with αE subunit to form αEβ7, which is primarily expressed on intraepithelial lymphocytes (IEL) in the intestine, lung and genitourinary tract. αEβ7 is also expressed on dendritic cells in the gut. The αEβ7 heterodimer binds to E-cadherin on the epithelial cells. The IEL cells are thought to provide a mechanism for immune surveillance within the epithelial compartment. Therefore, blocking αEβ7 and α4β7 together may be a useful method for treating inflammatory conditions of the intestine

[0005] Inhibitors of specific integrin-ligand interactions have been shown effective as anti-inflammatory agents for the treatment of various autoimmune diseases. For example, monoclonal antibodies displaying high binding affinity for α4β7 have displayed therapeutic benefits for gastrointestinal auto-inflammatory/autoimmune diseases, such as Crohn's disease, and ulcerative colitis. *Id.* However, one of these therapies interfered with α4β1 integrin-ligand interactions thereby resulting in dangerous side effects to the patient. Therapies utilizing a dual-specific small molecule antagonists have shown similar side effects in animal models.

[0006] Accordingly, there is a need in the art for integrin antagonist molecules having high affinity for the α4β7 integrin and high selectivity against the α4β1 integrin, as a therapy for various gastrointestinal autoimmune diseases.

[0007] Such integrin antagonist molecules and related compositions and methods are provided by the present invention.

SUMMARY

[0008] The present disclosure has been developed in response to the present state of the art, and in particular, in response to the problems and needs in the art that have not yet been fully solved by currently available integrin antagonists. Thus, the present disclosure provides α4β7 antagonist monomer and dimer peptides, e.g., for use as anti-inflammatory and/or immunosuppressive agents. Further, the present disclosure provides α4β7 antagonist monomer and dimer peptides for use in treating a condition that is associated with a biological function of α4β7 to tissues expressing MAdCAM.

[0009] The disclosure relates to novel peptidic compounds exhibiting integrin antagonist activity. The present disclosure further relates to novel peptidic compounds exhibiting high specificity for α4β7 integrin, and increased oral stability. In particular

embodiments, the present disclosure relates to novel compounds having activity useful for treating conditions which arise or are exacerbated by integrin binding, pharmaceutical compositions comprising the compounds, methods of treatment using the compounds, and methods of blocking or disrupting integrin binding. The compounds are integrin antagonist molecules having high affinity for the α4β7 integrin, which may be used as a therapy for various gastrointestinal autoimmune diseases.

[0010] In certain embodiments, compounds of the present disclosure are dimers comprising two paired subunits that are linked together by their C- or N-termini via a linking moiety. In certain embodiments, one or both of the dimer subunit peptides of the present disclosure further comprises two natural or unnatural amino acids that are capable of bridging to form a cyclized structure. Thus, particular compounds of the present disclosure comprise dimerized peptides, each subunit of the dimer containing a cyclized structure through at least one of a disulfide bridge, an amide bond, or another or equivalent connection. This feature provides increased stability to the compound when administered orally as a therapeutic agent. In addition, this feature further provides for increased specificity and potency.

[0011] One having skill in the art will appreciate that the C- and N-terminal linker moieties disclosed herein are non-limiting examples of suitable linkers, and that the present disclosure may include any suitable linker moiety. Thus, some embodiments of the present disclosure comprises a homo- or heterodimer molecule comprised of two monomer subunits selected from the peptide molecules described herein and in the accompanying figures and tables, wherein the C- or N-termini of the respective monomers are linked by any suitable linker moiety to provide a dimer molecule having superior integrin antagonist activity.

[0012] Disclosed is a composition for treating a subject in need of integrin-antagonist therapy comprising a dimer compound of Formula (I), or any other compound described herein or in the accompanying figures and tables, in combination with a pharmaceutically acceptable carrier.

[0013] Disclosed is a diagnostic method for visualizing and diagnosing a disease comprising administering an orally stable compound of Formula (I), or any other compound described herein or in the acompanying figures, that is further labeled with at least one of a chelating group and a detectable label for use as an *in vivo* imaging agent for non-invasive diagnostic procedures.

[0014] In certain embodiments, compounds of the present disclosure are monomers. Each monomer peptide of the present disclosure further comprises two natural or unnatural amino acids that are capable of bridging to form a cyclized structure. Thus, the compounds of the present disclosure comprise monomer peptides, each forming a cyclized structure through at least one of a disulfide salt bridge, an amide bond, or an equivalent connection. This feature provides increased stability to the compound when administered orally as a therapeutic agent. This feature further provides for increased specificity and potency as compared to non-cyclized analogs.

[0015] In one embodiment, the present disclosure includes a peptide dimer compound comprising two linked monomer subunits of Formula (I):

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))

or a pharmaceutically acceptable salt thereof,

[0016] wherein:

Xaa^1 is absent, Ac, or any amino acid;

Xaa^2 is absent, Ac, or any amino acid;

Xaa^3 is absent, Ac, or any amino acid;

Xaa^4 is any amino acid capable of forming a bond with Xaa^{10};

Xaa^5 is selected from the group consisting of: N-Me-Arg, Arg, N-Me-Lys, Phe(4-guanidinoguanidino), Phe(4-carbomyl), Cit, Phe(4-NH_2), N-Me-homoArg, homoArg, Tyr, Dap, Dab, Arg-Me-sym, Arg-Me-asym, Cav, and His;

Xaa^6 is Ser, Gly, Thr or Ile;

Xaa^7 is Asp, Asp(OMe) or N-Me-Asp;

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

Xaa^9 is selected from the group consisting of: Gln, Ser, Asp, Pro, Gly, Ala, Phe, Glu, Ile, Val, N-butyl Ala, N-pental Ala, N-hexyl Ala, cyclobutyl Ala, cyclopentylAla, Leu, Nle, Cba, homoLeu, Cpa, Aoc, and N-Me-Leu;

Xaa^{10} is any amino acid capable of forming a bond with Xaa^4;

group consisting of Leu, homoLeu, Nle and Val; Xaa^9 is selected from the group consisting of Cba, homoLeu, and Cpa; Xaa^{11} is selected from the group consisting of Tic, Phe(2-carbomyl), Phe(3-carbomyl), Phe(4-COOH), Phe(4-OMe), and Phe(4-tBu); Xaa^{12} is selected from the group consisting of Aic, Gln, Cit, Glu(OMe), D-His, Tic, Phe(3-COOH), D-Arg, Bip, D-Trp, Phe, D-Phe, D-Val, D-Thr, D-1-Nal, D-2-Nal, Thr, Val; or Xaa^{13} is Pro.

[0024] In certain embodiments of Formula (I), one or both monomer subunits of the peptide dimer compound comprises a disulfide bond, a lactam bond, an olefin bond, a 1,2,3-triazole ring, a selenoether bond, or a diselenide bond between Xaa^4 and Xaa^{10}.

[0025] In certain embodiments, Formula (I) represents a monomer subunit of a dimer molecule, wherein the monomer subunits are linked to form a dimer molecule in accordance with the present disclosure.

[0026] In certain embodiments, Xaa^4 is Cys or Pen. In certain embodiments, Xaa^{10} is Cys or Pen. In certain embodiments, both Xaa^4 and Xaa^{10} are Cys or Pen. In certain embodiments, Both Xaa^4 and Xaa^{10} are Pen. In certain embodiments, the amino acid residue directly C-terminal to Xaa^{10} is an aromatic amino acid.

[0027] In certain embodiments wherein the compound is a peptide dimer, Xaa^{14} is any amino acid with amine side chain, Lys, D-Lys, N-Me-Lys, D-N-Me-Lys, Orn, Dab, Dap, HomoLys, D-Dap, D-Dab, or D-Orn. In certain embodiments, Xaa^{14} is Lys, D-Lys, N-Me-Lys, D-N-Me-Lys, Orn, Dab, Dap, HomoLys, D-Dap, D-Dab, or D-Orn. In certain embodiments, Xaa^{14} is Cys, HomoCys, or Pen.

[0028] In certain embodiments, one or both monomer subunits of the peptide dimer comprise an intramolecular bind between Xaa^4 and Xaa^{10}. In particular embodiments, the intramolecular bond is a disulfide bond or a lactam bond.

[0029] In certain embodiments, a free amine in the C-terminal amino acid of the peptide monomer is capped, e.g., with an acetyl group

[0030] For some embodiments, any of Xaa^1-Xaa^5, Xaa^7-Xaa^9, and Xaa^{11}-Xaa^{12} are N(alpha)Methylated. Xaa^5 may further be Arg-Me-sym or Arg-Me-asym, and Xaa^{11} may be O-Me-Tyr, N-Me-Lys(Ac), or 4-Me-Phe. In some instances, any of Xaa^1-Xaa^4, and Xaa^{11}-Xaa^{14} are acylated. For example, in some instances one or more residues at positions Xaa^1-Xaa^4, and Xaa^{11}-Xaa^{14} are acylated with an acylating organic compound selected from the group consisting of 2-me-Trifluorobutyl, Trifluoropentyl, Acetyl, Octonyl, Butyl, Pentyl,

Hexyl, Palmityl, Lauryl, Oleoyl, and Lauryl, Trifluoromethyl butyric, cyclopentane carboxylic, cyclopropylacetic, 4-fluorobenzoic, 4-fluorophenyl acetic, 3-Phenylpropionic, tetrahedro-2H-pyran-4carboxylic, succinic acid, and glutaric acid. In some instances, small PEG (e.g., PEG4-PEG13) is used as spacer before acylations. In some instances Glu, IsoGlu, and/or Asp are used as spacers for acylations. In some instances, Glu or Asp are used as spacers for acylations.

[0031] In some embodiments, the N-terminal or C-terminal amino acids of both peptide monomer subunits of a peptide dimer, e.g., Xaa^1, Xaa^2, Xaa^3, Xaa^{12}, Xaa^{13} or Xaa^{14}, are modified with a suitable linker moiety to form a homo- or hetero-dimer molecule, wherein Formula (I) comprises a dimer formed from two subunits joined by a suitable C- or N-terminal linker.

[0032] In certain embodiments of Formula (I), both subunits comprise one of the following sequences:

Pen-(N-Me-Arg)-Ser-Asp-Thr-Leu-Pen-Trp-(β-homoGlu)-(D-Lys);
Pen-(N-Me-Arg)-Ser-Asp-Thr-Leu-Pen-(Phe-(4-COOH)-(β-homoGlu)-(D-Lys);
Pen-(N-Me-Arg)-Ser-Asp-Thr-Leu-Pen-Trp-Glu-(N-Me-Lys);
Pen-(N-Me-Arg)-Ser-Asp-Thr-Leu-Pen-2-Nal-(β-homoGlu)-(D-Lys);
Pen-(N-Me-Arg)-Ser-Asp-Thr-Leu-Pen-1-Nal-(β-homoGlu)-(D-Lys);
Pen-(N-Me-Arg)-Ser-Asp-Thr-Leu-Pen-2-Nal-Glu-(N-Me-Lys);
Pen-(N-Me-Arg)-Ser-Asp-Thr-Leu-Pen-Phe(4-tBu)-(β-homoGlu)-(D-Lys);
Pen-(N-Me-Arg)-Ser-Asp-Thr-Leu-Pen-Phe(4-tBu)-(β-homoGlu)-(N-Me-Lys);
Pen-(N-Me-Arg)-Ser-Asp-Thr-Leu-Pen-Trp-(β-homoGlu)-(N-Me-Lys);
Pen-(N-Me-Arg)-Ser-Asp-Thr-Leu-Pen-2-Nal-(β-homoGlu)-(N-Me-Lys);
Pen-(N-Me-Arg)-Ser-Asp-Thr-Leu-Pen-1-Nal-(β-homoGlu)-(D-Lys);
Pen-(N-Me-Arg)-Ser-Asp-Thr-Leu-Pen-1-Nal-(β-homoGlu)-(N-Me-Lys);
Pen-(N-Me-Arg)-Ser-Asp-Thr-Leu-Pen-Trp-(β-homoGlu)-(D-Lys); or
Pen-(N-Me-Arg)-Ser-Asp-Thr-Leu-Pen-Trp-Glu-(N-Me-D-Lys).

[0032a] In one aspect, there is provided a peptide comprising the amino acid sequence:

Pen-(N-Me-Arg)-Ser-Asp-Thr-Leu-Pen-Phe(4-tBu)-(β-homo-Glu)-(D-Lys).

[0032b] In another aspect, there is provided a peptide dimer compound comprising two peptides, each peptide comprising the amino acid sequence:

Pen-(N-Me-Arg)-Ser-Asp-Thr-Leu-Pen-Phe(4-tBu)-(β-homo-Glu)-(D-Lys),

or a pharmaceutically acceptable salt thereof,

[0033] wherein the two peptides are linked by a linker moiety.In certain embodiments, both subunits comprise the same sequences.In particular embodiments, the subunits are linked via DIG at their C-termini.

[0034] In particular embodiments the peptide dimer compound has one of the following structures:

[Ac-Pen-(N-Me-Arg)-Ser-Asp-Thr-Leu-Pen-Trp-(β-homoGlu)-(D-Lys)-OH]$_2$-DIG; or [Ac-Pen-(N-Me-Arg)-Ser-Asp-Thr-Leu-Pen-Trp-Glu-(N-Me-D-Lys)-OH]$_2$-DIG, wherein there is a disulfide bond between the two Pen residues in the monomer subunits.

[0035] In particular embodiments, the peptide dimer compound comprises an C-terminal OH.

[0036] In particular embodiments, the peptide dimer compound comprises N(alpha)methylation at one or more positions selected from the group consisting of Xaa^3, Xaa^5, Xaa^7-Xaa^9, and Xaa^{11}-Xaa^{13}; or acylation at one or more position selected from the group consisting of Xaa^1-Xaa^3 and Xaa^{11}-Xaa^{14}. In one embodiment, Xaa^1 and Xaa^2 are absent, and Xaa^3 is Ac. In one embodiment, one or more of Xaa^{11}, Xaa^{12} and Xaa^{13} is absent.

[0037] In a related embodiment, the present disclosure includes a peptide monomer compound of Formula (IV):

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 (IV))

[0038] or a pharmaceutically acceptable salt thereof,

[0039] wherein:

Xaa^1 is absent, Ac, or any amino acid;

Xaa^2 is absent, Ac, or any amino acid;

Xaa^3 is absent, Ac, or any amino acid;

Xaa^4 is any amino acid capable of binding to Xaa^{10};

Xaa^5 is selected from the group consisting of: N-Me-Arg, Arg, N-Me-Lys, Phe(4-guanidino), Phe(4-carbomylamino), Cit, Phe(4-NH_2), N-Me-homoArg, homoArg, Tyr, Dap, Dab, Arg-Me-sym, Arg-Me-asym, Cav, and His;

Xaa^6 is Ser, Gly, Thr, or Ile;

Xaa^7 is Asp, Asp(OMe), or N-Me-Asp;

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

[0050] In certain embodiments, Xaa^4 is Cys or Pen. In certain embodiments, Xaa^{10} is Cys or Pen. In certain embodiments, both Xaa^4 and Xaa^{10} are Cys or Pen. In certain embodiments, both Xaa^4 and Xaa^{10} are Pen.

[0051] In certain embodiments, the amino acid residue directly C-terminal to Xaa^{10} is an aromatic amino acid.

[0052] In certain embodiments, Xaa^{14} or the C-terminal amino acid does not comprise a free amine.

[0053] In certain embodiments, Xaa^{14} is absent or any amino acid with an amine side chain, Lys, D-Lys, N-Me-Lys, D-N-Me-Lys, Orn, Dab, Dap, HomoLys, D-Dap, D-Dab, or D-Orn. In certain embodiments, Xaa^{14} is Lys, D-Lys, N-Me-Lys, D-N-Me-Lys, Orn, Dab, Dap, HomoLys, D-Dap, D-Dab, or D-Orn.

[0054] In certain embodiments wherein the compound is peptide monomer, Xaa^{14} or the C-terminus comprises an NH_2 or an OH.

[0055] In certain embodiments, a free amine in the C-terminal amino acid of the peptide monomer is capped, e.g., with an acetyl group.

[0056] In certain embodiments, the peptide monomer comprises an intramolecular bind between Xaa^4 and Xaa^{10}. In particular embodiments, the intramolecular bond is a disulfide bond or a lactam bond.

[0057] For some embodiments, any of Xaa^1-Xaa^5, Xaa^7-Xaa^9, and Xaa^{11}-Xaa^{12} are N(alpha)Methylated. Xaa^5 may further be Arg-Me-sym or Arg-Me-asym, and Xaa^{11} may be O-Me-Tyr, N-Me-Lys(Ac), or 4-Me-Phe. In some instances, any of Xaa^1-Xaa^4, and Xaa^{11}-Xaa^{14} are acylated. For example, in some instances one or more residues at positions Xaa^1-Xaa^4, and Xaa^{11}-Xaa^{14} are acylated with an acylating organic compound selected from the group consisting of 2-me-Trifluorobutyl, Trifluoropentyl, Acetyl, Octonyl, Butyl, Pentyl, Hexyl, Palmityl, Lauryl, Oleoyl, and Lauryl, Trifluoromethyl butyric, cyclopentane carboxylic, cyclopropylacetic, 4-fluorobenzoic, 4-fluorophenyl acetic, 3-Phenylpropionic, tetrahedro-2H-pyran-4carboxylic, succinic acid, and glutaric acid. In some instances, small PEG (e.g., PEG4-PEG13) is used as spacer before acylations. In some instances Glu, IsoGlu, or Asp are used as spacer for acylations.

[0058] The disclosure also includes a peptide monomer compound of Formula (V):

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

Ac-Pen-(N-Me-Arg)-Ser-Asp-Thr-Leu-Pen-2-Nal-(β-homoGlu)-OH;

Ac-Pen-(N-Me-Arg)-Ser-Asp-Thr-Leu-Pen-1-Nal-(β-homoGlu)-OH;

Ac-Pen-(N-Me-Arg)-Ser-Asp-Thr-Leu-Pen-2-Nal-Glu-OH;

Ac-Pen-(N-Me-Arg)-Ser-Asp-Thr-Leu-Pen-Phe(4-tBu)-(β-homoGlu)-OH;

Ac-Pen-(N-Me-Arg)-Ser-Asp-Thr-Leu-Pen-Phe(4-tBu)-(β-homoGlu)-OH;

Ac-Pen-(N-Me-Arg)-Ser-Asp-Thr-Leu-Pen-Trp-(β-homoGlu)-OH;

Ac-Pen-(N-Me-Arg)-Ser-Asp-Thr-Leu-Pen-2-Nal-(β-homoGlu)-OH;

Ac-Pen-(N-Me-Arg)-Ser-Asp-Thr-Leu-Pen-1-Nal-(β-homoGlu)-OH;

Ac-Pen-(N-Me-Arg)-Ser-Asp-Thr-Leu-Pen-1-Nal-(β-homoGlu)-OH;

Ac-Pen-(N-Me-Arg)-Ser-Asp-Thr-Leu-Pen-Trp-(β-homoGlu)-OH;

Ac-Pen-(N-Me-Arg)-Ser-Asp-Thr-Leu-Pen-Trp-Glu-OH;

Ac-Pen-(N-Me-Arg)-Ser-Asp-Thr-Leu-Pen-Trp-(β-homoGlu)-NH_2;

Ac-Pen-(N-Me-Arg)-Ser-Asp-Thr-Leu-Pen-(Phe-(4-COOH)-(β-homoGlu)-NH_2;

Ac-Pen-(N-Me-Arg)-Ser-Asp-Thr-Leu-Pen-Trp-Glu-NH_2;

Ac-Pen-(N-Me-Arg)-Ser-Asp-Thr-Leu-Pen-2-Nal-(β-homoGlu)-NH_2;

Ac-Pen-(N-Me-Arg)-Ser-Asp-Thr-Leu-Pen-1-Nal-(β-homoGlu)-NH_2;

Ac-Pen-(N-Me-Arg)-Ser-Asp-Thr-Leu-Pen-2-Nal-Glu-NH_2;

Ac-Pen-(N-Me-Arg)-Ser-Asp-Thr-Leu-Pen-Phe(4-tBu)-(β-homoGlu)-NH_2;

Ac-Pen-(N-Me-Arg)-Ser-Asp-Thr-Leu-Pen-Phe(4-tBu)-(β-homoGlu)-NH_2;

Ac-Pen-(N-Me-Arg)-Ser-Asp-Thr-Leu-Pen-Trp-(β-homoGlu)-NH_2;

Ac-Pen-(N-Me-Arg)-Ser-Asp-Thr-Leu-Pen-2-Nal-(β-homoGlu)-NH_2;

Ac-Pen-(N-Me-Arg)-Ser-Asp-Thr-Leu-Pen-1-Nal-(β-homoGlu)-NH_2;

Ac-Pen-(N-Me-Arg)-Ser-Asp-Thr-Leu-Pen-1-Nal-(β-homoGlu)-NH_2;

Ac-Pen-(N-Me-Arg)-Ser-Asp-Thr-Leu-Pen-Trp-(β-homoGlu)-NH_2; or

Ac-Pen-(N-Me-Arg)-Ser-Asp-Thr-Leu-Pen-Trp-Glu-NH_2,

wherein in certain embodiments, there is a disulfide bond between the two Pen residues of the peptide or peptide monomer compound.

[0064] In certain embodiments, any of the compounds are detectably labeled.

[0065] The present disclosure further includes pharmaceutical composition comprising any of the compounds of the disclosure. In one embodiment, the pharmaceutical

composition comprises an enteric coating, wherein the enteric coating protects and releases the pharmaceutical composition within a subject's lower gastrointestinal system.

[0065a] In another aspect, there is provided a pharmaceutical composition comprising the peptide dimer compound as described herein and a pharmaceutically acceptable excipient, carrier or diluent.

[0066] The disclosure further includes a method for treating a subject afflicted with a condition that is associated with a biological function of an α4β7 integrin, the method comprising administering to the human an effective amount of a compound or compoids of the present disclosure.

[0066a] In another aspect, there is provided use of a pharmaceutical composition as described herein in the manufacture of a medicament for treating an inflammatory bowel disease in a subject, wherein the pharmaceutical composition comprises the peptide dimer compound as described herien and a pharmaceutically acceptable excipient, carrier or diluent, wherein peptide dimer compound comprises two peptides, each peptide comprising the amino acid sequence:Pen-(N-Me-Arg)-Ser-Asp-Thr-Leu-Pen-Phe(4-tBu)-(β-homo-Glu)-(D-Lys), or a pharmaceutically acceptable salt thereof, wherein the two peptides are linked by a linker moiety.

[0067] In certain embodiments, the condition is selected from the group consisting of Inflammatory Bowel Disease (IBD), ulcerative colitis, Crohn's disease, Celiac disease (*nontropical Sprue)*, enteropathy associated with seronegative arthropathies, microscopic colitis, collagenous colitis, eosinophilic gastroenteritis, radiotherapy, chemotherapy, pouchitis resulting after proctocolectomy and ileoanal anastomosis, gastrointestinal cancer, pancreatitis, insulin-dependent diabetes mellitus, mastitis, cholecystitis, cholangitis, pericholangitis, chronic bronchitis, chronic sinusitis, asthma, primary sclerosing cholangitis, human immunodeficiency virus (HIV) infection in the GI tract, eosinophilic asthma, eosinophilic esophagitis, gastritis, colitis, microscopic colitis, graft versus host disease, colitis associated with radio- or chemo-therapy, colitis associated with disorders of innate immunity as in leukocyte adhesion deficiency-1, chronic granulomatous disease, glycogen storage disease type 1b, Hermansky-Pudlak syndrome, Chediak-Higashi syndrome, and Wiskott-Aldrich Syndrome, or pouchitis resulting after proctocolectomy and ileoanal anastomosis and various forms of gastrointestinal cancer, osteoporosis, arthritis, multiple sclerosis, chronic pain, weight gain, and depression. In another embodiment, the condition is pancreatitis, insulin-dependent diabetes mellitus, mastitis, cholecystitis, cholangitis, pericholangitis, chronic bronchitis, chronic sinusitis, asthma or graft versus host disease. In particular embodiments, the condition is an inflammatory bowel disease, such as ulcerative colitis or Crohn's disease.

[0068] In particular embodiments, the peptide dimer compound or peptide monomer compound of the disclosure inhibits binding of α4β7 to MAdCAM, and/or selectively inhibits binding of α4β7 to MAdCAM.

[0069] In certain embodiments, the subject is a human.

[0070] In certain embodiments, the peptide dimer compound or peptide monomer compound is administered by a form of administration selected from the group consisting of

CLAIMS

1. A peptide comprising the amino acid sequence:
Pen-(N-Me-Arg)-Ser-Asp-Thr-Leu-Pen-Phe(4-tBu)-(β-homo-Glu)-(D-Lys).

2. The peptide of claim 1, comprising a disulfide bond between the two Pen amino acids.

3. The peptide of claim 1, further comprising a linker moiety.

4. The peptide of claim 3, wherein the linker moiety is bound to the D-Lys amino acid.

5. The peptide of claim 4, wherein the linker moiety is diglycolic acid (DIG).

6. The peptide of claim 1, wherein the N-terminus of the peptide is acylated.

7. The peptide of claim 1, comprising a C-terminal free amide.

8. The peptide of claim 1, comprising a disulfide bond between the two Pen amino acids and a linker moiety bound to the D-Lys amino acid, wherein the N-terminus of the peptide is acylated.

9. A peptide dimer compound comprising two peptides, each peptide comprising the amino acid sequence:
Pen-(N-Me-Arg)-Ser-Asp-Thr-Leu-Pen-Phe(4-tBu)-(β-homo-Glu)-(D-Lys),
or a pharmaceutically acceptable salt thereof,
wherein the two peptides are linked by a linker moiety.

10. The peptide dimer compound of claim 9, wherein the linker moiety is bound to the D-Lys amino acids of the two peptides.

11. The peptide dimer compound or pharmaceutically acceptable salt thereof of claim 9, wherein the linker moiety is diglycolic acid (DIG).

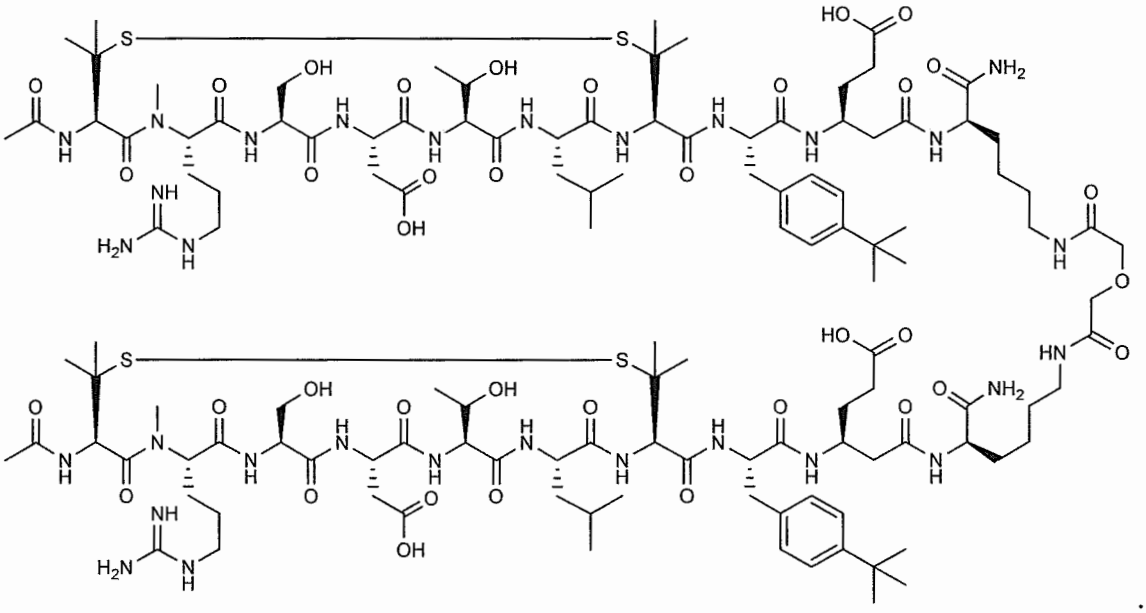
12. The peptide dimer compound or pharmaceutically acceptable salt thereof of claim 9, wherein each of the two peptides comprises a disulfide bond between the two Pen amino acids.

13. The peptide dimer compound or pharmaceutically acceptable salt thereof of claim 9, wherein the N-terminus of each of the two peptides is acylated.

14. The peptide dimer compound or pharmaceutically acceptable salt thereof of claim 9, wherein each of the two peptides comprises a C-terminal free amide.

15. The peptide dimer compound or pharmaceutically acceptable salt thereof of claim 9, where each of the two peptides comprises a disulfide bond between the two Pen amino acids and wherein the N-terminus of each of the two peptides is acylated.

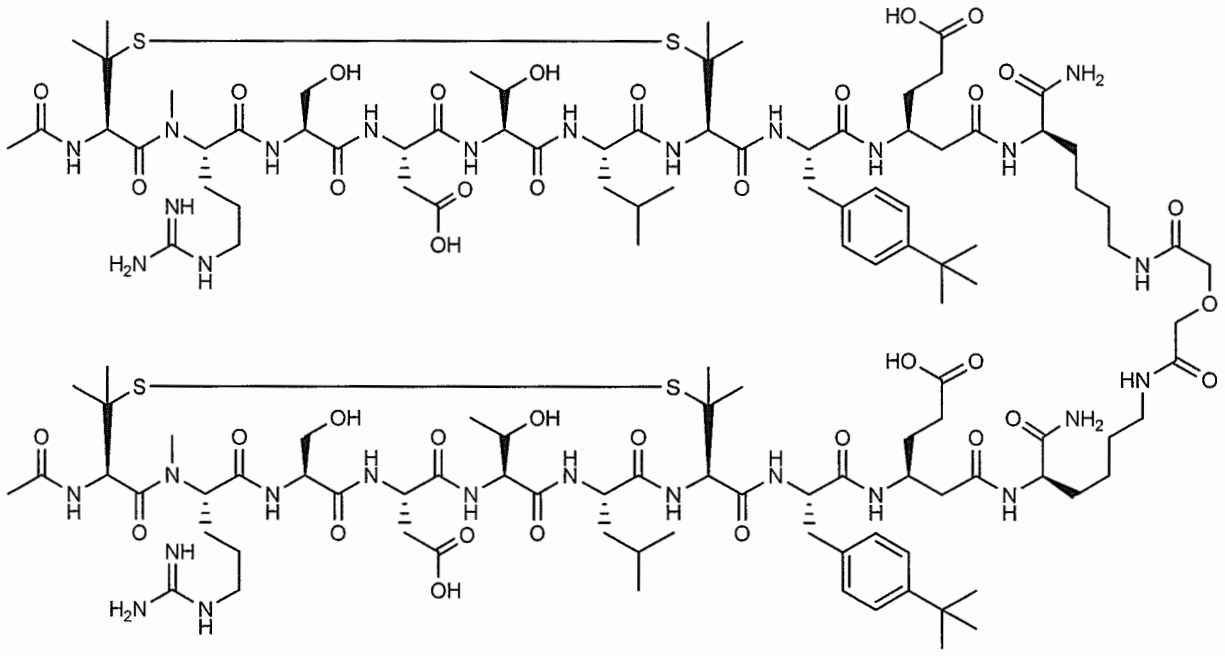
16. The peptide dimer compound or pharmaceutically acceptable salt thereof of claim 9, having the structure:



17. The peptide dimer compound or pharmaceutically acceptable salt thereof of claim 9, wherein the peptide dimer compound or pharmaceutically acceptable salt thereof is an acetate salt of the peptide dimer compound.

18. A pharmaceutical composition comprising the peptide dimer compound of claim 9 and a pharmaceutically acceptable excipient, carrier or diluent.

19. The pharmaceutical composition of claim 18, wherein the peptide dimer compound has the structure:



20. The pharmaceutical composition of claim 19, wherein the peptide dimer compound or pharmaceutically acceptable salt thereof is an acetate salt of the peptide dimer compound.

21. The pharmaceutical composition of claim 19, wherein the pharmaceutical composition comprises an enteric coating.

22. Use of a pharmaceutical composition of claim 18 in the manufacture of a medicament for treating an inflammatory bowel disease in a subject, wherein the pharmaceutical composition comprises the peptide dimer compound of claim 9 and a pharmaceutically acceptable excipient, carrier or diluent, wherein peptide dimer compound comprises two peptides, each peptide comprising the amino acid sequence:

Pen-(N-Me-Arg)-Ser-Asp-Thr-Leu-Pen-Phe(4-tBu)-(β-homo-Glu)-(D-Lys),

or a pharmaceutically acceptable salt thereof,

wherein the two peptides are linked by a linker moiety.

23. The use of claim 22, wherein the inflammatory bowel disease is ulcerative colitis.

24. The use of claim 22, wherein the pharmaceutical composition is to be administered orally.

25. The use of claim 22, wherein the linker moiety is bound to the D-Lys amino acids of the two peptides.

26. The use of claim 22, wherein the linker moiety is diglycolic acid (DIG).

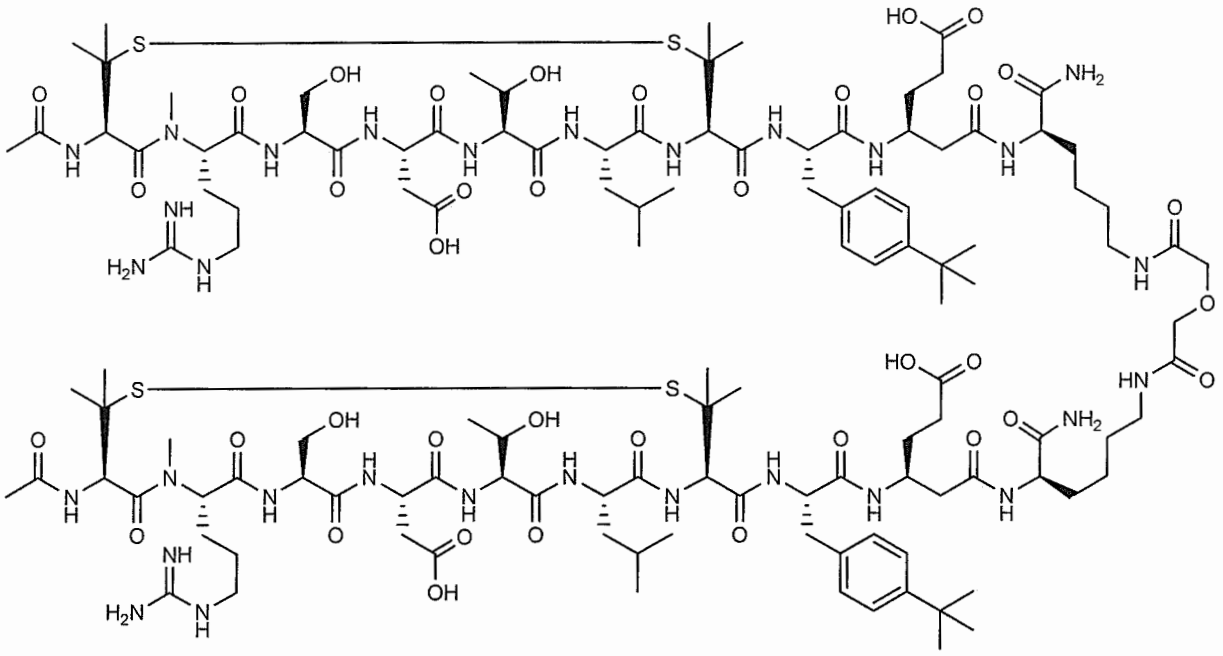
27. The use of claim 22, wherein each of the two peptides comprises a disulfide bond between the two Pen amino acids.

28. The use of claim 22, wherein the N-terminus of each of the two peptides is acylated.

29. The use of claim 22, wherein each of the two peptides comprises a C-terminal free amide.

30. The use of claim 22, where each of the two peptides comprises a disulfide bond between the two Pen amino acids and wherein the N-terminus of each of the two peptides is acylated.

31. The use of claim 22, wherein the peptide dimer compound or pharmaceutically acceptable salt thereof comprises the structure:



32. The use of claim 22, wherein the peptide dimer compound or pharmaceutically acceptable salt thereof is an acetate salt of the peptide dimer compound.

33. The use of claim 31, wherein the peptide dimer compound or pharmaceutically acceptable salt thereof is an acetate salt of the peptide dimer compound.

34. The use of claim 22, wherein the inflammatory bowel disease is Crohn's disease.

35. The use of claim 22, wherein the inflammatory bowel disease is microscopic colitis.