α4β7 INTEGRIN THIOETHER PEPTIDE ANTAGONISTS

CROSS REFERENCE TO RELATED APPLICATIONS

[0001] This application claims priority to U.S. Provisional Application No. 61/994,699, filed on May 16, 2014, U.S. Provisional Application No. 61/994,717, filed on May 16, 2014, U.S. Provisional Application No. 62/058,499, filed on October 1, 2014, and U.S. Provisional Application No.62/058,501, filed on October 1, 2014, all of which are incorporated by reference herein in their entireties.

SEQUENCE LISTING

[0002] The Sequence Listing associated with this application is provided in text format in lieu of a paper copy, and is hereby incorporated by reference into the specification.

FIELD OF THE INVENTION

[0003] The present invention relates to the field of engineered peptides, and to the field of peptides that bind to integrins. In particular, the present invention relates to thioether peptides (*e.g*. thioether peptide monomers and dimers) that inhibit binding of α4β7 to the mucosal addressin cell adhesion molecule (MAdCAM) in vitro, and show high selectivity against α4β1 binding.

BACKGROUND OF THE INVENTION

[0004] Integrins are noncovalently associated α/β heterodimeric cell surface receptors involved in numerous cellular processes ranging from cell adhesion and migration to gene regulation (Dubree, *et al.*, Selective α4β7 Integrin Antagonist and Their Potential as Anti-inflammatory Agents, *J. Med. Chem.* 2002, 45, 3451-3457). Differential expression of integrins can regulate a cell's adhesive properties, allowing different leukocyte populations to be recruited to specific organs in response to different inflammatory signals. If left unchecked, the integrin-mediated adhesion process can lead to chronic inflammation and autoimmune disease.

[0005] The α4 integrins, α4β1 and α4β7, play essential roles in lymphocyte migration throughout the gastrointestinal tract. They are expressed on most leukocytes, including B and

[0026] Xaa^{13} is absent or any amino acid; and

[0027] Xaa^{14} is absent or any amino acid;

[0028] wherein if the peptide molecule is a peptide dimer or subunit thereof, then Xaa^{14} is absent or selected from the group consisting of: any amino acid with an amine side chain, Lys, D-Lys, N-Me-Lys, D-N-Me-Lys, Orn, N-Me-Orn, Dab, N-Me-Dab, Dap, N-Me-Dap, Homo-Lys, D-Dap, D-Dab, D-Orn, Gln, Pro, Gly, His, Ala, Ile, Phe, Lys, Arg, Leu, Val, Tyr, Trp, Met, Glu, Ser, Asn, Gla, Cys, HomoCys, COOH, $CONH_2$, suitable isosteres, corresponding D-amino acids, and corresponding N-Methyl amino acids, and wherein the peptide molecule comprises a thioether bond between Xaa^4 and Xaa^{10}.

[0029] In particular examples, Xaa^1, Xaa^2 and Xaa^3 are absent. In certain examples, Xaa^4 is a 2-methylbenzoyl moiety. In certain embodiments, Xaa^5 is 2-Me-Arg. In particular examples, Xaa^8 is selected from the group consisting of Thr, Gln, Ser, Asp, Gly, His, Ala, Ile, Phe, Lys, Arg, Asn, Glu, Val, Tyr, Trp, Leu, Met, HomoLeu, Nle, and N-Methyl amino acids including N-Me-Thr. In particular examples, Xaa^9 is selected from the group consisting of Gln, Asn, Asp, Gly, Ala, Phe, Leu, Glu, Ile, Val, HLeu, n-Butyl Ala, n-Pentyl Ala, n-Hexyl Ala, Nle, cyclobutyl-Ala, Cpa, Aoc, N-Me-Leu, and suitable isostere replacements. In certain examples, Xaa^{14} is selected from the group consisting of: Lys, D-Lys, N-Me-Lys, D-N-Me-Lys, Orn, Dab, Dap, Homo-Lys, D-Dap, D-Dab, Cys, HomoCys, Pen, or D-Orn. In particular examples, Xaa^{14} is selected from the group consisting of: D-Lys, N-Me-Lys, and D-N-Me-Lys. In certain examples, the peptide molecule comprises N(alpha)methylation of at least one position selected from the group consisting of Xaa^3, Xaa^5, Xaa^7-Xaa^9, and Xaa^{11}-Xaa^{13}. In certain examples, the peptide molecule comprises acylation for at least one position selected from the group consisting of Xaa^1-Xaa^3 and Xaa^{11}-Xaa^{14}.

[0030] In a related example, the invention includes a peptide molecule comprising a structure of Formula (VI) (SEQ ID NO: 387):

$$Xaa^1\text{-}Xaa^2\text{-}Xaa^3\text{-}Xaa^4\text{-}Xaa^5\text{-}Xaa^6\text{-}Xaa^7\text{-}Xaa^8\text{-}Xaa^9\text{-}Xaa^{10}\text{-}Xaa^{11}$$

(Formula VI)

[0031] or a pharmaceutically acceptable salt thereof, wherein

[0032] Xaa^1 is a 2-Me-benzoyl group capable of forming a thioether bond with Xaa^7;

[0033] Xaa^2 is selected from the group consisting of N(alpha)-Me-Arg, Arg, HArg, Dap, Dab, Arg-Me-sym, Arg-Me-asym, 4-Guan, Cit, Cav, and suitable isostere replacements;

herein. For example, some peptides include Dab, Dap, Pen, Sar, Cit, Cav, HLeu, 2-Nal, D-1-Nal, D-2-Nal, Bip, O-Me-Tyr, β-HTrp, β-HPhe, Phe (4-CF3), 2-2-Indane, 1-1-Indane, Cyclobutyl, β-HPhe, HLeu, Gla, HPhe, 1-Nal, Nle, homo amino acids, D-amino acids, 3-3-diPhe, cyclobutyl-Ala, HCha, Phe(4-NH2), Bip, β-HPhe, β-Glu, 4-guan, and various N-methylated amino acids. One having skill in the art will appreciate that additional substitutions may be made to achieve similar desired results, and that such substitutions are within the teaching and spirit of the present invention. In certain embodiments, any of the peptides, *e.g.* peptide dimers and peptide monomer or subunits thereof, described herein or shown in the sequence listing or accompanying figures further comprises one or more amino acid substitutions, e.g., in certain embodiments, one or more amino acid residues is substituted with Dab, Dap, Pen, Sar, Cit, Cav, HLeu, 2-Nal, D-1-Nal, D-2-Nal, Bip, O-Me-Tyr, β-HTrp, β-HPhe, Phe (4-CF3), 2-2-Indane, 1-1-Indane, Cyclobutyl, β-HPhe, HLeu, Gla, HPhe, 1-Nal, Nle, homo amino acids, D-amino acids, 3-3-diPhe, cyclobutyl-Ala, HCha, Phe(4-NH2), Bip, β-HPhe, β-Glu, 4-guan, or an N-methylated amino acid, such as, e.g., N-methyl-Arg.

[00126] As used herein, "Xaa" can stand for one or more of any naturally occurring amino acids, unnatural amino acids, modified amino acids, and/or non-naturally occurring amino acids, including D- and L-amino acids, aminoacyl residues or any chemical moieity capable of substituting and amino acid position. In some embodiments, Xaa designates that more than one amino acid, aminoacyl residue, or chemical residency may occupy a given position in the peptide. In particular embodiments, Xaa designates that a single non-naturally occurring, unnatural, or modified amino acid, or an aminoacyl residue or a chemical moiety (e.g., a 2-methylbenzoyl moiety) occupies a given position in the polypeptide.

[00127] One aspect of the present invention relates to a thioether peptide monomer, a thioether peptide dimer, or a thioether subunit of a dimer molecule comprising the structure according to Formula (I):

[00128] Xaa^{1}-Xaa^{2}-Xaa^{3}-Xaa^{4}-Xaa^{5}-Xaa^{6}-Xaa^{7}-Xaa^{8}-Xaa^{9}-Xaa^{10}-Xaa^{11}-Xaa^{12}-Xaa^{13}-Xaa^{14} (Formula (I); SEQ ID NO: 388; Figure 1), or a pharmaceutically acceptable salt thereof, wherein the peptide monomer or one or both subunits of the thioether peptide dimer comprises a thioether bond between Xaa^{4} and Xaa^{10} to provide a cyclized structure, and wherein:

[00129] Xaa^{1} is absent, or selected from the group consisting of any naturally occurring amino acid, a suitable isostere, and corresponding D-amino acids;

[00145] In certain embodiments, a thioether peptide dimer comprises two peptide monomer subunit of Formula (I), wherein these subunits are linked via a linker moiety through their C- or N-termini. In one embodiment, they are linked via both their C-termini.

[00146] In another aspect, the present invention includes a thioether peptide molecule (e.g. a peptide monomer, peptide dimer, or a peptide dimer subunit) comprising the structure according to Formula (I-1) (SEQ ID NO: 389):

[00147] Xaa^1-Xaa^2-Xaa^3-Xaa^4-Xaa^5-Xaa^6-Xaa^7-Xaa^8-Xaa^9-Xaa^{10}-Xaa^{11}-Xaa^{12}-Xaa^{13}-Xaa^{14} (Formula (I-1)), or a pharmaceutically acceptable salt thereof, wherein the peptide comprises a thioether bond between Xaa^4 and Xaa^{10}, and wherein:

[00148] Xaa^1 is absent, or Xaa^1 is any amino acid;

[00149] Xaa^2 is absent, or Xaa^2 is any amino acid;

[00150] Xaa^3 is absent, or Xaa^3 is any amino acid;

[00151] Xaa^4 is an amino acid, aliphatic acid, alicyclic acid, or modified 2-methyl aromatic acid having a side chain with one or two carbons, and capable of forming a thioether bond with Xaa^{10};

[00152] Xaa^5 is selected from the group consisting of N(alpha)-Me-Arg, Arg, HomoArg, Dap, Dab, Arg-Me-sym, Arg-Me-asym, 4-Guan, Cit, Cav, N-Me-Lys, Phe(4-quanidino), Phe(4-carbamoyl amino), Phe(4-NH_2), N-Me-HomoArg, Tyr, His, and suitable isostere replacements;

[00153] Xaa^6 is selected from the group consisting of Ser, Gly, Thr, Ile, and suitable isostere replacements; wherein if Formula (I-1) is directed to a dimer peptide subunit, then in some embodiments, Xaa^6 is selected from the group consisting of Ser, Gly, Thr, and suitable isostere replacements;

[00154] Xaa^7 is selected from the group consisting of Asp, N-Me-Asp, Asp(OMe), D-Asp, and suitable isostere replacements;

[00155] Xaa^8 is selected from the group consisting of Thr, Gln, Ser, Asp, Pro, Gly, His, Ala, Ile, Phe, Lys, Arg, Asn, Glu, Val, Tyr, Trp, Leu, Met, HomoLeu, Nle, and N-Methyl amino acids including N-Me-Thr;

[00156] Xaa^9 is selected from the group consisting of Gln, Asn, Asp, Pro, Gly, Ala, Phe, Leu, Glu, Ile, Val, HLeu, n-Butyl Ala, n-Pentyl Ala, n-Hexyl Ala, Nle, cyclobutyl-Ala, Cpa, Aoc, N-Me-Leu, and suitable isostere replacements;

[00242] Xaa^6 is Ser, Gly, Thr, or Ile; wherein in some embodiments, if Formula (I-B) is directed to a peptide dimer subunit then Xaa^6 is Ser;

[00243] Xaa^7 is Asp or D-Asp;

[00244] Xaa^8 is selected from the group consisting of: Thr, Val, Ile, Leu, hLeu and Nle;

[00245] Xaa^9 is selected from the group consisting of: Leu, Nle, Cpa, Cba, HomoLeu, Aoc, and N-Me-Leu;

[00246] Xaa^{10} is Pen, Cys, D-Cys or HomoCys;

[00247] Xaa^{11} is selected from the group consisting of: Trp, Phe, 2-Nal, 1-Nal, Tyr, His, Phe(4-F), Phe(4-CF3), Phe (4-CH3), Phe (4-tBu), Bip, Phe(4-COOH), Gly, 3,3-DiPhenylGly, 3,3 diPhenyl Ala, Tic, b-homo-Trp, D-1-Nal, D-2-Nal, Phe(2,4-diCl), Phe(3,4-diCl), Phe(4-carbomyl), Phe(3-Carbomyl), Tyr(Me), HomoPhe, N-Me-Phe, N-Me-Tyr, Ser, Sar, Dihydro Trp, Ile, Leu, Ser, Arg, Thr, Sar, Ser and any substituted aromatic amono acid and corresponding D-amino acids; wherein in some embodiments, if Formula (I-B) is directed to a peptide dimer subunit, then Xaa^{11} is selected from the group consisting of: Trp, Phe, 2-Nal, 1-Nal, Tyr, His, Phe(4-F), Phe(4-CF3), Phe (4-CH3), Phe (4-tBu), Bip, Phe(4-COOH), Gly, 3,3-DiPhenylGly, 3,3 diPhenyl Ala, Tic, b-homo-Trp, D-1-Nal, D-2-Nal, Phe(2,4-diCl), Phe(3,4-diCl), Phe(4-carbomyl), Phe(3-Carbomyl), Tyr(Me), HomoPhe, N-Me-Phe, N-Me-Tyr, Dihydro Trp, Ile, Leu, Ser, Arg, Thr, Sar, and Ser;

[00248] Xaa^{12} is selected from the group consisting of: any aromatic amino acid, Glu, D-Glu, homoGlu, Asp, D-Asp, D-homoGlu, Gla, beta-homo-Glu, corresponding D-amino acid and isosteres;

[00249] Xaa^{13} is absent;

[00250] wherein some embodiments, if Formula (I-B) is directed to a peptide monomer, then Xaa^{14} is any amino acid; and

[00251] in other emboidiments, if Formula (I-B) is directed to a peptide dimer subunit, then Xaa^{14} is selected from the group consisting of: Lys, D-Lys, N-Me-Lys, D-N-Me-Lys, Orn, Dab, Dap, Homo-Lys, D-Dap, D-Dab, Cys, HomoCys, Pen, or D-Orn.

[00252] In one embodiment of Formula (I-1), herein referred to as Formula (I-C) (SEQ ID NO: 38),

[00253] Xaa^1 is absent or any amino acid;

[00254] Xaa^2 is absent or any amino acid;

[00255] Xaa^3 is absent or any amino acid;

[00256] Xaa^4 is a 2-methylbenzoyl moiety or a modified HomoSer, optionally Homo-Ser-Cl;

[00257] Xaa^5 is N-Me-Arg;

[00258] Xaa^6 is Ser, Gly, Thr, or Ile; wherein in some embodiments, if Formula (I-C) is directed to a peptide dimer subunit, then Xaa^6 is Ser;

[00259] Xaa^7 is Asp or D-Asp;

[00260] Xaa^8 is selected from the group consisting of: Thr, Val, Ile, Leu, hLeu and Nle;

[00261] Xaa^9 is selected from the group consisting of: Leu, Nle, Cpa, Cba, HomoLeu, Aoc, and N-Me-Leu;

[00262] Xaa^{10} is Pen, Cys, D-Cys or HomoCys;

[00263] Xaa^{11} is selected from the group consisting of: Trp, Phe, 2-Nal, 1-Nal, Tyr, His, Phe(4-F), Phe(4-CF3), Phe (4-CH3). Phe (4-tBu), Bip, Phe(4-COOH), Gly, 3,3-DiPhenylGly, 3,3 diPhenyl Ala, Tic, b-homo-Trp, D-1-Nal, D-2-Nal, Phe(2,4-diCl), Phe(3,4-diCl), Phe(4-carbomyl), Phe(3-Carbomyl), Tyr(Me), HomoPhe, N-Me-Phe, N-Me-Tyr, Sar, Dihydro Trp, Ile, Leu, Ser, Arg, Thr, Sar, and Ser; or

[00264] Xaa^{12} is selected from the group consisting of: any aromatic amino acid, Glu, D-Glu, homoGlu, Asp, D-Asp, D-homoGlu, Gla, beta-homo-Glu, corresponding D-amino acid and isosteres;

[00265] Xaa^{13} is absent or any amino acid; wherein in other embodiments, if Formula (I-C) is directed to a peptide dimer subunit, then Xaa^{13} is absent; and

[00266] wherein in some embodiments, if Formula (I-C) is directed to a peptide monomer subunit then Xaa^{14} is any amino acid; and

[00267] whererin in other embodiments, if Formula (I-C) is directed to a peptide dimer subunit then Xaa^{14} is selected from the group consisting of: Lys, D-Lys, N-Me-Lys, D-N-Me-Lys, Orn, Dab, Dap, Homo-Lys, D-Dap, D-Dab, Cys, HomoCys, Pen, or D-Orn.

[00268] In certain embodiments, Formula (I-C) is directed to a peptide monomer and Xaa^{13} is absent.

[00269] In one embodiment of Formula (I-1), herein referred to as Formula (I-D) (SEQ ID NO: 39),

[00270] Xaa^1 is absent or any amino acid;

[00271] Xaa^2 is absent or any amino acid;

[00272] Xaa^3 is absent or any amino acid;

[00273] Xaa^4 is a 2-methylbenzoyl moiety or a modified HomoSer, optionally Homo-Ser-Cl;

[00274] Xaa^5 is N-Me-Arg;

[00275] Xaa^6 is Ser;

[00276] Xaa^7 is Asp or D-Asp;

[00277] Xaa^8 is Thr or Val;

[00278] Xaa^9 is selected from the group consisting of: Leu, Nle, Cpa, Cba, HomoLeu, Aoc, and N-Me-Leu;

[00279] Xaa^{10} is Pen, Cys, D-Cys or HomoCys;

[00280] Xaa^{11} is selected from the group consisting of: Trp, Phe, 2-Nal, 1-Nal, Tyr, His, Phe(4-F), Phe(4-CF3), Phe (4-CH3), Phe (4-tBu), Bip, Phe(4-COOH), Gly, 3,3-DiPhenylGly, 3,3 diPhenyl Ala, Tic, b-homo-Trp, D-1-Nal, D-2-Nal, Phe(2,4-diCl), Phe(3,4-diCl), Phe(4-carbomyl), Phe(3-Carbomyl), Tyr(Me), HomoPhe, N-Me-Phe, N-Me-Tyr, Ser, Sar, Dihydro Trp, Ile, Leu, Ser, Arg, Thr, Sar, and Ser;

[00281] Xaa^{12} is absent or selected from the group consisting of: any aromatic amino acid, Glu, D-Glu, homoGlu, Asp, D-Asp, D-homoGlu, Gla, beta-homo-Glu, corresponding D-amino acid and isosteres;

[00282] Xaa^{13} is absent; and

[00283] wherein in some embodiments, if Formula (I-D) is directed to a peptide monomer then Xaa^{14} is any amino acid; and wherein in other embodiments, if Formula (I-D) is directed to a peptide dimer subunit, then Xaa^{14} is selected from the group consisting of: Lys, D-Lys, N-Me-Lys, D-N-Me-Lys, Orn, Dab, Dap, Homo-Lys, D-Dap, D-Dab, Cys, HomoCys, Pen, or D-Orn.

[00284] In one embodiment of Formula (I-1), herein referred to as Formula (I-E) (SEQ ID NO: 40),

[00285] Xaa^1 is absent or any amino acid;

[00286] Xaa^2 is absent or any amino acid;

[00287] Xaa^3 is absent or any amino acid;

[00288] Xaa^4 is a 2-methylbenzoyl moiety or a modified HomoSer, optionally Homo-Ser-Cl;

[00289] Xaa^5 is N-Me-Arg;

[00290] Xaa^6 is Ser;

[00291] Xaa^7 is Asp or D-Asp;

[00292] Xaa^8 is Thr or Val;

[00293] Xaa^9 is selected from the group consisting of: Leu, Nle, Cpa, Cba, HomoLeu, Aoc, and N-Me-Leu;

[00294] Xaa^{10} is Pen, Cys, D-Cys or HomoCys;

[00295] Xaa^{11} is selected from the group consisting of: Trp, Phe, 2-Nal, 1-Nal, Tyr, His, Phe(4-F), Phe(4-CF3), Phe (4-CH3). Phe (4-tBu), Bip, Phe(4-COOH), Gly, 3,3-DiPhenylGly, 3,3 diPhenyl Ala, Tic, b-homo-Trp, D-1-Nal, D-2-Nal, Phe(2,4-diCl), Phe(3,4-diCl), Phe(4-carbomyl), Phe(3-Carbomyl), Tyr(Me), HomoPhe, N-Me-Phe, N-Me-Tyr, Ser, Sar, Dihydro Trp, Ile, Leu, Ser, Arg, Thr, Sar, and Ser;

[00296] Xaa^{12} is absent or selected from the group consisting of: any aromatic amino acid, Glu, D-Glu, and beta-homo-Glu;

[00297] Xaa^{13} is absent; and,

[00298] wherein in some embodiments, if Formula (I-E) is directed to a peptide monomer, then Xaa^{14} is any amino acid; and in other embodiments, if Formula (I-E) is directed to a peptide dimer subunit, then Xaa^{14} is selected from the group consisting of: Lys, D-Lys, N-Me-Lys, D-N-Me-Lys, Orn, Dab, Dap, Homo-Lys, D-Dap, D-Dab, Cys, HomoCys, Pen, or D-Orn.

[00299] In one embodiment of Formula (I-1), herein referred to as Formula (I-F) (SEQ ID NO: 41),

[00300] Xaa^1 is absent or any amino acid;

[00301] Xaa^2 is absent or any amino acid;

[00302] Xaa^3 is absent or any amino acid;

[00303] Xaa^4 is a 2-methylbenzoyl moiety or a modified HomoSer, optionally Homo-Ser-Cl;

[00304] Xaa^5 is N-Me-Arg;

[00305] Xaa^6 is Ser;

[00306] Xaa^7 is Asp or D-Asp;

[00307] Xaa^8 is Thr or Val;

[00308] Xaa^9 is Leu;

[00309] Xaa^{10} is Pen, Cys, D-Cys or HomoCys;

[00310] Xaa^{11} is selected from the group consisting of: Trp, Phe, 2-Nal, 1-Nal, Tyr, His, Phe(4-F), Phe(4-CF3), Phe (4-CH3). Phe (4-tBu), Bip, Phe(4-COOH), Gly, 3,3-DiPhenylGly, 3,3 diPhenyl Ala, Tic, b-homo-Trp, D-1-Nal, D-2-Nal, Phe(2,4-diCl), Phe(3,4-

diCl), Phe(4-carbomyl), Phe(3-Carbomyl), Tyr(Me), HomoPhe, N-Me-Phe, N-Me-Tyr, Ser, Sar, Dihydro Trp, Ile, Leu, Ser, Arg, Thr, Sar, and Ser;

[00311] Xaa^{12} is selected from the group consisting of: any aromatic amino acid, Glu, D-Glu, beta-homo-Glu, corresponding D-amino acid and isosteres;

[00312] Xaa^{13} is absent; and

[00313] wherein in some embodiments, if Formula (I-F) is directed to a peptide monomer, then Xaa^{14} is any amino acid; and wherein in some embodiments, if Formula (I-F) is directed to a peptide dimer subunit, then Xaa^{14} is selected from the group consisting of: Lys, D-Lys, N-Me-Lys, D-N-Me-Lys, Orn, Dab, Dap, Homo-Lys, D-Dap, D-Dab, Cys, HomoCys, Pen, or D-Orn.

[00314] In certain embodiments, Xaa^{14} is selected from the group consisting of: Lys, D-Lys, N-Me-Lys, D-N-Me-Lys.

[00315] In one embodiment of Formula (I-1), herein referred to as Formula (I-G) (SEQ ID NO: 42),

[00316] Xaa^{1} is absent or any amino acid;

[00317] Xaa^{2} is absent or any amino acid;

[00318] Xaa^{3} is absent or any amino acid;

[00319] Xaa^{4} is a 2-methylbenzoyl moiety or a modified HomoSer, optionally Homo-Ser-Cl;

[00320] Xaa^{5} is N-Me-Arg;

[00321] Xaa^{6} is Ser;

[00322] Xaa^{7} is Asp or D-Asp;

[00323] Xaa^{8} is Thr or Val;

[00324] Xaa^{9} is Leu;

[00325] Xaa^{10} is Pen, Cys, D-Cys or HomoCys;

[00326] Xaa^{11} is selected from the group consisting of: Trp, Phe, 2-Nal, 1-Nal, Tyr, His, Phe(4-F), Phe(4-CF3), Phe (4-CH3). Phe (4-tBu), Bip, Phe(4-COOH), Gly, 3,3-DiPhenylGly, 3,3 diPhenyl Ala, Tic, b-homo-Trp, D-1-Nal, D-2-Nal, Phe(2,4-diCl), Phe(3,4-diCl), Phe(4-carbomyl), Phe(3-Carbomyl), Tyr(Me), HomoPhe, N-Me-Phe, N-Me-Tyr, Ser, Sar, Dihydro Trp, Ile, Leu, Ser, Arg, Thr, Sar, and Ser;

[00327] Xaa^{12} is selected from the group consisting of: any aromatic amino acid, Glu, D-Glu, and beta-homo-Glu;

[00328] Xaa^{13} is absent; and

[00329] wherein in some embodiments, if Formula I-G is directed to a peptide monomer, then Xaa^{14} is any amino acid; and wherein in other embodiments, if Formula I-G is directed to a peptide dimer subunit, then Xaa^{14} is selected from the group consisting of: Lys, D-Lys, N-Me-Lys, D-N-Me-Lys, Orn, Dab, Dap, Homo-Lys, D-Dap, D-Dab, Cys, HomoCys, Pen, or D-Orn.

[00330] In certain embodiments, Xaa^{14} is selected from the group consisting of: D-Lys, N-Me-Lys, and D-N-Me-Lys.

[00331] In one embodiment of Formula (I-1), herein referred to as Formula (I-H) (SEQ ID NO: 43),

[00332] Xaa^{1} is absent or any amino acid;

[00333] Xaa^{2} is absent or any amino acid;

[00334] Xaa^{3} is absent or any amino acid;

[00335] Xaa^{4} is a 2-methylbenzoyl moiety or a modified HomoSer, optionally Homo-Ser-Cl;

[00336] Xaa^{5} is N-Me-Arg;

[00337] Xaa^{6} is Ser;

[00338] Xaa^{7} is Asp;

[00339] Xaa^{8} is Thr or Val;

[00340] Xaa^{9} is Leu;

[00341] Xaa^{10} is Pen, Cys, D-Cys or HomoCys;

[00342] Xaa^{11} is selected from the group consisting of: Trp, Phe, 2-Nal, 1-Nal, Tyr, His, Phe(4-F), Phe(4-CF3), Phe (4-CH3). Phe (4-tBu), Bip, Phe(4-COOH), Gly, 3,3-DiPhenylGly, 3,3 diPhenyl Ala, Tic, b-homo-Trp, D-1-Nal, D-2-Nal, Phe(2,4-diCl), Phe(3,4-diCl), Phe(4-carbomyl), Phe(3-Carbomyl), Tyr(Me), HomoPhe, N-Me-Phe, N-Me-Tyr, Ser, Sar, Dihydro Trp, Ile, Leu, Ser, Arg, Thr, Sar, and Ser;

[00343] Xaa^{12} is selected from the group consisting of: any aromatic amino acid, Glu, D-Glu, and beta-homo-Glu;

[00344] Xaa^{13} is absent; and

[00345] wherein in some embodiments, if Formula I-H is directed to a peptide monomer, then Xaa^{14} is any amino acid; and wherein in some embodiments, if Formula I-H is directed to a peptide dimer subunit, then Xaa^{14} is selected from the group consisting of: D-Lys, N-Me-Lys, and D-N-Me-Lys.

[00346] In one embodiment of Formula (I-1), herein referred to as Formula (I-I) (SEQ ID NO: 44),

[00347] Xaa^1 is absent or any amino acid;

[00348] Xaa^2 is absent or any amino acid;

[00349] Xaa^3 is absent or any amino acid;

[00350] Xaa^4 is a 2-methylbenzoyl moiety or a modified HomoSer, optionally Homo-Ser-Cl;

[00351] Xaa^5 is N-Me-Arg;

[00352] Xaa^6 is Ser;

[00353] Xaa^7 is Asp or D-Asp;

[00354] Xaa^8 is Thr or Val;

[00355] Xaa^9 is Leu;

[00356] Xaa^{10} is Pen, Cys, D-Cys or HomoCys;

[00357] Xaa^{11} is selected from the group consisting of: Trp, Phe, 2-Nal, 1-Nal, Tyr, His, Phe(4-F), Phe(4-CF3), Phe (4-CH3). Phe (4-tBu), Bip, Phe(4-COOH), Gly, 3,3-DiPhenylGly, 3,3 diPhenyl Ala, Tic, b-homo-Trp, D-1-Nal, D-2-Nal, Phe(2,4-diCl), Phe(3,4-diCl), Phe(4-carbomyl), Phe(3-Carbomyl), Tyr(Me), and HomoPhe;

[00358] Xaa^{12} is selected from the group consisting of: any aromatic amino acid, Glu, D-Glu, and beta-homo-Glu;

[00359] Xaa^{13} is absent; and

[00360] wherein in some embodiments, if Formula I-I is directed to a peptide monomer then Xaa^{14} is any amino acid; and wherein in other embodiments, if Formula I-I is directed to a peptide dimer subunit, then Xaa^{14} is selected from the group consisting of: D-Lys, N-Me-Lys, and D-N-Me-Lys.

[00361] In certain embodiments of Formulas (I), (V), (I-1), (I-2), (I-3), (V), or any of (I-A), (I-B), I-C), (I-D), (I-E), (I-F), (I-G), (I-H), and (I-I), Xaa^{11} may also be Bpa, Phe(3-Me), Phe(2-Me), Phe(2-CF3), or β-Me-Phe.

[00362] In certain embodiments of Formulas (I), (V), (I-1), (I-2), (I-3), (V) or any of (I-A), (I-B), I-C), (I-D), (I-E), (I-F), (I-G), (I-H), and (I-I), Xaa^{12} may also be N-Me-Glu, N-Me-Asp, or alpha-H-Glu.

[00363] In particular embodiments of Formulas (I), (V), (I-1), (I-2), (I-3), (V), or any of (I-A), (I-B), I-C), (I-D), (I-E), (I-F), (I-G), (I-H), and (I-I), e.g., when the peptide is a dimer, Xaa^{14} is selected from the group consisting of: Lys, D-Lys, N-Me-Lys, D-N-Me-Lys,

DiPhenylGly, 3,3 diPhenyl Ala, Tic, b-homo-Trp, D-1-Nal, D-2-Nal, Phe(2,4-diCl), Phe(3,4-diCl), Phe(4-carbomyl), Phe(3-Carbomyl), Tyr(Me), HomoPhe, N-Me-Phe, N-Me-Tyr, Ser, Sar, Dihydro Trp, Ile, Leu, Ser, Arg, Thr, Sar, Bpa, Phe(3-Me), Phe(2-Me), Phe(2-CF3), β-Me-Phe, Ser and any substituted aromatic amono acid and corresponding D-amino acids;

[00404] Xaa^{12} is selected from the group consisting of: any aromatic amino acid, Glu, D-Glu, homoGlu, Asp, D-Asp, D-homoGlu, Gla, beta-homo-Glu, N-Me-Glu, N-Me-Asp, alpha-H-Glu , corresponding D-amino acid and isosteres;

[00405] Xaa^{13} is absent; and

[00406] Xaa^{14} is any amino acid.

[00407] In other embodiments,

[00408] Xaa^{1} is absent or any amino acid;

[00409] Xaa^{2} is absent or any amino acid;

[00410] Xaa^{3} is absent or any amino acid;

[00411] Xaa^{4} is a 2-methylbenzoyl moiety or a modified HomoSer, optionally Homo-Ser-Cl;

[00412] Xaa^{5} is N-Me-Arg;

[00413] Xaa^{6} is Ser, Gly, Thr, or Ile;

[00414] Xaa^{7} is Asp or D-Asp;

[00415] Xaa^{8} is selected from the group consisting of: Thr, Val, Ile, Leu, hLeu and Nle;

[00416] Xaa^{9} is selected from the group consisting of: Leu, Nle, Cpa, Cba, HomoLeu, Aoc, and N-Me-Leu;

[00417] Xaa^{10} is Pen, Cys, D-Cys or HomoCys;

[00418] Xaa^{11} is selected from the group consisting of: Trp, Phe, 2-Nal, 1-Nal, Tyr, His, Phe(4-F), Phe(4-CF3), Phe (4-CH3). Phe (4-tBu), Bip, Phe(4-COOH), Gly, 3,3-DiPhenylGly, 3,3 diPhenyl Ala, Tic, b-homo-Trp, D-1-Nal, D-2-Nal, Phe(2,4-diCl), Phe(3,4-diCl), Phe(4-carbomyl), Phe(3-Carbomyl), Tyr(Me), HomoPhe, N-Me-Phe, N-Me-Tyr, Sar,

Dihydro Trp, Ile, Leu, Ser, Arg, Thr, Sar, Bpa, Phe(3-Me), Phe(2-Me), Phe(2-CF3), β-Me-Phe, and Ser;

[00419] Xaa^{12} is selected from the group consisting of: any aromatic amino acid, Glu, D-Glu, homoGlu, Asp, D-Asp, D-homoGlu, Gla, beta-homo-Glu, N-Me-Glu, N-Me-Asp, alpha-H-Glu, corresponding D-amino acid and isosteres;

[00420] Xaa^{13} is absent or any amino acid; and

[00421] Xaa^{14} is any amino acid.

[00422] In other embodiments:

[00423] Xaa^{1} is absent or any amino acid;

[00424] Xaa^{2} is absent or any amino acid;

[00425] Xaa^{3} is absent or any amino acid;

[00426] Xaa^{4} is a 2-methylbenzoyl moiety or a modified HomoSer, optionally Homo-Ser-Cl;

[00427] Xaa^{5} is N-Me-Arg;

[00428] Xaa^{6} is Ser;

[00429] Xaa^{7} is Asp or D-Asp;

[00430] Xaa^{8} is Thr or Val;

[00431] Xaa^{9} is selected from the group consisting of: Leu, Nle, Cpa, Cba, HomoLeu, Aoc, and N-Me-Leu;

[00432] Xaa^{10} is Pen, Cys, D-Cys or HomoCys;

[00433] Xaa^{11} is selected from the group consisting of: Trp, Phe, 2-Nal, 1-Nal, Tyr, His, Phe(4-F), Phe(4-CF3), Phe (4-CH3), Phe (4-tBu), Bip, Phe(4-COOH), Gly, 3,3-DiPhenylGly, 3,3 diPhenyl Ala, Tic, b-homo-Trp, D-1-Nal, D-2-Nal, Phe(2,4-diCl), Phe(3,4-diCl), Phe(4-carbomyl), Phe(3-Carbomyl), Tyr(Me), HomoPhe, N-Me-Phe, N-Me-Tyr, Ser, Sar, Dihydro Trp, Ile, Leu, Ser, Arg, Thr, Sar, Bpa, Phe(3-Me), Phe(2-Me), Phe(2-CF3), β-Me-Phe, and Ser;

[00434] Xaa^{12} is absent or selected from the group consisting of: any aromatic amino acid, Glu, D-Glu, homoGlu, Asp, D-Asp, D-homoGlu, Gla, beta-homo-Glu, N-Me-Glu, N-Me-Asp, alpha-H-Glu, corresponding D-amino acid and isosteres;

[00435] Xaa^{13} is absent; and

[00436] Xaa^{14} is any amino acid.

[00437] In other embodiments:

[00438] Xaa^{1} is absent or any amino acid;

[00439] Xaa^{2} is absent or any amino acid;

[00440] Xaa^{3} is absent or any amino acid;

[00441] Xaa^{4} is a 2-methylbenzoyl moiety or a modified HomoSer, optionally Homo-Ser-Cl;

[00442] Xaa^{5} is N-Me-Arg;

[00443] Xaa^{6} is Ser;

[00444] Xaa^{7} is Asp or D-Asp;

[00445] Xaa^{8} is Thr or Val;

[00446] Xaa^{9} is selected from the group consisting of: Leu, Nle, Cpa, Cba, HomoLeu, Aoc, and N-Me-Leu;

[00447] Xaa^{10} is Pen, Cys, D-Cys or HomoCys;

[00448] Xaa^{11} is selected from the group consisting of: Trp, Phe, 2-Nal, 1-Nal, Tyr, His, Phe(4-F), Phe(4-CF3), Phe (4-CH3). Phe (4-tBu), Bip, Phe(4-COOH), Gly, 3,3-DiPhenylGly, 3,3 diPhenyl Ala, Tic, b-homo-Trp, D-1-Nal, D-2-Nal, Phe(2,4-diCl), Phe(3,4-diCl), Phe(4-carbomyl), Phe(3-Carbomyl), Tyr(Me), HomoPhe, N-Me-Phe, N-Me-Tyr, Ser, Sar, Dihydro Trp, Ile, Leu, Ser, Arg, Thr, Sar, Bpa, Phe(3-Me), Phe(2-Me), Phe(2-CF3), β-Me-Phe, and Ser;

[00449] Xaa^{12} is absent or selected from the group consisting of: any aromatic amino acid, Glu, D-Glu, beta-homo-Glu, N-Me-Glu, N-Me-Asp, alpha-H-Glu;

[00450] Xaa^{13} is absent; and

[00451] Xaa^{14} is any amino acid.

[00452] In other embodiments:

[00453] Xaa^{1} is absent or any amino acid;

[00454] Xaa^{2} is absent or any amino acid;

[00455] Xaa^{3} is absent or any amino acid;

[00456] Xaa^{4} is a 2-methylbenzoyl moiety or a modified HomoSer, optionally Homo-Ser-Cl;

[00457] Xaa^{5} is N-Me-Arg;

[00458] Xaa^{6} is Ser;

[00459] Xaa^{7} is Asp or D-Asp;

[00460] Xaa^{8} is Thr or Val;

[00461] Xaa^{9} is Leu;

[00462] Xaa^{10} is Pen, Cys, D-Cys or HomoCys;

[00463] Xaa^{11} is selected from the group consisting of: Trp, Phe, 2-Nal, 1-Nal, Tyr, His, Phe(4-F), Phe(4-CF3), Phe (4-CH3). Phe (4-tBu), Bip, Phe(4-COOH), Gly, 3,3-DiPhenylGly, 3,3 diPhenyl Ala, Tic, b-homo-Trp, D-1-Nal, D-2-Nal, Phe(2,4-diCl), Phe(3,4-diCl), Phe(4-carbomyl), Phe(3-Carbomyl), Tyr(Me), HomoPhe, N-Me-Phe, N-Me-Tyr, Ser, Sar, Dihydro Trp, Ile, Leu, Ser, Arg, Thr, Sar, Bpa, Phe(3-Me), Phe(2-Me), Phe(2-CF3), β-Me-Phe, and Ser;

[00464] Xaa^{12} is selected from the group consisting of: any aromatic amino acid, Glu, D-Glu, beta-homo-Glu, N-Me-Glu, N-Me-Asp, alpha-H-Glu, corresponding D-amino acid and isosteres;

[00465] Xaa^{13} is absent; and

[00466] Xaa^{14} is any amino acid.

[00467] In other embodiments:

[00468] Xaa^{1} is absent or any amino acid;

[00469] Xaa^{2} is absent or any amino acid;

[00470] Xaa^3 is absent or any amino acid;

[00471] Xaa^4 is a 2-methylbenzoyl moiety or a modified HomoSer, optionally Homo-Ser-Cl;

[00472] Xaa^5 is N-Me-Arg;

[00473] Xaa^6 is Ser;

[00474] Xaa^7 is Asp or D-Asp;

[00475] Xaa^8 is Thr or Val;

[00476] Xaa^9 is Leu;

[00477] Xaa^{10} is Pen, Cys, D-Cys or HomoCys;

[00478] Xaa^{11} is selected from the group consisting of: Trp, Phe, 2-Nal, 1-Nal, Tyr, His, Phe(4-F), Phe(4-CF3), Phe (4-CH3). Phe (4-tBu), Bip, Phe(4-COOH), Gly, 3,3-DiPhenylGly, 3,3 diPhenyl Ala, Tic, b-homo-Trp, D-1-Nal, D-2-Nal, Phe(2,4-diCl), Phe(3,4-diCl), Phe(4-carbomyl), Phe(3-Carbomyl), Tyr(Me), HomoPhe, N-Me-Phe, N-Me-Tyr, Ser, Sar, Dihydro Trp, Ile, Leu, Ser, Arg, Thr, Sar, Bpa, Phe(3-Me), Phe(2-Me), Phe(2-CF3), β-Me-Phe, and Ser;

[00479] Xaa^{12} is selected from the group consisting of: any aromatic amino acid, Glu, D-Glu, N-Me-Glu, N-Me-Asp, alpha-H-Glu, and beta-homo-Glu;

[00480] Xaa^{13} is absent; and

[00481] Xaa^{14} is any amino acid.

[00482] In other embodiments:

[00483] Xaa^1 is absent or any amino acid;

[00484] Xaa^2 is absent or any amino acid;

[00485] Xaa^3 is absent or any amino acid;

[00486] Xaa^4 is a 2-methylbenzoyl moiety or a modified HomoSer, optionally Homo-Ser-Cl;

[00487] Xaa^5 is N-Me-Arg;

[00488] Xaa^6 is Ser;

[00489] Xaa^7 is Asp;

[00490] Xaa^8 is Thr or Val;

[00491] Xaa^9 is Leu;

[00492] Xaa^{10} is Pen, Cys, D-Cys or HomoCys;

[00493] Xaa^{11} is selected from the group consisting of: Trp, Phe, 2-Nal, 1-Nal, Tyr, His, Phe(4-F), Phe(4-CF3), Phe (4-CH3). Phe (4-tBu), Bip, Phe(4-COOH), Gly, 3,3-DiPhenylGly, 3,3 diPhenyl Ala, Tic, b-homo-Trp, D-1-Nal, D-2-Nal, Phe(2,4-diCl), Phe(3,4-diCl), Phe(4-carbomyl), Phe(3-Carbomyl), Tyr(Me), HomoPhe, N-Me-Phe, N-Me-Tyr, Ser, Sar, Dihydro Trp, Ile, Leu, Ser, Arg, Thr, Sar, Bpa, Phe(3-Me), Phe(2-Me), Phe(2-CF3), β-Me-Phe, and Ser;

[00494] Xaa^{12} is selected from the group consisting of: any aromatic amino acid, Glu, D-Glu, N-Me-Glu, N-Me-Asp, alpha-H-Glu, and beta-homo-Glu;

[00495] Xaa^{13} is absent; and

[00496] Xaa^{14} is any amino acid.

[00497] In other embodiments:

[00498] Xaa^1 is absent or any amino acid;

[00499] Xaa^2 is absent or any amino acid;

[00500] Xaa^3 is absent or any amino acid;

[00501] Xaa^4 is a 2-methylbenzoyl moiety or a modified HomoSer, optionally Homo-Ser-Cl;

[00502] Xaa^5 is N-Me-Arg;

[00503] Xaa^6 is Ser;

[00504] Xaa^7 is Asp or D-Asp;

[00505] Xaa^8 is Thr or Val;

[00506] Xaa^9 is Leu;

[00507] Xaa^{10} is Pen, Cys, D-Cys or HomoCys;

[00508] Xaa^{11} is selected from the group consisting of: Trp, Phe, 2-Nal, 1-Nal, Tyr, His, Phe(4-F), Phe(4-CF3), Phe (4-CH3). Phe (4-tBu), Bip, Phe(4-COOH), Gly, 3,3-DiPhenylGly, 3,3 diPhenyl Ala, Tic, b-homo-Trp, D-1-Nal, D-2-Nal, Phe(2,4-diCl), Phe(3,4-diCl), Phe(4-carbomyl), Phe(3-Carbomyl), Tyr(Me), Bpa, Phe(3-Me), Phe(2-Me), Phe(2-CF3), β-Me-Phe, and HomoPhe;

[00509] Xaa^{12} is selected from the group consisting of: any aromatic amino acid, Glu, D-Glu, N-Me-Glu, N-Me-Asp, alpha-H-Glu, and beta-homo-Glu;

[00510] Xaa^{13} is absent; and

[00511] Xaa^{14} is any amino acid.

[00512] In some embodiments of any of the peptides (*e.g.* peptide monomers, or peptide dimers or subunits thereof) described herein, including but not limited to those of Formula (I) (including (I-A)-(I-I), (I-1), (I-2) and (I-3)) or Formula (V), Xaa^{7} is Asp.

[00513] In some embodiments of any of the peptides (*e.g.* peptide monomers, or peptide dimers or subunits thereof) described herein, including but not limited to those of Formula (I) (including (I-A)-(I-I), (I-1), (I-2) and (I-3) or Formula (V)), the N-terminus of the peptide is acylated.

[00514] In some embodiments of any of the peptides (*e.g.* peptide monomers or peptide dimers or subunits thereof) described herein, including but not limited to those of Formula (I) (including (I-A)-(I-I), (I-1), (I-2) and (I-3) or Formula (V)), Xaa^{14} or the C-terminal amino acid does not comprise a free amine.

[00515] In some embodiments of any of the peptides (*e.g.* peptide monomers or peptide dimers or subunits thereof) described herein, including but not limited to those of Formula (I) (including (I-A)-(I-I), (I-1), (I-2) and (I-3) or Formula (V)), Xaa^{14} or the C-terminus comprises an NH_2 or an OH. In particular embodiments, Xaa^{13} is D-Lys Xaa^{14} or the C-terminus is an OH.

[00516] In some embodiments of any of the peptide (*e.g.* peptide monomers or peptide dimers or subunits thereof) described herein, including but not limited to those of Formula (I) (including (I-A)-(I-I), (I-1), (I-2) and (I-3) or Formula (V)), a free amine in the C-terminal amino acid of the peptide monomer is capped, e.g., with an acetyl group.

[00517] In some embodiments of any of the peptides (*e.g.* peptide monomers or peptide dimers or subunits thereof) described herein, including but not limited to those of

[00668] In certain embodiments of Formulas (II), (II-A), (A), (III), (IV), (VI) or Formula (VI), Xaa^8 may also be Bpa, Phe(3-Me), Phe(2-Me), Phe(2-CF3), or β-Me-Phe.

[00669] In certain embodiments of Formulas (II), (II-A), (A), (III), (IV), (VI) or Formula (VI), Xaa^9 may also be N-Me-Glu, N-Me-Asp, or alpha-H-Glu.

[00670] In certain embodiments of Formulas (II), (II-A), (A), (III), (IV), (VI) or Formula (VI), e.g., when the peptide is a dimer, Xaa^{10} is selected from the group consisting of: Lys, D-Lys, N-Me-Lys, D-N-Me-Lys, Orn, Dab, Dap, Homo-Lys, D-Dap, D-Dab, Cys, HomoCys, Pen, or D-Orn, while in other embodiments, Xaa^{10} is selected from D-Lys, N-Me-Lys, and D-N-Me-Lys.

[00671] In certain embodiments of the peptide monomers or peptide dimers described herein, the N-terminus of the peptide is acylated.

[00672] In certain embodiments of the peptide monomers and dimer subunits, Xaa^{10} or the C-terminus of each peptide or peptide subunit comprises an NH_2 or an OH. In certain embodiments of the peptide dimer subunits, the C-terminus of comprises an NH_2 or an OH either before or after dimerization.

[00673] In certain embodiments of peptide monomers described herein, a free amine in the C-terminal amino acid is capped, e.g., with an acetyl group.

[00674] Particular aspects of the present invention relate to peptide inhibitors of α4β7 comprising the following core consensus sequence (shown left to right from N-term to C-term):

[00675] Y-(N-Me-Arg)-Ser-Glu-Thr-Leu-X (SEQ ID NO: 390)

[00676] wherein Y is a 2-methyl benzoyl moiety capable of forming a thioether bond with X, and wherein X is an amino acid residue selected from Pen, Cys, D-Cys and HomoCys. In particular embodiments, X is Pen. In particular embodiments, the core sequence comprises an intramoleculer thioether bond between X and Y. In particular embodiments, the peptide inhibitor is a monomer. In particular embodiments, the peptide inhibitor is a dimer comprising two peptide monomer subunits, each comprising this core sequence. In particular embodiments, the monomer peptide inhibitor comprises 7-15 amino acid residues. In particular embodiments, each monomer subunit of the dimer peptide inhibitor comprises 7-15 amino acid residues. In certain embodiments, the two monomer subunits are linker via their respective N- or C-termini. In particular embodiments, they are linker by each of their C-termini. In certain embodiments, the peptide inhibitor further comprises an aromatic amino acid immediately downstream of X. In particular

Table 4. Illustrative Thioether Monomers

SEQ ID NO	**Peptide sequence**	1	2	3	4	5	6	7	8	9	10	
391	(thioether)	Acetyl	N-Me-R	S	D	T	L	C	W	k	NH2	
392	(thioether)	Acetyl	N-Me-R	S	D	T	L	homoCys	W	k	NH2	
51	(thioether)	Propionyl	N-Me-R	S	D	T	L	C	W	k	NH2	
52	(thioether)	alpha-bromoispbutyryl	N-Me-R	S	D	T	L	C	W	k	NH2	
53	(thioether)	Acetyl	N-Me-R	S	D	T	L	Pen	W	k	NH2	
54	(thioether)	Propionyl	N-Me-R	S	D	T	L	Pen	W	k	NH2	
55	(thioether)	2-Benzyl	N-Me-R	S	D	T	L	C	W	E	k	NH2
56	(thioether)	2-Benzyl	N-Me-R	S	D	T	L	Pen	W	E	k	NH2
57	(thioether)	Propionyl	N-Me-R	S	D	T	L	hC	W	k	NH2	
58	((thioether)	Butyryl	N-Me-R	S	D	T	L	C	W	k	NH2)2	
59	(thioether)	2-Benzyl	R	S	D	T	L	C	W	k	NH2	
60	(thioether)	2-Benzyl	N-Me-R	S	D	T	L	Pen	W	e	k	NH2
61	(thioether)	2-Benzyl	N-Me-R	S	D	T	L	Pen	W	b-H-E	k	NH2
62	(thioether)	2-Benzyl	N-Me-R	S	D	T	L	Pen	W	E	N-Me-k	NH2
63	(thioether)	2-Benzyl	N-Me-R	S	D	T	L	Pen	W	Y	N-Me-K	NH2