.

[00290] In some embodiments, X4 is Asn, hE, Glu, Glu_OMe, or Thr.

[00291] In some embodiments, X5 and X13 are directly or indirectly cross-linked. In some embodiments, the direct cross-link can be a disulfide bond between X5Hhc and X13Hhc, a carbon-carbon single bond between X5O3S_Reduced- and X13O3S_Reduced or X13O3S_Me_Reduced, or a carbon-carbon double-bond between X5O3S and X13O3S or X5O3S and X13O3S_Methyl. In some embodiments, the indirect cross-link can be mediated by a Dimethylcyclopropane_Linkers, a Pentane_Linkers, or a Propane_Linkers with X5Hcy-X13Hcy or X5Cys-X13Cys.

[00292] In some embodiments, X6 is Oic.

[00293] In some embodiments, X6 is an Oic analog residue having the structure:



wherein either A or B or both are present, and wherein A and B are both attached to position 4 and/or 5. A and B can be identical or different, and comprises a small hydrophobic group. In one related embodiment, A and B result in a fused carbocyclic or heterocyclic ring system between positions 3 and 4, or 4 and 5.

[00294] In some embodiments, X6 is the Oic analog 45cHept_Pro, 45cOct_Pro, Oic_4CF3, Oic_5CF3, Oic_5Me, Oic_6Me, or Oic_6CF3.

[00295] In some embodiments, X7 is Acvc, Ala, Gln, Glu, Lys_Ac, Pro, Ser, or Tba.

[00296] In some embodiments, X8 is Asp or Gla.

[00297] In some embodiments, X9 is Dgl, Ogl, or an analog of Ogl with a hydrophobic side-chain comprising an alkane chain of 6-20 CH₂ moieties, either straight-chain or branched.

- [00298] In some embodiments, X9 is the Ogl analog Trifluoro_Ogl, Ddgl, or Phenyl_Hgl.
- [00299] In some embodiments, X6 is Oic and X9 is Dgl or Ogl.
- [00300] In some embodiments, X10 is 1Nal, 2Nal, or Trp.
- [00301] In some embodiments, X10 is Phe_4COOH, Phe_4ad, Trp_7Me, or Trp_7Phe.
- [00302] In some embodiments, X10 Aoc.
- [00303] In some embodiments, X11 is Aib, Asp, or Glu.
- [00304] In some embodiments, X11 is Ser or Phe_4ad.
- [00305] In some embodiments, X12 is aMe_Trp or Trp.
- [00306] In some embodiments, X12 is Trp_5Cl.
- [00307] In some embodiments, X14 is dK, Lys, Lys_PEG4_1PEG2_NH2, Lys_PEG8_NH2, or Lys_PEG4_PEG4_NH2.
- [00308] In some embodiments, X15 is dR.
- [00309] In some embodiments, X16 is dE.
- [00310] In some embodiments, a peptide has two intramolecular cross-links at X5-X13 and X10-X14. In related embodiments, X5-X13 are both O3S and are directly covalently attached through a carbon-carbon double bond, and X10-X14 are both Cys and are indirectly cross-linked through a Xylene_Linkers or a Propane_Linkers. In related embodiments, X5-X13 are both Hcy and are indirectly cross-linked through a Propane_Linkers, and X10-X14 are directly covalently linked through a carbon-carbon double bond and are individually, or both, O3S or O3S_Me.
- [00311] In some embodiments, X14 and X15 are absent (and any other residues C-terminal to X14 or X15 are also absent if present in a peptide to be modified).
- [00312] The invention contemplates that any monomer described in Figure 1 (e.g., by the SEQ ID NOs) or by any of the peptide Formulas herein, can be part of a homodimer or heterodimer or other multimeric composition. In other words, any peptide monomer of the invention may be part of homodimer or heterodimer or other multimeric complexes, including any combination of two or more different monomers from Figure 1. Likewise, any dimer or other multimeric compound of Figure 1 that has a monomer that is not already described as a separate monomeric compound, the invention encompasses such monomeric peptide compounds. The invention also extends to linear counterparts of the cyclic peptides of the invention. For

example, the linear counterparts would not have side chains or other reactive substituents cross-linked between X5-X13, X9-X13, X7-X11, and/or X10-14. Furthermore, the invention contemplates variants of the monomers described in Figure 1 (including if the monomer is part of a dimer or other multimeric compound), including variants with one conservative substitution at X00 through X16, two conservative substitutions at X00 through X16, or three or more conservative substitutions at X00 through X16. In some embodiments, the invention contemplates variants of the monomers described in Figure 1, where in some embodiments, conservative substitutions are not allowed at cyclization positions (if cross-linked residues are described for the peptide). In some embodiments, the invention includes variants of the monomers described in Figure 1, where 1, 2, 3, 4, 5, or more residues are substituted with an analog of the amino acid (e.g., if the residue is a Tyr, then it can be substituted with an analog of Tyr; if the residue is already an analog of Tyr, then it can be substituted with a different analog of Tyr). In some embodiments, the invention encompasses peptide compounds comprising a monomer peptide that has at least 90%, 91%, 92%, 93%, 94%, or 95% sequence identity, or the monomer peptide comprises at least 10, 11, 12, 13, or 14 identical amino acids when aligned to a primary monomer sequence of Figure 1 (i.e., alignment of linear sequences).

[00313] In some embodiments, as reflected by human IL-17 HEK Blue IC₅₀ values in the about 20 nM range or less, peptides comprising a cyclic structure can exhibit high potency against one or more human IL-17 cytokine isoforms. In some instances, a peptide of the invention has a human IL-17 HEK Blue IC₅₀ value less than about 10 nM, less than about 5 nM, or less than about 1 nM.

[00314] In some embodiments, a peptide of the invention has a half-life time greater than about 0.5 hours, 1.0 hours, 1.5 hours, or 2 hours in a SGF and/or SIF stability assay.

[00315] In some embodiments, a peptide of the invention has an IC₅₀ value in a human IL-17 HEK Blue assay of about 20 nM or less, of about 10 nM or less, of about 5 nM or less, or about 1 nM or less, *and* a half-life time greater than about 0.5 hours, 1.0 hours, 1.5 hours, or 2 hours in a SGF and/or SIF stability assay.

[00316] In some cases, peptides comprising a cyclic structure have greater potency as compared to a cyclic peptide's linear form (see, e.g., Figure 1 of compounds sharing the same

peptide sequence, i.e., SEQ ID NO, but where one of the compounds is linear and the other is cyclized).

[00317] In some embodiments, linear peptide compounds, whether in monomeric or dimeric form, are suitable for oral administration, as many exhibit half-lives greater than 0.5 hours, 1.0 hours, 1.5 hours, or 2 hours, in an SGF and/or SIF assay (see Figure 1).

[00318] In some embodiments, a peptide comprising a cyclic structure can be more suitable for oral administration as compared to the same peptide without intramolecular cross-links between two or more positions, when the cyclic compound exhibits more stability as compared to its linear form in a Simulated Gastric Fluid (SGF) and/or a Simulated Intestinal Fluid (SIF) assay (see e.g., Example 7 and Figure 1). A peptide compound exhibits stability in these assays if its half-life is greater than: 0.5 hours, 1.0 hours, 1.5 hours, or 2.0 hours. SGF and SIF stability assays are commonly used to assess the degradation of drugs in simulated stomach and intestinal environments, respectively. Accordingly, peptides that exhibit increasing stability times in these assays have potential as a pharmaceutical drug for oral administration. See Section 2C below. In some embodiments, peptides comprising a cyclic structure can exhibit both high potency and stability. See Section 2C.

[00319] In some embodiments, homodimeric peptide compounds can exhibit greater potency and/or stability as compared to their corresponding monomer compounds, whether the monomer comprises a cyclic structure or is linear. In some embodiments, homodimeric cyclic peptide compounds can exhibit greater potency and/or stability as compared to their corresponding cyclic peptide monomer compounds. (See, e.g., compare potency and stability data between dimer and monomer compounds having the same monomer SEQ ID NO.)

[00320] Thus, the peptide compounds of the invention can be organized or classified by one or more structural and/or functional features. To the extent that the instant teachings do not already explicitly describe structural or functional features for a peptide sequence Formula herein, then the Formula may be sub-categorized into progeny Formula based on structural and/or functional requirements. Typically, sub-category formulas generated by the requirement of additional structural and/or functional features narrows the available residue options set forth by a peptide sequence Formula. See, for example, Formula (III) and its related sub-category formulas Formula (III.A) *et al.* Therefore, any peptide sequence Formula described herein may

be divided into related sub-formulas by requiring the peptide to have one or more of the following structural or functional features (to the extent said Formula does not already require the features(s)): (1) cyclic structure or linear structure (no intramolecular cross-linking between different residues of the monomer peptide sequence), (2) for cyclic peptides, the position of the cross-linked pairs of residues in the peptide sequence Formula, *e.g.*, X5-X13, X7-X11, X9-X13, and X10-X14, (3) the type of chemical bond of the cross-link, *e.g.*, amide, disulfide, thioether, carbon-carbon single bond, carbon-carbon double bond, (4) a direct covalent link between the cross-linked pairs of residues or an indirect covalent link between the cross-linked pairs of residues, (5) the type of cyclization linker mediating the indirect covalent link, (6) if the peptide sequence underlies a monomer of a dimer, (7) for dimers, the position of the residue on each monomer that is linked to a dimerization linker, (8) the type of dimerization linker, (9) the level of potency in a human IL-17 HEK Blue assay, (10) the level of potency in a human IL-17 HEK Blue assay against one or more human IL-17 cytokine isoforms, and (11) the half-life time in an SGF and/or SIF assay.

[00321] 2A. Cyclic Structure

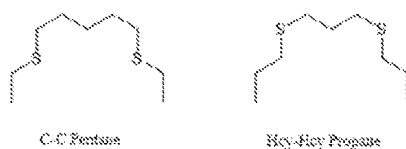
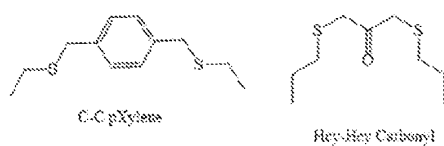
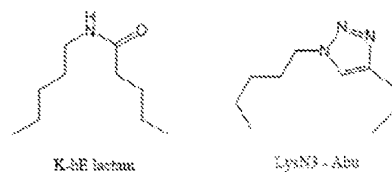
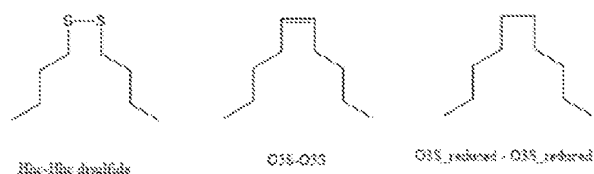
[00322] The instant peptides can have a “cyclic” structure that comprises a ring with greater than 8, 9, 10, 20, 30, 40, 50, 60, 70, 80, 90, or 100 atoms or more. The cyclic structure can comprise a single ring or multiple rings (*e.g.*, a bicyclic structure). Figure 1 identifies numerous peptide compounds of the invention with cyclic structures, and the two-dimensional (2D) chemical structure for such peptide compounds can be visualized through standard translation of their SMILES code, which is also present in Figure 1. In addition, Figure 1 includes linear peptides, *i.e.*, non-cyclic peptides, and in some embodiments, these can be cyclized according to whether their positional residue content corresponds to the X5-X13, X9-X13, X7-X11, and X10-X14 scaffold requirements described below.

[00323] In most embodiments, a peptide is cyclized by covalently linking, *i.e.*, “cross-linking,” any two positions of a peptide monomer (*i.e.*, R₁, X0 through X16, and R₂, of a peptide of Formula I), directly or indirectly through a cyclization linker to form a cyclic peptide. This can be done in different ways depending on the type of chemical moieties or amino acids to be cross-linked: head-to-tail cyclization (N- to C-terminal), head-to-side chain cyclization, side-chain-to-tail cyclization, and side-chain-to-side-chain cyclization.

[00324] In some embodiments, a peptide is cyclized by (a) directly linking the side chains of two amino acid residues to form an amide bond, (e.g., -NHC(O)- or -C(O)NH-, i.e., when an intramolecular cross-link between the side chains of two amino acids creates an amide bond and a cyclic structure for a portion of the peptide, this is referred to as a bond – which occurs when there is a coupling between an amine and a carboxylic acid within the same peptide molecule – whether side-chain to side-chain, head to side-chain, tail to side-chain, or head to tail), a disulfide bond (e.g., -S-S-), a thioether bond (e.g., -C-S-C-), a carbon-carbon single bond (e.g., -CH₂-CH₂-), or a carbon-carbon double bond (e.g., -CH=CH-); or (b) linking the side chains of two amino acids through a cyclization linker to form two thioether bonds, one between the side chain of one of the amino acids with a chemical group of the linker and one between the side chain of the other amino acid with a different chemical group of the linker. In other embodiments, a peptide has a cyclic structure comprising an intramolecular cross-link between two amino acid residues (or between two amino acid residues via a cyclization linker) that comprises a lactam, an olefin, a triazole (e.g., click chemistry), a selenoether, or a diselenide bond.

[00325] Whether the cyclization is direct or indirect, representative pairs of chemical moieties for cross-linking are: an amine group and a carboxylic acid group to form an amide bond (a lactam when the amide bond forms a cyclic structure, i.e., a cyclic amide; as opposed to amide bond based dimerization of peptide monomers, where the amide bond is not part of a linkage forming a cyclic structure); two thiols groups to form a disulfide bond; a thiol group and an alkyl group to form a thioether bond; two alkenyl groups to form a carbon-carbon double bond; and carbon-carbon double bond can be reduced to a carbon-carbon single bond.

[00326] In addition to Figure 1, which indicates the type of cyclization chemistry (if cyclized) for each peptide, and the person of ordinary skill can determine the structure and therefore type of bond(s) of the intramolecular cross-link through the conversion of the provided SMILES code of the peptide compound into two-dimensional structure. Figure 6 provides two-dimensional depictions of several compounds of the invention, and these chemical structures show some of the main types of cyclization chemistry used herein. In addition, representative cross-links of cyclized peptides are shown below:



[00327] In other embodiments, the peptide is cyclized by covalently linking two pairs of any two residues in the monomer, or any of three of the residues, directly or indirectly through a cyclization linker to form a bicyclic peptide.

[00328] In some embodiments, the peptide is cyclized at positions X5-X13 (herein, when describing cyclization, the notation X#-X# means that the residues at these two positions are cross-linked and it does not mean a range of positions), X7-X11, X9-X13, or X10-X14. These cyclization positions are sometimes referred to as “scaffolds” to describe different structural categories for cyclic peptides of the invention. Cyclization at these pairs of positions involve either direct side-chain to side-chain covalent linkages or “indirect” side-chain to linker

covalent linkages. For example, the notation X5-X13 indicates that the residues at position X5 and position X13 are directly or indirectly covalently linked or “cross-linked”, thereby forming a cyclic structure. If a peptide is described as having both X5-X13 and X7-X11 or X5-X7-X11, then this indicates two separate cross-links that form a bicyclic structure.

[00329] 2A.1 Cyclic Structure – Directly Cross-Linked Scaffold Structures

[00330] In some embodiments of the compounds of Formula (I), a peptide comprises a cyclic structure comprising two cross-linked amino acids at residues at X5 and X13, X7 and X11, X9 and X13, or X10 and X14, which two amino acid residues are directly covalently linked through a disulfide bond, a thioether bond, a carbon-carbon double bond, or a carbon-carbon single bond.

[00331] In some cases, when the two cross-linked amino acid residues are at X5 and X13 or X9 and X13, the two amino acids are directly covalently linked through a disulfide bond. The two amino acid residues cross-linked through a disulfide bond can be, for example, both or individually, Hhc, Hcy, Pen, hhPen, or Cys (or their D-amino acid or α -methyl variant form). Other residues with a free thiol group may also be suitable for disulfide bond cross-linking. In some cases, the disulfide bond cross-linked residues are: both Hhc at X5 and X13, both Hcy at X5 and X13, Hcy at X5 and Cys at X13, or Hcy at X9 and Hhc at X13. Representative examples of cyclic peptide compounds with these types of cross-linked monomers are listed in Figure 1 (see cyclization information); SEQ ID NOs are for the monomer sequence.

[00332] In some embodiments, for any of the Compounds that have a disulfide cross-link, these Compounds can be modified to include a Cyclization Linker connecting the side chains of the two cyclization residues such that the cross-link is indirect between the two residues and such that the cross-link comprises a thioether bond between the Cyclization Linker and each side-chain.

[00333] In some cases, when the two directly cross-linked amino acid residues are at X5 and X13, X7 and X11, X9 and X13, or X10 and X14, the two amino acids are directly covalently linked through a thioether bond. The two amino acid residues directly cross-linked through a thioether bond can be, for example, a residue with a free thiol in its side chain such as aMe_Cys, Cys, Hhc, Hcy, Pen, or HhPen, with a residue with a free alkyl in its side chain such as aMe_Lys_Ac, Dab_Acetyl, Dap_Ac, dLys_Ac, NMe_Lys_Ac, Lys_Ac, Lys_PEG12_Ac, LysPhAc, O2S_Reduced, O3S_Reduced, O4S_Reduced, or O5S_Reduced, or Orn_Acetyl. In

some cases, the D-form of the amino acid or its α -methyl variant can be used. The invention contemplates other types of residue pairs, where one member of the pair has a free thiol group and the other member of the pair has a free alkyl group, including an acetyl comprising a free alkyl group, such that direct cross-linking of these side chains results in a thioether bond. Figure 1 provides numerous representative examples of peptide compounds with side-chains directly cross-linked through a thioether bond.

[00334] In some cases, when the two directly cross-linked amino acid residues are at X5 and X13, X7 and X11, X9 and X13, or X10 and X14, the two amino acids are directly covalently linked through a carbon-carbon double bond. The two amino acid residues cross-linked through a carbon-carbon double bond can be, for example, both or individually, O2S, O2S_Methyl, O3S, O3S_Methyl, O4S, O4S_Methyl, O5S, or O5S_Methyl. Other residues with a free alkenyl group may also be suitable for carbon-carbon double bond cross-linking. Representative examples of cyclic peptide compounds with these types of cross-linked monomers are provided in Figure 1.

[00335] In some cases, when the two directly cross-linked amino acid residues are at X5 and X13, X7 and X11, X9 and X13, or X10 and X14, the two amino acids are directly covalently linked through a carbon-carbon single bond. The two amino acid residues cross-linked through a carbon-carbon single bond can be, for example, both or individually, O2S_Reduced, O3S_Reduced, O3S_Me_Reduced, O4S_Reduced, or O5S_Reduced. Other residues with a free alkyl group may also be suitable for carbon-carbon single bond cross-linking – where double bonds are first formed and then reduced to a single bond. Representative examples of cyclic peptide compounds with these types of cross-linked monomers are provided in Figure 1.

[00336] In another embodiment, when the two directly cross-linked amino acid residues at X5 and X13 (or at X7-X11, X9-X13, or X10-X14), the two amino acids are directly covalently linked through an amide bond (cyclic amide or lactam). The two amino acid residues are suitable for amide bond cyclization if one has a side chain with a free amine and the other with a free carboxylic acid, such as Lys paired with Glu, hE, or Asp. Hence, in one embodiment, one of X5 and X13 is Lys and the other is Glu, hE, or Asp. Representative examples are provided in Figure 1.

[00337] In another embodiment, when the two directly cross-linked amino acid residues at X5 and X13 (or at X7-X11, X9-X13, or X10-X14), two directly cross-linked amino acid residues are X5LysN3 and X13Abu, or X5Abu and X13 LysN3. The side chains of these two amino acids are directly covalently linked. Specifically, a hydrogen from theazole ring of LysN3 reacts with a free hydroxyl from Abu to form the cross-link as shown in paragraph [00324]. Representative examples are provided in Figure 1.

[00338] In one embodiment, the invention provides a peptide monomer comprising the sequence of Formula (I), but further comprises X17-X22, wherein: X16 is PEG4, PEG6, PEG8; X17 is Ile or Gly; X18 is His or Ile; X19 is His or Val; X20 is Thr or Val; X21 is Ile or Thr; and X22 is Ile or absent. In this embodiment, R2 would follow X22.

[00339] 2A.2 Cyclic Structure – Indirectly Cross-Linked Scaffold Structures

[00340] In some embodiments of the compounds of Formula (I), a peptide comprises a cyclic structure comprising two indirectly cross-linked amino acids at residues at X5 and X13, X7 and X11, X9 and X13, or X10 and X14, which two amino acid residues are indirectly covalently linked through a thioether bond with a cyclization linker that comprises at least two free methyl (CH₃) or alkyl groups that can form covalent bonds with a thiol group from the side chains of the two amino acid residues. Representative cyclization linkers suitable for (bis- or di-)thioether cross-linking include a Butane_Link, a Carbonyl_Link, a Dimethylcyclopropane_Link, a Ebutene_Link, a Hexane_Link, a Methylene_Link, an Oxetane_Link, a Pentane_Link, a Propane_Link, an mXylene_Link, a pXylene_Link, or an oXylene_Link, as described in Table 1. Other cyclization linkers are contemplated, such as other alkane or alkene linkers with terminal -CH₃ moieties, or linkers comprising a ring structure with at least two methyl groups on different carbon positions of a ring structure (or linkers with at least two free methyl groups that are situated at least two backbone carbons apart).

[00341] In some cases, when the two cross-linked amino acid residues are at X5 and X13, X7 and X11, X9 and X13, or X10 and X14, the two amino acids are indirectly cross-linked through a cyclization linker that is mXylene_Link, pXylene_Link, or oXylene_Link, and where each residue of the pair makes a direct covalent bond with the cyclization linker forming a thioether bond. The two amino acid residues cross-linked through a thioether bond with the

cyclization linker can be, for example, individually or both Cys dC, Hcy, Hhc, HhPen, or Pen. Other amino acids with a thiol side chain may be suitable. Representative examples are provided in Figure 1.

[00342] In some embodiments, when the two cross-linked amino acid residues are at X5 and X13, X7 and X11, X9 and X13, or X10 and X14, the two amino acids are indirectly cross-linked through a cyclization linker that comprises an alkane or an alkene with at least two free methyl (CH₃) or alkyl groups (at least one at each terminal end of the linker) that can form covalent bonds with a thiol group from the side chains of the two amino acid residues, such as a Butane_Link, a Carbonyl_Link, a Dimethylcyclopropane_Link, an Ebutene_Link, a Hexane_Link, a Methylene_Link, an Oxetane_Link, a Pentane_Link, or a Propane_Link, (see Table 1). The two amino acid residues cross-linked through a thioether bond with the cyclization linker can be, for example, individually or both Cys, dC, Hcy, Hhc, Pen, or hhPen. Other linkers and other amino acids with thiol containing side chains may be suitable as taught herein. Representative examples of cyclic peptide compounds with these types of cross-linked monomers are provided in Figure 1.

[00343] 2B. Dimers

[00344] The main subunit of the instant peptide-based compositions is a monomeric peptide. Any monomeric peptide can be readily made into a homodimer or heterodimer or other multimeric compound. Two monomer units can be directly or indirectly linked together at any position, i.e., R1-X00...X16-R2. For example, head-to-tail dimerization would involve forming a covalent bond between R1 of one monomer and R2 of the other monomer, whether directly or through a dimerization linker. Side-chain to side chain dimerization would involve forming a covalent bond between an X position side-chain of one monomer and an X position side-chain of the other monomer, whether directly or through a dimerization linker. Head to side-chain and tail to side-chain dimerization is also contemplated. The peptide dimer can comprise linear or cyclic monomers.

[00345] In another aspect, the present disclosure provides a dimeric peptide or a peptide dimer, which is formed by directly or indirectly covalently linking a peptide comprising or consisting of a sequence of Formula (I) with another peptide comprising or consisting of a sequence of

Formula (I). The two monomer peptides can have the same amino acid sequence (homodimer) or different amino acid sequences (heterodimer).

[00346] . In some embodiments, dimerization linkers for cyclic or linear monomers comprise an unbranched and unsaturated carbon backbone length of at least 10, 20, 30, 40, 50, 60, 70, 80, 90, or 100 carbons.

[00347] In some embodiments, for dimers with cyclic monomers cross-linked at X5-X13, X9-X13, X10-X14, or X7-X11, the monomer units each comprise an amino acid at X14, X15, or X16 that has a free amine group, such as Lys or dK or analogs of Lys (see, e.g., Table 1), that is covalently linked to a dimerization linker. The X14, X15, and X16 position are potentially suitable dimerization positions because they lie outside the cyclic structure formed by the cross-links at X5-X13, X9-X13, X10-X14, or X7-X11. Other potential dimerization positions include the terminal ends and the residues before and after the cyclization positions, e.g., for X5-X13 monomers, R1, X00, X0, X1, X2, X3, X4, X14, X15, X16, R2. The same rationale would apply for X9-X13, X7-X11, and also X10-X14. However, dimerization can occur at any position of a cyclic or a linear monomer given the variety of side-chain structures of natural and unnatural amino acids, the variety of potential linkers, and the option to integrate non-amino acid chemical moieties into the residue string of the monomer.

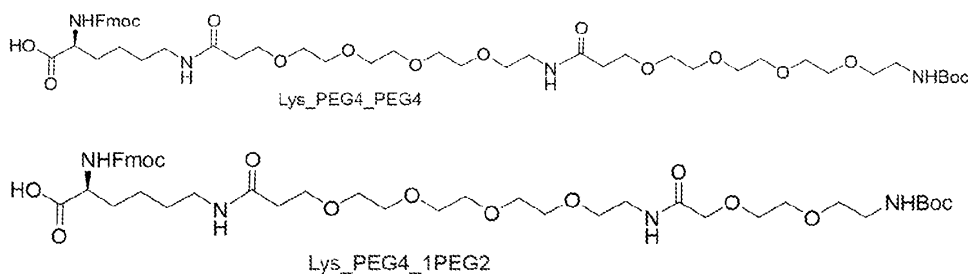
[00348] In some embodiments, whether for linear or cyclic monomers, a dimerization linker comprises a string of multiple PEG subunits $-(\text{OCH}_2\text{CH}_2)_n-$ with functionalized terminal ends. The functionalized terminal ends are covalently attached to each monomer, e.g., through an amide, a thiol, via click chemistry, a lactam, or via any other suitable means known in the art. In some embodiments, a PEG linker is attached through an amide bond and, as such, certain PEG derivatives used will be appropriately functionalized. For example, common PEG linkers have a free amine and/or a free carboxylic acid at their terminal ends for covalent attachment to peptides.

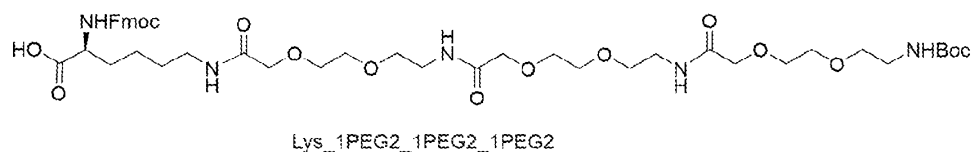
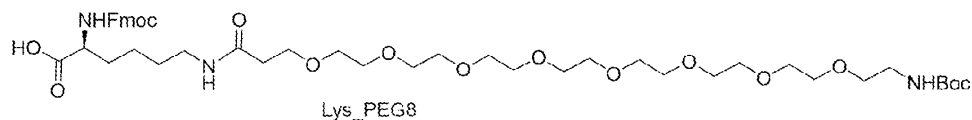
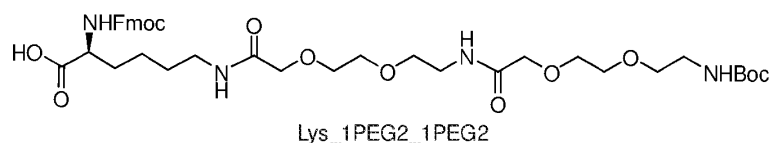
[00349] Accordingly, in some embodiments, dimers comprise two cyclic monomers, each monomer comprising a cyclic structure characterized by cross-links at X5-X13, X9-X13, X10-X14, or X7-X11, and each monomer comprising a Lys or dK at X14 or X16, wherein X14 or X16 is covalently linked to a terminal end of a PEGDA (PEG diacid) linker. In some embodiments, the PEGDA linker comprises between 10-50 PEG subunits (e.g., PEG10DA-

PEG50DA), 10-40 PEG subunits, 10-30 PEG subunits, or 15-25 PEG subunits. In some embodiments, X14 or X16 is Lys in each monomer, wherein X14 or X16 is covalently attached to a terminal end of a PEG21DA or a PEG25DA dimerization linker through an amide bond.

[00350] In some embodiments, two linear monomers are dimerized either directly or through a dimerization linker. For example, two linear monomers each comprising an amino acid residue comprising a free amine can (indirectly) dimerize through a dimerization linker with two free reactive groups (i.e., carboxylic acid groups) such that the amine and carboxylic acid groups can form an amide bond. In some embodiments, the residue is X14K or X14dK and the dimerization linker is a PEGDA linker. A large number of representative compounds have this type of dimerization structure (see Figure 1 for sequence and additional dimerization information).

[00351] In another embodiment, each monomer of a dimer can comprise a residue with a free amine in its side chain such that the free amine can react with a free hydroxyl of a dimerization linker to form an amide bond. For example, X14 can be Lys_PEG4_PEG4_NH₂, Lys_PEG4_1PEG2_NH₂, or Lys_PEG8_NH₂, which have a free amine in their side chains, and the free amine can react with a free hydroxyl at one of the terminal ends of the DIG_Linkers. If each monomer has X14Lys_PEG4_PEG4_NH₂ et al., then each monomer will form an amide bond with the DIG_Linkers, thereby forming a dimer. The ordinary artisan understands that other amino acids are suitable, including other variants of lysine with PEG side chains having a free amine. For example, the following lysine analogs have different combinations of PEG units in the side-chain (the NHFmoc protecting group and the Boc protecting group would be removed prior to dimerization such that NHFmoc becomes NH₂ and the terminal group would be a free amine, e.g., Lys_PEG4_PEG4 below would be Lys_PEG4_PEG4_NH₂):





[00352] Accordingly, in some embodiments, a dimer compound of the invention comprises two monomer peptides each comprising one of the modified Lys residues above (Lys_PEG4_PEG4_NH₂, Lys_PEG4_1PEG2_NH₂, Lys_1PEG2_1PEG2_NH₂, Lys_PEG8_NH₂, Lys_1PEG2_1PEG2_1PEG2_NH₂), wherein the modified Lys residue is attached through an amide bond with a DIG_Linkers.

[00353] In some aspects, a dimer of the instant invention with a PEG linker attached to a lysine can be modified such that the lysine is substituted with Lys_PEG4_PEG4_NH₂, Lys_PEG4_1PEG2_NH₂, or Lys_PEG8_NH₂, and the PEG linker is substituted with a DIG_Linkers.

[00354] In another example, two linear monomers each comprising a residue with a free thiol can be indirectly covalently attached to a dimerization linker with at least two free alkyl groups. For example, the free thiol group of a Cys from each monomer can be reacted with free alkyl groups of a dimerization linker such that each Cys is covalently attached to the dimerization linker through a thioether bond. Other amino acid residues with free thiol groups are suitable for this approach, for example, Hcy and Hhc. Exemplary dimerization linkers with two free and separated alkyl groups include the pBiphenyl_Linkers, the series of Xylene_Linkers, the Ebutene_Linkers, . Representative compounds having this type of dimerization structure include C16, C26, C28, C62, C77, C255, C277, C278, C279, and C280 (see Figure 1 for sequence and additional dimerization information).

[00355] In another examples, two linear monomers comprising a PEG molecule at an internal residue position (i.e., serving as a residue of the linear peptide string rather than as a dimerization linker or a half-life extension moiety) with a free carboxylic acid and an amino acid residue comprising a free amine group can directly dimerize. For example, the carboxylic acid and the free amine from residues on different monomers can form an amide bond. Representative compounds with this type of dimerization include C17 and C23.

[00356] In some embodiments, a homodimer peptide compound exhibits substantially more potency as compared to its corresponding monomeric peptide compound. For example, Table 2 shows a few representative hIL-17 HEK Blue IC50 comparisons between homodimer and monomeric compounds that comprise the same monomer peptide unit. Other comparisons can be made by examining the monomer and dimer peptide compounds in Figure 1 that have the same monomer SEQ ID NO. Potency ratios are with respect to hIL-17AA, unless otherwise noted. Furthermore, in some embodiments, a homodimer peptide compound exhibits more stability as compared to its corresponding monomeric peptide compound in an SGF and/or SIF assay – see Figure 1 and compare monomer and dimer compounds comprising the same SEQ ID NO. Thus, in some embodiments, a peptide homodimer compound exhibits greater than 2-fold, 3-fold, 5-fold, 10-fold, 25-fold, 50-fold, 100-fold, 200-fold, or 300-fold or more potency with respect to a lower IC50 value in a hIL-17 HEK Blue assay as compared to its monomeric form; and such homodimers may further require exhibiting an improved stability as compared to its monomeric form with respect to a greater half-life time in an SGF and/or SIF stability assay.

Table 2 – Exemplary Homodimer v. Monomer Potency Ratios

Dimer Compound	Corresponding Monomer Compound	HEK Blue human IL-17AA IC ₅₀ Potency Ratio (monomer IC ₅₀ divided by dimer IC ₅₀)
C45	(C# not listed in Fig. 1; SEQ ID NO:36 in monomeric form)	107
(C# not listed in Fig. 1; SEQ ID NO:70 in homodimeric form)	C81	349
C78	C82	48
C83	C79	31
(C# not listed in Fig. 1; SEQ ID NO:115 in homodimeric form)	C150	203

C147	C146	27
C86	(C# not listed in Fig. 1; SEQ ID NO:73 in monomeric form)	35
C217	C216	4
C219	C218	3
C314	C343	151
C517	C516	24
C532	C507	137

[00357] 2C. Functional Activity Against IL-17 & Stability

[00358] The peptide compounds of the invention can exhibit nanomolar or sub-nanomolar potency against human IL-17 cytokines, and in some instances, also exhibit stability in simulated gastrointestinal environments. The potency is shown by the nanomolar and sub-nanomolar IC₅₀ values in the human IL-17 HEK Blue Assay. Exemplary structures-function relationships are provided in the Formulas herein.

[00359] In some embodiments, a homodimer peptide compound exhibits an IC₅₀ equal to or less than 10 nM in a HEK Blue human IL-17 assay, wherein the compound has two monomer cyclic peptides both comprising or consisting of the same amino acid sequence from Formula (II):

R₁-X00-X0-X1-X2-X3-X4-X5-X6-X7-X8-X9-X10-X11-X12-X13-X14-X15-X16-R₂,

or a pharmaceutically acceptable salt or solvate thereof,

wherein:

R₁ is acetyl (Ac), 3-hydroxypropionic acid, C₆ diacid, cyclopropanecarboxylic acid, glutaric acid, isovaleric acid, methanesulfonyl acetic acid, 1PEG2_1PEG2_IsoGlu_Palm,

1PEG2_1PEG2_IsoGlu_C18_Diacid, 1PEG2_1PEG2_IsoGlu_C12, or absent;

R₂ is NH₂, OH, or absent;

X00 is dH or absent;

X0 is dE, dH, Gln, Glu, Glu_OMe, His, Ile, Lys_Me3, Sar, Tle, or absent;

X1 is Cha, Chg, Cyclopropyl-Ala, DIP, Ile, Lys_1PEG2_1PEG2_IsoGlu_C12, Ogl, Tba, or Val;

X2 is 2Pal, 3Pal, Agb, Agp, Cit, Dab_Ac, Dab2HyAc, DabMs, DabTs, dDab2HyAc, Gln, Glu, His, hR, Hse, Lys, Lys_1PEG2_1PEG2_C18_diacid, Lys_1PEG2_1PEG2_IsoGlu_C12, Lys_Ac, Lys_Dimethyl, Lys_Me3, Lys_PEG2_Me3, Lys1PEG2Ac, Lys2HyAc, LysMPA, LysMs, LysNs, LysTs, OrnAc, Orn2HyAc, OrnMs, OrnPVA, OrnTs, Phe_2Ad, Phe_3Ad,

Phe_4_Morph, Phe_4Ad, Phe_4COOH, Phe_4Guan, Phe_4OMe, Phe_pentaF, Q_NHMe, Q_NMe2, Q_Pyro, Q_EtOMe, Tet1, Thi, or Thr;

X3 is AlaCF3, AlaCHF2, Ala_cycBu, Aoc, Cha, Chg, Cpg, cyclopentyl_Al原因, cyclopropyl_Al原因, Cys, dV, H_Cha, Hcy, Hph, Igl, nVF3, Ogl, Phe_34diCl, Phe_4CF3, Phe_4Cl, Phe_4Me, Phe_4OMe, Phe_4tBu, Tba, Tle, or Val;

X4 is Asn, Gln, Glu, Glu_OMe, His, hE, hR, Lys_Me3, Phe4_COOH, Thr, or Thr_Me;

X5 is Abu, Cys, Cha, Chg, Dab_Acetyl, Glu, Hcy, hE, Hhc, Ile, Lys, Lys_Ac, LysN3, LysPhAc, O2S, O3S, O3S_Reduced, O4S, O4S_Reduced, Orn_Acetyl, or Pen;

X6 is 4RBenzyloxyPro, 4RPhePro, 4S_Amp_Cyclohex, 4S_Amp_Hex, 4S_Amp_IVA, 4S_Amp_tBu, 4SCF3Pro, 4SCyclohexPro, 5RPhePro, Azetidinone, Hpr, Oic, or Pro;

X7 is Ala, Acvc, Aib, aMe_Phe, Arg, Cys, Gln, Glu, His, hR,

Lys_1PEG2_1PEG2_Ahx_C18_diacid, Lys_1PEG2_1PEG2_IsoGlu_C12,

Lys_1PEG2_1PEG2_IsoGlu_C18_diacid, Lys_1PEG2_1PEG2_IsoGlu_Palm, Lys_Ac,

O3S_Me, Oic, Pro, Ser, or Tba

X8 is aMe_Glu, Asp, dD, Gla, Glu, Phe_3COOH, Phe_4COOH, Tet1, or Tet2;

X9 is Aoc, Dgl, Hcy, Leu, O3S, O3S_Reduced, or Ogl;

X10 is 1Nal, 2Nal, aMe_Phe, aMe_Trp, Cys, Hph, Lys_1PEG2_1PEG2_IsoGlu_C12, Phe_4COOH, Trp_4Cl, Trp_4Me, Trp_5Cl, Trp_5CONH2, Trp_5Et, Trp_5Me, Trp_6CF3, Trp_6Cl, Trp_6CONH2, Trp_6Me, Trp_7Cl, Trp_7Me, Trp_7Phe, or Trp;

X11 is Aib, Ala, aMe_Asp, aMe_Leu, aMe_Phe, Asn, Asp, Cys, Chg, Gln, Glu, Leu, Lys_1PEG2_1PEG2_IsoGlu_C12, Lys_Ac, Lys_Me3, O3S_Me, Phe_4Ad, Phe_4tBu, Ser, Tba, or Tle;

X12 is 1Nal, aMe_Trp, Orn_Bz, Trp, Trp_56diCl, Trp_56diMe, Trp_5Br, Trp_5Cl, Trp_5Et, Trp_5Me, Trp_6CF3, Trp_6Cl, or Trp6Me;

X13 is Abu, aMe_Cys, aMe_Lys_Ac, Cys, Cha, Dab_Acetyl, Glu, Hcy, hE, Hhc, Ile, Lys, Lys_Ac, LysN3, O2S, O3S, O3S_Me, O3S_Me_Reduced, O3S_Reduced, O4S, O4S_Reduced, Orn_Acetyl, or Pen;

X14 is Asn, dK, dR, Lys, Lys_Ac, Lys_PEG4_PEG4_NH2, Lys_PEG4_1PEG2_NH2, Lys_PEG8_NH2, Orn_Acetyl, or PEG12;

X15 is dR, dK, Lys, Lys_PEG4_PEG4_NH2, or Lys_Dimethyl, or absent;

X16 is dK, Lys, Lys_Ac, Lys_1PEG2_1PEG2_IsoGlu_C12, Lys_1PEG2_1PEG2_IsoGlu_Palm, Lys_PEG4_PEG4_NH2, or absent;

wherein:

(i) the monomer comprises a cyclic structure wherein two amino acid residues in the peptide monomer are directly covalently linked or indirectly covalently linked through a through an amide bond, a disulfide bond, a thioether bond, a carbon-carbon single bond, or a carbon-carbon double bond, wherein the two amino acid residues are at X5 and X13, X7 and X11, X9 and X13, or X10 and X14; and

(ii.a) each monomer is directly covalently linked to a polyethylene glycol (PEG) linker at X14, X15, or X16 through an amide bond, wherein X14, X15, or X16 is Lys or dK and the PEG linker comprises $-(OCH_2CH_2)_n-$, wherein n is between 5 and 25, and wherein one monomer is linked to one terminal end of the PEG linker and the other monomer is linked to the other terminal end of the PEG linker, or (ii.b) each monomer is directly covalently linked to a DIG_linker (diglycolic acid linker) at X14, X15, or X16 through an amide bond, where X14, X15, or X16 is Lys_PEG4_PEG4_NH2, Lys_PEG4_1PEG2_NH2, or Lys_PEG8_NH2.

(Formula (II).)

[00360] In other embodiments, a Formula (II) monomer may not be part of a homodimer compound. In this situation, because X14 (or X15 or X16) is often a residue that mediates dimerization, it can be substituted with another amino acid, for example, any of the residues listed at X14 in Formula (I). In some embodiments, for a Formula (II) monomer that is not part of a homodimer compound, X14 is Asn or Lys_Ac.

[00361] In others embodiments of Formula (II), the HEK Blue human IL-17 assay is a human IL-17AA, human IL-17AF, or human IL-17FF assay.

[00362] For any of the Formulas herein, R1 and R2 can be expanded to include the moieties specified for Formula (I).

[00363] In some embodiments, a monomer peptide of a homodimer compound comprises or consists of an amino acid sequence of Formula (II.A):

$R_1-X00-X0-X1-X2-X3-X4-X5-X6-X7-X8-X9-X10-X11-X12-X13-X14-X15-X16-R_2$,

wherein:

R1 is acetyl, 3-hydroxypropionic acid, C6_diacid, cyclopropanecarboxylic acid, glutaric acid, isovaleric acid, methanesulfonyl acetic acid, or absent; R2 is NH₂, OH, or absent;

X00 is dH or absent;

X0 is dH, Gln, Glu, Glu_OMe, His, Ile, Lys_Me3, Sar, Tle, or absent;

X1 is Chg, Ile, Lys_1PEG2_1PEG2_IsoGlu_C12, Ogl, or Val;

X2 is 2Pal, 3Pal, Agb, Agp, Dab_Acetyl, Dab_2HyAc, Dab_Ms, Dab_Ts, dDab_2HyAc, Gln, Glu, His, hR, Hse, Lys, Lys_1PEG2_1PEG2_C18_Diacid, Lys_1PEG2_1PEG2_IsoGlu_C12, Lys_Ac, Lys_Dimethyl, Lys_Me3, Lys1PEG2Ac, Lys2HyAc, LysMs, LysTs, OrnAc, OrnMs, OrnTs, Phe_2Ad, Phe_3Ad, Phe_4Ad, Phe_4Guan, Q_NHMe, Q_NMe2, Q_Pyro, Tet1, or Thr;;

X3 is Ala_cycBu, Aoc, Cha, Chg, Cpg, cyclopropyl_Alal, dV, H_Cha, Hph, Igl, Ogl, Phe_34diCl, Phe_4CF3, Phe_4Cl, Phe_4Me, Phe_4OMe, Phe_4tBu, Tba, Tle, or Val;

X4 is Glu, hR, or Thr;

X5 is Hhc;

X6 is Oic or Pro;

X7 is Ala, Acvc, aMe_Phe, Gln, Glu, His, hR, Lys_Ac, Pro, Ser, or Tba;

X8 is aMe_Glu, Asp, dD, Gla, Glu, Tet1, or Tet2;

X9 is Leu or Ogl;

X10 is 1Nal, aMe_Trp, Trp_7Phe, or Trp;

X11 is aMe_Phe, Asp, or Glu;

X12 is aMe_Trp, Trp_5Br, Trp_5Cl, Trp_5Me, Trp_6Cl, Trp_6Me, or Trp;

X13 is Hhc;

X14 is Asn, dR, dK, Lys, Lys_PEG4_1PEG2_NH₂, Lys_PEG8_NH₂, or Lys_PEG4_PEG4_NH₂;

X15 is dR, Lys, or absent;

X16 is absent;

wherein: (a) X5 and X13 are directly covalently linked through a disulfide bond; wherein each monomer is directly covalently linked to a PEG linker at X14 or X15 through an amide bond, and (b) X14 or X15 is dK or Lys, and wherein one monomer is linked to one terminal end of the PEG linker and the other monomer is linked to the other terminal end of the PEG linker, or

X2 is dK or Lys and wherein one monomer is linked to one terminal end of the PEG linker and the other monomer is linked to the other terminal end of the PEG linker, or X14 is Lys_PEG4_PEG4_NH2, Lys_PEG8_NH2, or Lys_PEG4_1PEG2_NH2, and wherein one monomer is linked to one terminal end of a DIG_Linkers and the other monomer is linked to the other terminal end of the DIG_Linkers. (Formula (II.A)).

[00364] Representative compounds of Formula (II.A) include: C45, C80, C81, C82, C83, C87, C88, C89, C120, C121, C122, C138, C139, C147, C162, C180, C182, C184, C186, C188, C190, C192, C194, C196, C206, C207, C208, C209, C210, C213, C215, C217, C219, C221, C222, C224, C256, C262, C281, C294, C295, C296, C297, C298, C300, C302, C303, C304, C305, C307, C308, C309, C310, C311, C312, C313, C314, C315, C316, C317, C318, C319, C328, C329, C330, C331, C332, C333, C334, C335, C336, C340, C345, C347, C388, C390, C412, C413, C414, C428, C429, C430, C431, C433, C434, C435, C531, C542, C543, C544, C545, C546, C547, C548, C571, C572, C645, C689, C690, C728, C729, C730, C731, C732, and C733.

[00365] As Formula (II.A) is a sub-formula of Formula (II), all of these representative homodimer compounds have an IC₅₀ equal to or less than 10 nM in a human HEK Blue IL-17 assay (see Fig. 1, AA, AF, or FF activity of ++, +++, or ++++) This dimer and potency cut-off also applies to the other Formula (II) sub-formulas herein.

[00366] Furthermore, in some embodiments, Formula (II) dimers (including Formula (II) subformulas) comprise Figure 1 monomers that do not have its homodimer form listed in Figure 1, where such monomers exhibit an IC₅₀ value of equal to or less than 10 nM or less (++++, +++, ++). For example, at least the C288 and C290 compounds are monomers that would fall under Formula II (others, see Fig. 1 monomer compounds), but for the homodimer requirement. Thus, in some embodiments, monomers with X14N are changed to X14Lys to allow for routine dimerization via a PEGDA linker.

[00367] In some embodiments, a monomer peptide of a homodimer compound comprises or consists of an amino acid sequence of Formula (II.B):

R₁-X00-X0-X1-X2-X3-X4-X5-X6-X7-X8-X9-X10-X11-X12-X13-X14-X15-X16--R₂,
wherein: R₁ is acetyl, 3-hydroxypropionic acid, C₆_diacid, cyclopropanecarboxylic acid, glutaric acid, isovaleric acid, methanesulfonyl acetic acid, or absent; R₂ is amine, hydroxyl,

or absent; X00 is dH or absent; X0 is dE, dH, Gln, Glu, Glu_OMe, His, Ile, Lys_Me3, Sar, Tle, or absent; X1 is Ile or Val; X2 is His or Lys_Me3; X3 is Tba or Val; X4 is Thr; X5 is Chg, Ile, or Tle; X6 is Azetidinone, Oic, or Pro; X7 is Ala; X8 is Asp or Gla; X9 is Hcy; X10 is Trp; X11 is Asp or Glu; X12 is Trp; X13 is Hhc; X14 is Lys, Lys_PEG4_1PEG2_NH2, Lys_PEG8_NH2, or Lys_PEG4_PEG4_NH2; X15 is dR; X16 is absent; wherein: (i) the cyclic structure of each monomer comprises X9 and X13 that are directly covalently linked through a disulfide bond; and (ii) each monomer is directly covalently linked to a PEG linker at X14Lys through an amide bond, wherein one monomer is linked to one terminal end of the PEG linker and the other monomer is linked to the other terminal end of the PEG linker; or each monomer is directly covalently linked to a DIG linker at X14Lys_PEG4_PEG4_NH2, X14Lys_PEG4_1PEG2_NH2, or X14Lys_PEG8_NH2, through an amide bond, wherein one monomer is linked to one terminal end of the DIG linker and the other monomer is linked to the other terminal end. (Formula (II.B)).

[00368] Representative compounds of Formula (II.B) include C46, C84, C85, C86, C140, and C145.

[00369] In other embodiments of a Formula (II) homodimer, the cyclic structure of each monomer comprises two amino acid residues directly covalently linked through a thioether bond at: (a) X5 and X13, wherein X5 is Cys, Dab_Acetyl, Hcy, Hcy_sulfoxide, Hhc, Lys_Ac, LysPhAc, Orn_Acetyl, or Pen, and X13 is aMe_Cys, aMe_Lys_Ac, Cys, Dab_Acetyl, Hcy, Hcy_sulfoxide, Hhc, Lys_Ac, Orn_Acetyl, or Pen; (b) X7 and X11, wherein X7 is Cys, Hcy, or Lys_Ac and X11 is Cys or Lys_Ac; or (c) X10 and X14, wherein X10 is Cys and X14 is Lys_Ac or Orn_Acetyl; and wherein aMe_Cys, Cys, Hcy, Hcy_sulfoxide, Hhc, or Pen is paired with aMe_Lys_Ac, Dab_Acetyl, Lys_Ac, LysPhAc, or Orn_Acetyl, and vice versa.

[00370] In some embodiments, a monomer peptide of a homodimer compound comprises or consists of an amino acid sequence of Formula (II.C):

$R_1\text{-X00-X0-X1-X2-X3-X4-X5-X6-X7-X8-X9-X10-X11-X12-X13-X14-X15-X16-R}_2$,
wherein: R1 is acetyl, 3-hydroxypropionic acid, C6_diacid, cyclopropanecarboxylic acid, glutaric acid, isovaleric acid, methanesulfonyl acetic acid, or absent; R2 is amine, hydroxyl, or absent; X00 is dH or absent, X0 is dE, dH, Gln, Glu, Glu_OMe, His, Ile, Lys_Me3, Sar, Tle, or absent; X1 is Chg, Ile, Lys_1PEG2_1PEG2_C18_diacid,

Lys_1PEG2_1PEG2_IsoGlu_Palm, Lys_1PEG2_1PEG2_IsoGlu_C12,
 Lys_1PEG2_1PEG2_IsoGlu_C18_Diacid, Ogl, or Val; X2 is 2Pal, 3Pal, Agb, Agp,
 aMe_Arg, Cit, Dab_Ac, Dab2HyAc, DabMs, DabTs, dDab2HyAc, Gln, Glu, His, hR, Hse,
 Lys, Lys_1PEG2_1PEG2_C18_diacid, Lys_1PEG2_1PEG2_IsoGlu_C12,
 Lys_1PEG2_1PEG2_IsoGlu_C18_Diacid, Lys_Ac, Lys_Dimethyl, Lys_Me3,
 Lys1PEG2Ac, Phe_4_Morph, Phe_4COOH, Phe_4OMe, Phe_pentaF, Thr, or Thi; or Thr; X3
 is Cha, H_Cha, Ogl, Phe_4tBu, Tba, or Tle, or Val; X4 is Asn, Gln, Glu, His, Phe_4COOH,
 Thr, or Thr_Me; X5 is Cys, Dab_Acetyl, Hcy, Lys_Ac, LysPhAc, Orn_Acetyl, or Pen; X6 is
 Oic, or Pro; X7 is Aib, Ala, Arg, His, Lys_1PEG2_1PEG2_Ahx_C18_Diacid,
 Lys_1PEG2_1PEG2_IsoGlu_C18_Diacid, Lys_1PEG2_1PEG2_IsoGlu_Palm; X8 is
 aMe_Glu, Asp, or Gla, Glu, or Tet1; X9 is Ogl; X10 is 1Nal, Trp, Trp_4Cl, Trp_4Me,
 Trp_5Cl, Trp_5CONH2, Trp_5Et, Trp_5Me, Trp_6CF3, Trp_6Cl, Trp_6CONH2, Trp_6Me,
 Trp_7Cl, Trp_7Me, or Trp_7Phe; X11 is aMe_Asp, Asp, Gln, or Glu; X12 is Trp,
 Trp_56diCl, Trp_56diMe, Trp_5Et, Trp_5Me, Trp_6CF3, Trp_6Cl, or Trp_6Me; X13 is
 aMe_Cys, aMe_Lys_Ac, Cys, Dab_Acetyl, Hcy, Hhc, Lys_Ac, Orn_Acetyl, or Pen; X14 is
 Lys, Lys_PEG4_1PEG2_NH2, Lys_PEG8_NH2, or Lys_PEG4_PEG4_NH2; X15 is dR;
 X16 is absent;

wherein: (i) the cyclic structure of each monomer comprises X5 and X13 that are directly covalently linked through a thioether bond; wherein aMe_Cys, Cys, Hcy, Hhc, or Pen is paired with aMe_Lys_Ac, Dab_Acetyl, Lys_Ac, LysPhAc, or Orn_Acetyl, and vice versa;
 and (ii) each monomer is directly covalently linked to a PEG linker at X14Lys through an amide bond, wherein one monomer is linked to one terminal end of the PEG linker and the other monomer is linked to the other terminal end of the PEG linker or each monomer is directly covalently linked to a PEG linker at X14Lys through an amide bond, wherein one monomer is linked to one terminal end of the PEG linker and the other monomer is linked to the other terminal end of the PEG linker; or each monomer is directly covalently linked to a DIG linker at X14Lys_PEG4_PEG4_NH2, X14Lys_PEG8_NH2, or X14Lys_PEG4_1PEG2_NH2, through an amide bond, wherein one monomer is linked to one terminal end of the DIG linker and the other monomer is linked to the other terminal end.

Formula (II.C)

[00371] Representative compounds of Formula (II.C) include: C124, C161, C225, C226, C227, C228, C229, C230, C263, C264, C265, C266, C267, C289, C291, C320, C321, C322, C323, C324, C325, C326, C327, C339, C341, C385, C405, C415, C416, C417, C418, C419, C420, C423, C424, C425, C426, C465, C466, C485, C486, C487, C488, C501, C502, C503, C504, C505, C523, C524, C525, C526, C527, C554, C555, C556, C557, C558, C559, C560, C561, and C562.

[00372] In some embodiments, a monomer peptide of a homodimer compound comprises or consists of an amino acid sequence of Formula (II.D):

R_1 -X00-X0-X1-X2-X3-X4-X5-X6-X7-X8-X9-X10-X11-X12-X13-X14-X15-X16- R_2 ,
wherein: R_1 is acetyl, 3-hydroxypropionic acid, C6_diacid, cyclopropanecarboxylic acid, glutaric acid, isovaleric acid, methanesulfonyl acetic acid, or absent; R_2 is amine, hydroxyl, or absent; X00 is dH or absent, X0 is dE, dH, Gln, Glu, Glu_OMe, His, Ile, Lys_Me3, Sar, Tle, or absent; X1 is Ile or Val; X2 is His, Lys_Me3, or Thr; X3 is Tba, Tle, or Val; X4 is Thr or Glu; X5 is Ile; X6 is Oic or Pro; X7 is Cys or Lys_Ac; X8 is Asp; X9 is Leu or Ogl; X10 is INal or Trp; X11 is Cys or Lys_Ac; X12 is aMe_Trp or Trp; X13 is Ile; X14 is Lys, Lys_PEG4_1PEG2_NH2, Lys_PEG8_NH2, or Lys_PEG4_PEG4_NH2; X15 is dR; X16 is absent; wherein X7 and X11 are not both Cys or Lys_Ac; and wherein: (i) the cyclic structure of each monomer comprises X7 and X11 that are directly covalently linked through a thioether bond; and (ii) each monomer is directly covalently linked to a PEG linker at X14Lys through an amide bond, wherein one monomer is linked to one terminal end of the PEG linker and the other monomer is linked to the other terminal end of the PEG linker or each monomer is directly covalently linked to a PEG linker at X14Lys through an amide bond, wherein one monomer is linked to one terminal end of the PEG linker and the other monomer is linked to the other terminal end of the PEG linker; or each monomer is directly covalently linked to a DIG linker at X14Lys_PEG4_PEG4_NH2, X14Lys_PEG4_1PEG2_NH2, X14Lys_PEG8_NH2, through an amide bond, wherein one monomer is linked to one terminal end of the DIG linker and the other monomer is linked to the other terminal end. (Formula (II.D)).

[00373] Representative compounds of Formula (II.D) include: C51, C52, C54, C56, and C62.

[00374] In some embodiments, a monomer peptide of a homodimer compound comprises or consists of an amino acid sequence of Formula (II.E):

R_1 -X00-X0-X1-X2-X3-X4-X5-X6-X7-X8-X9-X10-X11-X12-X13-X14-X15-X16- R_2 ,
 wherein: R_1 is 3-hydroxypropionic acid, C6_diacid, cyclopropanecarboxylic acid, glutaric acid, isovaleric acid, methanesulfonyl acetic acid, or absent; R_2 is amine, hydroxyl, or absent; X00 is dH or absent, X0 is dE, dH, Gln, Glu, Glu_OMe, His, Ile, Lys_Me3, Sar, Tle, or absent; X1 is Ile or Val; X2 is Thr or Lys_Me3; X3 is Tba or Tle; X4 is Thr or Glu; X5 is Chg or Ile; X6 is Oic or Pro; X7 is Ala; X8 is Asp; X9 is Ogl; X10 is Cys; X11 is Asp or Glu; X12 is Trp; X13 is Ile; X14 is Lys or Orn_Ac; X15 is dR; X16 is Lys, Lys_PEG4_1PEG2_NH2, Lys_PEG8_NH2, or Lys_PEG4_PEG4_NH2; wherein: (i) the cyclic structure of each monomer comprises X10 and X14 that are directly covalently linked through a thioether bond; and (ii) each monomer is directly covalently linked to a PEG linker at X16Lys through an amide bond, wherein one monomer is linked to one terminal end of the PEG linker and the other monomer is linked to the other terminal end of the PEG linker; or each monomer is directly covalently linked to a DIG linker at X16Lys_PEG4_PEG4_NH2, X16Lys_PEG4_1PEG2_NH2, or X14Lys_PEG8_NH2, through an amide bond, wherein one monomer is linked to one terminal end of the DIG linker and the other monomer is linked to the other terminal end. (Formula (II.E)).

[00375] Representative compounds of Formula (II.E) include C136 and C137.

[00376] In some embodiments, the cyclic structure of a monomer of Formula (II) comprises the two amino acid residues directly covalently linked through: (a) a carbon-carbon single bond (-C-C-) at X5 and X13, X9-X13, X7-X11, or X10-X14, wherein the residues of these pairs are individually or both O3S_Reduced, O3S_Methyl_Reduced, O4S_Reduced, or O4S_Methyl_Reduced; or (b) a carbon-carbon double bond (-C=C-) at X5 and X13, X9-X13, X7-X11, or X10-X14, wherein the residues of these pairs are individually or both O2S, O3S, O4S, O3S_methyl, or O4S_Methyl.

[00377] In some embodiments, a monomer peptide of a homodimer compound comprises or consists of an amino acid sequence of Formula (II.F):

R_1 -X00-X0-X1-X2-X3-X4-X5-X6-X7-X8-X9-X10-X11-X12-X13-X14-X15-X16- R_2 ,

wherein: R1 is acetyl, 3-hydroxypropionic acid, C6_diacid, cyclopropanecarboxylic acid, glutaric acid, isovaleric acid, methanesulfonyl acetic acid, or absent; R2 is amine, hydroxyl, or absent; X00 is dH or absent, X0 is dE, dH, Gln, Glu, Glu_OMe, His, Ile, Lys_Me3, Sar, Tle, or absent; X1 is Ile, Val, or Tba; X2 is Gln, His, Hse, Lys_Me3, or Thr; X3 is cyclopropyl_Ala, Tba, Tle, or Val; X4 is Glu or Thr; X5 is O3S_Reduced or O4S_Reduced; X6 is Pro or Oic; X7 is Ala; X8 is Asp or Gla; X9 is Ogl; X10 is 1Nal or Trp; X11 is Asp or Glu; X12 is Trp or Trp5Me; X13 is O3S_Reduced, O3S_Methyl_Reduced, O4S_Reduced; X14 is Lys, Lys_PEG4_1PEG2_NH2, Lys_PEG8_NH2, or Lys_PEG4_PEG4_NH2; X15 is dR; and X16 is absent; wherein: (i) the cyclic structure of each monomer comprises X5 and X13 that are directly covalently linked through a carbon-carbon single bond (-C-C-); and (ii) each monomer is directly covalently linked to a PEG linker at X14Lys through an amide bond, wherein one monomer is linked to one terminal end of the PEG linker and the other monomer is linked to the other terminal end of the PEG linker; or each monomer is directly covalently linked to a DIG linker at X14Lys_PEG4_PEG4_NH2, X14Lys_PEG4_1PEG2_NH2, or X14Lys_PEG8_NH2, through an amide bond, wherein one monomer is linked to one terminal end of the DIG linker and the other monomer is linked to the other terminal end. (Formula (II.F)).

[00378] Representative compounds of Formula (II.F) include: C135, C168, C169, C292, C349, C350, C367, C427, C528, C532, C533, C534, C566, C567, C568, C569, C570, C585, C586, C598, C699, C701, C758, C811, C813, C818, C819, C836, C837, C838, and C839.

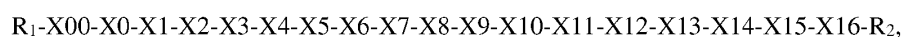
[00379] In some embodiments, a monomer peptide of a homodimer compound comprises or consists of an amino acid sequence of Formula (II.G):

R₁-X00-X0-X1-X2-X3-X4-X5-X6-X7-X8-X9-X10-X11-X12-X13-X14-X15-X16-R₂,
 wherein: R1 is acetyl, 3-hydroxypropionic acid, C6_diacid, cyclopropanecarboxylic acid, glutaric acid, isovaleric acid, methanesulfonyl acetic acid, or absent; R2 is amine, hydroxyl, or absent; X00 is dH or absent, X0 is dE, dH, Gln, Glu, Glu_OMe, His, Ile, Lys_Me3, Sar, Tle, or absent; X1 is Chg, Val, or Ile; X2 is His, Lys_Me3, or Thr; X3 is Ogl, Val, Tba, or Tle; X4 is Thr or Glu; X5 is Ile or Chg; X6 is Oic or Pro; X7 is O3S_Me; X8 is Asp or Gla; X9 is Ogl; X10 is 1Nal or Trp; X11 is O3S_Me; X12 is Trp; X13 is Ile; X14 is Asn; X15 is dR; and X16 is Lys, Lys_PEG4_1PEG2_NH2, Lys_PEG8_NH2, or Lys_PEG4_PEG4_NH2; wherein: (i)

the cyclic structure of each monomer comprises X7 and X11 that are directly covalently linked through a carbon-carbon double bond (-C=C-); and (ii) each monomer is directly covalently linked to a PEG linker at X16Lys through an amide bond, wherein one monomer is linked to one terminal end of the PEG linker and the other monomer is linked to the other terminal end of the PEG linker; or each monomer is directly covalently linked to a DIG linker at X16Lys_PEG4_PEG4_NH2, X16Lys_PEG4_1PEG2_NH2, or X16Lys_PEG8_NH2, through an amide bond, wherein one monomer is linked to one terminal end of the DIG linker and the other monomer is linked to the other terminal end. (Formula (II.G)).

[00380] Representative compounds of Formula (II.G) include C119 and C170.

[00381] In some embodiments, a monomer peptide of a homodimer compound comprises or consists of an amino acid sequence of Formula (II.H):



wherein R1 is acetyl, 3-hydroxypropionic acid, C6_diacid, cyclopropanecarboxylic acid, glutaric acid, isovaleric acid, methanesulfonyl acetic acid, or absent; R2 is amine, hydroxyl, or absent; X00 is dH or absent, X0 is dE, dH, Gln, Glu, Glu_OMe, His, Ile, Lys_Me3, Sar, Tle, or absent; X1 is Chg, Val, or Ile; X2 is His, Lys_Me3, or Thr; X3 is Ogl, Tba, Tle, or Val; X4 is Thr or Glu; X5 is Chg or Ile; X6 is Oic or Pro; X7 is Ala or Cys; X8 is Asp or Gla; X9 is O3S; X10 is 1Nal or Trp; X11 is Asp, Glu, or Lys_Ac; X12 is Trp; X13 is O3S; X14 is Lys, Lys_PEG4_1PEG2_NH2, Lys_PEG4_PEG4_NH2, or Lys_PEG8_NH2; X15 is dR; and X16 is absent; wherein: (i) the cyclic structure of each monomer comprises X9 and X13 that are directly covalently linked through a carbon-carbon double bond (-C=C-); and (ii) each monomer is directly covalently linked to a PEG linker at X14Lys through an amide bond, wherein one monomer is linked to one terminal end of the PEG linker and the other monomer is linked to the other terminal end of the PEG linker; or each monomer is directly covalently linked to a DIG linker at X14Lys_PEG4_PEG4_NH2, X14Lys_PEG4_1PEG2_NH2, or X14Lys_PEG8_NH2, through an amide bond, wherein one monomer is linked to one terminal end of the DIG linker and the other monomer is linked to the other terminal end. (Formula (II.H)).

[00382] Representative compounds of Formula (II.H) include: C163, C164, C165, C166, C223, C257, C258, C259, C260, C261, C306, C307, and C408.

[00383] In some embodiments, when the two cross-linked amino acid residues are at X5 and X13, X7 and X11, X9 and X13, or X10 and X14, the two amino acids are indirectly cross-linked through a cyclization linker that comprises an alkane or an alkene or at least two free methyl (CH₃) or alkyl groups that can form covalent bonds with a thiol group from the side chains of the two amino acid residues, such as a Butane_Linkers, a Carbonyl_Linkers, a Dimethylcyclopropane_Linkers, a Ebutene_Linkers, a Hexane_Linkers, an Oxetane_Linkers a Pentane_Linkers, Propane_Linkers, or a Xylene_Linkers. The two amino acid residues cross-linked through a thioether bond with the cyclization linker can be, for example, individually or both Cys, dC, Hcy, Hhc, Pen, or hhPen, their D-forms, and their α -methyl variants. Other amino acids with thiol containing side chains may be suitable.

[00384] In some embodiments of Formula (II), each monomer of the dimer has a cyclic structure comprising two amino acid residues that are indirectly covalently linked through: a thioether bond with one of the aforementioned linkers in the paragraph immediately above at: (a) X5 and X13, wherein X5 is Cys, Hcy, Hhc, or Pen, and X13 is Cys, Hcy, Hhc, or Pen; (b) X7 and X11, wherein both X7 and X11 are Cys, and with the a Xylene linker, or (c) X7 and X11, wherein X7 and X11 are individually or both Cys or Hcy and with the Propane_Linkers.

[00385] In some embodiments, a monomer peptide of a homodimer compound comprises or consists of an amino acid sequence of Formula (II.I):

R₁-X00-X0-X1-X2-X3-X4-X5-X6-X7-X8-X9-X10-X11-X12-X13-X14-X15-X16-R₂,

wherein: R₁ is acetyl, 3-hydroxypropionic acid, C₆_diacid, cyclopropanecarboxylic acid, glutaric acid, isovaleric acid, methanesulfonyl acetic acid, or absent; R₂ is amine, hydroxyl, or absent; X00 is dH or absent, X0 is dE, dH, Gln, Glu, Glu_OMe, His, Ile, Lys_Me3, Sar, Tle, or absent; X1 is Cha, Cyclopropyl_Ala, DIP, Ile, Tba, or Val; X2 is Gln, His, Hse, Lys_Me3, Lys_Dimethyl, Lys_PEG2_Me3, Lys2HyAc, LysMPA, LysNs, Orn_Ac, Orn2HyAc, OrnPVA, Phe_2Ad, Phe_3Ad, Q_NHMe, Q_NMe2, Q_Pyro, Q_EtOMe, or Tet1; X3 is AlaCF3, AlaCHF2, cyclopentyl_Ala, cyclopropyl_Ala, nVF3, Tba, Tle, or Val; X4 is Asn, Glu, Glu_OMe, hE, Lys_Me3, Phe_4COOH, or Thr; X5 is Cys, Hcy, or Pen; X6 is 4RBenzoyloxyPro, 4RPhePro, 4S_Amp_Cyclohex, 4S_Amp_Hex, 4S_Amp_IVA, 4S_Amp_tBu, 4SCF3Pro, 4SCyclohexPro, 5RPhePro, Oic, or Pro; X7 is Ala, Gln, His, Lys_1PEG2_1PEG2_IsoGlu_C18_diacid, Lys_Ac, Oic, or Pro; X8 is Asp, Gla, Glu,

Phe_3COOH, or Phe_4COOH; X9 is Aoc, Dgl, or Ogl; X10 is 1Nal, 2Nal, aMe_Phe, aMe_Trp, Hph, Phe_4COOH, or Trp; X11 is Aib, Ala, Asn, Asp, aMe_Leu, aMe_Phe, Chg, Glu, Leu, Lys_Me3, Phe_4Ad, Phe_4tBu, Ser, Tba, or Tle; X12 is 1Nal, aMe_Trp, Orn_Bz, Trp_6Cl, or Trp; X13 is Cys, Hcy, or Pen; X14 is dK, Lys, Lys_PEG4_1PEG2_NH2, Lys_PEG8_NH2, or Lys_PEG4_PEG4_NH2; X15 is dR; and X16 is absent; wherein: (i) the cyclic structure of each monomer comprises X5 and X13 that are indirectly covalently linked through a thioether bond with a Butane_Link, a Carbonyl_Link, Dimethylcyclopropane_Link, EButene linker, Hexane_Link, Oxetane_Link, Pentane_Link, Propane linker, oXylene linker, mXylene linker, or pXylene linker; and (ii) each monomer is directly covalently linked to a PEG linker at X14 through an amide bond, wherein one monomer is linked to one terminal end of the PEG linker and the other monomer is linked to the other terminal end of the PEG linker; or each monomer is directly covalently linked to a DIG linker at X14Lys_PEG4_PEG4_NH2, X14Lys_PEG4_1PEG2_NH2, X14Lys_PEG8_NH2, through an amide bond, wherein one monomer is linked to one terminal end of the DIG linker and the other monomer is linked to the other terminal end. (Formula (II.I)).

[00386] Representative compounds of Formula (II.I) include: C202, C203, C204, C268, C270, C282, C283, C284, C285, C299, C301, C337, C338, C346, C363, C386, C387, C391, C421, C422, C443, C444, C448, C449, C467, C472, C474, C493, C494, C495, C496, C497, C498, C499, C500, C508, C509, C510, C511, C513, C515, C517, C519, C520, C521, C522, C531, , C536, C537, C563, C572, C574, C575, C576, C577, C578, C579, C581, C583, C588, C589, C590, C591, C592, C593, C594, C595, C596, C597, C599, C600, C601, C686, C687, C688, C691, C693, C694, C695, C696, C697, C698, C703, C704, C705, C706, C707, C708, C709, C714, C715, C716, C717, C718, C719, C720, C721, C722, C723, C724, C725, C726, C727, C734, C735, C736, C737, C738, C739, C740, C741, C742, C743, C744, C745, C746, C747, C748, C749, C750, C751, C752, C753, C754, C760, C761, C764, C765, C789, C791, C792, C793, C794, C795, C796, C807, C808, C816, C817, C820, C821, C822, C823, C824, C825, C826, C827, C828, C829, C830, C831, C832, C833, C834, C835, C840, C841, C842, C843, C844, C845, C846, and C847.

[00387] In some embodiments, a monomer peptide of a homodimer compound comprises or consists of an amino acid sequence of Formula (II.J):

R_1 -X00-X0-X1-X2-X3-X4-X5-X6-X7-X8-X9-X10-X11-X12-X13-X14-X15-X16- R_2 ,

Wherein: R_1 is acetyl, 3-hydroxypropionic acid, C6_diacid, cyclopropanecarboxylic acid, glutaric acid, isovaleric acid, methanesulfonyl acetic acid, or absent; R_2 is amine, hydroxyl, or absent; X00 is dH or absent, X0 is dE, dH, Gln, Glu, Glu_OMe, His, Ile, Lys_Me3, Sar, Tle, or absent; X1 is Ile or Val; X2 is His, Lys_Me3, or Thr; X3 is Tle or Val; X4 is Glu or Thr; X5 is Ile; X6 is Pro or Oic; X7 is Cys; X8 is Asp or Gla; X9 is Leu or Ogl; X10 is 1Nal or Trp; X11 is Cys or Hcy; X12 is Trp; X13 is Ile; X14 is Asn, Lys, Lys_PEG4_1PEG2_NH2, Lys_PEG8_NH2, or Lys_PEG4_PEG4_NH2; X15 is dR; and X16 is Lys, Lys_PEG4_PEG4_NH2, or absent; wherein: (i) the cyclic structure of each monomer comprises X7 and X11 that are indirectly covalently linked through a bis-thioether bond with the a Xylene linker (m-, o-, or p-) or a Propane_Linkers; and (ii) each monomer is directly covalently linked to a PEG linker at X14 or X16 through an amide bond when X14 or X16 is Lys, wherein one monomer is linked to one terminal end of the PEG linker and the other monomer is linked to the other terminal end of the PEG linker; or each monomer is directly covalently linked to a DIG linker at X14 or X16 through an amide bond, wherein X14 or X16 is Lys_PEG4_PEG4_NH2, Lys_PEG4_1PEG2_NH2, or Lys_PEG8_NH2, wherein one monomer is linked to one terminal end of the DIG linker and the other monomer is linked to the other terminal end. (Formula (II.J)).

[00388] Representative compounds of Formula (II.J) include: C50 or C62.

[00389] In some embodiments, a peptide compound of the invention inhibits human IL-17AA, human IL-17AF, and human IL-17FF activity, or at least for each of hIL-17AA and hIL-17FF, with an IC_{50} for each isoform (IL-17 ---AA, -AF, -FF) or with an IC_{50} for at least the AA and FF isoforms, of about 10 nM or less in the human IL-17 HEK Blue assays, wherein the peptide compound comprises a monomer peptide comprising or consisting of the sequence of Formula (III):

R^1 -X00-X0-X1-X2-X3-X4-X5-X6-X7-X8-X9-X10-X11-X12-X13-X14-X15-X16- R^2 ,

wherein:

R^1 is 1Pip_AceticAcid, acetyl, 3-hydroxypropionic acid, C6_diacid, cyclopropanecarboxylic acid, glutaric acid, isovaleric acid, methanesulfonyl acetic acid, Mor_propanoic_acid, or absent; R^2 is NH_2 or OH or absent;

X00 is Cha, dH, Tle, or absent;

X0 is 2Pal, Asn, d2Pal, dE, dH, dQ, Gln, Glu, Glu_OMe, His, Ile, Lys, Lys_Me3, NMe_His, Orn, Sar, Tle, or absent;

X1 is 1Nal, Cha, Cyclopropyl_Ala, Dgl, DIP, hCha, hF, hhF, Ile, Ogl, Phe_4Me, Tba, Tle, or Val;

X2 is 2Pal, 3Pal, Dab_Ac, Dab2HyAc, DabMs, DabTs, Gln, Glu, His, Hse, Lys_Ac, Lys_Dimethyl, Lys_Me3, Lys_PEG2_Me3, Lys1PEG2Ac, Lys2HyAc, LysMPA, LysMs, Orn_Ac, Orn2HyAc, OrnAc, OrnMs, OrnPVA, Phe_2Ad, Phe_3Ad, Phe_4Ad, Q_NHMe, Q_NMe2, Q_Pyro, Q_EtoMe, Tet1, or Thr;

X3 is Ala_cycBu, AlaCF3, AlaCHF2, Aoc, Cha, Chg, Cyclopentyl_Ala, Cyclopropyl_Ala, hCha, nVF3, Ogl, Phe_4tBu, Tba, Tle, or Val;

X4 is Asn, Gln, Glu, Glu_OMe, hE, His, LysMe3, Phe_4COOH, or Thr;

X5 is Cys, Hcy, Hhc, Lys_Ac, LysN3, O2S, O3S, O3S_Reduced, O3S_Me, O3S_Me_Reduced, O4S, O4S_Reduced, O5S, O5S_Reduced, or Pen;

X6 is 4SCF3Pro, 4SCyclohexPro, Oic, or Pro;

X7 is Acvc, Ala, Dab, Gln, Glu, His, Hpr, hR, Lys_Ac, Oic, Pro, Ser, or Tba;

X8 is aMe_Glu, Asp, Gla, Glu, or Tet1;

X9 is Aoc, Dgl, or Ogl;

X10 is 1Nal, 2Nal, aMe_Phe, aMe_Trp, Aoc, Cys, hCha, Hph, Phe_4COOH, Trp, Trp_4Cl, Trp_4Me, Trp_5Cl, Trp_5CONH2, Trp_5Et, Trp_5Me, Trp_6Cl, Trp_6CONH2, Trp_6Me, Trp_7Cl, Trp_7Me, or Trp_7Phe;

X11 is Aib, Ala, aMe_Asp, aMe_Leu, aMe_Phe, Asn, Asp, Chg, Glu, Leu, Lys_Me3, O3S, Phe_4Ad, Phe_4tBu, Ser, Tba, or Tle;

X12 is aMe_Trp, Trp, Trp_56diCl, Trp_5Cl, Trp_5Me, or Trp_6Cl;

X13 is Abu, Cys, Dab_Acetyl, Hcy, Hhc, O2S, O3S, O3S_Reduced, O3S_Me, O3S_Me_Reduced, O4S, O4S_Reduced, O5S, O5S_Reduced, or Pen;

X14 is Aib, Asn, Cys, dK, dL, dN, dQ, dR, Gln, Lys, Lys_1PEG2_1PEG2_IsoGlu_C12, Lys_Ac, Lys_PEG4_PEG4_NH2, Lys_PEG4_1PEG2_NH2, Lys_PEG8_NH2, Tba, or absent;

X15 is dR, dE, or absent;

X16 is dE, dQ, or absent;

wherein the peptide comprises a cyclic structure wherein X5 and X13 are either: (a) directly covalently linked or (b) indirectly covalently linked through a cyclization linker;

and wherein:

(i) the peptide is optionally a monomer in a homodimer or heterodimer complex, wherein each monomer is directly covalently linked to each other or indirectly covalently linked to each other through a dimerization linker; and/or

(ii) the peptide is optionally conjugated with a half-life extension moiety.

(Formula (III))

[00390] Representative compounds of Formula (III) include: C203, C217, C219, C222, C225, C270, C271, C283, C285, C289, C291, C292, C294, C295, C296, C298, C299, C301, C302, C303, C304, C305, C307, C309, C310, C312, C313, C314, C315, C316, C317, C318, C320, C321, C322, C323, C331, C332, C333, C334, C335, C336, C337, C340, C341, C349, C350, C351, C352, C356, C357, C358, C363, C367, C457, C488, C491, C494, C495, C496, C497, C498, C499, C500, C501, C502, C503, C504, C505, C508, C509, C510, C511, C513, C515, C517, C519, C520, C521, C522, C525, C528, C529, C530, C531, C532, C533, C534, C535, C536, C537, C538, C539, C540, C541, C542, C543, C544, C545, C546, C547, C548, C557, C559, C560, C561, C562, C566, C567, C568, C569, C570, C571, C572, C574, C575, C576, C577, C578, C579, C580, C581, C583, C584, C585, C586, C587, C588, C589, C590, C591, C592, C593, C594, C595, C596, C597, C598, C599, C600, C601, C604, C605, C606, C607, C608, C609, C610, C611, C612, C613, C614, C615, C617, C618, C620, C621, C629, C631, C632, C634, C647, C648, C650, C651, C654, C658, C659, C660, C661, C662, C672, C675, C677, C682, C686, C687, C688, C689, C690, C691, C693, C694, C695, C696, C697, C698, C699, C700, C701, C702, C703, C704, C705, C706, C707, C708, C709, C710, C711, C712, C713, C714, C715, C716, C717, C718, C719, C721, C722, C723, C724, C726, C727, C728, C729, C730, C731, C732, C733, C734, C735, C736, C737, C738, C739, C740, C741, C742, C743, C744, C746, C747, C748, C750, C751, C752, C754, C755, C756, C757, C758, C759, C760, C761, C762, C763, C764, C767, C765, C768, C769, C770, C771, C772, C774, C777, C778, C780, C781, C782, C783, C784, C785, C786, C787, C788, C789, C791, C792, C793, C794, C795, C796, C797, C798, C799, C800, C801, C802, C803, C804, C805, C806, C807, C808, C809, C810, C811, C812, C813, C814, C816, C817, C818, C819, C820, C821, C822,

C823, C824, C825, C826, C827, C828, C829, C830, C831, C832, C833, C834, C835, C836, C837, C838, C839, C840, C841, C842, C843, C844, C845, C846, and C847.

[00391] It should be noted that representative compounds of the Formulas can be determined through the information provided in Figure 1. Figure 1 provides the necessary cyclization, dimerization, potency, and stability information to determine which compounds fall under a particular Formula. The representative compounds of the Formulas listed herein is not necessarily comprehensive relative to Figure 1.

[00392] In some embodiments of Formula (III), the peptides comprise X5Hhc and X13Hhc, wherein these two residues are directly covalently linked through a disulfide bond. Other pairs can be any combination of Hhc, Cys, Hcy, Pen, HhPen, and their D-isoforms, or X5 and X13 can both be any one of these residues.

[00393] In some embodiments, Formula (III) peptides comprise X5Lys_Ac and X13Cys, or X5Hhc and X13 is Dab_Acetyl, wherein these two residues are directly covalently linked through a thioether bond. Other pairs include Lys_Ac, Orn_Ac or Dab_Ac, for one residue of the pair, and Hhc, Cys, Pen, HhPen, and Hcy as the other residue of the pair.

[00394] In another embodiment of Formula (III), X5 is Lys and X13 is hE (or vice versa), and these two residues are directly covalently linked through an amide bond (lactam).

[00395] In another embodiment of Formula (III), X5 is LysN3 and X13 is Abu (or vice versa), and these two residue are directly covalently linked as shown in paragraph [00324].

[00396] In some embodiments, Formula (III) peptides comprise O3S_Reduced at both X5 and X13.

[00397] In some embodiments, Formula (III) peptides comprise Hcy, Hhc, Cys, or Pen at X5 and X13, wherein these two residues are indirectly covalently linked through an Ebutene_Linkers or a Propane_Linkers, such that each of X5 and X13 form a thioether bond with a terminal end of the Ebutene_Linkers or the Propane_Linkers. In some embodiments, X5 and X13 can be D-isoforms of Hcy, Cys, Hhc, or Pen. Residues with a free thiol in its side chain can be covalently attached to a cyclization linker with two free and separated alkyl groups (one for each thiol). Such cyclization linkers include, for example, a Butane_Linkers, a Carbonyl_Linkers, a Dimethylcyclopropane_Linkers, an EButene linker, a Hexane_Linkers, a

Methylene_Linker, an Oxetane_Linker, a Pentane_Linker, a Propane linker, an oXylene linker, an mXylene linker, or a pXylene linker.

[00398] In some embodiments of Formula (III), the peptide is a monomer of a homodimer compound, wherein X14K of each monomer is covalently linked to a dimerization linker. The dimerization linker can be, for example, a PEG linker comprising functional moieties at its terminal ends, *e.g.*, see Table for PEGDA linkers, including PEG21DA and PEG25DA.

[00399] In some embodiments of Formula (III), the peptide is a monomer of a homodimer compound, wherein X14Lys_PEG4_PEG4_NH2, Lys_PEG4_1PEG2_NH2, or Lys_PEG8_NH2, of each monomer is covalently linked to a DIG dimerization linker.

[00400] In some embodiments of Formula (III), the peptide compound, whether a monomer or a dimer, has a half-life ($T_{1/2}$) of at least 0.5 hours, or between 1-1.5 hours, 1.5-2, or greater than 2 hours in an SGF and/or SIF assay.

[00401] In another embodiment, the invention provides a peptide compound that has an IC_{50} for hIL-17AA that is less than about 1nM, and has an IC_{50} for hIL-17FF that is less than about 10 nM, in a human IL-17 HEK Blue assay, wherein the peptide compound comprises a monomer peptide comprises or consists of the sequence of Formula (IV):

R^1 -X00-X0-X1-X2-X3-X4-X5-X6-X7-X8-X9-X10-X11-X12-X13-X14-X15-X16- R^2 ,

R^1 is acetyl, 3-hydroxypropionic acid, C6_diacid, cyclopropanecarboxylic acid, glutaric acid, isovaleric acid, methanesulfonyl acetic acid, or absent; R^2 is NH_2 , OH, or absent;

X00 is dH, Tle, or absent;

X0 is 2Pal, d2Pal, Asn, dE, dH, dQ, Gln, Glu, Glu_OMe, His, Ile, Lys, Lys_Me3, NMe_His, Orn, Sar, Thr, Tle, or absent;

X1 is 1Nal, Cha, Cyclopropyl_Alal, Dgl, DIP, hCha, hF, hhF, Ile, Ogl, Phe_4Me, Tba, Tle, or Val;

X2 is 2Pal, 3Pal, Dab_Ac, Dab2HyAc, DabMs, DabTs, E, Gln, His, Hse, Lys_Ac, Lys_Dimethyl, Lys_Me3, Lys_PEG2_Me3, Lys1PEG2Ac, Lys2HyAc, LysMPA, LysMs, OrnAc, Orn2HyAc, OrnMs, OrnPVA, Phe_2Ad, Phe_3Ad, Phe_4Ad, Q_NHMe, Q_NMe2, Q_Pyro, Q_EtOMe, Tet1, or Thr;

X3 is Ala_cycBu, AlaCF3, AlaCHF2, Aoc, Cha, Chg, Cyclopentyl_Alal, Cyclopropyl_Alal, hCha, nVF3, Ogl, Phe_4tBu, Tba, Tle, or Val;

X4 is Asn, Gln, Glu, Glu_OMe, hE, His, LysMe3, Phe_4COOH, or Thr;

X5 is Cys, Hcy, Hhc, Lys_Ac, LysN3, O2S, O3S, O3S_Reduced, O3S_Me, O3S_Me_Reduced, O4S, O4S_Reduced, O5S, O5S_Reduced, or Pen;

X6 is 4SCF3Pro, 4SCyclohexPro, Oic, or Pro;

X7 is Acvc, Ala, Dab, Gln, Glu, His, hR, Lys_Ac, Oic, Pro, Ser, or Tba;

X8 is aMe_Glu, Asp, Gla, Glu, or Tet1;

X9 is Aoc, Dgl, or Ogl;

X10 is 1Nal, 2Nal, aMe_Phe, aMe_Trp, Aoc, Cys, hCha, Hph, Phe_4COOH, Trp, Trp_4Cl, Trp_4COOH, Trp_4Me, Trp_5CONH2, Trp_6CONH2, Trp_6Me, Trp_7Me, or Trp_7Phe;

X11 is Aib, Ala, aMe_Asp, aMe_Leu, aMe_Phe, Asn, Asp, Chg, Glu, Leu, Lys_Me3, Phe_4Ad, Ser, Tba, or Tle;

X12 is aMe_Trp, Trp, Trp_56diCl, Trp_5Cl, Trp_5Me, or Trp_6Cl;

X13 is Abu, Cys, Dab_Acetyl, Hcy, Hhc, O2S, O3S, O3S_Reduced, O3S_Me, O3S_Me_Reduced, O4S, O4S_Reduced, O5S, O5S, or Pen;

X14 is Aib, Asn, Cys, dK, dN, dQ, dR, Gln, Lys, Lys_Ac, Lys_PEG4_PEG4_NH2, Lys_PEG4_1PEG2_NH2, Lys_PEG8_NH2, Tba, or absent;

X15 is dE, dR, or absent; and

X16 is dE, dQ, or absent;

wherein the peptide comprises a cyclic structure wherein X5 and X13 are either: (a) directly covalently linked or (b) indirectly covalently linked through a cyclization linker; and wherein: (i) the peptide is optionally a monomer in a homodimer or heterodimer complex, wherein each monomer is directly covalently linked to each other or indirectly covalently linked to each other through a dimerization linker; and/or (ii) the peptide is optionally conjugated with a half-life extension moiety (Formula (IV)).

[00402] In one embodiment of Formula (IV), both X5 and X13 are Hhc, and these two residues are directly covalently linked through a disulfide bond.

[00403] In another embodiment of Formula (IV), X5 is Lys_Ac and X13 is Cys, and these two residues are directly covalently linked through a thioether bond.

[00404] In another embodiment of Formula (IV), X5 is Hhc and X13 is Dab_Acetyl, and these two residues are directly covalently linked through a thioether bond.

[00405] In another aspect of Formula (IV), X5 is O5S_Reduced and X13 is Dab_Acetyl, and these two residues are directly covalently linked through a thioether bond.

[00406] In another aspect of Formula (IV), X5 is O5S_Reduced and X13 is Hhc, and these two residues are directly covalently linked through a thioether bond.

[00407] In another embodiment of Formula (IV), X5 is Lys and X13 is hE, or vice versa, and these two residues are directly covalently linked through a lactam.

[00408] In another embodiment of Formula (IV), X5 is LysN3 or Lys and X13 is Abu or hE, and these two residues are directly covalently linked as shown in paragraph [00324].

[00409] In another aspect of Formula (IV), both X5 and X13 are individually, or both, O3S_Reduced, O3S_Methyl_Reduced, or O4S_Reduced, and these two residues are directly covalently linked through a carbon-carbon single bond.

[00410] In another aspect of Formula (IV), X5 and X13 are individually, or both, O2S, O3S, O3S_Me, or O4S, and these two residues are directly covalently linked through a carbon-carbon double bond.

[00411] In another aspect of Formula (IV), X5 and X13 are individually, or both, Cys, Hcy, Hhc, or Pen, wherein X5 and X13 are indirectly covalently linked through a thioether bond, wherein these two residues are indirectly covalently linked through a thioether bond with a terminal end of a Carbonyl_Linkers, a Dimethylcyclopropane_Linkers, an EButene_Linkers, a Methylene_Linkers, an Oxetane_Linkers, a Pentane_Linkers, a Propane_Linkers, or a pXylene_Linkers

[00412] In another embodiment of Formula (IV), the peptide is a monomer in a homodimer compound, and wherein each monomer is directly covalently linked to a PEG linker at X14 through an amide bond, wherein one monomer is linked to one terminal end of the PEG linker and the other monomer is linked to the other terminal end of the PEG linker. The PEG linker can be, for example, PEG5DA, PEG9DA, PEG13DA, PEG21DA, or PEG25DA. X14 can be Lys, dK, Lys_Hexy, Lys_PEG12_NH, or a Lys analog with a side chain comprising a free amine.

[00413] In another embodiment of Formula (IV), the peptide is a monomer in a homodimer compound, and wherein each monomer is directly covalently linked to a DIG_linkers at X14Lys_PEG4_PEG4_NH2, X14Lys_PEG4_1PEG2_NH2, or X14Lys_PEG8_NH2, through

an amide bond, wherein one monomer is linked to one terminal end of this linker and the other monomer is linked to the other terminal end.

[00414] In another embodiment of Formula (IV), the compound exhibits a half-life greater than about 0.5 hours, 1.0 hours, 1.5 hours, or 2.0 hours, in an SGF and/or SIF stability assay.

[00415] Representative Formula (IV) peptide compounds include: C203, C219, C225, C270, C271, C283, C285, C288, C289, C291, C292, C294, C295, C296, C298, C299, C301, C302, C303, C304, C305, C307, C309, C310, C312, C313, C314, C315, C316, C317, C318, C320, C321, C322, C323, C331, C332, C333, C334, C335, C336, C337, C340, C341, C349, C350, C351, C352, C356, C357, C358, C363, C367, C457, C488, C491, C494, C495, C496, C497, C498, C499, C500, C501, C502, C503, C504, C505, C508, C509, C510, C511, C513, C515, C517, C519, C520, C521, C522, C525, C528, C529, C530, C531, C532, C533, C534, C535, C536, C537, C538, C539, C540, C541, C542, C543, C544, C545, C546, C547, C548, C557, C559, C560, C561, C562, C566, C567, C568, C569, C570, C571, C572, C574, C575, C576, C577, C578, C579, C580, C581, C583, C584, C585, C586, C587, C588, C589, C590, C591, C592, C593, C594, C595, C596, C597, C598, C599, C600, C601, C605, C606, C607, C608, C609, C610, C611, C612, C613, C614, C615, C617, C618, C620, C621, C629, C631, C632, C634, C647, C648, C650, C651, C654, C658, C659, C660, C661, C662, C664, C667, C672, C675, C677, C682, C686, C687, C688, C689, C690, C691, C693, C694, C695, C696, C697, C698, C699, C700, C701, C702, C703, C704, C705, C706, C707, C708, C709, C710, C711, C712, C713, C714, C715, C716, C717, C718, C719, C721, C722, C723, C724, C726, C727, C728, C729, C730, C731, C732, C733, C734, C735, C736, C737, C738, C739, C740, C741, C742, C743, C744, C746, C747, C748, C750, C751, C752, C754, C755, C756, C757, C758, C759, C760, C761, C762, C763, C764, C765, C767, C769, C770, C771, C772, C774, C777, C778, C780, C781, C782, C783, C784, C785, C786, C788, C789, C791, C792, C793, C794, C795, C796, C797, C798, C799, C800, C801, C802, C803, C804, C805, C806, C808, C809, C810, C811, C812, C813, C814, C816, C817, C818, C819, C820, C821, C822, C823, C824, C825, C826, C827, C828, C829, C830, C831, C832, C833, C834, C835, C836, C837, C838, C839, C840, C841, C842, C843, C844, C845, C846, and C847.

[00416] In one embodiment, the invention provides a peptide compound that has an IC₅₀ for hIL-17AA that is less than about 1nM, and has an IC₅₀ for hIL-17FF that is less than about 5

nM, in a human IL-17 HEK Blue assay, wherein the peptide compound comprises a monomer peptide comprises or consists of the sequence of Formula (V):

R^1 -X00-X0-X1-X2-X3-X4-X5-X6-X7-X8-X9-X10-X11-X12-X13-X14-X15-X16- R^2 ,

wherein:

R^1 is acetyl, 3-hydroxypropionic acid, C6_diacid, cyclopropanecarboxylic acid, glutaric acid, isovaleric acid, methanesulfonyl acetic acid, or absent; R^2 is NH₂, OH, or absent;

X00 is dH, Tle or absent;

X0 is dE, dH, dQ, Gln, Glu, Glu_OMe, His, Ile, Lys, Lys_Me3, Orn, Sar, Thr, Tle, or absent;

X1 is Cha, Cyclopropyl_Alal, Dgl, DIP, hhF, Ile, Tba, Tle, or Val;

X2 is 2Pal, 3Pal, Dab_Ac, Dab2HyAc, DabMs, DabTs, Gln, Glu, His, Hse, Lys_Ac, Lys_Dimethyl, Lys_Me3, Lys_PEG2_Me3, Lys1PEG2Ac, Lys2HyAc, LysMPA, LysMs, OrnAc, Orn2HyAc, OrnMs, OrnPVA, Phe_3Ad, Phe_4Ad, Q_NHMe, Q_NMe2, Q_Pyro, Q_EtOMe, Tet1, or Thr;

X3 is Ala_cycBu, AlaCF3, AlaCHF2, Cha, Chg, Cyclopentyl_Alal, Cyclopropyl_Alal, hCha, nVF3, Ogl, Tba, Tle, or Val;

X4 is Asn, Gln, Glu, Glu_OMe, hE, His, Phe_4COOH, or Thr;

X5 is Cys, Hcy, Hhc, Lys_Ac, LysN3, O2S, O3S, O3S_Reduced, O3S_Me, O3S_Me_Reduced, O4S, O4S_Reduced, O5S_Reduced, or Pen;

X6 is 4SCF3Pro or Oic;

X7 is Acvc, Ala, Gln, Glu, Lys_Ac, Oic, Pro, Ser, or Tba;

X8 is aMe_Glu, Asp, Glal, Glu, or Tet1;

X9 is Aoc, Dgl, or Ogl;

X10 is 1Nal, 2Nal, Aoc, Hph, Phe_4COOH, Trp, Trp_4Cl, Trp_4COOH, Trp_6CONH2, Trp_6Me, Trp_7Me, or Trp_7Phe;

X11 is Aib, Ala, aMe_Leu, aMe_Phe, Asn, Asp, Chg, Glu, Leu, Lys_Me3, Phe_4Ad, Ser, Tba, or Tle;

X12 is aMe_Trp, Trp, Trp_56diCl, or Trp_6Cl;

X13 is Abu, Cys, Dab_Acetyl, Hcy, Hhc, O2S, O3S, O3S_Reduced, O3S_Me, O3S_Me_Reduced, O4S, O4S_Reduced, or Pen;

X14 Asn, dK, Gln, Lys, Lys_PEG4_PEG4_NH2, Lys_PEG4_1PEG2_NH2, Lys_PEG8_NH2, or absent;

X15 is dE, dR, or absent; and

X16 is dE or absent;

wherein the peptide comprises a cyclic structure wherein X5 and X13 are either: (a) directly covalently linked or (b) indirectly covalently linked through a cyclization linker; and wherein: (i) the peptide is optionally a monomer in a homodimer or heterodimer complex, wherein each monomer is directly covalently linked to each other or indirectly covalently linked to each other through a dimerization linker; and/or (ii) the peptide is optionally conjugated with a half-life extension moiety.

Formula (V).

[00417] In one embodiment of Formula (V), both X5 and X13 are Hhc, and these two residues are directly covalently linked through a disulfide bond.

[00418] In another embodiment of Formula (V), X5 is Lys_Ac and X13 is Cys, and these two residues are directly covalently linked through a thioether bond.

[00419] In another embodiment of Formula (V), X5 is Hhc and X13 is Dab_Acetyl, and these two residues are directly covalently linked through a thioether bond.

[00420] In another aspect of Formula (V), X5 is O5S_Reduced and X13 is Hhc, and these two residues are directly covalently linked through a thioether bond.

[00421] In another embodiment of Formula (V), X5 is LysN3 and X13 is Abu, and these two residues are directly covalently linked as shown in paragraph [00324].

[00422] In another embodiment of Formula (V), X5 is O2S, O3S, or O4S, and X13 is O2S, O3S, O4S, or O3S_Me, and these two residues are directly covalently linked through a carbon-carbon double bond.

[00423] In another embodiment of Formula (V), X5 is O3S_Reduced and X13 is O3S_Reduced or O3S_Me_Reduced, and these two residues are directly covalently linked through a carbon-carbon single bond.

[00424] In another embodiment of Formula (V), X5 is Cys or Hcy, and X13 is Cys or Hcy, wherein X5 and X13 are indirectly covalently linked through a thioether bond, wherein these two residues are indirectly covalently linked through a thioether bond with a terminal end of a

Butane_Linkers, a Carbonyl_Linkers, a Dimethylcyclopropane_Linkers, an EButene_Linkers, an Oxetane_Linkers, a Pentane_Linkers, Propane_Linkers, or a pXylene_Linkers.

[00425] In other embodiments of Formula (V), the peptide is a monomer in a homodimer compound, and wherein each monomer is directly covalently linked to a PEG linker at X14Lys through an amide bond, wherein one monomer is linked to one terminal end of the PEG linker and the other monomer is linked to the other terminal end of the PEG linker. The PEG linker can be, for example, PEG5DA, PEG9DA, PEG13DA, PEG21DA, or PEG25DA.

[00426] In another embodiment of Formula (V), the peptide is a monomer in a homodimer compound, and wherein each monomer is directly covalently linked to a DIG linker at X14Lys_PEG4_PEG4_NH2, X14Lys_PEG4_1PEG2_NH2, or X14Lys_PEG8_NH2, through an amide bond, wherein one monomer is linked to one terminal end of this linker and the other monomer is linked to the other terminal end.

[00427] In other embodiments of Formula (V), the compound exhibits a half-life greater than about 0.5 hours, 1.0 hours, 1.5 hours, or 2.0 hours, in an SGF and/or SIF stability assay.

[00428] Representative Formula (V) peptides include: C219, C225, C270, C271, C283, C285, C291, C292, C294, C295, C296, C298, C299, C301, C302, C303, C304, C305, C307, C309, C310, C312, C313, C314, C315, C316, C317, C320, C321, C331, C332, C333, C334, C335, C336, C337, C341, C349, C350, C351, C363, C367, C457, C488, C491, C494, C495, C496, C497, C498, C500, C501, C503, C505, C508, C509, C510, C511, C513, C515, C517, C519, C520, C521, C522, C528, C529, C530, C531, C532, C533, C534, C535, C536, C537, C538, C539, C540, C541, C542, C543, C544, C545, C546, C547, C548, C559, C560, C561, C562, C564, C565, C566, C567, C568, C569, C570, C571, C572, C574, C575, C576, C577, C578, C579, C581, C583, C584, C585, C586, C587, C589, C590, C591, C592, C593, C594, C597, C598, C599, C600, C601, C605, C606, C607, C608, C609, C610, C611, C612, C613, C614, C617, C618, C647, C675, C686, C687, C688, C689, C690, C691, C693, C694, C695, C696, C697, C698, C699, C700, C701, C702, C703, C704, C705, C706, C707, C708, C709, C710, C711, C712, C713, C715, C716, C717, C718, C719, C721, C722, C723, C724, C726, C727, C728, C729, C730, C731, C732, C733, C734, C735, C737, C738, C739, C741, C742, C743, C744, C746, C747, C748, C750, C751, C752, C754, C755, C756, C757, C758, C759, C760, C761, C762, C763, C764, C765, C768, C771, C783, C785, C786, C787, C788, C791, C792,

C793, C794, C795, C796, C797, C798, C799, C800, C801, C802, C803, C804, C805, C806, C808, C809, C810, C811, C812, C813, C814, C816, C817, C818, C819, C820, C821, C822, C823, C824, C825, C826, C827, C828, C829, C830, C831, C832, C833, C834, C835, C836, C837, C838, C839, C840, C841, C842, C843, C844, C845, C846, and C847.

[00429] In one embodiment, the invention provides a peptide compound that has an IC₅₀ for hIL-17AA that is less than about 1nM and for hIL-17FF that is less than about 1 nM in a human IL-17 HEK Blue assay, wherein the peptide compound comprises a monomer peptide comprising or consisting of the sequence of Formula (VI):

R¹-X00-X0-X1-X2-X3-X4-X5-X6-X7-X8-X9-X10-X11-X12-X13-X14-X15-X16-R²,

wherein:

R¹ is acetyl, 3-hydroxypropionic acid, C6_diacid, cyclopropanecarboxylic acid, glutaric acid, isovaleric acid, methanesulfonyl acetic acid, or absent; R² is NH₂, OH, or absent;

X00 is dH or absent;

X0 is dE, dH, Gln, Glu, Glu_OMe, His, Ile, Lys_Me3, Sar, Tle, or absent;

X1 is Cyclopropyl_Alal, Ile, Tba, or Val;

X2 is Dab_Ac, Gln, Glu, His, Hse, Lys_Ac, Lys_Me3, Lys1PEG2Ac, Lys2HyAc, LysMs, Orn2HyAc, OrnAc, Q_NHMe, Q_NMe2, Q_EtOMe, or Thr;

X3 is Cyclopropyl_Alal, Ogl, Tba, Tle, or Val;

X4 is Asn, Glu, Glu_OMe, hE, Phe_4COOH, or Thr;

X5 is Cys, Hcy, Hhc, O2S, O3S, O3S_Reduced, or O4S;

X6 is Oic;

X7 is Acvc, Ala, Gln, Glu, Lys_Ac, Pro, Ser, or Tba;

X8 is Asp or Gla;

X9 is Dgl, or Ogl;

X10 is 1Nal, 2Nal, or Trp;

X11 is Aib, Asp, or Glu;

X12 is aMe_Trp or Trp;

X13 is Cys, Hcy, Hhc, O2S, O3S, O3S_Me, O3S_Me_Reduced, O3S_Reduced, or O4S;

X14 Asn, Lys, Lys_PEG4_1PEG2_NH2, Lys_PEG8_NH2, or Lys_PEG4_PEG4_NH2;

X15 is dR; and

X16 is dE or absent;

wherein the peptide comprises a cyclic structure wherein X5 and X13 are either: (a) directly covalently linked or (b) indirectly covalently linked through a cyclization linker; and wherein: (i) the peptide is optionally a monomer in a homodimer or heterodimer complex, wherein each monomer is directly covalently linked to each other or indirectly covalently linked to each other through a dimerization linker; and/or (ii) the peptide is optionally conjugated with a half-life extension moiety (Formula (VI)).

[00430] In one embodiment of Formula (VI), both X5 and X13 are Hhc, and these two residues are directly covalently linked through a disulfide bond.

[00431] In another embodiment Formula (VI), X5 is O2S, O3S, or O4S, and X13 is O2S, O3S, O4S, or O3S_Me, and these two residues are directly covalently linked through a carbon-carbon double bond.

[00432] In another embodiment of Formula (VI), X5 is O3S_Reduced and X13 is O3S_Reduced or O3S_Me_Reduced, and these two residues are directly covalently linked through a carbon-carbon single bond.

[00433] In another embodiment of Formula (VI), X5 is Cys or Hcy, and X13 is Cys or Hcy, wherein X5 and X13 are indirectly covalently linked through a thioether bond, wherein these two residues are indirectly covalently linked through a thioether bond with a terminal end of a Butane_Linkers, a Carbonyl_Linkers, a Dimethylcyclopropane_Linkers, an EButene_Linkers, an Oxetane_Linkers, a Pentane_Linkers, or a Propane_Linkers.

[00434] In other embodiments of Formula (VI), the peptide is a monomer in a homodimer compound, and wherein each monomer is directly covalently linked to a PEG linker at X14Lys through an amide bond, wherein one monomer is linked to one terminal end of the PEG linker and the other monomer is linked to the other terminal end of the PEG linker. The PEG linker can be, for example, PEG5DA, PEG9DA, PEG13DA, PEG21DA, or PEG25DA.

[00435] In another embodiment of Formula (VI), the peptide is a monomer in a homodimer compound, and wherein each monomer is directly covalently linked to a DIG_linker at X14Lys_PEG4_PEG4_NH2, X14Lys_PEG4_1PEG2_NH2, or X14Lys_PEG8_NH2, through an amide bond, wherein one monomer is linked to one terminal end of this linker and the other monomer is linked to the other terminal end.

[00436] In other embodiments of Formula (VI), the compound exhibits a half-life greater than about 0.5 hours, 1.0 hours, 1.5 hours, or 2.0 hours, in an SGF and/or SIF stability assay.

[00437] In another embodiment of Formula (VI), R¹ is Acetyl or isovaleric acid, and R² is an amine.

[00438] Representative Formula (VI) compounds include: C270, C271, C302, C304, C305, C315, C316, C331, C332, C335, C494, C496, C503, C515, C517, C519, C520, C522, C529, C530, C531, C532, C533, C534, C535, C536, C537, C542, C543, C544, C545, C546, C547, C548, C566, C567, C570, C571, C574, C575, C581, C583, C584, C585, C586, C587, C590, C591, C592, C593, C598, C599, C600, C601, C604, C686, C687, C688, C690, C691, C693, C694, C695, C696, C699, C700, C701, C702, C703, C704, C705, C707, C708, C709, C710, C711, C712, C713, C722, C730, C731, C734, C737, C738, C742, C743, C744, C746, C747, C750, C751, C755, C756, C757, C758, C759, C760, C761, C762, C763, C764, C765, C787, C788, C789, C791, C792, C793, C796, C810, C811, C812, C813, C814, C816, C817, C818, C819, C820, C821, C823, C824, C825, C826, C827, C828, C829, C830, C831, C832, C833, C834, C835, C836, C837, C838, C839, C840, C841, C842, C844, C845, and C846.

[00439] In one embodiment, the invention provides a peptide compound that has an IC₅₀ for hIL-17AA that is less than about 1nM, wherein the peptide compound comprises a monomer peptide comprising or consisting of the sequence of Formula (VII):

R¹-X00-X0-X1-X2-X3-X4-X5-X6-X7-X8-X9-X10-X11-X12-X13-X14-X15-X16-X17-X18-X19-X20-X21-X22-X23-X24-R²,

wherein:

R¹ is acetyl, 3-hydroxypropionic acid, C6_diacid, cyclopropanecarboxylic acid, glutaric acid, glycolic acid, isovaleric acid, methanesulfonyl acetic acid, or absent; R² is NH₂ or OH or absent;

X00 is bA, dH, dK, Tle or absent;

X0 is 2Pal, Aib, Asn, d2Pal, d3Pal, dA, dE, dH, dL, dQ, dS, Gla, Gln, Glu, Glu_OMe, His, Ile, Lys, Lys_Me3, NMe_His, Orn, Pro, Sar, Thr, Tle, or absent;

X1 is 1Nal, Aph, Dgl, hCha, hF, hhF, Ile, Lys_1PEG2_1PEG2_IsoGluC12, Ogl, Phe_4Me, Tba, Tle, or Val;

X2 is 2Pal, 3Pal, Gln, His, Hse, Lys_1PEG2_1PEG2_IsoGluC12, Lys_Me3, Orn, Phe_3Ad, Phe_4_2ae, or Phe_4ad;

X3 is Cpg, Cyclopropyl-Ala, Dgl, Ogl, Phe_4tBu, Tba, Tle, or Val;

X4 is Asn, Glu, or Thr;

X5 is Cys, Hcy, Hhc, Ile, Lys_Ac, O3S, O3S_Reduced, or O5S_Reduced;

X6 is Oic or Pro;

X7 is Ala, Aze, Dab, His, Lys_Ac, O3S_Me, or Tic;

X8 is Asp or Gla;

X9 is Dgl, Ogl, or O3S;

X10 is 1Nal, 2Nal, aMe_Phe, aMe_Trp, Aoc, Cys, Gln, hCha, Hph, O3S, Phe_4Ad, Phe_4COOH, Tba, Tle, Trp, Trp_4Cl, Trp_4Me, Trp_5Cl, Trp_5Me, Trp_6Cl, Trp_6Me, Trp_7Cl, Trp_7Me, or Trp_7Phe;

X11 is Asp, dA, Glu, or O3S_Me;

X12 is aMe_Trp, Trp, Trp_5Cl, Trp_5Me, or Trp_6Cl;

X13 is Cys, Hcy, Hhc, Ile, O3S, O3S_Me, O3S_Reduced, or O4S;

X14 Aib, Arg, Asn, Asp, Cys, dE, dK, dN, dQ, dR, Gln, Glu, Gly, Lys, Lys_1PEG2_1PEG2_IsoGlu_C12, Lys_Ac, O3S_Me, Tba, or absent;

X15 is Ala, Asn, dE, dQ, dR, Gln, Gly, Leu, Pro, Ser, or absent;

X16 is Aad, dE, dH, dQ, PEG4, PEG6, PEG8, Ser, Thr, Val, or absent;

X17 is Asp, Gly, Glu, His, Ile, Pro, or absent;

X18 is His, Ile, Ser, Tle, Val, or absent;

X19 is His, Ile, Val, or absent;

X20 is His, Thr, Val, or absent;

X21 is Ile, Thr, Val, or absent;

X22 is Ile, Thr, or absent;

X23 is Ile or absent;

X24 is Oic, Pro, or absent;

wherein the peptide comprises a cyclic structure wherein X5 and X13, X9 and X13, or X7 and X11, are either: (a) directly covalently linked or (b) indirectly covalently linked through a cyclization linker.

(Formula (VII)).

[00440] In one embodiment of Formula (VII), the peptide compound is a monomer (not a multimer).

[00441] In one embodiment of Formula (VII), both X5 and X13 are Hhc, and these two residues are directly covalently linked through a disulfide bond.

[00442] In one embodiment of Formula (VII), X5 is Lys_Ac and X13 is Cys, and these two residues are directly covalently linked through a thioether bond

[00443] In one embodiment of Formula (VII), X5 is O5S_Reduced and X13 is Hhc, and these two residues are directly covalently linked through a thioether bond.

[00444] In another embodiment of Formula (VII), both X5 and X13 are O3S, or X5 and X13 are individually or both O3S, O4S, or O3S_Methyl, and these two residues are directly covalently linked through a carbon-carbon double bond.

[00445] In another embodiment of Formula (VII), both X5 and X13 are O3S_Reduced, and these two residues are directly covalently linked through a carbon-carbon single bond.

[00446] In another embodiment of Formula (VII), X5 is Cys or Hcy, and X13 is Cys or Hcy, wherein X5 and X13 are indirectly covalently linked through a thioether bond, wherein these two residues are indirectly covalently linked through a thioether bond with a terminal end of a Butane_Linkers, Dimethylcyclopropane_Linkers, an EButene_Linkers, a Hexane_Linkers, a Methylene_Linkers, an Oxetane_Linkers, a Pentane_Linkers, a Propane_Linkers, or a Xylene_Linkers.

[00447] In another embodiment of Formula (VII), X9 and X13 are both O3S, which are directly covalently linked through a carbon-carbon single bond.

[00448] In another embodiment of Formula (VII), X7 and X11 are both O3S_Me, which are directly covalently linked through a carbon-carbon double bond.

[00449] In another embodiment, each monomer is directly covalently linked to a PEG linker at X14Lys through an amide bond, wherein one monomer is linked to one terminal end of the PEG linker and the other monomer is linked to the other terminal end of the PEG linker. The PEG linker can be, for example, PEG5DA, PEG9DA, PEG13DA, PEG21DA, or PEG25DA.

[00450] In other embodiments, a peptide of Formula (VII) can be a monomer in a homodimer compound. As described herein, the monomer can be dimerized in multiple ways, such as

having a lysine at a residue prior to or after the cyclization residues. In one embodiment, a homodimer comprising a monomer of Formula (VII) can be dimerized by covalently attaching a PEG linker to each monomer through an amide bond to the side chain of a lysine.

[00451] In another embodiment, a homodimer comprising a monomer of Formula (VII) can be modified to have a lysine with a modified side-chain that comprises PEG units and a free amine, such that the amine can form an amide bond with a linker having free COOH groups, such as the DIG_Linkers.

[00452] In other embodiments of Formula (VII), the compound exhibits a half-life greater than about 0.5 hours, 1.0 hours, 1.5 hours, or 2.0 hours, in an SGF and/or SIF stability assay.

[00453] In another embodiment of Formula (VII), the compound has an IC₅₀ for hIL-17AA that is less than about 1nM and an IC₅₀ for hIL-17FF that is less than about 10 nM, wherein the peptide comprises the following:

R¹ is acetyl, glutaric acid, glycolic acid, or isovaleric acid; R² is NH₂;

X00 is bA or absent;

X0 is 2Pal, d2Pal, dE, dH, Gla, Glu, His, NMe_His, Tle, or absent;

X1 is 1Nal, Aph, Dgl, hF, hhF, Ile, Tle, or Val;

X2 is 2Pal, 3Pal, or His;

X3 is Tba or Tle;

X4 is Thr;

X5 is Cys, Hcy, Hhc, or O3S;

X6 is Oic;

X7 is Ala or Lys_Ac;

X8 is Asp;

X9 is Dgl or Ogl;

X10 is Cys, Trp, Trp_7Me, or Trp_7Phe;

X11 is Asp or Glu;

X12 is aMe_Trp or Trp;

X13 is Hcy, Hhc, O3S, O3S_Me, or O4S;

X14 Aib, Asn, Asp, Cys, Gln, Gly, Lys_1PEG2_1PEG2_IsoGlu_C12, or Lys_Ac;

X15 is Ala, Asn, dQ, dR, Gln, Gly, Leu, Ser, or absent;

X16 is Aad, dE, Ser, Thr, Val, or absent;

X17 is Asp, His, or absent; and

X18 is Ser, Val, or absent;

wherein the peptide comprises a cyclic structure wherein X5 and X13 are either: (a) directly covalently linked or (b) indirectly covalently linked through a cyclization linker.

[00454] In another embodiment of Formula (VII), the compound has an IC₅₀ for hIL-17AA that is less than about 1nM and an IC₅₀ for hIL-17FF that is less than about 10 nM, and the compound exhibits a half-life in both an SGF and an SIF assay greater than about 2 hours, wherein the peptide comprises the following:

R¹ is acetyl, glutaric acid, glycolic acid, or isovaleric acid; R² is NH₂;

X00 is bA or absent;

X0 is 2Pal, d2Pal, dE, dH, Glu, His, NMe_His, Tle, or absent;

X1 is 1Nal, Aph, Dgl, hF, hhF, Ile, Tle, or Val;

X2 is 2Pal, 3Pal, or His;

X3 is Tba or Tle;

X4 is Thr;

X5 is Cys, Hcy, Hhc, or O3S;

X6 is Oic;

X7 is Ala or Lys_Ac;

X8 is Asp;

X9 is Dgl or Ogl;

X10 is Cys, Trp, Trp_7Me, or Trp_7Phe;

X11 is Asp or Glu;

X12 is aMe_Trp or Trp;

X13 is Hcy, Hhc, O3S, O3S_Me, or O4S;

X14 Aib, Asn, Cys, Gln, Lys_1PEG2_1PEG2_IsoGlu_C12, or Lys_Ac;

X15 is Ala, dQ, dR, Gln, or absent;

X16 is Aad, dE, or absent;

X17-X24 are absent;

wherein the peptide comprises a cyclic structure wherein X5 and X13 are either: (a) directly covalently linked or (b) indirectly covalently linked through a cyclization linker.

[00455] Representative monomer peptide compounds (*i.e.*, not representative homodimer compounds that could fall under Formula (VII)) include: C218, C231, C269, C271, C273, C286, C288, C290, C342, C344, C348, C351, C352, C353, C354, C355, C357, C360, C362, C374, C375, C376, C378, C384, C397, C399, C402, C403, C406, C407, C409, C410, C411, C436, C438, C441, C447, C456, C457, C458, C459, C461, C462, C463, C468, C471, C482, C483, C484, C514, C529, C530, C538, C539, C540, C541, C549, C550, C551, C552, C553, C573, C582, C596, C597, C602, C603, C604, C605, C606, C607, C608, C609, C610, C611, C612, C613, C614, C615, C616, C617, C618, C619, C620, C621, C622, C623, C624, C625, C626, C627, C628, C629, C630, C631, C632, C633, C634, C635, C636, C637, C638, C639, C640, C641, C642, C643, C644, C645, C646, C647, C648, C649, C650, C641, C652, C653, C654, C655, C657, C658, C659, C660, C661, C662, C663, C664, C665, C666, C667, C668, C670, C671, C672, C673, C674, C675, C676, C677, C678, C679, C680, C681, C682, C683, C684, C685, C766, C767, C768, C769, C770, C771, C772, C773, C774, C775, C776, C777, C778, C779, C780, C781, C782, C783, C784, C785, C786, C790, C797, C798, C799, C800, C801, C802, C803, C804, C805, C806, C809, C855, C856, C857, C858, C859, C860, C861, C862, C863, C864, C865, C866, C867, C868, C869, C870, C871, C872, C873, C874, C875, C876, C877, C878, C879, C880, C881, C882, C883, C884, C885, C886, C887, C888, C889, C890, C891, C892, C893, C894, C895, C896, and C897..

[00456] In one embodiment, the invention provides a peptide compound that has an IC₅₀ for hIL-17AA and FF that is less than about 1nM in a human IL-17 HEK Blue assay, wherein the peptide compound exhibits a half-life in an SIF assay greater than about 2 hours, wherein the peptide compound comprises a monomer peptide comprising or consisting of the sequence of Formula (VIII):

R¹-X00-X0-X1-X2-X3-X4-X5-X6-X7-X8-X9-X10-X11-X12-X13-X14-X15-X16-R²,

wherein:

R¹ is acetyl, 3-hydroxypropionic acid, C₆ diacid, cyclopropanecarboxylic acid, glutaric acid, isovaleric acid, methanesulfonyl acetic acid, or absent; R² is NH₂, OH, or absent;

X00 is dH or absent;

X0 is dE, dH, Gln, Glu, His, Ile, Lys_Me3, Sar, Tle, or absent;

X1 is Cyclopropyl_Alal, Ile, Tba, or Val;

X2 is Dab_Ac, Gln, His, Lys_Ac, Lys_Me3, Lys1PEG2Ac, Lys2HyAc, Orn2HyAc, OrnAc, or Thr;

X3 is Cyclopropyl_Alal, Ogl, Tba, Tle, or Val;

X4 is Asn, Glu, Glu_OMe, hE, or Thr;

X5 is Cys, Hcy, Hhc, O2S, O3S, O3S_Reduced, or O4S;

X6 is Oic;

X7 is Acvc, Ala, Gln, Glu, Lys_Ac, Pro, Ser, or Tba;

X8 is Asp or Gla;

X9 is Dgl, or Ogl;

X10 is 1Nal, 2Nal, or Trp;

X11 is Aib, Asp, or Glu;

X12 is aMe_Trp or Trp;

X13 is Cys, Hcy, Hhc, O2S, O3S, O3S_Me, O3S_Reduced, or O4S;

X14 is Asn, Lys, , Lys_PEG4_1PEG2_NH2, Lys_PEG8_NH2, or Lys_PEG4_PEG4_NH2;

X15 is dR; and

X16 is absent;

wherein the peptide comprises a cyclic structure wherein X5 and X13 are either: (a) directly covalently linked or (b) indirectly covalently linked through a cyclization linker; and wherein: (i) the peptide is optionally a monomer in a homodimer or heterodimer complex, wherein each monomer is directly covalently linked to each other or indirectly covalently linked to each other through a dimerization linker; and/or (ii) the peptide is optionally conjugated with a half-life extension moiety (Formula (VIII)).

[00457] In one embodiment of Formula (VIII), both X5 and X13 are Hhc, and these two residues are directly covalently linked through a disulfide bond.

[00458] In another embodiment of Formula (VIII), both X5 and X13 are individually or both O2S, O3S, O3S_Methyl, or O4S, and these two residues are directly covalently linked through a carbon-carbon double bond.

[00459] In another embodiment of Formula (VIII), both X5 and X13 are O3S_Reduced, and these two residues are directly covalently linked through a carbon-carbon single bond.

[00460] In another embodiment of Formula (VIII), X5 is Cys or Hcy, and X13 is Cys or Hcy, wherein X5 and X13 are indirectly covalently linked through a thioether bond, wherein these two residues are indirectly covalently linked through a thioether bond with a terminal end of a Dimethylcyclopropane_Linker, an Oxetane_Linker, a Pentane_Linker, or a Propane_Linker.

[00461] In other embodiments of Formula (VIII), the peptide is a monomer in a homodimer compound, and wherein each monomer is directly covalently linked to a PEG linker at X14Lys through an amide bond, wherein one monomer is linked to one terminal end of the PEG linker and the other monomer is linked to the other terminal end of the PEG linker. The PEG linker can be, for example, PEG5DA, PEG9DA, PEG13DA, PEG21DA, or PEG25DA.

[00462] In other embodiments, a peptide of Formula (VIII) can be a monomer in a homodimer compound. As described herein, the monomer can be dimerized in multiple ways, such as having a lysine at a residue prior to or after the cyclization residues. In one embodiment, a homodimer comprising a monomer of Formula (VIII) can be dimerized by covalently attaching a PEG linker to each monomer through an amide bond to the side chain of a lysine.

[00463] In another embodiment, a homodimer comprising a monomer of Formula (VII) can be modified to have a lysine with a modified side-chain that comprises at least one PEG unit and a free amine, such that the amine can form an amide bond with a linker having free COOH groups at its terminal ends, such as the DIG_Linker. Thus, in one embodiment, X14 is Lys_PEG4_PEG4_NH2, Lys_PEG4_1PEG2_NH2, or Lys_PEG8_NH2, and the dimerization linker is a DIG_Linker.

[00464] In other embodiments of Formula (VIII), the compound exhibits a half-life greater than about 0.5 hours, 1.0 hours, 1.5 hours, or 2.0 hours, in an SGF stability assay.

[00465] Representative Formula (VIII) compounds include: C271, C302, C304, C331, C332, C335, C494, C496, C515, C517, C519, C530, C531, C532, C533, C534, C535, C537, C542, C543, C544, C545, C546, C547, C548, C566, C567, C570, C571, C574, C575, C581, C583, C584, C585, C586, C587, C590, C591, C592, C593, C598, C599, C600, C601, C604, C690, C693, C699, C700, C701, C702, C707, C708, C709, C710, C711, C712, C713, C722, C734, C737, C738, C742, C743, C744, C747, C750, C756, C757, C758, C760, C761, C762, C763,

C764, C765, C787, C788, C789, C791, C792, C793, C796, C816, C817, C818, C819, C820, C821, C823, C824, C825, C826, C827, C828, C829, C830, C831, C832, C833, C834, C835, C836, C837, C838, C839, C840, C841, C842, C844, C845, and C846.

[00466] In one embodiment, the invention provides a peptide compound that has an IC_{50} for hIL-17AA that is less than about 1 nM and for IL-17FF that is less than about 5nM, wherein the peptide compound exhibits a half-life in both an SGF and an SIF assay greater than about 2 hours, wherein the peptide compound comprises a monomer peptide comprising or consisting of the sequence of Formula (IX):

R^1 -X00-X0-X1-X2-X3-X4-X5-X6-X7-X8-X9-X10-X11-X12-X13-X14-X15-X16- R^2 ,

wherein:

R^1 is acetyl, 3-hydroxypropionic acid, C6_diacid, cyclopropanecarboxylic acid, glutaric acid, isovaleric acid, methanesulfonyl acetic acid, or absent; R^2 is NH_2 or OH or absent;

X00 is dH or absent;

X0 is dE, dH, Glu, His, Ile, Lys_Me3, Sar, Tle, or absent;

X1 is Ile or Val;

X2 is His, Lys_Me3, or Gln;

X3 is Tba, Tle, or Val;

X4 is Asn, Glu, Glu_OMe, hE, or Thr;

X5 is Cys, Hcy, Hhc, O3S, or O3S_Reduced;

X6 is Oic;

X7 is Acvc, Ala, Gln, Glu, Lys_Ac, Pro, Ser, or Tba;

X8 is Asp or Gla;

X9 is Dgl or Ogl;

X10 is 1Nal, 2Nal, or Trp;

X11 is Aib, Asp, or Glu;

X12 is aMe_Trp or Trp;

X13 is Cys, Hcy, Hhc, O3S, O3S_Me, or O3S_Reduced;

X14 is Lys, Lys_PEG4_1PEG2_NH2, Lys_PEG8_NH2, or Lys_PEG4_PEG4_NH2;

X15 is dR; and

X16 is absent;

wherein the peptide comprises a cyclic structure wherein X5 and X13 are either: (a) directly covalently linked or (b) indirectly covalently linked through a cyclization linker; and wherein: (i) the peptide is a monomer in a homodimer complex, wherein each monomer is covalently linked to a dimerization linker; and/or (ii) the peptide is optionally conjugated with a half-life extension moiety (Formula (IX)).

[00467] In one embodiment of Formula (IX), both X5 and X13 are Hhc, and these two residues are directly covalently linked through a disulfide bond.

[00468] In another embodiment of Formula (IX), both X5 and X13 are O3S and these two residues are directly covalently linked through a carbon-carbon double bond.

[00469] In another embodiment of Formula (IX), X5 is O3S and X13 is O3S or O3S_Me and these two residues are directly covalently linked through a carbon-carbon double bond.

[00470] In another embodiment of Formula (IX), both X5 and X13 are O3S_Reduced, and these two residues are directly covalently linked through a carbon-carbon single bond.

[00471] In another embodiment of Formula (IX), X5 is Cys or Hcy, and X13 is Cys or Hcy, wherein X5 and X13 are indirectly covalently linked through a thioether bond, wherein these two residues are indirectly covalently linked through a thioether bond with a terminal end of a Dimethylcyclopropane_Linkers, a Pentane_Linkers, or a Propane_Linkers.

[00472] In other embodiments of Formula (IX), the peptide is a monomer in a homodimer compound, and wherein each monomer is directly covalently linked to a PEG linker at X14Lys through an amide bond, wherein one monomer is linked to one terminal end of the PEG linker and the other monomer is linked to the other terminal end of the PEG linker. The PEG linker can be, for example, PEG5DA, PEG9DA, PEG13DA, PEG21DA, or PEG25DA.

[00473] In another aspect of Formula (IX), the peptide is a monomer in a homodimer compound, and wherein each monomer is directly covalently linked to a DIG_linkers at X14Lys_PEG4_PEG4_NH2, X14Lys_PEG4_1PEG2_NH2, or X14Lys_PEG8_NH2 (or its D-form, i.e., dK_PEG4_PEG4_NH2 et al.) through an amide bond, wherein one monomer is linked to one terminal end of this linker and the other monomer is linked to the other terminal end.

[00474] In other embodiments of Formula (IX), the peptide is a monomer in a homotrimer compound, and wherein the amine at the terminal end of the side chain of

X14Lys_PEG12_NH, X14Lys_PEG4_PEG4_NH2, X14Lys_PEG4_1PEG2_NH2, or X14Lys_PEG8_NH2, in each monomer is covalently linked to the same multimerization linker, TAEP, through an amide bond. The PEG portion in a lysine analog side-chain can be modified to increase or decrease the number of PEG units.

[00475] In other embodiments, any monomer peptide of the invention can be part of a homotrimer through this multimerization approach, i.e., X14Lys_PEG12_NH (or another Lys analog comprising a PEG unit and a free NH2 in its side-chain) with a TAEP multimerization linker.

[00476] In other embodiments, any monomer peptide of the invention can be part of a homotetramer compound, wherein the methyl at the terminal end of the side chain of a residue (for example, X14Lys_Hexy) in each monomer is covalently linked to the same multimerization linker, TetN3, through a carbon-carbon single bond.

[00477] Representative Formula (IX) compounds include: C292, C313, C314, C317, C349, C351, C498, C500, C513, C517, C533, C537, C542, C543, C544, C545, C546, C547, C548, C551, C564, C565, C570, C571, C572, C574, C575, C577, C581, C586, C587, C592, C593, C599, C601, C690, C693, C699, C722, C734, C737, C738, C707, C708, C709, C712, C713, C742, C743, C744, C750, C758, C760, C761, C762, C763, C764, C765, C787, C789, C791, C792, C793, C796, C816, C817, C818, C819, C820, C821, C822, C823, C824, C825, C826, C827, C828, C829, C830, C831, C832, C833, C834, C835, C836, C837, C838, C839, C840, C841, C842, C843, C844, C845, C846, and C847.

[00478] In some embodiments, a peptide compound comprising a monomer of any of the Formulas herein (including SEQ ID NO formulas) has an IC₅₀ less than 100, 90, 80, 70, 60, 50, 40, 30, 20, 10, 5, or 1 nM in a 3T3 Cell Line IL-6 secretion assay (see Example 3).

2D. Prodrug Forms of IL-17 Antagonist Peptides

[00479] A prodrug is a compound that undergoes chemical conversion by an enzymatic or non-enzymatic chemical process in vivo resulting in liberation of the parent drug. Herein, the parent drug is an IL-17 antagonist peptide of the invention, i.e., a peptide according to one of Formulas (I) et al., a peptide according to one of the compounds of Figure 1, or a peptide according to any of the SEQ ID NOs. An intact prodrug is not substantially pharmacologically active. Rather, herein, a dipeptide-based amide or ester extension is attached to the N-terminus, C-terminus, or side chain, of an IL-17 antagonist peptide of the invention, whereupon in vivo,

the extension is cleaved from the peptide of the invention, resulting in the liberation of the peptide in its free form.

[00480] Dipeptides are known in the art for prodrug development for targeting or targeted transport as they are substrates for enzymes or biotransport systems or for the non-enzymatic route for dipeptide prodrug formation, namely the ability to undergo intramolecular cyclization to form the corresponding diketopiperazine (DKP) or diketomorpholine (DKM) and release the active drug. See, e.g., US20110237493A1 and US20130137849A1, both of which are hereby incorporated-by-reference for their teachings on suitable dipeptide moieties that can be attached to the IL-17 antagonist peptides described herein. Potential susceptibility of dipeptide-based prodrugs to peptidases may be addressed by incorporating at least one non-natural amino acid in the dipeptide motif.

[00481] Such dipeptides may be attached to a drug via ester bonds. In this case, the cyclization reaction consists of a nucleophilic attack of the N-terminal amine of the peptide on the ester carbon atom to form a tetrahedral intermediate. This is followed by a proton transfer from the amine to the leaving group oxyanion with simultaneous formation of a peptide bond to give the cyclic DKP product and free drug. The reaction has been described for ester prodrugs for example for cyclosporin A (Hamel, A R; Hubler, F; Carrupt, A; Wenger, R M; Mutter, M, J. Pept. Res., vol. 63, num. 2 (2004), p. 147-154). WO-A 2009/99763 describes ester based dipeptide prodrugs of bioactive peptides such as GLP-1 capable of releasing the peptide through diketopiperazine formation of the dipeptidic extension.

[00482] DKP formation reaction also results from amide prodrugs. U.S. Pat. No. 5,952,294 details prodrug activation using diketopiperazine formation for dipeptidyl amide prodrugs of cytarabine. In this case, the temporary linkage was formed between the carbonyl of a dipeptide and the aromatic amino group of cytarabine. In another study, the utility of diketopiperazine activation was demonstrated for even more stable aliphatic amide prodrugs (Suaifan et al., Tetrahedron 62 (2006) 11245-11266).

[00483] Thus, in one embodiment, the invention provides DKP-forming or DKM-forming prodrugs of the peptides of the invention, wherein a DKP-forming moiety or a DKM-forming moiety, i.e., a dipeptide, is attached to the N-terminus, C-terminus, or a side-chain of the peptides of the invention. The dipeptide can be attached through an ester bond or an amide bond.

[00484] In one embodiment, the dipeptide can be attached via an amide bond between the dipeptide and an aliphatic amino group of an IL-17 antagonist peptide of the invention (e.g., a primary amine such as the N-terminal amine or the amino group of an amino acid side chain or via a linking moiety that comprises a primary amine bearing an acyl group or alkyl group).

In a related embodiment, the R1 or R2 group of an IL-17 antagonist peptide of the invention can be absent or modified to comprise an acyl or alkyl group with a free amine moiety.

[00485] The prodrug dipeptides can also have one or more biocompatible polymers attached to a side chain of one of the residues of the dipeptide. Polymers can have, for example, a size selected from a range of about 20,000 to 120,000 Daltons. In one embodiment the polymer has a size selected from a range of about 40,000 to 100,000 or about 40,000 to 80,000 Daltons. In one embodiment the polymer has a size of about 40,000, 50,000, 60,000, 70,000 or 80,000 Daltons. Suitable polymers include but are not limited to dextrans, polylactides, polyglycolides, caprolactone-based polymers, poly(caprolactone), polyanhydrides, polyamines, polyesteramides, polyorthoesters, polydioxanones, polyacetals, polyketals, polycarbonates, polyphosphoesters, polyesters, polybutylene terephthalate, polyorthocarbonates, polyphosphazenes, succinates, poly(malic acid), poly(amino acids), polyvinylpyrrolidone, polyethylene glycol, polyhydroxycellulose, polysaccharides, chitin, chitosan, hyaluronic acid, and copolymers, terpolymers and mixtures thereof, and biodegradable polymers and their copolymers including caprolactone-based polymers, polycaprolactones and copolymers which include polybutylene terephthalate. In one embodiment the polymer is selected from the group consisting of polyethylene glycol, dextran, polylactic acid, polyglycolic acid and a copolymer of lactic acid and glycolic acid. In one embodiment, the polymer is polyethylene glycol, and the polymer can comprise one or more polyethylene glycol chains linked to the dipeptide element wherein the combined molecular weight of polymer(s) is 40,000 to 80,000 Daltons.

[00486] In one embodiment, the attachment between the dipeptide and a peptide of the invention comprises an amide bond and the dipeptide can comprise a structure according to Dipeptide Formula (I):



wherein R1, R2, R4 and R8 are independently selected from the group consisting of H, C1-C18 alkyl, C2-C18 alkenyl, (C1-C18 alkyl)OH, (C1-C18 alkyl)SH, (C2-C3 alkyl)SCH₃, (C1-C4 alkyl)CONH₂, (C1-C4 alkyl)COOH, (C1-C4 alkyl)NH₂, (C1-C4 alkyl)NHC(NH₂⁺)NH₂, (C0-C4 alkyl)(C3-C6 cycloalkyl), (C0-C4 alkyl)(C2-C5 heterocyclic), (C0-C4 alkyl)(C6-C10 aryl)R7, (C1-C4 alkyl)(C3-C9 heteroaryl), and C1-C12 alkyl(W1)C1-C12 alkyl, wherein W1 is a heteroatom selected from the group consisting of N, S and O, or R1 and R2 together with the atoms to which they are attached form a C3-C12 cycloalkyl or aryl; or R4 and R8 together

with the atoms to which they are attached form a C3-C6 cycloalkyl; R3 is selected from the group consisting of C1-C18 alkyl, (C1-C18 alkyl)OH, (C1-C18 alkyl)NH₂, (C1-C18 alkyl)SH, (C0-C4 alkyl)(C3-C6)cycloalkyl, (C0-C4 alkyl)(C2-C5 heterocyclic), (C0-C4 alkyl)(C6-C10 aryl)R7, and (C1-C4 alkyl)(C3-C9 heteroaryl) or R4 and R3 together with the atoms to which they are attached form a 4, 5 or 6 member heterocyclic ring; R5 is NHR6 or OH; R6 is H, C1-C8 alkyl or R6 and R2 together with the atoms to which they are attached form a 4, 5 or 6 member heterocyclic ring; and R7 is selected from the group consisting of H and OH, with the proviso that when R4 and R3 together with the atoms to which they are attached form a 5 or 6 member heterocyclic ring, then at least one of R1 and R2 are other than hydrogen.

(Dipeptide Formula (I).)

[00487] In another embodiment, the dipeptide structure that is attached to a peptide of the invention through an amide bond comprises a structure according to Dipeptide Formula (II):



wherein

(I) R1 and R2 are independently selected from the group consisting of H, C1-C18 alkyl, C2-C18 alkenyl, (C1-C18 alkyl)OH, (C1-C18 alkyl)SH, (C2-C3 alkyl)SCH₃, (C1-C4 alkyl)CONH₂, (C1-C4 alkyl)COOH, (C1-C4 alkyl)NH₂, (C1-C4 alkyl)NHC(NH₂⁺)NH₂, (C0-C4 alkyl)(C3-C6 cycloalkyl), (C0-C4 alkyl)(C2-C5 heterocyclic), (C0-C4 alkyl)(C6-C10 aryl)R7, (C1-C4 alkyl)(C3-C9 heteroaryl), and C1-C12 alkyl(W1)C1-C12 alkyl, wherein W1 is a heteroatom selected from the group consisting of N, S and O, or R1 and R2 together with the atoms to which they are attached form a C3-C12 cycloalkyl; R3 is C1-C18 alkyl; R4 and R8 are each H; R5 is NHR6, or R5 and R2 together with the atoms to which they are attached form a 4, 5 or 6 member heterocyclic ring; R6 is H or C1-C4 alkyl; and, R7 is selected from the group consisting of H and OH; wherein the dipeptide is linked to an IL-17 antagonist peptide of the invention through an amide bond between the dipeptide and an aliphatic amino group (e.g., a primary amine such as the N-terminal amine or the amino group of an amino acid side chain or via a linking moiety that comprises a primary amine bearing acyl group or alkyl group) of the IL-17 antagonist peptide; with the proviso that when both R1 and R2 are H, R3 is C5-C18 alkyl;

(II) R1 and R2 are independently selected from the group consisting of H, C1-C18 alkyl, C2-C18 alkenyl, (C1-C18 alkyl)OH, (C1-C18 alkyl)SH, (C2-C3 alkyl)SCH₃, (C1-C4 alkyl)CONH₂, (C1-C4 alkyl)COOH, (C1-C4 alkyl)NH₂, (C1-C4 alkyl)NHC(NH₂⁺)NH₂, (C0-C4 alkyl)(C3-C6 cycloalkyl), (C0-C4 alkyl)(C2-C5 heterocyclic), (C0-C4 alkyl)(C6-C10 aryl)R7, (C1-C4 alkyl)(C3-C9 heteroaryl), and C1-C12 alkyl(W1)C1-C12 alkyl, wherein W1 is a heteroatom selected from the group consisting of N, S and O, or R1 and R2 together with the atoms to which they are attached form a C3-C12 cycloalkyl; R3 is C1-C18 alkyl; R4 is selected from the group consisting of CH₃, CH₂(C1-C10 alkyl), CH₂(C2-C10 alkenyl), CH₂(C0-C10 alkyl)OH, CH₂(C0-C10 alkyl)SH, CH₂(C0-C3 alkyl)SCH₃, CH₂(C0-C3 alkyl)CONH₂, CH₂(C0-C3 alkyl)COOH, CH₂(C0-C3 alkyl)NH₂, CH₂(C0-C3 alkyl)NHC(NH₂⁺)NH₂, CH₂(C0-C3 alkyl)(C3-C6 cycloalkyl), CH₂(C0-C3 alkyl)(C2-C5 heterocyclic), CH₂(C0-C3 alkyl)(C6-C10 aryl)R7, CH₂(C1-C3 alkyl)(C3-C9 heteroaryl), and CH₂(C0-C12 alkyl)(W1)C1-C12 alkyl, wherein W1 is a heteroatom selected from the group consisting of N, S and O, or R4 and R3 together with the atoms to which they are attached form a 4, 5 or 6 member heterocyclic ring; R8 is H; R5 is NHR6, or R5 and R2 together with the atoms to which they are attached form a 4, 5 or 6 member heterocyclic ring; R6 is H or C1-C4 alkyl; and, R7 is selected from the group consisting of H and OH; wherein the dipeptide is linked to an IL-17 antagonist peptide of the invention through an amide bond between the dipeptide and an aliphatic amino group (e.g., a primary amine such as the N-terminal amine or the amino group of an amino acid side chain or via a linking moiety that comprises a primary amine bearing acyl group or alkyl group) of the IL-17 antagonist peptide; with the proviso that when either R1 or R2 are H, then R4 and R3 together with the atoms to which they are attached do not form a 4, 5 or 6 member heterocyclic ring;

(III) R1 and R2 are independently selected from the group consisting of H, C1-C18 alkyl, C2-C18 alkenyl, (C1-C18 alkyl)OH, (C1-C18 alkyl)SH, (C2-C3 alkyl)SCH₃, (C1-C4 alkyl)CONH₂, (C1-C4 alkyl)COOH, (C1-C4 alkyl)NH₂, (C1-C4 alkyl)NHC(NH₂⁺)NH₂, (C0-C4 alkyl)(C3-C6 cycloalkyl), (C0-C4 alkyl)(C2-C5 heterocyclic), (C0-C4 alkyl)(C6-C10 aryl)R7, (C1-C4 alkyl)(C3-C9 heteroaryl), and C1-C12 alkyl(W1)C1-C12 alkyl, wherein W1 is a heteroatom selected from the group consisting of N, S and O, or R1 and R2 together with the atoms to which they are attached form a C3-C12 cycloalkyl; or R1 and R2 together with the atoms to which they are attached form a C3-C12 cycloalkyl; R3 is C1-C18 alkyl; R4 is independently selected from the group consisting of CH(C1-C8 alkyl)₂, CH(C2-C8 alkenyl)₂, CH(C1-C8 alkyl)(OH), CH(C1-C8 alkyl)((C1-C8 alkyl)SH), and CH(C1-C3 alkyl)((C1-C8 alkyl)(NH₂); R8 is H; R5 is NHR6, or R5 and R2 together with the atoms to which they are attached form a 4, 5 or 6 member heterocyclic ring; R6 is H or C1-C4 alkyl; and, R7 is selected

from the group consisting of H and OH; wherein the dipeptide is linked to an IL-17 antagonist peptide of the invention through an amide bond between the dipeptide and an aliphatic amino group of the IL-17 antagonist peptide;

(IV) R1 and R2 are independently selected from the group consisting of H, C1-C18 alkyl, C2-C18 alkenyl, (C1-C18 alkyl)OH, (C1-C18 alkyl)SH, (C2-C3 alkyl)SCH₃, (C1-C4 alkyl)CONH₂, (C1-C4 alkyl)COOH, (C1-C4 alkyl)NH₂, (C1-C4 alkyl)NHC(NH₂⁺)NH₂, (C0-C4 alkyl)(C3-C6 cycloalkyl), (C0-C4 alkyl)(C2-C5 heterocyclic), (C0-C4 alkyl)(C6-C10 aryl)R7, alkyl)(C3-C9 heteroaryl), and C12 alkyl(W1)C1-C12 alkyl, wherein W1 is a heteroatom selected from the group consisting of N, S and O, or R1 and R2 together with the atoms to which they are attached form a C3-C12 cycloalkyl; R3 is C1-C18 alkyl; R4 and R8 are each H; R5 is NHR6, or R5 and R2 together with the atoms to which they are attached form a 4, 5 or 6 member heterocyclic ring; R6 is H or C1-C4 alkyl; and, R7 is selected from the group consisting of H and OH; wherein A-B is linked to an IL-17 antagonist peptide of the invention through an amide bond between A-B and an aromatic amino group on an amino acid side chain of an IL-17 antagonist peptide;

(V) R1 and R2 are independently selected from the group consisting of H, C1-C18 alkyl, C2-C18 alkenyl, (C1-C18 alkyl)OH, (C1-C18 alkyl)SH, (C2-C3 alkyl)SCH₃, (C1-C4 alkyl)CONH₂, alkyl)COOH, alkyl)NH₂, (C1-C4 alkyl)NHC(NH₂⁺)NH₂, (C0-C4 alkyl)(C3-C6 cycloalkyl), (C0-C4 alkyl)(C2-C5 heterocyclic), (C0-C4 alkyl)(C6-C10 aryl)R7, (C1-C4 alkyl)(C3-C9 heteroaryl), and C1-C12 alkyl(W1)C1-C12 alkyl, wherein W1 is a heteroatom selected from the group consisting of N, S and O, or R1 and R2 together with the atoms to which they are attached form a C3-C12 cycloalkyl; R3 is C1-C18 alkyl; R4 is selected from the group consisting of CH₃, CH₂(C1-C10 alkyl), CH₂(C2-C10 alkenyl), CH₂(C0-C10 alkyl)OH, CH₂(C0-C10 alkyl)SH, CH₂(C0-C3 alkyl)SCH₃, CH₂(C0-C3 alkyl)CONH₂, CH₂(C0-C3 alkyl)COOH, CH₂(C0-C3 alkyl)NH₂, CH₂(C0-C3 alkyl)NHC(NH₂⁺)NH₂, CH₂(C0-C3 alkyl)(C3-C6 cycloalkyl), CH₂(C0-C3 alkyl)(C2-C5 heterocyclic), CH₂(C0-C3 alkyl)(C6-C10 aryl)R7, CH₂(C1-C3 alkyl)(C3-C9 heteroaryl), and CH₂(C0-C12 alkyl)(W1)C1-C12 alkyl, wherein W1 is a heteroatom selected from the group consisting of N, S and O, or R4 and R3 together with the atoms to which they are attached form a 4, 5 or 6 member heterocyclic ring; R8 is H; R5 is NHR6, or R5 and R2 together with the atoms to which they are attached form a 4, 5 or 6 member heterocyclic ring; R6 is H or C1-C4 alkyl; and, R7 is selected from the group consisting of H and OH. wherein the dipeptide is linked to an IL-17 antagonist peptide of the invention through an amide bond between the dipeptide and an aromatic amino group on an amino acid side chain of the IL-17 antagonist peptide of the invention;

(VI) R1 and R2 are independently selected from the group consisting of H, C1-C18 alkyl, C2-C18 alkenyl, (C1-C18 alkyl)OH, (C1-C18 alkyl)SH, (C2-C3 alkyl)SCH3, (C1-C4 alkyl)CONH2, (C1-C4 alkyl)COOH, (C1-C4 alkyl)NH2, (C1-C4 alkyl)NHC(NH2 +)NH2, (C0-C4 alkyl)(C3-C6 cycloalkyl), (C0-C4 alkyl)(C2-C5 heterocyclic), (C0-C4 alkyl)(C6-C10 aryl)R7, (C1-C4 alkyl)(C3-C9 heteroaryl), and C1-C12 alkyl(W1)C1-C12 alkyl, wherein W1 is a heteroatom selected from the group consisting of N, S and O, or R1 and R2 together with the atoms to which they are attached form a C3-C12 cycloalkyl; or R1 and R2 together with the atoms to which they are attached form a C3-C12 cycloalkyl; R3 is C1-C18 alkyl; R4 is independently selected from the group consisting of CH(C1-C8 alkyl)2, CH(C2-C8 alkenyl)2, CH(C1-C8 alkyl)(OH), CH(C1-C8 alkyl)((C1-C8 alkyl)SH), and CH(C1-C3 alkyl)((C1-C8 alkyl)(NH2)); R8 is H; R5 is NHR6, or R5 and R2 together with the atoms to which they are attached form a 4, 5 or 6 member heterocyclic ring; R6 is H or C1-C4 alkyl; and, R7 is selected from the group consisting of H and OH; wherein the dipeptide is linked to an IL-17 antagonist peptide of the invention through an amide bond between the dipeptide and an aromatic amino group on an amino acid side chain of the IL-17 antagonist peptide of the invention.

[00488] Suitable amino acids for the dipeptide (which can be referred to herein as “A-B”) include, but are not limited to:

- (1) for the first residue of the dipeptide (N-terminal residue of the dipeptide), or the “A” residue: Aib, Gly, Ala, Leu, Met, Asn, Glu, Asp, Gln, His, Lys, Arg, Ser, Cys, Pro, Phe, Tyr, Trp, Ile, Val, Thr, their corresponding D-forms, their N-methyl variant forms (N-methyl amino acids have a methyl group attached to the nitrogen), and D-forms of the N-methyl variants;
- (2) for the second residue of the dipeptide, or the “B” residue, modified amino acids are contemplated, where the modification comprises attaching an alkyl group to the amino group of the core amino acid structure, for example: Gly(N—C1-C8alkyl), Gly(N—C1-C8alkyl), Ala(N—C1-C8alkyl), Leu(N—C1-C8alkyl), Met(N—C1-C8alkyl), Asn(N—C1-C8alkyl), Glu(N—C1-C8alkyl), Asp(N—C1-C8alkyl), Gln(N—C1-C8alkyl), His(N—C1-C8alkyl), Lys(N—C1-C8alkyl), Arg(N—C1-C8alkyl), Ser(N—C1-C8alkyl), Cys(N—C1-C8alkyl), Pro, Phe(N—C1-C8alkyl), Tyr(N—C1-C8alkyl), Trp(N—C1-C8alkyl), Val(N—C1-C8alkyl), Thr(N—C1-C8alkyl), Gly(N-methyl), Ala(N-methyl), Leu(N-methyl), Met(N-methyl), Asn(N-methyl), Glu(N-methyl), Asp(N-methyl), Gln(N-methyl), His(N-methyl), Lys(N-methyl), Arg(N-methyl), Ser(N-methyl), Cys(N-methyl), Phe(N-methyl), Tyr(N-methyl), Trp(N-methyl), Ile(N-methyl), Val(N-methyl), Thr(N-methyl), Gly(N-hexyl), Ala(N-hexyl), Leu(N-hexyl), Met(N-hexyl), Asn(N-hexyl), Glu(N-hexyl), Asp(N-hexyl), Gln(N-hexyl), His(N-hexyl), Lys(N-hexyl), Arg(N-hexyl), Ser(N-hexyl), Cys(N-hexyl), Phe(N-hexyl),

Tyr(N-hexyl), Trp(N-hexyl), Ile(N-hexyl), Val(N-hexyl), Thr(N-hexyl), and their corresponding D-isoforms.

[00489] In some embodiments, the half-life of the prodrug, e.g., the chemical cleavage half-life ($t_{1/2}$) of A-B from a peptide of the invention under physiological conditions, is dependent on the presence and length of the N-alkyl substituent on the B amino acid. For example, a prodrug that has a shorter N-alkyl substituent on the B amino acid (e.g. Gly(N-methyl)), will undergo a slower rate of cleavage of A-B, and have a longer half-life, than a prodrug that has a longer N-alkyl substituent on the B amino acid (e.g., Gly(N-hexyl)).

[00490] In some embodiments, the half-life of the prodrug is dependent on the presence or absence of an alkyl side chain, and the degree of substitution at the beta position of the alkyl side chain, of the B amino acid of the dipeptide prodrug element. For example, a prodrug that has an N-alkylated B amino acid that is disubstituted at the beta position (e.g., N-alkylated isoleucine) will undergo slower cleavage of A-B, and have a longer half-life, than a prodrug that has an N-alkylated B amino acid that is monosubstituted at the beta position (e.g., N-alkylated leucine). Further, a prodrug that has an N-alkylated B amino acid that is monosubstituted at the beta position (e.g., N-alkylated leucine) will undergo slower cleavage of A-B, and have a longer half-life, than a prodrug that has an N-alkylated B amino acid that is unsubstituted at the beta position (e.g., N-alkylated alanine). Further still, a prodrug with an N-alkylated B amino acid that has an unsubstituted beta position (e.g., N-alkylated alanine) will undergo slower cleavage of A-B, and have a longer half-life, than a prodrug that has glycine or N-alkylated glycine as the B amino acid.

[00491] In some embodiments, the half-life of the prodrug is dependent on the bulkiness of the side chain of the B amino acid. For example, a prodrug that has a bulkier side chain on the B amino acid (e.g., N-alkylated phenylalanine), will undergo slower cleavage of A-B, and have a longer half-life, than a prodrug that has a less bulky side chain on the B amino acid (e.g., N-alkylated alanine). Cleavage rates of dipeptides can be further differentiated by the amine of the peptide to which they are attached. More particularly the same dipeptide will cleave at a faster rate when linked to an aromatic amine relative to an N-terminal amine, where the dipeptide linked to an N-terminal amine will cleave at a faster rate relative to when the dipeptide is linked to the side chain amine of a lysine residue.

[00492] In one embodiment, the dipeptide is Sar_isoDLys_1PEG2_1PEG2_isoGlu_C18_Diacid that is connected by an amide bond to dK, dH, or H, wherein dK, dH, or H is the N-terminal amino acid residue at X00, X0, or X1, or wherein dK, dH, or H, is the C-terminal residue at X14, X15, or X16.

[00493] In another embodiment, a half-life extension conjugate (see below) is attached to a side chain of the first or second amino acid of the dipeptide.

[00494] 2E. Peptide-Half-Life Extension Conjugates

[00495] In certain embodiments, IL-17 inhibitors of the present invention, including both monomers and dimers, comprise one or more conjugated chemical substituents, such as lipophilic substituents and polymeric moieties, collectively 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 IL-17 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, and in some cases enhance permeability through the epithelium and retention in the lamina propria. The skilled person will be well aware of suitable techniques for preparing the compounds employed in the context of the invention. For examples of non-limiting suitable chemistry, see, e.g., WO98/08871, WO00/55184, WO00/55119, Madsen et al (J. Med. Chem. 2007, 50, 6126-32), and Knudsen et al. 2000 (J. Med Chem. 43, 1664-1669).

[00496] In some embodiments, the side chains of one or more amino acid residues in an IL-17 inhibitor of the invention is further conjugated (e.g., covalently attached) to a lipophilic substituent or other half-life extension moiety. 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 or linker moieties. The spacer or linker moiety, when present, may provide spacing between the IL-17 inhibitor and the lipophilic substituent.

[00497] In certain embodiments, the lipophilic substituent or half-life extension moiety comprises 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.

[00498] A lipophilic substituent may be conjugated to any amino acid side chain in an IL-17 inhibitor of the invention. In one embodiment, a lipophilic substituent is conjugated to an N-terminus amino acid side chain. In certain embodiments, 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. Representative 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. In certain embodiments, the lipophilic substituent is conjugated to Lys, if Lys is not already conjugated to a dimerization linker. An amino acid shown as Lys in any of the Formulas provided herein may be replaced by, e.g., Dbu, Dpr or Orn where a lipophilic substituent is added.

[00499] In further embodiments of the present invention, alternatively or additionally, the side-chains of one or more amino acid residues in an IL-17 inhibitor of the invention may be conjugated to a polymeric moiety or other half-life extension 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. In one embodiment, a polymeric moiety or other half-life extension moiety is conjugated to an N-terminus amino acid side chain.

[00500] In some embodiments, suitable methods known in the art for determining solubility include incubating IL-17 inhibitors 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.

[00501] In some embodiments, the present disclosure includes an IL-17 inhibitor peptide (or a dimer thereof) conjugated with a PEG linker (in cases where there is already a PEG dimerization linker, an additional PEG linker may be added for half-life extension, solubility, and/or bioavailability) that is attached covalently, e.g., through an amide, a thiol, via click chemistry, or via any other suitable means known in the art.

[00502] 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.

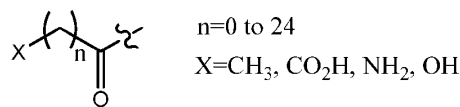
[00503] As used herein, disulfide bond oxidation can occur within a single step or is a two-step process. As used herein, for a single oxidation step, the trityl protecting group is often

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, Acn 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 Acn group is then performed. For native oxidation, the trityl protecting group is used for all cysteines, allowing for natural folding of the peptide.

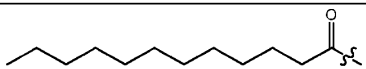
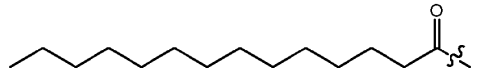
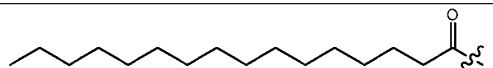
[00504] A skilled worker will be well aware of suitable techniques which can be used to perform the oxidation step.

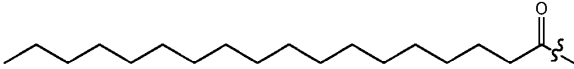
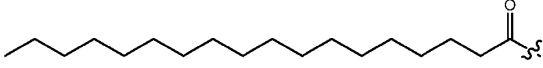
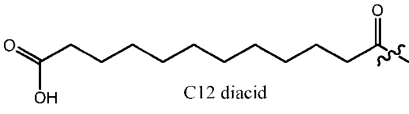
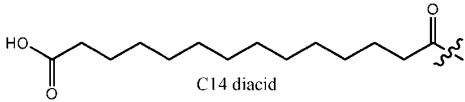
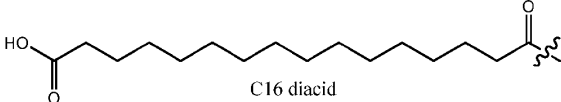
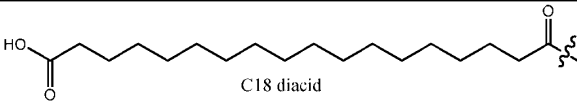
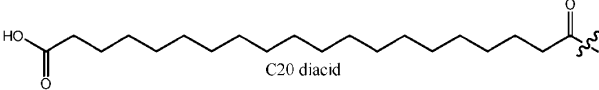
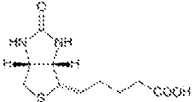
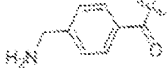
[00505] In certain embodiments, an IL-17 receptor antagonist or inhibitor of the present disclosure comprises a half-life extension moiety, which may be selected from but is not limited to the following: Ahx-Palm, PEG2-Palm, PEG11-Palm, isoGlu-Palm, dapa-Palm, isoGlu-Lauric acid, isoGlu-Mysteric acid, and isoGlu-Isovaleric acid.

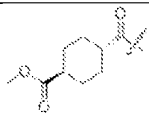
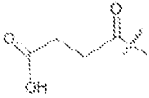
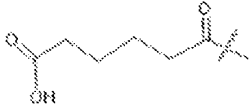
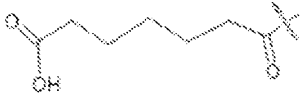
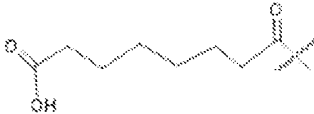
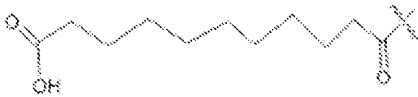
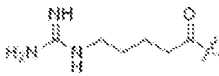
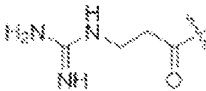
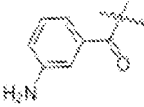
[00506] In certain embodiments, an IL-17 inhibitor comprises a half-life extension moiety having the structure shown below, wherein n=0 to 24 or n=14 to 24:

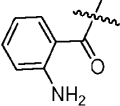
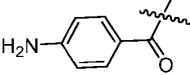


[00507] In certain embodiments, an IL-17 inhibitor of the present invention comprises a conjugated half-life extension moiety shown in Table 2 - Illustrative Half-Life Extension Moieties:

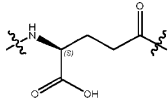
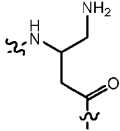
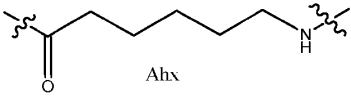
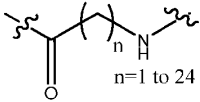
#	Half-Life Extension Moieties
H1	 C12 (Lauric acid)
H2	 C14 (Myristic acid)
H3	 C16 (Palm or Palmitic acid)

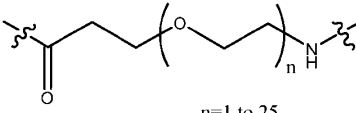
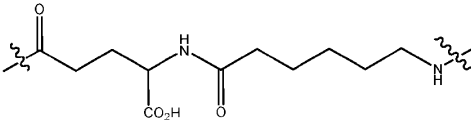
#	Half-Life Extension Moieties
H4	 C18 (Stearic acid)
H5	 C20
H6	 C12 diacid
H7	 C14 diacid
H8	 C16 diacid
H9	 C18 diacid
H10	 C20 diacid
H11	 Biotin
H12	 Isovaleric acid
H13	 4-(aminomethyl)benzoic acid

#	Half-Life Extension Moieties
H14	 (1r,4r)-4-(methoxycarbonyl)cyclohexane-1-carboxylic acid
H15	4-carboxybutanoyl 
H16	6-carboxyhexanoyl 
H17	7-carboxyheptanoyl 
H18	8-carboxyoctanoyl 
H19	11-carboxyundecanoyl 
H20	5-guanidinopentanoic acid 
H21	3-guanidinopropanoic acid 
H22	3-aminobenzoic acid 

#	Half-Life Extension Moieties
H23	2-aminobenzoic acid 
H24	4-aminobenzoic acid 

[00508] In certain embodiments, a half-life extension moiety is conjugated directly to an IL-17 inhibitor, while in other embodiments, a half-life extension moiety is conjugated to an IL-17 inhibitor peptide via a linker moiety, e.g., any of those depicted in Table 3 -- Illustrative Half-Life Extension Linker Moieties

#	Half-Life Extension Linker Moieties
L1	 IsoGlu
L2	 Dapa
L3	 Ahx
L4	Lipidic based linkers:  n=1 to 24

#	Half-Life Extension Linker Moieties
L5	 n=1 to 25 -[C(O)CH₂CH₂(OCH₂CH₂)_nN(H)]- PEG based linkers
L6	 IsoGlu-Ahx
L7	-[C(O)-CH ₂ -(Peg)2-NH]- or -[C(O)-CH ₂ -(OCH ₂ CH ₂)2-NH]- (1Peg2)
L8	-[C(O)-CH ₂ -(OCH ₂ CH ₂)2-NH-C(O)-CH ₂ -(OCH ₂ CH ₂)2-NH]- (1Peg2-1Peg2)
L9	-[C(O)-CH ₂ -CH ₂ -(Peg)2-NH]- or -[C(O)-CH ₂ -CH ₂ -(OCH ₂ CH ₂)2-NH]- (2Peg2)
L10	-[C(O)-CH ₂ -CH ₂ -(Peg)4-NH]- or -[C(O)-CH ₂ -CH ₂ -(OCH ₂ CH ₂)4-NH]- (2Peg4)
L11	-[C(O)-CH ₂ -(Peg)8-NH]- or -[C(O)-CH ₂ -(OCH ₂ CH ₂)8-NH]- (1Peg8)
L12	-[C(O)-CH ₂ -CH ₂ -(Peg)8-NH]- or -[C(O)-CH ₂ -CH ₂ -(OCH ₂ CH ₂)8-NH]- (2Peg8)
L17	-[C(O)-CH ₂ -(Peg)11-NH]- or -[C(O)-CH ₂ -(OCH ₂ CH ₂)11-NH]- (1Peg11)
L18	-[C(O)-CH ₂ -CH ₂ -(Peg)11-NH]- or -[C(O)-CH ₂ -CH ₂ -(OCH ₂ CH ₂)11-NH]- (2Peg11)
L19	-[C(O)-CH ₂ -CH ₂ -(Peg)12-NH]- or -[C(O)-CH ₂ -CH ₂ -(OCH ₂ CH ₂)12-NH]- (2Peg11' or 2Peg12)

*(Peg) is -(OCH₂CH₂)-

[00509] In some embodiments, an IL-17 antagonist of the present invention comprises any of the linker moieties shown in Table 3 and any of the half-life extension moieties shown in Table 2, including any of the following combinations shown in Table 4.

[00510] Table 4 - Illustrative Combinations of Linkers and Half-Life Extension Moieties

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
L16	C1		L16	C2		L16	C3
L17	C1		L17	C2		L17	C3
L18	C1		L18	C2		L18	C3
L19	C1		L19	C2		L18	C3

[00511] In some embodiments, the IL-17 inhibitor of the present invention exhibits increased stability (*e.g.*, as measured by half-life, rate of protein degradation) as compared to the same inhibitor without having an additional half-life extension moiety (*i.e.*, the “reference compound”). In certain embodiments, the stability of an IL-17 inhibitor of the present invention is increased at least about 1.5, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14, 15, 16, 17, 18, 19, 20, 30, 40, 50, 60, 70, 80, 90, 100, 120, 140, 160, 180, or 200-fold greater or at least about 10%, 20%, 30%, 40%, 50%, 60%, 70%, 80%, 90%, 100%, 200%, 300%, 400%, or 500% greater than the reference compound.

[00512] In certain embodiments, an IL-17 inhibitor of the present invention, comprising a conjugated half-life extension moiety, has an increased serum half-life following oral, intravenous or subcutaneous administration as compared to the same analogue but lacking the

conjugated half-life extension moiety. In some embodiments, the serum half-life of an IL-17 inhibitor of the present invention following any of oral, intravenous or subcutaneous administration is at least 12 hours, at least 24 hours, at least 30 hours, at least 36 hours, at least 48 hours, at least 72 hours or at least 168 h. In some embodiments, it is between 12 and 168 hours, between 24 and 168 hours, between 36 and 168 hours, or between 48 and 168 hours.

[00513] In some embodiments, the half-life is measured *in vitro* using any suitable method known in the art, e.g., the SGF and/or SIF assays described in the Examples, or in some embodiments, the stability of an IL-17 inhibitor of the present invention is determined by incubating the IL-17 inhibitor 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 IL-17 inhibitor from the serum proteins and then analyzing for the presence of the IL-17 inhibitor of interest using LC-MS.

[00514] In some embodiments, the stability of the IL-17 inhibitor is measured *in vivo* using any suitable method known in the art, e.g., in some embodiments, the stability of an IL-17 inhibitor is determined *in vivo* by administering the IL-17 inhibitor to a subject such as a human or any mammal (e.g., mouse) and then samples are taken from the subject via blood draw at various time points, typically up to 24 hours. Samples are then analyzed as described above in regard to the *in vitro* method of measuring half-life.

[00515] **3. Methods Based on Inhibition of IL-17/IL-17R Signaling**

[00516] The peptide compounds of the invention are potent inhibitors of IL-17 cytokine function. As discussed, over 290 representative peptide compounds have nanomolar or subnanomolar IC₅₀ values in human IL-17 HEK Blue Assays, which IC₅₀ values correspond to their binding affinities to human IL-17 cytokines. Furthermore, initial *in vivo* studies show the peptide compounds may exhibit dose response relationships with respect to the inhibition of IL-17 receptor activation gene expression. Specifically, as described in Example 6, increasing amounts of peptide compounds administered to mice (whether subcutaneously or oral) show a relationship with decreasing the levels of CXCL1 in the serum and ear tissue of the mice. As discussed, CXCL1 levels are upregulated by IL-17R activation.

[00517] Thus, in another aspect, the disclosure provides a method for inhibiting binding between an IL-17 cytokine and an IL-17 receptor, the method comprising contacting the IL-17 cytokine with a peptide as described herein, or a pharmaceutically acceptable salt or solvate thereof. In some embodiments, the method comprises contacting an IL-17 cytokine with a peptide *in vitro*. In other embodiments, the method comprises contacting an IL-17 cytokine with a peptide *in vivo*. The disclosure further provides a method of modulating an IL-17 receptor or inhibiting / reducing IL-17 receptor activation in a subject, the method comprising

administering to the subject a peptide as described herein, or a pharmaceutically acceptable salt or solvate thereof, or a pharmaceutical composition comprising a peptide as described herein or a pharmaceutically acceptable salt or solvate thereof, and a pharmaceutically acceptable carrier or excipient.

[00518] In some embodiments, an IL-17 inhibitor (*i.e.*, a peptide compound of the invention) as disclosed herein binds to IL-17 cytokine. The peptide inhibitors of the invention specifically bind to one or more human IL-17 cytokine isoforms. As used herein, "specifically binds" refers to a specific compound's preferential interaction with a human IL-17 cytokine over other molecules in a sample or in a subject.

[00519] In some embodiments, the present disclosure provides methods for treating, ameliorating or preventing a disease or disorder in a subject, wherein the disease or disorder is associated with, caused, mediated, or supported by IL-17, *e.g.*, overproduction of IL-17. The method comprises administering to the subject a peptide compound of the present invention, including by subcutaneous injection or by oral ingestion. In some embodiments, the IL-17 inhibitor that is administered to the subject is present in a pharmaceutical composition. In one embodiment, a method is provided for treating a subject afflicted with or suffered from a disease or disorder associated with, caused, mediated, or supported by IL-17 and/or by IL-17R, the method comprising administering to the subject an IL-17 inhibitor or a pharmaceutically acceptable salt or solvate thereof, or a pharmaceutical composition comprising the IL-17 inhibitor, wherein the IL-17 inhibitor inhibits, prevents, or reduces the binding of IL-17 to IL-17 receptors.

[00520] In certain embodiments, the disease or disorder treatable, ameliorable, or preventable with a peptide compound of the present invention is associated with an IL-17 connected inflammatory disease or an autoimmune disease. For example, the inflammatory or autoimmune disease associated with IL-17 can be: multiple sclerosis, asthma, rheumatoid arthritis, inflammation of the gut, inflammatory bowel diseases (IBDs), juvenile IBD, adolescent IBD, Crohn's disease, ulcerative colitis, sarcoidosis, Systemic Lupus Erythematosus, ankylosing spondylitis (axial spondyloarthritis), psoriatic arthritis, or psoriasis. In particular 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, graft versus host disease, ankylosing spondylitis, or nonradiographic axial spondyloarthritis.

[00521] In some embodiments, the disease or disorder treatable, ameliorable, or preventable with an IL-17 inhibitor of the present invention includes psoriasis, plaque psoriasis, guttate psoriasis, inverse psoriasis, pustular psoriasis, erythrodermic psoriasis, nail psoriasis, or psoriatic arthritis, ankylosing spondylitis, and nonradiographic axial spondyloarthritis. The initial mouse studies described in the Examples shows that the peptide compounds of the invention can decrease CXCL1 levels in the ear tissue, and elevated CXCL1 levels in the ear tissue after repeated IL-17 cytokine administration is associated with psoriasis-like conditions with the murine ear dermis.

[00522] In some embodiments, the disclosure provides a method for treating a disease or disorder as disclosed herein in a subject. The method comprises administering to the subject in need thereof an IL-17 inhibitor of the present invention in combination with one or more therapeutic agents or therapies. In certain embodiments, one or more therapeutic agents or therapies are provided to the subject before and/or simultaneously with and/or after the pharmaceutical composition is administered to the subject. In some embodiments, the second therapeutic agent is an IL-17 inhibitor.

[00523] The pharmaceutical compositions of the invention comprise a peptide compound per one of the Formulas (including SEQ ID NO formulas), which compositions can be administered to a subject with an autoimmune or inflammatory condition as described above. In some embodiments, when administration is by injection or by oral ingestion, the pharmaceutical composition comprises a peptide compound of the invention that exhibits an IC_{50} of 20 nM or less, 10 nM or less, 5 nM or less, or 1 nM or less, in a HEK Blue IL-17 assay (see Figure 1 for peptide compounds that satisfy these thresholds). In some embodiments, when administration is by oral ingestion, the pharmaceutical composition comprises a peptide compound of the invention that exhibits: (a) an IC_{50} of 20 nM or less, 10 nM or less, 5 nM or less, or 1 nM or less, in a HEK Blue IL-17 assay; and (b) exhibits a half-life of at least 0.5, 1, 1.5, or 2 hours in an SGF and/or SIF assay. (See Figure 1 for peptide compounds that satisfy these dual thresholds)

4. Pharmaceutical Compositions

[00524] The IL-17 inhibitors of the present invention may be formulated as pharmaceutical compositions which are suited for administration with or without storage, and which typically comprise a therapeutically effective amount of at least one IL-17 inhibitor of the invention, together with a pharmaceutically acceptable carrier, excipient or vehicle.

[00525] The present invention provides compositions (for example pharmaceutical compositions) comprising one or more IL-17 inhibitors of the present invention and a pharmaceutically acceptable carrier, excipient or diluent. 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.

[00526] The term “pharmaceutically acceptable carrier” includes any of the standard pharmaceutical carriers. Pharmaceutically acceptable carriers for therapeutic use are well known in the pharmaceutical art and are described, for example, in “Remington's Pharmaceutical Sciences”, 17th edition, Alfonso R. Gennaro (Ed.), Mark Publishing Company, Easton, PA, USA, 1985. For example, sterile saline and phosphate-buffered saline at slightly acidic or physiological pH may be used. Suitable pH-buffering agents may, e.g., be phosphate, citrate, acetate, tris(hydroxymethyl)aminomethane (TRIS), N-tris(hydroxymethyl)methyl-3-aminopropanesulfonic acid (TAPS), ammonium bicarbonate, diethanolamine, histidine, arginine, lysine or acetate (e.g. as sodium acetate), or mixtures thereof. The term further encompasses any carrier agents listed in the US Pharmacopeia for use in animals, including humans.

[00527] In certain embodiments, the compositions comprise two or more IL-17 inhibitors disclosed herein.

[00528] In some embodiments, the IL-17 inhibitor pharmaceutical compositions of the invention are in unit dosage form. In such forms, the composition is divided into unit doses containing appropriate quantities of the active component or components. The unit dosage form may be presented as a packaged preparation, the package containing discrete quantities of the preparation, for example, packaged tablets, capsules or powders in vials or ampoules. The unit dosage form may also be, e.g., a capsule, cachet or tablet in itself, or it may be an appropriate number of any of these packaged forms. A unit dosage form may also be provided in single-dose injectable form, for example in the form of a pen device containing a liquid-phase (typically aqueous) composition. Compositions may be formulated for any suitable route and

means of administration, e.g., any one of the routes and means of administration disclosed herein.

[00529] In some embodiments, the IL-17 inhibitor, or the pharmaceutical composition comprising an IL-17 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).

[00530] In certain embodiments, the compositions are administered parenterally, subcutaneously or orally. In particular embodiments, the compositions are administered orally, intracisternally, intravaginally, intraperitoneally, intrarectally, topically (as by powders, ointments, drops, suppository, or transdermal patch, including delivery intravitreally, intranasally, and via inhalation) or buccally. The term “parenteral” as used herein refers to modes of administration which include intravenous, intramuscular, intraperitoneal, intrasternal, subcutaneous, intradermal and intra-articular injection and infusion. Accordingly, in certain embodiments, the compositions are formulated for delivery by any of these routes of administration.

[00531] 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, beta-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. These 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.

[00532] Injectable depot forms include those made by forming microencapsule matrices of the IL-17 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 IL-17 inhibitor can be controlled. Depot injectable formulations are also prepared by entrapping the IL-17 inhibitor in liposomes or microemulsions compatible with body tissues.

[00533] 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.

[00534] IL-17 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 an IL-17 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.

[00535] Pharmaceutical compositions to be used in the invention suitable for parenteral administration may comprise sterile aqueous solutions and/or suspensions of the peptide inhibitors made isotonic with the blood of the recipient, generally using sodium chloride, glycerin, glucose, mannitol, sorbitol, and the like.

[00536] Compositions and IL-17 inhibitors of the instant invention can 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 IL-17 inhibitors of the invention can 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.

[00537] 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 IL-17 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.

[00538] In particular embodiments, oral dosage forms or unit doses compatible for use with the IL-17 inhibitors of the present invention may include a mixture of an IL-17 inhibitor(s) 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 an IL-17 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 IL-17 inhibitor in the subject's small intestine and/or colon.

[00539] In one embodiment, an oral pharmaceutical composition comprising an IL-17 inhibitor of the present invention comprises an enteric coating that is designed to delay release of the IL-17 inhibitor in the small intestine. In at least some embodiments, a pharmaceutical composition is provided which comprises an IL-17 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.

[00540] In one embodiment, a pharmaceutical composition comprising an IL-17 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 IL-17 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 an IL-17 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.

[00541] In some embodiments, the pharmaceutical compositions comprise a hydrogel polymer carrier system in which an IL-17 inhibitor of the present invention is contained, whereby the hydrogel polymer protects the IL-17 inhibitor from proteolysis or degradation in the small intestine and/or colon. The IL-17 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.

[00542] Various bioresponsive systems may also be combined with one or more IL-17 inhibitors of the present invention to provide a pharmaceutical agent for oral delivery. In some embodiments, an IL-17 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 an IL-17 inhibitor disclosed herein, wherein the surface of the IL-17 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 an IL-17 inhibitor.

[00543] In other embodiments, the disclosure provides a method for oral delivery of an IL-17 inhibitor of the present invention, wherein the IL-17 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. For example, a permeation enhancer is combined with an IL-17 inhibitor, wherein the permeation enhancer comprises at least one of a long-chain fatty acid, a bile salt, an amphiphilic surfactant, and a chelating agent. In one embodiment, a permeation enhancer comprising sodium N-[hydroxybenzoyl]amino] caprylate is used to form a weak noncovalent association with the IL-17 inhibitor of the instant invention, wherein the permeation enhancer favors membrane transport and further dissociation once reaching the blood circulation. In another embodiment, an IL-17 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 inhibitor 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 IL-17 inhibitor molecule.

Dosages and administrations

[00544] The total daily usage of the IL-17 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 IL-17 inhibitor employed; e) the duration of the treatment; f) drugs used in combination or coincidental with the specific IL-17 inhibitor employed, and like factors well known in the medical arts.

[00545] In some embodiments, the total daily dose of the IL-17 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. In certain embodiments, a dosage of an IL-17 inhibitor of the present invention is in the range from about 0.0001 to about 100 mg/kg body weight per day, such as from about 0.0005 to about 50 mg/kg body weight per day, such as from about 0.001 to about 10 mg/kg body weight per day, e.g. from about 0.01 to about 1 mg/kg body weight per day, administered in one or more doses, such as from one to three doses. In certain embodiments, a total dosage is about 1 mg, about 2 mg, about 3 mg, about 4 mg, about 5 mg, about 6 mg, about 7 mg, about 8 mg, about 9 mg, or about 10 mg about once or twice weekly, e.g., for a human patient. In certain embodiments, the total dosage is in the range of about 1 mg to about 5 mg, or about 1 mg to about 3 mg, or about 2 mg to about 3 mg per human patient, e.g., about once weekly.

[00546] In various embodiments, an IL-17 inhibitor of the invention may be administered continuously (e.g. by intravenous administration or another continuous drug administration method), or may be administered to a subject at intervals, typically at regular time intervals, depending on the desired dosage and the pharmaceutical composition selected by the skilled practitioner for the particular subject. Regular administration dosing intervals include, e.g., once daily, twice daily, once every two, three, four, five or six days, once or twice weekly, once or twice monthly, and the like.

[00547] Such regular IL-17 inhibitor administration regimens of the invention may, in certain circumstances such as, e.g., during chronic long-term administration, be advantageously

interrupted for a period of time so that the medicated subject reduces the level of or stops taking the medication, often referred to as taking a “drug holiday.” Drug holidays are useful for, e.g., maintaining or regaining sensitivity to a drug especially during long-term chronic treatment, or to reduce unwanted side-effects of long-term chronic treatment of the subject with the drug. The timing of a drug holiday depends on the timing of the regular dosing regimen and the purpose for taking the drug holiday (e.g., to regain drug sensitivity and/or to reduce unwanted side effects of continuous, long-term administration). In some embodiments, the drug holiday may be a reduction in the dosage of the drug (e.g. to below the therapeutically effective amount for a certain interval of time). In other embodiments, administration of the drug is stopped for a certain interval of time before administration is started again using the same or a different dosing regimen (e.g. at a lower or higher dose and/or frequency of administration). A drug holiday of the invention may thus be selected from a wide range of time-periods and dosage regimens. An exemplary drug holiday is two or more days, one or more weeks, or one or more months, up to about 24 months of drug holiday. So, for example, a regular daily dosing regimen with a peptide, a peptide analogue, or a dimer of the invention may, for example, be interrupted by a drug holiday of a week, or two weeks, or four weeks, after which time the preceding, regular dosage regimen (e.g. a daily or a weekly dosing regimen) is resumed. A variety of other drug holiday regimens are envisioned to be useful for administering the IL-17 inhibitors of the invention.

[00548] Thus, the IL-17 inhibitor may be delivered via an administration regime which comprises two or more administration phases separated by respective drug holiday phases.

[00549] During each administration phase, the IL-17 inhibitor is administered to the recipient subject in a therapeutically effective amount according to a pre-determined administration pattern. The administration pattern may comprise continuous administration of the drug to the recipient subject over the duration of the administration phase. Alternatively, the administration pattern may comprise administration of a plurality of doses of the IL-17 inhibitor to the recipient subject, wherein said doses are spaced by dosing intervals.

[00550] A dosing pattern may comprise at least two doses per administration phase, at least five doses per administration phase, at least 10 doses per administration phase, at least 20 doses per administration phase, at least 30 doses per administration phase, or more.

[00551] Said dosing intervals may be regular dosing intervals, which may be as set out above, including once daily, twice daily, once every two, three, four, five or six days, once or twice weekly, once or twice monthly, or a regular and even less frequent dosing interval, depending on the particular dosage formulation, bioavailability, and pharmacokinetic profile of the IL-17 inhibitor of the present invention.

[00552] An administration phase may have a duration of at least two days, at least a week, at least 2 weeks, at least 4 weeks, at least a month, at least 2 months, at least 3 months, at least 6 months, or more.

[00553] Where an administration pattern comprises a plurality of doses, the duration of the following drug holiday phase is longer than the dosing interval used in that administration pattern. Where the dosing interval is irregular, the duration of the drug holiday phase may be greater than the mean interval between doses over the course of the administration phase. Alternatively, the duration of the drug holiday may be longer than the longest interval between consecutive doses during the administration phase.

[00554] The duration of the drug holiday phase may be at least twice that of the relevant dosing interval (or mean thereof), at least 3 times, at least 4 times, at least 5 times, at least 10 times, or at least 20 times that of the relevant dosing interval or mean thereof.

[00555] Within these constraints, a drug holiday phase may have a duration of at least two days, at least a week, at least 2 weeks, at least 4 weeks, at least a month, at least 2 months, at least 3 months, at least 6 months, or more, depending on the administration pattern during the previous administration phase.

[00556] An administration regime comprises at least 2 administration phases. Consecutive administration phases are separated by respective drug holiday phases. Thus, the administration regime may comprise at least 3, at least 4, at least 5, at least 10, at least 15, at least 20, at least 25, or at least 30 administration phases, or more, each separated by respective drug holiday phases.

[00557] Consecutive administration phases may utilise the same administration pattern, although this may not always be desirable or necessary. However, if other drugs or active agents are administered in combination with an IL-17 inhibitor of the invention, then typically the same combination of drugs or active agents is given in consecutive administration phases. In certain embodiments, the recipient subject is human.

[00558] In some embodiments, the invention provides a device comprising at least one IL-17 inhibitor of the present invention, or pharmaceutically acceptable salt or solvate thereof for delivery of the IL-17 inhibitor to a subject.

[00559] In some embodiments, the present invention provides kits comprising at least one IL-17 inhibitor, or a composition (e.g., pharmaceutical composition) as disclosed herein packaged together with a reagent, a device, instructional material, or a combination thereof.

[00560] In some embodiments, the present invention provides a method of administering an IL-17 inhibitor or a composition (e.g., pharmaceutical composition) comprising an IL-17

inhibitor to a subject *via* implant or osmotic pump, by cartridge or micro pump, or by other means appreciated by the skilled artisan, as well-known in the art.

[00561] In some embodiments, the IL-17 inhibitor of the present invention has a measurement (e.g., an IC_{50}) of less than 20 nM within a human IL-17 HEK Blue Assay. As a skilled person will realize, the function of the IL-17 inhibitor is dependent on the tertiary structure of the IL-17 inhibitor and the binding surface presented. It is therefore possible to make minor changes to the sequence encoding the IL-17 inhibitor that do not affect the fold or are not on the binding surface and maintain function. In other embodiments, the present invention provides an IL-17 inhibitor having 85% or higher (e.g., 85%, 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99%, or 99.5%) identity or homology to an amino acid sequence of any IL-17 inhibitor described herein that exhibits an activity, or lessens a symptom of a disease or indication for which IL-17 is involved.

[00562] In some embodiments, an IL-17 inhibitor of the present invention may comprise functional fragments or variants thereof that have at most 10, 9, 8, 7, 6, 5, 4, 3, 2, or 1 amino acid substitutions compared to one or more of the specific peptide analogue sequences recited herein.

[00563] In addition to the methods described in the Examples herein, the IL-17 inhibitors of the present invention may be produced using methods known in the art including chemical synthesis, biosynthesis or in vitro synthesis using recombinant DNA methods, and solid phase synthesis. See e.g. Kelly & Winkler (1990) Genetic Engineering Principles and Methods, vol. 12, J. K. Setlow ed., Plenum Press, NY, pp. 1-19; Merrifield (1964) J Amer Chem Soc 85:2149; Houghten (1985) PNAS USA 82:5131-5135; and Stewart & Young (1984) Solid Phase Peptide Synthesis, 2ed. Pierce, Rockford, IL, which are herein incorporated by reference. The IL-17 inhibitors of the present invention may be purified using protein purification techniques known in the art such as reverse phase high-performance liquid chromatography (HPLC), ion-exchange or immunoaffinity chromatography, filtration or size exclusion, or electrophoresis. See Olsnes, S. and A. Pihl (1973) Biochem. 12(16):3121-3126; and Scopes (1982) Protein Purification, Springer-Verlag, NY, which are herein incorporated by reference.

EXAMPLES

[00564] The following examples demonstrate certain specific embodiments of the present invention. The following examples were carried out using standard techniques that are well known and routine to those of skill in the art, except where otherwise described in detail. It is to be understood that these examples are for illustrative purposes only and do not purport

to be wholly definitive as to conditions or scope of the invention. As such, they should not be construed in any way as limiting the scope of the present invention.

ABBREVIATIONS:

DCM: dichloromethane
DMF: N,N-dimethylformamide
NMP: N-methylpyrrolidone
HBTU: O-(Benzotriazol-1-yl)-N,N,N',N'-tetramethyluronium hexafluorophosphate
HATU: 2-(7-aza-1H-benzotriazole-1-yl)-1,1,3,3-tetramethyluronium hexafluorophosphate
DCC: Dicyclohexylcarbodiimide
NHS: N-hydroxysuccinimide
DIPEA: diisopropylethylamine
EtOH: ethanol
Et₂O: diethyl ether
Hy: hydrogen
TFA: trifluoroacetic acid
TIS: triisopropylsilane
ACN: acetonitrile
HPLC: high performance liquid chromatography
ESI-MS: electron spray ionization mass spectrometry
PBS: phosphate-buffered saline
Boc: t-butoxycarbonyl
Fmoc: Fluorenylmethyloxycarbonyl
Acm: acetamidomethyl
IVA: Isovaleric acid (or Isovaleryl)
Palm: Indicates conjugation of a palmitic acid (palmitoyl).

[00565] In the peptide sequences provided herein, wherein a compound or chemical group is connected by an underscore to an amino acid residue or a chemical moiety, it is to be understood that the compound or chemical group is a side chain or group bonded to the amino acid residue or the chemical moiety but is not connected to any other adjacent amino acid residue. For example, Leu-Trp_{5F}-Asp indicates the 5F substituent is only bonded to Trp but is not connected to Asp. The dash line between 5F and Asp denotes the bonding between Trp and Asp. Lys_Ac indicates the Ac group is conjugated to a side chain of the lysine residue.

General procedure for purification of peptides

[00566] Purification of the peptides of the invention was carried out using reverse-phase high performance liquid chromatography (RP-HPLC). A semi-preparative column - Gemini 5 μ m C18 column (21.2 mm $\times$ 250 mm) (Phenomenex[®]) was applied at the flow rate of 20 mL/min. The separation was achieved using linear gradients with mobile phase A (MPA = 0.1% TFA in water) and mobile phase B (MPB = 0.1% TFA in acetonitrile).

[00567] One of skill in the art will appreciate that standard methods of peptide synthesis may be used to generate the compounds of the invention.

[00568] The peptides disclosed herein were prepared in accordance with procedures and synthetic sequences similar to those set forth in the representative Examples that follow. The molecular weights of the peptides were determined by LC/MS.

[00569] **Example 1. Synthesis of Peptide Analogues**

[00570] Unless otherwise specified, reagents and solvents employed in the following were available commercially in standard laboratory reagent or analytical grade and were used without further purification. Additional teachings for peptide synthesis and isolation, including cyclization and dimerization chemistry, can be found in prior Protagonist patent publications, which are hereby incorporated-by-reference for such teachings – for example: US 10,030,061; US 10,059,744; US 11,807,674; US 9,624,268; US 11,840,581; US 11,845,808; US 10,407,468; and US 11,041,000.

General procedure for Fmoc solid-phase peptide synthesis (SPPS)

[00571] Peptides were synthesized utilizing the CEM liberty Blue Microwave assisted peptide synthesizer. Using the Liberty Blue, Fmoc-deprotection was carried out by addition of 20% piperidine in *N,N*-dimethylformamide (DMF) and then heating to 90° C using microwave irradiation for 80 sec. After DMF washes the Fmoc-protected amino acids were coupled by addition of 0.2 M amino acid (5 eq), 0.5 M *N,N'*-Diisopropylcarbodiimide (DIC; 5 eq) and 1.0 M ethyl cyanohydroxyiminoacetate (Oxyma; 5 eq) all dissolved in DMF. The coupling solution is heated using microwave radiation to 90° C for 160 sec. A second coupling was employed when coupling Arg or other sterically hindered amino acids. When coupling with histidine, the reaction was heated to 50° C for 10 min, double coupling. The cycles were repeated until the desired peptide was obtained.

General procedure for cleavage of peptides off resin and side chain deprotection

[00572] Side chain deprotection and cleavage off the resin for peptide analogues of the invention was achieved by stirring dry resin in a solution containing trifluoroacetic acid (TFA), water, 2,2'-(ethylenedioxy)diethanethiol (DODT) and triisopropylsilane (TIPS) (90:5:2.5:2.5) for 2 h. Following TFA removal, peptide was precipitated using ice-cold diethyl ether. The

solution was centrifuged (5,000 rpm, 4° C, 5 min), and the ether was decanted. The peptide was dissolved in an acetonitrile (MeCN) / water solution (1:1) and the resulting solution was filtered. The linear peptide quality was assessed using electrospray ionization mass spectrometry (ESI-MS).

General procedure for purification of peptides and final lyophilization

[00573] Purification of the peptides of the invention was carried out using reverse-phase high performance liquid chromatography (RP-HPLC). A semi-preparative column - Gemini 5 µm C18 column (21.2 mm × 250 mm) (Phenomenex®) was applied at the flow rate of 20 mL/min. The separation was achieved using linear gradients with mobile phase A (MPA = 0.1% TFA in water) and mobile phase B (MPB = 0.1% TFA in acetonitrile). The collected fractions were analyzed by analytical RP-HPLC, and all fractions >95% purity were combined and freeze-dried under lyophilizer.

General Procedure for Intramolecular Disulfide Bond Formation (Disulfide Bond Cyclization) via Oxidation

[00574] A peptide containing a free thiol at the desired cyclization positions can be 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

[00575] The crude, cleaved peptide was dissolved in 20 ml 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 is monitored with analytic HPLC and LCMS. When the reaction was complete, solid ascorbic acid was added until the solution becomes 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, 10 u, 100 A, 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 15 ml/min). Fractions containing pure product were then freeze-dried on a lyophilizer.

General Procedure for Intramolecular Thioether Bond Formation (Thioether Bond Cyclization)

[00576] A peptide containing a free thiol at the desired position and a free alkyl at the other desired residue position for cyclization was assembled on a Rink Amide-MBHA resin

following general Fmoc-SPPS procedure. Chlorination was carried out by treating the resin with PPh₃ (10 equiv.) and Cl₃CCN (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.

[00577] The crude peptide possessing a free thiol and an alkyl halide intermediate at the desired cyclization positions 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, 10 μ , 100 Å, 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 15 ml/min). Fractions containing pure product were then freeze-dried on a lyophilizer.

General Procedure for Intramolecular Bis-thioether Bond Formation (Cyclization Linker Mediated Cross-Linking)

[00578] After crude linear peptides purification, combine the desired fractions (~200 mL for 1.5 mmol scale). To this, 1 eq. of TCEP was added, then 15-20 eq. of base K₂CO₃ was added to adjust the pH to 10-11. Diiodide alkane (2-4 eq.) was then added batchwise over an hour to minimize the formation of double alkylated side products. Cyclization was generally completed within 1-2 hr, and can be monitored by LC-MS. Upon completion, the reaction mixture was then diluted to containing 30% ACN/H₂O, acidified by TFA, followed by purification using RP-HPLC.

General Procedure for Hydrocarbon Ring Close Metathesis (RCM) (Carbon-carbon single or double bond cross-linking)

[00579] After the coupling of second olefin residue, the resin was washed with DCM and dried under high vacuum. The dry resin was then placed in the round bottom flask and swollen in toluene (1 g resin per 20 mL toluene). To the reaction mixture was added Grubbs catalyst 1st generation (0.35 eq.). The resulting solution was bubbled with N₂ for 5 mins and capped with a small nitrogen balloon. It was heated to 60 °C overnight (O/N). Micro-cleavage test confirmed reaction completion. After cooling down to room temperature resin was filtered and washed with DMF x2, DMSO x1, DCM x3.

General Procedures for Olefin Reduction

[00580] After the RCM reaction, the dry resin was swollen in MeCN (1 g resin per 20 mL solvent). It was cooled by ice bath and charged with 2-nitrobenzenesulfonyl chloride (10 eq.). Hydrazine hydrate (25 eq.) was slowly added to the reaction mixture. After addition, it was allowed to warm up to room temperature and continued stirred overnight. Micro-cleavage test to confirm the reaction completion. Second round of treatment can be applied if the reaction was not yet completed.

[00581] Once the reaction was completed, the reaction mixture was filtered and washed with DMF x2, DMF/H₂O (1:1) x1, THF x1, DMF x1, DCM x2; then dried under vacuum and transferred back to the reaction vessel to continue the amino acid assembly using Fmoc SPPS until completion.

General Procedures for Linker Activation and Dimerization

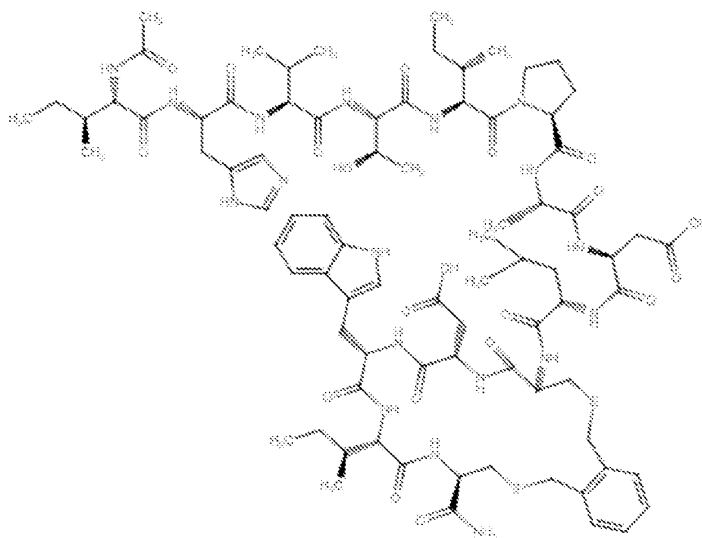
[00582] Peptide monomer subunits are linked to form peptide dimers as described below.

[00583] Small Scale DIG Linker Activation Procedure: 5 mL of NMP was added to a glass vial containing IDA diacid (304.2 mg, 1 mmol), N-hydroxysuccinimide (NHS, 253.2 mg, 2.2 eq. 2.2 mmol) and a stirring bar. The mixture was stirred at room temperature to completely dissolve the solid starting materials. N, N'-Dicyclohexylcarbodiimide (DCC, 453.9 mg, 2.2 eq., 2.2 mmol) was then added to the mixture. Precipitation appears within 10 min and the reaction mixture was further stirred at room temperature overnight. The reaction mixture was then filtered to remove the precipitated dicyclohexylurea (DCU). The activated linker was kept in a closed vial prior to use for dimerization. The nominal concentration of the activated linker was approximately 0.20 M.

[00584] For dimerization using PEG linkers, there was no pre-activation step involved. Commercially available pre-activated bi-functional PEG linkers were used.

[00585] Dimerization Procedure: 2 mL of anhydrous -DMF or DMSO was added to a vial containing peptide monomer (0.1 mmol). The pH of the peptide was then adjusted to 8-9 with DIEA. Activated linker (0.48 eq relative to monomer, 0.048 mmol) was then added to the monomer solution. The reaction mixture was stirred at room temperature for one hour. Completion of the dimerization reaction was monitored using analytical HPLC. The time for completion of dimerization reaction varies depending upon the linker. After the completion, the reaction mixture was diluted with MeCN by 20-100x fold and loaded on to RP-HPLC for purification.

[00586] **Example 2. Representative Synthesis of a Cyclized Peptide: Compound 10**
(SEQ ID NO. 10)



Cmpd 10, where Cys and Cys in the peptide are linked via an Xylene_linker to form a cyclized peptide.

[00587] The linear precursor of peptide with SEQ ID NO. 10 was constructed on Rink Amide MBHA resin (100-200 mesh, 0.68 mmol/g) using standard Fmoc-protection synthesis conditions on the CEM Liberty Blue Microwave assisted peptide synthesizer. 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 by RP-HPLC. Cyclisation of the peptide was achieved in solution using α,α' -Dibromo-m-xylene, followed by final purification via RP-HPLC. Lyophilization of pure fractions gave the final product of peptide 143 as a white powder of >95% purity.

[00588] Step 1: Resin Swelling: 150 mg of Rink Amide MBHA resin (100-200 mesh, 0.68 mmol/g) was transferred to a 50 mL Falcon tube. The resin was swelled with 15 mL of 1:1 dichloromethane (DCM):DMF (1 h) and attached to the HT12 module of the CEM Liberty Blue Microwave assisted peptide synthesizer.

[00589] Step 2: Coupling of Fmoc-Cys(Trt)-OH: Deprotection of the Fmoc group was accomplished using modified deprotection conditions on the Liberty Blue consisting of: treatment of 4 mL of 20% piperidine in DMF, 20sec, 75° C, 130 W to 80 sec, 90° C, 20 W.

After deprotection, the resin was washed with DMF (2x4 mL – 5 sec drain time, 1x5 mL – 10 sec drain time) which was followed by addition of 2.5 mL of Fmoc-Cys(Trt)-OH in DMF (0.2 M), 1 mL of DIC in DMF (0.5 M) and 0.5 mL of Oxyma in DMF (1.0 M). The coupling reaction was heated using a modified microwave method of: 15 sec, 75° C, 130 W to 160 sec, 90° C, 20 W. After completion of the cycle, the resin was washed with 4 mL of DMF (5 sec drain time) prior to starting the next deprotection/coupling cycle.

[00590] Step 3: Coupling of Fmoc-Ile-OH: Deprotection of the Fmoc group was accomplished using modified deprotection conditions on the Liberty Blue consisting of: treatment of 4 mL of 20% piperidine in DMF, 20 sec, 75° C, 130 W to 80 sec, 90° C, 20 W. After deprotection, the resin was washed with DMF (2x4 mL – 5 sec drain time, 1x5 mL – 10 sec drain time) which was followed by addition of 2.5 mL of Fmoc-Ile-OH in DMF (0.2 M), 1 mL of DIC in DMF (0.5 M) and 0.5 mL of Oxyma in DMF (1.0 M). The coupling reaction was heated using a modified microwave method of: 15 sec, 75° C, 130 W to 160 sec, 90° C, 20 W. After completion of the cycle, the resin was washed with 4 mL of DMF (5sec drain time) prior to starting the next deprotection/coupling cycle.

[00591] Step 4: Coupling of Fmoc-Trp(Boc)-OH: Deprotection of the Fmoc group was accomplished using modified deprotection conditions on the Liberty Blue consisting of: treatment of 4 mL of 20% piperidine in DMF, 20 sec, 75° C, 130 W to 80 sec, 90° C, 20 W. After deprotection, the resin was washed with DMF (2x4 mL – 5 sec drain time, 1x5 mL – 10 sec drain time) which was followed by addition of 2.5 mL of Fmoc- Trp(Boc)-OH in DMF (0.2 M), 1 mL of DIC in DMF (0.5 M) and 0.5 mL of Oxyma in DMF (1.0 M). The coupling reaction was heated using a modified microwave method of: 15 sec, 75° C, 130 W to 160 sec, 90° C, 20 W. After completion of the cycle, the resin was washed with 4 mL of DMF (5sec drain time) prior to starting the next deprotection/coupling cycle.

[00592] Step 5: Coupling of Fmoc-Asp(tBu)-OH: Deprotection of the Fmoc group was accomplished using modified deprotection conditions on the Liberty Blue consisting of: treatment of 4 mL of 20% piperidine in DMF, 20 sec, 75° C, 130 W to 80 sec, 90° C, 20 W. After deprotection, the resin was washed with DMF (2x4 mL – 5 sec drain time, 1x5 mL – 10sec drain time) which was followed by addition of 2.5 mL of Fmoc- Asp(tBu)-OH in DMF (0.2 M), 1 mL of DIC in DMF (0.5 M) and 0.5 mL of Oxyma in DMF (1.0 M). The coupling reaction was heated using a modified microwave method of: 15 sec, 75° C, 130 W to 160 sec, 90° C, 20 W. After completion of the cycle, the resin was washed with 4 mL of DMF (5 sec drain time) prior to starting the next deprotection/coupling cycle.

[00593] Step 6: Coupling of Fmoc-Cys(Trt)-OH: Deprotection of the Fmoc group was accomplished using modified deprotection conditions on the Liberty Blue consisting of:

treatment of 4 mL of 20% piperidine in DMF, 20 sec, 75° C, 130 W to 80 sec, 90° C, 20 W. After deprotection, the resin was washed with DMF (2x4 mL – 5 sec drain time, 1x5 mL – 10 sec drain time) which was followed by addition of 2.5 mL of Fmoc- Cys(Trt)-OH in DMF (0.2 M), 1 mL of DIC in DMF (0.5 M) and 0.5 mL of Oxyma in DMF (1.0 M). The coupling reaction was heated using a modified microwave method of: 15 sec, 75° C, 130 W to 160 sec, 90° C, 20 W. After completion of the cycle, the resin was washed with 4 mL of DMF (5 sec drain time) prior to starting the next deprotection/coupling cycle.

[00594] Step 7: Coupling of Fmoc-Leu-OH: Deprotection of the Fmoc group was accomplished using modified deprotection conditions on the Liberty Blue consisting of: treatment of 4 mL of 20% piperidine in DMF, 20 sec, 75° C, 130 W to 80 sec, 90° C, 20 W. After deprotection, the resin was washed with DMF (2x4 mL – 5 sec drain time, 1x5 mL – 10 sec drain time) which was followed by addition of 2.5 mL of Fmoc-Leu-OH in DMF (0.2 M), 1 mL of DIC in DMF (0.5 M) and 0.5 mL of Oxyma in DMF (1.0 M). The coupling reaction was heated using a modified microwave method of: 15 sec, 75° C, 130 W to 160 sec, 90° C, 20 W. After completion of the cycle, the resin was washed with 4 mL of DMF (5 sec drain time) prior to starting the next deprotection/coupling cycle.

[00595] Step 8: Coupling of Fmoc-Asp(tBu)-OH: Deprotection of the Fmoc group was accomplished using modified deprotection conditions on the Liberty Blue consisting of: treatment of 4 mL of 20% piperidine in DMF, 20 sec, 75° C, 130 W to 80 sec, 90° C, 20 W. After deprotection, the resin was washed with DMF (2x4 mL – 5 sec drain time, 1x5 mL – 10 sec drain time) which was followed by addition of 2.5 mL of Fmoc- Asp(tBu)-OH in DMF (0.2 M), 1 mL of DIC in DMF (0.5 M) and 0.5 mL of Oxyma in DMF (1.0 M). The coupling reaction was heated using a modified microwave method of: 15 sec, 75° C, 130 W to 160 sec, 90° C, 20 W. After completion of the cycle, the resin was washed with 4 mL of DMF (5 sec drain time) prior to starting the next deprotection/coupling cycle.

[00596] Step 9: Coupling of Fmoc-Ala-OH: Deprotection of the Fmoc group was accomplished using modified deprotection conditions on the Liberty Blue consisting of: treatment of 4 mL of 20% piperidine in DMF, 20 sec, 75° C, 130 W to 80 sec, 90° C, 20 W. After deprotection, the resin was washed with DMF (2x4 mL – 5 sec drain time, 1x5mL – 10 sec drain time) which was followed by addition of 2.5 mL of Fmoc- Ala-OH in DMF (0.2 M), 1 mL of DIC in DMF (0.5 M) and 0.5 mL of Oxyma in DMF (1.0 M). The coupling reaction was heated using a modified microwave method of: 15 sec, 75° C, 130 W to 160 sec, 90° C, 20 W. After completion of the cycle, the resin was washed with 4 mL of DMF (5 sec drain time) prior to starting the next deprotection/coupling cycle.

[00597] Step 10: Coupling of Fmoc-Pro-OH: Deprotection of the Fmoc group was accomplished using modified deprotection conditions on the Liberty Blue consisting of: treatment of 4 mL of 20% piperidine in DMF, 20 sec, 75° C, 130 W to 80 sec, 90° C, 20 W. After deprotection, the resin was washed with DMF (2x4 mL – 5 sec drain time, 1x5 mL – 10 sec drain time) which was followed by addition of 2.5 mL of Fmoc-Pro-OH in DMF (0.2 M), 1 mL of DIC in DMF (0.5 M) and 0.5 mL of Oxyma in DMF (1.0 M). The coupling reaction was heated using a modified microwave method of: 15 sec, 75° C, 130 W to 160 sec, 90° C, 20 W. After completion of the cycle, the resin was washed with 4 mL of DMF (5 sec drain time) prior to starting the next deprotection/coupling cycle.

[00598] Step 11: Coupling of Fmoc-Ile-OH: Deprotection of the Fmoc group was accomplished using modified deprotection conditions on the Liberty Blue consisting of: treatment of 4 mL of 20% piperidine in DMF, 20 sec, 75° C, 130 W to 80 sec, 90° C, 20 W. After deprotection, the resin was washed with DMF (2x4 mL – 5 sec drain time, 1x5 mL – 10 sec drain time) which was followed by addition of 2.5 mL of Fmoc-Ile-OH in DMF (0.2 M), 1 mL of DIC in DMF (0.5 M) and 0.5 mL of Oxyma in DMF (1.0 M). The coupling reaction was heated using a modified microwave method of: 15 sec, 75° C, 130 W to 160 sec, 90° C, 20 W. After completion of the cycle, the resin was washed with 4 mL of DMF (5 sec drain time) prior to starting the next deprotection/coupling cycle.

[00599] Step 12: Coupling of Fmoc-Thr(tBu)-OH: Deprotection of the Fmoc group was accomplished using modified deprotection conditions on the Liberty Blue consisting of: treatment of 4 mL of 20% piperidine in DMF, 20 sec, 75° C, 130 W to 80 sec, 90° C, 20 W. After deprotection, the resin was washed with DMF (2x4 mL – 5 sec drain time, 1x5 mL – 10 sec drain time) which was followed by addition of 2.5 mL of Fmoc-Thr(tBu)-OH in DMF (0.2 M), 1 mL of DIC in DMF (0.5 M) and 0.5 mL of Oxyma in DMF (1.0 M). The coupling reaction was heated using a modified microwave method of: 15 sec, 75° C, 130 W to 160 sec, 90° C, 20 W. After completion of the cycle, the resin was washed with 4 mL of DMF (5 sec drain time) prior to starting the next deprotection/coupling cycle.

[00600] Step 13: Coupling of Fmoc-Val-OH: Deprotection of the Fmoc group was accomplished using modified deprotection conditions on the Liberty Blue consisting of: treatment of 4 mL of 20% piperidine in DMF, 20 sec, 75° C, 130 W to 80 sec, 90° C, 20 W. After deprotection, the resin was washed with DMF (2x4 mL – 5 sec drain time, 1x5 mL – 10 sec drain time) which was followed by addition of 2.5 mL of Fmoc-Val-OH in DMF (0.2 M), 1 mL of DIC in DMF (0.5 M) and 0.5 mL of Oxyma in DMF (1.0 M). The coupling reaction was heated using a modified microwave method of: 15 sec, 75° C, 130 W to 160

sec, 90° C, 20 W. After completion of the cycle, the resin was washed with 4 mL of DMF (5 sec drain time) prior to starting the next deprotection/coupling cycle.

[00601] Step 14: Coupling of Fmoc-His(Trt)-OH: Deprotection of the Fmoc group was accomplished using modified deprotection conditions on the Liberty Blue consisting of: treatment of 4 mL of 20% piperidine in DMF, 20 sec, 75° C, 130 W to 80 sec, 90° C, 20 W. After deprotection, the resin was washed with DMF (2x4 mL – 5 sec drain time, 1x5 mL – 10 sec drain time) which was followed by addition of 2.5 mL of Fmoc-His(Trt)-OH in DMF (0.2 M), 1 mL of DIC in DMF (0.5 M) and 0.5 mL of Oxyma in DMF (1.0 M). The coupling reaction was heated using a modified microwave method of: 120 sec, 25° C, 0 W to 480 sec, 50° C, 20 W. This coupling protocol was repeated once (double coupling). After completion of the cycle, the resin was washed with 4 mL of DMF (5 sec drain time) prior to starting the next deprotection/coupling cycle.

[00602] Step 15: Coupling of Fmoc-Ile-OH: Deprotection of the Fmoc group was accomplished using modified deprotection conditions on the Liberty Blue consisting of: treatment of 4 mL of 20% piperidine in DMF, 20 sec, 75° C, 130 W to 80 sec, 90° C, 20 W. After deprotection, the resin was washed with DMF (2x4 mL – 5 sec drain time, 1x5 mL – 10 sec drain time) which was followed by addition of 2.5 mL of Fmoc-Ile-OH in DMF (0.2 M), 1 mL of DIC in DMF (0.5 M) and 0.5 mL of Oxyma in DMF (1.0 M). The coupling reaction was heated using a modified microwave method of: 15 sec, 75° C, 130 W to 160 sec, 90° C, 20 W. After completion of the cycle, the resin was washed with 4 mL of DMF (5 sec drain time) prior to starting the next deprotection/coupling cycle.

[00603] Step 16: Acetyl Capping: Deprotection of the Fmoc group was accomplished using modified deprotection conditions on the Liberty Blue consisting of: treatment of 4 mL of 20% piperidine in DMF, 20 sec, 75° C, 130 W to 80 sec, 90° C, 20 W. After deprotection, the resin was washed with DMF (2x4 mL – 5 sec drain time, 1x5 mL – 10 sec drain time) which was followed by addition of 2.5 mL of acetic anhydride in DMF (0.5 M) and 2 mL of DIPEA in DMF (1.0 M). The coupling reaction was heated using a modified microwave method of: 60 sec, 50° C, 50 W to 540 sec, 60° C, 20 W. After completion of the cycle, the resin was washed with 4 mL of DMF (5 sec drain time) and transferred to the HT12 module of the CEM Liberty Blue Microwave assisted peptide synthesizer in a mixture of 1:1 DCM:DMF.

[00604] Step 17: Drying the Resin: After completion of the synthesis the resin was filtered to remove 1:1 DCM:DMF transfer solvent and washed with DCM (4x 10 mL). The resin was subsequently dried *via* a stream of N₂ (1 – 2h) prior to cleavage.

[00605] Step 18: TFA Cleavage and Et₂O precipitation of linear precursor: 10 mL of the cleavage cocktail [TFA cleavage cocktail (90/5/2.5/2.5 of TFA/water/TIPS/DODT)] was added to the dried, protected resin bound peptide and stirred for 2 h. The cleavage mixture was removed *via* a stream of N₂ (reduced to ~1 mL), after which cold Et₂O was added. The resulting white suspension was then centrifuged (5,000 rpm, 4° C, 5 min) and the Et₂O was decanted to waste. The white precipitate cake was dissolved in MeCN / water (1:1) and filtered before purification.

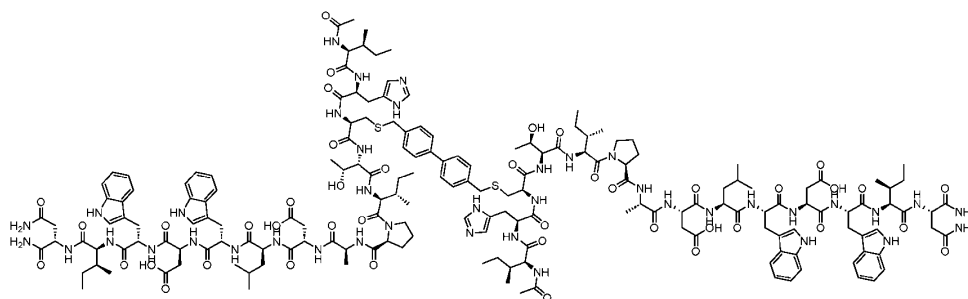
[00606] Step 19: RP-HPLC purification of linear precursor: a semi-preparative column - Gemini 5 µm C18 column (21.2 mm × 250 mm) (Phenomenex®) was applied. The separation was achieved using linear gradients of 25-55% MPB over 30 min at 20 mL/min with mobile phase A (MPA = 0.1% TFA in water) and mobile phase B (MPB = 0.1% TFA in acetonitrile).

[00607] Step 20: Lyophilization of linear precursor: The collected fractions were analyzed by analytical RP-HPLC, and all fractions >90% purity were combined. Lyophilization of the combined fractions gave the linear precursor of PEPTIDE 143 as a white powder (0.060 g).

[00608] Step 21: Bis-thioether formation: The linear intermediate (0.030 g, 1 eq.) was dissolved in 50 mL of 1:1 MeCN/0.2 M aqueous NH₄HCO₃ buffer. To this, 700 µL α,α'-Dibromo-o-xylene (10 mg/mL in MeCN, 1.5 eq.) was added, and the reaction mixture was stirred at ambient temperature for 1 h. Once complete, the reaction was diluted with water (100 mL total volume) and loaded for RP-HPLC purification.

[00609] Step 22: 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 with SEQ ID NO. 10 as a white powder (0.015 g, 98 % purity). Low resolution LC/MS of purified compound 10 displayed both the [M+H]⁺ and [M+2H]²⁺ ions at 1743.0 Da and 872.0 Da, respectively. The experimental mass agrees with the theoretical molecular weight of 1742.09 Da.

[00610] Example 3. Representative Synthesis of a Dimeric Peptide: Compound 16 (SEQ ID NO. 12)



[00611] The dimeric peptide 16 is formed by covalently linking the thiol groups on the side chains of the cysteine residues in the two peptide fragments with pBiphenyl_linker

[00612] The linear precursor peptide (SEQ ID NO:12) was constructed on Rink amide resin (100-200 mesh, 0.69 mmol/g) using standard Fmoc-protection synthesis conditions on the CEM Liberty Blue Microwave assisted peptide synthesizer. Dimerization of the peptide was achieved in solution with 4,4'-bis(bromomethyl)-1,1'-biphenyl. The constructed dimeric peptide was then purified by RP-HPLC. Lyophilization of pure fractions gave the final product peptide 162 as a white powder of > 95% purity.

Peptide Assembly

[00613] Step 1 – TFA Cleavage and Et₂O precipitation of monomeric precursor: After assembly of the peptide 162 monomer, peptide Ac-I-H-C-T-I-P-A-D-L-W-D-W-I-N-NH₂ (SEQ ID NO:12) *via* the CEM Liberty Blue Microwave assisted peptide synthesizer, 10 mL of the cleavage cocktail [TFA cleavage cocktail (90/5/2.5/2.5 of TFA/water/TIPS/DODT)] was added to the dried, protected, resin bound peptide and stirred for 2 h. The cleavage mixture was removed *via* a stream of N₂ (reduced to ~1 mL), after which cold Et₂O was added. The resulting white suspension was then centrifuged (5,000 rpm, 4° C, 5 min) and the Et₂O was decanted to waste. The white precipitate cake was dissolved in MeCN / water (1:1) and filtered before purification.

[00614] Step 2 – RP-HPLC purification: Semi-Preparative reverse phase HPLC was performed on a Gemini® 10 µm C18 column (22 mm x 250 mm) (Phenomenex). Separations were achieved using linear gradients of buffer B in A (Mobile phase A: water containing 0.05% TFA, mobile phase B: MeCN containing 0.05% TFA), at a flow rate of 20 mL/min (preparative).

[00615] Step 3 – Lyophilization of monomeric intermediate: The collected fractions were analyzed by analytical RP-HPLC, and all fractions >95% purity were combined. Lyophilization of the combined fractions gave the monomeric precursor of peptide 162 as a white powder (0.158 g).

[00616] Step 4 – Cyclisation: The monomeric intermediate (0.030 g, 1 eq.) was dissolved in 2 mL of 1:1 MeCN/0.2 M aqueous NH₄HCO₃ buffer. To this solution, 4,4'-bis(bromomethyl)-1,1'-biphenyl (0.003 g, 0.5 eq.) dissolved in DMSO (1 mL) was added, and the reaction monitored via MS. Once complete, the reaction was diluted with water (100 mL total volume) and loaded for RP-HPLC purification as described above in Step 2.

[00617] Step 5 – 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 the dimeric peptide 162 as a white powder. Low resolution LC/MS of purified peptide 162 dimer displayed the $[M+3H]^{3+}$ ion at 1218.1 Da. The experimental mass agrees with the theoretical molecular weight of 3654.2 Da.

[00618] Example 4. NIH 3T3 IL-6 Secretion Assay Protocol

[00619] Fibroblast cell line isolated from mouse NIH/Swiss embryo (ATCC: CRL-1658) were cultured in Dulbecco's Modified Eagle's Medium supplemented with 10% of heat-inactivated fetal bovine serum and 2mM L-glutamine (Invitrogen). Cells were grown in T150 flasks until 60–80% confluent and removed using 0.25% Trypsin-EDTA and resuspended in cultured media at 1,000,000 cells per mL. 100uL of cells were seeded in a 96-well plate and rested for 1hr at 37°C with 5% CO₂ before addition of cytokines and peptides. 50uL of 4X peptide stocks were pretreated with cells for 10 minutes at room temperature then 50uL of 4X human 20ng/mL TNFa (PeproTech) containing 3ng/mL human IL-17A (PeproTech) or 10ng/mL human IL-17AF (SinoBiological). Cell assay plates were incubated for 22-24hrs at 37°C incubator containing 5% CO₂. Culture supernatants were harvested for IL-6 analysis using MSD mouse IL-6 Kit (MesoScale). Dose response curves were generated in GraphPad Prism using a 4-parameter fit; plotting IL-6 levels against inhibitor concentrations. Peptides were ranked based on the IC₅₀ value.

[00620] Example 5. Human IL-17 HEK Blue assay (Invivogen)

[00621] Either human IL-17AA, AF, or FF is contacted with HEK Blue cells, with or without incubation with a peptide compound of the invention. The inhibitory (or neutralizing / antagonist) potency of the compounds of the invention can be determined by calculating the amount (in moles, *e.g.*, micromolar, nanomolar, or picomolar amounts) of the compound needed to reduce the IL-17 dependent SEAP activity by half, *i.e.*, the IC₅₀ of the compound.

[00622] A schematic of the assay is shown in Figure 2, and the results for representative peptide compounds of the invention are provided in Figure 1. The assay was conducted in accordance with manufacturer's instructions.

[00623] Materials: HEK Blue IL-17 Cells (Invivogen: HKB-IL-17); Culture Medium (DMEM containing 4mM L-glutamine, 4500 mg/L glucose, 1mM sodium pyruvate, and 1500 mg/L sodium bicarbonate + 10% HI FBS+ 1x HEK Blue Selection + 100ug/mL Normocin); Assay Medium (DMEM + 10% FBS); Quanti-Blue Solution; Recombinant Human IL-17A (or -AF, -FF) (PeproTech: 200-17-100UG); Synergy HTX Instrument.

[00624] Day 1: Dosing Peptide on HEK Blue IL-17 cells.

[00625] (1) Prepare the peptide dosing solution by preparing 10 mM DMSO of lyophilized peptide and 400x DMSO of the peptide sample in a microtiter plate. A series of limiting dilutions for each sample and controls were then made in the microtiter plate. A dose response curve in DMSO was conducted with a 1:4 serial dilution (5 uL DMSO stock serial dilution + 15 uL of DMSO). The 400x DMSO plate was incubated on a shaker.

[00626] (2) Prepare EC50 IL-17. Prepare 4x of 1 ng/mL human IL-17 (-AA, -AF, -FF), 50 uL are added per well.

[00627] (3) Prepare HEK Blue IL-17 cells. Cells are cultured in T150 Flask (Do not let cells reach >90% confluency). Remove flask from incubator and discard culture medium. Rinse the cell layer 1x with 5mL DPBS. Aspirate the DPBS and add 5mL of Versene T175 Flask. Incubate at 37C for 2mins. Add 5mL of culture medium and resuspend the cells up and down. Transfer the cells to 50mL conical tube. Centrifuge at 1500rpm for 3mins at RT. Resuspend cells in 5mL of culture medium. Count the cells using Countess (10uL of cells + 10uL of Trypan Blue--> Add 10uL of mixture to Countess Cassette). Resuspend cells to 0.25e6c/mL in assay medium (25k cells per 100uL per well).

[00628] (4) Dosing HEK Blue IL-17 Cells. Prepare 4x Dosing Solution of Test Peptides (Add 2uL of 400x DMSO Stock + 198uL of assay medium). Incubate the plate on a shaker for a few minutes. Add 100uL of HEK Blue IL-17 (25k cells/well) to a flat bottom 96-well tissue culture plate. Then add 50uL of 4x Test Sample. Lastly, add 50uL of 4x human IL-17 or assay medium alone. Incubate the plate in the incubator at 37C, 5% CO₂ for 20-24 hrs.

[00629] Day 2. Quantify and Determine SEAP Levels.

[00630] Remove Quanti-Blue Solution from -20C and thaw at room temperature in water. Add 180uL of Quanti-Blue Solution to each well on a new 96 well tissue culture plate (Prepare Quanti-Blue Solution according to Invivogen's Specification). At 20-24 hrs, transfer 20uL of induced HEK Blue IL-17 cells supernatant to the plate containing Quanti-Blue Solution. Incubate the plate in the incubator at 37C with 5% CO₂ for 1hr. Determine SEAP levels using Synergy HTX Instrument (Read OD at 655nm).

[00631] Analysis. Calculate % Inhibition using the following equation: $100 * (1 - (\text{OD Test Sample} - \text{OD Average negative control}) / (\text{OD Average 1ng/mL Human IL-17} - \text{OD Average negative control}))$

negative control). Graph % Inhibition in GraphPad Prism. Fit curve using 4-parameter fit (if needed, constrain data to 0 and 100%). Use Macro File to generate IC₅₀ values.

[00632] Example 6. In Vivo IL-17 Mouse Model Experiments

[00633] Figure 3 presents an in vivo model and data for evaluating pharmacodynamic and pharmacokinetic properties of the peptide-based compounds of the invention. The in vivo model is a murine inflammation/psoriasis model with human IL-17. Recombinant human IL-17A (rhIL-17A) is administered by subcutaneously to the mice. The rhIL-17A upregulates the expression of CXCL1, which is a chemokine produced by keratinocytes. By monitoring CXCL1 levels in the serum (and if desired, ear tissue), one can assess the pharmacodynamic properties of the peptide-based compounds of the invention by determining the levels needed to reduce the rhIL-17A-triggered upregulation of CXCL1 levels. Furthermore, repeated administration of rhIL-17A triggers a psoriasis-like cutaneous phenotype characterized by erythema and ear thickness.

[00634] The top panel of Figure 3 shows the design of the initial experiments conducted with the in vivo model. There are three treatment groups for each experiment, where mice were treated with either: (a) vehicle (no active ingredient – otherwise same formulation solution as with PO or SC), (b) Compound 82 through oral administration (“PO”), and (c) Compound 82 by subcutaneous injection (“SC” or “sc”). Different amounts of Compound 82 were administered to assess dose response. After 0.5 hours, mice in each treatment group were then given 0.2 mg/animal of rhIL-17A subcutaneously. Two - (2) hours after rhIL-17A administration, serum samples were collected and analyzed for CXCL1 levels (ear and serum) and for Compound levels (ear and serum).

[00635] The data in the bottom panel of Figure 3 presents in the results from the first round of experiments. This data shows that there is a significant reduction of rhIL-17 induced CXCL-1 secretion after a single PO (oral) dose of Compound 82. A dose-response relationship was also observed -- the amount of CXCL-1 reduction was in relationship to the amount of Compound 82 orally administered (see Figure 3, bottom panel, 500 mg/kg, 300 mg/kg and 150 mg/kg). Further, the CXCL-1 reduction through oral administration was similar to the reduction seen with subcutaneous (sc) administration of Compound 82. For all dosage amounts, serum

concentrations of Compound 82 (3 hours after administration) were at least 2-5-fold above the IC₉₀ concentration of rhIL-17 (36 ng/mL).

[00636] Initial experiments also included testing with other peptide compounds using the Figure 3 experimental scheme. For example, Compound 285 showed significant reduction of serum CXCL-1 secretion when it was administered subcutaneously at 0.3 mg/kg. (Fig. 4.) The serum concentration of Compound 285 (3 hours after administration) was 197 ng/mL, well above the target concentration of > 100 ng/mL and the IC₉₀ concentration of rhIL-17. Another example was with the oral administration (PO) of Compound 288. Figure 5 shows significant reduction of serum and ear CXCL-1 secretion after PO 100 mg/kg dose. Serum concentrations of 40 ng/mL and 18 ng/mL were measured for Compound 288 at 3 hours after PO 100 mg/kg and 30 mg/kg dosing, respectively.

[00637] Additional experiments included testing peptide compounds 829, 834, and 836 using a modified Figure 3 experimental scheme, where the time after peptide administration and rhIL-17AA administration was changed from 0.5 hours to 2.0 hours, and the amount of rhIL-17AA administered was changed from 0.2 micrograms per mouse to 2.0 micrograms per mouse. As shown in Figures 7A-C, compounds 829, 834 (serum data only), and 836 significantly reduced serum and skin CXCL-1 levels even with oral administration of these compounds at 80 mg/kg.

[00638] Another additional experiment examined whether Compounds 829, 834, and 836 were efficacious in a rat IL-23-induced skin inflammation efficacy model. The IL-23/IL-17 axis activation contributes to the development of several inflammatory diseases, such as psoriasis. Thus, this rat 5-day IL-23 efficacy model was used to assess IL-17 target engagement with these Compounds. IL-23 was administered ID (intradermal) in the ear (1.5 micrograms/ear) daily for 5 days to induce psoriasis-like phenotype in rats. Such repeated IL-23 administration causes ear erythema and thickening. The peptide compounds were dosed 2 hours before IL-23. Daily ear thickness and erythema were scored, and at day 5, serum, skin, and ears were collected for analysis. Figure 8 shows that Compounds 829 and 836 significantly reduced ear thickness.

[00639] **Example 7: Stability Assays - Simulated Gastrointestinal Assays**

[00640] **Simulated Gastric Fluid (SGF) Assay**

[00641] Blank SGF was prepared by adding 2 g sodium chloride, 7 mL hydrochloric acid (37%) in a final volume of 1 L water, and adjusted pH to 1.2.

[00642] SGF was prepared by dissolving 320 mg Pepsin (Sigma®, P6887, from Porcine Stomach Mucosa) in 100 mL Blank SGF and stirred at room temperature for 30 minutes. The solution was filtered through 0.45 µm membrane and aliquot and stored at -20 °C.

[00643] Experimental: peptides of interest (20 µM) were incubated with pre-warmed SGF 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.

[00644] Simulated Intestinal Fluid (SIF) Stability Assay

[00645] Blank FaSSIF (Fasted State Simulated Intestinal Fluid) was prepared by dissolving 0.348 g NaOH, 3.954 g sodium phosphate monobasic monohydrate and 6.186 g NaCl in a final volume of 1 liter water (pH adjusted to 6.5).

[00646] FaSSIF was prepared by dissolving 1.2 g porcine pancreatin (Chem-supply, PL378) in 100 mL Blank FaSSIF and stirred at room temperature for 30 minutes. The solution was filtered through 0.45 µm membrane and aliquot and stored at -20 °C.

[00647] Experimental: peptides of interest (20 µM) were incubated with pre-warmed FaSSIF (1% pancreatin in final incubation mixture) 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.

[00648] Plasma Stability Assay

[00649] Peptides of interest (20 μ M) are incubated with pre-warmed plasma (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 μ M internal standard). Quenched samples were stored at 4 °C until the end of the experiment and centrifuged at 17,000 g for 15 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.

* * * * *

[00650] 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.

[00651] At least some of the chemical names or sequences of compounds of the invention as given and set forth in this application, may have been generated on an automated basis by use of a commercially available chemical naming software program, and have not been independently verified. In the instance where the indicated chemical name or sequence and the depicted structure differ, the depicted structure will control. In the chemical structures where a chiral center exists in a structure, but no specific stereochemistry is shown for the chiral center, both enantiomers associated with the chiral structure are encompassed by the structure. Similarly, for the peptides where E/Z isomers exist but are not specifically mentioned, both isomers are specifically disclosed and covered.

[00652] 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.

What is claimed is:

1. A peptide comprising or consisting of a sequence of Formula (I):

R^1 -X00-X0-X1-X2-X3-X4-X5-X6-X7-X8-X9-X10-X11-X12-X13-X14-X15-X16- R^2 ,

wherein:

R^1 is R^a -C(O)- or hydrogen, wherein R^a is C_{1-20} alkyl or C_{3-8} cycloalkyl; or R^1 is acetyl, IPip_AceticAcid, 3-hydroxypropionic acid, C6_diacid, cyclopropanecarboxylic acid, cyclohexanecarboxylic acid, glutaric_acid, isovaleric acid, methanesulfonyl acetic acid, Mor_propanoic_acid, pivalic acid (PVA), 1PEG2_1PEG2_IsoGlu_C12, 1PEG2_1PEG2_IsoGlu_C12_Diacid, 1PEG2_1PEG2_IsoGlu_C18_diacid, 1PEG2_1PEG2_IsoGlu_Palm, 1PEG2_1PEG2_Ahx_C18_Diacid, 1PEG2_PEG2_Ahx_Palm, or absent;

R^2 is NH_2 or OH or absent;

X00 is Cha, dH, dK, Ogl, Tle or absent;

X0 is 2Pal, 3Pal, Aib, Asn, d2Pal, d3Pal, dA, dE, dF, dH, dK, dL, dQ, dS, Gln, Glu,

Glu_OMe, His, Ile, Lys, Lys_1PEG2_1PEG2_IsoGlu_C12,

Lys_1PEG2_1PEG2_IsoGlu_C18_diacid, Lys_1PEG2_1PEG2_IsoGlu_Palm, Lys_Me3,

NMe_His, Orn, Pro, Sar, Thr, Tle, or absent;

X1 is 1Nal, Bip, Cha, Chg, Cyclopropyl_Ala, Dgl, DIP, dI, hCha, hF, hhF, Ile, Lys,

Lys_1PEG2_1PEG2_IsoGlu_C18_diacid, Lys_1PEG2_1PEG2_IsoGlu_C12,

Lys_1PEG2_1PEG2_IsoGlu_Palm, Ogl, Phe_4Me, Tba, Tle, Val, or absent;

X2 is 2Pal, 3Pal, aMe_Arg, Agb, Agp, bhF, Cit, Dab, Dab_Ac, Dab_2HyAc, Dab_Ms,

Dab_Ts, dDab2HyAc, dH, dT, Glu, Gln, His, hR, Hse, Lys, Lys_1PEG2_Ac,

Lys_1PEG2_1PEG2_C18_diacid, Lys_1PEG2_1PEG2_IsoGlu_C12, Lys_Ac,

Lys_Dimethyl, Lys_Me3, Lys_PEG2_Me3, Lys_1PEG2Ac, Lys_2HyAc, LysMPA, Lys_Ms,

Lys_Ns, Lys_Ts, NMe_Thr, Orn, Orn_Ac, Orn_Ms, OrnPVA, Orn_Ts, Phe_2Ad, Phe_3Ad,

Phe_4Ad, Phe_4_2ae, Phe_4_COOH, Phe_4_Cl, Phe_4guan, Phe_4OMe, Phe_4_Morph,

Phe_pentaF, Q_NHMe, Q_NMe2, Q_Pyro, Q_EtOMe, Q_MecPro, Tet1, Thr, or Thi;

X3 is Ala_cycBu, AlaCF3, AlaCHF2, Aoc, bhV, Cha, Chg, Cprg, Cpg, cyclopentyl_Ala,

cyclopropyl_Ala, Cys, Dgl, DiethylGly, dL, dV, H_Cha, Hcy, hL, Hph, Igl, Nle, NMe_Leu,

nVF3, O4S, O5S, Ogl, Phe_4tBu, Phe_4Cl, Phe_4_OMe, Phe_4_Me, Phe_3_4_C12,

Phe_4_CF3, Peptoid_CH2_V, Pra, Tba, Tle, or Val;

X4 is Asn, dT, Dab, Gln, Glu, Glu_OMe, hE, His, hR, Lys_Me3, Orn, Phe4_COOH,

Phe_4_Morph, Tet1, Thr, or Thr_Me;

X5 is Abu, aMe_Lys_Ac, Cha, Cys, Chg, Dab_Acetyl, dI, dLys_Ac, Glu, Hcy, hE, Hhc, HhPen, Ile, Lys, Lys_Ac, LysN3, LysPhAc, NMe_Lys_Ac, O2S, O3S, O3S_Reduced, O4S_Reduced, O5S, O5S_Reduced, Orn_Acetyl, or Pen;

X6 is 4R_BenzyloxyPro, 4RPhePro, 4S_Amp, 4S_Amp_Cyclhex, 4S_Amp_Hex, 4S_Amp_IVA, 4S_Amp_tBu, 4SCF3Pro, 4ScyclohexPro, 5RPhePro, Azetidinone, Dfp, dP, Hpr, Oic, or Pro;

X7 is Acvc, Aib, Ala, aMe_Phe, Arg, Aze, Cys, Dab, dC, Gln, Glu, His, Hpr, hR, Lys_1PEG2_1PEG2_Ahx_C18_Diacid, Lys_1PEG2_1PEG2_IsoGlu_C12, Lys_1PEG2_1PEG2_IsoGlu_C18_diacid, Lys_1PEG2_1PEG2_IsoGlu_Palm, Lys_Ac, O3S, O3S_Me, O4S, Pro, Ser, Tba, or Tic;

X8 is aMe_Asp, aMe_Glu, Asp, dD, Gla, Gln, Glu, Phe_3COOH, Phe_4COOH, Tet1, or Tet2;

X9 is Aoc, Cha, Cys, Dgl, hCha, Hcy, Leu, Nle, O3S, O3S_Reduced, O6S, Ogl, Phe_34diF, Phe_4CF3, or Tba;

X10 is 1Nal, 2Nal, Aib, aMe_Phe, aMe_Trp, Aoc, Cys, DIP, dW, hCha, Gln, Hph, Lys_1PEG2_1PEG2_IsoGlu_C12, Phe, Phe_34diCl, Phe_3Ad, Phe_4ad, Phe4_COOH, Phe_4OMe, Phg, Tba, Tle, Trp_4Cl, Trp_4Me, Trp_5Cl, Trp_5CONH2, Trp_5Et, Trp_5Me, Trp_6CF3, Trp_6Cl, Trp_6CONH2, Trp_6Me, Trp_7Cl, Trp_7Me, Trp_7Phe, or Trp;

X11 is Aib, aMe_Asp, aMe_Leu, aMe_Phe, Asn, Asp, Cys, Chg, dA, dS, Gln, Glu, Hcy, Leu, Lys_1PEG2_1PEG2_IsoGlu_C12, Lys_Ac, Lys_Me3, O3S, O3S_Me, O4S, Phe_4Ad, Phe_4tBu, Ser, Tba, or Tle;

X12 is 1Nal, aMe_Trp, Hph_34diCl, Orn_Bz, Trp, Trp_4Cl, Trp_5Br, Trp_5Cl, Trp_5Et, Trp_5Me, Trp_56diCl, Trp_56diMe, Trp_6Cl, Trp_6CF3, Trp_6Me, or Trp_7Cl;

X13 is Abu, aMe_Cys, aMe_Lys_Ac, Cys, Cha, Dab_Acetyl, Glu, Hcy, hE, Hhc, HhPen, Ile, Lys, Lys_Ac, LysN3, O2S, O3S, O3S_Me, O3S_Me_Reduced, O3S_Reduced, O4S_Reduced, Orn_Acetyl, or Pen;

X14 is Aib, Arg, Asn, Cys, dE, dF, dH, dK, dL, dN, dQ, dR, Gln, Glu, Lys,

Lys_1PEG2_1PEG2_NH2, Lys_1PEG2_1PEG2_1PEG2_NH2,

Lys_1PEG2_1PEG2_IsoGlu_C12, Lys_Ac, Lys_Hexy, Lys_PEG12_NH,

Lys_PEG4_1PEG2_NH2, Lys_PEG4_PEG4_NH2, Lys_PEG8_NH2, O3S, O3S_Me,

Orn_Acetyl, PEG12, Tba, or absent;

X15 is dE, dK, dR, Glu, Lys, Lys_PEG4_PEG4_NH2, Lys_Dimethyl, Pro, or absent; and

X16 is dE, dF, dH, dK, dL, dR, dQ, Lys, Lys_1PEG2_1PEG2_IsoGlu_C12,

Lys_1PEG2_1PEG2_IsoGlu_Palm, Lys_PEG4_PEG4_NH2, Lys_Ac, or absent;

wherein:

- (i) the peptide optionally comprises a cyclic structure wherein at least two amino acid residues in the peptide (monomer) are either: (a) directly covalently linked, or (b) indirectly covalently linked through a cyclization linker;
- (ii) the peptide is optionally a monomer in a homodimer or heterodimer complex, wherein each monomer is directly covalently linked to each other, or indirectly covalently linked to each other through a dimerization linker; and/or
- (iii) the peptide is optionally conjugated with a half-life extension moiety.

Formula (I).

2. The peptide of claim 1, wherein the peptide comprises a cyclic structure characterized by an intramolecular cross-link between residues X5 and X13 (X5-X13), X7 and X11 (X7-X11), X9 and X13 (X9-X13), or X10 and X14 (X10-X14).

3. The peptide of claim 2, wherein the intramolecular cross-link comprises a covalent bond directly or indirectly between the cross-linked residues, wherein the covalent bond comprises an amide bond, a disulfide bond, a thioether bond, a carbon-carbon single bond, or a carbon-carbon double bond.

4. The peptide of claim 3, wherein the intramolecular cross-link is a direct covalent bond between the cross-linked residues.

5. The peptide of claim 4, wherein the two cross-linked amino acid residues are at X5 and X13 or X9 and X13, and the two amino acids are directly covalently linked through a disulfide bond.

6. The peptide of claim 5, wherein the two amino acid residues cross-linked through a disulfide bond are both, or individually, Cys, Hcy, Hhc, Pen, or HhPen.

7. The peptide of claim 4, wherein the two directly cross-linked amino acid residues are at X5 and X13, X7 and X11, X9 and X13, or X10 and X14, and wherein these two amino acids are directly covalently linked through a thioether bond.

8. The peptide of claim 7, wherein the two amino acid residues directly cross-linked through a thioether bond are: Cys, Hcy, Hhc, Pen, or hhPen, their D-forms, and their α -methyl variants, for one residue of the pair; and aMe_Lys_Ac, Dab_Acetyl, Dap_Ac, dLys_Ac,

NMe_Lys_Ac, Lys_Ac, Lys_PEG12_Ac, LysPhAc, or Orn_Acetyl, for the other residue of the pair, in either order.

9. The peptide of claim 4, wherein the two directly cross-linked amino acid residues are at X5 and X13, and the two amino acids are directly covalently linked through a cyclic amide bond (lactam).

10. The peptide of claim 9, wherein the two amino acid residues cross-linked through a cyclic amide bond are Lys paired with Glu, hE, or Asp.

11. The peptide of claim 4, wherein the two directly cross-linked amino acid residues are at X5 and X11, or X9 and X13, and the two amino acids are directly covalently linked through a carbon-carbon double bond.

12. The peptide of claim 11, wherein the two amino acid residues cross-linked through a carbon-carbon double bond are both, or individually, O2S, O3S, O3S_Me, O4S, O5S, or O6S.

13. The peptide of claim 4, wherein the two directly cross-linked amino acid residues are at X5 and X13, or at X9 and X13, and the two amino acids are directly covalently linked through a carbon-carbon single bond.

14. The peptide of claim 13, wherein the two amino acid residues cross-linked through a carbon-carbon single bond are both, or individually, O3S_Reduced, O3S_Me_Reduced, or O4S_Reduced.

15. The peptide of claim 3, wherein the intramolecular cross-link is an indirect covalent bond between the cross-linked residues, wherein each of the cross-linked residues form a direct covalent bond with a cyclization linker.

16. The peptide of claim 15, wherein the two amino acid residues are indirectly covalently linked through a thioether bond with a cyclization linker.

17. The peptide of claim 16, wherein the cyclization linker comprises an alkane or an alkene with two free alkyl groups, a Butane_Linkers, a Carbonyl_Linkers, a

Dimethylcyclopropane_Linker, an Ebutene_Linker, a Hexane_Linker, a Methylene_Linker, an Oxetane_Linker, a Pentane_Linker, a Propane_Linker, an mXylene_Linker, a pXylene_Linker, or an oXylene_Linker..

18. The peptide of claim 17, wherein the cyclization linker comprises one of the Xylene_Linkers, and wherein the two amino acid residues cross-linked through a thioether bond with the cyclization linker are at X5 and X13, X7 and X11, X9 and X13, or X10 and X14, wherein the residues are both, or individually, Cys or dC.

19. The peptide of claim 17, wherein the cyclization linker comprises a Carbonyl_Linker, a Dimethylcyclopropane_Linker, a Ebutene_Linker, a Hexane_Linker, an Oxetane_Linker a Pentane_Linker, or a Propane_Linker, and wherein the two amino acid residues cross-linked through a thioether bond with the cyclization linker can be both, or individually, Cys, dC, Hcy, Hhc, Pen, or HhPen.

20. The peptide of any one of claims 1-19, wherein the peptide is a monomer of a homodimer or heterodimer.

21. The peptide of claim 20, wherein the homodimer comprises each monomer having a direct covalent attachment to a dimerization linker.

22. The peptide of claim 21, wherein each monomer comprises Lys or dK at X14, X15, or X16 that is directly covalently linked to a PEG linker, or wherein each monomer comprises Lys_PEG4_PEG4_NH2, Lys_PEG4_1PEG2_NH2, or Lys_PEG8_NH2, at X14, X15, or X16 that is directly covalently linked to a DIG_Linkers.

23. The peptide of claim 22, wherein the PEG linker comprises $-(OCH_2CH_2)_n-$, wherein n is between 5 and 25.

24. The peptide of claim 23, wherein each monomer is directly covalently linked to the PEG linker through an amide bond, wherein one monomer is linked to one terminal end of the PEG linker and the other monomer is linked to the other terminal end of the PEG linker.

25. The peptide of claim 24, wherein the PEG linker is PEG5DA, PEG9DA, PEG13DA, PEG21DA, or PEG25DA.

26. The peptide of any one of claims 1-25, wherein the monomer or homodimer exhibits an IC_{50} value of less than about 20 nM in a human IL-17 HEK Blue assay.
27. The peptide of any one of claims 1-25, wherein the monomer or homodimer exhibits a half-life greater than 0.5 hours in an SGF and/or SIF stability assay.
28. The peptide of claim 26, wherein the homodimer exhibits at least a 2-fold improvement in its IC_{50} value in a human IL-17 HEK Blue assay as compared to its monomeric form.
29. The peptide of claim 27, wherein the homodimer exhibits at least an improvement in its half-life in an SGF and/or an SIF stability assay as compared to its monomeric form.
30. A homodimer peptide compound that exhibits an IC_{50} equal to or less than 10 nM in a HEK Blue IL-17 assay, wherein the compound has two monomer cyclic peptides both comprising or consisting of the same amino acid sequence from Formula (II):
R1-X00-X0-X1-X2-X3-X4-X5-X6-X7-X8-X9-X10-X11-X12-X13-X14-X15-X16-R2,
R1 is acetyl (Ac), 3-hydroxypropionic acid, C6_diacid, cyclopropanecarboxylic acid, glutaric acid, isovaleric acid, methanesulfonyl acetic acid, 1PEG2_1PEG2_IsoGlu_Palm, 1PEG2_1PEG2_IsoGlu_C18_Diacid, 1PEG2_1PEG2_IsoGlu_C12, or absent;
R2 is NH₂, OH, or absent;
X00 is dH or absent;
X0 is dE, dH, Gln, Glu, Glu_OMe, His, Ile, Lys_Me3, Sar, Tle, or absent;
X1 is Cha, Chg, Cyclopropyl_Ala, DIP, Ile, Lys_1PEG2_1PEG2_IsoGlu_C12, Ogl, Tba, or Val;
X2 is 2Pal, 3Pal, Agb, Agp, Cit, Dab_Ac, Dab2HyAc, DabMs, DabTs, dDab2HyAc, Gln, Glu, His, hR, Hse, Lys, Lys_1PEG2_1PEG2_C18_diacid, Lys_1PEG2_1PEG2_IsoGlu_C12, Lys_Ac, Lys_Dimethyl, Lys_Me3, Lys_PEG2_Me3, Lys1PEG2Ac, Lys2HyAc, LysMPA, LysMs, LysNs, LysTs, OrnAc, Orn2HyAc, OrnMs, OrnPVA, OrnTs, Phe_2Ad, Phe_3Ad, Phe_4_Morph, Phe_4Ad, Phe_4COOH, Phe_4Guan, Phe_4OMe, Phe_pentaF, Q_NHMe, Q_NMe2, Q_Pyro, Q_EtOMe, Tet1, Thi, or Thr;
X3 is AlaCF3, AlaCHF2, Ala_cycBu, Aoc, Cha, Chg, Cpg, cyclopentyl_Ala, cyclopropyl_Ala, Cys, dV, H_ChA, Hcy, Hph, Igl, nVF3, Ogl, Phe_34diCl, Phe_4CF3, Phe_4Cl, Phe_4Me, Phe_4OMe, Phe_4tBu, Tba, Tle, or Val;
X4 is Asn, Gln, Glu, Glu_OMe, His, hE, hR, Lys_Me3, Phe4_COOH, Thr, or Thr_Me;

X5 is Abu, Cys, Cha, Chg, Dab_Acetyl, Glu, Hcy, hE, Hhc, Ile, Lys, Lys_Ac, LysN3, LysPhAc, O2S, O3S, O3S_Reduced, O4S, O4S_Reduced, Orn_Acetyl, or Pen;

X6 is 4RBenzyloxyPro, 4RPhePro, 4S_Amp_Cyclohex, 4S_Amp_Hex, 4S_Amp_IVA, 4S_Amp_tBu, 4SCF3Pro, 4SCyclohexPro, 5RPhePro, Azetidinone, Hpr, Oic, or Pro;

X7 is Ala, Acvc, Aib, aMe_Phe, Arg, Cys, Gln, Glu, His, hR,

Lys_1PEG2_1PEG2_Ahx_C18_diacid, Lys_1PEG2_1PEG2_IsoGlu_C12,

Lys_1PEG2_1PEG2_IsoGlu_C18_diacid, Lys_1PEG2_1PEG2_IsoGlu_Palm, Lys_Ac,

O3S_Me, Oic, Pro, Ser, or Tba

X8 is aMe_Glu, Asp, dD, Gla, Glu, Phe_3COOH, Phe_4COOH, Tet1, or Tet2;

X9 is Aoc, Dgl, Hcy, Leu, O3S, O3S_Reduced, or Ogl;

X10 is 1Nal, 2Nal, aMe_Phe, aMe_Trp, Cys, Hph, Lys_1PEG2_1PEG2_IsoGlu_C12, Phe_4COOH, Trp_4Cl, Trp_4Me, Trp_5Cl, Trp_5CONH2, Trp_5Et, Trp_5Me, Trp_6CF3, Trp_6Cl, Trp_6CONH2, Trp_6Me, Trp_7Cl, Trp_7Me, Trp_7Phe, or Trp;

X11 is Aib, Ala, aMe_Asp, aMe_Leu, aMe_Phe, Asn, Asp, Cys, Chg, Gln, Glu, Leu, Lys_1PEG2_1PEG2_IsoGlu_C12, Lys_Ac, Lys_Me3, O3S_Me, Phe_4Ad, Phe_4tBu, Ser, Tba, or Tle;

X12 is 1Nal, aMe_Trp, Orn_Bz, Trp, Trp_56diCl, Trp_56diMe, Trp_5Br, Trp_5Cl, Trp_5Et, Trp_5Me, Trp_6CF3, Trp_6Cl, or Trp6Me;

X13 is Abu, aMe_Cys, aMe_Lys_Ac, Cys, Cha, Dab_Acetyl, Glu, Hcy, hE, Hhc, Ile, Lys, Lys_Ac, LysN3, O2S, O3S, O3S_Me, O3S_Me_Reduced, O3S_Reduced, O4S, O4S_Reduced, Orn_Acetyl, or Pen;

X14 is Asn, dK, dR, Lys, Lys_Ac, Lys_PEG4_PEG4_NH2, Orn_Acetyl, or PEG12;

X15 is dR, dK, Lys, Lys_PEG4_PEG4_NH2, or Lys_Dimethyl, or absent;

X16 is dK, Lys, Lys_Ac, Lys_1PEG2_1PEG2_IsoGlu_C12,

Lys_1PEG2_1PEG2_IsoGlu_Palm, Lys_PEG4_PEG4_NH2, or absent;

wherein:

(i) the monomer comprises a cyclic structure wherein two amino acid residues in the peptide monomer are directly covalently linked or indirectly covalently linked through a through an amide bond, a disulfide bond, a thioether bond, a carbon-carbon single bond, or a carbon-carbon double bond, wherein the two amino acid residues are at X5 and X13, X7 and X11, X9 and X13, or X10 and X14; and

(ii.a) each monomer is directly covalently linked to a polyethylene glycol (PEG) linker at X14, X15, or X16 through an amide bond, wherein the PEG linker comprises $-(OCH_2CH_2)_n-$, wherein n is between 5 and 25, and wherein one monomer is linked to one terminal end of the PEG linker and the other monomer is linked to the other terminal end of the PEG linker,

wherein X14, X15, or X16 is Lys or dK, or (ii.b) each monomer is directly covalently linked to a DIG_linker (diglycolic acid linker) at X14, X15, or X16 through an amide bond, where X14, X15, or X16 is Lys_PEG4_PEG4_NH2, Lys_PEG4_1PEG2_NH2, or Lys_PEG8_NH2. (Formula (II).)

31. The homodimer compound of claim 30, wherein the cyclic structure of each monomer comprises two amino acid residues directly or indirectly covalently linked at X5 and X13.

32. The homodimer compound of claim 30, wherein a monomer peptide of the homodimer compound comprises or consists of an amino acid sequence of Formula (II.A):

R1-X00-X0-X1-X2-X3-X4-X5-X6-X7-X8-X9-X10-X11-X12-X13-X14-X15-X16-R2,

wherein:

R1 is acetyl, 3-hydroxypropionic acid, C6_diacid, cyclopropanecarboxylic acid, glutaric acid, isovaleric acid, methanesulfonyl acetic acid, or absent; R2 is NH2, OH, or absent;

X00 is dH or absent,

X0 is dE, dH, Gln, Glu, Glu_OMe, His, Ile, Lys_Me3, Sar, Tle, or absent;

X1 is Chg, Ile, Lys_1PEG2_1PEG2_IsoGlu_C12, Ogl, or Val;

X2 is 2Pal, 3Pal, Agb, Agp, Dab_Acetyl, Dab_2HyAc, Dab_Ms, Dab_Ts, dDab_2HyAc, Gln, Glu, His, hR, Hse, Lys, Lys_1PEG2_1PEG2_C18_Diacid, Lys_1PEG2_1PEG2_IsoGlu_C12, Lys_Ac, Lys_Dimethyl, Lys_Me3, Lys1PEG2Ac, Lys2HyAc, LysMs, LysTs, OrnAc, OrnMs, OrnTs, Phe_2Ad, Phe_3Ad, Phe_4Ad, Phe_4Guan, Q_NHMe, Q_NMe2, Q_Pyro, Tet1, or Thr;;

X3 is Ala_cycBu, Aoc, Cha, Chg, Cpg, cyclopropyl_Alal, dV, H_Cha, Hph, Igl, Ogl, Phe_34diCl, Phe_4CF3, Phe_4Cl, Phe_4Me, Phe_4OMe, Phe_4tBu, Tba, Tle, or Val;

X4 is Glu, hR, or Thr;

X5 is Hhc;

X6 is Oic or Pro;

X7 is Ala, Acvc, aMe_Phe, Gln, Glu, His, hR, Lys_Ac, Pro, Ser, or Tba;

X8 is aMe_Glu, Asp, dD, Gla, Glu, Tet1, or Tet2;

X9 is Leu or Ogl;

X10 is 1Nal, aMe_Trp, Trp_7Phe, or Trp;

X11 is aMe_Phe, Asp, or Glu;

X12 is aMe_Trp, Trp_5Br, Trp_5Cl, Trp_5Me, Trp_6Cl, Trp_6Me, or Trp;

X13 is Hhc;

X14 is Asn, dR, dK, Lys, Lys_PEG4_1PEG2_NH2, Lys_PEG8_NH2, or Lys_PEG4_PEG4_NH2;

X15 is dR, Lys, or absent;

X16 is absent;

wherein: (a) X5 and X13 are directly covalently linked through a disulfide bond; wherein each monomer is directly covalently linked to a PEG linker at X14 or X15 through an amide bond, and (b) X14 or X15 is dK or Lys, and wherein one monomer is linked to one terminal end of the PEG linker and the other monomer is linked to the other terminal end of the PEG linker, or X2 is dK or Lys and wherein one monomer is linked to one terminal end of the PEG linker and the other monomer is linked to the other terminal end of the PEG linker, or X14 is Lys_PEG4_PEG4_NH2, Lys_PEG8_NH2, or Lys_PEG4_1PEG2_NH2, and wherein one monomer is linked to one terminal end of a DIG_Linker and the other monomer is linked to the other terminal end of the DIG_Linker. (Formula (II.A)).

33. The homodimer compound of claim 30, wherein a monomer peptide of the homodimer compound comprises or consists of an amino acid sequence of Formula (II.B):

R1-X00-X0-X1-X2-X3-X4-X5-X6-X7-X8-X9-X10-X11-X12-X13-X14-X15-X16-R2,

wherein: R1 is acetyl, 3-hydroxypropionic acid, C6_diacid, cyclopropanecarboxylic acid, glutaric acid, isovaleric acid, methanesulfonyl acetic acid, or absent; R2 is amine, hydroxyl, or absent; X00 is dH or absent; X0 is dE, dH, Gln, Glu, Glu_OMe, His, Ile, Lys_Me3, Sar, Tle, or absent; X1 is Ile or Val; X2 is His or Lys_Me3; X3 is Tba or Val; X4 is Thr; X5 is Chg, Ile, or Tle; X6 is Azetidinone, Oic, or Pro; X7 is Ala; X8 is Asp or Gla; X9 is Hcy; X10 is Trp; X11 is Asp or Glu; X12 is Trp; X13 is Hhc; X14 is Lys, Lys_PEG4_1PEG2_NH2, Lys_PEG8_NH2, or Lys_PEG4_PEG4_NH2; X15 is dR; X16 is absent;

wherein: (i) the cyclic structure of each monomer comprises X9 and X13 that are directly covalently linked through a disulfide bond; and (ii) each monomer is directly covalently linked to a PEG linker at X14Lys through an amide bond, wherein one monomer is linked to one terminal end of the PEG linker and the other monomer is linked to the other terminal end of the PEG linker; or each monomer is directly covalently linked to a DIG linker at X14Lys_PEG4_PEG4_NH2, X14Lys_PEG4_1PEG2_NH2, or X14Lys_PEG8_NH2, through an amide bond, wherein one monomer is linked to one terminal end of the DIG linker and the other monomer is linked to the other terminal end. (Formula (II.B)).

34. The homodimer compound of claim 30, wherein the cyclic structure of each monomer comprises the two amino acid residues directly covalently linked through a thioether bond at:

(a) X5 and X13, wherein X5 is Cys, Dab_Acetyl, Hcy, Hhc, Lys_Ac, LysPhAc, Orn_Acetyl, or Pen, and X13 is aMe_Cys, aMe_Lys_Ac, Cys, Dab_Acetyl, Hcy, Hhc, Lys_Ac, Orn_Acetyl, or Pen; (b) X7 and X11, wherein X7 is Cys or Lys_Ac and X11 is Cys or Lys_Ac; or (c) X10 and X14, wherein X10 is Cys and X14 is Lys_Ac or Orn_Acetyl; and wherein aMe_Cys, Cys, Hcy, Hhc, or Pen is paired with aMe_Lys_Ac, Dab_Acetyl, Lys_Ac, LysPhAc, or Orn_Acetyl, and vice versa.

35. The homodimer compound of claim 30, a monomer peptide of the homodimer compound comprises or consists of an amino acid sequence of Formula (II.C):

R1-X00-X0-X1-X2-X3-X4-X5-X6-X7-X8-X9-X10-X11-X12-X13-X14-X15-X16-R2,
wherein:

R1 is acetyl, 3-hydroxypropionic acid, C6_diacid, cyclopropanecarboxylic acid, glutaric acid, isovaleric acid, methanesulfonyl acetic acid, or absent;

R2 is amine, hydroxyl, or absent;

X00 is dH or absent,

X0 is dE, dH, Gln, Glu, Glu_OMe, His, Lys_Me3, Sar, Tle, or absent;

X1 is Chg, Ile, Lys_1PEG2_1PEG2_C18_diacid, Lys_1PEG2_1PEG2_IsoGlu_Palm, Lys_1PEG2_1PEG2_IsoGlu_C12, Lys_1PEG2_1PEG2_IsoGlu_C18_Diacid, Ogl, or Val;

X2 is 2Pal, 3Pal, Agb, Agp, aMe_Arg, Cit, Dab_Ac, Dab2HyAc, DabMs, DabTs, dDab2HyAc, Gln, Glu, His, hR, Hse, Lys, Lys_1PEG2_1PEG2_C18_diacid, Lys_1PEG2_1PEG2_IsoGlu_C12, Lys_1PEG2_1PEG2_IsoGlu_C18_Diacid, Lys_Ac, Lys_Dimethyl, Lys_Me3, Lys1PEG2Ac, Phe_4_Morph, Phe_4COOH, Phe_4OMe, Phe_pentaF, Thr, or Thi; or Thr;

X3 is Cha, H_Cha, Ogl, Phe_4tBu, Tba, or Tle, or Val;

X4 is Asn, Gln, Glu, His, Phe_4COOH, Thr, or Thr_Me;

X5 is Cys, Dab_Acetyl, Hcy, Lys_Ac, LysPhAc, Orn_Acetyl, or Pen;

X6 is Oic, or Pro;

X7 is Aib, Ala, Arg, His, Lys_1PEG2_1PEG2_Ahx_C18_Diacid, Lys_1PEG2_1PEG2_IsoGlu_C18_Diacid, Lys_1PEG2_1PEG2_IsoGlu_Palm;

X8 is aMe_Glu, Asp, Gla, Glu, or Tet1;

X9 is Ogl;

X10 is 1Nal, Trp, Trp_4Cl, Trp_4Me, Trp_5Cl, Trp_5CONH2, Trp_5Et, Trp_5Me, Trp_6CF3, Trp_6Cl, Trp_6CONH2, Trp_6Me, Trp_7Cl, Trp_7Me, or Trp_7Phe;

X11 is aMe_Asp, Asp, Gln, or Glu;

X12 is Trp, Trp_56diCl, Trp_56diMe, Trp_5Et, Trp_5Me, Trp_6CF3, Trp_6Cl, or Trp_6Me;

X13 is aMe_Cys, aMe_Lys_Ac, Cys, Dab_Acetyl, Hcy, Hhc, Lys_Ac, Orn_Acetyl, or Pen;

X14 is Lys, Lys_PEG4_1PEG2_NH2, Lys_PEG8_NH2, or Lys_PEG4_PEG4_NH2;

X15 is dR;

X16 is absent;

wherein: (i) the cyclic structure of each monomer comprises X5 and X13 that are directly covalently linked through a thioether bond; wherein aMe_Cys, Cys, Hcy, Hhc, or Pen is paired with aMe_Lys_Ac, Dab_Acetyl, Lys_Ac, LysPhAc, or Orn_Acetyl, and vice versa;

and (ii) each monomer is directly covalently linked to a PEG linker at X14Lys through an amide bond, wherein one monomer is linked to one terminal end of the PEG linker and the other monomer is linked to the other terminal end of the PEG linker or each monomer is directly covalently linked to a PEG linker at X14Lys through an amide bond, wherein one monomer is linked to one terminal end of the PEG linker and the other monomer is linked to the other terminal end of the PEG linker; or each monomer is directly covalently linked to a DIG linker at X14Lys_PEG4_PEG4_NH2, X14Lys_PEG8_NH2, or X14Lys_PEG4_1PEG2_NH2, through an amide bond, wherein one monomer is linked to one terminal end of the DIG linker and the other monomer is linked to the other terminal end.

(Formula (II.C)).

36. The homodimer compound of claim 30, wherein a monomer peptide of the homodimer compound comprises or consists of an amino acid sequence of Formula (II.D):

R^1 -X00-X0-X1-X2-X3-X4-X5-X6-X7-X8-X9-X10-X11-X12-X13-X14-X15-X16- R^2 ,

wherein: R1 is acetyl, 3-hydroxypropionic acid, C6_diacid, cyclopropanecarboxylic acid, glutaric acid, isovaleric acid, methanesulfonyl acetic acid, or absent; R2 is amine, hydroxyl, or absent; X00 is dH or absent, X0 is dE, dH, Gln, Glu, Glu_OMe, His, Ile, Lys_Me3, Sar, Tle, or absent; X1 is Ile or Val; X2 is His, Lys_Me3, or Thr; X3 is Tba, Tle, or Val; X4 is Thr or Glu; X5 is Ile; X6 is Oic or Pro; X7 is Cys or Lys_Ac; X8 is Asp; X9 is Leu or Ogl; X10 is 1Nal or Trp; X11 is Cys or Lys_Ac; X12 is aMe_Trp or Trp; X13 is Ile; X14 is Lys, Lys_PEG4_1PEG2_NH2, Lys_PEG8_NH2, or Lys_PEG4_PEG4_NH2; X15 is dR; X16 is absent; wherein X7 and X11 are not both Cys or Lys_Ac; and

wherein: (i) the cyclic structure of each monomer comprises X7 and X11 that are directly covalently linked through a thioether bond; and (ii) each monomer is directly covalently linked to a PEG linker at X14Lys through an amide bond, wherein one monomer is linked to one terminal end of the PEG linker and the other monomer is linked to the other terminal end of the PEG linker or each monomer is directly covalently linked to a PEG linker at X14Lys

through an amide bond, wherein one monomer is linked to one terminal end of the PEG linker and the other monomer is linked to the other terminal end of the PEG linker; or each monomer is directly covalently linked to a DIG linker at X14Lys_PEG4_PEG4_NH2, X14Lys_PEG4_1PEG2_NH2, or X14Lys_PEG8_NH2, through an amide bond, wherein one monomer is linked to one terminal end of the DIG linker and the other monomer is linked to the other terminal end.

(Formula (II.D).)

37. The homodimer compound of claim 30, a monomer peptide of the homodimer compound comprises or consists of an amino acid sequence of Formula (II.E):

R1-X00-X0-X1-X2-X3-X4-X5-X6-X7-X8-X9-X10-X11-X12-X13-X14-X15-X16-R2,

wherein: R1 is acetyl3-hydroxypropionic acid, C6_diacid, cyclopropanecarboxylic acid, glutaric acid, isovaleric acid, methanesulfonyl acetic acid, or absent; R2 is amine, hydroxyl, or absent; X00 is dH or absent, X0 is dE, dH, Gln, Glu, Glu_OMe, His, Ile, Lys_Me3, Sar, Tle, or absent; X1 is Ile or Val; X2 is Thr or Lys_Me3; X3 is Tba or Tle; X4 is Thr or Glu; X5 is Chg or Ile; X6 is Oic or Pro; X7 is Ala; X8 is Asp; X9 is Ogl; X10 is Cys; X11 is Asp or Glu; X12 is Trp; X13 is Ile; X14 is Lys or Orn_Ac; X15 is dR; X16 is Lys, Lys_PEG4_1PEG2_NH2, Lys_PEG8_NH2, or Lys_PEG4_PEG4_NH2;

wherein: (i) the cyclic structure of each monomer comprises X10 and X14 that are directly covalently linked through a thioether bond; and (ii) each monomer is directly covalently linked to a PEG linker at X14Lys through an amide bond, wherein one monomer is linked to one terminal end of the PEG linker and the other monomer is linked to the other terminal end of the PEG linker; or each monomer is directly covalently linked to a DIG linker at X16Lys_PEG4_PEG4_NH2, X16Lys_PEG4_1PEG2_NH2, or X14Lys_PEG8_NH2, through an amide bond, wherein one monomer is linked to one terminal end of the DIG linker and the other monomer is linked to the other terminal end.

(Formula (II.E)).

38. The homodimer compound of claim 30, a monomer peptide of the homodimer compound comprises or consists of an amino acid sequence of Formula (II.F):

R1-X00-X0-X1-X2-X3-X4-X5-X6-X7-X8-X9-X10-X11-X12-X13-X14-X15-X16-R2,

R1 is acetyl, 3-hydroxypropionic acid, C6_diacid, cyclopropanecarboxylic acid, glutaric acid, isovaleric acid, methanesulfonyl acetic acid, or absent; R2 is amine, hydroxyl, or absent; X00 is dH or absent, X0 is dE, dH, Gln, Glu, Glu_OMe, His, Ile, Lys_Me3, Sar, Tle, or absent; X1 is Ile, Val, or Tba; X2 is Gln, His, Hse, Lys_Me3, or Thr; X3 is cyclopropyl_Alal, Tba, Tle, or

Val; X4 is Glu or Thr; X5 is O3S_Reduced or O4S_Reduced; X6 is Pro or Oic; X7 is Ala; X8 is Asp or Glu; X9 is Ogl; X10 is 1Nal or Trp; X11 is Asp or Glu; X12 is Trp or Trp5Me; X13 is O3S_Reduced, O3S_Methyl_Reduced, O4S_Reduced; X14 is Lys, Lys_PEG4_1PEG2_NH2, Lys_PEG8_NH2, or Lys_PEG4_PEG4_NH2; X15 is dR; and X16 is absent;

wherein: (i) the cyclic structure of each monomer comprises X5 and X13 that are directly covalently linked through a carbon-carbon single bond (-C-C-); and (ii) each monomer is directly covalently linked to a PEG linker at X14Lys through an amide bond, wherein one monomer is linked to one terminal end of the PEG linker and the other monomer is linked to the other terminal end of the PEG linker; or each monomer is directly covalently linked to a DIG linker at X14Lys_PEG4_PEG4_NH2, X14Lys_PEG4_1PEG2_NH2, or X14Lys_PEG8_NH2, through an amide bond, wherein one monomer is linked to one terminal end of the DIG linker and the other monomer is linked to the other terminal end. (Formula (II.F)).

39. The homodimer compound of claim 30, a monomer peptide of the homodimer compound comprises or consists of an amino acid sequence of Formula (II.G):

R^1 -X00-X0-X1-X2-X3-X4-X5-X6-X7-X8-X9-X10-X11-X12-X13-X14-X15-X16- R^2 ,

wherein R1 is acetyl, 3-hydroxypropionic acid, C6_diacid, cyclopropanecarboxylic acid, glutaric acid, isovaleric acid, methanesulfonyl acetic acid, or absent; R2 is amine, hydroxyl, or absent; X00 is dH or absent, X0 is dE, dH, Gln, Glu, Glu_OMe, His, Ile, Lys_Me3, Sar, Tle, or absent; X1 is Chg, Val, or Ile; X2 is His, Lys_Me3, or Thr; X3 is Ogl, Val, Tba, or Tle; X4 is Thr or Glu; X5 is Ile or Chg; X6 is Oic or Pro; X7 is O3S_Me; X8 is Asp or Glu; X9 is Ogl; X10 is 1Nal or Trp; X11 is O3S_Me; X12 is Trp; X13 is Ile; X14 is Asn; X15 is dR; and X16 is Lys, Lys_PEG4_1PEG2_NH2, Lys_PEG8_NH2, or Lys_PEG4_PEG4_NH2;

wherein: (i) the cyclic structure of each monomer comprises X7 and X11 that are directly covalently linked through a carbon-carbon double bond (-C=C-); and (ii) each monomer is directly covalently linked to a PEG linker at X16Lys through an amide bond, wherein one monomer is linked to one terminal end of the PEG linker and the other monomer is linked to the other terminal end of the PEG linker; or each monomer is directly covalently linked to a DIG linker at X16Lys_PEG4_PEG4_NH2, X16Lys_PEG4_1PEG2_NH2, or X16Lys_PEG8_NH2, through an amide bond, wherein one monomer is linked to one terminal end of the DIG linker and the other monomer is linked to the other terminal end.

(Formula (II.G)).

40. The homodimer compound of claim 30, a monomer peptide of a homodimer compound comprises or consists of an amino acid sequence of Formula (II.H):

R1-X00-X0-X1-X2-X3-X4-X5-X6-X7-X8-X9-X10-X11-X12-X13-X14-X15-X16-R2,

wherein R1 is acetyl, 3-hydroxypropionic acid, C6_diacid, cyclopropanecarboxylic acid, glutaric acid, isovaleric acid, methanesulfonyl acetic acid, or absent; R2 is amine, hydroxyl, or absent; X00 is dH or absent, X0 is dE, dH, Gln, Glu, Glu_OMe, His, Ile, Lys_Me3, Sar, Tle, or absent; X1 is Chg, Val, or Ile; X2 is His, Lys_Me3, or Thr; X3 is Ogl, Tba, Tle, or Val; X4 is Thr or Glu; X5 is Chg or Ile; X6 is Oic or Pro; X7 is Ala or Cys; X8 is Asp or Gla; X9 is O3S; X10 is Trp or 1Nal; X11 is Asp, Glu, or Lys_Ac; X12 is Trp; X13 is O3S; X14 is Lys, Lys_PEG4_1PEG2_NH2, Lys_PEG4_PEG4_NH2, or Lys_PEG8_NH2; X15 is dR; and X16 is absent;

wherein: (i) the cyclic structure of each monomer comprises X9 and X13 that are directly covalently linked through a carbon-carbon double bond (-C=C-); and (ii) each monomer is directly covalently linked to a PEG linker at X14Lys through an amide bond, wherein one monomer is linked to one terminal end of the PEG linker and the other monomer is linked to the other terminal end of the PEG linker; or each monomer is directly covalently linked to a DIG linker at X14Lys_PEG4_PEG4_NH2, X14Lys_PEG4_1PEG2_NH2, or X14Lys_PEG8_NH2, through an amide bond, wherein one monomer is linked to one terminal end of the DIG linker and the other monomer is linked to the other terminal end.

(Formula (II.H)).

41. The homodimer compound of claim 30, wherein each monomer of the dimer has a cyclic structure comprising two amino acid residues with a side-chain comprising a free thiol that are indirectly covalently linked through a thioether bond with a Butane_Linkers, a Carbonyl_Linkers, a Dimethylcyclopropane_Linkers, an Ebutene_Linkers, a Hexane_Linkers, a Methylene_Linkers, an Oxetane_Linkers, a Pentane_Linkers, a Propane_Linkers, an mXylene_Linkers, a pXylene_Linkers, or an oXylene_Linkers. at: (a) X5 and X13, wherein the residues are individually or both, Cys, Hcy, Hhc, or Pen, (b) X7 and X11, wherein both X7 and X11 are Cys, and with a Xylene linker, or (c) X7 and X11, wherein X7 and X11 are individually or both Cys or Hcy and with the Propane_Linkers.

42. The homodimer compound of claim 30, wherein a monomer peptide of the homodimer compound comprises or consists of an amino acid sequence of Formula (II.I):

R1-X00-X0-X1-X2-X3-X4-X5-X6-X7-X8-X9-X10-X11-X12-X13-X14-X15-X16-R2,

wherein: R1 is acetyl, 3-hydroxypropionic acid, C6_diacid, cyclopropanecarboxylic acid, glutaric acid, isovaleric acid, methanesulfonyl acetic acid, or absent; R2 is amine, hydroxyl, or absent; X00 is dH or absent, X0 is dE, dH, Gln, Glu, Glu_OMe, His, Ile, Lys_Me3, Sar, Tle, or absent; X1 is Cha, Cyclopropyl_Al原因, DIP, Ile, Tba, or Val; X2 is Gln, His, Hse, Lys_Me3, Lys_Dimethyl, Lys_PEG2_Me3, Lys2HyAc, LysMPA, LysNs, Orn_Ac, Orn2HyAc, OrnPVA, Phe_2Ad, Phe_3Ad, Q_NHMe, Q_NMe2, Q_Pyro, Q_EtOMe, or Tet1; X3 is AlaCF3, AlaCHF2, cyclopentyl_Al原因, cyclopropyl_Al原因, nVF3, Tba, Tle, or Val; X4 is Asn, Glu, Glu_OMe, hE, Lys_Me3, Phe_4COOH, or Thr; X5 is Cys, Hcy, or Pen; X6 is 4RBenzoyloxyPro, 4RPhePro, 4S_Amp_Cyclohex, 4S_Amp_Hex, 4S_Amp_IVA, 4S_Amp_tBu, 4SCF3Pro, 4SCyclohexPro, 5RPhePro, Oic, or Pro; X7 is Ala, Gln, His, Lys_1PEG2_1PEG2_IsoGlu_C18_diacid, Lys_Ac, Oic, or Pro; X8 is Asp, Gla, Glu, Phe_3COOH, or Phe_4COOH; X9 is Aoc, Dgl, or Ogl; X10 is 1Nal, 2Nal, aMe_Phe, aMe_Trp, Hph, Phe_4COOH, or Trp; X11 is Aib, Ala, Asn, Asp, aMe_Leu, aMe_Phe, Chg, Glu, Leu, Lys_Me3, Phe_4Ad, Phe_4tBu, Ser, Tba, or Tle; X12 is 1Nal, aMe_Trp, Orn_Bz, Trp_6Cl, or Trp; X13 is Cys, Hcy, or Pen; X14 is dK, Lys, , Lys_PEG4_1PEG2_NH2, Lys_PEG8_NH2, or Lys_PEG4_PEG4_NH2; X15 is dR; and X16 is absent;

wherein: (i) the cyclic structure of each monomer comprises X5 and X13 that are indirectly covalently linked through a thioether bond with a Butane_Linkers, a Carbonyl_Linkers, Dimethylcyclopropane_Linkers, EButene linker, Hexane_Linkers, Oxetane_Linkers, Pentane_Linkers, Propane linker, oXylene linker, mXylene linker, or pXylene_linkers; and (ii) each monomer is directly covalently linked to a PEG linker at X14 through an amide bond, wherein one monomer is linked to one terminal end of the PEG linker and the other monomer is linked to the other terminal end of the PEG linker; or each monomer is directly covalently linked to a DIG linker at X14Lys_PEG4_PEG4_NH2, X14Lys_PEG4_1PEG2_NH2, or X14Lys_PEG8_NH2, through an amide bond, wherein one monomer is linked to one terminal end of the DIG linker and the other monomer is linked to the other terminal end. (Formula (II.I)).

43. The homodimer compound of claim 30, wherein a monomer peptide of the homodimer compound comprises or consists of an amino acid sequence of Formula (II.J):

R1-X00-X0-X1-X2-X3-X4-X5-X6-X7-X8-X9-X10-X11-X12-X13-X14-X15-X16-R2,

wherein R1 is acetyl, 3-hydroxypropionic acid, C6_diacid, cyclopropanecarboxylic acid, glutaric acid, isovaleric acid, methanesulfonyl acetic acid, or absent; R2 is amine, hydroxyl, or absent; X00 is dH or absent, X0 is dE, dH, Gln, Glu, Glu_OMe, His, Lys_Me3, Sar, Tle, or absent; X1 is Ile or Val; X2 is His, Lys_Me3, or Thr; X3 is Tle or Val; X4 is Glu or Thr; X5 is

Ile; X6 is Pro or Oic; X7 is Cys; X8 is Asp or Gla; X9 is Leu or Ogl; X10 is 1Nal or Trp; X11 is Cys or Hcy; X12 is Trp; X13 is Ile; X14 is Asn, Lys, Lys_PEG4_1PEG2_NH2, Lys_PEG8_NH2, or Lys_PEG4_PEG4_NH2; X15 is dR; and X16 is Lys, Lys_PEG4_PEG4_NH2, Lys_PEG4_1PEG2_NH2, Lys_PEG8_NH2, or absent;

wherein: (i) the cyclic structure of each monomer comprises X7 and X11 that are indirectly covalently linked through a bis-thioether bond with the a Xylene linker (m-, o-, or p-) or a Propane_Linkers; and (ii) each monomer is directly covalently linked to a PEG linker at X14 or X16 through an amide bond when X14 or X16 is Lys, wherein one monomer is linked to one terminal end of the PEG linker and the other monomer is linked to the other terminal end of the PEG linker; or each monomer is directly covalently linked to a DIG linker at X14 or X16 through an amide bond, wherein X14 or X16 is Lys_PEG4_PEG4_NH2, Lys_PEG4_1PEG2_NH2, or Lys_PEG8_NH2, wherein one monomer is linked to one terminal end of the DIG linker and the other monomer is linked to the other terminal end. (Formula (II.J)).

44. The homodimer compound of any one of claims 30-43, wherein the PEG linker is PEG5DA, PEG9DA, PEG13DA, PEG21DA, or PEG25DA.

45. The homodimer compound of any one of claims 30-43, wherein the homodimer exhibits an IC₅₀ value of less than about 5 nM in a human IL-17 HEK Blue assay.

46. The homodimer compound of any one of claims 30-45, wherein the homodimer exhibits a half-life greater than 0.5 hours in an SGF and/or SIF stability assay.

47. The homodimer compound of any one of claims 30-46, wherein R¹ is acetyl, glutaric acid, or isovaleric acid, and R² is an amine.

48. A peptide compound that has an IC₅₀ for each of hIL-17AA, hIL-17AF, and hIL-17FF, or at least for each of hIL-17AA and hIL-17FF, that is less than about 10 nM in a human IL-17 HEK Blue assay, wherein the peptide compound comprises a monomer peptide comprising or consisting of the sequence of Formula (III):

R¹-X00-X0-X1-X2-X3-X4-X5-X6-X7-X8-X9-X10-X11-X12-X13-X14-X15-X16-R²,

wherein:

R¹ is 1Pip_AceticAcid, acetyl, 3-hydroxypropionic acid, C6_diacid, cyclopropanecarboxylic acid, glutaric acid, isovaleric acid, methanesulfonyl acetic acid, Mor_propanoic_acid, or absent; R² is NH₂ or OH or absent;

X00 is Cha, dH, or Tle

X0 is 2Pal, Asn, d2Pal, dE, dH, dQ, Gln, Glu, Glu_OMe, His, Ile, Lys, Lys_Me3, NMe_His, Orn, Sar, Tle, or absent;

X1 is 1Nal, Cha, Cyclopropyl_Alal, Dgl, DIP, hCha, hF, hhF, Ile, Ogl, Phe_4Me, Tba, Tle, or Val;

X2 is 2Pal, 3Pal, Dab_Ac, Dab2HyAc, DabMs, DabTs, Gln, Glu, His, Hse, Lys_Ac, Lys_Dimethyl, Lys_Me3, Lys_PEG2_Me3, Lys1PEG2Ac, Lys2HyAc, LysMPA, LysMs, Orn_Ac, Orn2HyAc, OrnAc, OrnMs, OrnPVA, Phe_2Ad, Phe_3Ad, Phe_4Ad, Q_NHMe, Q_NMe2, Q_Pyro, Q_EtoMe, Tet1, or Thr;

X3 is Ala_cycBu, AlaCF3, AlaCHF2, Aoc, Cha, Chg, Cyclopentyl_Alal, Cyclopropyl_Alal, hCha, nVF3, Ogl, Phe_4tBu, Tba, Tle, or Val;

X4 is Asn, Gln, Glu, Glu_OMe, hE, His, LysMe3, Phe_4COOH, or Thr;

X5 is Cys, Hcy, Hhc, Lys_Ac, LysN3, O2S, O3S, O3S_Reduced, O3S_Me, O3S_Me_Reduced, O4S, O4S_Reduced, O5S, O5S_Reduced, or Pen;

X6 is 4SCF3Pro, 4SCyclohexPro, Oic, or Pro;

X7 is Acvc, Ala, Dab, Gln, Glu, His, Hpr, hR, Lys_Ac, Oic, Pro, Ser, or Tba;

X8 is aMe_Glu, Asp, Gla, Glu, or Tet1;

X9 is Aoc, Dgl, or Ogl;

X10 is 1Nal, 2Nal, aMe_Phe, aMe_Trp, Aoc, Cys, hCha, Hph, Phe_4COOH, Trp, Trp_4Cl, Trp_4Me, Trp_5Cl, Trp_5CONH2, Trp_5Et, Trp_5Me, Trp_6Cl, Trp_6CONH2, Trp_6Me, Trp_7Cl, Trp_7Me, or Trp_7Phe;

X11 is Aib, Ala, aMe_Asp, aMe_Leu, aMe_Phe, Asn, Asp, Chg, Glu, Leu, Lys_Me3, O3S, Phe_4Ad, Phe_4tBu, Ser, Tba, or Tle;

X12 is aMe_Trp, Trp, Trp_56diCl, Trp_5Cl, Trp_5Me, or Trp_6Cl;

X13 is Abu, Cys, Dab_Acetyl, Hcy, Hhc, O2S, O3S, O3S_Reduced, O3S_Me, O3S_Me_Reduced, O4S, O4S_Reduced, O5S, O5S_Reduced, or Pen;

X14 is Aib, Asn, Cys, dK, dL, dN, dQ, dR, Gln, Lys, Lys_1PEG2_1PEG2_IsoGlu_C12, Lys_Ac, Lys_PEG4_PEG4_NH2, Lys_PEG4_1PEG2_NH2, Lys_PEG8_NH2, Tba, or absent;

X15 is dR, dE, or absent;

X16 is dE, dQ, or absent;

wherein the peptide comprises a cyclic structure wherein X5 and X13 are either: (a) directly covalently linked or (b) indirectly covalently linked through a cyclization linker; and

wherein: (i) the peptide is optionally a monomer in a homodimer or heterodimer complex, wherein each monomer is directly covalently linked to each other or indirectly covalently linked to each other through a dimerization linker; and/or (ii) the peptide is optionally conjugated with a half-life extension moiety.

(Formula (III)).

49. The peptide compound of claim 48, wherein both X5 and X13 are Hhc, and wherein these two residues are directly covalently linked through a disulfide bond

50. The peptide compound of claim 48, wherein X5 is Lys_Ac and X13 is Cys, or X5 is Hhc and X13 is Dab_Acetyl, and wherein these two residues are directly covalently linked through a thioether bond.

51. The peptide compound of claim 48, wherein X5 is Lys and X13 is hE (or vice versa), and these two residues are directly covalently linked through an amide bond (lactam).

52. The peptide compound of claim 48, wherein X5 is LysN3 and X13 is Abu (or vice versa), and these two residue are directly covalently linked as shown in paragraph [00324].

53. The peptide compound of claim 48, wherein X5 and X13 are individually or both O3S_Reduced, O3S_Me_Reduced, O4S_Reduced, or O5S_Reduced, and these two residues are directly covalently linked through a carbon-carbon single bond.

54. The peptide compound of claim 48, wherein X5 and X13 are individually or both O2S, O3S, O3S_Methyl, or O4S, and these two residues are directly covalently linked through a carbon-carbon double bond.

55. The peptide compound of claim 48, wherein X5 and X13 are both, or individually, Hcy, Cys, Hhc, or Pen, wherein X5 and X13 are indirectly covalently linked through a thioether bond, wherein these two residues are indirectly covalently linked through a thioether bond with a terminal end of a Butane_Linkers, a Carbonyl_Linkers, a Dimethylcyclopropane_Linkers, an EButene_Linkers, a Methylene_Linkers, an Oxetane_Linkers, a Pentane_Linkers, a Propane_Linkers, or a Xylene_Linkers.

56. The peptide compound of any one of claims 48-55, wherein the peptide is a monomer in a homodimer compound, and wherein each monomer is directly covalently linked to either a (a) PEG linker at X14Lys or X14 dK through an amide bond, wherein one monomer is linked to one terminal end of the PEG linker and the other monomer is linked to the other terminal end of the PEG linker, or (b) a DIG linker at X14Lys_PEG4_PEG4_NH₂, X14Lys_PEG4_1PEG2_NH₂, or X14Lys_PEG8_NH₂ through an amide bond, wherein one monomer is linked to one terminal end of the DIG linker and the other monomer is linked to the other terminal end of the PEG linker..

57. The homodimer compound of claim 56, wherein the PEG linker is PEG5DA, PEG9DA, PEG13DA, PEG21DA, or PEG25DA.

58. The homodimer compound of any one of claims 48-57, wherein the homodimer exhibits an IC₅₀ value of less than about 5 nM in a human IL-17 HEK Blue assay.

59. The homodimer compound of any one of claims 48-58, wherein the homodimer exhibits a half-life greater than 0.5 hours in an SGF and/or SIF stability assay.

60. A peptide of any one of claims 48-59, wherein R¹ is acetyl, glutaric acid, or isovaleric acid, and R² is an amine.

61. A peptide compound that has an IC₅₀ for hIL-17AA that is less than about 1nM and for hIL-17FF that is less than about 10 nM in a human IL-17 HEK Blue assay, wherein the peptide compound comprises a monomer peptide that comprises or consists of the sequence of Formula (IV):

R¹-X00-X0-X1-X2-X3-X4-X5-X6-X7-X8-X9-X10-X11-X12-X13-X14-X15-X16-R²,

wherein:

R¹ is acetyl, 3-hydroxypropionic acid, C6_diacid, cyclopropanecarboxylic acid, glutaric acid, isovaleric acid, methanesulfonyl acetic acid, or absent; R² is NH₂, OH, or absent;

X00 is dH, Tle, or absent;

X0 is 2Pal, d2Pal, Asn, dE, dH, dQ, Gln, Glu, Glu_OMe, His, Ile, Lys, Lys_Me3, NMe_His, Orn, Sar, Thr, Tle, or absent;

X1 is 1Nal, Cha, Cyclopropyl_Ala, Dgl, DIP, hCha, hF, hhF, Ile, Ogl, Phe_4Me, Tba, Tle, or Val;

X2 is 2Pal, 3Pal, Dab_Ac, Dab2HyAc, DabMs, DabTs, E, Gln, His, Hse, Lys_Ac, Lys_Dimethyl, Lys_Me3, Lys_PEG2_Me3, Lys1PEG2Ac, Lys2HyAc, LysMPA, LysMs, OrnAc, Orn2HyAc, OrnMs, OrnPVA, Phe_2Ad, Phe_3Ad, Phe_4Ad, Q_NHMe, Q_NMe2, Q_Pyro, Q_EtOMe, Tet1, or Thr;

X3 is Ala_cycBu, AlaCF3, AlaCHF2, Aoc, Cha, Chg, Cyclopentyl_Ala, Cyclopropyl_Ala, hCha, nVF3, Ogl, Phe_4tBu, Tba, Tle, or Val;

X4 is Asn, Gln, Glu, Glu_OMe, hE, His, LysMe3, Phe_4COOH, or Thr;

X5 is Cys, Hcy, Hhc, Lys_Ac, LysN3, O2S, O3S, O3S_Reduced, O3S_Me, O3S_Me_Reduced, O4S, O4S_Reduced, O5S, O5S_Reduced, or Pen;

X6 is 4SCF3Pro, 4SCyclohexPro, Oic, or Pro;

X7 is Acvc, Ala, Dab, Gln, Glu, His, hR, Lys_Ac, Oic, Pro, Ser, or Tba;

X8 is aMe_Glu, Asp, Gla, Glu, or Tet1;

X9 is Aoc, Dgl, or Ogl;

X10 is 1Nal, 2Nal, aMe_Phe, aMe_Trp, Aoc, Cys, hCha, Hph, Phe_4COOH, Trp, Trp_4Cl, Trp_4COOH, Trp_4Me, Trp_5CONH2, Trp_6CONH2, Trp_6Me, Trp_7Me, or Trp_7Phe;

X11 is Aib, Ala, aMe_Asp, aMe_Leu, aMe_Phe, Asn, Asp, Chg, Glu, Leu, Lys_Me3, Phe_4Ad, Ser, Tba, or Tle;

X12 is aMe_Trp, Trp, Trp_56diCl, Trp_5Cl, Trp_5Me, or Trp_6Cl;

X13 is Abu, Cys, Dab_Acetyl, Hcy, Hhc, O2S, O3S, O3S_Reduced, O3S_Me, O3S_Me_Reduced, O4S, O4S_Reduced, O5S, O5S, or Pen;

X14 is Aib, Asn, Cys, dK, dN, dQ, dR, Gln, Lys, Lys_Ac, Lys_PEG4_PEG4_NH2, Lys_PEG4_1PEG2_NH2, Lys_PEG8_NH2, Tba, or absent;

X15 is dE, dR, or absent; and

X16 is dE, dQ, or absent;

wherein the peptide comprises a cyclic structure wherein X5 and X13 are either: (a) directly covalently linked or (b) indirectly covalently linked through a cyclization linker; and

wherein: (i) the peptide is optionally a monomer in a homodimer or heterodimer complex, wherein each monomer is directly covalently linked to each other or indirectly covalently linked to each other through a dimerization linker; and/or (ii) the peptide is optionally conjugated with a half-life extension moiety.

(Formula (IV)).

62. The peptide compound of claim 61, wherein both X5 and X13 are Hhc, and these two residues are directly covalently linked through a disulfide bond.

63. The peptide compound of claim 61, wherein X5 is Lys_Ac and X13 is Cys, and these two residues are directly covalently linked through a thioether bond.

64. The peptide compound of claim 61, wherein X5 is Hhc and X13 is Dab_Acetyl, and these two residues are directly covalently linked through a thioether bond, or wherein X5 is O5S_Reduced and X13 is Dab_Acetyl, and these two residues are directly covalently linked through a thioether bond.

65. The peptide compound of claim 61, wherein X5 is Lys and X13 is hE, or vice versa, and these two residues are directly covalently linked through a lactam.

66. The peptide compound of claim 61, wherein X5 is LysN3 or Lys and X13 is Abu or hE, and these two residues are directly covalently linked as shown in paragraph [00324].

67. The peptide compound of claim 61, wherein X5 and X13 are individually, or both, O3S_Reduced, O3S_Methyl_Reduced, or O4S_Reduced, and these two residues are directly covalently linked through a carbon-carbon single bond.

68. The peptide compound of claim 61, wherein both X5 and X13 are individually, or both, O2S, O3S, O3S_Me, or O4S, and these two residues are directly covalently linked through a carbon-carbon double bond.

69. The peptide compound of claim 61, wherein X15 and X13 are individually, or both, Cys, Hcy, Hhc, or Pen, wherein X5 and X13 are indirectly covalently linked through a thioether bond, wherein these two residues are indirectly covalently linked through a thioether bond with a terminal end of a Carbonyl_Linkers, a Dimethylcyclopropane_Linkers, an EButene_Linkers, a Methylene_Linkers, an Oxetane_Linkers, a Pentane_Linkers, a Propane_Linkers, or a pXylene_Linkers.

70. The peptide compound of claim 69, wherein X5 and X13 are Hcy, wherein X5 and X13 are indirectly covalently linked through a thioether bond, wherein these two residues are indirectly covalently linked through a thioether bond with a terminal end of a Pentane_Linkers, a Propane_Linkers, or Dimethylcyclopropane_Linkers.

71. The peptide compound of claim 61, wherein the peptide is a monomer in a homodimer compound, and wherein each monomer is directly covalently linked to either: (a) a PEG linker at X14Lys through an amide bond, wherein one monomer is linked to one terminal end of the PEG linker and the other monomer is linked to the other terminal end of the PEG linker, or (b) a DIG_linker at X14Lys_PEG4_PEG4_NH2, X14Lys_PEG4_1PEG2_NH2, or X14Lys_PEG8_NH2, through an amide bond, wherein one monomer is linked to one terminal end of the DIG linker and the other monomer is linked to the other terminal end.

72. The peptide compound of any one of claims 61-72, wherein the peptide is a monomer in a homodimer compound, and wherein each monomer is directly covalently linked to a PEG linker at X14 through an amide bond, wherein one monomer is linked to one terminal end of the PEG linker and the other monomer is linked to the other terminal end of the PEG linker.

73. The peptide compound of claim 72, wherein the PEG linker is PEG5DA, PEG9DA, PEG13DA, PEG21DA, or PEG25DA and X14 is Lys.

74. The peptide compound of any one of claims 61-73, wherein the peptide exhibits a half-life greater than about 0.5 hours, 1.0 hours, 1.5 hours, or 2.0 hours, in an SGF and/or SIF stability assay.

75. The peptide compound of any one of claims 61-74, wherein R¹ is acetyl or isovaleric acid, and R² is an amine.

76. A peptide compound that has an IC₅₀ for hIL-17AA that is less than about 1nM, and an IC₅₀ for hIL-17FF that is less than about 5 nM, in a human IL-17 HEK Blue assay, wherein the peptide compound comprises a monomer peptide that comprises or consists of the sequence of Formula (V):

R¹-X00-X0-X1-X2-X3-X4-X5-X6-X7-X8-X9-X10-X11-X12-X13-X14-X15-X16-R²,

wherein:

R¹ is acetyl, 3-hydroxypropionic acid, C6_diacid, cyclopropanecarboxylic acid, glutaric acid, isovaleric acid, methanesulfonyl acetic acid, or absent; R² is NH₂, OH, or absent;

X00 is dH, Tle or absent;

X0 is dH, dQ, Gln, Glu, Glu_OMe, His, Ile, Lys, Lys_Me3, Orn, Sar, Thr, Tle, or absent;

X1 is Cha, Cyclopropyl_Ala, Dgl, DIP, hhF, Ile, Tba, Tle, or Val;

X2 is 2Pal, 3Pal, Dab_Ac, Dab2HyAc, DabMs, DabTs, Gln, Glu, His, Hse, Lys_Ac, Lys_Dimethyl, Lys_Me3, Lys_PEG2_Me3, Lys1PEG2Ac, Lys2HyAc, LysMPA, LysMs, OrnAc, Orn2HyAc, OrnMs, OrnPVA, Phe_3Ad, Phe_4Ad, Q_NHMe, Q_NMe2, Q_Pyro, Q_EtOMe, Tet1, or Thr;

X3 is Ala_cycBu, AlaCF3, AlaCHF2, Cha, Chg, Cyclopentyl_Ala, Cyclopropyl_Ala, hCha, nVF3, Ogl, Tba, Tle, or Val;

X4 is Asn, Gln, Glu, Glu_OMe, hE, His, Phe_4COOH, or Thr;

X5 is Cys, Hcy, Hhc, Lys_Ac, LysN3, O2S, O3S, O3S_Reduced, O3S_Me, O3S_Me_Reduced, O4S, O4S_Reduced, O5S_Reduced, or Pen;

X6 is 4SCF3Pro or Oic;

X7 is Acvc, Ala, Gln, Glu, Lys_Ac, Oic, Pro, Ser, or Tba;

X8 is aMe_Glu, Asp, Gla, Glu, or Tet1;

X9 is Aoc, Dgl, or Ogl;

X10 is 1Nal, 2Nal, Aoc, Hph, Phe_4COOH, Trp, Trp_4Cl, Trp_4COOH, Trp_6CONH2, Trp_6Me, Trp_7Me, or Trp_7Phe;

X11 is Aib, Ala, aMe_Leu, aMe_Phe, Asn, Asp, Chg, Glu, Leu, Lys_Me3, Phe_4Ad, Ser, Tba, or Tle;

X12 is aMe_Trp, Trp, Trp_56diCl, or Trp_6Cl;

X13 is Abu, Cys, Dab_Acetyl, Hcy, Hhc, O2S, O3S, O3S_Reduced, O3S_Me, O3S_Me_Reduced, O4S, O4S_Reduced, or Pen;

X14 Asn, dK, Gln, Lys, Lys_PEG4_PEG4_NH2, Lys_PEG4_1PEG2_NH2, Lys_PEG8_NH2, or absent;

X15 is dE, dR, or absent; and

X16 is dE or absent;

wherein the peptide comprises a cyclic structure wherein X5 and X13 are either: (a) directly covalently linked or (b) indirectly covalently linked through a cyclization linker; and

wherein: (i) the peptide is optionally a monomer in a homodimer or heterodimer complex, wherein each monomer is directly covalently linked to each other or indirectly covalently linked to each other through a dimerization linker; and/or (ii) the peptide is optionally conjugated with a half-life extension moiety.

(Formula (V)).

77. The peptide compound of claim 76, wherein both X5 and X13 are Hhc, and these two residues are directly covalently linked through a disulfide bond.

78. The peptide compound of claim 76, wherein X5 is Lys_Ac and X13 is Cys, and these two residues are directly covalently linked through a thioether bond.

79. The peptide compound of claim 76, wherein X5 is Hhc and X13 is Dab_Acetyl, and these two residues are directly covalently linked through a thioether bond.

80. The peptide compound of claim 76, wherein X5 is LysN3 and X13 is Abu, and these two residues are directly covalently linked as shown in paragraph [00324].

81. The peptide compound of claim 76, wherein X5 is O2S, O3S, or O4S, and X13 is O2S, O3S, O4S, or O3S_Me, and these two residues are directly covalently linked through a carbon-carbon double bond.

82. The peptide compound of claim 76, wherein X5 is O3S_Reduced and X13 is O3S_Reduced or O3S_Me_Reduced, and these two residues are directly covalently linked through a carbon-carbon single bond.

83. The peptide compound of claim 76, wherein X5 is Cys or Hcy, and X13 is Cys or Hcy, wherein X5 and X13 are indirectly covalently linked through a thioether bond, wherein these two residues are indirectly covalently linked through a thioether bond with a terminal end of a Butane_Linkers, a Carbonyl_Linkers, a Dimethylcyclopropane_Linkers, an EButene_Linkers, an Oxetane_Linkers, a Pentane_Linkers, Propane_Linkers, or a pXylene_Linkers.

84. The peptide compound of claim 76, wherein the peptide is a monomer in a homodimer compound, and wherein each monomer is directly covalently linked to a DIG linker at X14Lys_PEG4_PEG4_NH2, X14Lys_PEG4_1PEG2_NH2, or X14Lys_PEG8_NH2, through an amide bond, wherein one monomer is linked to one terminal end of this linker and the other monomer is linked to the other terminal end.

85. The peptide compound of any one of claims 76-83, wherein the peptide is a monomer in a homodimer compound, and wherein each monomer is directly covalently linked to a PEG linker at X14Lys through an amide bond, wherein one monomer is linked to one terminal end of the PEG linker and the other monomer is linked to the other terminal end of the PEG linker.

86. The peptide compound of claim 85, wherein the PEG linker is PEG5DA, PEG9DA, PEG13DA, PEG21DA, or PEG25DA.

87. The peptide compound of any one of claims 76-86, wherein the compound exhibits a half-life greater than about 0.5 hours, 1.0 hours, 1.5 hours, or 2.0 hours, in an SGF and/or SIF stability assay.

88. The peptide compound of any one of claims 76-87, wherein R¹ is acetyl or isovaleric acid, and R² is an amine.

89. A peptide compound that has an IC₅₀ for hIL-17AA that is less than about 1nM and for hIL-17FF that is less than about 1 nM in a human IL-17 HEK Blue assay, wherein the peptide compound comprises a monomer peptide comprising or consisting of the sequence of Formula (VI):

R¹-X00-X0-X1-X2-X3-X4-X5-X6-X7-X8-X9-X10-X11-X12-X13-X14-X15-X16-R²,

wherein:

R¹ is acetyl, 3-hydroxypropionic acid, C6_diacid, cyclopropanecarboxylic acid, glutaric acid, isovaleric acid, methanesulfonyl acetic acid, or absent; R² is NH₂, OH, or absent;

X00 is dH or absent;

X0 is dE, dH, Gln, Glu, Glu_OMe, His, Ile, Lys_Me3, Sar, Tle, or absent;

X1 is Cyclopropyl_Alal, Ile, Tba, or Val;

X2 is Dab_Ac, Gln, Glu, His, Hse, Lys_Ac, Lys_Me3, Lys1PEG2Ac, Lys2HyAc, LysMs, Orn2HyAc, OrnAc, Q_NHMe, Q_NMe2, Q_EtOMe, or Thr;

X3 is Cyclopropyl_Alal, Ogl, Tba, Tle, or Val;

X4 is Asn, Glu, Glu_OMe, hE, Phe_4COOH, or Thr;

X5 is Cys, Hcy, Hhc, O2S, O3S, O3S_Reduced, or O4S;

X6 is Oic;

X7 is Acvc, Ala, Gln, Glu, Lys_Ac, Pro, Ser, or Tba;

X8 is Asp or Glal;

X9 is Dgl, or Ogl;

X10 is 1Nal, 2Nal, or Trp;

X11 is Aib, Asp, or Glu;

X12 is aMe_Trp or Trp;

X13 is Cys, Hcy, Hhc, O2S, O3S, O3S_Me, O3S_Me_Reduced, O3S_Reduced, or O4S;

X14 Asn, Lys, Lys_PEG4_1PEG2_NH2, Lys_PEG8_NH2, or Lys_PEG4_PEG4_NH2;

X15 is dR; and

X16 is dE or absent;

wherein the peptide comprises a cyclic structure wherein X5 and X13 are either: (a) directly covalently linked or (b) indirectly covalently linked through a cyclization linker; and

wherein: (i) the peptide is optionally a monomer in a homodimer or heterodimer complex, wherein each monomer is directly covalently linked to each other or indirectly covalently linked to each other through a dimerization linker; and/or (ii) the peptide is optionally conjugated with a half-life extension moiety.

(Formula (VI)).

90. The peptide compound of claim 89, wherein both X5 and X13 are Hhc, and these two residues are directly covalently linked through a disulfide bond.

91. The peptide compound of claim 89, wherein X5 is O3S_Reduced and X13 is O3S_Reduced or O3S_Me_Reduced, and these two residues are directly covalently linked through a carbon-carbon single bond.

92. The peptide compound of claim 89, wherein X5 is O2S, O3S, or O4S, and X13 is O2S, O3S, O4S, or O3S_Me, and these two residues are directly covalently linked through a carbon-carbon double bond.

93. The peptide compound of claim 89, wherein X5 is Cys or Hcy, and X13 is Cys or Hcy, wherein X5 and X13 are indirectly covalently linked through a thioether bond, wherein these two residues are indirectly covalently linked through a thioether bond with a terminal end of a Butane_Link, a Carbonyl_Link, a Dimethylcyclopropane_Link, an EButene_Link, an Oxetane_Link, a Pentane_Link, or a Propane_Link.

94. The peptide compound of any one of claims 89-93, wherein the peptide is a monomer in a homodimer compound, and wherein each monomer is directly covalently linked to either: (a) a PEG linker at X14Lys through an amide bond, wherein one monomer is linked to one terminal end of the PEG linker and the other monomer is linked to the other terminal end of the PEG linker, or (b) a DIG_linker at X14Lys_PEG4_PEG4_NH2, X14Lys_PEG4_1PEG2_NH2, or X14Lys_PEG8_NH2, through an amide bond, wherein one monomer is linked to one terminal end of the DIG linker and the other monomer is linked to the other terminal end.

95. The peptide compound of claim 94, wherein the PEG linker is PEG5DA, PEG9DA, PEG13DA, PEG21DA, or PEG25DA.

96. The peptide compound of any one of claims 89-95, wherein the compound exhibits a half-life greater than about 0.5 hours, 1.0 hours, 1.5 hours, or 2.0 hours, in an SGF and/or SIF stability assay.

97. The peptide compound of any one of claims 89-96, wherein R¹ is acetyl or isovaleric acid, and R² is an amine.

98. A peptide compound that has an IC₅₀ for hIL-17AA that is less than about 1nM, wherein the peptide compound comprises a monomer peptide comprising or consisting of the sequence of Formula (VII):

R¹-X00-X0-X1-X2-X3-X4-X5-X6-X7-X8-X9-X10-X11-X12-X13-X14-X15-X16-X17-X18-X19-X20-X21-X22-X23-X24-R²,

wherein:

R¹ is acetyl, 3-hydroxypropionic acid, C6_diacid, cyclopropanecarboxylic acid, glutaric acid, glycolic acid, isovaleric acid, methanesulfonyl acetic acid, or absent; R² is NH₂ or OH or absent;

X00 is bA, dH, dK, Tle or absent;

X0 is 2Pal, Aib, Asn, d2Pal, d3Pal, dA, dE, dH, dL, dQ, dS, Gla, Gln, Glu, Glu_OMe, His, Ile, Lys, Lys_Me3, NMe_His, Orn, Pro, Sar, Thr, Tle, or absent;

X1 is 1Nal, Aph, Dgl, hCha, hF, hhF, Ile, Lys_1PEG2_1PEG2_IsoGlu_C12, Ogl, Phe_4Me, Tba, Tle, or Val;

X2 is 2Pal, 3Pal, Gln, His, Hse, Lys_1PEG2_1PEG2_IsoGlu_C12, Lys_Me3, Orn, Phe_3Ad, Phe_4_2ae, or Phe_4ad;

X3 is Cpg, Cyclopropyl_Ala, Dgl, Ogl, Phe_4tBu, Tba, Tle, or Val;

X4 is Asn, Glu, or Thr;

X5 is Cys, Hcy, Hhc, Ile, Lys_Ac, O3S, O3S_Reduced, or O5S_Reduced;

X6 is Oic or Pro;

X7 is Ala, Aze, Dab, His, Lys_Ac, O3S_Me, or Tic;

X8 is Asp or Gla;

X9 is Dgl, Ogl, or O3S;

X10 is 1Nal, 2Nal, aMe_Phe, aMe_Trp, Aoc, Cys, Gln, hCha, Hph, O3S, Phe_4Ad, Phe_4COOH, Tba, Tle, Trp, Trp_4Cl, Trp_4Me, Trp_5Cl, Trp_5Me, Trp_6Cl, Trp_6Me, Trp_7Cl, Trp_7Me, or Trp_7Phe;

X11 is Asp, dA, Glu, or O3S_Me;

X12 is aMe_Trp, Trp, Trp_5Cl, Trp_5Me, or Trp_6Cl;

X13 is Cys, Hcy, Hhc, Ile, O3S, O3S_Me, O3S_Reduced, or O4S;

X14 Aib, Arg, Asn, Asp, Cys, dE, dK, dN, dQ, dR, Glu, Gln, Gly, Lys, Lys_1PEG2_1PEG2_IsoGlu_C12, Lys_Ac, O3S_Me, Tba, or absent;

X15 is Ala, Asn, dE, dR, dQ, Gln, Gly, Leu, Pro, Ser, or absent;

X16 is Aad, dE, dH, dQ, PEG4, PEG6, PEG8, Ser, Thr, Val, or absent;

X17 is Asp, Gly, Glu, His, Ile, Pro, or absent;

X18 is His, Ile, Ser, Tle, Val, or absent; X19 is His, Ile, Val, or absent;

X20 is His, Thr, Val, or absent;

X21 is Ile, Thr, Val, or absent;

X22 is Ile, Thr, or absent;

X23 is Ile or absent;

X24 is Oic, Pro, or absent;

wherein the peptide comprises a cyclic structure wherein X5 and X13, X9 and X13, or X7 and X11, are either: (a) directly covalently linked or (b) indirectly covalently linked through a cyclization linker.

(Formula (VII)).

99. The peptide compound of claim 98, wherein the peptide compound is a monomer and not a multimer.

100. The peptide compound of claim 98, wherein both X5 and X13 are Hhc, and these two residues are directly covalently linked through a disulfide bond.

101. The peptide compound of claim 98, wherein X5 is Lys_Ac and X13 is Cys, and these two residues are directly covalently linked through a thioether bond.

102. The peptide compound of claim 98, wherein X5 and X13 are O3S, or X5 and X13 are individually or both O3S or O3S_Methyl, and these two residues are directly covalently linked through a carbon-carbon double bond.

103. The peptide compound of claim 98, wherein both X5 and X13 are O3S_Reduced, and these two residues are directly covalently linked through a carbon-carbon single bond.

104. The peptide compound of claim 98, wherein X5 is Cys or Hcy, and X13 is Cys or Hcy, wherein X5 and X13 are indirectly covalently linked through a thioether bond, wherein these two residues are indirectly covalently linked through a thioether bond with a terminal end of a Butane_Linkers, Dimethylcyclopropane_Linkers, an EButene_Linkers, a Hexane_Linkers, a Methylene_Linkers, an Oxetane_Linkers, a Pentane_Linkers, a Propane_Linkers, or a Xylene_Linkers.

105. The peptide compound of claim 98, wherein X16-X24 are absent.

106. The peptide compound of claim 98, wherein X17-X24 are absent.

107. The peptide compound of any one of claims 98-106, wherein the peptide is a monomer in a homodimer compound, and wherein each monomer is directly covalently linked to a PEG linker at X14Lys through an amide bond, wherein one monomer is linked to one terminal end of the PEG linker and the other monomer is linked to the other terminal end of the PEG linker.

108. The peptide compound of claim 107, wherein the PEG linker is PEG5DA, PEG9DA, PEG13DA, PEG21DA, or PEG25DA.

109. The peptide compound of any one of claims 98-108, wherein the compound exhibits a half-life greater than about 0.5 hours, 1.0 hours, 1.5 hours, or 2.0 hours, in an SGF and/or SIF stability assay.

110. The peptide compound of any one of claims 98-106, wherein the peptide is a monomer in a homodimer compound, and wherein each monomer is directly covalently linked to a DIG linker at X14Lys_PEG4_PEG4_NH2, X14Lys_PEG4_1PEG2_NH2, or X14Lys_PEG8_NH2 through an amide bond, wherein one monomer is linked to one terminal end of the DIG_linkers and the other monomer is linked to the other terminal end of the DIG_linkers.

111. A peptide compound that has an IC₅₀ for hIL-17AA and FF that is less than about 1nM, wherein the peptide compound exhibits a half-life in an SIF assay greater than about 2 hours,

wherein the peptide compound comprises a monomer peptide comprising or consisting of the sequence of Formula (VIII):

R^1 -X00-X0-X1-X2-X3-X4-X5-X6-X7-X8-X9-X10-X11-X12-X13-X14-X15-X16- R^2 ,

wherein:

R^1 is acetyl, 3-hydroxypropionic acid, C6_diacid, cyclopropanecarboxylic acid, glutaric acid, isovaleric acid, methanesulfonyl acetic acid, or absent; R^2 is NH_2 , OH, or absent;

X00 is dH or absent;

X0 is dE, dH, Gln, Glu, His, Ile, Lys_Me3, Sar, Tle, or absent;

X1 is Cyclopropyl_Alal, Ile, Tba, or Val;

X2 is Dab_Ac, Gln, His, Lys_Ac, Lys_Me3, Lys1PEG2Ac, Lys2HyAc, Orn2HyAc, OrnAc, or Thr;

X3 is Cyclopropyl_Alal, Ogl, Tba, Tle, or Val;

X4 is Asn, Glu, Glu_OMe, hE, or Thr;

X5 is Cys, Hcy, Hhc, O2S, O3S, O3S_Reduced, or O4S;

X6 is Oic;

X7 is Acvc, Ala, Gln, Glu, Lys_Ac, Pro, Ser, or Tba;

X8 is Asp or Glal;

X9 is Dgl, or Ogl;

X10 is 1Nal, 2Nal, or Trp;

X11 is Aib, Asp, or Glu;

X12 is aMe_Trp or Trp;

X13 is Cys, Hcy, Hhc, O2S, O3S, O3S_Me, O3S_Reduced, or O4S;

X14 is Asn, Lys, Lys_PEG4_1PEG2_NH2, Lys_PEG8_NH2, or Lys_PEG4_PEG4_NH2;

X15 is dR; and

X16 is absent;

wherein the peptide comprises a cyclic structure wherein X5 and X13 are either: (a) directly covalently linked or (b) indirectly covalently linked through a cyclization linker; and

wherein the peptide is optionally a monomer in a homodimer complex, wherein each monomer is directly covalently linked to each other or indirectly covalently linked to each other through a dimerization linker.

(Formula (VIII)).

112. The peptide compound of claim 111, wherein both X5 and X13 are Hhc, and these two residues are directly covalently linked through a disulfide bond.

113. The peptide compound of claim 111, wherein X5 and X13 are individually, or both, O2S, O3S, O3S_Me, or O4S, and these two residues are directly covalently linked through a carbon-carbon double bond.

114. The peptide compound of claim 111, wherein X5 and X13 are O3S_Reduced, and these two residues are directly covalently linked through a carbon-carbon single bond.

115. The peptide compound of claim 111, wherein X5 is Cys or Hcy, and X13 is Cys or Hcy, wherein X5 and X13 are indirectly covalently linked through a thioether bond, wherein these two residues are indirectly covalently linked through a thioether bond with a terminal end of a Dimethylcyclopropane_Linker, an Oxetane_Linker, a Pentane_Linker, or a Propane_Linker.

116. The peptide compound of any one of claims 111-115, wherein the peptide is a monomer in a homodimer compound, and wherein each monomer is directly covalently linked to a PEG linker at X14Lys through an amide bond, wherein one monomer is linked to one terminal end of the PEG linker and the other monomer is linked to the other terminal end of the PEG linker.

117. The peptide compound of claim 116, wherein the PEG linker is PEG5DA, PEG9DA, PEG13DA, PEG21DA, or PEG25DA.

118. The peptide compound of any one of claims 111-117, wherein the compound exhibits a half-life greater than about 0.5 hours, 1.0 hours, 1.5 hours, or 2.0 hours, in an SGF stability assay.

119. The peptide compound of any one of claims 111-118, wherein the peptide is a monomer in a homodimer compound, and wherein each monomer is directly covalently linked to a DIG_linker at X14Lys_PEG4_PEG4_NH2, X14Lys_PEG4_1PEG2_NH2, or X14Lys_PEG8_NH2, through an amide bond, wherein one monomer is linked to one terminal end of this linker and the other monomer is linked to the other terminal end.

120. A peptide compound that has an IC₅₀ for hIL-17AA that is less than about 1 nM and for IL-17FF that is less than about 5nM, wherein the peptide compound exhibits a half-life in both an SGF and an SIF assay greater than about 2 hours, wherein the peptide compound comprises a monomer peptide comprising or consisting of the sequence of Formula (IX):

R¹-X00-X0-X1-X2-X3-X4-X5-X6-X7-X8-X9-X10-X11-X12-X13-X14-X15-X16-R²,

wherein:

R¹ is acetyl, 3-hydroxypropionic acid, C6_diacid, cyclopropanecarboxylic acid, glutaric acid, isovaleric acid, methanesulfonyl acetic acid, or absent; R² is NH₂ or OH or absent;

X00 is dH or absent;

X0 is dE, dH, Glu, His, Ile, Lys_Me3, Sar, Tle, or absent;

X1 is Ile or Val;

X2 is His, Lys_Me3, or Gln;

X3 is Tba, Tle, or Val;

X4 is Asn, Glu, Glu_OMe, hE, or Thr;

X5 is Cys, Hcy, Hhc, O3S, or O3S_Reduced;

X6 is Oic;

X7 is Acvc, Ala, Gln, Glu, Lys_Ac, Pro, Ser, or Tba;

X8 is Asp or Gla;

X9 is Dgl or Ogl;

X10 is 1Nal, 2Nal, or Trp;

X11 is Aib, Asp, or Glu;

X12 is aMe_Trp or Trp;

X13 is Cys, Hcy, Hhc, O3S, O3S_Me, or O3S_Reduced;

X14 is Lys, Lys_PEG4_1PEG2_NH2, Lys_PEG8_NH2, or Lys_PEG4_PEG4_NH2;

X15 is dR; and

X16 is absent;

wherein the peptide comprises a cyclic structure wherein X5 and X13 are either: (a) directly covalently linked or (b) indirectly covalently linked through a cyclization linker; and

wherein: (i) the peptide is a monomer in a homodimer complex, wherein each monomer is covalently linked to a dimerization linker; and/or (ii) the peptide is optionally conjugated with a half-life extension moiety.

(Formula (IX)).

121. The peptide compound of claim 120, wherein both X5 and X13 are Hhc, and these two residues are directly covalently linked through a disulfide bond.

122. The peptide compound of claim 120, wherein X5 is O3S, and X13 is O3S or O3S_Me, and these two residues are directly covalently linked through a carbon-carbon double bond.

123. The peptide compound of claim 120, wherein X5 is O3S_Reduced and X13 is O3S_Reduced, and these two residues are directly covalently linked through a carbon-carbon single bond.

124. The peptide compound of claim 120, wherein X5 is Cys or Hcy, and X13 is Cys or Hcy, wherein X5 and X13 are indirectly covalently linked through a thioether bond, wherein these two residues are indirectly covalently linked through a thioether bond with a terminal end of a Dimethylcyclopropane_Linkers, a Pentane_Linkers, or a Propane_Linkers.

125. The peptide compound of any one of claims 120-124, wherein the peptide is a monomer in a homodimer compound, and wherein each monomer is directly covalently linked to a PEG linker at X14Lys through an amide bond, wherein one monomer is linked to one terminal end of the PEG linker and the other monomer is linked to the other terminal end of the PEG linker.

126. The peptide compound of claim 125, wherein the PEG linker is PEG5DA, PEG9DA, PEG13DA, PEG21DA, or PEG25DA.

127. The peptide compound of any one of claims 120-124, wherein the peptide is a monomer in a homodimer compound, and wherein each monomer is directly covalently linked to a DIG_Linkers at X14Lys_PEG4_PEG4_NH2, X14Lys_PEG4_1PEG2_NH2, or X14Lys_PEG8_NH2, through an amide bond, wherein one monomer is linked to one terminal end of the PEG linker and the other monomer is linked to the other terminal end of the DIG_Linkers.

128. A peptide compound comprising a peptide monomer comprising or consisting of the sequence of any one of SEQ ID NO:1-720.

129. A peptide compound having the two-dimensional chemical structure as encoded by a SMILES formula as listed in Figure 1.

130. A peptide compound having the two-dimensional chemical structure as depicted by one of Figures 6A-6Z.

131. A pharmaceutical composition comprising a peptide of any one of the Formulas herein (including SEQ ID NO formulas), any of the peptide compounds of Figure 1 (i.e., compounds

1-897) or a pharmaceutically acceptable salt thereof and a pharmaceutically acceptable carrier or excipient.

132. A pharmaceutical composition comprising a peptide of any one of claims 1-130 or a pharmaceutically acceptable salt thereof and a pharmaceutically acceptable carrier or excipient.

133. A method of inhibiting the binding of a human IL-17 cytokine to a human IL-17 receptor, the method comprising contacting the human IL-17 cytokine with a peptide of any one of claims 1-132, or a pharmaceutically acceptable salt or solvate thereof.

134. A method for treating an IL-17 related inflammatory disease or an autoimmune disease in a subject, the method comprising: administering to the subject an effective amount of a peptide of any one of claims 1-132.

135. The method of claim 134, wherein the inflammatory disease or autoimmune disease is psoriasis, psoriatic arthritis, rheumatoid arthritis, ankylosing spondylitis, or nonradiographic axial spondyloarthritis.