

ANTIVIRAL STRUCTURALLY STAPLED INFLUENZA PEPTIDES AND USES THEREOF

RELATED APPLICATIONS

[0001] This application claims priority to and benefit of U.S. Application No. 63/599,361, filed November 15, 2023, the entire contents of which are hereby incorporated by reference.

BACKGROUND

[0002] Influenza infection is one of the most common viral infections throughout the world every year. Influenza viruses infect host cells when the lipid envelope fuses with the endosomal membrane in host cells to release the viral genome into the cells. Specifically, the envelope glycoprotein hemagglutinin (HA) mediates binding of the virus envelope with the endosomal membrane of the host cell, leading to membrane fusion, viral genome replication, and infection. Influenza HA is divided into two domains, HA1 and HA2, with HA1 mediating host cell receptor binding and HA2 mediating fusion of the viral membrane to the endosomal membrane. Fusion of an influenza virus particle with the endosomal membrane of a host cell is mediated by conformational shifts in HA, which are driven by the lower pH in the endosome.

[0003] Cryo EM studies at pH 5.5 (endosomal pH) have highlighted several conformational changes of influenza HA during the host cell fusion process. In the final conformational change, the HA2 domain C-terminal helix, residues 106-125, folds back onto the HR2 portion of the longer HA2 helix to bring the viral membrane in proximity to the endosomal membrane and fusion takes place. Further, the C-terminal helix of HA2 is highly conserved among influenza A subtypes.

[0004] Although influenza vaccines and treatments are available, there are still millions of cases of influenza illnesses, hundreds of thousands of influenza hospitalizations, and thousands of influenza deaths every year.

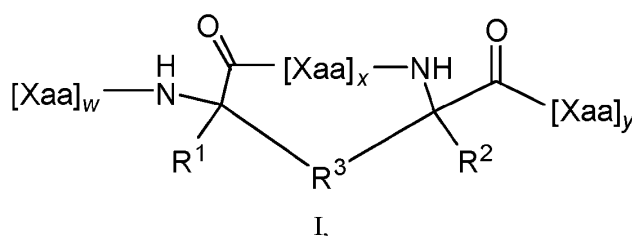
SUMMARY

[0005] The present disclosure provides modified peptides that are useful for the treatment and/or prevention of influenza virus infections (e.g., influenza A or influenza B infections). In some embodiments, provided peptides are crosslinked (e.g., stapled) to stabilize the helical structure of the peptide. The peptides provided herein are particularly advantageous because they

are not limited to treating or preventing a particular influenza subtype and thus can be used to treat or prevent more than one subtype of influenza.

[0006] The present disclosure encompasses the recognition that blocking the final conformational change in HA may inhibit influenza fusion with the host cell and provides a new strategy for preventing and/or treating influenza infections that is not limited to a specific influenza subtype. The modified peptides provided herein are believed to prevent this conformational change in the HA2 domain of influenza HA (e.g., the fold back of the HA2 C-terminal helix to the HR2 region), and thus prevent influenza fusion with the host cell.

[0007] In some embodiments, the present disclosure provides modified peptides of Formula I:



or a pharmaceutically acceptable salt thereof, wherein R^1 , R^2 , R^3 , Xaa, x, w, and y are as defined herein.

[0008] The present disclosure also provides methods of treating and/or preventing an influenza viral infection, comprising administering to a patient in need thereof a therapeutically effective amount of a modified peptide provided herein, such as a peptide of Formula I, or a pharmaceutically acceptable salt thereof.

BRIEF DESCRIPTION OF THE DRAWINGS

[0009] **FIG. 1** is a schematic showing the mapping of the C-terminal helix interactions on influenza A subtype sequences. The consensus sequence for each subtype is shown and colored to reflect conservation. Most residues for a given subtype were conserved at 95% or better. A proposed therapeutic peptide is shown in a box and the residues that interact between the C-terminal helix and the HA2 are in bold font.

[0010] **FIG. 2** is a schematic showing an interaction map of the H3N3 C-terminal helix. The sequence of the C-terminal helix is shown for loop regions and for the helical region. Connections are made within the C-terminal helix or with external boxes. The connections are shown for hydrogen bonds, for hydrophobic interactions, and for the potential staple position. The residues

within the boxes show the conservation of H1N1, H3N2, and influenza B for the C-terminal helix contacts.

[0011] FIG. 3 shows a synthetic scheme of the steps for on-resin derivatization of a stapled peptide sequence with a PEG-linked cholesterol moiety.

DETAILED DESCRIPTION

Compounds & Definitions

[0012] Compounds (e.g., modified peptides) of the present disclosure 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.

[0013] For purposes of this disclosure, 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.

[0014] Unless otherwise stated, structures depicted herein are meant to include all stereoisomeric (e.g., enantiomeric or diastereomeric) forms of the structure, as well as all geometric or conformational isomeric forms of the structure. For example, the R and S configurations of each stereocenter are contemplated as part of the disclosure. Therefore, single stereochemical isomers, as well as enantiomeric, diastereomeric, and geometric (or conformational) mixtures of provided compounds are within the scope of the disclosure. Unless otherwise stated, all tautomeric forms of provided compounds are within the scope of the disclosure.

[0015] Unless otherwise indicated, structures depicted herein are meant to include compounds that differ only in the presence of one or more isotopically enriched atoms. For example, compounds having the present structures including replacement of hydrogen by deuterium or tritium, or replacement of a carbon by ¹³C- or ¹⁴C-enriched carbon are within the scope of this disclosure.

[0016] 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. 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.

[0017] The term “alkyl”, used alone or as part of a larger moiety, refers to a saturated, optionally substituted straight or branched hydrocarbon group having (unless otherwise specified) 1-12, 1-10, 1-8, 1-6, 1-4, 1-3, or 1-2 carbon atoms (e.g., C₁₋₁₂, C₁₋₁₀, C₁₋₈, C₁₋₆, C₁₋₄, C₁₋₃, or C₁₋₂). Exemplary alkyl groups include methyl, ethyl, propyl, butyl, pentyl, hexyl, and heptyl.

[0018] The term “alkylene” refers to a bivalent alkyl group. An “alkylene chain” is a polymethylene group, i.e., $-(CH_2)_n-$, 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 herein for a substituted aliphatic group.

[0019] The term “alkenyl”, used alone or as part of a larger moiety, refers to an optionally substituted straight or branched hydrocarbon chain having at least one double bond and having (unless otherwise specified) 2-12, 2-10, 2-8, 2-6, 2-4, or 2-3 carbon atoms (e.g., C₂₋₁₂, C₂₋₁₀, C₂₋₈, C₂₋₆, C₂₋₄, or C₂₋₃). Exemplary alkenyl groups include ethenyl, propenyl, butenyl, pentenyl, hexenyl, and heptenyl.

[0020] The term “alkenylene” refers to a bivalent alkenyl group. A substituted alkenylene chain is a bivalent hydrocarbon chain containing at least one double bond, in which one or more hydrogen atoms are replaced with a substituent. Suitable substituents include those described herein for a substituted aliphatic group.

[0021] The term “alkynyl”, used alone or as part of a larger moiety, refers to an optionally substituted straight or branched chain hydrocarbon group having at least one triple bond and

having (unless otherwise specified) 2-12, 2-10, 2-8, 2-6, 2-4, or 2-3 carbon atoms (e.g., C₂₋₁₂, C₂₋₁₀, C₂₋₈, C₂₋₆, C₂₋₄, or C₂₋₃). Exemplary alkynyl groups include ethynyl, propynyl, butynyl, pentynyl, hexynyl, and heptynyl.

[0022] As used herein, the term “alkynylene” refers to a bivalent alkynyl group. A substituted alkynylene chain is a bivalent hydrocarbon chain containing at least one triple bond, in which one or more hydrogen atoms are replaced with a substituent. Suitable substituents include those described herein for a substituted aliphatic group.

[0023] 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 six 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 disclosure, “aryl” refers to an aromatic ring system which includes, but not limited to, phenyl, naphthyl, anthracyl and the like, which may bear one or more substituents. Unless otherwise specified, “aryl” groups are hydrocarbons.

[0024] 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.

[0025] The term “halogen” or “halo” means F, Cl, Br, or I.

[0026] 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)).

[0027] 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 (e.g., 1-5 heteroatoms independently selected from nitrogen, oxygen, and sulfur). Heteroaryl groups include, without limitation, thienyl, furanyl, pyrrolyl, imidazolyl, pyrazolyl, triazolyl, tetrazolyl, oxazolyl, isoxazolyl, oxadiazolyl, thiazolyl, isothiazolyl, thiadiazolyl, pyridyl, pyridazinyl, pyrimidinyl, pyrazinyl, indoliziny, 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. Nonlimiting examples include indolyl, isoindolyl, benzothienyl, benzofuranyl, dibenzofuranyl, indazolyl, benzimidazolyl, benzthiazolyl, quinolyl, isoquinolyl, cinnolyl, phthalazinyl, quinazolinyl, quinoxalinyl, 4*H*-quinoliziny, carbazolyl, acridinyl, phenazinyl, phenothiazinyl, phenoxazinyl, tetrahydroquinolyl, and tetrahydroisoquinolyl. 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.

[0028] As used herein, the terms “heterocycle,” “heterocyclyl,” and “heterocyclic ring” are used interchangeably and refer to a stable 3- to 7-membered monocyclic or 5- to 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). 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, tetrahydrothienyl, piperidinyl, decahydroquinolyl, oxazolidinyl, piperazinyl, dioxanyl, dioxolanyl, diazepinyl, oxazepinyl, thiazepinyl, morpholyl, and thiamorpholyl. A heterocyclyl group may be mono-, bi-, tri-, or polycyclic, preferably mono-, bi-, or tricyclic, more preferably mono- or bicyclic. A bicyclic heterocyclic ring also includes groups in which the heterocyclic ring is fused to one or more aryl, heteroaryl, or cycloaliphatic rings. Exemplary bicyclic heterocyclic groups include indolyl, isoindolyl, benzodioxolyl, 1,3-dihydroisobenzofuranyl, 2,3-dihydrobenzofuranyl, and

tetrahydroquinoliny. A bicyclic heterocyclic ring can also be a spirocyclic ring system (e.g., 7- to 11-membered spirocyclic heterocyclic ring having, in addition to carbon atoms, one or more heteroatoms as defined above (e.g., one, two, three or four heteroatoms)).

[0029] As used herein, the term “partially unsaturated,” when used in reference to a ring moiety, 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] The term “unsaturated,” as used herein, means that a moiety has one or more units of unsaturation.

[0031] As described herein, compounds of the present disclosure 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 disclosure are 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.

[0032] 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° ; $-NO_2$; $-CN$; $-N_3$; $-(CH_2)_{0-4}N(R^\circ)_2$; $-(CH_2)_{0-4}N(R^\circ)C(O)R^\circ$; $-N(R^\circ)C(S)R^\circ$; $-(CH_2)_{0-4}N(R^\circ)C(O)NR^\circ_2$; $-N(R^\circ)C(S)NR^\circ_2$; $-(CH_2)_{0-4}N(R^\circ)C(O)OR^\circ$; $-N(R^\circ)N(R^\circ)C(O)R^\circ$; $-N(R^\circ)N(R^\circ)C(O)NR^\circ_2$; $-N(R^\circ)N(R^\circ)C(O)OR^\circ$; $-(CH_2)_{0-4}C(O)R^\circ$; $-C(S)R^\circ$; $-(CH_2)_{0-4}C(O)OR^\circ$; $-(CH_2)_{0-4}C(O)SR^\circ$; $-(CH_2)_{0-4}C(O)OSiR^\circ_3$; $-(CH_2)_{0-4}OC(O)R^\circ$; $-OC(O)(CH_2)_{0-4}SR^\circ$; $-SC(S)SR^\circ$; $-(CH_2)_{0-4}SC(O)R^\circ$; $-(CH_2)_{0-4}C(O)NR^\circ_2$; $-C(S)NR^\circ_2$; $-$

$C(S)SR^{\circ}$; $-(CH_2)_{0-4}OC(O)NR^{\circ}_2$; $-C(O)N(OR^{\circ})R^{\circ}$; $-C(O)C(O)R^{\circ}$; $-C(O)CH_2C(O)R^{\circ}$; $-C(NOR^{\circ})R^{\circ}$; $-(CH_2)_{0-4}SSR^{\circ}$; $-(CH_2)_{0-4}S(O)_2R^{\circ}$; $-(CH_2)_{0-4}S(O)_2OR^{\circ}$; $-(CH_2)_{0-4}OS(O)_2R^{\circ}$; $-S(O)_2NR^{\circ}_2$; $-(CH_2)_{0-4}S(O)R^{\circ}$; $-N(R^{\circ})S(O)_2NR^{\circ}_2$; $-N(R^{\circ})S(O)_2R^{\circ}$; $-N(OR^{\circ})R^{\circ}$; $-C(NH)NR^{\circ}_2$; $-P(O)(OR^{\circ})R^{\circ}$; $-P(O)R^{\circ}_2$; $-OP(O)R^{\circ}_2$; $-OP(O)(OR^{\circ})_2$; $-SiR^{\circ}_3$; $-(C_{1-4}$ 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.

[0033] 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 $=S$.

[0034] 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.

[0035] Suitable substituents on the aliphatic group of R^* include 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.

[0036] Suitable substituents on a substitutable nitrogen of an “optionally substituted” group include $-R^\dagger$, $-\text{NR}^\dagger_2$, $-\text{C}(\text{O})R^\dagger$, $-\text{C}(\text{O})\text{OR}^\dagger$, $-\text{C}(\text{O})\text{C}(\text{O})R^\dagger$, $-\text{C}(\text{O})\text{CH}_2\text{C}(\text{O})R^\dagger$, $-\text{S}(\text{O})_2R^\dagger$, $-\text{S}(\text{O})_2\text{NR}^\dagger_2$, $-\text{C}(\text{S})\text{NR}^\dagger_2$, $-\text{C}(\text{NH})\text{NR}^\dagger_2$, or $-\text{N}(R^\dagger)\text{S}(\text{O})_2R^\dagger$; wherein each $R^\dagger$ is independently hydrogen, C_{1-6} aliphatic which may be substituted as defined below, unsubstituted $-\text{OPh}$, 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.

[0037] 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.

[0038] 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 or other 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.

[0039] 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, which are, within the scope of sound medical judgment, suitable for use in contact with the tissues of human beings and/or animals without excessive toxicity, irritation, allergic response, or other problems or complication, commensurate with a reasonable benefit/risk ratio. For examples of carriers, as well as stabilizers and adjuvants, *see e.g.*, Martin, Remington's Pharmaceutical Sciences, 15th Ed., Mack Publ. Co., Easton, PA [1975].

[0040] As used herein, the terms "prevent" or "prevention", when used in connection with the occurrence of a disease, disorder, and/or condition, refer to reducing the risk of developing the disease, disorder and/or condition and/or to delaying onset of one or more characteristics or symptoms of the disease, disorder or condition.

[0041] 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.

[0042] The phrase "therapeutically effective amount," as used herein, means that amount of an active agent which is effective for producing some desired therapeutic effect in at least a sub-population of cells in an animal and/or a sub-population of subjects at a reasonable benefit/risk ratio applicable to any medical treatment.

[0043] As used herein, the term "treat" (also "treatment" or "treating") refers to any administration of a therapy that partially or completely alleviates, ameliorates, relieves, inhibits, delays onset of, reduces severity of, and/or reduces incidence of one or more symptoms, features, and/or causes of a particular disease, disorder, and/or condition.

Influenza Peptides

[0044] The present disclosure provides modified peptides that are useful for the treatment and/or prevention of influenza virus infections (*e.g.*, influenza A or influenza B infections). In some embodiments, provided peptides are crosslinked (*e.g.*, stapled) to stabilize the helical structure of the peptide. The modified peptides provided herein are particularly advantageous because they are not limited to treating or preventing a particular influenza subtype and thus can be used to treat or prevent more than one subtype of influenza.

[0045] In some embodiments, the present disclosure provides a modified peptide comprising an amino acid sequence of an influenza HA protein, or a variant thereof. In some embodiments, the present disclosure provides a modified peptide comprising an amino acid sequence of an influenza HA protein, or a variant thereof, wherein at least two amino acids comprise side chains that are linked together (e.g., to form a staple).

[0046] In some embodiments, a provided modified peptide comprises an amino acid sequence that is substantially identical to an amino acid sequence selected from Table 1. In some embodiments, a provided modified peptide comprises an amino acid sequence that is substantially identical to an amino acid sequence selected from Table 1, wherein at least two amino acids of the sequence comprise side chains that are linked together (e.g., to form a staple).

Table 1.

SEMKNLFEKTRRQLRENA	SEQ ID NO: 1
SEMKNLFEKVRRQLRENA	SEQ ID NO: 2
SEMKNLFEKTRRELRENA	SEQ ID NO: 3
SEMKNLYEKVRSQLENA	SEQ ID NO: 4
DLTDSEMKNLFEKTRRQLRENA	SEQ ID NO: 5
SEMKNLFEKVRSQLRN	SEQ ID NO: 6

[0047] In some embodiments, provided modified peptides 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 selected from Table 1, wherein at least two amino acids of the sequence comprise side chains that are linked together (e.g., to form a staple). In some embodiments, provided modified peptides comprise an amino acid sequence that is at least 30% identical to a sequence selected from Table 1. In some embodiments, provided modified peptides comprise an amino acid sequence that is at least 35% identical to a sequence selected from Table 1. In some embodiments, provided modified peptides comprise an amino acid sequence that is at least 40% identical to a sequence selected from Table 1. In some embodiments, provided modified peptides comprise an amino acid sequence that is at least 45% identical to a sequence selected from Table 1. In some embodiments, provided modified peptides comprise an amino acid sequence that is at least 50% identical to a sequence selected from Table 1. In some embodiments, provided modified peptides comprise an amino acid sequence that is at least 55% identical to a

sequence selected from Table 1. In some embodiments, provided modified peptides comprise an amino acid sequence that is at least 60% identical to a sequence selected from Table 1. In some embodiments, provided modified peptides comprise an amino acid sequence that is at least 65% identical to a sequence selected from Table 1. In some embodiments, provided modified peptides comprise an amino acid sequence that is at least 70% identical to a sequence selected from Table 1. In some embodiments, provided modified peptides comprise an amino acid sequence that is at least 75% identical to a sequence selected from Table 1. In some embodiments, provided modified peptides comprise an amino acid sequence that is at least 80% identical to a sequence selected from Table 1. In some embodiments, provided modified peptides comprise an amino acid sequence that is at least 85% identical to a sequence selected from Table 1. In some embodiments, provided modified peptides comprise an amino acid sequence that is at least 90% identical to a sequence selected from Table 1. In some embodiments, provided modified peptides comprise an amino acid sequence that is at least 95% identical to a sequence selected from Table 1. In some embodiments, provided modified peptides comprise an amino acid sequence that is at least 98% identical to a sequence selected from Table 1.

[0048] In some embodiments, the present disclosure provides a modified peptide comprising an amino acid sequence that has 0-10 substitutions, insertions, and/or deletions relative to a sequence selected from Table 1, wherein at least two amino acids comprise side chains that are linked together (e.g., to form a staple). In some embodiments, provided modified peptides comprise 0-5 substitutions, insertions, and/or deletions relative to a sequence selected from Table 1. In some embodiments, provided modified peptides comprise 0-2 substitutions, insertions, and/or deletions relative to a sequence selected from Table 1. In some embodiments, provided modified peptides comprise 1-5 substitutions, insertions, and/or deletions relative to a sequence selected from Table 1. In some embodiments, provided modified peptides comprise 1-2 substitutions, insertions, and/or deletions relative to a sequence selected from Table 1.

[0049] In some embodiments, when a modified peptide comprises an amino acid sequence that has a substitution relative to a sequence selected from Table 1, the substitution is a conservative amino acid substitution. 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).

[0050] In some embodiments, when a modified peptide comprises an amino acid sequence that has a substitution relative to a sequence selected from Table 1, the substitution is methionine to norleucine. In some embodiments, when a modified peptide comprises an amino acid sequence that has a substitution relative to a sequence selected from Table 1, the substitution is threonine to valine. In some embodiments, when a modified peptide comprises an amino acid sequence that has a substitution relative to a sequence selected from Table 1, the substitution is glutamine to glutamate. In some embodiments, when a modified peptide comprises an amino acid sequence that has a substitution relative to a sequence selected from Table 1, the substitution is phenylalanine to tyrosine. In some embodiments, when a modified peptide comprises an amino acid sequence that has a substitution relative to a sequence selected from Table 1, the substitution is arginine to serine.

[0051] In some embodiments, provided modified peptides comprise an amino acid sequence:

SE-Xaa¹-NKL-Xaa²-EK-Xaa³-R-Xaa⁴-Xaa⁵-LRENA (SEQ ID NO: 7)

wherein:

Xaa¹ is methionine or norleucine;

Xaa² is phenylalanine or tyrosine;

Xaa³ is threonine or valine;

Xaa⁴ is arginine or serine; and

Xaa⁵ is glutamine or glutamate.

[0052] In some embodiments, provided modified peptides comprise an amino acid sequence:

SE-Xaa¹-NKL-Xaa²-EKVR-Xaa⁴-Xaa⁵-LRENA (SEQ ID NO: 8)

wherein:

Xaa¹ is methionine or norleucine;

Xaa² is phenylalanine or tyrosine;

Xaa⁴ is arginine or serine; and

Xaa⁵ is glutamine or glutamate.

[0053] In some embodiments, provided modified peptides comprise an amino acid sequence:

SEMNKL-Xaa²-EK-Xaa³-R-Xaa⁴-Xaa⁵-LRENA (SEQ ID NO: 9)

wherein:

Xaa² is phenylalanine or tyrosine;

Xaa³ is threonine or valine;

Xaa⁴ is arginine or serine; and

Xaa⁵ is glutamine or glutamate.

[0054] In some embodiments, provided modified peptides comprise an amino acid sequence:

SE-Xaa¹-NKL-Xaa²-EK-Xaa³-R-Xaa⁴-Xaa⁵-LRENA (SEQ ID NO: 10)

wherein:

Xaa¹ is norleucine;

Xaa² is phenylalanine or tyrosine;

Xaa³ is threonine or valine;

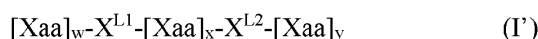
Xaa⁴ is arginine or serine; and

Xaa⁵ is glutamine or glutamate.

[0055] In some embodiments, provided modified peptides comprise at least two amino acid side chains that are linked together (e.g., to form a staple). In some embodiments, two amino acid side chains that are linked together span one to two turns of an alpha helix of the modified peptide. In some embodiments, two amino acid side chains that are linked together span one turn of an alpha helix of the modified peptide. In some embodiments, two amino acid side chains that are linked together span two turns of an alpha helix of the modified peptide.

[0056] In some embodiments, provided modified peptides comprise at least two amino acid side chains that are linked together, wherein the two amino acids are 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 of amino acids at positions i and i+7). In some embodiments, provided modified peptides comprise at least two amino acid side chains that are linked together, wherein the two amino acids are separated by 3 amino acids (e.g., side chains of amino acids at positions i and i+4). In some embodiments, provided modified peptides comprise at least two amino acid side chains that are linked together, wherein the two amino acids are separated by 6 amino acids (e.g., side chains of amino acids at positions i and i+7).

[0057] In some embodiments, the present disclosure provides a modified peptide of Formula I':



or a pharmaceutically acceptable salt thereof, wherein:

each Xaa independently represents a natural or unnatural amino acid;

w, x, and y are independently 0-50, inclusive;

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

[Xaa]_x represents an amino acid sequence comprising at least 3 contiguous amino acids of:

an amino acid sequence selected from Table 1; or

an amino acid sequence that is (i) at least 30% identical to an amino acid sequence selected from Table 1 and/or (ii) has 1-10 substitutions, insertions, and/or deletions relative to an amino acid sequence selected from Table 1;

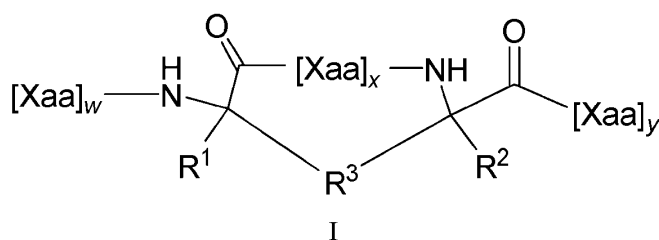
each of [Xaa]_w and [Xaa]_y independently represents an amino acid sequence comprising one or more contiguous amino acids of:

an amino acid sequence selected from Table 1; or

an amino acid sequence that is (i) at least 30% identical to an amino acid sequence selected from Table 1 and/or (ii) has 1-10 substitutions, insertions, and/or deletions relative to an amino acid sequence selected from Table 1,

optionally wherein the N-terminal amino acid in [Xaa]_w and/or the C-terminal amino acid in [Xaa]_y is conjugated to a moiety described herein.

[0058] In some embodiments, the present disclosure provides a modified peptide of Formula I:



or a pharmaceutically acceptable salt thereof, wherein:

R¹ and R² are each independently hydrogen or an optionally substituted C₁₋₁₀ aliphatic group;

R³ represents linked side chain groups and is an optionally substituted bivalent, C₃₋₂₀ hydrocarbon chain, wherein one or more methylene units of the hydrocarbon chain are

optionally and independently replaced with $-\text{O}-$, $-\text{S}-$, $-\text{S}-\text{S}-$, $-\text{N}(\text{R}')-$, $-\text{C}(\text{O})-$, $-\text{C}(\text{S})-$, $-\text{C}(\text{NR}')-$, $-\text{C}(\text{O})\text{N}(\text{R}')-$, $-\text{N}(\text{R}')\text{C}(\text{O})\text{N}(\text{R}')-$, $-\text{N}(\text{R}')\text{C}(\text{O})\text{O}-$, $-\text{S}(\text{O})-$, $-\text{S}(\text{O})_2-$, $-\text{S}(\text{O})_2\text{N}(\text{R}')-$, $-\text{C}(\text{O})\text{S}-$, or $-\text{C}(\text{O})\text{O}-$;
 each R' is independently hydrogen or optionally substituted C_{1-12} aliphatic;
 each Xaa independently represents a natural or unnatural amino acid;
 w and y are each independently 0-50;
 x is 3-10; and

$[\text{Xaa}]_x$ represents an amino acid sequence comprising at least 3 contiguous amino acids of:

an amino acid sequence selected from Table 1; or

an amino acid sequence that is (i) at least 30% identical to an amino acid sequence selected from Table 1 and/or (ii) has 1-10 substitutions, insertions, and/or deletions relative to an amino acid sequence selected from Table 1;

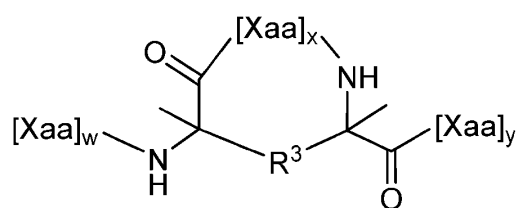
each of $[\text{Xaa}]_w$ and $[\text{Xaa}]_y$ independently represents an amino acid sequence comprising one or more contiguous amino acids of:

an amino acid sequence selected from Table 1; or

an amino acid sequence that is (i) at least 30% identical to an amino acid sequence selected from Table 1 and/or (ii) has 1-10 substitutions, insertions, and/or deletions relative to an amino acid sequence selected from Table 1,

optionally wherein the N-terminal amino acid in $[\text{Xaa}]_w$ and/or the C-terminal amino acid in $[\text{Xaa}]_y$ is conjugated to a moiety described herein.

[0059] In some embodiments, the present disclosure provides a modified peptide of Formula I-A:

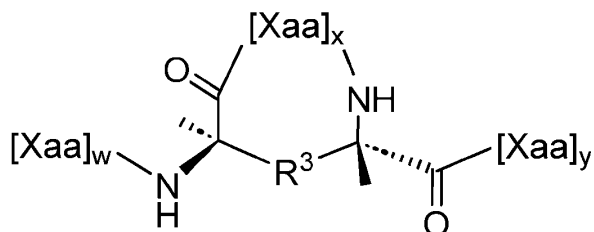


I-A

or a pharmaceutically acceptable salt thereof, wherein R^3 , $[\text{Xaa}]_w$, $[\text{Xaa}]_x$, and $[\text{Xaa}]_y$ are as defined above for Formula I and described in classes and subclasses herein, both singly and in combination.

[0060] In some embodiments, the present disclosure provides a modified peptide of Formula

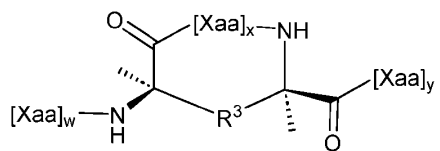
I-B:



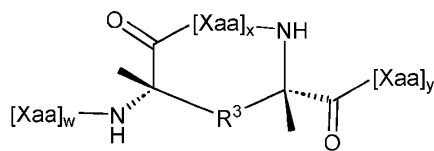
I-B

or a pharmaceutically acceptable salt thereof, wherein R^3 , $[Xaa]_w$, $[Xaa]_x$, and $[Xaa]_y$ are as defined above for Formula I and described in classes and subclasses herein, both singly and in combination.

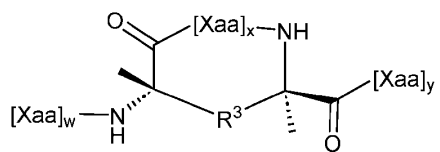
[0061] In some embodiments, the present disclosure provides a modified peptide selected from:



(I-B1),



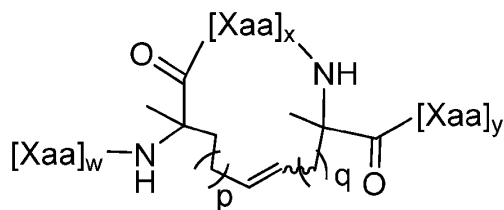
(I-B2), or



(I-B3)

or a pharmaceutically acceptable salt thereof, wherein R^3 , $[Xaa]_w$, $[Xaa]_x$, and $[Xaa]_y$ are as defined above for Formula I and described in classes and subclasses herein, both singly and in combination.

[0062] In some embodiments, the present disclosure provides a modified peptide of Formula I-C:

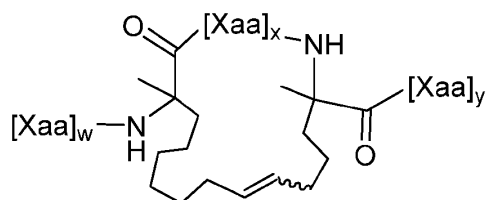


I-C

or a pharmaceutically acceptable salt thereof, wherein $[Xaa]_w$, $[Xaa]_x$, and $[Xaa]_y$ are as defined above for Formula I and described in classes and subclasses herein, both singly and in combination;

p is 2, 3, 4, 5, 6, 7, or 8; and q is 2, 3, 4, 5, or 6.

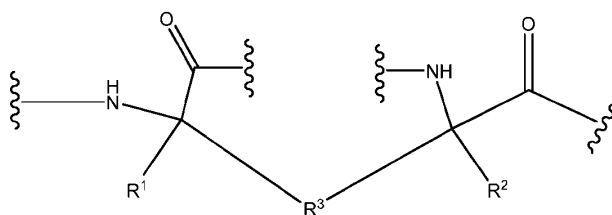
[0063] In some embodiments, the present disclosure provides a modified peptide of Formula I-Ci:



I-Ci

or a pharmaceutically acceptable salt thereof, wherein $[Xaa]_w$, $[Xaa]_x$, and $[Xaa]_y$ are as defined above for Formula I and described in classes and subclasses herein, both singly and in combination.

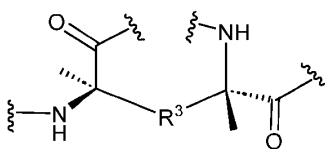
[0064] As defined generally above, in Formula I', X^{L1} and X^{L2} are amino acids comprising side chains that are linked together. In some embodiments, X^{L1} and X^{L2} (e.g., two amino acids comprising side chains that are linked together) have the structure of Formula XI:



XI

wherein R^1 , R^2 , and R^3 are as defined above for Formula I and described in classes and subclasses herein, both singly and in combination.

[0065] In some embodiments, X^{L1} and X^{L2} (e.g., two amino acids comprising side chains that are linked together) have the structure of Formula XIa:

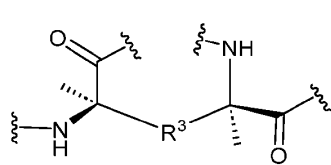


XIa

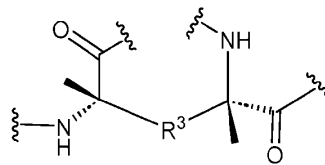
wherein R^3 is as defined above for Formula I and described in classes and subclasses herein, both singly and in combination.

[0066] In some embodiments, X^{L1} and X^{L2} (e.g., two amino acids comprising side chains that

are linked together) have the structure selected from:

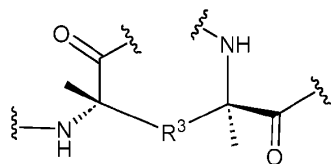


(XIb),



(XIc),

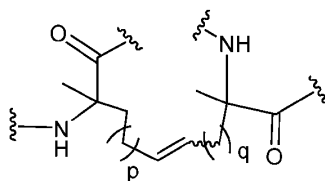
or



(XId),

wherein R^3 is as defined above for Formula I and described in classes and subclasses herein, both singly and in combination.

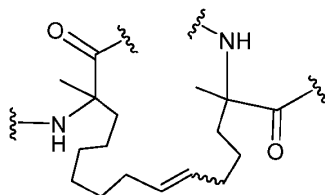
[0067] In some embodiments, X^{L1} and X^{L2} (e.g., two amino acids comprising side chains that are linked together) have the structure of Formula XII:



XII

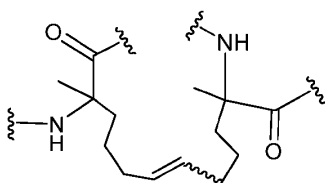
wherein p is 2, 3, 4, 5, 6, 7, or 8; and q is 2, 3, 4, 5, or 6.

[0068] In some embodiments, X^{L1} and X^{L2} (e.g., two amino acids comprising side chains that are linked together) have the structure of Formula XIIa:



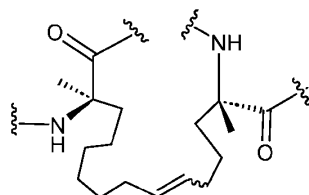
XIIa.

[0069] In some embodiments, X^{L1} and X^{L2} (e.g., two amino acids comprising side chains that are linked together) have the structure of Formula XIIb:



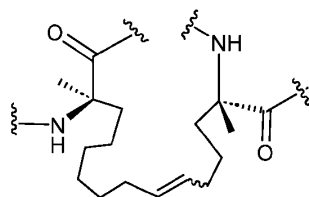
XIIb.

[0070] In some embodiments, X^{L1} and X^{L2} (e.g., two amino acids comprising side chains that are linked together) have the structure of Formula XIIc:



XIIc.

[0071] In some embodiments, X^{L1} and X^{L2} (e.g., two amino acids comprising side chains that are linked together) have the structure of Formula XIIId:



XIIId.

[0072] In some embodiments of any Formulae described herein, R^1 is hydrogen or C_{1-10} aliphatic. In some embodiments, R^1 is hydrogen. In some embodiments, R^1 is optionally substituted C_{1-10} aliphatic (e.g., optionally substituted with one or more halo, hydroxyl, or C_{1-3} alkoxy). In some embodiments, R^1 is optionally substituted C_{1-10} alkyl (e.g., optionally substituted with one or more halo, hydroxyl, or C_{1-3} alkoxy). In some embodiments, R^1 is optionally substituted C_{2-10} alkenyl (e.g., optionally substituted with one or more halo, hydroxyl, or C_{1-3} alkoxy). In certain embodiments, R^1 is optionally substituted C_{2-10} alkynyl (e.g., optionally substituted with one or more halo, hydroxyl, or C_{1-3} alkoxy). In some embodiments, R^1 is C_{1-10} alkyl. In some embodiments, R^1 is C_{2-10} alkenyl. In some embodiments, R^1 is C_{2-10} alkynyl. In some embodiments, R^1 is optionally substituted C_{1-4} alkyl (e.g., optionally substituted with one or more halo, hydroxyl, or C_{1-3} alkoxy). In some embodiments, R^1 is optionally substituted C_{2-4}

alkenyl (e.g., optionally substituted with one or more halo, hydroxyl, or C₁₋₃ alkoxy). In some embodiments, R¹ is optionally substituted C₂₋₄ alkynyl (e.g., optionally substituted with one or more halo, hydroxyl, or C₁₋₃ alkoxy). In some embodiments, R¹ is C₁₋₄ alkyl. In some embodiments, R¹ is C₂₋₄ alkenyl. In some embodiments, R¹ is C₂₋₄ alkynyl. In some embodiments, R¹ is methyl.

[0073] In some embodiments of any Formulae described herein, R² is hydrogen or C₁₋₁₀ aliphatic. In some embodiments, R² is hydrogen. In some embodiments, R² is optionally substituted C₁₋₁₀ aliphatic (e.g., optionally substituted with one or more halo, hydroxyl, or C₁₋₃ alkoxy). In some embodiments, R² is optionally substituted C₁₋₁₀ alkyl (e.g., optionally substituted with one or more halo, hydroxyl, or C₁₋₃ alkoxy). In some embodiments, R² is optionally substituted C₂₋₁₀ alkenyl (e.g., optionally substituted with one or more halo, hydroxyl, or C₁₋₃ alkoxy). In certain embodiments, R² is optionally substituted C₂₋₁₀ alkynyl (e.g., optionally substituted with one or more halo, hydroxyl, or C₁₋₃ alkoxy). In some embodiments, R² is C₁₋₁₀ alkyl. In some embodiments, R² is C₂₋₁₀ alkenyl. In some embodiments, R² is C₂₋₁₀ alkynyl. In some embodiments, R² is optionally substituted C₁₋₄ alkyl (e.g., optionally substituted with one or more halo, hydroxyl, or C₁₋₃ alkoxy). In some embodiments, R² is optionally substituted C₂₋₄ alkenyl (e.g., optionally substituted with one or more halo, hydroxyl, or C₁₋₃ alkoxy). In some embodiments, R² is optionally substituted C₂₋₄ alkynyl (e.g., optionally substituted with one or more halo, hydroxyl, or C₁₋₃ alkoxy). In some embodiments, R² is C₁₋₄ alkyl. In some embodiments, R² is C₂₋₄ alkenyl. In some embodiments, R² is C₂₋₄ alkynyl. In some embodiments, R² is methyl.

[0074] In some embodiments of any Formulae described herein, R¹ and R² are each hydrogen. In some embodiments, R¹ and R² are each independently optionally substituted C₁₋₁₀ aliphatic (e.g., optionally substituted with one or more halo, hydroxyl, or C₁₋₃ alkoxy). In some embodiments, R¹ and R² are each independently optionally substituted C₁₋₁₀ alkyl (e.g., optionally substituted with one or more halo, hydroxyl, or C₁₋₃ alkoxy). In some embodiments, R¹ and R² are each independently optionally substituted C₂₋₁₀ alkenyl (e.g., optionally substituted with one or more halo, hydroxyl, or C₁₋₃ alkoxy). In some embodiments, R¹ and R² are each independently optionally substituted C₂₋₁₀ alkynyl (e.g., optionally substituted with one or more halo, hydroxyl, or C₁₋₃ alkoxy). In some embodiments, R¹ and R² are each independently C₁₋₁₀ aliphatic. In some embodiments, R¹ and R² are each independently C₁₋₁₀ alkyl. In some embodiments, R¹ and R² are

each independently C₂₋₁₀ alkenyl. In some embodiments, R¹ and R² are each independently C₂₋₁₀ alkynyl. In some embodiments, R¹ and R² are each independently optionally substituted C₁₋₄ aliphatic (e.g., optionally substituted with one or more halo, hydroxyl, or C₁₋₃ alkoxy). In some embodiments, R¹ and R² are each independently optionally substituted C₁₋₄ alkyl (e.g., optionally substituted with one or more halo, hydroxyl, or C₁₋₃ alkoxy). In some embodiments, R¹ and R² are each independently optionally substituted C₂₋₄ alkenyl (e.g., optionally substituted with one or more halo, hydroxyl, or C₁₋₃ alkoxy). In some embodiments, R¹ and R² are each independently optionally substituted C₂₋₄ alkynyl (e.g., optionally substituted with one or more halo, hydroxyl, or C₁₋₃ alkoxy). In some embodiments, R¹ and R² are each independently C₁₋₄ aliphatic. In some embodiments, R¹ and R² are each independently C₁₋₄ alkyl. In some embodiments, R¹ and R² are each independently C₂₋₄ alkenyl. In some embodiments, R¹ and R² are each independently C₂₋₄ alkynyl. In certain embodiments, R¹ and R² are each methyl.

[0075] In some embodiments of any Formulae described herein, R³ is an optionally substituted bivalent, C₇₋₁₆ hydrocarbon chain, wherein one or more methylene units of the hydrocarbon chain 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—. In some embodiments, R³ is an optionally substituted bivalent, C₇₋₁₂ hydrocarbon chain, wherein one or more methylene units of the hydrocarbon chain 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—.

[0076] In some embodiments of any Formulae described herein, R³ is an optionally substituted bivalent, C₃₋₂₀ hydrocarbon chain comprising at least one double bond, wherein one or more methylene units of the hydrocarbon chain 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—. In some embodiments, R³ is an optionally substituted bivalent, C₇₋₁₆ hydrocarbon chain comprising at least one double bond, wherein one or more methylene units of the hydrocarbon chain 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—. In some embodiments, R³ is

an optionally substituted bivalent, C₇₋₁₂ hydrocarbon chain comprising at least one double bond, wherein one or more methylene units of the hydrocarbon chain 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—.

[0077] In some embodiments of any Formulae described herein, R³ is an optionally substituted bivalent, C₃₋₂₀ hydrocarbon chain. In some embodiments, R³ is an optionally substituted bivalent, C₇₋₁₆ hydrocarbon chain. In some embodiments, R³ is an optionally substituted bivalent, C₇₋₁₂ hydrocarbon chain. In some embodiments, R³ is an optionally substituted bivalent, C₃₋₂₀ hydrocarbon chain comprising at least one double bond. In some embodiments, R³ is an optionally substituted bivalent, C₇₋₁₆ hydrocarbon chain comprising at least one double bond. In some embodiments, R³ is an optionally substituted bivalent, C₇₋₁₂ hydrocarbon chain comprising at least one double bond.

[0078] In some embodiments of any Formulae described herein, R³ is a bivalent, C₃₋₂₀ hydrocarbon chain, wherein one or more methylene units of the hydrocarbon chain 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—. In some embodiments, R³ is a bivalent, C₇₋₁₆ hydrocarbon chain, wherein one or more methylene units of the hydrocarbon chain 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—. In some embodiments, R³ is a bivalent, C₇₋₁₂ hydrocarbon chain, wherein one or more methylene units of the hydrocarbon chain 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—.

[0079] In some embodiments of any Formulae described herein, R³ is a bivalent, C₃₋₂₀ hydrocarbon chain comprising at least one double bond, wherein one or more methylene units of the hydrocarbon chain 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—. In some

embodiments, R^3 is a bivalent, C_{7-16} hydrocarbon chain comprising at least one double bond, wherein one or more methylene units of the hydrocarbon chain 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 $-C(O)O-$. In some embodiments, R^3 is a bivalent, C_{7-12} hydrocarbon chain comprising at least one double bond, wherein one or more methylene units of the hydrocarbon chain 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 $-C(O)O-$.

[0080] In some embodiments of any Formulae described herein, R^3 is a bivalent, C_{3-20} hydrocarbon chain. In some embodiments, R^3 is a bivalent, C_{7-16} hydrocarbon chain. In some embodiments, R^3 is a bivalent, C_{7-12} hydrocarbon chain. In some embodiments, R^3 is a bivalent, C_{3-20} hydrocarbon chain comprising at least one double bond. In some embodiments, R^3 is a bivalent, C_{7-16} hydrocarbon chain comprising at least one double bond. In some embodiments, R^3 is a bivalent, C_{7-12} hydrocarbon chain comprising at least one double bond.

[0081] In some embodiments of any Formulae described herein, R^3 is C_{7-12} alkenylene. In some embodiments, R^3 is C_8 alkenylene. In some embodiments, R^3 is C_{11} alkenylene. In some embodiments, R^3 is $-(CH_2)_{1-7}-CH=CH-(CH_2)_{1-7}-$. In some embodiments, R^3 is $-(CH_2)_{3-7}-CH=CH-(CH_2)_{3-4}-$. In some embodiments, R^3 is $-(CH_2)_6-CH=CH-(CH_2)_3-$. In some embodiments, R^3 is $-(CH_2)_3-CH=CH-(CH_2)_3-$.

[0082] In some embodiments of any Formulae described herein, R^3 spans one to two turns of an alpha helix. In some embodiments, R^3 spans one turn of an alpha helix. In some embodiments, R^3 spans two turns of an alpha helix.

[0083] In some embodiments of any Formulae described herein, each R' is independently hydrogen or optionally substituted C_{1-6} aliphatic. In some embodiments, R' is hydrogen. In some embodiments, R' is optionally substituted C_{1-12} aliphatic. In some embodiments, R' is optionally substituted C_{1-6} aliphatic. In some embodiments, R' is C_{1-12} aliphatic. In some embodiments, R' is C_{1-6} aliphatic. In some embodiments, R' is optionally substituted C_{1-12} alkyl. In some embodiments, R' is optionally substituted C_{1-6} alkyl. In some embodiments, R' is C_{1-12} alkyl. In some embodiments, R' is C_{1-6} alkyl.

[0084] In some embodiments of any Formulae described herein, p is 2. In some embodiments,

p is 3. In some embodiments, p is 4. In some embodiments, p is 5. In some embodiments, p is 6. In some embodiments, p is 7. In some embodiments, p is 8.

[0085] In some embodiments of any Formulae described herein, q is 2. In some embodiments, q is 3. In some embodiments, q is 4. In some embodiments, q is 5. In some embodiments, q is 6.

[0086] In some embodiments of any Formulae described herein, p is 5 and q is 3. In some embodiments, p is 2 and q is 3.

[0087] In some embodiments of any Formulae described herein, each Xaa is independently a natural amino acid. In some embodiments, Xaa is a natural amino acid. In some embodiments, Xaa is an unnatural amino acid. In some embodiments, 1-5 instances of Xaa are an unnatural amino acid, such as norleucine. In some embodiments, 1-3 instances of Xaa are an unnatural amino acid, such as norleucine. In some embodiments, one instance of Xaa is an unnatural amino acid, such as norleucine. In some embodiments, Xaa is an *N*-acyl amino acid (e.g., when Xaa is at the N-terminus of a peptide). In some embodiments, Xaa is an alpha-amino amide (e.g., when Xaa is at the C-terminus of a peptide).

[0088] In some embodiments of any Formulae described herein, w is an integer from 2-50. In some embodiments, w is an integer from 2-25. In some embodiments, w is an integer from 2-10. In some embodiments, w is 7. In some embodiments, w is 11.

[0089] In some embodiments of any Formulae described herein, [Xaa]_w represents an amino acid sequence comprising one or more contiguous amino acids of: an amino acid sequence selected from Table 1; or an amino acid sequence that is (i) at least 30% identical to an amino acid sequence selected from Table 1 and/or (ii) has 1-10 substitutions, insertions, and/or deletions relative to an amino acid sequence selected from Table 1. In some embodiments, [Xaa]_w represents an amino acid sequence comprising at least 2 contiguous amino acids of: an amino acid sequence selected from Table 1; or an amino acid sequence that is (i) at least 30% identical to an amino acid sequence selected from Table 1 and/or (ii) has 1-10 substitutions, insertions, and/or deletions relative to an amino acid sequence selected from Table 1. In some embodiments, [Xaa]_w represents an amino acid sequence comprising at least 3 contiguous amino acids of: an amino acid sequence selected from Table 1; or an amino acid sequence that is (i) at least 30% identical to an amino acid sequence selected from Table 1 and/or (ii) has 1-10 substitutions, insertions, and/or deletions relative to an amino acid sequence selected from Table 1. In some embodiments, [Xaa]_w represents an amino acid sequence comprising at least 5 contiguous amino acids of: an amino acid sequence selected

from Table 1; or an amino acid sequence that is (i) at least 30% identical to an amino acid sequence selected from Table 1 and/or (ii) has 1-10 substitutions, insertions, and/or deletions relative to an amino acid sequence selected from Table 1. In some embodiments, [Xaa]_w represents an amino acid sequence comprising at least 7 contiguous amino acids of: an amino acid sequence selected from Table 1; or an amino acid sequence that is (i) at least 30% identical to an amino acid sequence selected from Table 1 and/or (ii) has 1-10 substitutions, insertions, and/or deletions relative to an amino acid sequence selected from Table 1. In some embodiments, [Xaa]_w is absent (i.e., when w is 0).

[0090] In some embodiments of any Formulae described herein, [Xaa]_w represents an amino acid sequence comprising one or more contiguous amino acids of: an amino acid sequence selected from Table 1; or an amino acid sequence that is (i) at least 70% identical to an amino acid sequence selected from Table 1 and/or (ii) has 1-10 substitutions, insertions, and/or deletions relative to an amino acid sequence selected from Table 1. In some embodiments, [Xaa]_w represents an amino acid sequence comprising at least 2 contiguous amino acids of: an amino acid sequence selected from Table 1; or an amino acid sequence that is (i) at least 70% identical to an amino acid sequence selected from Table 1 and/or (ii) has 1-10 substitutions, insertions, and/or deletions relative to an amino acid sequence selected from Table 1. In some embodiments, [Xaa]_w represents an amino acid sequence comprising at least 3 contiguous amino acids of: an amino acid sequence selected from Table 1; or an amino acid sequence that is (i) at least 70% identical to an amino acid sequence selected from Table 1 and/or (ii) has 1-10 substitutions, insertions, and/or deletions relative to an amino acid sequence selected from Table 1. In some embodiments, [Xaa]_w represents an amino acid sequence comprising at least 5 contiguous amino acids of: an amino acid sequence selected from Table 1; or an amino acid sequence that is (i) at least 70% identical to an amino acid sequence selected from Table 1 and/or (ii) has 1-10 substitutions, insertions, and/or deletions relative to an amino acid sequence selected from Table 1. In some embodiments, [Xaa]_w represents an amino acid sequence comprising at least 7 contiguous amino acids of: an amino acid sequence selected from Table 1; or an amino acid sequence that is (i) at least 70% identical to an amino acid sequence selected from Table 1 and/or (ii) has 1-10 substitutions, insertions, and/or deletions relative to an amino acid sequence selected from Table 1.

[0091] In some embodiments of any Formulae described herein, [Xaa]_w represents an amino acid sequence comprising one or more contiguous amino acids of: an amino acid sequence selected

from Table 1; or an amino acid sequence that is (i) at least 90% identical to an amino acid sequence selected from Table 1 and/or (ii) has 1-10 substitutions, insertions, and/or deletions relative to an amino acid sequence selected from Table 1. In some embodiments, [Xaa]_w represents an amino acid sequence comprising at least 2 contiguous amino acids of: an amino acid sequence selected from Table 1; or an amino acid sequence that is (i) at least 90% identical to an amino acid sequence selected from Table 1 and/or (ii) has 1-10 substitutions, insertions, and/or deletions relative to an amino acid sequence selected from Table 1. In some embodiments, [Xaa]_w represents an amino acid sequence comprising at least 3 contiguous amino acids of: an amino acid sequence selected from Table 1; or an amino acid sequence that is (i) at least 90% identical to an amino acid sequence selected from Table 1 and/or (ii) has 1-10 substitutions, insertions, and/or deletions relative to an amino acid sequence selected from Table 1. In some embodiments, [Xaa]_w represents an amino acid sequence comprising at least 5 contiguous amino acids of: an amino acid sequence selected from Table 1; or an amino acid sequence that is (i) at least 90% identical to an amino acid sequence selected from Table 1 and/or (ii) has 1-10 substitutions, insertions, and/or deletions relative to an amino acid sequence selected from Table 1. In some embodiments, [Xaa]_w represents an amino acid sequence comprising at least 7 contiguous amino acids of: an amino acid sequence selected from Table 1; or an amino acid sequence that is (i) at least 90% identical to an amino acid sequence selected from Table 1 and/or (ii) has 1-10 substitutions, insertions, and/or deletions relative to an amino acid sequence selected from Table 1.

[0092] In some embodiments of any Formulae described herein, [Xaa]_w represents an amino acid sequence comprising one or more contiguous amino acids of an amino acid sequence selected from Table 1. In some embodiments, [Xaa]_w represents an amino acid sequence comprising at least 2 contiguous amino acids of an amino acid sequence selected from Table 1. In some embodiments, [Xaa]_w represents an amino acid sequence comprising at least 3 contiguous amino acids of an amino acid sequence selected from Table 1. In some embodiments, [Xaa]_w represents an amino acid sequence comprising at least 5 contiguous amino acids of an amino acid sequence selected from Table 1. In some embodiments, [Xaa]_w represents an amino acid sequence comprising at least 7 contiguous amino acids of an amino acid sequence selected from Table 1.

[0093] In some embodiments of any Formulae described herein, [Xaa]_w represents an amino acid sequence comprising at least 3 contiguous amino acids of an amino acid sequence that is at least 30% identical to an amino acid sequence selected from Table 1. In some embodiments,

[Xaa]_w represents an amino acid sequence comprising at least 3 contiguous amino acids of an amino acid sequence that is at least 70% identical to an amino acid sequence selected from Table 1. In some embodiments, [Xaa]_w represents an amino acid sequence comprising at least 3 contiguous amino acids of an amino acid sequence that is at least 90% identical to an amino acid sequence selected from Table 1.

[0094] In some embodiments of any Formulae described herein, [Xaa]_w represents an amino acid sequence comprising at least 3 contiguous amino acids of an amino acid sequence that has 1-10 substitutions, insertions, and/or deletions relative to an amino acid sequence selected from Table 1. In some embodiments, [Xaa]_w represents an amino acid sequence comprising at least 3 contiguous amino acids of an amino acid sequence that has 1-5 substitutions, insertions, and/or deletions relative to an amino acid sequence selected from Table 1. In some embodiments, [Xaa]_w represents an amino acid sequence comprising at least 3 contiguous amino acids of an amino acid sequence that has 1-3 substitutions, insertions, and/or deletions relative to an amino acid sequence selected from Table 1.

[0095] In some embodiments of any Formulae described herein, x is an integer from 3-50. In some embodiments, x is an integer from 3-25. In some embodiments, x is an integer from 3-10. In some embodiments, x is an integer from 3-5. In some embodiments, x is an integer from 5-10. In some embodiments, x is 3 or 6. In some embodiments, x is 3. In some embodiments, x is 6.

[0096] In some embodiments of any Formulae described herein, [Xaa]_x represents an amino acid sequence comprising at least 3 contiguous amino acids of: an amino acid sequence selected from Table 1; or an amino acid sequence that is (i) at least 30% identical to an amino acid sequence selected from Table 1 and/or (ii) has 1-10 substitutions, insertions, and/or deletions relative to an amino acid sequence selected from Table 1. In some embodiments, [Xaa]_x represents an amino acid sequence comprising at least 5 contiguous amino acids of: an amino acid sequence selected from Table 1; or an amino acid sequence that is (i) at least 30% identical to an amino acid sequence selected from Table 1 and/or (ii) has 1-10 substitutions, insertions, and/or deletions relative to an amino acid sequence selected from Table 1. In some embodiments, [Xaa]_x represents an amino acid sequence comprising at least 6 contiguous amino acids of: an amino acid sequence selected from Table 1; or an amino acid sequence that is (i) at least 30% identical to an amino acid sequence selected from Table 1 and/or (ii) has 1-10 substitutions, insertions, and/or deletions relative to an amino acid sequence selected from Table 1. In some embodiments, [Xaa]_x represents an amino

acid sequence comprising at least 7 contiguous amino acids of: an amino acid sequence selected from Table 1; or an amino acid sequence that is (i) at least 30% identical to an amino acid sequence selected from Table 1 and/or (ii) has 1-10 substitutions, insertions, and/or deletions relative to an amino acid sequence selected from Table 1.

[0097] In some embodiments of any Formulae described herein, [Xaa]_x represents an amino acid sequence comprising at least 3 contiguous amino acids of: an amino acid sequence selected from Table 1; or an amino acid sequence that is (i) at least 70% identical to an amino acid sequence selected from Table 1 and/or (ii) has 1-10 substitutions, insertions, and/or deletions relative to an amino acid sequence selected from Table 1. In some embodiments, [Xaa]_x represents an amino acid sequence comprising at least 5 contiguous amino acids of: an amino acid sequence selected from Table 1; or an amino acid sequence that is (i) at least 70% identical to an amino acid sequence selected from Table 1 and/or (ii) has 1-10 substitutions, insertions, and/or deletions relative to an amino acid sequence selected from Table 1. In some embodiments, [Xaa]_x represents an amino acid sequence comprising at least 6 contiguous amino acids of: an amino acid sequence selected from Table 1; or an amino acid sequence that is (i) at least 70% identical to an amino acid sequence selected from Table 1 and/or (ii) has 1-10 substitutions, insertions, and/or deletions relative to an amino acid sequence selected from Table 1. In some embodiments, [Xaa]_x represents an amino acid sequence comprising at least 7 contiguous amino acids of: an amino acid sequence selected from Table 1; or an amino acid sequence that is (i) at least 70% identical to an amino acid sequence selected from Table 1 and/or (ii) has 1-10 substitutions, insertions, and/or deletions relative to an amino acid sequence selected from Table 1.

[0098] In some embodiments of any Formulae described herein, [Xaa]_x represents an amino acid sequence comprising at least 3 contiguous amino acids of: an amino acid sequence selected from Table 1; or an amino acid sequence that is (i) at least 90% identical to an amino acid sequence selected from Table 1 and/or (ii) has 1-10 substitutions, insertions, and/or deletions relative to an amino acid sequence selected from Table 1. In some embodiments, [Xaa]_x represents an amino acid sequence comprising at least 5 contiguous amino acids of: an amino acid sequence selected from Table 1; or an amino acid sequence that is (i) at least 90% identical to an amino acid sequence selected from Table 1 and/or (ii) has 1-10 substitutions, insertions, and/or deletions relative to an amino acid sequence selected from Table 1. In some embodiments, [Xaa]_x represents an amino acid sequence comprising at least 6 contiguous amino acids of: an amino acid sequence selected

from Table 1; or an amino acid sequence that is (i) at least 90% identical to an amino acid sequence selected from Table 1 and/or (ii) has 1-10 substitutions, insertions, and/or deletions relative to an amino acid sequence selected from Table 1. In some embodiments, [Xaa]_x represents an amino acid sequence comprising at least 7 contiguous amino acids of: an amino acid sequence selected from Table 1; or an amino acid sequence that is (i) at least 90% identical to an amino acid sequence selected from Table 1 and/or (ii) has 1-10 substitutions, insertions, and/or deletions relative to an amino acid sequence selected from Table 1.

[0099] In some embodiments of any Formulae described herein, [Xaa]_x represents an amino acid sequence comprising at least 3 contiguous amino acids of an amino acid sequence selected from Table 1. In some embodiments, [Xaa]_x represents an amino acid sequence comprising at least 5 contiguous amino acids of an amino acid sequence selected from Table 1. In some embodiments, [Xaa]_x represents an amino acid sequence comprising at least 6 contiguous amino acids of an amino acid sequence selected from Table 1. In some embodiments, [Xaa]_x represents an amino acid sequence comprising at least 7 contiguous amino acids of an amino acid sequence selected from Table 1.

[0100] In some embodiments of any Formulae described herein, [Xaa]_x represents an amino acid sequence comprising at least 3 contiguous amino acids of an amino acid sequence that is at least 30% identical to an amino acid sequence selected from Table 1. In some embodiments, [Xaa]_x represents an amino acid sequence comprising at least 3 contiguous amino acids of an amino acid sequence that is at least 70% identical to an amino acid sequence selected from Table 1. In some embodiments, [Xaa]_x represents an amino acid sequence comprising at least 3 contiguous amino acids of an amino acid sequence that is at least 90% identical to an amino acid sequence selected from Table 1.

[0101] In some embodiments of any Formulae described herein, [Xaa]_x represents an amino acid sequence comprising at least 3 contiguous amino acids of an amino acid sequence that has 1-10 substitutions, insertions, and/or deletions relative to an amino acid sequence selected from Table 1. In some embodiments, [Xaa]_x represents an amino acid sequence comprising at least 3 contiguous amino acids of an amino acid sequence that has 1-5 substitutions, insertions, and/or deletions relative to an amino acid sequence selected from Table 1. In some embodiments, [Xaa]_x represents an amino acid sequence comprising at least 3 contiguous amino acids of an amino acid sequence that has 1-3 substitutions, insertions, and/or deletions relative to an amino acid sequence

selected from Table 1.

[0102] In some embodiments of any Formulae described herein, y is an integer from 2-50. In some embodiments, y is an integer from 2-25. In some embodiments, y is an integer from 2-10. In some embodiments, y is an integer from 0-5. In some embodiments, y is an integer from 2-5. In some embodiments, y is 1. In some embodiments, y is 2. In some embodiments, y is 3. In some embodiments, y is 4.

[0103] In some embodiments of any Formulae described herein, $[Xaa]_y$ represents an amino acid sequence comprising one or more contiguous amino acids of: an amino acid sequence selected from Table 1; or an amino acid sequence that is (i) at least 30% identical to an amino acid sequence selected from Table 1 and/or (ii) has 1-10 substitutions, insertions, and/or deletions relative to an amino acid sequence selected from Table 1. In some embodiments, $[Xaa]_y$ represents an amino acid sequence comprising at least 2 contiguous amino acids of: an amino acid sequence selected from Table 1; or an amino acid sequence that is (i) at least 30% identical to an amino acid sequence selected from Table 1 and/or (ii) has 1-10 substitutions, insertions, and/or deletions relative to an amino acid sequence selected from Table 1. In some embodiments, $[Xaa]_y$ represents an amino acid sequence comprising at least 3 contiguous amino acids of: an amino acid sequence selected from Table 1; or an amino acid sequence that is (i) at least 30% identical to an amino acid sequence selected from Table 1 and/or (ii) has 1-10 substitutions, insertions, and/or deletions relative to an amino acid sequence selected from Table 1. In some embodiments, $[Xaa]_y$ represents an amino acid sequence comprising at least 5 contiguous amino acids of: an amino acid sequence selected from Table 1; or an amino acid sequence that is (i) at least 30% identical to an amino acid sequence selected from Table 1 and/or (ii) has 1-10 substitutions, insertions, and/or deletions relative to an amino acid sequence selected from Table 1. In some embodiments, $[Xaa]_y$ represents an amino acid sequence comprising at least 7 contiguous amino acids of: an amino acid sequence selected from Table 1; or an amino acid sequence that is (i) at least 30% identical to an amino acid sequence selected from Table 1 and/or (ii) has 1-10 substitutions, insertions, and/or deletions relative to an amino acid sequence selected from Table 1. In some embodiments, $[Xaa]_y$ is absent (i.e., when y is 0).

[0104] In some embodiments of any Formulae described herein, $[Xaa]_y$ represents an amino acid sequence comprising one or more contiguous amino acids of: an amino acid sequence selected from Table 1; or an amino acid sequence that is (i) at least 70% identical to an amino acid sequence

selected from Table 1 and/or (ii) has 1-10 substitutions, insertions, and/or deletions relative to an amino acid sequence selected from Table 1. In some embodiments, [Xaa]_y represents an amino acid sequence comprising at least 2 contiguous amino acids of: an amino acid sequence selected from Table 1; or an amino acid sequence that is (i) at least 70% identical to an amino acid sequence selected from Table 1 and/or (ii) has 1-10 substitutions, insertions, and/or deletions relative to an amino acid sequence selected from Table 1. In some embodiments, [Xaa]_y represents an amino acid sequence comprising at least 3 contiguous amino acids of: an amino acid sequence selected from Table 1; or an amino acid sequence that is (i) at least 70% identical to an amino acid sequence selected from Table 1 and/or (ii) has 1-10 substitutions, insertions, and/or deletions relative to an amino acid sequence selected from Table 1. In some embodiments, [Xaa]_y represents an amino acid sequence comprising at least 5 contiguous amino acids of: an amino acid sequence selected from Table 1; or an amino acid sequence that is (i) at least 70% identical to an amino acid sequence selected from Table 1 and/or (ii) has 1-10 substitutions, insertions, and/or deletions relative to an amino acid sequence selected from Table 1. In some embodiments, [Xaa]_y represents an amino acid sequence comprising at least 7 contiguous amino acids of: an amino acid sequence selected from Table 1; or an amino acid sequence that is (i) at least 70% identical to an amino acid sequence selected from Table 1 and/or (ii) has 1-10 substitutions, insertions, and/or deletions relative to an amino acid sequence selected from Table 1.

[0105] In some embodiments of any Formulae described herein, [Xaa]_y represents an amino acid sequence comprising one or more contiguous amino acids of: an amino acid sequence selected from Table 1; or an amino acid sequence that is (i) at least 90% identical to an amino acid sequence selected from Table 1 and/or (ii) has 1-10 substitutions, insertions, and/or deletions relative to an amino acid sequence selected from Table 1. In some embodiments, [Xaa]_y represents an amino acid sequence comprising at least 2 contiguous amino acids of: an amino acid sequence selected from Table 1; or an amino acid sequence that is (i) at least 90% identical to an amino acid sequence selected from Table 1 and/or (ii) has 1-10 substitutions, insertions, and/or deletions relative to an amino acid sequence selected from Table 1. In some embodiments, [Xaa]_y represents an amino acid sequence comprising at least 3 contiguous amino acids of: an amino acid sequence selected from Table 1; or an amino acid sequence that is (i) at least 90% identical to an amino acid sequence selected from Table 1 and/or (ii) has 1-10 substitutions, insertions, and/or deletions relative to an amino acid sequence selected from Table 1. In some embodiments, [Xaa]_y represents an amino

acid sequence comprising at least 5 contiguous amino acids of: an amino acid sequence selected from Table 1; or an amino acid sequence that is (i) at least 90% identical to an amino acid sequence selected from Table 1 and/or (ii) has 1-10 substitutions, insertions, and/or deletions relative to an amino acid sequence selected from Table 1. In some embodiments, [Xaa]_y represents an amino acid sequence comprising at least 7 contiguous amino acids of: an amino acid sequence selected from Table 1; or an amino acid sequence that is (i) at least 90% identical to an amino acid sequence selected from Table 1 and/or (ii) has 1-10 substitutions, insertions, and/or deletions relative to an amino acid sequence selected from Table 1.

[0106] In some embodiments of any Formulae described herein, [Xaa]_y represents an amino acid sequence comprising one or more contiguous amino acids of an amino acid sequence selected from Table 1. In some embodiments, [Xaa]_y represents an amino acid sequence comprising at least 2 contiguous amino acids of an amino acid sequence selected from Table 1. In some embodiments, [Xaa]_y represents an amino acid sequence comprising at least 3 contiguous amino acids of an amino acid sequence selected from Table 1. In some embodiments, [Xaa]_y represents an amino acid sequence comprising at least 5 contiguous amino acids of an amino acid sequence selected from Table 1. In some embodiments, [Xaa]_y represents an amino acid sequence comprising at least 7 contiguous amino acids of an amino acid sequence selected from Table 1.

[0107] In some embodiments of any Formulae described herein, [Xaa]_y represents an amino acid sequence comprising at least 3 contiguous amino acids of an amino acid sequence that is at least 30% identical to an amino acid sequence selected from Table 1. In some embodiments, [Xaa]_y represents an amino acid sequence comprising at least 3 contiguous amino acids of an amino acid sequence that is at least 70% identical to an amino acid sequence selected from Table 1. In some embodiments, [Xaa]_y represents an amino acid sequence comprising at least 3 contiguous amino acids of an amino acid sequence that is at least 90% identical to an amino acid sequence selected from Table 1.

[0108] In some embodiments of any Formulae described herein, [Xaa]_y represents an amino acid sequence comprising at least 3 contiguous amino acids of an amino acid sequence that has 1-10 substitutions, insertions, and/or deletions relative to an amino acid sequence selected from Table 1. In some embodiments, [Xaa]_y represents an amino acid sequence comprising at least 3 contiguous amino acids of an amino acid sequence that has 1-5 substitutions, insertions, and/or deletions relative to an amino acid sequence selected from Table 1. In some embodiments, [Xaa]_y

represents an amino acid sequence comprising at least 3 contiguous amino acids of an amino acid sequence that has 1-3 substitutions, insertions, and/or deletions relative to an amino acid sequence selected from Table 1.

[0109] In some embodiments of any Formulae described herein, the N-terminal amino acid in [Xaa]_w is conjugated to a moiety described herein. In some embodiments, the C-terminal amino acid in [Xaa]_y is conjugated to a moiety described herein. In some embodiments, the N-terminal amino acid in [Xaa]_w and the C-terminal amino acid in [Xaa]_y is conjugated to a moiety described herein.

[0110] In some embodiments of any Formulae described herein, [Xaa]_w is selected from Table 2.

Table 2.

Sequence	SEQ ID NO:
SEMKNLFEKTRR	11
SEMKNLFEKTR	12
SEMKNLFEKT	13
SEMKNLFEK	14
SEMKNLFE	15
SEMKNLKF	16
SEMKNKL	17
SEMKNK	18
SEMKN	19
SEM	20
SE	21
S	22
SEMKNLFEKVRR	23
SEMKNLFEKVR	24
SEMKNLFEKV	25
SEMKNLYEKVRS	26
SEMKNLYEKVR	27
SEMKNLYEKV	28

SEMKNLYEK	29
SEMKNLYE	30
SEMKNLY	31
DLTDSEMKNLFKTRR	32
DLTDSEMKNLFKTR	33
DLTDSEMKNLFKFT	34
DLTDSEMKNLFK	35
DLTDSEMKNLFE	36
DLTDSEMKNLF	37
DLTDSEMKNL	38
DLTDSEMKN	39
DLTDSEMN	40
DLTDSEM	41
DLTDSE	42
DLTDS	43
DLTD	44
DLT	45
DL	46
D	47

[0111] In some embodiments of any Formulae described herein, [Xaa]_x is selected from Table 3.

Table 3.

Sequence	SEQ ID NO:
SEMKNL	17
EMNKLF	48
MNKLFE	49
NKLFK	50
KLFKFT	51
LFKTR	52

FEKTRR	53
EKTRRQ	54
KTRRQL	55
TRRQLR	56
RRQLRE	57
RQLREN	58
QLRENA	59
KLFEKV	60
LFEKVR	61
FEKVRR	62
EKVRRQ	63
KVRRQL	64
VRRQLR	65
EKTRRE	66
KTRREL	67
TRREL R	68
RRELRE	69
RELREN	70
ELRENA	71
EMNKLY	72
MNKLYE	73
NKLYEK	74
KLYEKV	75
LYEKVR	76
YEKVRS	77
EKVRSQ	78
KVRSQL	79
VRSQLR	80
RSQLRE	81
SQLREN	82

DLTDSE	42
LTDSEM	83
TDSEMN	84
DSEMNK	85
FEKVRS	86
RSQLRN	87

[0112] In some embodiments of any Formulae described herein, [Xaa]_y is selected from Table 4.

Table 4.

Sequence	SEQ ID NO:
A	88
NA	89
ENA	90
RENA	91
LRENA	92
QLRENA	59
RQLRENA	93
RRQLRENA	94
TRRQLRENA	95
KTRRQLRENA	96
EKTRRQLRENA	97
FEKTRRQLRENA	98
VRRQLRENA	99
KVRRQLRENA	100
EKVRRQLRENA	101
FEKVRRQLRENA	102
ELRENA	71
RELRENA	103
RRELRENA	104

TRRELRENA	105
KTRRELRENA	106
EKTRRELRENA	107
FEKTRRELRENA	108
SQLRENA	109
RSQLENA	110
VRSQLENA	111
KVRSQLENA	112
EKVRSQLENA	113
YEKVRSQLENA	114
LFEKTRRQLENA	115
KLFEKTRRQLENA	116
NKLFEKTRRQLENA	117
MNKLFEKTRRQLENA	118
N	119
RN	120
LRN	121
QLRN	122
SQLRN	123
RSQLRN	87
VRSQLRN	124
KVRSQLRN	125
EKVRSQLRN	126
FEKVRSQLRN	127

[0113] In some embodiments of any Formulae described herein, [Xaa]_w, [Xaa]_x, and [Xaa]_y are selected from Table 5.

Table 5.

[Xaa] _w	SEQ ID NO:	[Xaa] _x	SEQ ID NO:	[Xaa] _y	SEQ ID NO:
SEMNKLF	16	KTRRRL	144	ENA	90
SEB*NKLF	128	KTRRRL	144	ENA	90
SAMNKLF	129	KTRRQL	55	ENA	90
SAB*NKLF	130	KTRRQL	55	ENA	90
SVMNKLF	131	KTRRQL	55	ENA	90
SVB*NKLF	132	KTRRQL	55	ENA	90
SEMNKLF	16	KTRREL	67	ENA	90
SEB*NKLF	128	KTRREL	67	ENA	90
SEMNKLF	16	KTARQL	145	ENA	90
SEB*NKLF	128	KTARQL	145	ENA	90
SEMNNLF	133	KTRRQL	55	ENA	90
SEB*NNLF	134	KTRRQL	55	ENA	90
SEMNKLF	16	KVRRQL	64	ENA	90
SEB*NKLF	128	KVRRQL	64	ENA	90
SEMNKLF	16	KTRSQL	146	ENA	90
SEB*NKLF	128	KTRSQL	146	ENA	90
SEMKNL	17	EKTRSQ	147	RENA	91
SEB*NKL	135	EKTRSQ	147	RENA	91
SNVKNLY	136	KVRSQL	148	NNA	151
SEMKNLY	31	KVRSQL	148	ENA	90
SEB*NKLY	137	KVRSQL	148	ENA	90
SEMNKLF	16	KVRSQL	148	N	119
SEB*NKLF	128	KVRSQL	148	N	119
DLTDSEMKNLF	37	KTRRQL	55	ENA	90
DLTDSEB*NKLF	138	KTRRQL	55	ENA	90
DLTDSEM	41	KLFEKT	51	RQLRENA	93
DLTDSEB*	139	KLFEKT	51	RQLRENA	93
DLTQSEM	140	KLFEKT	51	RQLRENA	93

[Xaa] _w	SEQ ID NO:	[Xaa] _x	SEQ ID NO:	[Xaa] _y	SEQ ID NO:
DLTQSEB*	141	KLFEKT	51	RQLRENA	93
DLTDSEM	41	KLFEKV	60	RQLRENA	93
DLTDSEB*	139	KLFEKV	60	RQLRENA	93
SEB*NKLF	128	KTRRQL	55	E	152
SEMNKLF	16	KTRRQL	55	E	152
DQB*NYLA	142	KTRFQI	149	NAA	153
DQMNYLA	143	KTRFQI	149	NAA	153
SEMNKLF	16	KVSRQL	79	ENA	90
SEB*NKLF	128	KVSRQL	79	ENA	90
SEMNKLF	16	KVARQL	150	ENA	90
SEB*NKLF	128	KVARQL	150	ENA	90

B* = norleucine

[0114] It should be understood that the amino acid sequences of [Xaa]_w, [Xaa]_x, and [Xaa]_y in Tables 2-5 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 2-5 include one or more variants. In some embodiments, 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 2-5. In some embodiments, the amino acid sequences of [Xaa]_w, [Xaa]_x, and [Xaa]_y described herein (e.g., the sequences of Tables 2-5) 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 2-5), e.g., one or more (e.g., 1, 2, 3, 4, or 5) conservative and/or non-conservative amino acid substitutions.

[0115] In some embodiments of any Formulae described herein, modified peptides described herein are at most 50 amino acids in length (i.e., $w+x+y+2 \leq 50$). In some embodiments, modified peptides described herein are at most 45 amino acids in length (i.e., $w+x+y+2 \leq 45$). In some embodiments, modified peptides described herein are at most 30 amino acids in length (i.e., $w+x+y+2 \leq 30$). In some embodiments, modified peptides described herein are 22 amino acids in

length (i.e., $w+x+y+2 = 22$). In some embodiments, modified peptides described herein are 22 amino acids in length (i.e., $w+x+y+2 = 18$).

[0116] In some embodiments, modified peptides described herein comprise peptide staples. “Peptide stapling” is a term coined from a synthetic methodology wherein two amino acid side chains are covalently joined (e.g., “stapled together”). For example, two olefin-containing side chains (e.g., cross-linkable side chains) present in a peptide chain may be 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). Peptide stapling may impart structural stabilization (see, e.g., Walensky, *J. Med. Chem.*, 57:6275-6288 (2014)). In some cases, the staple is a hydrocarbon staple.

[0117] 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; Orner 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; Horne 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).

[0118] In some embodiments, a stapled peptide is structurally stabilized. 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.

[0119] Non-limiting examples of 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'-octeny)glycine.

[0120] 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.

[0121] In addition, other methods of performing different types of stapling are well known in the art and can be employed with the modified 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. Spokoyny *et al.*, *J. Am. Chem. Soc.*, 135:5946–5949 (2013)).

Conjugates

[0122] In some embodiments, modified peptides provided herein are conjugated to one or more moieties. In some embodiments, a conjugated moiety is one that imparts a useful characteristic to the modified peptide, such as improved pharmacokinetic or pharmacodynamic properties. In some embodiments, a conjugated moiety is or comprises a lipid (*e.g.*, cholesterol). In some embodiments, a conjugated moiety is or comprises a carbohydrate. In some embodiments, a conjugated moiety is or comprises a peptide (*e.g.*, a second modified peptide described herein). In some embodiments, a conjugated moiety is attached to a modified peptide via a linker (*e.g.*, a linker comprising polyethylene glycol (PEG)).

[0123] In some embodiments, a moiety is conjugated at or near the N-terminus of the peptide. For example, in some embodiments, a moiety is conjugated to the alpha-amino group of the N-

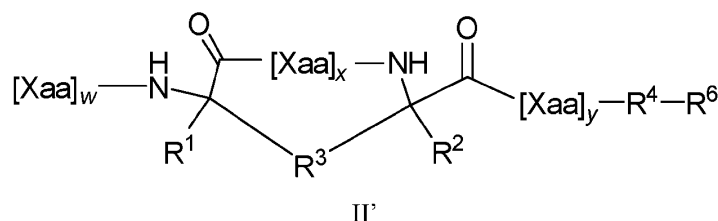
terminal amino acid. In some embodiments, a moiety is conjugated at or near the C-terminus of the peptide. For example, in some embodiments, a lysine residue is appended to the C-terminus of a peptide and a moiety is conjugated to the lysine side chain (e.g., via the amino group).

[0124] In some embodiments, a provided modified peptide comprises: $-(\text{linker})-(\text{lipid moiety})$. In some embodiments, a linker comprises PEG, a peptide (e.g., one or more amino acids), or a combination thereof. In some embodiments, a linker comprises a peptide. In some embodiments, a linker comprises one or more PEG units. In some embodiments, a linker comprises PEG units linked by amide bonds. In some embodiments, an amino acid at the C-terminus of a provided modified peptide is conjugated to a lipid moiety via a linker group, i.e., $-(\text{linker})-(\text{lipid moiety})$. In some embodiments, an amino acid at the N-terminus of a provided modified peptide is conjugated to a lipid moiety via a linker group, i.e., $-(\text{linker})-(\text{lipid moiety})$.

[0125] In some embodiments, the linker comprises PEG. In some 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.

[0126] In some embodiments, a lipid moiety is C_5 - C_{100} aliphatic lipid moiety. In some embodiments, a lipid moiety is a fatty acid, phospholipid, sphingolipid, or a sterol. In some embodiments, a fatty acid is palmitic acid or stearic acid. In some embodiments, a phospholipid is phosphatidylcholine or phosphatidylethanolamine. In some embodiments, a sphingolipid is sphingosine or ceramide. In some embodiments, a sterol is cholesterol, thiocholesterol, sitosterol, ergosterol, or tocopherol. In some embodiments, a lipid moiety is cholesterol.

[0127] In some embodiments, the present disclosure provides a modified peptide of Formula II':



or a pharmaceutically acceptable salt thereof, wherein R^1 , R^2 , R^3 , $[\text{Xaa}]_w$, $[\text{Xaa}]_x$, and $[\text{Xaa}]_y$ are

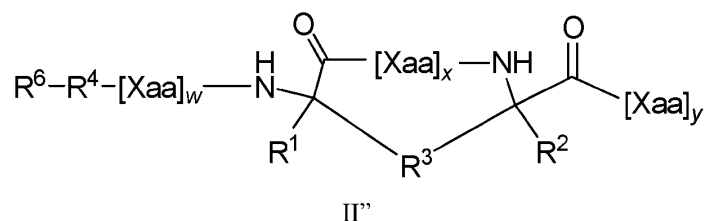
as defined above for Formula I and described in classes and subclasses herein, both singly and in combination; and

R^4 is a bivalent, straight or branched, saturated or unsaturated, optionally substituted C_{1-30} 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]_n, wherein n is 1-20;

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

R^6 is a conjugated moiety (e.g., a lipid, carbohydrate, or peptide).

[0128] In some embodiments, the present disclosure provides a modified peptide of Formula II':



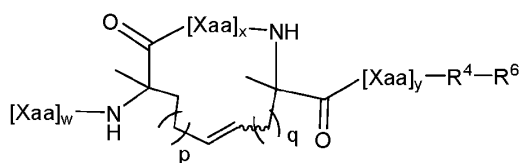
or a pharmaceutically acceptable salt thereof, wherein R^1 , R^2 , R^3 , $[Xaa]_w$, $[Xaa]_x$, and $[Xaa]_y$ are as defined above for Formula I and described in classes and subclasses herein, both singly and in combination; and

R^4 is a bivalent, straight or branched, saturated or unsaturated, optionally substituted C_{1-30} 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]_n, wherein n is 1-20;

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

R^6 is a conjugated moiety (e.g., a lipid, carbohydrate, or peptide).

[0129] In some embodiments, the present disclosure provides a modified peptide of Formula II:



II

or a pharmaceutically acceptable salt thereof, wherein $[Xaa]_w$, $[Xaa]_x$, and $[Xaa]_y$ are as defined above for Formula I and described in classes and subclasses herein, both singly and in combination; and

R^4 is a bivalent, straight or branched, saturated or unsaturated, optionally substituted C_{1-30} 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 $-[O-CH_2CH_2]_n$, wherein n is 1-20;

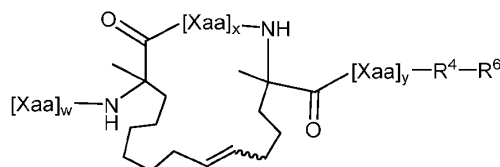
each R' is independently hydrogen or optionally substituted C_{1-12} aliphatic;

R^6 is a conjugated moiety (e.g., a lipid, carbohydrate, or peptide);

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

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

[0130] In some embodiments, the present disclosure provides a modified peptide of Formula IIa:



IIa

or a pharmaceutically acceptable salt thereof, wherein $[Xaa]_w$, $[Xaa]_x$, and $[Xaa]_y$ are as defined above for Formula I and described in classes and subclasses herein, both singly and in combination; and

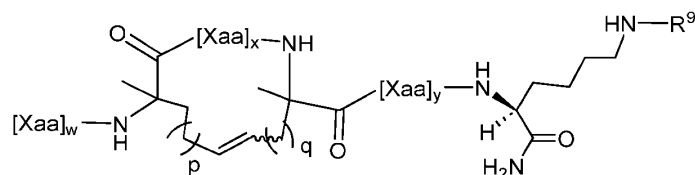
R^4 is a bivalent, straight or branched, saturated or unsaturated, optionally substituted C_{1-30} hydrocarbon chain, wherein 1-10 methylene units of the hydrocarbon chain are independently replaced by $-O-$, $-N(R')$, $-S-$, $-OC(O)-$, $-C(O)O-$, $-C(O)-$, $-S(O)-$, $-S(O)_2-$, $-N(R')S(O)_2-$, $-S(O)_2N(R')$, $-N(R')C(O)-$, $-C(O)N(R')$, $-OC(O)N(R')$, $-N(R')C(O)O-$, or $-[O-CH_2CH_2]_n$, wherein n is 1-20;

$[\text{O}-\text{CH}_2\text{CH}_2]_n$, wherein n is 1-20;

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

R^6 is a conjugated moiety (e.g., a lipid, carbohydrate, or peptide).

[0131] In some embodiments, the present disclosure provides a modified peptide of Formula IIb:



IIb

or a pharmaceutically acceptable salt thereof, wherein $[\text{Xaa}]_w$, $[\text{Xaa}]_x$, and $[\text{Xaa}]_y$ are as defined above for Formula I and described in classes and subclasses herein, both singly and in combination; and

R^9 is $-\text{C}(\text{O})-(\text{CH}_2\text{CH}_2)-[\text{O}-\text{CH}_2\text{CH}_2]_m-\text{N}(\text{R}^5)\text{C}(\text{O})-(\text{CH}_2)_{0-6}-\text{R}^6$;

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

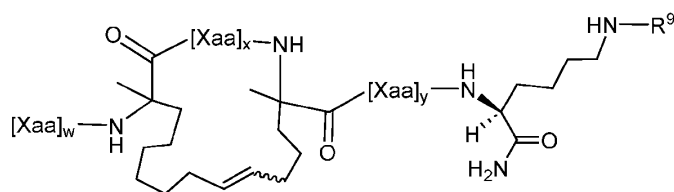
R^6 is a conjugated moiety (e.g., a lipid, carbohydrate, or peptide);

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

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

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

[0132] In some embodiments, the present disclosure provides a modified peptide of Formula IIc:



IIc

or a pharmaceutically acceptable salt thereof, wherein $[\text{Xaa}]_w$, $[\text{Xaa}]_x$, and $[\text{Xaa}]_y$ are as defined above for Formula I and described in classes and subclasses herein, both singly and in combination; and

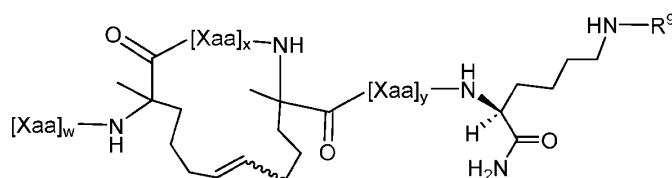
R^9 is $-\text{C}(\text{O})-(\text{CH}_2\text{CH}_2)-[\text{O}-\text{CH}_2\text{CH}_2]_m-\text{N}(\text{R}^5)\text{C}(\text{O})-(\text{CH}_2)_{0-6}-\text{R}^6$;

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

R^6 is a conjugated moiety (e.g., a lipid, carbohydrate, or peptide); and

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

[0133] In some embodiments, the present disclosure provides a modified peptide of Formula IVc:



IVc

or a pharmaceutically acceptable salt thereof, wherein $[Xaa]_w$, $[Xaa]_x$, and $[Xaa]_y$ are as defined above for Formula I and described in classes and subclasses herein, both singly and in combination; and

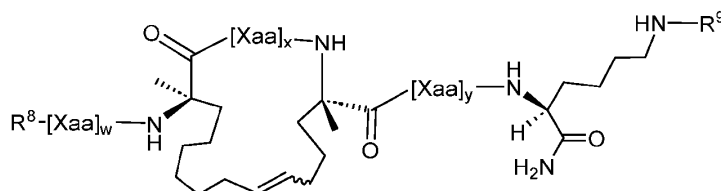
R^9 is $-C(O)-(CH_2CH_2)-[O-CH_2CH_2]_m-N(R^5)C(O)-(CH_2)_{0-6}-R^6$;

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

R^6 is a conjugated moiety (e.g., a lipid, carbohydrate, or peptide); and

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

[0134] In some embodiments, the present disclosure provides a modified peptide of Formula Va:



Va

or a pharmaceutically acceptable salt thereof, wherein $[Xaa]_w$, $[Xaa]_x$, and $[Xaa]_y$ are as defined above for Formula I and described in classes and subclasses herein, both singly and in combination; and

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

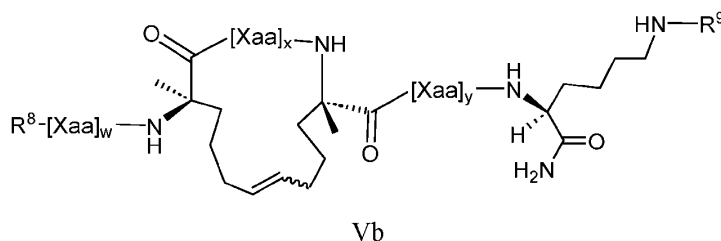
R^9 is $-C(O)-(CH_2CH_2)-[O-CH_2CH_2]_m-N(R^5)C(O)-(CH_2)_{0-6}-R^6$;

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

R^6 is a conjugated moiety (e.g., a lipid, carbohydrate, or peptide); and

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

[0135] In some embodiments, the present disclosure provides a modified peptide of Formula Vb:



or a pharmaceutically acceptable salt thereof, wherein [Xaa]_w, [Xaa]_x, and [Xaa]_y are as defined above for Formula I and described in classes and subclasses herein, both singly and in combination; and

R⁸ is -C(O)(C₁₋₄ alkyl);

R⁹ is -C(O)-(CH₂CH₂)-[O-CH₂CH₂]_m-N(R⁵)C(O)-(CH₂)₀₋₆-R⁶;

R⁵ is hydrogen or C₁₋₄ alkyl;

R⁶ is a conjugated moiety (e.g., a lipid, carbohydrate, or peptide); and

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

[0136] In some embodiments of any Formulae described herein, R⁴ is a bivalent, straight or branched, saturated or unsaturated, optionally substituted C₁₋₃₀ 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]_n, wherein n is 1-20. In some embodiments, R⁴ is a bivalent, straight or branched, saturated or unsaturated, optionally substituted C₆₋₃₀ 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]_n, wherein n is 1-20. In some embodiments, R⁴ is a bivalent, straight or branched, saturated or unsaturated, optionally substituted C₃₋₂₀ 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]_n, wherein n is 1-20.

[0137] In some embodiments of any Formulae described herein, R⁴ is a bivalent, straight or

branched, saturated or unsaturated, optionally substituted C_{1-30} hydrocarbon chain, wherein 1-10 methylene units of the hydrocarbon chain are independently replaced by $-N(R')C(O)-$, $-C(O)N(R')-$, or $-[O-CH_2CH_2]_n$, wherein n is 1-20. In some embodiments, R^4 is a bivalent, straight or branched, saturated or unsaturated, optionally substituted C_{6-30} hydrocarbon chain, wherein 1-10 methylene units of the hydrocarbon chain are independently replaced by $-N(R')C(O)-$, $-C(O)N(R')-$, or $-[O-CH_2CH_2]_n$, wherein n is 1-20. In some embodiments, R^4 is a bivalent, straight or branched, saturated or unsaturated, optionally substituted C_{3-20} hydrocarbon chain, wherein 1-10 methylene units of the hydrocarbon chain are independently replaced by $-N(R')C(O)-$, $-C(O)N(R')-$, or $-[O-CH_2CH_2]_n$, wherein n is 1-20.

[0138] In some embodiments of any Formulae described herein, R^4 is $-N(H)-C(H)((CH_2)_4N(H)(C(O)-(C_{2-6} \text{ alkylene})-[O-CH_2CH_2]_n-N(R^5)C(O)-(C_{0-6} \text{ alkylene})-R^6))-C(O)-NH_2$. In some embodiments, R^4 is $-N(H)-C(H)((CH_2)_4N(H)(C(O)-(C_{2-3} \text{ alkylene})-[O-CH_2CH_2]_n-N(R^5)C(O)-(C_{0-2} \text{ alkylene})-R^6))-C(O)-NH_2$. In some embodiments, R^4 is $-N(H)-C(H)((CH_2)_4N(H)(C(O)-CH_2CH_2-[O-CH_2CH_2]_n-N(R^5)C(O)-CH_2-R^6))-C(O)-NH_2$. In some embodiments, R^4 is $-N(H)-C(H)((CH_2)_4N(H)(C(O)-(C_{2-3} \text{ alkylene})-[O-CH_2CH_2]_n-N(R^5)C(O)-(C_{0-2} \text{ alkylene})-R^6))-C(O)-NH_2$. In some embodiments, R^4 is $-N(H)-C(H)((CH_2)_4N(H)(C(O)-CH_2CH_2-[O-CH_2CH_2]_n-N(R^5)C(O)-CH_2-R^6))-C(O)-NH_2$. In some embodiments, R^4 is $-N(H)-C(H)((CH_2)_4N(H)(C(O)-(C_{2-3} \text{ alkylene})-[O-CH_2CH_2]_n-N(R^5)C(O)-(C_{0-2} \text{ alkylene})-R^6))-C(O)-NH_2$. In some embodiments, R^4 is $-N(H)-C(H)((CH_2)_4N(H)(C(O)-CH_2CH_2-[O-CH_2CH_2]_n-N(R^5)C(O)-R^6))-C(O)-NH_2$. In some embodiments, R^4 is $-N(H)-C(H)((CH_2)_4N(H)(C(O)-CH_2CH_2-[O-CH_2CH_2]_n-N(R^5)C(O)-R^6))-C(O)-NH_2$.

[0139] In some embodiments of any Formulae described herein, R^4 is a bivalent peptide. In some embodiments, R^4 comprises an amino acid residue (e.g., lysine).

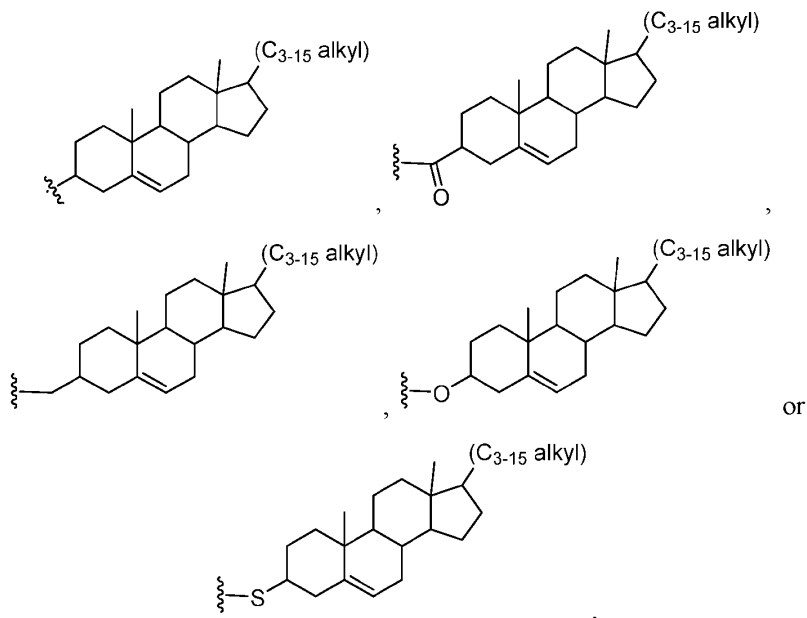
[0140] In some embodiments of any Formulae described herein, R^5 is hydrogen. In some embodiments, R^5 is C_{1-4} alkyl. In some embodiments, R^5 is methyl.

[0141] In some embodiments of any Formulae described herein, R^6 is a lipid. In some embodiments, R^6 is a carbohydrate. In some embodiments, R^6 is a peptide.

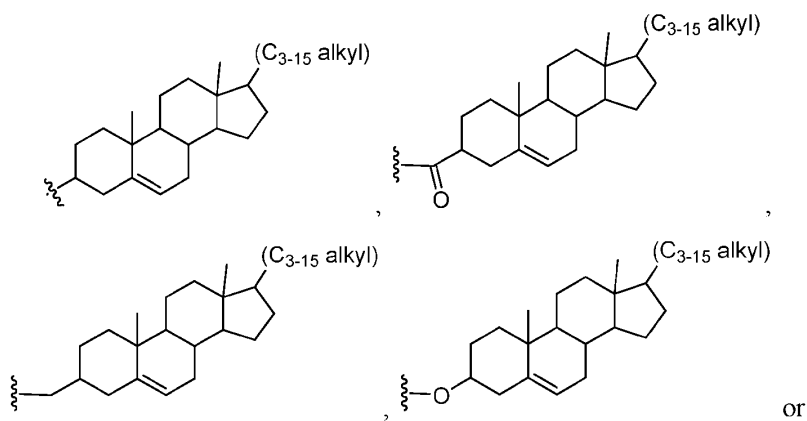
[0142] In some embodiments of any Formulae described herein, R^6 is an optionally substituted C_5-C_{100} aliphatic lipid moiety. In some embodiments, R^6 is a fatty acid, phospholipid, sphingolipid, or a sterol. In some embodiments, R^6 is palmitic acid or stearic acid. In some embodiments, R^6 is phosphatidylcholine or phosphatidylethanolamine. In some embodiments, R^6 is sphingosine or

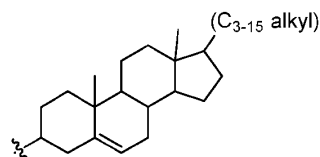
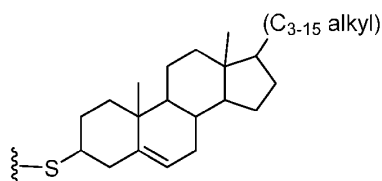
ceramide. In some embodiments, R^6 is cholesterol, thiocholesterol, sitosterol, ergosterol, or tocopherol.

[0143] In some embodiments of any Formulae described herein, R^6 is one of the following:

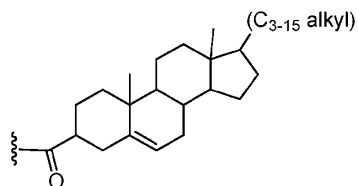


each of which may be optionally substituted (e.g., with one or more halo, C₁₋₃ alkyl, hydroxyl or C₁₋₃ alkoxy). In some embodiments, R^6 is

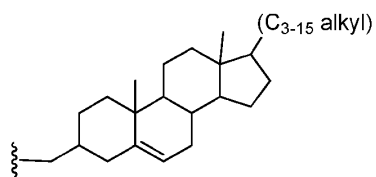




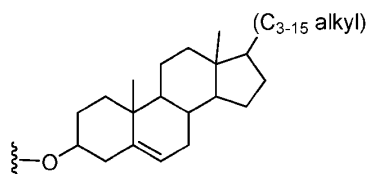
[0144] In some embodiments, R⁶ is , which may be optionally substituted (e.g., with halo, C₁₋₃ alkyl, hydroxyl or C₁₋₃ alkoxy). In some embodiments, R⁶ is



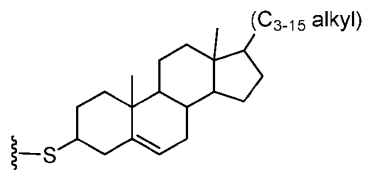
, which may be optionally substituted (e.g., with one or more halo, C₁₋₃ alkyl, hydroxyl or C₁₋₃ alkoxy). In some embodiments, R⁶ is



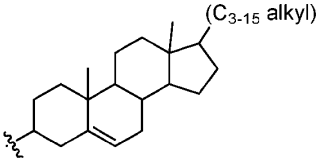
, which may be optionally substituted (e.g., with one or more halo, C₁₋₃ alkyl, hydroxyl or C₁₋₃ alkoxy). In some embodiments, R⁶ is

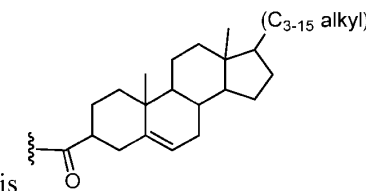
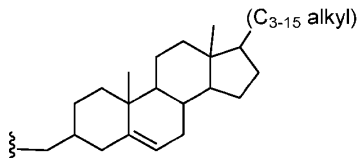


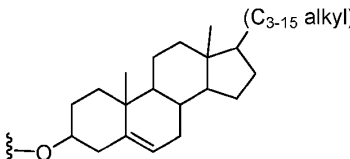
, which may be optionally substituted (e.g., with one or more halo, C₁₋₃ alkyl, hydroxyl or C₁₋₃ alkoxy). In some embodiments, R⁶ is

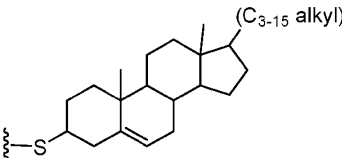
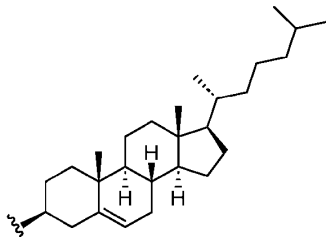


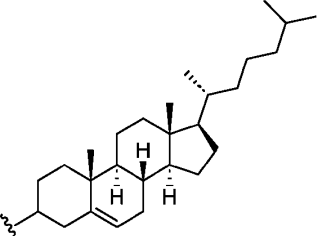
, which may be optionally substituted (e.g., with one or more halo, C₁₋₃ alkyl, hydroxyl or C₁₋₃ alkoxy).

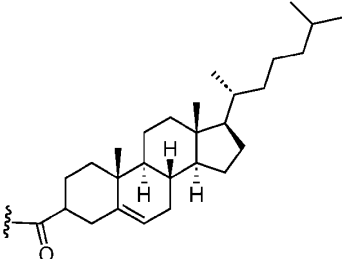
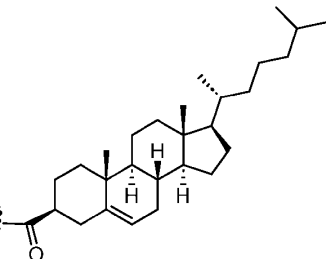
[0145] In some embodiments, R⁶ is . In some embodiments, R⁶

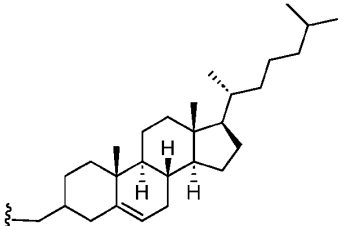
is . In some embodiments, R⁶ is .

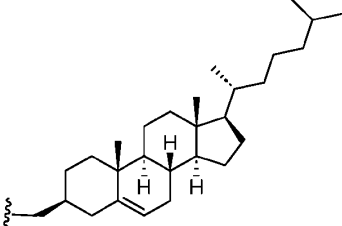
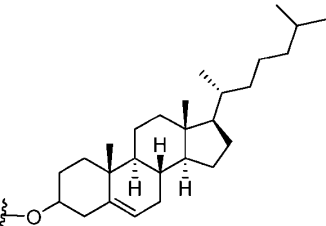
In some embodiments, R⁶ is . In some embodiments, R⁶ is

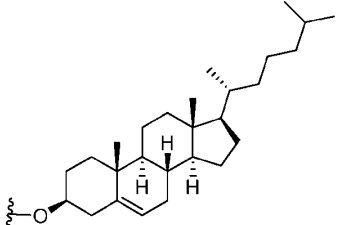
. In some embodiments, R⁶ is . In

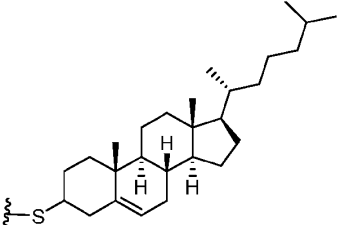
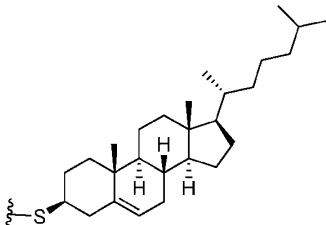
some embodiments, R⁶ is . In some embodiments, R⁶ is

. In some embodiments, R⁶ is . In

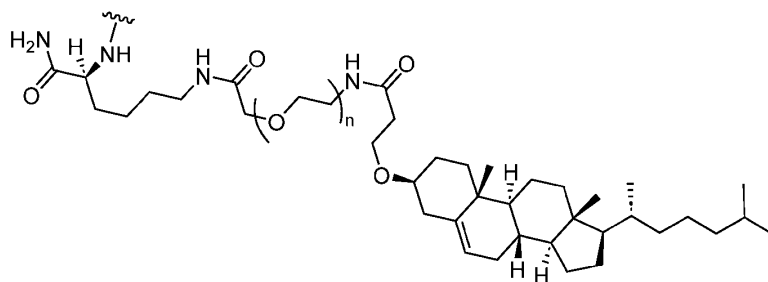
some embodiments, R^6 is . In some embodiments, R^6 is

. In some embodiments, R^6 is . In

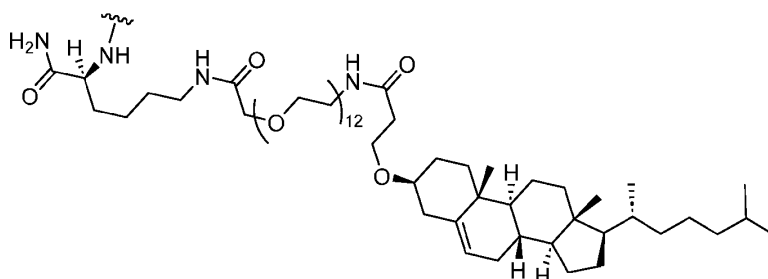
some embodiments, R^6 is . In some embodiments, R^6 is

. In some embodiments, R^6 is .

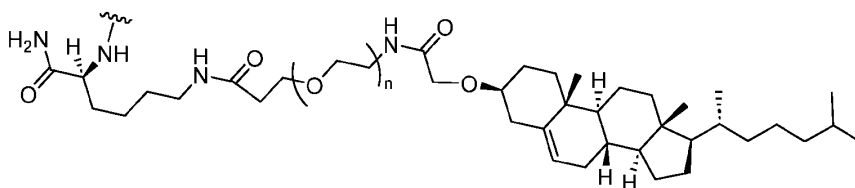
[0146] In some embodiments of any Formulae described herein, $-R^4-R^6$ is:



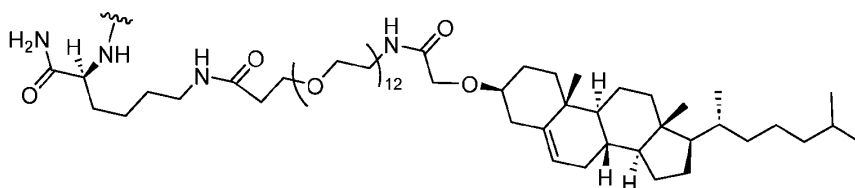
[0147] In some embodiments of any Formulae described herein, $-R^4-R^6$ is:



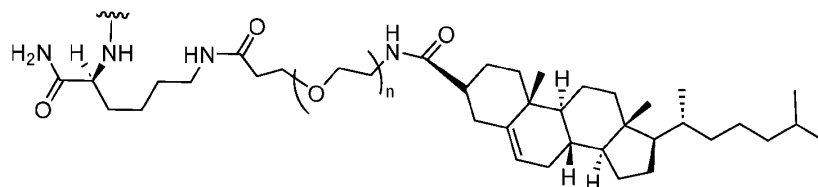
[0148] In some embodiments of any Formulae described herein, $-R^4-R^6$ is:



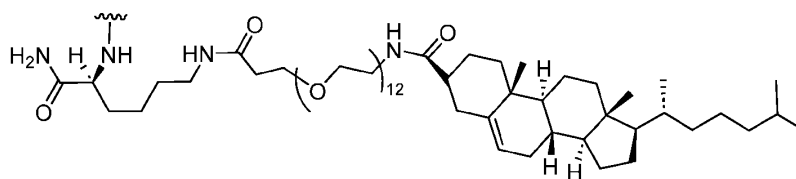
[0149] In some embodiments of any Formulae described herein, $-R^4-R^6$ is:



[0150] In some embodiments of any Formulae described herein, $-R^4-R^6$ is:



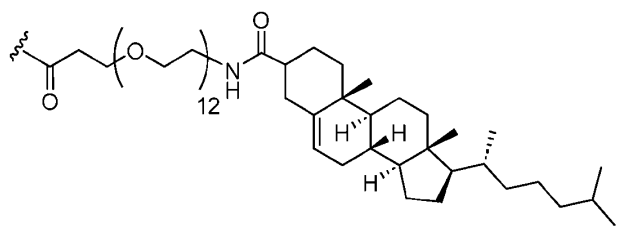
[0151] In some embodiments of any Formulae described herein, $-R^4-R^6$ is:



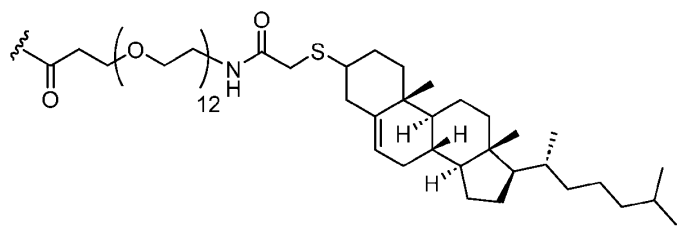
[0152] In some embodiments of any Formulae described herein, R^9 is $-C(O)-(CH_2CH_2)-[O-CH_2CH_2]_m-N(R^5)C(O)-(CH_2)-R^6$. In some embodiments, R^9 is $-C(O)-(CH_2CH_2)-[O-CH_2CH_2]_{12}-N(R^5)C(O)-(CH_2)-R^6$. In some embodiments, R^9 is $-C(O)-(CH_2CH_2)-[O-CH_2CH_2]_8-N(R^5)C(O)-$

$(\text{CH}_2)\text{-R}^6$. In some embodiments, R^9 is $\text{-C(O)-(CH}_2\text{CH}_2\text{)-[O-CH}_2\text{CH}_2\text{]}_m\text{-N(R}^5\text{)C(O)-R}^6$. In some embodiments, R^9 is $\text{-C(O)-(CH}_2\text{CH}_2\text{)-[O-CH}_2\text{CH}_2\text{]}_{12}\text{-N(R}^5\text{)C(O)-R}^6$. In some embodiments, R^9 is $\text{-C(O)-(CH}_2\text{CH}_2\text{)-[O-CH}_2\text{CH}_2\text{]}_8\text{-N(R}^5\text{)C(O)-R}^6$.

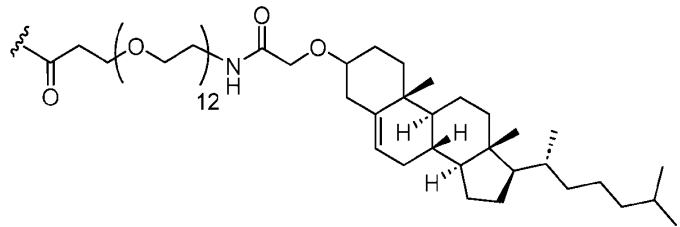
[0153] In some embodiments of any Formulae described herein, $\text{-R}^9\text{-R}^6$ is:



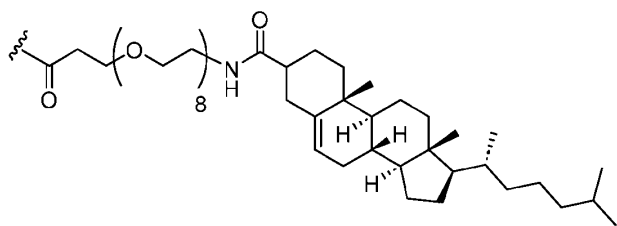
[0154] In some embodiments of any Formulae described herein, $\text{-R}^9\text{-R}^6$ is:



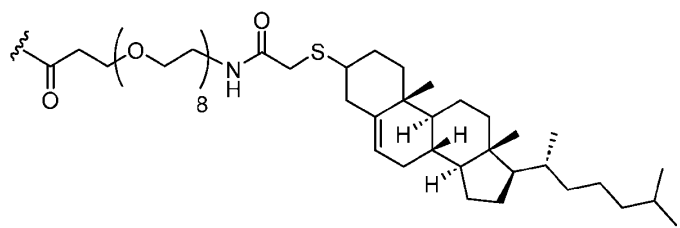
[0155] In some embodiments of any Formulae described herein, $\text{-R}^9\text{-R}^6$ is:



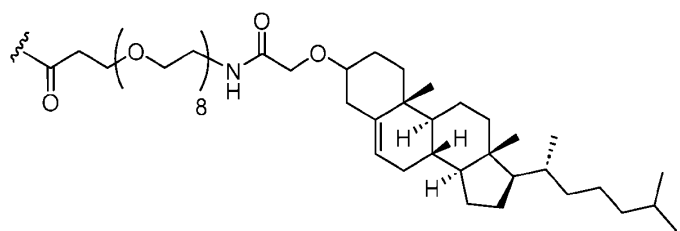
[0156] In some embodiments of any Formulae described herein, $\text{-R}^9\text{-R}^6$ is:



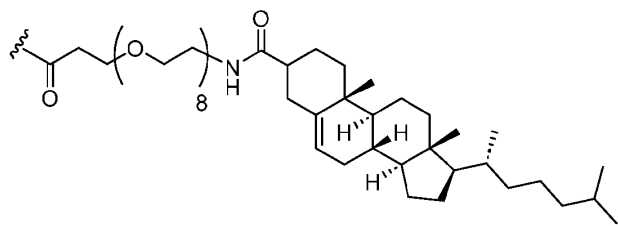
[0157] In some embodiments of any Formulae described herein, $\text{-R}^9\text{-R}^6$ is:



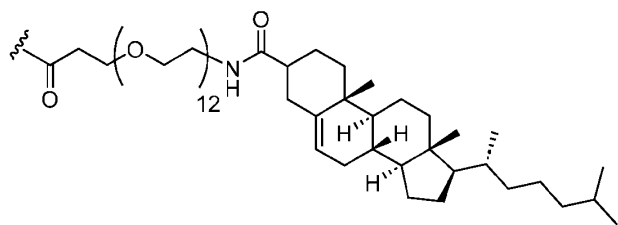
[0158] In some embodiments of any Formulae described herein, $-R^9-R^6$ is:



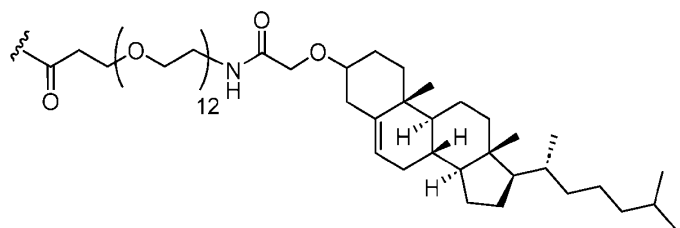
[0159] In some embodiments of any Formulae described herein, $-R^9-R^6$ is:



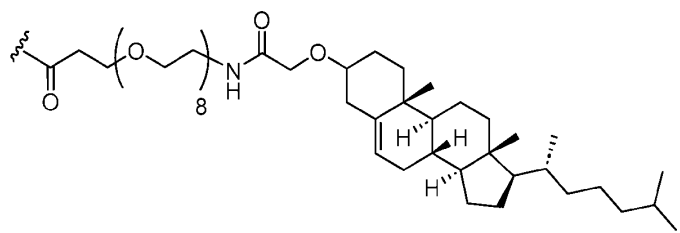
[0160] In some embodiments of any Formulae described herein, $-R^9-R^6$ is:



[0161] In some embodiments of any Formulae described herein, $-R^9-R^6$ is:



[0162] In some embodiments of any Formulae described herein, $-R^9-R^6$ is:



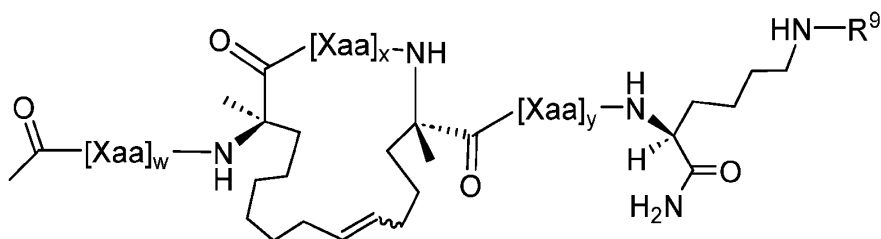
[0163] In some embodiments of any Formulae described herein, m is 6, 7, 8, 9, 10, 11, 12, 13, 14, 15, or 16. In some embodiments, m is 6, 7, 8, 9, 10, 11, 12, 13, or 14. In some embodiments, m is 8. In some embodiments, m is 12.

[0164] In some embodiments of any Formulae described herein, n is 6, 7, 8, 9, 10, 11, 12, 13, 14, 15, or 16. In some embodiments, n is 6, 7, 8, 9, 10, 11, 12, 13, or 14. In some embodiments, n is 8. In some embodiments, n is 12.

[0165] In some embodiments of any Formulae described herein, R^8 is $-C(O)(C_{1-2} \text{ alkyl})$. In some embodiments, R^8 is $-C(O)CH_3$.

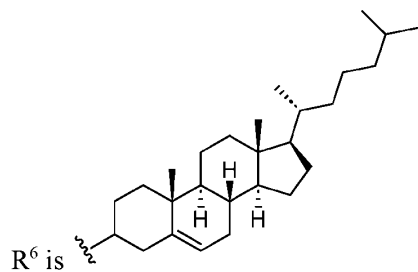
[0166] In some embodiments, the present disclosure provides a modified peptide selected from Table 6.

Table 6.



wherein

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



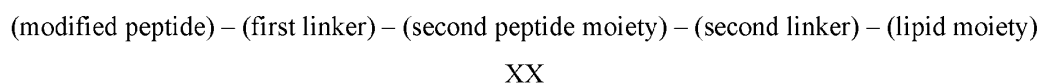
Cmpd. No.	Cmpd. SEQ ID NO:	[Xaa] _w	[Xaa] _w SEQ ID NO:	[Xaa] _x	[Xaa] _x SEQ ID NO:	[Xaa] _y	[Xaa] _y SEQ ID NO:
1	154	SEMKNLF	16	KTRRRL	144	ENA	90
2	155	SEB*KNLF	128	KTRRRL	144	ENA	90
3	156	SAMKNLF	129	KTRRQL	55	ENA	90
4	157	SAB*KNLF	130	KTRRQL	55	ENA	90
5	158	SVMKNLF	131	KTRRQL	55	ENA	90
6	159	SVB*KNLF	132	KTRRQL	55	ENA	90
7	160	SEMKNLF	16	KTRREL	67	ENA	90
8	161	SEB*KNLF	128	KTRREL	67	ENA	90
9	162	SEMKNLF	16	KTARQL	145	ENA	90
10	163	SEB*KNLF	128	KTARQL	145	ENA	90
11	164	SEMNNLF	133	KTRRQL	55	ENA	90
12	165	SEB*NNLF	134	KTRRQL	55	ENA	90
13	166	SEMKNLF	16	KVRRQL	64	ENA	90
14	167	SEB*KNLF	128	KVRRQL	64	ENA	90
15	168	SEMKNLF	16	KTRSQL	146	ENA	90
16	169	SEB*KNLF	128	KTRSQL	146	ENA	90
17	170	SEMKNL	17	EKTRSQ	147	RENA	91
18	171	SEB*KNL	135	EKTRSQ	147	RENA	91
19	172	SNVKNLY	136	KVRSQL	148	NNA	151
20	173	SEMKNLY	31	KVRSQL	148	ENA	90
21	174	SEB*KNLY	137	KVRSQL	148	ENA	90
22	175	SEMKNLF	16	KVRSQL	148	N	119
23	176	SEB*KNLF	128	KVRSQL	148	N	119
24	177	DLTDSEMKNLF	37	KTRRQL	55	ENA	90
25	178	DLTDSEB*KNLF	138	KTRRQL	55	ENA	90
26	179	DLTDSEM	41	KLFEKT	51	RQLRENA	93
27	180	DLTDSEB*	139	KLFEKT	51	RQLRENA	93
28	181	DLTQSEM	140	KLFEKT	51	RQLRENA	93
29	182	DLTQSEB*	141	KLFEKT	51	RQLRENA	93
30	183	DLTDSEM	41	KLFEKV	60	RQLRENA	93
31	184	DLTDSEB*	139	KLFEKV	60	RQLRENA	93

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:
32	185	SEB*NKLF	128	KTRRQL	55	ENA	90
33	186	SEMKNLF	16	KTRRQL	55	ENA	90
34	187	SEB*NKLF	128	KTRRQL	55	E	152
35	188	SEMKNLF	16	KTRRQL	55	E	152
36	189	DQB*NYLA	142	KTRFQI	149	NAA	153
37	190	DQMNYLA	143	KTRFQI	149	NAA	153
38	191	SEMKNLF	16	KVSRQL	79	ENA	90
39	192	SEB*NKLF	128	KVSRQL	79	ENA	90
40	193	SEMKNLF	16	KVARQL	150	ENA	90
41	194	SEB*NKLF	128	KVARQL	150	ENA	90

B* = norleucine

[0167] In some embodiments, a provided modified peptide is a peptide conjugate further comprising: -(linker)-(peptide moiety). In some embodiments, a linker comprises PEG, a peptide (e.g., one or more amino acids), or a combination thereof. In some embodiments, a linker comprises a peptide. In some embodiments, a linker comprises one or more PEG units. In some embodiments, a linker comprises PEG units linked by amide bonds. In some embodiments, an amino acid at the C-terminus of a provided modified peptide is conjugated to a second peptide moiety via a linker group, i.e., -(linker)-(peptide moiety). In some embodiments, a second peptide moiety is further conjugated to a lipid moiety, i.e., -(linker)-(second peptide moiety)-(linker)-(lipid moiety). In some such embodiments, a lipid moiety is one described herein. In some embodiments, a second peptide moiety has the same or different sequence as the modified peptide. In some embodiments, a second peptide moiety comprises a sequence of amino acids capable of binding a portion of influenza HA.

[0168] In some embodiments, a provided modified peptide is a part of a peptide conjugate of Formula XX:



or a pharmaceutically acceptable salt thereof, wherein:

modified peptide is a modified peptide as described herein;

first linker is a bivalent, straight or branched, saturated or unsaturated, optionally substituted C₁₋₃₀

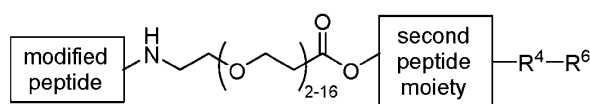
hydrocarbon chain, wherein 1-10 methylene units of the hydrocarbon chain are independently replaced by -O-, -N(R')-, -S-, -OC(O)-, -C(O)O-, -C(O)-, -S(O)-, -S(O)₂-, -N(R')S(O)₂-, -S(O)₂N(R')-, -N(R')C(O)-, -C(O)N(R')-, -OC(O)N(R')-, -N(R')C(O)O-, or -[O-CH₂CH₂]_n, wherein n is 1-20;

second peptide moiety is a peptide having 10-30 amino acids;

second linker is R⁴ or R⁹ as described herein; and

lipid moiety is R⁶ as described herein.

[0169] In some embodiments, a provided modified peptide is a part of a peptide conjugate of Formula XXI:



XXI

or a pharmaceutically acceptable salt thereof, wherein:

modified peptide is a modified peptide as described herein;

second peptide moiety is a peptide having 10-30 amino acids;

R⁴ is as described herein; and

R⁶ is as described herein.

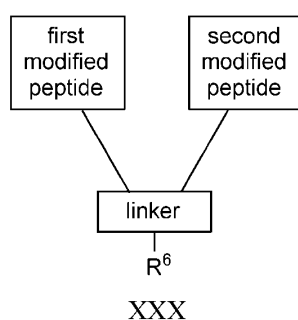
[0170] In some embodiments of Formula XX and XXI, a second peptide moiety comprises the following sequence: GTYDHDVYRDEALNNRFQI (SEQ ID NO: 195). In some embodiments, a second peptide moiety comprises a sequence that is 30% identical to SEQ ID NO: 195. In some embodiments, a second peptide moiety comprises a sequence that is 70% identical to SEQ ID NO: 195. In some embodiments, a second peptide moiety comprises a sequence that is 90% identical to SEQ ID NO: 195. In some embodiments, a second peptide moiety comprises a sequence that is 95% identical to SEQ ID NO: 195. In some embodiments, a second peptide moiety comprises a sequence that is 98% identical to SEQ ID NO: 195. In some embodiments, a second peptide moiety comprises a sequence that has 0-10 substitutions, insertions, and/or deletions relative to SEQ ID NO: 195. In some embodiments, a second peptide moiety comprises a sequence that has 0-5 substitutions, insertions, and/or deletions relative to SEQ ID NO: 195. In some embodiments, a second peptide moiety comprises a sequence that has 0-2 substitutions, insertions, and/or deletions relative to SEQ ID NO: 195. In some embodiments, a second peptide moiety comprises a sequence that has 1-5 substitutions, insertions, and/or deletions relative to SEQ ID NO: 195. In

some embodiments, a second peptide moiety comprises a sequence that has 1-2 substitutions, insertions, and/or deletions relative to SEQ ID NO: 195.

Multimers

[0171] The present disclosure also provides multimeric constructs comprising more than one modified peptide as described herein. In some embodiments, a multimeric construct comprises two modified peptides as described herein.

[0172] In some embodiments, a multimeric construct comprises Formula XXX:



or a pharmaceutically acceptable salt thereof, wherein:

first modified peptide and second modified peptide are each independently a modified peptide described herein;

linker is a linking group; and

R^6 is as defined herein.

[0173] In some embodiments, a first modified peptide and a second modified peptide comprise the same amino acid sequence. In some embodiments, a first modified peptide and a second modified peptide comprise different amino acid sequences.

Compositions

[0174] The present disclosure also provides compositions comprising a modified peptide provided herein with one or more other components. In some embodiments, provided compositions comprise and/or deliver a modified peptide described herein.

[0175] In some embodiments, a provided composition is a pharmaceutical composition that comprises and/or delivers a modified peptide provided herein and further comprises a pharmaceutically acceptable carrier.

[0176] Provided 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) intravaginal or intrarectal administration, for example, as a pessary, cream or foam; (5) sublingual administration; (6) ocular administration; (7) transdermal administration; (8) nasal administration; or (9) administration via inhalation (*e.g.*, as an aerosol or for use with a nebulizer).

[0177] In some embodiments, provided pharmaceutical compositions comprise a modified peptide described herein and one or more fillers, disintegrants, lubricants, glidants, anti-adherents, and/or anti-statics, etc. Provided pharmaceutical compositions can be in a variety of forms including oral dosage forms, topical creams, topical patches, iontophoresis forms, suppository, nasal spray and/or inhaler, eye drops, intraocular injection forms, depot forms, as well as injectable and infusible solutions. Methods of preparing pharmaceutical compositions are well known in the art.

Uses

[0178] In some embodiments, the present disclosure provides methods of using any of the peptides or pharmaceutical compositions described herein for the treatment and/or prevention of an influenza virus infection.

[0179] In some embodiments, the present disclosure provides a method of inhibiting influenza fusion to a host cell in a subject in need thereof, the method comprising administering to the subject a therapeutically effective amount of a peptide comprising an amino acid sequence of an influenza hemagglutinin (HA) protein or a variant thereof.

[0180] In some embodiments, the present disclosure provides a method of inhibiting a conformational change in an influenza hemagglutinin (HA) protein in a subject in need thereof, the method comprising administering to the subject a therapeutically effective amount of a peptide comprising an amino acid sequence of an influenza hemagglutinin (HA) protein or a variant

thereof. In some embodiments, the conformation change in an influenza hemagglutinin (HA) protein that is inhibited is the fold back of the native influenza HA2 C-terminal helix (as described in Example 1).

[0181] In some embodiments, the present disclosure provides a method of preventing and/or treating an influenza virus infection in a subject in need thereof, the method comprising administering to the subject a therapeutically effective amount of a peptide comprising an amino acid sequence of an influenza hemagglutinin (HA) protein or a variant thereof.

[0182] In some embodiments, the present disclosure provides a method of preventing an influenza virus infection in a subject in need thereof, the method comprising administering to the subject a therapeutically effective amount of a peptide comprising an amino acid sequence of an influenza hemagglutinin (HA) protein or a variant thereof.

[0183] In some embodiments, the present disclosure provides a method of treating an influenza virus infection in a subject in need thereof, the method comprising administering to the subject a therapeutically effective amount of a peptide comprising an amino acid sequence of an influenza hemagglutinin (HA) protein or a variant thereof.

[0184] In some embodiments, a peptide comprising an amino acid sequence of an influenza hemagglutinin (HA) protein or a variant thereof inhibits fusion of an influenza virus particle to an endosomal membrane in a host cell. In some embodiments, the peptide comprises an amino acid sequence of an HA2 domain of influenza HA. In some embodiments, the peptide comprises an amino acid sequence of the C-terminal helix of an HA2 domain of influenza HA. In some embodiments, the peptide comprises at least 5 contiguous amino acids of an amino acid sequence selected from Table 1, or an amino acid sequence that is (i) at least 30% identical to an amino acid sequence selected from Table 1; and/or (ii) has 1-10 substitutions, insertions, and/or deletions relative to an amino acid sequence selected from Table 1. In some embodiments, the peptide is any one of the peptides disclosed herein.

[0185] In some embodiments, provided herein is a method of inhibiting influenza virus particle fusion to a host cell in a subject in need thereof, the method comprising administering to the subject a therapeutically effective amount of a modified peptide disclosed herein. In some embodiments, the modified peptide inhibits fusion to a host cell of more than one (e.g., two, three, four, five, six, seven, eight, nine, ten, or more than ten) influenza A virus subtype. In some embodiments, the modified peptide inhibits fusion to a host cell of both influenza A and B viruses.

[0186] In some embodiments, provided herein is a method of inhibiting a conformational change in an influenza hemagglutinin (HA) protein in a subject in need thereof, the method comprising administering to the subject a therapeutically effective amount of a modified peptide disclosed herein. In some embodiments, the conformation change in an influenza hemagglutinin (HA) protein that is inhibited is the fold back of the native influenza HA2 C-terminal helix (as described in Example 1). In some embodiments, the modified peptide or a pharmaceutically acceptable salt thereof inhibits a conformational change in an influenza hemagglutinin (HA) protein of more than one (e.g., two, three, four, five, six, seven, eight, nine, ten, or more than ten) influenza A virus subtype. In some embodiments, the modified peptide or a pharmaceutically acceptable salt thereof inhibits a conformational change in an influenza hemagglutinin (HA) protein of both influenza A and B viruses.

[0187] In some embodiments, provided herein is a method of preventing and/or treating an influenza virus infection in a subject in need thereof, the method comprising administering to the subject a therapeutically effective amount of a modified peptide disclosed herein. In some embodiments, provided herein is a method of preventing an influenza virus infection in a subject in need thereof, the method comprising administering to the subject a therapeutically effective amount of a modified peptide disclosed herein. In some embodiments, provided herein is a method of treating an influenza virus infection in a subject in need thereof, the method comprising administering to the subject a therapeutically effective amount of a modified peptide disclosed herein.

[0188] In some embodiments, provided herein is a method of preventing and/or treating an influenza virus infection in a subject in need thereof, the method comprising administering to the subject a therapeutically effective amount of a modified peptide disclosed herein, wherein the modified peptide treats or prevents influenza virus infection caused by more than one (e.g., two, three, four, five, six, seven, eight, nine, ten, or more than ten) influenza A virus subtype. In some embodiments, the modified peptide or a pharmaceutically acceptable salt thereof treats or prevents influenza virus infection caused by both influenza A and B viruses.

[0189] In some embodiments, an influenza HA is from an influenza A virus. In some embodiments, an influenza A is subtype H10N4, subtype H10N5, subtype H10N7, subtype H10N8, subtype H10N9, subtype H11N1, subtype H11N13, subtype H11N2, subtype H11N4, subtype H11N6, subtype H11N8, subtype H11N9, subtype H12N1, subtype H12N4, subtype

H12N5, subtype H12N8, subtype H13N2, subtype H13N3, subtype H13N6, subtype H13N7, subtype H14N5, subtype H14N6, subtype H15N8, subtype H15N9, subtype H16N3, subtype H1N1, subtype H1N2, subtype H1N3, subtype H1N6, subtype H1N9, subtype H2N1, subtype H2N2, subtype H2N3, subtype H2N5, subtype H2N7, subtype H2N8, subtype H2N9, subtype H3N1, subtype H3N2, subtype H3N3, subtype H3N4, subtype H3N5, subtype H3N6, subtype H3N8, subtype H3N9, subtype H4N1, subtype H4N2, subtype H4N3, subtype H4N4, subtype H4N5, subtype H4N6, subtype H4N8, subtype H4N9, subtype H5N1, subtype H5N2, subtype H5N3, subtype H5N4, subtype H5N6, subtype H5N7, subtype H5N8, subtype H5N9, subtype H6N1, subtype H6N2, subtype H6N3, subtype H6N4, subtype H6N5, subtype H6N6, subtype H6N7, subtype H6N8, subtype H6N9, subtype H7N1, subtype H7N2, subtype H7N3, subtype H7N4, subtype H7N5, subtype H7N7, subtype H7N8, subtype H7N9, subtype H8N4, subtype H8N5, subtype H9N1, subtype H9N2, subtype H9N3, subtype H9N5, subtype H9N6, subtype H9N7, subtype H9N8, or subtype H9N9. In some embodiments, an influenza A is subtype H1N1 or H3N2. In some embodiments, an influenza HA is from an influenza B virus.

[0190] In some embodiments, the subject has or is at risk of having an influenza infection. In some embodiments, an influenza infection is from an influenza A virus. In some embodiments, an influenza A virus is subtype H10N4, subtype H10N5, subtype H10N7, subtype H10N8, subtype H10N9, subtype H11N1, subtype H11N13, subtype H11N2, subtype H11N4, subtype H11N6, subtype H11N8, subtype H11N9, subtype H12N1, subtype H12N4, subtype H12N5, subtype H12N8, subtype H13N2, subtype H13N3, subtype H13N6, subtype H13N7, subtype H14N5, subtype H14N6, subtype H15N8, subtype H15N9, subtype H16N3, subtype H1N1, subtype H1N2, subtype H1N3, subtype H1N6, subtype H1N9, subtype H2N1, subtype H2N2, subtype H2N3, subtype H2N5, subtype H2N7, subtype H2N8, subtype H2N9, subtype H3N1, subtype H3N2, subtype H3N3, subtype H3N4, subtype H3N5, subtype H3N6, subtype H3N8, subtype H3N9, subtype H4N1, subtype H4N2, subtype H4N3, subtype H4N4, subtype H4N5, subtype H4N6, subtype H4N8, subtype H4N9, subtype H5N1, subtype H5N2, subtype H5N3, subtype H5N4, subtype H5N6, subtype H5N7, subtype H5N8, subtype H5N9, subtype H6N1, subtype H6N2, subtype H6N3, subtype H6N4, subtype H6N5, subtype H6N6, subtype H6N7, subtype H6N8, subtype H6N9, subtype H7N1, subtype H7N2, subtype H7N3, subtype H7N4, subtype H7N5, subtype H7N7, subtype H7N8, subtype H7N9, subtype H8N4, subtype H8N5, subtype H9N1, subtype H9N2, subtype H9N3, subtype H9N5, subtype H9N6, subtype H9N7, subtype H9N8, or

subtype H9N9. In some embodiments, an influenza A virus is subtype H1N1 or H3N2. In some embodiments, an influenza infection is from an influenza B virus.

[0191] In some embodiments, 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 embodiments, the subject is a domesticated animal (*e.g.*, a dog or cat). In some embodiments, the subject is a human.

[0192] In some embodiments, the subject is infected with an influenza virus (*e.g.*, influenza A or influenza B). In some embodiments, the subject is at risk of being infected with an influenza virus (*e.g.*, influenza A or influenza B).

[0193] Provided modified peptides can be administered using any suitable means. In some embodiments, a peptide is administered to a subject orally, intranasally, intravenously, subcutaneously, intramuscularly, or topically, including skin, nasal, sinus, ocular, oropharynx, respiratory tree, and lung administration (*e.g.*, via inhalation). In some embodiments, a peptide is administered by a topical respiratory application, which includes application to the nasal mucosa, sinus mucosa, oropharyngeal mucosa, or respiratory tree, including the lungs. In some embodiments, a peptide is administered by topical application to the skin or eyes.

[0194] An effective amount of provided modified peptides can be administered in one or more administrations, applications or dosages. A therapeutically effective amount of a therapeutic peptide (*i.e.*, an effective dosage) depends on the therapeutic peptide selected. Provided compositions (*e.g.*, comprising one or more modified peptides described herein) can be administered from one or more times per day to one or more times per week. Treatment of a subject with a therapeutically effective amount of a therapeutic peptide described herein can include a single treatment or a series of treatments. For example, effective amounts can be administered at least once.

[0195] In some embodiments, provided modified peptides (including conjugates and multimeric constructs described herein) demonstrate a particular effect in one or more assays described herein. In some embodiments, provided modified peptides demonstrate an EC₅₀ value of less than 5 μ M in the assays of Examples 3-5. In some embodiments, provided modified peptides demonstrate an EC₅₀ value of less than 2 μ M in the assays of Examples 3-5. In some embodiments, provided modified peptides demonstrate an EC₅₀ value of less than 1 μ M in the assays of Examples 3-5. In some embodiments, provided modified peptides demonstrate a

selective index (SI) of greater than 1.5 in the assays of Examples 3-5. In some embodiments, provided modified peptides demonstrate a SI of greater than 2 in the assays of Examples 3-5. In some embodiments, provided modified peptides demonstrate a SI of greater than 4 in the assays of Examples 3-5. In some embodiments, provided modified peptides demonstrate a SI of greater than 5 in the assays of Examples 3-5.

Methods of Preparing Provided Peptides

[0196] The present disclosure also provides a method of making a modified peptide disclosed herein, the method comprising: (a) providing a peptide comprising the amino acid sequence set forth in Table 1, or a variant thereof, optionally wherein the amino acid sequence comprises 2 non-naturally occurring amino acids; and (b) cross-linking the peptide, and optionally purifying the peptide.

[0197] In some embodiments, the present disclosure provides a method of synthesizing a conjugate comprising a modified peptide disclosed herein, the method comprising: (a) providing the modified peptide; and (b) derivatizing a resin bound amine of the modified peptide with a conjugated moiety on a resin. In some embodiments, a conjugated moiety is one described herein.

[0198] In some embodiments, provided herein is a method of making a peptide derivatized with a PEG(n)-thiocholesterol, PEG(n)-cholesterol, thiocholesterol-PEG(n), or cholesterol-PEG(n) moiety. The fully on-resin synthetic method involves (a) providing a peptide comprising at least 3 contiguous amino acids of a sequence selected from Table 1, or a variant thereof, and two non-naturally occurring amino acids, (b) cross-linking the peptide, for example, by a ruthenium catalyzed metathesis reaction, and (c) derivatizing the N-terminus and/or C-terminus on resin with a PEG linker of variable length connected to a thiocholesterol or cholesterol moiety.

[0199] In some embodiments, Fmoc-based solid-phase peptide synthesis is used to synthesize modified peptides disclosed herein. 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 is added to the resin-bound peptides. One or more rounds, for example three to five rounds, of stapling may be performed to ensure complete stapling. After appending the PEG(n)-thiocholesterol, PEG(n)-cholesterol, thiocholesterol-PEG(n), or cholesterol-PEG(n) moiety, the peptides are

cleaved off of the resin using trifluoroacetic acid, precipitated using a hexane:ether (1:1) mixture, air dried, and purified by LC-MS.

[0200] In some embodiments, the peptides disclosed herein are made by chemical synthesis methods, which are well known to the ordinarily skilled artisan. The 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.

[0201] In some embodiments, the peptides disclosed herein are made by 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.

[0202] Peptides (e.g., peptides described herein) 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.

[0203] The peptides disclosed herein 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), stearylation, succinylation and sulfurylation.

[0204] In some embodiments, the molecules are substantially free of 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 some embodiments, the resin is washed with NMP. Shaking and bubbling an inert gas into the solution may be performed.

Assays to Characterize Stapled Peptide Conjugates

[0205] 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).

[0206] 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).

[0207] 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.

[0208] 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 Turbovap 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.

[0209] 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.

[0210] 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.

[0211] 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).

[0212] 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.

[0213] 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

[0214] 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. Design of Anti-Influenza Stapled Peptides

[0215] The following example describes the process of designing therapeutic peptides that are believed to prevent a conformational change in the influenza virus haemagglutinin (HA) protein and inhibit influenza virus particle fusion with a host cell endosomal membrane. These therapeutic peptides were designed for use in several different influenza subtypes and thus, could be a pan-influenza treatment and/or prevention.

[0216] A cascade of conformational changes of the influenza virus HA protein mediates viral particle fusion with a host cell and is triggered by the pH drop from neutral to acidic conditions in the endosome of the host cell. In the critical final conformational change, the HA2 C-terminal helix (residues 106-125 of HA2) folds back to the HR2 region (residues 77-101 of HA2) to bring the viral membrane and host endosomal membrane into close proximity simultaneous with the cleavage of the HA1 domain (Benton et al., *Nature*. 2020 Jul;583(7814):150-153). Similar to the HR1/HR2 interaction in other viruses, the C-terminal helix/HR2 interaction supports the post-fusion structure that is needed for influenza infection. Thus, inhibiting the fold back of the HA2 C-terminal helix is a possible target to prevent influenza infection.

[0217] Based on the final conformational change of influenza HA, a therapeutic peptide that mimics the structure of the influenza HA2 C-terminal helix may interact with the HR2 domain and block the fold back of the native influenza HA2 C-terminal helix, thus preventing virus particle fusion and infection. For the initial design of a therapeutic peptide, a portion of the H3N2 HA2 C-terminal helix (DLTDSEMKNLF EKTRRQLRENA, SEQ ID NO: 5) was chosen as the basis for the design. To this end, the amino acid sequence of SEQ ID NO: 5 was analyzed for its conservation across subtypes of influenza, in order to determine if this peptide sequence could be applicable to more than one influenza subtype. Table 7 shows the % homology of the HA region corresponding to the amino acid of SEQ ID NO: 5, between subtypes H3N2, H1N1, and influenza B.

Table 7. C-terminal Helix Residue Conservation

Residue	H1N1 Conservation	H3N2 Conservation	Influenza B Conservation
109	D – 99.5%	D – 99.8%	N – 99.9%
110	Y – 81.3%	L – 99.8%	S – 99.9%
111	H – 99.9%	T – 99.9%	E – 100%
112	D – 99.4%	D – 99.9%	D – 99.9%
113	S – 99.6%	S – 99.6%	E – 99.9%
114*	N – 99.4%	E – 99.9%	H – 100%
115*	V – 99.7%	M – 99.9%	L – 99.9%
116	K – 99.7%	N – 99.5%	L – 99.9%
117	N – 99.0%	K – 99.9%	A – 99.9%
118*	L – 100%	L – 100%	L – 99.9%
119*	Y – 99.9%	F – 100%	E – 100%
120	E – 99.8%	E – 99.9%	R – 99.5%
121*	K – 99.6%	K – 86.0% otherwise R	K – 99.9%

Residue	H1N1 Conservation	H3N2 Conservation	Influenza B Conservation
122*	V – 99.5%	T – 100%	L – 100%
123	R – 81.0% otherwise K	K – 92.3% otherwise R	K – 99.9%
124	S – 60.2% otherwise K/N	K – 98.3%	K – 99.9%
125*	Q – 99.8%	Q – 99.9%	M – 99.9%
126*	L – 99.5%	L – 99.8%	L – 100%
127	K – 99.2%	R – 99.9%	G – 100%
128	N – 99.1%	E – 100%	P – 100%
129	N – 100%	N – 100%	S – 99.9%
130*	A – 100%	A – 100%	A – 99.9%

*Residues involved in interaction of the HA2 C-terminal helix to the HR2 region of HA.

[0218] The data in Table 7 show that the amino acids of the H3N2 HA2 C-terminal helix, including those that contact the HR2 region, are highly conserved between H1N1 and H3N2, with more variation in influenza B.

[0219] To further analyze the conservation of SEQ ID NO: 5 across influenza virus subtypes, the NCBI Influenza Virus Resource (NIVR) database was reviewed. The NIVR database has 77,280 influenza A sequences and 26,225 influenza B sequences, which have been isolated from human hosts. This database shows that H1 and H3 HA proteins account for 92.5% of identified human influenza A infections. Analysis of the sequences of the influenza A subtypes listed in the database that have at least 50 sequences demonstrates that the amino acids involved in the C-terminal helix interactions are highly conserved (**FIG. 1**). Among the influenza A subtypes, the residues which interact with the H3N2 HA2 C-terminal helix-based peptide are identical, with the exception of residues 105, 108, and 140, which have the highly conserved residues, E vs Q, L vs I, and F vs I, respectively.

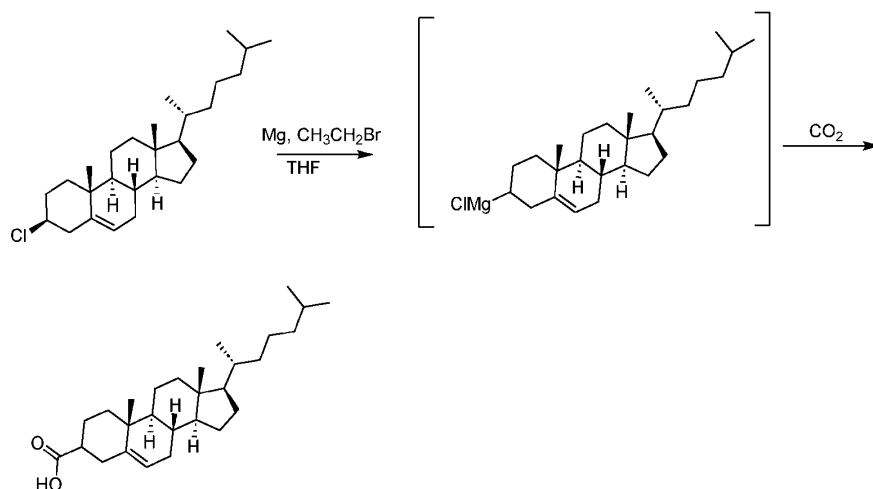
[0220] Based on this sequence analysis, therapeutic peptides were designed with an amino acid sequence similar to all or a portion of SEQ ID NO: 5, with two amino acids replaced with non-naturally occurring amino acids to cross-link or staple the peptide and stabilize the helical structure of the peptide. For example, the hydrogen bond between E120 and R127 appeared as a plausible staple position in the helical region based on mapping internal contacts within the C-terminal helix and its interactions with the HA2 domain (**FIG. 2**). In order to generate the stapled peptide, Glu12 of SEQ ID NO: 5 was replaced by R8 (R-octenyl alanine) and Arg19 of SEQ ID NO: 5 was replaced by S5 (S-pentenyl alanine).

Example 2. Preparation of Stapled Anti-Influenza Peptide Conjugates

[0221] Based on the general design of anti-influenza peptides described in Example 1, several exemplary peptides were prepared. Stapled peptide conjugates 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-octenyl alanine (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).

[0222] Briefly, a 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 of the non-natural amino acids (e.g., R8 and S5) 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 (prepared as described below). 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**.

[0223] Carboxy-cholesterol was prepared according to the following scheme:



[0224] Magnesium turnings were 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.

Example 3. In Vitro Evaluation of Stapled Peptides Against Influenza A (H3N2) in MDCK Cells

[0225] Compounds (e.g., modified peptides described herein) were tested for in vitro antiviral activity against influenza A/Perth/16/2009 (H3N2) in MDCK cells. Test media was minimum essential medium (MEM) supplemented with 10 U/mL trypsin, 1 µg/mL EDTA, and 50 µg/mL gentamicin. Cell plates were prepared the day before treatment and infection, seeding cells at 3e4 per well in 96-well plates, and incubating overnight at 37±2 °C, 5% CO₂.

[0226] Compounds were received as 10 mM solutions. Compounds were serially diluted using

eight 2-fold dilutions in test media so that the starting (high) test concentration was 10 μ M. Each dilution was added to 5 wells of a 96-well plate containing cells. Three wells of each concentration were infected with virus, and two wells remained uninfected as toxicity controls. Six wells were infected and untreated as virus controls, and six wells were uninfected and untreated as cell controls. Virus was prepared to achieve a MOI of 0.001. Ribavirin was tested in parallel as a positive control. Plates were incubated at 37 ± 2 °C, 5% CO₂.

[0227] On day 4 post-infection, once untreated virus control wells reached maximum CPE, plates were stained with neutral red dye for approximately 2 hours (± 15 minutes). Supernatant dye was removed and wells rinsed with PBS. The incorporated dye was extracted in 50:50 Sorensen citrate buffer/ethanol for >30 minutes, and the optical density was read on a spectrophotometer at 540 nm. Optical densities were converted to percent of cell controls and normalized to the virus control, then the concentration of test compound required to inhibit CPE by 50% (EC₅₀) was calculated by regression analysis. The concentration of compound that would cause 50% cell death in the absence of virus was similarly calculated (CC₅₀). The selective index (SI) is the CC₅₀ divided by EC₅₀.

[0228] The results of this analysis are summarized in Table 8.

Table 8.

Compound	EC ₅₀	CC ₅₀	SI
32 (μ M)	4.1	7	1.7
36 (μ M)	>10	>10	0
R1 (μ M)	>3.9	3.9	0
Ribavirin (μ g/mL)	15	>1000	>67

R1 is a modified peptide having [Xaa]_w = SEB*¹NKLF (SEQ ID NO: 128); [Xaa]_x = KTRRQL (SEQ ID NO: 55); [Xaa]_y = E; and an N-terminal conjugate having the structure: -N(H)-C(H)((CH₂)₄N(H)C(O)-CH₂CH₂-[O-CH₂CH₂]₁₀-N(R⁵)C(O)-(CH₂)-O-cholesterol))-C(O)-NH₂, wherein B* is norleucine.

Example 4. In Vitro Evaluation of Stapled Peptides Against Influenza A (H3N2) in MA-104 Cells

[0229] Compounds (e.g., modified peptides described herein) were tested for in vitro antiviral activity against influenza A/Perth/16/2009(H3N2) in MA-104 cells. Test media was MEM

supplemented with 10 U/mL trypsin, 1 µg/mL EDTA, and 50 µg/mL gentamicin. Cell plates were prepared the day before treatment and infection, seeding cells at 6e4 per well in 96-well plates, and incubating overnight at 37±2 °C, 5% CO₂.

[0230] Compounds were received as 10 mM solutions. Compound was serially diluted using four 2-fold dilutions in test media so that the starting (high) test concentration was 5 µM. Each dilution was added to 5 wells of a 96-well plate containing cells. Three wells of each concentration were infected with virus, and two wells remained uninfected as toxicity controls. Six wells were infected and untreated as virus controls, and six wells were uninfected and untreated as cell controls. Virus was prepared to achieve a MOI < 0.001. Ribavirin was tested in parallel as a positive control. Plates were incubated at 37±2 °C, 5% CO₂.

[0231] On day 3 post-infection, once untreated virus control wells reached maximum CPE, plates were stained with neutral red dye for approximately 2 hours (±15 minutes). Supernatant dye was removed and wells rinsed with PBS. The incorporated dye was extracted in 50:50 Sorensen citrate buffer/ethanol for >30 minutes, and the optical density was read on a spectrophotometer at 540 nm. Optical densities were converted to percent of cell controls and normalized to the virus control, then the concentration of test compound required to inhibit CPE by 50% (EC₅₀) was calculated by regression analysis. The concentration of compound that would cause 50% cell death in the absence of virus was similarly calculated (CC₅₀). The selective index (SI) is the CC₅₀ divided by EC₅₀.

[0232] The results of this analysis are summarized in Table 9.

Table 9.

Compound	EC ₅₀	CC ₅₀	SI
7 (µM)	1.2	5	4.2
13 (µM)	<0.63	2.7	>4.3
17 (µM)	>5	>5	0
20 (µM)	1.7	>5	>2.9
Ribavirin (µg/mL)	3.9	>1000	>260

Example 5. In Vitro Evaluation of Stapled Peptides Against Influenza A and B

[0233] A compound (e.g., a modified peptide described herein) was tested for in vitro antiviral activity against influenza A/California/07/2009(H1N1)pdm09, influenza A/Perth/16/2009(H3N2),

and influenza B/Brisbane/60/2008 (Victoria lineage) in MDCK cells. Test media was MEM supplemented with 10 U/mL trypsin, 1 µg/mL EDTA, and 50 µg/mL gentamicin. Cell plates were prepared the day before treatment and infection, seeding cells at 6e4 per well in 96-well plates, and incubating overnight at 37±2 °C, 5% CO₂.

[0234] Compound was received as a 10 mM solution. Compound was serially diluted using eight half-log₁₀ dilutions in test media so that the starting (high) test concentration was 10 µM. Each dilution was added to 5 wells of a 96-well plate containing cells. Three wells of each concentration were infected with virus, and two wells remained uninfected as toxicity controls. Six wells were infected and untreated as virus controls, and six wells were uninfected and untreated as cell controls. Virus was prepared to achieve a MOI < 0.001. Ribavirin was tested in parallel as a positive control. Plates were incubated at 37±2 °C, 5% CO₂.

[0235] On day 4-5 post-infection, once untreated virus control wells reached maximum CPE, plates were stained with neutral red dye for approximately 2 hours (±15 minutes). Supernatant dye was removed and wells rinsed with PBS. The incorporated dye was extracted in 50:50 Sorensen citrate buffer/ethanol for >30 minutes, and the optical density was read on a spectrophotometer at 540 nm. Optical densities were converted to percent of cell controls and normalized to the virus control, then the concentration of test compound required to inhibit CPE by 50% (EC₅₀) was calculated by regression analysis. The concentration of compound that would cause 50% cell death in the absence of virus was similarly calculated (CC₅₀). The selective index (SI) is the CC₅₀ divided by EC₅₀.

[0236] The results of this analysis are summarized in Table 10.

Table 10.

Influenza Virus	Compound 13 (µM)			Ribavirin (µg/mL)		
	EC ₅₀	CC ₅₀	SI	EC ₅₀	CC ₅₀	SI
A(H1N1)	0.5	2.7	5.1	20	>1000	>50
A(H3N2)	0.3	3.0	10	12	>1000	>83
B	0.6	2.4	4.2	5.9	>1000	>170

[0237] While we have described a number of embodiments of this invention, it is apparent that our basic examples may be altered to provide other embodiments that utilize the peptides and methods of this invention. Therefore, it will be appreciated that the scope of this invention is to be

defined by the appended claims rather than by the specific embodiments that have been represented by way of example.

CLAIMS

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:

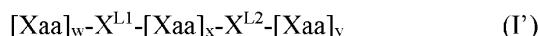
SEMNKLF EKTRRQLRENA	SEQ ID NO: 1
SEMNKLF EKVRRQLRENA	SEQ ID NO: 2
SEMNKLF EKTRRELRENA	SEQ ID NO: 3
SEMNKLYEKVRSQ LRENA	SEQ ID NO: 4
DLTDSEM NKLF EKTRRQLRENA	SEQ ID NO: 5
SEMNKLF EKVRSQ LRN	SEQ ID NO: 6

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 0-10 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 claim 1 or 2, 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 of amino acids at positions i and $i+7$).
4. The modified peptide of claim 3, wherein the side chains that are linked together are side chains of two amino acids separated by 3 amino acids (e.g., side chains of amino acids at positions i and $i+4$).
5. The modified peptide of claim 3, wherein the side chains that are linked together are side chains of two amino acids separated by 6 amino acids (e.g., side chains of amino acids at positions i and $i+7$).

6. 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.
7. 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.
8. 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.
9. 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.
10. 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.
11. The modified peptide of any one of claims 1-10, wherein the amino acid sequence is SEQ ID NO: 1.
12. The modified peptide of any one of claims 1-10, wherein the amino acid sequence is SEQ ID NO: 2.
13. The modified peptide of any one of claims 1-10, wherein the amino acid sequence is SEQ ID NO: 3.
14. The modified peptide of any one of claims 1-10, wherein the amino acid sequence is SEQ ID NO: 4.

15. The modified peptide of any one of claims 1-10, wherein the amino acid sequence is SEQ ID NO: 5.
16. The modified peptide of any one of claims 1-10, wherein the amino acid sequence is SEQ ID NO: 6.
17. The modified peptide of any one of the preceding claims, wherein the modified peptide is conjugated to a lipid, carbohydrate, or peptide moiety.
18. The modified peptide of claim 17, wherein the modified peptide is conjugated to a lipid, carbohydrate, or peptide moiety via a PEG moiety.
19. The modified peptide of claim 18, wherein the PEG moiety is attached at or near the C-terminus of the amino acid sequence.
20. The modified peptide of claim 18, wherein the PEG moiety is attached at or near the N-terminus of the amino acid sequence.
21. The modified peptide of any one of claims 17-20, wherein the modified peptide further comprises an optionally substituted C₅-C₁₀₀ aliphatic lipid moiety.
22. The modified peptide of claim 21, wherein the lipid moiety is a fatty acid, phospholipid, sphingolipid, or a sterol.
23. The modified peptide of claim 21 or 22, wherein the lipid moiety is cholesterol, thiocholesterol, sitosterol, ergosterol, or tocopherol.
24. The modified peptide of claim 23, wherein the lipid moiety is cholesterol.
25. A modified peptide, wherein the modified peptide is of the formula I':



or a pharmaceutically acceptable salt thereof, wherein:

each Xaa independently represents a natural or unnatural amino acid;

w, x, and y are independently 0-50, inclusive;

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

[Xaa]_x represents an amino acid sequence comprising at least 3 contiguous amino acids of:

an amino acid sequence selected from Table 1; or

an amino acid sequence that is (i) at least 30% identical to an amino acid sequence selected from Table 1 and/or (ii) has 1-10 substitutions, insertions, and/or deletions relative to an amino acid sequence selected from Table 1;

each of [Xaa]_w and [Xaa]_y independently represents an amino acid sequence comprising one or more contiguous amino acids of:

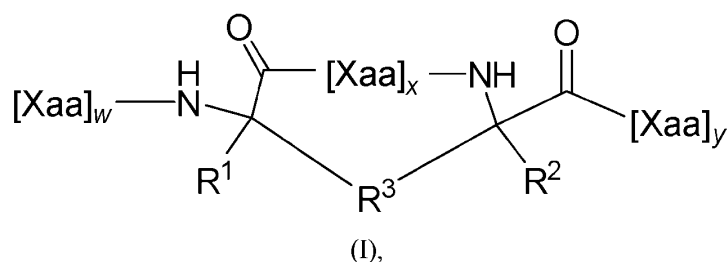
an amino acid sequence selected from Table 1; or

an amino acid sequence that is (i) at least 30% identical to an amino acid sequence selected from Table 1 and/or (ii) has 1-10 substitutions, insertions, and/or deletions relative to an amino acid sequence selected from Table 1,

optionally wherein the N-terminal amino acid in [Xaa]_w and/or the C-terminal amino acid in

[Xaa]_y is conjugated to a lipid, carbohydrate, or peptide moiety.

26. A modified peptide, wherein the modified peptide is of Formula I:



or a pharmaceutically acceptable salt thereof, wherein:

R¹ and R² are each independently hydrogen or an optionally substituted C₁₋₁₀ aliphatic group;

R³ represents linked side chain groups and is an optionally substituted bivalent, C₃₋₂₀ hydrocarbon chain, wherein one or more methylene units of the hydrocarbon chain 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 independently hydrogen or optionally substituted C₁₋₁₂ aliphatic;

each Xaa independently represents a natural or unnatural amino acid;

w and y are each independently 0-50;

x is 3-10; and

[Xaa]_x represents an amino acid sequence comprising at least 3 contiguous amino acids of:

an amino acid sequence selected from Table 1; or

an amino acid sequence that is (i) at least 30% identical to an amino acid sequence selected from Table 1 and/or (ii) has 1-10 substitutions, insertions, and/or deletions relative to an amino acid sequence selected from Table 1;

each of [Xaa]_w and [Xaa]_y independently represents an amino acid sequence comprising one or more contiguous amino acids of:

an amino acid sequence selected from Table 1; or

an amino acid sequence that is (i) at least 30% identical to an amino acid sequence selected from Table 1 and/or (ii) has 1-10 substitutions, insertions, and/or deletions relative to an amino acid sequence selected from Table 1,

optionally wherein the N-terminal amino acid in [Xaa]_w and/or the C-terminal amino acid in [Xaa]_y is conjugated to a lipid, carbohydrate, or peptide moiety.

27. The modified peptide of claim 25 or 26, wherein each of [Xaa]_w, [Xaa]_x, and [Xaa]_y represents an amino acid sequence comprising at least 3 contiguous amino acids of:

an amino acid sequence selected from SEQ ID NO: 1-6; or

an amino acid sequence that is (i) at least 90% identical to an amino acid sequence selected from SEQ ID NO: 1-6 and/or (ii) has 1-10 substitutions, insertions, and/or deletions relative to an amino acid sequence selected from SEQ ID NO: 1-6,

optionally wherein the N-terminal amino acid in [Xaa]_w and/or the C-terminal amino acid in [Xaa]_y is conjugated to a lipid, carbohydrate, or peptide moiety.

28. The modified peptide of any one of claims 25-27, wherein each of [Xaa]_w, [Xaa]_x, and [Xaa]_y represents an amino acid sequence comprising at least 3 contiguous amino acids of an amino acid sequence selected from SEQ ID NO: 1-6.
29. The modified peptide of any one of claims 25-27, wherein each of [Xaa]_w, [Xaa]_x, and [Xaa]_y represents an amino acid sequence comprising at least 3 contiguous amino acids of an amino acid sequence that is (i) at least 90% identical to an amino acid sequence selected from SEQ ID NO: 1-6 and/or (ii) has 1-10 substitutions, insertions, and/or deletions relative to an amino acid sequence selected from SEQ ID NO: 1-6.
30. The modified peptide of any one of claims 25-29, wherein the C-terminal amino acid in [Xaa]_y is conjugated to a lipid, carbohydrate, or peptide moiety.
31. The modified peptide of any one of claims 25-30, wherein the N-terminal amino acid in [Xaa]_w is conjugated to a lipid, carbohydrate, or peptide moiety.
32. The modified peptide of any one of claims 25-31, wherein w is 7.
33. The modified peptide of any one of claims 25-32, wherein x is 6.
34. The modified peptide of any one of claims 25-33, wherein y is 0-5.
35. The modified peptide of any one of claims 25-34, wherein [Xaa]_w is selected from Table 2.
36. The modified peptide of any one of claims 25-35, wherein [Xaa]_x is selected from Table 3.
37. The modified peptide of any one of claims 25-35, wherein [Xaa]_y is selected from Table 4.

38. The modified peptide of any one of claims 25-37, wherein $[Xaa]_w$, $[Xaa]_x$, and $[Xaa]_y$ are selected from Table 5.

39. The modified peptide of any one of claims 1-38, wherein the modified peptide is at most 50 amino acids in length (i.e., $w+x+y+2 \leq 50$).

40. The modified peptide of any one of claims 1-39, wherein the modified peptide is at most 30 amino acids in length (i.e., $w+x+y+2 \leq 30$).

41. The modified peptide of any one of claims 26-40, wherein R^1 and R^2 are each independently hydrogen or C_{1-10} aliphatic optionally substituted with one or more halo, hydroxyl, or C_{1-3} alkoxy.

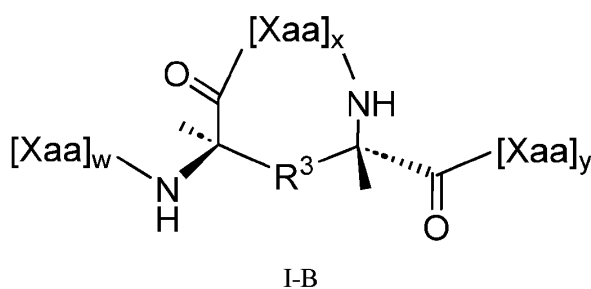
42. The modified peptide of any one of claims 26-41, wherein R^1 is C_{1-10} alkyl.

43. The modified peptide of any one of claims 26-42, wherein R^1 is methyl.

44. The modified peptide of any one of claims 26-43, wherein R^2 is C_{1-10} alkyl.

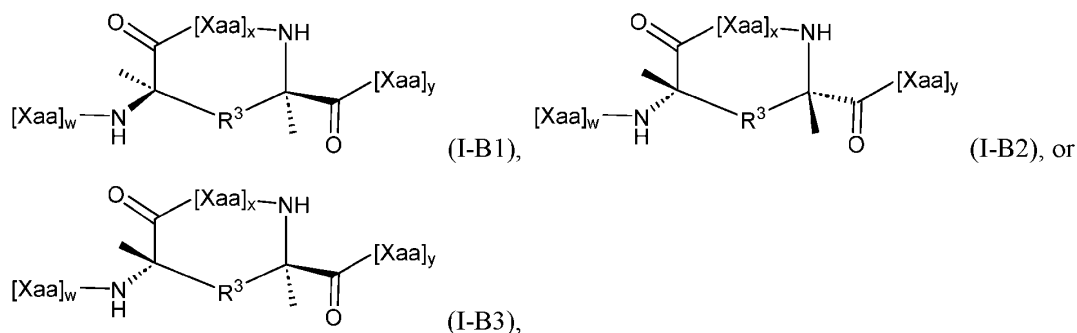
45. The modified peptide of any one of claims 26-44, wherein R^2 is methyl.

46. The modified peptide of any one of claims 26-45, wherein the modified peptide is of Formula I-B:



or a pharmaceutically acceptable salt thereof.

47. The modified peptide of any one of claims 26-45, wherein the modified peptide is selected from:



or a pharmaceutically acceptable salt thereof.

48. The modified peptide of any one of claims 26-47, wherein R^3 is an optionally substituted bivalent, C_{3-20} hydrocarbon chain comprising at least one double bond, wherein one or more methylene units of the hydrocarbon chain 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 $—C(O)O—$.

49. The modified peptide of any one of claims 26-48, wherein R^3 is an optionally substituted bivalent, C_{3-20} hydrocarbon chain.

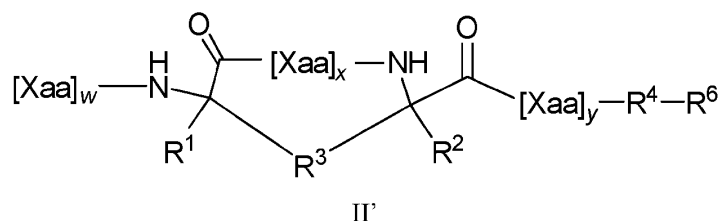
50. The modified peptide of any one of claims 26-49, wherein R^3 is C_{7-12} alkenylene.

51. The modified peptide of any one of claims 26-50, wherein R^3 is C_8 alkenylene.

52. The modified peptide of any one of claims 26-50, wherein R^3 is C_{11} alkenylene.

53. The modified peptide of any one of claims 26-48, wherein R^3 is $-(CH_2)_{1-7}-CH=CH-(CH_2)_{1-7}-$.

54. The modified peptide of any one of claims 26-48, wherein R^3 is $-(CH_2)_{3-7}-CH=CH-(CH_2)_{3-4}-$.
55. The modified peptide of any one of claims 26-48, wherein R^3 is $-(CH_2)_6-CH=CH-(CH_2)_3-$.
56. The modified peptide of any one of claims 26-48, wherein R^3 is $-(CH_2)_3-CH=CH-(CH_2)_3-$.
57. The modified peptide of any one of claims 26-56, wherein the modified peptide is of Formula II':



or a pharmaceutically acceptable salt thereof, wherein:

- R^4 is a bivalent, straight or branched, saturated or unsaturated, optionally substituted C_{1-30} 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 $-[O-CH_2CH_2]_n$, wherein n is 1-20; and
- R^6 is a conjugated moiety (e.g., a lipid, carbohydrate, or peptide).

58. The modified peptide of claim 57, wherein R^4 is a bivalent, straight or branched, saturated or unsaturated, optionally substituted C_{1-30} hydrocarbon chain, wherein 1-10 methylene units of the hydrocarbon chain are independently replaced by $-N(R')C(O)-$, $-C(O)N(R')$, or $-[O-CH_2CH_2]_n$, wherein n is 1-20.
59. The modified peptide of claim 57 or 58, wherein R^6 is a lipid moiety.

60. The modified peptide of any one of claims 57-59, wherein:

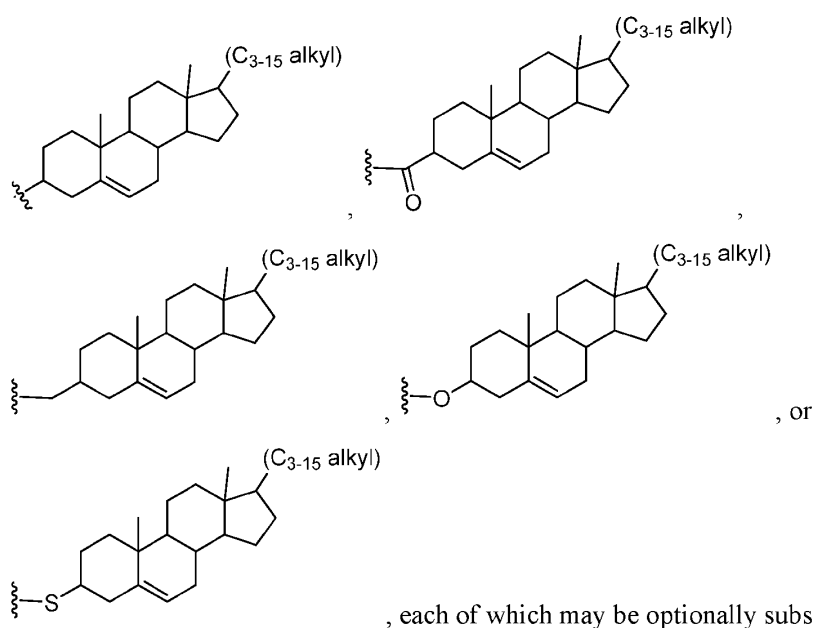
R^4 is $-N(H)-C(H)((CH_2)_4N(H)(C(O)-(C_{2-6} \text{ alkylene})-[O-CH_2CH_2]_n-N(R^5)C(O)-(C_{0-6} \text{ alkylene})-R^6))-C(O)-NH_2$;

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

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

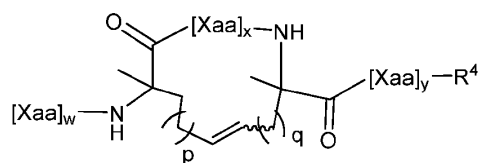
n is 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14, 15, or 16.

61. The modified peptide of any one of claims 57-60, wherein R^6 is selected from:



62. The modified peptide of claim 60 or 61, wherein R^6 is optionally substituted with one or more halo, C_{1-3} alkyl, hydroxyl, or C_{1-3} alkoxy.

63. The modified peptide of any one of claims 57-62, wherein the modified peptide is of Formula IIa1:



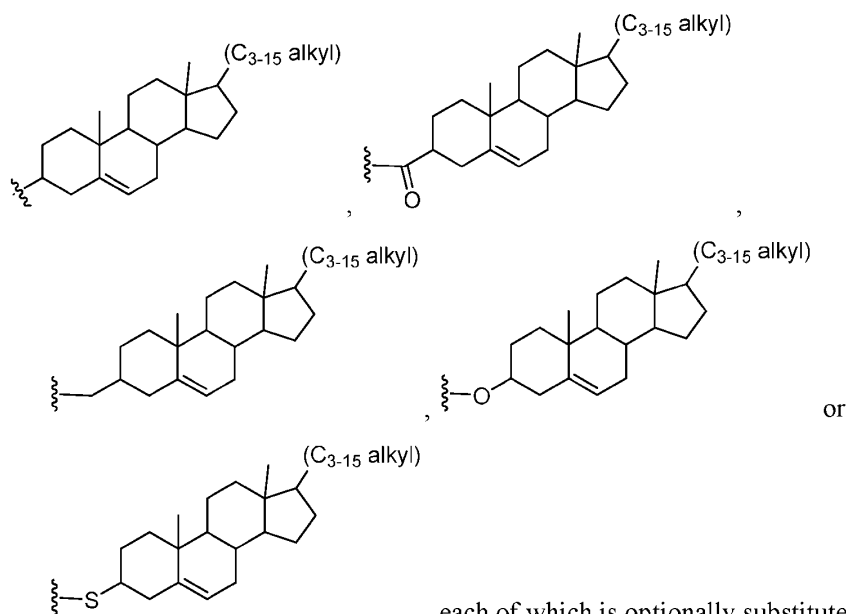
IIa1

or a pharmaceutically acceptable salt thereof, wherein:

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

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

R^6 is one of the following:



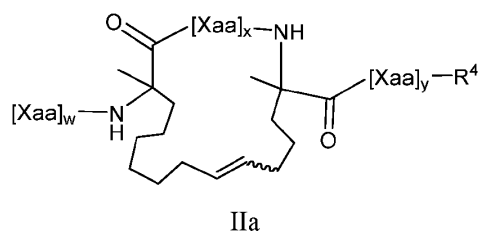
, each of which is optionally substituted with one or more occurrences of halo, C_{1-3} alkyl, hydroxyl, or C_{1-3} alkoxy;

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

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

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

64. The modified peptide of claim 63, wherein the modified peptide is of Formula IIa:

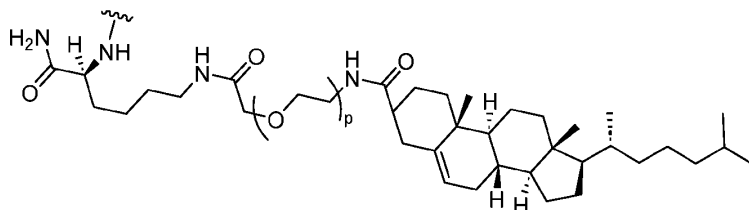


or a pharmaceutically acceptable salt thereof.

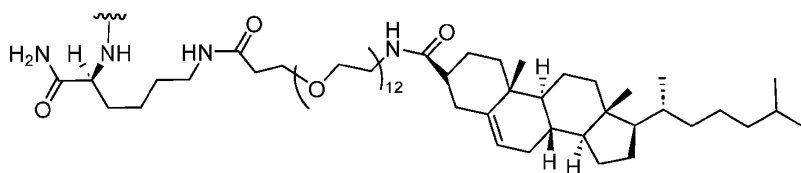
65. The modified peptide of any one of claims 57-64, wherein R^4 is $-N(H)-C(H)((CH_2)_4N(H)(C(O)-(C_{2-3} \text{ alkylene})-[O-CH_2CH_2]_n-N(R^5)C(O)-(C_{0-2} \text{ alkylene})-R^6))-C(O)-NH_2$.

66. The modified peptide of any one of claims 57-64, wherein R^4 is $-N(H)-C(H)((CH_2)_4N(H)(C(O)-CH_2CH_2-[O-CH_2CH_2]_n-N(R^5)C(O)-R^6))-C(O)-NH_2$.

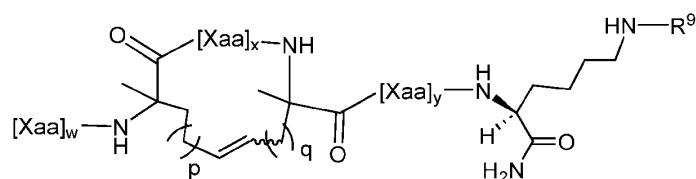
67. The modified peptide of any one of claims 57-64, wherein $-R^4-R^6$ is



68. The modified peptide of any one of claims 57-64, wherein $-R^4-R^6$ is



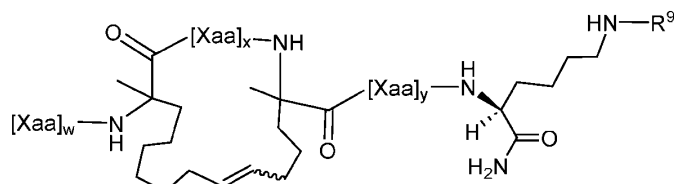
69. The modified peptide of any one of claims 57-62, wherein the modified peptide is of Formula IIb:



IIb

or a pharmaceutically acceptable salt thereof, wherein R^9 is $-\text{C}(\text{O})-(\text{CH}_2\text{CH}_2)-[\text{O}-\text{CH}_2\text{CH}_2]_n-\text{N}(\text{R}^5)\text{C}(\text{O})-\text{R}^6$.

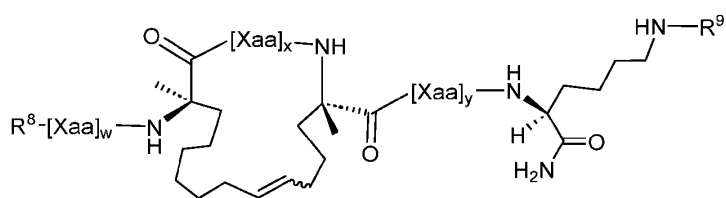
70. The modified peptide of claim 69, wherein the modified peptide is of Formula IIc:



IIc

or a pharmaceutically acceptable salt thereof, wherein R^9 is $-\text{C}(\text{O})-(\text{CH}_2\text{CH}_2)-[\text{O}-\text{CH}_2\text{CH}_2]_n-\text{N}(\text{R}^5)\text{C}(\text{O})-\text{R}^6$.

71. The modified peptide of any one of claims 57-70, wherein the modified peptide is of Formula V:

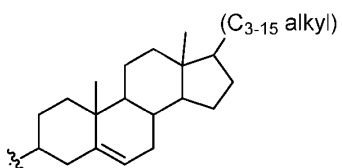


V

wherein

R^9 is $-\text{C}(\text{O})-(\text{C}_{2-6} \text{ alkylene})-[\text{O}-\text{CH}_2\text{CH}_2]_n-\text{N}(\text{R}^5)\text{C}(\text{O})-(\text{C}_{0-6} \text{ alkylene})-\text{R}^6$;

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

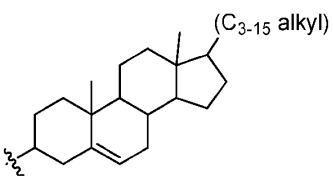


 R^6 is , which is optionally substituted with one or more halo, C_{1-3} alkyl, hydroxyl, or C_{1-3} alkoxy;

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

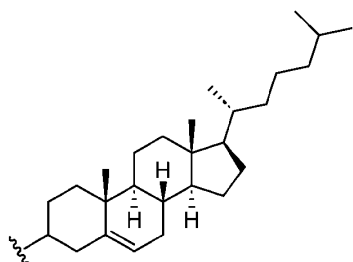
 n is 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14, 15, or 16.

72. The modified peptide of any one of claims 57-71, wherein R^6 is

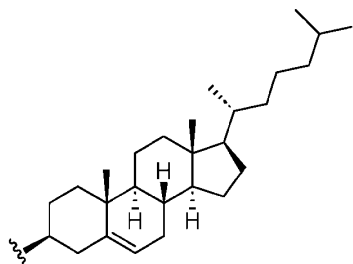


, substituted with one or more halo, C_{1-3} alkyl, hydroxyl, or C_{1-3} alkoxy.

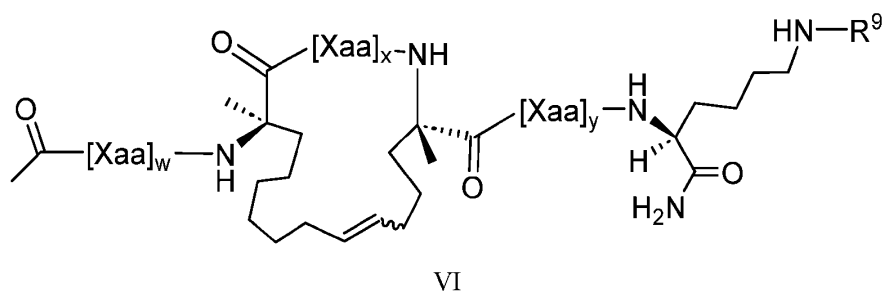
73. The modified peptide of any one of claims 57-71, wherein R^6 is



74. The modified peptide of any one of claims 57-71, wherein R^6 is

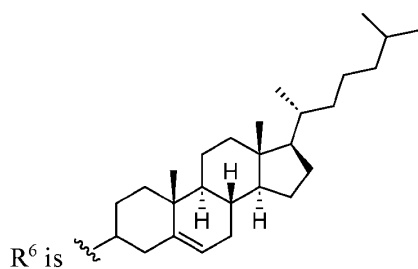


75. The modified peptide of any one of claims 71-74, wherein R^8 is $-C(O)CH_3$.
76. The modified peptide of any one of claims 60-75, wherein R^5 is hydrogen.
77. The modified peptide of any one of claims 57-76, wherein n is 4.
78. The modified peptide of any one of claims 57-76, wherein n is 8.
79. The modified peptide of any one of claims 57-76, wherein n is 12.
80. The modified peptide of any one of claims 71-79, wherein the modified peptide is of 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



81. A modified peptide selected from Table 6, or a pharmaceutically acceptable salt thereof.
82. The modified peptide of any one of the preceding claims, wherein the peptide is structurally stabilized.

83. The modified peptide of any one of the preceding claims, wherein the two amino acid side chains are linked together to form a staple that spans one to two turns of an alpha helix of the modified peptide.
84. A pharmaceutical composition comprising the modified peptide of any one of claims 1-83, or pharmaceutically acceptable salt thereof, and a pharmaceutically acceptable carrier.
85. A method of treating or preventing an influenza virus infection in a subject in need thereof, the method comprising administering to the subject a therapeutically effective amount of the modified peptide of any one of claims 1-83, or a pharmaceutically acceptable salt thereof, or the pharmaceutical composition of claim 84.
86. A method of inhibiting influenza virus particle fusion to a host cell in a subject in need thereof, the method comprising administering to the subject a therapeutically effective amount of the modified peptide of any one of claims 1-83, or a pharmaceutically acceptable salt thereof, or the pharmaceutical composition of claim 84.
87. A method of inhibiting a conformational change in an influenza hemagglutinin (HA) protein in a subject in need thereof, the method comprising administering to the subject a therapeutically effective amount of the modified peptide of any one of claims 1-83, or a pharmaceutically acceptable salt thereof, or the pharmaceutical composition of claim 84.
88. The method of any one of claims 85-87, wherein the influenza is an influenza A virus.
89. The method of claim 88, wherein the influenza A virus is subtype H10N4, subtype H10N5, subtype H10N7, subtype H10N8, subtype H10N9, subtype H11N1, subtype H11N13, subtype H11N2, subtype H11N4, subtype H11N6, subtype H11N8, subtype H11N9, subtype H12N1, subtype H12N4, subtype H12N5, subtype H12N8, subtype H13N2, subtype H13N3, subtype H13N6, subtype H13N7, subtype H14N5, subtype H14N6, subtype H15N8, subtype H15N9, subtype H16N3, subtype H1N1, subtype H1N2, subtype H1N3, subtype H1N6, subtype

H1N9, subtype H2N1, subtype H2N2, subtype H2N3, subtype H2N5, subtype H2N7, subtype H2N8, subtype H2N9, subtype H3N1, subtype H3N2, subtype H3N3, subtype H3N4, subtype H3N5, subtype H3N6, subtype H3N8, subtype H3N9, subtype H4N1, subtype H4N2, subtype H4N3, subtype H4N4, subtype H4N5, subtype H4N6, subtype H4N8, subtype H4N9, subtype H5N1, subtype H5N2, subtype H5N3, subtype H5N4, subtype H5N6, subtype H5N7, subtype H5N8, subtype H5N9, subtype H6N1, subtype H6N2, subtype H6N3, subtype H6N4, subtype H6N5, subtype H6N6, subtype H6N7, subtype H6N8, subtype H6N9, subtype H7N1, subtype H7N2, subtype H7N3, subtype H7N4, subtype H7N5, subtype H7N7, subtype H7N8, subtype H7N9, subtype H8N4, subtype H8N5, subtype H9N1, subtype H9N2, subtype H9N3, subtype H9N5, subtype H9N6, subtype H9N7, subtype H9N8, or subtype H9N9, or a combination thereof.

90. The method of any one of claims 85-87, wherein the influenza is an influenza B virus.

91. The method of any one of claims 85, 88, or 89, wherein the modified peptide or a pharmaceutically acceptable salt thereof treats or prevents influenza virus infection caused by more than one (e.g., two, three, four, five, six, seven, eight, nine, ten, or more than ten) influenza A virus subtype.

92. The method of claim 85 or 91, wherein the modified peptide or a pharmaceutically acceptable salt thereof treats or prevents influenza virus infection caused by both influenza A and B viruses.

93. The method of any one of claims 86, 88, or 89, wherein the modified peptide or a pharmaceutically acceptable salt thereof inhibits fusion to a host cell of more than one (e.g., two, three, four, five, six, seven, eight, nine, ten, or more than ten) influenza A virus subtype.

94. The method of claim 86 or 93, wherein the modified peptide or a pharmaceutically acceptable salt thereof inhibits fusion to a host cell of both influenza A and B viruses.

95. The method of any one of claims 87, 88, or 89, wherein the modified peptide or a pharmaceutically acceptable salt thereof inhibits a conformational change in an influenza hemagglutinin (HA) protein of more than one (e.g., two, three, four, five, six, seven, eight, nine, ten, or more than ten) influenza A virus subtype.
96. The method of claim 87 or 95, wherein the modified peptide or a pharmaceutically acceptable salt thereof inhibits a conformational change in an influenza hemagglutinin (HA) protein of both influenza A and B viruses.
97. The method of any one of claims 91, 93, or 95, wherein the influenza A virus subtypes comprise H1N1 and H3N2.