

**ANTIVIRAL STRUCTURALLY-STAPLED PARAMYXOVIRIDAE PEPTIDE-
CHOLESTEROL CONJUGATES AND USES THEREOF**

RELATED APPLICATIONS

[0001] This application claims priority to and benefit of U.S. Application No. 63/593,818, filed October 27, 2023, the entire contents of which are hereby incorporated by reference.

SEQUENCE LISTING

[0002] A Sequence Listing conforming to the rules of WIPO Standard ST.26 is hereby incorporated by reference. Said Sequence Listing has been filed as an electronic document via Patent Center encoded as XML in UTF-8 text. The electronic document, created on October 25, 2024, is entitled "406693-004USP1-201906_ST26.xml", and is 2,886,061 bytes in size.

TECHNICAL FIELD

[0003] This disclosure relates to modified Paramyxoviridae antiviral peptides alone or conjugated with a PEG(n)-cholesterol or cholesterol derivative to further optimize activity and methods for making and using such stapled peptide cholesterol conjugates in the prevention and treatment of a Paramyxoviridae infection.

BACKGROUND

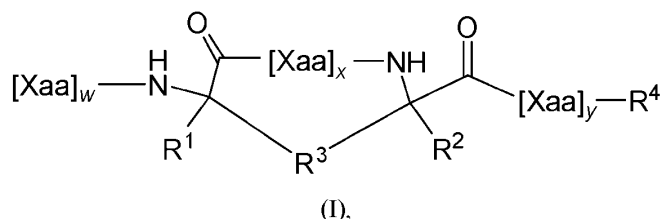
[0004] Paramyxoviridae contain a surface glycoprotein that undergoes a conformational change upon engagement with a host cell, resulting in formation of a bundle that fuses the host and viral membranes together enabling the formation of a fusion pore. This fusion pore allows the negative-stranded viral RNA to enter cells and initiate the replication of the virus. Although peptide-based inhibition of viral fusion processes is mechanistically feasible and clinically effective (e.g., enfuvirtide), the biophysical and pharmacologic liabilities of peptides, including loss of bioactive shape and rapid proteolysis in vivo (e.g., 100 mg self-injected twice daily), have limited broader application of this validated approach. Thus, new strategies for the prophylaxis and/or treatment of Paramyxoviridae infection are urgently required to effectively mitigate outbreaks.

SUMMARY

[0005] According to one aspect of the present disclosure, modified peptides having amino acids with side chains linked together (e.g., to form a staple) are provided for use in treating

Paramyxoviridae infection. For example, hydrocarbon-stapled and PEG(n)-cholesterol or cholesterol derivatized peptide inhibitors of Paramyxoviridae are disclosed. These structurally stabilized peptide inhibitors can be used to prevent and/or treat Paramyxoviridae infection such as Nipah virus, Hendra Virus, and Parainfluenza virus.

[0006] According to one aspect, this disclosure provides modified (e.g., structurally stabilized) peptides of Formula I:



or a pharmaceutically acceptable salt thereof, where the variables are as defined herein. Further description of additional collections of modified (e.g., structurally stabilized) peptides are described herein. The compounds may be part of a pharmaceutical composition comprising a pharmaceutically acceptable carrier.

[0007] Another aspect of the disclosure provides a method of treating or preventing a viral infection caused by a Paramyxoviridae virus. The method comprises administering to a patient in need thereof a therapeutically effective amount of a compound described herein, such as a compound of Formula I, to treat or prevent the viral infection.

BRIEF DESCRIPTION OF DRAWINGS

[0008] FIG. 1 shows a variety of non-natural amino acids containing olefinic sidechains that can be used to generate hydrocarbon stapled peptides bearing staples spanning i, i+3; i, i+4; and i, i+7 positions. The resultant structurally stabilized, alpha-helical peptides are shown.

[0009] FIG. 2 is an illustration of an exemplary approach to designing, synthesizing, and identifying optimal stapled peptide conjugates, including the generation of Ala scan, staple scan, and variable N- and C-terminal deletion, addition, and derivatization libraries for conjugation to PEG-thiocholesterol or PEG-cholesterol moieties.

[0010] FIG. 3 show a synthetic schema of the steps for on-resin derivatization of the stapled peptide sequence (VALDPIDI8IVLNKIXSDLEESKEWIRRSNKILDSI SEQ ID NO: 624) with a PEG-linked cholesterol moiety.

DETAILED DESCRIPTION

[0011] In some embodiments, provided are compositions and methods for peptide stabilizing technology (e.g., stapling) that recapitulates and fortifies the structure of bioactive helices, combined with a method for PEG(n)-cholesterol or thiocholesterol derivatization to generate an optimized and targeted prophylactic and therapeutic agent for prevention and/or treatment of Paramyxoviridae (e.g. Nipah virus, Hendra virus, Parainfluenza virus, Measles virus, Respiratory Syncytial Virus, Newcastle disease virus, etc.) infection. For example, by inserting “staples” into natural peptides, bioactive-helical structure can be restored and remarkable protease resistance can be conferred by burying the otherwise labile amide bonds at the core of the helical structure and/or restraining amide bonds in a manner that precludes their recognition and proteolysis by the body’s proteases.

[0012] The present disclosure provides modified peptides, pharmaceutical compositions, and their use in treating a viral infection. In some embodiments, a modified peptide is a structurally stabilized peptide. In some embodiments, a modified peptide is a stapled peptide. In some embodiments, a modified peptide is a peptide conjugate.

[0013] The practice of the present invention employs, unless otherwise indicated, conventional techniques of organic chemistry, pharmacology, molecular biology (including recombinant techniques), cell biology, biochemistry, and immunology. Such techniques are explained in the literature, such as in “Comprehensive Organic Synthesis” (B.M. Trost & I. Fleming, eds., 1991-1992); “Handbook of experimental immunology” (D.M. Weir & C.C. Blackwell, eds.); “Current protocols in molecular biology” (F.M. Ausubel *et al.*, eds., 1987, and periodic updates); and “Current protocols in immunology” (J.E. Coligan *et al.*, eds., 1991), each of which is herein incorporated by reference in its entirety.

Definitions

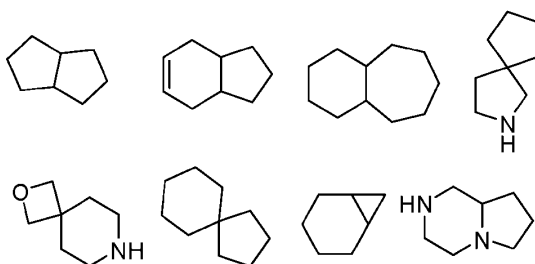
[0014] Compounds (i.e., modified peptides) of the present invention include those described generally herein, and are further illustrated by the classes, subclasses, and species disclosed herein. As used herein, the following definitions shall apply unless otherwise indicated. These definitions apply regardless of whether a term is used by itself or in combination with other terms, unless otherwise indicated. Hence, the definition of “alkyl” applies to “alkyl” as well as the “alkyl” portions of “-O-alkyl” etc. For purposes of this invention, the chemical elements are identified in accordance with the Periodic Table of the Elements, CAS version, Handbook of Chemistry and Physics, 75th Ed. Additionally, general principles of organic chemistry are described in “Organic Chemistry”, Thomas Sorrell,

University Science Books, Sausalito: 1999, and “March’s Advanced Organic Chemistry”, 5th Ed., Ed.: Smith, M.B. and March, J., John Wiley & Sons, New York: 2001, the entire contents of which are hereby incorporated by reference.

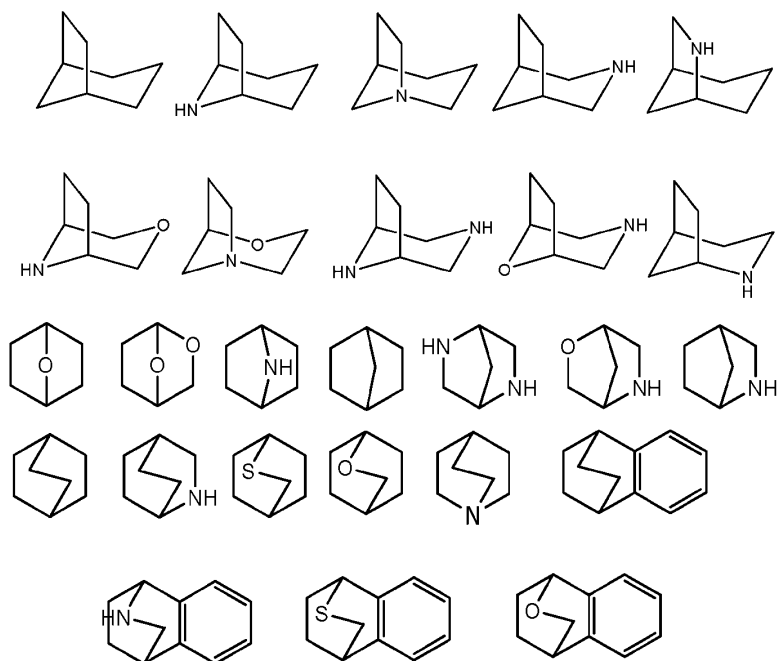
[0015] The term “aliphatic” or “aliphatic group”, as used herein, means a straight-chain (i.e., unbranched) or branched, substituted or unsubstituted hydrocarbon chain that is completely saturated or that contains one or more units of unsaturation, or a monocyclic hydrocarbon or bicyclic hydrocarbon that is completely saturated or that contains one or more units of unsaturation, but which is not aromatic (also referred to herein as “cycloaliphatic”), that has a single point of attachment to the rest of the molecule. Unless otherwise specified, aliphatic groups contain 1-6 aliphatic carbon atoms. In some embodiments, aliphatic groups contain 1-5 aliphatic carbon atoms. In other embodiments, aliphatic groups contain 1-4 aliphatic carbon atoms. In still other embodiments, aliphatic groups contain 1-3 aliphatic carbon atoms, and in yet other embodiments, aliphatic groups contain 1-2 aliphatic carbon atoms. In some embodiments, “cycloaliphatic” refers to a monocyclic C₃-C₆ hydrocarbon that is completely saturated or that contains one or more units of unsaturation, but which is not aromatic, that has a single point of attachment to the rest of the molecule. Suitable aliphatic groups include, but are not limited to, linear or branched, substituted or unsubstituted alkyl, alkenyl, alkynyl groups and hybrids thereof such as (cycloalkyl)alkyl, (cycloalkenyl)alkyl or (cycloalkyl)alkenyl.

[0016] As used herein, the term “bicyclic ring” or “bicyclic ring system” refers to any bicyclic ring system, i.e., carbocyclic or heterocyclic, saturated or having one or more units of unsaturation, having one or more atoms in common between the two rings of the ring system. Thus, the term includes any permissible ring fusion, such as *ortho*-fused or spirocyclic. As used herein, the term “heterobicyclic” is a subset of “bicyclic” that requires that one or more heteroatoms are present in one or both rings of the bicycle. Such heteroatoms may be present at ring junctions and are optionally substituted, and may be selected from nitrogen (including N-oxides), oxygen, sulfur (including oxidized forms such as sulfones and sulfonates), phosphorus (including oxidized forms such as phosphates), boron, etc. In some embodiments, a bicyclic group has 7-12 ring members and 0-4 heteroatoms independently selected from nitrogen, oxygen, or sulfur. As used herein, the term “bridged bicyclic” refers to any bicyclic ring system, i.e., carbocyclic or heterocyclic, saturated or partially unsaturated, having at least one bridge. As defined by IUPAC, a “bridge” is an unbranched chain of atoms or an atom or a valence bond connecting two bridgeheads, where a “bridgehead” is any skeletal atom of the ring system which is bonded to three or more skeletal atoms (excluding hydrogen). In some

embodiments, a bridged bicyclic group has 7-12 ring members and 0-4 heteroatoms independently selected from nitrogen, oxygen, or sulfur. Such bridged bicyclic groups are well known in the art and include those groups set forth below where each group is attached to the rest of the molecule at any substitutable carbon or nitrogen atom. Unless otherwise specified, a bridged bicyclic group is optionally substituted with one or more substituents as set forth for aliphatic groups. Additionally or alternatively, any substitutable nitrogen of a bridged bicyclic group is optionally substituted. Exemplary bicyclic rings include:



Exemplary bridged bicyclics include:



[0017] The term “heteroatom” means one or more of oxygen, sulfur, nitrogen, phosphorus, or silicon (including, any oxidized form of nitrogen, sulfur, phosphorus, or silicon; the quaternized form of any basic nitrogen or; a substitutable nitrogen of a heterocyclic ring, for

example N (as in 3,4-dihydro-2*H*-pyrrolyl), NH (as in pyrrolidinyl) or NR⁺ (as in N-substituted pyrrolidinyl)).

[0018] The term “unsaturated,” as used herein, means that a moiety has one or more units of unsaturation.

[0019] As used herein, the term “bivalent C₁₋₈ (or C₁₋₆) saturated or unsaturated, straight or branched, hydrocarbon chain”, refers to bivalent alkylene, alkenylene, and alkynylene chains that are straight or branched as defined herein.

[0020] The term “alkylene” refers to a bivalent alkyl group. An “alkylene chain” is a polymethylene group, i.e., -(CH₂)_n-, wherein n is a positive integer, preferably from 1 to 6, from 1 to 4, from 1 to 3, from 1 to 2, or from 2 to 3. A substituted alkylene chain is a polymethylene group in which one or more methylene hydrogen atoms are replaced with a substituent. Suitable substituents include those described below for a substituted aliphatic group.

[0021] The term “-(C₀ alkylene)-” refers to a bond. Accordingly, the term “-(C₀₋₃ alkylene)-” encompasses a bond (i.e., C₀) and a -(C₁₋₃ alkylene)- group.

[0022] The term “alkenylene” refers to a bivalent alkenyl group. A substituted alkenylene chain is a polymethylene group containing at least one double bond in which one or more hydrogen atoms are replaced with a substituent. Suitable substituents include those described below for a substituted aliphatic group.

[0023] The term “halogen” or “halo” means F, Cl, Br, or I.

[0024] The term “aryl” used alone or as part of a larger moiety as in “aralkyl,” “aralkoxy,” or “aryloxyalkyl,” refers to monocyclic or bicyclic ring systems having a total of five to fourteen ring members, wherein at least one ring in the system is aromatic and wherein each ring in the system contains 3 to 7 ring members. The term “aryl” may be used interchangeably with the term “aryl ring.” In certain embodiments of the present invention, “aryl” refers to an aromatic ring system which includes, but not limited to, phenyl, biphenyl, naphthyl, anthracyl and the like, which may bear one or more substituents. Also included within the scope of the term “aryl,” as it is used herein, is a group in which an aromatic ring is fused to one or more non-aromatic rings, such as indanyl, phthalimidyl, naphthimidyl, phenanthridinyl, or tetrahydronaphthyl, and the like. The term “haloaryl” refers to an aryl group that is substituted with at least one halogen. Exemplary haloaryl groups include chlorophenyl (e.g., 3-chlorophenyl, 4-chlorophenyl), fluorophenyl, and the like. The term “phenylene” refers to a bivalent phenyl group.

[0025] The terms “heteroaryl” and “heteroar-,” used alone or as part of a larger moiety, e.g., “heteroaralkyl,” or “heteroaralkoxy,” refer to groups having 5 to 10 ring atoms, preferably 5, 6, or 9 ring atoms; having 6, 10, or 14 π electrons shared in a cyclic array; and having, in addition to carbon atoms, from one to five heteroatoms. The term “heteroatom” refers to nitrogen, oxygen, or sulfur, and includes any oxidized form of nitrogen or sulfur, and any quaternized form of a basic nitrogen. Heteroaryl groups include, without limitation, thienyl, furanyl, pyrrolyl, imidazolyl, pyrazolyl, triazolyl, tetrazolyl, oxazolyl, isoxazolyl, oxadiazolyl, thiazolyl, isothiazolyl, thiadiazolyl, pyridyl, pyridazinyl, pyrimidinyl, pyrazinyl, indolizynyl, purinyl, naphthyridinyl, and pteridinyl. The terms “heteroaryl” and “heteroar-”, as used herein, also include groups in which a heteroaromatic ring is fused to one or more aryl, cycloaliphatic, or heterocyclyl rings, where unless otherwise specified, the radical or point of attachment is on the heteroaromatic ring or on one of the rings to which the heteroaromatic ring is fused. Nonlimiting examples include indolyl, isoindolyl, benzothienyl, benzofuranyl, dibenzofuranyl, indazolyl, benzimidazolyl, benzthiazolyl, quinolyl, isoquinolyl, cinnolynyl, phthalazinyl, quinazolinyl, quinoxalinyl, 4*H*-quinolizynyl, carbazolyl, acridinyl, phenazinyl, phenothiazinyl, phenoxazinyl, tetrahydroquinolynyl, and tetrahydroisoquinolynyl. A heteroaryl group may be mono- or bicyclic. The term “heteroaryl” may be used interchangeably with the terms “heteroaryl ring,” “heteroaryl group,” or “heteroaromatic,” any of which terms include rings that are optionally substituted. The term “heteroaralkyl” refers to an alkyl group substituted by a heteroaryl, wherein the alkyl and heteroaryl portions independently are optionally substituted. The term “haloheteroaryl” refers to a heteroaryl group that is substituted with at least one halogen. Exemplary haloheteroaryl groups include chloropyridine, fluoropyridine, chloropyrazole, fluoropyrazole, and the like. The term “heteroarylene” refers to a bivalent heteroaryl group. Similarly, the terms “pyrazolylene”, “imidazolylene”, and “pyrrolylene”, respectively refer to bivalent pyrazolyl, imidazolyl, and pyrrolyl groups. Similarly, the terms “pyridazinylene,” “pyrimidinylene,” “pyrazinylene,” and “pyridinylene,” respectively refer to bivalent pyridazinyl, pyrimidinyl, pyrazinyl, and pyridinyl groups.

[0026] As used herein, the terms “heterocycle,” “heterocyclyl,” “heterocyclic radical,” and “heterocyclic ring” are used interchangeably and refer to a stable 4- to 7-membered monocyclic or 7-10-membered bicyclic heterocyclic moiety that is either saturated or partially unsaturated, and having, in addition to carbon atoms, one or more, preferably one to four, heteroatoms, as defined above. When used in reference to a ring atom of a heterocycle, the term “nitrogen” includes a substituted nitrogen. As an example, in a saturated or partially unsaturated

ring having 0–3 heteroatoms selected from oxygen, sulfur or nitrogen, the nitrogen may be N (as in 3,4-dihydro-2*H*-pyrrolyl), NH (as in pyrrolidinyl), or ⁺NR (as in *N*-substituted pyrrolidinyl).

[0027] A heterocyclic ring can be attached to its pendant group at any heteroatom or carbon atom that results in a stable structure and any of the ring atoms can be optionally substituted. Examples of such saturated or partially unsaturated heterocyclic radicals include, without limitation, tetrahydrofuranyl, tetrahydrothiophenyl, pyrrolidinyl, piperidinyl, pyrrolinyl, tetrahydroquinolinyl, tetrahydroisoquinolinyl, decahydroquinolinyl, oxazolidinyl, piperazinyl, dioxanyl, dioxolanyl, diazepinyl, oxazepinyl, thiazepinyl, morpholinyl, 2-oxa-6-azaspiro[3.3]heptane, and quinuclidinyl. The terms “heterocycle,” “heterocyclyl,” “heterocyclyl ring,” “heterocyclic group,” “heterocyclic moiety,” and “heterocyclic radical,” are used interchangeably herein, and also include groups in which a heterocyclyl ring is fused to one or more aryl, heteroaryl, or cycloaliphatic rings, such as indolinyl, 3*H*-indolyl, chromanyl, phenanthridinyl, or tetrahydroquinolinyl. A heterocyclyl group may be mono- or bicyclic. The term “heterocyclylalkyl” refers to an alkyl group substituted by a heterocyclyl, wherein the alkyl and heterocyclyl portions independently are optionally substituted. The term “heterocyclylene” refers to a bivalent heterocyclyl group. The terms “piperidinylene,” “piperazinylene,” and “azetidylene”, respectively refer to bivalent piperidinyl, piperazinyl, and azetidiny groups.

[0028] As used herein, the term “heterocycloalkyl” refers to a saturated heterocyclyl. The term “heterocycloalkylene” refers to a bivalent heterocycloalkyl group.

[0029] As used herein, the term “partially unsaturated” refers to a ring moiety that includes at least one double or triple bond. The term “partially unsaturated” is intended to encompass rings having multiple sites of unsaturation, but is not intended to include aryl or heteroaryl moieties, as herein defined.

[0030] As described herein, compounds of the invention may contain “optionally substituted” moieties. In general, the term “substituted,” whether preceded by the term “optionally” or not, means that one or more hydrogens of the designated moiety are replaced with a suitable substituent. Unless otherwise indicated, an “optionally substituted” group may have a suitable substituent at each substitutable position of the group, and when more than one position in any given structure may be substituted with more than one substituent selected from a specified group, the substituent may be either the same or different at every position. Combinations of substituents envisioned by this invention are preferably those that result in the formation of stable or chemically feasible compounds. The term “stable,” as used herein, refers

to compounds that are not substantially altered when subjected to conditions to allow for their production, detection, and, in certain embodiments, their recovery, purification, and use for one or more of the purposes disclosed herein.

[0031] Suitable monovalent substituents on a substitutable carbon atom of an “optionally substituted” group are independently halogen; $-(CH_2)_{0-4}R^\circ$; $-(CH_2)_{0-4}OR^\circ$; $-O(CH_2)_{0-4}R^\circ$; $-O-(CH_2)_{0-4}C(O)OR^\circ$; $-(CH_2)_{0-4}CH(OR^\circ)_2$; $-(CH_2)_{0-4}SR^\circ$; $-(CH_2)_{0-4}Ph$, which may be substituted with R° ; $-(CH_2)_{0-4}O(CH_2)_{0-1}Ph$ which may be substituted with R° ; $-CH=CHPh$, which may be substituted with R° ; $-(CH_2)_{0-4}O(CH_2)_{0-1}pyridyl$ which may be substituted with R° ; $-NO_2$; $-CN$; $-N_3$; $-(CH_2)_{0-4}N(R^\circ)_2$; $-(CH_2)_{0-4}N(R^\circ)C(O)R^\circ$; $-N(R^\circ)C(S)R^\circ$; $-(CH_2)_{0-4}N(R^\circ)C(O)NR^\circ_2$; $-N(R^\circ)C(S)NR^\circ_2$; $-(CH_2)_{0-4}N(R^\circ)C(O)OR^\circ$; $-N(R^\circ)N(R^\circ)C(O)R^\circ$; $-N(R^\circ)N(R^\circ)C(O)NR^\circ_2$; $-N(R^\circ)N(R^\circ)C(O)OR^\circ$; $-(CH_2)_{0-4}C(O)R^\circ$; $-C(S)R^\circ$; $-(CH_2)_{0-4}C(O)OR^\circ$; $-(CH_2)_{0-4}C(O)SR^\circ$; $-(CH_2)_{0-4}C(O)OSiR^\circ_3$; $-(CH_2)_{0-4}OC(O)R^\circ$; $-OC(O)(CH_2)_{0-4}SR^\circ$; $-SC(S)SR^\circ$; $-(CH_2)_{0-4}SC(O)R^\circ$; $-(CH_2)_{0-4}C(O)NR^\circ_2$; $-C(S)NR^\circ_2$; $-C(S)SR^\circ$; $-SC(S)SR^\circ$; $-(CH_2)_{0-4}OC(O)NR^\circ_2$; $-C(O)N(OR^\circ)R^\circ$; $-C(O)C(O)R^\circ$; $-C(O)CH_2C(O)R^\circ$; $-C(NOR^\circ)R^\circ$; $-(CH_2)_{0-4}SSR^\circ$; $-(CH_2)_{0-4}S(O)_2R^\circ$; $-(CH_2)_{0-4}S(O)_2OR^\circ$; $-(CH_2)_{0-4}OS(O)_2R^\circ$; $-S(O)_2NR^\circ_2$; $-(CH_2)_{0-4}S(O)R^\circ$; $-N(R^\circ)S(O)_2NR^\circ_2$; $-N(R^\circ)S(O)_2R^\circ$; $-N(OR^\circ)R^\circ$; $-C(NH)NR^\circ_2$; $-P(O)(OR^\circ)R^\circ$; $-P(O)R^\circ_2$; $-OP(O)R^\circ_2$; $-OP(O)(OR^\circ)_2$; $-SiR^\circ_3$; $-(C_{1-4}$ straight or branched alkylene) $O-N(R^\circ)_2$; or $-(C_{1-4}$ straight or branched alkylene) $C(O)O-N(R^\circ)_2$, wherein each R° may be substituted as defined below and is independently hydrogen, C_{1-6} aliphatic, $-CH_2Ph$, $-O(CH_2)_{0-1}Ph$, $-CH_2$ -(5-6 membered heteroaryl ring), or a 3-6-membered saturated, partially unsaturated, or aryl ring having 0-4 heteroatoms independently selected from nitrogen, oxygen, or sulfur, or, notwithstanding the definition above, two independent occurrences of R° , taken together with their intervening atom(s), form a 3-12-membered saturated, partially unsaturated, or aryl mono- or bicyclic ring having 0-4 heteroatoms independently selected from nitrogen, oxygen, or sulfur, which may be substituted as defined below.

[0032] Suitable monovalent substituents on R° (or the ring formed by taking two independent occurrences of R° together with their intervening atoms), are independently halogen, $-(CH_2)_{0-2}R^\bullet$, $-(haloR^\bullet)$, $-(CH_2)_{0-2}OH$, $-(CH_2)_{0-2}OR^\bullet$, $-(CH_2)_{0-2}CH(OR^\bullet)_2$, $-O(haloR^\bullet)$, $-CN$, $-N_3$, $-(CH_2)_{0-2}C(O)R^\bullet$, $-(CH_2)_{0-2}C(O)OH$, $-(CH_2)_{0-2}C(O)OR^\bullet$, $-(CH_2)_{0-2}SR^\bullet$, $-(CH_2)_{0-2}SH$, $-(CH_2)_{0-2}NH_2$, $-(CH_2)_{0-2}NHR^\bullet$, $-(CH_2)_{0-2}NR^\bullet_2$, $-NO_2$, $-SiR^\bullet_3$, $-OSiR^\bullet_3$, $-C(O)SR^\bullet$, $-(C_{1-4}$ straight or branched alkylene) $C(O)OR^\bullet$, or $-SSR^\bullet$.

wherein each $R^\bullet$ is unsubstituted or where preceded by “halo” is substituted only with one or more halogens, and is independently selected from C_{1-4} aliphatic, $-CH_2Ph$, $-O(CH_2)_{0-1}Ph$, or a 5–6–membered saturated, partially unsaturated, or aryl ring having 0–4 heteroatoms independently selected from nitrogen, oxygen, or sulfur. Suitable divalent substituents on a saturated carbon atom of R° include $=O$ and $=S$.

[0033] Suitable divalent substituents on a saturated carbon atom of an “optionally substituted” group include the following: $=O$, $=S$, $=NNR^{*2}$, $=NNHC(O)R^*$, $=NNHC(O)OR^*$, $=NNHS(O)_2R^*$, $=NR^*$, $=NOR^*$, $-O(C(R^{*2}))_{2-3}O-$, or $-S(C(R^{*2}))_{2-3}S-$, wherein each independent occurrence of R^* is selected from hydrogen, C_{1-6} aliphatic which may be substituted as defined below, or an unsubstituted 5–6–membered saturated, partially unsaturated, or aryl ring having 0–4 heteroatoms independently selected from nitrogen, oxygen, or sulfur. Suitable divalent substituents that are bound to vicinal substitutable carbons of an “optionally substituted” group include: $-O(CR^{*2})_{2-3}O-$, wherein each independent occurrence of R^* is selected from hydrogen, C_{1-6} aliphatic which may be substituted as defined below, or an unsubstituted 5–6–membered saturated, partially unsaturated, or aryl ring having 0–4 heteroatoms independently selected from nitrogen, oxygen, or sulfur.

[0034] Suitable substituents on the aliphatic group of R^* include halogen, $-R^\bullet$, $-(haloR^\bullet)$, $-OH$, $-OR^\bullet$, $-O(haloR^\bullet)$, $-CN$, $-C(O)OH$, $-C(O)OR^\bullet$, $-NH_2$, $-NHR^\bullet$, $-NR^{*2}$, or $-NO_2$, wherein each $R^\bullet$ is unsubstituted or where preceded by “halo” is substituted only with one or more halogens, and is independently C_{1-4} aliphatic, $-CH_2Ph$, $-O(CH_2)_{0-1}Ph$, or a 5–6–membered saturated, partially unsaturated, or aryl ring having 0–4 heteroatoms independently selected from nitrogen, oxygen, or sulfur.

[0035] Suitable substituents on a substitutable nitrogen of an “optionally substituted” group include $-R^\dagger$, $-NR^{\dagger2}$, $-C(O)R^\dagger$, $-C(O)OR^\dagger$, $-C(O)C(O)R^\dagger$, $-C(O)CH_2C(O)R^\dagger$, $-S(O)_2R^\dagger$, $-S(O)_2NR^{\dagger2}$, $-C(S)NR^{\dagger2}$, $-C(NH)NR^{\dagger2}$, or $-N(R^\dagger)S(O)_2R^\dagger$; wherein each $R^\dagger$ is independently hydrogen, C_{1-6} aliphatic which may be substituted as defined below, unsubstituted $-OPh$, or an unsubstituted 5–6–membered saturated, partially unsaturated, or aryl ring having 0–4 heteroatoms independently selected from nitrogen, oxygen, or sulfur, or, notwithstanding the definition above, two independent occurrences of $R^\dagger$, taken together with their intervening atom(s) form an unsubstituted 3–12–membered saturated, partially unsaturated, or aryl mono- or bicyclic ring having 0–4 heteroatoms independently selected from nitrogen, oxygen, or sulfur.

[0036] Suitable substituents on the aliphatic group of $R^{\dagger}$ are independently halogen, $-R^{\bullet}$, $-(\text{halo}R^{\bullet})$, $-\text{OH}$, $-\text{OR}^{\bullet}$, $-\text{O}(\text{halo}R^{\bullet})$, $-\text{CN}$, $-\text{C}(\text{O})\text{OH}$, $-\text{C}(\text{O})\text{OR}^{\bullet}$, $-\text{NH}_2$, $-\text{NHR}^{\bullet}$, $-\text{NR}^{\bullet}_2$, or $-\text{NO}_2$, wherein each $R^{\bullet}$ is unsubstituted or where preceded by "halo" is substituted only with one or more halogens, and is independently C_{1-4} aliphatic, $-\text{CH}_2\text{Ph}$, $-\text{O}(\text{CH}_2)_{0-1}\text{Ph}$, or a 5–6-membered saturated, partially unsaturated, or aryl ring having 0–4 heteroatoms independently selected from nitrogen, oxygen, or sulfur.

[0037] As used herein, the term "pharmaceutically acceptable salt" refers to those salts which are, within the scope of sound medical judgment, suitable for use in contact with the tissues of humans and lower animals without undue toxicity, irritation, allergic response and the like, and are commensurate with a reasonable benefit/risk ratio. Pharmaceutically acceptable salts are well known in the art. For example, S. M. Berge *et al.*, describe pharmaceutically acceptable salts in detail in J. Pharmaceutical Sciences, 1977, 66, 1–19, incorporated herein by reference.

[0038] Unless otherwise stated, structures depicted herein are also meant to include all isomeric (e.g., enantiomeric, diastereomeric, and geometric (or conformational)) forms of the structure; for example, the R and S configurations for each asymmetric center, Z and E double bond isomers, and Z and E conformational isomers. Therefore, single stereochemical isomers as well as enantiomeric, diastereomeric, and geometric (or conformational) mixtures of the present compounds are within the scope of the invention. Unless otherwise stated, all tautomeric forms of the compounds of the invention are within the scope of the invention. The invention includes compounds that differ only in the presence of one or more isotopically enriched atoms. For example, compounds having the present structures including the replacement of hydrogen by deuterium or tritium, or the replacement of a carbon by a ^{13}C - or ^{14}C -enriched carbon are within the scope of this invention. Such compounds are useful, for example, as analytical tools, as probes in biological assays, or as therapeutic agents in accordance with the present invention.

[0039] Diastereomeric mixtures can be separated into their individual diastereomers on the basis of their physical chemical differences by methods known to those skilled in the art, such as, for example, by chromatography and/or fractional crystallization. Enantiomers can be separated by converting the enantiomeric mixture into a diastereomeric mixture by reaction with an appropriate optically active compound (e.g., chiral auxiliary such as a chiral alcohol or Mosher's acid chloride), separating the diastereomers and converting (e.g., hydrolyzing) the individual diastereomers to the corresponding pure enantiomers. Alternatively, a particular enantiomer of a compound of the present invention may be prepared by asymmetric synthesis.

Still further, where the molecule contains a basic functional group (such as amino) or an acidic functional group (such as carboxylic acid) diastereomeric salts are formed with an appropriate optically-active acid or base, followed by resolution of the diastereomers thus formed by fractional crystallization or chromatographic means known in the art, and subsequent recovery of the pure enantiomers.

[0040] Individual stereoisomers of the compounds of the invention may, for example, be substantially free of other isomers, or may be admixed, for example, as racemates or with all other, or other selected, stereoisomers. Chiral center(s) in a compound of the present invention can have the *S* or *R* configuration as defined by the *IUPAC* 1974 Recommendations. Further, to the extent a compound described herein may exist as a atropisomer (*e.g.*, substituted biaryls), all forms of such atropisomer are considered part of this invention.

[0041] Chemical names, common names, and chemical structures may be used interchangeably to describe the same structure. If a chemical compound is referred to using both a chemical structure and a chemical name, and an ambiguity exists between the structure and the name, the structure predominates. It should also be noted that any carbon as well as heteroatom with unsatisfied valences in the text, schemes, examples and tables herein is assumed to have the sufficient number of hydrogen atom(s) to satisfy the valences.

[0042] The terms “a” and “an” as used herein mean “one or more” and include the plural unless the context is inappropriate.

[0043] The term “alkyl” refers to a saturated straight or branched hydrocarbon, such as a straight or branched group of 1-12, 1-10, or 1-6 carbon atoms, referred to herein as C₁-C₁₂ alkyl, C₁-C₁₀ alkyl, and C₁-C₆ alkyl, respectively. Exemplary alkyl groups include, but are not limited to, methyl, ethyl, propyl, isopropyl, 2-methyl-1-propyl, 2-methyl-2-propyl, 2-methyl-1-butyl, 3-methyl-1-butyl, 2-methyl-3-butyl, 2,2-dimethyl-1-propyl, 2-methyl-1-pentyl, 3-methyl-1-pentyl, 4-methyl-1-pentyl, 2-methyl-2-pentyl, 3-methyl-2-pentyl, 4-methyl-2-pentyl, 2,2-dimethyl-1-butyl, 3,3-dimethyl-1-butyl, 2-ethyl-1-butyl, butyl, isobutyl, t-butyl, pentyl, isopentyl, neopentyl, hexyl, heptyl, octyl, etc.

[0044] The term “cycloalkyl” refers to a monovalent saturated cyclic, bicyclic, or bridged cyclic (*e.g.*, adamantyl) hydrocarbon group of 3-12, 3-8, 4-8, or 4-6 carbons, referred to herein, *e.g.*, as “C₃-C₆ cycloalkyl,” derived from a cycloalkane. Exemplary cycloalkyl groups include cyclohexyl, cyclopentyl, cyclobutyl, and cyclopropyl. The term “cycloalkylene” refers to a bivalent cycloalkyl group.

[0045] The term “haloalkyl” refers to an alkyl group that is substituted with at least one halogen. Exemplary haloalkyl groups include -CH₂F, -CHF₂, -CF₃, -CH₂CF₃, -CF₂CF₃, and

the like. The term “chloroalkyl” refers to an alkyl group that is substituted with at least one chloro. The term “bromoalkyl” refers to an alkyl group that is substituted with at least one bromo. The term “haloalkylene” refers to a bivalent haloalkyl group.

[0046] The term “hydroxyalkyl” refers to an alkyl group that is substituted with at least one hydroxyl. Exemplary hydroxyalkyl groups include $-\text{CH}_2\text{CH}_2\text{OH}$, $-\text{C}(\text{H})(\text{OH})\text{CH}_3$, $-\text{CH}_2\text{C}(\text{H})(\text{OH})\text{CH}_2\text{CH}_2\text{OH}$, and the like.

[0047] The term “heteroalkyl” refers to an alkyl group in which one or more carbon atoms has been replaced by a heteroatom (e.g., N, O, or S). Exemplary heteroalkyl groups include $-\text{OCH}_3$, $-\text{CH}_2\text{OCH}_3$, $-\text{CH}_2\text{CH}_2\text{N}(\text{CH}_3)_2$, and $-\text{CH}_2\text{CH}_2\text{OH}$. The heteroalkyl group may contain, for example, from 2-4, 2-6, or 2-8 atoms selected from the group consisting of carbon and a heteroatom (e.g., N, O, or S). The phrase 3-8 membered heteroalkyl refers to a heteroalkyl group having from 3 to 8 atoms selected from the group consisting of carbon and a heteroatom. The term “heteroalkylene” refers to a bivalent heteroalkyl group.

[0048] The terms “alkenyl” and “alkynyl” are art-recognized and refer to unsaturated aliphatic groups analogous in length and possible substitution to the alkyls described above, but that contain at least one double or triple bond respectively. The term “haloalkenyl” refers to an alkenyl group that is substituted with at least one halogen. The term “fluoroalkenyl” refers to an alkenyl group that is substituted with at least one fluoro. The term “nitroalkenyl” refers to an alkenyl group that is substituted with at least one nitro.

[0049] The terms “alkoxyl” or “alkoxy” are art-recognized and refer to an alkyl group, as defined above, having an oxygen radical attached thereto. Representative alkoxyl groups include methoxy, ethoxy, propyloxy, *tert*-butoxy and the like. The term “haloalkoxyl” refers to an alkoxyl group that is substituted with at least one halogen. Exemplary haloalkoxyl groups include $-\text{OCH}_2\text{F}$, $-\text{OCHF}_2$, $-\text{OCF}_3$, $-\text{OCH}_2\text{CF}_3$, $-\text{OCF}_2\text{CF}_3$, and the like.

[0050] The symbol “ $\sim$ ” indicates a point of attachment.

[0051] When any substituent or variable occurs more than one time in any constituent or the compound of the invention, its definition on each occurrence is independent of its definition at every other occurrence, unless otherwise indicated.

[0052] As used herein, the terms “subject” and “patient” are used interchangeable and refer to organisms to be treated by the methods of the present invention. Such organisms preferably include, but are not limited to, mammals (e.g., murines, simians, equines, bovines, porcines, canines, felines, and the like), and most preferably includes humans.

[0053] The term “ IC_{50} ” is art-recognized and refers to the concentration of a compound that is required to achieve 50% inhibition of the target.

[0054] As used herein, the term “treating” includes any effect, *e.g.*, lessening, reducing, modulating, ameliorating or eliminating, that results in the improvement of the condition, disease, disorder, and the like, or ameliorating a symptom thereof.

[0055] As used herein, the term “pharmaceutical composition” refers to the combination of an active agent with a carrier, inert or active, making the composition especially suitable for diagnostic or therapeutic use *in vivo* or *ex vivo*.

[0056] As used herein, the term “pharmaceutically acceptable carrier” refers to any of the standard pharmaceutical carriers, such as a phosphate buffered saline solution, water, emulsions (*e.g.*, such as an oil/water or water/oil emulsions), and various types of wetting agents. The compositions also can include stabilizers and preservatives. For examples of carriers, stabilizers and adjuvants, *see e.g.*, Martin, Remington’s Pharmaceutical Sciences, 15th Ed., Mack Publ. Co., Easton, PA [1975].

[0057] For therapeutic use, salts of the compounds of the present invention are contemplated as being pharmaceutically acceptable. However, salts of acids and bases that are non-pharmaceutically acceptable may also find use, for example, in the preparation or purification of a pharmaceutically acceptable compound.

[0058] In addition, when a compound of the invention contains both a basic moiety (such as, but not limited to, a pyridine or imidazole) and an acidic moiety (such as, but not limited to, a carboxylic acid) zwitterions (“inner salts”) may be formed. Such acidic and basic salts used within the scope of the invention are pharmaceutically acceptable (*i.e.*, non-toxic, physiologically acceptable) salts. Such salts of the compounds of the invention may be formed, for example, by reacting a compound of the invention with an amount of acid or base, such as an equivalent amount, in a medium such as one in which the salt precipitates or in an aqueous medium followed by lyophilization.

[0059] Throughout the description, where compositions are described as having, including, or comprising specific components, or where processes and methods are described as having, including, or comprising specific steps, it is contemplated that, additionally, there are compositions of the present invention that consist essentially of, or consist of, the recited components, and that there are processes and methods according to the present invention that consist essentially of, or consist of, the recited processing steps.

[0060] As a general matter, compositions specifying a percentage are by weight unless otherwise specified.

Paramyxoviridae Peptides

[0061] The modified (e.g., structurally stabilized) peptides described herein are derived from the heptad repeat domain 2 (HR2) sequences of several Paramyxoviridae viruses. Exemplary amino acid sequences of the HR2 of several Paramyxoviridae viruses are shown below in Table 1.

Table 1: Paramyxoviridae HR2 Peptides

Genus	Species	Subfamily	SEQUENCE	SEQ ID NO:
Respirovirus	Human respirovirus 3	Orthoparamyxovirinae	VALDPIDISIVLNKIKSD LEESKEWIRRSNKILDSI	1
Henipavirus	Nipah henipavirus	Orthoparamyxovirinae	VFTDKVDISSQISSMNQS LQQSKDYIKEAQRLLDT V	2
Morbillivirus	Measles Morbillivirus		ISLERLDVGTNLGNAIA KLEDAKELLESSDQILRS MK	3
Orthorubulavirus	Mumps Orthorubulavirus	Rubulavirinae	INTQPIDISTELSKVNAS LQNAVKYIKESNHQLQS V	4
Orthoavulavirus	Avian orthoavulavirus 1	Avulavirinae	VTGN- LDISTELGNVNNISNAL DKLEESNSKLDKV	5
Henipavirus	Hendra henipavirus		VDISSQISSMNQSLQQSK DYIKEAQKILDTV	6

[0062] In certain embodiments, the Paramyxoviridae HR2 modified peptides described herein may contain one or more (e.g., 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14, 15, 16, 17, or 18) amino acid substitutions (relative to an amino acid sequence set forth in any one of SEQ ID NOs: 1-6), e.g., one or more (e.g., 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14, 15, 16, 17, or 18) conservative and/or non-conservative amino acid substitutions.

[0063] A “conservative amino acid substitution” means that the substitution replaces one amino acid with another amino acid residue having a similar side chain. Families of amino acid residues having similar side chains have been defined in the art. These families include amino acids with basic side chains (e.g., lysine, arginine, histidine), acidic side chains (e.g., aspartic acid, glutamic acid), uncharged polar side chains (e.g., glycine, asparagine, glutamine, serine, threonine, tyrosine, cysteine), nonpolar side chains (e.g., alanine, valine, leucine, isoleucine, proline, phenylalanine, methionine, tryptophan), beta-branched side chains (e.g., threonine, valine, isoleucine), aromatic side chains (e.g., tyrosine, phenylalanine, tryptophan, histidine), and acidic side chains and their amides (e.g., aspartic acid, glutamic acid, asparagine, glutamine).

[0064] In some instances, the Paramyxoviridae HR2 modified peptides described herein (e.g., SEQ ID NOs: 1-6) may also contain at least one, at least 2, at least 3, at least 4, or at least 5 amino acids added to the N-terminus of the peptide. In some instances, the Paramyxoviridae HR2 modified peptides described herein (e.g., SEQ ID NO: 1-6) may also contain at least one, at least 2, at least 3, at least 4, or at least 5 amino acids added to the C-terminus of the peptide. In some instances, the Paramyxoviridae HR2 peptides described herein (e.g., SEQ ID NO: 1-6) may also contain at least one, at least 2, at least 3, at least 4, or at least 5 amino acids deleted at the N-terminus of the peptide. In some instances, the Paramyxoviridae HR2 modified peptides described herein (e.g., SEQ ID NO: 1-6) may also contain at least one, at least 2, at least 3, at least 4, or at least 5 amino acids deleted at the C-terminus of the peptide.

[0065] In some instances, the modified peptides described herein comprise an amino acid sequence that is at least 30%, 35%, 40%, 45%, 50%, 55%, 60%, 65%, 70%, 75%, 80%, 85%, 90%, 95%, or 98% identical to a sequence set forth in SEQ ID NO:1-6.

[0066] In some instances, the modified peptides include an amino acid sequence that has 2 to 18, 2 to 17, 2 to 16, 2 to 15, 2 to 14, 2 to 13, 2 to 12, 2 to 11, 2 to 10, 2 to 9, 2 to 8, 2 to 7, 2 to 6, 2 to 5, 2 to 4, 2 to 3, or 2 substitutions, insertions, and/or deletions relative to SEQ ID NO: 1-6. In some instances, the peptides include 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14, 15, 16, 17, or 18 substitutions, insertions, and/or deletions relative to SEQ ID NO: 1-6.

Modified Peptides

[0067] In some embodiments, the present disclosure provides a modified peptide comprising an amino acid sequence that is at least 30% identical to an amino acid sequence selected from the group consisting of SEQ ID NO: 1-6, wherein at least two amino acids comprise side chains that are linked together (e.g., to form a staple).

[0068] In some embodiments, the present disclosure provides a modified peptide comprising an amino acid sequence that has 1-18 substitutions, insertions, and/or deletions relative to SEQ ID NO: 1-6, wherein at least two amino acids comprise side chains that are linked together (e.g., to form a staple). In some embodiments, the staple spans one to two turns of an alpha helix.

[0069] In some embodiments, the present disclosure provides a modified peptide, wherein side chains that are linked together are side chains of two amino acids separated by:

- i) 3 amino acids (e.g., side chains of amino acids at positions i and i+4) or
- ii) 6 amino acids (e.g., side chains amino acids at positions i and i+7).

[0070] In some embodiments, amino acid side chains that are linked together span one to two turns of an alpha helix.

[0071] In some embodiments, the present disclosure provides a modified peptide wherein the amino acid sequence is at least 70% identical to an amino acid sequence selected from the group consisting of SEQ ID NO: 1-6. In some embodiments, the present disclosure provides a modified peptide wherein the amino acid sequence is at least 80% identical to an amino acid sequence selected from the group consisting of SEQ ID NO: 1-6. In some embodiments, the present disclosure provides a modified peptide wherein the amino acid sequence is at least 90% identical to an amino acid sequence selected from the group consisting of SEQ ID NO: 1-6. In some embodiments, the present disclosure provides a modified peptide wherein the amino acid sequence is at least 95% identical to an amino acid sequence selected from the group consisting of SEQ ID NO: 1-6. In some embodiments, the present disclosure provides a modified peptide wherein the amino acid sequence is at least 98% identical to an amino acid sequence selected from the group consisting of SEQ ID NO: 1-6.

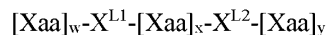
[0072] In some embodiments, the present disclosure provides a modified peptide wherein the amino acid sequence is SEQ ID NO: 1. In some embodiments, the present disclosure provides a modified peptide wherein the amino acid sequence is SEQ ID NO: 2. In some embodiments, the present disclosure provides a modified peptide wherein the amino acid sequence is SEQ ID NO: 3. In some embodiments, the present disclosure provides a modified peptide wherein the amino acid sequence is SEQ ID NO: 4. In some embodiments, the present disclosure provides a modified peptide wherein the amino acid sequence is SEQ ID NO: 5. In some embodiments, the present disclosure provides a modified peptide wherein the amino acid sequence is SEQ ID NO: 6.

[0073] In some embodiments, the present disclosure provides a modified peptide wherein the two amino acids with side chain group linked together are at the *i* and *i*+4 positions. In some embodiments, the two amino acids with side chain group linked together are at the *i* and *i*+7 positions.

[0074] In some embodiments, the present disclosure provides a modified peptide wherein the modified peptide further comprises a PEG moiety.

[0075] In some embodiments, the present disclosure provides a modified peptide wherein the modified peptide further comprises an optionally substituted C₅-C₁₀₀ aliphatic lipid moiety. In some embodiments, the lipid moiety is a fatty acid, phospholipid, sphingolipid, or a sterol. In some embodiments, the fatty acid is palmitic acid or stearic acid. In some embodiments, the phospholipid is phosphatidylcholine or phosphatidylethanolamine. In some embodiments, the sphingolipid is sphingosine or ceramide. In some embodiments, the sterol is cholesterol, thiocholesterol, sitosterol, ergosterol, or tocopherol.

[0076] In some embodiments, the present disclosure provides a modified peptide wherein the modified peptide is of the formula:



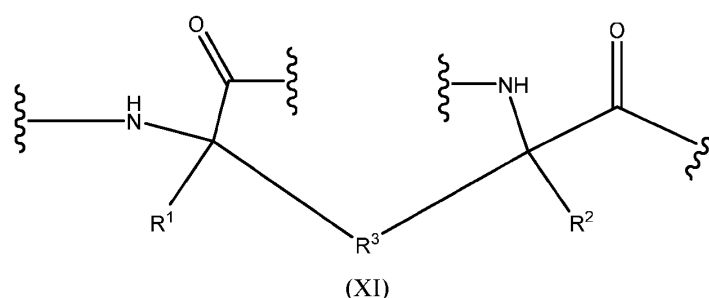
or a pharmaceutically acceptable salt thereof, wherein:

each Xaa independently represents a natural or unnatural amino acid;

w, x, and y are independently 0-100, inclusive; and

X^{L1} and X^{L2} are amino acids comprising side chains that are linked together.

[0077] In certain embodiments, the two amino acids with side chain groups linked together are of formula (XI):



or a pharmaceutically acceptable salt thereof, wherein:

R¹ and R² are each independently hydrogen or an optionally substituted group selected from C₁₋₁₀ alkyl, C₂₋₁₀ alkenyl, and C₂₋₁₀ alkynyl;

R³ represents the linked side chain groups and is an optionally substituted bivalent, C₃₋₂₀ aliphatic group wherein one or more methylene units of the aliphatic group are optionally and independently replaced with —O—, —S—, —S—S—, —N(R')—, —C(O)—, —C(S)—, —C(NR')—, —C(O)N(R')—, —N(R')C(O)N(R')—, —N(R')C(O)O—, —S(O)—, —S(O)₂—, —S(O)₂N(R')—, —C(O)S—, or —C(O)O—; and

each R' is hydrogen or optionally substituted C₁₋₁₂ aliphatic.

[0078] As defined generally above, R¹ and R² are each independently hydrogen, or an optionally substituted group selected from C₁₋₁₀ alkyl, C₂₋₁₀ alkenyl, or C₂₋₁₀ alkynyl. In certain embodiments, R¹ and R² are each hydrogen. In certain embodiments, R¹ and R² are each independently optionally substituted C₁₋₁₀ alkyl. In certain embodiments, R¹ and R² are each independently optionally substituted C₂₋₁₀ alkenyl. In certain embodiments, R¹ and R² are each independently optionally substituted C₂₋₁₀ alkynyl. In certain embodiments, R¹ and R² are each C₁₋₁₀ alkyl. In certain embodiments, R¹ and R² are methyl.

[0079] In certain embodiments, R¹ is hydrogen, or an optionally substituted group selected from C₁₋₁₀ alkyl, C₂₋₁₀ alkenyl, or C₂₋₁₀ alkynyl. In certain embodiments, R¹ is hydrogen. In

certain embodiments, R^1 is optionally substituted C_{1-10} alkyl. In certain embodiments, R^1 is optionally substituted C_{2-10} alkenyl. In certain embodiments, R^1 is optionally substituted C_{2-10} alkynyl.

[0080] In certain embodiments, R^1 is hydrogen, C_{1-10} alkyl, C_{2-10} alkenyl, or C_{2-10} alkynyl. In certain embodiments, R^1 is C_{1-10} alkyl. In certain embodiments, R^1 is C_{2-10} alkenyl. In certain embodiments, R^1 is C_{2-10} alkynyl. In certain embodiments, R^1 is methyl.

[0081] In certain embodiments, R^2 is hydrogen, or an optionally substituted group selected from C_{1-10} alkyl, C_{2-10} alkenyl, or C_{2-10} alkynyl. In certain embodiments, R^2 is hydrogen. In certain embodiments, R^2 is optionally substituted C_{1-10} alkyl. In certain embodiments, R^2 is optionally substituted C_{2-10} alkenyl. In certain embodiments, R^2 is optionally substituted C_{2-10} alkynyl.

[0082] In certain embodiments, R^2 is hydrogen, C_{1-10} alkyl, C_{2-10} alkenyl, or C_{2-10} alkynyl. In certain embodiments, R^2 is C_{1-10} alkyl. In certain embodiments, R^2 is C_{2-10} alkenyl. In certain embodiments, R^2 is C_{2-10} alkynyl. In certain embodiments, R^2 is methyl.

[0083] In certain embodiments, R^1 and R^2 are each independently optionally substituted with 1-3 groups selected from C_{1-3} alkyl, hydroxyl, or C_{1-3} alkoxy. In certain embodiments, R^1 and R^2 are each independently substituted with 1-3 groups selected from C_{1-3} alkyl, hydroxyl, or C_{1-3} alkoxy.

[0084] In certain embodiments, R^1 is substituted with C_{1-3} alkyl. In certain embodiments, R^1 is substituted with C_{1-3} alkoxy. In certain embodiments, R^1 is substituted with hydroxyl. In certain embodiments, R^1 is substituted with methyl.

[0085] In certain embodiments, R^2 is substituted with C_{1-3} alkyl. In certain embodiments, R^2 is substituted with C_{1-3} alkoxy. In certain embodiments, R^2 is substituted with hydroxyl. In certain embodiments, R^2 is substituted with methyl.

[0086] As defined generally above, R^3 represents linked side chain groups and is an optionally substituted bivalent, C_{3-20} aliphatic group wherein one or more methylene units of the aliphatic group are optionally and independently replaced with —O—, —S—, —S—S—, —N(R')—, —C(O)—, —C(S)—, —C(NR')—, —C(O)N(R')—, —N(R')C(O)N(R')—, —N(R')C(O)O—, —S(O)—, —S(O)₂—, —S(O)₂N(R')—, —C(O)S—, or —C(O)O—.

[0087] In certain embodiments, R^3 represents linked side chain groups and is an optionally substituted bivalent, C_{7-12} aliphatic group wherein one or more methylene units of the aliphatic group are optionally and independently replaced with —O—, —S—, —S—S—, —N(R')—, —C(O)—, —C(S)—, —C(NR')—, —C(O)N(R')—, —N(R')C(O)N(R')—, —N(R')C(O)O—, —S(O)—, —S(O)₂—, —S(O)₂N(R')—, —C(O)S—, or —C(O)O—.

[0088] In certain embodiments, R^3 represents linked side chain groups and is an optionally substituted bivalent, C_{7-12} aliphatic group. In certain embodiments, R^3 is C_{7-12} alkenylene. In certain embodiments, R^3 is C_8 alkenylene. In certain embodiments, R^3 is C_{11} alkenylene. In certain embodiments, R^3 is $-(CH_2)_{1-7}-CH=CH-(CH_2)_{1-7}-$. In certain embodiments, R^3 is $-(CH_2)_3-7-CH=CH-(CH_2)_{3-4}-$. In certain embodiments, R^3 is $-(CH_2)_6-CH=CH-(CH_2)_3-$. In certain embodiments, R^3 is $-(CH_2)_3-CH=CH-(CH_2)_3-$.

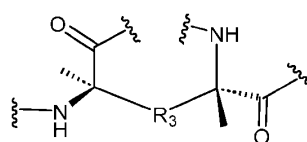
[0089] In some embodiments, R^3 spans one to two turns of an alpha helix.

[0090] As defined generally above, each R' is hydrogen or optionally substituted C_{1-12} aliphatic. In certain embodiments, R' is hydrogen. In certain embodiments, R' is C_{1-12} aliphatic. In certain embodiments, R' is C_{1-4} aliphatic.

[0091] As defined generally above, each X_{aa} independently represents a natural or unnatural amino acid.

[0092] As defined generally above, w , x , and y are independently 0-100, inclusive. In certain embodiments, w , x , and y are independently 0-30 inclusive. In certain embodiments, w , x , and y are independently 4-30 inclusive. In certain embodiments, w is 0 to 100 inclusive. In certain embodiments, w is 0 to 30, inclusive. In certain embodiments, w is 4 to 30, inclusive. In certain embodiments, y is 0 to 100 inclusive. In certain embodiments, y is 0 to 30, inclusive. In certain embodiments, y is 4 to 30, inclusive. In certain embodiments, x is 0 to 10, inclusive. In certain embodiments, x is 3. In certain embodiments, x is 6. In certain embodiments, w is 4-30 inclusive, x is 3 or 6, and y is 4-30 inclusive.

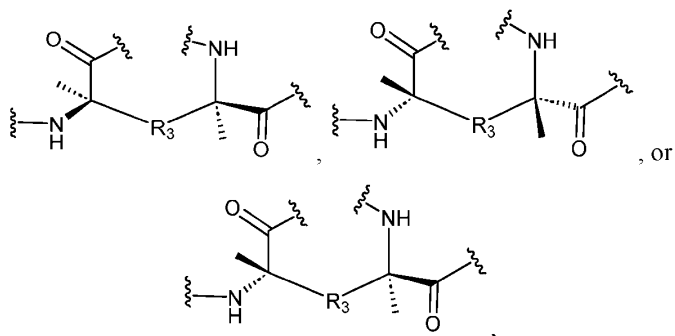
[0093] In certain embodiments, Formula XI is further defined by Formula XIa:



XIa

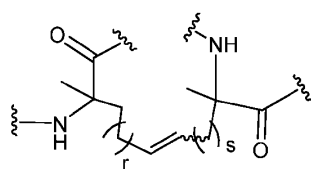
wherein R^3 is as defined above and described in classes and subclasses herein.

[0094] In certain embodiments, Formula XI is further defined by:



wherein R^3 is as defined above and described in classes and subclasses herein.

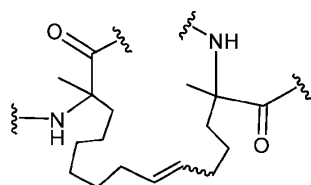
[0095] In certain embodiments, Formula XI is further defined by Formula XII:



XII

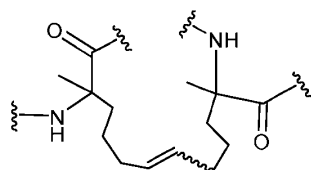
wherein r is 2, 3, 4, 5, 6, 7, or 8, and s is 2, 3, 4, 5, or 6.

[0096] In certain embodiments, Formula XI is further defined by Formula XIIa:



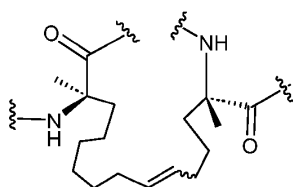
XIIa.

[0097] In certain embodiments, Formula XI is further defined by Formula XIIb:



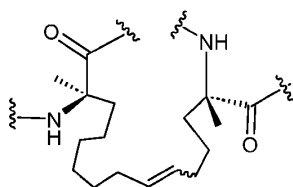
XIIb.

[0098] In certain embodiments, Formula XI is further defined by Formula XIIc:



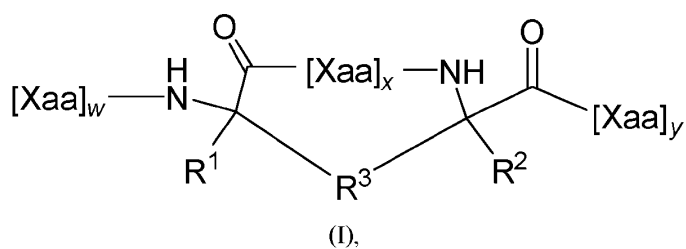
XIIc.

[0099] In certain embodiments, Formula XI is further defined by Formula XIId:



XIId.

[0100] In certain embodiments, the present disclosure provides a modified peptide comprising Formula (I):



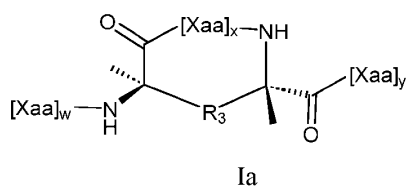
or a pharmaceutically acceptable salt thereof, wherein:

R^1 , R^2 , and R^3 are as defined above and described in classes and subclasses herein;

each Xaa independently represents a natural or unnatural amino acid; and

w, x, and y are independently 0-100, inclusive.

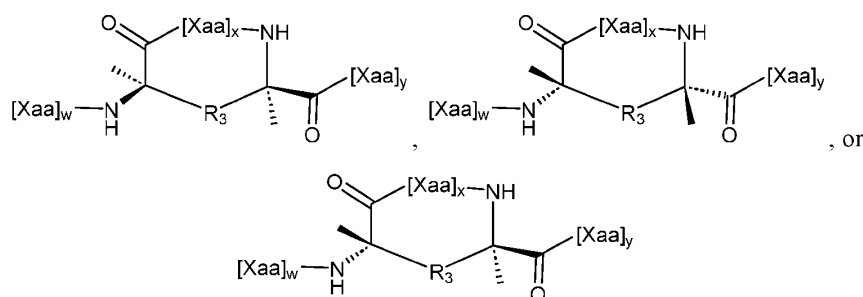
[0101] In certain embodiments, a modified peptide comprises Formula Ia:



or a pharmaceutically acceptable salt thereof, wherein each variable is as defined above and described in classes and subclasses herein.

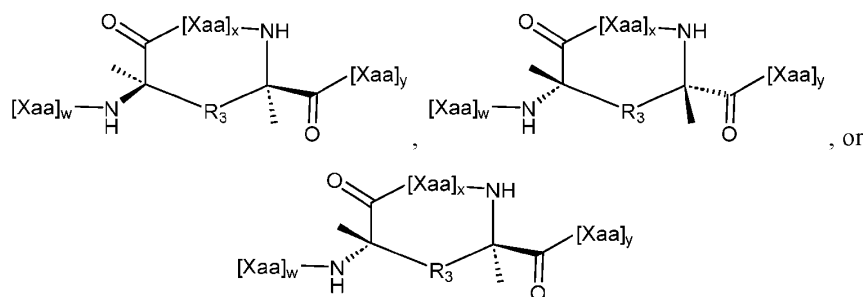
[0102] In certain embodiments, a modified peptide consists of Formula Ia.

[0103] In certain embodiments, a modified peptide comprises:



or a pharmaceutically acceptable salt thereof, wherein each variable is as defined above and described in classes and subclasses herein.

[0104] In certain embodiments, a modified peptide consists of:



or a pharmaceutically acceptable salt thereof, wherein each variable is as defined above and described in classes and subclasses herein.

[0105] In certain embodiments, for provided modified peptides, the modified peptide further comprises a PEG moiety. In certain embodiments, for provided modified peptides, the modified peptide further comprises an optionally substituted C₅-C₁₀₀ aliphatic lipid moiety.

[0106] In certain embodiments, for provided modified peptides, the modified peptide further comprises -(LINKER)-(LIPID MOIETY). In some embodiments, a linker comprises PEG, a peptide (e.g., sequence of amino acids), or a combination thereof. In some embodiments, a linker comprises a peptide. In some embodiments, a linker comprises PEG units linked by amide bonds. In certain embodiments, for provided modified peptides, the C-terminus is conjugated to a lipid moiety via a linker group, i.e., -(LINKER)-(LIPID MOIETY). It is also contemplated by the present disclosure that multimeric conjugates can be made comprising two or more modified peptides described herein, a linker moiety, and a lipid moiety.

[0107] In certain embodiments, the linker comprises PEG. In certain embodiments, the linker is a peptide comprising 3-20 amino acids. The linkers considered herein include those disclosed in Chen, X. et al. Fusion protein linkers: property, design and functionality. Adv Drug

Deliv Rev. 2013 Oct;65(10):1357-69 and Zhou, J. et al. A highly potent and stable pan-coronavirus fusion inhibitor as a candidate prophylactic and therapeutic for COVID-19 and other coronavirus diseases, Acta Pharm. Sinica B; 2022;12(4): 1652-1661, the contents of each of which are hereby incorporated by reference.

[0108] In some embodiments, the lipid moiety is C₅-C₁₀₀ aliphatic lipid moiety. In some embodiments, the lipid moiety is a fatty acid, phospholipid, sphingolipid, or a sterol. In some embodiments, the fatty acid is palmitic acid or stearic acid. In some embodiments, the phospholipid is phosphatidylcholine or phosphatidylethanolamine. In some embodiments, the sphingolipid is sphingosine or ceramide. In some embodiments, the sterol is cholesterol, thiocholesterol, sitosterol, ergosterol, or tocopherol.

[0109] In certain embodiments, the C-terminus of a modified peptide is attached to a lipid moiety via R⁴, wherein R⁴ is a bivalent, saturated or unsaturated, straight or branched C₁₋₂₀ hydrocarbon chain, wherein 1-10 methylene units of the hydrocarbon chain are independently replaced by -O-, -N(R)-, -S-, -OC(O)-, -C(O)O-, -C(O)-, -S(O)-, -S(O)₂-, -N(R)S(O)₂-, -S(O)₂N(R)-, -N(R)C(O)-, -C(O)N(R)-, -OC(O)N(R)-, -N(R)C(O)O-, or -[O-CH₂CH₂]_p, wherein p is 1-20 and each R is independently hydrogen or optionally substituted C₁₋₆ aliphatic.

[0110] In some embodiments, R⁴ is a bivalent peptide.

[0111] In certain embodiments, the C-terminus of a modified peptide is attached to R⁴, wherein:

R⁴ is -N(H)-C(H)((CH₂)₄N(H)(C(O)-(C₂₋₆ alkylene)-[O-CH₂CH₂]_p-N(R⁵)C(O)-(C₀₋₆ alkylene)-R⁶))-C(O)-NH₂;

R⁵ is hydrogen or C₁₋₄ alkyl;

R⁶ is an optionally substituted C₅-C₁₀₀ aliphatic lipid moiety; and

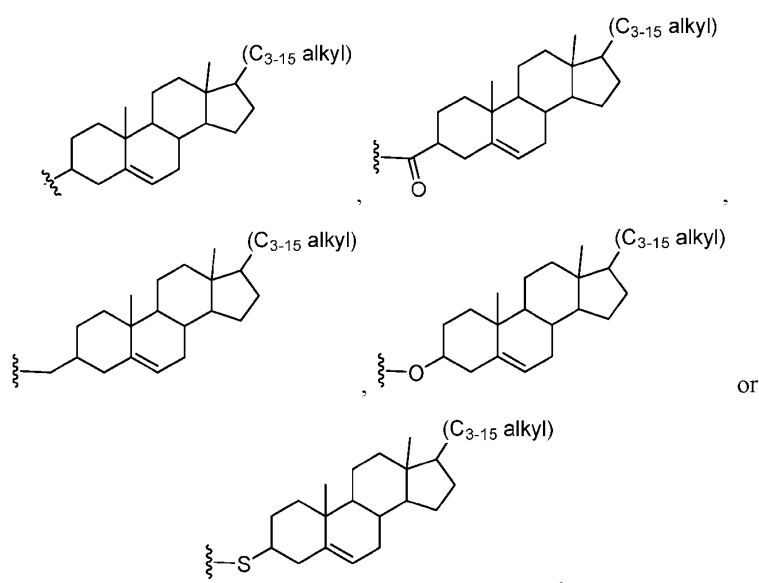
p is 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14, 15, or 16.

[0112] In certain embodiments, R⁴ is -N(H)-C(H)((CH₂)₄N(H)(C(O)-(C₂₋₆ alkylene)-[O-CH₂CH₂]_p-N(R⁵)C(O)-(C₀₋₆ alkylene)-R⁶))-C(O)-NH₂. In certain embodiments, R⁴ is -N(H)-C(H)((CH₂)₄N(H)(C(O)-(C₂₋₃ alkylene)-[O-CH₂CH₂]_p-N(R⁵)C(O)-(C₀₋₂ alkylene)-R⁶))-C(O)-NH₂. In certain embodiments, R⁴ is -N(H)-C(H)((CH₂)₄N(H)(C(O)-CH₂CH₂-[O-CH₂CH₂]_p-N(R⁵)C(O)-CH₂-R⁶))-C(O)-NH₂. In certain embodiments, R⁴ is -N(H)-C(H)((CH₂)₄N(H)(C(O)-(C₂₋₃ alkylene)-[O-CH₂CH₂]_p-N(R⁵)C(O)-(C₀₋₂ alkylene)-R⁶))-C(O)-NH₂. In certain embodiments, R⁴ is -N(H)-C(H)((CH₂)₄N(H)(C(O)-CH₂CH₂-[O-CH₂CH₂]_p-N(R⁵)C(O)-CH₂-R⁶))-C(O)-NH₂. In certain embodiments, R⁴ is -N(H)-C(H)((CH₂)₄N(H)(C(O)-(C₂₋₃ alkylene)-[O-CH₂CH₂]_p-N(R⁵)C(O)-(C₀₋₂ alkylene)-R⁶))-C(O)-NH₂.

[0113] As defined generally above, R^5 is hydrogen or C_{1-4} alkyl. In certain embodiments, R^5 is hydrogen. In certain embodiments, R^5 is C_{1-4} alkyl. In certain embodiments, R^5 is methyl.

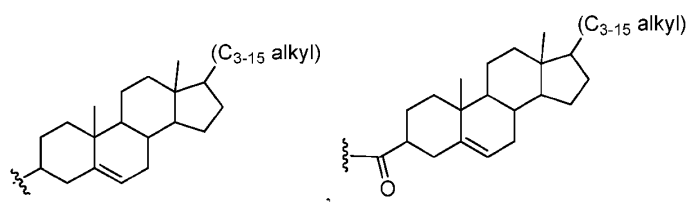
[0114] As defined generally above, R^6 is an optionally substituted C_5 - C_{100} aliphatic lipid moiety. In some embodiments, R^6 is a fatty acid, phospholipid, sphingolipid, or a sterol. In some embodiments, R^6 is palmitic acid or stearic acid. In some embodiments, R^6 is phosphatidylcholine or phosphatidylethanolamine. In some embodiments, R^6 is sphingosine or ceramide. In some embodiments, R^6 is cholesterol, thiocholesterol, sitosterol, ergosterol, or tocopherol.

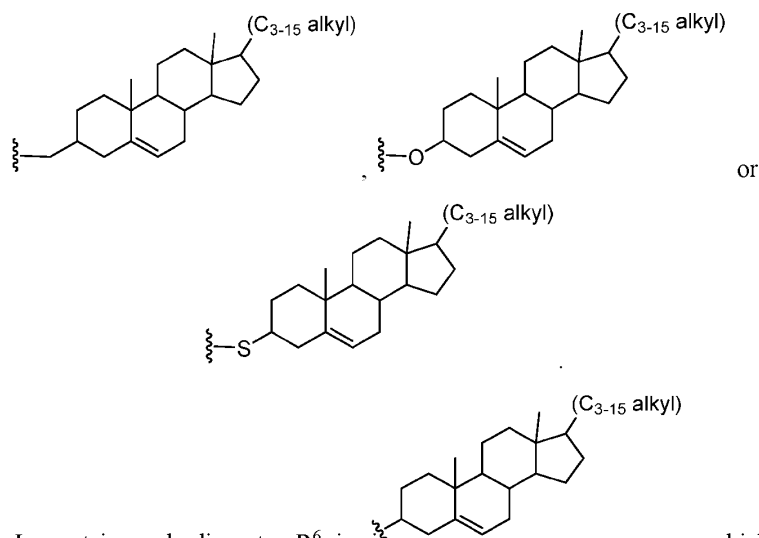
[0115] In certain embodiments, R^6 is one of the following:



each of which may be optionally substituted.

[0116] In certain embodiments, R^6 is:





[0117] In certain embodiments, R⁶ is , which may be

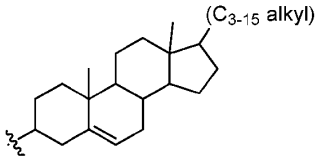
optionally substituted. In certain embodiments, R⁶ is , which

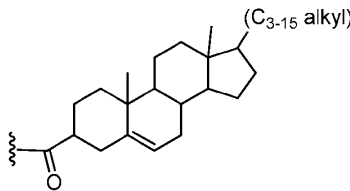
may be optionally substituted. In certain embodiments, R⁶ is , which may be optionally substituted. In certain embodiments, R⁶ is

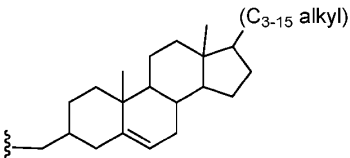
, which may be optionally substituted. In certain

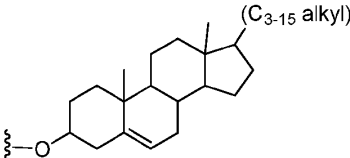
embodiments, R⁶ is , which may be optionally substituted.

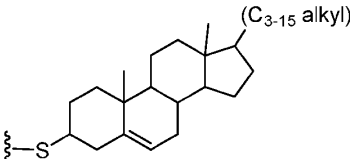
[0118] In certain embodiments, R⁶ is optionally substituted with 1-3 groups independently selected from C₁₋₃ alkyl, hydroxyl, or C₁₋₃ alkoxy.

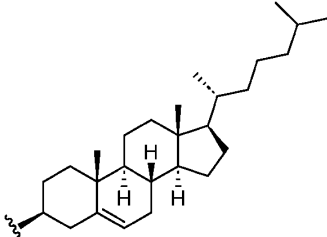
[0119] In certain embodiments, R^6 is . In certain

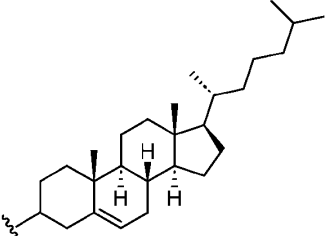
embodiments, R^6 is . In certain embodiments, R^6 is

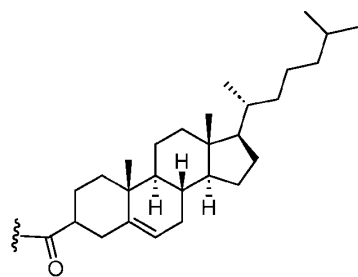
. In certain embodiments, R^6 is

. In certain embodiments, R^6 is

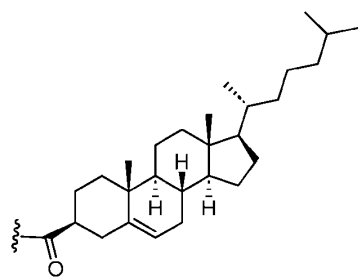


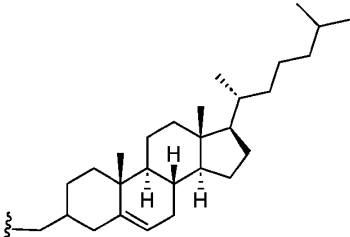
[0120] In certain embodiments, R^6 is . In certain

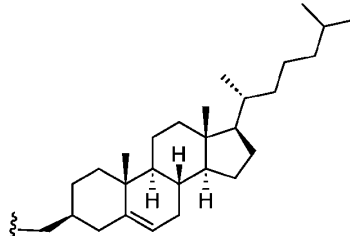
embodiments, R^6 is . In certain embodiments, R^6 is

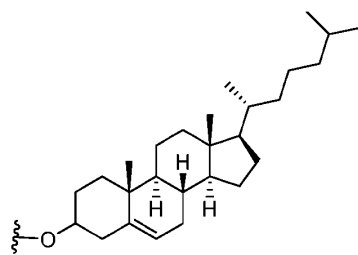


In certain embodiments, R^6 is

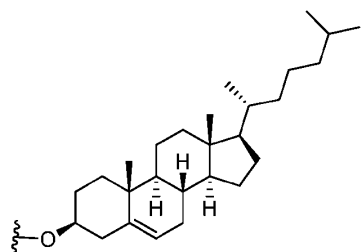


[0121] In certain embodiments, R^6 is . In certain

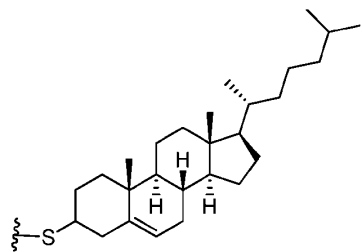
embodiments, R^6 is . In certain embodiments, R^6 is



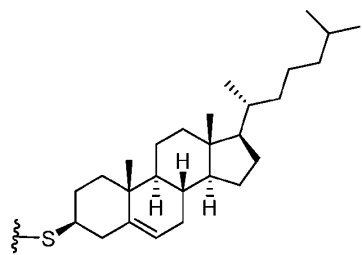
In certain embodiments, R^6 is



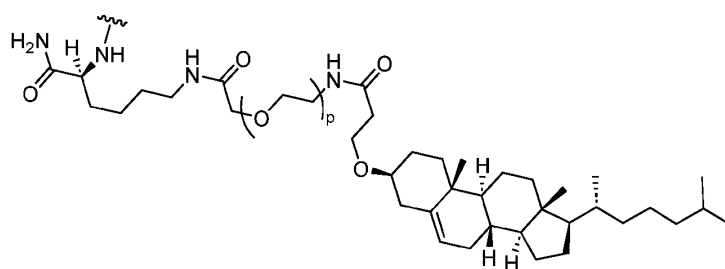
In certain embodiments, R^6 is



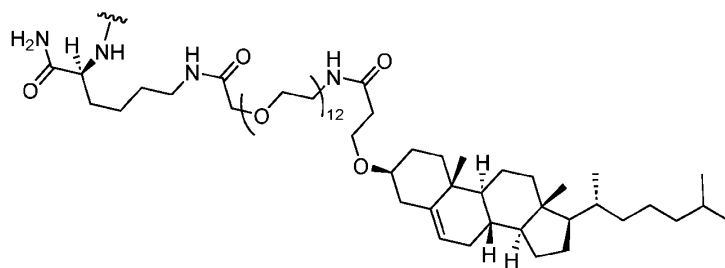
In certain embodiments, R^6 is



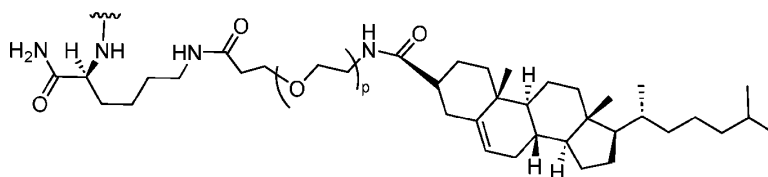
[0122] In certain embodiments, R^4 is:



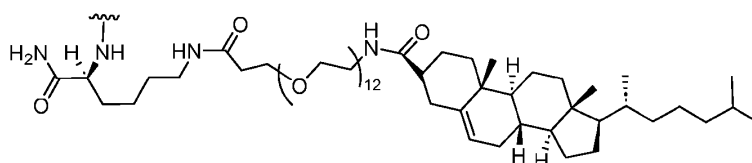
[0123] In certain embodiments, R^4 is:



[0124] In certain embodiments, R^4 is:



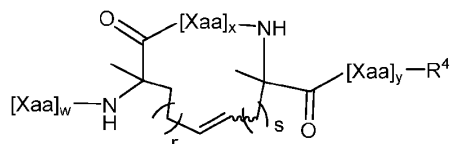
[0125] In certain embodiments, R^4 is:



[0126] In certain embodiments, R^6 is substituted with hydroxyl or C_{1-3} alkoxy. In certain embodiments, R^6 is substituted with C_{1-3} alkyl or C_{1-3} alkoxy. In certain embodiments, R^6 is substituted with C_{1-3} alkyl or hydroxyl.

[0127] In certain embodiments, R^6 is substituted with C_{1-3} alkyl. In certain embodiments, R^6 is substituted with C_{1-3} alkoxy. In certain embodiments, R^6 is substituted with hydroxyl. In certain embodiments, R^6 is substituted with methyl.

[0128] In certain embodiments, a modified peptide comprises Formula II:

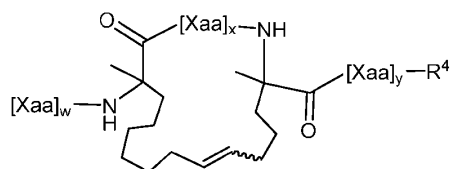


II

or a pharmaceutically acceptable salt thereof, wherein each variable is as defined above and described in classes and subclasses herein.

[0129] In certain embodiments, a modified peptide consists of Formula II.

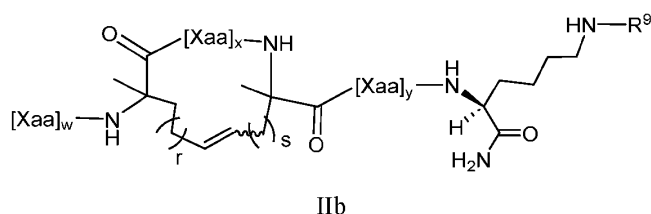
[0130] In certain embodiments, Formula II is further defined by Formula IIa:



IIa

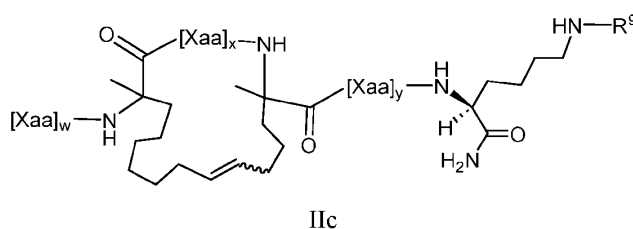
or a pharmaceutically acceptable salt thereof, wherein each variable is as defined above and described in classes and subclasses herein.

[0131] In some embodiments, a modified peptide comprises Formula IIb or a pharmaceutically acceptable salt thereof:



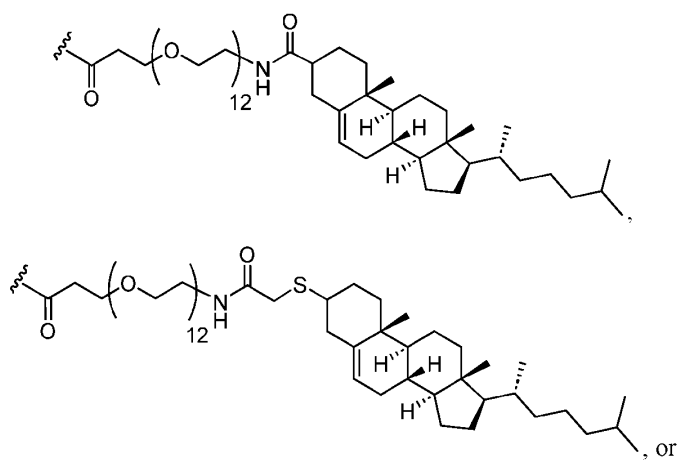
wherein R^9 is $-C(O)-(CH_2CH_2)-[O-CH_2CH_2]_m-N(R^5)C(O)-(CH_2)-R^6$, and each variable is as defined above and described in classes and subclasses herein.

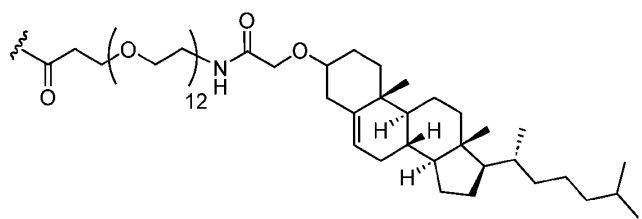
[0132] In some embodiments, a modified peptide comprises Formula IIc or a pharmaceutically acceptable salt thereof:



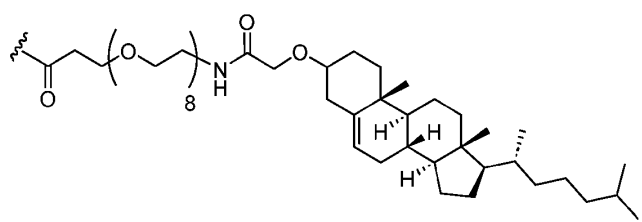
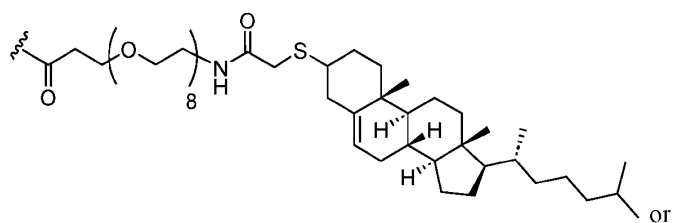
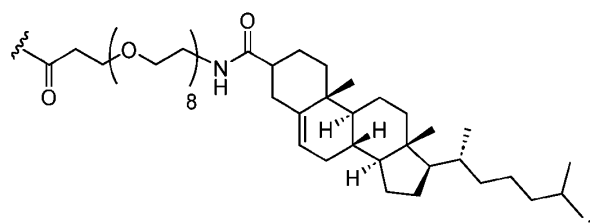
wherein each variable is as defined above and described in classes and subclasses herein.

[0133] In some embodiments, R^9 is:

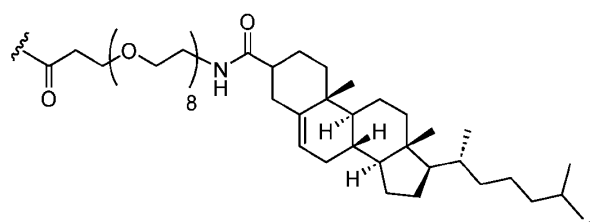




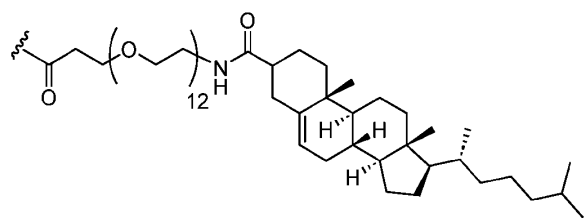
[0134] In some embodiments, R^9 is:



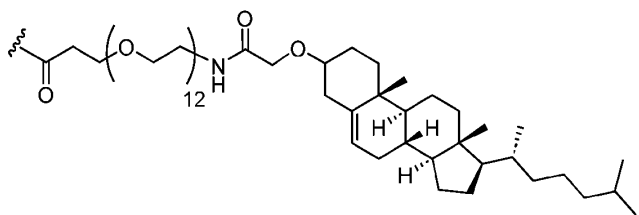
[0135] In some embodiments, R^9 is:



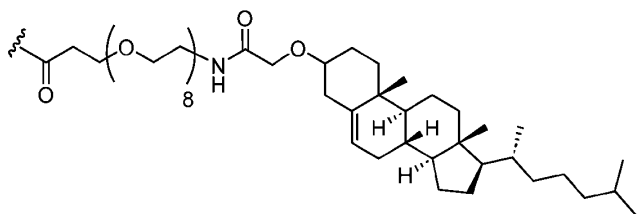
[0136] In some embodiments, R^9 is:



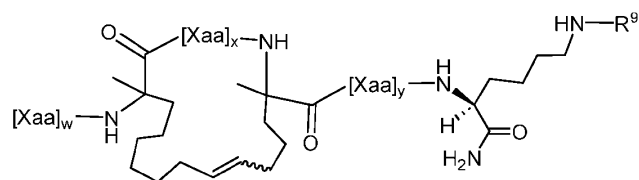
[0137] In certain embodiments, R⁹ is:



[0138] In certain embodiments, R⁹ is:



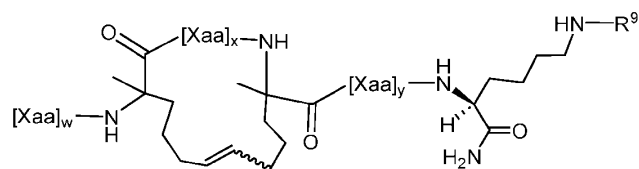
[0139] In some embodiments, a provided modified peptide is of Formula IVb:



IVb

or a pharmaceutically acceptable salt thereof, wherein each variable is as defined above and described in classes and subclasses herein.

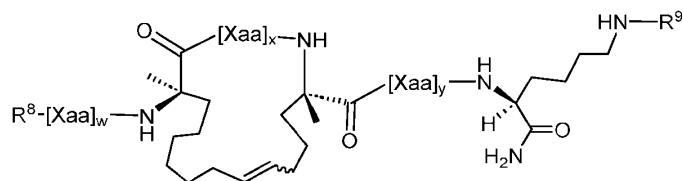
[0140] In some embodiments, a provided modified peptide is of Formula IVc:



IVc

or a pharmaceutically acceptable salt thereof, wherein each variable is as defined above and described in classes and subclasses herein.

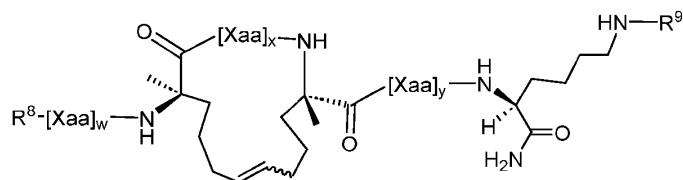
[0141] In some embodiments, a provided modified peptide is of Formula Va:



Va

or a pharmaceutically acceptable salt thereof, wherein R^8 is $-C(O)-(C_{1-4} \text{ alkyl})$ and each variable is as defined above and described in classes and subclasses herein.

[0142] In some embodiments, a provided modified peptide is of Formula Vb:

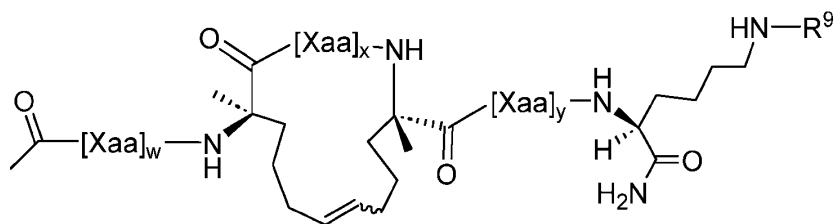


Vb

or a pharmaceutically acceptable salt thereof, wherein R^8 is $-C(O)-(C_{1-4} \text{ alkyl})$ and each variable is as defined above and described in classes and subclasses herein.

[0143] In certain embodiments, R^8 is $-C(O)CH_3$.

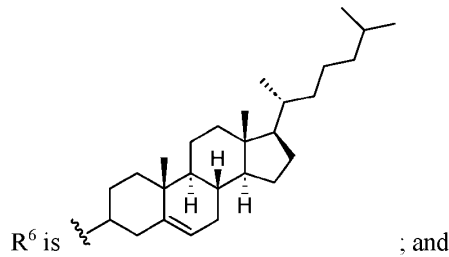
[0144] In some embodiments, a provided modified peptide is of Formula VIa:



VIa

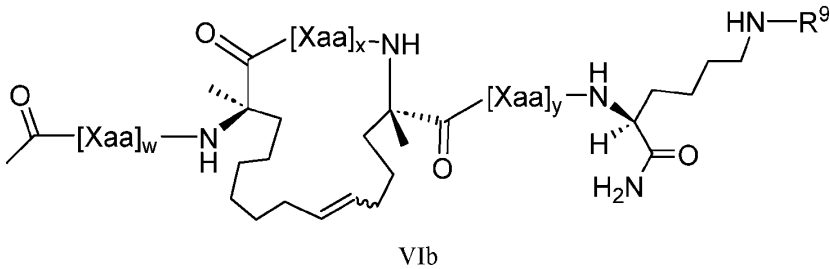
or a pharmaceutically acceptable salt thereof, wherein

R^9 is $-C(O)-(CH_2CH_2)-[O-CH_2CH_2]_{12}-N(H)C(O)-R^6$;



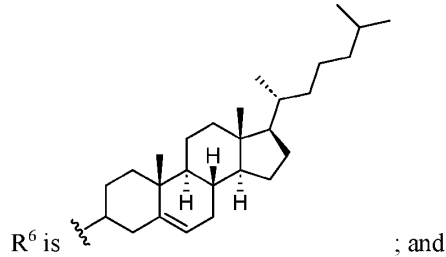
each variable is as defined above and described in classes and subclasses herein.

[0145] In some embodiments, a provided modified peptide is of Formula VIb:



or a pharmaceutically acceptable salt thereof, wherein

R⁹ is -C(O)-(CH₂CH₂)-[O-CH₂CH₂]₁₂-N(H)C(O)-R⁶;



each variable is as defined above and described in classes and subclasses herein.

[0146] As defined generally above, each Xaa of [Xaa]_w, [Xaa]_x, and [Xaa]_y represents independently a natural or unnatural amino acid.

[0147] In certain embodiments, [Xaa]_w is selected from Table 2a.

Table 2a.

Sequence	SEQ ID NO:
V	1401
VA	1402
VAL	1403
VALD	1404
VALDP	1405
VALDPI	1406
VALDPID	1407

Sequence	SEQ ID NO:
VALDPIDI	1408
VALDPIDIS	1409
VALDPIDISI	1410
VALDPIDISIV	1411
VALDPIDISIVL	1412
VALDPIDISIVLN	1413
VALDPIDISIVLNK	1414
VALDPIDISIVLNKI	1415
VALDPIDISIVLNKIK	1416
VALDPIDISIVLNKIKS	1417
VALDPIDISIVLNKIKSD	1418
VALDPIDISIVLNKIKSDL	1419
VALDPIDISIVLNKIKSDLE	1420
VALDPIDISIVLNKIKSDLEE	1421
VALDPIDISIVLNKIKSDLEES	1422
VALDPIDISIVLNKIKSDLEESK	1423
VALDPIDISIVLNKIKSDLEESKE	1424
VALDPIDISIVLNKIKSDLEESKEW	1425
VALDPIDISIVLNKIKSDLEESKEWI	1426
VALDPIDISIVLNKIKSDLEESKEWIR	1427
VALDPIDISIVLNKIKSDLEESKEWIRR	1428
VALDPIDISIVLNKIKSDLEESKEWIRRS	1429
VALDPIDISIVLNKIKSDLEESKEWIRRSN	1430

[0148] In certain embodiments, [Xaa]_s is selected from Table 2b.

Table 2b.

Sequence	SEQ ID NO:
LDP	2401
DPI	2402
PID	2403
IDI	2404
DIS	2405
ISI	2406
SIV	2407
IVL	2408
VLN	2409
LNK	2410
NKI	2411
KIK	2412
IKS	2413
KSD	2414
SDL	2415
DLE	2416
LEE	2417
EES	2418
ESK	2419

Sequence	SEQ ID NO:
SKE	2420
KEW	2421
EWI	2422
WIR	2423
IRR	2424
RRS	2425
RSN	2426
SNK	2427
KIL	2428
ILD	2429
LDPIDI	2430
DPIDIS	2431
PIDISI	2432
IDISIV	2433
DISIVL	2434
ISIVLN	2435
SIVLNK	2436
IVLNKI	2437
VLNKIK	2438
LNKIKS	2439
NKIKSD	2440
KIKSDL	2441
IKSDLE	2442
KSDLEE	2443
SDLEES	2444
DLEESK	2445
LEESKE	2446
EESKEW	2447
ESKEWI	2448
SKEWIR	2449
KEWIRR	2450
EWIRRS	2451
WIRRSN	2452
IRRSNK	2453
RRSNKI	2454
RSNKIL	2455
SNKILD	2456

[0149] In certain embodiments, [Xaa]_y is selected from Table 2c.

Table 2c.

Sequence	SEQ ID NO:
I	3401
SI	3402
DSI	3403
LDSI	3404

Sequence	SEQ ID NO:
ILDSI	3405
KILDSI	3406
NKILDSI	3407
SNKILDSI	3408
RSNKILDSI	3409
RRSNKILDSI	3410
IRRSNKILDSI	3411
WIRRSNKILDSI	3412
EWIRRSNKILDSI	3413
KEWIRRSNKILDSI	3414
SKEWIRRSNKILDSI	3415
ESKEWIRRSNKILDSI	3416
EESKEWIRRSNKILDSI	3417
LEESKEWIRRSNKILDSI	3418
DLEESKEWIRRSNKILDSI	3419
SDLEESKEWIRRSNKILDSI	3420
KSDLEESKEWIRRSNKILDSI	3421
IKSDLEESKEWIRRSNKILDSI	3422
KIKSDLEESKEWIRRSNKILDSI	3423
NKIKSDLEESKEWIRRSNKILDSI	3424
LNKIKSDLEESKEWIRRSNKILDSI	3425
VLNLIKSDLEESKEWIRRSNKILDSI	3426
IVLNLIKSDLEESKEWIRRSNKILDSI	3427
SIVLNLIKSDLEESKEWIRRSNKILDSI	3428
ISIVLNLIKSDLEESKEWIRRSNKILDSI	3429
DISIVLNLIKSDLEESKEWIRRSNKILDSI	3430

[0150] In certain embodiments, [Xaa]_w, [Xaa]_x, and [Xaa]_y are selected from i-viii:

	SEQ ID NO:	[Xaa] _w	[Xaa] _x	[Xaa] _y
i)	11	VALDPIDI	IVLNKI	SDLEESKEWIRRSNKILDSI;
ii)	12	VALDPIDISIVL	KIKSDL	ESKEWIRRSNKILDSI;
iii)	13	VALDPIDIS	VLNLIK	DLEESKEWIRRSNKILDSI;
iv)	14	VALDPIDISIVLN	IKSDLE	SKEWIRRSNKILDSI;
v)	15	VALDPIDISIVLNKIKSDL	ESKEWI	RSNKILDSI;
vi)	16	VALDPIDISIVLNKI	SDLEES	EWIRRSNKILDSI;
vii)	17	VALDPIDISIVLNKIK	DLEESK	WIRASNKILDSI; and
viii)	18	VALDPIDISIVLNKIKSDLE	SKEWIR	SNKILDSI.

[0151] In certain embodiments, [Xaa]_w is selected from Table 3a.

Table 3a.

Sequence	SEQ ID NO:
V	1501
VF	1502
VFT	1503
VFTD	1504
VFTDK	1505
VFTDKV	1506
VFTDKVD	1507
VFTDKVDI	1508
VFTDKVDIS	1509
VFTDKVDISS	1510
VFTDKVDISSQ	1511
VFTDKVDISSQI	1512
VFTDKVDISSQIS	1513
VFTDKVDISSQISS	1514
VFTDKVDISSQISSM	1515
VFTDKVDISSQISSMN	1516
VFTDKVDISSQISSMNQ	1517
VFTDKVDISSQISSMNQS	1518
VFTDKVDISSQISSMNQSL	1519
VFTDKVDISSQISSMNQSLQ	1520
VFTDKVDISSQISSMNQSLQQ	1521
VFTDKVDISSQISSMNQSLQQS	1522
VFTDKVDISSQISSMNQSLQQSK	1523
VFTDKVDISSQISSMNQSLQQSKD	1524
VFTDKVDISSQISSMNQSLQQSKDY	1525
VFTDKVDISSQISSMNQSLQQSKDYI	1526
VFTDKVDISSQISSMNQSLQQSKDYIK	1527
VFTDKVDISSQISSMNQSLQQSKDYIKE	1528
VFTDKVDISSQISSMNQSLQQSKDYIKEA	1529
VFTDKVDISSQISSMNQSLQQSKDYIKEAQ	1530

[0152] In certain embodiments, [Xaa]_s is selected from Table 3b.

Table 3b.

Sequence	SEQ ID NO:
TDK	2501
DKV	2502
KVD	2503
VDI	2504

Sequence	SEQ ID NO:
DIS	2505
ISS	2506
SSQ	2507
SQI	2508
QIS	2509
SSM	2510
SMN	2511
MNQ	2512
NQS	2513
QSL	2514
SLQ	2515
LQQ	2516
QQS	2517
QSK	2518
SKD	2519
KDY	2520
DYI	2521
YIK	2522
IKE	2523
KEA	2524
EAQ	2525
AQR	2526
QRL	2527
RLL	2528
LLD	2529
TDKVDI	2530
DKVDIS	2531
KVDISS	2532
VDISSQ	2533
DISSQI	2534
ISSQIS	2535
SSQISS	2536
SQISSM	2537
QISSMN	2538
ISSMNQ	2539
SSMNQS	2540
SMNQSL	2541
MNQSLQ	2542
NQSLQQ	2543
QSLQQS	2544
SLQQSK	2545

Sequence	SEQ ID NO:
LQSKD	2546
QSKDY	2547
QSKDYI	2548
SKDYIK	2549
KDYIKE	2550
DYIKEA	2551
YIKEAQ	2552
IKEAQR	2553
KEAQL	2554
EAQRL	2555
AQRLD	2556

[0153] In certain embodiments, $[Xaa]_y$ is selected from Table 3c.

Table 3c.

Sequence	SEQ ID NO:
V	3501
TV	3502
DTV	3503
LDTV	3504
LLDTV	3505
RLLDTV	3506
QRLDTV	3507
AQRLDTV	3508
EAQRLDTV	3509
KEAQRLDTV	3510
IKEAQRLDTV	3511
YIKEAQRLDTV	3512
DYIKEAQRLDTV	3513
KDYIKEAQRLDTV	3514
SKDYIKEAQRLDTV	3515
QSKDYIKEAQRLDTV	3516
QSKDYIKEAQRLDTV	3517
LQSKDYIKEAQRLDTV	3518
SLQSKDYIKEAQRLDTV	3519
QSLQSKDYIKEAQRLDTV	3520
NQSLQSKDYIKEAQRLDTV	3521
MNQSLQSKDYIKEAQRLDTV	3522
SMNQSLQSKDYIKEAQRLDTV	3523
SSMNQSLQSKDYIKEAQRLDTV	3524

Sequence	SEQ ID NO:
ISSMNQSLQQSKDYIKEAQRLLDTV	3525
QISSMNQSLQQSKDYIKEAQRLLDTV	3526
SQISSMNQSLQQSKDYIKEAQRLLDTV	3527
SSQISSMNQSLQQSKDYIKEAQRLLDTV	3528
ISSQISSMNQSLQQSKDYIKEAQRLLDTV	3529
DISSQISSMNQSLQQSKDYIKEAQRLLDTV	3530
VDISSQISSMNQSLQQSKDYIKEAQRLLDTV	3531

[0154] In certain embodiments, [Xaa]_w, [Xaa]_x, and [Xaa]_y are selected from i-viii:

	SEQ ID NO:	[Xaa] _w	[Xaa] _x	[Xaa] _y
i)	21	VFTDKVDI	SQISSM	QSLQQSKDYIKEAQRLLDTV;
ii)	22	VFTDKVDISSQI	SMNQSL	QSKDYIKEAQRLLDTV;
iii)	23	VFTDKVDIS	QISSMN	SLQQSKDYIKEAQRLLDTV;
iv)	24	VFTDKVDISSQIS	MNQSLQ	SKDYIKEAQRLLDTV;
v)	25	VFTDKVDISSQISSMNQSL	QSKDYI	EAQRLLDTV;
vi)	26	VFTDKVDISSQISSM	QSLQQS	DYIKEAQRLLDTV;
vii)	27	VFTDKVDISSQISSMN	SLQQSK	YIKEAQRLLDTV; and
viii)	28	VFTDKVDISSQISSMNQSLQ	SKDYIK	AQRLLDTV

[0155] In certain embodiments, [Xaa]_w is selected from Table 4a.

Table 4a.

Sequence	SEQ ID NO:
I	1601
IS	1602
ISL	1603
ISLE	1604
ISLER	1605
ISLERL	1606
ISLERLD	1607
ISLERLDV	1608
ISLERLDVG	1609
ISLERLDVGT	1610
ISLERLDVGTN	1611
ISLERLDVGTNL	1612
ISLERLDVGTNLG	1613

Sequence	SEQ ID NO:
ISLERLDVGTNLGN	1614
ISLERLDVGTNLGNA	1615
ISLERLDVGTNLGNAI	1616
ISLERLDVGTNLGNAIA	1617
ISLERLDVGTNLGNAIAK	1618
ISLERLDVGTNLGNAIAKL	1619
ISLERLDVGTNLGNAIAKLE	1620
ISLERLDVGTNLGNAIAKLED	1621
ISLERLDVGTNLGNAIAKLEDA	1622
ISLERLDVGTNLGNAIAKLEDAK	1623
ISLERLDVGTNLGNAIAKLEDAKE	1624
ISLERLDVGTNLGNAIAKLEDAKEL	1625
ISLERLDVGTNLGNAIAKLEDAKELL	1626
ISLERLDVGTNLGNAIAKLEDAKELLE	1627
ISLERLDVGTNLGNAIAKLEDAKELLES	1628
ISLERLDVGTNLGNAIAKLEDAKELLESS	1629
ISLERLDVGTNLGNAIAKLEDAKELLESSD	1630
ISLERLDVGTNLGNAIAKLEDAKELLESSDQ	1091
ISLERLDVGTNLGNAIAKLEDAKELLESSDQI	1632

[0156] In certain embodiments, [Xaa]_x is selected from Table 4b.

Table 4b.

Sequence	SEQ ID NO:
LER	2601
ERL	2602
RLD	2603
LDV	2604
DVG	2605
VGT	2606
GTN	2607
TNL	2608
NLG	2609
LGN	2610
GNA	2611
NAI	2612
AIA	2613
IAK	2614
AKL	2615
KLE	2616
LED	2617

Sequence	SEQ ID NO:
EDA	2618
DAK	2619
AKE	2620
KEL	2621
ELL	2622
LLE	2623
LES	2624
ESS	2625
SSD	2626
SDQ	2627
DQI	2628
QIL	2629
ILR	2630
LRS	2631
RSM	2632
LERLDV	2633
ERLDVG	2634
RLDVGT	2635
LDVGTN	2636
DVGTNL	2637
VGTNLG	2638
GTNLGN	2639
TNLGNA	2640
NLGNAI	2641
LGNAIA	2642
GNAIAK	2643
NAIAKL	2644
AIACLE	2645
IAKLED	2646
AKLEDA	2647
KLEDAK	2648
LEDAKE	2649
EDAKEL	2650
DAKELL	2651
AKELLE	2652
KELLES	2653
ELLESS	2654
LLESSD	2655
LESSDQ	2656
ESSDQI	2254
SSDQIL	2255

Sequence	SEQ ID NO:
SDQILR	2256
DQILRS	2257
QILRSM	2661

[0157] In certain embodiments, [Xaa]_y is selected from Table 4c.

Table 4c.

Sequence	SEQ ID NO:
K	3601
MK	3602
SMK	3603
RSMK	3604
LRSMK	3605
ILRSMK	3606
QILRSMK	3607
DQILRSMK	3608
SDQILRSMK	3609
SSDQILRSMK	3610
ESSDQILRSMK	3611
LESSDQILRSMK	3612
LLESSDQILRSMK	3613
ELLESSDQILRSMK	3614
KELLESSDQILRSMK	3615
AKELLESSDQILRSMK	3616
DAKELLESSDQILRSMK	3617
EDAKELLESSDQILRSMK	3618
LEDAKELLESSDQILRSMK	3619
KLEDAKELLESSDQILRSMK	3620
AKLEDAKELLESSDQILRSMK	3621
IAKLEDAKELLESSDQILRSMK	3622
AIAKLEDAKELLESSDQILRSMK	3623
NAIAKLEDAKELLESSDQILRSMK	3624
GNIAKLEDAKELLESSDQILRSMK	3625
LGNAIAKLEDAKELLESSDQILRSMK	3626
NLGNAIAKLEDAKELLESSDQILRSMK	3627
TNLGNAIAKLEDAKELLESSDQILRSMK	3628
GTNLGNAIAKLEDAKELLESSDQILRSMK	3629
VGTNLGNAIAKLEDAKELLESSDQILRSMK	3630
DVGTNLGNAIAKLEDAKELLESSDQILRSMK	3061

[0158] In certain embodiments, [Xaa]_w, [Xaa]_x, and [Xaa]_y are selected from i-viii:

	SEQ ID NO	[Xaa] _w	[Xaa] _x	[Xaa] _y
i)	31	ISLERLDV	TNLGNA	AKLEDAKELLESSDQILRSMK;
ii)	32	ISLERLDVGTNL	NAIAKL	DAKELLESSDQILRSMK;
iii)	33	ISLERLDVG	NLGNAI	KLEDAKELLESSDQILRSMK;
iv)	34	ISLERLDVGTNLG	AIAKLE	AKELLESSDQILRSMK;
v)	35	ISLERLDVGTNLGNIAIAKL	DAKELL	SSDQILRSMK;
vi)	36	ISLERLDVGTNLGNA	AKLEDA	ELLESSDQILRSMK;
vii)	37	ISLERLDVGTNLGNAI	KLEDAK	LLESSDQILRSMK; and
viii)	38	ISLERLDVGTNLGNIAIAKLE	AKELLE	SDQILRSMK.

[0159] In certain embodiments, [Xaa]_w is selected from Table 5a.

Table 5a.

Sequence	SEQ ID NO:
I	1701
IN	1702
INT	1703
INTQ	1704
INTQP	1705
INTQPI	1706
INTQPID	1707
INTQPIDI	1708
INTQPIDIS	1709
INTQPIDIST	1710
INTQPIDISTE	1711
INTQPIDISTEL	1712
INTQPIDISTELS	1713
INTQPIDISTELSK	1714
INTQPIDISTELSKV	1715
INTQPIDISTELSKVN	1716
INTQPIDISTELSKVNA	1717
INTQPIDISTELSKVNAS	1718
INTQPIDISTELSKVNASL	1719
INTQPIDISTELSKVNASLQ	1720
INTQPIDISTELSKVNASLQN	1721
INTQPIDISTELSKVNASLQNA	1722

Sequence	SEQ ID NO:
INTQPIDISTELSKVNASLQNAV	1723
INTQPIDISTELSKVNASLQNAVK	1724
INTQPIDISTELSKVNASLQNAVKY	1725
INTQPIDISTELSKVNASLQNAVKYI	1726
INTQPIDISTELSKVNASLQNAVKYIK	1727
INTQPIDISTELSKVNASLQNAVKYIKE	1728
INTQPIDISTELSKVNASLQNAVKYIKES	1729
INTQPIDISTELSKVNASLQNAVKYIKESN	1730

[0160] In certain embodiments, [Xaa]_x is selected from Table 5b.

Table 5b.

Sequence	SEQ ID NO:
TQP	2701
QPI	2702
PID	2703
IDI	2704
DIS	2705
IST	2706
STE	2707
TEL	2708
ELS	2709
LSK	2710
SKV	2711
KVN	2712
VNA	2713
NAS	2714
ASL	2715
SLQ	2716
LQN	2717
QNA	2718
NAV	2719
AVK	2720
VKY	2721
KYI	2722
YIK	2723
IKE	2724
KES	2725
ESN	2726
SNH	2727

Sequence	SEQ ID NO:
NHQ	2728
HQL	2729
QLQ	2730
NTQPID	2731
TQPIDI	2732
QPIDIS	2733
PIDIST	2734
IDISTE	2735
DISTEL	2736
ISTELS	2737
STELSK	2738
TELSKV	2739
ELSKVN	2740
LSKVNA	2741
SKVNAS	2742
KVNASL	2743
VNASLQ	2744
NASLQN	2745
ASLQNA	2746
SLQNAV	2747
LQNAVK	2748
QNAVKY	2749
NAVKYI	2750
AVKYIK	2751
VKYIKE	2752
KYIKES	2753
YIKESN	2754
IKESNH	2755
KESNHQ	2756
ESNHQL	2283
SNHQLQ	2284

[0161] In certain embodiments, [Xaa]_y is selected from Table 5c.

Table 5c.

Sequence	SEQ ID NO:
V	3701
SV	3702
QSV	3703
LQSV	3704

Sequence	SEQ ID NO:
QLQSV	3705
HQLQSV	3706
NHQLQSV	3707
SNHQLQSV	3708
ESNHQLQSV	3709
KESNHQLQSV	3710
IKESNHQLQSV	3711
YIKESNHQLQSV	3712
KYIKESNHQLQSV	3713
VKYIKESNHQLQSV	3714
AVKYIKESNHQLQSV	3715
NAVKYIKESNHQLQSV	3716
QNAVKYIKESNHQLQSV	3717
LQNAVKYIKESNHQLQSV	3718
SLQNAVKYIKESNHQLQSV	3719
ASLQNAVKYIKESNHQLQSV	3720
NASLQNAVKYIKESNHQLQSV	3721
VNASLQNAVKYIKESNHQLQSV	3722
KVNASLQNAVKYIKESNHQLQSV	3723
SKVNASLQNAVKYIKESNHQLQSV	3724
LSKVNASLQNAVKYIKESNHQLQSV	3725
ELSKVNASLQNAVKYIKESNHQLQSV	3726
TELSKVNASLQNAVKYIKESNHQLQSV	3727
STELSKVNASLQNAVKYIKESNHQLQSV	3728
ISTELSKVNASLQNAVKYIKESNHQLQSV	3729
DISTELSKVNASLQNAVKYIKESNHQLQSV	3730

[0162] In certain embodiments, [Xaa]_w, [Xaa]_x, and [Xaa]_y are selected from i-viii:

	SEQ ID NO	[Xaa] _w	[Xaa] _x	[Xaa] _y
i)	41	INTQPIDI	TELSKV	ASLQNAVKYIKESNHQLQSV;
ii)	42	INTQPIDISTEL	KVNASL	NAVKYIKESNHQLQSV;
iii)	43	INTQPIDIS	ELSKVN	SLQNAVKYIKESNHQLQSV;
iv)	44	INTQPIDISTELS	VNASLQ	AVKYIKESNHQLQSV;
v)	45	INTQPIDISTELSKVNASL	NAVKYI	ESNHQLQSV;
vi)	46	INTQPIDISTELSKV	ASLQNA	KYIKESNHQLQSV;
vii)	47	INTQPIDISTELSKVN	SLQNAV	YIKESNHQLQSV; and
viii)	48	INTQPIDISTELSKVNASLQ	AVKYIK	SNHQLQSV.

[0163] In certain embodiments, [Xaa]_w is selected from Table 6a.

Table 6a.

Sequence	SEQ ID NO:
V	1801
VT	1802
VTG	1803
VTGN	1804
VTGNL	1805
VTGNLD	1806
VTGNLDI	1807
VTGNLDIS	1808
VTGNLDIST	1809
VTGNLDISTE	1810
VTGNLDISTEL	1811
VTGNLDISTELG	1812
VTGNLDISTELGN	1813
VTGNLDISTELGNV	1814
VTGNLDISTELGNVN	1815
VTGNLDISTELGNVNN	1816
VTGNLDISTELGNVNNS	1817
VTGNLDISTELGNVNNSI	1818
VTGNLDISTELGNVNNSIS	1819
VTGNLDISTELGNVNNSISN	1820
VTGNLDISTELGNVNNSISNA	1821
VTGNLDISTELGNVNNSISNAL	1822
VTGNLDISTELGNVNNSISNALD	1823
VTGNLDISTELGNVNNSISNALDK	1824

Sequence	SEQ ID NO:
VTGNLDISTELGNVNNSISNALDKL	1825
VTGNLDISTELGNVNNSISNALDKLE	1826
VTGNLDISTELGNVNNSISNALDKLEE	1827
VTGNLDISTELGNVNNSISNALDKLEES	1828
VTGNLDISTELGNVNNSISNALDKLEESN	1829
VTGNLDISTELGNVNNSISNALDKLEESNS	1830

[0164] In certain embodiments, [Xaa]_x is selected from Table 6b.

Table 6b.

Sequence	SEQ ID NO:
GNL	2801
NLD	2802
LDI	2803
DIS	2804
IST	2805
STE	2806
TEL	2807
ELG	2808
LGN	2809
GNV	2810
NVN	2811
VNN	2812
NNS	2813
NSI	2814
SIS	2815
ISN	2816
SNA	2817
NAL	2818
ALD	2819
LDK	2820
DKL	2821
KLE	2822
LEE	2823
EES	2824
ESN	2825
SNS	2826
NSK	2827
SKL	2828
KLD	2829
GNLDIS	2830

Sequence	SEQ ID NO:
NLDIST	2831
LDISTE	2832
DISTEL	2833
ISTELG	2834
STELGN	2835
TELGNV	2836
ELGNVN	2837
LGNVNN	2838
GNVNNS	2839
NVNNSI	2840
VNNSIS	2841
NNSISN	2842
NSISNA	2843
SISNAL	2844
ISNALD	2845
SNALDK	2846
NALDKL	2847
ALDKLE	2848
LDKLEE	2849
DKLEES	2850
KLEESN	2851
LEESNS	2852
EESNSK	2853
ESNSKL	2854
SNSKLD	2855
NSKLDK	2856

[0165] In certain embodiments, [Xaa]_y is selected from Table 6c.

Table 6c.

Sequence	SEQ ID NO:
V	3801
KV	3802
DKV	3803
LDKV	3804
KLDKV	3805
SKLDKV	3806
NSKLDKV	3807
SNSKLDKV	3808
ESNSKLDKV	3809

Sequence	SEQ ID NO:
EESNSKLDKV	3810
LEESNSKLDKV	3811
KLEESNSKLDKV	3812
DKLEESNSKLDKV	3813
LDKLEESNSKLDKV	3814
ALDKLEESNSKLDKV	3815
NALDKLEESNSKLDKV	3816
SNALDKLEESNSKLDKV	3817
ISNALDKLEESNSKLDKV	3818
SISNALDKLEESNSKLDKV	3819
NSISNALDKLEESNSKLDKV	3820
NNISNALDKLEESNSKLDKV	3821
VNNISNALDKLEESNSKLDKV	3822
NVNNISNALDKLEESNSKLDKV	3823
GNVNNISNALDKLEESNSKLDKV	3824
LGNVNNISNALDKLEESNSKLDKV	3825
ELGNVNNISNALDKLEESNSKLDKV	3826
TELGNVNNISNALDKLEESNSKLDKV	3827
STELGNVNNISNALDKLEESNSKLDKV	3828
ISTELGNVNNISNALDKLEESNSKLDKV	3829

[0166] In certain embodiments, [Xaa]_w, [Xaa]_x, and [Xaa]_y are selected from i-viii:

	SEQ ID NO	[Xaa] _w	[Xaa] _x	[Xaa] _y
i)	51	VTGNLDI	TELGNV	NSISNALDKLEESNSKLDKV;
ii)	52	VTGNLDISTEL	NVNNISI	NALDKLEESNSKLDKV;
iii)	53	VTGNLDIS	ELGNVN	SISNALDKLEESNSKLDKV;
iv)	54	VTGNLDISTELG	VNNISIS	ALDKLEESNSKLDKV;
v)	55	VTGNLDISTELGNVNNISIS	ALDKLE	NSKLDKV;
vi)	56	VTGNLDISTELGNV	NSISNA	LDKLEESNSKLDKV;
vii)	57	VTGNLDISTELGNVN	SISNAL	KLEESNSKLDKV; and
viii)	58	VTGNLDISTELGNVNNISIN	LDKLEE	NSKLDKV.

[0167] In certain embodiments, [Xaa]_w is selected from Table 7a.

Table 7a.

Sequence	SEQ ID NO:
V	1901
VD	1902
VDI	1903
VDIS	1904
VDISS	1905
VDISSQ	1906
VDISSQI	1907
VDISSQIS	1908
VDISSQISS	1909
VDISSQISSM	1910
VDISSQISSMN	1911
VDISSQISSMNQ	1912
VDISSQISSMNQS	1913
VDISSQISSMNQSL	1914
VDISSQISSMNQSLQ	1915
VDISSQISSMNQSLQQ	1916
VDISSQISSMNQSLQQS	1917
VDISSQISSMNQSLQQSK	1918
VDISSQISSMNQSLQQSKD	1919
VDISSQISSMNQSLQQSKDY	1920
VDISSQISSMNQSLQQSKDYI	1921
VDISSQISSMNQSLQQSKDYIK	1922
VDISSQISSMNQSLQQSKDYIKE	1923
VDISSQISSMNQSLQQSKDYIKEA	1924
VDISSQISSMNQSLQQSKDYIKEAQ	1925
VDISSQISSMNQSLQQSKDYIKEAQK	1926

[0168] In certain embodiments, [Xaa]_x is selected from Table 7b.

Table 7b.

Sequence	SEQ ID NO:
ISS	2901
SSQ	2902
SQI	2903
QIS	2904
SSM	2905
SMN	2906
MNQ	2907
NQS	2908

Sequence	SEQ ID NO:
QSL	2909
SLQ	2910
LQQ	2911
QQS	2912
QSK	2913
SKD	2914
KDY	2915
DYI	2916
YIK	2917
IKE	2918
KEA	2919
EAQ	2920
AQK	2921
QKI	2922
KIL	2923
ILD	2924
ISSQIS	2925
SSQISS	2926
SQISSM	2927
QISSMN	2928
ISSMNQ	2929
SSMNQS	2930
SMNQSL	2931
MNQSLQ	2932
NQSLQQ	2933
QSLQQS	2934
SLQQSK	2935
LQQSKD	2936
QQSKDY	2937
QSKDYI	2938
SKDYIK	2939
KDYIKE	2940
DYIKEA	2941
YIKEAQ	2942
IKEAQK	2943
KEAQKI	2944
EAQKIL	2945
AQKILD	2946
QKILDT	2947

[0169] In certain embodiments, [Xaa]_y is selected from Table 7c.

Table 7c.

Sequence	SEQ ID NO:
V	3901
TV	3902
DTV	3903
LDTV	3904
ILDTV	3905
KILDTV	3906
QKILDTV	3907
AKKILDTV	3908
EAKKILDTV	3909
KEAKKILDTV	3910
IKKAKKILDTV	3911
YIKKAKKILDTV	3912
DYIKKAKKILDTV	3913
KDYIKKAKKILDTV	3914
SKDYIKKAKKILDTV	3915
QSKDYIKKAKKILDTV	3916
QQSKDYIKKAKKILDTV	3917
LQQSKDYIKKAKKILDTV	3918
SLQQSKDYIKKAKKILDTV	3919
QSLQQSKDYIKKAKKILDTV	3920
NQSLQQSKDYIKKAKKILDTV	3921
MNQSLQQSKDYIKKAKKILDTV	3922
SMNQSLQQSKDYIKKAKKILDTV	3923
SSMNQSLQQSKDYIKKAKKILDTV	3924
ISSMNQSLQQSKDYIKKAKKILDTV	3925
QISSMNQSLQQSKDYIKKAKKILDTV	3926

[0170] In certain embodiments, [Xaa]_w, [Xaa]_x, and [Xaa]_y are selected from i-viii:

	SEQ ID NO	[Xaa] _w	[Xaa] _x	[Xaa] _y
i)	61	VDI	SQISSM	QSLQQSKDYIKEAQRLLDTV;
ii)	62	VDISSQI	SMNQSL	QSKDYIKEAQRLLDTV;
iii)	63	VDIS	QISSMN	SLQQSKDYIKEAQRLLDTV;
iv)	64	VDISSQIS	MNQSLQ	SKDYIKEAQRLLDTV;
v)	65	VDISSQISSMNQSL	QSKDYI	EAQRLLDTV;
vi)	66	VDISSQISSM	QSLQQS	DYIKEAQRLLDTV;
vii)	67	VDISSQISSMN	SLQQSK	YIKEAQRLLDTV; and
viii)	68	VDISSQISSMNQSLQ	SKDYIK	AQRLLDTV.

[0171] It should be understood that the above amino acid sequences of [Xaa]_w, [Xaa]_x, and [Xaa]_y above can be modified to include additional amino acids (e.g., 1, 2, 3, 4, 5, 6, 7, 8, 9, 10 amino acids added) at the N and/or C-terminus, and/or to have N and/or C terminal deletions (e.g., 1, 2, 3, 4, 5, 6, 7, 8, 9, 10 amino acids deleted). In some instances, the sequences of Tables 2a, 2b, 2c, 3a, 3b, 3c, 4a, 4b, 4c, 5a, 5b, 5c, 6a, 6b, 6c, 7a, 7b, and 7c include one or more variants. In some instances, the amino acid sequence has 2 to 18, 2 to 17, 2 to 16, 2 to 15, 2 to 14, 2 to 13, 2 to 12, 2 to 11, 2 to 10, 2 to 9, 2 to 8, 2 to 7, 2 to 6, 2 to 5, 2 to 4, 2 to 3, or 2 substitutions, insertions, and/or deletions relative to the sequences of Tables 2a, 2b, 2c, 3a, 3b, 3c, 4a, 4b, 4c, 5a, 5b, 5c, 6a, 6b, 6c, 7a, 7b, and 7c.

[0172] In certain instances, the amino acid sequences of [Xaa]_w, [Xaa]_x, and [Xaa]_y described herein (e.g., the sequences of Tables 2a, 2b, 2c, 3a, 3b, 3c, 4a, 4b, 4c, 5a, 5b, 5c, 6a, 6b, 6c, 7a, 7b, and 7c) may also contain one or more (e.g., 1, 2, 3, 4, or 5) amino acid substitutions (relative to an amino acid sequence set forth in any one of the sequences of Tables 2a, 2b, 2c, 3a, 3b, 3c, 4a, 4b, 4c, 5a, 5b, 5c, 6a, 6b, 6c, 7a, 7b, and 7c), e.g., one or more (e.g., 1, 2, 3, 4, or 5) conservative and/or non-conservative amino acid substitutions. In some instances, amino acid sequences of [Xaa]_w, [Xaa]_x, and [Xaa]_y described herein (e.g., the sequences of Tables 2a, 2b, 2c, 3a, 3b, 3c, 4a, 4b, 4c, 5a, 5b, 5c, 6a, 6b, 6c, 7a, 7b, and 7c) may also contain at least one, at least 2, at least 3, at least 4, or at least 5 amino acids added to the N-terminus of the peptide. In some instances, the amino acid sequences of [Xaa]_w, [Xaa]_x, and [Xaa]_y (e.g., the sequences of Tables 2a, 2b, 2c, 3a, 3b, 3c, 4a, 4b, 4c, 5a, 5b, 5c, 6a, 6b, 6c, 7a, 7b, and 7c) may also contain at least one, at least 2, at least 3, at least 4, or at least 5 amino acids added to the C-terminus of the peptide.

[0173] As defined generally above, the amino group of the N-terminal amino acid in [Xaa]_w is optionally replaced with -N(H)C(O)-(C₁₋₄ alkyl). In certain embodiments, the amino group of the N-terminal amino acid in [Xaa]_w is replaced with -N(H)C(O)-(C₁₋₄ alkyl). In certain embodiments, the amino group of the N-terminal aspartic acid in [Xaa]_w is replaced with -N(H)C(O)CH₃.

[0174] As defined generally above, p is 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14, 15, or 16. In certain embodiments, p is 3. In certain embodiments, p is 4. In certain embodiments, p is 5. In certain embodiments, p is 6. In certain embodiments, p is 7. In certain embodiments, p is 8. In certain embodiments, p is 9. In certain embodiments, p is 10. In certain embodiments, p is 11. In certain embodiments, p is 12. In certain embodiments, p is 13. In certain embodiments, p is 14. In certain embodiments, p is 15. In certain embodiments, p is 16.

[0175] In certain embodiments, p is 4, 8, 12, or 16. In certain embodiments, p is 8 or 12.

[0176] It will be understood that the above modified (e.g., structurally stabilized) peptides can be modified to include additional amino acids (e.g., 1, 2, 3, 4, 5, 6, 7, 8, 9, 10 amino acids added) at the N and/or C-terminus, and/or to have N and/or C terminal deletions (e.g., 1, 2, 3, 4, 5, 6, 7, 8, 9, 10 amino acids deleted).

[0177] The disclosure encompasses each and every modified peptide and structurally stabilized peptide listed in Table 8 and Table 9 as well as variants thereof. In some instances, the modified peptide is 19 to 50 (e.g., 19, 20, 21, 22, 23, 24, 25, 26, 27, 28, 29, 30, 31, 32, 33, 34, 35, 36, 37, 38, 39, 40, 41, 42, 43, 44, 45, 46, 47, 48, 49, or 50) amino acids in length. In some instances, the modified peptide is 19 to 60 (e.g., 19, 20, 21, 22, 23, 24, 25, 26, 27, 28, 29, 30, 31, 32, 33, 34, 35, 36, 37, 38, 39, 40, 41, 42, 43, 44, 45, 46, 47, 48, 49, 50, 51, 52, 53, 54, 55, 56, 57, 58, 59, or 60) amino acids in length. In some instances, the modified peptide ranges from 19 to 100, 38 to 100, 19 to 60, 38 to 60, 19 to 50, 38 to 50, 19 to 45, 38 to 45, 19 to 40 and 38 to 40 amino acids in length. In some instances, the modified peptide described above has one or more (1, 2, 3, 4, 5, 6) of the properties listed below: (i) is alpha-helical; (ii) is protease resistant; (iii) inhibits fusion of Paramyxoviridae with a host cell; and/or (iv) inhibits infection of a cell by Paramyxoviridae. In some instances, the modified peptide inhibits infection of a cell by Paramyxoviridae in pseudovirus and/or live Paramyxoviridae virus assays and/or wherein the modified peptide prevents infection of a cell by Paramyxoviridae in the pseudovirus and/or the live Paramyxoviridae virus assays.

[0178] In some instances, the modified peptide includes an amino acid sequence that has 2 to 18, 2 to 17, 2 to 16, 2 to 15, 2 to 14, 2 to 13, 2 to 12, 2 to 11, 2 to 10, 2 to 9, 2 to 8, 2 to 7, 2 to 6, 2 to 5, 2 to 4, 2 to 3, or 2 substitutions, insertions, and/or deletions relative to SEQ ID

NOs: 1-6. In some instances, a modified peptide having substitutions, insertions, and/or deletions relative to SEQ ID NOs: 1-6 as described above (i) is alpha-helical; (ii) is protease resistant; (iii) inhibits fusion of Paramyxoviridae with a host cell; and/or (iv) inhibits infection of a cell by Paramyxoviridae. In some instances, the modified peptide inhibits infection of a cell by Paramyxoviridae in pseudovirus and/or live Paramyxoviridae virus assays and/or wherein the modified peptide prevents infection of a cell by Paramyxoviridae in the pseudovirus and/or the live Paramyxoviridae virus assays.

[0179] In some instances, disclosed herein are peptides that comprise 0-10 (0, 1, 2, 3, 4, 5, 6, 7, 8, 9, 10) amino acid substitutions compared to one of the Paramyxoviridae HR2 peptides (e.g., SEQ ID NOs: 1-6) in Table 1. In some instances, disclosed herein are peptides that are at least 30% (e.g., at least 40%, at least 50%, at least 60%, at least 70%, at least 75%, at least 80%, at least 85%, at least 90%, at least 94%, at least 95% identical) to one of the Paramyxoviridae HR2 peptides (e.g., SEQ ID NOs: 1-6) in Table 1. In some instances, the modified peptide is 19 to 50 (e.g., 19, 20, 21, 22, 23, 24, 25, 26, 27, 28, 29, 30, 31, 32, 33, 34, 35, 36, 37, 38, 39, 40, 41, 42, 43, 44, 45, 46, 47, 48, 49, or 50) amino acids in length. In some instances, the modified peptide is 19 to 60 (e.g., 19, 20, 21, 22, 23, 24, 25, 26, 27, 28, 29, 30, 31, 32, 33, 34, 35, 36, 37, 38, 39, 40, 41, 42, 43, 44, 45, 46, 47, 48, 49, 50, 51, 52, 53, 54, 55, 56, 57, 58, 59, 60) amino acids in length. In some instances, the modified peptide ranges from 19 to 100, 38 to 100, 19 to 60, 38 to 60, 19 to 50, 38 to 50, 19 to 45, 38 to 45, 19 to 40 and 38 to 40 amino acids in length. In some instances, the modified peptide described above has one or more (1, 2, 3, 4, 5, 6) of the properties listed below: (i) is alpha-helical; (ii) is protease resistant; (iii) inhibits fusion of a Paramyxoviridae virus with a host cell; and/or (iv) inhibits infection of a cell by a Paramyxoviridae virus. In some instances, the modified peptide inhibits infection of a cell by Paramyxoviridae in pseudovirus and/or live Paramyxoviridae virus assays and/or wherein the modified peptide prevents infection of a cell by Paramyxoviridae in the pseudovirus and/or the live Paramyxoviridae virus assays.

[0180] In some instances, any substitution as described herein can be a conservative substitution. In some instances, any substitution as described herein is a non-conservative substitution.

[0181] In certain instances, the Paramyxoviridae HR2 peptides described herein may also contain one or more (e.g., 1, 2, 3, 4, or 5) amino acid substitutions (relative to an amino acid sequence set forth in any one of SEQ ID NOs: 1-6), e.g., one or more (e.g., 1, 2, 3, 4, or 5) conservative and/or non-conservative amino acid substitutions. In some instances, the Paramyxoviridae HR2 peptides described herein (e.g., SEQ ID NOs: 1-6) may also contain at

least one, at least 2, at least 3, at least 4, or at least 5 amino acids added to the N-terminus of the peptide. In some instances, the Paramyxoviridae HR2 peptides described herein (*e.g.*, SEQ ID NOs: 1-6) may also contain at least one, at least 2, at least 3, at least 4, or at least 5 amino acids added to the C-terminus of the peptide.

[0182] In some embodiments, a modified peptide comprising an amino acid sequence is at least 30%, at least 40%, at least 50%, at least 60%, at least 70%, at least 80%, at least 90%, at least 95%, at least 98%, or is identical to an amino acid sequence selected from:

VALDPIDISIVLNKIKSDLEESKEWIRRSNKILDSI (SEQ ID NO: 1)

VFTDKVDISSQISSMNQSLQQSKDYIKEAQRLLDTV (SEQ ID NO: 2)

ISLERLDVGTNLGNIAKLEDAKELLESDQILRSMK (SEQ ID NO: 3)

INTQPIDISTELSKVNASLQNAVKYIKESNHQLQSV (SEQ ID NO: 4)

VTGN-LDISTELGNVNNISNALDKLEESNSKLDKV (SEQ ID NO: 5) and

VDISSQISSMNQSLQQSKDYIKEAQKILDTV (SEQ ID NO: 6).

[0183] In certain embodiments, the amino acid sequence is SEQ ID NO: 1. In certain embodiments the amino acid sequence is SEQ ID NO: 2. In certain embodiments the amino acid sequence is SEQ ID NO: 3. In certain embodiments the amino acid sequence is SEQ ID NO: 4. In certain embodiments the amino acid sequence is SEQ ID NO: 5. In certain embodiments the amino acid sequence is SEQ ID NO: 6.

Structurally Stabilized Peptide Conjugates

[0184] In some embodiments, structurally stabilized peptides described herein comprise peptide staples. “Peptide stapling” is a term coined from a synthetic methodology wherein two olefin-containing side-chains (*e.g.*, cross-linkable side chains) present in a peptide chain are covalently joined (*e.g.*, “stapled together”) using a ring-closing metathesis (RCM) reaction to form a cross-linked ring (see, *e.g.*, Blackwell et al., *J. Org. Chem.*, 66: 5291-5302, 2001; Angew et al., *Chem. Int. Ed.* 37:3281, 1994). The structural-stabilization may be by, *e.g.*, stapling the peptide (see, *e.g.*, Walensky, *J. Med. Chem.*, 57:6275-6288 (2014), the contents of which are incorporated by reference herein in its entirety). In some cases, the staple is a hydrocarbon staple.

[0185] In some instances, a staple used herein is a lactam staple; a UV-cycloaddition staple; an oxime staple; a thioether staple; a double-click staple; a bis-lactam staple; a bis-arylation staple; or a combination of any two or more thereof. Stabilized peptides as described herein include stapled peptides as well as peptides containing multiple staples or any other chemical strategies for structural reinforcement (see, *e.g.*, Balaram P. *Cur. Opin. Struct. Biol.* 1992;2:845; Kemp DS, et al., *J. Am. Chem. Soc.* 1996;118:4240; Ormer BP, et al., *J. Am. Chem.*

Soc. 2001;123:5382; Chin JW, et al., *Int. Ed.* 2001;40:3806; Chapman RN, et al., *J. Am. Chem. Soc.* 2004;126:12252; Home WS, et al., *Chem. Int. Ed.* 2008;47:2853; Madden et al., *Chem Commun* (Camb). 2009 Oct 7; (37): 5588–5590; Lau et al., *Chem. Soc. Rev.*, 2015,44:91-102; and Gunnoo et al., *Org. Biomol. Chem.*, 2016,14:8002-8013; each of which is incorporated by reference herein in its entirety).

[0186] A peptide is “structurally stabilized” in that it maintains its native secondary structure. For example, stapling allows a peptide, predisposed to having an α -helical secondary structure, to maintain its native α -helical conformation. This secondary structure increases resistance of the peptide to proteolytic cleavage and heat, and may increase target binding affinity, hydrophobicity, plasma membrane binding, and/or cell permeability. Accordingly, modified (e.g., stapled) peptides described herein have improved biological activity and pharmacology relative to a corresponding unmodified (e.g., non-stapled (un-cross-linked)) peptides.

[0187] In some instances, the non-natural amino acids that may be used as stapling amino acids are: (R)-2-(2'-propenyl)alanine; (R)-2-(4'-pentenyl)alanine; (R)- α -(7'-octenyl)alanine; (S)- α -(2'-propenyl)alanine; (S)- α -(4'-pentenyl)alanine; (S)-2-(7'-octenyl)alanine; α,α -Bis(4'-pentenyl)glycine; and α,α -Bis(7'-octenyl)glycine.

[0188] In some embodiments, a staple is between two amino acids separated by, for example, 6 amino acids. In some embodiments, the amino acids forming the staple are positions i and $i+7$. For example, where a peptide has the sequence . . . X1, X2, X3, X4, X5, X6, X7, X8, X9, X10 . . . , a staple can be placed between X2 and X9 or X3 and X10, etc. (i and $i+7$). Where a peptide has the sequence . . . X1, X2, X3, X4, X5, X6, X7, X8, X9 . . . , a staple can be placed between X2 and X6, X3 and X7, or X4 and X8, etc. (i and $i+4$). Additional description regarding making and use of hydrocarbon-stapled peptides can be found, e.g., in U.S. Patent Publication Nos. 2012/0172285, 2010/0286057, and 2005/0250680, the contents of all of which are incorporated by reference herein in their entireties.

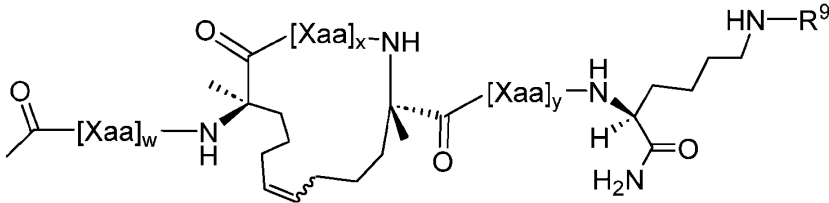
[0189] In addition, other methods of performing different types of stapling are well known in the art and can be employed with the Paramyxoviridae HR2 peptides described herein (*see, e.g., Lactam stapling*: Shepherd et al., *J. Am. Chem. Soc.*, 127:2974–2983 (2005); *UV-cycloaddition stapling*: Madden et al., *Bioorg. Med. Chem. Lett.*, 21:1472–1475 (2011); *Disulfide stapling*: Jackson et al., *Am. Chem. Soc.*, 113:9391–9392 (1991); *Oxime stapling*: Haney et al., *Chem. Commun.*, 47:10915–10917 (2011); *Thioether stapling*: Brunel and Dawson, *Chem. Commun.*, 552–2554 (2005); *Photoswitchable stapling*: J. R. Kumita et al., *Proc. Natl. Acad. Sci. U. S. A.*, 97:3803–3808 (2000); *Double-click stapling*: Lau et al., *Chem.*

Sci., 5:1804–1809 (2014); *Bis-lactam stapling*: J. C. Phelan *et al.*, *J. Am. Chem. Soc.*, 119:455–460 (1997); and *Bis-arylation stapling*: A. M. Spokoiny *et al.*, *J. Am. Chem. Soc.*, 135:5946–5949 (2013)).

Exemplary Specific Compounds

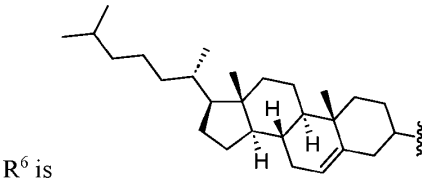
[0190] In certain embodiments, the compound is a compound in Table 8 or 9, or a pharmaceutically acceptable salt thereof. In certain embodiments, the compound is a compound in Table 8 or 9. In certain embodiments, the compound is a compound in Table 8, or a pharmaceutically acceptable salt thereof. In certain embodiments, the compound is a compound in Table 8. In certain embodiments, the compound is a compound in Table 9, or a pharmaceutically acceptable salt thereof. In certain embodiments, the compound is a compound in Table 9. In certain embodiments, the compound is selected from I-1 to I-337, or a pharmaceutically acceptable salt thereof. In certain embodiments, the compound is a compound selected from I-1 to I-337.

Table 8. Exemplary Modified Peptides



wherein

R⁹ is -C(O)-(CH₂CH₂)-[O-CH₂CH₂]₁₂-N(H)C(O)-R⁶; and



R⁶ is

Cmpd. No.	Cmpd. SEQ ID NO:	[Xaa] _w	[Xaa] _w SEQ ID NO:	[Xaa] _x	[Xaa] _x SEQ ID NO:	[Xaa] _y	[Xaa] _y SEQ ID NO:
I-1	101	V	1001	LDP	2001	DISIVLNKIKSD LEESKEWIRRSN KILDSI	3001
I-2	102	VA	1002	DPI	2002	ISIVLNKIKSDL EESKEWIRRSNK ILDSI	3002
I-3	103	VAL	1003	PID	2003	SIVLNKIKSDLE ESKEWIRRSNKI LDSI	3003

Cmpd. No.	Cmpd. SEQ ID NO:	[Xaa] _w	[Xaa] _w SEQ ID NO:	[Xaa] _x	[Xaa] _x SEQ ID NO:	[Xaa] _y	[Xaa] _y SEQ ID NO:
I-4	104	VALD	1004	IDI	2004	IVLNKIKSDLEE SKEWIRRSNKIL DSI	3004
I-5	105	VALDP	1005	DIS	2005	VLNLIKSDLEES KEWIRRSNKILD SI	3005
I-6	106	VALDPI	1006	ISI	2006	LNKIKSDLEESK EWIRRSNKILDS I	3006
I-7	107	VALDPID	1007	SIV	2007	NKIKSDLEESKE WIRRSNKILDSI	3007
I-8	108	VALDPIDI	1008	IVL	2008	KIKSDLEESKEW IRRSNKILDSI	3008
I-9	109	VALDPIDIS	1009	VLN	2009	IKSDLEESKEWI RRSNKILDSI	3009
I-10	110	VALDPIDISI	1010	LNK	2010	KSDLEESKEWIR RSNKILDSI	3010
I-11	111	VALDPIDISIV	1011	NKI	2011	SDLEESKEWIRR SNKILDSI	3011
I-12	112	VALDPIDISIV L	1012	KIK	2012	DLEESKEWIRRS NKILDSI	3012
I-13	113	VALDPIDISIV LN	1013	IKS	2013	LEESKEWIRRSN KILDSI	3013
I-14	114	VALDPIDISIV LNK	1014	KSD	2014	EESKEWIRRSNK ILDSI	3014
I-15	115	VALDPIDISIV LNKI	1015	SDL	2015	ESKEWIRRSNKI LDSI	3015
I-16	116	VALDPIDISIV LNKIK	1016	DLE	2016	SKEWIRRSNKIL DSI	3016
I-17	117	VALDPIDISIV LNKIKS	1017	LEE	2017	KEWIRRSNKILD SI	3017
I-18	118	VALDPIDISIV LNKIKSD	1018	EES	2018	EWIRRSNKILDS I	3018
I-19	119	VALDPIDISIV LNKIKSDL	1019	ESK	2019	WIRRSNKILDSI	3019
I-20	120	VALDPIDISIV LNKIKSDLE	1020	SKE	2020	IRRSNKILDSI	3020
I-21	121	VALDPIDISIV LNKIKSDLEE	1021	KEW	2021	RRSNKILDSI	3021
I-22	122	VALDPIDISIV LNKIKSDLEES	1022	EWI	2022	RSNKILDSI	3022
I-23	123	VALDPIDISIV LNKIKSDLEES K	1023	WIR	2023	SNKILDSI	3023
I-24	124	VALDPIDISIV LNKIKSDLEES KE	1024	IRR	2024	NKILDSI	3024
I-25	125	VALDPIDISIV LNKIKSDLEES KEW	1025	RRS	2025	KILDSI	3025

Cmpd. No.	Cmpd. SEQ ID NO:	[Xaa] _w	[Xaa] _w SEQ ID NO:	[Xaa] _x	[Xaa] _x SEQ ID NO:	[Xaa] _y	[Xaa] _y SEQ ID NO:
I-26	126	VALDPIDISIV LNKIKSDLEES KEWI	1026	RSN	2026	ILDSI	3026
I-27	127	VALDPIDISIV LNKIKSDLEES KEWIR	1027	SNK	2027	LDSI	3027
I-28	128	VALDPIDISIV LNKIKSDLEES KEWIRR	1028	NKI	2028	DSI	3028
I-29	129	VALDPIDISIV LNKIKSDLEES KEWIRRS	1029	KIL	2029	SI	3029
I-30	130	VALDPIDISIV LNKIKSDLEES KEWIRRSN	1030	ILD	2030	I	3030
I-31	131	V	1031	TDK	2031	DISSQISSMNQS LQSKDYIKEAQ RLLDTV	3031
I-32	132	VF	1032	DKV	2032	ISSQISSMNQSL QSKDYIKEAQR LLDTV	3032
I-33	133	VFT	1033	KVD	2033	SSQISSMNQSLQ QSKDYIKEAQR LDTV	3033
I-34	134	VFTD	1034	VDI	2034	SQISSMNQSLQQ SKDYIKEAQRLL DTV	3034
I-35	135	VFTDK	1035	DIS	2035	QISSMNQSLQQS KDYIKEAQRLLD TV	3035
I-36	136	VFTDKV	1036	ISS	2036	ISSMNQSLQQSK DYIKEAQRLLDT V	3036
I-37	137	VFTDKVD	1037	SSQ	2037	SSMNQSLQQSKD YIKEAQRLLDTV	3037
I-38	138	VFTDKVDI	1038	SQI	2038	SMNQSLQQSKDY IKEAQRLLDTV	3038
I-39	139	VFTDKVDIS	1039	QIS	2039	MNQSLQQSKDYI KEAQRLLDTV	3039
I-40	140	VFTDKVDISS	1040	ISS	2040	NQSLQQSKDYIK EAQRLLDTV	3040
I-41	141	VFTDKVDISSQ	1041	SSM	2041	QSLQQSKDYIKE AQRLLDTV	3041
I-42	142	VFTDKVDISSQ I	1042	SMN	2042	SLQQSKDYIKEA QRLLDTV	3042
I-43	143	VFTDKVDISSQ IS	1043	MNQ	2043	LQSKDYIKEAQ RLLDTV	3043
I-44	144	VFTDKVDISSQ ISS	1044	NQS	2044	QSKDYIKEAQR LLDTV	3044
I-45	145	VFTDKVDISSQ ISSM	1045	QSL	2045	QSKDYIKEAQR LDTV	3045

Cmpd. No.	Cmpd. SEQ ID NO:	[Xaa] _w	[Xaa] _w SEQ ID NO:	[Xaa] _x	[Xaa] _x SEQ ID NO:	[Xaa] _y	[Xaa] _y SEQ ID NO:
I-46	146	VFTDKVDISSQ ISSMN	1046	SLQ	2046	SKDYIKEAQRLLD DTV	3046
I-47	147	VFTDKVDISSQ ISSMNQ	1047	LQQ	2047	KDYIKEAQRLLD TV	3047
I-48	148	VFTDKVDISSQ ISSMNQS	1048	QQS	2048	DYIKEAQRLLD TV	3048
I-49	149	VFTDKVDISSQ ISSMNQSL	1049	QSK	2049	YIKEAQRLLD TV	3049
I-50	150	VFTDKVDISSQ ISSMNQSLQ	1050	SKD	2050	IKEAQRLLD TV	3050
I-51	151	VFTDKVDISSQ ISSMNQSLQQ	1051	KDY	2051	KEAQRLLD TV	3051
I-52	152	VFTDKVDISSQ ISSMNQSLQQS	1052	DYI	2052	EAQRLLD TV	3052
I-53	153	VFTDKVDISSQ ISSMNQSLQQS K	1053	YIK	2053	AQRLLD TV	3053
I-54	154	VFTDKVDISSQ ISSMNQSLQQS KD	1054	IKE	2054	QRLLD TV	3054
I-55	155	VFTDKVDISSQ ISSMNQSLQQS KDY	1055	KEA	2055	RLLD TV	3055
I-56	156	VFTDKVDISSQ ISSMNQSLQQS KDYI	1056	EAQ	2056	LLD TV	3056
I-57	157	VFTDKVDISSQ ISSMNQSLQQS KDYIK	1057	AQR	2057	L D TV	3057
I-58	158	VFTDKVDISSQ ISSMNQSLQQS KDYIKE	1058	QRL	2058	D TV	3058
I-59	159	VFTDKVDISSQ ISSMNQSLQQS KDYIKEA	1059	RLL	2059	T V	3059
I-60	160	VFTDKVDISSQ ISSMNQSLQQS KDYIKEAQ	1060	LLD	2060	V	3060
I-61	161	I	1061	LER	2061	DVGTNLGNIAIAK LEDAKELLESD QILRSMK	3061
I-62	162	IS	1062	ERL	2062	VGTTNLGNIAIAKL EDAKELLESDQ ILRSMK	3062
I-63	163	ISL	1063	RLD	2063	GTNLGNIAIAKLE DAKELLESDQI LRSMK	3063
I-64	164	ISLE	1064	LDV	2064	TNLGNIAIAKLED AKELLESDQIL RSMK	3064

Cmpd. No.	Cmpd. SEQ ID NO:	[Xaa] _w	[Xaa] _w SEQ ID NO:	[Xaa] _x	[Xaa] _x SEQ ID NO:	[Xaa] _y	[Xaa] _y SEQ ID NO:
I-65	165	ISLER	1065	DVG	2065	NLGNAIAKLEDA KELLESSDQILR SMK	3065
I-66	166	ISLERL	1066	VGT	2066	LGNAIAKLEDAK ELLESSDQILRS MK	3066
I-67	167	ISLERLD	1067	GTN	2067	GNAIAKLEDAKE LLESSDQILRSM K	3067
I-68	168	ISLERLDV	1068	TNL	2068	NAIAKLEDAKEL LESSDQILRSMK	3068
I-69	169	ISLERLDVG	1069	NLG	2069	AIKLEDAKELL ESSDQILRSMK	3069
I-70	170	ISLERLDVGT	1070	LGN	2070	IAKLEDAKELLE SSDQILRSMK	3070
I-71	171	ISLERLDVGTN	1071	GNA	2071	AKLEDAKELLES SDQILRSMK	3071
I-72	172	ISLERLDVGTN L	1072	NAI	2072	KLEDAKELLESS DQILRSMK	3072
I-73	173	ISLERLDVGTN LG	1073	AIA	2073	LEDAKELLESSD QILRSMK	3073
I-74	174	ISLERLDVGTN LGN	1074	IAK	2074	EDAKELLESSDQ ILRSMK	3074
I-75	175	ISLERLDVGTN LGNA	1075	AKL	2075	DAKELLESSDQI LRSMK	3075
I-76	176	ISLERLDVGTN LGNAI	1076	KLE	2076	AKELLESSDQIL RSMK	3076
I-77	177	ISLERLDVGTN LGNAIA	1077	LED	2077	KELLESSDQILR SMK	3077
I-78	178	ISLERLDVGTN LGNAIAK	1078	EDA	2078	ELLESSDQILRS MK	3078
I-79	179	ISLERLDVGTN LGNAIAKL	1079	DAK	2079	LLESSDQILRSM K	3079
I-80	180	ISLERLDVGTN LGNAIAKLE	1080	AKE	2080	LESSDQILRSMK	3080
I-81	181	ISLERLDVGTN LGNAIAKLED	1081	KEL	2081	ESSDQILRSMK	3081
I-82	182	ISLERLDVGTN LGNAIAKLEDA	1082	ELL	2082	SSDQILRSMK	3082
I-83	183	ISLERLDVGTN LGNAIAKLEDA K	1083	LLE	2083	SDQILRSMK	3083
I-84	184	ISLERLDVGTN LGNAIAKLEDA KE	1084	LES	2084	DQILRSMK	3084
I-85	185	ISLERLDVGTN LGNAIAKLEDA KEL	1085	ESS	2085	QILRSMK	3085
I-86	186	ISLERLDVGTN LGNAIAKLEDA KELL	1086	SSD	2086	ILRSMK	3086

Cmpd. No.	Cmpd. SEQ ID NO:	[Xaa] _w	[Xaa] _w SEQ ID NO:	[Xaa] _x	[Xaa] _x SEQ ID NO:	[Xaa] _y	[Xaa] _y SEQ ID NO:
I-87	187	ISLERLDVGTN LGNAIAKLEDA KELLE	1087	SDQ	2087	LRSMK	3087
I-88	188	ISLERLDVGTN LGNAIAKLEDA KELLES	1088	DQI	2088	RSMK	3088
I-89	189	ISLERLDVGTN LGNAIAKLEDA KELLESS	1089	QIL	2089	SMK	3089
I-90	190	ISLERLDVGTN LGNAIAKLEDA KELLESSD	1090	ILR	2090	MK	3090
I-91	191	ISLERLDVGTN LGNAIAKLEDA KELLESSDQ	1091	LRS	2091	K	3091
I-92	192	I	1092	TQP	2092	DISTELSKVNAS LQNAVKYIKESN HQLQSV	3092
I-93	193	IN	1093	QPI	2093	ISTELSKVNASL QNAVKYIKESNH QLQSV	3093
I-94	194	INT	1094	PID	2094	STELSKVNASLQ NAVKYIKESNHQ LQSV	3094
I-95	195	INTQ	1095	IDI	2095	TELSKVNASLQN AVKYIKESNHQL QSV	3095
I-96	196	INTQP	1096	DIS	2096	ELSKVNASLQNA VKYIKESNHQLQ SV	3096
I-97	197	INTQPI	1097	IST	2097	LSKVNASLQNAV KYIKESNHQLQS V	3097
I-98	198	INTQPID	1098	STE	2098	SKVNASLQNAV YIKESNHQLQSV	3098
I-99	199	INTQPIDI	1099	TEL	2099	KVNASLQNAV IKESNHQLQSV	3099
I-100	200	INTQPIDIS	1100	ELS	2100	VNASLQNAV IKESNHQLQSV	3100
I-101	201	INTQPIDIST	1101	LSK	2101	NASLQNAV IKESNHQLQSV	3101
I-102	202	INTQPIDISTE	1102	SKV	2102	ASLQNAV IKESNHQLQSV	3102
I-103	203	INTQPIDISTE L	1103	KVN	2103	SLQNAV IKESNHQLQSV	3103
I-104	204	INTQPIDISTE LS	1104	VNA	2104	LQNAV IKESNHQLQSV	3104
I-105	205	INTQPIDISTE LSK	1105	NAS	2105	QNAV IKESNHQLQSV	3105
I-106	206	INTQPIDISTE LSKV	1106	ASL	2106	NAV IKESNHQLQSV	3106

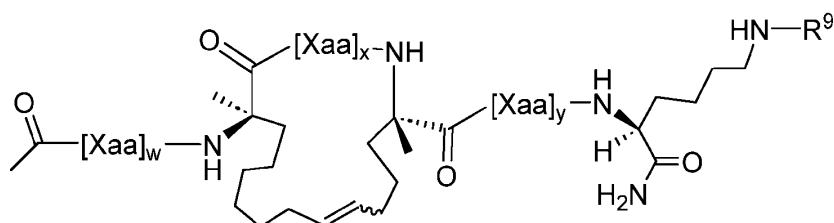
Cmpd. No.	Cmpd. SEQ ID NO:	[Xaa] _w	[Xaa] _w SEQ ID NO:	[Xaa] _x	[Xaa] _x SEQ ID NO:	[Xaa] _y	[Xaa] _y SEQ ID NO:
I-107	207	INTQPIDISTE LSKVN	1107	SLQ	2107	AVKYIKESNHQL QSV	3107
I-108	208	INTQPIDISTE LSKVNA	1108	LQN	2108	VKYIKESNHQLQ SV	3108
I-109	209	INTQPIDISTE LSKVNAS	1109	QNA	2109	KYIKESNHQLQS V	3109
I-110	210	INTQPIDISTE LSKVNASL	1110	NAV	2110	YIKESNHQLQSV	3110
I-111	211	INTQPIDISTE LSKVNASLQ	1111	AVK	2111	IKESNHQLQSV	3111
I-112	212	INTQPIDISTE LSKVNASLQN	1112	VKY	2112	KESNHQLQSV	3112
I-113	213	INTQPIDISTE LSKVNASLQNA	1113	KYI	2113	ESNHQLQSV	3113
I-114	214	INTQPIDISTE LSKVNASLQNA V	1114	YIK	2114	SNHQLQSV	3114
I-115	215	INTQPIDISTE LSKVNASLQNA VK	1115	IKE	2115	NHQLQSV	3115
I-116	216	INTQPIDISTE LSKVNASLQNA VKY	1116	KES	2116	HQLQSV	3116
I-117	217	INTQPIDISTE LSKVNASLQNA VKYI	1117	ESN	2117	QLQSV	3117
I-118	218	INTQPIDISTE LSKVNASLQNA VKYIK	1118	SNH	2118	LQSV	3118
I-119	219	INTQPIDISTE LSKVNASLQNA VKYIKE	1119	NHQ	2119	QSV	3119
I-120	220	INTQPIDISTE LSKVNASLQNA VKYIKES	1120	HQL	2120	SV	3120
I-121	221	INTQPIDISTE LSKVNASLQNA VKYIKESN	1121	QLQ	2121	V	3121
I-122	222	V	1122	GNL	2122	ISTELGNVNNSI SNALDKLEESNS KLDKV	3122
I-123	223	VT	1123	NLD	2123	STELGNVNNSIS NALDKLEESNSK LDKV	3123
I-124	224	VTG	1124	LDI	2124	TELGNVNNSISN ALDKLEESNSKL DKV	3124
I-125	225	VTGN	1125	DIS	2125	ELGNVNNSISNA LDKLEESNSKLD KV	3125

Cmpd. No.	Cmpd. SEQ ID NO:	[Xaa] _w	[Xaa] _w SEQ ID NO:	[Xaa] _x	[Xaa] _x SEQ ID NO:	[Xaa] _y	[Xaa] _y SEQ ID NO:
I-126	226	VTGNL	1126	IST	2126	LGNVNNSISNAL DKLEESNSKLDK V	3126
I-127	227	VTGNLD	1127	STE	2127	GNVNNSISNALD KLEESNSKLDKV	3127
I-128	228	VTGNLDI	1128	TEL	2128	NVNNSISNALDK LEESNSKLDKV	3128
I-129	229	VTGNLDIS	1129	ELG	2129	VNNSISNALDKL EESNSKLDKV	3129
I-130	230	VTGNLDIST	1130	LGN	2130	NNSISNALDKLE ESNSKLDKV	3130
I-131	231	VTGNLDISTE	1131	GNV	2131	NSISNALDKLEE SNSKLDKV	3131
I-132	232	VTGNLDISTEL	1132	NVN	2132	SISNALDKLEES NSKLDKV	3132
I-133	233	VTGNLDISTEL G	1133	VNN	2133	ISNALDKLEESN SKLDKV	3133
I-134	234	VTGNLDISTEL GN	1134	NNS	2134	SNALDKLEESNS KLDKV	3134
I-135	235	VTGNLDISTEL GNV	1135	NSI	2135	NALDKLEESNSK LDKV	3135
I-136	236	VTGNLDISTEL GNVN	1136	SIS	2136	ALDKLEESNSKL DKV	3136
I-137	237	VTGNLDISTEL GNVNN	1137	ISN	2137	LDKLEESNSKLD KV	3137
I-138	238	VTGNLDISTEL GNVNNS	1138	SNA	2138	DKLEESNSKLDK V	3138
I-139	239	VTGNLDISTEL GNVNNSI	1139	NAL	2139	KLEESNSKLDKV	3139
I-140	240	VTGNLDISTEL GNVNNSIS	1140	ALD	2140	LEESNSKLDKV	3140
I-141	241	VTGNLDISTEL GNVNNSISN	1141	LDK	2141	EESNSKLDKV	3141
I-142	242	VTGNLDISTEL GNVNNSISNA	1142	DKL	2142	ESNSKLDKV	3142
I-143	243	VTGNLDISTEL GNVNNSISNAL	1143	KLE	2143	SNSKLDKV	3143
I-144	244	VTGNLDISTEL GNVNNSISNAL D	1144	LEE	2144	NSKLDKV	3144
I-145	245	VTGNLDISTEL GNVNNSISNAL DK	1145	EES	2145	SKLDKV	3145
I-146	246	VTGNLDISTEL GNVNNSISNAL DKL	1146	ESN	2146	KLDKV	3146
I-147	247	VTGNLDISTEL GNVNNSISNAL DKLE	1147	SNS	2147	LDKV	3147

Cmpd. No.	Cmpd. SEQ ID NO:	[Xaa] _w	[Xaa] _w SEQ ID NO:	[Xaa] _x	[Xaa] _x SEQ ID NO:	[Xaa] _y	[Xaa] _y SEQ ID NO:
I-148	248	VTGNLDISTEL GNVNNSISNAL DKLEE	1148	NSK	2148	DKV	3148
I-149	249	VTGNLDISTEL GNVNNSISNAL DKLEES	1149	SKL	2149	KV	3149
I-150	250	VTGNLDISTEL GNVNNSISNAL DKLEESN	1150	KLD	2150	V	3150
I-151	251	V	1151	ISS	2151	ISSMNQSLQQSK DYIKEAQKILDT V	3151
I-152	252	VD	1152	SSQ	2152	SSMNQSLQQSKD YIKEAQKILDTV	3152
I-153	253	VDI	1153	SQI	2153	SMNQSLQQSKDY IKEAQKILDTV	3153
I-154	254	VDIS	1154	QIS	2154	MNQSLQQSKDYI KEAQKILDTV	3154
I-155	255	VDISS	1155	ISS	2155	NQSLQQSKDYIK EAQKILDTV	3155
I-156	256	VDISSQ	1156	SSM	2156	QSLQQSKDYIKE AQKILDTV	3156
I-157	257	VDISSQI	1157	SMN	2157	SLQQSKDYIKEA QKILDTV	3157
I-158	258	VDISSQIS	1158	MNQ	2158	LQQSKDYIKEAQ KILDTV	3158
I-159	259	VDISSQISS	1159	NQS	2159	QQSKDYIKEAQK ILDTV	3159
I-160	260	VDISSQISSM	1160	QSL	2160	QSKDYIKEAQKI LDTV	3160
I-161	261	VDISSQISSMN	1161	SLQ	2161	SKDYIKEAQKIL DTV	3161
I-162	262	VDISSQISSMN Q	1162	LQQ	2162	KDYIKEAQKILD TV	3162
I-163	263	VDISSQISSMN QS	1163	QQS	2163	DYIKEAQKILDT V	3163
I-164	264	VDISSQISSMN QSL	1164	QSK	2164	YIKEAQKILDTV	3164
I-165	265	VDISSQISSMN QSLQ	1165	SKD	2165	IKEAQKILDTV	3165
I-166	266	VDISSQISSMN QSLQQ	1166	KDY	2166	KEAQKILDTV	3166
I-167	267	VDISSQISSMN QSLQQS	1167	DYI	2167	EAQKILDTV	3167
I-168	268	VDISSQISSMN QSLQQSK	1168	YIK	2168	AQKILDTV	3168
I-169	269	VDISSQISSMN QSLQQSKD	1169	IKE	2169	QKILDTV	3169
I-170	270	VDISSQISSMN QSLQQSKDY	1170	KEA	2170	KILDTV	3170

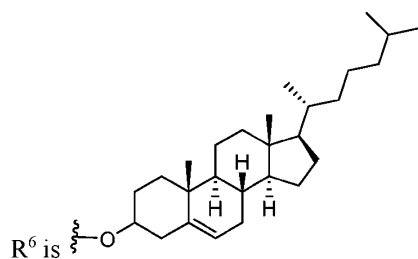
Cmpd. No.	Cmpd. SEQ ID NO:	[Xaa] _w	[Xaa] _w SEQ ID NO:	[Xaa] _x	[Xaa] _x SEQ ID NO:	[Xaa] _y	[Xaa] _y SEQ ID NO:
I-171	271	VDISSQISSMN QSLQQSKDYI	1171	EAQ	2171	ILDTV	3171
I-172	272	VDISSQISSMN QSLQQSKDYIK	1172	AQK	2172	LDTV	3172
I-173	273	VDISSQISSMN QSLQQSKDYIK E	1173	QKI	2173	DTV	3173
I-174	274	VDISSQISSMN QSLQQSKDYIK EA	1174	KIL	2174	TV	3174
I-175	275	VDISSQISSMN QSLQQSKDYIK EAQ	1175	ILD	2175	V	3175

Table 9. Exemplary Modified Peptides



wherein

R⁹ is -C(O)-(CH₂CH₂)-[O-CH₂CH₂]₁₂-N(H)C(O)-(CH₂)-R⁶; and



Cmpd. No.	Cmpd. SEQ ID NO:	[Xaa] _w	[Xaa] _w SEQ ID NO:	[Xaa] _x	[Xaa] _x SEQ ID NO:	[Xaa] _y	[Xaa] _y SEQ ID NO:
I-176	276	V	1176	LDPIDI	2176	IVLNKIKSDLE ESKEWIRRSNK ILDSI	3176
I-177	277	VA	1177	DPIDIS	2177	VLNLIKSDLEE SKEWIRRSNKI LDSI	3177
I-178	278	VAL	1178	PIDISI	2178	LNKIKSDLEES KEWIRRSNKIL DSI	3178

Cmpd. No.	Cmpd. SEQ ID NO:	[Xaa] _w	[Xaa] _w SEQ ID NO:	[Xaa] _x	[Xaa] _x SEQ ID NO:	[Xaa] _y	[Xaa] _y SEQ ID NO:
I-179	279	VALD	1179	IDISIV	2179	NKIKSDLEESK EWIRRSNKILD SI	3179
I-180	280	VALDP	1180	DISIVL	2180	KIKSDLEESKE WIRRSNKILDS I	3180
I-181	281	VALDPI	1181	ISIVLN	2181	IKSDLEESKEW IRRSNKILDSI	3181
I-182	282	VALDPID	1182	SIVLNK	2182	KSDLEESKEWI RRSNKILDSI	3182
I-183	283	VALDPIDI	1183	IVLNKI	2183	SDLEESKEWIR RSNKILDSI	3183
I-184	284	VALDPIDIS	1184	VLNKIK	2184	DLEESKEWIRR SNKILDSI	3184
I-185	285	VALDPIDISI	1185	LNKIKS	2185	LEESKEWIRRS NKILDSI	3185
I-186	286	VALDPIDISIV	1186	NKIKSD	2186	EESKEWIRRSN KILDSI	3186
I-187	287	VALDPIDISIV L	1187	KIKSDL	2187	ESKEWIRRSNK ILDSI	3187
I-188	288	VALDPIDISIV LN	1188	IKSDLE	2188	SKEWIRRSNKI LDSI	3188
I-189	289	VALDPIDISIV LNK	1189	KSDLEE	2189	KEWIRRSNKIL DSI	3189
I-190	290	VALDPIDISIV LNKI	1190	SDLEES	2190	EWIRRSNKILD SI	3190
I-191	291	VALDPIDISIV LNKIK	1191	DLEESK	2191	WIRRSNKILDS I	3191
I-192	292	VALDPIDISIV LNKIKS	1192	LEESKE	2192	IRRSNKILDSI	3192
I-193	293	VALDPIDISIV LNKIKSD	1193	EESKEW	2193	RRSNKILDSI	3193
I-194	294	VALDPIDISIV LNKIKSDL	1194	ESKEWI	2194	RSNKILDSI	3194
I-195	295	VALDPIDISIV LNKIKSDLE	1195	SKEWIR	2195	SNKILDSI	3195
I-196	296	VALDPIDISIV LNKIKSDLEE	1196	KEWIRR	2196	NKILDSI	3196
I-197	297	VALDPIDISIV LNKIKSDLEES	1197	EWIRRS	2197	KILDSI	3197
I-198	298	VALDPIDISIV LNKIKSDLEES K	1198	WIRRSN	2198	ILDSI	3198
I-199	299	VALDPIDISIV LNKIKSDLEES KE	1199	IRRSNK	2199	LDSI	3199
I-200	300	VALDPIDISIV LNKIKSDLEES KEW	1200	RRSNKI	2200	DSI	3200

Cmpd. No.	Cmpd. SEQ ID NO:	[Xaa] _w	[Xaa] _w SEQ ID NO:	[Xaa] _x	[Xaa] _x SEQ ID NO:	[Xaa] _y	[Xaa] _y SEQ ID NO:
I-201	301	VALDPIDISIV LNKIKSDLEES KEWI	1201	RSNKIL	2201	SI	3201
I-202	302	VALDPIDISIV LNKIKSDLEES KEWIR	1202	SNKILD	2202	I	3202
I-203	303	V	1203	TDKVDI	2203	SQISSMNQSLQ QSKDYIKEAQR LLDTV	3203
I-204	304	VF	1204	DKVDIS	2204	QISSMNQSLQQ SKDYIKEAQRLL LDTV	3204
I-205	305	VFT	1205	KVDISS	2205	ISSMNQSLQQS KDYIKEAQRLL DTV	3205
I-206	306	VFTD	1206	VDISSQ	2206	SSMNQSLQQSK DYIKEAQRLLD TV	3206
I-207	307	VFTDK	1207	DISSQI	2207	SMNQSLQQSKD YIKEAQRLLDT V	3207
I-208	308	VFTDKV	1208	ISSQIS	2208	MNQSLQQSKDY IKEAQRLLDTV	3208
I-209	309	VFTDKVD	1209	SSQISS	2209	NQSLQQSKDYI KEAQRLLDTV	3209
I-210	310	VFTDKVDI	1210	SQISSM	2210	QSLQQSKDYIK EAQRLLDTV	3210
I-211	311	VFTDKVDIS	1211	QISSMN	2211	SLQQSKDYIKE AQRLLDTV	3211
I-212	312	VFTDKVDISS	1212	ISSMNQ	2212	LQQSKDYIKEA QRLLDTV	3212
I-213	313	VFTDKVDISSQ	1213	SSMNQS	2213	QQSKDYIKEAQ RLLDTV	3213
I-214	314	VFTDKVDISSQ I	1214	SMNQSL	2214	QSKDYIKEAQR LLDTV	3214
I-215	315	VFTDKVDISSQ IS	1215	MNQSLQ	2215	SKDYIKEAQRLL LDTV	3215
I-216	316	VFTDKVDISSQ ISS	1216	NQSLQQ	2216	KDYIKEAQRLL DTV	3216
I-217	317	VFTDKVDISSQ ISSM	1217	QSLQQS	2217	DYIKEAQRLLD TV	3217
I-218	318	VFTDKVDISSQ ISSMN	1218	SLQQSK	2218	YIKEAQRLLDT V	3218
I-219	319	VFTDKVDISSQ ISSMNQ	1219	LQQSKD	2219	IKEAQRLLDTV	3219
I-220	320	VFTDKVDISSQ ISSMNQS	1220	QQSKDY	2220	KEAQRLLDTV	3220
I-221	321	VFTDKVDISSQ ISSMNQSL	1221	QSKDYI	2221	EAQRLLDTV	3221
I-222	322	VFTDKVDISSQ ISSMNQSLQ	1222	SKDYIK	2222	AQRLLDTV	3222

Cmpd. No.	Cmpd. SEQ ID NO:	[Xaa] _w	[Xaa] _w SEQ ID NO:	[Xaa] _x	[Xaa] _x SEQ ID NO:	[Xaa] _y	[Xaa] _y SEQ ID NO:
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I-224	324	VFTDKVDISSQ ISSMNQSLQQS	1224	DYIKEA	2224	RLLDTV	3224
I-225	325	VFTDKVDISSQ ISSMNQSLQQS K	1225	YIKEAQ	2225	LLDTV	3225
I-226	326	VFTDKVDISSQ ISSMNQSLQQS KD	1226	IKEAQR	2226	LDTV	3226
I-227	327	VFTDKVDISSQ ISSMNQSLQQS KDY	1227	KEAQRL	2227	DTV	3227
I-228	328	VFTDKVDISSQ ISSMNQSLQQS KDYI	1228	EAQRLL	2228	TV	3228
I-229	329	VFTDKVDISSQ ISSMNQSLQQS KDYIK	1229	AQRLLD	2229	V	3229
I-230	330	I	1230	LERLDV	2230	TNLGNAIAKLE DAKELLESDQ ILRSMK	3230
I-231	331	IS	1231	ERLDVG	2231	NLGNAIAKLED AKELLESDQI LRSMK	3231
I-232	332	ISL	1232	RLDVGT	2232	LGNAIAKLEDA KELLESDQIL RSMK	3232
I-233	333	ISLE	1233	LDVGTN	2233	GNAIAKLEDAK ELLESDQILR SMK	3233
I-234	334	ISLER	1234	DVGTNL	2234	NAIAKLEDAKE LLESDQILRS MK	3234
I-235	335	ISLERL	1235	VGTNLG	2235	AIKLEDAKEL LESSDQILRSM K	3235
I-236	336	ISLERLD	1236	GTNLGN	2236	IAKLEDAKELL ESSDQILRSMK	3236
I-237	337	ISLERLDV	1237	TNLGNA	2237	AKLEDAKELLE SSDQILRSMK	3237
I-238	338	ISLERLDVG	1238	NLGNAI	2238	KLEDAKELLES SDQILRSMK	3238
I-239	339	ISLERLDVGT	1239	LGNAIA	2239	LEDAKELLE DQILRSMK	3239
I-240	340	ISLERLDVGTN	1240	GNAIAK	2240	EDAKELLESD QILRSMK	3240
I-241	341	ISLERLDVGTN L	1241	NAIAKL	2241	DAKELLESDQ ILRSMK	3241
I-242	342	ISLERLDVGTN LG	1242	AIKLE	2242	AKELLESDQI LRSMK	3242

Cmpd. No.	Cmpd. SEQ ID NO:	[Xaa] _w	[Xaa] _w SEQ ID NO:	[Xaa] _x	[Xaa] _x SEQ ID NO:	[Xaa] _y	[Xaa] _y SEQ ID NO:
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I-244	344	ISLERLDVGTN LGNA	1244	AKLEDA	2244	ELLESSDQILR SMK	3244
I-245	345	ISLERLDVGTN LGNAI	1245	KLEDAK	2245	LLESSDQILRS MK	3245
I-246	346	ISLERLDVGTN LGNAIA	1246	LEDAKE	2246	LESSDQILRSM K	3246
I-247	347	ISLERLDVGTN LGNAIAK	1247	EDAKEL	2247	ESSDQILRSMK	3247
I-248	348	ISLERLDVGTN LGNAIAKL	1248	DAKELL	2248	SSDQILRSMK	3248
I-249	349	ISLERLDVGTN LGNAIAKLE	1249	AKELLE	2249	SDQILRSMK	3249
I-250	350	ISLERLDVGTN LGNAIAKLED	1250	KELLES	2250	DQILRSMK	3250
I-251	351	ISLERLDVGTN LGNAIAKLEDA	1251	ELLESS	2251	QILRSMK	3251
I-252	352	ISLERLDVGTN LGNAIAKLEDA K	1252	LLESSD	2252	ILRSMK	3252
I-253	353	ISLERLDVGTN LGNAIAKLEDA KE	1253	LESSDQ	2253	LRSRK	3253
I-254	354	ISLERLDVGTN LGNAIAKLEDA KEL	1254	ESSDQI	2254	RSMK	3254
I-255	355	ISLERLDVGTN LGNAIAKLEDA KELL	1255	SSDQIL	2255	SMK	3255
I-256	356	ISLERLDVGTN LGNAIAKLEDA KELLE	1256	SDQILR	2256	MK	3256
I-257	357	ISLERLDVGTN LGNAIAKLEDA KELLES	1257	DQILRS	2257	K	3257
I-258	358	I	1258	TQPIDI	2258	TELSKVNASIQ NAVKYIKESNH QLQSV	3258
I-259	359	IN	1259	QPIDIS	2259	ELSKVNASLQN AVKYIKESNHQ LQSV	3259
I-260	360	INT	1260	PIDIST	2260	LSKVNASLQNA VKYIKESNHQL QSV	3260
I-261	361	INTQ	1261	IDISTE	2261	SKVNASLQNAV KYIKESNHQLQ SV	3261
I-262	362	INTQP	1262	DISTEL	2262	KVNASLQNAV KYIKESNHQLQS V	3262

Cmpd. No.	Cmpd. SEQ ID NO:	[Xaa] _w	[Xaa] _w SEQ ID NO:	[Xaa] _x	[Xaa] _x SEQ ID NO:	[Xaa] _y	[Xaa] _y SEQ ID NO:
I-263	363	INTQPI	1263	ISTELS	2263	VNASLQNAVKY IKESNHQLQSV	3263
I-264	364	INTQPID	1264	STELSK	2264	NASLQNAVKYI KESNHQLQSV	3264
I-265	365	INTQPIDI	1265	TELSKV	2265	ASLQNAVKYIK ESNHQLQSV	3265
I-266	366	INTQPIDIS	1266	ELSKVN	2266	SLQNAVKYIKE SNHQLQSV	3266
I-267	367	INTQPIDIST	1267	LSKVNA	2267	LQNAVKYIKES NHQLQSV	3267
I-268	368	INTQPIDISTE	1268	SKVNAS	2268	QNAVKYIKESN HQLQSV	3268
I-269	369	INTQPIDISTE L	1269	KVNASL	2269	NAVKYIKESNH QLQSV	3269
I-270	370	INTQPIDISTE LS	1270	VNASLQ	2270	AVKYIKESNHQ LQSV	3270
I-271	371	INTQPIDISTE LSK	1271	NASLQN	2271	VKYIKESNHQL QSV	3271
I-272	372	INTQPIDISTE LSKV	1272	ASLQNA	2272	KYIKESNHQLQ SV	3272
I-273	373	INTQPIDISTE LSKVN	1273	SLQNAV	2273	YIKESNHQLQS V	3273
I-274	374	INTQPIDISTE LSKVNA	1274	LQNAVK	2274	IKESNHQLQSV	3274
I-275	375	INTQPIDISTE LSKVNAS	1275	QNAVKY	2275	KESNHQLQSV	3275
I-276	376	INTQPIDISTE LSKVNASL	1276	NAVKYI	2276	ESNHQLQSV	3276
I-277	377	INTQPIDISTE LSKVNASLQ	1277	AVKYIK	2277	SNHQLQSV	3277
I-278	378	INTQPIDISTE LSKVNASLQN	1278	VKYIKE	2278	NHQLQSV	3278
I-279	379	INTQPIDISTE LSKVNASLQNA	1279	KYIKES	2279	HQLQSV	3279
I-280	380	INTQPIDISTE LSKVNASLQNA V	1280	YIKESN	2280	QLQSV	3280
I-281	381	INTQPIDISTE LSKVNASLQNA VK	1281	IKESNH	2281	LQSV	3281
I-282	382	INTQPIDISTE LSKVNASLQNA VKY	1282	KESNHQ	2282	QSV	3282
I-283	383	INTQPIDISTE LSKVNASLQNA VKYI	1283	ESNHQL	2283	SV	3283
I-284	384	INTQPIDISTE LSKVNASLQNA VKYIK	1284	SNHQLQ	2284	V	3284

Cmpd. No.	Cmpd. SEQ ID NO:	[Xaa] _w	[Xaa] _w SEQ ID NO:	[Xaa] _x	[Xaa] _x SEQ ID NO:	[Xaa] _y	[Xaa] _y SEQ ID NO:
I-285	385	V	1285	GNLDIS	2285	ELGNVNNSISN ALDKLEESNSK LDKV	3285
I-286	386	VT	1286	NLDIST	2286	LGNVNNSISNA LDKLEESNSKL DKV	3286
I-287	387	VTG	1287	LDISTE	2287	GNVNNSISNAL DKLEESNSKLD KV	3287
I-288	388	VTGN	1288	DISTEL	2288	NVNNSISNALD KLEESNSKLDK V	3288
I-289	389	VTGNL	1289	ISTELG	2289	VNNSISNALDK LEESNSKLDKV	3289
I-290	390	VTGNLD	1290	STELGN	2290	NNSISNALDKL EESNSKLDKV	3290
I-291	391	VTGNLDI	1291	TELGNV	2291	NSISNALDKLE ESNSKLDKV	3291
I-292	392	VTGNLDIS	1292	ELGNVN	2292	SISNALDKLEE SNSKLDKV	3292
I-293	393	VTGNLDIST	1293	LGNVNN	2293	ISNALDKLEES NSKLDKV	3293
I-294	394	VTGNLDISTE	1294	GNVNNS	2294	SNALDKLEESN SKLDKV	3294
I-295	395	VTGNLDISTEL	1295	NVNNSI	2295	NALDKLEESNS KLDKV	3295
I-296	396	VTGNLDISTEL G	1296	VNNSIS	2296	ALDKLEESNSK LDKV	3296
I-297	397	VTGNLDISTEL GN	1297	NNSISN	2297	LDKLEESNSKL DKV	3297
I-298	398	VTGNLDISTEL GNV	1298	NSISNA	2298	DKLEESNSKLD KV	3298
I-299	399	VTGNLDISTEL GNVN	1299	SISNAL	2299	KLEESNSKLDK V	3299
I-300	400	VTGNLDISTEL GNVNN	1300	ISNALD	2300	LEESNSKLDKV	3300
I-301	401	VTGNLDISTEL GNVNNS	1301	SNALDK	2301	EESNSKLDKV	3301
I-302	402	VTGNLDISTEL GNVNNSI	1302	NALDKL	2302	ESNSKLDKV	3302
I-303	403	VTGNLDISTEL GNVNNSIS	1303	ALDKLE	2303	SNSKLDKV	3303
I-304	404	VTGNLDISTEL GNVNNSISN	1304	LDKLEE	2304	NSKLDKV	3304
I-305	405	VTGNLDISTEL GNVNNSISNA	1305	DKLEES	2305	SKLDKV	3305
I-306	406	VTGNLDISTEL GNVNNSISNAL	1306	KLEESN	2306	KLDKV	3306
I-307	407	VTGNLDISTEL GNVNNSISNAL D	1307	LEESNS	2307	LDKV	3307

Cmpd. No.	Cmpd. SEQ ID NO:	[Xaa] _w	[Xaa] _w SEQ ID NO:	[Xaa] _x	[Xaa] _x SEQ ID NO:	[Xaa] _y	[Xaa] _y SEQ ID NO:
I-308	408	VTGNLDISTEL GNVNNSISNAL DK	1308	EESNSK	2308	DKV	3308
I-309	409	VTGNLDISTEL GNVNNSISNAL DKL	1309	ESNSKL	2309	KV	3309
I-310	410	VTGNLDISTEL GNVNNSISNAL DKLE	1310	SNSKLD	2310	V	3310
I-311	411	V	1311	ISSQIS	2311	MNQLQQSKDY IKEAQKILDTV	3311
I-312	412	VD	1312	SSQISS	2312	NQLQQSKDYI KEAQKILDTV	3312
I-313	413	VDI	1313	SQISSM	2313	QSLQQSKDYIK EAQKILDTV	3313
I-314	414	VDIS	1314	QISSMN	2314	SLQQSKDYIKE AQKILDTV	3314
I-315	415	VDISS	1315	ISSMNQ	2315	LQQSKDYIKEA QKILDTV	3315
I-316	416	VDISSQ	1316	SSMNQS	2316	QQSKDYIKEAQ KILDTV	3316
I-317	417	VDISSQI	1317	SMNQL	2317	QSKDYIKEAQK ILDTV	3317
I-318	418	VDISSQIS	1318	MNQLSQ	2318	SKDYIKEAQKI LDTV	3318
I-319	419	VDISSQISS	1319	NQLQQ	2319	KDYIKEAQKIL DTV	3319
I-320	420	VDISSQISSM	1320	QSLQQS	2320	DYIKEAQKILD TV	3320
I-321	421	VDISSQISSMN	1321	SLQQSK	2321	YIKEAQKILDT V	3321
I-322	422	VDISSQISSMN Q	1322	LQQSKD	2322	IKEAQKILDTV	3322
I-323	423	VDISSQISSMN QS	1323	QQSKDY	2323	KEAQKILDTV	3323
I-324	424	VDISSQISSMN QSL	1324	QSKDYI	2324	EAQKILDTV	3324
I-325	425	VDISSQISSMN QSLQ	1325	SKDYIK	2325	AQKILDTV	3325
I-326	426	VDISSQISSMN QSLQQ	1326	KDYIKE	2326	QKILDTV	3326
I-327	427	VDISSQISSMN QSLQQS	1327	DYIKEA	2327	KILDTV	3327
I-328	428	VDISSQISSMN QSLQQSK	1328	YIKEAQ	2328	ILDTV	3328
I-329	429	VDISSQISSMN QSLQQSKD	1329	IKEAQK	2329	LDTV	3329
I-330	430	VDISSQISSMN QSLQQSKDY	1330	KEAQKI	2330	DTV	3330
I-331	431	VDISSQISSMN QSLQQSKDYI	1331	EAQKIL	2331	TV	3331

Cmpd. No.	Cmpd. SEQ ID NO:	[Xaa] _w	[Xaa] _w SEQ ID NO:	[Xaa] _x	[Xaa] _x SEQ ID NO:	[Xaa] _y	[Xaa] _y SEQ ID NO:
I-332	432	VDISSQISSMN QSLQQSKDYIK	1332	AQKILD	2332	V	3332

[0191] It should be understood that the above amino acid sequences of [Xaa]_w, [Xaa]_x, and [Xaa]_y above can be modified to include additional amino acids (e.g., 1, 2, 3, 4, 5, 6, 7, 8, 9, 10 amino acids added) at the N and/or C-terminus, and/or to have N and/or C terminal deletions (e.g., 1, 2, 3, 4, 5, 6, 7, 8, 9, 10 amino acids deleted). In some instances, Compounds I-1 to I-337 includes one or more variants. In some instances, the amino acid sequence that has 2 to 18, 2 to 17, 2 to 16, 2 to 15, 2 to 14, 2 to 13, 2 to 12, 2 to 11, 2 to 10, 2 to 9, 2 to 8, 2 to 7, 2 to 6, 2 to 5, 2 to 4, 2 to 3, or 2 substitutions, insertions, and/or deletions relative to Compounds I-1 to I-337.

[0192] In certain instances, the amino acid sequences of [Xaa]_w, [Xaa]_x, and [Xaa]_y described herein may also contain one or more (e.g., 1, 2, 3, 4, or 5) amino acid substitutions (relative to an amino acid sequence set forth in in Tables 8 or 9), e.g., one or more (e.g., 1, 2, 3, 4, or 5) conservative and/or non-conservative amino acid substitutions. In some instances, amino acid sequences of [Xaa]_w, [Xaa]_x, and [Xaa]_y set forth in in Tables 8 or 9 may also contain at least one, at least 2, at least 3, at least 4, or at least 5 amino acids added to the N-terminus of the peptide. In some instances, the amino acid sequences of [Xaa]_w, [Xaa]_x, and [Xaa]_y set forth in Tables 8 or 9 may also contain at least one, at least 2, at least 3, at least 4, or at least 5 amino acids added to the C-terminus of the peptide.

[0193] In certain embodiments, the amino group of the N-terminal amino acid in [Xaa]_w of any one of Compound I-1 to I-337 is optionally replaced with -N(H)C(O)-(C₁₋₄ alkyl). In certain embodiments, the amino group of the N-terminal amino acid in [Xaa]_w of any one of Compound I-1 to I-337 is replaced with -N(H)C(O)-(C₁₋₄ alkyl). In certain embodiments, the amino group of the N-terminal amino acid in [Xaa]_w of any one of Compound I-1 to I-337 is replaced with -N(H)C(O)CH₃.

Methods of Treatment

[0194] The disclosure provides methods of using any of the structurally stabilized peptide conjugates, and pharmaceutical compositions comprising said structurally stabilized peptide conjugates, described herein for the prevention and/or treatment of infection by a virus of the Paramyxoviridae family.

[0195] The terms "treat" or "treating," as used herein, refer to alleviating, inhibiting, or ameliorating the disease or infection from which the subject (*e.g.*, human) or other species (*e.g.*, pets; farm animals; domestic animals) is suffering. In some instances, the subject is an animal. In some embodiments, the subject is a mammal such as a non-primate (*e.g.*, cow, pig, horse, cat, dog, rat, etc.) or a primate (*e.g.*, monkey or human). In some instances, the subject is a domesticated animal (*e.g.*, a dog or cat). In some instances, the subject is a human. In certain embodiments, such terms refer to a non-human animal (*e.g.*, a non-human animal such as a pig, horse, cow, cat or dog). In some embodiments, such terms refer to a pet or farm animal. In some embodiments, such terms refer to a human.

[0196] The structurally stabilized peptide conjugates, or compositions comprising the peptides described herein can be useful for treating a subject (*e.g.*, human subject or a species as described above) infected by a Paramyxoviridae virus. The structurally stabilized peptide-cholesterol conjugates or compositions comprising the peptide-cholesterol conjugates described herein can also be useful for treating a subject infected by a Paramyxoviridae virus, wherein the subject is a mammal such as a non-primate (*e.g.*, cow, pig, horse, cat, dog, rat, etc.) or a primate (*e.g.*, monkey or human). In certain embodiments, the subject is a human.

[0197] In some embodiments, the human subject or a subject from another species provided herein is infected with a paramyxoviridae virus. In some embodiments, the human subject or a subject from another species provided herein is at risk of being infected with a paramyxoviridae virus.

[0198] In certain embodiments, the paramyxoviridae virus is selected from Measles virus (MeV), Mumps virus (MuV), Respiratory Syncytial Virus (RSV), Parainfluenza virus 1 (PIV-1), Parainfluenza virus 2 (PIV-2), Parainfluenza virus 3 (PIV-3), Parainfluenza virus 4 (PIV-4), Human Metapneumovirus (HMPV), Nipah virus (NiV), Hendra virus (HeV), Human parainfluenza-like virus (HPIV), Human metapneumovirus-like virus (HMPV-like virus), Human respirovirus 1 (HRV1), Human respirovirus 2 (HRV2), Human respirovirus 3 (HRV3), Human respirovirus 4 (HRV4), Avian metapneumovirus (aMPV), Avian Paramyxovirus Type 1 (APMV-1), Tioman virus (TioV), Tuhoko virus (TuhV), Mossman virus (MosV), Menangle virus (MenV), Mapuera virus (MapV), and J virus (JV).

[0199] In certain embodiments, the virus is Measles virus (MeV). In certain embodiments, the virus is Mumps virus (MuV). In certain embodiments, the virus is Respiratory Syncytial Virus (RSV). In certain embodiments, the virus is Parainfluenza virus 1(PIV-1). In certain embodiments, the virus is Parainfluenza virus 2 (PIV-2). In certain embodiments, the virus is Parainfluenza virus 3 (PIV-3). In certain embodiments, the virus is Parainfluenza virus 4 (PIV-

4). In certain embodiments, the virus is Human Metapneumovirus (HMPV). In certain embodiments, the virus is Nipah virus (NiV). In certain embodiments, the virus is Hendra virus (HeV). In certain embodiments, the virus is Human parainfluenza-like virus (HPIV). In certain embodiments, the virus is Human metapneumovirus-like virus (HMPV-like virus). In certain embodiments, the virus is Human respirovirus 1 (HRV1). In certain embodiments, the virus is Human respirovirus 2 (HRV2). In certain embodiments, the virus is Human respirovirus 3 (HRV3). In certain embodiments, the virus is Human respirovirus 4 (HRV4). In certain embodiments, the virus is Avian metapneumovirus (aMPV). In certain embodiments, the virus is Avian Paramyxovirus Type 1 (APMV-1). In certain embodiments, the virus is Tioman virus (TioV). In certain embodiments, the virus is Tuhoko virus (TuhV). In certain embodiments, the virus is Mossman virus (MosV). In certain embodiments, the virus is Menangle virus (MenV). In certain embodiments, the virus is Mapuera virus (MapV). In certain embodiments, the virus is J virus (JV).

[0200] In general, methods include selecting a subject or a subject from another species provided herein and administering to the subject or a subject from another species provided herein an effective amount of one or more of the structurally stabilized peptide conjugates herein, *e.g.*, in or as a pharmaceutical composition, and optionally repeating administration as required for the prevention or treatment of a Paramyxoviridae viral infection and can be administered orally, intranasally, intravenously, intradermally, subcutaneously, intramuscularly, or topically, including skin, nasal, sinus, ocular, oropharynx, respiratory tree, and lung administration. In some instances, the administration is by a topical respiratory application which includes application to the nasal mucosa, sinus mucosa, oropharyngeal mucosa, or respiratory tree, including the lungs. In some instances, topical application includes application to the skin or eyes. A subject can be selected for treatment based on, *e.g.*, determining that the subject is at risk to acquire or has a Paramyxoviridae viral infection.

[0201] Specific dosage and treatment regimens for any particular patient or subject will depend upon a variety of factors, including the activity of the specific compound employed, the age, body weight, general health status, sex, diet, time of administration, rate of excretion, drug combination, the severity and course of the disease, condition or symptoms, the patient's or subject's disposition to the disease, condition or symptoms, and the judgment of the treating physician or veterinarian.

[0202] An effective amount can be administered in one or more administrations, applications or dosages. A therapeutically effective amount of a therapeutic compound (*i.e.*, an effective dosage) depends on the therapeutic compounds selected. The compositions can be

administered from one or more times per day to one or more times per week, including once every other day. The skilled artisan will appreciate that certain factors may influence the dosage and timing required to effectively treat a subject, including but not limited to the risk to acquire or severity of the disease or disorder, previous treatments, the general health and/or age of the subject, and other diseases present. Moreover, treatment of a subject with a therapeutically effective amount of the therapeutic compounds described herein can include a single treatment or a series of treatments. For example, effective amounts can be administered at least once.

Pharmaceutical Compositions

[0203] As indicated above, the invention provides pharmaceutical compositions, which comprise a therapeutically-effective amount of one or more of the structurally stabilized peptide conjugates described above, formulated together with one or more pharmaceutically acceptable carriers (additives) and/or diluents. The pharmaceutical compositions may be specially formulated for administration in solid or liquid form, including those adapted for the following: (1) oral administration, for example, drenches (aqueous or non-aqueous solutions or suspensions), tablets, *e.g.*, those targeted for buccal, sublingual, and systemic absorption, boluses, powders, granules, pastes for application to the tongue; (2) parenteral administration, for example, by subcutaneous, intramuscular, intravenous or epidural injection as, for example, a sterile solution or suspension, or sustained-release formulation; (3) topical application, for example, as a cream, ointment, or a controlled-release patch or spray applied to the skin; (4) intravaginally or intrarectally, for example, as a pessary, cream or foam; (5) sublingually; (6) ocularly; (7) transdermally; (8) nasally; or (9) inhalation. In certain embodiments, the invention provides a pharmaceutical composition comprising a compound described herein and a pharmaceutically acceptable carrier.

[0204] In certain embodiments, the invention provides a pharmaceutical composition comprising a structurally stabilized peptide conjugate comprising Formula XI and a pharmaceutically acceptable carrier.

[0205] In certain embodiments, the invention provides a pharmaceutical composition comprising a structurally stabilized peptide conjugate of Formula I and a pharmaceutically acceptable carrier.

[0206] The phrase “therapeutically effective amount” as used herein means that amount of a compound, material, or composition comprising a compound of the present invention which

is effective for producing some desired therapeutic effect in at least a sub-population of cells in an animal at a reasonable benefit/risk ratio applicable to any medical treatment.

[0207] The phrase “pharmaceutically acceptable” is employed herein to refer to those compounds, materials, compositions, and/or dosage forms which are, within the scope of sound medical judgment, suitable for use in contact with the tissues of human beings and animals without excessive toxicity, irritation, allergic response, or other problem or complication, commensurate with a reasonable benefit/risk ratio.

[0208] Wetting agents, emulsifiers and lubricants, as well as coloring agents, release agents, coating agents, sweetening, flavoring and perfuming agents, preservatives and antioxidants can also be present in the compositions.

[0209] Formulations of the present invention include those suitable for oral, nasal, topical (including buccal and sublingual), rectal, vaginal and/or parenteral administration. The formulations may conveniently be presented in unit dosage form and may be prepared by any methods well known in the art of pharmacy. The amount of active ingredient which can be combined with a carrier material to produce a single dosage form will vary depending upon the host being treated, the particular mode of administration. The amount of active ingredient which can be combined with a carrier material to produce a single dosage form will generally be that amount of the compound which produces a therapeutic effect. Generally, out of one hundred percent, this amount will range from about 0.1 percent to about ninety-nine percent of active ingredient, preferably from about 5 percent to about 70 percent, most preferably from about 10 percent to about 30 percent.

[0210] Methods of preparing these formulations or compositions include the step of bringing into association a compound of the present invention with the carrier and, optionally, one or more accessory ingredients. In general, the formulations are prepared by uniformly and intimately bringing into association a compound of the present invention with liquid carriers, or finely divided solid carriers, or both, and then, if necessary, shaping the product.

[0211] Formulations of the invention suitable for oral administration may be in the form of capsules, cachets, pills, tablets, lozenges (using a flavored basis, usually sucrose and acacia or tragacanth), powders, granules, or as a solution or a suspension in an aqueous or non-aqueous liquid, or as an oil-in-water or water-in-oil liquid emulsion, or as an elixir or syrup, or as pastilles (using an inert base, such as gelatin and glycerin, or sucrose and acacia) and/or as mouth washes and the like, each containing a predetermined amount of a compound of the present invention as an active ingredient. A compound of the present invention may also be administered as a bolus, electuary or paste.

[0212] In solid dosage forms of the invention for oral administration (capsules, tablets, pills, dragees, powders, granules, trouches and the like), the active ingredient is mixed with one or more pharmaceutically-acceptable carriers, and/or any of the following: (1) fillers or extenders; (2) binders; (3) humectants; (4) disintegrating agents; (5) solution retarding agents; (6) absorption accelerators; (7) wetting agents; (8) absorbents; (9) lubricants; (10) coloring agents; and (11) controlled release agents. In the case of capsules, tablets and pills, the pharmaceutical compositions may also comprise buffering agents. Solid compositions of a similar type may also be employed as fillers in soft and hard-shelled gelatin capsules.

[0213] A tablet may be made by compression or molding, optionally with one or more accessory ingredients. Compressed tablets may be prepared using binder, lubricant, inert diluent, preservative, disintegrant, surface-active or dispersing agent. Molded tablets may be made by molding in a suitable machine a mixture of the powdered compound moistened with an inert liquid diluent.

[0214] The tablets, and other solid dosage forms of the pharmaceutical compositions of the present invention, such as dragees, capsules, pills and granules, may optionally be scored or prepared with coatings and shells, such as enteric coatings and other coatings well known in the pharmaceutical-formulating art. They may also be formulated so as to provide slow or controlled release of the active ingredient therein to provide the desired release profile, other polymer matrices, liposomes and/or microspheres. They may be formulated for rapid release, *e.g.*, freeze-dried. They may be sterilized by, for example, filtration through a bacteria-retaining filter, or by incorporating sterilizing agents in the form of sterile solid compositions which can be dissolved in sterile water, or some other sterile injectable medium immediately before use. These compositions may also optionally contain opacifying agents and may be of a composition that they release the active ingredient(s) only, or preferentially, in a certain portion of the gastrointestinal tract, optionally, in a delayed manner. Examples of embedding compositions which can be used include polymeric substances and waxes. The active ingredient can also be in micro-encapsulated form, if appropriate, with one or more of the above-described excipients.

[0215] Liquid dosage forms for oral administration of the structurally stabilized peptide conjugates of the invention include pharmaceutically acceptable emulsions, microemulsions, solutions, suspensions, syrups and elixirs. In addition to the active ingredient, the liquid dosage forms may contain inert diluents commonly used in the art, such as, for example, water or other solvents, solubilizing agents and emulsifiers, and mixtures thereof.

[0216] Besides inert diluents, the oral compositions can also include adjuvants such as wetting agents, emulsifying and suspending agents, sweetening, flavoring, coloring, perfuming and preservative agents.

[0217] Suspensions, in addition to the active structurally stabilized peptide conjugates, may contain suspending agents.

[0218] Formulations of the pharmaceutical compositions of the invention for rectal or vaginal administration may be presented as a suppository, which may be prepared by mixing one or more structurally stabilized peptide conjugates of the invention with one or more suitable nonirritating excipients or carriers comprising, for example, cocoa butter, polyethylene glycol, a suppository wax or a salicylate, and which is solid at room temperature, but liquid at body temperature and, therefore, will melt in the rectum or vaginal cavity and release the active compound.

[0219] Formulations of the present invention which are suitable for vaginal administration also include pessaries, tampons, creams, gels, pastes, foams or spray formulations containing such carriers as are known in the art to be appropriate.

[0220] Dosage forms for the topical or transdermal administration of a compound of this invention include powders, sprays, ointments, pastes, creams, lotions, gels, solutions, patches and inhalants. The active compound may be mixed under sterile conditions with a pharmaceutically-acceptable carrier, and with any preservatives, buffers, or propellants which may be required.

[0221] Transdermal patches have the added advantage of providing controlled delivery of a compound of the present invention to the body. Such dosage forms can be made by dissolving or dispersing the compound in the proper medium. Absorption enhancers can also be used to increase the flux of the compound across the skin. The rate of such flux can be controlled by either providing a rate controlling membrane or dispersing the compound in a polymer matrix or gel.

[0222] Ophthalmic formulations, eye ointments, powders, solutions and the like, are also contemplated as being within the scope of this invention.

[0223] Pharmaceutical compositions of this invention suitable for parenteral administration comprise one or more structurally stabilized peptide conjugates of the invention in combination with one or more pharmaceutically-acceptable sterile isotonic aqueous or nonaqueous solutions, dispersions, suspensions or emulsions, or sterile powders which may be reconstituted into sterile injectable solutions or dispersions just prior to use, which may contain

sugars, alcohols, antioxidants, buffers, bacteriostats, solutes which render the formulation isotonic with the blood of the intended recipient or suspending or thickening agents.

[0224] These compositions may also contain adjuvants such as preservatives, wetting agents, emulsifying agents and dispersing agents. Prevention of the action of microorganisms upon the subject structurally stabilized peptide conjugates may be ensured by the inclusion of various antibacterial and antifungal agents. It may also be desirable to include isotonic agents, such as sugars, sodium chloride, and the like into the compositions. In addition, prolonged absorption of the injectable pharmaceutical form may be brought about by the inclusion of agents which delay absorption.

[0225] In some cases, in order to prolong the effect of a drug, it is desirable to slow the absorption of the drug from subcutaneous or intramuscular injection. This may be accomplished by the use of a liquid suspension of crystalline or amorphous material having poor water solubility. The rate of absorption of the drug then depends upon its rate of dissolution which, in turn, may depend upon crystal size and crystalline form. Alternatively, delayed absorption of a parenterally-administered drug form is accomplished by dissolving or suspending the drug in an oil vehicle.

[0226] Injectable depot forms are made by forming microencapsule matrices of the subject structurally stabilized peptide conjugates in biodegradable polymers such as polylactide-polyglycolide. Depending on the ratio of drug to polymer, and the nature of the particular polymer employed, the rate of drug release can be controlled. Depot injectable formulations are also prepared by entrapping the drug in liposomes or microemulsions which are compatible with body tissue.

[0227] When the structurally stabilized peptide conjugates of the present invention are administered as pharmaceuticals, to humans and animals, they can be given per se or as a pharmaceutical composition containing, for example, 0.1 to 99% (more preferably, 10 to 30%) of active ingredient in combination with a pharmaceutically acceptable carrier.

[0228] The preparations of the present invention may be given orally, parenterally, topically, or rectally. They are of course given in forms suitable for each administration route. For example, they are administered in tablets or capsule form, by injection, inhalation, eye lotion, ointment, suppository, etc. administration by injection, infusion or inhalation; topical by lotion or ointment; and rectal by suppositories.

[0229] The phrases "parenteral administration" and "administered parenterally" as used herein means modes of administration other than enteral and topical administration, usually by injection, and includes, without limitation, intravenous, intramuscular, intraarterial, intrathecal,

intracapsular, intraorbital, intracardiac, intradermal, intraperitoneal, transtracheal, subcutaneous, subcuticular, intraarticular, subcapsular, subarachnoid, intraspinal and intrasternal injection and infusion.

[0230] The phrases “systemic administration,” “administered systemically,” “peripheral administration” and “administered peripherally” as used herein mean the administration of a compound, drug or other material other than directly into the central nervous system, such that it enters the patient’s system and, thus, is subject to metabolism and other like processes, for example, subcutaneous administration.

[0231] These structurally stabilized peptide conjugates may be administered to humans and other animals for therapy by any suitable route of administration, including orally, nasally, as by, for example, a spray, rectally, intravaginally, parenterally, intracisternally and topically, as by powders, ointments or drops, including buccally and sublingually.

[0232] Regardless of the route of administration selected, the structurally stabilized peptide conjugates of the present invention, which may be used in a suitable hydrated form, and/or the pharmaceutical compositions of the present invention, are formulated into pharmaceutically-acceptable dosage forms by conventional methods known to those of skill in the art.

[0233] Actual dosage levels of the active ingredients in the pharmaceutical compositions of this invention may be varied so as to obtain an amount of the active ingredient which is effective to achieve the desired therapeutic response for a particular patient, composition, and mode of administration, without being toxic to the patient.

[0234] The selected dosage level will depend upon a variety of factors including the activity of the particular compound of the present invention employed, or the ester, salt or amide thereof, the route of administration, the time of administration, the rate of excretion or metabolism of the particular compound being employed, the rate and extent of absorption, the duration of the treatment, other drugs, compounds and/or materials used in combination with the particular compound employed, the age, sex, weight, condition, general health and prior medical history of the patient being treated, and like factors well known in the medical arts.

[0235] A physician or veterinarian having ordinary skill in the art can readily determine and prescribe the effective amount of the pharmaceutical composition required. For example, the physician or veterinarian could start doses of the structurally stabilized peptide conjugates of the invention employed in the pharmaceutical composition at levels lower than that required in order to achieve the desired therapeutic effect and gradually increase the dosage until the desired effect is achieved.

[0236] In general, a suitable daily dose of a compound of the invention will be that amount of the compound which is the lowest dose effective to produce a therapeutic effect. Such an effective dose will generally depend upon the factors described above. Preferably, the structurally stabilized peptide conjugates are administered at about 0.01 mg/kg to about 200 mg/kg, more preferably at about 0.1 mg/kg to about 100 mg/kg, even more preferably at about 0.5 mg/kg to about 50 mg/kg. When the structurally stabilized peptide conjugates described herein are co-administered with another agent (*e.g.*, as sensitizing agents), the effective amount may be less than when the agent is used alone.

[0237] The invention further provides a unit dosage form (such as a tablet or capsule) comprising a structurally stabilized peptide conjugate or related compound described herein in a therapeutically effective amount for the treatment of a medical disorder described herein.

[0238] Another aspect of this invention is a kit comprising (i) a structurally stabilized peptide conjugate described herein, such as a structurally stabilized peptide conjugate of Formula I, and (ii) instructions for use, such as treating a viral infection.

[0239] Another aspect of this invention is a kit comprising (i) a structurally stabilized peptide conjugate described herein, such as a structurally stabilized peptide conjugate of Formula XI, and (ii) instructions for use, such as treating a viral infection.

Methods of Making Structurally Stabilized Peptide Conjugates

[0240] *Stapled peptide synthesis:* Fmoc-based solid-phase peptide synthesis was used to synthesize stapled peptide fusion inhibitors in accordance with reported methods for generating all-hydrocarbon stapled peptides (Bird et al., *Curr. Protocol. Chem. Biol.*, 3(3):99-117 (2011); Bird et al., *Methods Enzymol.*, 446:369-86(2008). To achieve the various staple lengths, α -methyl, α -alkenyl amino acids were installed in specific pairings at discrete positions, such as for i, i+7 positioning the use of one S-pentenyl alanine residue (S5) and one R-octenyl alanine residue (R8). For the stapling reaction, Grubbs 1st generation ruthenium catalyst dissolved in dichloroethane was added to the resin-bound peptides. To ensure maximal conversion, three to five rounds of stapling were performed. After appending the PEG(n)-thiocholesterol or PEG(n)-cholesterol moiety (see below), the peptides were then cleaved off of the resin using trifluoroacetic acid, precipitated using a hexane:ether (1:1) mixture, air dried, and purified by LC-MS. All peptides were quantified by amino acid analysis.

[0241] *Stitched peptide synthesis:* Methods of synthesizing the stitched peptides described herein are known in the art. Nevertheless, the following exemplary method may be used. Synthetic chemistry transformations and protecting group methodologies (protection and

deprotection) useful in synthesizing the structurally stabilized peptide conjugates described herein are known in the art and include, for example, those such as described in Bird et al., ACS Chem Biol. (2020) 15(6):1340-1348; Hilinski et al., J Am Chem Soc. (2014) 136(35):12314-22; R. Larock, Comprehensive Organic Transformations, VCH Publishers (1989); T.W. Greene and P.G.M. Wuts, Protective Groups in Organic Synthesis, 3d. Ed., John Wiley and Sons (1999); L. Fieser and M. Fieser, Fieser and Fieser's Reagents for Organic Synthesis, John Wiley and Sons (1994); and L. Paquette, ed., Encyclopedia of Reagents for Organic Synthesis, John Wiley and Sons (1995), and subsequent editions thereof.

[0242] *C-terminal derivatization of stapled or stitched peptides with PEG(n)-thiocholesterol or PEG(n)-cholesterol using an on-resin synthetic approach:* To generate the carboxy thiocholesterol or carboxy cholesterol reagent for peptide derivatization by solid phase synthesis, thiocholesterol was dissolved in dichloromethane (DCM) or cholesterol was dissolved in tetrahydrofuran (THF) at 0.1 M and added to a round bottom flask. 3 eq of a base (diisopropylethylamine for thiocholesterol or sodium hydride or potassium t-butoxide for cholesterol) was added with stirring. 5 eq of the t-butyl ester of bromoacetic acid was added next and the reaction was stirred for 2 hours at room temperature followed by 30 min at 40 °C. Two volumes of trifluoroacetic acid (relative to solvent) was added and the reaction was stirred at room temperature for 30 min. The reaction progress was monitored by TLC (19:1 Hex:EtOAc for thiocholesterol and 3:1 Hex:EtOAc for cholesterol) with KMnO₄ staining. (Thio)cholesterol, for example, migrated with the solvent front with (thio)ether slowing migration by ~20% and TFA hydrolysis brought the spot to baseline. The reaction mixture was added to 5 vol water and the 1 vol DCM was added. The solvent layer was washed with 0.1M HCl, brine and dried with sodium sulfate. Removal of the solvent by Rotovap yielded an orange heavy oil that was used without further purification. The yield was near quantitative. Purity was determined to be greater than 90% by NMR of the olefin proton vs the new CH₂ singlet. For peptide derivatization with thiocholesterol or cholesterol, the completed resin bound peptide sequence was treated with 20% piperidine/DMF followed by capping with acetic anhydride to block the N-terminal amine before the C-terminal side chain lysine amine was revealed by treatment with 2% hydrazine in DMF, 5x for 10 min each. The amine was acylated with an Fmoc-protected PEG(n) amino acid (e.g., n = 1-36 (e.g., 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14, 15, 16, 17, 18, 19, 20, 21, 22, 23, 24, 25, 26, 27, 28, 29, 30, 31, 32, 33, 34, 35, or 36)) at which point the olefins were crosslinked by treating with Grubbs(I) catalyst, 3x for 2 h each. Upon completion, the Fmoc was removed from the C-terminal NH of the PEG reagent and the amine was acylated with carboxy-thiocholesterol (or carboxy-cholesterol) for

30 min. TFA cleavage yielded a crude product of excellent purity that was further purified using semi-prep HPLC.

[0243] The peptide sequences of this invention can be made by chemical synthesis methods, which are well known to the ordinarily skilled artisan. See, for example, Fields et al., Chapter 3 in *Synthetic Peptides: A User's Guide*, ed. Grant, W. H. Freeman & Co., New York, N.Y., 1992, p. 77. Hence, peptides can be synthesized using the automated Merrifield techniques of solid phase synthesis with the α -NH₂ protected by either t-Boc or Fmoc chemistry using side chain protected amino acids on, for example, an Applied Biosystems Peptide Synthesizer Model 430A or 431.

[0244] One manner of making of the peptides described herein is using solid phase peptide synthesis (SPPS). The C-terminal amino acid is attached to a cross-linked polystyrene resin via an acid labile bond with a linker molecule. This resin is insoluble in the solvents used for synthesis, making it relatively simple and fast to wash away excess reagents and by-products. The N-terminus is protected with the Fmoc group, which is stable in acid, but removable by base. Any side chain functional groups are protected with base stable, acid labile groups.

[0245] Longer peptides could be made by conjoining individual synthetic peptides using native chemical ligation. Insertion of a linking amino acid may be performed as described in, *e.g.*, Young and Schultz, *J Biol Chem.* 2010 Apr 9; 285(15): 11039–11044. Alternatively, the longer synthetic peptides can be synthesized by well-known recombinant DNA techniques. Such techniques are provided in well-known standard manuals with detailed protocols. To construct a gene encoding a peptide of this invention, the amino acid sequence is reverse translated to obtain a nucleic acid sequence encoding the amino acid sequence, preferably with codons that are optimal for the organism in which the gene is to be expressed. Next, a synthetic gene is made, typically by synthesizing oligonucleotides which encode the peptide and any regulatory elements, if necessary. The synthetic gene is inserted in a suitable cloning vector and transfected into a host cell. The peptide is then expressed under suitable conditions appropriate for the selected expression system and host. The peptide is purified and characterized by standard methods.

[0246] The peptides can be made in a high-throughput, combinatorial fashion, *e.g.*, using a high-throughput multiple channel combinatorial synthesizer available from, *e.g.*, Advanced Chemtech or Gyros Protein Technologies. Peptide bonds can be replaced, *e.g.*, to increase physiological stability of the peptide, by: a retro-inverso bonds (C(O)-NH); a reduced amide bond (NH-CH₂); a thiomethylene bond (S-CH₂ or CH₂-S); an oxomethylene bond (O-CH₂ or CH₂-O); an ethylene bond (CH₂-CH₂); a thioamide bond (C(S)-NH); a trans-olefin bond

(CH=CH); a fluoro substituted trans-olefin bond (CF=CH); a ketomethylene bond (C(O)-CHR) or CHR-C(O) wherein R is H or CH₃; and a fluoro-ketomethylene bond (C(O)-CFR or CFR-C(O) wherein R is H or F or CH₃).

[0247] The peptides can be further modified by: acetylation, amidation, biotinylation, cinnamoylation, farnesylation, fluoresceination, formylation, myristoylation, palmitoylation, and other lipidation, specifically including thiocholesterol or cholesterol modification using the on-resin method disclosed herein, phosphorylation (Ser, Tyr or Thr), stearoylation, succinylation and sulfurylation. As indicated above, peptides can be conjugated to or contain linker atoms or moieties of variable length, for example, polyethylene glycol (PEG) moieties of variable length; alkyl groups (*e.g.*, C1-C20 straight or branched alkyl groups); fatty acid radicals; and combinations thereof. α,α -Disubstituted non-natural amino acids containing olefinic side chains of varying length can be synthesized by known methods (Williams et al. J. Am. Chem. Soc., 113:9276, 1991; Schafmeister et al., J. Am. Chem Soc., 122:5891, 2000; and Bird et al., Methods Enzymol., 446:369, 2008; Bird et al, Current Protocols in Chemical Biology, 2011). In some instances, the amino acids forming the staple or stitch are (R)-2-(4'-pentenyl)Alanine, 2,2-bis(4-pentenyl)glycine, and (S)-2-(4'-pentenyl)alanine at positions i, i+4, and i+8, respectively, of the stitch. In some instances for peptides where an i linked to i+7, i+7 linked to i+14 stitch is used (four turns of the helix stabilized): one R-octenyl alanine (*e.g.*, (R)- α -(7'-octenyl)alanine), one bis-pentenyl glycine (*e.g.*, α,α -Bis(4'-pentenyl)glycine), and one R-octenyl alanine (*e.g.*, (R)- α -(7'-octenyl)alanine) is used. In some instances for peptides where an i linked to i+7, i+7 linked to i+14 stitch is used (four turns of the helix stabilized): one S-octenyl alanine (*e.g.*, (S)- α -(7'-octenyl)alanine), one bis-pentenyl glycine (*e.g.*, α,α -Bis(4'-pentenyl)glycine), and one R-octenyl alanine (*e.g.*, (R)- α -(7'-octenyl)alanine) is used. In some instances for peptides where an i linked to i+7, i+7 linked to i+14 stitch is used (four turns of the helix stabilized): one S-octenyl alanine (*e.g.*, (S)- α -(7'-octenyl)alanine), one bis-pentenyl glycine (*e.g.*, α,α -Bis(4'-pentenyl)glycine), and one S-octenyl alanine (*e.g.*, (S)- α -(7'-octenyl)alanine) is used. In some instances for peptides where an i linked to i+7, i+7 linked to i+14 stitch is used (four turns of the helix stabilized): one R-pentenyl alanine (*e.g.*, (R)- α -(4'-pentenyl)alanine), one bis-octenyl glycine (*e.g.*, α,α -Bis(7'-octenyl)glycine), and one S-pentenyl alanine (*e.g.*, (S)- α -(4'-pentenyl)alanine) is used. In some instances for peptides where an i linked to i+7, i+7 linked to i+14 stitch is used (four turns of the helix stabilized): one R-pentenyl alanine (*e.g.*, (R)- α -(4'-pentenyl)alanine), one bis-octenyl glycine (*e.g.*, α,α -Bis(7'-octenyl)glycine), and one R-pentenyl alanine (*e.g.*, (R)- α -(4'-pentenyl)alanine) is used. In some instances for peptides where an i linked to i+7, i+7 linked

to i+14 stitch is used (four turns of the helix stabilized): one S-pentenyl alanine (*e.g.*, (S)- α -(4'-pentenyl)alanine), one bis-octenyl glycine (*e.g.*, α,α -Bis(7'-octenyl)glycine), and one R-pentenyl alanine (*e.g.*, (R)- α -(4'-pentenyl)alanine) is used. In some instances for peptides where an i linked to i+7, i+7 linked to i+14 stitch is used (four turns of the helix stabilized): one S-pentenyl alanine (*e.g.*, (S)- α -(4'-pentenyl)alanine), one bis-octenyl glycine (*e.g.*, α,α -Bis(7'-octenyl)glycine), and one S-pentenyl alanine (*e.g.*, (S)- α -(4'-pentenyl)alanine) is used. R-octenyl alanine is synthesized using the same route, except that the starting chiral auxiliary confers the R-alkyl-stereoisomer. Also, 8-iodooctene is used in place of 5-iodopentene. Inhibitors are synthesized on a solid support using solid-phase peptide synthesis (SPPS) on MBHA resin or Rink Amide AM resin (see, *e.g.*, WO 2010/148335).

[0248] Fmoc-protected α -amino acids (other than the olefinic amino acids N-Fmoc- α,α -Bis(4'-pentenyl)glycine, (S)-N-Fmoc- α -(4'-pentenyl)alanine, (R)-N-Fmoc- α -(7'-octenyl)alanine, (R)-N-Fmoc- α -(7'-octenyl)alanine, and (R)-N-Fmoc- α -(4'-pentenyl)alanine), 2-(6-chloro-1-H-benzotriazole-1-yl)-1,1,3,3-tetramethylaminium hexafluorophosphate (HCTU), and Rink Amide MBHA are commercially available from, *e.g.*, Novabiochem (San Diego, CA). Dimethylformamide (DMF), N-methyl-2-pyrrolidinone (NMP), N,N-diisopropylethylamine (DIEA), trifluoroacetic acid (TFA), 1,2-dichloroethane (DCE), fluorescein isothiocyanate (FITC), and piperidine are commercially available from, *e.g.*, Sigma-Aldrich. Olefinic amino acid synthesis is reported in the art (Williams et al., *Org. Synth.*, 80:31, 2003).

[0249] Again, methods suitable for obtaining (*e.g.*, synthesizing), stitching, and purifying the peptides disclosed herein are also known in the art (see, *e.g.*, Bird et al., *Methods in Enzymol.*, 446:369-386 (2008); Bird et al., *Current Protocols in Chemical Biology*, 2011; Walensky et al., *Science*, 305:1466-1470 (2004); Schafmeister et al., *J. Am. Chem. Soc.*, 122:5891-5892 (2000); U.S. Patent Application No. 12/525,123, filed March 18, 2010; and U.S. Patent No. 7,723,468, issued May 25, 2010, each of which are hereby incorporated by reference in their entirety).

[0250] In some instances, the peptides are substantially free of non-stitched or non-stapled peptide contaminants or are isolated. Methods for purifying peptides include, for example, synthesizing the peptide on a solid-phase support. Following cyclization, multiple alternative solvent and purification schemes are known in the art for peptide and stapled peptide isolation and purification and may use solvents that include, but are not limited to, DMSO, DMSO/dichloromethane mixture, DMSO/NMP mixture, or a mixture/solution that does not include DMSO. The DMSO/dichloromethane or DMSO/NMP mixture may comprise about

30%, 40%, 50% or 60% DMSO. In a specific instance, a 50%/50% DMSO/NMP solution is used. The solution may be incubated for a period of 1, 6, 12 or 24 hours, following which the resin may be washed, for example with dichloromethane or NMP. In one instance, the resin is washed with NMP. Shaking and bubbling an inert gas into the solution may be performed.

[0251] Properties of the stitched or stapled peptides derivatized with a C-terminal PEG(n)-thiocholesterol or PEG(n)-cholesterol of the disclosure can be assayed, for example, using the methods described below and in the Examples.

Assays to Determine Characteristics of Stapled HR2 Peptide Conjugates

[0252] *Assays to Determine α -Helicity*: Compounds are dissolved in an aqueous solution (e.g. 5 μ M potassium phosphate solution at pH 7, or distilled H₂O, to concentrations of 25-50 μ M). Circular dichroism (CD) spectra are obtained on a spectropolarimeter (e.g., Jasco J-710, Aviv) using standard measurement parameters (e.g. temperature, 20°C; wavelength, 190-260 nm; step resolution, 0.5 nm; speed, 20 nm/sec; accumulations, 10; response, 1 sec; bandwidth, 1 nm; path length, 0.1 cm). The α -helical content of each peptide is calculated by dividing the mean residue ellipticity by the reported value for a model helical decapeptide (Yang et al., *Methods Enzymol.*, 1986).

[0253] *Assays to Determine Melting Temperature (T_m)*: Cross-linked or the unmodified template peptides are dissolved in distilled H₂O or other buffer or solvent (e.g. at a final concentration of 50 μ M) and T_m is determined by measuring the change in ellipticity over a temperature range (e.g. 4 to 95 °C) on a spectropolarimeter (e.g., Jasco J-710, Aviv) using standard parameters (e.g. wavelength 222 nm; step resolution, 0.5 nm; speed, 20 nm/sec; accumulations, 10; response, 1 sec; bandwidth, 1 nm; temperature increase rate: 1 °C/min; path length, 0.1 cm).

[0254] *In Vitro Protease Resistance Assays*: The amide bond of the peptide backbone is susceptible to hydrolysis by proteases, thereby rendering peptidic compounds vulnerable to rapid degradation in vivo. Peptide helix formation, however, typically buries and/or twists and/or shields the amide backbone and therefore may prevent or substantially retard proteolytic cleavage. The peptidomimetic macrocycles of the present invention may be subjected to in vitro enzymatic proteolysis (e.g. trypsin, chymotrypsin, pepsin) to assess for any change in degradation rate compared to a corresponding uncrosslinked or alternatively stapled polypeptide. For example, the peptidomimetic macrocycle and a corresponding uncrosslinked polypeptide are incubated with trypsin agarose and the reactions quenched at various time points by centrifugation and subsequent HPLC injection to quantitate the residual substrate by

ultraviolet absorption at 280 nm. Briefly, the peptidomimetic macrocycle and peptidomimetic precursor (5 mcg) are incubated with trypsin agarose (Pierce) (S/E ~125) for 0, 10, 20, 90, and 180 minutes. Reactions are quenched by tabletop centrifugation at high speed; remaining substrate in the isolated supernatant is quantified by HPLC-based peak detection at 280 nm. The proteolytic reaction displays first order kinetics and the rate constant, k , is determined from a plot of $\ln[S]$ versus time.

[0255] Peptidomimetic macrocycles and/or a corresponding uncrosslinked polypeptide can be each incubated with fresh mouse, rat and/or human serum (*e.g.* 1-2 mL) at 37 °C for, *e.g.*, 0, 1, 2, 4, 8, and 24 hours. Samples of differing macrocycle concentration may be prepared by serial dilution with serum. To determine the level of intact compound, the following procedure may be used: The samples are extracted, for example, by transferring 100 μ L of sera to 2 ml centrifuge tubes followed by the addition of 10 μ L of 50% formic acid and 500 μ L acetonitrile and centrifugation at 14,000 RPM for 10 min at 4 $\pm$ 2 °C. The supernatants are then transferred to fresh 2 ml tubes and evaporated on Turbopap under N_2 <10 psi, 37 °C. The samples are reconstituted in 100 μ L of 50:50 acetonitrile:water and submitted to LC-MS/MS analysis. Equivalent or similar procedures for testing *ex vivo* stability are known and may be used to determine stability of macrocycles in serum.

[0256] *Plasma Stability Assay:* Stapled peptide stability can be tested in freshly drawn mouse plasma collected in lithium heparin tubes. Triplicate incubations are set up with 500 μ L of plasma spiked with 10 μ M of the individual peptides. Samples are gently shaken in an orbital shaker at 37 °C and 25 μ L aliquots are removed at 0, 5, 15, 30, 60, 240, 360 and 480 min and added to 100 μ L of a mixture containing 10% methanol:10% water:80% acetonitrile to stop further degradation of the peptides. The samples are allowed to sit on ice for the duration of the assay and then transferred to a MultiScreen Solvinert 0.45 μ m low-binding hydrophilic PTFE plate (Millipore). The filtrate is directly analyzed by LC-MS/MS. The peptides are detected as double or triple charged ions using a Sciex 5500 mass spectrometer. The percentage of remaining peptide is determined by the decrease in chromatographic peak area and log transformed to calculate the half-life.

[0257] *In Vivo Protease Resistance Assays:* Liquid chromatography/mass spectrometry-based analytical assays are used to detect and quantitate stapled peptide levels in plasma. For pharmacokinetic analysis, peptides are dissolved in sterile aqueous 5% dextrose (1 mg/mL) and administered to C57BL/6 mice (Jackson Laboratory) by bolus tail vein or intraperitoneal injection (*e.g.* 5, 10, 25, 50 mg/kg). Blood is collected by retro-orbital puncture at 5, 30, 60, 120, and 240 minutes after dosing 5 animals at each time point. Plasma is harvested after

centrifugation (2,500 x g, 5 minutes, 4 °C) and stored at -70 °C until assayed. Peptide concentrations in plasma are determined by reversed-phase high performance liquid chromatography with electrospray ionization mass spectrometric detection (Aristoteli *et al.*, *Journal of Proteome Res.*, 2007; Walden *et al.*, *Analytical and Bioanalytical Chem.*, 2004). Study samples are assayed together with a series of 7 calibration standards of peptide in plasma at concentrations ranging from 1.0 to 50.0 µg/mL, drug-free plasma assayed with and without addition of an internal standard, and 3 quality control samples (*e.g.* 3.75, 15.0, and 45.0 µg/mL). Standard curves are constructed by plotting the analyte/internal standard chromatographic peak area ratio against the known drug concentration in each calibration standard. Linear least squares regression is performed with weighting in proportion to the reciprocal of the analyte concentration normalized to the number of calibration standards. Values of the slope and y-intercept of the best-fit line are used to calculate the drug concentration in study samples. Plasma concentration-time curves are analyzed by standard noncompartmental methods using WinNonlin Professional 5.0 software (Pharsight Corp., Cary, NC), yielding pharmacokinetic parameters such as initial and terminal phase plasma half-life, peak plasma levels, total plasma clearance, and apparent volume of distribution.

[0258] *In vitro Binding Assays:* To assess the binding and affinity of peptidomimetic macrocycles and peptidomimetic precursors to acceptor proteins, a fluorescence polarization assay (FPA) can be used, for example. The FPA technique measures the molecular orientation and mobility using polarized light and fluorescent tracer. When excited with polarized light, fluorescent tracers (*e.g.*, FITC) attached to molecules or peptides and then bound to proteins of high apparent molecular weights (*e.g.* FITC-labeled peptides bound to a large protein) emit higher levels of polarized fluorescence due to their slower rates of rotation upon protein binding as compared to fluorescent tracers attached to smaller molecules or peptides alone (*e.g.* FITC-labeled peptides that are free in solution).

[0259] *In vitro Displacement Assays to Characterize Antagonists of Peptide-Protein Interactions:* To assess the binding and affinity of compounds that antagonize the interaction between a peptide and an acceptor protein, a fluorescence polarization assay (FPA) utilizing a fluoresceinated peptide or peptidomimetic macrocycle derived from a template peptide sequence is used, for example. The FPA technique measures the molecular orientation and mobility using polarized light and fluorescent tracer. When excited with polarized light, fluorescent tracers (*e.g.*, FITC) attached to molecules that are then bound to proteins with high apparent molecular weights (*e.g.* FITC-labeled peptides bound to a large protein) emit higher levels of polarized fluorescence due to their slower rates of rotation as compared to the FITC-

derivatized molecules alone (e.g. FITC-labeled peptides that are free in solution). Compounds such as unlabeled stapled peptides and their conjugates that antagonize the interaction between the fluoresceinated peptide and an acceptor protein will be detected in a competitive binding FPA experiment and the differential potency of compounds in disrupting the interaction can be quantified and compared.

[0260] *Cellular Localization Assays:* To measure the localization of peptides or crosslinked polypeptides on or in cells, intact cells are incubated with fluoresceinated crosslinked polypeptides derivatized with PEG(n)-thiocholesterol or PEG(n)-cholesterol (5 μ M) for 4 hours in serum-free media or in media supplemented with human serum at 37 °C, washed twice with media and incubated with trypsin (0.25%) for 10 min at 37 °C. The cells are washed again and resuspended in PBS. Cellular fluorescence is analyzed, for example, by using either a FACSCalibur flow cytometer or Cellomics' KineticScan^{RTM} HCS Reader.

EXAMPLES

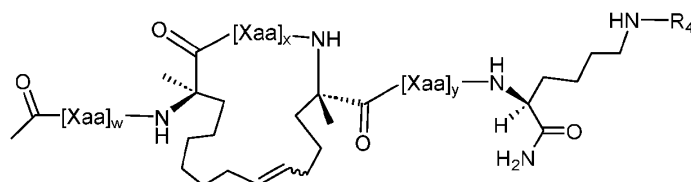
[0261] The following examples are provided to better illustrate the claimed invention and are not to be interpreted as limiting the scope of the invention. To the extent that specific materials are mentioned, it is merely for purposes of illustration and is not intended to limit the invention. One skilled in the art can develop equivalent means or reactants without the exercise of inventive capacity and without departing from the scope of the invention.

Example 1: Preparation of Stapled HPIV3 Peptide Conjugates

[0262] To design peptides that could block the fusion of the Paramyxoviridae virus to a host cell, a series of modified peptides bearing differentially localized chemical staples and derivatized with PEG(n)-cholesterol moieties at the C-termini were designed. The differentially localized staples are located within the Paramyxoviridae HR2 domain of the sequences of the surface (S) glycoprotein of the Paramyxoviridae virus (see, **FIG. 1**), by replacing native residues with α,α -disubstituted non-natural olefinic residues (e.g., S-pentenyl alanine and R-octenyl alanine installed at select i , $i+7$ positions or S-pentenyl alanine installed at each of select i , $i+4$ positions) and combinations thereof, followed by ruthenium-catalyzed olefin metathesis (see, **FIG. 1**). One approach to designing, synthesizing, and identifying optimal stapled peptide constructs to target the Paramyxoviridae fusion apparatus includes the generation of Ala scan (e.g. mutants), staple scan, and variable N- and C-terminal deletion, addition, and derivatization libraries for conjugation to PEG-thiocholesterol or PEG-cholesterol moieties (see, **FIG. 2**). Stapled Paramyxoviridae HR2 constructs bearing C-

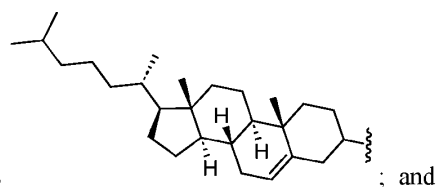
terminal derivatization with PEG(n)-thiocholesterol or PEG(n)-cholesterol moieties were designed by replacing two naturally occurring amino acids with the non-natural (R)-2-(((9H-fluoren-9-yl)methoxy)carbonylamino)-2-methyl-dec-9-enoic acid (R8) and S-2-(4'-pentenyl) alanine (S5) amino acids at i , $i+7$ positions (*i.e.* flanking 7 amino acids) to generate a staple spanning two α -helical turns, or with two S5 non-natural amino acids at i , $i+4$ positions to generate a staple spanning one α -helical turn. Asymmetric syntheses of α,α -disubstituted amino acids were performed as previously described in detail (Schafmeister et al., *J. Am. Chem. Soc.*, 2000; Walensky et al., *Science*, 2004; Bird et al. *Current Protocols in Chemical Biology*, 2011, each of which is incorporated by reference in its entirety).

[0263] The following compounds were prepared based on the procedure described above and additional details below:



wherein

R_4 is $-\text{C}(\text{O})-(\text{CH}_2\text{CH}_2)-[\text{O}-\text{CH}_2\text{CH}_2]_{12}-\text{N}(\text{H})\text{C}(\text{O})-\text{R}_6$;



R_6 is

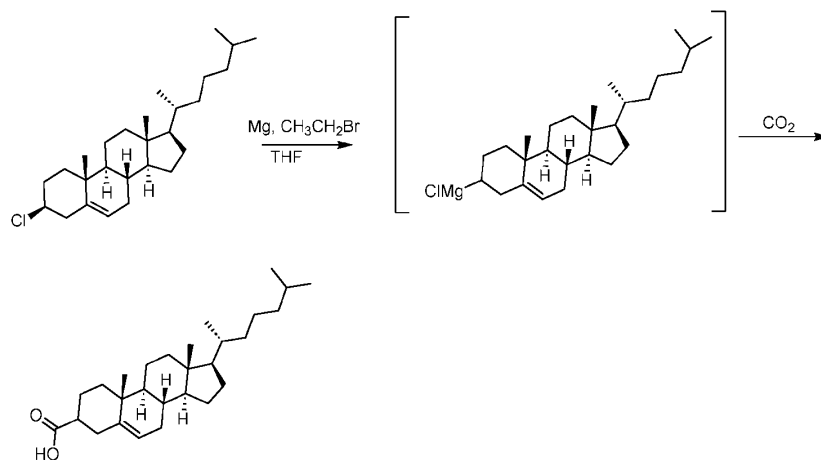
$[\text{Xaa}]_w$, $[\text{Xaa}]_x$, and $[\text{Xaa}]_y$ are as defined below in Table 10.

Table 10

Cmpd. No.	Cmpd. SEQ ID NO:	[Xaa] _w	[Xaa] _w SEQ ID NO:	[Xaa] _x	[Xaa] _x SEQ ID NO:	[Xaa] _y	[Xaa] _y SEQ ID NO:
I-183	283	VALDPIDI	1183	IVLNKI	2183	SDLEESKEWIRRSNKILDSI	3183
I-187	287	VALDPIDISI VL	1187	KIKSDL	2187	ESKEWIRRSNKILDSI	3187
I-184	284	VALDPIDIS	1184	VLNKKI	2184	DLEESKEWIRRSNKILDSI	3184
I-188	288	VALDPIDISI VLN	1188	IKSDLE	2188	SKEWIRRSNKILDSI	3188
I-194	294	VALDPIDISI VLNKKISDL	1194	ESKEWI	2194	RSNKILDSI	3194
I-190	290	VALDPIDISI VLNKKI	1190	SDLEES	2190	EWIRRSNKILDSI	3190
I-191	291	VALDPIDISI VLNKKI	1191	DLEESK	2191	WIRASNKILDSI	3191
I-195	295	VALDPIDISI VLNKKISDLE	1195	SKEWIR	2195	SNKILDSI	3195
I-333	433	IQLDYIDISV ETNSAKAWL	1333	FSGQIL	2333	BSNKRLDSIK	3333
I-334	434	IQLDNIDIS	1334	ETNSAK	2334	YLAFSIEQLW ESNQRLDSIK	3334
I-335	435	VALDPIDISI VL	1335	KIKSQL	2335	ESKEWIRRSNKILDSIK	3335
I-336	436	VALDPIDISI EL	1336	KAKSDL	2336	ESKEWIRRSNQKILDSI	3336
I-337	437	VALDPIDISI VL	1337	KAKSDL	2337	ESKEWIRRSNGKILDSI	3337
I-338	438	IQLDYIDISV ETNSAKAWL	1338	FSGQIL	2338	BSNKRLDSI	3338
I-339	439	IQLDNIDIS	1339	ETNSAK	2339	YLAFSIEQLW ESNQRLDSI	3339
I-340	440	VALDPIDISI VL	1340	KIKSQL	2340	ESKEWIRRSNKILDSI	3340

Part I- Procedure

[0264] Cholesterol was converted into a carboxylic acid for facile on-resin derivatization of stapled peptides with cholesterol-containing moieties:



[0265] Cholesteryl chloride and anhydrous THF was purchased from Sigma-Aldrich, magnesium turning, ethyl bromide, Conc Sulfuric acid and solvents for extraction were purchased from Oakwood chemicals.

[0266] Magnesium turning was oven dried before reaction. Ultra-pure grade argon and carbon dioxide gas was used. In an oven dried 3 neck-flask fitted with appropriate septum, reflux condenser and dropping funnel under an atmosphere of dry argon was placed magnesium turnings (1.95 g, 0.080 mole) in dry anhydrous THF (450 mL). Ethyl bromide (1.81 g, 0.016 mole) was added dropwise (20 min) via a syringe and the mixture was allowed to stir while being slowly heated. Cholesteryl chloride (25 g, 0.061 mole) in anhydrous THF (350 mL) was then added dropwise via the dropping funnel while maintaining the temperature at gentle reflux. The mixture was then allowed to stir at gentle reflux. The reaction mixture was then cooled to RT and dry carbon dioxide was gently bubbled. The mixture was then poured into ice cold solution of 10 % sulfuric acid (500 mL). The mixture was then extracted with EtOAc (750 mL x 3) and the combined EtOAc extracts were dried on sodium sulfate, filtered and EtOAc distilled off under reduced pressure. The crude residue obtained was triturated with benzene (150 ml x 2) and collected by filtration to give white solid (7.1 g). The solid was air dried under vacuum.

[0267] To enable peptide derivatization with cholesterol on resin, carboxy-cholesterol was synthesized according to the procedure described above. The completed resin-bound peptide was capped with an acetyl group (by use of acetic anhydride) followed by deprotection of the C-terminal side chain lysine amine by treatment with 2% hydrazine. The amine was acylated with an Fmoc-protected PEG(n) amino acid (e.g., n = 1-36; e.g., 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14, 15, 16, 17, 18, 19, 20, 21, 22, 23, 24, 25, 26, 27, 28, 29, 30, 31, 32, 33, 34, 35, or

36) at which point the olefins were crosslinked by treating with Grubbs(I) catalyst. The Fmoc was removed from the C-terminal NH of the PEG(n) amino acid and the amine acylated with carboxy-cholesterol. The final peptide product was obtained after peptide deprotection and cleavage, and purification by reverse phase high performance liquid chromatography/mass spectrometry (LC/MS). See the full synthetic scheme in **FIG. 3**.

Example 2: Broad Paramyxoviridae Anti-viral Activity Across Variants of a Structurally Stabilized Parainfluenza 3 Peptide Conjugate

[0268] Structurally stabilized peptides were tested in a pseudoviral assay against NiV and HPIV3.

Part I – Procedure

[0269] The control peptide “CNTRL” was the unstapled and unconjugated native PIV3 sequence:

VALDPIDISIVLNKIKSDLEESKEWIRRSNKILDSIK (SEQ ID NO. 625).

[0270] Primary human bronchial epithelial (NHBE) cells (Lonza Bioscience, CC-2540) were trypsinized and counted. The cells were then diluted to 2×10^5 /mL in BEGM media (Lonza Bioscience, CC-3170). The experimental peptide was then added at the desired concentrations. 20,000 cells/100 μ L containing peptides were transferred to 96-well white solid plate with 1.25 μ L Nipah pseudovirus (Integral Molecular, RVP-1801L, Lot# HNL-516A). The plates were incubated for 24 hrs and replaced with fresh BEGM media. Cells were incubated for another 72 hrs and bioluminescence were measured using ViviRen™ Live Cell Substrate (Promega, E6492) in GloMax® plate reader (Promega).

Part II – Results

[0271] The EC₅₀ values for the structurally stabilized peptide conjugates were calculated. Results are provided in the table below.

[0272] In the table, EC₅₀ values are represented as follows: EC₅₀ ≤ 5 nM is represented by “++++”, 5 nM > EC₅₀ ≤ 10 nM is represented by “+++”, 10 nM > EC₅₀ ≤ 20 nM is represented by “++”, and EC₅₀ > 20 nM is represented by “+”.

Compound No.	EC ₅₀
I-183	+++
I-187	++++
I-184	++++
I-188	+++
I-194	+++

Compound No.	EC ₅₀
I-190	+++
I-191	+++
I-195	++
CNTRL	+

WHAT IS CLAIMED IS:

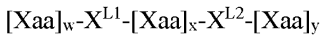
1. A modified peptide comprising an amino acid sequence that is at least 30% identical to an amino acid sequence selected from the group consisting of SEQ ID NO: 1-6, wherein at least two amino acids comprise side chains that are linked together (e.g., to form a staple).
2. A modified peptide comprising an amino acid sequence that has 1-18 substitutions, insertions, and/or deletions relative to SEQ ID NO: 1-6, wherein at least two amino acids comprise side chains that are linked together (e.g., to form a staple).
3. The modified peptide of any one of the preceding claims, wherein the side chains that are linked together are side chains of two amino acids separated by:
 - i) 3 amino acids (e.g., side chains of amino acids at positions i and i+4) or
 - ii) 6 amino acids (e.g., side chains amino acids at positions i and i+7).
4. The modified peptide of any one of the preceding claims, wherein the amino acid sequence is at least 70% identical to an amino acid sequence selected from the group consisting of SEQ ID NO: 1-6.
5. The modified peptide of any one of the preceding claims, wherein the amino acid sequence is at least 80% identical to an amino acid sequence selected from the group consisting of SEQ ID NO: 1-6.
6. The modified peptide of any one of the preceding claims, wherein the amino acid sequence is at least 90% identical to an amino acid sequence selected from the group consisting of SEQ ID NO: 1-6.
7. The modified peptide of any one of the preceding claims, wherein the amino acid sequence is at least 95% identical to an amino acid sequence selected from the group consisting of SEQ ID NO: 1-6.
8. The modified peptide of any one of the preceding claims, wherein the amino acid sequence is at least 98% identical to an amino acid sequence selected from the group consisting of SEQ ID NO: 1-6.

9. The modified peptide of any one of claims 1-8, wherein the amino acid sequence is SEQ ID NO: 1.
10. The modified peptide of any one of claims 1-8, wherein the amino acid sequence is SEQ ID NO: 2.
11. The modified peptide of any one of claims 1-8, wherein the amino acid sequence is SEQ ID NO: 3.
12. The modified peptide of any one of claims 1-8, wherein the amino acid sequence is SEQ ID NO: 4.
13. The modified peptide of any one of claims 1-8, wherein the amino acid sequence is SEQ ID NO: 5.
14. The modified peptide of any one of claims 1-8, wherein the amino acid sequence is SEQ ID NO: 6.
15. The modified peptide of any one of the preceding claims, wherein the two amino acids with side chains that are linked together are at the i and i+4 positions.
16. The modified peptide of any one of the preceding claims, wherein the two amino acids with side chains that are linked together are at the i and i+7 positions.
17. The modified peptide of any one of the preceding claims, wherein the modified peptide further comprises a PEG moiety.
18. The modified peptide of any one of the preceding claims, wherein the modified peptide further comprises an optionally substituted C₅-C₁₀₀ aliphatic lipid moiety.
19. The modified peptide of claim 18, wherein the lipid moiety is a fatty acid, phospholipid, sphingolipid, or a sterol.

20. The modified peptide of claim 18 or 19, wherein the lipid moiety is cholesterol, thiocholesterol, sitosterol, ergosterol, or tocopherol.

21. The modified peptide of any one of claims 18-20, wherein the lipid moiety is cholesterol.

22. The modified peptide of any one of the preceding claims, wherein the modified peptide is or comprises the formula:



or a pharmaceutically acceptable salt thereof, wherein:

- each Xaa independently represents a natural or unnatural amino acid;
- w, x, and y are independently 0-100, inclusive; and
- X^{L1} and X^{L2} are amino acids comprising side chains that are linked together.

23. The modified peptide of claim 22, wherein [Xaa]_x comprises a sequence selected from Table 2b.

24. The modified peptide of claim 22, wherein [Xaa]_w comprises a sequence selected from Table 2a.

25. The modified peptide of claim 22, wherein [Xaa]_y comprises a sequence selected from Table 2c.

26. The modified peptide of claim 22 wherein [Xaa]_w, [Xaa]_x, and [Xaa]_y are selected from i-viii:

	SEQ ID NO:	[Xaa] _w	[Xaa] _x	[Xaa] _y
i)	11	VALDPIDI	IVLNKI	SDLEESKEWIRRSNKILDSI;
ii)	12	VALDPIDISIVL	KIKSDL	ESKEWIRRSNKILDSI;
iii)	13	VALDPIDIS	VLNLIK	DLEESKEWIRRSNKILDSI;
iv)	14	VALDPIDISIVLN	IKSDLE	SKEWIRRSNKILDSI;
v)	15	VALDPIDISIVLNKIKSDL	ESKEWI	RSNKILDSI;
vi)	16	VALDPIDISIVLNKI	SDLEES	EWIRRSNKILDSI;
vii)	17	VALDPIDISIVLNKIK	DLEESK	WIRASNKILDSI; and

	SEQ ID NO:	[Xaa] _w	[Xaa] _x	[Xaa] _y
viii)	18	VALDPIDISIVLNKIKSDLE	SKEWIR	SNKILDSI.

27. The modified peptide of claim 22, wherein [Xaa]_w comprises a sequence selected from Table 3a.

28. The modified peptide of claim 22, wherein [Xaa]_x comprises a sequence selected from Table 3b.

29. The modified peptide of claim 22, wherein [Xaa]_y comprises a sequence selected from Table 3c.

30. The modified peptide of claim 22 wherein [Xaa]_w, [Xaa]_x, and [Xaa]_y are selected from i-viii:

	SEQ ID NO:	[Xaa] _w	[Xaa] _x	[Xaa] _y
i)	21	VFTDKVDI	SQISSM	QSLQQSKDYIKEAQRLLDTV;
ii)	22	VFTDKVDISSQI	SMNQSL	QSKDYIKEAQRLLDTV;
iii)	23	VFTDKVDIS	QISSMN	SLQQSKDYIKEAQRLLDTV;
iv)	24	VFTDKVDISSQIS	MNQSLQ	SKDYIKEAQRLLDTV;
v)	25	VFTDKVDISSQISSMNQSL	QSKDYI	EAQRLLDTV;
vi)	26	VFTDKVDISSQISSM	QSLQQS	DYIKEAQRLLDTV;
vii)	27	VFTDKVDISSQISSMN	SLQQSK	YIKEAQRLLDTV; and
viii)	28	VFTDKVDISSQISSMNQSLQ	SKDYIK	AQRLLDTV.

31. The modified peptide of claim 22, wherein [Xaa]_w comprises a sequence selected from Table 4a.

32. The modified peptide of claim 22, wherein [Xaa]_x comprises a sequence selected from Table 4b.

33. The modified peptide of claim 22, wherein [Xaa]_y comprises a sequence selected from Table 4c.

34. The modified peptide of claim 22 wherein [Xaa]_w, [Xaa]_x, and [Xaa]_y are selected from i-viii:

	SEQ ID NO:	[Xaa] _w	[Xaa] _x	[Xaa] _y
i)	31	ISLERLDV	TNLGNA	AKLEDAKELLESSDQILRSMK;
ii)	32	ISLERLDVGTNL	NAIAKL	DAKELLESSDQILRSMK;
iii)	33	ISLERLDVG	NLGNAI	KLEDAKELLESSDQILRSMK;
iv)	34	ISLERLDVGTNLG	AIAKLE	AKELLESSDQILRSMK;
v)	35	ISLERLDVGTNLGNAIAKL	DAKELL	SSDQILRSMK;
vi)	36	ISLERLDVGTNLGNA	AKLEDA	ELLESSDQILRSMK;
vii)	37	ISLERLDVGTNLGNAI	KLEDAK	LLESSDQILRSMK; and
viii)	38	ISLERLDVGTNLGNAIAKLE	AKELLE	SDQILRSMK.

35. The modified peptide of claim 22, wherein [Xaa]_w comprises a sequence selected from Table 5a.

36. The modified peptide of claim 22, wherein [Xaa]_x comprises a sequence selected from Table 5b.

37. The modified peptide of claim 22, wherein [Xaa]_y comprises a sequence selected from Table 5c.

38. The modified peptide of claim 22 wherein [Xaa]_w, [Xaa]_x, and [Xaa]_y are selected from i-viii:

	SEQ ID NO	[Xaa] _w	[Xaa] _x	[Xaa] _y
i)	41	INTQPIDI	TELSKV	ASLQNAVKYIKESNHQLQSV;
ii)	42	INTQPIDISTEL	KVNASL	NAVKYIKESNHQLQSV;
iii)	43	INTQPIDIS	ELSKVN	SLQNAVKYIKESNHQLQSV;
iv)	44	INTQPIDISTELS	VNASLQ	AVKYIKESNHQLQSV;
v)	45	INTQPIDISTELSKVNASL	NAVKYI	ESNHQLQSV;
vi)	46	INTQPIDISTELSKV	ASLQNA	KYIKESNHQLQSV;
vii)	47	INTQPIDISTELSKVN	SLQNAV	YIKESNHQLQSV; and

	SEQ ID NO	[Xaa] _w	[Xaa] _x	[Xaa] _y
viii)	48	INTQPIDISTELSKVNASLQ	AVKYIK	SNHQLQSV.

39. The modified peptide of claim 22, wherein [Xaa]_w comprises a sequence selected from Table 6a.

40. The modified peptide of claim 22, wherein [Xaa]_x comprises a sequence selected from Table 6b.

41. The modified peptide of claim 22, wherein [Xaa]_y comprises sequence selected from Table 6c.

42. The modified peptide of claim 22 wherein [Xaa]_w, [Xaa]_x, and [Xaa]_y are selected from i-viii:

	SEQ ID NO:	[Xaa] _w	[Xaa] _x	[Xaa] _y
i)	51	VTGNLDI	TELGNV	NSISNALDKLEESNSKLDKV;
ii)	52	VTGNLDISTEL	NVNNSI	NALDKLEESNSKLDKV;
iii)	53	VTGNLDIS	ELGNVN	SISNALDKLEESNSKLDKV;
iv)	54	VTGNLDISTELG	VNNSIS	ALDKLEESNSKLDKV;
v)	55	VTGNLDISTELGNVNNSIS	ALDKLE	SNSKLDKV;
vi)	56	VTGNLDISTELGNV	NSISNA	LDKLEESNSKLDKV;
vii)	57	VTGNLDISTELGNVN	SISNAL	KLEESNSKLDKV; and
viii)	58	VTGNLDISTELGNVNNSISN	LDKLEE	NSKLDKV.

43. The modified peptide of claim 22, wherein [Xaa]_w comprises a sequence selected from Table 7a.

44. The modified peptide of claim 22, wherein [Xaa]_x comprises a sequence selected from Table 7b.

45. The modified peptide of claim 22, wherein [Xaa]_y comprises a sequence selected from Table 7c.

46. The modified peptide of claim 22 wherein [Xaa]_w, [Xaa]_x, and [Xaa]_y are selected from i-viii:

	SEQ ID NO:	[Xaa] _w	[Xaa] _x	[Xaa] _y
i)	61	VDI	SQISSM	QSLQQSKDYIKEAQRLLDTV;
ii)	62	VDISSQI	SMNQSL	QSKDYIKEAQRLLDTV;
iii)	63	VDIS	QISSMN	SLQQSKDYIKEAQRLLDTV;
iv)	64	VDISSQIS	MNQSLQ	SKDYIKEAQRLLDTV;
v)	65	VDISSQISSMNQSL	QSKDYI	EAQRLLDTV;
vi)	66	VDISSQISSM	QSLQQS	DYIKEAQRLLDTV;
vii)	67	VDISSQISSMN	SLQQSK	YIKEAQRLLDTV; and
viii)	68	VDISSQISSMNQSLQ	SKDYIK	AQRLLDTV.

47. The modified peptide of any one of claims 22-46, wherein w, x, and y are independently 0-30, inclusive.

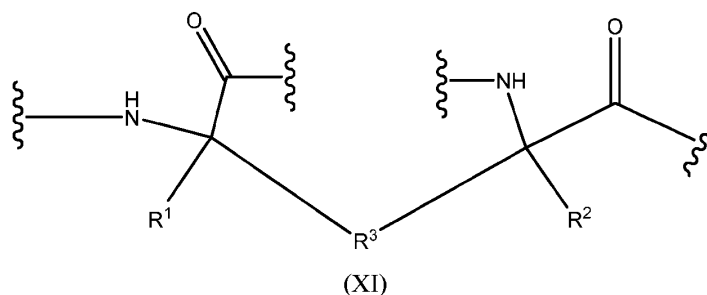
48. The modified peptide of any one of claims 22-47, wherein w is 4-30, inclusive.

49. The modified peptide of any one of claims 22-48, wherein y is 4-30, inclusive.

50. The modified peptide of any one of claims 22-49, wherein x is 3.

51. The modified peptide of any one of claims 22-49, wherein x is 6.

52. The modified peptide of any one of the preceding claims, wherein the two amino acids with side chains that are linked together are of formula (XI):

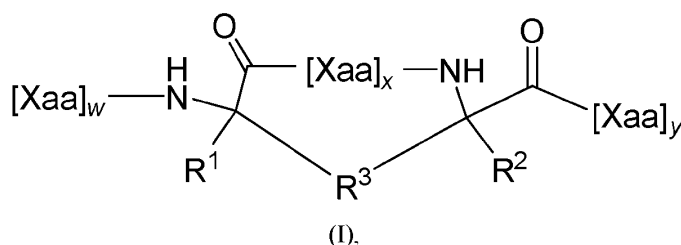


or a pharmaceutically acceptable salt thereof, wherein:

R^1 and R^2 are each independently hydrogen or an optionally substituted group selected from C_{1-10} alkyl, C_{2-10} alkenyl, and C_{2-10} alkynyl;

R^3 represents the linked side chain groups and is an optionally substituted bivalent, saturated or unsaturated, C_{3-20} aliphatic group wherein one or more methylene units of the aliphatic group are optionally and independently replaced with $—O—$, $—S—$, $—S—S—$, $—N(R')—$, $—C(O)—$, $—C(S)—$, $—C(NR')—$, $—C(O)N(R')—$, $—N(R')C(O)N(R')—$, $—N(R')C(O)O—$, $—S(O)—$, $—S(O)_2—$, $—S(O)_2N(R')—$, $—C(O)S—$, or $—C(O)O—$; and each R' is hydrogen or optionally substituted C_{1-12} aliphatic.

53. The modified peptide of any one of the preceding claims, wherein the modified peptide is or comprises Formula I:



or a pharmaceutically acceptable salt thereof, wherein:

R^1 and R^2 are each independently hydrogen or an optionally substituted group selected from C_{1-10} alkyl, C_{2-10} alkenyl, and C_{2-10} alkynyl;

R^3 represents the linked side chain groups and is an optionally substituted bivalent, C_{3-20} aliphatic group wherein one or more methylene units of the aliphatic group are optionally and independently replaced with $—O—$, $—S—$, $—S—S—$, $—N(R')—$, $—C(O)—$, $—C(S)—$, $—C(NR')—$, $—C(O)N(R')—$, $—N(R')C(O)N(R')—$, $—N(R')C(O)O—$, $—S(O)—$, $—S(O)_2—$, $—S(O)_2N(R')—$, $—C(O)S—$, or $—C(O)O—$;

each R' is hydrogen or optionally substituted C_{1-12} aliphatic;

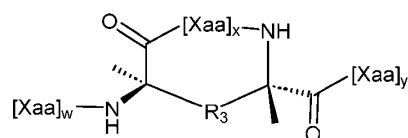
each Xaa independently represents a natural or unnatural amino acid; and

w, x, and y are independently 0-100, inclusive.

54. The modified peptide of claim 52 or 53, wherein R^1 and R^2 are each independently optionally substituted with 1-3 groups selected from C_{1-3} alkyl, hydroxyl, and C_{1-3} alkoxy.

55. The modified peptide of any one of claims 52-54, wherein R^1 is C_{1-10} alkyl.

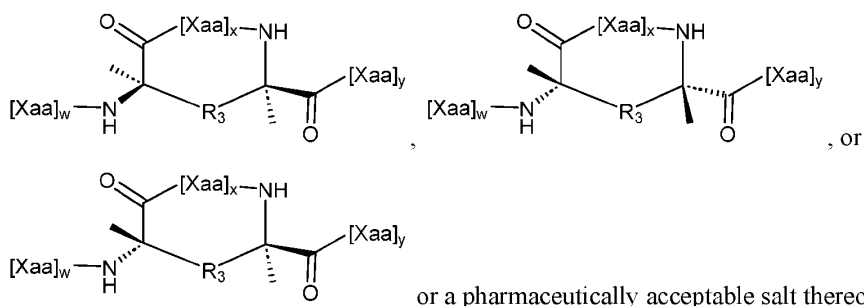
56. The modified peptide of any one of claims 52-54, wherein R^1 is methyl.
57. The modified peptide of any one of claims 52-56, wherein R^2 is C_{1-10} alkyl.
58. The modified peptide of any one of claims 52-56, wherein R^2 is methyl.
59. The modified peptide of claim 52 or 53, wherein the peptide comprises Formula Ia:



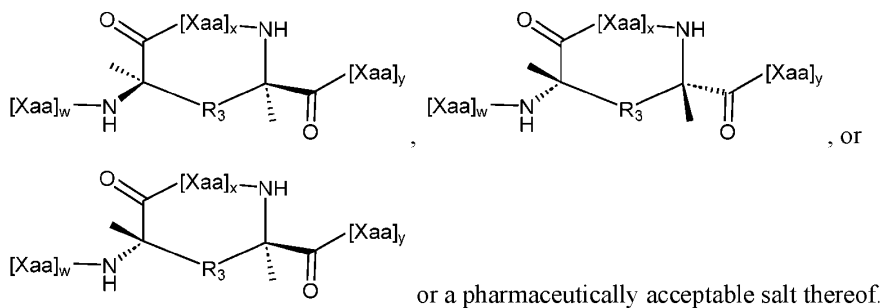
Ia

or a pharmaceutically acceptable salt thereof.

60. The modified peptide of claim 59, wherein the peptide consists of Formula Ia.
61. The modified peptide of claim 52 or 53, wherein the peptide comprises



62. The peptide of claim 61, wherein the peptide consists of



63. The modified peptide of any one of claims 52-62, wherein R^3 is optionally substituted C_{3-20} alkylene, C_{3-20} alkenylene, or C_{3-20} alkynylene, wherein one or more methylene units of the aliphatic group are optionally and independently replaced with $-O-$, $-S-$, $-S-S-$, $-N(R')$, $-C(O)-$, $-C(S)-$, $-C(NR')$, $-C(O)N(R')$, $-N(R')C(O)N(R')$, $-N(R')C(O)O-$, $-S(O)-$, $-S(O)_2-$, $-S(O)_2N(R')$, $-C(O)S-$, or $-C(O)O-$.
64. The modified peptide of any one of claims 52-62, wherein R^3 is C_{7-12} alkenylene.
65. The modified peptide of any one of claims 52-62, wherein R^3 is C_8 alkenylene.
66. The modified peptide of any one of claims 52-62, wherein R^3 is C_{11} alkenylene.
67. The modified peptide of any one of claims 52-62, wherein R^3 is $-(CH_2)_{1-7}-CH=CH-(CH_2)_{1-7}-$.
68. The modified peptide of any one of claims 52-62, wherein R^3 is $-(CH_2)_{3-7}-CH=CH-(CH_2)_{3-4}-$.
69. The modified peptide of any one of claims 52-62, wherein R^3 is $-(CH_2)_6-CH=CH-(CH_2)_3-$.
70. The modified peptide of any one of claims 52-62, wherein R^3 is $-(CH_2)_3-CH=CH-(CH_2)_3-$.
71. The modified peptide of any one of the preceding claims, wherein the C-terminus is conjugated to a PEG-cholesterol moiety.
72. The modified peptide of any one of the preceding claims, wherein the C-terminus is attached to a lipid moiety via R^4 , wherein R^4 is a bivalent, saturated or unsaturated, straight or branched C_{1-20} hydrocarbon chain, wherein 1-10 methylene units of the hydrocarbon chain are independently replaced by $-O-$, $-N(R)-$, $-S-$, $-OC(O)-$, $-C(O)O-$, $-C(O)-$, $-S(O)-$, $-S(O)_2-$, $-N(R)S(O)_2-$, $-S(O)_2N(R)-$, $-N(R)C(O)-$, $-C(O)N(R)-$, $-OC(O)N(R)-$, $-N(R)C(O)O-$, or $-[O-CH_2CH_2]_p$, wherein p is 1-20.

73. The modified peptide of any one of the preceding claims, wherein the C-terminus is attached to R^4 , wherein:

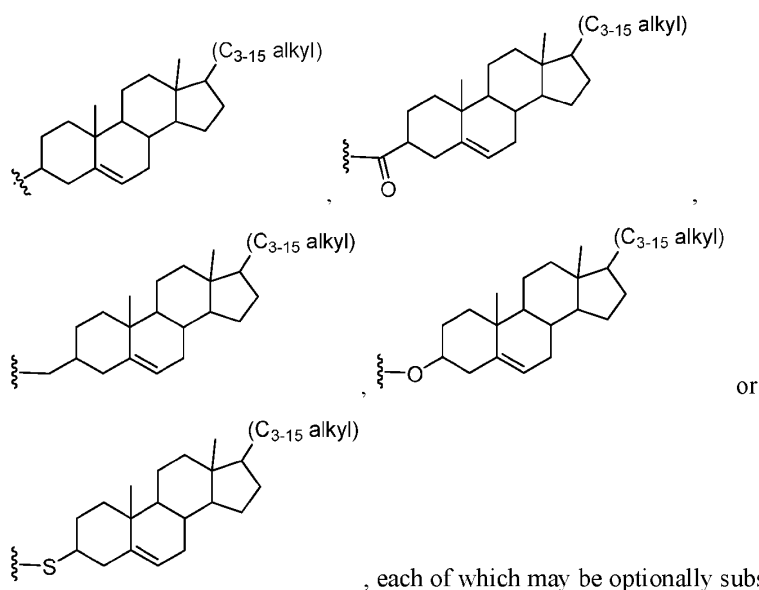
R^4 is $-N(H)-C(H)((CH_2)_4N(H)(C(O)-(C_{2-6} \text{ alkylene})-[O-CH_2CH_2]_p-N(R^5)C(O)-(C_{0-6} \text{ alkylene})-R^6))-C(O)-NH_2$;

R^5 is hydrogen or C_{1-4} alkyl;

R^6 is an optionally substituted C_5-C_{100} aliphatic lipid moiety; and

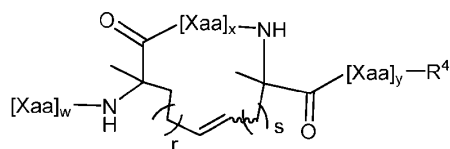
p is 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14, 15, or 16.

74. The modified peptide of claim 73, wherein R^6 is one of the following:



75. The modified peptide of claim 73 or 74, wherein R^6 is optionally substituted with 1-3 groups selected from C_{1-3} alkyl, hydroxyl, or C_{1-3} alkoxy.

76. The modified peptide of any one of claims 1-53, wherein the peptide comprises
Formula II:



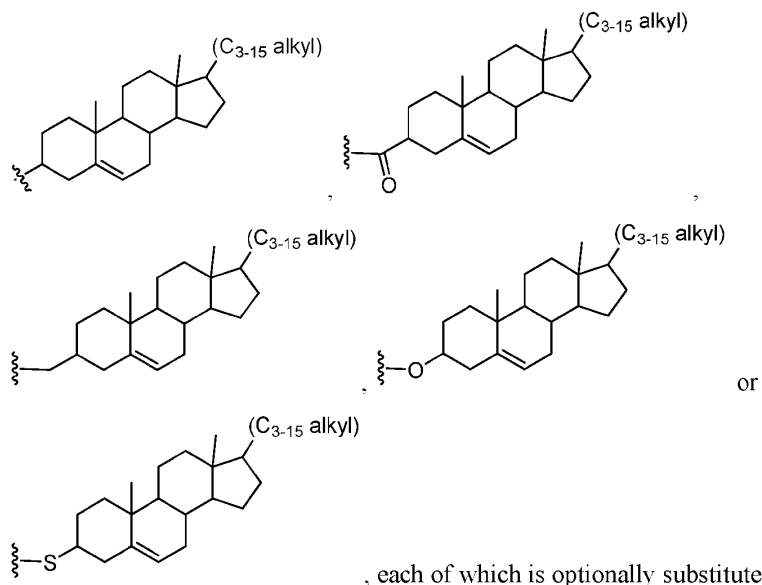
II

or a pharmaceutically acceptable salt thereof, wherein:

R^4 is $-N(H)-C(H)((CH_2)_4N(H)(C(O)-(C_{2-6} \text{ alkylene})-[O-CH_2CH_2]_p-N(R^5)C(O)-(C_{0-6} \text{ alkylene})-R^6))-C(O)-NH_2$;

R^5 is hydrogen or C_{1-4} alkyl;

R^6 is one of the following:



, each of which is optionally substituted with 1-3 occurrences of C_{1-3} alkyl, hydroxyl, or C_{1-3} alkoxy;

each Xaa independently represents a natural or unnatural amino acid,

wherein optionally the amino group of the N-terminal amino acid in $[Xaa]_w$ is replaced with $-N(H)C(O)-(C_{1-4} \text{ alkyl})$;

w, x, and y are independently 0-100, inclusive;

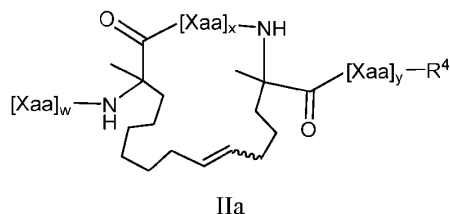
p is 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14, 15, or 16;

r is 2, 3, 4, 5, 6, 7, or 8; and

s is 2, 3, 4, 5, or 6.

77. The modified peptide of claim 76, wherein the peptide consists of Formula II.

78. The modified peptide of claim 76 or 77, wherein Formula II is further defined by Formula IIa:

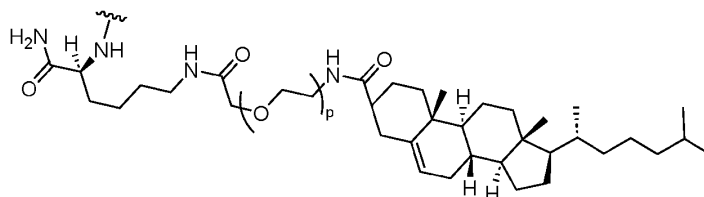


or a pharmaceutically acceptable salt thereof.

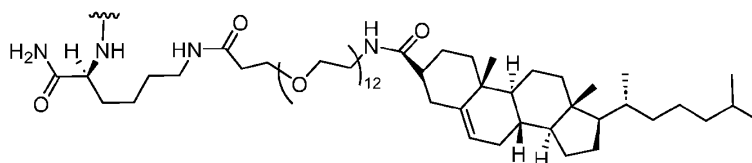
79. The modified peptide of any one of claims 75-78, wherein R^4 is $-N(H)-C(H)((CH_2)_4N(H)(C(O)-(C_{2-3} \text{ alkylene})-[O-CH_2CH_2]_p-N(R^5)C(O)-(C_{0-2} \text{ alkylene})-R^6))-C(O)-NH_2$.

80. The modified peptide of any one of claims 75-78, wherein R^4 is $-N(H)-C(H)((CH_2)_4N(H)(C(O)-CH_2CH_2-[O-CH_2CH_2]_p-N(R^5)C(O)-CH_2-R^6))-C(O)-NH_2$.

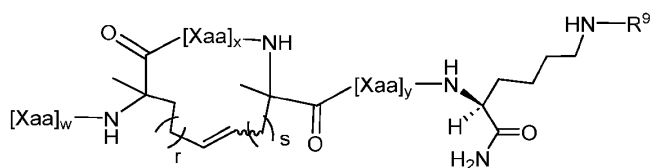
81. The modified peptide of any one of claims 75-78, wherein R^4 is



82. The modified peptide of any one of claims 75-78, wherein R^4 is



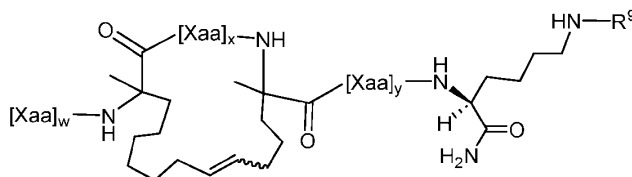
83. The modified peptide of claim 76 or 77, wherein Formula II is further defined by Formula IIb:



IIb

or a pharmaceutically acceptable salt thereof, wherein R^9 is $-C(O)-(CH_2CH_2)-[O-CH_2CH_2]_p-N(R^5)C(O)-R^6$.

84. The modified peptide of claim 76 or 77, wherein Formula II is further defined by Formula IIc:



IIc

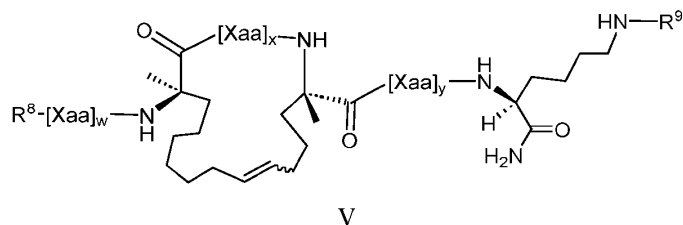
or a pharmaceutically acceptable salt thereof, wherein R^9 is $-C(O)-(CH_2CH_2)-[O-CH_2CH_2]_p-N(R^5)C(O)-R^6$.

85. The modified peptide of any one of claims 53-84, wherein the amino group of the N-terminal amino acid in $[Xaa]_w$ is replaced with $-N(H)C(O)-(C_{1-4} \text{ alkyl})$.

86. The modified peptide of any one of claims 22-84, wherein the amino group of the N-terminal amino acid in $[Xaa]_w$ is replaced with $-N(H)C(O)CH_3$.

87. The modified peptide of any one of claims 53-84, wherein the amino group of the N-terminal aspartic acid in $[Xaa]_w$ is replaced with $-N(H)C(O)CH_3$.

88. The modified peptide of any one of claims 1-53 comprising Formula V:

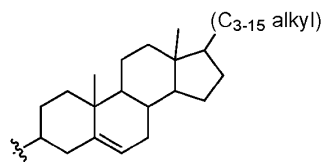


or a pharmaceutically acceptable salt thereof, wherein

R^9 is $-C(O)-(C_{2-6} \text{ alkylene})-[O-CH_2CH_2]_p-N(R^5)C(O)-(C_{0-6} \text{ alkylene})-R^6$;

R^5 is hydrogen or C_{1-4} alkyl;

R^6 is



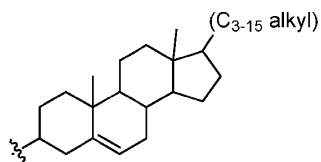
, which is optionally substituted 1-3 occurrences of C_{1-3}

alkyl, hydroxyl, or C_{1-3} alkoxy;

R^8 is $-C(O)-(C_{1-4} \text{ alkyl})$; and

p is 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14, 15, or 16.

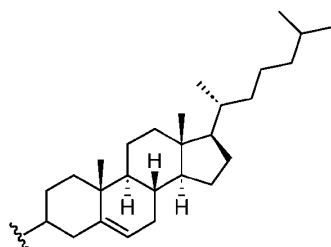
89. The modified peptide of any one of claims 73-80 or 83-88, wherein R^6 is



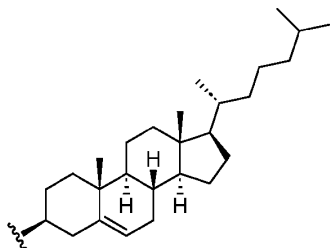
, substituted with 1-3 groups selected from C_{1-3} alkyl,

hydroxyl, or C_{1-3} alkoxy.

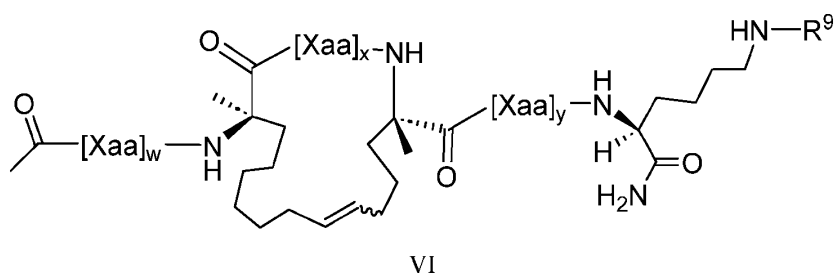
90. The modified peptide of any one of claims 73-80 or 83-88, wherein R^6 is



91. The modified peptide of any one of claims 73-80 or 83-88, wherein R^6 is

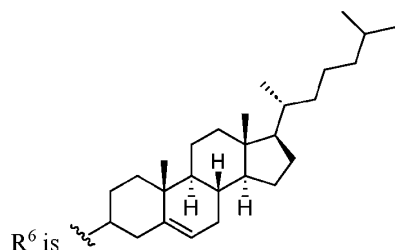


92. The modified peptide of any one of claims 88-91, wherein R^8 is $-C(O)CH_3$.
93. The modified peptide of any one of claims 73-80 or 83-88, wherein R^5 is hydrogen.
94. The modified peptide of any one of claims 73-81 or 83-93, wherein p is 4.
95. The modified peptide of any one of claims 73-81 or 83-93, wherein p is 8.
96. The modified peptide of any one of claims 73-81 or 83-93, wherein p is 12.
97. The modified peptide of any one of claims 23-78, comprising Formula VI or a pharmaceutically acceptable salt thereof:



wherein

R^9 is $-C(O)-(CH_2CH_2)-[O-CH_2CH_2]_{12}-N(H)C(O)-R^6$; and



98. A modified peptide selected from Table 8, Table 9, or Table 10, or a pharmaceutically acceptable salt thereof.
99. The modified peptide of any one of claims 1-21, wherein optionally the amino group of the N-terminal amino acid of the peptide is replaced with -N(H)C(O)-(C₁₋₄ alkyl).
100. The modified peptide of one of claims 1-21, wherein the amino group of the N-terminal amino acid of the peptide is replaced with -N(H)C(O)CH₃.
101. The modified peptide of any one of the preceding claims, wherein the amino acid side chains that are linked together span one to two turns of an alpha helix.
102. The modified peptide of any one of the preceding claims, wherein the peptide is structurally stabilized.
103. The modified peptide of any one of the preceding claims, wherein the peptide is stapled.
104. The modified peptide of claim 103, wherein the staple spans one to two turns of an alpha helix.
105. A multimeric conjugate comprising two or more peptides, a linker moiety, and a lipid moiety, wherein each peptide is independently a modified peptide of any one of the preceding claims.
106. The multimeric conjugate of claim 105, wherein the linker moiety comprises PEG.

107. The multimeric conjugate of claim 105 or 106, wherein the lipid moiety is a fatty acid, phospholipid, sphingolipid, or a sterol.

108. A pharmaceutically acceptable salt of the modified peptide of any one of claims 1-104 or of the multimeric conjugate of any one of claims 105-107, wherein the pharmaceutically acceptable salt comprises hydrochloride, sodium, sulfate, acetate, phosphate or diphosphate, chloride, potassium, maleate, calcium, citrate, mesylate, nitrate, tartrate, aluminum, gluconate, or any combination thereof.

109. A pharmaceutical composition comprising the modified peptide or pharmaceutically acceptable salt thereof, of any one of claims 1-104 or the multimeric conjugate of any one of claims 105-107, and a pharmaceutically acceptable carrier.

110. A method of treating or preventing a paramyxoviridae virus infection in a subject in need thereof, the method comprising administering to the subject a therapeutically effective amount of the modified peptide or a pharmaceutically acceptable salt thereof, of any one of claims 1-104 or the multimeric conjugate of any one of claims 105-107.

111. A method of treating or preventing a paramyxoviridae virus infection in a subject in need thereof, the method comprising administering to the subject a therapeutically-effective amount of the pharmaceutical composition of claim 109.

112. The method of any one of claims 110 or 111, wherein the paramyxoviridae virus is selected from Measles virus (MeV), Mumps virus (MuV), Respiratory Syncytial Virus (RSV), Parainfluenza virus 1(PIV-1), Parainfluenza virus 2 (PIV-2), Parainfluenza virus 3(PIV-3), Parainfluenza virus 4(PIV-4), Human Metapneumovirus (HMPV), Nipah virus (NiV), Hendra virus (HeV), Human parainfluenza-like virus (HPIV), Human metapneumovirus-like virus (HMPV-like virus), Human respirovirus 1 (HRV1), Human respirovirus 2 (HRV2), Human respirovirus 3 (HRV3), Human respirovirus 4 (HRV4), Avian metapneumovirus (aMPV), Tioman virus (TioV), Tuhoko virus (TuhV), Mossman virus (MosV), Menangle virus (MenV), Mapuera virus (MapV), or J virus (JV).