PEPTIDOMIMETIC MACROCYCLES AND FORMULATIONS THEREOF

CROSS REFERENCE

[0001] This application calims priority to U.S. Provisional Application No. 62/054,842, filed September 24, 2014, which is incorporated herein by reference in its entirety.

BACKGROUND OF THE DISCLOSURE

[0002] The human transcription factor protein p53 induces cell cycle arrest and apoptosis in response to DNA damage and cellular stress, and thereby plays a critical role in protecting cells from malignant transformation. The E3 ubiquitin ligase MDM2 (also known as HDM2 or human double minute 2) negatively regulates p53 function through a direct binding interaction that neutralizes the p53 transactivation activity, leads to export from the nucleus of p53 protein, and targets p53 for degradation via the ubiquitylation-proteasomal pathway. Loss of p53 activity, either by deletion, mutation, or MDM2 overexpression, is the most common defect in human cancers. Tumors that express wild type p53 are vulnerable to pharmacologic agents that stabilize or increase the concentration of active p53. In this context, inhibition of the activities of MDM2 has emerged as a validated approach to restore p53 activity and resensitize cancer cells to apoptosis *in vitro* and *in vivo.* MDMX(also known as MDM4, HDM4 or human double minute 4) has more recently been identified as a similar negative regulator of p53, and studies have revealed significant structural homology between the p53 binding interfaces of MDM2 and MDMX. MDMX has also been observed to be overexpressed in human tumors. The p53-MDM2 and p53-MDMX protein-protein interactions are mediated by the same 15-residue alpha-helical transactivation domain of p53, which inserts into hydrophobic clefts on the surface of MDM2 and MDMX. Three residues within this domain of wild type p53 (F19, W23, and L26) are essential for binding to MDM2 and MDMX.

[0003] There remains a considerable need for compounds capable of binding to and modulating the activity of p53, MDM2 and/or MDMX. Provided herein are aqueous pharmaceutical formulations comprising p53-based peptidomimetic macrocycles that modulate an activity of p53. Also provided herein are aqueous pharmaceutical formulations comprising p53-based peptidomimetic macrocycles that inhibit the interactions between p53, MDM2 and/or MDMX proteins. Further, provided herein are aqueous pharmaceutical formulations comprising p53-based peptidomimetic macrocycles that can be used for treating diseases including but not limited to cancer and other hyperproliferative diseases.

SUMMARY OF THE DISCLOSURE

[0004] In one aspect, the disclosure provides an aqueous pharmaceutical formulation comprising a peptidomimetic macrocycle that binds to MDM2 and/or MDMX proteins or a pharmaceutically acceptable salt thereof, a buffering agent, a tonicity agent, and a stabilizing agent wherein the amount of the peptidomimetic macrocycle in the aqueous pharmaceutical formulation is equal to or greater than15 mg/mL and wherein the

aqueous pharmaceutical formulation comprises less than 2 % w/v of any micelle forming agent. The micelle forming agent can be solutol-HS-15. In some examples, the peptidomimetic macrocycle forms a micelle in absence of a surfactant.

[0005] In another aspect, the disclosure provides an aqueous pharmaceutical formulation comprising (i) a peptidomimetic macrocycle or a pharmaceutically acceptable salt thereof, wherein the amount of the peptidomimetic macrocycle in the aqueous pharmaceutical formulation is equal to or greater than15 mg/mL; (ii) a buffering agent; (iii) a stabilizing agent; and (iv) a tonicity agent, wherein the molar ratio of the peptidomimetic macrocycle to the buffering agent is in the range of 0.01-2.5.

[0006] In another aspect, the disclosure provides an aqueous pharmaceutical formulation comprising a peptidomimetic macrocycle that binds to a target protein with a K_D value of $1x10^{-7}$ M or less, or a pharmaceutically acceptable salt thereof, a buffering agent, a tonicity agent, and a stabilizing agent wherein the amount of the peptidomimetic macrocycle in the aqueous pharmaceutical formulation is equal to or greater than15 mg/mL and wherein the aqueous pharmaceutical formulation comprises less than 2 % w/v of any micelle forming agent, wherein the peptidomimetic macrocycle or pharmaceutically acceptable salt thereof has: (a) a length value of from 10 to 24 amino acids, (b) a von Heijne value of from 2 to 10, (c) a net charge of from -4 to +2, (d) a per cent alanine content of from 15% to 50%, (e) or any combination of (a)-(d).

[0007] In some embodiments, the peptidomimetic macrocycle or pharmaceutically acceptable salt thereof is not precipitated in the formulation. In some embodiments, an aqueous solubility of the peptidomimetic macrocycle is determined by evaluating the turbidity of a solution comprising the peptidomimetic macrocycle. In some embodiments, the peptidomimetic macrocycle or pharmaceutically acceptable salt thereof has an amphipathicity that falls in a range that is optimal for cell permeability.

[0008] In some embodiments, the peptidomimetic macrocycle or pharmaceutically acceptable salt thereof has a length value of from 14 to 20 amino acids. In some embodiments, the peptidomimetic macrocycle or pharmaceutically acceptable salt thereof has a von Heijne value of from 2 to 9. In some embodiments, the peptidomimetic macrocycle or pharmaceutically acceptable salt thereof has a von Heijne value of from 3 to 8. In some embodiments, the peptidomimetic macrocycle or pharmaceutically acceptable salt thereof has a von Heijne value of from 4 to 7. In some embodiments, the peptidomimetic macrocycle or pharmaceutically acceptable salt thereof has a net charge of from -2 to 0. In some embodiments, the peptidomimetic macrocycle or pharmaceutically acceptable salt thereof has a per cent alanine content of from 15% to 40%. In some embodiments, the peptidomimetic macrocycle or pharmaceutically acceptable salt thereof has a per cent alanine content of from 20% to 40%. In some embodiments, the peptidomimetic macrocycle or pharmaceutically acceptable salt thereof has a per cent alanine content of from 25% to 40%. In some embodiments, the peptidomimetic macrocycle or pharmaceutically acceptable salt thereof has a length value of from 14 to 20 amino acids, a von Heijne value of from 4 to 7, a net charge of from -2 to 0, and a per cent alanine content of from 25%

to 40%. In some embodiments, the peptidomimetic macrocycle or pharmaceutically acceptable salt thereof is soluble, does not have off-target effects, or a combination thereof.

[0009] In some embodiments, the peptidomimetic macrocycle or pharmaceutically acceptable salt thereof comprises a first C-terminal amino acid that is hydrophobic. In some embodiments, the peptidomimetic macrocycle or pharmaceutically acceptable salt thereof comprises a second C-terminal amino acid that is hydrophobic. In some embodiments, the peptidomimetic macrocycle or pharmaceutically acceptable salt thereof comprises a third C-terminal amino acid that is hydrophobic. In some embodiments, the peptidomimetic macrocycle or pharmaceutically acceptable salt thereof comprises a fourth C-terminal amino acid that is hydrophobic. In some embodiments, the peptidomimetic macrocycle or pharmaceutically acceptable salt thereof comprises a fifth C-terminal amino acid that is hydrophobic. In some embodiments, the peptidomimetic macrocycle or pharmaceutically acceptable salt thereof comprises a sixth C-terminal amino acid that is hydrophobic.

[0010] In some embodiments, the first amino acid connected to the crosslinker is N-terminal to the second amino acid connected to the crosslinker, and wherein the peptidomimetic macrocycle or pharmaceutically acceptable salt thereof comprises 1, 2, 3, 4, 5, 6, 7, or 8 amino acids that are C-terminal to the second amino acid connected to the crosslinker.

[0011] In some embodiments, the first amino acid connected to the crosslinker is N-terminal to the second amino acid connected to the crosslinker, and wherein the peptidomimetic macrocycle or pharmaceutically acceptable salt thereof comprises 1, 2, 3, 4, 5, or 6 hydrophobic amino acids that are C-terminal to the second amino acid connected to the crosslinker.

[0012] In some embodiments, the first amino acid connected to the crosslinker is N-terminal to the second amino acid connected to the crosslinker, and wherein the peptidomimetic macrocycle or pharmaceutically acceptable salt thereof comprises 1, 2, or 3 glutamines that are C-terminal to the second amino acid connected to the crosslinker.

[0013] In some embodiments, the amino acid that is hydrophobic is a small hydrophobic amino acid. In some embodiments, the amino acid that is hydrophobic is an alanine, a D-alanine, or an Aib.

[0014] In some embodiments, the peptidomimetic macrocycle or pharmaceutically acceptable salt thereof is a helical polypeptide. In some embodiments, the peptidomimetic macrocycle or pharmaceutically acceptable salt thereof comprises an α-helix. In some embodiments, the peptidomimetic macrocycle or pharmaceutically acceptable salt thereof comprises an amphipathic α-helix.

[0015] In some embodiments, the first amino acid connected to the crosslinker or the second amino acid connected to the crosslinker is an α,α-disubstituted amino acid. In some embodiments, the first amino acid connected to the crosslinker and the second amino acid connected to the crosslinker are α,α-disubstituted amino acids. In some embodiments, the first amino acid connected to the crosslinker and the second amino acid connected to the crosslinker are separated by two amino acids. In some embodiments, the first amino acid connected to the crosslinker and the second amino acid connected to the crosslinker are separated by three amino

acids. In some embodiments, the first amino acid connected to the crosslinker and the second amino acid connected to the crosslinker are separated by six amino acids. In some embodiments, the crosslinker spans 1 turn of an α-helix of the peptidomimetic macrocycle. In some embodiments, the crosslinker spans 2 turns of an α-helix of the peptidomimetic macrocycle. In some embodiments, the length of the crosslinker is from about 5 Å to about 9 Å per turn of an α-helix of the peptidomimetic macrocycle. In some embodiments, the peptidomimetic macrocycle or pharmaceutically acceptable salt thereof provides a therapeutic effect. In some embodiments, an ability of the peptidomimetic macrocycle or pharmaceutically acceptable salt thereof to penetrate cell membranes by an energy-dependent process is improved relative to a corresponding uncrosslinked peptidomimetic macrocycle. In some embodiments, the ability of the peptidomimetic macrocycle or pharmaceutically acceptable salt thereof to penetrate cell membranes by an energy-independent process is improved relative to a corresponding uncrosslinked peptidomimetic macrocycle. In some embodiments, the energy-dependent process is primary active transport, secondary transport, endocytosis, or a combination thereof. In some embodiments, the energy-dependent process is active transport. In some embodiments, the energy-independent process is passive diffusion, facilitated diffusion, filtration, or a combination thereof. In some embodiments, the energy-independent process is passive transport.

[0016] In some embodiments, the peptidomimetic macrocycle or pharmaceutically acceptable salt thereof binds to HDM2 with a K_D value of $1x10^{-7}$ M or less. In some embodiments, the peptidomimetic macrocycle or pharmaceutically acceptable salt thereof binds to HDM2 or HDM4 with a K_D value of $1x10^{-7}$ M or less. In some embodiments, the peptidomimetic macrocycle or pharmaceutically acceptable salt thereof binds to HDM4 with a K_D value of $1x10^{-7}$ M or less. In some embodiments, the peptidomimetic macrocycle or pharmaceutically acceptable salt thereof binds to a PB1 peptide binding site of a PA protein with a K_D value of $1x10^{-7}$ M or less. In some embodiments, the peptidomimetic macrocycle or pharmaceutically acceptable salt thereof binds to a PB2 peptide binding site of a PB1 protein with a K_D value of $1x10^{-7}$ M or less. In some embodiments, the peptidomimetic macrocycle or pharmaceutically acceptable salt thereof binds to viral polymerase, for example, a RNA-dependent RNA polymerase with a K_D value of $1x10^{-7}$ M or less. In some embodiments, the peptidomimetic macrocycle or pharmaceutically acceptable salt thereof inhibits an influenza RNA-dependent RNA polymerase. In some embodiments, the virus is influenza virus. In some embodiments, the peptidomimetic macrocycle is capable of competing with the binding of a peptide of the sequence MDVNPTLLFLKVPAQ or MERIKELRNLM to the viral RNA-dependent RNA polymerase. In some embodiments, the peptidomimetic macrocycle or pharmaceutically acceptable salt thereof binds to MCL-1, BCL-X_L, BCL-2, or a combination thereof with a K_D value of $1x10^{-7}$ M or less. In some embodiments, the peptidomimetic macrocycle or pharmaceutically acceptable salt thereof binds to MCL-1 with a K_D value of $1x10^{-7}$ M or less. In some embodiments, the peptidomimetic macrocycle or pharmaceutically acceptable salt thereof binds to BCL-X_L with a K_D value of $1x10^{-7}$ M or less. In some embodiments, the peptidomimetic macrocycle or pharmaceutically acceptable salt thereof binds to BCL-2 with a K_D value of $1x10^{-7}$ M or less.

[0017] In some embodiments, the peptidomimetic macrocycle or pharmaceutically acceptable salt thereof has an IC_{50} value of 100 nM or less to a target protein. In some embodiments, the peptidomimetic macrocycle or pharmaceutically acceptable salt thereof has an EC_{50} value of 100 μM or less.

[0018] In some embodiments, the peptidomimetic macrocycle or pharmaceutically acceptable salt thereof has an IC_{50} value of 10 nM or less to a target protein. In some embodiments, the peptidomimetic macrocycle or pharmaceutically acceptable salt thereof has an EC_{50} value of 10 μM or less. In some embodiments, the peptidomimetic macrocycle or pharmaceutically acceptable salt thereof has an IC_{50} value of 1 nM or less to a target protein. In some embodiments, the peptidomimetic macrocycle or pharmaceutically acceptable salt thereof has an EC_{50} value of 1 μM or less.

[0019] In some embodiments, the peptidomimetic macrocycle or pharmaceutically acceptable salt thereof has a penetration efficiency value of 100 or less. In some embodiments, the peptidomimetic macrocycle or pharmaceutically acceptable salt thereof has a penetration efficiency value of 10 or less. In some embodiments, the peptidomimetic macrocycle or pharmaceutically acceptable salt thereof has a penetration efficiency value of 1 or less.

[0020] In some embodiments, the peptidomimetic macrocycle penetrates cell membranes by an energy-dependent process and binds to an intracellular target with a K_D value of $1x10^{-7}$ M or less. In some embodiments, the energy-dependent process comprises primary active transport, secondary transport, or endocytosis. In some embodiments, the energy-dependent process comprises active transport. In some embodiments, the peptidomimetic macrocycle penetrates cell membranes by an energy-independent process and binds to an intracellular target with a K_D value of $1x10^{-7}$ M or less. In some embodiments, the energy-independent process comprises passive diffusion, facilitated diffusion, or filtration. In some embodiments, the energy-independent process comprises passive transport.

[0021] In some embodiments, the amount of the buffering agent in the aqueous pharmaceutical formulations of the disclosure is 0.001-10% w/v, the stabilizing agent in the aqueous pharmaceutical formulations of the disclosure is 0.001-10% w/v and , the amount of the tonicity agent in the aqueous pharmaceutical formulations of the disclosure 1.0-10% w/v.

[0022] The pharmaceutically acceptable salt of the peptidomimetic macrocycle can be a sodium salt. In some examples, the pharmaceutically acceptable salt of the peptidomimetic macrocycle can be a potassium, lithium, calcium, zinc or magnesium salt.

[0023] Any suitable amount of the peptidomimetic macrocycle can be used in the aqueous pharmaceutical formulations of the disclosure. In some examples, the amount of the peptidomimetic macrocycle present in the aqueous pharmaceutical formulation can be from about 0.1-10% w/v. For example, the amount of the peptidomimetic macrocycle present in the aqueous pharmaceutical formulation can be about 1% w/v, 1.5% w/v, or 2% w/v. In some examples, the concentration of the peptidomimetic macrocycle present in the aqueous pharmaceutical formulation is about 15-100 mg/mL. In some examples, the concentration of the peptidomimetic

macrocycle present in the aqueous pharmaceutical formulation is about 15-50 mg/mL. In some examples, the concentration of the peptidomimetic macrocycle present in the aqueous pharmaceutical formulation is about 15, 20, 25, or 50 mg/mL.

[0024] Any suitable buffering agent can be used in the aqueous pharmaceutical formulations described herein. In some examples, the buffering agent is selected from a group consisting of ammonia solution, calcium carbonate, tribasic calcium phosphate, citric acid dihydrate, citric acid monohydrate, dibasic sodium phosphate, diethanolamine, malic acid, monobasic sodium phosphate, monoethanolamine, monosodium glutamate, phosphoric acid, phosphate-citrate buffer (dibasic sodium phosphate and citric acid), potassium citrate, sodium acetate, sodium bicarbonate, sodium borate, sodium citrate dehydrate, sodium hydroxide, sodium lactate, sodium carbonate, and triethanolamine (tris(hydroxymethyl)aminomethane). In some examples, the buffering agent is a phosphate buffer. In some examples, the buffering agent is selected from a group consisting of phosphoric acid, dibasic sodium phosphate, monobasic sodium phosphate or a mixture thereof. In some examples, the buffering agent is 20 mM phosphate buffer

[0025] The amount of the buffering agent in the aqueous pharmaceutical formulations of the disclosure can be from about 0.001-10% w/v. In some examples, the amount of the buffering agent in the aqueous pharmaceutical formulations of the disclosure is from about 0.01-10% w/v. In some examples, the amount of the buffering agent in the aqueous pharmaceutical formulations of the disclosure is from about 0.01-5% w/v. In some examples, the amount of the buffering agent in the aqueous pharmaceutical formulations of the disclosure is from about 0.01-1% w/v. In some examples, the amount of the buffering agent present in the aqueous pharmaceutical formulations of the disclosure is about 0.2% w/v.

[0026] The stabilizing agent in the aqueous pharmaceutical formulations of the disclosure can be a non-ionic stabilizing agent. In some examples, the stabilizing agent is a fatty acid ester. In some examples, the stabilizing agent can be a surfactant. In some for examples, the stabilizing agent is a non-ionic surfactant. In some for examples, the stabilizing agent is an anti-oxidant. In some examples the stabilizing agent can be selected from a group consisting of polyoxyethylene glycol alkyl ethers, polyoxypropylene glycol alkyl ethers, glucoside alkyl ethers, polyoxyethylene glycol octylphenol ethers, polyoxyethylene glycol alkylphenol ethers, glycerol alkyl esters, polyoxyethylene glycol sorbitan alkyl esters, sorbitan alkyl esters, cocamide MEA, cocamide DEA, dodecyldimethylamine oxide, block copolymers of polyethylene glycol and polypropylene glycol, and polyethoxylated tallow amine. In some examples, the stabilizing agent can be a polyoxyethylene sorbitan fatty acid ester. In some examples, stabilizing agent can be polysorbate 20, polysorbate 21, polysorbate 40, polysorbate 60, polysorbate 61, polysorbate 65, polysorbate 80, polysorbate 81, polysorbate 85 or polysorbate 120. In some examples, the stabilizing agent can be polysorbate 20.

[0027] The amount of the stabilizing agent present in the aqueous pharmaceutical formulation is from about 0.001-10 % w/v, for example from about 0.01-.05% w/v. In some examples, the amount of the stabilizing agent present in the aqueous pharmaceutical formulations is about 0.03% w/v. In some examples, the aqueous

pharmaceutical formulations comprise 250-350 ppm polysorbate 20.The aqueous pharmaceutical formulation of the disclosure can be a solution. In some examples, the aqueous pharmaceutical formulations can be sterile. In some examples, the aqueous pharmaceutical formulations can be colorless. In some examples, the aqueous pharmaceutical formulations can be a frozen solution. In some examples, the aqueous pharmaceutical formulation can be refrigerated solution.

[0028] In some examples, the aqueous pharmaceutical formulations can be particulate-free. In some examples, the aqueous pharmaceutical formulations comprise less than about 6,000 particles of size ≥ 10 μm in about 5 mL of the aqueous formulation. In some examples, the aqueous pharmaceutical formulations comprise less than about 600 particles of size ≥ 25 μm in about 5 mL of the aqueous formulation.

[0029] In some examples, the aqueous pharmaceutical formulations are dissolved into a diluent prior to administration into a subject. The diluent can be water for injection. In some examples, thee diluent can be solution of dextrose in water. The amount of the diluent can be from about 50-99% w/v. In some examples, the amount of the diluent can be about 90% w/v.

[0030] In some examples, the tonicity agent in the aqueous pharmaceutical formulations of the disclosure can be a non-ionic tonicity agent. In some examples, the tonicity agent can be a sugar or a sugar alcohol. In some examples, the tonicity agent can be a mono- or a disaccharide. In some cases, the tonicity agent can be selected from a groups consisting of glucose, fructose, galactose, sucrose, lactose, maltose, trehalose, and mixtures thereof. In some examples, the tonicity agent can be mannitol, glycerin, or a combination thereof. In some examples the tonicity agent can be D-trehalose.

[0031] The amount of the tonicity agent present in the aqueous pharmaceutical formulations can be from about 1-15% w/v. In some examples, the amount of the tonicity agent present in the aqueous pharmaceutical formulations can be about 8% w/v. The concentration of the tonicity agent can be from about 200-300 mM. In some examples, the concentration of the tonicity agent is 240 mM.

[0032] The pH of the aqueous pharmaceutical formulations of the disclosure can be from about 4.0-9.0. In some examples the pH of the aqueous pharmaceutical formulations of the disclosure is from about 4.5-8.5. In some examples the pH of the aqueous pharmaceutical formulations of the disclosure is from about 5.0-8.0. In some examples the pH of the aqueous pharmaceutical formulations of the disclosure is from about 5.5-7.5. In some examples the pH of the aqueous pharmaceutical formulations of the disclosure is from about 7.0-7.5.

[0033] The aqueous pharmaceutical formulations of the disclosure can be stable for at least two years at a temperature of about -20 °C-25 °C. In some examples, the aqueous pharmaceutical formulations can be stable for at least one year at a temperature of about -20 °C-25 °C. In some examples, the aqueous pharmaceutical formulations can be stable for at least 6 months at a temperature of about -20 °C-25 °C. In some examples, the aqueous pharmaceutical formulations can be stable for at least 3 months at a temperature of about -20 °C-25 °C. In some examples, the aqueous pharmaceutical formulations can be stable for at least 3 months at a temperature of about 45 °C. In some examples, the aqueous pharmaceutical formulations can be stable for at least 6 months at a

temperature of about 45 °C. In some examples, the aqueous pharmaceutical formulations can be stable for at least 3 weeks at a temperature of about 75 °C. In some examples, the aqueous pharmaceutical formulations can be stable for at least 1.5 weeks at a temperature of about 75 °C.

[0034] In some examples, the aqueous pharmaceutical formulations upon storage for 24 months at from about 2 °C- 8 °C can comprise at least 95% of the initial amount of the peptidomimetic macrocycle. In some examples, the aqueous pharmaceutical formulations upon storage for 12 months at from about 2 °C- 8 °C can comprise at least 95% of the initial amount of the peptidomimetic macrocycle. In some examples, the aqueous pharmaceutical formulations upon storage for 6 months at from about 2 °C- 8 °C can comprise at least 95% of the initial amount of the peptidomimetic macrocycle. In some cases, the aqueous pharmaceutical formulations upon storage for 3 months at from about 2 °C- 8 °C can comprise at least 95% of the initial amount of the peptidomimetic macrocycle.

[0035] The osmolality of the aqueous pharmaceutical formulations of the disclosure can be from about 100-600 milliosmoles per kilogram, for example from about 220-400 milliosmoles per kilogram.

[0036] The endotoxin level of the aqueous pharmaceutical formulations of the disclosure can be at most 2.0, 4.0, 6.0, 8.0 or 10 EU/mL^2. In some examples, the endotoxin level of the aqueous pharmaceutical formulations can be at most 4.5 EU/mL^2.

[0037] The aqueous pharmaceutical formulations of the disclosure can be contained in a container. The container can be a single use container or a multi-use container. In some examples, the container can be a glass vial. In some examples, the container is a pre-filled syringe to be used alone or in an injection device. In some examples, the container is a cartridge for a pen injection system, or a glass ampoule. In some examples, the container is a 20 mL, 10 mL, or a 5 mL glass serum vial. The glass vial can comprise borosilicate glass or polycarbonate. The container can comprise stopper and/or cap. The stopper can be a rubber stopper. The container can comprise a seal for example an aluminum seal.

[0038] The aqueous pharmaceutical formulations of the disclosure can be prepared by adding the peptidomimetic macrocycle or a pharmaceutically acceptable salt thereof to water or an aqueous solution, wherein the peptidomimetic macrocycle is capable of binding to the MDM2 and/or MDMX proteins. The pharmaceutically acceptable salt can be a sodium salt, potassium salt or calcium salt. In some examples, the aqueous pharmaceutical formulations can be prepared by dissolving a sodium salt of the peptidomimetic macrocycle in water. The method can further comprise adding a buffering agent and a stabilizing agent.

[0039] The aqueous pharmaceutical formulations of the disclosure can be suitable for administration to a subject without reconstitution or dilution. In some examples, the aqueous pharmaceutical formulations can require reconstitution prior to administration to a subject. Reconstitution can involve dilution with an aqueous solution, for example with a solution of dextrose in water.

[0040] In some embodiments, the micelle forming agent in solutol-HS-15. In some embodiments, the peptidomimetic macrocycle forms a micelle in absence of a surfactant. In some embodiments, the the aqueous pharmaceutical formulation does not form micelle.

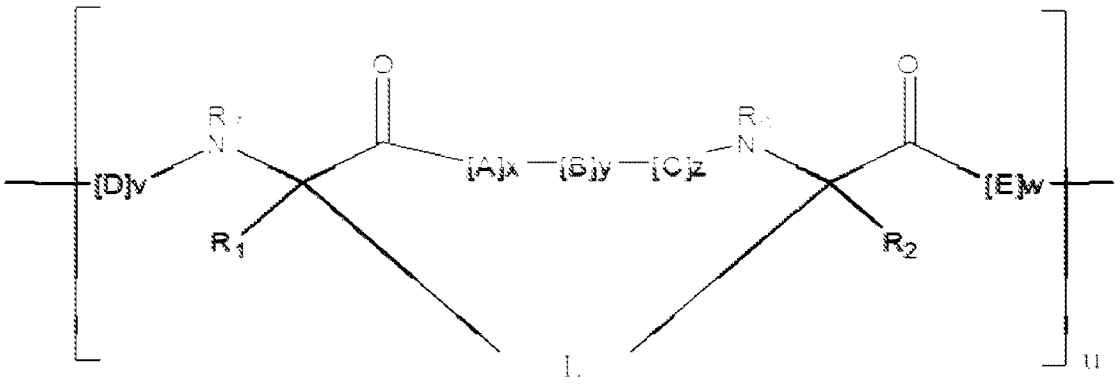
[0041] The aqueous pharmaceutical formulations of the disclosure can further comprise a preservative. The preservative can be selected from a group consisting of benzalkonium chloride, EDTA and combination thereof. In some examples, the preservative can be selected from a group consisting of phenol, meta-cresol and combination thereof.

[0042] The aqueous pharmaceutical formulations of the disclosure can further comprise a co-solvent. The co-solvent can be selected from a group consisting of dimethyl sulfoxide (DMSO), N-methylpyrrolidone (NMP), dimethylacetamide (DMA) and combinations thereof.

[0043] The molecular weight of the peptidomimetic macrocycle can be in the range of 1800-2000 D. In some examples, the peptidomimetic macrocycle has an observed mass (m/e) in the range of 900-1000 D.

[0044] In another aspect the disclosure provides an aqueous pharmaceutical formulation comprising a peptidomimetic macrocycle that binds to MDM2 and/or MDMX proteins or a pharmaceutically acceptable salt thereof, phosphate buffering agent, D-trehalose, and polysorbate 20, wherein the peptidomimetic macrocycle comprises an amino acid sequence which is at least about 60%, 65%, 70%, 75%, 80%, 85%, 90%, 95% identical to an amino acid sequence in any of **Table 1**, **Table 1a**, **Table 1b**, and **Table 1c**, In some examples, the amount of the peptidomimetic macrocycle in the aqueous pharmaceutical formulation can be equal to or greater than15 mg/mL. In some examples, the amount of D-trehalose in the aqueous pharmaceutical formulations can be about 8% w/v. The amount of polysorbate 20 in the aqueous pharmaceutical formulations can be about 0.03% w/v. In some examples, the aqueous pharmaceutical formulations comprise less than 2 % w/v of any micelle forming agent.

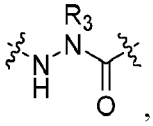
[0045] The peptidomimetic macrocycle in the aqueous pharmaceutical formulations can comprise an amino acid sequence which is at least about 60%, 65%, 70%, 75%, 80%, 85%, 90%, 95% identical to an amino acid sequence in any of **Table 1**, **Table 1a**, **Table 1b**, and **Table 1c**, and wherein the peptidomimetic macrocycle has the formula:



Formula (I)

wherein:

each A, C, and D is independently an amino acid;

each B is independently an amino acid, , [–NH–L_3–CO–], [–NH–L_3–SO_2–], or [–NH–L_3–];

each E is independently an amino acid selected from the group consisting of Ala (alanine), D–Ala (D–alanine), Aib (α–aminoisobutyric acid), Sar (N–methyl glycine), and Ser (serine);

each R_1 and R_2 is independently –H, alkyl, alkenyl, alkynyl, arylalkyl, cycloalkyl, cycloalkylalkyl, heteroalkyl, or heterocycloalkyl, unsubstituted or substituted with halo; or forms a macrocycle–forming linker L' connected to the alpha position of one of said D or E amino acids;

each R_3 independently is hydrogen, alkyl, alkenyl, alkynyl, arylalkyl, heteroalkyl, cycloalkyl, heterocycloalkyl, cycloalkylalkyl, cycloaryl, or heterocycloaryl, optionally substituted with R_5;

each L and L' is independently a macrocycle–forming linker;

each L_3 is independently alkylene, alkenylene, alkynylene, heteroalkylene, cycloalkylene, heterocycloalkylene, cycloarylene, heterocycloarylene, or $[-R_4-K-R_4-]_n$, each being optionally substituted with R_5;

each R_4 is independently alkylene, alkenylene, alkynylene, heteroalkylene, cycloalkylene, heterocycloalkylene, arylene, or heteroarylene;

each K is independently O, S, SO, SO_2, CO, CO_2, or $CONR_3$;

each R_5 is independently halogen, alkyl, $–OR_6$, $–N(R_6)_2$, $–SR_6$, $–SOR_6$, $–SO_2R_6$, $–CO_2R_6$, a fluorescent moiety, a radioisotope or a therapeutic agent;

each R_6 is independently –H, alkyl, alkenyl, alkynyl, arylalkyl, cycloalkylalkyl, heterocycloalkyl, a fluorescent moiety, a radioisotope or a therapeutic agent;

each R_7 is independently –H, alkyl, alkenyl, alkynyl, arylalkyl, cycloalkyl, heteroalkyl, cycloalkylalkyl, heterocycloalkyl, cycloaryl, or heterocycloaryl, optionally substituted with R_5, or part of a cyclic structure with a D residue;

each R_8 is independently –H, alkyl, alkenyl, alkynyl, arylalkyl, cycloalkyl, heteroalkyl, cycloalkylalkyl, heterocycloalkyl, cycloaryl, or heterocycloaryl, optionally substituted with R_5, or part of a cyclic structure with an E residue;

each v is independently an integer from 1–1000;

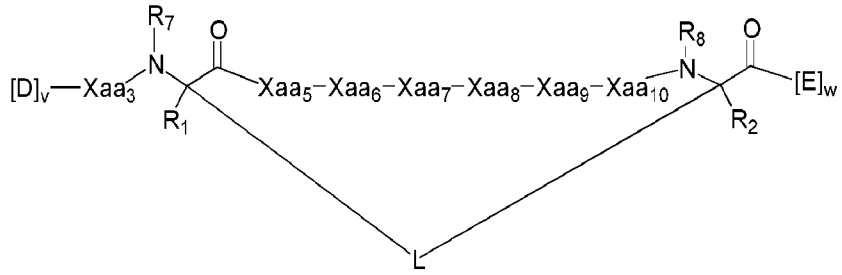
each w is independently an integer from 3–1000;

u is an integer from 1–10;

each x, y and z is independently an integer from 0–10; and

each n is independently an integer from 1–5.

[0046] In some embodiments, the peptidomimetic macrocycle has formula:



wherein:

each of Xaa_3, Xaa_5, Xaa_6, Xaa_7, Xaa_8, Xaa_9, and Xaa_{10} is individually an amino acid, wherein at least three of Xaa_3, Xaa_5, Xaa_6, Xaa_7, Xaa_8, Xaa_9, and Xaa_{10} are the same amino acid as the amino acid at the corresponding position of the sequence Phe_3-X_4-His_5-Tyr_6-Trp_7-Ala_8-Gln_9-Leu_{10}-X_{11}-Ser_{12} or Phe_3-X_4-Glu_5-Tyr_6-Trp_7-Ala_8-Gln_9-Leu_{10}/Cba_{10}-X_{11}-Ala_{12}, where each X is an amino acid;

each D and E is independently an amino acid;

each R_1 and R_2 are independently –H, alkyl, alkenyl, alkynyl, arylalkyl, cycloalkyl, cycloalkylalkyl, heteroalkyl, or heterocycloalkyl, unsubstituted or substituted with halo–; or at least one of R_1 and R_2 forms a macrocycle-forming linker L' connected to the alpha position of one of said D or E amino acids;

each L or L' is independently a macrocycle-forming linker;

each R_5 is independently halogen, alkyl, $-OR_6$, $-N(R_6)_2$, $-SR_6$, $-SOR_6$, $-SO_2R_6$, $-CO_2R_6$, a fluorescent moiety, a radioisotope or a therapeutic agent;

each R_6 is independently –H, alkyl, alkenyl, alkynyl, arylalkyl, cycloalkylalkyl, heterocycloalkyl, a fluorescent moiety, a radioisotope or a therapeutic agent;

R_7 is –H, alkyl, alkenyl, alkynyl, arylalkyl, cycloalkyl, heteroalkyl, cycloalkylalkyl, heterocycloalkyl, cycloaryl, or heterocycloaryl, optionally substituted with R_5, or part of a cyclic structure with a D residue;

R_8 is –H, alkyl, alkenyl, alkynyl, arylalkyl, cycloalkyl, heteroalkyl, cycloalkylalkyl, heterocycloalkyl, cycloaryl, or heterocycloaryl, optionally substituted with R_5, or part of a cyclic structure with an E residue;

v is an integer from 1-1000; and

w is an integer from 0-1000.

[0047] In some examples, at least one of the macrocycle-forming linker in the Formulas provided herein has a formula $–L_1–L_2–$, wherein

L_1 and L_2 are independently alkylene, alkenylene, alkynylene, heteroalkylene, cycloalkylene, heterocycloalkylene, cycloarylene, heterocycloarylene, or $[-R_4-K-R_4-]_n$, each being optionally substituted with R_5;

each R_4 is independently alkylene, alkenylene, alkynylene, heteroalkylene, cycloalkylene, heterocycloalkylene, arylene, or heteroarylene;

each K is independently O, S, SO, SO_2, CO, CO_2, or $CONR_3$; and

each R_3 independently is hydrogen, alkyl, alkenyl, alkynyl, arylalkyl, heteroalkyl, cycloalkyl, heterocycloalkyl, cycloalkylalkyl, cycloaryl, or heterocycloaryl, optionally substituted with R_5;
each n is independently an integer from 1-5.

[0048] In some embodiments w is an integer from 3-1000, for example 3-500, 3-200, 3-100, 3-50, 3-30, 3-20, or 3-10. In some examples, Xaa_5 is Glu or an amino acid analog thereof. In some examples each E is independently an amino acid selected from Ala (alanine), D-Ala (D-alanine), Aib (α–aminoisobutyric acid), Sar (N-methyl glycine), and Ser (serine). In some examples, $[D]_v$ is $–Leu_1\text{-}Thr_2$. In some examples, w is 3-6. In some examples, w is 6-10. In some examples, w is 6. In some examples, v is 1-10. In some examples, v is 2-10. In some examples, v is 2-5. In some examples, v is 2.

[0049] In some examples, L_1 and L_2 in the Formulas above are independently alkylene, alkenylene, alkynylene, heteroalkylene, cycloalkylene, heterocycloalkylene, cycloarylene, or heterocycloarylene, each being optionally substituted with R_5. In some examples, L_1 and L_2 are independently alkylene or alkenylene. In some examples, L is alkylene, alkenylene, or alkynylene. In some examples, L is alkylene. In some examples, L is C_3-C_{16} alkylene. In some examples, L is C_{10}-C_{14} alkylene.

[0050] In some examples, R_1 and R_2 in the Formulas above are independently –H, alkyl, alkenyl, alkynyl, arylalkyl, cycloalkyl, cycloalkylalkyl, heteroalkyl, or heterocycloalkyl, unsubstituted or substituted with halo–. In some examples, R_1 and R_2 are H. In some examples, R_1 and R_2 are independently alkyl. In some examples, R_1 and R_2 are methyl.

[0051] In some examples, x+y+z in the Formulas here is 6.

[0052] In some examples, in the Formulas here, u is 1.

[0053] In some examples, each E is Ser or Ala or an analog thereof.

[0054] In some examples, the aqueous pharmaceutical formulations comprise at least one amino acid which is an amino acid analog.

[0055] In some examples, the peptidomimetic macrocycle in the aqueous pharmaceutical formulations is a peptidomimetic macrocycle shown in **Table 1c**.

[0056] In another aspect, the disclosure provides a method of treating cancer in a subject, the method comprising administering to the subject a therapeutically effective amount of an aqueous pharmaceutical formulation of the disclosure.

[0057] In another aspect, the disclosure provides a method of treating cancer in a subject comprising administering to the subject an aqueous pharmaceutical formulation a peptidomimetic macrocycle peptidomimetic macrocycle that is capable of binding to the MDM2 and/or MDMX proteins and wherein the amount of the peptidomimetic macrocycle in the aqueous pharmaceutical formulation is greater than15 mg/mL and wherein the aqueous pharmaceutical formulation contains less than 2% w/v of any micelle forming agent. The aqueous pharmaceutical formulation can further comprise a buffering agent, a stabilizing agent, and/or tonicity agent.

[0058] The cancer can be selected from the group consisting of head and neck cancer, melanoma, lung cancer, breast cancer, and glioma. In some examples, the cancer is selected from a group consisting of bladder cancer, bone cancer, breast cancer, cervical cancer, CNS cancer, colon cancer, ocular tumor, renal cancer, liver cancer, lung cancer, pancreatic cancer, choriocarcinoma (tumor of the placenta), prostate cancer, sarcoma, skin cancer, soft tissue cancer, gastric cancer, gall bladder cancer, biliary cancer, renal cancer, neoblastoma, or neuroendocrine cancer.

[0042] In another aspect, the disclosure provides a method of modulating the activity of p53 and/or MDM2 and/or MDMX in a subject comprising administering to the subject an aqueous pharmaceutical formulation comprising a peptidomimetic macrocycle capable of binding to the MDM2 and/or MDMX proteins, wherein the amount of the peptidomimetic macrocycle in the aqueous pharmaceutical formulation is greater than15 mg/mL and wherein the aqueous pharmaceutical formulation contains less than 2% w/v of any micelle forming agent. The aqueous pharmaceutical formulation can further comprise a buffering agent, a tonicity agent, and/or a stabilizing agent.

[0043] In another aspect, the disclosure provides a method of antagonizing the interaction between p53 and MDM2 and/or between p53 and MDMX proteins in a subject, the method comprising administering to the subject a aqueous pharmaceutical formulation comprising a peptidomimetic macrocycle capable of binding to the MDM2 and/or MDMX proteins, wherein the amount of the peptidomimetic macrocycle in the aqueous pharmaceutical formulation is greater than15 mg/mL and wherein the aqueous pharmaceutical formulation contains less than 2% w/v of any micelle forming agent. The aqueous pharmaceutical formulation can further comprise a buffering agent, a stabilizing agent and/or a tonicity agent.

[0044] In another aspect, the disclosure provides a method of making an aqueous pharmaceutical formulation comprising adding greater than 15 mg/mL of a peptidomimetic macrocycle or a pharmaceutically acceptable salt thereof to water or an aqueous solution, wherein the peptidomimetic macrocycle is capable of binding to the MDM2 and/or MDMX proteins and wherein the aqueous pharmaceutical formulation comprises less than 2% w/v of any micelle forming agent. In some examples, the method comprises adding a sodium salt of the peptidomimetic macrocycle to water or an aqueous solution. The aqueous solution can comprise a buffering agent. The aqueous solution can also comprise a tonicity agent. The aqueous solution can further comprise a stabilizing agent.

[0045] The method can further comprise adjusting the pH of the solution comprising the buffering agent and the stabilizing agent during the addition of the peptidomimetic macrocycle. The pH can be adjusted by addition of a pH adjusting agent. In some examples, the pH is adjusted to be in the range of from about 6.0-8.0.

[0046] The amount of the pH adjusting agent added can be from about 0.01-10% w/v, for example about 0.09% w/v. The pH adjusting agent can comprise an acid or a base. In some examples, the pH adjusting agent comprises phosphoric acid. In some examples, the pH adjusting agent comprises sodium hydroxide, for example 0.1 N NaOH.

[0047] The method can further comprise filtration of the aqueous pharmaceutical formulation obtained after the addition of the peptidomimetic macrocycle to the aqueous solution. The filtration is performed under vacuum or under pressure. The filtration can comprise sterilizing filtration. In some examples, the filtration comprises use of membrane filter. In some examples, the membrane filter comprises cellulose or cellulose derivative, cellulosic ester (MCE), comprise polytetrafluoroethylene (PTFE), polyvinylidene, polyvinylidene chloride, or polyvinylidene fluoride. The membrane filter can have a pore size in the range from about 10 nm – 10 μm, for example 0.2 μm. The filtration can result in clarification of the aqueous formulation. The filtering can involve passing the aqueous pharmaceutical formulation through one or more membrane filters.

[0048] In another aspect, the disclosure provides a kit comprising, in suitable container means, an aqueous pharmaceutical formulation comprising a peptidomimetic macrocycle and instructions for administration of the aqueous pharmaceutical formulation to a human subject, wherein the peptidomimetic macrocycle is capable of binding to MDM2 and/or MDMX proteins and wherein the amount of the peptidomimetic macrocycle in the aqueous pharmaceutical formulation is greater than15 mg/mL and the aqueous pharmaceutical formulation comprises less than 2% w/v of any micelle forming agent. The instructions can be for intravenous administration of the aqueous formulation.

[0049] In some embodiments, the amount of aqueous pharmaceutical formulation made is about 1 liter to about 100 liters. In some embodiments, the amount of aqueous pharmaceutical formulation made is about 10 litres to about 100 litres. In some embodiments the amount of aqueous pharmaceutical formulation made is about 10 liters to about 50 liters.

[0050] A kit for formulating an aqueous pharmaceutical formulation comprising, in suitable container means, a peptidomimetic macrocycle capable of binding to the MDM2 and/or MDMX proteins or a pharmaceutically acceptable salt thereof, wherein the amount of the peptidomimetic macrocycle in the aqueous pharmaceutical formulation is greater than15 mg/mL and the aqueous pharmaceutical formulation comprises less than 2% w/v of any micelle forming agent.

INCORPORATION BY REFERENCE

[0051] All publications, patents, and patent applications mentioned in this specification are herein incorporated by reference to the same extent as if each individual publication, patent, or patent application was specifically and individually indicated to be incorporated by reference.

BRIEF DESCRIPTION OF THE DRAWINGS

[0052] The novel features of the disclosure are set forth with particularity in the appended claims. A better understanding of the features and advantages of the present disclosure will be obtained by reference to the following detailed description that sets forth illustrative embodiments, in which the principles of the disclosure are utilized, and the accompanying drawings of which:

[0053] **Figure 1**. Shows a flow diagram of the manufacturing process of an exemplary aqueous pharmaceutical formulation of the disclosure.

[0054] **Figure 2.** Shows the observation pictures for Example 5.

[0055] **Figure 3** Shows a plot of viable SJSA-1 cells (%) vs. log concentration (μM) of indicated peptide after incubation of the cells with the peptide for 72 hr in 10% serum.

[0056] **Figure 4** Shows the 12-month stability results for Aileron peptide-1. The data support greater than 2 year shelf life at -20 – 5 °C.

DETAILED DESCRIPTION OF THE DISCLOSURE

[0057] While preferred embodiments of the present disclosure have been shown and described herein, it will be obvious to those skilled in the art that such embodiments are provided by way of example only. Numerous variations, changes, and substitutions will now occur to those skilled in the art without departing from the disclosure. It should be understood that various alternatives to the embodiments of the disclosure described herein can be employed in practicing the disclosure. It is intended that the following claims define the scope of the disclosure and that methods and structures within the scope of these claims and their equivalents be covered thereby.

[0001] Definitions

[0058] As used herein, the term "macrocycle" refers to a molecule having a chemical structure including a ring or cycle formed by at least 9 covalently bonded atoms.

[0059] As used herein, the term "peptidomimetic macrocycle" or "crosslinked polypeptide" refers to a compound comprising a plurality of amino acid residues joined by a plurality of peptide bonds and at least one macrocycle-forming linker which forms a macrocycle between a first naturally-occurring or non-naturally-occurring amino acid residue (or analog) and a second naturally-occurring or non-naturally-occurring amino acid residue (or analog) within the same molecule. Peptidomimetic macrocycle include embodiments where the macrocycle-forming linker connects the α carbon of the first amino acid residue (or analog) to the α carbon of the second amino acid residue (or analog). The peptidomimetic macrocycles optionally include one or more non-peptide bonds between one or more amino acid residues and/or amino acid analog residues, and optionally include one or more non-naturally-occurring amino acid residues or amino acid analog residues in addition to any which form the macrocycle. A "corresponding uncrosslinked polypeptide" when referred to in the context of a peptidomimetic macrocycle is understood to relate to a polypeptide of the same length as the macrocycle and comprising the equivalent natural amino acids of the wild-type sequence corresponding to the macrocycle.

[0060] As used herein, the term "pharmaceutically acceptable salt" refers to those salts which are suitable for pharmaceutical use, preferably for use in humans and lower animals without undue irritation, allergic response and the like. Pharmaceutically acceptable salts of amines, carboxylic acids, and other types of compounds, are

well known in the art. For example, S. M. Berge, *et al.*, describe pharmaceutically acceptable salts in detail in J Pharmaceutical Sciences, 66: 1-19 (1977), incorporated herein by reference. The salts can be prepared in situ during the final isolation and purification of the peptidomimetic macrocycles of the invention, or separately by reacting a free base or free acid function with a suitable reagent, as described generally below. For example, a free base function can be reacted with a suitable acid. Suitable pharmaceutically acceptable salts can, include metal salts such as alkali metal salts, e. g. sodium, potassium, and lithium salts; and alkaline earth metal salts, e. g. calcium or magnesium salts. Examples of pharmaceutically acceptable, nontoxic acid addition salts are salts of an amino group formed with inorganic acids such as hydrochloric acid, hydrobromic acid, hydroiodic acid, phosphoric acid, sulfuric acid and perchloric acid or with organic acids such as acetic acid, oxalic acid, maleic acid, tartaric acid, citric acid, succinic acid or malonic acid or by using other methods used in the art such as ion exchange. Other pharmaceutically acceptable salts include adipate, alginate, ascorbate, aspartate, benzoate, bisulfate, borate, butyrate, camphorate, camphorsulfonate, citrate, cyclopentanepropionate, digluconate, dodecylsulfate, formate, fumarate, glucoheptonate, glycerophosphate, gluconate, hernisulfate, heptanoate, hexanoate, hydroiodide, 2-hydroxy-ethanesulfonate, lactobionate, lactate, laurate, lauryl sulfate, malate, maleate, malonate, methanesulfonate, nicotinate, nitrate, oleate, oxalate, palmitate, pectinate, persulfate, 3-phenylpropionate, phosphate, picrate, pivalate, propionate, stearate, succinate, sulfate, tartrate, thiocyanate, p-toluenesulfonate, undecanoate, valerate salts, and the like.

[0061] As used herein, the term "stability" can refer to chemical stability and/or physical stability. As used herein, the phrase chemical stability means the ability of a compound to maintain its chemical identity over time. Accordingly, stability implies the ability of a chemical species to resist oxidation or other degradation, for example. As used herein, the phrase physical stability means the ability of a composition to maintain consistent physical properties over time. The ability of a composition to maintain a consistent disintegration time over time is exemplary of physical stability. In some embodiments, stability can also refer to the maintenance of a defined secondary structure in solution by a peptidomimetic macrocycle as measured by circular dichroism, NMR or another biophysical measure, or resistance to proteolytic degradation *in vitro* or *in vivo*. Non-limiting examples of secondary structures contemplated herein are α-helices, 3_{10} helices, β-turns, and β-pleated sheets.

[0062] The term "amino acid" refers to a molecule containing both an amino group and a carboxyl group. Suitable amino acids include, without limitation, both the D-and L-isomers of the naturally-occurring amino acids, as well as non-naturally occurring amino acids prepared by organic synthesis or other metabolic routes. The term amino acid, as used herein, includes, without limitation, α-amino acids, natural amino acids, non-natural amino acids, and amino acid analogs.

[0063] The term "α-amino acid" refers to a molecule containing both an amino group and a carboxyl group bound to a carbon which is designated the α-carbon.

[0064] The term "β-amino acid" refers to a molecule containing both an amino group and a carboxyl group in a β configuration.

[0065] The term "naturally occurring amino acid" refers to any one of the twenty amino acids commonly found in peptides synthesized in nature, and known by the one letter abbreviations A, R, N, C, D, Q, E, G, H, I, L, K, M, F, P, S, T, W, Y and V.

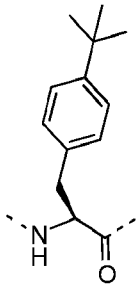
[0066] The following table shows a summary of the properties of natural amino acids:

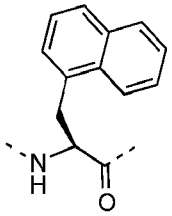
Amino Acid	3-Letter Code	1-Letter Code	Side-chain Polarity	Side-chain charge (pH 7.4)	Hydropathy Index
Alanine	Ala	A	nonpolar	neutral	1.8
Arginine	Arg	R	polar	positive	−4.5
Asparagine	Asn	N	polar	neutral	−3.5
Aspartic acid	Asp	D	polar	negative	−3.5
Cysteine	Cys	C	polar	neutral	2.5
Glutamic acid	Glu	E	polar	negative	−3.5
Glutamine	Gln	Q	polar	neutral	−3.5
Glycine	Gly	G	nonpolar	neutral	−0.4
Histidine	His	H	polar	positive(10%) neutral(90%)	−3.2
Isoleucine	Ile	I	nonpolar	neutral	4.5
Leucine	Leu	L	nonpolar	neutral	3.8
Lysine	Lys	K	polar	positive	−3.9
Methionine	Met	M	nonpolar	neutral	1.9
Phenylalanine	Phe	F	nonpolar	neutral	2.8
Proline	Pro	P	nonpolar	neutral	−1.6
Serine	Ser	S	polar	neutral	−0.8
Threonine	Thr	T	polar	neutral	−0.7
Tryptophan	Trp	W	nonpolar	neutral	−0.9
Tyrosine	Tyr	Y	polar	neutral	−1.3
Valine	Val	V	nonpolar	neutral	4.2

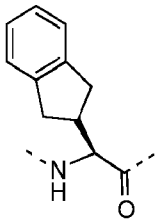
[0067] "Hydrophobic amino acids" include small hydrophobic amino acids and large hydrophobic amino acids. "Small hydrophobic amino acid" are glycine, alanine, proline, and analogs thereof. "Large hydrophobic amino acids" are valine, leucine, isoleucine, phenylalanine, methionine, tryptophan, and analogs thereof. "Polar amino acids" are serine, threonine, asparagine, glutamine, cysteine, tyrosine, and analogs thereof. "Charged amino acids" are lysine, arginine, histidine, aspartate, glutamate, and analogs thereof.

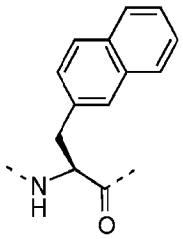
[0068] The term "amino acid analog" refers to a molecule which is structurally similar to an amino acid and which can be substituted for an amino acid in the formation of a peptidomimetic macrocycle. Amino acid analogs include, without limitation, β-amino acids and amino acids where the amino or carboxy group is substituted by a similarly reactive group (*e.g.*, substitution of the primary amine with a secondary or tertiary amine, or substitution of the carboxy group with an ester).

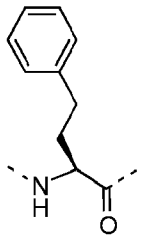
[0069] The term "non-natural amino acid" refers to an amino acid which is not one of the twenty amino acids commonly found in peptides synthesized in nature, and known by the one letter abbreviations A, R, N, C, D, Q, E, G, H, I, L, K, M, F, P, S, T, W, Y and V. Non-natural amino acids or amino acid analogs include, without limitation, structures according to the following:

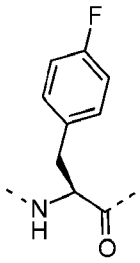

4-t-butylphenylalanine
(F4tBu)

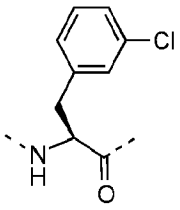

1-Naphthylalanine
(1Nal)

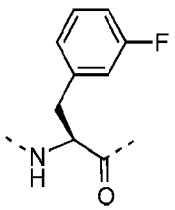

Indanyl glycine
(Igl)

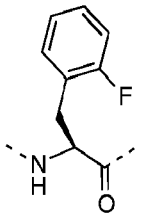

2-Naphthylalanine
(2Nal)

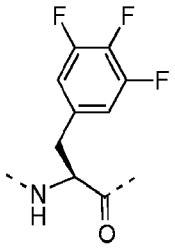

homophenylalanine
(hF)

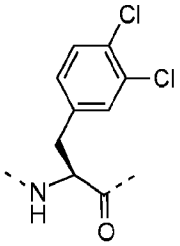

4-fluorophenylalanine
(F4F)

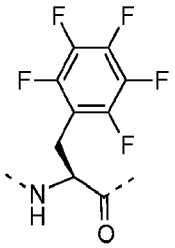

3-chlorohenylalanine
(F3Cl=3cf)

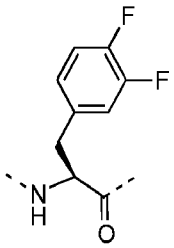

3-fluorophenylalanine
(F3F=3ff)

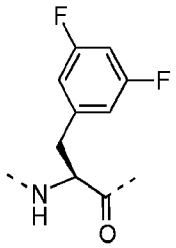

2-fluorophenylalanine
(F2F=2ff)

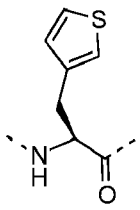

3,4,5-trifluoro
phenylalanine
(F345F3)

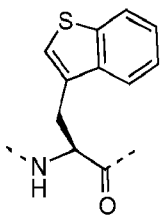

3,4-difluoro
phenylalanine
(F34Cl2)

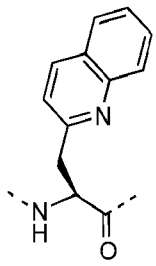

pentafluoro
phenylalanine
(F5F)

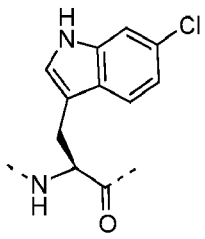

3,4-difluoro
phenylalanine
(F34F2)

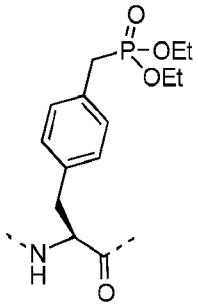

3,5-difluoro
phenylalanine
(F35F2)

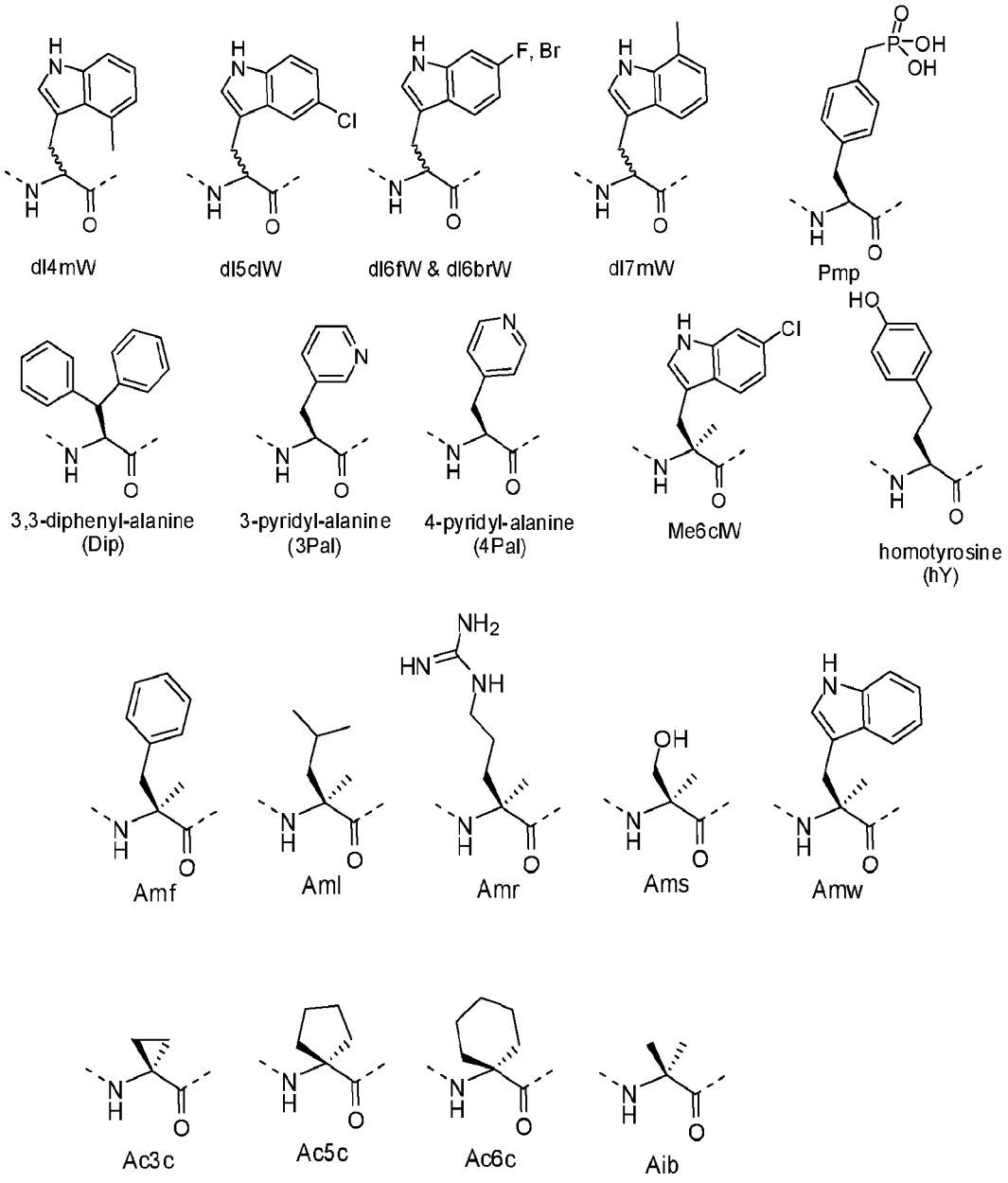

3-thienylalanine
(2Thi)

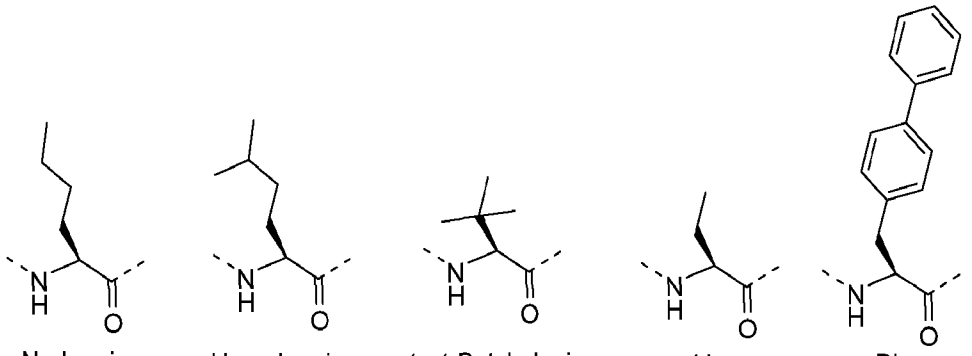

3-(1-Benzothiophen-3-yl)
alanine
(3BthA)

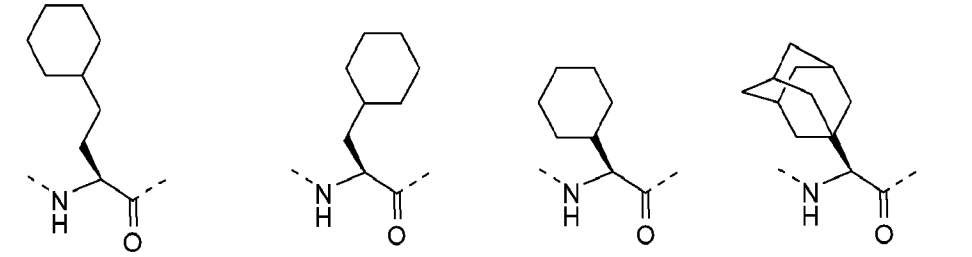

3-(2-quinolyl)
alanine
(2qA)

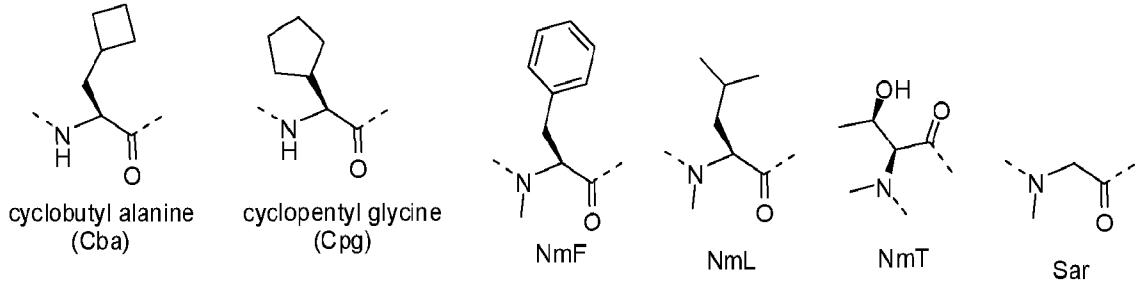

6-chlorotryptophan
(6clW)

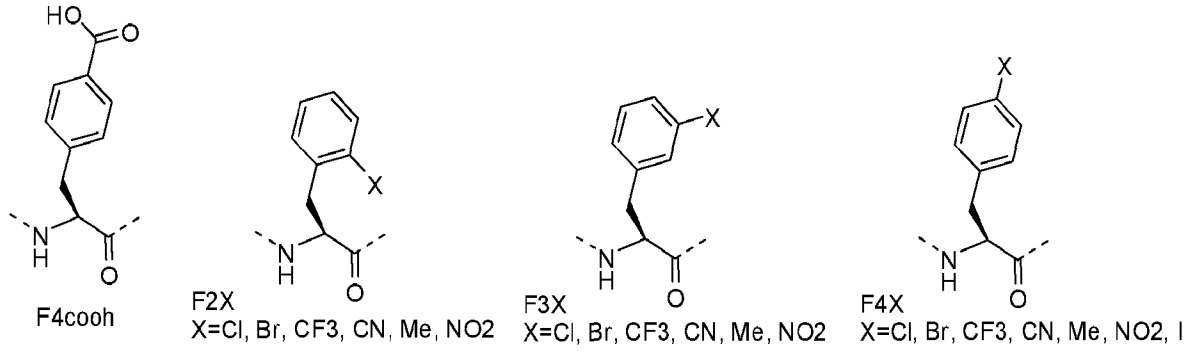

4-[di-(ethyl)phosphono
methyl]phenylalanine
(pmpEt)

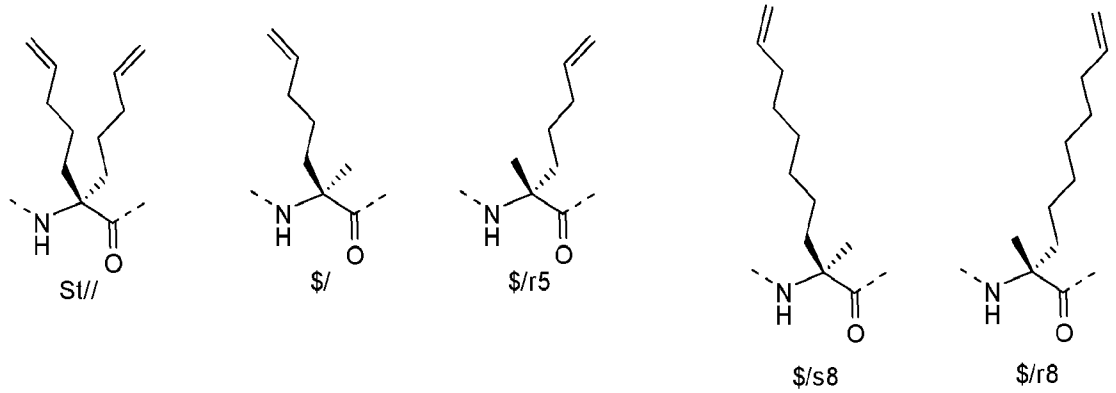

dl4mW
dl5clW
dl6fW & dl6brW
F, Br
dl7mW
Pmp
3,3-diphenyl-alanine
(Dip)
3-pyridyl-alanine
(3Pal)
4-pyridyl-alanine
(4Pal)
Me6clW
homotyrosine
(hY)
Amf
Aml
Amr
Ams
Amw
Ac3c
Ac5c
Ac6c
Aib

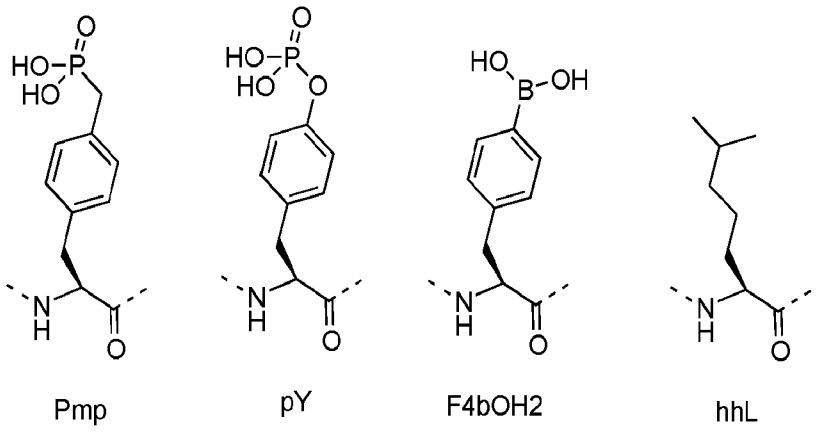

Norleucine
(Nle)
Homoleucine
(hL)
tert-Butyl glycine
(Tle)
Abu
Bip

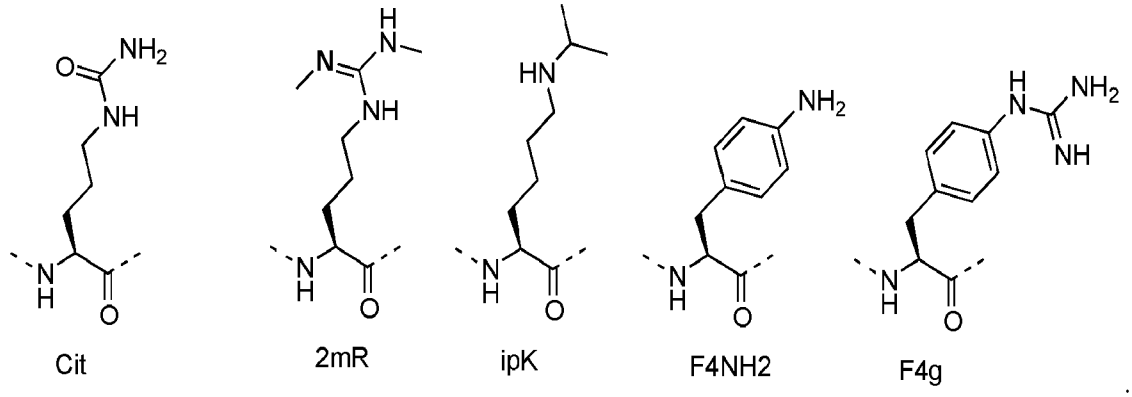

homocyclohexyl alanine
(hCha)
cyclohexyl alanine
(Cha)
cyclohexyl glycine
(Chg)
Adamantyl glycine
(Adm)


cyclobutyl alanine
(Cba)
cyclopentyl glycine
(Cpg)
NmF
NmL
NmT
Sar


F4cooh
F2X
X=Cl, Br, CF3, CN, Me, NO2
F3X
X=Cl, Br, CF3, CN, Me, NO2
F4X
X=Cl, Br, CF3, CN, Me, NO2, I


St//
$/
$/r5
$/s8
$/r8





[0070] Amino acid analogs include β-amino acid analogs. Examples of β-amino acid analogs include, but are not limited to, the following: cyclic β-amino acid analogs; β – alanine; (R) - β – phenylalanine; (R) - 1,2,3,4 - tetrahydro - isoquinoline - 3 - acetic acid; (R) - 3 - amino - 4 - (1 - naphthyl) - butyric acid; (R) - 3 - amino - 4 - (2,4 - dichlorophenyl)butyric acid; (R) - 3 - amino - 4 - (2 - chlorophenyl) - butyric acid; (R) - 3 - amino - 4 - (2 - cyanophenyl) - butyric acid; (R) - 3 - amino - 4 - (2 - fluorophenyl) - butyric acid; (R) - 3 - amino - 4 - (2 - furyl) - butyric acid; (R) - 3 - amino - 4 - (2 - methylphenyl) - butyric acid; (R) - 3 - amino - 4 - (2 - naphthyl) - butyric acid; (R) - 3 - amino - 4 - (2 - thienyl) - butyric acid; (R) - 3 - amino - 4 - (2 - trifluoromethylphenyl) - butyric acid; (R) - 3 - amino - 4 - (3,4 - dichlorophenyl)butyric acid; (R) - 3 - amino - 4 - (3,4 - difluorophenyl)butyric acid; (R) - 3 - amino - 4 - (3 - benzothienyl) - butyric acid; (R) - 3 - amino - 4 - (3 - chlorophenyl) - butyric acid; (R) - 3 - amino - 4 - (3 - cyanophenyl) - butyric acid; (R) - 3 - amino - 4 - (3 - fluorophenyl) - butyric acid; (R) - 3 - amino - 4 - (3 - methylphenyl) - butyric acid; (R) - 3 - amino - 4 - (3 - pyridyl) - butyric acid; (R) - 3 - amino - 4 - (3 - thienyl) - butyric acid; (R) - 3 - amino - 4 - (3 - trifluoromethylphenyl) - butyric acid; (R) - 3 - amino - 4 - (4 - bromophenyl) - butyric acid; (R) - 3 - amino - 4 - (4 - chlorophenyl) - butyric acid; (R) - 3 - amino - 4 - (4 - cyanophenyl) - butyric acid; (R) - 3 - amino - 4 - (4 - fluorophenyl) - butyric acid; (R) - 3 - amino - 4 - (4 - iodophenyl) - butyric acid; (R) - 3 - amino - 4 - (4 - methylphenyl) - butyric acid; (R) - 3 - amino - 4 - (4 - nitrophenyl) - butyric acid; (R) - 3 - amino - 4 - (4 - pyridyl) - butyric acid; (R) - 3 - amino - 4 - (4 - trifluoromethylphenyl) - butyric acid; (R) - 3 - amino - 4 - pentafluoro - phenylbutyric acid; (R) - 3 - amino - 5 -

hexenoic acid; (R) - 3 - amino - 5 - hexynoic acid; (R) - 3 - amino - 5 - phenylpentanoic acid; (R) - 3 - amino - 6 - phenyl - 5 - hexenoic acid; (S) - 1,2,3,4 - tetrahydro - isoquinoline - 3 - acetic acid; (S) - 3 - amino - 4 - (1 - naphthyl) - butyric acid; (S) - 3 - amino - 4 - (2,4 - dichlorophenyl)butyric acid; (S) - 3 - amino - 4 - (2 - chlorophenyl) - butyric acid; (S) - 3 - amino - 4 - (2 - cyanophenyl) - butyric acid; (S) - 3 - amino - 4 - (2 - fluorophenyl) - butyric acid; (S) - 3 - amino - 4 - (2 - furyl) - butyric acid; (S) - 3 - amino - 4 - (2 - methylphenyl) - butyric acid; (S) - 3 - amino - 4 - (2 - naphthyl) - butyric acid; (S) - 3 - amino - 4 - (2 - thienyl) - butyric acid; (S) - 3 - amino - 4 - (2 - trifluoromethylphenyl) - butyric acid;

(S) - 3 - amino - 4 - (3,4 - dichlorophenyl)butyric acid; (S) - 3 - amino - 4 - (3,4 - difluorophenyl)butyric acid; (S) - 3 - amino - 4 - (3 - benzothienyl) - butyric acid; (S) - 3 - amino - 4 - (3 - chlorophenyl) - butyric acid; (S) - 3 - amino - 4 - (3 - cyanophenyl) - butyric acid; (S) - 3 - amino - 4 - (3 - fluorophenyl) - butyric acid; (S) - 3 - amino - 4 - (3 - methylphenyl) - butyric acid; (S) - 3 - amino - 4 - (3 - pyridyl) - butyric acid; (S) - 3 - amino - 4 - (3 - thienyl) - butyric acid; (S) - 3 - amino - 4 - (3 - trifluoromethylphenyl) - butyric acid; (S) - 3 - amino - 4 - (4 - bromophenyl) - butyric acid; (S) - 3 - amino - 4 - (4 - chlorophenyl) - butyric acid; (S) - 3 - amino - 4 - (4 - cyanophenyl) - butyric acid; (S) - 3 - amino - 4 - (4 - fluorophenyl) - butyric acid; (S) - 3 - amino - 4 - (4 - iodophenyl) - butyric acid; (S) - 3 - amino - 4 - (4 - methylphenyl) - butyric acid; (S) - 3 - amino - 4 - (4 - nitrophenyl) - butyric acid; (S) - 3 - amino - 4 - (4 - pyridyl) - butyric acid; (S) - 3 - amino - 4 - (4 - trifluoromethylphenyl) - butyric acid; (S) - 3 - amino - 4 - pentafluoro - phenylbutyric acid; (S) - 3 - amino - 5 - hexenoic acid; (S) - 3 - amino - 5 - hexynoic acid; (S) - 3 - amino - 5 - phenylpentanoic acid; (S) - 3 - amino - 6 - phenyl - 5 - hexenoic acid; 1,2,5,6 - tetrahydropyridine - 3 - carboxylic acid; 1,2,5,6 - tetrahydropyridine - 4 - carboxylic acid; 3 - amino - 3 - (2 - chlorophenyl) - propionic acid; 3 - amino - 3 - (2 - thienyl) - propionic acid; 3 - amino - 3 - (3 - bromophenyl) - propionic acid; 3 - amino - 3 - (4 - chlorophenyl) - propionic acid; 3 - amino - 3 - (4 - methoxyphenyl) - propionic acid; 3 - amino - 4,4,4 - trifluoro - butyric acid; 3 - aminoadipic acid; D- β – phenylalanine; β – leucine; L - β – homoalanine; L - β - homoaspartic acid γ - benzyl ester; L - β - homoglutamic acid δ - benzyl ester; L - β – homoisoleucine; L - β – homoleucine; L - β – homomethionine; L - β – homophenylalanine; L - β – homoproline; L - β – homotryptophan; L - β – homovaline; L - Nω - benzyloxycarbonyl - β – homolysine; Nω - L - β – homoarginine; O - benzyl - L - β – homohydroxyproline; O - benzyl - L - β – homoserine; O - benzyl - L - β – homothreonine; O - benzyl - L - β – homotyrosine; γ - trityl - L - β – homoasparagine; (R) - β – phenylalanine; L - β - homoaspartic acid γ - t - butyl ester; L - β - homoglutamic acid δ - t - butyl ester; L - Nω - β – homolysine; Nδ - trityl - L - β – homoglutamine; Nω - 2,2,4,6,7 - pentamethyl - dihydrobenzofuran - 5 - sulfonyl - L - β – homoarginine; O - t - butyl - L - β - homohydroxy – proline; O - t - butyl - L - β – homoserine; O - t - butyl - L - β – homothreonine; O - t - butyl - L - β – homotyrosine; 2-aminocyclopentane carboxylic acid; and 2-aminocyclohexane carboxylic acid.

[0071] Amino acid analogs include analogs of alanine, valine, glycine or leucine. Examples of amino acid analogs of alanine, valine, glycine, and leucine include, but are not limited to, the following: α – methoxyglycine; α - allyl - L – alanine; α - aminoisobutyric acid; α - methyl – leucine; β - (1 - naphthyl) - D – alanine; β - (1 -

naphthyl) - L – alanine; β - (2 - naphthyl) - D – alanine; β - (2 - naphthyl) - L – alanine; β - (2 - pyridyl) - D – alanine; β - (2 - pyridyl) - L – alanine; β - (2 - thienyl) - D – alanine; β - (2 - thienyl) - L – alanine; β - (3 - benzothienyl) - D – alanine; β - (3 - benzothienyl) - L – alanine; β - (3 - pyridyl) - D – alanine; β - (3 - pyridyl) - L – alanine; β - (4 - pyridyl) - D – alanine; β - (4 - pyridyl) - L – alanine; β - chloro - L – alanine; β - cyano - L – alanin; β - cyclohexyl - D – alanine; β - cyclohexyl - L – alanine; β - cyclopenten - 1 - yl - alanine; β - cyclopentyl – alanine; β - cyclopropyl - L - Ala – OH • dicyclohexylammonium salt; β - t - butyl - D – alanine; β - t - butyl - L – alanine; γ - aminobutyric acid; L - α,β - diaminopropionic acid; 2,4 - dinitro – phenylglycine; 2,5 - dihydro - D – phenylglycine; 2 - amino - 4,4,4 - trifluorobutyric acid; 2 - fluoro – phenylglycine; 3 - amino - 4,4,4 - trifluoro - butyric acid; 3 - fluoro – valine; 4,4,4 - trifluoro – valine; 4,5 - dehydro - L - leu – OH • dicyclohexylammonium salt; 4 - fluoro - D – phenylglycine; 4 - fluoro - L – phenylglycine; 4 - hydroxy - D – phenylglycine; 5,5,5 - trifluoro – leucine; 6 - aminohexanoic acid; cyclopentyl - D - Gly – OH • dicyclohexylammonium salt; cyclopentyl - Gly – OH • dicyclohexylammonium salt; D - α,β - diaminopropionic acid; D - α - aminobutyric acid; D - α - t – butylglycine; D - (2 - thienyl)glycine; D - (3 - thienyl)glycine; D - 2 - aminocaproic acid; D - 2 – indanylglycine; D – allylglycine•dicyclohexylammonium salt; D – cyclohexylglycine; D – norvaline; D – phenylglycine; β - aminobutyric acid; β - aminoisobutyric acid; (2 - bromophenyl)glycine; (2 - methoxyphenyl)glycine; (2 - methylphenyl)glycine; (2 - thiazoyl)glycine; (2 - thienyl)glycine; 2 - amino - 3 - (dimethylamino) - propionic acid; L - α,β - diaminopropionic acid; L - α - aminobutyric acid; L - α - t – butylglycine; L - (3 - thienyl)glycine; L - 2 - amino - 3 - (dimethylamino) - propionic acid; L - 2 - aminocaproic acid dicyclohexyl - ammonium salt; L - 2 – indanylglycine; L - allylglycine•dicyclohexyl ammonium salt; L – cyclohexylglycine; L – phenylglycine; L – propargylglycine; L – norvaline; N - α - aminomethyl - L – alanine; D - α,γ - diaminobutyric acid; L - α,γ - diaminobutyric acid; β - cyclopropyl - L – alanine; (N - β - (2,4 - dinitrophenyl)) - L - α,β - diaminopropionic acid; (N - β - 1 - (4,4 - dimethyl - 2,6 - dioxocyclohex - 1 - ylidene)ethyl) - D - α,β - diaminopropionic acid; (N - β - 1 - (4,4 - dimethyl - 2,6 - dioxocyclohex - 1 - ylidene)ethyl) - L - α,β - diaminopropionic acid; (N - β - 4 - methyltrityl) - L - α,β - diaminopropionic acid; (N - β - allyloxycarbonyl) - L - α,β - diaminopropionic acid; (N - γ - 1 - (4,4 - dimethyl - 2,6 - dioxocyclohex - 1 - ylidene)ethyl) - D - α,γ - diaminobutyric acid; (N - γ - 1 - (4,4 - dimethyl - 2,6 - dioxocyclohex - 1 - ylidene)ethyl) - L - α,γ - diaminobutyric acid; (N - γ - 4 - methyltrityl) - D - α,γ - diaminobutyric acid; (N - γ - 4 - methyltrityl) - L - α,γ - diaminobutyric acid; (N - γ - allyloxycarbonyl) - L - α,γ - diaminobutyric acid; D - α,γ - diaminobutyric acid; 4,5 - dehydro - L – leucine; cyclopentyl - D - Gly – OH; cyclopentyl - Gly – OH; D – allylglycine; D – homocyclohexylalanine; L - 1 – pyrenylalanine; L - 2 - aminocaproic acid; L – allylglycine; L – homocyclohexylalanine; and N - (2 - hydroxy - 4 - methoxy - Bzl) - Gly – OH.

[0072] Amino acid analogs include analogs of arginine or lysine. Examples of amino acid analogs of arginine and lysine include, but are not limited to, the following: citrulline; L - 2 - amino - 3 - guanidinopropionic acid; L - 2 - amino - 3 - ureidopropionic acid; L – citrulline; $Lys(Me)_2$ – OH; $Lys(N_3)$ – OH; Nδ - benzyloxycarbonyl - L – ornithine; Nω - nitro - D – arginine; Nω - nitro - L – arginine; α - methyl – ornithine; 2,6 - diaminoheptanedioic

acid; L – ornithine; (Nδ - 1 - (4,4 - dimethyl - 2,6 - dioxo - cyclohex - 1 - ylidene)ethyl) - D – ornithine; (Nδ - 1 - (4,4 - dimethyl - 2,6 - dioxo - cyclohex - 1 - ylidene)ethyl) - L – ornithine; (Nδ - 4 - methyltrityl) - D – ornithine; (Nδ - 4 - methyltrityl) - L – ornithine; D – ornithine; L – ornithine; Arg(Me)(Pbf) – OH; $Arg(Me)_2$ – OH (asymmetrical); Arg(Me)2 - OH (symmetrical); Lys(ivDde) – OH; Lys(Me)2 - OH • HCl; Lys(Me3) - OH chloride; Nω - nitro - D – arginine; and Nω - nitro - L – arginine.

[0073] Amino acid analogs include analogs of aspartic or glutamic acids. Examples of amino acid analogs of aspartic and glutamic acids include, but are not limited to, the following: α - methyl - D - aspartic acid; α - methyl - glutamic acid; α - methyl - L - aspartic acid; γ - methylene - glutamic acid; (N - γ - ethyl) - L – glutamine; [N - α - (4 - aminobenzoyl)] - L - glutamic acid; 2,6 - diaminopimelic acid; L - α - aminosuberic acid; D - 2 - aminoadipic acid; D - α - aminosuberic acid; α - aminopimelic acid; iminodiacetic acid; L - 2 - aminoadipic acid; threo - β - methyl - aspartic acid; γ - carboxy - D - glutamic acid γ,γ - di - t - butyl ester; γ - carboxy - L - glutamic acid γ,γ - di - t - butyl ester; Glu(OAll) – OH; L - Asu(OtBu) – OH; and pyroglutamic acid.

[0074] Amino acid analogs include analogs of cysteine and methionine. Examples of amino acid analogs of cysteine and methionine include, but are not limited to, Cys(farnesyl) – OH, Cys(farnesyl) – OMe, α - methyl – methionine, Cys(2 - hydroxyethyl) – OH, Cys(3 - aminopropyl) – OH, 2 - amino - 4 - (ethylthio)butyric acid, buthionine, buthioninesulfoximine, ethionine, methionine methylsulfonium chloride, selenomethionine, cysteic acid, [2 - (4 - pyridyl)ethyl] - DL – penicillamine, [2 - (4 - pyridyl)ethyl] - L – cysteine, 4 - methoxybenzyl - D – penicillamine, 4 - methoxybenzyl - L – penicillamine, 4 - methylbenzyl - D - penicillamine, 4 - methylbenzyl - L – penicillamine, benzyl-D-cysteine, benzyl – L – cysteine, benzyl – DL – homocysteine, carbamoyl – L – cysteine, carboxyethyl – L – cysteine, carboxymethyl – L – cysteine, diphenylmethyl – L – cysteine, ethyl – L – cysteine, methyl – L – cysteine, t-butyl – D – cysteine, trityl – L- homocysteine, trityl – D – penicillamine, cystathionine, homocystine, L-homocystine, (2-aminoethyl) – L – cysteine, seleno – L – cystine, cystathionine, Cys(StBu) – OH, and acetamidomethyl - D – penicillamine.

[0075] Amino acid analogs include analogs of phenylalanine and tyrosine. Examples of amino acid analogs of phenylalanine and tyrosine include β - methyl – phenylalanine, β – hydroxyphenylalanine, α - methyl - 3 - methoxy - DL – phenylalanine, α - methyl - D – phenylalanine, α - methyl - L – phenylalanine, 1,2,3,4 - tetrahydroisoquinoline - 3 - carboxylic acid, 2,4 - dichloro – phenylalanine, 2 - (trifluoromethyl) – D - phenylalanine, 2 - (trifluoromethyl) - L – phenylalanine, 2 - bromo - D – phenylalanine, 2 - bromo - L – phenylalanine, 2 - chloro - D – phenylalanine, 2 - chloro - L – phenylalanine, 2 - cyano - D – phenylalanine, 2 - cyano - L – phenylalanine, 2 - fluoro - D – phenylalanine, 2 - fluoro - L – phenylalanine, 2 - methyl - D – phenylalanine, 2 - methyl - L – phenylalanine, 2 - nitro - D – phenylalanine, 2 - nitro - L – phenylalanine, 2;4;5 - trihydroxy – phenylalanine, 3,4,5 - trifluoro - D – phenylalanine, 3,4,5 - trifluoro - L – phenylalanine, 3,4 - dichloro - D – phenylalanine, 3,4 - dichloro - L – phenylalanine, 3,4 - difluoro - D – phenylalanine, 3,4 - difluoro - L – phenylalanine, 3,4 - dihydroxy - L – phenylalanine, 3,4 - dimethoxy - L – phenylalanine, 3,5,3' - triiodo - L – thyronine, 3,5 - diiodo - D – tyrosine, 3,5 - diiodo - L – tyrosine, 3,5 - diiodo - L – thyronine, 3 -

(trifluoromethyl) - D – phenylalanine, 3 - (trifluoromethyl) - L – phenylalanine, 3 - amino - L – tyrosine, 3 - bromo - D – phenylalanine, 3 - bromo - L – phenylalanine, 3 – chloro – D – phenylalanine, 3 – chloro – L – phenylalanine, 3 - chloro - L – tyrosine, 3 - cyano - D – phenylalanine, 3 - cyano - L – phenylalanine, 3 - fluoro - D – phenylalanine, 3 - fluoro - L – phenylalanine, 3 - fluoro – tyrosine, 3 - iodo - D – phenylalanine, 3 - iodo - L – phenylalanine, 3 - iodo - L – tyrosine, 3 - methoxy - L – tyrosine, 3 - methyl - D – phenylalanine, 3 - methyl - L – phenylalanine, 3 - nitro - D – phenylalanine, 3 - nitro - L – phenylalanine, 3 - nitro - L – tyrosine, 4 - (trifluoromethyl) - D – phenylalanine, 4 - (trifluoromethyl) - L – phenylalanine, 4 - amino - D – phenylalanine, 4 - amino - L – phenylalanine, 4 - benzoyl - D – phenylalanine, 4 - benzoyl - L – phenylalanine, 4 - bis(2 - chloroethyl)amino - L – phenylalanine, 4 - bromo - D – phenylalanine, 4 - bromo - L – phenylalanine, 4 - chloro - D – phenylalanine, 4 - chloro - L – phenylalanine, 4 - cyano - D – phenylalanine, 4 - cyano - L – phenylalanine, 4 - fluoro - D – phenylalanine, 4 - fluoro - L – phenylalanine, 4 - iodo - D – phenylalanine, 4 - iodo - L – phenylalanine, homophenylalanine, thyroxine, 3,3 – diphenylalanine, thyronine, ethyl-tyrosine, and methyl-tyrosine.

[0076] Amino acid analogs include analogs of proline. Examples of amino acid analogs of proline include, but are not limited to, 3,4-dehydro-proline, 4-fluoro-proline, cis-4-hydroxy-proline, thiazolidine-2-carboxylic acid, and trans-4-fluoro-proline.

[0077] Amino acid analogs include analogs of serine and threonine. Examples of amino acid analogs of serine and threonine include, but are not limited to, 3 - amino - 2 - hydroxy - 5 - methylhexanoic acid, 2 - amino - 3 - hydroxy - 4 - methylpentanoic acid, 2 - amino - 3 - ethoxybutanoic acid, 2 - amino - 3 - methoxybutanoic acid, 4 - amino - 3 - hydroxy - 6 - methylheptanoic acid, 2 - amino - 3 - benzyloxypropionic acid, 2 - amino - 3 - benzyloxypropionic acid, 2 - amino - 3 - ethoxypropionic acid, 4 - amino - 3 - hydroxybutanoic acid, and α–methylserine.

[0078] Amino acid analogs include analogs of tryptophan. Examples of amino acid analogs of tryptophan include, but are not limited to, the following: α - methyl - tryptophan; β - (3 - benzothienyl) - D - alanine; β - (3 - benzothienyl) - L - alanine; 1 - methyl - tryptophan; 4 - methyl - tryptophan; 5 - benzyloxy - tryptophan; 5 - bromo - tryptophan; 5 - chloro - tryptophan; 5 - fluoro - tryptophan; 5 - hydroxy - tryptophan; 5 - hydroxy - L - tryptophan; 5 - methoxy - tryptophan; 5 - methoxy - L - tryptophan; 5 - methyl - tryptophan; 6 - bromo - tryptophan; 6 - chloro - D - tryptophan; 6 - chloro - tryptophan; 6 - fluoro - tryptophan; 6 - methyl - tryptophan; 7 - benzyloxy - tryptophan; 7 - bromo - tryptophan; 7 - methyl - - tryptophan; D - 1,2,3,4 - tetrahydro - norharman - 3 - carboxylic acid; 6 - methoxy - 1,2,3,4 - tetrahydronorharman - 1 - carboxylic acid; 7 - azatryptophan; L - 1,2,3,4 - tetrahydro - norharman - 3 - carboxylic acid; 5 - methoxy - 2 - methyl - tryptophan; and 6 - chloro - L - tryptophan.

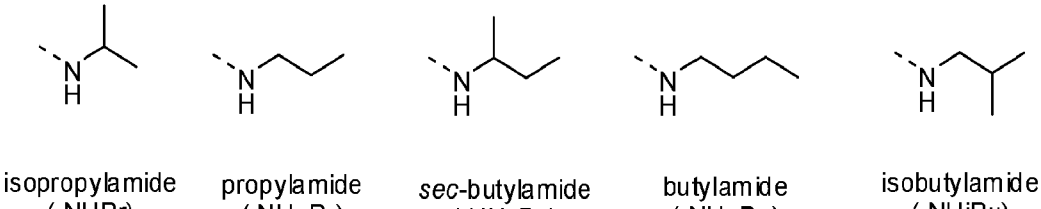
[0079] In some embodiments, amino acid analogs are racemic. In some embodiments, the D isomer of the amino acid analog is used. In some embodiments, the L isomer of the amino acid analog is used. In other embodiments, the amino acid analog comprises chiral centers that are in the R or S configuration. In still other embodiments, the

amino group(s) of a β-amino acid analog is substituted with a protecting group, *e.g.*, tert-butyloxycarbonyl (BOC group), 9-fluorenylmethyloxycarbonyl (FMOC), tosyl, and the like. In yet other embodiments, the carboxylic acid functional group of a β-amino acid analog is protected, *e.g.*, as its ester derivative. In some embodiments the salt of the amino acid analog is used.

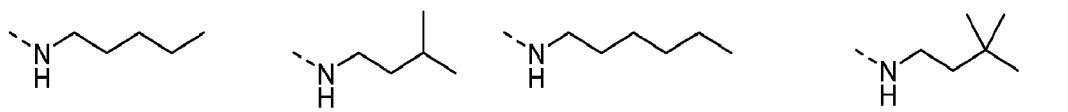
[0080] A "non-essential" amino acid residue is a residue that can be altered from the wild-type sequence of a polypeptide without abolishing or substantially altering its essential biological or biochemical activity (*e.g.*, receptor binding or activation). An "essential" amino acid residue is a residue that, when altered from the wild-type sequence of the polypeptide, results in abolishing or substantially abolishing the polypeptide's essential biological or biochemical activity.

[0081] A "conservative amino acid substitution" is one in which the amino acid residue is replaced with an 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.*, K, R, H), acidic side chains (*e.g.*, D, E), uncharged polar side chains (*e.g.*, G, N, Q, S, T, Y, C), nonpolar side chains (*e.g.*, A, V, L, I, P, F, M, W), beta-branched side chains (*e.g.*, T, V, I) and aromatic side chains (*e.g.*, Y, F, W, H). Thus, a predicted nonessential amino acid residue in a polypeptide, for example, is replaced with another amino acid residue from the same side chain family. Other examples of acceptable substitutions are substitutions based on isosteric considerations (e.g. norleucine for methionine) or other properties (e.g. 2-thienylalanine for phenylalanine, or 6-Cl-tryptophan for tryptophan).

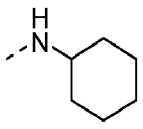
[0082] The term "capping group" refers to the chemical moiety occurring at either the carboxy or amino terminus of the polypeptide chain of the subject peptidomimetic macrocycle. The capping group of a carboxy terminus includes an unmodified carboxylic acid (ie –COOH) or a carboxylic acid with a substituent. For example, the carboxy terminus can be substituted with an amino group to yield a carboxamide at the C-terminus. Various substituents include but are not limited to primary and secondary amines, including pegylated secondary amines. Representative secondary amine capping groups for the C-terminus include:



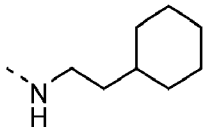
isopropylamide (-NHPr) | propylamide (-NHnPr) | *sec*-butylamide (-NHsBu) | butylamide (-NHnBu) | isobutylamide (-NHiBu)



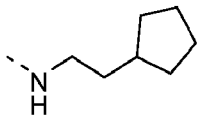
amylamide (-NHAm) | isoamylamide (-NHiAm) | hexylamide (-NHHex) | 3,3-dimethylbutylamide (-NH*n*Bu3,3Me)



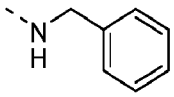
cyclohexylamide
(-NHChx)



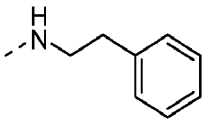
2-cyclohexylethylamide
(-NHnEt2Ch)



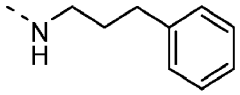
2-cyclopentylethylamide
(-NHnEt2Cp)



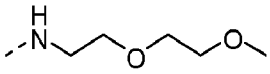
benzylamide
(-NHBn)



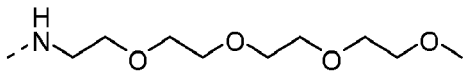
phenetylamide
(-NHPe)



3-phenyl-1-propylamide
(-NHnPr3Ph)

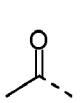


n-diPeg2-amide
(-NHmdPeg2)

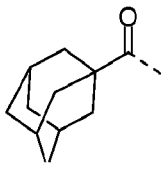


n-diPeg4-amide
(-NHmdPeg4)

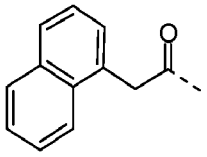
[0083] The capping group of an amino terminus includes an unmodified amine (ie $-NH_2$) or an amine with a substituent. For example, the amino terminus can be substituted with an acyl group to yield a carboxamide at the N-terminus. Various substituents include but are not limited to substituted acyl groups, including C_1-C_6 carbonyls, C_7-C_{30} carbonyls, and pegylated carbamates. Representative capping groups for the N-terminus include, but are not limited to, 4-FBzl (4-fluoro-benzyl) and the following:



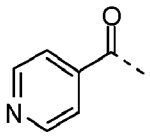
Ac-



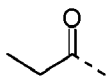
Adamantylcarbonyl
(Admac-)



1-Napthylacetyl
(Napac-)



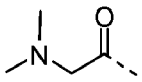
Isonicotinyl
(Isonac-)



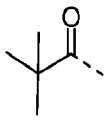
Pr-



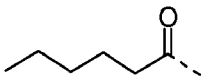
H-



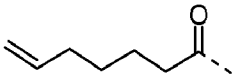
N,N-Dimethylaminoacetyl



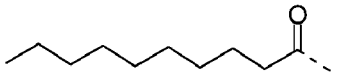
Trimethylacetyl



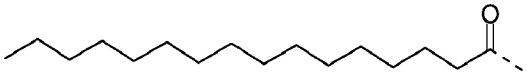
Hexanoyl



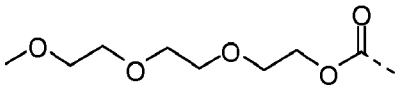
1-oxo-6-heptenyl
(uncapped)



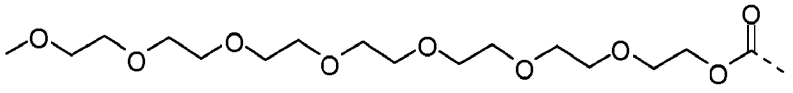
Decanoyl
(Decac)



Palmityl
(Pam)



mdPEG3



mdPEG7

[0084] The term "member" as used herein in conjunction with macrocycles or macrocycle-forming linkers refers to the atoms that form or can form the macrocycle, and excludes substituent or side chain atoms. By analogy, cyclodecane, 1,2-difluoro-decane and 1,3-dimethyl cyclodecane are all considered ten-membered macrocycles as the hydrogen or fluoro substituents or methyl side chains do not participate in forming the macrocycle.

[0085] The symbol "$\diagup\!\!\diagup$" when used as part of a molecular structure refers to a single bond or a *trans* or *cis* double bond.

[0086] The term "amino acid side chain" refers to a moiety attached to the α-carbon (or another backbone atom) in an amino acid. For example, the amino acid side chain for alanine is methyl, the amino acid side chain for phenylalanine is phenylmethyl, the amino acid side chain for cysteine is thiomethyl, the amino acid side chain for aspartate is carboxymethyl, the amino acid side chain for tyrosine is 4-hydroxyphenylmethyl, etc. Other non-naturally occurring amino acid side chains are also included, for example, those that occur in nature (*e.g.*, an amino acid metabolite) or those that are made synthetically (*e.g.*, an α,α di-substituted amino acid).

[0087] The term "α,α di-substituted amino" acid refers to a molecule or moiety containing both an amino group and a carboxyl group bound to a carbon (the α-carbon) that is attached to two natural or non-natural amino acid side chains.

[0088] The term "polypeptide" encompasses two or more naturally or non-naturally-occurring amino acids joined by a covalent bond (*e.g.*, an amide bond). Polypeptides as described herein include full length proteins (*e.g.*, fully processed proteins) as well as shorter amino acid sequences (*e.g.*, fragments of naturally-occurring proteins or synthetic polypeptide fragments).

[0089] The term "first C-terminal amino acid" refers to the amino acid which is closest to the C-terminus. The term "second C-terminal amino acid" refers to the amino acid attached at the N-terminus of the first C-terminal amino acid.

[0090] The term "macrocyclization reagent" or "macrocycle-forming reagent" as used herein refers to any reagent which can be used to prepare a peptidomimetic macrocycle by mediating the reaction between two reactive groups. Reactive groups can be, for example, an azide and alkyne, in which case macrocyclization reagents include, without limitation, Cu reagents such as reagents which provide a reactive Cu(I) species, such as CuBr, CuI or CuOTf, as well as Cu(II) salts such as $Cu(CO_2CH_3)_2$, $CuSO_4$, and $CuCl_2$ that can be converted in

situ to an active Cu(I) reagent by the addition of a reducing agent such as ascorbic acid or sodium ascorbate. Macrocyclization reagents can additionally include, for example, Ru reagents known in the art such as $Cp^*RuCl(PPh_3)_2$, $[Cp^*RuCl]_4$ or other Ru reagents which can provide a reactive Ru(II) species. In other cases, the reactive groups are terminal olefins. In such embodiments, the macrocyclization reagents or macrocycle-forming reagents are metathesis catalysts including, but not limited to, stabilized, late transition metal carbene complex catalysts such as Group VIII transition metal carbene catalysts. For example, such catalysts are Ru and Os metal centers having a +2 oxidation state, an electron count of 16 and pentacoordinated. In other examples, catalysts have W or Mo centers. Various catalysts are disclosed in Grubbs et al., "Ring Closing Metathesis and Related Processes in Organic Synthesis" Acc. Chem. Res. 1995, 28, 446-452, U.S. Pat. No. 5,811,515; U.S. Pat. No. 7,932,397; U.S. Application No. 2011/0065915; U.S. Application No. 2011/0245477; Yu et al., "Synthesis of Macrocyclic Natural Products by Catalyst-Controlled Stereoselective Ring-Closing Metathesis," Nature 2011, 479, 88; and Peryshkov et al., "Z-Selective Olefin Metathesis Reactions Promoted by Tungsten Oxo Alkylidene Complexes," J. Am. Chem. Soc. 2011, 133, 20754. In yet other cases, the reactive groups are thiol groups. In such embodiments, the macrocyclization reagent is, for example, a linker functionalized with two thiol-reactive groups such as halogen groups. In some examples, the macrocyclization reagent include palladium reagents, for example $Pd(PPh_3)_4$, $Pd(PPh_3)_2Cl_2$, Pd(dppe)Cl, $Pd(dppp)Cl_2$, and $Pd(dppf)Cl_2$.The term "halo" or "halogen" refers to fluorine, chlorine, bromine or iodine or a radical thereof.

[0091] The term "alkyl" refers to a hydrocarbon chain that is a straight chain or branched chain, containing the indicated number of carbon atoms. For example, C_1-C_{10} indicates that the group has from 1 to 10 (inclusive) carbon atoms in it. In the absence of any numerical designation, "alkyl" is a chain (straight or branched) having 1 to 20 (inclusive) carbon atoms in it.

[0092] The term "alkylene" refers to a divalent alkyl (*i.e.*, -R-).

[0093] The term "alkenyl" refers to a hydrocarbon chain that is a straight chain or branched chain having one or more carbon-carbon double bonds. The alkenyl moiety contains the indicated number of carbon atoms. For example, C_2-C_{10} indicates that the group has from 2 to 10 (inclusive) carbon atoms in it. The term "lower alkenyl" refers to a C_2-C_6 alkenyl chain. In the absence of any numerical designation, "alkenyl" is a chain (straight or branched) having 2 to 20 (inclusive) carbon atoms in it.

[0094] The term "alkynyl" refers to a hydrocarbon chain that is a straight chain or branched chain having one or more carbon-carbon triple bonds. The alkynyl moiety contains the indicated number of carbon atoms. For example, C_2-C_{10} indicates that the group has from 2 to 10 (inclusive) carbon atoms in it. The term "lower alkynyl" refers to a C_2-C_6 alkynyl chain. In the absence of any numerical designation, "alkynyl" is a chain (straight or branched) having 2 to 20 (inclusive) carbon atoms in it.

[0095] The term "aryl" refers to a 6-carbon monocyclic or 10-carbon bicyclic aromatic ring system wherein 0, 1, 2, 3, or 4 atoms of each ring are substituted by a substituent. Examples of aryl groups include phenyl, naphthyl and the like. The term "arylalkoxy" refers to an alkoxy substituted with aryl.

[0096] "Arylalkyl" refers to an aryl group, as defined above, wherein one of the aryl group's hydrogen atoms has been replaced with a C_1-C_5 alkyl group, as defined above. Representative examples of an arylalkyl group include, but are not limited to, 2-methylphenyl, 3-methylphenyl, 4-methylphenyl, 2-ethylphenyl, 3-ethylphenyl, 4-ethylphenyl, 2-propylphenyl, 3-propylphenyl, 4-propylphenyl, 2-butylphenyl, 3-butylphenyl, 4-butylphenyl, 2-pentylphenyl, 3-pentylphenyl, 4-pentylphenyl, 2-isopropylphenyl, 3-isopropylphenyl, 4-isopropylphenyl, 2-isobutylphenyl, 3-isobutylphenyl, 4-isobutylphenyl, 2-sec-butylphenyl, 3-sec-butylphenyl, 4-sec-butylphenyl, 2-t-butylphenyl, 3-t-butylphenyl and 4-t-butylphenyl.

[0097] "Arylamido" refers to an aryl group, as defined above, wherein one of the aryl group's hydrogen atoms has been replaced with one or more -$C(O)NH_2$ groups. Representative examples of an arylamido group include 2-C(O)NH2-phenyl, 3-$C(O)NH_2$-phenyl, 4-$C(O)NH_2$-phenyl, 2-$C(O)NH_2$-pyridyl, 3-$C(O)NH_2$-pyridyl, and 4-$C(O)NH_2$-pyridyl,

[0098] "Alkylheterocycle" refers to a C_1-C_5 alkyl group, as defined above, wherein one of the C_1-C_5 alkyl group's hydrogen atoms has been replaced with a heterocycle. Representative examples of an alkylheterocycle group include, but are not limited to, -CH_2CH_2-morpholine, -CH_2CH_2-piperidine, -$CH_2CH_2CH_2$-morpholine, and -$CH_2CH_2CH_2$-imidazole.

[0099] "Alkylamido" refers to a C_1-C_5 alkyl group, as defined above, wherein one of the C_1-C_5 alkyl group's hydrogen atoms has been replaced with a -$C(O)NH_2$ group. Representative examples of an alkylamido group include, but are not limited to, -CH_2-$C(O)NH_2$, -CH_2CH_2-$C(O)NH_2$, -$CH_2CH_2CH_2C(O)NH_2$, -$CH_2CH_2CH_2CH_2C(O)NH_2$, -$CH_2CH_2CH_2CH_2CH_2C(O)NH_2$, -$CH_2CH(C(O)NH_2)CH_3$, -$CH_2CH(C(O)NH_2)CH_2CH_3$, -$CH(C(O)NH_2)CH_2CH_3$, -$C(CH_3)_2CH_2C(O)NH_2$, –$CH_2$-$CH_2$–NH-C(O)-$CH_3$, –$CH_2$-$CH_2$–NH-C(O)-$CH_3$-CH3, and –$CH_2$-$CH_2$–NH-C(O)-$CH$=$CH_2$.

[00100] "Alkanol" refers to a C_1-C_5 alkyl group, as defined above, wherein one of the C_1-C_5 alkyl group's hydrogen atoms has been replaced with a hydroxyl group. Representative examples of an alkanol group include, but are not limited to, -CH_2OH, -CH_2CH_2OH, -$CH_2CH_2CH_2OH$, -$CH_2CH_2CH_2CH_2OH$, -$CH_2CH_2CH_2CH_2CH_2OH$, -$CH_2CH(OH)CH_3$, -$CH_2CH(OH)CH_2CH_3$, -$CH(OH)CH_3$ and -$C(CH_3)_2CH_2OH$.

[00101] "Alkylcarboxy" refers to a C_1-C_5 alkyl group, as defined above, wherein one of the C_1-C_5 alkyl group's hydrogen atoms has been replaced with a --COOH group. Representative examples of an alkylcarboxy group include, but are not limited to, -CH_2COOH, -CH_2CH_2COOH, -$CH_2CH_2CH_2COOH$, -$CH_2CH_2CH_2CH_2COOH$, -$CH_2CH(COOH)CH_3$, -$CH_2CH_2CH_2CH_2CH_2COOH$, -$CH_2CH(COOH)CH_2CH_3$, -$CH(COOH)CH_2CH_3$ and -$C(CH_3)_2CH_2COOH$.

[00102] The term "cycloalkyl" as employed herein includes saturated and partially unsaturated cyclic hydrocarbon groups having 3 to 12 carbons, preferably 3 to 8 carbons, and more preferably 3 to 6 carbons, wherein the cycloalkyl group additionally is optionally substituted. Some cycloalkyl groups include, without limitation, cyclopropyl, cyclobutyl, cyclopentyl, cyclopentenyl, cyclohexyl, cyclohexenyl, cycloheptyl, and cyclooctyl.

[00103] The term "heteroaryl" refers to an aromatic 5-8 membered monocyclic, 8-12 membered bicyclic, or 11-14 membered tricyclic ring system having 1-3 heteroatoms if monocyclic, 1-6 heteroatoms if bicyclic, or 1-9 heteroatoms if tricyclic, said heteroatoms selected from O, N, or S (*e.g.*, carbon atoms and 1-3, 1-6, or 1-9 heteroatoms of O, N, or S if monocyclic, bicyclic, or tricyclic, respectively), wherein 0, 1, 2, 3, or 4 atoms of each ring are substituted by a substituent. Examples of heteroaryl groups include pyridyl, furyl or furanyl, imidazolyl, benzimidazolyl, pyrimidinyl, thiophenyl or thienyl, quinolinyl, indolyl, thiazolyl, and the like.

[00104] The term "heteroarylalkyl" or the term "heteroaralkyl" refers to an alkyl substituted with a heteroaryl. The term "heteroarylalkoxy" refers to an alkoxy substituted with heteroaryl.

[00105] The term "heteroarylalkyl" or the term "heteroaralkyl" refers to an alkyl substituted with a heteroaryl. The term "heteroarylalkoxy" refers to an alkoxy substituted with heteroaryl.

[00106] The term "heterocyclyl" refers to a nonaromatic 5-8 membered monocyclic, 8-12 membered bicyclic, or 11-14 membered tricyclic ring system having 1-3 heteroatoms if monocyclic, 1-6 heteroatoms if bicyclic, or 1-9 heteroatoms if tricyclic, said heteroatoms selected from O, N, or S (*e.g.*, carbon atoms and 1-3, 1-6, or 1-9 heteroatoms of O, N, or S if monocyclic, bicyclic, or tricyclic, respectively), wherein 0, 1, 2 or 3 atoms of each ring are substituted by a substituent. Examples of heterocyclyl groups include piperazinyl, pyrrolidinyl, dioxanyl, morpholinyl, tetrahydrofuranyl, and the like.

[00107] The term "substituent" refers to a group replacing a second atom or group such as a hydrogen atom on any molecule, compound or moiety. Suitable substituents include, without limitation, halo, hydroxy, mercapto, oxo, nitro, haloalkyl, alkyl, alkaryl, aryl, aralkyl, alkoxy, thioalkoxy, aryloxy, amino, alkoxycarbonyl, amido, carboxy, alkanesulfonyl, alkylcarbonyl, and cyano groups.

[00108] In some embodiments, the compounds disclosed herein contain one or more asymmetric centers and thus occur as racemates and racemic mixtures, single enantiomers, individual diastereomers and diastereomeric mixtures. All such isomeric forms of these compounds are included unless expressly provided otherwise. In some embodiments, the compounds disclosed herein are also represented in multiple tautomeric forms, in such instances, the compounds include all tautomeric forms of the compounds described herein (*e.g.*, if alkylation of a ring system results in alkylation at multiple sites, the disclosure includes all such reaction products). All such isomeric forms of such compounds are included unless expressly provided otherwise. All crystal forms of the compounds described herein are included unless expressly provided otherwise.

[00109] As used herein, the terms "increase" and "decrease" mean, respectively, to cause a statistically significantly (*i.e.*, $p < 0.1$) increase or decrease of at least 5%.

[00110] As used herein, the recitation of a numerical range for a variable is intended to convey that the variable is equal to any of the values within that range. Thus, for a variable which is inherently discrete, the variable is equal to any integer value within the numerical range, including the end-points of the range. Similarly, for a variable which is inherently continuous, the variable is equal to any real value within the numerical range, including the end-points of the range. As an example, and without limitation, a variable which is described as having values

between 0 and 2 takes the values 0, 1 or 2 if the variable is inherently discrete, and takes the values 0.0, 0.1, 0.01, 0.001, or any other real values ≥ 0 and ≤ 2 if the variable is inherently continuous.

[00111] As used herein, unless specifically indicated otherwise, the word "or" is used in the inclusive sense of "and/or" and not the exclusive sense of "either/or."

[00112] The term "on average" represents the mean value derived from performing at least three independent replicates for each data point.

[00113] The term "biological activity" encompasses structural and functional properties of a macrocycle. Biological activity is, for example, structural stability, alpha-helicity, affinity for a target, resistance to proteolytic degradation, cell penetrability, intracellular stability, *in vivo* stability, or any combination thereof.

[00114] The term "binding affinity" refers to the strength of a binding interaction, for example between a peptidomimetic macrocycle and a target. Binding affinity can be expressed, for example, as an equilibrium dissociation constant ("K_D"), which is expressed in units which are a measure of concentration (e.g. M, mM, μM, nM etc). Numerically, binding affinity and K_D values vary inversely, such that a lower binding affinity corresponds to a higher K_D value, while a higher binding affinity corresponds to a lower K_D value. Where high binding affinity is desirable, "improved" binding affinity refers to higher binding affinity and therefore lower K_D values.

[00115] The term "in vitro efficacy" refers to the extent to which a test compound, such as a peptidomimetic macrocycle, produces a beneficial result in an in vitro test system or assay. In vitro efficacy can be measured, for example, as an "IC_{50}" or "EC_{50}" value, which represents the concentration of the test compound which produces 50% of the maximal effect in the test system.

[00116] The term "ratio of in vitro efficacies" or "in vitro efficacy ratio" refers to the ratio of IC_{50} or EC_{50} values from a first assay (the numerator) versus a second assay (the denominator). Consequently, an improved in vitro efficacy ratio for Assay 1 versus Assay 2 refers to a lower value for the ratio expressed as IC_{50}(Assay 1)/IC_{50}(Assay 2) or alternatively as EC_{50}(Assay 1)/EC_{50}(Assay 2). This concept can also be characterized as "improved selectivity" in Assay 1 versus Assay 2, which can be due either to a decrease in the IC_{50} or EC_{50} value for Target 1 or an increase in the value for the IC_{50} or EC_{50} value for Target 2.

[00117] "Micelle forming agent" as used herein can be an amphiphilic compound meaning a compound that contains both hydrophobic groups (tails) and hydrophilic groups (heads). Micelle forming agents include surfactant, for examples ionic, non-ionic, and zwitterionic surfactants.

[00118] The details of one or more particular embodiments of the invention are set forth in the accompanying drawings and the description below. Other features, objects, and advantages of the invention will be apparent from the description and drawings, and from the claims.

The term "Xaa" is used in the Formulas described herein to refer to any amino acids. This term can sometimes be followed by a number subscript, for e.g. "Xaa_6." The number subscript in these cases may or may not refer to the

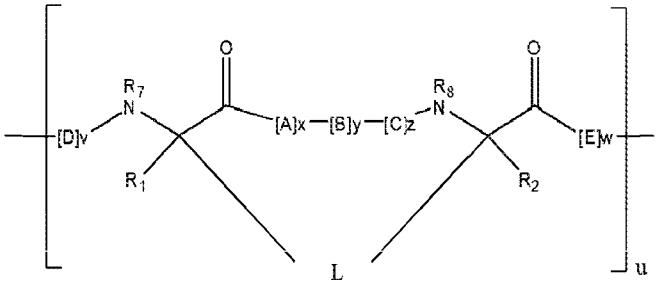
position of the amino acids "Xaa" in a sequence. For example in some but not all cases Xaa_6 can mean that the amino acid "Xaa" is present at the sixth position in a sequence.

OVERVIEW

[00119] In one aspect the disclosure provides aqueous pharmaceutical formulations, for parenteral administration, comprising peptidomimetic macrocycle or a pharmaceutically acceptable salt thereof, wherein the peptidomimetic macrocycle binds to MDM2 and/or MDMX proteins. The aqueous pharmaceutical formulations provided herein are aqueous solution ready for injection (for example intravenously) or aqueous concentrations ready for dilution and injection. In some embodiments, the aqueous pharmaceutical formulations disclosed herein do not contain micelles or are essentially free of micelles. In various embodiments, the aqueous pharmaceutical formulations disclosed herein comprise less than 2% w/v of a micelle forming agent. In some examples the aqueous pharmaceutical formulations disclosed herein comprise less than 2%, 1.9%, 1.8%, 1.7%,1 .6%, 1.5%, 1.4%, 1.3%, 1.2%, 1.1%, 1.0%, 0.9%, 08%, 0.7%, 0.6%, 0.5%, 0.4%, 0.3%, 0.2%, 0.1%, 0.09%, 0.08%, 0.07%, 0.06%, or 0.05% w/v of a micelle forming agent. In some embodiments, the micelle forming agent is sorbitol. In some embodiments, the micelle forming agent is polyethylene glycol-poly(lactic acid). In some embodiments, the micelle forming agent is 1,2-distearoyl-phosphatidylethanolamine-methyl-polyethyleneglycol conjugate. In some embodiments, no micelle forming agent is used, yet the molecule has micelle forming properties.

[00120] The aqueous pharmaceutical formulations comprise an aqueous diluent. In some examples, the diluent is water, purified water, water for injection, bacteriostatic water for injection, sterile water for injection, water for parenterals, PBS, and/or, sterile water for irrigation. In some embodiments, the diluent is water for injection. In some embodiments, the diluent is PBS. In some embodiments, the diluent is a solution of dextrose in water, for example 5% dextrose in water.

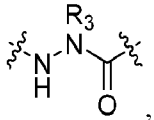
[00121] In various embodiments, the peptidomimetic macrocycle is a cross-linked peptide comprising at least one macrocycle-forming linker which forms a macrocycle between a first amino acid residue (or analog) and a second amino acid residue. In some embodiments, a peptidomimetic macrocycle has the Formula (I):



Formula (I)

wherein:

each A, C, and D is independently an amino acid;

each B is independently an amino acid, , [–NH–L_3–CO–], [–NH–L_3–SO_2–], or

[–NH–L_3–];

each E is independently an amino acid selected from the group consisting of Ala (alanine), D–Ala (D–alanine), Aib (α–aminoisobutyric acid), Sar (N–methyl glycine), and Ser (serine);

each R_1 and R_2 is independently –H, alkyl, alkenyl, alkynyl, arylalkyl, cycloalkyl, cycloalkylalkyl, heteroalkyl, or heterocycloalkyl, unsubstituted or substituted with halo; or forms a macrocycle–forming linker L' connected to the alpha position of one of said D or E amino acids;

each R_3 is independently hydrogen, alkyl, alkenyl, alkynyl, arylalkyl, heteroalkyl, cycloalkyl, heterocycloalkyl, cycloalkylalkyl, cycloaryl, or heterocycloaryl, optionally substituted with R_5;

each L and L' is independently a macrocycle–forming linker;

each L_3 is independently alkylene, alkenylene, alkynylene, heteroalkylene, cycloalkylene, heterocycloalkylene, cycloarylene, heterocycloarylene, or $[-R_4\text{-}K\text{-}R_4-]_n$, each being optionally substituted with R_5;

each R_4 is independently alkylene, alkenylene, alkynylene, heteroalkylene, cycloalkylene, heterocycloalkylene, arylene, or heteroarylene;

each K is independently O, S, SO, SO_2, CO, CO_2, or $CONR_3$;

each R_5 is independently halogen, alkyl, $–OR_6$, $–N(R_6)_2$, $–SR_6$, $–SOR_6$, $–SO_2R_6$, $–CO_2R_6$, a fluorescent moiety, a radioisotope or a therapeutic agent;

each R_6 is independently –H, alkyl, alkenyl, alkynyl, arylalkyl, cycloalkylalkyl, heterocycloalkyl, a fluorescent moiety, a radioisotope or a therapeutic agent;

each R_7 is independently –H, alkyl, alkenyl, alkynyl, arylalkyl, cycloalkyl, heteroalkyl, cycloalkylalkyl, heterocycloalkyl, cycloaryl, or heterocycloaryl, optionally substituted with R_5, or part of a cyclic structure with a D residue;

each R_8 is independently –H, alkyl, alkenyl, alkynyl, arylalkyl, cycloalkyl, heteroalkyl, cycloalkylalkyl, heterocycloalkyl, cycloaryl, or heterocycloaryl, optionally substituted with R_5, or part of a cyclic structure with an E residue;

each v is independently an integer from 1–1000;

each w is independently an integer from 3–1000;

u is an integer from 1–10;

each x, y and z is independently an integer from 0–10; and

each n is independently an integer from 1–5.

[00122] In some embodiments, the macrocycle-forming linker (L or L') has a formula $–L_1–L_2–$, wherein

L_1 and L_2 are independently alkylene, alkenylene, alkynylene, heteroalkylene, cycloalkylene, heterocycloalkylene, cycloarylene, heterocycloarylene, or $[-R_4\text{-}K\text{-}R_4-]_n$, each being optionally substituted with R_5;

each R_4 is independently alkylene, alkenylene, alkynylene, heteroalkylene, cycloalkylene, heterocycloalkylene, arylene, or heteroarylene;

each K is independently O, S, SO, SO_2, CO, CO_2, or $CONR_3$; and

each R_3 independently is hydrogen, alkyl, alkenyl, alkynyl, arylalkyl, heteroalkyl, cycloalkyl, heterocycloalkyl, cycloalkylalkyl, cycloaryl, or heterocycloaryl, optionally substituted with R_5;
each n is an integer from 1-5.

[00123] In some embodiments the peptidomimetic macrocycle is a p53 –based peptidomimetic macrocycle capable of binding to and modulating the activity of p53, MDM2 and/or MDMX. In some embodiments the peptidomimetic macrocycle is a p53-based peptidomimetic macrocycle that inhibits the interactions between p53, MDM2 and/or MDMX proteins. In some embodiments the peptidomimetic macrocycle is a p53-based peptidomimetic macrocycle that can be used for treating diseases including but not limited to cancer and other hyperproliferative diseases. In some examples, the peptidomimetic macrocycle has a Formula I and comprises an amino acid sequence which is at least about 60%, 65%, 70%, 75%, 80%, 85%, 90%, 95%, 99% or more identical to an amino acid sequence in any of **Table 1**, **Table 1a**, **Table 1b**, and **Table 1c**. In some examples, the peptidomimetic macrocycle in a peptidomimetic macrocycle from the any of **Table 1**, **Table 1a**, **Table 1b**, and **Table 1c**.

[00124] Any suitable dosage of peptidomimetic macrocycles can be formulated in the aqueous pharmaceutical formulations of the present disclosure. Generally, the peptidomimetic macrocycle (or, in embodiments comprising two or more peptidomimetic macrocycles, each of the peptidomimetic macrocycle) is present in the aqueous pharmaceutical formulation in an amount greater than or equal to 1mg/mL. For example greater than or equal to 5 mg/mL, 10 mg/mL, 15 mg/mL, 20 mg/mL, 30 mg/mL, 40 mg/mL, and 50 mg/mL. In some examples, the peptidomimetic macrocycle is present in the aqueous pharmaceutical formulation in an amount ranging from about 15 mg/mL to about 100 mg/mL. In some embodiments, the peptidomimetic macrocycle is present in the aqueous pharmaceutical formulation in an amount ranging from about 15 mg/mL to about 60 mg/mL. In some embodiments, the peptidomimetic macrocycle is present in the aqueous pharmaceutical formulation in an amount ranging from about 20 mg/mL to about 50 mg/mL. In some embodiments, the peptidomimetic macrocycle is present in the aqueous pharmaceutical formulation in an amount ranging from about 50 mg/mL to about 100 mg/mL. In some embodiments, the peptidomimetic macrocycles is present in the aqueous pharmaceutical formulation in an amount ranging from about 15 mg/mL to about 20 mg/mL. In some embodiments, the peptidomimetic macrocycles is present in the aqueous pharmaceutical formulation in an amount ranging from about 15 mg/mL to about 30 mg/mL. It will be readily apparent to those of skill that the peptidomimetic macrocycle dosage can be varied depending on several conditions including the peptidomimetic macrocycle used, the subject to be treated, and the disease, disorder or condition to be treated.

[00125] The aqueous pharmaceutical formulations disclosed herein can additionally comprise a buffering agent. The buffering agent can be any agent capable of maintaining the pH of the aqueous formulation in the range of 4.0-9.0. For example, the buffering agent is selected from a group consisting of ammonia solution, calcium carbonate, tribasic calcium phosphate, citric acid monohydrate, dibasic sodium phosphate, diethanolamine, malic acid, monobasic sodium phosphate, monoethanolamine, monosodium glutamate, phosphoric acid, potassium

citrate, sodium acetate, sodium bicarbonate, sodium borate, sodium citrate dehydrate, sodium hydroxide, sodium lactate and triethanolamine. In some embodiments, the buffering agent can be monobasic sodium phosphate, dibasic sodium phosphate, or a mixture thereof. The pH of the formulation can be in the range of 4.0-9.0. For example, the pH can be in the range of about 4.5-8.5, about 5.0-8.0, about 5.5-7.5, about 7.0-7.5, about 7.0-8.0, about 7.0-9.0, or about 8.0-9.0. In some embodiments, the pH of the formulations is about 7.0. In some embodiments, the pH of the formulations is about 7.5. In some embodiments, the pH of the formulations is about 8.0.

[00126] The aqueous pharmaceutical formulations disclosed herein can comprise a stabilizing agent. The stabilizing agent can be any pharmaceutically acceptable stabilizing agent. Such stabilizing agent can include, for example antioxidants and/or surfactants. In some embodiments, the stabilizing agent is a non-ionic stabilizing agent, for example as non-ionic surfactant. In some embodiments, the stabilizing agent is a fatty acid ester. The stabilizing agent can be selected from a group consisting of polyoxyethylene glycol alkyl ethers, polyoxypropylene glycol alkyl ethers, glucoside alkyl ethers, polyoxyethylene glycol octylphenol ethers, polyoxyethylene glycol alkylphenol ethers, glycerol alkyl esters, polyoxyethylene glycol sorbitan alkyl esters, sorbitan alkyl esters, cocamide MEA, cocamide DEA, dodecyldimethylamine oxide, block copolymers of polyethylene glycol and polypropylene glycol, and polyethoxylated tallow amine. In some examples, the stabilizing agent is a polyoxyethylene sorbitan fatty acid ester, for example polysorbate 20, polysorbate 21, polysorbate 40, polysorbate 60, polysorbate 61, polysorbate 65, polysorbate 80, polysorbate 81, polysorbate 85 or polysorbate 120.

[00127] In some embodiments, the tonicity of the instant aqueous pharmaceutical formulations can be adjusted, for example the tonicity of the formulations can be such that the formulations are isotonic with the physiologic fluid. Such formulations can further comprise one or more tonicity adjusting agent (tonicity agent) to adjust the tonicity of the formulations. Any pharmaceutically acceptable tonicity agent can be used. In some examples the tonicity agents are selected from a group consisting of electrolytes, monosaccharides, disaccharides, polysaccharides, and water-soluble glucans. In some examples the tonicity agent in NaCl or KCl. In some examples the tonicity agent is selected from a group consisting of fructose, glucose, mannose, mannitol, sorbose, xylose, maltose, lactose, sucrose, trehalose, dextran, pullulan, dextrin, cyclodextrin, soluble starch, hydroxyethyl starch and carboxymethylcellulose. In some embodiments, the tonicity agent is trehalose.

[00128] In some examples, the formulations of the present disclosure further comprise one or more additional excipients. For example a preservative or a co-solvent.

[00129] Also provided herein are methods of making the aqueous pharmaceutical formulations disclosed herein. The method comprises adding a peptidomimetic macrocycle or a pharmaceutically acceptable salt thereof to an aqueous solution. The aqueous solution can comprise one or more of a buffering agent, a stabilizing agent, and a tonicity agent. The method can further comprise adding a pH adjusting agent to maintain the pH of the mixture at a specified level. In some embodiments, the method comprises adding a desired amount of the peptidomimetic

macrocycle or a pharmaceutically acceptable salt (for example sodium, potassium or lithium salt) thereof to water. In some embodiments, the method comprises adding a desired amount of the peptidomimetic macrocycle or a pharmaceutically acceptable salt thereof to an aqueous solution comprising a buffering agent, a stabilizing agent, and a tonicity agent.

[00130] Also provided herein is a method for treating a disease, condition or disorder that can be treated, alleviated, or prevented by administering to a subject an aqueous pharmaceutical formulation as described herein. The method comprises, administering to the subject the aqueous pharmaceutical formulation in an amount effective to treat, alleviate or prevent the disease, condition, or disorder. In some embodiments, the disease, condition, or disorder is a p53 mediated disease, condition, or disorder. In some embodiments, the disease, condition, or disorder is a MDM2 and/or MDMX mediated disease, condition, or disorder. In some embodiments, the disease, condition, or disorder is a hyperproliferative disease and/or an inflammatory disorder. In some embodiments, the disease, condition, or disorder is cancers and neoplastic conditions. In some examples, the cancer is selected from a group consisting of pancreatic cancer, bladder cancer, colon cancer, liver cancer, colorectal cancer, breast cancer, prostate cancer, renal cancer, hepatocellular cancer, lung cancer, ovarian cancer, cervical cancer, gastric cancer, esophageal cancer, head and neck cancer, melanoma, neuroendocrine cancers, CNS cancers, brain tumors, bone cancer, skin cancer, ocular tumor, rectal cancer, choriocarcinoma (tumor of the placenta), sarcoma and soft tissue cancer, testicular cancer, gall bladder cancer, and biliary cancer. In some examples, the cancer is selected from a group consisting of bladder cancer, bone cancer, breast cancer, cervical cancer, CNS cancer, colon cancer, ocular tumor, renal cancer, liver cancer, lung cancer, pancreatic cancer, choriocarcinoma (tumor of the placenta), prostate cancer, sarcoma, skin cancer, soft tissue cancer, gastric cancer, gall bladder cancer, biliary cancer, renal cancer, neoblastoma, or neuroendocrine cancer. Non-limiting examples of ocular tumor include choroidal nevus, choroidal melanoma, choroidal metastasis, choroidal hemangioma, choroidal osteoma, iris melanoma, uveal melanoma, melanocytoma, metastasis retinal capillary hemangiomas, congenital hypertrophy of the RPE, RPE adenoma or retinoblastoma. In some cases, the cancer is selected from non-small cell lung cancer, small-cell lung cancer, colon cancer, CNS cancer, melanoma, ovarian cancer, renal cancer, prostate cancer and breast cancer. In some examples, the cancer is breast cancer. In some examples, the cancer is gall bladder cancer. In some examples, the cancer is biliary cancer. In some examples, the cancer is neuroendocrine cancer. In some examples, the cancer is bone cancer. In some examples, the cancer is the bone cancer is osteosarcoma. In some examples, the cancer is skin cancer. In some examples, the cancer is melanoma.

[00131] In another aspect, the present disclosure provides kits for treating a disease, condition or disorder, wherein the kit comprises the aqueous pharmaceutical disclosed herein. The formulations can be packaged in any suitable container, for example a bottle or a vial. In some examples, the formulations can be packed in glass serum vial. In some examples, the formulations can be packed in serum vials composed of borosilicate glass. In some examples, the formulations are packed in a 1 mL, a 2 mL, a 3 mL, a 4 mL, a 5 mL, a 10 mL, a 20 mL, a 30 mL, or a 50 mL glass vial. The bottles and/or vials can be equipped with stoppers and/or seals. For example, the formulations can

be packaged into glass vials equipped with Teflon stoppers and/or a flip-off cap. The flip-off cap can be a plastic cap. The glass container can be an ampoule. The formulations can be packaged in multidose form or in single dose form. In some cases, the formulations are packaged in multidose forms. In some embodiments the formulations are packaged as single dose units. In some embodiments, the kit further comprises instructions, wherein the instructions direct the administration of the formulation to treat the subject in need thereof. The kit can also include a device for administration of the formulation.

AQUEOUS PHARMACEUTICAL FORMULATIONS OF PEPTIDOMIMETIC MACROCYCLES FOR PARENTERAL ADMINISTRATION

[00132] In one aspect, the disclosure provides aqueous pharmaceutical formulations, suitable for parenteral administration, comprising peptidomimetic macrocycles, as described herein and an aqueous diluent. The aqueous pharmaceutical formulations provided herein can be suitable for intravenous, intra-arterial, intrathecal, or subcutaneous administration. In some embodiments, the aqueous pharmaceutical formulations are suitable for intravenous administration.The aqueous pharmaceutical formulations described herein can provide improved solubility and/or stability of the peptidomimetic macrocycle. In particular embodiments, the aqueous pharmaceutical formulations provide increased solubility of the peptidomimetic macrocycles compared to the solubility of the peptidomimetic macrocycles peptide in water alone.

[00133] In some examples, the aqueous diluent is water, purified water, water for injection, bacteriostatic water for injection, sterile water for injection, water for parenterals, sterile water for irrigation, various sterile solution of electrolytes and or dextrose. In some embodiments, the diluent is a pH buffered solution (e.g. phosphate-buffered saline), sterile saline solution, Ringer's solution or dextrose solution. In some embodiments, the diluent is water for injection. In some embodiments, the diluent is a solution of dextrose in water, for example 5% dextrose in water.

[00134] The aqueous pharmaceutical formulations my further comprise a co-solvent. A co-solvent is any solvent that facilitates/enhances the solubility of the peptidomimetic macrocycles (or of the one or more excipients) in the aqueous diluent. The co-solvent is preferably water miscible. In some embodiments, the co-solvent is ethyl alcohol, glycerin, polyethylene glycol, or propylene glycol. In some embodiments, the co-solvent is dimethyl sulfoxide (DMSO), N-methylpyrrolidone (NMP), dimethylacetamide (DMA) or a combination thereof.

[00135] The aqueous pharmaceutical formulations provided herein are aqueous solution ready for injection (for example intravenously) or aqueous concentrations ready for dilution and injection. In some embodiments, the aqueous pharmaceutical formulations disclosed herein do not contain micelles or are essentially free of micelles. In various embodiments, the aqueous pharmaceutical formulations disclosed herein comprise less than 2% w/v of a micelle forming agent. In some examples the aqueous pharmaceutical formulations disclosed herein comprise less than 2%, 1.9%, 1.8%, 1.7%,1 .6%, 1.5%, 1.4%, 1.3%, 1.2%, 1.1%, 1.0%, 0.9%, 08%, 0.7%, 0.6%, 0.5%, 0.4%, 0.3%, 0.2%, 0.1%, 0.09%, 0.08%, 0.07%, 0.06%, or 0.05% w/v of a micelle forming agent. In some

examples the aqueous pharmaceutical formulations disclosed herein comprise 0.0001%-2%, 0.0005%-2%, 0.001%-2%, 0.005%-2%, 0.01%-2%, 0.05%-2%, 0.1%-2%, 0.2%-2%, 0.3%-2%, 0.4%-2%, 0.5%-2%, 0.6%-2%, 0.7%-2%, 0.8%-2%, 0.9%-2%, 1.0%-2%, 1.1%-2%, 1.2%-2%, 1.3%-2%, 1.4%-2%, 1.5%-2%,1.6%-2%, 1.7%-2%, 1.8%-2%, 1.9%-2%, 0.0001%-1.8%, 0.0005%-1.8%, 0.001%-1.8%, 0.005%-1.8%, 0.01%-1.8%, 0.05%-1.8%, 0.1%-1.8%, 0.2%-1.8%, 0.3%-1.8%, 0.4%-1.8%, 0.5%-1.8%, 0.6%-1.8%, 0.7%-1.8%, 0.8%-1.8%, 0.9%-1.8%, 1.0%-1.8%, 1.1%-1.8%, 1.2%-1.8%, 1.3%-1.8%, 1.4%-1.8%, 1.5%-1.8%,1.6%-1.8%, 0.0001%-1.6%, 0.0005%-1.6%, 0.001%-1.6%, 0.005%-1.6%, 0.01%-1.6%, 0.05%-1.6%, 0.1%-1.6%, 0.2%-1.6%, 0.3%-1.6%, 0.4%-1.6%, 0.5%-1.6%, 0.6%-1.6%, 0.7%-1.6%, 0.8%-1.6%, 0.9%-1.6%, 1.0%-1.6%, 1.1%-1.6%, 1.2%-1.6%, 1.3%-1.6%, 1.4%-1.6%, 1.5%-1.6%, 0.0001%-1.4%, 0.0005%-1.4%, 0.001%-1.4%, 0.005%-1.4%, 0.01%-1.4%, 0.05%-1.4%, 0.1%-1.4%, 0.2%-1.4%, 0.3%-1.4%, 0.4%-1.4%, 0.5%-1.4%, 0.6%-1.4%, 0.7%-1.4%, 0.8%-1.4%, 0.9%-1.4%, 1.0%-1.4%, 1.1%-1.4%, 1.2%-1.4%, 1.3%-1.4%, 0.0001%-1.2%, 0.0005%-1.2%, 0.001%-1.2%, 0.005%-1.2%, 0.01%-1.2%, 0.05%-1.2%, 0.1%-1.2%, 0.2%-1.2%, 0.3%-1.2%, 0.4%-1.2%, 0.5%-1.2%, 0.6%-1.2%, 0.7%-1.2%, 0.8%-1.2%, 0.9%-1.2%, 1.0%-1.2%, 1.1%-1.2%, 0.0001%-1%, 0.0005%-1%, 0.001%-1%, 0.005%-1%, 0.01%-1%, 0.05%-1%, 0.1%-1%, 0.2%-1%, 0.3%-1%, 0.4%-1%, 0.5%-1%, 0.6%-1%, 0.7%-1%, 0.0001%-0.8%, 0.0005%-0.8%, 0.001%-0.8%, 0.005%-0.8%, 0.01%-0.8%, 0.05%-0.8%, 0.1%-0.8%, 0.2%-0.8%, 0.3%-0.8%, 0.4%-0.8%, 0.5%-0.8%, 0.6%-0.8%, 0.7%-0.8%, 0.0001%-0.6%, 0.0005%-0.6%, 0.001%-0.6%, 0.005%-0.6%, 0.01%-0.6%, 0.05%-0.6%, 0.1%-0.6%, 0.2%-0.6%, 0.3%-0.6%, 0.4%-0.6%, 0.5%-0.6%, 0.0001%-0.4%, 0.0005%-0.4%, 0.001%-0.4%, 0.005%-0.4%, 0.01%-0.4%, 0.05%-0.4%, 0.1%-0.4%, 0.2%-0.4%, 0.3%-0.4%, 0.0001%-0.2%, 0.0005%-0.2%, 0.001%-0.2%, 0.005%-0.2%, 0.01%-0.2%, 0.05%-0.2%, 0.1%-0.2%, 0.0001%-0.1%, 0.0005%-0.1%, 0.001%-0.1%, 0.005%-0.1%, 0.01%-0.1%, 0.05%-0.1, 0.0001%-0.05%, 0.0005%-0.05%, 0.001%-0.05%, 0.005%-0.05%, 0.01%-0.05%, 0.0001%-0.01%, 0.0005%-0.01%, 0.001%-0.01%, 0.005%-0.01%, 0.0001%-0.005%, 0.0005%-0.005%, 0.001%-0.005%, 0.0001%-0.001%, 0.0005%-0.001%, or 0.0001%-0.0005% w/v of a micelle forming agent. In some embodiments, the micelle forming agent is sorbitol. In some embodiments, the micelle forming agent is Polyethylene glycol-Poly(lactic acid). In some embodiments, the micelle forming agent is 1,2-Distearoyl-phosphatidylethanolamine-methyl-polyethyleneglycol conjugate. In some embodiments, no micelle-forming agent is added in the formulation, but the molecule has micelle-forming properties.

[00136] The aqueous pharmaceutical formulations disclosed herein can additionally comprise one or more excipients suitable for aqueous pharmaceutical formulations. Exemplary excipients that can be present in the aqueous pharmaceutical formulations described herein are described below.

Buffering agents

[00137] The aqueous pharmaceutical formulation of the disclosure can comprise one or more buffering agent, for example a pharmaceutically acceptable buffering agent. Buffering agent can be used to control pH of the formulation and/or to maintain stability of the peptidomimetic macrocycle. The pH range of the aqueous pharmaceutical formulation can be pH 2 to pH 12, pH 4 to pH 9, pH 5 to pH9, or pH 6 to pH 8. In some

embodiments the aqueous solution is buffered to a pH of about 5.0-9.0. In some embodiments the aqueous pharmaceutical formulation is buffered to a pH of about 6.0-8.0. In some embodiments the pH of the aqueous pharmaceutical formulation is in the range of about 6.5-8.0, about 7.0-8.0, about 7.5-8.0, about 6.0-7.5, about 6.5-7.5, about 7.0-7.5, 6.0-7.0, about 6.5-7.0, about 7.0-7.5, or about 7.5-8.0. In some embodiments the aqueous solution is buffered to a pH of about 6.0, about 6.5, about 7.0, about 7.5, about 8.0 or about 8.5. In some embodiments the aqueous pharmaceutical formulation is buffered to a pH of about 7.0, about 7.1, about 7.2, about 7.3, about 7.4, about 7.5, about 7.6, about 7.7, about 7.8, about 7.9, or about 8.0. In some embodiments the aqueous pharmaceutical formulation is buffered to a pH of about 7.3-7.5.

[00138] Any buffering that can be safe for injection into mammalian tissue, particularly into humans, can be used in the pharmaceutical formulation of the disclosure. Buffering agent can be any agent capable of driving an acidic or basic solution to a certain pH state, and then preventing a change from that state. Buffering agents that can be used in the instant aqueous pharmaceutical formulations include citrate, acetate, phosphate, maleate, tartrate, borate, carbonate, bicarbonate, succinate, or glutamate buffers.

[00139] In some examples, the buffering agent is lithium lactate, magnesium lactate, sodium lactate, potassium lactate, calcium lactate, lithium phosphate, sodium phosphate, potassium phosphate, calcium phosphate, sodium polyphosphate, potassium polyphosphate, sodium pyrophosphate, potassium pyrophosphate, disodium hydrogenphosphate, dipotassium hydrogenphosphate, trisodium phosphate, tripotassium phosphate, potassium metaphosphate, lithium maleate, sodium maleate, potassium maleate, calcium maleate, lithium tartarate, sodium tartarate, potassium tartarate, calcium tartarate, lithium succinate, sodium succinate, potassium succinate, calcium succinate, lithium acetate, sodium acetate, potassium acetate, calcium acetate, sodium bicarbonate, potassium bicarbonate, magnesium hydroxide, magnesium glucomate, aluminum hydroxide, aluminum hydroxide/ sodium bicarbonate coprecipitate, sodium citrate, sodium tartarate, sodium carbonate, magnesium oxide, magnesium hydroxide, magnesium carbonate, magnesium silicate, calcium glycerophosphate, calcium cholride, calcium hydroxide, calcium lactate, calcium carbonate, calcium bicarbonate, or mixture thereof.

[00140] In some examples, the buffering agent is a citrate buffer. Non-limiting examples of suitable citrate buffers include lithium citrate monohydrate, sodium citrate monohydrate, potassium citrate monohydrate, calcium citrate monohydrate, lithium citrate dihydrate, sodium citrate dihydrate, potassium citrate dihydrate, calcium citrate dihydrate, lithium citrate trihydrate, sodium citrate trihydrate, potassium citrate trihydrate, calcium citrate trihydrate, lithium citrate tetrahydrate, sodium citrate tetrahydrate, potassium citrate tetrahydrate, calcium citrate tetrahydrate, lithium citrate pentahydrate, sodium citrate pentahydrate, potassium citrate pentahydrate, calcium citrate pentahydrate, lithium citrate hexahydrate, sodium citrate hexahydrate, potassium citrate hexahydrate, calcium citrate hexahydrate, lithium citrate heptahydrate, sodium citrate heptahydrate, potassium citrate heptahydrate, or calcium citrate heptahydrate.

[00141] In some examples, the buffering agent is a phosphate buffer. Non-limiting examples of suitable phosphate buffering agents that can be used in the formulations of the instant disclosure include, without limitation,

monobasic sodium phosphate, dibasic sodium phosphate, monobasic potassium phosphate, dibasic potassium phosphate, sodium pyrophosphate, potassium pyrophosphate, disodium hydrogenphosphate, dipotassium hydrogenphosphate, potassium metaphosphate, calcium phosphate, tribasic, calcium phosphate, dibasic anhydrous, calcium phosphate dibasic, hydrate, In one embodiment, the buffering agent is a phosphate buffer. In one embodiment buffering agent is NaH_2PO_4. In one embodiment, the buffering agent is Na_2HPO_4. In one embodiment the buffering agent is a mixture of NaH_2PO_4 and Na_2HPO_4. In one embodiment buffering agent is KH_2PO_4. In one embodiment, the buffering agent is K_2HPO_4. In one embodiment the buffering agent is a mixture of KH_2PO_4 and K_2HPO_4.

Tonicity adjusting agents

[00142] The aqueous pharmaceutical formulations disclosed herein can comprise one or more tonicity adjusting agents in order to adjust the tonicity/osmolarity of the formulations. For example, the tonicity/osmolarity of the aqueous pharmaceutical formulations can be adjusted to be isotonic with human plasma. This can help to avoid damage to the tissues. In various embodiments, the osmolarity of the aqueous pharmaceutical formulations disclosed herein can be in the range of 250 to 1000 mOsM. For example, the osmolarity of the formulations can be about 250-300 mOsM, 250-350 mOsM, 250-400 mOsM, 250-450 mOsM, 250-500 mOsM, 250-550 mOsM, 250-600 mOsM, 250-650 mOsM, 250-700 mOsM, 250-750 mOsM, 250-800 mOsM, 250-850 mOsM, 250-900 mOsM, 250-950 mOsM, 300-350 mOsM, 300-400 mOsM, 300-450 mOsM, 300-500 mOsM, 300-550 mOsM, 300-600 mOsM, 300-650 mOsM, 300-700 mOsM, 300-750 mOsM, 300-800 mOsM, 300-850 mOsM, 300-900 mOsM, 300-950 mOsM, 300-1000 mOsM, 350-400 mOsM, 350-450 mOsM, 350-500 mOsM, 350-550 mOsM, 350-600 mOsM, 350-650 mOsM, 350-700 mOsM, 350-750 mOsM, 350-800 mOsM, 350-850 mOsM, 350-900 mOsM, 350-950 mOsM, 350-1000 mOsM, 400-450 mOsM, 400-500 mOsM, 400-550 mOsM, 400-600 mOsM, 400-650 mOsM, 400-700 mOsM, 400-750 mOsM, 400-800 mOsM, 400-850 mOsM, 400-900 mOsM, 400-950 mOsM, 400-1000 mOsM, 450-500 mOsM, 450-550 mOsM, 450-600 mOsM, 450-650 mOsM, 450-700 mOsM, 450-750 mOsM, 450-800 mOsM, 450-850 mOsM, 450-900 mOsM, 450-950 mOsM, 450-1000 mOsM, 500-550 mOsM, 500-600 mOsM, 500-650 mOsM, 500-700 mOsM, 500-750 mOsM, 500-800 mOsM, 500-850 mOsM, 500-900 mOsM, 500-950 mOsM, 500-1000 mOsM, 550-600 mOsM, 550-650 mOsM, 550-700 mOsM, 550-750 mOsM, 550-800 mOsM, 550-850 mOsM, 550-900 mOsM, 550-950 mOsM, 550-1000 mOsM, 600-650 mOsM, 600-700 mOsM, 600-750 mOsM, 600-800 mOsM, 600-850 mOsM, 600-900 mOsM, 600-950 mOsM, 600-1000 mOsM, 650-700 mOsM, 650-750 mOsM, 650-800 mOsM, 650-850 mOsM, 650-900 mOsM, 650-950 mOsM, 650-1000 mOsM, 700-750 mOsM, 700-800 mOsM, 700-850 mOsM, 700-900 mOsM, 700-950 mOsM, 700-1000 mOsM, 750-800 mOsM, 750-850 mOsM, 750-900 mOsM, 750-950 mOsM, 750-1000 mOsM, 800-850 mOsM, 800-900 mOsM, 800-950 mOsM, 800-1000 mOsM, 850-900 mOsM, 850-950 mOsM, 850-1000 mOsM, 900-950 mOsM, 900-1000 mOsM, or 950-1000 mOsM. In some embodiments, the osmolarity of the formulations is in the range of 250 to 450 mOsM. For example the osmolarity of the formulations can be about 250 mOsM, about 300

mOsM, about 350 mOsM, about 400 mOsM, or about 450 mOsM. In some embodiments, the formulation is isotonic with biologic fluids, i.e., the osmolarity is about 300 mOsM.

[00143] The tonicity adjusting agents can be ionic tonicity adjusting agents or non-ionic tonicity adjusting agents. In some embodiments, the isotonic agent is an ionic-isotonic agent. In some embodiments, the isotonic agent is a non-ionic isotonic agent. In some embodiments, the isotonic agent is a mixture of one or more ionic and/or non-ionic isotonic agent. In a some embodiment of the disclosure the isotonic agent is selected from the group consisting of a salt (e.g. sodium chloride, boric acid, sodium nitrate, potassium nitrate), a sugar or sugar alcohol, an amino acid (e.g. L-glycine, L-histidine, arginine, lysine, isoleucine, aspartic acid, tryptophan, threonine), an alditol (e.g. glycerol (glycerine), 1,2-propanediol (propyleneglycol), 1,3-propanediol, 1,3-butanediol, polyethyleneglycol (e.g. PEG400), or mixtures thereof. Any sugar such as mono-, di-, or polysaccharides, or water-soluble glucans, including for example fructose, glucose, mannose, sorbose, xylose, maltose, lactose, sucrose, trehalose, dextran, pullulan, dextrin, cyclodextrin, soluble starch, hydroxyethyl starch and carboxymethylcellulose-Na can be used. In some examples, the tonicity adjusting agent is selected from a group consisting of dextrose, glycerin, mannitol, trehalose, potassium chloride and sodium chloride. In some example, the tonicity adjusting agent is trehalose, for example D- trehalose. In some example, the tonicity adjusting agent is sodium chloride. In some example, the tonicity adjusting agent is potassium chloride. The use of an tonicity adjusting agent in aqueous pharmaceutical formulations is well-known to the skilled person. For convenience reference is made to Remington: *The Science and Practice of Pharmacy,* 19th edition, 1995.

Stabilizing agent

[00144] The aqueous pharmaceutical formulations described herein comprise a stabilizing agent. Non-limiting examples of stabilizing agents that can be used include acacia, agar, albumin, alginic acid, aluminum stearate, ammonium alginate, arabinose, arginine HCL, ascorbic acid, ascorbyl palmitate, bentonite, butylated hydroxytoluene, calcium alginate, calcium stearate, carboxymethylcellulose calcium, carboxymethylcellulose sodium, carrageenan, cellobiose, cellulose ceratonia, colloidal silicon dioxide, cyclodextrins, diethanolamine, dextran, edentates, ethylcellulose, ethylene glycol palmitostearate, fructose, gentiobiose, glucose, glucosamine, glycine, glycerin monostearate, hydroxypropyl cellulose, hydroxyethyl starch, hypromellose, hyaluronic acid, invert sugar, isomaltose, lactose, lecithin, magnesium aluminum silicate, mannose, mannitol, maltose, mineral oil and lanolin alcohols, monoethanolamine, N-methyl pyrollidone, pectin, polacrilin potassium, poloxamer (for example poloxamer 124, poloxamer 188, poloxamer 237, poloxamer 338, or poloxamer 407), polyoxyethylene sobitan fatty acid esters, polyvinyl alcohol, potassium alginate, potassium chloride, povidone (for example povidone K-12, povidone K-15, povidone K-17, povidone K-25, povidone K-20, povidone K-60, povidone K-90, or povidone K-120), propyl gallate, propylene glycol, propylene glycol alginate, raffinose, sodium acetate, sodium alginate, sodium borate, sodium chloride, sodium stearyl fumarate, sorbitol, stearyl alcohol, sucrose, sulfobutylether β-cyclodextrin, starch, trehalose, white wax, xanthan gum, xylitol, yellow wax and zinc acetate.

[00145] In some embodiments, the stabilizing agent is a polyoxyethylene sobitan fatty acid ester, for example polysorbate 20, polysorbate 21, polysorbate 40, polysorbate 60, polysorbate 61, polysorbate 65, polysorbate 80, polysorbate 81, polysorbate 85 or polysorbate 120. In some embodiments, the stabilizing agent is polysorbate 20. In some embodiments, the stabilizing agent is polysorbate 21. In some embodiments, the stabilizing agent is polysorbate 40. In some embodiments, the stabilizing agent is polysorbate 60. In some embodiments, the stabilizing agent is polysorbate 61. In some embodiments, the stabilizing agent is polysorbate 65. In some embodiments, the stabilizing agent is polysorbate 80. In some embodiments, the stabilizing agent is polysorbate 81. In some embodiments, the stabilizing agent is polysorbate 85. In some embodiments, the stabilizing agent is polysorbate 120.

Preservatives-Antioxidants, Antimicrobial and Chelating Agents

[00146] The aqueous pharmaceutical formulations disclosed herein can comprise one or more antioxidants in order to prevent/minimize the oxidation of the peptidomimetic macrocycle and/or the excipients present in the formulation The antioxidants can also be used as a stabilizing agent. The anti-oxidants which can be used to form aqueous pharmaceutical formulations the disclosure include, but are not limited to, propyl, octyl and dodecyl esters of gallic acid, butylated hydroxyanisole (BHA, usually purchased as a mixture of ortho and meta isomers), green tea extract, uric acid, cysteine, pyruvate, nordihydroguaiaretic acid, ascorbic acid, salts of ascorbic acid such as ascorbyl palmitate and sodium ascorbate, ascorbyl glucosamine, vitamin E (i.e., tocopherols such as a-tocopherol), derivatives of vitamin E (e.g., tocopheryl acetate), retinoids such as retinoic acid, retinol, trans-retinol, cis-retinol, mixtures of trans-retinol and cis-retinol, 3-dehydroretinol and derivatives of vitamin A (e.g., retinyl acetate, retinal and retinyl palmitate, also known as tetinyl palmitate), sodium citrate, sodium sulfite, sodium thiosulfate, sodium bisulfate, lycopene, anthocyanids, bioflavinoids (e.g., hesperitin, naringen, rutin and quercetin), superoxide dismutase, glutathione peroxidase, butylated hydroxytoluene (BHT), indole-3-carbinol, pycnogenol, melatonin, sulforaphane, pregnenolone, lipoic acid and 4-hydroxy-5-methyl-3[2H]-furanone. In various embodiments, one or more of the above antioxidants are excluded, or are present in less than effective amounts.

[00147] In some embodiments the antioxidant is ascorbic acid, citric acid, acetylcysteine, sulfurous acid salts (such as bisulfite, metasulfite), and monothioglyercol.

[00148] The aqueous pharmaceutical formulations can comprise one or more antimicrobial agent. Suitable antimicrobial agents that can be used include alcohol, benzalkonium chloride, benzyl alcohol, boric acid, bronopol, butylated hydroxyanisole, butylparaben, carbon dioxide, bentonite, cetrimide, cetylpyridinium chloride, chlorbutanol, chlorhexidine, chlorobutanol, chlorocresol, chloroxylenol, cresol (meta cresol), dimethyl ether, ethylparaben, glycerin, hexetidine, imidurea, inactivation by magnesium trisilicate, isopropyl alcohol, lactic acid, methylparaben, monothioglycerol, parabens (methyl, propyl, butyl), phenol, phenoxyethanol, phenylethyl alcohol, phenylmercuric salts (acetate, borate, nitrate) phenylmercuric borate, phenylmercuric nitrate, potassium benzoate, potassium metabisulfite, potassium sorbate, propionic acid, propyl gallate, propylene glycol, propylparaben,

sodium acetate, sodium benzoate, sodium borate, sodium lactate, sodium metabisulfite, sodium propionate, sodium sulfite, sorbic acid, synergists, edetic acid, thimerosal, xylitol, or other agents known to those skilled in the art. In some embodiments, the antimicrobial agent used is methyl paraben, ethyl paraben, propyl paraben, or a combination thereof. In some embodiments, the antimicrobial agent used is benzalkonium chloride.

[00149] The aqueous pharmaceutical formulations disclosed herein can comprise one or more chelating agents. Non-limiting examples of chelating agents which can be used to form aqueous pharmaceutical formulations of the disclosure include, but are not limited to, ethylene diaminetetraacetic acid (EDTA), EDTA disodium, calcium disodium edetate, EDTA trisodium, albumin, transferrin, desferoxamine, desferal, desferoxamine mesylate, EDTA tetrasodium and EDTA dipotassium, sodium metasilicate, citric acid monohydrate, fumaric acid, malic acid, maltol, or combinations of any of these. In some embodiments, the formulations of the current disclosure contain no or essentially no chelating agents. In some further embodiments, the formulations are solutions containing no chelating agents.

[00150] In some embodiments, the aqueous pharmaceutical formulations of the disclosure comprise no or essentially no preservatives. In some further embodiments, the aqueous pharmaceutical formulations are solutions containing no preservatives.

Surfactants

[00151] The solubility of the components of the present formulations can be enhanced by a surfactant or other appropriate co-solvent in the composition. Such co-solvents include polysorbate 20, 60, and 80, Pluronic® F68, F-84 and P-103, cyclodextrin, or other agents known to those skilled in the art. Such co-solvents can be employed at a level of from about 0.01% to 2% by weight. In addition, the surfactant can be used to prevent aggregation of the compound.

[00152] Surfactants which can be used to form aqueous pharmaceutical formulations include, but are not limited to, hydrophilic surfactants, lipophilic surfactants, and mixtures thereof. That is, a mixture of hydrophilic surfactants can be employed, a mixture of lipophilic surfactants can be employed, or a mixture of at least one hydrophilic surfactant and at least one lipophilic surfactant can be employed.

[00153] In some embodiments of the disclosure, the surfactant can be the sodium salt form of the compound, which can include the monosodium salt form. Suitable sodium salt surfactants can be selected based on desirable properties, including high speed of polymerization, small resultant particle sizes suitable for delivery, good polymerization yields, stability including freeze-thaw and shelf-life stability, improved surface tension properties, and lubrication properties.

[00154] The surfactant can be any suitable, non-toxic compound that is non-reactive with the medicament and that substantially reduces the surface tension between the medicament, the excipient and the site of administration. Some useful surfactants are: oleic acid available under the trade names Mednique 6322 and Emersol 6321 (from Cognis Corp., Cincinnati, Ohio); cetylpyridinium chloride (from Arrow Chemical, Inc. Westwood, N.J.); soya lecithin available under the trade name Epikuron 200 (from Lucas Meyer Decatur, Ill.); polyoxyethylene(20)

sorbitan monolaurate available under the tradename Tween 20 (from ICI Specialty Chemicals, Wilmington, Del.); polyoxyethylene(20) sorbitan monostearate available under the tradename Tween 60 (from ICI); polyoxyethylene(20) sorbitan monooleate available under the tradename Tween 80 (from ICI); polyoxyethylene (10) stearyl ether available under the tradename Brij 76 (from ICI); polyoxyethylene (2) oleyl ether available under the tradename Brij 92 (frown ICI); Polyoxyethylene-polyoxypropylene-ethylenediamine block copolymer available under the tradename Tetronic 150 R1 (from BASF); polyoxypropylene-polyoxyethylene block copolymers available under the trade names Pluronic L-92, Pluronic L-121 end Pluronic F 68 (from BASF); castor oil ethoxylate available under the tradename Alkasurf CO-40 (from Rhone-Poulenc Mississauga Ontario, Canada); and mixtures thereof.

[00155] A suitable hydrophilic surfactant can generally have an HLB value of at least 10, while suitable lipophilic surfactants can generally have an HLB value of or less than about 10. An empirical parameter used to characterize the relative hydrophilicity and hydrophobicity of non-ionic amphiphilic compounds is the hydrophilic-lipophilic balance (" HLB" value). Surfactants with lower HLB values are more lipophilic or hydrophobic, and have greater solubility in oils, while surfactants with higher HLB values are more hydrophilic, and have greater solubility in aqueous solutions. Hydrophilic surfactants are generally considered to be those compounds having an HLB value greater than about 10, as well as anionic, cationic, or zwitterionic compounds for which the HLB scale is not generally applicable. Similarly, lipophilic (i.e., hydrophobic) surfactants are compounds having an HLB value equal to or less than about 10. However, HLB value of a surfactant is merely a rough guide generally used to enable formulation of industrial, pharmaceutical and cosmetic emulsions.

[00156] Hydrophilic surfactants can be either ionic or non-ionic. Suitable ionic surfactants include, but are not limited to, alkylammonium salts; fusidic acid salts; fatty acid derivatives of amino acids, oligopeptides, and polypeptides; glyceride derivatives of amino acids, oligopeptides, and polypeptides; lecithins and hydrogenated lecithins; lysolecithins and hydrogenated lysolecithins; phospholipids and derivatives thereof; lysophospholipids and derivatives thereof; carnitine fatty acid ester salts; salts of alkylsulfates; fatty acid salts; sodium docusate; acyl lactylates; mono- and di-acetylated tartaric acid esters of mono- and di-glycerides; succinylated mono- and di-glycerides; citric acid esters of mono- and di-glycerides; and mixtures thereof.

[00157] Within the aforementioned group, some ionic surfactants include, by way of example: lecithins, lysolecithin, phospholipids, lysophospholipids and derivatives thereof; carnitine fatty acid ester salts; salts of alkylsulfates; fatty acid salts; sodium docusate; acyl lactylates; mono- and di-acetylated tartaric acid esters of mono- and di-glycerides; succinylated mono- and di-glycerides; citric acid esters of mono- and di-glycerides; and mixtures thereof.

[00158] Ionic surfactants can be the ionized forms of lecithin, lysolecithin, phosphatidylcholine, phosphatidylethanolamine, phosphatidylglycerol, phosphatidic acid, phosphatidylserine, lysophosphatidylcholine, lysophosphatidylethanolamine, lysophosphatidylglycerol, lysophosphatidic acid, lysophosphatidylserine, PEG-phosphatidylethanolamine, PVP-phosphatidylethanolamine, lactylic esters of fatty acids, stearoyl-2-lactylate,

stearoyl lactylate, succinylated monoglycerides, mono/diacetylated tartaric acid esters of mono/diglycerides, citric acid esters of mono/diglycerides, cholylsarcosine, caproate, caprylate, caprate, laurate, myristate, palmitate, oleate, ricinoleate, linoleate, linolenate, stearate, lauryl sulfate, teracecyl sulfate, docusate, lauroyl carnitines, palmitoyl carnitines, myristoyl carnitines, and salts and mixtures thereof.

[00159] Hydrophilic non-ionic surfactants can include, but not limited to, alkylglucosides; alkylmaltosides; alkylthioglucosides; lauryl macrogolglycerides; polyoxyalkylene alkyl ethers such as polyethylene glycol alkyl ethers; polyoxyalkylene alkylphenols such as polyethylene glycol alkyl phenols; polyoxyalkylene alkyl phenol fatty acid esters such as polyethylene glycol fatty acids monoesters and polyethylene glycol fatty acids diesters; polyethylene glycol glycerol fatty acid esters; polyglycerol fatty acid esters; polyoxyalkylene sorbitan fatty acid esters such as polyethylene glycol sorbitan fatty acid esters; hydrophilic transesterification products of a polyol with at least one member of the group consisting of glycerides, vegetable oils, hydrogenated vegetable oils, fatty acids, and sterols; polyoxyethylene sterols, derivatives, and analogues thereof; polyoxyethylated vitamins and derivatives thereof; polyoxyethylene-polyoxypropylene block copolymers; and mixtures thereof; polyethylene glycol sorbitan fatty acid esters and hydrophilic transesterification products of a polyol with at least one member of the group consisting of triglycerides, vegetable oils, and hydrogenated vegetable oils. The polyol can be glycerol, ethylene glycol, polyethylene glycol, sorbitol, propylene glycol, pentaerythritol, or a saccharide.

[00160] Other hydrophilic-non-ionic surfactants include, without limitation, PEG-10 laurate, PEG-12 laurate, PEG-20 laurate, PEG-32 laurate, PEG-32 dilaurate, PEG-12 oleate, PEG-15 oleate, PEG-20 oleate, PEG-20 dioleate, PEG-32 oleate, PEG-200 oleate, PEG-400 oleate, PEG-15 stearate, PEG-32 distearate, PEG-40 stearate, PEG-100 stearate, PEG-20 dilaurate, PEG-25 glyceryl trioleate, PEG-32 dioleate, PEG-20 glyceryl laurate, PEG-30 glyceryl laurate, PEG-20 glyceryl stearate, PEG-20 glyceryl oleate, PEG-30 glyceryl oleate, PEG-30 glyceryl laurate, PEG-40 glyceryl laurate, PEG-40 palm kernel oil, PEG-50 hydrogenated castor oil, PEG-40 castor oil, PEG-35 castor oil, PEG-60 castor oil, PEG-40 hydrogenated castor oil, PEG-60 hydrogenated castor oil, PEG-60 corn oil, PEG-6 caprate/caprylate glycerides, PEG-8 caprate/caprylate glycerides, polyglyceryl-10 laurate, PEG-30 cholesterol, PEG-25 phyto sterol, PEG-30 soya sterol, PEG-20 trioleate, PEG-40 sorbitan oleate, PEG-80 sorbitan laurate, polysorbate 20, polysorbate 80, POE-9 lauryl ether, POE-23 lauryl ether, POE-10 oleyl ether, POE-20 oleyl ether, POE-20 stearyl ether, tocopheryl PEG-100 succinate, PEG-24 cholesterol, polyglyceryl-10oleate, Tween 40, Tween 60, sucrose monostearate, sucrose monolaurate, sucrose monopalmitate, PEG 10-100 nonyl phenol series, PEG 15-100 octyl phenol series, and poloxamers.

[00161] Suitable lipophilic surfactants include, by way of example only: fatty alcohols; glycerol fatty acid esters; acetylated glycerol fatty acid esters; lower alcohol fatty acids esters; propylene glycol fatty acid esters; sorbitan fatty acid esters; polyethylene glycol sorbitan fatty acid esters; sterols and sterol derivatives; polyoxyethylated sterols and sterol derivatives; polyethylene glycol alkyl ethers; sugar esters; sugar ethers; lactic acid derivatives of mono- and di-glycerides; hydrophobic transesterification products of a polyol with at least one member of the group consisting of glycerides, vegetable oils, hydrogenated vegetable oils, fatty acids and sterols; oil-soluble

vitamins/vitamin derivatives; and mixtures thereof. Within this group, some lipophilic surfactants include glycerol fatty acid esters, propylene glycol fatty acid esters, and mixtures thereof, or are hydrophobic transesterification products of a polyol with at least one member of the group consisting of vegetable oils, hydrogenated vegetable oils, and triglycerides.

[00162] In some embodiments the formulations of the disclosure contain no surfactants. In some embodiments, the formulations of the disclosure are intravenous formulations containing no surfactants. In some further embodiments the formulations contain substantially no surfactant, i.e. contain less than approximately 0.0001% by weight of surfactants. In some embodiments, the formulations contain essentially no surfactants.

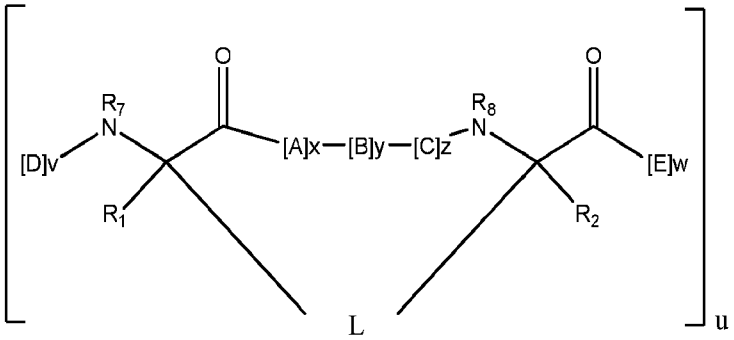
[00163] If desired, however, the formulations can contain surface-active agents conventionally employed, such as oleic acid, lecithin, sorbitan trioleate, cetylpyridinium chloride, benzalkonium chloride, polyoxyethylene (20) sorbitan monolaurate, polyoxyethylene (20) sorbitan monostearate, polyoxyethylene (20) sorbitan mono-oleate, polyoxypropylene/polyoxyethylene block copolymers, polyoxypropylene/polyoxyethylene/ethylene diamine block copolymers, ethoxylated castor oil and the like, where the proportion of surface-active agents, if present, can be about 0.0001 to 1% by weight, or about 0.001 to 0.1% by weight, based on the total formulation. Other suitable surfactant/emulsifying agents would be known to one of skill in the art and are listed in the CTFA International Cosmetic Ingredient Dictionary and Handbook, Vol. 2, 7th Edition (1997).

[00164] The aqueous pharmaceutical formulations of the disclosure can further include other pharmacological active ingredients as far as they do not contradict the purpose of the present disclosure. The aqueous pharmaceutical formulations for example can comprise solubilizing agents, bulking agents, dissolution enhancers, wetting agents, emulsifiers, suspending agents, antibacterial agents, sweeteners, perfuming agents, flavoring agents, and combinations thereof.

[00165] Some of the excipients or additives can have more than one possible function or use, depending on their properties and the nature of the formulation. In a combination of plural active ingredients, their respective contents can be suitably increased or decreased in consideration of their effects and safety.

Peptidomimetic macrocycles

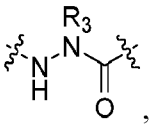
[00166] In some embodiments, a peptidomimetic macrocycle has the Formula (I):



Formula I

wherein:

each A, C, and D is independently an amino acid;

each B is independently an amino acid, , [–NH–L_3–CO–], [–NH–L_3–SO_2–], or [–NH–L_3–];

each E is independently an amino acid selected from the group consisting of Ala (alanine), D–Ala (D–alanine), Aib (α–aminoisobutyric acid), Sar (N–methyl glycine), and Ser (serine);

each R_3 independently is hydrogen, alkyl, alkenyl, alkynyl, arylalkyl, heteroalkyl, cycloalkyl, heterocycloalkyl, cycloalkylalkyl, cycloaryl, or heterocycloaryl, optionally substituted with R_5;

each R_1 and R_2 is independently –H, alkyl, alkenyl, alkynyl, arylalkyl, cycloalkyl, cycloalkylalkyl, heteroalkyl, or heterocycloalkyl, unsubstituted or substituted with halo–; or forms a macrocycle–forming linker L' connected to the alpha position of one of said D or E amino acids;

each L and L' is independently a macrocycle–forming linker;

each L_3 is independently alkylene, alkenylene, alkynylene, heteroalkylene, cycloalkylene, heterocycloalkylene, cycloarylene, heterocycloarylene, or $[-R_4-K-R_4-]_n$, each being optionally substituted with R_5;

each R_4 is independently alkylene, alkenylene, alkynylene, heteroalkylene, cycloalkylene, heterocycloalkylene, arylene, or heteroarylene;

each K is independently O, S, SO, SO_2, CO, CO_2, or $CONR_3$;

each R_5 is independently halogen, alkyl, $–OR_6$, $–N(R_6)_2$, $–SR_6$, $–SOR_6$, $–SO_2R_6$, $–CO_2R_6$, a fluorescent moiety, a radioisotope or a therapeutic agent;

each R_6 is independently –H, alkyl, alkenyl, alkynyl, arylalkyl, cycloalkylalkyl, heterocycloalkyl, a fluorescent moiety, a radioisotope or a therapeutic agent;

each R_7 is independently –H, alkyl, alkenyl, alkynyl, arylalkyl, cycloalkyl, heteroalkyl, cycloalkylalkyl, heterocycloalkyl, cycloaryl, or heterocycloaryl, optionally substituted with R_5, or part of a cyclic structure with a D residue;

each R_8 is independently –H, alkyl, alkenyl, alkynyl, arylalkyl, cycloalkyl, heteroalkyl, cycloalkylalkyl, heterocycloalkyl, cycloaryl, or heterocycloaryl, optionally substituted with R_5, or part of a cyclic structure with an E residue;

each v is independently an integer;

each w is independently an integer from 3–1000;

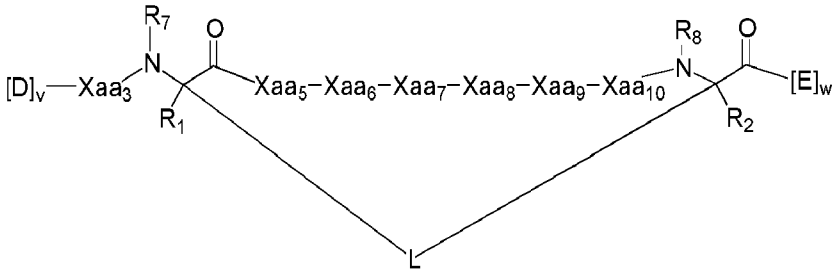
u is an integer from 1–10;

each x, y and z is independently an integer from 0–10; and

each n is independently an integer from 1–5.

[00167] In some embodiments, each v and w is independently integers between 1-30. In some embodiments, w is an integer from 3-1000, for example 3-500, 3-200, 3-100, 3-50, 3-30, 3-20, or 3-10. In some embodiments, the sum of x+y+z is 3 or 6. In some embodiments, the sum of x+y+z is 3. In other embodiments, the sum of x+y+z is 6.

[00168] In some embodiments, peptidomimetic macrocycles are also provided of the formula:



wherein:

each of Xaa_3, Xaa_5, Xaa_6, Xaa_7, Xaa_8, Xaa_9, and Xaa_{10} is individually an amino acid, wherein at least three of Xaa_3, Xaa_5, Xaa_6, Xaa_7, Xaa_8, Xaa_9, and Xaa_{10} are the same amino acid as the amino acid at the corresponding position of the sequence Phe_3-X_4-His_5-Tyr_6-Trp_7-Ala_8-Gln_9-Leu_{10}-X_{11}-Ser_{12}, where each X is an amino acid;

each D and E is independently an amino acid;

each R_1 and R_2 is independently –H, alkyl, alkenyl, alkynyl, arylalkyl, cycloalkyl, cycloalkylalkyl, heteroalkyl, or heterocycloalkyl, unsubstituted or substituted with halo–; or at least one of R_1 and R_2 forms a macrocycle-forming linker L' connected to the alpha position of one of said D or E amino acids;

each L or L' is independently a macrocycle-forming linker;

each R_5 is independently halogen, alkyl, $-OR_6$, $-N(R_6)_2$, $-SR_6$, $-SOR_6$, $-SO_2R_6$, $-CO_2R_6$, a fluorescent moiety, a radioisotope or a therapeutic agent;

each R_6 is independently –H, alkyl, alkenyl, alkynyl, arylalkyl, cycloalkylalkyl, heterocycloalkyl, a fluorescent moiety, a radioisotope or a therapeutic agent;

each R_7 is independently –H, alkyl, alkenyl, alkynyl, arylalkyl, cycloalkyl, heteroalkyl, cycloalkylalkyl, heterocycloalkyl, cycloaryl, or heterocycloaryl, optionally substituted with R_5, or part of a cyclic structure with a D residue;

each R_8 is independently –H, alkyl, alkenyl, alkynyl, arylalkyl, cycloalkyl, heteroalkyl, cycloalkylalkyl, heterocycloalkyl, cycloaryl, or heterocycloaryl, optionally substituted with R_5, or part of a cyclic structure with an E residue;

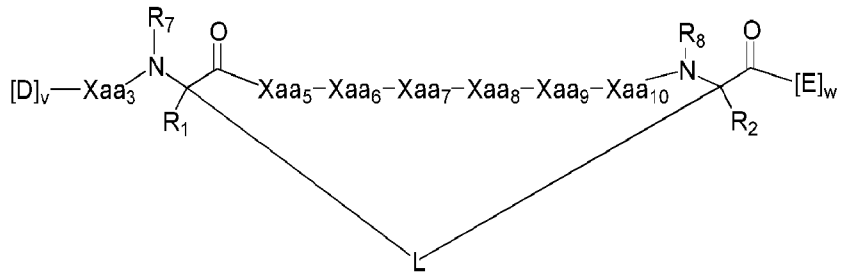
v is an integer from 1-1000, for example 1-500, 1-200, 1-100, 1-50, 1-30, 1-20 or 1-10; and

w is an integer from 3-1000, for example 3-500, 3-200, 3-100, 3-50, 3-30, 3-20, or 3-10.

[00169] In some embodiments, each v and w is independently an integer between 1-30. In some embodiments, w is an integer from 3-1000, for example 3-500, 3-200, 3-100, 3-50, 3-30, 3-20, or 3-10. In some embodiments, the sum of x+y+z is 3 or 6. In some embodiments, the sum of x+y+z is 3. In other embodiments, the sum of x+y+z is 6.

[00170] In some embodiments of any of the Formulas described herein, at least three of Xaa_3, Xaa_5, Xaa_6, Xaa_7, Xaa_8, Xaa_9, and Xaa_{10} are the same amino acid as the amino acid at the corresponding position of the sequence Phe_3-X_4-His_5-Tyr_6-Trp_7-Ala_8-Gln_9-Leu_{10}-X_{11}-Ser_{12}. In other embodiments, at least four of Xaa_3, Xaa_5, Xaa_6, Xaa_7, Xaa_8, Xaa_9, and Xaa_{10} are the same amino acid as the amino acid at the corresponding position of the sequence Phe_3-X_4-His_5-Tyr_6-Trp_7-Ala_8-Gln_9-Leu_{10}-X_{11}-Ser_{12}. In other embodiments, at least five of Xaa_3, Xaa_5, Xaa_6, Xaa_7, Xaa_8, Xaa_9, and Xaa_{10} are the same amino acid as the amino acid at the corresponding position of the sequence Phe_3-X_4-His_5-Tyr_6-Trp_7-Ala_8-Gln_9-Leu_{10}-X_{11}-Ser_{12}. In other embodiments, at least six of Xaa_3, Xaa_5, Xaa_6, Xaa_7, Xaa_8, Xaa_9, and Xaa_{10} are the same amino acid as the amino acid at the corresponding position of the sequence Phe_3-X_4-His_5-Tyr_6-Trp_7-Ala_8-Gln_9-Leu_{10}-X_{11}-Ser_{12}. In other embodiments, at least seven of Xaa_3, Xaa_5, Xaa_6, Xaa_7, Xaa_8, Xaa_9, and Xaa_{10} are the same amino acid as the amino acid at the corresponding position of the sequence Phe_3-X_4-His_5-Tyr_6-Trp_7-Ala_8-Gln_9-Leu_{10}-X_{11}-Ser_{12}.

[00171] In some embodiments, a peptidomimetic macrocycle has the Formula:



wherein:

each Xaa_3, Xaa_5, Xaa_6, Xaa_7, Xaa_8, Xaa_9, and Xaa_{10} is individually an amino acid, wherein at least three of Xaa_3, Xaa_5, Xaa_6, Xaa_7, Xaa_8, Xaa_9, and Xaa_{10} are the same amino acid as the amino acid at the corresponding position of the sequence Phe_3-X_4-Glu_5-Tyr_6-Trp_7-Ala_8-Gln_9-Leu_{10}/Cba_{10}-X_{11}-Ala_{12}, where each X is an amino acid;

each D is independently an amino acid;

each E is independently an amino acid, for example an amino acid selected from Ala (alanine), D-Ala (D-alanine), Aib (α–aminoisobutyric acid), Sar (N-methyl glycine), and Ser (serine);

each R_1 and R_2 are independently –H, alkyl, alkenyl, alkynyl, arylalkyl, cycloalkyl, cycloalkylalkyl, heteroalkyl, or heterocycloalkyl, unsubstituted or substituted with halo–; or at least one of R_1 and R_2 forms a macrocycle-forming linker L' connected to the alpha position of one of said D or E amino acids;

each L or L' is independently a macrocycle-forming linker;

each R_5 is independently halogen, alkyl, $-OR_6$, $-N(R_6)_2$, $-SR_6$, $-SOR_6$, $-SO_2R_6$, $-CO_2R_6$, a fluorescent moiety, a radioisotope or a therapeutic agent;

each R_6 is independently –H, alkyl, alkenyl, alkynyl, arylalkyl, cycloalkylalkyl, heterocycloalkyl, a fluorescent moiety, a radioisotope or a therapeutic agent;

each R_7 is independently –H, alkyl, alkenyl, alkynyl, arylalkyl, cycloalkyl, heteroalkyl, cycloalkylalkyl, heterocycloalkyl, cycloaryl, or heterocycloaryl, optionally substituted with R_5, or part of a cyclic structure with a D residue;

each R_8 is independently –H, alkyl, alkenyl, alkynyl, arylalkyl, cycloalkyl, heteroalkyl, cycloalkylalkyl, heterocycloalkyl, cycloaryl, or heterocycloaryl, optionally substituted with R_5, or part of a cyclic structure with an E residue;

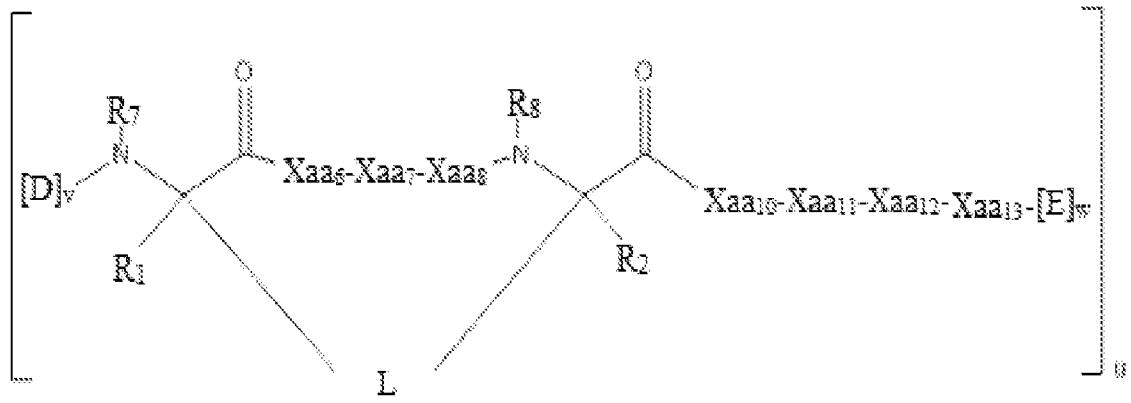
v is an integer from 1-1000, for example 1-500, 1-200, 1-100, 1-50, 1-30, 1-20, or 1-10;

w is an integer from 3-1000, for example 3-500, 3-200, 3-100, 3-50, 3-30, 3-20, or 3-10; and.

[00172] In some embodiments of the above Formula, at least three of Xaa_3, Xaa_5, Xaa_6, Xaa_7, Xaa_8, Xaa_9, and Xaa_{10} are the same amino acid as the amino acid at the corresponding position of the sequence Phe_3-X_4-Glu_5-Tyr_6-Trp_7-Ala_8-Gln_9-Leu_{10}/Cba_{10}-X_{11}-Ala_{12}. In other embodiments of the above Formula, at least four of Xaa_3, Xaa_5, Xaa_6, Xaa_7, Xaa_8, Xaa_9, and Xaa_{10} are the same amino acid as the amino acid at the corresponding position of the sequence Phe_3-X_4-Glu_5-Tyr_6-Trp_7-Ala_8-Gln_9-Leu_{10}/Cba_{10}-X_{11}-Ala_{12}. In other embodiments of the above Formula, at least five of Xaa_3, Xaa_5, Xaa_6, Xaa_7, Xaa_8, Xaa_9, and Xaa_{10} are the same amino acid as the amino acid at the corresponding position of the sequence Phe_3-X_4-Glu_5-Tyr_6-Trp_7-Ala_8-Gln_9-Leu_{10}/Cba_{10}-X_{11}-Ala_{12}. In other embodiments of the above Formula, at least six of Xaa_3, Xaa_5, Xaa_6, Xaa_7, Xaa_8, Xaa_9, and Xaa_{10} are the same amino acid as the amino acid at the corresponding position of the sequence Phe_3-X_4-Glu_5-Tyr_6-Trp_7-Ala_8-Gln_9-Leu_{10}/Cba_{10}-X_{11}-Ala_{12}. In other embodiments of the above Formula, at least seven of Xaa_3, Xaa_5, Xaa_6, Xaa_7, Xaa_8, Xaa_9, and Xaa_{10} are the same amino acid as the amino acid at the corresponding position of the sequence Phe_3-X_4-Glu_5-Tyr_6-Trp_7-Ala_8-Gln_9-Leu_{10}/Cba_{10}-X_{11}-Ala_{12}.

[00173] In some embodiments, w is an integer from 3-10, for example 3-6, 3-8, 6-8, or 6-10. In some embodiments, w is 3. In other embodiments, w is 6. In some embodiments, v is an integer from 1-10, for example 2-5. In some embodiments, v is 2.

[00174] In one embodiment, the peptidomimetic macrocycle of Formula (I) is Formula (Ia):

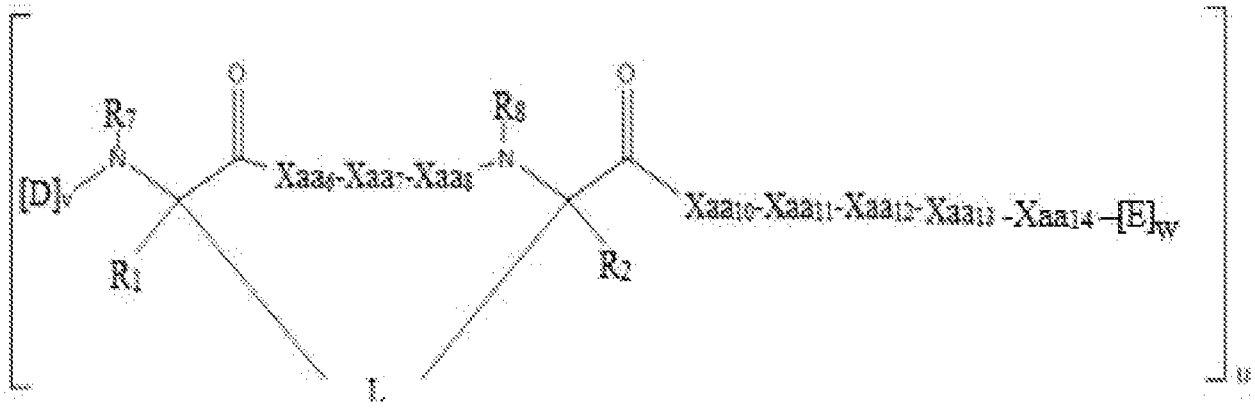


Formula (Ia)

or a pharmaceutically-acceptable salt thereof wherein:

each of Xaa_6, Xaa_7, Xaa_8, Xaa_{10}, Xaa_{11}, Xaa_{12}, and Xaa_{13} is independently an amino acid, wherein at least three, four, five, or each of Xaa_6, Xaa_7, Xaa_8, Xaa_{10}, Xaa_{11}, Xaa_{12}, are the same amino acid as the amino acid at the corresponding position of the sequence X_5–Thr_6– Leu_7–Leu_8–X_9–Leu_{10}– Lys_{11}/Ala_{11}–Val_{12}/Ala_{12}, where each of X_5 and X_9 is independently an amino acid.

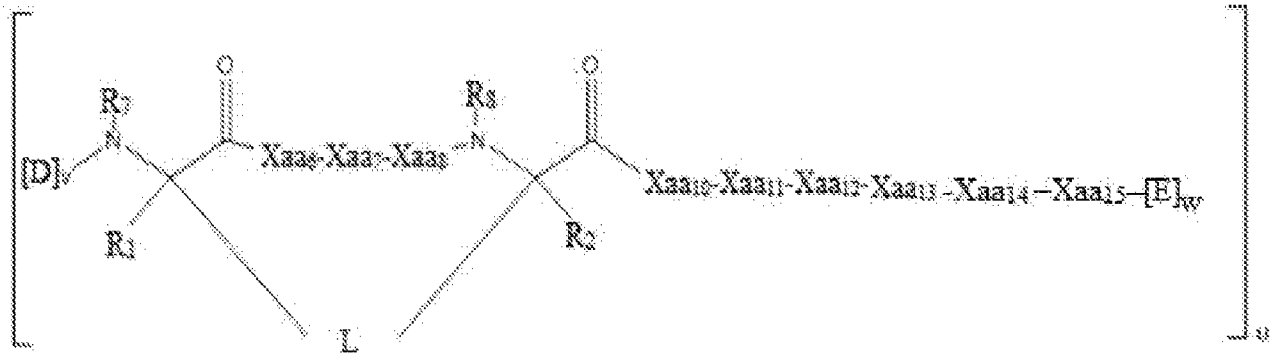
[00175] In some embodiments, the peptidomimetic macrocycle of Formula (Ia) is Formula (Ia-1):



Formula (Ia-1)

or a pharmaceutically-acceptable salt thereof, wherein each Xaa_{14} is independently an amino acid.

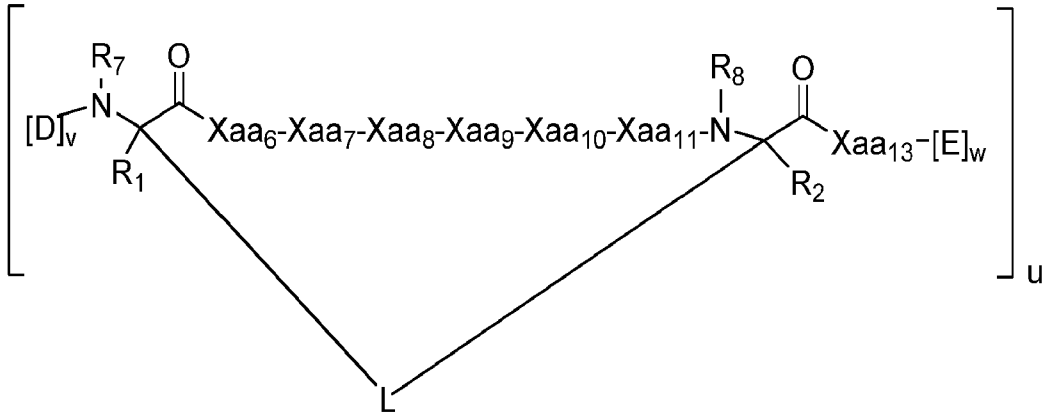
[00176] In some embodiments, the peptidomimetic macrocycle of Formula (Ia) is Formula (Ia-2):



Formula (Ia-2)

or a pharmaceutically-acceptable salt thereof, wherein each Xaa_{14} and Xaa_{15} is independently an amino acid.

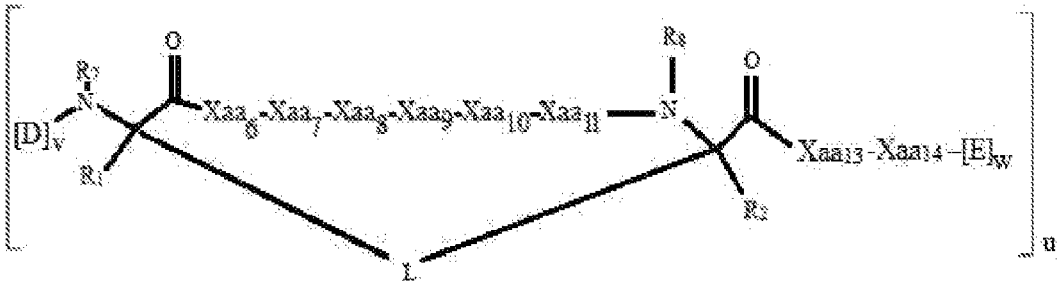
[00177] In one embodiment, the peptidomimetic macrocycle of Formula (I) is Formula (Ib):



Formula (Ib)

or a pharmaceutically-acceptable salt thereof, wherein: each of Xaa_6, Xaa_7, Xaa_8, Xaa_9, Xaa_{10}, Xaa_{11} and Xaa_{13} is independently an amino acid, wherein at least three, four, five, or each of Xaa_6, Xaa_7, Xaa_8, Xaa_9, Xaa_{10}, and Xaa_{11} are the same amino acid as the amino acid at the corresponding position of the sequence X_5-Thr_6–Leu_7–Leu_8–Phe_9–Leu_{10}–Lys_{11}/Ala_{11}–X_{12} , where each of X_5 and X_{12} is independently an amino acid.

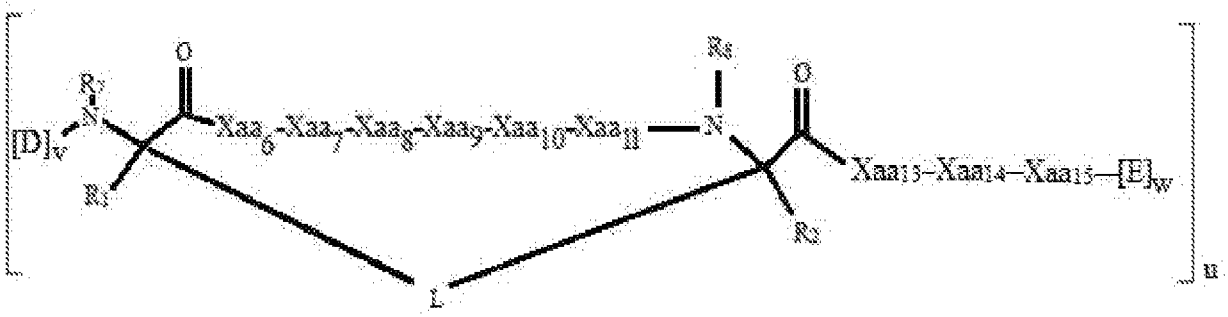
[00178] In some embodiments, the peptidomimetic macrocycle of Formula (Ib) is Formula (Ib-1):



Formula (Ib-1)

or a pharmaceutically-acceptable salt thereof, wherein each Xaa_{14} is independently an amino acid..

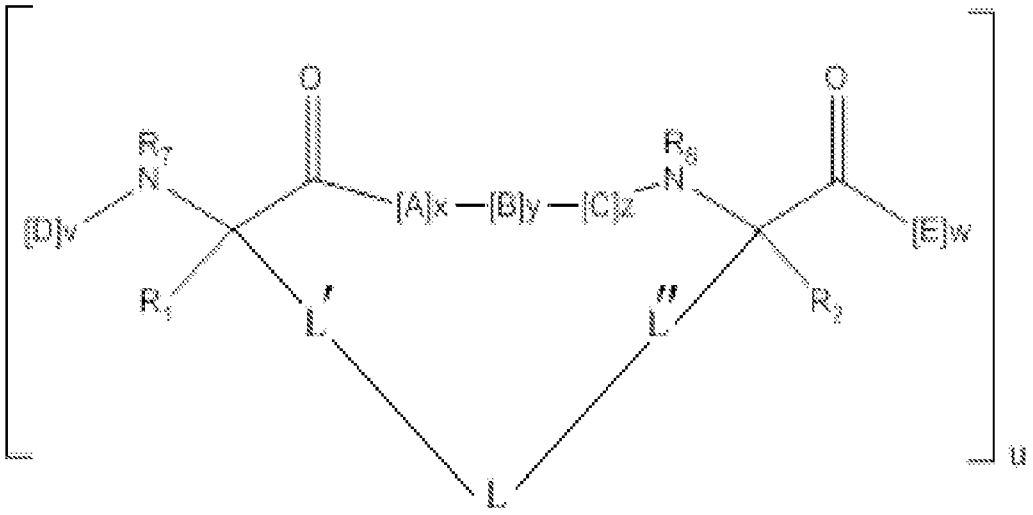
[00179] In some embodiments, the peptidomimetic macrocycle of Formula (Ib) is Formula (Ib-2):



Formula (Ib-2)

or a pharmaceutically-acceptable salt thereof, wherein each Xaa_{14} and Xaa_{15} is independently an amino acid.

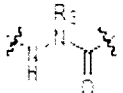
[00180] In some embodiments, the invention provides a peptidomimetic macrocycle of Formula (IX):



Formula (IX)

wherein the peptidomimetic macrocycle binds MCL-1 selectively over another protein that has a BH3 domain, wherein:

each A, C, D, and E is independently a natural or non-natural amino acid;

each B is independently a natural or non-natural amino acid, amino acid analog, , [-NH-L_3-CO-], [-NH-L_3-SO_2-], or [-NH-L_3-];

each L is independently a macrocycle-forming linker;

each L′ is independently alkylene, alkenylene, alkynylene, heteroalkylene, cycloalkylene, heterocycloalkylene, arylene, or heteroarylene, each being optionally substituted with R_5, or a bond, or together with R_1 and the atom to which both R_1 and L′ are bound forms a ring;

each L″ is independently alkylene, alkenylene, alkynylene, heteroalkylene, cycloalkylene, heterocycloalkylene, arylene, or heteroarylene, each being optionally substituted with R_5, or a bond, or together with R_2 and the atom to which both R_2 and L″ are bound forms a ring;

each R_1 is independently –H, alkyl, alkenyl, alkynyl, arylalkyl, cycloalkyl, cycloalkylalkyl, heteroalkyl, or heterocycloalkyl, unsubstituted or substituted with halo–, or together with L′ and the atom to which both R_1 and L′ are bound forms a ring;

each R_2 is independently –H, alkyl, alkenyl, alkynyl, arylalkyl, cycloalkyl, cycloalkylalkyl, heteroalkyl, or heterocycloalkyl, unsubstituted or substituted with halo–, or together with L″ and the atom to which both R_2 and L″ are bound forms a ring;

each R_3 is independently hydrogen, alkyl, alkenyl, alkynyl, arylalkyl, heteroalkyl, cycloalkyl, heterocycloalkyl, cycloalkylalkyl, aryl, or heteroaryl, optionally substituted with R_5;

each L_3 is independently alkylene, alkenylene, alkynylene, heteroalkylene, cycloalkylene, heterocycloalkylene, arylene, heteroarylene, or $[-R_4\text{-}K\text{-}R_4\text{-}]_n$, each being optionally substituted with R_5;

each R_4 is independently alkylene, alkenylene, alkynylene, heteroalkylene, cycloalkylene, heterocycloalkylene, arylene, or heteroarylene;

each K is independently O, S, SO, SO_2, CO, CO_2, or $CONR_3$;

each n is independently an integer from 1-5;

each R_5 is independently halogen, alkyl, $-OR_6$, $-N(R_6)_2$, $-SR_6$, $-SOR_6$, $-SO_2R_6$, $-CO_2R_6$, a fluorescent moiety, a radioisotope, or a therapeutic agent;

each R_6 is independently –H, alkyl, alkenyl, alkynyl, arylalkyl, cycloalkylalkyl, heterocycloalkyl, a fluorescent moiety, a radioisotope, or a therapeutic agent;

each R_7 is independently –H, alkyl, alkenyl, alkynyl, arylalkyl, cycloalkyl, heteroalkyl, cycloalkylalkyl, heterocycloalkyl, aryl, or heteroaryl, optionally substituted with R_5, or part of a cyclic structure with a D residue;

each R_8 is independently –H, alkyl, alkenyl, alkynyl, arylalkyl, cycloalkyl, heteroalkyl, cycloalkylalkyl, heterocycloalkyl, aryl, or heteroaryl, optionally substituted with R_5, or part of a cyclic structure with an E residue;

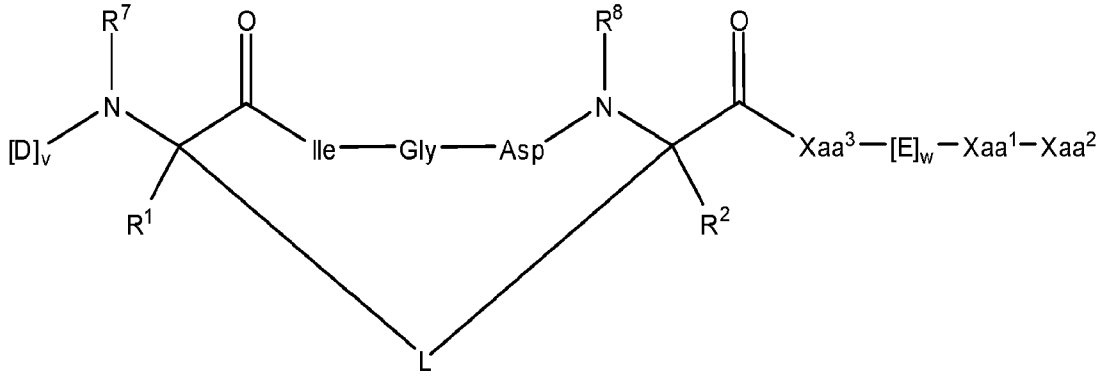
each v and w is independently an integer from 1-1000;

u is an integer from 1-10; and

each x, y and z is independently an integer from 0-10, or

a pharmaceutically-acceptable salt thereof.

[00181] In some embodiments, the invention provides a peptidomimetic macrocycle having the formula:



wherein:

each D and E is independently an amino acid residue;

each R^1 and R^2 are independently alkyl, alkenyl, alkynyl, arylalkyl, cycloalkyl, cycloalkylalkyl, heteroalkyl, or heterocycloalkyl, each being optionally substituted with halo–; –H, or at least one of R^1 and R^2 forms a macrocycle-forming linker L′ connected to the alpha position of one of the D or E amino acid residues;

each L is a macrocycle-forming linker of the formula $–L^1–L^2–$ or $–L^1–L^2–L^3–$;

each L^1, L^2, and L^3 are independently alkylene, alkenylene, alkynylene, heteroalkylene, cycloalkylene, heterocycloalkylene, arylene, heteroarylene, or $[-R^4\text{-}K\text{-}R^4-]_n$, each being optionally substituted with R^5;

each R^3 is independently –H, alkyl, alkenyl, alkynyl, arylalkyl, cycloalkyl, heteroalkyl, cycloalkylalkyl, heterocycloalkyl, aryl, or heteroaryl, each being optionally substituted with R^5;

each R^4 is independently alkylene, alkenylene, alkynylene, heteroalkylene, cycloalkylene,

heterocycloalkylene, arylene, or heteroarylene, each being optionally substituted with R^5;

each K is independently O, S, SO, SO_2, CO, CO_2, or $CONR^3$;

each R^5 is independently halogen, alkyl, $-OR^6$, $-N(R^6)_2$, $-SR^6$, $-SOR^6$, $-SO_2R^6$, $-CO_2R^6$, a fluorescent moiety, a radioisotope, or a therapeutic agent;

each R^6 is independently –H, alkyl, alkenyl, alkynyl, arylalkyl, cycloalkylalkyl, heterocycloalkyl, a fluorescent moiety, a radioisotope, or a therapeutic agent;

R^7 is –H, alkyl, alkenyl, alkynyl, arylalkyl, cycloalkyl, heteroalkyl, cycloalkylalkyl, heterocycloalkyl, aryl, or heteroaryl, each being optionally substituted with R^5, or part of a cyclic structure with a D residue;

R^8 is –H, alkyl, alkenyl, alkynyl, arylalkyl, cycloalkyl, heteroalkyl, cycloalkylalkyl, heterocycloalkyl, aryl, or heteroaryl, each being optionally substituted with R^5, or part of a cyclic structure with an E residue;

each of Xaa^1 and Xaa^2 is independently an amino acid residue or absent;

Xaa^3 is Ala, Aib, Asp, Asn, Cys, Glu, Gln, His, Ile, Lys, Leu, Met, Arg, Ser, Thr, Val, Trp, Tyr, or an analog of any of the foregoing;

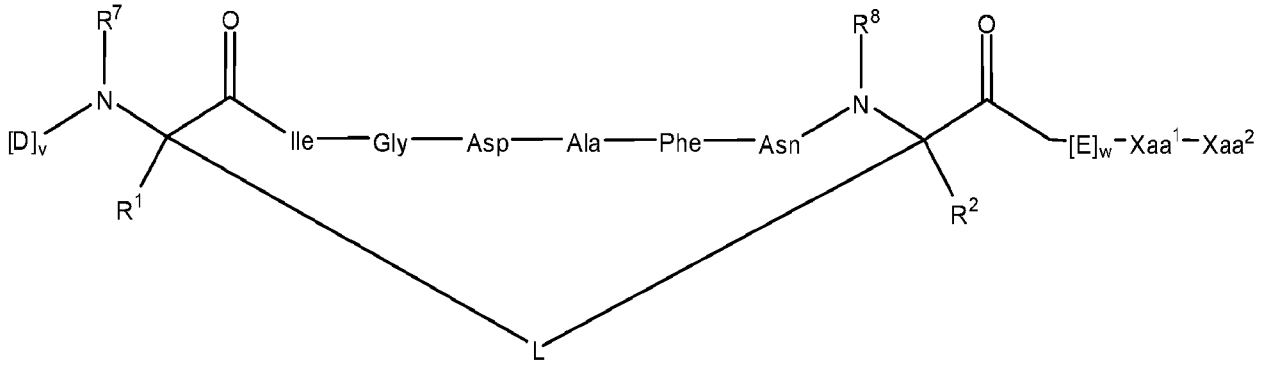
v is an integer from 1-1000;

w is an integer from 0-1000; and

n is an integer from 1-5, or

a pharmaceutically-acceptable salt thereof.

[00182] In some embodiments, the invention provides a peptidomimetic macrocycle of the formula:



wherein:

each D and E is independently an amino acid residue;

R^1 and R^2 are independently alkyl, alkenyl, alkynyl, arylalkyl, cycloalkyl, cycloalkylalkyl, heteroalkyl, or heterocycloalkyl, each being optionally substituted with halo–; –H, or at least one of R^1 and R^2 forms a macrocycle-forming linker L′ connected to the alpha position of one of the D or E amino acid residues;

each L or L′ is independently a macrocycle-forming linker of the formula $-L^1-L^2-$ or $-L^1-L^2-L^3-$;

L^1, L^2, and L^3 are independently alkylene, alkenylene, alkynylene, heteroalkylene, cycloalkylene, heterocycloalkylene, arylene, heteroarylene, or $[-R^4-K-R^4-]_n$, each being optionally substituted with R^5;

each R^3 is independently –H, alkyl, alkenyl, alkynyl, arylalkyl, cycloalkyl, heteroalkyl, cycloalkylalkyl, heterocycloalkyl, aryl, or heteroaryl, each being optionally substituted with R^5;

each R^4 is independently alkylene, alkenylene, alkynylene, heteroalkylene, cycloalkylene, heterocycloalkylene, arylene, or heteroarylene, each being optionally substituted with R^5;

each K is independently O, S, SO, SO_2, CO, CO_2, or $CONR^3$;

each R^5 is independently halogen, alkyl, $-OR^6$, $-N(R^6)_2$, $-SR^6$, $-SOR^6$, $-SO_2R^6$, $-CO_2R^6$, a fluorescent moiety, a radioisotope, or a therapeutic agent;

each R^6 is independently –H, alkyl, alkenyl, alkynyl, arylalkyl, cycloalkylalkyl, heterocycloalkyl, a fluorescent moiety, a radioisotope, or a therapeutic agent;

R^7 is –H, alkyl, alkenyl, alkynyl, arylalkyl, cycloalkyl, heteroalkyl, cycloalkylalkyl, heterocycloalkyl, aryl, or heteroaryl, each being optionally substituted with R^5, or part of a cyclic structure with a D residue;

R^8 is –H, alkyl, alkenyl, alkynyl, arylalkyl, cycloalkyl, heteroalkyl, cycloalkylalkyl, heterocycloalkyl, aryl, or heteroaryl, each being optionally substituted with R^5, or part of a cyclic structure with an E residue;

each of Xaa^1 and Xaa^2 is independently an amino acid residue or absent;

v is an integer from 1-1000;

w is an integer from 0-1000; and

n is an integer from 1-5, or

a pharmaceutically-acceptable salt thereof.

[00183] In some embodiments, the invention provides a peptidomimetic macrocycle comprising an amino acid sequence of formula:

X_1-X_2-X_3-X_4-X_5-X_6-X_7-X_8-X_9-X_{10}-X_{11}-X_{12}-X_{13}-X_{14}-X_{15}-X_{16}-X_{17}-X_{18}-X_{19}-X_{20}-X_{21}

wherein:

X_1 is Ile, Arg, Ala, Lys, Pro, Leu, Asp, Glu, His, Ser, Gln, Phe, an analog thereof, or absent;

X_2 is Trp, Arg, Ala, Asn, Phe, Pro, Leu, Ser, Lys, Tyr, His, Cou, Cou2, Cou4, Cou7, an analog thereof, a crosslinked amino acid, or absent;

X3 is Ile, Ala, Leu, Phe, Tyr, Val, Asp, Trp, Pro, Gln, Chg, Ac5c, Ac6c, Tba, Bip, Cha, Adm, hCha, an analog thereof, or absent;

X_4 is Ala, Gln, Asp, Val, Gly, Ser, Leu, Phe, Cha, A4, an analog, thereof, a crosslinked amino acid, or absent;

X_5 is Gln, Ala, Leu, Phe, Tyr, Gly, Ile, Val, Arg, Glu, Pro, Asp, MO, MO2, an analog thereof, a crosslinked amino acid, or absent;

X_6 is Glu, Gln, His, Ala, Ser, Arg, Ile, Leu, Thr, Phe, Val, Tyr, Gly, Nle, St, an analog thereof, or absent;

X_7 is Ala, Leu, Phe, Ile, 2Nal, 1Nal, 3cf, Chg, Cha, Adm, hCha, Igl, Bip, an analog thereof, or absent;

X_8 is Arg, Ala, Asp, Glu, Thr, His, Gln, Gly, Asn, Phe, Cit, St, an analog thereof, a crosslinked amino acid, or absent;

X_9 is Arg, Ala, Asp, Lys, Asn, Gly, Ser, Gln, Cys, Nle, St, an analog thereof, or a crosslinked amino acid;

X_{10} is Ile, Val, Ala, Asp, Asn, Phe, Tba, hL, hhL, Nle, Chg, Cha, an analog thereof, or a crosslinked amino acid;

X_{11} is Gly, Val, Ala, Leu, Ile, Asp, Glu, Cha, Aib, Abu, an analog thereof, or a crosslinked amino acid;

X_{12} is Asp, Ala, Asn, Gly, Arg, Glu, Lys, Leu, Nle, an analog thereof, or a crosslinked amino acid;

X_{13} is Ala, Glu, Gln, Leu, Lys, Asp, Tyr, Ile, Ser, Cys, St, Sta5, Aib, Nle, an analog thereof, or a crosslinked amino acid;

X_{14} is Phe, Ala, Leu, Val, Tyr, Glu, His, Ile, Nle, 1Nal, 2Nal, Chg, Cha, BiP, an analog thereof, or a crosslinked amino acid;

X_{15} is Asn, Gln, Ser, His, Glu, Asp, Ala, Leu, Ile, St, Nle, Aib, an analog thereof, a crosslinked amino acid, or absent;

X_{16} is Ala, Glu, Asp, Arg, Lys, Phe, Gly, Gln, Aib, Cha, St, an analog thereof, a crosslinked amino acid, or absent;

X_{17} is Phe, Tyr, Ala, Leu, Asn, Ser, Gln, Arg, His, Thr, Cou2, Cou3, Cou7, Dpr, Amf, Damf, Amye, an analog thereof, a crosslinked amino acid, or absent;

X_{18} is Tyr, Ala, Ile, Phe, His, Arg, Lys, Trp, Orn, Amf, Amye, Cha, 2Nal, an analog thereof, or absent;

X_{19} is Ala, Lys, Arg, His, Ser, Gln, Glu, Asp, Thr, Aib, Cha, an analog thereof, a crosslinked amino acid, or absent; and

X_{20} is Arg, His, Ala, Thr, Lys, Amr, an analog thereof, a crosslinked amino acid, or absent; and

X_{21} is Arg, His, Ala, Amr, an analog thereof, or absent, or

a pharmaceutically-acceptable salt thereof,

wherein at least two of the amino acids of the amino acid sequence are a crosslinked amino acid.

[00184] In some embodiments, the invention provides a peptidomimetic macrocycle comprising an amino acid sequence with C-terminal amino acid residues that are –His-His, wherein the peptidomimetic macrocycle comprises a crosslink connecting at least two amino acid residues, or a pharmaceutically-acceptable salt thereof.In an embodiment of any of the Formulas described herein, of the macrocycle-forming linker (L or L') has a formula $–L_1–L_2–$, wherein

L_1 and L_2 are independently alkylene, alkenylene, alkynylene, heteroalkylene, cycloalkylene, heterocycloalkylene, cycloarylene, heterocycloarylene, or $[-R_4-K-R_4-]_n$, each being optionally substituted with R_5;

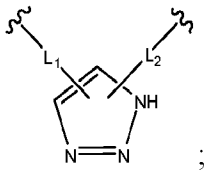
each R_4 is independently alkylene, alkenylene, alkynylene, heteroalkylene, cycloalkylene, heterocycloalkylene, arylene, or heteroarylene;

each K is independently O, S, SO, SO_2, CO, CO_2, or $CONR_3$;

each R_3 independently is hydrogen, alkyl, alkenyl, alkynyl, arylalkyl, heteroalkyl, cycloalkyl, heterocycloalkyl, cycloalkylalkyl, cycloaryl, or heterocycloaryl, optionally substituted with R_5; and

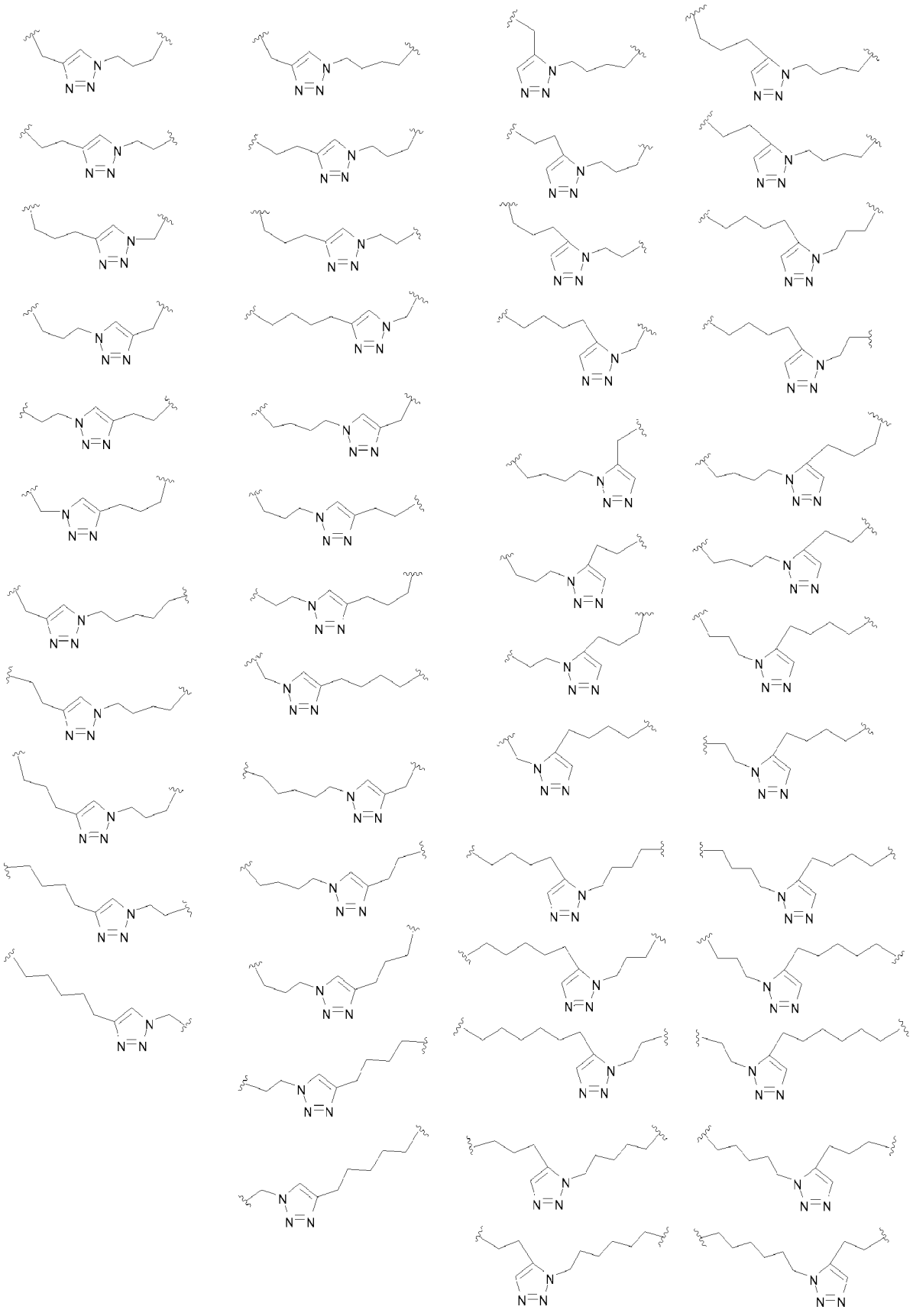
n is an integer from 1-5.

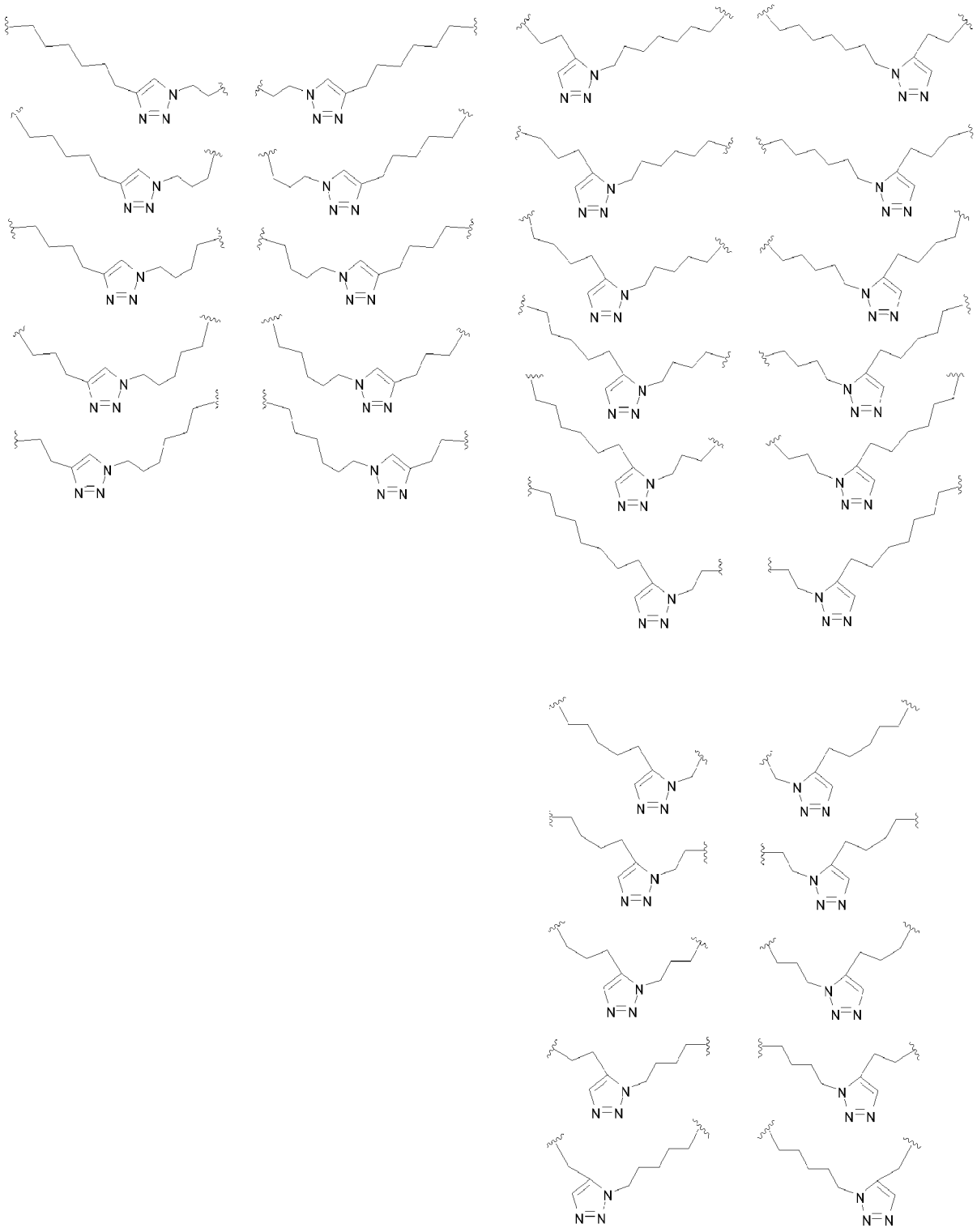
[00185] In some embodiments, L (or L') is a macrocycle-forming linker of the formula



;

[00186] Exemplary embodiments of such macrocycle-forming linkers L are shown below.





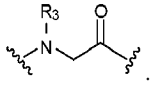
[00187] In an embodiment of any of the Formulas described herein, L_1 and L_2, either alone or in combination, form a triazole or a thioether.

[00188] In an embodiment of any of the Formulas described herein, L_1 and L_2, either alone or in combination, do not form a triazole or a thioether.

[00189] In one example, at least one of R_1 and R_2 is alkyl, unsubstituted or substituted with halo–. In another example, both R_1 and R_2 are independently alkyl, unsubstituted or substituted with halo–. In some embodiments, at least one of R_1 and R_2 is methyl. In other embodiments, R_1 and R_2 are methyl.

[00190] In some embodiments, x+y+z is at least 3. In other embodiments, x+y+z is 1, 2, 3, 4, 5, 6, 7, 8, 9 or 10. In some embodiments, the sum of x+y+z is 3 or 6. In some embodiments, the sum of x+y+z is 3. In other embodiments, the sum of x+y+z is 6. Each occurrence of A, B, C, D or E in a macrocycle or macrocycle precursor is independently selected. For example, a sequence represented by the formula $[A]_x$, when x is 3, encompasses embodiments where the amino acids are not identical, e.g. Gln–Asp–Ala as well as embodiments where the amino acids are identical, e.g. Gln–Gln–Gln. This applies for any value of x, y, or z in the indicated ranges. Similarly, when u is greater than 1, each compound can encompass peptidomimetic macrocycles which are the same or different. For example, a compound can comprise peptidomimetic macrocycles comprising different linker lengths or chemical compositions.

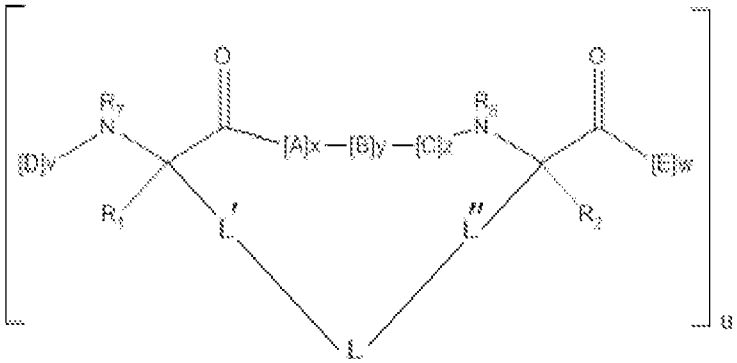
[00191] In some embodiments, the peptidomimetic macrocycle comprises a secondary structure which is an α-helix and R_8 is –H, allowing intrahelical hydrogen bonding. In some embodiments, at least one of A, B, C, D or E is an α,α-disubstituted amino acid. In one example, B is an α,α-disubstituted amino acid. For instance, at least one of A, B, C, D or E is 2-aminoisobutyric acid. In other embodiments, at least one of A, B, C, D or E is



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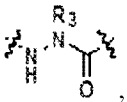
[00192] In other embodiments, the length of the macrocycle-forming linker L as measured from a first Cα to a second Cα is selected to stabilize a desired secondary peptide structure, such as an α-helix formed by residues of the peptidomimetic macrocycle including, but not necessarily limited to, those between the first Cα to a second Cα.

[00193] In some embodiments, a peptidomimetic macrocycle of Formula (I) has Formula :



wherein:

each A, C, D, and E is independently a natural or non-natural amino acid;

each B is independently a natural or non-natural amino acid, amino acid analog, , [-NH-L_3-CO-], [-NH-L_3-SO_2-], or [-NH-L_3-];

each L is independently a macrocycle-forming linker;

each L' is independently alkylene, alkenylene, alkynylene, heteroalkylene, cycloalkylene, heterocycloalkylene, arylene, or heteroarylene, each being optionally substituted with R_5, or a bond, or together with R_1 and the atom to which both R_1 and L' are bound forms a ring;

each L'' is independently alkylene, alkenylene, alkynylene, heteroalkylene, cycloalkylene, heterocycloalkylene, arylene, or heteroarylene, each being optionally substituted with R_5, or a bond, or together with R_2 and the atom to which both R_2 and L'' are bound forms a ring;

each R_1 is independently –H, alkyl, alkenyl, alkynyl, arylalkyl, cycloalkyl, cycloalkylalkyl, heteroalkyl, or heterocycloalkyl, unsubstituted or substituted with halo–, or together with L' and the atom to which both R_1 and L' are bound forms a ring;

each R_2 is independently –H, alkyl, alkenyl, alkynyl, arylalkyl, cycloalkyl, cycloalkylalkyl, heteroalkyl, or heterocycloalkyl, unsubstituted or substituted with halo–, or together with L'' and the atom to which both R_2 and L'' are bound forms a ring;

each R_3 is independently hydrogen, alkyl, alkenyl, alkynyl, arylalkyl, heteroalkyl, cycloalkyl, heterocycloalkyl, cycloalkylalkyl, aryl, or heteroaryl, optionally substituted with R_5;

each L_3 is independently alkylene, alkenylene, alkynylene, heteroalkylene, cycloalkylene, heterocycloalkylene, arylene, heteroarylene, or $[-R_4\text{-}K\text{-}R_4-]_n$, each being optionally substituted with R_5;

each R_4 is alkylene, alkenylene, alkynylene, heteroalkylene, cycloalkylene, heterocycloalkylene, arylene, or heteroarylene;

each K is independently O, S, SO, SO_2, CO, CO_2, or $CONR_3$;

each n is independently an integer from 1-5;

each R_5 is independently halogen, alkyl, $-OR_6$, $-N(R_6)_2$, $-SR_6$, $-SOR_6$, $-SO_2R_6$, $-CO_2R_6$, a fluorescent moiety, a radioisotope or a therapeutic agent;

each R_6 is independently –H, alkyl, alkenyl, alkynyl, arylalkyl, cycloalkylalkyl, heterocycloalkyl, a fluorescent moiety, a radioisotope or a therapeutic agent;

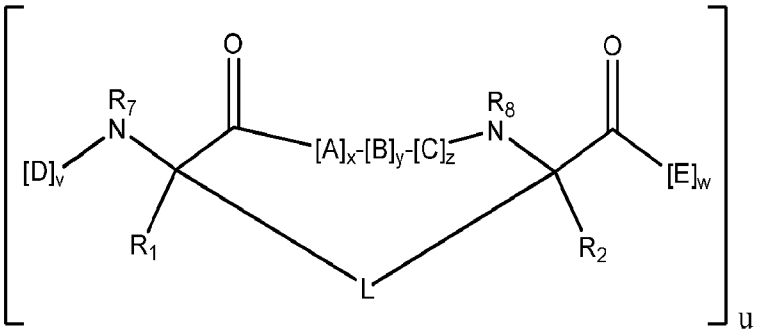
each R_7 is independently –H, alkyl, alkenyl, alkynyl, arylalkyl, cycloalkyl, heteroalkyl, cycloalkylalkyl, heterocycloalkyl, aryl, or heteroaryl, optionally substituted with R_5, or part of a cyclic structure with a D residue;

each R_8 is independently –H, alkyl, alkenyl, alkynyl, arylalkyl, cycloalkyl, heteroalkyl, cycloalkylalkyl, heterocycloalkyl, aryl, or heteroaryl, optionally substituted with R_5, or part of a cyclic structure with an E residue;

each v and w is independently an integer from 1-1000, for example 1-500, 1-200, 1-100, 1-50, 1-40, 1-25, 1-20, 1-15, or 1-10; and

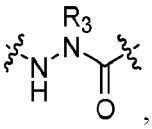
each u, x, y and z is independently an integer from 0-10.

[00194] In some embodiments, the peptidomimetic macrocycles have the Formula I:



wherein:

each A, C, D, and E is independently a natural or non-natural amino acid;

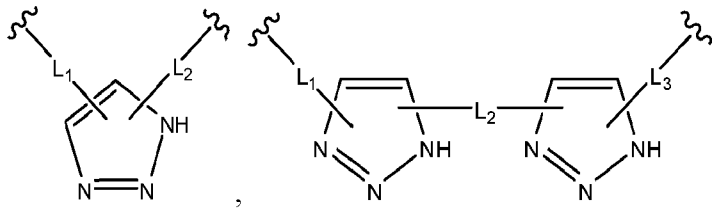
each B is independently a natural or non-natural amino acid, amino acid analog, ,

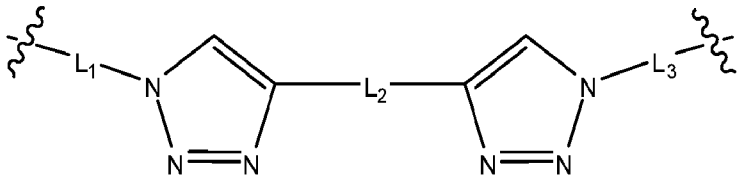
[-NH-L_3-CO-], [-NH-L_3-SO_2-], or [-NH-L_3-];

each R_1 and R_2 is independently –H, alkyl, alkenyl, alkynyl, arylalkyl, cycloalkyl, cycloalkylalkyl, heteroalkyl, or heterocycloalkyl, unsubstituted or substituted with halo–;

each R_3 is independently hydrogen, alkyl, alkenyl, alkynyl, arylalkyl, heteroalkyl, cycloalkyl, heterocycloalkyl, cycloalkylalkyl, aryl, or heteroaryl, optionally substituted with R_5;

each L is independently a macrocycle-forming linker of the formula

, or

;

each L_1, L_2 and L_3 is independently alkylene, alkenylene, alkynylene, heteroalkylene, cycloalkylene, heterocycloalkylene, arylene, heteroarylene, or [-R_4-K-R_4-]$_n$, each being optionally substituted with R_5;

each R_4 is alkylene, alkenylene, alkynylene, heteroalkylene, cycloalkylene, heterocycloalkylene, arylene, or heteroarylene;

each K is independently O, S, SO, SO_2, CO, CO_2, or $CONR_3$;

each R_5 is independently halogen, alkyl, -OR_6, -$N(R_6)_2$, -SR_6, -SOR_6, -SO_2R_6, -CO_2R_6, a fluorescent moiety, a radioisotope or a therapeutic agent;

each R_6 is independently –H, alkyl, alkenyl, alkynyl, arylalkyl, cycloalkylalkyl, heterocycloalkyl, a fluorescent moiety, a radioisotope or a therapeutic agent;

each R_7 is independently –H, alkyl, alkenyl, alkynyl, arylalkyl, cycloalkyl, heteroalkyl, cycloalkylalkyl, heterocycloalkyl, aryl, or heteroaryl, optionally substituted with R_5, or part of a cyclic structure with a D residue;

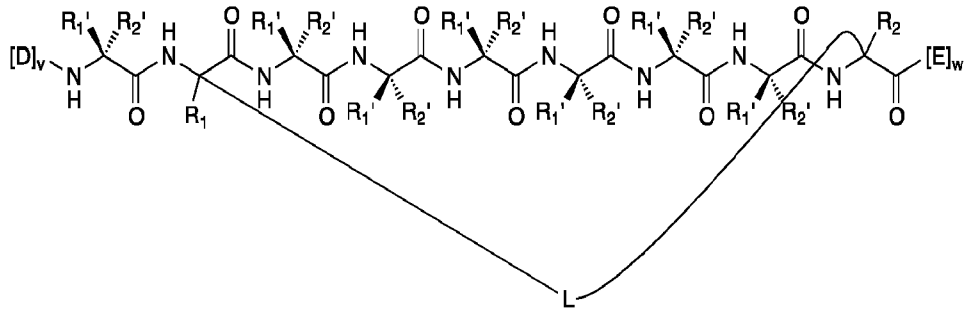
each R_8 is independently –H, alkyl, alkenyl, alkynyl, arylalkyl, cycloalkyl, heteroalkyl, cycloalkylalkyl, heterocycloalkyl, aryl, or heteroaryl, optionally substituted with R_5, or part of a cyclic structure with an E residue;

each v and w is independently an integer from 1-1000;

each u, x, y and z is independently integers from 0-10; and

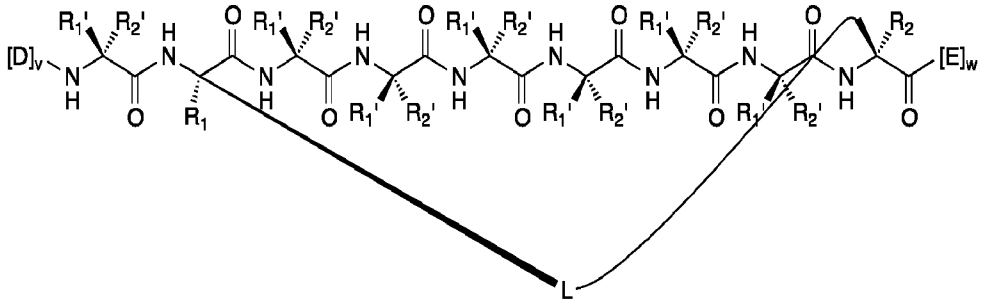
n is an integer from 1-5.

[00195] In one embodiment, the peptidomimetic macrocycle of Formula (I) is:



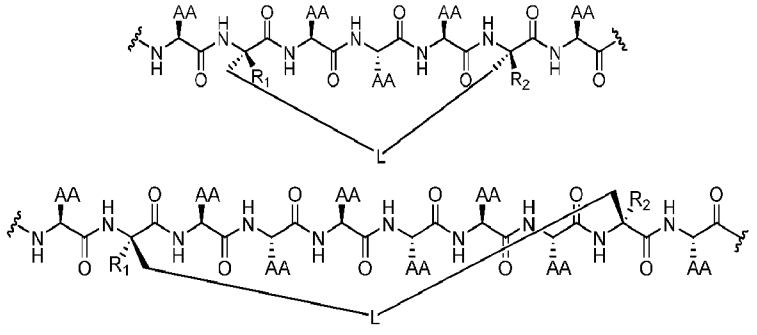
wherein each R_1 and R_2 is independently independently –H, alkyl, alkenyl, alkynyl, arylalkyl, cycloalkyl, cycloalkylalkyl, heteroalkyl, or heterocycloalkyl, unsubstituted or substituted with halo–.

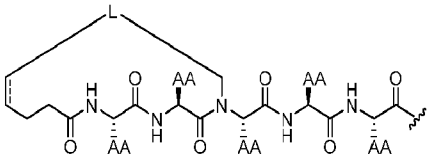
[00196] In related embodiments, the peptidomimetic macrocycle of Formula (I) is:

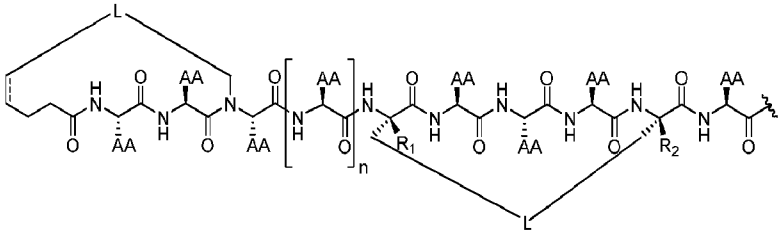


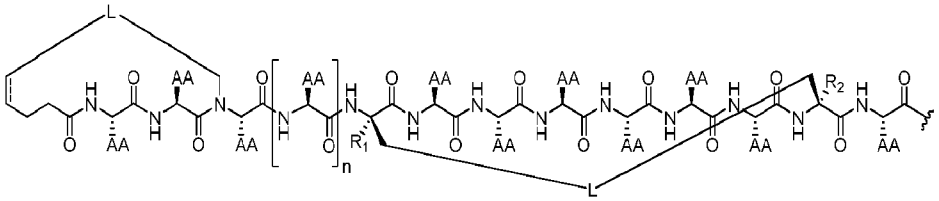
wherein each R_1' and R_2' is independently an amino acid.

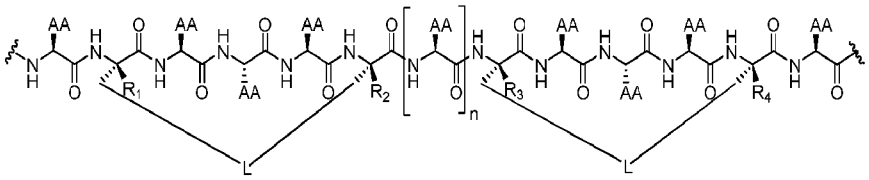
In other embodiments, the peptidomimetic macrocycle of Formula (I) is a compound of any of the formulas shown below:

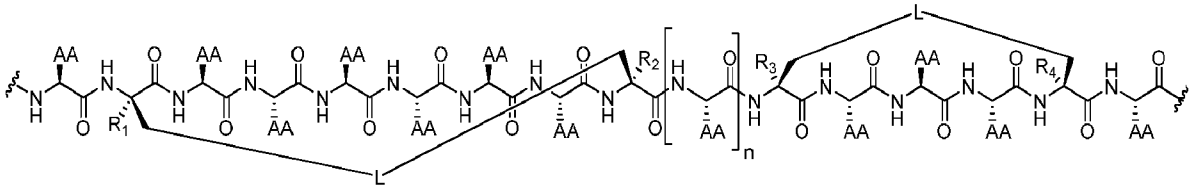


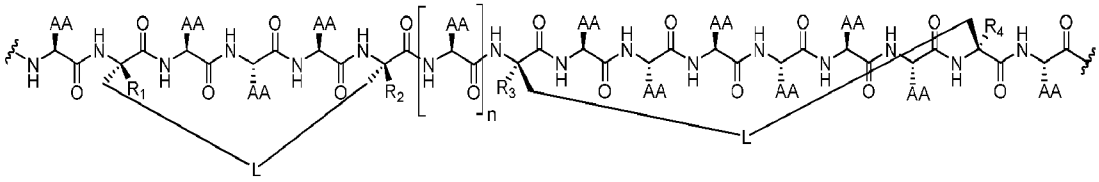


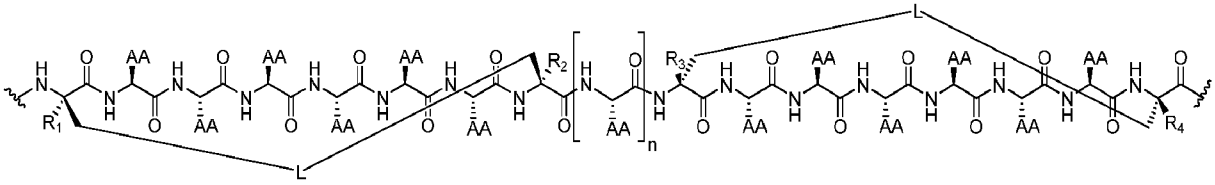


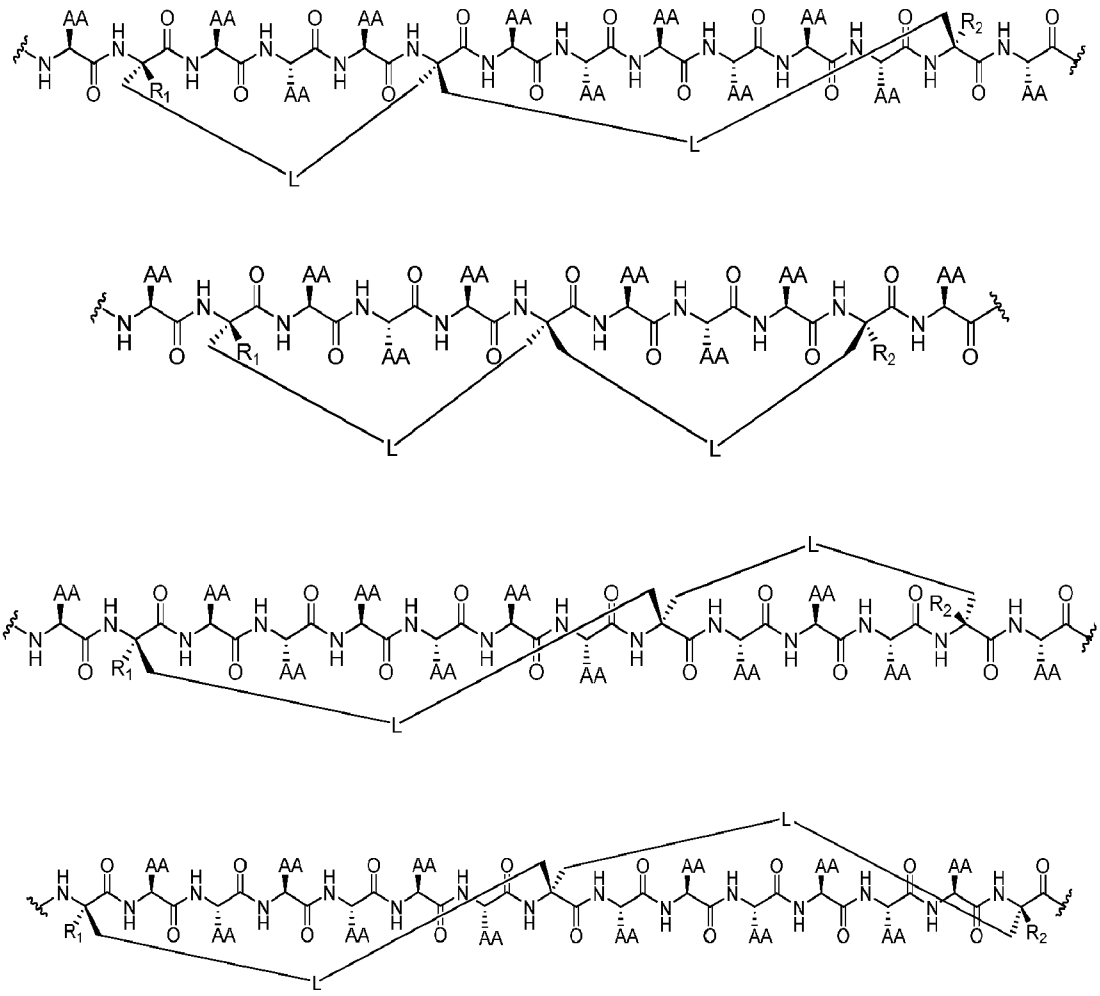






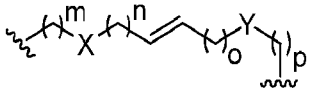




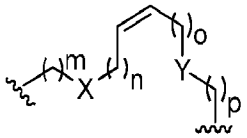


wherein "AA" represents any natural or non-natural amino acid side chain and "~" is $[D]_v$, $[E]_w$ as defined above, and n is an integer between 0 and 20, 50, 100, 200, 300, 400 or 500. In some embodiments, n is 0. In other embodiments, n is less than 50.

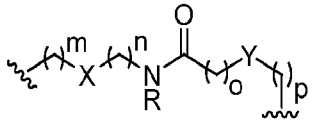
[00197] Exemplary embodiments of the macrocycle-forming linker L are shown below.



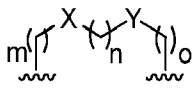
where X, Y = -CH_2-, O, S, or NH
m, n, o, p = 0-10



where X, Y = -CH_2-, O, S, or NH
m, n, o, p = 0-10



where X, Y = -CH_2-, O, S, or NH
m, n, o, p = 0-10
R = H, alkyl, other substituent



where X, Y = -CH_2-, O, S, or NH
m, n, o = 0-10

[00198] In other embodiments, D and/or E in the compound of Formula I are further modified in order to facilitate cellular uptake. In some embodiments, lipidating or PEGylating a peptidomimetic macrocycle facilitates cellular uptake, increases bioavailability, increases blood circulation, alters pharmacokinetics, decreases immunogenicity and/or decreases the needed frequency of administration.

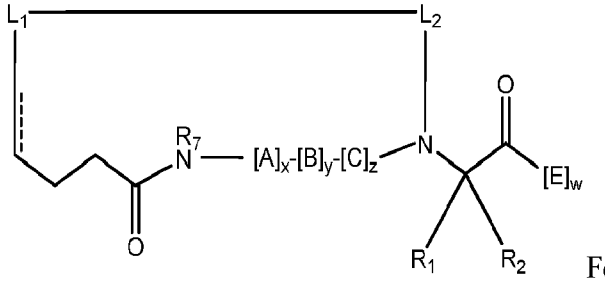
[00199] In other embodiments, at least one of [D] and [E] in the compound of Formula I represents a moiety comprising an additional macrocycle-forming linker such that the peptidomimetic macrocycle comprises at least two macrocycle-forming linkers. In a specific embodiment, a peptidomimetic macrocycle comprises two macrocycle-forming linkers. In an embodiment, u is 2.

[00200] In some embodiments, any of the macrocycle-forming linkers described herein can be used in any combination with any of the sequences shown in **Table 1**, **Table 1a**, **Table 1b**, and **Table 1c** and also with any of the R– substituents indicated herein.

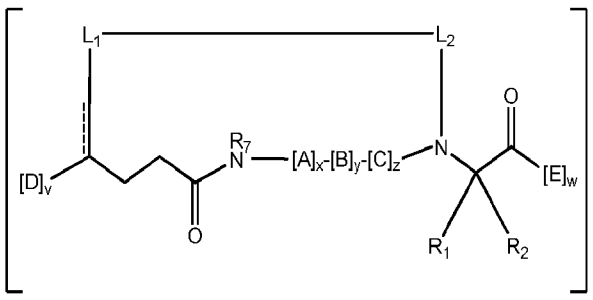
[00201] In some embodiments, the peptidomimetic macrocycle comprises at least one α-helix motif. For example, A, B and/or C in the compound of Formula I include one or more α-helices. As a general matter, α-helices include between 3 and 4 amino acid residues per turn. In some embodiments, the α-helix of the peptidomimetic macrocycle includes 1 to 5 turns and, therefore, 3 to 20 amino acid residues. In specific embodiments, the α-helix includes 1 turn, 2 turns, 3 turns, 4 turns, or 5 turns. In some embodiments, the macrocycle-forming linker stabilizes an α-helix motif included within the peptidomimetic macrocycle. Thus, in some embodiments, the length of the macrocycle-forming linker L from a first Cα to a second Cα is selected to increase the stability of an α-helix. In some embodiments, the macrocycle-forming linker spans from 1 turn to 5 turns of the α-helix. In some embodiments, the macrocycle-forming linker spans approximately 1 turn, 2 turns, 3 turns, 4 turns, or 5 turns of the α-helix. In some embodiments, the length of the macrocycle-forming linker is approximately 5 Å to 9 Å per turn of the α-helix, or approximately 6 Å to 8 Å per turn of the α-helix. Where the macrocycle-forming linker spans approximately 1 turn of an α-helix, the length is equal to approximately 5 carbon-carbon bonds to 13 carbon-carbon bonds, approximately 7 carbon-carbon bonds to 11 carbon-carbon bonds, or approximately 9 carbon-carbon bonds. Where the macrocycle-forming linker spans approximately 2 turns of an α-helix, the length is equal to approximately 8 carbon-carbon bonds to 16 carbon-carbon bonds, approximately 10 carbon-carbon bonds to 14 carbon-carbon bonds, or approximately 12 carbon-carbon bonds. Where the macrocycle-forming linker spans approximately 3 turns of an α-helix, the length is equal to approximately 14 carbon-carbon bonds to 22 carbon-carbon bonds, approximately 16 carbon-carbon bonds to 20 carbon-carbon bonds, or approximately 18 carbon-carbon bonds. Where the macrocycle-forming linker spans approximately 4 turns of an α-helix, the length is equal to approximately 20 carbon-carbon bonds to 28 carbon-carbon bonds, approximately 22 carbon-carbon bonds to 26 carbon-carbon bonds, or approximately 24 carbon-carbon bonds. Where the macrocycle-forming linker spans approximately 5 turns of an α-helix, the length is equal to approximately 26 carbon-carbon bonds to 34 carbon-carbon bonds, approximately 28 carbon-carbon bonds to 32 carbon-carbon bonds, or approximately 30

carbon-carbon bonds. Where the macrocycle-forming linker spans approximately 1 turn of an α-helix, the linkage contains approximately 4 atoms to 12 atoms, approximately 6 atoms to 10 atoms, or approximately 8 atoms. Where the macrocycle-forming linker spans approximately 2 turns of the α-helix, the linkage contains approximately 7 atoms to 15 atoms, approximately 9 atoms to 13 atoms, or approximately 11 atoms. Where the macrocycle-forming linker spans approximately 3 turns of the α-helix, the linkage contains approximately 13 atoms to 21 atoms, approximately 15 atoms to 19 atoms, or approximately 17 atoms. Where the macrocycle-forming linker spans approximately 4 turns of the α-helix, the linkage contains approximately 19 atoms to 27 atoms, approximately 21 atoms to 25 atoms, or approximately 23 atoms. Where the macrocycle-forming linker spans approximately 5 turns of the α-helix, the linkage contains approximately 25 atoms to 33 atoms, approximately 27 atoms to 31 atoms, or approximately 29 atoms. Where the macrocycle-forming linker spans approximately 1 turn of the α-helix, the resulting macrocycle forms a ring containing approximately 17 members to 25 members, approximately 19 members to 23 members, or approximately 21 members. Where the macrocycle-forming linker spans approximately 2 turns of the α-helix, the resulting macrocycle forms a ring containing approximately 29 members to 37 members, approximately 31 members to 35 members, or approximately 33 members. Where the macrocycle-forming linker spans approximately 3 turns of the α-helix, the resulting macrocycle forms a ring containing approximately 44 members to 52 members, approximately 46 members to 50 members, or approximately 48 members. Where the macrocycle-forming linker spans approximately 4 turns of the α-helix, the resulting macrocycle forms a ring containing approximately 59 members to 67 members, approximately 61 members to 65 members, or approximately 63 members. Where the macrocycle-forming linker spans approximately 5 turns of the α-helix, the resulting macrocycle forms a ring containing approximately 74 members to 82 members, approximately 76 members to 80 members, or approximately 78 members.

[00202] In other embodiments, provided are peptidomimetic macrocycles of Formula (IV) or (IVa):



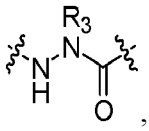
Formula (IV)



Formula (IVa)

wherein:

each A, C, D, and E is independently a natural or non-natural amino acid, and the terminal D and E independently optionally include a capping group;

each B is independently a natural or non-natural amino acid, amino acid analog, , [-NH-L_3-CO-], [-NH-L_3-SO_2-], or [-NH-L_3-];

each R_1 and R_2 are independently –H, alkyl, alkenyl, alkynyl, arylalkyl, cycloalkyl, cycloalkylalkyl, heteroalkyl, or heterocycloalkyl, unsubstituted or substituted with halo–; or at least one of R_1 and R_2 forms a macrocycle-forming linker L' connected to the alpha position of one of said D or E amino acids;

each R_3 independently is hydrogen, alkyl, alkenyl, alkynyl, arylalkyl, heteroalkyl, cycloalkyl, heterocycloalkyl, cycloalkylalkyl, cycloaryl, or heterocycloaryl, optionally substituted with R_5;

each L independently is a macrocycle-forming linker of the formula –L_1–L_2–;

each L_1, L_2 and L_3 are independently alkylene, alkenylene, alkynylene, heteroalkylene, cycloalkylene, heterocycloalkylene, cycloarylene, heterocycloarylene, or [-R_4-K-R_4-]$_n$, each being optionally substituted with R_5;

each R_4 is independently alkylene, alkenylene, alkynylene, heteroalkylene, cycloalkylene, heterocycloalkylene, arylene, or heteroarylene;

each K is independently O, S, SO, SO_2, CO, CO_2, or $CONR_3$;

each R_5 is independently halogen, alkyl, -OR_6, -$N(R_6)_2$, -SR_6, -SOR_6, -SO_2R_6, -CO_2R_6, a fluorescent moiety, a radioisotope or a therapeutic agent;

each R_6 is independently –H, alkyl, alkenyl, alkynyl, arylalkyl, cycloalkylalkyl, heterocycloalkyl, a fluorescent moiety, a radioisotope or a therapeutic agent;

each R_7 is independently –H, alkyl, alkenyl, alkynyl, arylalkyl, cycloalkyl, heteroalkyl, cycloalkylalkyl, heterocycloalkyl, cycloaryl, or heterocycloaryl, optionally substituted with R_5;

each v and w are independently integers from 1-1000;

u is an integer from 1-10;

each x, y and z are independently integers from 0-10; and

each n independently is an integer from 1-5.

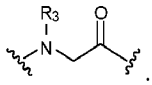
[00203] In one example, L_1 and L_2, either alone or in combination, do not form a triazole or a thioether.

[00204] In one example, at least one of R_1 and R_2 is alkyl, unsubstituted or substituted with halo–. In another example, both R_1 and R_2 are independently alkyl, unsubstituted or substituted with halo–. In some embodiments, at least one of R_1 and R_2 is methyl. In other embodiments, R_1 and R_2 are methyl.

[00205] In some embodiments, x+y+z is at least 1. In other embodiments, x+y+z is at least 2. In other embodiments, x+y+z is 1, 2, 3, 4, 5, 6, 7, 8, 9 or 10. Each occurrence of A, B, C, D or E in a macrocycle or macrocycle precursor is independently selected. For example, a sequence represented by the formula $[A]_x$, when x

is 3, encompasses embodiments where the amino acids are not identical, e.g. Gln–Asp–Ala as well as embodiments where the amino acids are identical, e.g. Gln–Gln–Gln. This applies for any value of x, y, or z in the indicated ranges.

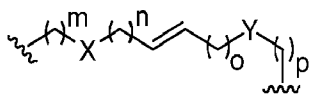
[00206] In some embodiments, the peptidomimetic macrocycle comprises a secondary structure which is an α-helix and R_8 is –H, allowing intrahelical hydrogen bonding. In some embodiments, at least one of A, B, C, D or E is an α,α-disubstituted amino acid. In one example, B is an α,α-disubstituted amino acid. For instance, at least one of A, B, C, D or E is 2-aminoisobutyric acid. In other embodiments, at least one of A, B, C, D or E is



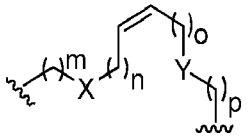
.

[00207] In other embodiments, the length of the macrocycle-forming linker L as measured from a first Cα to a second Cα is selected to stabilize a desired secondary peptide structure, such as an α-helix formed by residues of the peptidomimetic macrocycle including, but not necessarily limited to, those between the first Cα to a second Cα.

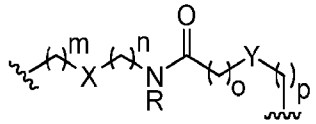
[00208] Exemplary embodiments of the macrocycle-forming linker $-L_1-L_2-$ are shown below.



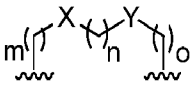
where X, Y = $-CH_2-$, O, S, or NH
m, n, o, p = 0-10



where X, Y = $-CH_2-$, O, S, or NH
m, n, o, p = 0-10

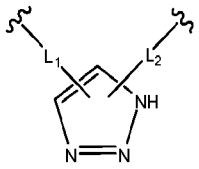


where X, Y = $-CH_2-$, O, S, or NH
m, n, o, p = 0-10
R = H, alkyl, other substituent

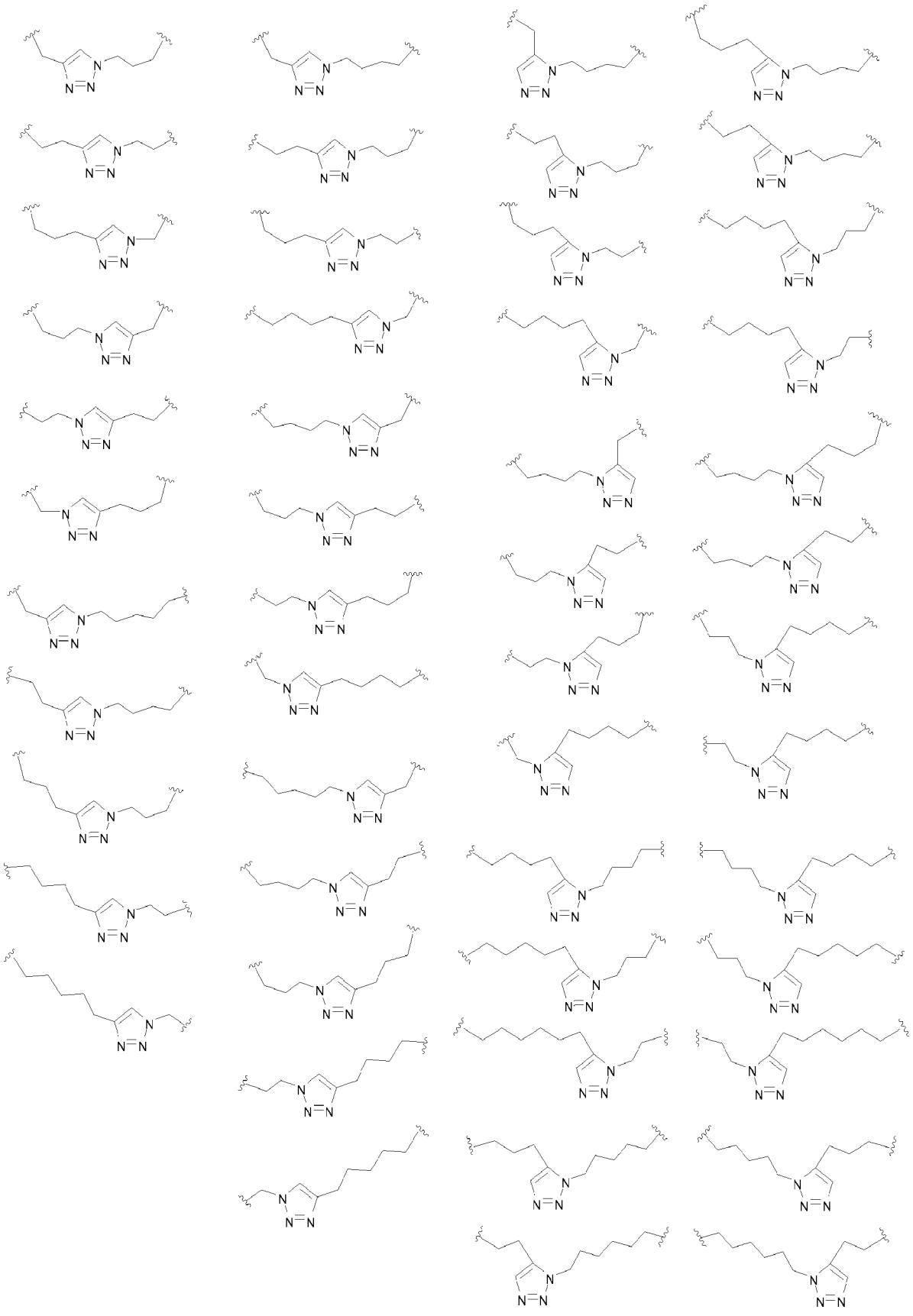


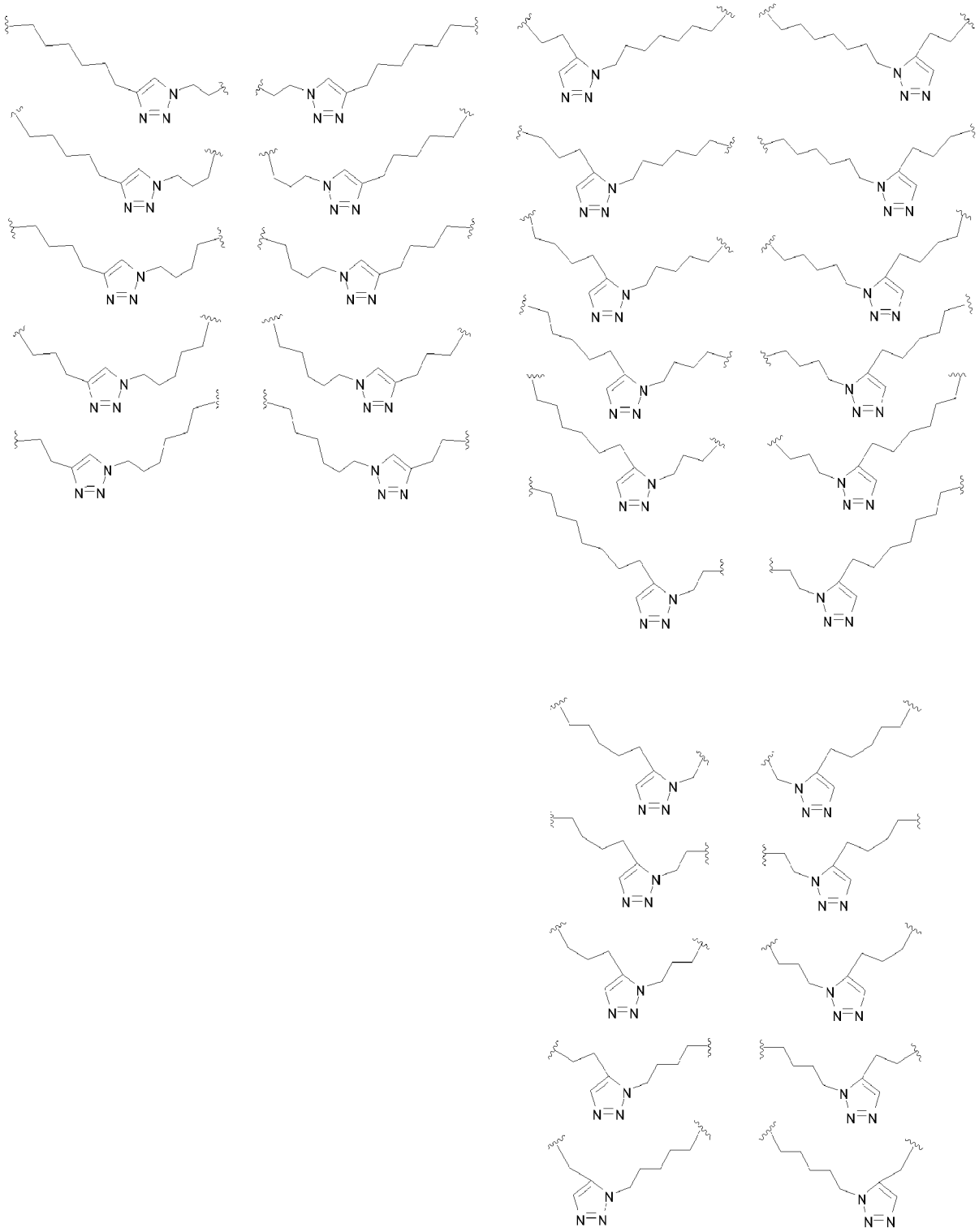
where X, Y = $-CH_2-$, O, S, or NH
m, n, o = 0-10

[00209] In some embodiments, L is a macrocycle-forming linker of the formula



. Exemplary embodiments of such macrocycle-forming linkers L are shown below.





[00210] Unless otherwise stated, any compounds (including peptidomimetic macrocycles, macrocycle precursors, and other compositions) are also meant to encompass compounds which differ only in the presence of one or more isotopically enriched atoms. For example, compounds having the described structures except for the replacement of a hydrogen by a deuterium or tritium, or the replacement of a carbon by ^{13}C- or ^{14}C-enriched carbon are within the scope of this disclosure.

[00211] In some embodiments, the compounds disclosed herein can contain unnatural proportions of atomic isotopes at one or more of atoms that constitute such compounds. For example, the compounds can be radiolabeled with radioactive isotopes, such as for example tritium (^{3}H), iodine-125 (^{125}I) or carbon-14 (^{14}C). In other embodiments, one or more carbon atoms is replaced with a silicon atom. The compounds (including peptidomimetic macrocycles, macrocycle precursors, and other compositions) also include salts thereof. For example, salts of acidic and basic amino acids. All isotopic variations of the compounds disclosed herein, whether radioactive or not, are contemplated herein.

[00212] The compound or peptidomimetic macrocycles described herein can be at least 1% pure, at least 2% pure, at least 3% pure, at least 4% pure, at least 5% pure, at least 6% pure, at least 7% pure, at least 8% pure, at least 9% pure, at least 10% pure, at least 11% pure, at least 12% pure, at least 13% pure, at least 14% pure, at least 15% pure, at least 16% pure, at least 17% pure, at least 18% pure, at least 19% pure, at least 20% pure, at least 21% pure, at least 22% pure, at least 23% pure, at least 24% pure, at least 25% pure, at least 26% pure, at least 27% pure, at least 28% pure, at least 29% pure, at least 30% pure, at least 31% pure, at least 32% pure, at least 33% pure, at least 34% pure, at least 35% pure, at least 36% pure, at least 37% pure, at least 38% pure, at least 39% pure, at least 40% pure, at least 41% pure, at least 42% pure, at least 43% pure, at least 44% pure, at least 45% pure, at least 46% pure, at least 47% pure, at least 48% pure, at least 49% pure, at least 50% pure, at least 51% pure, at least 52% pure, at least 53% pure, at least 54% pure, at least 55% pure, at least 56% pure, at least 57% pure, at least 58% pure, at least 59% pure, at least 60% pure, at least 61% pure, at least 62% pure, at least 63% pure, at least 64% pure, at least 65% pure, at least 66% pure, at least 67% pure, at least 68% pure, at least 69% pure, at least 70% pure, at least 71% pure, at least 72% pure, at least 73% pure, at least 74% pure, at least 75% pure, at least 76% pure, at least 77% pure, at least 78% pure, at least 79% pure, at least 80% pure, at least 81% pure, at least 82% pure, at least 83% pure, at least 84% pure, at least 85% pure, at least 86% pure, at least 87% pure, at least 88% pure, at least 89% pure, at least 90% pure, at least 91% pure, at least 92% pure, at least 93% pure, at least 94% pure, at least 95% pure, at least 96% pure, at least 97% pure, at least 98% pure, at least 99% pure, at least 99.1% pure, at least 99.2% pure, at least 99.3% pure, at least 99.4% pure, at least 99.5% pure, at least 99.6% pure, at least 99.7% pure, at least 99.8% pure, or at least 99.9% pure on a chemical, optical, isomeric, enantiomeric, or diastereomeric basis. Purity can be assessed, for example, by HPLC, MS, LC/MS, melting point, or NMR.

[00213] Two or more peptides can share a degree of homology. A pair of peptides can have, for example, up to about 20% pairwise homology, up to about 25% pairwise homology, up to about 30% pairwise homology, up to about 35% pairwise homology, up to about 40% pairwise homology, up to about 45% pairwise homology, up to about 50% pairwise homology, up to about 55% pairwise homology, up to about 60% pairwise homology, up to about 65% pairwise homology, up to about 70% pairwise homology, up to about 75% pairwise homology, up to about 80% pairwise homology, up to about 85% pairwise homology, up to about 90% pairwise homology, up to about 95% pairwise homology, up to about 96% pairwise homology, up to about 97% pairwise homology, up to about 98% pairwise homology, up to about 99% pairwise homology, up to about 99.5% pairwise homology, or up to about 99.9% pairwise homology. A pair of peptides can have, for example, at least about 20% pairwise homology, at least about 25% pairwise homology, at least about 30% pairwise homology, at least about 35% pairwise homology, at least about 40% pairwise homology, at least about 45% pairwise homology, at least about 50% pairwise homology, at least about 55% pairwise homology, at least about 60% pairwise homology, at least about 65% pairwise homology, at least about 70% pairwise homology, at least about 75% pairwise homology, at least about 80%

pairwise homology, at least about 85% pairwise homology, at least about 90% pairwise homology, at least about 95% pairwise homology, at least about 96% pairwise homology, at least about 97% pairwise homology, at least about 98% pairwise homology, at least about 99% pairwise homology, at least about 99.5% pairwise homology, at least about 99.9% pairwise homology.

[00214] Various methods and software programs can be used to determine the homology between two or more peptides, such as NCBI BLAST, Clustal W, MAFFT, Clustal Omega, AlignMe, Praline, or another suitable method or algorithm.

[00215] The circulating half-life of the peptidomimetic macrocycles in human blood can be about 1-24 h. For example the circulating half-life of the peptidomimetic macrocycles in human blood can me about 2-24 h, 4-24 h, 6-24 h, 8-24 h, 10- 24 h, 12- 24 h, 14-24 h, 16-24 h, 18-24 h, 20-24 h, 22-24 h, 1- 20 h, 4-20 h, 6-20 h, 8-20 h, 10-20 h, 12- 20 h, 14-20 h, 16-20 h, 18-20 h, 1- 16 h, 4-16 h, 6-16 h, 8-16 h, 10- 16 h, 12-16 h, 14-16 h, 1- 12 h, 4-12 h, 6-12 h, 8-12 h, 10- 12 h, 1- 8 h, 4-8 h, 6-8 h, or 1-4 h. In some examples, the circulating half-life of the peptidomimetic macrocycles in human blood can be bout 1-12 h, for example about 1 h, 2 h, 3 h, 4 h, 5 h, 6 h, 7 h, 8 h, 9 h, 10 h, 11 h, or 12 h. In some examples, the circulating half-life of the peptidomimetic macrocycles in human blood is about 2 h. In some examples, the circulating half-life of the peptidomimetic macrocycles in human blood is about 4 h. In some examples, the circulating half-life of the peptidomimetic macrocycles in human blood is about 6 h. In some examples, the circulating half-life of the peptidomimetic macrocycles in human blood is about 8 h. In some examples, the circulating half-life of the peptidomimetic macrocycles in human blood is about 10 h.

[00216] The half-life of the peptidomimetic macrocycles in biological tissue can be about 1-24 h. For example the circulating half-life of the peptidomimetic macrocycles in human blood can me about 1-24 h, 5-24 h, 10-24 h, 15-24 h, 20- 24 h, 1-22 h, 5-22 h, 10-22 h, 15-22 h, 20- 22 h, 1- 20 h, 5-20 h, 15-20 h, 1- 18 h, 5-18 h, 10-18 h, 15-18 h, 1- 16 h, 5-16 h, 10-16 h, 15-16 h, 1- 14 h, 5-14 h, 10-14 h, 1- 12 h, 5-12 h, 10-12 h, 1-10 h, 5-10h, 1-8 h, 5-8 h, 1-6 h, 5-6h, or 1-4 h. In some examples, the circulating half-life of the peptidomimetic macrocycles in human blood can be bout 5-20 h, for example about 5 h, 6 h, 7 h, 8 h, 9 h, 10 h, 11 h, 12 h, 13 h, 14 h, 15 h, 16 h, 17 h, 18 h, 19 h or 20 h. In some examples, the circulating half-life of the peptidomimetic macrocycles in human blood is about 2 h. In some examples, the circulating half-life of the peptidomimetic macrocycles in human blood is about 4 h. In some examples, the circulating half-life of the peptidomimetic macrocycles in human blood is about 6 h. In some examples, the circulating half-life of the peptidomimetic macrocycles in human blood is about 8 h. In some examples, the circulating half-life of the peptidomimetic macrocycles in human blood is about 10 h.

[00217] The circulating half-life of the peptidomimetic macrocycles in human blood can be greater than, equal to, or less than the half -life of the peptidomimetic macrocycles in biological tissue. In some examples, the circulating half-life of the peptidomimetic macrocycles in human blood can be greater than the half -life of the peptidomimetic macrocycles in biological tissue. In some examples, the circulating half-life of the peptidomimetic macrocycles in human blood can be equal to the half -life of the peptidomimetic macrocycles in biological tissue. In some examples, the half -life of the peptidomimetic macrocycles in biological tissue is greater

than the circulating half-life of the peptidomimetic macrocycles in human blood. This can facilitate administration of the peptidomimetic macrocycles at a lower dose and/or at lower frequency. In some embodiments, the half -life of the peptidomimetic macrocycles in biological tissue is at least 1 h, 2 h, 3 h, 4 h, 5 h , 6 h, 7 h, 8 h, 9 h, 10 h, 11 h, or 12 h greater than the than the circulating half-life of the peptidomimetic macrocycles in human blood. In some examples, the circulating half-life of the peptidomimetic macrocycles in human blood is about 4 h and the half -life of the in biological tissue is about 10 h. In some examples, the circulating half-life of the peptidomimetic macrocycles in human blood is about 6 h and the half -life of the in biological tissue is about 10 h.

[00218] The cross-linked peptides of the disclosure can be modeled after the N-terminal transactivation domain of p53 ("p53 peptidomimetic macrocycles"). These cross-linked peptides contain at least two modified amino acids that together form an intramolecular cross-link that can help to stabilize the α-helical secondary structure of a portion of p53 that is thought to be important for binding of p53 to MDM2 and for binding of p53 to MDMX. Accordingly, a cross-linked polypeptide described herein can have improved biological activity relative to a corresponding polypeptide that is not cross-linked. The p53 peptidomimetic macrocycles are thought to interfere with binding of p53 to MDM2 and/or of p53 to MDMX, thereby liberating functional p53 and inhibiting its destruction. The p53 peptidomimetic macrocycles described herein can be used therapeutically, for example to treat cancers and other disorders characterized by an undesirably low level or a low activity of p53, and/or to treat cancers and other disorders characterized by an undesirably high level of activity of MDM2 or MDMX. The p53 peptidomimetic macrocycles can also be useful for treatment of any disorder associated with disrupted regulation of the p53 transcriptional pathway, leading to conditions of excess cell survival and proliferation such as cancer and autoimmunity, in addition to conditions of inappropriate cell cycle arrest and apoptosis such as neurodegeneration and immune deficiencies. In some embodiments, the p53 peptidomimetic macrocycles bind to MDM2 (*e.g.*, GenBank® Accession No.: 228952; GI:228952) and/or MDMX (also referred to as MDM4; GenBank® Accession_No.: 88702791; GI:88702791).

[00219] **Table** 1 shows a list of peptidomimetic macrocycles derived from the MDM2/MDMX-binding helix of p53 that were prepared. **Tables 1a, 1b, 1c**, **1d** and **1e** show a list of selected peptidomimetic macrocycles from **Table 1**. **Table 1f** shows a list of selected peptidomimetic macrocycles from **Table 1e**. A partial staple scan was performed on the linear peptide p-CF_3-Phe7-D-PMI-β. SP-757, a potent and selective MDM2 antagonist, was prepared by including an i, i+7 crosslink to the sequence of p-CF3-Phe-7-D-PMI-b. SP-757 exhibited SJSA-1 sarcoma cell killing activity at a single digit micromolar concentration (EC_{50}= 1.5 mM). (**Figure 3**). SP-763 was prepared by increasing the alanine content to 35% while maintaining the net charge and Von Heijne score by adding four alanine residues to the C-terminus of SP-757. SP-763 exhibited improved SJSA-1 sarcoma cell killing activity (EC_{50}= 0.15 mM) compared to SP-757 (**Figure 3**). SP-763 exhibited similar cell killing activity as SP-449.

[00220] **Table 1:** List of peptidomimetic macrocycles derived from the MDM2/MDMX-binding helix of p53 that were prepared.

SP	Sequence	Isomer	Exact Mass	Found Mass	Calc (M+1)/1	Calc (M+2)/2	Calc (M+3)/3
SP1	Ac-F$r8AYWEAc3cL$AAA-NH2		1456.78	729.44	1457.79	729.4	486.6
SP2	Ac-F$r8AYWEAc3cL$AAibA-NH2		1470.79	736.4	1471.8	736.4	491.27
SP3	Ac-LTF$r8AYWAQL$SANle-NH2		1715.97	859.02	1716.98	858.99	573
SP4	Ac-LTF$r8AYWAQL$SAL-NH2		1715.97	859.02	1716.98	858.99	573
SP5	Ac-LTF$r8AYWAQL$SAM-NH2		1733.92	868.48	1734.93	867.97	578.98
SP6	Ac-LTF$r8AYWAQL$SAhL-NH2		1729.98	865.98	1730.99	866	577.67
SP7	Ac-LTF$r8AYWAQL$SAF-NH2		1749.95	876.36	1750.96	875.98	584.32
SP8	Ac-LTF$r8AYWAQL$SAI-NH2		1715.97	859.02	1716.98	858.99	573
SP9	Ac-LTF$r8AYWAQL$SAChg-NH2		1741.98	871.98	1742.99	872	581.67
SP10	Ac-LTF$r8AYWAQL$SAAib-NH2		1687.93	845.36	1688.94	844.97	563.65
SP11	Ac-LTF$r8AYWAQL$SAA-NH2		1673.92	838.01	1674.93	837.97	558.98
SP12	Ac-LTF$r8AYWA$LSNle-NH2		1767.04	884.77	1768.05	884.53	590.02
SP13	Ac-LTF$r8AYWA$LSA-NH2		1724.99	864.23	1726	863.5	576
SP14	Ac-F$r8AYWEAc3cL$AANle-NH2		1498.82	750.46	1499.83	750.42	500.61
SP15	Ac-F$r8AYWEAc3cL$AAL-NH2		1498.82	750.46	1499.83	750.42	500.61
SP16	Ac-F$r8AYWEAc3cL$AAM-NH2		1516.78	759.41	1517.79	759.4	506.6
SP17	Ac-F$r8AYWEAc3cL$AAhL-NH2		1512.84	757.49	1513.85	757.43	505.29
SP18	Ac-F$r8AYWEAc3cL$AAF-NH2		1532.81	767.48	1533.82	767.41	511.94
SP19	Ac-F$r8AYWEAc3cL$AAI-NH2		1498.82	750.39	1499.83	750.42	500.61
SP20	Ac-F$r8AYWEAc3cL$AAChg-NH2		1524.84	763.48	1525.85	763.43	509.29
SP21	Ac-F$r8AYWEAc3cL$AACha-NH2		1538.85	770.44	1539.86	770.43	513.96
SP22	Ac-F$r8AYWEAc3cL$AAAib-NH2		1470.79	736.84	1471.8	736.4	491.27
SP23	Ac-LTF$r8AYWAQL$AAAibV-NH2		1771.01	885.81	1772.02	886.51	591.34
SP24	Ac-LTF$r8AYWAQL$AAAibV-NH2	iso2	1771.01	886.26	1772.02	886.51	591.34
SP25	Ac-LTF$r8AYWAQL$SAibAA-NH2		1758.97	879.89	1759.98	880.49	587.33
SP26	Ac-LTF$r8AYWAQL$SAibAA-NH2	iso2	1758.97	880.34	1759.98	880.49	587.33
SP27	Ac-HLTF$r8HHWHQL$AANleNle-NH2		2056.15	1028.86	2057.16	1029.08	686.39
SP28	Ac-DLTF$r8HHWHQL$RRLV-NH2		2190.23	731.15	2191.24	1096.12	731.08
SP29	Ac-HHTF$r8HHWHQL$AAML-NH2		2098.08	700.43	2099.09	1050.05	700.37
SP30	Ac-F$r8HHWHQL$RRDCha-NH2		1917.06	959.96	1918.07	959.54	640.03
SP31	Ac-F$r8HHWHQL$HRFV-NH2		1876.02	938.65	1877.03	939.02	626.35
SP32	Ac-HLTF$r8HHWHQL$AAhLA-NH2		2028.12	677.2	2029.13	1015.07	677.05

SP	Sequence	Isomer	Exact Mass	Found Mass	Calc (M+1)/1	Calc (M+2)/2	Calc (M+3)/3
SP33	Ac-DLTF$r8HHWHQL$RRChgl-NH2		2230.26	1115.89	2231.27	1116.14	744.43
SP34	Ac-DLTF$r8HHWHQL$RRChgl-NH2	iso2	2230.26	1115.96	2231.27	1116.14	744.43
SP35	Ac-HHTF$r8HHWHQL$AAChav-NH2		2106.14	1053.95	2107.15	1054.08	703.05
SP36	Ac-F$r8HHWHQL$RRDa-NH2		1834.99	918.3	1836	918.5	612.67
SP37	Ac-F$r8HHWHQL$HRAibG-NH2		1771.95	886.77	1772.96	886.98	591.66
SP38	Ac-F$r8AYWAQL$HHNleL-NH2		1730.97	866.57	1731.98	866.49	578
SP39	Ac-F$r8AYWSAL$HQANle-NH2		1638.89	820.54	1639.9	820.45	547.3
SP40	Ac-F$r8AYWVQL$QHChgl-NH2		1776.01	889.44	1777.02	889.01	593.01
SP41	Ac-F$r8AYWTAL$QQNlev-NH2		1671.94	836.97	1672.95	836.98	558.32
SP42	Ac-F$r8AYWYQL$HAibAa-NH2		1686.89	844.52	1687.9	844.45	563.3
SP43	Ac-LTF$r8AYWAQL$HHLa-NH2		1903.05	952.27	1904.06	952.53	635.36
SP44	Ac-LTF$r8AYWAQL$HHLa-NH2	iso2	1903.05	952.27	1904.06	952.53	635.36
SP45	Ac-LTF$r8AYWAQL$HQNlev-NH2		1922.08	962.48	1923.09	962.05	641.7
SP46	Ac-LTF$r8AYWAQL$HQNlev-NH2	iso2	1922.08	962.4	1923.09	962.05	641.7
SP47	Ac-LTF$r8AYWAQL$QQMl-NH2		1945.05	973.95	1946.06	973.53	649.36
SP48	Ac-LTF$r8AYWAQL$QQMl-NH2	iso2	1945.05	973.88	1946.06	973.53	649.36
SP49	Ac-LTF$r8AYWAQL$HAibhLV-NH2		1893.09	948.31	1894.1	947.55	632.04
SP50	Ac-LTF$r8AYWAQL$AHFA-NH2		1871.01	937.4	1872.02	936.51	624.68
SP51	Ac-HLTF$r8HHWHQL$AANlel-NH2		2056.15	1028.79	2057.16	1029.08	686.39
SP52	Ac-DLTF$r8HHWHQL$RRLa-NH2		2162.2	721.82	2163.21	1082.11	721.74
SP53	Ac-HHTF$r8HHWHQL$AAMv-NH2		2084.07	1042.92	2085.08	1043.04	695.7
SP54	Ac-F$r8HHWHQL$RRDA-NH2		1834.99	612.74	1836	918.5	612.67
SP55	Ac-F$r8HHWHQL$HRFCha-NH2		1930.06	966.47	1931.07	966.04	644.36
SP56	Ac-F$r8AYWEAL$AA-NHAm		1443.82	1445.71	1444.83	722.92	482.28
SP57	Ac-F$r8AYWEAL$AA-NHiAm		1443.82	723.13	1444.83	722.92	482.28
SP58	Ac-F$r8AYWEAL$AA-NHnPr3Ph		1491.82	747.3	1492.83	746.92	498.28
SP59	Ac-F$r8AYWEAL$AA-NHnBu33Me		1457.83	1458.94	1458.84	729.92	486.95
SP60	Ac-F$r8AYWEAL$AA-NHnPr		1415.79	709.28	1416.8	708.9	472.94
SP61	Ac-F$r8AYWEAL$AA-NHnEt2Ch		1483.85	1485.77	1484.86	742.93	495.62
SP62	Ac-F$r8AYWEAL$AA-NHnEt2Cp		1469.83	1470.78	1470.84	735.92	490.95
SP63	Ac-F$r8AYWEAL$AA-NHHex		1457.83	730.19	1458.84	729.92	486.95
SP64	Ac-LTF$r8AYWAQL$AAIA-NH2		1771.01	885.81	1772.02	886.51	591.34

SP	Sequence	Isomer	Exact Mass	Found Mass	Calc (M+1)/1	Calc (M+2)/2	Calc (M+3)/3
SP65	Ac-LTF$r8AYWAQL$AAIA-NH2	iso2	1771.01	866.8	1772.02	886.51	591.34
SP66	Ac-LTF$r8AYWAAL$AAMA-NH2		1731.94	867.08	1732.95	866.98	578.32
SP67	Ac-LTF$r8AYWAAL$AAMA-NH2	iso2	1731.94	867.28	1732.95	866.98	578.32
SP68	Ac-LTF$r8AYWAQL$AANleA-NH2		1771.01	867.1	1772.02	886.51	591.34
SP69	Ac-LTF$r8AYWAQL$AANleA-NH2	iso2	1771.01	886.89	1772.02	886.51	591.34
SP70	Ac-LTF$r8AYWAQL$AAIa-NH2		1771.01	886.8	1772.02	886.51	591.34
SP71	Ac-LTF$r8AYWAQL$AAIa-NH2	iso2	1771.01	887.09	1772.02	886.51	591.34
SP72	Ac-LTF$r8AYWAAL$AAMa-NH2		1731.94	867.17	1732.95	866.98	578.32
SP73	Ac-LTF$r8AYWAAL$AAMa-NH2	iso2	1731.94	867.37	1732.95	866.98	578.32
SP74	Ac-LTF$r8AYWAQL$AANlea-NH2		1771.01	887.08	1772.02	886.51	591.34
SP75	Ac-LTF$r8AYWAQL$AANlea-NH2	iso2	1771.01	887.08	1772.02	886.51	591.34
SP76	Ac-LTF$r8AYWAAL$AAIv-NH2		1742.02	872.37	1743.03	872.02	581.68
SP77	Ac-LTF$r8AYWAAL$AAIv-NH2	iso2	1742.02	872.74	1743.03	872.02	581.68
SP78	Ac-LTF$r8AYWAQL$AAMv-NH2		1817	910.02	1818.01	909.51	606.67
SP79	Ac-LTF$r8AYWAAL$AANlev-NH2		1742.02	872.37	1743.03	872.02	581.68
SP80	Ac-LTF$r8AYWAAL$AANlev-NH2	iso2	1742.02	872.28	1743.03	872.02	581.68
SP81	Ac-LTF$r8AYWAQL$AAIl-NH2		1813.05	907.81	1814.06	907.53	605.36
SP82	Ac-LTF$r8AYWAQL$AAIl-NH2	iso2	1813.05	907.81	1814.06	907.53	605.36
SP83	Ac-LTF$r8AYWAAL$AAMl-NH2		1773.99	887.37	1775	888	592.34
SP84	Ac-LTF$r8AYWAQL$AANlel-NH2		1813.05	907.61	1814.06	907.53	605.36
SP85	Ac-LTF$r8AYWAQL$AANlel-NH2	iso2	1813.05	907.71	1814.06	907.53	605.36
SP86	Ac-F$r8AYWEAL$AAMA-NH2		1575.82	789.02	1576.83	788.92	526.28
SP87	Ac-F$r8AYWEAL$AANleA-NH2		1557.86	780.14	1558.87	779.94	520.29
SP88	Ac-F$r8AYWEAL$AAIa-NH2		1557.86	780.33	1558.87	779.94	520.29
SP89	Ac-F$r8AYWEAL$AAMa-NH2		1575.82	789.3	1576.83	788.92	526.28
SP90	Ac-F$r8AYWEAL$AANlea-NH2		1557.86	779.4	1558.87	779.94	520.29
SP91	Ac-F$r8AYWEAL$AAIv-NH2		1585.89	794.29	1586.9	793.95	529.64
SP92	Ac-F$r8AYWEAL$AAMv-NH2		1603.85	803.08	1604.86	802.93	535.62
SP93	Ac-F$r8AYWEAL$AANlev-NH2		1585.89	793.46	1586.9	793.95	529.64
SP94	Ac-F$r8AYWEAL$AAIl-NH2		1599.91	800.49	1600.92	800.96	534.31
SP95	Ac-F$r8AYWEAL$AAMl-NH2		1617.86	809.44	1618.87	809.94	540.29
SP96	Ac-F$r8AYWEAL$AANlel-NH2		1599.91	801.7	1600.92	800.96	534.31

SP	Sequence	Isomer	Exact Mass	Found Mass	Calc (M+1)/1	Calc (M+2)/2	Calc (M+3)/3
SP97	Ac-F$r8AYWEAL$AANlel-NH2	iso2	1599.91	801.42	1600.92	800.96	534.31
SP98	Ac-LTF$r8AY6clWAQL$SAA-NH2		1707.88	855.72	1708.89	854.95	570.3
SP99	Ac-LTF$r8AY6clWAQL$SAA-NH2	iso2	1707.88	855.35	1708.89	854.95	570.3
SP100	Ac-WTF$r8FYWSQL$AVAa-NH2		1922.01	962.21	1923.02	962.01	641.68
SP101	Ac-WTF$r8FYWSQL$AVAa-NH2	iso2	1922.01	962.49	1923.02	962.01	641.68
SP102	Ac-WTF$r8VYWSQL$AVA-NH2		1802.98	902.72	1803.99	902.5	602
SP103	Ac-WTF$r8VYWSQL$AVA-NH2	iso2	1802.98	903	1803.99	902.5	602
SP104	Ac-WTF$r8FYWSQL$SAAa-NH2		1909.98	956.47	1910.99	956	637.67
SP105	Ac-WTF$r8FYWSQL$SAAa-NH2	iso2	1909.98	956.47	1910.99	956	637.67
SP106	Ac-WTF$r8VYWSQL$AVAaa-NH2		1945.05	974.15	1946.06	973.53	649.36
SP107	Ac-WTF$r8VYWSQL$AVAaa-NH2	iso2	1945.05	973.78	1946.06	973.53	649.36
SP108	Ac-LTF$r8AYWAQL$AVG-NH2		1671.94	837.52	1672.95	836.98	558.32
SP109	Ac-LTF$r8AYWAQL$AVG-NH2	iso2	1671.94	837.21	1672.95	836.98	558.32
SP110	Ac-LTF$r8AYWAQL$AVQ-NH2		1742.98	872.74	1743.99	872.5	582
SP111	Ac-LTF$r8AYWAQL$AVQ-NH2	iso2	1742.98	872.74	1743.99	872.5	582
SP112	Ac-LTF$r8AYWAQL$SAa-NH2		1673.92	838.23	1674.93	837.97	558.98
SP113	Ac-LTF$r8AYWAQL$SAa-NH2	iso2	1673.92	838.32	1674.93	837.97	558.98
SP114	Ac-LTF$r8AYWAQhL$SAA-NH2		1687.93	844.37	1688.94	844.97	563.65
SP115	Ac-LTF$r8AYWAQhL$SAA-NH2	iso2	1687.93	844.81	1688.94	844.97	563.65
SP116	Ac-LTF$r8AYWEQLStSA$-NH2		1826	905.27	1827.01	914.01	609.67
SP117	Ac-LTF$r8AYWAQL$SLA-NH2		1715.97	858.48	1716.98	858.99	573
SP118	Ac-LTF$r8AYWAQL$SLA-NH2	iso2	1715.97	858.87	1716.98	858.99	573
SP119	Ac-LTF$r8AYWAQL$SWA-NH2		1788.96	895.21	1789.97	895.49	597.33
SP120	Ac-LTF$r8AYWAQL$SWA-NH2	iso2	1788.96	895.28	1789.97	895.49	597.33
SP121	Ac-LTF$r8AYWAQL$SVS-NH2		1717.94	859.84	1718.95	859.98	573.65
SP122	Ac-LTF$r8AYWAQL$SAS-NH2		1689.91	845.85	1690.92	845.96	564.31
SP123	Ac-LTF$r8AYWAQL$SVG-NH2		1687.93	844.81	1688.94	844.97	563.65
SP124	Ac-ETF$r8VYWAQL$SAa-NH2		1717.91	859.76	1718.92	859.96	573.64
SP125	Ac-ETF$r8VYWAQL$SAA-NH2		1717.91	859.84	1718.92	859.96	573.64
SP126	Ac-ETF$r8VYWAQL$SVA-NH2		1745.94	873.82	1746.95	873.98	582.99
SP127	Ac-ETF$r8VYWAQL$SLA-NH2		1759.96	880.85	1760.97	880.99	587.66
SP128	Ac-ETF$r8VYWAQL$SWA-NH2		1832.95	917.34	1833.96	917.48	611.99

SP	Sequence	Isomer	Exact Mass	Found Mass	Calc (M+1)/1	Calc (M+2)/2	Calc (M+3)/3
SP129	Ac-ETF$r8KYWAQL$SWA-NH2		1861.98	931.92	1862.99	932	621.67
SP130	Ac-ETF$r8VYWAQL$SVS-NH2		1761.93	881.89	1762.94	881.97	588.32
SP131	Ac-ETF$r8VYWAQL$SAS-NH2		1733.9	867.83	1734.91	867.96	578.97
SP132	Ac-ETF$r8VYWAQL$SVG-NH2		1731.92	866.87	1732.93	866.97	578.31
SP133	Ac-LTF$r8VYWAQL$SSa-NH2		1717.94	859.47	1718.95	859.98	573.65
SP134	Ac-ETF$r8VYWAQL$SSa-NH2		1733.9	867.83	1734.91	867.96	578.97
SP135	Ac-LTF$r8VYWAQL$SNa-NH2		1744.96	873.38	1745.97	873.49	582.66
SP136	Ac-ETF$r8VYWAQL$SNa-NH2		1760.91	881.3	1761.92	881.46	587.98
SP137	Ac-LTF$r8VYWAQL$SAa-NH2		1701.95	851.84	1702.96	851.98	568.32
SP138	Ac-LTF$r8VYWAQL$SVA-NH2		1729.98	865.53	1730.99	866	577.67
SP139	Ac-LTF$r8VYWAQL$SVA-NH2	iso2	1729.98	865.9	1730.99	866	577.67
SP140	Ac-LTF$r8VYWAQL$SWA-NH2		1816.99	909.42	1818	909.5	606.67
SP141	Ac-LTF$r8VYWAQL$SVS-NH2		1745.98	873.9	1746.99	874	583
SP142	Ac-LTF$r8VYWAQL$SVS-NH2	iso2	1745.98	873.9	1746.99	874	583
SP143	Ac-LTF$r8VYWAQL$SAS-NH2		1717.94	859.84	1718.95	859.98	573.65
SP144	Ac-LTF$r8VYWAQL$SAS-NH2	iso2	1717.94	859.91	1718.95	859.98	573.65
SP145	Ac-LTF$r8VYWAQL$SVG-NH2		1715.97	858.87	1716.98	858.99	573
SP146	Ac-LTF$r8VYWAQL$SVG-NH2	iso2	1715.97	858.87	1716.98	858.99	573
SP147	Ac-LTF$r8EYWAQCha$SAA-NH2		1771.96	886.85	1772.97	886.99	591.66
SP148	Ac-LTF$r8EYWAQCha$SAA-NH2	iso2	1771.96	886.85	1772.97	886.99	591.66
SP149	Ac-LTF$r8EYWAQCpg$SAA-NH2		1743.92	872.86	1744.93	872.97	582.31
SP150	Ac-LTF$r8EYWAQCpg$SAA-NH2	iso2	1743.92	872.86	1744.93	872.97	582.31
SP151	Ac-LTF$r8EYWAQF$SAA-NH2		1765.91	883.44	1766.92	883.96	589.64
SP152	Ac-LTF$r8EYWAQF$SAA-NH2	iso2	1765.91	883.89	1766.92	883.96	589.64
SP153	Ac-LTF$r8EYWAQCba$SAA-NH2		1743.92	872.42	1744.93	872.97	582.31
SP154	Ac-LTF$r8EYWAQCba$SAA-NH2	iso2	1743.92	873.39	1744.93	872.97	582.31
SP155	Ac-LTF3Cl$r8EYWAQL$SAA-NH2		1765.89	883.89	1766.9	883.95	589.64
SP156	Ac-LTF3Cl$r8EYWAQL$SAA-NH2	iso2	1765.89	883.96	1766.9	883.95	589.64
SP157	Ac-LTF34F2$r8EYWAQL$SAA-NH2		1767.91	884.48	1768.92	884.96	590.31
SP158	Ac-LTF34F2$r8EYWAQL$SAA-NH2	iso2	1767.91	884.48	1768.92	884.96	590.31
SP159	Ac-LTF34F2$r8EYWAQhL$SAA-NH2		1781.92	891.44	1782.93	891.97	594.98
SP160	Ac-LTF34F2$r8EYWAQhL$SAA-NH2	iso2	1781.92	891.88	1782.93	891.97	594.98

SP	Sequence	Isomer	Exact Mass	Found Mass	Calc (M+1)/1	Calc (M+2)/2	Calc (M+3)/3
SP161	Ac-ETF$r8EYWAQL$SAA-NH2		1747.88	874.34	1748.89	874.95	583.63
SP162	Ac-LTF$r8AYWVQL$SAA-NH2		1701.95	851.4	1702.96	851.98	568.32
SP163	Ac-LTF$r8AHWAQL$SAA-NH2		1647.91	824.83	1648.92	824.96	550.31
SP164	Ac-LTF$r8AEWAQL$SAA-NH2		1639.9	820.39	1640.91	820.96	547.64
SP165	Ac-LTF$r8ASWAQL$SAA-NH2		1597.89	799.38	1598.9	799.95	533.64
SP166	Ac-LTF$r8AEWAQL$SAA-NH2	iso2	1639.9	820.39	1640.91	820.96	547.64
SP167	Ac-LTF$r8ASWAQL$SAA-NH2	iso2	1597.89	800.31	1598.9	799.95	533.64
SP168	Ac-LTF$r8AF4coohWAQL$SAA-NH2		1701.91	851.4	1702.92	851.96	568.31
SP169	Ac-LTF$r8AF4coohWAQL$SAA-NH2	iso2	1701.91	851.4	1702.92	851.96	568.31
SP170	Ac-LTF$r8AHWAQL$AAIa-NH2		1745	874.13	1746.01	873.51	582.67
SP171	Ac-ITF$r8FYWAQL$AAIa-NH2		1847.04	923.92	1848.05	924.53	616.69
SP172	Ac-ITF$r8EHWAQL$AAIa-NH2		1803.01	903.17	1804.02	902.51	602.01
SP173	Ac-ITF$r8EHWAQL$AAIa-NH2	iso2	1803.01	903.17	1804.02	902.51	602.01
SP174	Ac-ETF$r8EHWAQL$AAIa-NH2		1818.97	910.76	1819.98	910.49	607.33
SP175	Ac-ETF$r8EHWAQL$AAIa-NH2	iso2	1818.97	910.85	1819.98	910.49	607.33
SP176	Ac-LTF$r8AHWVQL$AAIa-NH2		1773.03	888.09	1774.04	887.52	592.02
SP177	Ac-ITF$r8FYWVQL$AAIa-NH2		1875.07	939.16	1876.08	938.54	626.03
SP178	Ac-ITF$r8EYWVQL$AAIa-NH2		1857.04	929.83	1858.05	929.53	620.02
SP179	Ac-ITF$r8EHWVQL$AAIa-NH2		1831.04	916.86	1832.05	916.53	611.35
SP180	Ac-LTF$r8AEWAQL$AAIa-NH2		1736.99	869.87	1738	869.5	580
SP181	Ac-LTF$r8AF4coohWAQL$AAIa-NH2		1799	900.17	1800.01	900.51	600.67
SP182	Ac-LTF$r8AF4coohWAQL$AAIa-NH2	iso2	1799	900.24	1800.01	900.51	600.67
SP183	Ac-LTF$r8AHWAQL$AHFA-NH2		1845.01	923.89	1846.02	923.51	616.01
SP184	Ac-ITF$r8FYWAQL$AHFA-NH2		1947.05	975.05	1948.06	974.53	650.02
SP185	Ac-ITF$r8FYWAQL$AHFA-NH2	iso2	1947.05	976.07	1948.06	974.53	650.02
SP186	Ac-ITF$r8FHWAQL$AEFA-NH2		1913.02	958.12	1914.03	957.52	638.68
SP187	Ac-ITF$r8FHWAQL$AEFA-NH2	iso2	1913.02	957.86	1914.03	957.52	638.68
SP188	Ac-ITF$r8EHWAQL$AHFA-NH2		1903.01	952.94	1904.02	952.51	635.34
SP189	Ac-ITF$r8EHWAQL$AHFA-NH2	iso2	1903.01	953.87	1904.02	952.51	635.34
SP190	Ac-LTF$r8AHWVQL$AHFA-NH2		1873.04	937.86	1874.05	937.53	625.35
SP191	Ac-ITF$r8FYWVQL$AHFA-NH2		1975.08	988.83	1976.09	988.55	659.37
SP192	Ac-ITF$r8EYWVQL$AHFA-NH2		1957.05	979.35	1958.06	979.53	653.36

SP	Sequence	Isomer	Exact Mass	Found Mass	Calc (M+1)/1	Calc (M+2)/2	Calc (M+3)/3
SP193	Ac-ITF$r8EHWVQL$AHFA-NH2		1931.05	967	1932.06	966.53	644.69
SP194	Ac-ITF$r8EHWVQL$AHFA-NH2	iso2	1931.05	967.93	1932.06	966.53	644.69
SP195	Ac-ETF$r8EYWAAL$SAA-NH2		1690.86	845.85	1691.87	846.44	564.63
SP196	Ac-LTF$r8AYWVAL$SAA-NH2		1644.93	824.08	1645.94	823.47	549.32
SP197	Ac-LTF$r8AHWAAL$SAA-NH2		1590.89	796.88	1591.9	796.45	531.3
SP198	Ac-LTF$r8AEWAAL$SAA-NH2		1582.88	791.9	1583.89	792.45	528.63
SP199	Ac-LTF$r8AEWAAL$SAA-NH2	iso2	1582.88	791.9	1583.89	792.45	528.63
SP200	Ac-LTF$r8ASWAAL$SAA-NH2		1540.87	770.74	1541.88	771.44	514.63
SP201	Ac-LTF$r8ASWAAL$SAA-NH2	iso2	1540.87	770.88	1541.88	771.44	514.63
SP202	Ac-LTF$r8AYWAAL$AAIa-NH2		1713.99	857.39	1715	858	572.34
SP203	Ac-LTF$r8AYWAAL$AAIa-NH2	iso2	1713.99	857.84	1715	858	572.34
SP204	Ac-LTF$r8AYWAAL$AHFA-NH2		1813.99	907.86	1815	908	605.67
SP205	Ac-LTF$r8EHWAQL$AHIa-NH2		1869.03	936.1	1870.04	935.52	624.02
SP206	Ac-LTF$r8EHWAQL$AHIa-NH2	iso2	1869.03	937.03	1870.04	935.52	624.02
SP207	Ac-LTF$r8AHWAQL$AHIa-NH2		1811.03	906.87	1812.04	906.52	604.68
SP208	Ac-LTF$r8EYWAQL$AHIa-NH2		1895.04	949.15	1896.05	948.53	632.69
SP209	Ac-LTF$r8AYWAQL$AAFa-NH2		1804.99	903.2	1806	903.5	602.67
SP210	Ac-LTF$r8AYWAQL$AAFa-NH2	iso2	1804.99	903.28	1806	903.5	602.67
SP211	Ac-LTF$r8AYWAQL$AAWa-NH2		1844	922.81	1845.01	923.01	615.67
SP212	Ac-LTF$r8AYWAQL$AAVa-NH2		1756.99	878.86	1758	879.5	586.67
SP213	Ac-LTF$r8AYWAQL$AAVa-NH2	iso2	1756.99	879.3	1758	879.5	586.67
SP214	Ac-LTF$r8AYWAQL$AALa-NH2		1771.01	886.26	1772.02	886.51	591.34
SP215	Ac-LTF$r8AYWAQL$AALa-NH2	iso2	1771.01	886.33	1772.02	886.51	591.34
SP216	Ac-LTF$r8EYWAQL$AAIa-NH2		1829.01	914.89	1830.02	915.51	610.68
SP217	Ac-LTF$r8EYWAQL$AAIa-NH2	iso2	1829.01	915.34	1830.02	915.51	610.68
SP218	Ac-LTF$r8EYWAQL$AAFa-NH2		1863	932.87	1864.01	932.51	622.01
SP219	Ac-LTF$r8EYWAQL$AAFa-NH2	iso2	1863	932.87	1864.01	932.51	622.01
SP220	Ac-LTF$r8EYWAQL$AAVa-NH2		1815	908.23	1816.01	908.51	606.01
SP221	Ac-LTF$r8EYWAQL$AAVa-NH2	iso2	1815	908.31	1816.01	908.51	606.01
SP222	Ac-LTF$r8EHWAQL$AAIa-NH2		1803.01	903.17	1804.02	902.51	602.01
SP223	Ac-LTF$r8EHWAQL$AAIa-NH2	iso2	1803.01	902.8	1804.02	902.51	602.01
SP224	Ac-LTF$r8EHWAQL$AAWa-NH2		1876	939.34	1877.01	939.01	626.34

SP	Sequence	Isomer	Exact Mass	Found Mass	Calc (M+1)/1	Calc (M+2)/2	Calc (M+3)/3
SP225	Ac-LTF$r8EHWAQL$AAWa-NH2	iso2	1876	939.62	1877.01	939.01	626.34
SP226	Ac-LTF$r8EHWAQL$AALa-NH2		1803.01	902.8	1804.02	902.51	602.01
SP227	Ac-LTF$r8EHWAQL$AALa-NH2	iso2	1803.01	902.9	1804.02	902.51	602.01
SP228	Ac-ETF$r8EHWVQL$AALa-NH2		1847	924.82	1848.01	924.51	616.67
SP229	Ac-LTF$r8AYWAQL$AAAa-NH2		1728.96	865.89	1729.97	865.49	577.33
SP230	Ac-LTF$r8AYWAQL$AAAa-NH2	iso2	1728.96	865.89	1729.97	865.49	577.33
SP231	Ac-LTF$r8AYWAQL$AAAibA-NH2		1742.98	872.83	1743.99	872.5	582
SP232	Ac-LTF$r8AYWAQL$AAAibA-NH2	iso2	1742.98	872.92	1743.99	872.5	582
SP233	Ac-LTF$r8AYWAQL$AAAAa-NH2		1800	901.42	1801.01	901.01	601.01
SP234	Ac-LTF$r5AYWAQL$s8AAIa-NH2		1771.01	887.17	1772.02	886.51	591.34
SP235	Ac-LTF$r5AYWAQL$s8SAA-NH2		1673.92	838.33	1674.93	837.97	558.98
SP236	Ac-LTF$r8AYWAQCba$AANleA-NH2		1783.01	892.64	1784.02	892.51	595.34
SP237	Ac-ETF$r8AYWAQCba$AANleA-NH2		1798.97	900.59	1799.98	900.49	600.66
SP238	Ac-LTF$r8EYWAQCba$AANleA-NH2		1841.01	922.05	1842.02	921.51	614.68
SP239	Ac-LTF$r8AYWAQCba$AWNleA-NH2		1898.05	950.46	1899.06	950.03	633.69
SP240	Ac-ETF$r8AYWAQCba$AWNleA-NH2		1914.01	958.11	1915.02	958.01	639.01
SP241	Ac-LTF$r8EYWAQCba$AWNleA-NH2		1956.06	950.62	1957.07	979.04	653.03
SP242	Ac-LTF$r8EYWAQCba$SAFA-NH2		1890.99	946.55	1892	946.5	631.34
SP243	Ac-LTF34F2$r8EYWAQCba$SANleA-NH2		1892.99	947.57	1894	947.5	632
SP244	Ac-LTF$r8EF4coohWAQCba$SANleA-NH2		1885	943.59	1886.01	943.51	629.34
SP245	Ac-LTF$r8EYWSQCba$SANleA-NH2		1873	937.58	1874.01	937.51	625.34
SP246	Ac-LTF$r8EYWWQCba$SANleA-NH2		1972.05	987.61	1973.06	987.03	658.36
SP247	Ac-LTF$r8EYWAQCba$AAIa-NH2		1841.01	922.05	1842.02	921.51	614.68
SP248	Ac-LTF34F2$r8EYWAQCba$AAIa-NH2		1876.99	939.99	1878	939.5	626.67
SP249	Ac-LTF$r8EF4coohWAQCba$AAIa-NH2		1869.01	935.64	1870.02	935.51	624.01
SP250	Pam-ETF$r8EYWAQCba$SAA-NH2		1956.1	979.57	1957.11	979.06	653.04
SP251	Ac-LThF$r8EFWAQCba$SAA-NH2		1741.94	872.11	1742.95	871.98	581.65
SP252	Ac-LTA$r8EYWAQCba$SAA-NH2		1667.89	835.4	1668.9	834.95	556.97
SP253	Ac-LTF$r8EYAAQCba$SAA-NH2		1628.88	815.61	1629.89	815.45	543.97
SP254	Ac-LTF$r8EY2NalAQCba$SAA-NH2		1754.93	879.04	1755.94	878.47	585.98
SP255	Ac-LTF$r8AYWAQCba$SAA-NH2		1685.92	844.71	1686.93	843.97	562.98
SP256	Ac-LTF$r8EYWAQCba$SAF-NH2		1819.96	911.41	1820.97	910.99	607.66

SP	Sequence	Isomer	Exact Mass	Found Mass	Calc (M+1)/1	Calc (M+2)/2	Calc (M+3)/3
SP257	Ac-LTF$r8EYWAQCba$SAFa-NH2		1890.99	947.41	1892	946.5	631.34
SP258	Ac-LTF$r8AYWAQCba$SAF-NH2		1761.95	882.73	1762.96	881.98	588.32
SP259	Ac-LTF34F2$r8AYWAQCba$SAF-NH2		1797.93	900.87	1798.94	899.97	600.32
SP260	Ac-LTF$r8AF4coohWAQCba$SAF-NH2		1789.94	896.43	1790.95	895.98	597.65
SP261	Ac-LTF$r8EY6clWAQCba$SAF-NH2		1853.92	929.27	1854.93	927.97	618.98
SP262	Ac-LTF$r8AYWSQCba$SAF-NH2		1777.94	890.87	1778.95	889.98	593.65
SP263	Ac-LTF$r8AYWWQCba$SAF-NH2		1876.99	939.91	1878	939.5	626.67
SP264	Ac-LTF$r8AYWAQCba$AAIa-NH2		1783.01	893.19	1784.02	892.51	595.34
SP265	Ac-LTF34F2$r8AYWAQCba$AAIa-NH2		1818.99	911.23	1820	910.5	607.34
SP266	Ac-LTF$r8AY6clWAQCba$AAIa-NH2		1816.97	909.84	1817.98	909.49	606.66
SP267	Ac-LTF$r8AF4coohWAQCba$AAIa-NH2		1811	906.88	1812.01	906.51	604.67
SP268	Ac-LTF$r8EYWAQCba$AAFa-NH2		1875	938.6	1876.01	938.51	626.01
SP269	Ac-LTF$r8EYWAQCba$AAFa-NH2	iso2	1875	938.6	1876.01	938.51	626.01
SP270	Ac-ETF$r8AYWAQCba$AWNlea-NH2		1914.01	958.42	1915.02	958.01	639.01
SP271	Ac-LTF$r8EYWAQCba$AWNlea-NH2		1956.06	979.42	1957.07	979.04	653.03
SP272	Ac-ETF$r8EYWAQCba$AWNlea-NH2		1972.01	987.06	1973.02	987.01	658.34
SP273	Ac-ETF$r8EYWAQCba$AWNlea-NH2	iso2	1972.01	987.06	1973.02	987.01	658.34
SP274	Ac-LTF$r8AYWAQCba$SAFa-NH2		1832.99	917.89	1834	917.5	612
SP275	Ac-LTF$r8AYWAQCba$SAFa-NH2	iso2	1832.99	918.07	1834	917.5	612
SP276	Ac-ETF$r8AYWAQL$AWNlea-NH2		1902.01	952.22	1903.02	952.01	635.01
SP277	Ac-LTF$r8EYWAQL$AWNlea-NH2		1944.06	973.5	1945.07	973.04	649.03
SP278	Ac-ETF$r8EYWAQL$AWNlea-NH2		1960.01	981.46	1961.02	981.01	654.34
SP279	Dmaac-LTF$r8EYWAQhL$SAA-NH2		1788.98	896.06	1789.99	895.5	597.33
SP280	Hexac-LTF$r8EYWAQhL$SAA-NH2		1802	902.9	1803.01	902.01	601.67
SP281	Napac-LTF$r8EYWAQhL$SAA-NH2		1871.99	937.58	1873	937	625
SP282	Decac-LTF$r8EYWAQhL$SAA-NH2		1858.06	930.55	1859.07	930.04	620.36
SP283	Admac-LTF$r8EYWAQhL$SAA-NH2		1866.03	934.07	1867.04	934.02	623.02
SP284	Tmac-LTF$r8EYWAQhL$SAA-NH2		1787.99	895.41	1789	895	597
SP285	Pam-LTF$r8EYWAQhL$SAA-NH2		1942.16	972.08	1943.17	972.09	648.39
SP286	Ac-LTF$r8AYWAQCba$AANleA-NH2	iso2	1783.01	892.64	1784.02	892.51	595.34
SP287	Ac-LTF34F2$r8EYWAQCba$AAIa-NH2	iso2	1876.99	939.62	1878	939.5	626.67
SP288	Ac-LTF34F2$r8EYWAQCba$SAA-NH2		1779.91	892.07	1780.92	890.96	594.31

SP	Sequence	Isomer	Exact Mass	Found Mass	Calc (M+1)/1	Calc (M+2)/2	Calc (M+3)/3
SP289	Ac-LTF34F2$r8EYWAQCba$SAA-NH2	iso2	1779.91	891.61	1780.92	890.96	594.31
SP290	Ac-LTF$r8EF4coohWAQCba$SAA-NH2		1771.92	887.54	1772.93	886.97	591.65
SP291	Ac-LTF$r8EF4coohWAQCba$SAA-NH2	iso2	1771.92	887.63	1772.93	886.97	591.65
SP292	Ac-LTF$r8EYWSQCba$SAA-NH2		1759.92	881.9	1760.93	880.97	587.65
SP293	Ac-LTF$r8EYWSQCba$SAA-NH2	iso2	1759.92	881.9	1760.93	880.97	587.65
SP294	Ac-LTF$r8EYWAQhL$SAA-NH2		1745.94	875.05	1746.95	873.98	582.99
SP295	Ac-LTF$r8AYWAQhL$SAF-NH2		1763.97	884.02	1764.98	882.99	589
SP296	Ac-LTF$r8AYWAQhL$SAF-NH2	iso2	1763.97	883.56	1764.98	882.99	589
SP297	Ac-LTF34F2$r8AYWAQhL$SAA-NH2		1723.92	863.67	1724.93	862.97	575.65
SP298	Ac-LTF34F2$r8AYWAQhL$SAA-NH2	iso2	1723.92	864.04	1724.93	862.97	575.65
SP299	Ac-LTF$r8AF4coohWAQhL$SAA-NH2		1715.93	859.44	1716.94	858.97	572.98
SP300	Ac-LTF$r8AF4coohWAQhL$SAA-NH2	iso2	1715.93	859.6	1716.94	858.97	572.98
SP301	Ac-LTF$r8AYWSQhL$SAA-NH2		1703.93	853.96	1704.94	852.97	568.98
SP302	Ac-LTF$r8AYWSQhL$SAA-NH2	iso2	1703.93	853.59	1704.94	852.97	568.98
SP303	Ac-LTF$r8EYWAQL$AANleA-NH2		1829.01	915.45	1830.02	915.51	610.68
SP304	Ac-LTF34F2$r8AYWAQL$AANleA-NH2		1806.99	904.58	1808	904.5	603.34
SP305	Ac-LTF$r8AF4coohWAQL$AANleA-NH2		1799	901.6	1800.01	900.51	600.67
SP306	Ac-LTF$r8AYWSQL$AANleA-NH2		1787	894.75	1788.01	894.51	596.67
SP307	Ac-LTF34F2$r8AYWAQhL$AANleA-NH2		1821	911.79	1822.01	911.51	608.01
SP308	Ac-LTF34F2$r8AYWAQhL$AANleA-NH2	iso2	1821	912.61	1822.01	911.51	608.01
SP309	Ac-LTF$r8AF4coohWAQhL$AANleA-NH2		1813.02	907.95	1814.03	907.52	605.35
SP310	Ac-LTF$r8AF4coohWAQhL$AANleA-NH2	iso2	1813.02	908.54	1814.03	907.52	605.35
SP311	Ac-LTF$r8AYWSQhL$AANleA-NH2		1801.02	901.84	1802.03	901.52	601.35
SP312	Ac-LTF$r8AYWSQhL$AANleA-NH2	iso2	1801.02	902.62	1802.03	901.52	601.35
SP313	Ac-LTF$r8AYWAQhL$AAAAa-NH2		1814.01	908.63	1815.02	908.01	605.68
SP314	Ac-LTF$r8AYWAQhL$AAAAa-NH2	iso2	1814.01	908.34	1815.02	908.01	605.68
SP315	Ac-LTF$r8AYWAQL$AAAAAa-NH2		1871.04	936.94	1872.05	936.53	624.69
SP316	Ac-LTF$r8AYWAQL$AAAAAAa-NH2	iso2	1942.07	972.5	1943.08	972.04	648.37
SP317	Ac-LTF$r8AYWAQL$AAAAAAa-NH2	iso1	1942.07	972.5	1943.08	972.04	648.37
SP318	Ac-LTF$r8EYWAQhL$AANleA-NH2		1843.03	922.54	1844.04	922.52	615.35
SP319	Ac-AATF$r8AYWAQL$AANleA-NH2		1800	901.39	1801.01	901.01	601.01
SP320	Ac-LTF$r8AYWAQL$AANleAA-NH2		1842.04	922.45	1843.05	922.03	615.02

SP	Sequence	Isomer	Exact Mass	Found Mass	Calc (M+1)/1	Calc (M+2)/2	Calc (M+3)/3
SP321	Ac-ALTF$r8AYWAQL$AANleAA-NH2		1913.08	957.94	1914.09	957.55	638.7
SP322	Ac-LTF$r8AYWAQCba$AANleAA-NH2		1854.04	928.43	1855.05	928.03	619.02
SP323	Ac-LTF$r8AYWAQhL$AANleAA-NH2		1856.06	929.4	1857.07	929.04	619.69
SP324	Ac-LTF$r8EYWAQCba$SAAA-NH2		1814.96	909.37	1815.97	908.49	605.99
SP325	Ac-LTF$r8EYWAQCba$SAAA-NH2	iso2	1814.96	909.37	1815.97	908.49	605.99
SP326	Ac-LTF$r8EYWAQCba$SAAAA-NH2		1886	944.61	1887.01	944.01	629.67
SP327	Ac-LTF$r8EYWAQCba$SAAAA-NH2	iso2	1886	944.61	1887.01	944.01	629.67
SP328	Ac-ALTF$r8EYWAQCba$SAA-NH2		1814.96	909.09	1815.97	908.49	605.99
SP329	Ac-ALTF$r8EYWAQCba$SAAA-NH2		1886	944.61	1887.01	944.01	629.67
SP330	Ac-ALTF$r8EYWAQCba$SAA-NH2	iso2	1814.96	909.09	1815.97	908.49	605.99
SP331	Ac-LTF$r8EYWAQL$AAAAAa-NH2	iso2	1929.04	966.08	1930.05	965.53	644.02
SP332	Ac-LTF$r8EY6clWAQCba$SAA-NH2		1777.89	890.78	1778.9	889.95	593.64
SP333	Ac-LTF$r8EF4cooh6clWAQCba$SANleA-NH2		1918.96	961.27	1919.97	960.49	640.66
SP334	Ac-LTF$r8EF4cooh6clWAQCba$SANleA-NH2	iso2	1918.96	961.27	1919.97	960.49	640.66
SP335	Ac-LTF$r8EF4cooh6clWAQCba$AAIa-NH2		1902.97	953.03	1903.98	952.49	635.33
SP336	Ac-LTF$r8EF4cooh6clWAQCba$AAIa-NH2	iso2	1902.97	953.13	1903.98	952.49	635.33
SP337	Ac-LTF$r8AY6clWAQL$AAAAAa-NH2		1905	954.61	1906.01	953.51	636.01
SP338	Ac-LTF$r8AY6clWAQL$AAAAAa-NH2	iso2	1905	954.9	1906.01	953.51	636.01
SP339	Ac-F$r8AY6clWEAL$AAAAAAa-NH2		1762.89	883.01	1763.9	882.45	588.64
SP340	Ac-ETF$r8EYWAQL$AAAAAa-NH2		1945	974.31	1946.01	973.51	649.34
SP341	Ac-ETF$r8EYWAQL$AAAAAa-NH2	iso2	1945	974.49	1946.01	973.51	649.34
SP342	Ac-LTF$r8EYWAQL$AAAAAAa-NH2		2000.08	1001.6	2001.09	1001.05	667.7
SP343	Ac-LTF$r8EYWAQL$AAAAAAa-NH2	iso2	2000.08	1001.6	2001.09	1001.05	667.7
SP344	Ac-LTF$r8AYWAQL$AANleAAa-NH2		1913.08	958.58	1914.09	957.55	638.7
SP345	Ac-LTF$r8AYWAQL$AANleAAa-NH2	iso2	1913.08	958.58	1914.09	957.55	638.7
SP346	Ac-LTF$r8EYWAQCba$AAAAAa-NH2		1941.04	972.55	1942.05	971.53	648.02
SP347	Ac-LTF$r8EYWAQCba$AAAAAa-NH2	iso2	1941.04	972.55	1942.05	971.53	648.02
SP348	Ac-LTF$r8EF4coohWAQCba$AAAAAa-NH2		1969.04	986.33	1970.05	985.53	657.35
SP349	Ac-LTF$r8EF4coohWAQCba$AAAAAa-NH2	iso2	1969.04	986.06	1970.05	985.53	657.35
SP350	Ac-LTF$r8EYWSQCba$AAAAAa-NH2		1957.04	980.04	1958.05	979.53	653.35

SP	Sequence	Isomer	Exact Mass	Found Mass	Calc (M+1)/1	Calc (M+2)/2	Calc (M+3)/3
SP351	Ac-LTF$r8EYWSQCba$AAAAAa-NH2	iso2	1957.04	980.04	1958.05	979.53	653.35
SP352	Ac-LTF$r8EYWAQCba$SAAa-NH2		1814.96	909	1815.97	908.49	605.99
SP353	Ac-LTF$r8EYWAQCba$SAAa-NH2	iso2	1814.96	909	1815.97	908.49	605.99
SP354	Ac-ALTF$r8EYWAQCba$SAAa-NH2		1886	944.52	1887.01	944.01	629.67
SP355	Ac-ALTF$r8EYWAQCba$SAAa-NH2	iso2	1886	944.98	1887.01	944.01	629.67
SP356	Ac-ALTF$r8EYWAQCba$SAAAa-NH2		1957.04	980.04	1958.05	979.53	653.35
SP357	Ac-ALTF$r8EYWAQCba$SAAAa-NH2	iso2	1957.04	980.04	1958.05	979.53	653.35
SP358	Ac-AALTF$r8EYWAQCba$SAAAa-NH2		2028.07	1016.1	2029.08	1015.04	677.03
SP359	Ac-AALTF$r8EYWAQCba$SAAAa-NH2	iso2	2028.07	1015.57	2029.08	1015.04	677.03
SP360	Ac-RTF$r8EYWAQCba$SAA-NH2		1786.94	895.03	1787.95	894.48	596.65
SP361	Ac-LRF$r8EYWAQCba$SAA-NH2		1798.98	901.51	1799.99	900.5	600.67
SP362	Ac-LTF$r8EYWRQCba$SAA-NH2		1828.99	916.4	1830	915.5	610.67
SP363	Ac-LTF$r8EYWARCba$SAA-NH2		1771.97	887.63	1772.98	886.99	591.66
SP364	Ac-LTF$r8EYWAQCba$RAA-NH2		1812.99	908.08	1814	907.5	605.34
SP365	Ac-LTF$r8EYWAQCba$SRA-NH2		1828.99	916.12	1830	915.5	610.67
SP366	Ac-LTF$r8EYWAQCba$SAR-NH2		1828.99	916.12	1830	915.5	610.67
SP367	5-FAM-BaLTF$r8EYWAQCba$SAA-NH2		2131	1067.09	2132.01	1066.51	711.34
SP368	5-FAM-BaLTF$r8AYWAQL$AANleA-NH2		2158.08	1080.6	2159.09	1080.05	720.37
SP369	Ac-LAF$r8EYWAQL$AANleA-NH2		1799	901.05	1800.01	900.51	600.67
SP370	Ac-ATF$r8EYWAQL$AANleA-NH2		1786.97	895.03	1787.98	894.49	596.66
SP371	Ac-AAF$r8EYWAQL$AANleA-NH2		1756.96	880.05	1757.97	879.49	586.66
SP372	Ac-AAAF$r8EYWAQL$AANleA-NH2		1827.99	915.57	1829	915	610.34
SP373	Ac-AAAAF$r8EYWAQL$AANleA-NH2		1899.03	951.09	1900.04	950.52	634.02
SP374	Ac-AATF$r8EYWAQL$AANleA-NH2		1858	930.92	1859.01	930.01	620.34
SP375	Ac-AALTF$r8EYWAQL$AANleA-NH2		1971.09	987.17	1972.1	986.55	658.04
SP376	Ac-AAALTF$r8EYWAQL$AANleA-NH2		2042.12	1023.15	2043.13	1022.07	681.71
SP377	Ac-LTF$r8EYWAQL$AANleAA-NH2		1900.05	952.02	1901.06	951.03	634.36
SP378	Ac-ALTF$r8EYWAQL$AANleAA-NH2		1971.09	987.63	1972.1	986.55	658.04
SP379	Ac-AALTF$r8EYWAQL$AANleAA-NH2		2042.12	1022.69	2043.13	1022.07	681.71
SP380	Ac-LTF$r8EYWAQCba$AANleAA-NH2		1912.05	958.03	1913.06	957.03	638.36
SP381	Ac-LTF$r8EYWAQhL$AANleAA-NH2		1914.07	958.68	1915.08	958.04	639.03
SP382	Ac-ALTF$r8EYWAQhL$AANleAA-NH2		1985.1	994.1	1986.11	993.56	662.71

SP	Sequence	Isomer	Exact Mass	Found Mass	Calc (M+1)/1	Calc (M+2)/2	Calc (M+3)/3
SP383	Ac-LTF$r8ANmYWAQL$AANleA-NH2		1785.02	894.11	1786.03	893.52	596.01
SP384	Ac-LTF$r8ANmYWAQL$AANleA-NH2	iso2	1785.02	894.11	1786.03	893.52	596.01
SP385	Ac-LTF$r8AYNmWAQL$AANleA-NH2		1785.02	894.11	1786.03	893.52	596.01
SP386	Ac-LTF$r8AYNmWAQL$AANleA-NH2	iso2	1785.02	894.11	1786.03	893.52	596.01
SP387	Ac-LTF$r8AYAmwAQL$AANleA-NH2		1785.02	894.01	1786.03	893.52	596.01
SP388	Ac-LTF$r8AYAmwAQL$AANleA-NH2	iso2	1785.02	894.01	1786.03	893.52	596.01
SP389	Ac-LTF$r8AYWAibQL$AANleA-NH2		1785.02	894.01	1786.03	893.52	596.01
SP390	Ac-LTF$r8AYWAibQL$AANleA-NH2	iso2	1785.02	894.01	1786.03	893.52	596.01
SP391	Ac-LTF$r8AYWAQL$AAibNleA-NH2		1785.02	894.38	1786.03	893.52	596.01
SP392	Ac-LTF$r8AYWAQL$AAibNleA-NH2	iso2	1785.02	894.38	1786.03	893.52	596.01
SP393	Ac-LTF$r8AYWAQL$AaNleA-NH2		1771.01	887.54	1772.02	886.51	591.34
SP394	Ac-LTF$r8AYWAQL$AaNleA-NH2	iso2	1771.01	887.54	1772.02	886.51	591.34
SP395	Ac-LTF$r8AYWAQL$ASarNleA-NH2		1771.01	887.35	1772.02	886.51	591.34
SP396	Ac-LTF$r8AYWAQL$ASarNleA-NH2	iso2	1771.01	887.35	1772.02	886.51	591.34
SP397	Ac-LTF$r8AYWAQL$AANleAib-NH2		1785.02	894.75	1786.03	893.52	596.01
SP398	Ac-LTF$r8AYWAQL$AANleAib-NH2	iso2	1785.02	894.75	1786.03	893.52	596.01
SP399	Ac-LTF$r8AYWAQL$AANleNmA-NH2		1785.02	894.6	1786.03	893.52	596.01
SP400	Ac-LTF$r8AYWAQL$AANleNmA-NH2	iso2	1785.02	894.6	1786.03	893.52	596.01
SP401	Ac-LTF$r8AYWAQL$AANleSar-NH2		1771.01	886.98	1772.02	886.51	591.34
SP402	Ac-LTF$r8AYWAQL$AANleSar-NH2	iso2	1771.01	886.98	1772.02	886.51	591.34
SP403	Ac-LTF$r8AYWAQL$AANleAAib-NH2		1856.06		1857.07	929.04	619.69
SP404	Ac-LTF$r8AYWAQL$AANleAAib-NH2	iso2	1856.06		1857.07	929.04	619.69
SP405	Ac-LTF$r8AYWAQL$AANleANmA-NH2		1856.06	930.37	1857.07	929.04	619.69
SP406	Ac-LTF$r8AYWAQL$AANleANmA-NH2	iso2	1856.06	930.37	1857.07	929.04	619.69
SP407	Ac-LTF$r8AYWAQL$AANleAa-NH2		1842.04	922.69	1843.05	922.03	615.02
SP408	Ac-LTF$r8AYWAQL$AANleAa-NH2	iso2	1842.04	922.69	1843.05	922.03	615.02
SP409	Ac-LTF$r8AYWAQL$AANleASar-NH2		1842.04	922.6	1843.05	922.03	615.02
SP410	Ac-LTF$r8AYWAQL$AANleASar-NH2	iso2	1842.04	922.6	1843.05	922.03	615.02
SP411	Ac-LTF$/r8AYWAQL$/AANleA-NH2		1799.04	901.14	1800.05	900.53	600.69
SP412	Ac-LTFAibAYWAQLAibAANleA-NH2		1648.9	826.02	1649.91	825.46	550.64
SP413	Ac-LTF$r8Cou4YWAQL$AANleA-NH2		1975.05	989.11	1976.06	988.53	659.36
SP414	Ac-LTF$r8Cou4YWAQL$AANleA-NH2	iso2	1975.05	989.11	1976.06	988.53	659.36

SP	Sequence	Isomer	Exact Mass	Found Mass	Calc (M+1)/1	Calc (M+2)/2	Calc (M+3)/3
SP415	Ac-LTF$r8AYWCou4QL$AANleA-NH2		1975.05	989.11	1976.06	988.53	659.36
SP416	Ac-LTF$r8AYWAQL$Cou4ANleA-NH2		1975.05	989.57	1976.06	988.53	659.36
SP417	Ac-LTF$r8AYWAQL$Cou4ANleA-NH2	iso2	1975.05	989.57	1976.06	988.53	659.36
SP418	Ac-LTF$r8AYWAQL$ACou4NleA-NH2		1975.05	989.57	1976.06	988.53	659.36
SP419	Ac-LTF$r8AYWAQL$ACou4NleA-NH2	iso2	1975.05	989.57	1976.06	988.53	659.36
SP420	Ac-LTF$r8AYWAQL$AANleA-OH		1771.99	887.63	1773	887	591.67
SP421	Ac-LTF$r8AYWAQL$AANleA-OH	iso2	1771.99	887.63	1773	887	591.67
SP422	Ac-LTF$r8AYWAQL$AANleA-NHnPr		1813.05	908.08	1814.06	907.53	605.36
SP423	Ac-LTF$r8AYWAQL$AANleA-NHnPr	iso2	1813.05	908.08	1814.06	907.53	605.36
SP424	Ac-LTF$r8AYWAQL$AANleA-NHnBu33Me		1855.1	929.17	1856.11	928.56	619.37
SP425	Ac-LTF$r8AYWAQL$AANleA-NHnBu33Me	iso2	1855.1	929.17	1856.11	928.56	619.37
SP426	Ac-LTF$r8AYWAQL$AANleA-NHHex		1855.1	929.17	1856.11	928.56	619.37
SP427	Ac-LTF$r8AYWAQL$AANleA-NHHex	iso2	1855.1	929.17	1856.11	928.56	619.37
SP428	Ac-LTA$r8AYWAQL$AANleA-NH2		1694.98	849.33	1695.99	848.5	566
SP429	Ac-LThL$r8AYWAQL$AANleA-NH2		1751.04	877.09	1752.05	876.53	584.69
SP430	Ac-LTF$r8AYAAQL$AANleA-NH2		1655.97	829.54	1656.98	828.99	553
SP431	Ac-LTF$r8AY2NalAQL$AANleA-NH2		1782.01	892.63	1783.02	892.01	595.01
SP432	Ac-LTF$r8EYWCou4QCba$SAA-NH2		1947.97	975.8	1948.98	974.99	650.33
SP433	Ac-LTF$r8EYWCou7QCba$SAA-NH2		16.03	974.9	17.04	9.02	6.35
SP434	Ac-LTF%r8EYWAQCba%SAA-NH2		1745.94	874.8	1746.95	873.98	582.99
SP435	Dmaac-LTF$r8EYWAQCba$SAA-NH2		1786.97	894.8	1787.98	894.49	596.66
SP436	Dmaac-LTF$r8AYWAQL$AAAAAa-NH2		1914.08	958.2	1915.09	958.05	639.03
SP437	Dmaac-LTF$r8AYWAQL$AAAAAa-NH2	iso2	1914.08	958.2	1915.09	958.05	639.03
SP438	Dmaac-LTF$r8EYWAQL$AAAAAa-NH2		1972.08	987.3	1973.09	987.05	658.37
SP439	Dmaac-LTF$r8EYWAQL$AAAAAa-NH2	iso2	1972.08	987.3	1973.09	987.05	658.37
SP440	Dmaac-LTF$r8EF4coohWAQCba$AAIa-NH2		1912.05	957.4	1913.06	957.03	638.36
SP441	Dmaac-LTF$r8EF4coohWAQCba$AAIa-NH2	iso2	1912.05	957.4	1913.06	957.03	638.36
SP442	Dmaac-LTF$r8AYWAQL$AANleA-NH2		1814.05	908.3	1815.06	908.03	605.69
SP443	Dmaac-LTF$r8AYWAQL$AANleA-NH2	iso2	1814.05	908.3	1815.06	908.03	605.69
SP444	Ac-LTF%r8AYWAQL%AANleA-NH2		1773.02	888.37	1774.03	887.52	592.01
SP445	Ac-LTF%r8EYWAQL%AAAAAa-NH2		1931.06	966.4	1932.07	966.54	644.69
SP446	Cou6BaLTF$r8EYWAQhL$SAA-NH2		2018.05	1009.9	2019.06	1010.03	673.69

SP	Sequence	Isomer	Exact Mass	Found Mass	Calc (M+1)/1	Calc (M+2)/2	Calc (M+3)/3
SP447	Cou8BaLTF$r8EYWAQhL$SAA-NH2		1962.96	982.34	1963.97	982.49	655.32
SP448	Ac-LTF4I$r8EYWAQL$AAAAAa-NH2		2054.93	1028.68	2055.94	1028.47	685.98
SP449	Ac-LTF$r8EYWAQL$AAAAAa-NH2		1929.04	966.17	1930.05	965.53	644.02
SP550	Ac-LTF$r8EYWAQL$AAAAAa-OH		1930.02	966.54	1931.03	966.02	644.35
SP551	Ac-LTF$r8EYWAQL$AAAAAa-OH	iso2	1930.02	965.89	1931.03	966.02	644.35
SP552	Ac-LTF$r8EYWAEL$AAAAAa-NH2		1930.02	966.82	1931.03	966.02	644.35
SP553	Ac-LTF$r8EYWAEL$AAAAAa-NH2	iso2	1930.02	966.91	1931.03	966.02	644.35
SP554	Ac-LTF$r8EYWAEL$AAAAAa-OH		1931.01	967.28	1932.02	966.51	644.68
SP555	Ac-LTF$r8EY6clWAQL$AAAAAa-NH2		1963	983.28	1964.01	982.51	655.34
SP556	Ac-LTF$r8EF4bOH2WAQL$AAAAAa-NH2		1957.05	980.04	1958.06	979.53	653.36
SP557	Ac-AAALTF$r8EYWAQL$AAAAAa-NH2		2142.15	1072.83	2143.16	1072.08	715.06
SP558	Ac-LTF34F2$r8EYWAQL$AAAAAa-NH2		1965.02	984.3	1966.03	983.52	656.01
SP559	Ac-RTF$r8EYWAQL$AAAAAa-NH2		1972.06	987.81	1973.07	987.04	658.36
SP560	Ac-LTA$r8EYWAQL$AAAAAa-NH2		1853.01	928.33	1854.02	927.51	618.68
SP561	Ac-LTF$r8EYWAibQL$AAAAAa-NH2		1943.06	973.48	1944.07	972.54	648.69
SP562	Ac-LTF$r8EYWAQL$AAibAAAa-NH2		1943.06	973.11	1944.07	972.54	648.69
SP563	Ac-LTF$r8EYWAQL$AAAibAAa-NH2		1943.06	973.48	1944.07	972.54	648.69
SP564	Ac-LTF$r8EYWAQL$AAAAibAa-NH2		1943.06	973.48	1944.07	972.54	648.69
SP565	Ac-LTF$r8EYWAQL$AAAAAiba-NH2		1943.06	973.38	1944.07	972.54	648.69
SP566	Ac-LTF$r8EYWAQL$AAAAAiba-NH2	iso2	1943.06	973.38	1944.07	972.54	648.69
SP567	Ac-LTF$r8EYWAQL$AAAAAAib-NH2		1943.06	973.01	1944.07	972.54	648.69
SP568	Ac-LTF$r8EYWAQL$AaAAAa-NH2		1929.04	966.54	1930.05	965.53	644.02
SP569	Ac-LTF$r8EYWAQL$AAaAAa-NH2		1929.04	966.35	1930.05	965.53	644.02
SP570	Ac-LTF$r8EYWAQL$AAAaAa-NH2		1929.04	966.54	1930.05	965.53	644.02
SP571	Ac-LTF$r8EYWAQL$AAAaAa-NH2	iso2	1929.04	966.35	1930.05	965.53	644.02
SP572	Ac-LTF$r8EYWAQL$AAAAaa-NH2		1929.04	966.35	1930.05	965.53	644.02
SP573	Ac-LTF$r8EYWAQL$AAAAAA-NH2		1929.04	966.35	1930.05	965.53	644.02
SP574	Ac-LTF$r8EYWAQL$ASarAAAa-NH2		1929.04	966.54	1930.05	965.53	644.02
SP575	Ac-LTF$r8EYWAQL$AASarAAa-NH2		1929.04	966.35	1930.05	965.53	644.02
SP576	Ac-LTF$r8EYWAQL$AAASarAa-NH2		1929.04	966.35	1930.05	965.53	644.02
SP577	Ac-LTF$r8EYWAQL$AAAASara-NH2		1929.04	966.35	1930.05	965.53	644.02
SP578	Ac-LTF$r8EYWAQL$AAAAASar-NH2		1929.04	966.08	1930.05	965.53	644.02

SP	Sequence	Isomer	Exact Mass	Found Mass	Calc (M+1)/1	Calc (M+2)/2	Calc (M+3)/3
SP579	Ac-7LTF$r8EYWAQL$AAAAAa-NH2		1918.07	951.99	1919.08	960.04	640.37
SP581	Ac-TF$r8EYWAQL$AAAAAa-NH2		1815.96	929.85	1816.97	908.99	606.33
SP582	Ac-F$r8EYWAQL$AAAAAa-NH2		1714.91	930.92	1715.92	858.46	572.64
SP583	Ac-LVF$r8EYWAQL$AAAAAa-NH2		1927.06	895.12	1928.07	964.54	643.36
SP584	Ac-AAF$r8EYWAQL$AAAAAa-NH2		1856.98	859.51	1857.99	929.5	620
SP585	Ac-LTF$r8EYWAQL$AAAAa-NH2		1858	824.08	1859.01	930.01	620.34
SP586	Ac-LTF$r8EYWAQL$AAAa-NH2		1786.97	788.56	1787.98	894.49	596.66
SP587	Ac-LTF$r8EYWAQL$AAa-NH2		1715.93	1138.57	1716.94	858.97	572.98
SP588	Ac-LTF$r8EYWAQL$Aa-NH2		1644.89	1144.98	1645.9	823.45	549.3
SP589	Ac-LTF$r8EYWAQL$a-NH2		1573.85	1113.71	1574.86	787.93	525.62
SP590	Ac-LTF$r8EYWAQL$AAA-OH		1716.91	859.55	1717.92	859.46	573.31
SP591	Ac-LTF$r8EYWAQL$A-OH		1574.84	975.14	1575.85	788.43	525.95
SP592	Ac-LTF$r8EYWAQL$AAA-NH2		1715.93	904.75	1716.94	858.97	572.98
SP593	Ac-LTF$r8EYWAQCba$SAA-OH		1744.91	802.49	1745.92	873.46	582.64
SP594	Ac-LTF$r8EYWAQCba$S-OH		1602.83	913.53	1603.84	802.42	535.28
SP595	Ac-LTF$r8EYWAQCba$S-NH2		1601.85	979.58	1602.86	801.93	534.96
SP596	4-FBzl-LTF$r8EYWAQL$AAAAAa-NH2		2009.05	970.52	2010.06	1005.53	670.69
SP597	4-FBzl-LTF$r8EYWAQCba$SAA-NH2		1823.93	965.8	1824.94	912.97	608.98
SP598	Ac-LTF$r8RYWAQL$AAAAAa-NH2		1956.1	988.28	1957.11	979.06	653.04
SP599	Ac-LTF$r8HYWAQL$AAAAAa-NH2		1937.06	1003.54	1938.07	969.54	646.69
SP600	Ac-LTF$r8QYWAQL$AAAAAa-NH2		1928.06	993.92	1929.07	965.04	643.69
SP601	Ac-LTF$r8CitYWAQL$AAAAAa-NH2		1957.08	987	1958.09	979.55	653.37
SP602	Ac-LTF$r8GlaYWAQL$AAAAAa-NH2		1973.03	983	1974.04	987.52	658.68
SP603	Ac-LTF$r8F4gYWAQL$AAAAAa-NH2		2004.1	937.86	2005.11	1003.06	669.04
SP604	Ac-LTF$r82mRYWAQL$AAAAAa-NH2		1984.13	958.58	1985.14	993.07	662.38
SP605	Ac-LTF$r8ipKYWAQL$AAAAAa-NH2		1970.14	944.52	1971.15	986.08	657.72
SP606	Ac-LTF$r8F4NH2YWAQL$AAAAAa-NH2		1962.08	946	1963.09	982.05	655.03
SP607	Ac-LTF$r8EYWAAL$AAAAAa-NH2		1872.02	959.32	1873.03	937.02	625.01
SP608	Ac-LTF$r8EYWALL$AAAAAa-NH2		1914.07	980.88	1915.08	958.04	639.03
SP609	Ac-LTF$r8EYWAAibL$AAAAAa-NH2		1886.03	970.61	1887.04	944.02	629.68
SP610	Ac-LTF$r8EYWASL$AAAAAa-NH2		1888.01	980.51	1889.02	945.01	630.34
SP611	Ac-LTF$r8EYWANL$AAAAAa-NH2		1915.02	1006.41	1916.03	958.52	639.35

SP	Sequence	Isomer	Exact Mass	Found Mass	Calc (M+1)/1	Calc (M+2)/2	Calc (M+3)/3
SP612	Ac-LTF$r8EYWACitL$AAAAAa-NH2		1958.07		1959.08	980.04	653.7
SP613	Ac-LTF$r8EYWAHL$AAAAAa-NH2		1938.04	966.24	1939.05	970.03	647.02
SP614	Ac-LTF$r8EYWARL$AAAAAa-NH2		1957.08		1958.09	979.55	653.37
SP615	Ac-LTF$r8EpYWAQL$AAAAAa-NH2		2009.01		2010.02	1005.51	670.68
SP616	Cbm-LTF$r8EYWAQCba$SAA-NH2		1590.85		1591.86	796.43	531.29
SP617	Cbm-LTF$r8EYWAQL$AAAAAa-NH2		1930.04		1931.05	966.03	644.35
SP618	Ac-LTF$r8EYWAQL$SAAAAa-NH2		1945.04	1005.11	1946.05	973.53	649.35
SP619	Ac-LTF$r8EYWAQL$AAAASa-NH2		1945.04	986.52	1946.05	973.53	649.35
SP620	Ac-LTF$r8EYWAQL$SAAASa-NH2		1961.03	993.27	1962.04	981.52	654.68
SP621	Ac-LTF$r8EYWAQTba$AAAAAa-NH2		1943.06	983.1	1944.07	972.54	648.69
SP622	Ac-LTF$r8EYWAQAdm$AAAAAa-NH2		2007.09	990.31	2008.1	1004.55	670.04
SP623	Ac-LTF$r8EYWAQCha$AAAAAa-NH2		1969.07	987.17	1970.08	985.54	657.36
SP624	Ac-LTF$r8EYWAQhCha$AAAAAa-NH2		1983.09	1026.11	1984.1	992.55	662.04
SP625	Ac-LTF$r8EYWAQF$AAAAAa-NH2		1963.02	957.01	1964.03	982.52	655.35
SP626	Ac-LTF$r8EYWAQhF$AAAAAa-NH2		1977.04	1087.81	1978.05	989.53	660.02
SP627	Ac-LTF$r8EYWAQL$AANleAAa-NH2		1971.09	933.45	1972.1	986.55	658.04
SP628	Ac-LTF$r8EYWAQAdm$AANleAAa-NH2		2049.13	1017.97	2050.14	1025.57	684.05
SP629	4-FBz-BaLTF$r8EYWAQL$AAAAAa-NH2		2080.08		2081.09	1041.05	694.37
SP630	4-FBz-BaLTF$r8EYWAQCba$SAA-NH2		1894.97		1895.98	948.49	632.66
SP631	Ac-LTF$r5EYWAQL$s8AAAAAa-NH2		1929.04	1072.68	1930.05	965.53	644.02
SP632	Ac-LTF$r5EYWAQCba$s8SAA-NH2		1743.92	1107.79	1744.93	872.97	582.31
SP633	Ac-LTF$r8EYWAQL$AAhhLAAa-NH2		1999.12		2000.13	1000.57	667.38
SP634	Ac-LTF$r8EYWAQL$AAAAAAAa-NH2		2071.11		2072.12	1036.56	691.38
SP635	Ac-LTF$r8EYWAQL$AAAAAAAAa-NH2		2142.15	778.1	2143.16	1072.08	715.06
SP636	Ac-LTF$r8EYWAQL$AAAAAAAAAa-NH2		2213.19	870.53	2214.2	1107.6	738.74
SP637	Ac-LTA$r8EYAAQCba$SAA-NH2		1552.85		1553.86	777.43	518.62
SP638	Ac-LTA$r8EYAAQL$AAAAAa-NH2		1737.97	779.45	1738.98	869.99	580.33
SP639	Ac-LTF$r8EPmpWAQL$AAAAAa-NH2		2007.03	779.54	2008.04	1004.52	670.02
SP640	Ac-LTF$r8EPmpWAQCba$SAA-NH2		1821.91	838.04	1822.92	911.96	608.31
SP641	Ac-ATF$r8HYWAQL$S-NH2		1555.82	867.83	1556.83	778.92	519.61
SP642	Ac-LTF$r8HAWAQL$S-NH2		1505.84	877.91	1506.85	753.93	502.95
SP643	Ac-LTF$r8HYWAQA$S-NH2		1555.82	852.52	1556.83	778.92	519.61

SP	Sequence	Isomer	Exact Mass	Found Mass	Calc (M+1)/1	Calc (M+2)/2	Calc (M+3)/3
SP644	Ac-LTF$r8EYWAQCba$SA-NH2		1672.89	887.18	1673.9	837.45	558.64
SP645	Ac-LTF$r8EYWAQL$SAA-NH2		1731.92	873.32	1732.93	866.97	578.31
SP646	Ac-LTF$r8HYWAQCba$SAA-NH2		1751.94	873.05	1752.95	876.98	584.99
SP647	Ac-LTF$r8SYWAQCba$SAA-NH2		1701.91	844.88	1702.92	851.96	568.31
SP648	Ac-LTF$r8RYWAQCba$SAA-NH2		1770.98	865.58	1771.99	886.5	591.33
SP649	Ac-LTF$r8KYWAQCba$SAA-NH2		1742.98	936.57	1743.99	872.5	582
SP650	Ac-LTF$r8QYWAQCba$SAA-NH2		1742.94	930.93	1743.95	872.48	581.99
SP651	Ac-LTF$r8EYWAACba$SAA-NH2		1686.9	1032.45	1687.91	844.46	563.31
SP652	Ac-LTF$r8EYWAQCba$AAA-NH2		1727.93	895.46	1728.94	864.97	576.98
SP653	Ac-LTF$r8EYWAQL$AAAAA-OH		1858.99	824.54	1860	930.5	620.67
SP654	Ac-LTF$r8EYWAQL$AAAA-OH		1787.95	894.48	1788.96	894.98	596.99
SP655	Ac-LTF$r8EYWAQL$AA-OH		1645.88	856	1646.89	823.95	549.63
SP656	Ac-LTF$r8AF4bOH2WAQL$AAAAAa-NH2						
SP657	Ac-LTF$r8AF4bOH2WAAL$AAAAAa-NH2						
SP658	Ac-LTF$r8EF4bOH2WAQCba$SAA-NH2						
SP659	Ac-LTF$r8ApYWAQL$AAAAAa-NH2						
SP660	Ac-LTF$r8ApYWAAL$AAAAAa-NH2						
SP661	Ac-LTF$r8EpYWAQCba$SAA-NH2						
SP662	Ac-LTF$rda6AYWAQL$da5AAAAAa-NH2		1974.06	934.44			
SP663	Ac-LTF$rda6EYWAQCba$da5SAA-NH2		1846.95	870.52		869.94	
SP664	Ac-LTF$rda6EYWAQL$da5AAAAAa-NH2						
SP665	Ac-LTF$ra9EYWAQL$a6AAAAAa-NH2			936.57		935.51	
SP666	Ac-LTF$ra9EYWAQL$a6AAAAAa-NH2						
SP667	Ac-LTF$ra9EYWAQCba$a6SAA-NH2						
SP668	Ac-LTA$ra9EYWAQCba$a6SAA-NH2						
SP669	5-FAM-BaLTF$ra9EYWAQCba$a6SAA-NH2						
SP670	5-FAM-BaLTF$r8EYWAQL$AAAAAa-NH2		2316.11				
SP671	5-FAM-BaLTF$/r8EYWAQL$/AAAAAa-NH2		2344.15				
SP672	5-FAM-BaLTA$r8EYWAQL$AAAAAa-NH2		2240.08				
SP673	5-FAM-BaLTF$r8AYWAQL$AAAAAa-NH2		2258.11				
SP674	5-FAM-BaATF$r8EYWAQL$AAAAAa-NH2		2274.07				
SP675	5-FAM-BaLAF$r8EYWAQL$AAAAAa-NH2		2286.1				

SP	Sequence	Isomer	Exact Mass	Found Mass	Calc (M+1)/1	Calc (M+2)/2	Calc (M+3)/3
SP676	5-FAM-BaLTF$r8EAWAQL$AAAAAa-NH2		2224.09				
SP677	5-FAM-BaLTF$r8EYAAQL$AAAAAa-NH2		2201.07				
SP678	5-FAM-BaLTA$r8EYAAQL$AAAAAa-NH2		2125.04				
SP679	5-FAM-BaLTF$r8EYWAAL$AAAAAa-NH2		2259.09				
SP680	5-FAM-BaLTF$r8EYWAQA$AAAAAa-NH2		2274.07				
SP681	5-FAM-BaLTF$/r8EYWAQCba$/SAA-NH2		2159.03				
SP682	5-FAM-BaLTA$r8EYWAQCba$SAA-NH2		2054.97				
SP683	5-FAM-BaLTF$r8EYAAQCba$SAA-NH2		2015.96				
SP684	5-FAM-BaLTA$r8EYAAQCba$SAA-NH2		1939.92				
SP685	5-FAM-BaQSQQTF$r8NLWRLL$QN-NH2		2495.23				
SP686	5-TAMRA-BaLTF$r8EYWAQCba$SAA-NH2		2186.1				
SP687	5-TAMRA-BaLTA$r8EYWAQCba$SAA-NH2		2110.07				
SP688	5-TAMRA-BaLTF$r8EYAAQCba$SAA-NH2		2071.06				
SP689	5-TAMRA-BaLTA$r8EYAAQCba$SAA-NH2		1995.03				
SP690	5-TAMRA-BaLTF$/r8EYWAQCba$/SAA-NH2		2214.13				
SP691	5-TAMRA-BaLTF$r8EYWAQL$AAAAAa-NH2		2371.22				
SP692	5-TAMRA-BaLTA$r8EYWAQL$AAAAAa-NH2		2295.19				
SP693	5-TAMRA-BaLTF$/r8EYWAQL$/AAAAAa-NH2		2399.25				
SP694	Ac-LTF$r8EYWCou7QCba$SAA-OH		1947.93				
SP695	Ac-LTF$r8EYWCou7QCba$S-OH		1805.86				
SP696	Ac-LTA$r8EYWCou7QCba$SAA-NH2		1870.91				
SP697	Ac-LTF$r8EYACou7QCba$SAA-NH2		1831.9				
SP698	Ac-LTA$r8EYACou7QCba$SAA-NH2		1755.87				
SP699	Ac-LTF$/r8EYWCou7QCba$/SAA-NH2		1974.98				
SP700	Ac-LTF$r8EYWCou7QL$AAAAAa-NH2		2132.06				
SP701	Ac-LTF$/r8EYWCou7QL$/AAAAAa-NH2		2160.09				
SP702	Ac-LTF$r8EYWCou7QL$AAAAA-OH		2062.01				
SP703	Ac-LTF$r8EYWCou7QL$AAAA-OH		1990.97				

SP	Sequence	Isomer	Exact Mass	Found Mass	Calc (M+1)/1	Calc (M+2)/2	Calc (M+3)/3
SP704	Ac-LTF$r8EYWCou7QL$AAA-OH		1919.94				
SP705	Ac-LTF$r8EYWCou7QL$AA-OH		1848.9				
SP706	Ac-LTF$r8EYWCou7QL$A-OH		1777.86				
SP707	Ac-LTF$r8EYWAQL$AAAASa-NH2	iso2		974.4		973.53	
SP708	Ac-LTF$r8AYWAAL$AAAAAa-NH2	iso2	1814.01	908.82	1815.02	908.01	605.68
SP709	Biotin-BaLTF$r8EYWAQL$AAAAAa-NH2		2184.14	1093.64	2185.15	1093.08	729.05
SP710	Ac-LTF$r8HAWAQL$S-NH2	iso2	1505.84	754.43	1506.85	753.93	502.95
SP711	Ac-LTF$r8EYWAQCba$SA-NH2	iso2	1672.89	838.05	1673.9	837.45	558.64
SP712	Ac-LTF$r8HYWAQCba$SAA-NH2	iso2	1751.94	877.55	1752.95	876.98	584.99
SP713	Ac-LTF$r8SYWAQCba$SAA-NH2	iso2	1701.91	852.48	1702.92	851.96	568.31
SP714	Ac-LTF$r8RYWAQCba$SAA-NH2	iso2	1770.98	887.45	1771.99	886.5	591.33
SP715	Ac-LTF$r8KYWAQCba$SAA-NH2	iso2	1742.98	872.92	1743.99	872.5	582
SP716	Ac-LTF$r8EYWAQCba$AAA-NH2	iso2	1727.93	865.71	1728.94	864.97	576.98
SP717	Ac-LTF$r8EYWAQL$AAAAAaBaC-NH2		2103.09	1053.12	2104.1	1052.55	702.04
SP718	Ac-LTF$r8EYWAQL$AAAAAadPeg4C-NH2		2279.19	1141.46	2280.2	1140.6	760.74
SP719	Ac-LTA$r8AYWAAL$AAAAAa-NH2		1737.98	870.43	1738.99	870	580.33
SP720	Ac-LTF$r8AYAAAL$AAAAAa-NH2		1698.97	851	1699.98	850.49	567.33
SP721	5-FAM-BaLTF$r8AYWAAL$AAAAAa-NH2		2201.09	1101.87	2202.1	1101.55	734.7
SP722	Ac-LTA$r8AYWAQL$AAAAAa-NH2		1795	898.92	1796.01	898.51	599.34
SP723	Ac-LTF$r8AYAAQL$AAAAAa-NH2		1755.99	879.49	1757	879	586.34
SP724	Ac-LTF$rda6AYWAAL$da5AAAAAa-NH2		1807.97		1808.98	904.99	603.66
SP725	FITC-BaLTF$r8EYWAQL$AAAAAa-NH2		2347.1	1174.49	2348.11	1174.56	783.37
SP726	FITC-BaLTF$r8EYWAQCba$SAA-NH2		2161.99	1082.35	2163	1082	721.67
SP733	Ac-LTF$r8EYWAQL$EAAAAa-NH2		1987.05	995.03	1988.06	994.53	663.36
SP734	Ac-LTF$r8AYWAQL$EAAAAa-NH2		1929.04	966.35	1930.05	965.53	644.02
SP735	Ac-LTF$r8EYWAQL$AAAAAaBaKbio-NH2		2354.25	1178.47	2355.26	1178.13	785.76
SP736	Ac-LTF$r8AYWAAL$AAAAAa-NH2		1814.01	908.45	1815.02	908.01	605.68
SP737	Ac-LTF$r8AYAAAL$AAAAAa-NH2	iso2	1698.97	850.91	1699.98	850.49	567.33
SP738	Ac-LTF$r8AYAAQL$AAAAAa-NH2	iso2	1755.99	879.4	1757	879	586.34
SP739	Ac-LTF$r8EYWAQL$EAAAAa-NH2	iso2	1987.05	995.21	1988.06	994.53	663.36
SP740	Ac-LTF$r8AYWAQL$EAAAAa-NH2	iso2	1929.04	966.08	1930.05	965.53	644.02
SP741	Ac-LTF$r8EYWAQCba$SAAAAa-NH2		1957.04	980.04	1958.05	979.53	653.35

SP	Sequence	Isomer	Exact Mass	Found Mass	Calc (M+1)/1	Calc (M+2)/2	Calc (M+3)/3
SP742	Ac-LTF$r8EYWAQLStAAA$r5AA-NH2		2023.12	1012.83	2024.13	1012.57	675.38
SP743	Ac-LTF$r8EYWAQL$AAAAA-NH2		2108.17	1055.44	2109.18	1055.09	703.73
SP744	Ac-LTF$r8EYWAQL$AAAAAA-NH2		2179.21	1090.77	2180.22	1090.61	727.41
SP745	Ac-LTF$r8EYWAQL$AAAAAAA-NH2		2250.25	1126.69	2251.26	1126.13	751.09
SP746	Ac-AAALTF$r8EYWAQL$AAA-OH		1930.02		1931.03	966.02	644.35
SP747	Ac-AAALTF$r8EYWAQL$AAA-NH2		1929.04	965.85	1930.05	965.53	644.02
SP748	Ac-AAAALTF$r8EYWAQL$AAA-NH2		2000.08	1001.4	2001.09	1001.05	667.7
SP749	Ac-AAAAALTF$r8EYWAQL$AAA-NH2		2071.11	1037.13	2072.12	1036.56	691.38
SP750	Ac-AAAAAALTF$r8EYWAQL$AAA-NH2		2142.15		2143.16	1072.08	715.06
SP751	Ac-LTF$rda6EYWAQCba$da6SAA-NH2	iso2	1751.89	877.36	1752.9	876.95	584.97
SP752	Ac-t$r5wya$r5f4CF3ekllr-NH2			844.25			
SP753	Ac-tawy$r5nf4CF3e$r5llr-NH2			837.03			
SP754	Ac-tawya$r5f4CF3ek$r5lr-NH2			822.97			
SP755	Ac-tawyanf4CF3e$r5llr$r5a-NH2			908.35			
SP756	Ac-t$s8wyanf4CF3e$r5llr-NH2			858.03			
SP757	Ac-tawy$s8nf4CF3ekll$r5a-NH2			879.86			
SP758	Ac-tawya$s8f4CF3ekllr$r5a-NH2			936.38			
SP759	Ac-tawy$s8naekll$r5a-NH2			844.25			
SP760	5-FAM-Batawy$s8nf4CF3ekll$r5a-NH2						
SP761	5-FAM-Batawy$s8naekll$r5a-NH2						
SP762	Ac-tawy$s8nf4CF3eall$r5a-NH2						
SP763	Ac-tawy$s8nf4CF3ekll$r5aaaaa-NH2						
SP764	Ac-tawy$s8nf4CF3eall$r5aaaaa-NH2						

[00221] Table 1a shows a selection of peptidomimetic macrocycles.

[00222] Table 1a

SP	Sequence	Isomer	Exact Mass	Found Mass	Calc (M+1)/1	Calc (M+2)/2	Calc (M+3)/3
SP244	Ac-LTF$r8EF4coohWAQCba$SANleA-NH2		1885	943.59	1886.01	943.51	629.34
SP331	Ac-LTF$r8EYWAQL$AAAAAa-NH2	iso2	1929.04	966.08	1930.05	965.53	644.02
SP555	Ac-LTF$r8EY6clWAQL$AAAAAa-NH2		1963	983.28	1964.01	982.51	655.34
SP557	Ac-AAALTF$r8EYWAQL$AAAAAa-NH2		2142.15	1072.83	2143.16	1072.08	715.06

SP558	Ac-LTF34F2$r8EYWAQL$AAAAAa-NH2		1965.02	984.3	1966.03	983.52	656.01
SP562	Ac-LTF$r8EYWAQL$AAibAAAa-NH2		1943.06	973.11	1944.07	972.54	648.69
SP564	Ac-LTF$r8EYWAQL$AAAAibAa-NH2		1943.06	973.48	1944.07	972.54	648.69
SP566	Ac-LTF$r8EYWAQL$AAAAAiba-NH2	iso2	1943.06	973.38	1944.07	972.54	648.69
SP567	Ac-LTF$r8EYWAQL$AAAAAAib-NH2		1943.06	973.01	1944.07	972.54	648.69
SP572	Ac-LTF$r8EYWAQL$AAAAaa-NH2		1929.04	966.35	1930.05	965.53	644.02
SP573	Ac-LTF$r8EYWAQL$AAAAAA-NH2		1929.04	966.35	1930.05	965.53	644.02
SP578	Ac-LTF$r8EYWAQL$AAAAASar-NH2		1929.04	966.08	1930.05	965.53	644.02
SP551	Ac-LTF$r8EYWAQL$AAAAAa-OH	iso2	1930.02	965.89	1931.03	966.02	644.35
SP662	Ac-LTF$rda6AYWAQL$da5AAAAAa-NH2		1974.06	934.44		933.49	
SP367	5-FAM-BaLTF$r8EYWAQCba$SAA-NH2		2131	1067.09	2132.01	1066.51	711.34
SP349	Ac-LTF$r8EF4coohWAQCba$AAAAAa-NH2	iso2	1969.04	986.06	1970.05	985.53	657.35
SP347	Ac-LTF$r8EYWAQCba$AAAAAa-NH2	iso2	1941.04	972.55	1942.05	971.53	648.02

[00223] Table 1b shows a further selection of peptidomimetic macrocycles.

Table 1b

SP	Sequence	Isomer	Exact Mass	Found Mass	Calc (M+1)/1	Calc (M+2)/2	Calc (M+3)/3
SP581	Ac-TF$r8EYWAQL$AAAAAa-NH2		1815.96	929.85	1816.97	908.99	606.33
SP582	Ac-F$r8EYWAQL$AAAAAa-NH2		1714.91	930.92	1715.92	858.46	572.64
SP583	Ac-LVF$r8EYWAQL$AAAAAa-NH2		1927.06	895.12	1928.07	964.54	643.36
SP584	Ac-AAF$r8EYWAQL$AAAAAa-NH2		1856.98	859.51	1857.99	929.5	620
SP585	Ac-LTF$r8EYWAQL$AAAAa-NH2		1858	824.08	1859.01	930.01	620.34
SP586	Ac-LTF$r8EYWAQL$AAAa-NH2		1786.97	788.56	1787.98	894.49	596.66
SP587	Ac-LTF$r8EYWAQL$AAa-NH2		1715.93	1138.57	1716.94	858.97	572.98
SP588	Ac-LTF$r8EYWAQL$Aa-NH2		1644.89	1144.98	1645.9	823.45	549.3
SP589	Ac-LTF$r8EYWAQL$a-NH2		1573.85	1113.71	1574.86	787.93	525.62
SP590	Ac-LTF$r8AYWAQL$A-NH_2			758.97		758.93	

[00224] **Table 1d** shows a list of selected peptidomimetic macrocycles. **Table 1d -** Selected peptidomimetic macrocycles derived from the MDM2/MDMX-binding helix of p53.

SP#	L	RT*	Ala (%)	IC_{50} MDM2 (nM)	SJSA-1 EC_{50} (μM)**	Solubility (mg/mL)
590	12	74.2	25	140.7	6	≤ 1
68	15	91.5	33	29.02	1.12	3

SP#	L	RT*	Ala (%)	IC_{50} MDM2 (nM)	SJSA-1 EC_{50} (μM)**	Solubility (mg/mL)
315	17	≥ 100	47	30.77	0.18	4.5
317	18	≥ 100	50	10	0.1	5

* Normalized and calculated according to Example 11 (*see* table and equation).
**10% serum, 72 hr
L = length in amino acids; RT= retention time; Ala= alanine content

[00225] **Table 1e** - Peptidomimetic macrocycles that inhibit the MDM2/MDMX and p53 interaction.

SP#	Sequence	Calc. (M + 2)/2	Found Mass
778	Ac-tawyanfekllr-NH_2	776.92	777.46
779	Ac-tawyanf4CF3ekllr- NH_2	810.91	811.41
752	Ac-t$r5wya$r5f4CF3ekllr-NH_2		844.25
753	Ac-tawy$r5nf4CF3e$r5llr-NH_2		837.03
754	Ac-tawya$r5f4CF3ek$r5lr-NH_2		822.97
755	Ac-tawyanf4CF3e$r5llr$r5a-NH_2		908.35
756	Ac-t$s8wyanf4CF3e$r5llr-NH_2		858.03
757	Ac-tawy$s8nf4CF3ekll$r5a-NH_2	878.97	879.86
758	Ac-tawya$s8f4CF3ekllr$r5a-NH_2		936.38
763	Ac-tawy$s8nf4CF3ekll$r5aaaaa-NH_2		

[00226] **Table 1f** - Selected peptidomimetic macrocycles that inhibit the MDM2/MDMX and p53 interaction.

SP#	Ch	L	VH	RT (min)*	Ala (%)	Ki MDM2 (nM)	SJSA-1 EC_{50} (μM)**
778	1	12	9.8	5.53	17	19251.34	>30
779	1	12	9.8	6.52	17	48.16	*ND*
757	0	13	6.3	7.99	15	2.92	1.5
763	0	17	6.7	8.74	35	10.9	0.34

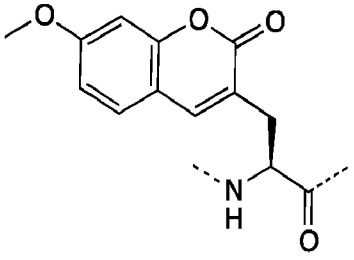
[00227] * *See* Example 11 table
[00228] **10% serum, 72 hr
[00229] Ch = net charge; L = length in amino acids; VH= von Heijne; RT= retention time; Ala= alanine content

[00230] In some embodiments, the invention provides a peptidomimetic macrocycle that comprises an amino acid sequence that has at least 60%, 70%, 80%, 90%, 95%, 97%, or 100% identity to any one of the amino acid sequences in **Table 1**, **1a**, **1b**, **1c**, **1e** or **1f**.

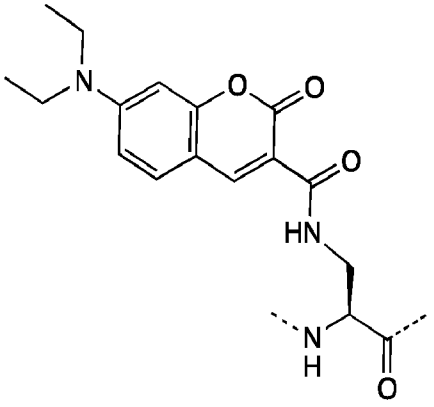
[00231] In the sequences shown above and elsewhere, the following abbreviations are used: "Nle" represents norleucine, "Aib" represents 2-aminoisobutyric acid, "Ac" represents acetyl, and "Pr" represents propionyl. Amino acids represented as "$" are alpha-Me S5-pentenyl-alanine olefin amino acids connected by an all-carbon crosslinker comprising one double bond. Amino acids represented as "$r5" are alpha-Me R5-pentenyl-alanine olefin amino acids connected by an all-carbon comprising one double bond. Amino acids represented as "$s8" are alpha-Me S8-octenyl-alanine olefin amino acids connected by an all-carbon crosslinker comprising one double bond. Amino acids represented as "$r8" are alpha-Me R8-octenyl-alanine olefin amino acids connected by an all-carbon crosslinker comprising one double bond. "Ahx" represents an aminocyclohexyl linker. The crosslinkers are linear all-carbon crosslinker comprising eight or eleven carbon atoms between the alpha carbons of each

amino acid. Amino acids represented as "$/" are alpha-Me S5-pentenyl-alanine olefin amino acids that are not connected by any crosslinker. Amino acids represented as "$/r5" are alpha-Me R5-pentenyl-alanine olefin amino acids that are not connected by any crosslinker. Amino acids represented as "$/s8" are alpha-Me S8-octenyl-alanine olefin amino acids that are not connected by any crosslinker. Amino acids represented as "$/r8" are alpha-Me R8-octenyl-alanine olefin amino acids that are not connected by any crosslinker. Amino acids represented as "Amw" are alpha-Me tryptophan amino acids. Amino acids represented as "Aml" are alpha-Me leucine amino acids. Amino acids represented as "Amf" are alpha-Me phenylalanine amino acids. Amino acids represented as "2ff" are 2-fluoro-phenylalanine amino acids. Amino acids represented as "3ff" are 3-fluoro-phenylalanine amino acids. Amino acids represented as "St" are amino acids comprising two pentenyl-alanine olefin side chains, each of which is crosslinked to another amino acid as indicated. Amino acids represented as "St//" are amino acids comprising two pentenyl-alanine olefin side chains that are not crosslinked. Amino acids represented as "%St" are amino acids comprising two pentenyl-alanine olefin side chains, each of which is crosslinked to another amino acid as indicated via fully saturated hydrocarbon crosslinks. Amino acids represented as "Ba" are beta-alanine. The lower-case character "e" or "z" within the designation of a crosslinked amino acid (e.g. "$er8" or "$zr8") represents the configuration of the double bond (*E* or *Z*, respectively). In other contexts, lower-case letters such as "a" or "f" represent D amino acids (e.g. D-alanine, or D-phenylalanine, respectively). Amino acids designated as "NmW" represent N-methyltryptophan. Amino acids designated as "NmY" represent N-methyltyrosine. Amino acids designated as "NmA" represent N-methylalanine. "Kbio" represents a biotin group attached to the side chain amino group of a lysine residue. Amino acids designated as "Sar" represent sarcosine. Amino acids designated as "Cha" represent cyclohexyl alanine. Amino acids designated as "Cpg" represent cyclopentyl glycine. Amino acids designated as "Chg" represent cyclohexyl glycine. Amino acids designated as "Cba" represent cyclobutyl alanine. Amino acids designated as "F4I" represent 4-iodo phenylalanine. "7L" represents N15 isotopic leucine. Amino acids designated as "F3Cl" represent 3-chloro phenylalanine. Amino acids designated as "F4cooh" represent 4-carboxy phenylalanine. Amino acids designated as "F34F2" represent 3,4-difluoro phenylalanine. Amino acids designated as "6clW" represent 6-chloro tryptophan. Amino acids designated as "$rda6" represent alpha-Me R6-hexynyl-alanine alkynyl amino acids, crosslinked via a dialkyne bond to a second alkynyl amino acid. Amino acids designated as "$da5" represent alpha-Me S5-pentynyl-alanine alkynyl amino acids, wherein the alkyne forms one half of a dialkyne bond with a second alkynyl amino acid. Amino acids designated as "$ra9" represent alpha-Me R9-nonynyl-alanine alkynyl amino acids, crosslinked via an alkyne metathesis reaction with a second alkynyl amino acid. Amino acids designated as "$a6" represent alpha-Me S6-hexynyl-alanine alkynyl amino acids, crosslinked via an alkyne metathesis reaction with a second alkynyl amino acid. The designation "iso1" or "iso2" indicates that the peptidomimetic macrocycle is a single isomer.

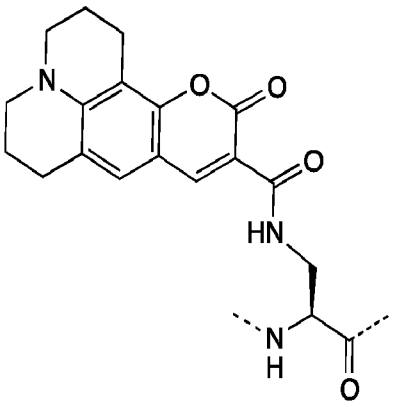
[00232] Amino acids designated as "Cit" represent citrulline. Amino acids designated as "Cou4", "Cou6", "Cou7" and "Cou8", respectively, represent the following structures:



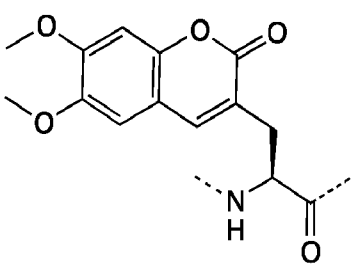
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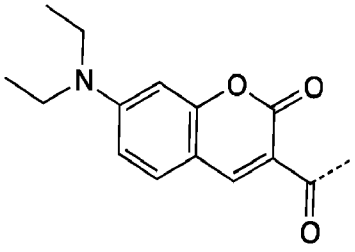
Cou2



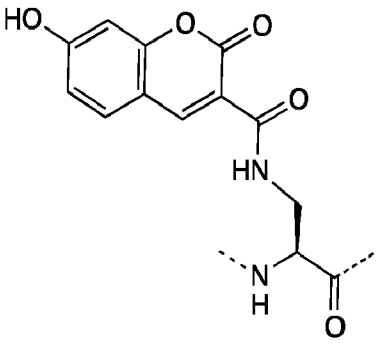
Cou3



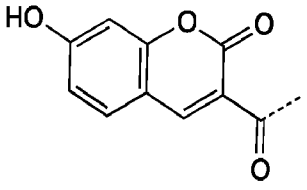
Cou4



Cou6



Cou7

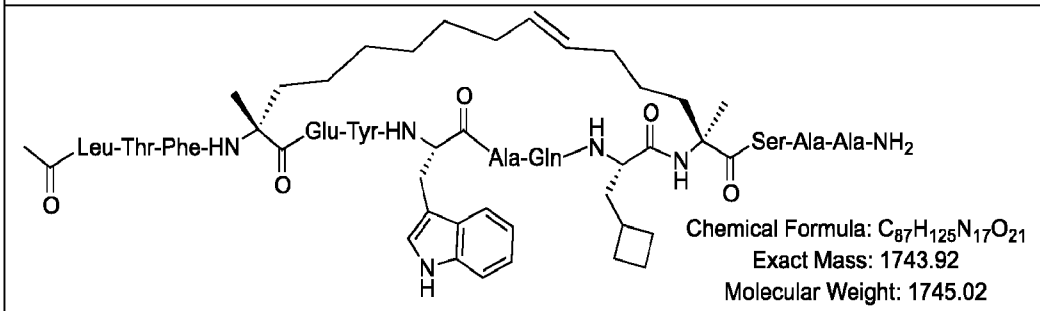
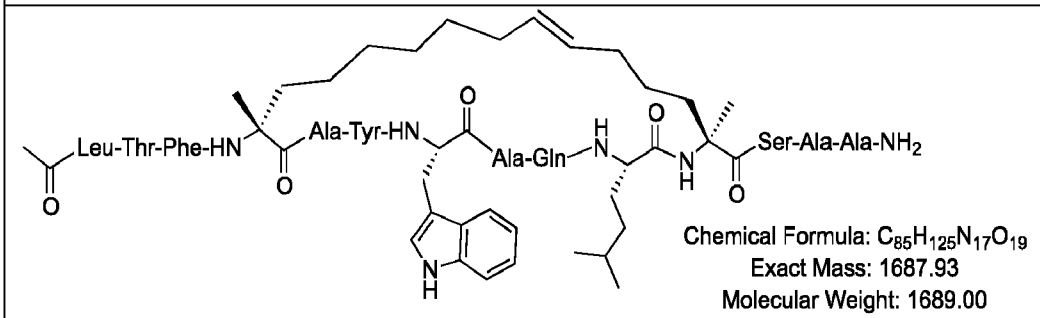
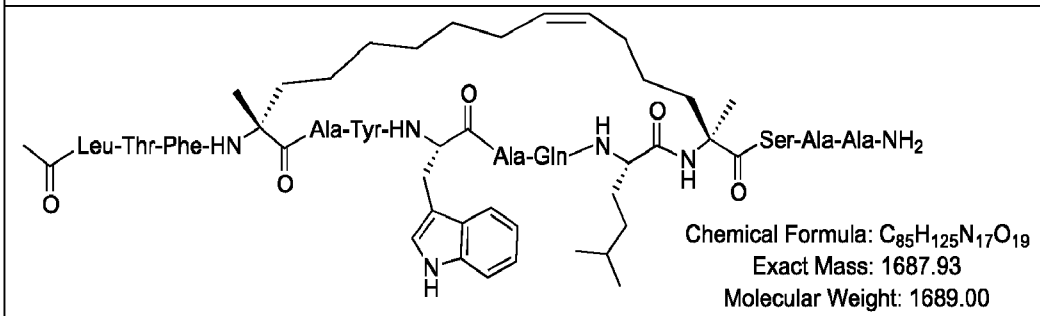


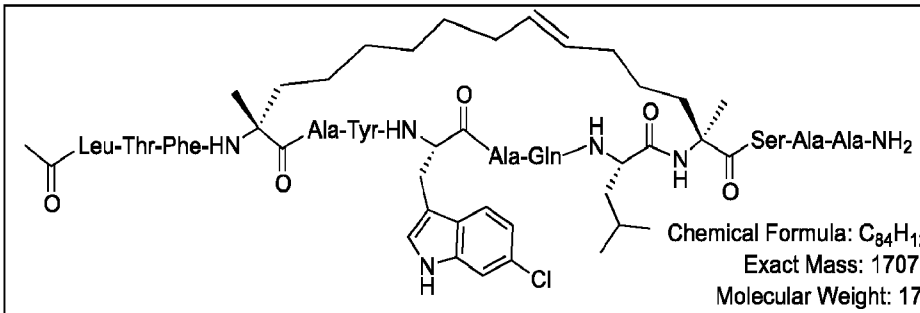
Cou8

[00233] In some embodiments, a peptidomimetic macrocycle is obtained in more than one isomer, for example due to the configuration of a double bond within the structure of the crosslink (*E* vs *Z*). Such isomers can or cannot be separable by conventional chromatographic methods. In some embodiments, one isomer has improved biological properties relative to the other isomer. In one embodiment, an *E* crosslink olefin isomer of a peptidomimetic macrocycle has better solubility, better target affinity, better in vivo or in vitro efficacy, higher helicity, or improved cell permeability relative to its *Z* counterpart. In another embodiment, a *Z* crosslink olefin isomer of a peptidomimetic macrocycle has better solubility, better target affinity, better in vivo or in vitro efficacy, higher helicity, or improved cell permeability relative to its *E* counterpart.

[00234] **Table 1c** shows exemplary peptidomimetic macrocycle:

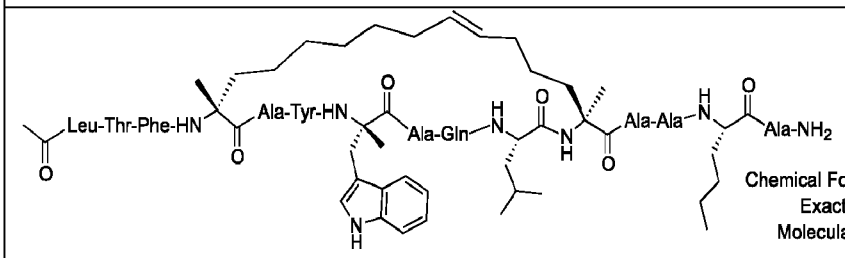
[00235] **Table 1c**

Structure
 Ac-L T F $er8 E Y W A Q Cba $e S A A -NH2
 Ac-L T F $er8 A Y W A Q hL $e S A A -NH2
 Ac-L T F $zr8 A Y W A Q hL $z S A A -NH2



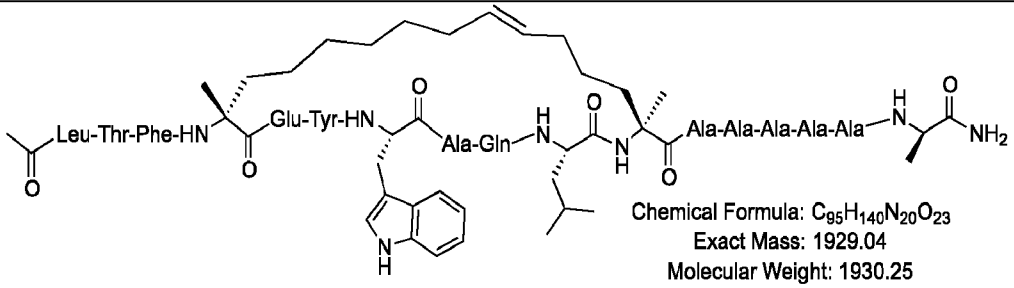
Chemical Formula: $C_{84}H_{122}ClN_{17}O_{19}$
Exact Mass: 1707.88
Molecular Weight: 1709.42

Ac-L T F $er8 A Y6clW AQL $e SAA -NH2



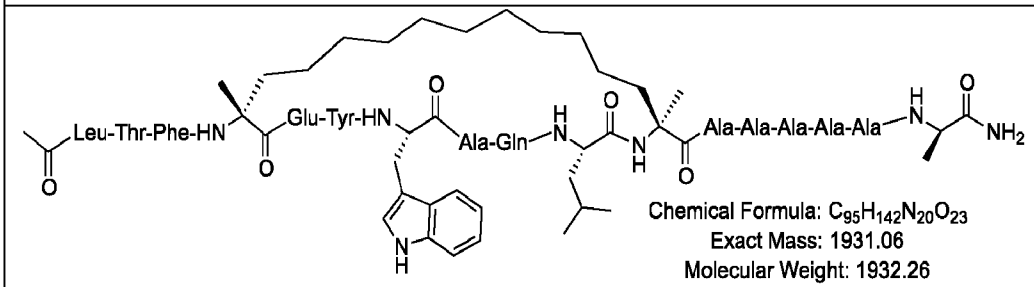
Chemical Formula: $C_{91}H_{136}N_{18}O_{19}$
Exact Mass: 1785.02
Molecular Weight: 1786.16

Ac-L T F $er8 A Y **Amw** AQL $e AA Nle A -NH2



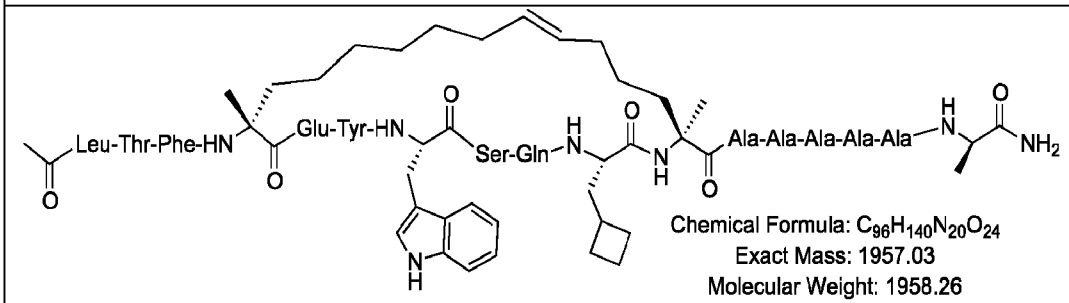
Chemical Formula: $C_{95}H_{140}N_{20}O_{23}$
Exact Mass: 1929.04
Molecular Weight: 1930.25

Ac-L T F $er8 E YW AQL $e AAAAA a -NH2



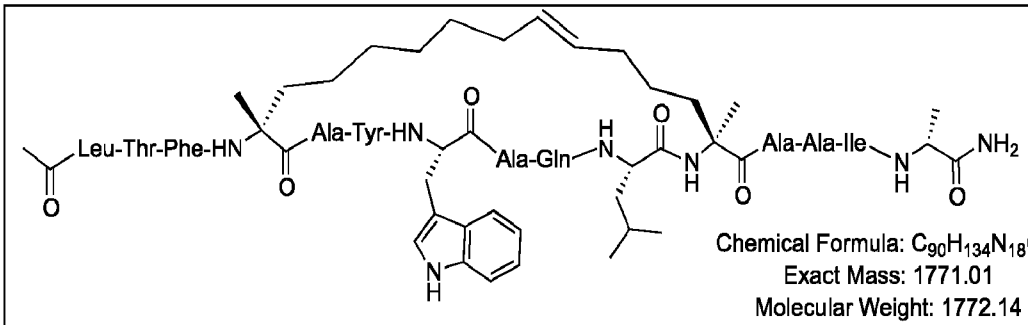
Chemical Formula: $C_{95}H_{142}N_{20}O_{23}$
Exact Mass: 1931.06
Molecular Weight: 1932.26

Ac-L T F %r8 E YW AQL % AAAAA a -NH2



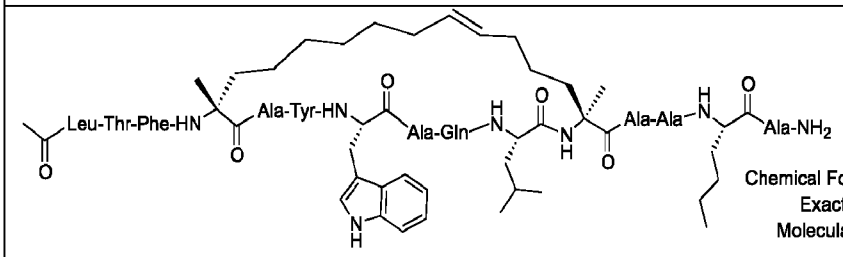
Chemical Formula: $C_{96}H_{140}N_{20}O_{24}$
Exact Mass: 1957.03
Molecular Weight: 1958.26

Ac-L T F $er8 E YW SQ Cba $e AAAAA a -NH2



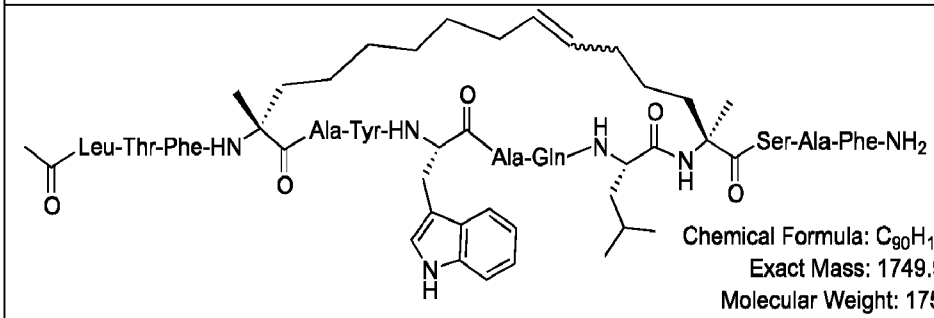
Chemical Formula: $C_{90}H_{134}N_{18}O_{19}$
Exact Mass: 1771.01
Molecular Weight: 1772.14

Ac-L T F $er8 A Y W A Q L $e AA I a-NH2



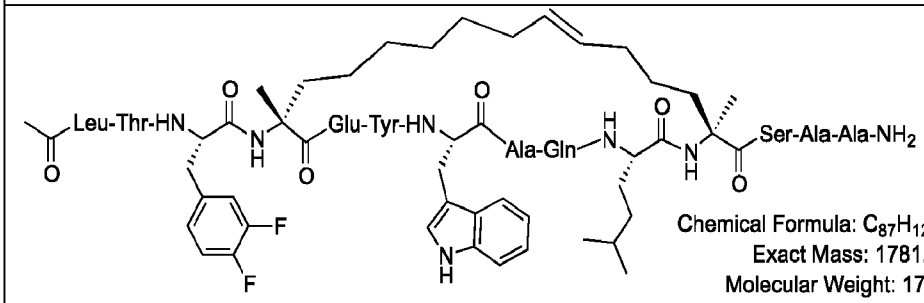
Chemical Formula: $C_{90}H_{134}N_{18}O_{19}$
Exact Mass: 1771.01
Molecular Weight: 1772.14

Ac-L T F $er8 A Y W A Q L $e AA Nle A-NH2



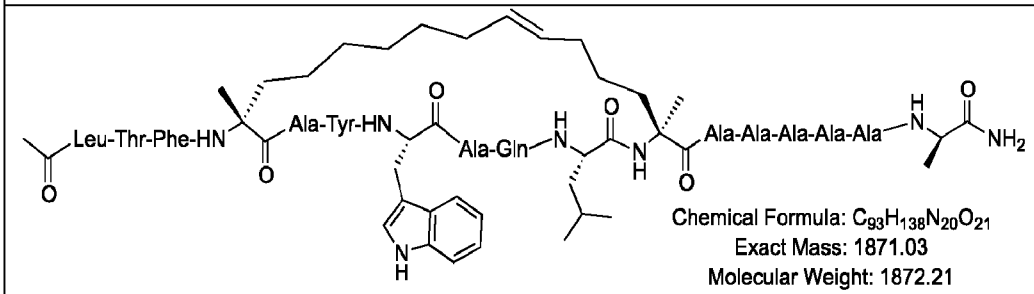
Chemical Formula: $C_{90}H_{127}N_{17}O_{19}$
Exact Mass: 1749.95
Molecular Weight: 1751.07

Ac-L T F $r8 A Y W A Q L $ SA F-NH2



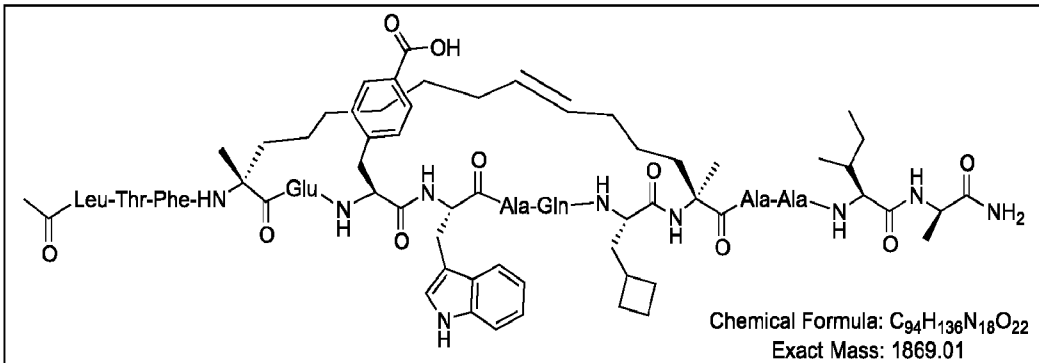
Chemical Formula: $C_{87}H_{125}F_2N_{17}O_{21}$
Exact Mass: 1781.92
Molecular Weight: 1783.02

Ac-L T F34F2 $er8 E Y W A Q hL $e SAA -NH2



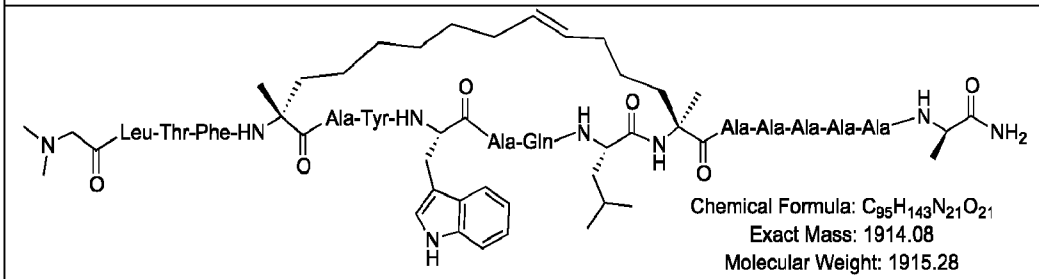
Chemical Formula: $C_{93}H_{138}N_{20}O_{21}$
Exact Mass: 1871.03
Molecular Weight: 1872.21

Ac-L T F $er8 A Y W A Q L $e AA A A A a-NH2



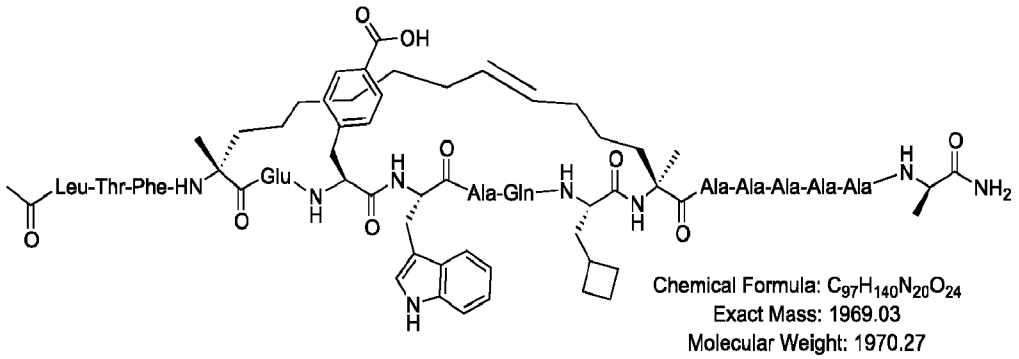
Chemical Formula: $C_{94}H_{136}N_{18}O_{22}$
Exact Mass: 1869.01
Molecular Weight: 1870.19

Ac-L T F $er8 E F4cooh W AQCba $e A A-l-a -NH2



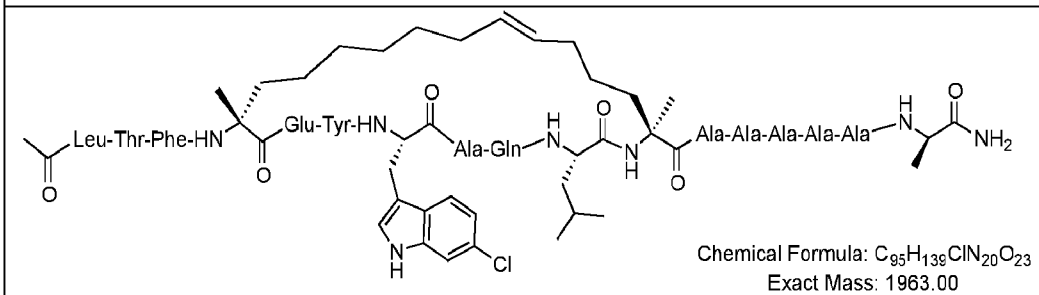
Chemical Formula: $C_{95}H_{143}N_{21}O_{21}$
Exact Mass: 1914.08
Molecular Weight: 1915.28

Dmaac- L T F $er8 A Y W AQL $e AAAAA a -NH2



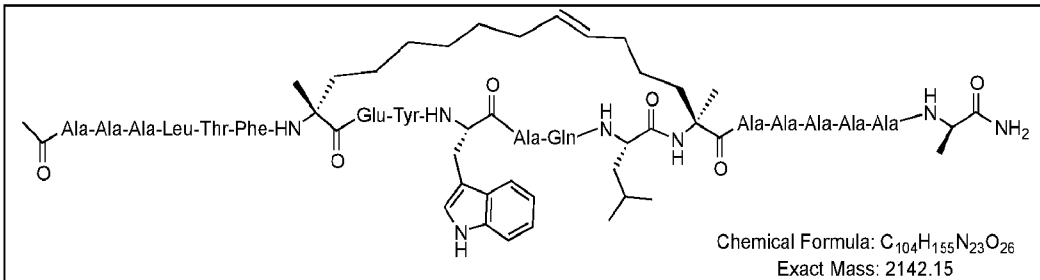
Chemical Formula: $C_{97}H_{140}N_{20}O_{24}$
Exact Mass: 1969.03
Molecular Weight: 1970.27

Ac-L T F $er8 E F4cooh W AQCba $e A A A A A a-NH2



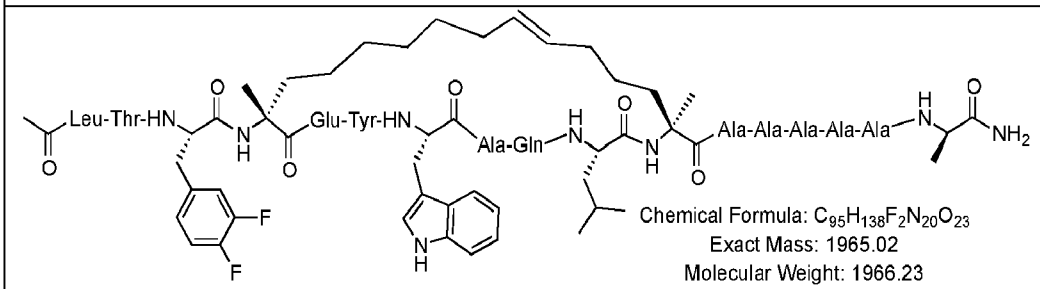
Chemical Formula: $C_{95}H_{139}ClN_{20}O_{23}$
Exact Mass: 1963.00
Molecular Weight: 1964.69

Ac-L T F $er8 E Y6clW AQL $e AA A A A a -NH2



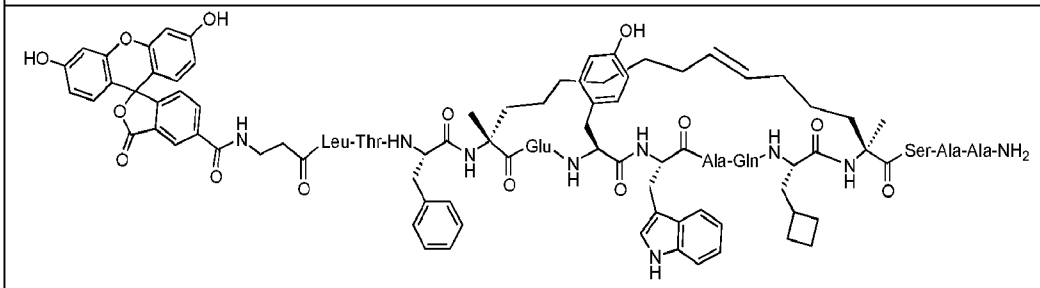
Chemical Formula: $C_{104}H_{155}N_{23}O_{26}$
Exact Mass: 2142.15
Molecular Weight: 2143.48

Ac-A A A L T F $er8 E YWAQL $e AA A A A a -NH2

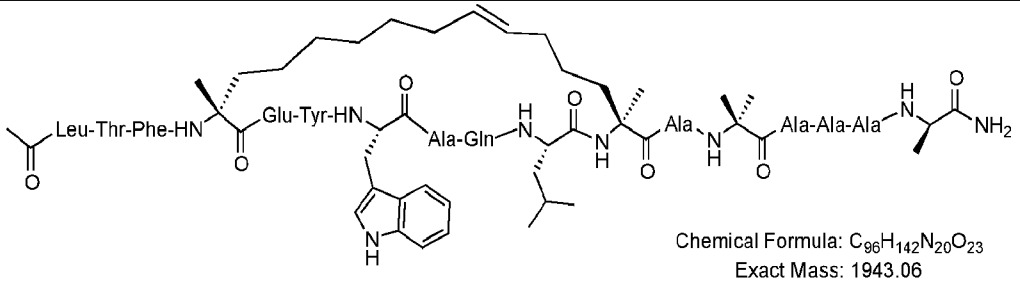


Chemical Formula: $C_{95}H_{138}F_2N_{20}O_{23}$
Exact Mass: 1965.02
Molecular Weight: 1966.23

Ac-L T F34F2 $er8 E YWAQL $e AAA A A a -NH2

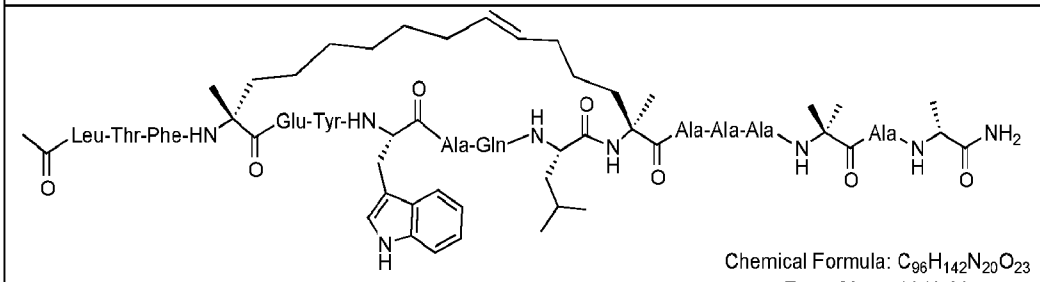


5-FAM- Ba L T F $er8 E YWAQCba $e SAA -NH2



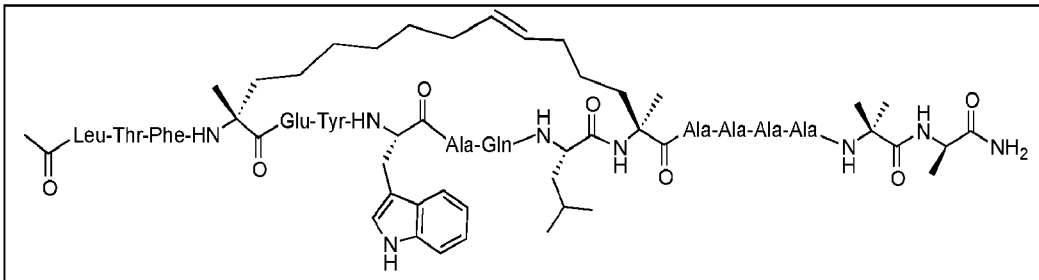
Chemical Formula: $C_{96}H_{142}N_{20}O_{23}$
Exact Mass: 1943.06
Molecular Weight: 1944.27

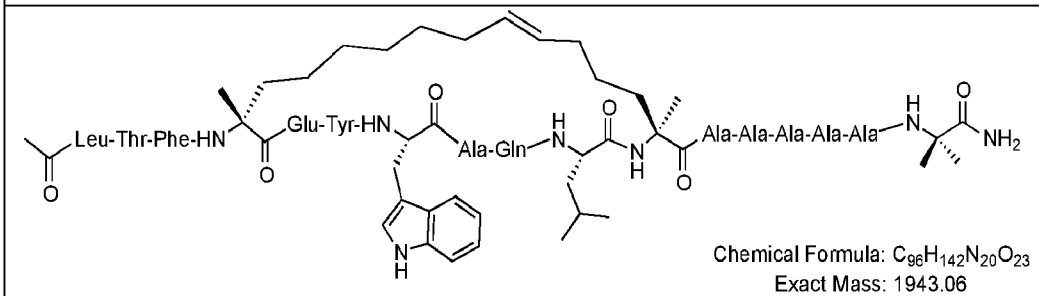
Ac-L T F $er8 E YWAQL $e AAib A A A a -NH2



Chemical Formula: $C_{96}H_{142}N_{20}O_{23}$
Exact Mass: 1943.06
Molecular Weight: 1944.27

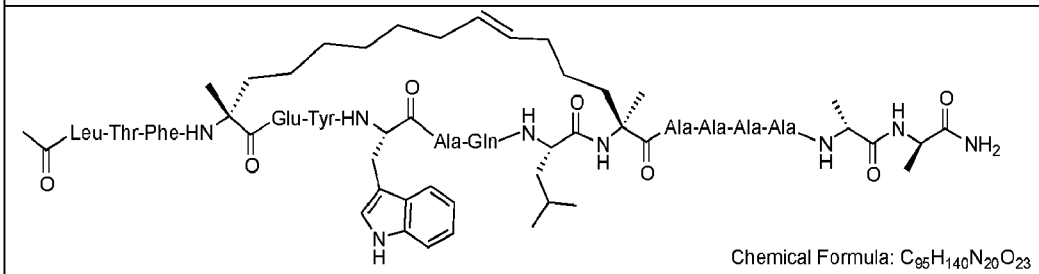
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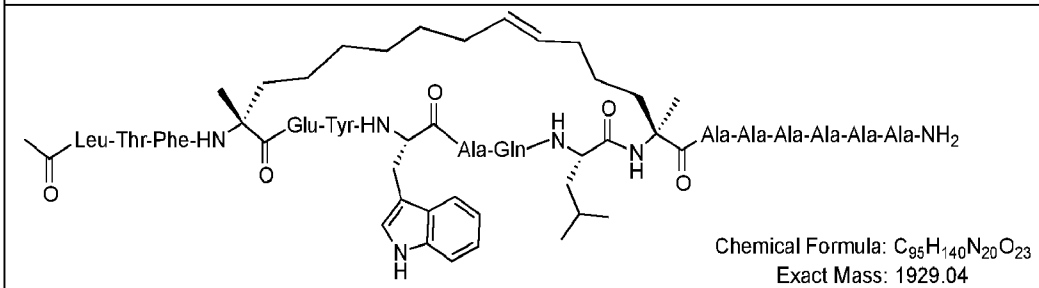
Chemical Formula: $C_{96}H_{142}N_{20}O_{23}$
Exact Mass: 1943.06
Molecular Weight: 1944.27

Ac-L T F $er8 E Y W A Q L $e A A A A A Aib -NH2



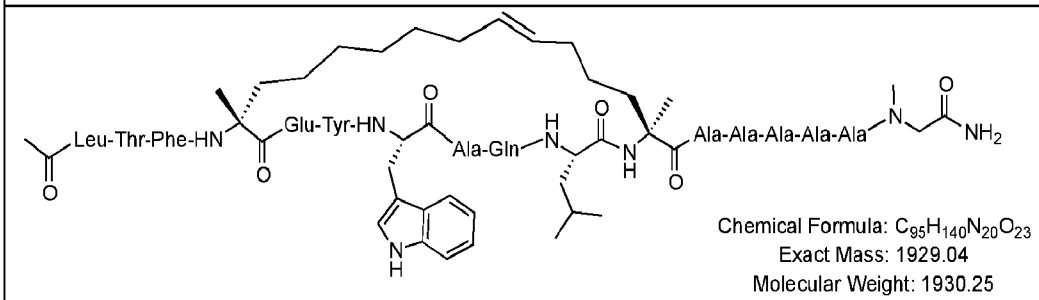
Chemical Formula: $C_{95}H_{140}N_{20}O_{23}$
Exact Mass: 1929.04
Molecular Weight: 1930.25

Ac-L T F $er8 E Y W A Q L $e A A A A a a -NH2



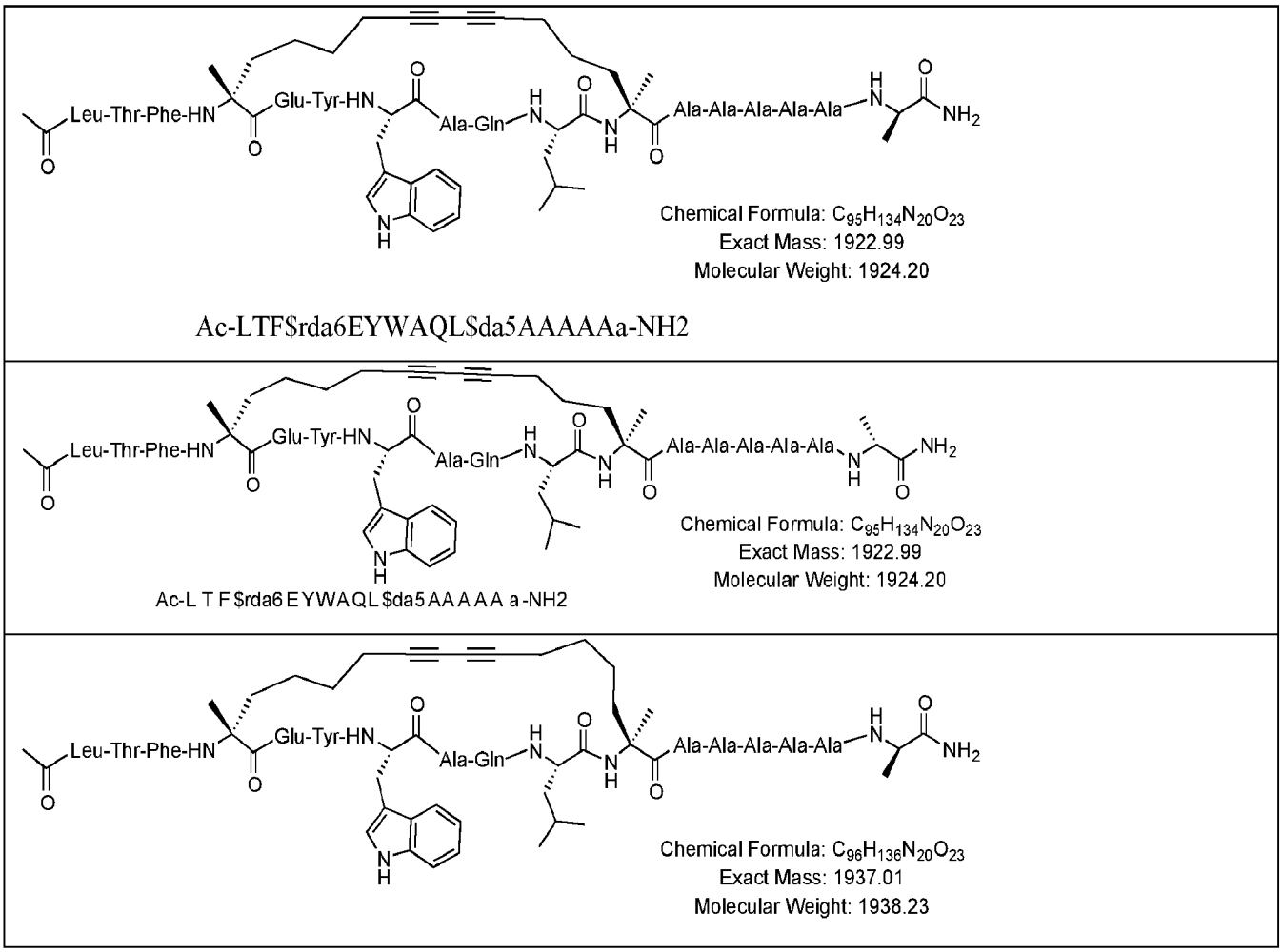
Chemical Formula: $C_{95}H_{140}N_{20}O_{23}$
Exact Mass: 1929.04
Molecular Weight: 1930.25

Ac-L T F $er8 E Y W A Q L $e A A A A A A -NH2



Chemical Formula: $C_{95}H_{140}N_{20}O_{23}$
Exact Mass: 1929.04
Molecular Weight: 1930.25

Ac-L T F $er8 E Y W A Q L $e A A A A A Sar-NH2



[00236] In some embodiments, peptidomimetic macrocycles exclude peptidomimetic macrocycles shown in **Table 2a**:

Table 2a

Number	Sequence
1	L$r5QETFSD$s8WKLLPEN
2	LSQ$r5TFSDLW$s8LLPEN
3	LSQE$r5FSDLWK$s8LPEN
4	LSQET$r5SDLWKL$s8PEN
5	LSQETF$r5DLWKLL$s8EN
6	LXQETFS$r5LWKLLP$s8N
7	LSQETFSD$r5WKLLPE$s8
8	LSQQTF$r5DLWKLL$s8EN
9	LSQETF$r5DLWKLL$s8QN
10	LSQQTF$r5DLWKLL$s8QN
11	LSQETF$r5NLWKLL$s8QN

12	LSQQTF$r5NLWKLL$s8QN
13	LSQQTF$r5NLWRLL$s8QN
14	QSQQTF$r5NLWKLL$s8QN
15	QSQQTF$r5NLWRLL$s8QN
16	QSQQTA$r5NLWRLL$s8QN
17	L$r8QETFSD$WKLLPEN
18	LSQ$r8TFSDLW$LLPEN
19	LSQE$r8FSDLWK$LPEN
20	LSQET$r8SDLWKL$PEN
21	LSQETF$r8DLWKLL$EN
22	LXQETFS$r8LWKLLP$N
23	LSQETFSD$r8WKLLPE$
24	LSQQTF$r8DLWKLL$EN
25	LSQETF$r8DLWKLL$QN
26	LSQQTF$r8DLWKLL$QN
27	LSQETF$r8NLWKLL$QN
28	LSQQTF$r8NLWKLL$QN
29	LSQQTF$r8NLWRLL$QN
30	QSQQTF$r8NLWKLL$QN
31	QSQQTF$r8NLWRLL$QN
32	QSQQTA$r8NLWRLL$QN
33	QSQQTF$r8NLWRKK$QN
34	QQTF$r8DLWRLL$EN
35	QQTF$r8DLWRLL$
36	LSQQTFDLWLL
37	QQTFDLWLL
38	QQTA$r8DLWRLL$EN
39	QSQQTF$r5NLWRLL$s8QN (dihydroxylated olefin)
40	QSQQTA$r5NLWRLL$s8QN (dihydroxylated olefin)
41	QSQQTF$r8DLWRLL$QN
42	QTF$r8NLWRLL$
43	QSQQTFNLWLLPQN

44	QSQTFNLWRLLPQN
45	TFSLWKLL
46	ETFDLWLL
47	QTFNLWLL
48	SQEFSNLWKLL

[00237] In **Table 2a**, X represents S or any amino acid. Peptides shown can comprise an N-terminal capping group such as acetyl or an additional linker such as beta-alanine between the capping group and the start of the peptide sequence.

[00238] In some embodiments, peptidomimetic macrocycles do not comprise a peptidomimetic macrocycle structure as shown in **Table 2a**.

[00239] In other embodiments, peptidomimetic macrocycles exclude peptidomimetic macrocycles shown in **Table 2b**:

Table 2b

Number	Sequence	Exact Mass	M+2	Observed mass (m/e)
1	Ac-LSQETF$r8DLWKLL$EN-NH2	2068.13	1035.07	1035.36
2	Ac-LSQETF$r8NLWKLL$QN-NH2	2066.16	1034.08	1034.31
3	Ac-LSQQTF$r8NLWRLL$QN-NH2	2093.18	1047.59	1047.73
4	Ac-QSQQTF$r8NLWKLL$QN-NH2	2080.15	1041.08	1041.31
5	Ac-QSQQTF$r8NLWRLL$QN-NH2	2108.15	1055.08	1055.32
6	Ac-QSQQTA$r8NLWRLL$QN-NH2	2032.12	1017.06	1017.24
7	Ac-QAibQQTF$r8NLWRLL$QN-NH2	2106.17	1054.09	1054.34
8	Ac-QSQQTFSNLWRLLPQN-NH2	2000.02	1001.01	1001.26
9	Ac-QSQQTF$/r8NLWRLL$/QN-NH2	2136.18	1069.09	1069.37
10	Ac-QSQAibTF$r8NLWRLL$QN-NH2	2065.15	1033.58	1033.71
11	Ac-QSQQTF$r8NLWRLL$AN-NH2	2051.13	1026.57	1026.70
12	Ac-ASQQTF$r8NLWRLL$QN-NH2	2051.13	1026.57	1026.90
13	Ac-QSQQTF$r8ALWRLL$QN-NH2	2065.15	1033.58	1033.41
14	Ac-QSQETF$r8NLWRLL$QN-NH2	2109.14	1055.57	1055.70
15	Ac-RSQQTF$r8NLWRLL$QN-NH2	2136.20	1069.10	1069.17
16	Ac-RSQQTF$r8NLWRLL$EN-NH2	2137.18	1069.59	1069.75

17	Ac-LSQETFSDLWKLLPEN-NH2	1959.99	981.00	981.24
18	Ac-QSQTFSLWRLLPQN-NH2	2008.09	1005.05	1004.97
19	Ac-QSQQFSNWRLLPQN-NH2	2036.06	1019.03	1018.86
20	Ac-QSQQTSNLRLLPQN-NH2	1917.04	959.52	959.32
21	Ac-QSQQTFNLWLLPQN-NH2	2007.06	1004.53	1004.97
22	Ac-RTQATF$r8NQWAibANle$TNAibTR-NH2	2310.26	1156.13	1156.52
23	Ac-QSQQTF$r8NLWRLL$RN-NH2	2136.20	1069.10	1068.94
24	Ac-QSQRTF$r8NLWRLL$QN-NH2	2136.20	1069.10	1068.94
25	Ac-QSQQTF$r8NNleWRLL$QN-NH2	2108.15	1055.08	1055.44
26	Ac-QSQQTF$r8NLWRNleL$QN-NH2	2108.15	1055.08	1055.84
27	Ac-QSQQTF$r8NLWRLNle$QN-NH2	2108.15	1055.08	1055.12
28	Ac-QSQQTY$r8NLWRLL$QN-NH2	2124.15	1063.08	1062.92
29	Ac-RAibQQTF$r8NLWRLL$QN-NH2	2134.22	1068.11	1068.65
30	Ac-MPRFMDYWEGLN-NH2	1598.70	800.35	800.45
31	Ac-RSQQRF$r8NLWRLL$QN-NH2	2191.25	1096.63	1096.83
32	Ac-QSQQRF$r8NLWRLL$QN-NH2	2163.21	1082.61	1082.87
33	Ac-RAibQQRF$r8NLWRLL$QN-NH2	2189.27	1095.64	1096.37
34	Ac-RSQQRF$r8NFWRLL$QN-NH2	2225.23	1113.62	1114.37
35	Ac-RSQQRF$r8NYWRLL$QN-NH2	2241.23	1121.62	1122.37
36	Ac-RSQQTF$r8NLWQLL$QN-NH2	2108.15	1055.08	1055.29
37	Ac-QSQQTF$r8NLWQAmlL$QN-NH2	2094.13	1048.07	1048.32
38	Ac-QSQQTF$r8NAmlWRLL$QN-NH2	2122.17	1062.09	1062.35
39	Ac-NlePRF$r8DYWEGL$QN-NH2	1869.98	935.99	936.20
40	Ac-NlePRF$r8NYWRLL$QN-NH2	1952.12	977.06	977.35
41	Ac-RF$r8NLWRLL$Q-NH2	1577.96	789.98	790.18
42	Ac-QSQQTF$r8N2ffWRLL$QN-NH2	2160.13	1081.07	1081.40
43	Ac-QSQQTF$r8N3ffWRLL$QN-NH2	2160.13	1081.07	1081.34
44	Ac-QSQQTF#r8NLWRLL#QN-NH2	2080.12	1041.06	1041.34
45	Ac-RSQQTA$r8NLWRLL$QN-NH2	2060.16	1031.08	1031.38
46	Ac-QSQQTF%r8NLWRLL%QN-NH2	2110.17	1056.09	1056.55
47	HepQSQ$TFSNLWRLLPQN-NH2	2051.10	1026.55	1026.82
48	HepQSQTFr8NLWRLL$QN-NH2	2159.23	1080.62	1080.89

49	Ac-QSQQTF$r8NL6clWRLL$QN-NH2	2142.11	1072.06	1072.35
50	Ac-QSQQTF$r8NLMe6clwRLL$QN-NH2	2156.13	1079.07	1079.27
51	Ac-LTFEHYWAQLTS-NH2	1535.74	768.87	768.91
52	Ac-LTFHYWQLTS-NH2	1585.83	793.92	794.17
53	Ac-LTFEYWALTS-NH2	1520.79	761.40	761.67
54	Ac-LTF$zr8HYWAQL$zS-NH2	1597.87	799.94	800.06
55	Ac-LTF$r8HYWRQL$S-NH2	1682.93	842.47	842.72
56	Ac-QS$QTFStNLWRLL$s8QN-NH2	2145.21	1073.61	1073.90
57	Ac-QSQQTASNLWRLLPQN-NH2	1923.99	963.00	963.26
58	Ac-QSQQTA$/r8NLWRLL$/QN-NH2	2060.15	1031.08	1031.24
59	Ac-ASQQTF$/r8NLWRLL$/QN-NH2	2079.16	1040.58	1040.89
60	Ac-SQQFSNLWRLLAibQN-NH2	2009.09	1005.55	1005.86
61	Ac-QSQTFNLWRLLAibQN-NH2	2023.10	1012.55	1012.79
62	Ac-QSQQFSNWRLLAibQN-NH2	2024.06	1013.03	1013.31
63	Ac-QSQQTFNLWLLAibQN-NH2	1995.06	998.53	998.87
64	Ac-QSQQTFSLWRLAibQN-NH2	2011.06	1006.53	1006.83
65	Ac-QSQQTFSNLWLLAN-NH2	1940.02	971.01	971.29
66	Ac-$/SQQ$/FSNLWRLLAibQN-NH2	2037.12	1019.56	1019.78
67	Ac-QS$/QTF$/NLWRLLAibQN-NH2	2051.13	1026.57	1026.90
68	Ac-QSQQ$/FSN$/WRLLAibQN-NH2	2052.09	1027.05	1027.36
69	Ac-QSQQTF$/NLW$/LLAibQN-NH2	2023.09	1012.55	1013.82
70	Ac-QSQTFSLWRLLAibQN-NH2	1996.09	999.05	999.39
71	Ac-QSQ$/TFS$/LWRLLAibQN-NH2	2024.12	1013.06	1013.37
72	Ac-QS$/QTFSt//NLWRLL$/s8QN-NH2	2201.27	1101.64	1102.00
73	Ac-$r8SQQTFS$LWRLLAibQN-NH2	2038.14	1020.07	1020.23
74	Ac-QSQ$r8TFSNLW$LLAibQN-NH2	1996.08	999.04	999.32
75	Ac-QSQQTFS$r8LWRLLA$N-NH2	2024.12	1013.06	1013.37
76	Ac-QS$r5QTFStNLW$LLAibQN-NH2	2032.12	1017.06	1017.39
77	Ac-$/r8SQQTFS$/LWRLLAibQN-NH2	2066.17	1034.09	1034.80
78	Ac-QSQ$/r8TFSNLW$/LLAibQN-NH2	2024.11	1013.06	1014.34
79	Ac-QSQQTFS$/r8LWRLLA$/N-NH2	2052.15	1027.08	1027.16
80	Ac-QS$/r5QTFSt//NLW$/LLAibQN-NH2	2088.18	1045.09	1047.10
81	Ac-QSQQTFSNLWRLLAibQN-NH2	1988.02	995.01	995.31

82	Hep/QSQ$/TF$/r8NLWRLL$/QN-NH2	2215.29	1108.65	1108.93
83	Ac-ASQQTF$r8NLRWLL$QN-NH2	2051.13	1026.57	1026.90
84	Ac-QSQQTF$/r8NLWRLL$/Q-NH2	2022.14	1012.07	1012.66
85	Ac-QSQQTF$r8NLWRLL$Q-NH2	1994.11	998.06	998.42
86	Ac-AAARAA$r8AAARAA$AA-NH2	1515.90	758.95	759.21
87	Ac-LTFEHYWAQLTSA-NH2	1606.78	804.39	804.59
88	Ac-LTF$r8HYWAQL$SA-NH2	1668.90	835.45	835.67
89	Ac-ASQQTFSNLWRLLPQN-NH2	1943.00	972.50	973.27
90	Ac-QS$QTFStNLW$r5LLAibQN-NH2	2032.12	1017.06	1017.30
91	Ac-QSQQTFAibNLWRLLAibQN-NH2	1986.04	994.02	994.19
92	Ac-QSQQTFNleNLWRLLNleQN-NH2	2042.11	1022.06	1022.23
93	Ac-QSQQTF$/r8NLWRLLAibQN-NH2	2082.14	1042.07	1042.23
94	Ac-QSQQTF$/r8NLWRLLNleQN-NH2	2110.17	1056.09	1056.29
95	Ac-QSQQTFAibNLWRLL$/QN-NH2	2040.09	1021.05	1021.25
96	Ac-QSQQTFNleNLWRLL$/QN-NH2	2068.12	1035.06	1035.31
97	Ac-QSQQTF%r8NL6clWRNleL%QN-NH2	2144.13	1073.07	1073.32
98	Ac-QSQQTF%r8NLMe6clWRLL%QN-NH2	2158.15	1080.08	1080.31
101	Ac-FNleYWEL-NH2	1160.63	-	1161.70
102	Ac-F$r8AYWELL$A-NH2	1344.75	-	1345.90
103	Ac-F$r8AYWQLL$A-NH2	1343.76	-	1344.83
104	Ac-NlePRF$r8NYWELL$QN-NH2	1925.06	963.53	963.69
105	Ac-NlePRF$r8DYWRLL$QN-NH2	1953.10	977.55	977.68
106	Ac-NlePRF$r8NYWRLL$Q-NH2	1838.07	920.04	920.18
107	Ac-NlePRF$r8NYWRLL$-NH2	1710.01	856.01	856.13
108	Ac-QSQQTF$r8DLWRLL$QN-NH2	2109.14	1055.57	1055.64
109	Ac-QSQQTF$r8NLWRLL$EN-NH2	2109.14	1055.57	1055.70
110	Ac-QSQQTF$r8NLWRLL$QD-NH2	2109.14	1055.57	1055.64
111	Ac-QSQQTF$r8NLWRLL$S-NH2	1953.08	977.54	977.60
112	Ac-ESQQTF$r8NLWRLL$QN-NH2	2109.14	1055.57	1055.70
113	Ac-LTF$r8NLWRNleL$Q-NH2	1635.99	819.00	819.10
114	Ac-LRF$r8NLWRNleL$Q-NH2	1691.04	846.52	846.68
115	Ac-QSQQTF$r8NWWRNleL$QN-NH2	2181.15	1091.58	1091.64
116	Ac-QSQQTF$r8NLWRNleL$Q-NH2	1994.11	998.06	998.07

117	Ac-QTF$r8NLWRNleL$QN-NH2	1765.00	883.50	883.59
118	Ac-NlePRF$r8NWWRLL$QN-NH2	1975.13	988.57	988.75
119	Ac-NlePRF$r8NWWRLL$A-NH2	1804.07	903.04	903.08
120	Ac-TSFAEYWNLLNH2	1467.70	734.85	734.90
121	Ac-QTF$r8HWWSQL$S-NH2	1651.85	826.93	827.12
122	Ac-FMYWEL-NH2	1178.58	-	1179.64
123	Ac-QTFEHWWSQLLS-NH2	1601.76	801.88	801.94
124	Ac-QSQQTF$r8NLAmwRLNle$QN-NH2	2122.17	1062.09	1062.24
125	Ac-FMAibY6clWEAc3cL-NH2	1130.47	-	1131.53
126	Ac-FNle$Y6clWE$L-NH2	1194.59	-	1195.64
127	Ac-F$zr8AY6clWEAc3cL$z-NH2	1277.63	639.82	1278.71
128	Ac-F$r8AY6clWEAc3cL$A-NH2	1348.66	-	1350.72
129	Ac-NlePRF$r8NY6clWRLL$QN-NH2	1986.08	994.04	994.64
130	Ac-AF$r8AAWALA$A-NH2	1223.71	-	1224.71
131	Ac-TF$r8AAWRLA$Q-NH2	1395.80	698.90	399.04
132	Pr-TF$r8AAWRLA$Q-NH2	1409.82	705.91	706.04
133	Ac-QSQQTF%r8NLWRNleL%QN-NH2	2110.17	1056.09	1056.22
134	Ac-LTF%r8HYWAQL%SA-NH2	1670.92	836.46	836.58
135	Ac-NlePRF%r8NYWRLL%QN-NH2	1954.13	978.07	978.19
136	Ac-NlePRF%r8NY6clWRLL%QN-NH2	1988.09	995.05	995.68
137	Ac-LTF%r8HY6clWAQL%S-NH2	1633.84	817.92	817.93
138	Ac-QS%QTF%StNLWRLL%s8QN-NH2	2149.24	1075.62	1075.65
139	Ac-LTF%r8HY6clWRQL%S-NH2	1718.91	860.46	860.54
140	Ac-QSQQTF%r8NL6clWRLL%QN-NH2	2144.13	1073.07	1073.64
141	Ac-%r8SQQTFS%LWRLLAibQN-NH2	2040.15	1021.08	1021.13
142	Ac-LTF%r8HYWAQL%S-NH2	1599.88	800.94	801.09
143	Ac-TSF%r8QYWNLL%P-NH2	1602.88	802.44	802.58
147	Ac-LTFEHYWAQLTS-NH2	1535.74	768.87	769.5
152	Ac-F$er8AY6clWEAc3cL$e-NH2	1277.63	639.82	1278.71
153	Ac-AF$r8AAWALA$A-NH2	1277.63	639.82	1277.84
154	Ac-TF$r8AAWRLA$Q-NH2	1395.80	698.90	699.04
155	Pr-TF$r8AAWRLA$Q-NH2	1409.82	705.91	706.04
156	Ac-LTF$er8HYWAQL$eS-NH2	1597.87	799.94	800.44

159	Ac-CCPGCCBaQSQQTF$r8NLWRLL$QN-NH2	2745.30	1373.65	1372.99
160	Ac-CCPGCCBaQSQQTA$r8NLWRLL$QN-NH2	2669.27	1335.64	1336.09
161	Ac-CCPGCCBaNlePRF$r8NYWRLL$QN-NH2	2589.26	1295.63	1296.2
162	Ac-LTF$/r8HYWAQL$/S-NH2	1625.90	813.95	814.18
163	Ac-F%r8HY6clWRAc3cL%-NH2	1372.72	687.36	687.59
164	Ac-QTF%r8HWWSQL%S-NH2	1653.87	827.94	827.94
165	Ac-LTA$r8HYWRQL$S-NH2	1606.90	804.45	804.66
166	Ac-Q$r8QQTFSN$WRLLAibQN-NH2	2080.12	1041.06	1041.61
167	Ac-QSQQ$r8FSNLWR$LAibQN-NH2	2066.11	1034.06	1034.58
168	Ac-F$r8AYWEAc3cL$A-NH2	1314.70	658.35	1315.88
169	Ac-F$r8AYWEAc3cL$S-NH2	1330.70	666.35	1331.87
170	Ac-F$r8AYWEAc3cL$Q-NH2	1371.72	686.86	1372.72
171	Ac-F$r8AYWEAibL$S-NH2	1332.71	667.36	1334.83
172	Ac-F$r8AYWEAL$S-NH2	1318.70	660.35	1319.73
173	Ac-F$r8AYWEQL$S-NH2	1375.72	688.86	1377.53
174	Ac-F$r8HYWEQL$S-NH2	1441.74	721.87	1443.48
175	Ac-F$r8HYWAQL$S-NH2	1383.73	692.87	1385.38
176	Ac-F$r8HYWAAc3cL$S-NH2	1338.71	670.36	1340.82
177	Ac-F$r8HYWRAc3cL$S-NH2	1423.78	712.89	713.04
178	Ac-F$r8AYWEAc3cL#A-NH2	1300.69	651.35	1302.78
179	Ac-NlePTF%r8NYWRLL%QN-NH2	1899.08	950.54	950.56
180	Ac-TF$r8AAWRAL$Q-NH2	1395.80	698.90	699.13
181	Ac-TSF%r8HYWAQL%S-NH2	1573.83	787.92	787.98
184	Ac-F%r8AY6clWEAc3cL%A-NH2	1350.68	676.34	676.91
185	Ac-LTF$r8HYWAQI$S-NH2	1597.87	799.94	800.07
186	Ac-LTF$r8HYWAQNle$S-NH2	1597.87	799.94	800.07
187	Ac-LTF$r8HYWAQL$A-NH2	1581.87	791.94	792.45
188	Ac-LTF$r8HYWAQL$Abu-NH2	1595.89	798.95	799.03
189	Ac-LTF$r8HYWAbuQL$S-NH2	1611.88	806.94	807.47

190	Ac-LTF$er8AYWAQL$eS-NH2	1531.84	766.92	766.96
191	Ac-LAF$r8HYWAQL$S-NH2	1567.86	784.93	785.49
192	Ac-LAF$r8AYWAQL$S-NH2	1501.83	751.92	752.01
193	Ac-LTF$er8AYWAQL$eA-NH2	1515.85	758.93	758.97
194	Ac-LAF$r8AYWAQL$A-NH2	1485.84	743.92	744.05
195	Ac-LTF$r8NLWANleL$Q-NH2	1550.92	776.46	776.61
196	Ac-LTF$r8NLWANleL$A-NH2	1493.90	747.95	1495.6
197	Ac-LTF$r8ALWANleL$Q-NH2	1507.92	754.96	755
198	Ac-LAF$r8NLWANleL$Q-NH2	1520.91	761.46	761.96
199	Ac-LAF$r8ALWANleL$A-NH2	1420.89	711.45	1421.74
200	Ac-A$r8AYWEAc3cL$A-NH2	1238.67	620.34	1239.65
201	Ac-F$r8AYWEAc3cL$AA-NH2	1385.74	693.87	1386.64
202	Ac-F$r8AYWEAc3cL$Abu-NH2	1328.72	665.36	1330.17
203	Ac-F$r8AYWEAc3cL$Nle-NH2	1356.75	679.38	1358.22
204	Ac-F$r5AYWEAc3cL$s8A-NH2	1314.70	658.35	1315.51
205	Ac-F$AYWEAc3cL$r8A-NH2	1314.70	658.35	1315.66
206	Ac-F$r8AYWEAc3cI$A-NH2	1314.70	658.35	1316.18
207	Ac-F$r8AYWEAc3cNle$A-NH2	1314.70	658.35	1315.66
208	Ac-F$r8AYWEAmlL$A-NH2	1358.76	680.38	1360.21
209	Ac-F$r8AYWENleL$A-NH2	1344.75	673.38	1345.71
210	Ac-F$r8AYWQAc3cL$A-NH2	1313.72	657.86	1314.7
211	Ac-F$r8AYWAAc3cL$A-NH2	1256.70	629.35	1257.56
212	Ac-F$r8AYWAbuAc3cL$A-NH2	1270.71	636.36	1272.14
213	Ac-F$r8AYWNleAc3cL$A-NH2	1298.74	650.37	1299.67
214	Ac-F$r8AbuYWEAc3cL$A-NH2	1328.72	665.36	1329.65
215	Ac-F$r8NleYWEAc3cL$A-NH2	1356.75	679.38	1358.66
216	5-FAM-BaLTFEHYWAQLTS-NH2	1922.82	962.41	962.87
217	5-FAM-BaLTF%r8HYWAQL%S-NH2	1986.96	994.48	994.97
218	Ac-LTF$r8HYWAQhL$S-NH2	1611.88	806.94	807
219	Ac-LTF$r8HYWAQTle$S-NH2	1597.87	799.94	799.97
220	Ac-LTF$r8HYWAQAdm$S-NH2	1675.91	838.96	839.09
221	Ac-LTF$r8HYWAQhCha$S-NH2	1651.91	826.96	826.98
222	Ac-LTF$r8HYWAQCha$S-NH2	1637.90	819.95	820.02

223	Ac-LTF$r8HYWAc6cQL$S-NH2	1651.91	826.96	826.98
224	Ac-LTF$r8HYWAc5cQL$S-NH2	1637.90	819.95	820.02
225	Ac-LThF$r8HYWAQL$S-NH2	1611.88	806.94	807
226	Ac-LTIgl$r8HYWAQL$S-NH2	1625.90	813.95	812.99
227	Ac-LTF$r8HYWAQChg$S-NH2	1623.88	812.94	812.99
228	Ac-LTF$r8HYWAQF$S-NH2	1631.85	816.93	816.99
229	Ac-LTF$r8HYWAQIgl$S-NH2	1659.88	830.94	829.94
230	Ac-LTF$r8HYWAQCba$S-NH2	1609.87	805.94	805.96
231	Ac-LTF$r8HYWAQCpg$S-NH2	1609.87	805.94	805.96
232	Ac-LTF$r8HhYWAQL$S-NH2	1611.88	806.94	807
233	Ac-F$r8AYWEAc3chL$A-NH2	1328.72	665.36	665.43
234	Ac-F$r8AYWEAc3cTle$A-NH2	1314.70	658.35	1315.62
235	Ac-F$r8AYWEAc3cAdm$A-NH2	1392.75	697.38	697.47
236	Ac-F$r8AYWEAc3chCha$A-NH2	1368.75	685.38	685.34
237	Ac-F$r8AYWEAc3cCha$A-NH2	1354.73	678.37	678.38
238	Ac-F$r8AYWEAc6cL$A-NH2	1356.75	679.38	679.42
239	Ac-F$r8AYWEAc5cL$A-NH2	1342.73	672.37	672.46
240	Ac-hF$r8AYWEAc3cL$A-NH2	1328.72	665.36	665.43
241	Ac-Igl$r8AYWEAc3cL$A-NH2	1342.73	672.37	671.5
243	Ac-F$r8AYWEAc3cF$A-NH2	1348.69	675.35	675.35
244	Ac-F$r8AYWEAc3cIgl$A-NH2	1376.72	689.36	688.37
245	Ac-F$r8AYWEAc3cCba$A-NH2	1326.70	664.35	664.47
246	Ac-F$r8AYWEAc3cCpg$A-NH2	1326.70	664.35	664.39
247	Ac-F$r8AhYWEAc3cL$A-NH2	1328.72	665.36	665.43
248	Ac-F$r8AYWEAc3cL$Q-NH2	1371.72	686.86	1372.87
249	Ac-F$r8AYWEAibL$A-NH2	1316.72	659.36	1318.18
250	Ac-F$r8AYWEAL$A-NH2	1302.70	652.35	1303.75
251	Ac-LAF$r8AYWAAL$A-NH2	1428.82	715.41	715.49
252	Ac-LTF$r8HYWAAc3cL$S-NH2	1552.84	777.42	777.5
253	Ac-NleTF$r8HYWAQL$S-NH2	1597.87	799.94	800.04
254	Ac-VTF$r8HYWAQL$S-NH2	1583.85	792.93	793.04
255	Ac-FTF$r8HYWAQL$S-NH2	1631.85	816.93	817.02
256	Ac-WTF$r8HYWAQL$S-NH2	1670.86	836.43	836.85

257	Ac-RTF$r8HYWAQL$S-NH2	1640.88	821.44	821.9
258	Ac-KTF$r8HYWAQL$S-NH2	1612.88	807.44	807.91
259	Ac-LNleF$r8HYWAQL$S-NH2	1609.90	805.95	806.43
260	Ac-LVF$r8HYWAQL$S-NH2	1595.89	798.95	798.93
261	Ac-LFF$r8HYWAQL$S-NH2	1643.89	822.95	823.38
262	Ac-LWF$r8HYWAQL$S-NH2	1682.90	842.45	842.55
263	Ac-LRF$r8HYWAQL$S-NH2	1652.92	827.46	827.52
264	Ac-LKF$r8HYWAQL$S-NH2	1624.91	813.46	813.51
265	Ac-LTF$r8NleYWAQL$S-NH2	1573.89	787.95	788.05
266	Ac-LTF$r8VYWAQL$S-NH2	1559.88	780.94	780.98
267	Ac-LTF$r8FYWAQL$S-NH2	1607.88	804.94	805.32
268	Ac-LTF$r8WYWAQL$S-NH2	1646.89	824.45	824.86
269	Ac-LTF$r8RYWAQL$S-NH2	1616.91	809.46	809.51
270	Ac-LTF$r8KYWAQL$S-NH2	1588.90	795.45	795.48
271	Ac-LTF$r8HNleWAQL$S-NH2	1547.89	774.95	774.98
272	Ac-LTF$r8HVWAQL$S-NH2	1533.87	767.94	767.95
273	Ac-LTF$r8HFWAQL$S-NH2	1581.87	791.94	792.3
274	Ac-LTF$r8HWWAQL$S-NH2	1620.88	811.44	811.54
275	Ac-LTF$r8HRWAQL$S-NH2	1590.90	796.45	796.52
276	Ac-LTF$r8HKWAQL$S-NH2	1562.90	782.45	782.53
277	Ac-LTF$r8HYWNleQL$S-NH2	1639.91	820.96	820.98
278	Ac-LTF$r8HYWVQL$S-NH2	1625.90	813.95	814.03
279	Ac-LTF$r8HYWFQL$S-NH2	1673.90	837.95	838.03
280	Ac-LTF$r8HYWWQL$S-NH2	1712.91	857.46	857.5
281	Ac-LTF$r8HYWKQL$S-NH2	1654.92	828.46	828.49
282	Ac-LTF$r8HYWANleL$S-NH2	1582.89	792.45	792.52
283	Ac-LTF$r8HYWAVL$S-NH2	1568.88	785.44	785.49
284	Ac-LTF$r8HYWAFL$S-NH2	1616.88	809.44	809.47
285	Ac-LTF$r8HYWAWL$S-NH2	1655.89	828.95	829
286	Ac-LTF$r8HYWARL$S-NH2	1625.91	813.96	813.98
287	Ac-LTF$r8HYWAQL$Nle-NH2	1623.92	812.96	813.39
288	Ac-LTF$r8HYWAQL$V-NH2	1609.90	805.95	805.99
289	Ac-LTF$r8HYWAQL$F-NH2	1657.90	829.95	830.26

290	Ac-LTF$r8HYWAQL$W-NH2	1696.91	849.46	849.5
291	Ac-LTF$r8HYWAQL$R-NH2	1666.94	834.47	834.56
292	Ac-LTF$r8HYWAQL$K-NH2	1638.93	820.47	820.49
293	Ac-Q$r8QQTFSN$WRLLAibQN-NH2	2080.12	1041.06	1041.54
294	Ac-QSQQ$r8FSNLWR$LAibQN-NH2	2066.11	1034.06	1034.58
295	Ac-LT2Pal$r8HYWAQL$S-NH2	1598.86	800.43	800.49
296	Ac-LT3Pal$r8HYWAQL$S-NH2	1598.86	800.43	800.49
297	Ac-LT4Pal$r8HYWAQL$S-NH2	1598.86	800.43	800.49
298	Ac-LTF2CF3$r8HYWAQL$S-NH2	1665.85	833.93	834.01
299	Ac-LTF2CN$r8HYWAQL$S-NH2	1622.86	812.43	812.47
300	Ac-LTF2Me$r8HYWAQL$S-NH2	1611.88	806.94	807
301	Ac-LTF3Cl$r8HYWAQL$S-NH2	1631.83	816.92	816.99
302	Ac-LTF4CF3$r8HYWAQL$S-NH2	1665.85	833.93	833.94
303	Ac-LTF4tBu$r8HYWAQL$S-NH2	1653.93	827.97	828.02
304	Ac-LTF5F$r8HYWAQL$S-NH2	1687.82	844.91	844.96
305	Ac-LTF$r8HY3BthAAQL$S-NH2	1614.83	808.42	808.48
306	Ac-LTF2Br$r8HYWAQL$S-NH2	1675.78	838.89	838.97
307	Ac-LTF4Br$r8HYWAQL$S-NH2	1675.78	838.89	839.86
308	Ac-LTF2Cl$r8HYWAQL$S-NH2	1631.83	816.92	816.99
309	Ac-LTF4Cl$r8HYWAQL$S-NH2	1631.83	816.92	817.36
310	Ac-LTF3CN$r8HYWAQL$S-NH2	1622.86	812.43	812.47
311	Ac-LTF4CN$r8HYWAQL$S-NH2	1622.86	812.43	812.47
312	Ac-LTF34Cl2$r8HYWAQL$S-NH2	1665.79	833.90	833.94
313	Ac-LTF34F2$r8HYWAQL$S-NH2	1633.85	817.93	817.95
314	Ac-LTF35F2$r8HYWAQL$S-NH2	1633.85	817.93	817.95
315	Ac-LTDip$r8HYWAQL$S-NH2	1673.90	837.95	838.01
316	Ac-LTF2F$r8HYWAQL$S-NH2	1615.86	808.93	809
317	Ac-LTF3F$r8HYWAQL$S-NH2	1615.86	808.93	809
318	Ac-LTF4F$r8HYWAQL$S-NH2	1615.86	808.93	809
319	Ac-LTF4I$r8HYWAQL$S-NH2	1723.76	862.88	862.94
320	Ac-LTF3Me$r8HYWAQL$S-NH2	1611.88	806.94	807.07
321	Ac-LTF4Me$r8HYWAQL$S-NH2	1611.88	806.94	807
322	Ac-LT1Nal$r8HYWAQL$S-NH2	1647.88	824.94	824.98

323	Ac-LT2Nal$r8HYWAQL$S-NH2	1647.88	824.94	825.06
324	Ac-LTF3CF3$r8HYWAQL$S-NH2	1665.85	833.93	834.01
325	Ac-LTF4NO2$r8HYWAQL$S-NH2	1642.85	822.43	822.46
326	Ac-LTF3NO2$r8HYWAQL$S-NH2	1642.85	822.43	822.46
327	Ac-LTF$r82ThiYWAQL$S-NH2	1613.83	807.92	807.96
328	Ac-LTF$r8HBipWAQL$S-NH2	1657.90	829.95	830.01
329	Ac-LTF$r8HF4tBuWAQL$S-NH2	1637.93	819.97	820.02
330	Ac-LTF$r8HF4CF3WAQL$S-NH2	1649.86	825.93	826.02
331	Ac-LTF$r8HF4ClWAQL$S-NH2	1615.83	808.92	809.37
332	Ac-LTF$r8HF4MeWAQL$S-NH2	1595.89	798.95	799.01
333	Ac-LTF$r8HF4BrWAQL$S-NH2	1659.78	830.89	830.98
334	Ac-LTF$r8HF4CNWAQL$S-NH2	1606.87	804.44	804.56
335	Ac-LTF$r8HF4NO2WAQL$S-NH2	1626.86	814.43	814.55
336	Ac-LTF$r8H1NalWAQL$S-NH2	1631.89	816.95	817.06
337	Ac-LTF$r8H2NalWAQL$S-NH2	1631.89	816.95	816.99
338	Ac-LTF$r8HWAQL$S-NH2	1434.80	718.40	718.49
339	Ac-LTF$r8HY1NalAQL$S-NH2	1608.87	805.44	805.52
340	Ac-LTF$r8HY2NalAQL$S-NH2	1608.87	805.44	805.52
341	Ac-LTF$r8HYWAQI$S-NH2	1597.87	799.94	800.07
342	Ac-LTF$r8HYWAQNle$S-NH2	1597.87	799.94	800.44
343	Ac-LTF$er8HYWAQL$eA-NH2	1581.87	791.94	791.98
344	Ac-LTF$r8HYWAQL$Abu-NH2	1595.89	798.95	799.03
345	Ac-LTF$r8HYWAbuQL$S-NH2	1611.88	806.94	804.47
346	Ac-LAF$r8HYWAQL$S-NH2	1567.86	784.93	785.49
347	Ac-LTF$r8NLWANleL$Q-NH2	1550.92	776.46	777.5
348	Ac-LTF$r8ALWANleL$Q-NH2	1507.92	754.96	755.52
349	Ac-LAF$r8NLWANleL$Q-NH2	1520.91	761.46	762.48
350	Ac-F$r8AYWAAc3cL$A-NH2	1256.70	629.35	1257.56
351	Ac-LTF$r8AYWAAL$S-NH2	1474.82	738.41	738.55
352	Ac-LVF$r8AYWAQL$S-NH2	1529.87	765.94	766
353	Ac-LTF$r8AYWAbuQL$S-NH2	1545.86	773.93	773.92
354	Ac-LTF$r8AYWNleQL$S-NH2	1573.89	787.95	788.17
355	Ac-LTF$r8AbuYWAQL$S-NH2	1545.86	773.93	773.99

356	Ac-LTF$r8AYWHQL$S-NH2	1597.87	799.94	799.97
357	Ac-LTF$r8AYWKQL$S-NH2	1588.90	795.45	795.53
358	Ac-LTF$r8AYWOQL$S-NH2	1574.89	788.45	788.5
359	Ac-LTF$r8AYWRQL$S-NH2	1616.91	809.46	809.51
360	Ac-LTF$r8AYWSQL$S-NH2	1547.84	774.92	774.96
361	Ac-LTF$r8AYWRAL$S-NH2	1559.89	780.95	780.95
362	Ac-LTF$r8AYWRQL$A-NH2	1600.91	801.46	801.52
363	Ac-LTF$r8AYWRAL$A-NH2	1543.89	772.95	773.03
364	Ac-LTF$r5HYWAQL$s8S-NH2	1597.87	799.94	799.97
365	Ac-LTF$HYWAQL$r8S-NH2	1597.87	799.94	799.97
366	Ac-LTF$r8HYWAAL$S-NH2	1540.84	771.42	771.48
367	Ac-LTF$r8HYWAAbuL$S-NH2	1554.86	778.43	778.51
368	Ac-LTF$r8HYWALL$S-NH2	1582.89	792.45	792.49
369	Ac-F$r8AYWHAL$A-NH2	1310.72	656.36	656.4
370	Ac-F$r8AYWAAL$A-NH2	1244.70	623.35	1245.61
371	Ac-F$r8AYWSAL$A-NH2	1260.69	631.35	1261.6
372	Ac-F$r8AYWRAL$A-NH2	1329.76	665.88	1330.72
373	Ac-F$r8AYWKAL$A-NH2	1301.75	651.88	1302.67
374	Ac-F$r8AYWOAL$A-NH2	1287.74	644.87	1289.13
375	Ac-F$r8VYWEAc3cL$A-NH2	1342.73	672.37	1343.67
376	Ac-F$r8FYWEAc3cL$A-NH2	1390.73	696.37	1392.14
377	Ac-F$r8WYWEAc3cL$A-NH2	1429.74	715.87	1431.44
378	Ac-F$r8RYWEAc3cL$A-NH2	1399.77	700.89	700.95
379	Ac-F$r8KYWEAc3cL$A-NH2	1371.76	686.88	686.97
380	Ac-F$r8ANleWEAc3cL$A-NH2	1264.72	633.36	1265.59
381	Ac-F$r8AVWEAc3cL$A-NH2	1250.71	626.36	1252.2
382	Ac-F$r8AFWEAc3cL$A-NH2	1298.71	650.36	1299.64
383	Ac-F$r8AWWEAc3cL$A-NH2	1337.72	669.86	1338.64
384	Ac-F$r8ARWEAc3cL$A-NH2	1307.74	654.87	655
385	Ac-F$r8AKWEAc3cL$A-NH2	1279.73	640.87	641.01
386	Ac-F$r8AYWVAc3cL$A-NH2	1284.73	643.37	643.38
387	Ac-F$r8AYWFAc3cL$A-NH2	1332.73	667.37	667.43
388	Ac-F$r8AYWWAc3cL$A-NH2	1371.74	686.87	686.97

389	Ac-F$r8AYWRAc3cL$A-NH2	1341.76	671.88	671.94
390	Ac-F$r8AYWKAc3cL$A-NH2	1313.75	657.88	657.88
391	Ac-F$r8AYWEVL$A-NH2	1330.73	666.37	666.47
392	Ac-F$r8AYWEFL$A-NH2	1378.73	690.37	690.44
393	Ac-F$r8AYWEWL$A-NH2	1417.74	709.87	709.91
394	Ac-F$r8AYWERL$A-NH2	1387.77	694.89	1388.66
395	Ac-F$r8AYWEKL$A-NH2	1359.76	680.88	1361.21
396	Ac-F$r8AYWEAc3cL$V-NH2	1342.73	672.37	1343.59
397	Ac-F$r8AYWEAc3cL$F-NH2	1390.73	696.37	1392.58
398	Ac-F$r8AYWEAc3cL$W-NH2	1429.74	715.87	1431.29
399	Ac-F$r8AYWEAc3cL$R-NH2	1399.77	700.89	700.95
400	Ac-F$r8AYWEAc3cL$K-NH2	1371.76	686.88	686.97
401	Ac-F$r8AYWEAc3cL$AV-NH2	1413.77	707.89	707.91
402	Ac-F$r8AYWEAc3cL$AF-NH2	1461.77	731.89	731.96
403	Ac-F$r8AYWEAc3cL$AW-NH2	1500.78	751.39	751.5
404	Ac-F$r8AYWEAc3cL$AR-NH2	1470.80	736.40	736.47
405	Ac-F$r8AYWEAc3cL$AK-NH2	1442.80	722.40	722.41
406	Ac-F$r8AYWEAc3cL$AH-NH2	1451.76	726.88	726.93
407	Ac-LTF2NO2$r8HYWAQL$S-NH2	1642.85	822.43	822.54
408	Ac-LTA$r8HYAAQL$S-NH2	1406.79	704.40	704.5
409	Ac-LTF$r8HYAAQL$S-NH2	1482.82	742.41	742.47
410	Ac-QSQQTF$r8NLWALL$AN-NH2	1966.07	984.04	984.38
411	Ac-QAibQQTF$r8NLWALL$AN-NH2	1964.09	983.05	983.42
412	Ac-QAibQQTF$r8ALWALL$AN-NH2	1921.08	961.54	961.59
413	Ac-AAAATF$r8AAWAAL$AA-NH2	1608.90	805.45	805.52
414	Ac-F$r8AAWRAL$Q-NH2	1294.76	648.38	648.48
415	Ac-TF$r8AAWAAL$Q-NH2	1310.74	656.37	1311.62
416	Ac-TF$r8AAWRAL$A-NH2	1338.78	670.39	670.46
417	Ac-VF$r8AAWRAL$Q-NH2	1393.82	697.91	697.99
418	Ac-AF$r8AAWAAL$A-NH2	1223.71	612.86	1224.67
420	Ac-TF$r8AAWKAL$Q-NH2	1367.80	684.90	684.97
421	Ac-TF$r8AAWOAL$Q-NH2	1353.78	677.89	678.01
422	Ac-TF$r8AAWSAL$Q-NH2	1326.73	664.37	664.47

423	Ac-LTF$r8AAWRAL$Q-NH2	1508.89	755.45	755.49
424	Ac-F$r8AYWAQL$A-NH2	1301.72	651.86	651.96
425	Ac-F$r8AWWAAL$A-NH2	1267.71	634.86	634.87
426	Ac-F$r8AWWAQL$A-NH2	1324.73	663.37	663.43
427	Ac-F$r8AYWEAL$-NH2	1231.66	616.83	1232.93
428	Ac-F$r8AYWAAL$-NH2	1173.66	587.83	1175.09
429	Ac-F$r8AYWKAL$-NH2	1230.72	616.36	616.44
430	Ac-F$r8AYWOAL$-NH2	1216.70	609.35	609.48
431	Ac-F$r8AYWQAL$-NH2	1230.68	616.34	616.44
432	Ac-F$r8AYWAQL$-NH2	1230.68	616.34	616.37
433	Ac-F$r8HYWDQL$S-NH2	1427.72	714.86	714.86
434	Ac-F$r8HFWEQL$S-NH2	1425.74	713.87	713.98
435	Ac-F$r8AYWHQL$S-NH2	1383.73	692.87	692.96
436	Ac-F$r8AYWKQL$S-NH2	1374.77	688.39	688.45
437	Ac-F$r8AYWOQL$S-NH2	1360.75	681.38	681.49
438	Ac-F$r8HYWSQL$S-NH2	1399.73	700.87	700.95
439	Ac-F$r8HWWEQL$S-NH2	1464.76	733.38	733.44
440	Ac-F$r8HWWAQL$S-NH2	1406.75	704.38	704.43
441	Ac-F$r8AWWHQL$S-NH2	1406.75	704.38	704.43
442	Ac-F$r8AWWKQL$S-NH2	1397.79	699.90	699.92
443	Ac-F$r8AWWOQL$S-NH2	1383.77	692.89	692.96
444	Ac-F$r8HWWSQL$S-NH2	1422.75	712.38	712.42
445	Ac-LTF$r8NYWANleL$Q-NH2	1600.90	801.45	801.52
446	Ac-LTF$r8NLWAQL$Q-NH2	1565.90	783.95	784.06
447	Ac-LTF$r8NYWANleL$A-NH2	1543.88	772.94	773.03
448	Ac-LTF$r8NLWAQL$A-NH2	1508.88	755.44	755.49
449	Ac-LTF$r8AYWANleL$Q-NH2	1557.90	779.95	780.06
450	Ac-LTF$r8ALWAQL$Q-NH2	1522.89	762.45	762.45
451	Ac-LAF$r8NYWANleL$Q-NH2	1570.89	786.45	786.5
452	Ac-LAF$r8NLWAQL$Q-NH2	1535.89	768.95	769.03
453	Ac-LAF$r8AYWANleL$A-NH2	1470.86	736.43	736.47
454	Ac-LAF$r8ALWAQL$A-NH2	1435.86	718.93	719.01
455	Ac-LAF$r8AYWAAL$A-NH2	1428.82	715.41	715.41

456	Ac-F$r8AYWEAc3cL$AAib-NH2	1399.75	700.88	700.95
457	Ac-F$r8AYWAQL$AA-NH2	1372.75	687.38	687.78
458	Ac-F$r8AYWAAc3cL$AA-NH2	1327.73	664.87	664.84
459	Ac-F$r8AYWSAc3cL$AA-NH2	1343.73	672.87	672.9
460	Ac-F$r8AYWEAc3cL$AS-NH2	1401.73	701.87	701.84
461	Ac-F$r8AYWEAc3cL$AT-NH2	1415.75	708.88	708.87
462	Ac-F$r8AYWEAc3cL$AL-NH2	1427.79	714.90	714.94
463	Ac-F$r8AYWEAc3cL$AQ-NH2	1442.76	722.38	722.41
464	Ac-F$r8AFWEAc3cL$AA-NH2	1369.74	685.87	685.93
465	Ac-F$r8AWWEAc3cL$AA-NH2	1408.75	705.38	705.39
466	Ac-F$r8AYWEAc3cL$SA-NH2	1401.73	701.87	701.99
467	Ac-F$r8AYWEAL$AA-NH2	1373.74	687.87	687.93
468	Ac-F$r8AYWENleL$AA-NH2	1415.79	708.90	708.94
469	Ac-F$r8AYWEAc3cL$AbuA-NH2	1399.75	700.88	700.95
470	Ac-F$r8AYWEAc3cL$NleA-NH2	1427.79	714.90	714.86
471	Ac-F$r8AYWEAibL$NleA-NH2	1429.80	715.90	715.97
472	Ac-F$r8AYWEAL$NleA-NH2	1415.79	708.90	708.94
473	Ac-F$r8AYWENleL$NleA-NH2	1457.83	729.92	729.96
474	Ac-F$r8AYWEAibL$Abu-NH2	1330.73	666.37	666.39
475	Ac-F$r8AYWENleL$Abu-NH2	1358.76	680.38	680.39
476	Ac-F$r8AYWEAL$Abu-NH2	1316.72	659.36	659.36
477	Ac-LTF$r8AFWAQL$S-NH2	1515.85	758.93	759.12
478	Ac-LTF$r8AWWAQL$S-NH2	1554.86	778.43	778.51
479	Ac-LTF$r8AYWAQI$S-NH2	1531.84	766.92	766.96
480	Ac-LTF$r8AYWAQNle$S-NH2	1531.84	766.92	766.96
481	Ac-LTF$r8AYWAQL$SA-NH2	1602.88	802.44	802.48
482	Ac-LTF$r8AWWAQL$A-NH2	1538.87	770.44	770.89
483	Ac-LTF$r8AYWAQI$A-NH2	1515.85	758.93	759.42
484	Ac-LTF$r8AYWAQNle$A-NH2	1515.85	758.93	759.42
485	Ac-LTF$r8AYWAQL$AA-NH2	1586.89	794.45	794.94
486	Ac-LTF$r8HWWAQL$S-NH2	1620.88	811.44	811.47
487	Ac-LTF$r8HRWAQL$S-NH2	1590.90	796.45	796.52
488	Ac-LTF$r8HKWAQL$S-NH2	1562.90	782.45	782.53

489	Ac-LTF$r8HYWAQL$W-NH2	1696.91	849.46	849.5
491	Ac-F$r8AYWAbuAL$A-NH2	1258.71	630.36	630.5
492	Ac-F$r8AbuYWEAL$A-NH2	1316.72	659.36	659.51
493	Ac-NlePRF%r8NYWRLL%QN-NH2	1954.13	978.07	978.54
494	Ac-TSF%r8HYWAQL%S-NH2	1573.83	787.92	787.98
495	Ac-LTF%r8AYWAQL%S-NH2	1533.86	767.93	768
496	Ac-HTF$r8HYWAQL$S-NH2	1621.84	811.92	811.96
497	Ac-LHF$r8HYWAQL$S-NH2	1633.88	817.94	818.02
498	Ac-LTF$r8HHWAQL$S-NH2	1571.86	786.93	786.94
499	Ac-LTF$r8HYWHQL$S-NH2	1663.89	832.95	832.38
500	Ac-LTF$r8HYWAHL$S-NH2	1606.87	804.44	804.48
501	Ac-LTF$r8HYWAQL$H-NH2	1647.89	824.95	824.98
502	Ac-LTF$r8HYWAQL$S-NHPr	1639.91	820.96	820.98
503	Ac-LTF$r8HYWAQL$S-NHsBu	1653.93	827.97	828.02
504	Ac-LTF$r8HYWAQL$S-NHiBu	1653.93	827.97	828.02
505	Ac-LTF$r8HYWAQL$S-NHBn	1687.91	844.96	844.44
506	Ac-LTF$r8HYWAQL$S-NHPe	1700.92	851.46	851.99
507	Ac-LTF$r8HYWAQL$S-NHChx	1679.94	840.97	841.04
508	Ac-ETF$r8AYWAQL$S-NH2	1547.80	774.90	774.96
509	Ac-STF$r8AYWAQL$S-NH2	1505.79	753.90	753.94
510	Ac-LEF$r8AYWAQL$S-NH2	1559.84	780.92	781.25
511	Ac-LSF$r8AYWAQL$S-NH2	1517.83	759.92	759.93
512	Ac-LTF$r8EYWAQL$S-NH2	1589.85	795.93	795.97
513	Ac-LTF$r8SYWAQL$S-NH2	1547.84	774.92	774.96
514	Ac-LTF$r8AYWEQL$S-NH2	1589.85	795.93	795.9
515	Ac-LTF$r8AYWAEL$S-NH2	1532.83	767.42	766.96
516	Ac-LTF$r8AYWASL$S-NH2	1490.82	746.41	746.46
517	Ac-LTF$r8AYWAQL$E-NH2	1573.85	787.93	787.98
518	Ac-LTF2CN$r8HYWAQL$S-NH2	1622.86	812.43	812.47
519	Ac-LTF3Cl$r8HYWAQL$S-NH2	1631.83	816.92	816.99
520	Ac-LTDip$r8HYWAQL$S-NH2	1673.90	837.95	838.01
521	Ac-LTF$r8HYWAQTle$S-NH2	1597.87	799.94	800.04
522	Ac-F$r8AY6clWEAL$A-NH2	1336.66	669.33	1338.56

523	Ac-F$r8AYdl6brWEAL$A-NH2	1380.61	691.31	692.2
524	Ac-F$r8AYdl6fWEAL$A-NH2	1320.69	661.35	1321.61
525	Ac-F$r8AYdl4mWEAL$A-NH2	1316.72	659.36	659.36
526	Ac-F$r8AYdl5clWEAL$A-NH2	1336.66	669.33	669.35
527	Ac-F$r8AYdl7mWEAL$A-NH2	1316.72	659.36	659.36
528	Ac-LTF%r8HYWAQL%A-NH2	1583.89	792.95	793.01
529	Ac-LTF$r8HCouWAQL$S-NH2	1679.87	840.94	841.38
530	Ac-LTFEHCouWAQLTS-NH2	1617.75	809.88	809.96
531	Ac-LTA$r8HCouWAQL$S-NH2	1603.84	802.92	803.36
532	Ac-F$r8AYWEAL$AbuA-NH2	1387.75	694.88	694.88
533	Ac-F$r8AYWEAI$AA-NH2	1373.74	687.87	687.93
534	Ac-F$r8AYWEANle$AA-NH2	1373.74	687.87	687.93
535	Ac-F$r8AYWEAmlL$AA-NH2	1429.80	715.90	715.97
536	Ac-F$r8AYWQAL$AA-NH2	1372.75	687.38	687.48
537	Ac-F$r8AYWAAL$AA-NH2	1315.73	658.87	658.92
538	Ac-F$r8AYWAbuAL$AA-NH2	1329.75	665.88	665.95
539	Ac-F$r8AYWNleAL$AA-NH2	1357.78	679.89	679.94
540	Ac-F$r8AbuYWEAL$AA-NH2	1387.75	694.88	694.96
541	Ac-F$r8NleYWEAL$AA-NH2	1415.79	708.90	708.94
542	Ac-F$r8FYWEAL$AA-NH2	1449.77	725.89	725.97
543	Ac-LTF$r8HYWAQhL$S-NH2	1611.88	806.94	807
544	Ac-LTF$r8HYWAQAdm$S-NH2	1675.91	838.96	839.04
545	Ac-LTF$r8HYWAQIgl$S-NH2	1659.88	830.94	829.94
546	Ac-F$r8AYWAQL$AA-NH2	1372.75	687.38	687.48
547	Ac-LTF$r8ALWAQL$Q-NH2	1522.89	762.45	762.52
548	Ac-F$r8AYWEAL$AA-NH2	1373.74	687.87	687.93
549	Ac-F$r8AYWENleL$AA-NH2	1415.79	708.90	708.94
550	Ac-F$r8AYWEAibL$Abu-NH2	1330.73	666.37	666.39
551	Ac-F$r8AYWENleL$Abu-NH2	1358.76	680.38	680.38
552	Ac-F$r8AYWEAL$Abu-NH2	1316.72	659.36	659.36
553	Ac-F$r8AYWEAc3cL$AbuA-NH2	1399.75	700.88	700.95
554	Ac-F$r8AYWEAc3cL$NleA-NH2	1427.79	714.90	715.01
555	H-LTF$r8AYWAQL$S-NH2	1489.83	745.92	745.95

556	mdPEG3-LTF$r8AYWAQL$S-NH2	1679.92	840.96	840.97
557	mdPEG7-LTF$r8AYWAQL$S-NH2	1856.02	929.01	929.03
558	Ac-F$r8ApmpEt6clWEAL$A-NH2	1470.71	736.36	788.17
559	Ac-LTF3Cl$r8AYWAQL$S-NH2	1565.81	783.91	809.18
560	Ac-LTF3Cl$r8HYWAQL$A-NH2	1615.83	808.92	875.24
561	Ac-LTF3Cl$r8HYWWQL$S-NH2	1746.87	874.44	841.65
562	Ac-LTF3Cl$r8AYWWQL$S-NH2	1680.85	841.43	824.63
563	Ac-LTF$r8AYWWQL$S-NH2	1646.89	824.45	849.98
564	Ac-LTF$r8HYWWQL$A-NH2	1696.91	849.46	816.67
565	Ac-LTF$r8AYWWQL$A-NH2	1630.89	816.45	776.15
566	Ac-LTF4F$r8AYWAQL$S-NH2	1549.83	775.92	776.15
567	Ac-LTF2F$r8AYWAQL$S-NH2	1549.83	775.92	776.15
568	Ac-LTF3F$r8AYWAQL$S-NH2	1549.83	775.92	785.12
569	Ac-LTF34F2$r8AYWAQL$S-NH2	1567.83	784.92	785.12
570	Ac-LTF35F2$r8AYWAQL$S-NH2	1567.83	784.92	1338.74
571	Ac-F3Cl$r8AYWEAL$A-NH2	1336.66	669.33	705.28
572	Ac-F3Cl$r8AYWEAL$AA-NH2	1407.70	704.85	680.11
573	Ac-F$r8AY6clWEAL$AA-NH2	1407.70	704.85	736.83
574	Ac-F$r8AY6clWEAL$-NH2	1265.63	633.82	784.1
575	Ac-LTF$r8HYWAQLSt/S-NH2	16.03	9.02	826.98
576	Ac-LTF$r8HYWAQL$S-NHsBu	1653.93	827.97	828.02
577	Ac-STF$r8AYWAQL$S-NH2	1505.79	753.90	753.94
578	Ac-LTF$r8AYWAEL$S-NH2	1532.83	767.42	767.41
579	Ac-LTF$r8AYWAQL$E-NH2	1573.85	787.93	787.98
580	mdPEG3-LTF$r8AYWAQL$S-NH2	1679.92	840.96	840.97
581	Ac-LTF$r8AYWAQhL$S-NH2	1545.86	773.93	774.31
583	Ac-LTF$r8AYWAQCha$S-NH2	1571.88	786.94	787.3
584	Ac-LTF$r8AYWAQChg$S-NH2	1557.86	779.93	780.4
585	Ac-LTF$r8AYWAQCba$S-NH2	1543.84	772.92	780.13
586	Ac-LTF$r8AYWAQF$S-NH2	1565.83	783.92	784.2
587	Ac-LTF4F$r8HYWAQhL$S-NH2	1629.87	815.94	815.36
588	Ac-LTF4F$r8HYWAQCha$S-NH2	1655.89	828.95	828.39
589	Ac-LTF4F$r8HYWAQChg$S-NH2	1641.87	821.94	821.35

590	Ac-LTF4F$r8HYWAQCba$S-NH2	1627.86	814.93	814.32
591	Ac-LTF4F$r8AYWAQhL$S-NH2	1563.85	782.93	782.36
592	Ac-LTF4F$r8AYWAQCha$S-NH2	1589.87	795.94	795.38
593	Ac-LTF4F$r8AYWAQChg$S-NH2	1575.85	788.93	788.35
594	Ac-LTF4F$r8AYWAQCba$S-NH2	1561.83	781.92	781.39
595	Ac-LTF3Cl$r8AYWAQhL$S-NH2	1579.82	790.91	790.35
596	Ac-LTF3Cl$r8AYWAQCha$S-NH2	1605.84	803.92	803.67
597	Ac-LTF3Cl$r8AYWAQChg$S-NH2	1591.82	796.91	796.34
598	Ac-LTF3Cl$r8AYWAQCba$S-NH2	1577.81	789.91	789.39
599	Ac-LTF$r8AYWAQhF$S-NH2	1579.84	790.92	791.14
600	Ac-LTF$r8AYWAQF3CF3$S-NH2	1633.82	817.91	818.15
601	Ac-LTF$r8AYWAQF3Me$S-NH2	1581.86	791.93	791.32
602	Ac-LTF$r8AYWAQ1Nal$S-NH2	1615.84	808.92	809.18
603	Ac-LTF$r8AYWAQBip$S-NH2	1641.86	821.93	822.13
604	Ac-LTF$r8FYWAQL$A-NH2	1591.88	796.94	797.33
605	Ac-LTF$r8HYWAQL$S-NHAm	1667.94	834.97	835.92
606	Ac-LTF$r8HYWAQL$S-NHiAm	1667.94	834.97	835.55
607	Ac-LTF$r8HYWAQL$S-NHnPr3Ph	1715.94	858.97	859.79
608	Ac-LTF$r8HYWAQL$S-NHnBu3,3Me	1681.96	841.98	842.49
610	Ac-LTF$r8HYWAQL$S-NHnPr	1639.91	820.96	821.58
611	Ac-LTF$r8HYWAQL$S-NHnEt2Ch	1707.98	854.99	855.35
612	Ac-LTF$r8HYWAQL$S-NHHex	1681.96	841.98	842.4
613	Ac-LTF$r8AYWAQL$S-NHmdPeg2	1633.91	817.96	818.35
614	Ac-LTF$r8AYWAQL$A-NHmdPeg2	1617.92	809.96	810.3
615	Ac-LTF$r8AYWAQL$A-NHmdPeg4	1705.97	853.99	854.33
616	Ac-F$r8AYdl4mWEAL$A-NH2	1316.72	659.36	659.44
617	Ac-F$r8AYdl5clWEAL$A-NH2	1336.66	669.33	669.43
618	Ac-LThF$r8AYWAQL$S-NH2	1545.86	773.93	774.11
619	Ac-LT2Nal$r8AYWAQL$S-NH2	1581.86	791.93	792.43
620	Ac-LTA$r8AYWAQL$S-NH2	1455.81	728.91	729.15
621	Ac-LTF$r8AYWVQL$S-NH2	1559.88	780.94	781.24
622	Ac-LTF$r8HYWAAL$A-NH2	1524.85	763.43	763.86
623	Ac-LTF$r8VYWAQL$A-NH2	1543.88	772.94	773.37

624	Ac-LTF$r8IYWAQL$S-NH2	1573.89	787.95	788.17
625	Ac-FTF$r8VYWSQL$S-NH2	1609.85	805.93	806.22
626	Ac-ITF$r8FYWAQL$S-NH2	1607.88	804.94	805.2
627	Ac-2NalTF$r8VYWSQL$S-NH2	1659.87	830.94	831.2
628	Ac-ITF$r8LYWSQL$S-NH2	1589.89	795.95	796.13
629	Ac-FTF$r8FYWAQL$S-NH2	1641.86	821.93	822.13
630	Ac-WTF$r8VYWAQL$S-NH2	1632.87	817.44	817.69
631	Ac-WTF$r8WYWAQL$S-NH2	1719.88	860.94	861.36
632	Ac-VTF$r8AYWSQL$S-NH2	1533.82	767.91	768.19
633	Ac-WTF$r8FYWSQL$S-NH2	1696.87	849.44	849.7
634	Ac-FTF$r8IYWAQL$S-NH2	1607.88	804.94	805.2
635	Ac-WTF$r8VYWSQL$S-NH2	1648.87	825.44	824.8
636	Ac-FTF$r8LYWSQL$S-NH2	1623.87	812.94	812.8
637	Ac-YTF$r8FYWSQL$S-NH2	1673.85	837.93	837.8
638	Ac-LTF$r8AY6clWEAL$A-NH2	1550.79	776.40	776.14
639	Ac-LTF$r8AY6clWSQL$S-NH2	1581.80	791.90	791.68
640	Ac-F$r8AY6clWSAL$A-NH2	1294.65	648.33	647.67
641	Ac-F$r8AY6clWQAL$AA-NH2	1406.72	704.36	703.84
642	Ac-LHF$r8AYWAQL$S-NH2	1567.86	784.93	785.21
643	Ac-LTF$r8AYWAQL$S-NH2	1531.84	766.92	767.17
644	Ac-LTF$r8AHWAQL$S-NH2	1505.84	753.92	754.13
645	Ac-LTF$r8AYWAHL$S-NH2	1540.84	771.42	771.61
646	Ac-LTF$r8AYWAQL$H-NH2	1581.87	791.94	792.15
647	H-LTF$r8AYWAQL$A-NH2	1473.84	737.92	737.29
648	Ac-HHF$r8AYWAQL$S-NH2	1591.83	796.92	797.35
649	Ac-aAibWTF$r8VYWSQL$S-NH2	1804.96	903.48	903.64
650	Ac-AibWTF$r8HYWAQL$S-NH2	1755.91	878.96	879.4
651	Ac-AibAWTF$r8HYWAQL$S-NH2	1826.95	914.48	914.7
652	Ac-fWTF$r8HYWAQL$S-NH2	1817.93	909.97	910.1
653	Ac-AibWWTF$r8HYWAQL$S-NH2	1941.99	972.00	972.2
654	Ac-WTF$r8LYWSQL$S-NH2	1662.88	832.44	832.8
655	Ac-WTF$r8NleYWSQL$S-NH2	1662.88	832.44	832.6
656	Ac-LTF$r8AYWSQL$a-NH2	1531.84	766.92	767.2

657	Ac-LTF$r8EYWARL$A-NH2	1601.90	801.95	802.1
658	Ac-LTF$r8EYWAHL$A-NH2	1582.86	792.43	792.6
659	Ac-aTF$r8AYWAQL$S-NH2	1489.80	745.90	746.08
660	Ac-AibTF$r8AYWAQL$S-NH2	1503.81	752.91	753.11
661	Ac-AmfTF$r8AYWAQL$S-NH2	1579.84	790.92	791.14
662	Ac-AmwTF$r8AYWAQL$S-NH2	1618.86	810.43	810.66
663	Ac-NmLTF$r8AYWAQL$S-NH2	1545.86	773.93	774.11
664	Ac-LNmTF$r8AYWAQL$S-NH2	1545.86	773.93	774.11
665	Ac-LSarF$r8AYWAQL$S-NH2	1501.83	751.92	752.18
667	Ac-LGF$r8AYWAQL$S-NH2	1487.82	744.91	745.15
668	Ac-LTNmF$r8AYWAQL$S-NH2	1545.86	773.93	774.2
669	Ac-TF$r8AYWAQL$S-NH2	1418.76	710.38	710.64
670	Ac-ETF$r8AYWAQL$A-NH2	1531.81	766.91	767.2
671	Ac-LTF$r8EYWAQL$A-NH2	1573.85	787.93	788.1
672	Ac-LT2Nal$r8AYWSQL$S-NH2	1597.85	799.93	800.4
673	Ac-LTF$r8AYWAAL$S-NH2	1474.82	738.41	738.68
674	Ac-LTF$r8AYWAQhCha$S-NH2	1585.89	793.95	794.19
675	Ac-LTF$r8AYWAQChg$S-NH2	1557.86	779.93	780.97
676	Ac-LTF$r8AYWAQCba$S-NH2	1543.84	772.92	773.19
677	Ac-LTF$r8AYWAQF3CF3$S-NH2	1633.82	817.91	818.15
678	Ac-LTF$r8AYWAQ1Nal$S-NH2	1615.84	808.92	809.18
679	Ac-LTF$r8AYWAQBip$S-NH2	1641.86	821.93	822.32
680	Ac-LT2Nal$r8AYWAQL$S-NH2	1581.86	791.93	792.15
681	Ac-LTF$r8AYWVQL$S-NH2	1559.88	780.94	781.62
682	Ac-LTF$r8AWWAQL$S-NH2	1554.86	778.43	778.65
683	Ac-FTF$r8VYWSQL$S-NH2	1609.85	805.93	806.12
684	Ac-ITF$r8FYWAQL$S-NH2	1607.88	804.94	805.2
685	Ac-ITF$r8LYWSQL$S-NH2	1589.89	795.95	796.22
686	Ac-FTF$r8FYWAQL$S-NH2	1641.86	821.93	822.41
687	Ac-VTF$r8AYWSQL$S-NH2	1533.82	767.91	768.19
688	Ac-LTF$r8AHWAQL$S-NH2	1505.84	753.92	754.31
689	Ac-LTF$r8AYWAQL$H-NH2	1581.87	791.94	791.94
690	Ac-LTF$r8AYWAHL$S-NH2	1540.84	771.42	771.61

691	Ac-aAibWTF$r8VYWSQL$S-NH2	1804.96	903.48	903.9
692	Ac-AibWTF$r8HYWAQL$S-NH2	1755.91	878.96	879.5
693	Ac-AibAWTF$r8HYWAQL$S-NH2	1826.95	914.48	914.7
694	Ac-fWTF$r8HYWAQL$S-NH2	1817.93	909.97	910.2
695	Ac-AibWWTF$r8HYWAQL$S-NH2	1941.99	972.00	972.7
696	Ac-WTF$r8LYWSQL$S-NH2	1662.88	832.44	832.7
697	Ac-WTF$r8NleYWSQL$S-NH2	1662.88	832.44	832.7
698	Ac-LTF$r8AYWSQL$a-NH2	1531.84	766.92	767.2
699	Ac-LTF$r8EYWARL$A-NH2	1601.90	801.95	802.2
700	Ac-LTF$r8EYWAHL$A-NH2	1582.86	792.43	792.6
701	Ac-aTF$r8AYWAQL$S-NH2	1489.80	745.90	746.1
702	Ac-AibTF$r8AYWAQL$S-NH2	1503.81	752.91	753.2
703	Ac-AmfTF$r8AYWAQL$S-NH2	1579.84	790.92	791.2
704	Ac-AmwTF$r8AYWAQL$S-NH2	1618.86	810.43	810.7
705	Ac-NmLTF$r8AYWAQL$S-NH2	1545.86	773.93	774.1
706	Ac-LNmTF$r8AYWAQL$S-NH2	1545.86	773.93	774.4
707	Ac-LSarF$r8AYWAQL$S-NH2	1501.83	751.92	752.1
708	Ac-TF$r8AYWAQL$S-NH2	1418.76	710.38	710.8
709	Ac-ETF$r8AYWAQL$A-NH2	1531.81	766.91	767.4
710	Ac-LTF$r8EYWAQL$A-NH2	1573.85	787.93	788.2
711	Ac-WTF$r8VYWSQL$S-NH2	1648.87	825.44	825.2
713	Ac-YTF$r8FYWSQL$S-NH2	1673.85	837.93	837.3
714	Ac-F$r8AY6clWSAL$A-NH2	1294.65	648.33	647.74
715	Ac-ETF$r8EYWVQL$S-NH2	1633.84	817.92	817.36
716	Ac-ETF$r8EHWAQL$A-NH2	1563.81	782.91	782.36
717	Ac-ITF$r8EYWAQL$S-NH2	1589.85	795.93	795.38
718	Ac-ITF$r8EHWVQL$A-NH2	1575.88	788.94	788.42
719	Ac-ITF$r8EHWAQL$S-NH2	1563.85	782.93	782.43
720	Ac-LTF4F$r8AYWAQCba$S-NH2	1561.83	781.92	781.32
721	Ac-LTF3Cl$r8AYWAQhL$S-NH2	1579.82	790.91	790.64
722	Ac-LTF3Cl$r8AYWAQCha$S-NH2	1605.84	803.92	803.37
723	Ac-LTF3Cl$r8AYWAQChg$S-NH2	1591.82	796.91	796.27
724	Ac-LTF3Cl$r8AYWAQCba$S-NH2	1577.81	789.91	789.83

725	Ac-LTF$r8AY6clWSQL$S-NH2	1581.80	791.90	791.75
726	Ac-LTF4F$r8HYWAQhL$S-NH2	1629.87	815.94	815.36
727	Ac-LTF4F$r8HYWAQCba$S-NH2	1627.86	814.93	814.32
728	Ac-LTF4F$r8AYWAQhL$S-NH2	1563.85	782.93	782.36
729	Ac-LTF4F$r8AYWAQChg$S-NH2	1575.85	788.93	788.35
730	Ac-ETF$r8EYWVAL$S-NH2	1576.82	789.41	788.79
731	Ac-ETF$r8EHWAAL$A-NH2	1506.79	754.40	754.8
732	Ac-ITF$r8EYWAAL$S-NH2	1532.83	767.42	767.75
733	Ac-ITF$r8EHWVAL$A-NH2	1518.86	760.43	760.81
734	Ac-ITF$r8EHWAAL$S-NH2	1506.82	754.41	754.8
735	Pam-LTF$r8EYWAQL$S-NH2	1786.07	894.04	894.48
736	Pam-ETF$r8EYWAQL$S-NH2	1802.03	902.02	902.34
737	Ac-LTF$r8AYWLQL$S-NH2	1573.89	787.95	787.39
738	Ac-LTF$r8EYWLQL$S-NH2	1631.90	816.95	817.33
739	Ac-LTF$r8EHWLQL$S-NH2	1605.89	803.95	804.29
740	Ac-LTF$r8VYWAQL$S-NH2	1559.88	780.94	781.34
741	Ac-LTF$r8AYWSQL$S-NH2	1547.84	774.92	775.33
742	Ac-ETF$r8AYWAQL$S-NH2	1547.80	774.90	775.7
743	Ac-LTF$r8EYWAQL$S-NH2	1589.85	795.93	796.33
744	Ac-LTF$r8HYWAQL$S-NHAm	1667.94	834.97	835.37
745	Ac-LTF$r8HYWAQL$S-NHiAm	1667.94	834.97	835.27
746	Ac-LTF$r8HYWAQL$S-NHnPr3Ph	1715.94	858.97	859.42
747	Ac-LTF$r8HYWAQL$S-NHnBu3,3Me	1681.96	841.98	842.67
748	Ac-LTF$r8HYWAQL$S-NHnBu	1653.93	827.97	828.24
749	Ac-LTF$r8HYWAQL$S-NHnPr	1639.91	820.96	821.31
750	Ac-LTF$r8HYWAQL$S-NHnEt2Ch	1707.98	854.99	855.35
751	Ac-LTF$r8HYWAQL$S-NHHex	1681.96	841.98	842.4
752	Ac-LTF$r8AYWAQL$S-NHmdPeg2	1633.91	817.96	855.35
753	Ac-LTF$r8AYWAQL$A-NHmdPeg2	1617.92	809.96	810.58
754	Ac-LTF$r5AYWAAL$s8S-NH2	1474.82	738.41	738.79
755	Ac-LTF$r8AYWCouQL$S-NH2	1705.88	853.94	854.61
756	Ac-LTF$r8CouYWAQL$S-NH2	1705.88	853.94	854.7
757	Ac-CouTF$r8AYWAQL$S-NH2	1663.83	832.92	833.33

758	H-LTF$r8AYWAQL$A-NH2	1473.84	737.92	737.29
759	Ac-HHF$r8AYWAQL$S-NH2	1591.83	796.92	797.72
760	Ac-LT2Nal$r8AYWSQL$S-NH2	1597.85	799.93	800.68
761	Ac-LTF$r8HCouWAQL$S-NH2	1679.87	840.94	841.38
762	Ac-LTF$r8AYWCou2QL$S-NH2	1789.94	895.97	896.51
763	Ac-LTF$r8Cou2YWAQL$S-NH2	1789.94	895.97	896.5
764	Ac-Cou2TF$r8AYWAQL$S-NH2	1747.90	874.95	875.42
765	Ac-LTF$r8ACou2WAQL$S-NH2	1697.92	849.96	850.82
766	Dmaac-LTF$r8AYWAQL$S-NH2	1574.89	788.45	788.82
767	Hexac-LTF$r8AYWAQL$S-NH2	1587.91	794.96	795.11
768	Napac-LTF$r8AYWAQL$S-NH2	1657.89	829.95	830.36
769	Pam-LTF$r8AYWAQL$S-NH2	1728.06	865.03	865.45
770	Ac-LT2Nal$r8HYAAQL$S-NH2	1532.84	767.42	767.61
771	Ac-LT2Nal$/r8HYWAQL$/S-NH2	1675.91	838.96	839.1
772	Ac-LT2Nal$r8HYFAQL$S-NH2	1608.87	805.44	805.9
773	Ac-LT2Nal$r8HWAAQL$S-NH2	1555.86	778.93	779.08
774	Ac-LT2Nal$r8HYAWQL$S-NH2	1647.88	824.94	825.04
775	Ac-LT2Nal$r8HYAAQW$S-NH2	1605.83	803.92	804.05
776	Ac-LTW$r8HYWAQL$S-NH2	1636.88	819.44	819.95
777	Ac-LT1Nal$r8HYWAQL$S-NH2	1647.88	824.94	825.41

[00240] In some embodiments, the peptidomimetic macrocycles disclosed herein do not comprise a peptidomimetic macrocycle structure as shown in **Table 2b**.

[00241] **Table 2c** shows examples of non-crosslinked polypeptides comprising D-amino acids.

Table 2c

SP	Sequence	Isomer	Exact Mass	Found Mass	Calc (M+1)/1	Calc (M+2)/2	Calc (M+3)/3
SP778	Ac-tawyanfekllr-NH2			777.46			
SP779	Ac-tawyanf4CF3ekllr-NH2			811.41			

[00242] Peptidomimetic macrocycles can also be prepared that target or interact with proteins that a virus needs for infection or replication within a host cell. Such viruses can be, for example, influenza viruses belonging to Orthomyxoviridae family of viruses. This family also includes Thogoto viruses and Dhoriviruses. There are

several types and subtypes of influenza viruses known, which infect humans and other species. Influenza type A viruses infect people, birds, pigs, horses, seals and other animals, but wild birds are the natural hosts for these viruses. Influenza type A viruses are divided into subtypes and named on the basis of two proteins on the surface of the virus: hemagglutinin (HA) and neuraminidase (NA). For example, an "H7N2 virus" designates an influenza A subtype that has an HA7 protein and an NA2 protein. Similarly an "H5N1" virus has an HA 5 protein and an NA1 protein. There are 16 known HA subtypes and 9 known NA subtypes. Many different combinations of HA and NA proteins are possible. Only some influenza A subtypes (i.e., H1N1, H1N2, and H3N2) are currently in general circulation among people. Other subtypes are found most commonly in other animal species. For example, H7N7 and H3N8 viruses cause illness in horses, and H3N8 also has recently been shown to cause illness in dogs.

[00243] Antiviral agents according to the invention can be used to protect high-risk groups (hospital units, institutes caring for elderly, immuno-suppressed individuals), and on a case by case basis. A potential use for antiviral agents is to limit the spread and severity of the future pandemics whether caused by avian H5N1 or other strains of influenza virus. Avian influenza A viruses of the subtypes H5 and H7, including H5N1, H7N7, and H7N3 viruses, have been associated with high pathogenicity, and human infection with these viruses have ranged from mild (H7N3, H7N7) to severe and fatal disease (H7N7, H5N1). Human illness due to infection with low pathogenicity viruses has been documented, including very mild symptoms (*e.g.*, conjunctivitis) to influenza-like illness. Examples of low pathogenicity viruses that have infected humans include H7N7, H9N2, and H7N2.

[00244] Influenza B viruses are usually found in humans but can also infect seals. Unlike influenza A viruses, these viruses are not classified according to subtype. Influenza B viruses can cause morbidity and mortality among humans, but in general are associated with less severe epidemics than influenza A viruses. Although influenza type B viruses can cause human epidemics, they have not caused pandemics.

[00245] Influenza type C viruses cause mild illness in humans and do not cause epidemics or pandemics. These viruses can also infect dogs and pigs. These viruses are not classified according to subtype.

[00246] Influenza viruses differ from each other in respect to cell surface receptor specificity and cell tropism, however they use common entry pathways. Charting these pathways and identification of host cell proteins involved in virus influenza transmission, entry, replication, biosynthesis, assembly, or exit allows the development of general agents against existing and emerging strains of influenza. The agents can also prove useful against unrelated viruses that use similar pathways. For example, the agents can protect airway epithelial cells against a number of different viruses in addition to influenza viruses.

[00247] In one embodiment the targeted virus is an adenovirus. Adenoviruses most commonly cause respiratory illness; symptoms of respiratory illness caused by adenovirus infection range from the common cold syndrome to pneumonia, croup, and bronchitis. Patients with compromised immune systems are especially susceptible to severe complications of adenovirus infection. Acute respiratory disease (ARD), first recognized among military recruits during World War II, can be caused by adenovirus infections during conditions of crowding and stress.

Adenoviruses are medium-sized (90-100 nm), nonenveloped icosohedral viruses containing double-stranded DNA. There are 49 immunologically distinct types (6 subgenera: A through F) that can cause human infections. Adenoviruses are unusually stable to chemical or physical agents and adverse pH conditions, allowing for prolonged survival outside of the body. Some adenoviruses, such as AD2 and Ad5 (species C) use clathrin mediated endocytosis and macropinocytosis for infectious entry. Other adenoviruses, such as Ad3 (species B) use dynamin dependent endocytosis and macropinocytosis for infectious entry.

[00248] In one embodiment the targeted virus is a respiratory syncytial virus (RSV). RSV is the most common cause of bronchiolitis and pneumonia among infants and children under 1 year of age. Illness begins most frequently with fever, runny nose, cough, and sometimes wheezing. During their first RSV infection, between 25% and 40% of infants and young children have signs or symptoms of bronchiolitis or pneumonia, and 0.5% to 2% require hospitalization. Most children recover from illness in 8 to 15 days. The majority of children hospitalized for RSV infection are under 6 months of age. RSV also causes repeated infections throughout life, usually associated with moderate-to-severe cold-like symptoms; however, severe lower respiratory tract disease can occur at any age, especially among the elderly or among those with compromised cardiac, pulmonary, or immune systems. RSV is a negative-sense, enveloped RNA virus. The virion is variable in shape and size (average diameter of between 120 and 300 nm), is unstable in the environment (surviving only a few hours on environmental surfaces), and is readily inactivated with soap and water and disinfectants.

[00249] In one embodiment the targeted virus is a human parainfluenza virus (HPIV). HPIVs are second to respiratory syncytial virus (RSV) as a common cause of lower respiratory tract disease in young children. Similar to RSV, HPIVs can cause repeated infections throughout life, usually manifested by an upper respiratory tract illness (*e.g.*, a cold and/or sore throat). HPIVs can also cause serious lower respiratory tract disease with repeat infection (*e.g.*, pneumonia, bronchitis, and bronchiolitis), especially among the elderly, and among patients with compromised immune systems. Each of the four HPIVs has different clinical and epidemiologic features. The most distinctive clinical feature of HPIV-1 and HPIV-2 is croup (i.e., laryngotracheobronchitis); HPIV-1 is the leading cause of croup in children, whereas HPIV-2 is less frequently detected. Both HPIV-1 and -2 can cause other upper and lower respiratory tract illnesses. HPIV-3 is more often associated with bronchiolitis and pneumonia. HPIV-4 is infrequently detected, possibly because it is less likely to cause severe disease. The incubation period for HPIVs is generally from 1 to 7 days. HPIVs are negative-sense, single-stranded RNA viruses that possess fusion and hemagglutinin-neuraminidase glycoprotein "spikes" on their surface. There are four serotypes types of HPIV (1 through 4) and two subtypes (4a and 4b). The virion varies in size (average diameter between 150 and 300 nm) and shape, is unstable in the environment (surviving a few hours on environmental surfaces), and is readily inactivated with soap and water.

[00250] In one embodiment the targeted virus is a coronavirus. Coronavirus is a genus of animal virus belonging to the family Coronaviridae. Coronaviruses are enveloped viruses with a positive-sense single-stranded RNA genome and a helical symmetry. The genomic size of coronaviruses ranges from approximately 16 to 31

kilobases, extraordinarily large for an RNA virus. The name "coronavirus" is derived from the Latin corona, meaning crown, as the virus envelope appears under electron microscopy to be crowned by a characteristic ring of small bulbous structures. This morphology is actually formed by the viral spike peplomers, which are proteins that populate the surface of the virus and determine host tropism. Coronaviruses are grouped in the order Nidovirales, named for the Latin nidus, meaning nest, as all viruses in this order produce a 3' co-terminal nested set of subgenomic mRNAs during infection. Proteins that contribute to the overall structure of all coronaviruses are the spike, envelope, membrane and nucleocapsid. In the specific case of SARS a defined receptor-binding domain on S mediates the attachment of the virus to its cellular receptor, angiotensin-converting enzyme 2.

[00251] In one embodiment the targeted virus is a rhinovirus. Rhinovirus is a genus of the Picornaviridae family of viruses. Rhinoviruses are the most common viral infective agents in humans, and a causative agent of the common cold. There are over 105 serologic virus types that cause cold symptoms, and rhinoviruses are responsible for approximately 50% of all cases. Rhinoviruses have single-stranded positive sense RNA genomes of between 7.2 and 8.5kb in length. At the 5′ end of the genome is a virus-encoded protein, and like mammalian mRNA, there is a 3' poly-A tail. Structural proteins are encoded in the 5′ region of the genome and nonstructural at the end. This is the same for all picornaviruses. The viral particles themselves are not enveloped and are icosahedral in structure.

[00252] Any secondary structure of a viral protein (or of a host cell protein involved in viral infectivity) can form the basis of the methods. For example, a viral protein comprising a secondary structure which is a helix can be used to design peptidomimetic macrocycles based on the helix.

[00253] In one embodiment, the peptidomimetic macrocycle is designed based on the PB1 or PB2 sequence of an influenza virus. The PB1 sequence is highly conserved across all known strains of influenza A virus, which can result in less drug resistance should than that observed with the current standard of care. An alignment of the first 25 N-terminal amino acids of PB1 from the NCBI data bank's 2,485 influenza A virus strains (Ghanem, 2007) demonstrates the remarkable sequence conservation in the PA interaction domain of PB1. Therefore, antiviral therapies based on the PB1 sequence can block most, if not all, influenza A virus strains. Additionally, sequence modification of a peptidomimetic macrocycle based on these few variations in PB1 can enable an antiviral cocktail of PB1 inhibitors to eliminate resistance due to escape mutants.

[00254] **Table 3a** shows a list of peptidomimetic macrocycles derived from the PA-binding helix of PB1 that were prepared.

[00255] **Table 3b** shows a list of selected peptidomimetic macrocycles from **Table 3a**. SP-791 and SP-794 were prepared by increasing the length and alanine content (%) of the SP-786 sequence. These modifications led to a five-fold increase in antiviral activity compared to that of SP-786. SP-798 was prepared by incorporating an i, i+7 crosslink instead of the i, i+4 crosslink of SP-786. SP-192 exhibited improved anti-viral activity (EC_{50}= 4.5 mM) compared to that of SP-786.

[00256] In some embodiments, the invention provides a peptidomimetic macrocycle that comprises an amino acid sequence that has at least 60%, 70%, 80%, 90%, 95%, 97%, or 100% identity to any one of the amino acid sequences in **Table 3a** or **3b**.

Table 3a - Prepared peptidomimetic macrocycles derived from the PA-binding helix of pB1.

SP#			1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17	
780	Ac-		Nle	D	V	N	$	T	L	L	$	L	K	V	Aib	A	Q			$-NH_2$
781	Ac-		Nle	D	V	N	$	T	L	L	$	L	K	A	Aib	A	Q			$-NH_2$
782	Ac-		Nle	D	V	N	$	T	L	L	$	L	K	V	Aib	A	A			$-NH_2$
783	Ac-		Nle	D	V	N	$	T	L	L	$	L	K	V	P	Aib	Q			$-NH_2$
784	Ac-		F	D	V	N	$	T	L	L	$	L	K	V	Aib	A	Q			$-NH_2$
785	5-FAM-	Ba	Nle	D	V	N	$	T	L	L	$	L	A	V	Aib	A	Q			$-NH_2$
786	Ac-		Nle	D	V	N	$	T	L	L	$	L	A	V	Aib	A	Q			$-NH_2$
787	Ac-		Nle	D	V	N	$	T	L	L	$	L	A	V	Aib	A	Q	A	A	$-NH_2$
788	Ac-		Nle	D	V	N	$	T	L	L	$	L	A	V	A	A	Q	A	A	$-NH_2$
789	Ac-		Nle	D	V	N	$	T	L	L	$	L	A	V	A	A	A	A	A	$-NH_2$
790	Ac-		Nle	D	V	N	$	T	L	L	$	L	A	V	S	A	Q	A	A	$-NH_2$
791	Ac-		Nle	D	V	N	$	T	L	L	$	L	A	V	Q	A	Q	A	A	$-NH_2$
792	Ac-		Nle	D	V	N	$	T	L	L	$	L	A	V	E	A	Q	A	A	$-NH_2$
793	Ac-		Nle	D	V	N	$	T	L	L	$	L	A	V	S	A	A	A	A	$-NH_2$
794	Ac-		Nle	D	V	N	$	T	L	L	$	L	A	V	Q	A	A	A	A	$-NH_2$
795	Ac-		Nle	D	V	N	$	T	L	L	$	L	A	V	E	A	A	A	A	$-NH_2$
796	Ac-		Nle	D	V	N	$	T	L	L	$	L	A	V	Aib	A	Q	A	a	$-NH_2$
797	Ac-		Nle	D	V	N	$	T	L	L	$	L	A	V	Aib	A	Q	A	a	-OH
798	Ac-		Nle	D	V	N	$r8	T	L	L	F	L	A	$	A	A	Q			$-NH_2$
799	Ac-		Nle	D	V	N	$	T	L	L	$	L	A	V	Q	Aib	Q	A	A	$-NH_2$
800	Ac-		Nle	D	V	N	$	T	L	L	$	L	A	V	Q	A	Q	Aib	A	$-NH_2$
801	Ac-		Nle	D	V	N	$	T	L	L	$	L	A	V	Q	Aib	A	A	A	$-NH_2$
802	Ac-		Nle	D	V	N	$	T	L	L	$	L	A	V	Q	A	A	Aib	A	$-NH_2$
803	Ac-		Nle	D	V	N	$	T	L	L	$	L	A	V	Q	A	Aib	A	A	$-NH_2$
804	Ac-		Nle	D	V	N	$r8	T	L	L	F	L	A	$	A	A	Q	A	A	$-NH_2$
805	Ac-		Nle	D	V	N	$r8	T	L	L	F	L	A	$	A	A	A	A	A	$-NH_2$
806	Ac-		Nle	D	V	N	$r8	T	L	L	F	L	A	$	Q	A	Q	A	A	$-NH_2$
807	Ac-		Nle	D	V	N	$r8	T	L	L	F	L	A	$	Q	A	A	A	A	$-NH_2$

Table 3b - Selected peptidomimetic macrocycles derived from the PA-binding helix of pB1.

SP#	Crosslink	Ch	L	VH	RT (min)*	Ala (%)	CPE, EC_{50} (μM)**
786	i, i+4	-1	15	4.7	10.68	13	23
791	i, i+4	-1	17	7.2	8.02	24	4.1
794	i, i+4	-1	17	5.1	9.54	29	6.1
799	i, i+4	-1	17	7		18	< 6.1***
800	i, i+4	-1	17	7	8.47	18	< 6.1***
801	i, i+4	-1	17	4.9	10.01	24	< 6.1***
802	i, i+4	-1	17	4.9	10.18	24	< 6.1***
803	i, i+4	-1	17	4.9	10.26	24	< 6.1***
798	i, i+7	-1	15	4.9	10.18	20	4.5
804	i, i+7	-1	17	5.1	10.92	29	< 4.5***
805	i, i+7	-1	17	3	13.03	35	< 4.5***

SP#	Crosslink	Ch	L	VH	RT (min)*	Ala (%)	CPE, EC_{50} (μM)**
806	i, i+7	-1	17	7.2	8.86	24	< 4.5***
807	i, i+7	-1	17	5.1	10.83	29	< 4.5***

* *See* Example 11 table
** By Neutral Red assay (Influenza A Virus H1N1 California/07/2009)
*** Predicted
Ch = net charge; L = length in amino acids; VH= von Heijne; RT= retention time; Ala= alanine content

[00257] In some embodiments of the invention, the peptide sequence is derived from the BCL-2 family of proteins. The BCL-2 family is defined by the presence of up to four conserved BCL-2 homology (BH) domains designated BH1, BH2, BH3, and BH4, all of which include α-helical segments (Chittenden *et al.* (1995), *EMBO* 14:5589; Wang *et al.* (1996), *Genes Dev.* 10:2859). Anti-apoptotic proteins, such as BCL-2 and BCL-X_L, display sequence conservation in all BH domains. Pro-apoptotic proteins are divided into "multidomain" family members (*e.g.*, BAK, BAX), which possess homology in the BH1, BH2, and BH3 domains, and "BH3-domain only" family members (*e.g.*, BID, BAD, BIM, BIK, NOXA, PUMA), that contain sequence homology exclusively in the BH3 amphipathic α-helical segment. BCL-2 family members have the capacity to form homo- and heterodimers, suggesting that competitive binding and the ratio between pro- and anti-apoptotic protein levels dictates susceptibility to death stimuli. Anti-apoptotic proteins function to protect cells from pro-apoptotic excess, *i.e.*, excessive programmed cell death. Additional "security" measures include regulating transcription of pro-apoptotic proteins and maintaining them as inactive conformers, requiring either proteolytic activation, dephosphorylation, or ligand-induced conformational change to activate pro-death functions. In certain cell types, death signals received at the plasma membrane trigger apoptosis via a mitochondrial pathway. The mitochondria can serve as a gatekeeper of cell death by sequestering cytochrome c, a critical component of a cytosolic complex which activates caspase 9, leading to fatal downstream proteolytic events. Multidomain proteins such as BCL-2/BCL-X_L and BAK/BAX play dueling roles of guardian and executioner at the mitochondrial membrane, with their activities further regulated by upstream BH3-only members of the BCL-2 family. For example, BID is a member of the BH3-domain only family of pro-apoptotic proteins, and transmits death signals received at the plasma membrane to effector pro-apoptotic proteins at the mitochondrial membrane. BID has the capability of interacting with both pro- and anti-apoptotic proteins, and upon activation by caspase 8, triggers cytochrome c release and mitochondrial apoptosis. Deletion and mutagenesis studies determined that the amphipathic α-helical BH3 segment of pro-apoptotic family members can function as a death domain and thus can represent a critical structural motif for interacting with multidomain apoptotic proteins. Structural studies have shown that the BH3 helix can interact with anti-apoptotic proteins by inserting into a hydrophobic groove formed by the interface of BH1, 2 and 3 domains. Activated BID can be bound and sequestered by anti-apoptotic proteins (*e.g.*, BCL-2 and BCL-X_L) and can trigger activation of the pro-apoptotic proteins BAX and BAK, leading to cytochrome c release and a mitochondrial apoptosis program. BAD is also a BH3-domain only pro-apoptotic family member whose expression triggers the activation of BAX/BAK. In contrast to BID, however, BAD displays preferential binding

to anti-apoptotic family members, BCL-2 and BCL-X_L. Whereas the BAD BH3 domain exhibits high affinity binding to BCL-2, BAD BH3 peptide is unable to activate cytochrome c release from mitochondria *in vitro*, suggesting that BAD is not a direct activator of BAX/BAK. Mitochondria that over-express BCL-2 are resistant to BID-induced cytochrome c release, but co-treatment with BAD can restore BID sensitivity. Induction of mitochondrial apoptosis by BAD appears to result from either: (1) displacement of BAX/BAK activators, such as BID and BID-like proteins, from the BCL-2/BCL-X_L binding pocket, or (2) selective occupation of the BCL-2/BCL-X_L binding pocket by BAD to prevent sequestration of BID-like proteins by anti-apoptotic proteins. Thus, two classes of BH3-domain only proteins have emerged, BID-like proteins that directly activate mitochondrial apoptosis, and BAD-like proteins, that have the capacity to sensitize mitochondria to BID-like pro-apoptotics by occupying the binding pockets of multidomain anti-apoptotic proteins. Various α-helical domains of BCL-2 family member proteins amenable to the methodology disclosed herein have been disclosed (Walensky *et al.* (2004), *Science* 305:1466; and Walensky *et al.*, U.S. Patent Publication No. 2005/0250680, the entire disclosures of which are incorporated herein by reference).

[00258] Myeloid cell leukemia 1 (MCL-1) is a protein that inhibits cell death through the binding and inhibition of pro-death factors such as BCL-2 interacting mediator (BIM). When MCL-1 is over-expressed, the rate of cell death in a cell or tissue is reduced. In some embodiments, the peptide sequences are derived from BIM. In some embodiments, a peptidomimetic macrocycle peptide derived from a human BIM peptide can be a peptide comprising 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14, 15, 16, 17, 18, 19, 20, 21, or 22 amino acids from a BIM peptide sequence.

[00259] In some embodiments, a peptidomimetic macrocycle peptide derived from a human BIM peptide sequence can be a peptide comprising 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14, 15, 16, 17, 18, 19, 20, 21, or 22 amino acids that are different from the selected sequences from which the peptide is derived. In some embodiments, a peptidomimetic macrocycle peptide derived from a human BIM peptide sequence can be a peptide comprising a mutation at amino acid position 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14, 15, 16, 17, 18, 19, 20, 21, or 22. In some embodiments, mutations are mutations of non-essential amino acids. In some embodiments, mutations are mutations of essential amino acids. In some embodiments, mutations are mutations of hydrophobic amino acids. In some embodiments, mutations are mutations of naturally occurring amino acids. In some embodiments, mutations are mutations to a conservative amino acid. In some embodiments, a peptidomimetic macrocycle peptide derived from a human BIM peptide sequence can be a peptide comprising 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14, 15, 16, 17, 18, 19, 20, 21, or 22 amino acid analogues. In some embodiments, a peptidomimetic macrocycle peptide derived from a human BIM peptide sequence can be a peptide comprising 1 or 2 capping groups.

[00260] In some embodiments, the peptidomimetic macrocycle comprises a C-terminal truncation of 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 or 30 amino acids from an amino acid sequence of BIM In some embodiments, the peptidomimetic macrocycle comprises a N-terminal

truncation of 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14, 15, 16, 17, 18, 19, 20, 21, or 22 amino acids from the sequence of BIM.

[00261] A non-limiting list of suitable BIM macrocycles for use in the present disclosure are given in **Tables 4a** and **4b**. In **Tables 4a** and **4b**, at the C-terminus, some peptides possess a carboxamide terminus (shown as $-NH_2$); some peptides possess a hydroxyl terminus (shown as –OH); some peptides possess a 5-carboxyfluorescein terminus (shown as –5-FAM); some peptides possess a isobutylamide terminus (shown as –NHiBu); some peptides possess a cyclohexylamide terminus (shown as –NHChx); some peptides possess a cyclohexylmethylamide terminus (shown as –NHMeChx); some peptides possess a phenethylamide terminus (shown as –NHPe); some peptides possess a n-butylamide terminus (shown as –NHBu); some peptides possess a *sec*-butylamide terminus (shown as –NHsBu); and some peptides possess an uncapped terminus (shown as no terminal modification).

[00262] In **Tables 4a** and **4b**, at the N-terminus, some peptides possess an acetyl terminus (shown as Ac–); some peptides possess a fluorescein isothiocyanate terminus (shown as FITC–); some peptides possess a single-unit polyethylene glycol terminus (shown as dPEG1–); some peptides possess a five-unit polyethylene glycol terminus (shown as dPEG5–); some peptides possess an eleven-unit polyethylene glycol terminus (shown as dPEG11–); some peptides possess a propyl terminus (shown as Pr–); some peptides possess a biotin terminus (shown as Biotin–); some peptides possess a KLH terminus (shown as KLH–); some peptides possess an ovalbumin terminus (shown as OVA–); some peptides possess an uncapped terminus (shown as H–); some peptides possess a isobutyl terminus (shown as iBu–); some peptides possess a decanoyl terminus (shown as Decac–); some peptides possess a benzyl terminus (shown as Bz–); some peptides possess a cyclohexyl terminus (shown as Chx–); some peptides possess a benzyl terminus (shown as Bz–); some peptides possess a Vrl terminus (shown as Vrl–); some peptides possess a HBS terminus (shown as HBS–); some peptides possess a MeIm terminus (shown as MeImC–); some peptides possess a *tert*-butyl terminus (shown as t-Bu-U–); some peptides possess a nonanoyl terminus (shown as non-U–); some peptides possess a ethyl terminus (shown as Et-U–); some peptides possess a cyclohexyl terminus (shown as Chx-U–); some peptides possess a isopropyl terminus (shown as iPr-U–); some peptides possess a phenyl terminus (shown as Ph-U–); some peptides possess a uric terminus (shown as NH2CO–); some peptides possess a palmitoyl terminus (shown as Pam–); some peptides possess a heptenoic terminus (shown as Hep–); and some peptides possess a 5-carboxytetramethylrhodamine terminus (shown as 5-TAMRA–).

[00263] **Table 4a** shows a list of peptidomimetic macrocycles derived from the MCL-1/ BCL-X_L /BCL-2-binding helix of BIM that were prepared. **Table 4b** shows a list of selected peptidomimetic macrocycles from **Table 4a.** SP-809 was prepared by incorporating an i, i+7 crosslink into the sequence of the linear peptide LP-2. SP-815 was prepared by removal of the two terminal arginine residues and an alanine substitution at position 13 of SP-809. SP-962 was prepared by a homoleucine substitution at position 9 and a F4F at position 17 of SP-815.

[00264] In some embodiments, the invention provides a peptidomimetic macrocycle that comprises an amino acid sequence that has at least 60%, 70%, 80%, 90%, 95%, 97%, or 100% identity to any one of the amino acid sequences in **Table 4a** or **4b**.

Table 4a - Prepared peptidomimetic macrocycles derived from the MCL-1/ BCL-X_L/BCL-2-binding helix of BIM

SP#			1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17	18	19	20	21		Calc.(M + 2) / 2	Fou ma
LP2	Ac-		I	W	I	A	Q	E	L	R	R	I	G	D	E	F	N	A	Y	Y	A	R	R	-NH_2		
808	Ac-		I	W	I	A	Q	E	L	R	$r8	I	G	D	E	F	N	$	Y	Y	A	R	R	-NH_2		
809	Ac-		I	W	I	A	Q	A	L	R	$r8	I	G	D	E	F	N	$	Y	Y	A	R	R	-NH_2	1344.74	134
810	Ac-		I	W	I	A	Q	E	L	R	$r8	I	G	D	E	F	N	$	Y	Y	A	R	R	-NH_2	1373.75	1373
812	Ac-			W	I	A	Q	A	L	R	$r8	I	G	D	A	F	N	$	Y	Y	A			-NH_2	1103.1	1103
813	Ac-				I	A	Q	A	L	R	$r8	I	G	D	A	F	A	$	Y	Y	A			-NH_2	988.55	988.
814	Ac-				I	A	Q	A	L	R	$r8	I	G	D	A	F	N	$	Y	A	A			-NH_2	964.04	963.
815	Ac-		I	W	I	A	Q	A	L	R	$r8	I	G	D	A	F	N	$	Y	Y	A			-NH_2	1159.64	1159
816	Ac-			W	I	A	Q	A	L	R	$r8	I	G	D	A	F	N	$	Y	Y	A			-NH_2	1103.1	1102
817	Ac-				I	A	Q	A	L	R	$r8	I	G	D	A	F	N	$	Y	Y	A			-NH_2	1010.06	100
818	Ac-				I	A	A	A	L	R	$r8	I	G	D	A	F	N	$	Y	Y	A			-NH_2	981.55	981.
819	Ac-				I	A	Q	A	L	A	$r8	I	G	D	A	F	N	$	Y	Y	A			-NH_2	967.53	967.
820	Ac-				I	A	Q	A	L	R	$r8	I	A	D	A	F	N	$	Y	Y	A			-NH_2	1017.07	1016
821	Ac-				I	A	Q	A	L	R	$r8	I	G	D	A	A	N	$	Y	Y	A			-NH_2	972.04	971.
822	Ac-				I	A	Q	A	L	R	$r8	I	G	D	A	F	N	$	A	Y	A			-NH_2	964.04	963.
823	Ac-		I	$	I	A	Q	$	L	R	$r8	I	G	D	E	F	N	$	Y	Y	A			-NH_2	1185.17	1185
824	Ac-		I	W	I	A	Q	A	L	R	%r8	I	G	D	A	F	N	%	Y	Y	A			-NH_2	1160.14	1161
825	Ac-		I	W	I	A	Q	A	L	R	$r8	I	G	D	E	F	A	$	Y	Y	A			-NH_2	1167.14	116
826	Ac-		I	W	I	A	Q	A	L	R	$r8	I	G	D	Q	A	N	$	Y	Y	A			-NH_2	1150.13	1151
827	FITC-	Ba	I	W	I	A	Q	A	L	R	$r8	I	G	D	A	F	N	$	Y	Y	A			-NH_2	1368.67	1369
828	5-FAM-	Ba	I	W	I	A	Q	A	L	R	$r8	I	G	D	A	F	N	$	Y	Y	A			-NH_2	1353.18	1354
829	5-FAM-	Ba	I	W	I	A	Q	A	L	R	$r8	I	G	D	E	F	N	$	Y	Y	A			-NH_2	1382.18	1382
830	Ac-		I	A	I	A	Q	A	L	R	$r8	I	G	D	A	F	N	$	Y	Y	A			-NH_2	1102.12	1103
831	Ac-		I	W	I	A	Q	A	L	R	$r8	I	G	D	E	F	N	$	Y	Y	A			-NH_2	1188.64	1189

SP#			1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17	18	19	20	21		Calc.(M + 2) / 2	Fou mas
832	Ac-		I	W	I	A	Q	A	L	R	$r8	I	G	D	Q	F	N	$	Y	Y	A			-NH_2	1188.15	1189
833	Ac-		I	W	I	A	A	A	L	R	$r8	I	G	D	E	F	N	$	Y	Y	A			-NH_2	1160.13	1161
834	Ac-		I	W	I	A	A	A	L	R	$r8	I	G	D	Q	F	N	$	Y	Y	A			-NH_2	1159.64	1160
835	Ac-		I	W	I	A	A	A	L	R	$r8	I	G	D	A	F	N	$	Y	Y	A			-NH_2	1131.13	1132
836	Ac-		I	W	I	A	Q	A	L	R	$r8	I	G	D	A	F	A	$	Y	Y	A			-NH_2	1138.14	1139
837	Ac-		I	W	I	A	Q	A	L	Cit	$r8	I	G	D	A	F	N	$	Y	Y	A			-NH_2	1160.13	1160
838	Ac-		I	W	I	A	Q	A	L	Cit	$r8	I	G	D	Q	F	N	$	Y	Y	A			-NH_2	1188.64	1189
839	Ac-		I	W	I	A	Q	A	L	H	$r8	I	G	D	A	F	N	$	Y	Y	A			-NH_2	1150.12	1151
840	Ac-		I	W	I	A	Q	A	L	H	$r8	I	G	D	Q	F	N	$	Y	Y	A			-NH_2	1178.63	1179
841	Ac-		I	W	I	A	Q	A	L	Q	$r8	I	G	D	A	F	N	$	Y	Y	A			-NH_2	1145.62	1146
842	Ac-		I	W	I	A	Q	A	L	Q	$r8	I	G	D	Q	F	N	$	Y	Y	A			-NH_2	1174.13	1175
843	Ac-		I	W	I	A	Q	A	L	R	$r8	I	G	D	A	A	N	$	Y	Y	A			-NH_2	1121.62	1122
844	Ac-		I	W	I	A	Q	A	L	R	$r8	I	G	D	A	I	N	$	Y	Y	A			-NH_2	1142.65	1143
845	Ac-		I	W	I	A	Q	A	L	R	$r8	I	G	D	Q	I	N	$	Y	Y	A			-NH_2	1171.16	1171
846	Ac-		I	W	I	A	Q	A	A	R	$r8	I	G	D	A	A	N	$	Y	Y	A			-NH_2	1100.6	1101
847	Ac-		I	W	I	A	Q	A	L	R	$r8	I	A	D	A	F	N	$	Y	Y	A			-NH_2	1166.65	1167
848	Ac-		I	W	I	A	Q	A	L	R	$r8	I	A	D	Q	F	N	$	Y	Y	A			-NH_2	1195.16	1196
849	Ac-		I	W	I	A	Q	A	L	R	$r8	A	G	D	A	F	N	$	Y	Y	A			-NH_2	1138.62	1139
850	Ac-		I	W	I	A	Q	A	L	R	$r8	A	G	D	Q	F	N	$	Y	Y	A			-NH_2	1167.13	1168
851	Ac-		I	W	I	A	Q	A	L	R	$r8	F	G	D	A	F	N	$	Y	Y	A			-NH_2	1176.63	1177
852	Ac-		I	W	I	A	Q	A	L	R	$r8	F	G	D	Q	F	N	$	Y	Y	A			-NH_2	1205.14	1205
853	Ac-		I	W	F	A	Q	A	L	R	$r8	I	G	D	A	F	N	$	Y	Y	A			-NH_2	1176.63	1177
854	Ac-		I	W	F	A	Q	A	L	R	$r8	I	G	D	Q	F	N	$	Y	Y	A			-NH_2	1205.14	1206
855	Ac-		I	W	I	A	Q	A	L	A	$r8	I	G	D	A	F	N	$	Y	Y	A			-NH_2	1117.11	1118
856	Ac-		I	W	I	A	Q	A	L	R	$r8	I	G	N	A	F	N	$	Y	Y	A			-NH_2	1159.15	1159
857	Ac-		I	W	I	A	Q	A	A	R	$r8	I	G	D	A	F	N	$	Y	Y	A			-NH_2	1138.62	1139
858	Ac-		I	W	I	A	Q	A	L	R	$r8	I	G	D	Q	F	A	$	Y	Y	A			-NH_2	1166.65	1167
859	Ac-		I	W	Cha	A	Q	A	L	R	$r8	I	G	D	A	F	N	$	Y	Y	A			-NH_2	1179.65	1180
860	Ac-		I	W	hhL	A	Q	A	L	R	$r8	I	G	D	A	F	N	$	Y	Y	A			-NH_2	1173.65	1174
861	Ac-		I	W	Adm	A	Q	A	L	R	$r8	I	G	D	A	F	N	$	Y	Y	A			-NH_2	1198.66	1199

SP#			1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17	18	19	20	21		Calc.(M + 2) / 2	Fou ma
862	Ac-		I	W	hCha	A	Q	A	L	R	$r8	I	G	D	A	F	N	$	Y	Y	A			-NH_2	1186.66	1186
863	Ac-		I	W	hF	A	Q	A	L	R	$r8	I	G	D	A	F	N	$	Y	Y	A			-NH_2	1183.64	1184
864	Ac-		I	W	Igl	A	Q	A	L	R	$r8	I	G	D	A	F	N	$	Y	Y	A			-NH_2	1190.65	1190
865	Ac-		I	W	F4CF3	A	Q	A	L	R	$r8	I	G	D	A	F	N	$	Y	Y	A			-NH_2	1210.62	1211
866	Ac-		I	W	F4tBu	A	Q	A	L	R	$r8	I	G	D	A	F	N	$	Y	Y	A			-NH_2	1204.66	1205
867	Ac-		I	W	2Nal	A	Q	A	L	R	$r8	I	G	D	A	F	N	$	Y	Y	A			-NH_2	1201.64	1202
868	Ac-		I	W	Bip	A	Q	A	L	R	$r8	I	G	D	A	F	N	$	Y	Y	A			-NH_2	1214.65	1215
869	Ac-		I	W	I	A	Q	A	Cha	R	$r8	I	G	D	A	F	N	$	Y	Y	A			-NH_2	1179.65	1180
870	Ac-		I	W	I	A	Q	A	hhL	R	$r8	I	G	D	A	F	N	$	Y	Y	A			-NH_2	1173.65	1174
871	Ac-		I	W	I	A	Q	A	Adm	R	$r8	I	G	D	A	F	N	$	Y	Y	A			-NH_2	1198.66	1199
872	Ac-		I	W	I	A	Q	A	hCha	R	$r8	I	G	D	A	F	N	$	Y	Y	A			-NH_2	1186.66	1187
873	Ac-		I	W	I	A	Q	A	hAdm	R	$r8	I	G	D	A	F	N	$	Y	Y	A			-NH_2	1205.67	1206
874	Ac-		I	W	I	A	Q	A	hF	R	$r8	I	G	D	A	F	N	$	Y	Y	A			-NH_2	1183.64	1184
875	Ac-		I	W	I	A	Q	A	Igl	R	$r8	I	G	D	A	F	N	$	Y	Y	A			-NH_2	1190.65	1190
876	Ac-		I	W	I	A	Q	A	F4CF3	R	$r8	I	G	D	A	F	N	$	Y	Y	A			-NH_2	1210.62	1210
877	Ac-		I	W	I	A	Q	A	F4tBu	R	$r8	I	G	D	A	F	N	$	Y	Y	A			-NH_2	1204.66	1205
878	Ac-		I	W	I	A	Q	A	2Nal	R	$r8	I	G	D	A	F	N	$	Y	Y	A			-NH_2	1201.64	1202
879	Ac-		I	W	I	A	Q	A	Bip	R	$r8	I	G	D	A	F	N	$	Y	Y	A			-NH_2	1214.65	1214
880	Ac-		I	W	I	A	Q	A	L	R	$r8	Cba	G	D	A	F	N	$	Y	Y	A			-NH_2	1165.64	1166
881	Ac-		I	W	I	A	Q	A	L	R	$r8	hL	G	D	A	F	N	$	Y	Y	A			-NH_2	1166.65	1167
882	Ac-		I	W	I	A	Q	A	L	R	$r8	Cha	G	D	A	F	N	$	Y	Y	A			-NH_2	1179.65	1180
883	Ac-		I	W	I	A	Q	A	L	R	$r8	Tba	G	D	A	F	N	$	Y	Y	A			-NH_2	1166.65	1167
884	Ac-		I	W	I	A	Q	A	L	R	$r8	hhL	G	D	A	F	N	$	Y	Y	A			-NH_2	1173.65	1173
885	Ac-		I	AmW	I	A	Q	A	L	R	$r8	I	G	D	A	F	N	$	Y	Y	A			-NH_2	1166.65	1167
886	Ac-		I	Aib	I	A	Q	A	L	R	$r8	I	G	D	A	F	N	$	Y	Y	A			-NH_2	1109.13	1109
887	Ac-		AmL	W	I	A	Q	A	L	R	$r8	I	G	D	A	F	N	$	Y	Y	A			-NH_2	1166.65	1167
888	Ac-		I	W	AmL	A	Q	A	L	R	$r8	I	G	D	A	F	N	$	Y	Y	A			-NH_2	1166.65	1137
889	Ac-		I	W	I	Aib	Q	A	L	R	$r8	I	G	AmD	A	F	N	$	Y	Y	A			-NH_2	1173.65	1173
890	Ac-		I	W	I	A	Aib	A	L	R	$r8	I	G	D	A	F	N	$	Y	Y	A			-NH_2	1138.14	1138
891	Ac-		I	W	I	A	Q	A	L	R	$r8	I	G	AmD	A	F	N	$	Y	Y	A			-NH_2	1166.65	1167

SP#			1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17	18	19	20	21		Calc.(M + 2) / 2	Fou mas
892	Ac-		I	W	I	A	Q	A	L	R	$r8	I	G	D	A	F	N	$	Y	F4F	A			-NH_2	1160.64	1161
896	Ac-		I	W	Tba	A	Q	A	L	R	$r8	I	G	D	A	F	N	$	Y	Y	A			-NH_2	1166.65	1167
897	Ac-		I	W	hL	A	Q	A	L	R	$r8	I	G	D	A	F	N	$	Y	Y	A			-NH_2	1166.65	1167
898	Ac-		I	W	Chg	A	Q	A	L	R	$r8	I	G	D	A	F	N	$	Y	Y	A			-NH_2	1172.65	1173
899	Ac-		I	W	Ac6c	A	Q	A	L	R	$r8	I	G	D	A	F	N	$	Y	Y	A			-NH_2	1165.64	1166
900	Ac-		I	W	Ac5c	A	Q	A	L	R	$r8	I	G	D	A	F	N	$	Y	Y	A			-NH_2	1158.63	1159
901	Ac-		E	W	I	A	A	A	L	R	$r8	I	G	D	A	F	N	$	Y	Y	A			-NH_2	1139.11	1139
902	Ac-		R	W	I	A	A	A	L	R	$r8	I	G	D	A	F	N	$	Y	Y	A			-NH_2	1152.64	1153
903	Ac-		K	W	I	A	A	A	L	R	$r8	I	G	D	A	F	N	$	Y	Y	A			-NH_2	1138.63	1138
904	Ac-		H	W	I	A	A	A	L	R	$r8	I	G	D	A	F	N	$	Y	Y	A			-NH_2	1143.12	1143
905	Ac-		S	W	I	A	A	A	L	R	$r8	I	G	D	A	F	N	$	Y	Y	A			-NH_2	1118.1	1118
906	Ac-		Q	W	I	A	A	A	L	R	$r8	I	G	D	A	F	N	$	Y	Y	A			-NH_2	1138.62	1139
907	Ac-		A	W	I	A	A	A	L	R	$r8	I	G	D	A	F	N	$	Y	Y	A			-NH_2	1110.1	1110
908	Ac-		Aib	W	I	A	A	A	L	R	$r8	I	G	D	A	F	N	$	Y	Y	A			-NH_2	1117.11	1117
909	Ac-		F	W	I	A	A	A	L	R	$r8	I	G	D	A	F	N	$	Y	Y	A			-NH_2	1148.12	1148
910	Ac-		I	D	I	A	A	A	L	R	$r8	I	G	D	A	F	N	$	Y	Y	A			-NH_2	1095.6	1096
911	Ac-		I	R	I	A	A	A	L	R	$r8	I	G	D	A	F	N	$	Y	Y	A			-NH_2	1116.14	1116
912	Ac-		I	H	I	A	A	A	L	R	$r8	I	G	D	A	F	N	$	Y	Y	A			-NH_2	1106.62	1107
913	Ac-		I	S	I	A	A	A	L	R	$r8	I	G	D	A	F	N	$	Y	Y	A			-NH_2	1081.6	1181
914	Ac-		I	N	I	A	A	A	L	R	$r8	I	G	D	A	F	N	$	Y	Y	A			-NH_2	1095.11	1095
915	Ac-		I	L	I	A	A	A	L	R	$r8	I	G	D	A	F	N	$	Y	Y	A			-NH_2	1094.63	1095
916	Ac-		I	F	I	A	A	A	L	R	$r8	I	G	D	A	F	N	$	Y	Y	A			-NH_2	1111.62	1112
917	Ac-		I	2Nal	I	A	A	A	L	R	$r8	I	G	D	A	F	N	$	Y	Y	A			-NH_2	1136.63	1137
918	Ac-		I	W	I	S	A	A	L	R	$r8	I	G	D	A	F	N	$	Y	Y	A			-NH_2	1139.13	1139
919	Ac-		I	W	I	L	A	A	L	R	$r8	I	G	D	A	F	N	$	Y	Y	A			-NH_2	1152.15	1152
920	Ac-		I	W	I	F	A	A	L	R	$r8	I	G	D	A	F	N	$	Y	Y	A			-NH_2	1169.14	1169
921	Ac-		I	W	I	A	L	A	L	R	$r8	I	G	D	A	F	N	$	Y	Y	A			-NH_2	1152.15	1152
922	Ac-		I	W	I	A	A	A	L	K	$r8	I	G	D	A	F	N	$	Y	Y	A			-NH_2	1117.13	1117
923	Ac-		I	W	I	A	A	A	L	R	$r8	I	Abu	D	A	F	N	$	Y	Y	A			-NH_2	1145.14	1145
924	Ac-		I	W	I	A	A	A	L	R	$r8	I	V	D	A	F	N	$	Y	Y	A			-NH_2	1152.15	1152

SP#			1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17	18	19	20	21		Calc.(M + 2) / 2	Fou ma
925	Ac-		I	W	I	A	A	A	L	R	$r8	I	G	E	A	F	N	$	Y	Y	A			-NH_2	1138.14	1138
926	Ac-		I	W	I	A	A	A	L	R	$r8	I	G	D	A	G	N	$	Y	Y	A			-NH_2	1086.1	1086
927	Ac-		I	W	I	A	Q	A	L	R	$r8	I	G	D	A	W	N	$	Y	Y	A			-NH_2	1179.14	1180
928	Ac-		I	W	I	A	Q	A	L	R	$r8	I	G	D	A	hF	N	$	Y	Y	A			-NH_2	1166.65	1167
929	Ac-		I	W	I	A	Q	A	L	R	$r8	I	G	D	A	F4CF3	N	$	Y	Y	A			-NH_2	1193.63	1194
930	Ac-		I	W	I	A	Q	A	L	R	$r8	I	G	D	A	F4tBu	N	$	Y	Y	A			-NH_2	1187.67	1188
931	Ac-		I	W	I	A	Q	A	L	R	$r8	I	G	D	A	2Nal	N	$	Y	Y	A			-NH_2	1184.65	118
932	Ac-		I	W	I	A	Q	A	L	R	$r8	I	G	D	A	Bip	N	$	Y	Y	A			-NH_2	1197.65	1198
933	Ac-		I	W	I	A	A	A	L	R	$r8	I	G	D	A	F	D	$	Y	Y	A			-NH_2	1131.62	113
934	Ac-		I	W	I	A	A	A	L	R	$r8	I	G	D	A	F	E	$	Y	Y	A			-NH_2	1138.63	1139
935	Ac-		I	W	I	A	A	A	L	R	$r8	I	G	D	A	F	Q	$	Y	Y	A			-NH_2	1138.14	1138
936	Ac-		I	W	I	A	A	A	L	R	$r8	I	G	D	A	F	S	$	Y	Y	A			-NH_2	1117.62	111
937	Ac-		I	W	I	A	A	A	L	R	$r8	I	G	D	A	F	H	$	Y	Y	A			-NH_2	1142.64	1143
938	Ac-		I	W	I	A	A	A	L	R	$r8	I	G	D	A	F	N	$	L	Y	A			-NH_2	1106.14	1107
939	Ac-		I	W	I	A	Q	A	L	R	$r8	I	G	D	A	F	N	$	Y	A	A			-NH_2	1113.63	1114
940	Ac-		I	W	I	A	Q	A	L	R	$r8	I	G	D	A	F	N	$	Y	L	A			-NH_2	1134.65	1135
941	Ac-		I	W	I	A	Q	A	L	R	$r8	I	G	D	A	F	N	$	Y	Cha	A			-NH_2	1154.66	1155
942	Ac-		I	W	I	A	Q	A	L	R	$r8	I	G	D	A	F	N	$	Y	hF	A			-NH_2	1158.65	115
943	Ac-		I	W	I	A	Q	A	L	R	$r8	I	G	D	A	F	N	$	Y	W	A			-NH_2	1171.15	1171
944	Ac-		I	W	I	A	Q	A	L	R	$r8	I	G	D	A	F	N	$	Y	2Nal	A			-NH_2	1176.65	117
945	Ac-		I	W	I	A	A	A	L	R	$r8	I	G	D	A	F	N	$	Y	Y	D			-NH_2	1153.12	1153
946	Ac-		I	W	I	A	A	A	L	R	$r8	I	G	D	A	F	N	$	Y	Y	E			-NH_2	1160.13	116
947	Ac-		I	W	I	A	A	A	L	R	$r8	I	G	D	A	F	N	$	Y	Y	Q			-NH_2	1159.64	1160
948	Ac-		I	W	I	A	A	A	L	R	$r8	I	G	D	A	F	N	$	Y	Y	S			-NH_2	1139.13	1139
949	Ac-		I	W	I	A	A	A	L	R	$r8	I	G	D	A	F	N	$	Y	Y	H			-NH_2	1164.14	1165
950	Ac-		I	W	I	A	A	A	L	R	$r8	I	G	D	A	F	N	$	Y	Y	R			-NH_2	1173.66	117
951	Ac-		I	W	I	A	A	A	L	R	$r8	I	G	D	A	F	N	$	Y	Y	K			-NH_2	1159.66	1160
952	Ac-		I	W	I	A	Q	A	AmL	R	$r8	I	G	D	A	F	N	$	Y	Y	A			-NH_2	1166.65	1167
953	Ac-		I	W	I	A	Q	A	L	R	$r8	I	G	AmD	A	F	N	$	Y	Y	A			-NH_2	1166.65	1167
954	Ac-		I	W	I	A	Q	A	L	R	$r8	I	G	D	A	F	N	$	F4F	Y	A			-NH_2	1160.64	1161

SP#			1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17	18	19	20	21		Calc.(M + 2) / 2	Fou ma
955	Ac-		I	W	I	A	Q	A	L	R	$r8	I	G	D	A	F	N	$	Y	Y	Aib			-NH_2	1166.65	1167
956	Ac-		I	W	I	A	Q	A	A	Cit	$r8	I	G	D	A	F	N	$	Y	Y	A			-NH_2	1139.11	1139
957	Ac-		I	W	I	A	Q	A	L	Cit	$r8	I	G	N	A	F	N	$	Y	Y	A			-NH_2	1159.64	116(
958	Ac-		I	W	I	A	Q	A	L	Cit	$r8	I	G	D	A	A	N	$	Y	Y	A			-NH_2	1122.12	1122
959	Ac-		I	W	I	A	Q	A	L	Cit	$r8	I	G	D	A	V	N	$	Y	Y	A			-NH_2	1136.13	1136
960	Ac-		I	W	I	A	Q	A	L	R	$r8	I	G	D	A	F	N	$	A	Y	A			-NH_2	1113.63	111
961	Ac-		I	W	I	A	Q	A	L	R	$r8	hL	G	D	A	F	N	$	F4F	Y	A			-NH_2	1167.64	1168
962	Ac-		I	W	I	A	Q	A	L	R	$r8	hL	G	D	A	F	N	$	Y	F4F	A			-NH_2	1167.64	116
963	Ac-		I	W	I	A	Q	A	L	R	$r8	hL	G	D	A	F	N	$	F4F	F4F	A			-NH_2	1168.64	1169
964	Ac-		A	W	I	A	A	A	L	R	$r8	hL	G	D	A	F	N	$	Y	F4F	A			-NH_2	1118.11	1118
965	Ac-		A	W	I	A	A	A	L	R	$r8	hL	G	D	A	F	N	$	A	F4F	A			-NH_2	1072.1	1072
966	Ac-		I	W	I	A	Q	A	A	R	$r8	hL	G	D	A	F	N	$	F4F	F4F	A			-NH_2	1147.62	1148
893	Ac-		I	$r8	I	A	Q	A	L	R	St	I	G	D	E	F	N	$s8	Y	Y	A			-NH_2	1199.18	1199
894	Ac-		I	W	I	A	$	A	L	R	St	I	G	D	E	F	N	$s8	Y	Y	A			-NH_2	1207.17	120
895	Ac-		I	W	I	A	Q	A	L	R	$r8	I	G	D	E	F	N	St	Y	Y	A	$r5	A	-NH_2	1306.72	1307

[00265] Table 4b - Selected peptidomimetic macrocycles derived from the MCL-1/ BCL-X_L/BCL-2-binding helix of BIM.

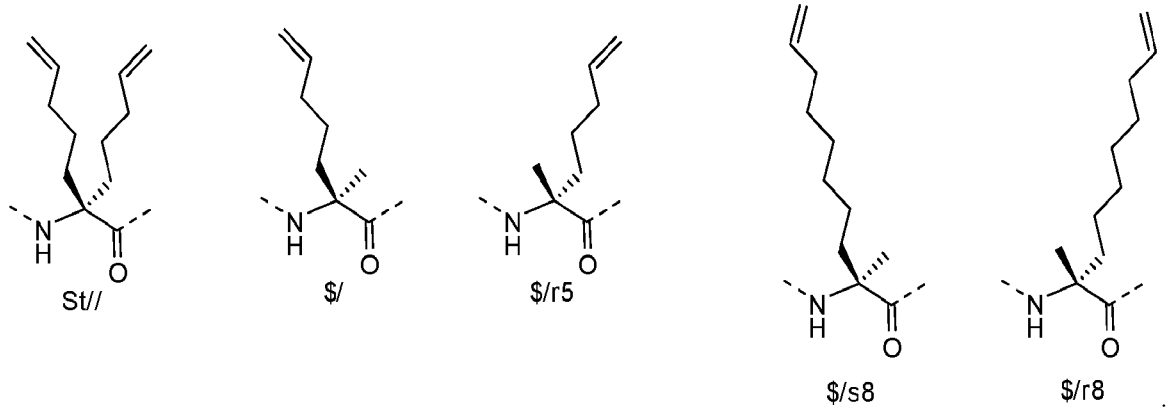
SP#	Ch	L	VH	RT (min)*	Ala (%)	IC_{50} (nM)		Raji Cell Viability EC_{50} (μM)**
						MCL-1	BCL-X_L	
810	0	21	18.9	9.07	9.5	*ND*	9.2	>30
809	1	21	16.5	10.56	14.3	10.6	3.9	>30
815	0	19	9.1	15.07	21	8.4	22.4	6.6
962	0	19	8.3	17.69	21	27.0	13.0	0.7

* *See* Example 11 table
**5% serum, 48 hr
Ch = net charge; L = length in amino acids; VH= von Heijne; RT= retention time; Ala= alanine content

Preparation of Peptidomimetic Macrocycles

[00266] Peptidomimetic macrocycles can be prepared by any of a variety of methods known in the art. For example, any of the residues indicated by "$" or "$r8" in **Table 1**, **Table 1a**, **Table 1b**, or **Table 1c** can be substituted with a residue capable of forming a crosslinker with a second residue in the same molecule or a precursor of such a residue.

[00267] Various methods to effect formation of peptidomimetic macrocycles are known in the art. For example, the preparation of peptidomimetic macrocycles of Formula I is described in Schafmeister et al., J. Am. Chem. Soc. 122:5891-5892 (2000); Schafmeister & Verdine, J. Am. Chem. Soc. 122:5891 (2005); Walensky et al., Science 305:1466-1470 (2004); US Patent No. 7,192,713 and PCT application WO 2008/121767. The α,α-disubstituted amino acids and amino acid precursors disclosed in the cited references can be employed in synthesis of the peptidomimetic macrocycle precursor polypeptides. For example, the "S5-olefin amino acid" is (S)-α-(2'-pentenyl) alanine and the "R8 olefin amino acid" is (R)-α-(2'-octenyl) alanine. Following incorporation of such amino acids into precursor polypeptides, the terminal olefins are reacted with a metathesis catalyst, leading to the formation of the peptidomimetic macrocycle. In various embodiments, the following amino acids can be employed in the synthesis of the peptidomimetic macrocycle:



[00268] In other embodiments, the peptidomimetic macrocycles are of Formula IV or IVa. Methods for the preparation of such macrocycles are described, for example, in US Patent No. 7,202,332.

[00269] Additional methods of forming peptidomimetic macrocycles which are envisioned as suitable include those disclosed by Mustapa, M. Firouz Mohd et al., J. Org. Chem (2003), 68, pp. 8193-8198; Yang, Bin et al. Bioorg Med. Chem. Lett. (2004), 14, pp. 1403-1406; U.S. Patent No. 5,364,851; U.S. Patent No. 5,446,128; U.S. Patent No. 5,824,483; U.S. Patent No. 6,713,280; and U.S. Patent No. 7,202,332. In such embodiments, amino acid precursors are used containing an additional substituent R- at the alpha position. Such amino acids are incorporated into the macrocycle precursor at the desired positions, which can be at the positions where the crosslinker is substituted or, alternatively, elsewhere in the sequence of the macrocycle precursor. Cyclization of the precursor is then effected according to the indicated method.

Assays

[00270] The properties of peptidomimetic macrocycles are assayed, for example, by using the methods described below. In some embodiments, a peptidomimetic macrocycle has improved biological properties relative to a corresponding polypeptide lacking the substituents described herein.

[00271] A peptidomimetic macrocycle with enhanced cell penetrability can be prepared based on one or more properties of the polypeptide. In some embodiments, a peptidomimetic macrocycle with enhanced cell penetrability can be prepared based on a length of the amino acid sequence of the polypeptide. In some embodiments, a peptidomimetic macrocycle with enhanced cell penetrability can be prepared based on a von Heijne value of the polypeptide. In some embodiments, a peptidomimetic macrocycle with enhanced cell penetrability can be prepared based on a net charge carried by the polypeptide.

[00272] In some embodiments, a peptidomimetic macrocycle with enhanced cell penetrability can be prepared based on an alanine content in the amino acid sequence of the polypeptide. In some embodiments, a peptidomimetic macrocycle with enhanced cell penetrability can be prepared based on an amphipathicity of the polypeptide. In some embodiments, a peptidomimetic macrocycle with enhanced cell penetrability can be prepared based on a solubility of the polypeptide. In some embodiments, a peptidomimetic macrocycle with enhanced cell penetrability can be prepared based on a reverse-phase HPLC retention time of the polypeptide. In some embodiments, a peptidomimetic macrocycle with enhanced cell penetrability can be prepared based on a length of the amino acid sequence of the polypeptide, a von Heijne value of the polypeptide, a net charge carried by the polypeptide, an alanine content in the amino acid sequence of the polypeptide, an amphipathicity of the polypeptide, a solubility of the polypeptide, a reverse-phase HPLC retention time of the polypeptide, or any combination thereof.

[00273] A peptidomimetic macrocycle with enhanced cell penetrability can be prepared based on the length of the polypeptide. In some embodiments, the length of the prepared peptidomimetic macrocycle ranges from 10-24 amino acids. For example, the length of the prepared peptidomimetic macrocycle is 10 amino acids, 11 amino acids, 12 amino acids, 13 amino acids, 14 amino acids, 15 amino acids, 16 amino acids, 17 amino acids, 18 amino acids, 19 amino acids, 20 amino acids, 21 amino acids, 22 amino acids, 23 amino acids, or 24 amino acids. For example, the length of the prepared peptidomimetic macrocycle ranges from 10-23, 10-22, 10-21, 10-20, 10-19, 10-18, 10-17, 10-16, 10-15, 10-14, 10-13, or 10-12 amino acids. For example, the length of the prepared peptidomimetic macrocycle ranges from 11-24, 12-24, 13-24, 14-24, 15-24, 16-24, 17-24, 18-24, 19-24, 20-24, 21-24, or 22-24 amino acids. In some embodiments, the length of the prepared peptidomimetic macrocycle ranges from 11 amino acids to 23 amino acids. For example, the length of the prepared peptidomimetic macrocycle ranges from 11-22, 11-21, 11-20, 11-19, 11-18, 11-17, 11-16, 11-15, 11-14, or 11-13 amino acids. For example, the length of the prepared peptidomimetic macrocycle ranges from 12-23, 13-23, 14-23, 15-23, 16-23, 17-23, 18-23, 19-23, 20-23, or 21-23 amino acids. In some embodiments, the length of the prepared peptidomimetic macrocycle ranges from 12 amino acids to 22 amino acids. For example, the length of the prepared peptidomimetic macrocycle ranges from 12-21, 12-20, 12-19, 12-18, 12-17, 12-16, 12-15, or 12-14 amino acids. For example, the length of the prepared peptidomimetic macrocycle ranges from 13-22, 14-22, 15-22, 16-22, 17-22, 18-22, 19-22, or 20-22 amino acids. In some embodiments, the length of the prepared peptidomimetic macrocycle ranges from 13 amino acids to 21 amino acids. For example, the length of the prepared

peptidomimetic macrocycle ranges from 13-20, 13-19, 13-18, 13-17, 13-16, or 13-15 amino acids. For example, the length of the prepared peptidomimetic macrocycle ranges from 14-21, 15-21, 16-21, 17-21, 18-21, or 19-21 amino acids. In some embodiments, the length of the prepared peptidomimetic macrocycle ranges from 14 amino acids to 20 amino acids. For example, the length of the prepared peptidomimetic macrocycle ranges from -19, 14-18, 14-17, or 14-16 amino acids. For example, the length of the prepared peptidomimetic macrocycle ranges from 15-20, 16-20, 17-20, or 18-20 amino acids. In some embodiments, the length of the prepared peptidomimetic macrocycle ranges from 15 amino acids to 19 amino acids. For example, the length of the prepared peptidomimetic macrocycle ranges from 15-18 or 15-17 amino acids. For example, the length of the prepared peptidomimetic macrocycle ranges from 16-19 or 17-19 amino acids. In some embodiments, the length of the prepared peptidomimetic macrocycle ranges from 16 amino acids to 18 amino acids. For example, the length of the prepared peptidomimetic macrocycle is 17. In some embodiments, the length of the prepared peptidomimetic macrocycle is 14. In some embodiments, the length of the prepared peptidomimetic macrocycle is 15. In some embodiments, the length of the prepared peptidomimetic macrocycle is 16. In some embodiments, the length of the prepared peptidomimetic macrocycle is 17. In some embodiments, the length of the prepared peptidomimetic macrocycle is 18. In some embodiments, the length of the prepared peptidomimetic macrocycle is 19. In some embodiments, the length of the prepared peptidomimetic macrocycle is 20. In some embodiments, the length of the prepared peptidomimetic macrocycle is 21.

[00274] A peptidomimetic macrocycle with enhanced cell penetrability can be prepared based on the von Heijne value of the polypeptide. In some embodiments, the von Heijne value of the prepared peptidomimetic macrocycle ranges from 2 to 9. For example, the von Heijne value of the prepared peptidomimetic macrocycle is 2, 3, 4, 5, 6, 7, 8, or 9, along with all values in between. For example, the von Heijne value of the prepared peptidomimetic macrocycle ranges from 2-8, 2-7, 2-6, 2-5, 2-4, or 2-3. For example, the von Heijne value of the prepared peptidomimetic macrocycle ranges from 3-9, 4-9, 5-9, 6-9, 7-9, or 8-9. In some embodiments, the von Heijne value of the prepared peptidomimetic macrocycle ranges from 3 to 8. For example, the von Heijne value of the prepared peptidomimetic macrocycle ranges from 3-7, 3-6, 3-5, or 3-4. For example, the von Heijne value of the prepared peptidomimetic macrocycle ranges from 4-8, 5-8, 6-8, or 7-9.

[00275] In some embodiments, the von Heijne value of the prepared peptidomimetic macrocycle ranges from 4 to 7. For example, the von Heijne value of the prepared peptidomimetic macrocycle ranges from 4-6 or 4-5. For example, the von Heijne value of the prepared peptidomimetic macrocycle ranges from 5-7 or 5-6. In some embodiments, the von Heijne value of the prepared peptidomimetic macrocycle ranges from 4-6. In some embodiments, the von Heijne value of the prepared peptidomimetic macrocycle ranges from 4-5. In some embodiments, the von Heijne value of the prepared peptidomimetic macrocycle ranges from 4.5-5.5, including 4.5, 4.6, 4.7, 4.8, 4.9, 5.0, 5.1, 5.2, 5.3, 5.4, and 5.5 along with all values in between. In some embodiments, the von Heijne value of the prepared peptidomimetic macrocycle ranges from 4.5-9.5. For example, the von Heijne

value of the prepared peptidomimetic macrocycle ranges from 4.5-8.5, 4.5-7.5, 4.5-6.5, 5.5-9.5, 5.5-8.5, 5.5-7.5, 5.5-6.5, 6.5-9.5, 6.5-8.5, 6.5-7.5, 7.5-9.5, or 7.5-8.5.

[00276] A peptidomimetic macrocycle with enhanced cell penetrability can be prepared based on the net charge carried by a peptide. For example, peptidomimetic macrocycles carrying a high number of negative charges can have poor cell permeability. A peptidomimetic macrocycle carrying a high number of positive charges can have good cell permeability, but can cause undesired cell damage (*e.g.*, cell lysis). A prepared peptidomimetic macrocycle can carry a net charge such that the polypeptide is cell permeable, but not damaging to cells (*e.g.*, does not cause cell lysis). In some embodiments, the net charge of the prepared peptidomimetic macrocycle ranges from -4 to +2, including -4, -3, -2, -1, 0, +1, and +2. In some embodiments, the net charge of the prepared peptidomimetic macrocycle ranges from -3 to +1, including -3, -2, -1, 0 and +1.

[00277] In some embodiments, the net charge of the prepared peptidomimetic macrocycle ranges from -2 to 0, including -2, -1, and 0. In some embodiments, the net charge of the prepared peptidomimetic macrocycle is zero or negative. In some embodiments, the net charge of the prepared peptidomimetic macrocycle is not positive. In some embodiments, the net charge of the prepared peptidomimetic macrocycle is zero or is not positive. In some embodiments, the net charge of the prepared peptidomimetic macrocycle is -2. In some embodiments, the net charge of the prepared peptidomimetic macrocycle is -1. In some embodiments, the net charge of the prepared peptidomimetic macrocycle is 0.

[00278] A peptidomimetic macrocycle with enhanced cell penetrability can be prepared based on the alanine content of the polypeptide. In some embodiments, the alanine content of the prepared peptidomimetic macrocycle ranges from 15% to 50%. For example, the alanine content of the prepared peptidomimetic macrocycle can be 15%, 16%, 17%, 18%, 19%, 20%, 21%, 22%, 23%, 24%, 25%, 26%, 27%, 28%, 29%, 30%, 31%, 32%, 33%, 34%, 35%, 36%, 37%, 38%, 39%, 40%, 41%, 42%, 43%, 44%, 45%, 46%, 47%, 48%, 49%, and 50%, along with all values in between. In some embodiments, the alanine content of the prepared peptidomimetic macrocycle ranges from 15% to 45%. In some embodiments, the alanine content of the prepared peptidomimetic macrocycle ranges from 15% to 40%. In some embodiments, the alanine content of the prepared peptidomimetic macrocycle ranges from 15% to 35%. In some embodiments, the alanine content of the prepared peptidomimetic macrocycle ranges from 20% to 50%. In some embodiments, the alanine content of the prepared peptidomimetic macrocycle ranges from 20% to 45%. In some embodiments, the alanine content of the prepared peptidomimetic macrocycle ranges from 20% to 40%. In some embodiments, the alanine content of the prepared peptidomimetic macrocycle ranges from 20% to 35%. In some embodiments, the alanine content of the prepared peptidomimetic macrocycle ranges from 20% to 30%. In some embodiments, the alanine content of the prepared peptidomimetic macrocycle ranges from 20% to 25%. In some embodiments, the alanine content of the prepared peptidomimetic macrocycle ranges from 25% to 50%. In some embodiments, the alanine content of the prepared peptidomimetic macrocycle ranges from 25% to 45%. In some embodiments, the alanine content of the prepared peptidomimetic macrocycle ranges from 25% to 40%. For example, the alanine content of the prepared peptidomimetic macrocycle can be

25%, 26%, 27%, 28%, 29%, 30%, 31%, 32%, 33%, 34%, 35%, 36%, 37%, 38%, 39%, and 40% along with all values in between. In some embodiments, the alanine content of the prepared peptidomimetic macrocycle ranges from 25% to 35%. In some embodiments, the alanine content of the prepared peptidomimetic macrocycle ranges from 25% to 30%. In some embodiments, the alanine content of the prepared peptidomimetic macrocycle ranges from 30% to 50%. In some embodiments, the alanine content of the prepared peptidomimetic macrocycle ranges from 30% to 45%. In some embodiments, the alanine content of the prepared peptidomimetic macrocycle ranges from 30% to 40%. In some embodiments, the alanine content of the prepared peptidomimetic macrocycle ranges from 30% to 35%. In some embodiments, the alanine content of the prepared peptidomimetic macrocycle ranges from 35% to 50%. In some embodiments, the alanine content of the prepared peptidomimetic macrocycle ranges from 35% to 45%. In some embodiments, the alanine content of the prepared peptidomimetic macrocycle ranges from 35% to 40%.

[00279] A peptidomimetic macrocycle with enhanced cell penetrability can be prepared based on the length and the von Heijne value of the polypeptide. For example, the length of the prepared peptidomimetic macrocycle ranges from 10 amino acids to 24 amino acids, from 11 amino acids to 23 amino acids, from 12 amino acids to 22 amino acids, from 13 amino acids to 21 amino acids, from 14 amino acids to 20 amino acids, from 15 amino acids to 19 amino acids, or from 16 amino acids to 18 amino acids, and the von Heijne value of the prepared peptidomimetic macrocycle ranges from 2 to 9, from 3 to 8, from 4 to 7, from 4 to 6, or from 4 to 5. For example, the length of the prepared peptidomimetic macrocycle is 10 amino acids, 11 amino acids, 12 amino acids, 13 amino acids, 14 amino acids, 15 amino acids, 16 amino acids, 17 amino acids, 18 amino acids, 19 amino acids, 20 amino acids, or 21 amino acids, and the von Heijne value of the prepared peptidomimetic macrocycle ranges from 4.5 to 5.5. For example, the prepared peptidomimetic macrocycle has a length ranging from 14 amino acids to 20 amino acids, and a von Heijne value ranging from 4 and 7.

[00280] A peptidomimetic macrocycle with enhanced cell penetrability can be prepared based on the length and the alanine content of the polypeptide. For example, the length of the prepared peptidomimetic macrocycle ranges from 10 amino acids to 24 amino acids, from 11 amino acids to 23 amino acids, from 12 amino acids to 22 amino acids, from 13 amino acids to 21 amino acids, from 14 amino acids to 20 amino acids, from 15 amino acids to 19 amino acids, or from 16 amino acids to 18 amino acids, and the alanine content of the prepared peptidomimetic macrocycle ranges from 15% to 50%, including 15%, 16%, 17%, 18%, 19%, 20%, 21%, 22%, 23%, 24%, 25%, 26%, 27%, 28%, 29%, 30%, 31%, 32%, 33%, 34%, 35%, 36%, 37%, 38%, 39%, 40%, 41%, 42%, 43%, 44%, 45%, 46%, 47%, 48%, 49%, and 50% along with all values in between. For example, the length of the prepared peptidomimetic macrocycle is 10 amino acids, 11 amino acids, 12 amino acids, 13 amino acids, 14 amino acids, 15 amino acids, 16 amino acids, 17 amino acids, 18 amino acids, 19 amino acids, 20 amino acids, or 21 amino acids, and the alanine content of the prepared peptidomimetic macrocycle ranges from 25% to 40%, including 25%, 26%, 27%, 28%, 29%, 30%, 31%, 32%, 33%, 34%, 35%, 36%, 37%, 38%, 39%, and 40% along with all

values in between. For example, the prepared peptidomimetic macrocycle has a length ranging from 14 amino acids to 20 amino acids, and an alanine content ranging from 25% to 40%.

[00281] A peptidomimetic macrocycle with enhanced cell penetrability can be prepared based on the length and the net charge of the polypeptide. For example, the length of the prepared peptidomimetic macrocycle ranges from 10 amino acids to 24 amino acids, from 11 amino acids to 23 amino acids, from 12 amino acids to 22 amino acids, from 13 amino acids to 21 amino acids, from 14 amino acids to 20 amino acids, from 15 amino acids to 19 amino acids, or from 16 amino acids to 18 amino acids, and the net charge of the prepared peptidomimetic macrocycle ranges from -3 to 1, including -3, -2, -1, 0 and 1. For example, the length of the prepared peptidomimetic macrocycle is 10 amino acids, 11 amino acids, 12 amino acids, 13 amino acids, 14 amino acids, 15 amino acids, 16 amino acids, 17 amino acids, 18 amino acids, 19 amino acids, 20 amino acids, or 21 amino acids, and the net charge of the prepared peptidomimetic macrocycle ranges from -3 to 1, including -3, -2, -1, 0 and 1. For example, the prepared peptidomimetic macrocycle has a length ranging from 14 amino acids to 20 amino acids, and a net charge ranging from -2 to 0.

[00282] A peptidomimetic macrocycle with enhanced cell penetrability can be prepared based on the von Heijne value and the net charge of the polypeptide. For example, the von Heijne value of the prepared peptidomimetic macrocycle ranges from 2 to 9, from 3 to 8, from 4 to 7, from 4 to 6, or from 4 to 5, and the net charge of the prepared peptidomimetic macrocycle ranges from -3 to 1, including -3, -2, -1, 0 and 1. For example, the von Heijne value of the prepared peptidomimetic macrocycle ranges from 4.5 to 5.5, including 4.5, 4.6, 4.7, 4.8, 4.9, 5.0, 5.1, 5.2, 5.3, 5.4, and 5.5 along with all values in between, and the net charge of the prepared peptidomimetic macrocycle ranges from -3 to 1, including -3, -2, -1, 0 and 1. For example, the prepared peptidomimetic macrocycle has a von Heijne value ranging from 4 and 7, and a net charge ranging from -2 to 0.

[00283] A peptidomimetic macrocycle with enhanced cell penetrability can be prepared based on the von Heijne value and the alanine content of the polypeptide. For example, the von Heijne value of the prepared peptidomimetic macrocycle ranges from 2 to 9, from 3 to 8, from 4 to 7, from 4 to 6, or from 4 to 5, and the alanine content of the prepared peptidomimetic macrocycle ranges from 15% to 50%, including 15%, 16%, 17%, 18%, 19%, 20%, 21%, 22%, 23%, 24%, 25%, 26%, 27%, 28%, 29%, 30%, 31%, 32%, 33%, 34%, 35%, 36%, 37%, 38%, 39%, 40%, 41%, 42%, 43%, 44%, 45%, 46%, 47%, 48%, 49%, and 50% along with all values in between. For example, the von Heijne value of the prepared peptidomimetic macrocycle ranges from 4.5 to 5.5, including 4.5, 4.6, 4.7, 4.8, 4.9, 5.0, 5.1, 5.2, 5.3, 5.4, and 5.5 along with all values in between, and the alanine content of the prepared peptidomimetic macrocycle ranges from 25% to 40%, including 25%, 26%, 27%, 28%, 29%, 30%, 31%, 32%, 33%, 34%, 35%, 36%, 37%, 38%, 39%, and 40% along with all values in between. For example, the prepared peptidomimetic macrocycle has a von Heijne value ranging from 4 and 7, and an alanine content ranging from 25% to 40%.

[00284] A peptidomimetic macrocycle with enhanced cell penetrability can be prepared based on length, von Heijne value and alanine content of the polypeptide. For example, the prepared peptidomimetic macrocycle has a

length ranging from 14 amino acids to 20 amino acids, a von Heijne value ranging from 4 and 7, and an alanine content ranging from 25% to 40%.

[00285] A peptidomimetic macrocycle with enhanced cell penetrability can be prepared based on the von Heijne value and the net charge of the polypeptide. For example, the prepared peptidomimetic macrocycle has a length ranging from 14 amino acids to 20 amino acids, a von Heijne value ranging from 4 and 7, and a net charge ranging from -2 to 0.

[00286] A peptidomimetic macrocycle with enhanced cell penetrability can be prepared based on the von Heijne value, the net charge, and the alanine content of the polypeptide. For example, the prepared peptidomimetic macrocycle has a von Heijne value ranging from 4 and 7, a net charge ranging from -2 to 0, and an alanine content ranging from 25% to 40%.

[00287] A peptidomimetic macrocycle with enhanced cell penetrability can be prepared based on the length, the net charge, and the alanine content of the polypeptide. For example, the prepared peptidomimetic macrocycle has a length ranging from 14 amino acids to 20 amino acids, a net charge ranging from -2 to 0, and an alanine content ranging from 25% to 40%.

[00288] A peptidomimetic macrocycle with enhanced cell penetrability can be prepared based on the length of its amino acid sequence, its von Heijne value, its net charge, and the alanine content of its amino acid sequence. For example, the prepared peptidomimetic macrocycle has a length ranging from 14 amino acids to 20 amino acids, a von Heijne value ranging from 4 and 7, a net charge ranging from -2 to 0, and an alanine content ranging from 25% to 40%.

[00289] In some embodiments, a peptidomimetic macrocycle with enhanced cell penetrability can be prepared based on the reverse-phase HPLC retention time of the polypeptide.

[00290] In some embodiments, a peptidomimetic macrocycle with enhanced cell penetrability can be prepared based on amphipathicity of the polypeptide.

[00291] In some embodiments, a peptidomimetic macrocycle with enhanced cell penetrability can be prepared based on solubility of the polypeptide, for example if the prepared peptidomimetic macrocycle is determined to be soluble based on visual examination of the turbidity of a solution of the polypeptide.

[00292] Assay to Determine α-helicity

[00293] In solution, the secondary structure of polypeptides with α-helical domains will reach a dynamic equilibrium between random coil structures and α-helical structures, often expressed as a "percent helicity". Thus, for example, alpha-helical domains are predominantly random coils in solution, with α-helical content usually under 25%. Peptidomimetic macrocycles with optimized linkers, on the other hand, possess, for example, an alpha-helicity that is at least two-fold greater than that of a corresponding uncrosslinked polypeptide. In some embodiments, macrocycles will possess an alpha-helicity of greater than 50%. To assay the helicity of peptidomimetic macrocycles, the compounds are dissolved in an aqueous solution (e.g. 50 mM potassium phosphate solution at pH 7, or distilled H_2O, to concentrations of 25-50 μM). Circular dichroism (CD) spectra are

obtained on a spectropolarimeter (*e.g.*, Jasco J-710) 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 (e.g. [Φ]222obs) by the reported value for a model helical decapeptide (Yang *et al.* (1986), *Methods Enzymol.* 130:208)).

[00294] Assay to Determine Melting Temperature (Tm)

[00295] A peptidomimetic macrocycle comprising a secondary structure such as an α-helix exhibits, for example, a higher melting temperature than a corresponding uncrosslinked polypeptide. Typically peptidomimetic macrocycles exhibit Tm of > 60°C representing a highly stable structure in aqueous solutions. To assay the effect of macrocycle formation on melting temperature, peptidomimetic macrocycles or unmodified peptides are dissolved in distilled H_2O (e.g. at a final concentration of 50 μM) and the Tm 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) using standard parameters (e.g. wavelength 222nm; 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).

[00296] Protease Resistance Assay

[00297] 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 the amide backbone and therefore can shield it from proteolytic cleavage. The peptidomimetic macrocycles can be subjected to *in vitro* trypsin proteolysis to assess for any change in degradation rate compared to a corresponding uncrosslinked 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 (k=-1Xslope).

[00298] *Ex Vivo* Stability Assay

[00299] Peptidomimetic macrocycles with optimized linkers possess, for example, an *ex vivo* half-life that is at least two-fold greater than that of a corresponding uncrosslinked polypeptide, and possess an *ex vivo* half-life of 12 hours or more. For *ex vivo* serum stability studies, a variety of assays can be used. For example, a peptidomimetic macrocycle and a corresponding uncrosslinked polypeptide (2 mcg) are incubated with fresh mouse, rat and/or human serum (2 mL) at 37°C for 0, 1, 2, 4, 8, and 24 hours. To determine the level of intact compound, the following procedure can be used: The samples are extracted by transferring 100 μl of sera to 2 ml centrifuge tubes followed by the addition of 10 μL of 50 % formic acid and 500μL acetonitrile and centrifugation

at 14,000 RPM for 10 min at 4 ± 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 100µL of 50:50 acetonitrile:water and submitted to LC-MS/MS analysis.

[00300] *In vitro* Binding Assays

[00301] To assess the binding and affinity of peptidomimetic macrocycles and peptidomimetic precursors to acceptor proteins, a fluorescence polarization assay (FPA) 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 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 fluorescent tracers attached to smaller molecules (*e.g.* FITC- labeled peptides that are free in solution).

[00302] For example, fluoresceinated peptidomimetic macrocycles (25 nM) are incubated with the acceptor protein (25- 1000nM) in binding buffer (140mM NaCl, 50 mM Tris-HCL, pH 7.4) for 30 minutes at room temperature. Binding activity is measured, for example, by fluorescence polarization on a luminescence spectrophotometer (e.g. Perkin-Elmer LS50B). Kd values can be determined by nonlinear regression analysis using, for example, Graphpad Prism software (GraphPad Software, Inc., San Diego, CA). A peptidomimetic macrocycle shows, In some embodiments, similar or lower Kd than a corresponding uncrosslinked polypeptide.

[00303] *In vitro* Displacement Assays To Characterize Antagonists of Peptide-Protein Interactions

[00304] 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 peptidomimetic macrocycle derived from a peptidomimetic precursor 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 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 fluorescent tracers attached to smaller molecules (*e.g.* FITC-labeled peptides that are free in solution). A compound that antagonizes the interaction between the fluoresceinated peptidomimetic macrocycle and an acceptor protein will be detected in a competitive binding FPA experiment.

[00305] For example, putative antagonist compounds (1 nM to 1 mM) and a fluoresceinated peptidomimetic macrocycle (25 nM) are incubated with the acceptor protein (50 nM) in binding buffer (140mM NaCl, 50 mM Tris-HCL, pH 7.4) for 30 minutes at room temperature. Antagonist binding activity is measured, for example, by fluorescence polarization on a luminescence spectrophotometer (e.g. Perkin-Elmer LS50B). Kd values can be determined by nonlinear regression analysis using, for example, Graphpad Prism software (GraphPad Software, Inc., San Diego, CA).

Any class of molecule, such as small organic molecules, peptides, oligonucleotides or proteins can be examined as putative antagonists in this assay.

Assay for Protein-ligand binding by Affinity Selection-Mass Spectrometry

To assess the binding and affinity of test compounds for proteins, an affinity-selection mass spectrometry assay is used, for example. Protein-ligand binding experiments are conducted according to the following representative procedure outlined for a system-wide control experiment using 1 μM peptidomimetic macrocycle plus 5 μM hMDM2. A 1 μL DMSO aliquot of a 40 μM stock solution of peptidomimetic macrocycle is dissolved in 19 μL of PBS (Phosphate-buffered saline: 50 mM, pH 7.5 Phosphate buffer containing 150 mM NaCl). The resulting solution is mixed by repeated pipetting and clarified by centrifugation at 10 000g for 10 min. To a 4 μL aliquot of the resulting supernatant is added 4 μL of 10 μM hMDM2 in PBS. Each 8.0 μL experimental sample thus contains 40 pmol (1.5 μg) of protein at 5.0 μM concentration in PBS plus 1 μM peptidomimetic macrocycle and 2.5% DMSO. Duplicate samples thus prepared for each concentration point are incubated for 60 min at room temperature, and then chilled to 4 °C prior to size-exclusion chromatography-LC-MS analysis of 5.0 μL injections. Samples containing a target protein, protein–ligand complexes, and unbound compounds are injected onto an SEC column, where the complexes are separated from non-binding component by a rapid SEC step. The SEC column eluate is monitored using UV detectors to confirm that the early-eluting protein fraction, which elutes in the void volume of the SEC column, is well resolved from unbound components that are retained on the column. After the peak containing the protein and protein–ligand complexes elutes from the primary UV detector, it enters a sample loop where it is excised from the flow stream of the SEC stage and transferred directly to the LC-MS via a valving mechanism. The $(M + 3H)^{3+}$ ion of the peptidomimetic macrocycle is observed by ESI-MS at the expected m/z, confirming the detection of the protein-ligand complex.

[00306] Assay for Protein-ligand Kd Titration Experiments

[00307] To assess the binding and affinity of test compounds for proteins, a protein-ligand Kd titration experiment is performed, for example. Protein-ligand K_d titrations experiments are conducted as follows: 2 μL DMSO aliquots of a serially diluted stock solution of titrant peptidomimetic macrocycle (5, 2.5, ..., 0.098 mM) are prepared then dissolved in 38 μL of PBS. The resulting solutions are mixed by repeated pipetting and clarified by centrifugation at 10 000g for 10 min. To 4.0 μL aliquots of the resulting supernatants is added 4.0 μL of 10 μM hMDM2 in PBS. Each 8.0 μL experimental sample thus contains 40 pmol (1.5 μg) of protein at 5.0 μM concentration in PBS, varying concentrations (125, 62.5, ..., 0.24 μM) of the titrant peptide, and 2.5% DMSO. Duplicate samples thus prepared for each concentration point are incubated at room temperature for 30 min, then chilled to 4 °C prior to SEC-LC-MS analysis of 2.0 μL injections. The $(M + H)^{1+}$, $(M + 2H)^{2+}$, $(M + 3H)^{3+}$, and/or $(M + Na)^{1+}$ ion is observed by ESI-MS; extracted ion chromatograms are quantified, then fit to equations to derive the binding affinity K_d as described in "*A General Technique to Rank Protein-Ligand Binding Affinities and Determine Allosteric vs. Direct Binding Site Competition in Compound Mixtures*." Annis, D. A.; Nazef, N.; Chuang, C. C.; Scott, M. P.; Nash, H. M. *J. Am. Chem. Soc.* **2004**, *126*, 15495-15503; also in "*ALIS: An Affinity Selection-Mass Spectrometry System for the Discovery and Characterization of Protein-Ligand Interactions*" D. A. Annis, C.-C. Chuang, and N. Nazef. In Mass Spectrometry in Medicinal Chemistry. Edited by Wanner K,

Höfner G: Wiley-VCH; **2007**:121-184. Mannhold R, Kubinyi H, Folkers G (Series Editors): Methods and Principles in Medicinal Chemistry.

[00308] Assay for Competitive Binding Experiments by Affinity Selection-Mass Spectrometry

[00309] To determine the ability of test compounds to bind competitively to proteins, an affinity selection mass spectrometry assay is performed, for example. A mixture of ligands at 40 μM per component is prepared by combining 2 μL aliquots of 400 μM stocks of each of the three compounds with 14 μL of DMSO. Then, 1 μL aliquots of this 40 μM per component mixture are combined with 1 μL DMSO aliquots of a serially diluted stock solution of titrant peptidomimetic macrocycle (10, 5, 2.5, ..., 0.078 mM). These 2 μL samples are dissolved in 38 μL of PBS. The resulting solutions were mixed by repeated pipetting and clarified by centrifugation at 10 000g for 10 min. To 4.0 μL aliquots of the resulting supernatants is added 4.0 μL of 10 μM hMDM2 protein in PBS. Each 8.0 μL experimental sample thus contains 40 pmol (1.5 μg) of protein at 5.0 μM concentration in PBS plus 0.5 μM ligand, 2.5% DMSO, and varying concentrations (125, 62.5, ..., 0.98 μM) of the titrant peptidomimetic macrocycle. Duplicate samples thus prepared for each concentration point are incubated at room temperature for 60 min, then chilled to 4 °C prior to SEC-LC-MS analysis of 2.0 μL injections. Additional details on these and other methods are provided in "*A General Technique to Rank Protein-Ligand Binding Affinities and Determine Allosteric vs. Direct Binding Site Competition in Compound Mixtures*." Annis, D. A.; Nazef, N.; Chuang, C. C.; Scott, M. P.; Nash, H. M. *J. Am. Chem. Soc.* **2004**, *126*, 15495-15503; also in "*ALIS: An Affinity Selection-Mass Spectrometry System for the Discovery and Characterization of Protein-Ligand Interactions*" D. A. Annis, C.-C. Chuang, and N. Nazef. In Mass Spectrometry in Medicinal Chemistry. Edited by Wanner K, Höfner G: Wiley-VCH; **2007**:121-184. Mannhold R, Kubinyi H, Folkers G (Series Editors): Methods and Principles in Medicinal Chemistry.

[00310] Binding Assays in Intact Cells

[00311] It is possible to measure binding of peptides or peptidomimetic macrocycles to their natural acceptors in intact cells by immunoprecipitation experiments. For example, intact cells are incubated with fluoresceinated (FITC-labeled) compounds for 4 hrs in the absence of serum, followed by serum replacement and further incubation that ranges from 4-18 hrs. Cells are then pelleted and incubated in lysis buffer (50mM Tris [pH 7.6], 150 mM NaCl, 1% CHAPS and protease inhibitor cocktail) for 10 minutes at 4°C. Extracts are centrifuged at 14,000 rpm for 15 minutes and supernatants collected and incubated with 10 μl goat anti-FITC antibody for 2 hrs, rotating at 4°C followed by further 2 hrs incubation at 4°C with protein A/G Sepharose (50 μl of 50% bead slurry). After quick centrifugation, the pellets are washed in lysis buffer containing increasing salt concentration (*e.g.*, 150, 300, 500 mM). The beads are then re-equilibrated at 150 mM NaCl before addition of SDS-containing sample buffer and boiling. After centrifugation, the supernatants are optionally electrophoresed using 4%-12% gradient Bis-Tris gels followed by transfer into Immobilon-P membranes. After blocking, blots are optionally incubated with an antibody that detects FITC and also with one or more antibodies that detect proteins that bind to the peptidomimetic macrocycle.

[00312] Cellular Penetrability Assays

[00313] A peptidomimetic macrocycle is, for example, more cell penetrable compared to a corresponding uncrosslinked macrocycle. Peptidomimetic macrocycles with optimized linkers possess, for example, cell penetrability that is at least two-fold greater than a corresponding uncrosslinked macrocycle, and often 20% or more of the applied peptidomimetic macrocycle will be observed to have penetrated the cell after 4 hours. To measure the cell penetrability of peptidomimetic macrocycles and corresponding uncrosslinked macrocycle, intact cells are incubated with fluorescently-labeled (e.g. fluoresceinated) peptidomimetic macrocycles or corresponding uncrosslinked macrocycle (10 μM) for 4 hrs in serum free media 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 ® HCS Reader.

[00314] Cellular Efficacy Assays

[00315] The efficacy of certain peptidomimetic macrocycles is determined, for example, in cell-based killing assays using a variety of tumorigenic and non-tumorigenic cell lines and primary cells derived from human or mouse cell populations. Cell viability is monitored, for example, over 24-96 hrs of incubation with peptidomimetic macrocycles (0.5 to 50 μM) to identify those that kill at EC_{50}<10 μM. Several standard assays that measure cell viability are commercially available and are optionally used to assess the efficacy of the peptidomimetic macrocycles. In addition, assays that measure Annexin V and caspase activation are optionally used to assess whether the peptidomimetic macrocycles kill cells by activating the apoptotic machinery. For example, the Cell Titer-glo assay is used which determines cell viability as a function of intracellular ATP concentration.

[00316] *In Vivo* Stability Assay

[00317] To investigate the *in vivo* stability of the peptidomimetic macrocycles, the compounds are, for example, administered to mice and/or rats by IV, IP, PO or inhalation routes at concentrations ranging from 0.1 to 50 mg/kg and blood specimens withdrawn at 0', 5', 15', 30', 1 hr, 4 hrs, 8 hrs and 24 hours post-injection. Levels of intact compound in 25 μL of fresh serum are then measured by LC-MS/MS as above.

[00318] *In vivo* Efficacy in Animal Models

[00319] To determine the anti-oncogenic activity of peptidomimetic macrocycles *in vivo*, the compounds are, for example, given alone (IP, IV, PO, by inhalation or nasal routes) or in combination with sub-optimal doses of relevant chemotherapy (*e.g.*, cyclophosphamide, doxorubicin, etoposide). In one example, 5 x 10^6 RS4;11 cells (established from the bone marrow of a patient with acute lymphoblastic leukemia) that stably express luciferase are injected by tail vein in NOD-SCID mice 3 hrs after they have been subjected to total body irradiation. If left untreated, this form of leukemia is fatal in 3 weeks in this model. The leukemia is readily monitored, for example, by injecting the mice with D-luciferin (60 mg/kg) and imaging the anesthetized animals (*e.g.*, Xenogen In Vivo Imaging System, Caliper Life Sciences, Hopkinton, MA). Total body bioluminescence is quantified by integration

of photonic flux (photons/sec) by Living Image Software (Caliper Life Sciences, Hopkinton, MA). Peptidomimetic macrocycles alone or in combination with sub-optimal doses of relevant chemotherapeutics agents are, for example, administered to leukemic mice (10 days after injection/day 1 of experiment, in bioluminescence range of 14-16) by tail vein or IP routes at doses ranging from 0.1mg/kg to 50 mg/kg for 7 to 21 days. Optionally, the mice are imaged throughout the experiment every other day and survival monitored daily for the duration of the experiment. Expired mice are optionally subjected to necropsy at the end of the experiment. Another animal model is implantation into NOD-SCID mice of DoHH2, a cell line derived from human follicular lymphoma, that stably expresses luciferase. These *in vivo* tests optionally generate preliminary pharmacokinetic, pharmacodynamic and toxicology data.

[00320] Clinical Trials

[00321] To determine the suitability of the peptidomimetic macrocycles for treatment of humans, clinical trials are performed. For example, patients diagnosed with solid tumor and in need of treatment can be selected and separated in treatment and one or more control groups, wherein the treatment group is administered a peptidomimetic macrocycle, while the control groups receive a placebo or a known anti-cancer drug. The treatment safety and efficacy of the peptidomimetic macrocycles can thus be evaluated by performing comparisons of the patient groups with respect to factors such as survival and quality-of-life. In this example, the patient group treated with a peptidomimetic macrocycle can show improved long-term survival compared to a patient control group treated with a placebo.

[00322] Chemical Stability

[00323] To assay the chemical stability of the aqueous pharmaceutical formulations disclosed herein, 1 mL of the aqueous pharmaceutical formulation is filled in 2-mL vials with 13-mm Ø stoppers. The smaller vial size can help provide a greater surface-to-volume ratio which would amplify any container/closure effects on product stability. To assure that all surfaces of the vials were challenged, the vials can be stored in an inverted position. The vials are stored at the desired assay temperature, for example -20 °C, 5 °C, 20 °C, and 40 °C for the desired assay time. For example for 1, 2, 3 or 6 months. The samples are analyzed by reverse phase HPLC. **Tables 8-12** and **14-17** depict the results of this study. The samples can also be analyzed for particulate matter.

[00324] In vitro Testing for Inhibition of Influenza Replication

[00325] This influenza antiviral evaluation assay examines the effects of compounds at designated dose-response concentrations. See also Noah, J.W., W. Severson, D.L. Noah, L. Rasmussen, E.L. White, and C.B. Jonsson, Antiviral Res, 2007. 73(1): p. 50-9. Madin Darby canine kidney (MDCK) cells are used in the assay to test the efficacy of the compounds in preventing the cytopathic effect (CPE) induced by influenza infection. Either Ribavirin or Tamiflu is included in each run as a positive control compound. Subconfluent cultures of MDCK cells are plated into 96-well plates for the analysis of cell viability (cytotoxicity) and antiviral activity (CPE). Drugs are added to the cells 24 hr later. At a designated time, the CPE wells also receive 100 tissue culture infectious doses (100 TCID50s) of titered influenza virus. 72 hr later the cell viability is determined. The effective compound concentrations which reduce viral-induced CPE by 25% (IC25), 50% (IC50), and 90% (IC90) are calculated by regression analysis with semi-log curve fitting. Cell viability is assessed using CellTiter-Glo (Promega). The toxic concentration of drug that reduces cell numbers by 50% and 90% (TC50 and TC90, respectively) are calculated as well. Selectivity (therapeutic) indices (SI = TC/IC) are also calculated.

[00326] In vivo Testing for Inhibition of Influenza Replication

[00327] In vivo testing of compounds can be performed, including testing on mammals such as rats or ferrets. Because ferrets (Mustela putorius furo) are naturally susceptible to infection with human influenza A and B viruses and their disease resembles that of human influenza, these animals have been widely used as a model for influenza virus pathogenesis and immunity studies. See Sidwell, R.W. and D.F. Smee, Antiviral Res, 2000. 48(1): p. 1-16; and Colacino, J.M., D.C. DeLong, J.R. Nelson, W.A. Spitzer, J. Tang, F. Victor, and C.Y. Wu, Antimicrob Agents Chemother, 1990. 34(11): p. 2156-63. Ferrets are also the model of choice for the study of avian influenza virus H5N1 pathogenesis in mammals. See also Zitzow, L.A., T. Rowe, T. Morken, W.-J. Shieh, S. Zaki, and J.M. Katz, Pathogenesis of Avian Influenza A (H5N1) Viruses in Ferrets. 2002. p. 4420-4429. The activities of the PB1 Stapled Peptides can be compared to Ribavirin or Oseltamivir as a positive control.

[00328] Briefly, young adult male or female ferrets (five ferrets for each treatment group) that are serologically negative by hemagglutination inhibition assay for currently circulating human influenza A or B viruses are quarantined at least 4 days prior to infection in a BSL-3+ animal holding area, where they are housed in cages contained in bioclean portable laminar flow clean room enclosures (Lab Products, Seaford, Del.). Prior to infection, baseline temperatures are measured twice daily for at least 3 days. Ferrets are anesthetized with ketamine (25 mg/kg), xylazine (2 mg/kg), and atropine (0.05 mg/kg) by the intramuscular route and infected intranasally (i.n.) with virus/mL in phosphate-buffered saline (PBS) delivered to the nostrils. Control animals are mock-infected with an equivalent dilution (1:30) of noninfectious allantoic fluid. Stapled Peptides are administered i.v. or i.p. one hour after virus infection. Temperatures are measured twice daily using either a rectal thermometer or a subcutaneous implantable temperature transponder (BioMedic Data Systems, Inc., Seaford, Del.) with pre-infection values averaged to obtain a baseline temperature for each ferret. The change in temperature (in degrees Celsius) is calculated at each time point for each animal. Clinical signs of sneezing (before anesthesia), inappetence, dyspnea, and level of activity are assessed. A scoring system is also used to assess the activity level, and based on the daily scores for each animal in a group a relative inactivity index will be calculated. Rectal temperature and activity scores are used to assess the severity of influenza infection and the ability of Stapled Peptides to prevent flu symptoms

[00329] Assaying inhibition of viral polymerase complex assembly and activity

[00330] The technique of Bimolecular Fluorescence Complementation ("BiFC") can be used to assay the compounds. In this technique, N- and C-terminal fragments of fluorescent proteins (e.g. GFP or its derivatives) are fused to interacting proteins. The two non-functional halves of the fluorophore, following the expression in cells, are brought into close proximity as a result of the specific protein interactions, which initiates folding of the fragments into an active protein and results in a detectable fluorescent signal at the site of the protein-protein complex. Thus, through BiFC, the specific interaction between PB1 and PA subunits can be visualized, quantified and localized within live cells. By disrupting PB1-PA interaction with a compound, the BiFC signal will be reduced, indicative of the presence of potential inhibitors targeting the assembly of PB1-PA complex. See Hemerka et. al., J. Virol. 2009, 3944-3955.

MANUFACTURING OF THE AQUEOUS PHARMACEUTICAL FORMULATION

[00331] In another aspect of the disclosure relates to a method of making the aqueous pharmaceutical formulations disclosed herein. The method comprising the steps of dissolving at least one peptidomimetic macrocycle, or a pharmaceutically acceptable salt thereof in an aqueous solution. The method can further comprise of stirring the peptide mixture for some additional time. For example, the peptide mixture can be allowed to be stirred for an additional period of 1 min, 2 min, 3 min, 4 min, 5 min, 6 min, 7 min, 8 min, 9 min, 10 min, 15 min, 30 min, 45 min, 1 h, 1.5 h, 2 h or more.

[00332] In some embodiments, the peptidomimetic macrocycle is added to the aqueous solution at once. In some embodiments, the peptidomimetic macrocycle is added slowly to the aqueous solution, for example over a period

of at least about 1 min, 2 min, 3 min, 4 min, 5 min, 6 min, 7 min, 8 min, 9 min, 10 min, 15 min, 30 min, 45 min, 1 h, 1.5 h, 2 h or more. In some embodiments, the peptidomimetic macrocycle is added slowly over a period of at most about 2 h, 1.5 h, 1 h, 45 min, 30 min, 15 min, 10 min, 9 min, 8 min, 7 min, 6 min, 5 min, 4 min, 3 min, 2 min, 1 min or less.

[00333] The aqueous solution comprises an aqueous diluent. The amount of the aqueous diluent can be in the range of about 10-99% w/v of formulation. In some embodiments, the amount of aqueous diluent in the formulation is about 50-99% w/v. For example, the amount of aqueous diluent is in the range of about 50-95% w/v, about 50-90% w/v, about 50-85% w/v, about 50-80% w/v, about 50- 75% w/v, about 50-70% w/v, about 50-65% w/v, about 50-60% w/v, about 50-55% w/v, about 55-95% w/v, about 55-90% w/v, about 55-85% w/v, about 55-80% w/v, about 55-75% w/v, about 55-70% w/v, about 55-65% w/v, about 55-60% w/v, about 60-95% w/v, about 60-90% w/v, about 60-85% w/v, about 60-80% w/v, about 60-75% w/v, about 60-70% w/v, about 60-65% w/v, about 65-95% w/v, about 65-90% w/v, about 65-85% w/v, about 65-80% w/v, about 65-75% w/v, about 65-70% w/v, about 70-95% w/v, about 70-90% w/v, about 70-85% w/v, 70-80% w/v, about 70-75% w/v, about 75-95% w/v, about 75-90% w/v, about 75-85% w/v, about 75-80% w/v, about 70-95% w/v, about 70-90% w/v, about 70-85% w/v, about 70-80% w/v, about 70-75% w/v, about 75-95% w/v, about 75-90% w/v, about 75-85% w/v, about 75-80% w/v, about 80-95% w/v, about 80-90% w/v, about 80-85% w/v, about 85-95% w/v, about 85-90% w/v, or about 90-95% w/v. In some embodiments, the amount of aqueous diluent in a formulation is about 85-99 % w/v. In some embodiments, the amount of the aqueous diluent in a formulation is about 85% w/v, about 86% w/v, about 87 % w/v, about 88% w/v, about 89% w/v, about 90% w/v, about 91% w/v, about 92% w/v, about 93% w/v, about 94% w/v, about 95% w/v, about 96% w/v, about 97% w/v, about 98% w/v, or about 99% w/v. In some embodiments, the amount of the aqueous diluent in the formulation is about 90 % w/v. In some embodiments, the amount of the diluent in the formulation is about 10% w/v, about 20% w/v, about 30% w/v, about 40% w/v, about 50% w/v, about 60% w/v, about 70% w/v, about 80% w/v, or about 90% w/v. In some embodiments the diluent is water (for example, water for injection) and it comprises about 90% w/v of the formulation.

[00334] The amount of a peptidomimetic macrocycle in the aqueous pharmaceutical formulations disclosed herein can range from about 0.0001-50.0% w/v. For example, the amount of the a peptidomimetic macrocycle can be about 0.0001-10.0 w/v %, about 0.005-10.0% w/v, about 0.01-10.0% w/v, about 0.05-10.0% w/v, about 0.1-10.0% w/v, about 0.5-10.0 % w/v, about 1.0-10.0 % w/v, about 2.0-10.0 % w/v, about 3.0-10.0 % w/v, about 4.0-10.0 % w/v, about 5.0-10.0 % w/v, 6.0-10.0 % w/v, about 7.0-10.0 % w/v, about 8.0-10.0 % w/v, about 9.0-10.0 % w/v, about 0.0001-5.0 w/v %, about 0.005-5.0% w/v, about 0.01-5.0% w/v, about 0.05-5.0% w/v, about 0.1-5.0% w/v, about 0.5-5.0 % w/v, about 1.0-5.0 % w/v, about 2.0-5.0 % w/v, about 3.0-5.0 % w/v, about 4.0-5.0 % w/v, about 0.0001-2.0 w/v %, about 0.005-2.0% w/v, about 0.01-2.0% w/v, about 0.05-2.0% w/v, about 0.1-2.0% w/v, about 0.5-2.0 % w/v, or about 1.0-2.0 % w/v. In some embodiments, the peptidomimetic macrocycle is a

p53-based peptidomimetic macrocycle and the amount is about 0.1-5.0% w/v, for example about 1.0% w/v, about 1.5% w/v, or about 2.0% w/v.

[00335] In some embodiments, the amount of the peptidomimetic macrocycle is in the range of about 1- 20.0 %w/v, 5-20.0 %w/v, about 7-20.0 %w/v, about 10-20.0 %w/v, about 12-20.0 %w/v, 15-20.0 %w/v, 17- 20.0 %w/v, about 5- 25.0 %w/v, 7-25.0 %w/v, 10-25.0 %w/v, 12-25.0 %w/v, 15-25.0 %w/v, 17-25.0 %w/v, 20-25.0 %w/v, or 22-25.0 %w/v; 5- 35.0 %w/v, 7-35.0 %w/v, 10-35.0 %w/v, 12-35.0 %w/v, 15-35.0 %w/v, 17-35.0 %w/v, 20-35.0 %w/v, 22-35.0 %w/v, 25-35.0 %w/v, 27-35.0 %w/v, 30-35.0 %w/v, or 32-35.0 %w/v; 5-40.0 %w/v, 7-40.0 %w/v, about 10-40.0 %w/v, about 12-40.0 %w/v, about 15-40.0 %w/v, about 17-40.0 %w/v, about 20-40.0 %w/v, 22-40.0 %w/v, 25-40.0 %w/v, 27-40.0 %w/v, 30-40.0 %w/v, 33-40.0 %w/v, 35-40.0 %w/v, or 37-40.0 %w/v; 5-50.0 %w/v, 10-50.0 %w/v, 12-50.0 %w/v, 15-50.0 %w/v, 20-50.0 %w/v, 22-50.0 %w/v, 25-50.0 %w/v, 27-50.0 %w/v, 30-50.0 %w/v, 32-50.0 %w/v, 35-50.0 %w/v, 37-50.0 %w/v, 40-50.0 %w/v, 42-50.0 %w/v, 45-50.0 %w/v, or 47-50.0 %w/v.

[00336] In some embodiments, the amount of peptidomimetic macrocycle is about 0.5%, about 1.0%, about 1.5%, about 2.0%, about 2.5%, about 3.0%, about 3.5%, about 4.0%, about 4.5%, about 5.0%, about 5.5%, about 6.0%, about 6.5%, about 7.0%, about 7.5%, about 8.0%, about 8.5%, about 9.0%, about 9.5, about 10%, about 15%, about 20%, about 25%, about 30%, about 35%, about 40%, about 45%, or about 50% w/v.

[00337] The concentration of a peptidomimetic macrocycle in the aqueous pharmaceutical formulations disclosed herein can be in the range of about 1-100 mg/mL. In some embodiments, the amount of a peptidomimetic macrocycle in the formulation is about 1-5 mg/mL, about 1-10 mg/mL, about 1-15 mg/mL, about 1-20 mg/mL, about 1-25 mg/mL, about 1-30 mg/mL, about 1-35 mg/mL, about 1-40 mg/mL, about 1-45 mg/mL, about 1-50 mg/mL, about 1-60 mg/mL, about 1-70 mg/mL, about 1-80 mg/mL, about 1-90 mg/mL, about 5-10 mg/mL, about 5-15 mg/mL, about 5-20 mg/mL, about 5-25 mg/mL, about 5-30 mg/mL, about 5-35 mg/mL, about 5-40 mg/mL, about 5-45 mg/mL, about 5-50 mg/mL, about 5-60 mg/mL, about 5-70 mg/mL, about 5-80 mg/mL, about 5-90 mg/mL, about 5-100 mg/mL, about 10-15 mg/mL, about 10-20 mg/mL, about 10-25 mg/mL, about 10-30 mg/mL, about 10-35 mg/mL, about 10-40 mg/mL, about 10-45 mg/mL, about 10-50 mg/mL, about 10-60 mg/mL, about 10-70 mg/mL, about 10-80 mg/mL, about 10-90 mg/mL, about 10-100 mg/mL, about 15-20 mg/mL, about 15-25 mg/mL, about 15-30 mg/mL, about 15-35 mg/mL, about 15-40 mg/mL, about 15-45 mg/mL, about 15-50 mg/mL, about 15-60 mg/mL, about 15-70 mg/mL, about 15-80 mg/mL, about 15-90 mg/mL, about 15-100 mg/mL, about 20-25 mg/mL, about 20-30 mg/mL, about 20-35 mg/mL, about 20-40 mg/mL, about 20-45 mg/mL, about 20-50 mg/mL, about 20-60 mg/mL, about 20-70 mg/mL, about 20-80 mg/mL, about 20-90 mg/mL, about 20-100 mg/mL, about 25-30 mg/mL, about 25-35 mg/mL, about 25-40 mg/mL, about 25-45 mg/mL, about 25-50 mg/mL, about 25-60 mg/mL, about 25-70 mg/mL, about 25-80 mg/mL, about 25-90 mg/mL, about 25-100 mg/mL, about 30-35 mg/mL, about 30-40 mg/mL, about 30-45 mg/mL, about 30-50 mg/mL, about 30-60 mg/mL, about 30-70 mg/mL, about 30-80 mg/mL, about 30-90 mg/mL, about 30-100 mg/mL, about 35-40 mg/mL, about 35-45 mg/mL, about 35-50 mg/mL, about 35-60 mg/mL, about 35-70 mg/mL, about 35-80 mg/mL, about 35-90 mg/mL,

about 35-100 mg/mL, about 40-45 mg/mL, about 40-50 mg/mL, about 40-60 mg/mL, about 40-70 mg/mL, about 40-80 mg/mL, about 40-90 mg/mL, about 45-50 mg/mL, about 45-60 mg/mL, about 45-70 mg/mL, about 45-80 mg/mL, about 45-90 mg/mL, about 40-100 mg/mL, about 50-60 mg/mL, about 50-70 mg/mL, about 50-80 mg/mL, about 50-90 mg/mL, about 50-100 mg/mL, about 60-70 mg/mL, about 60-80 mg/mL, about 60-90 mg/mL, about 60-100 mg/mL, about 70-80 mg/mL, about 70-90 mg/mL, about 70-100 mg/mL, about 80-90 mg/mL, about 80-100 mg/mL or about 90-100 mg/mL. In some embodiments, the amount of the peptidomimetic macrocycles in the formulations of the disclosure can be about 1 mg/mL, about 2 mg/mL, about 3 mg/mL, about 4 mg/mL, about 5 mg/mL, about 6 mg/mL, about 7 mg/mL, about 8 mg/mL, about 9 mg/mL, about 10 mg/mL, about 11 mg/mL, about 12 mg/mL, about 13 mg/mL, about 14 mg/mL, about 15 mg/mL, about 16 mg/mL, about 17 mg/mL, about 18 mg/mL, about 19 mg/mL, or about 20 mg/mL. In some embodiments, the amount of the peptidomimetic macrocycles is about 5 mg/mL, about 10 mg/mL, about 15 mg/mL or about 20 mg/mL. In some embodiments, the peptidomimetic macrocycle is a p53-based peptidomimetic macrocycle and the amount is about 1-20 mg/mL, for example about 1.0 mg/mL, about 5 mg/mL, about 10 mg/mL, about 15 mg/mL or about 20 mg/mL.

[00338] In some embodiments, the aqueous solution further comprises a buffering agent. In such embodiments, the method of making the aqueous pharmaceutical formulations disclosed herein comprises dissolving at least one buffering agent in the aqueous diluent, and adding at least one peptidomimetic macrocycle or a pharmaceutically acceptable salt thereof. In some embodiments, the peptidomimetic macrocycle is added at once. In some embodiments, the peptidomimetic macrocycle is added slowly over a period of time as described above. As described above, the method can further comprise of stirring the peptide mixture for some additional time.

[00339] The concentration of the buffering solution can be about 0.01-100 mM. In some embodiments the concentration of the buffering solution is at least 0.1 mM, 1 mM, 10 mM, 20 mM, 30 mM, 40 mM, 50 mM, 60 mM, 70 mM, 80 mM, 90 mM, 100 mM. In some embodiments the concentration of the buffering solution is at most 0.1 mM, 1 mM, 10 mM, 20 mM, 30 mM, 40 mM, 50 mM, 60 mM, 70 mM, 80 mM, 90 mM, 100 mM. In some embodiments, the concentration of the buffering agent is about 1 mM, 2 mM, 3 mM, 4 mM, 5 mM, 6 mM, 7 mM, 8 mM, 9 mM, 10 mM, 11 mM, 12 mM, 13 mM, 14 mM, 15 mM, 16 mM, 17 mM, 18 mM, 19 mM, 20 mM, 21 mM, 22 mM, 23 mM, 24 mM, 25 mM, 26 mM, 27 mM, 28 mM, 29 mM, 30 mM, 31 mM, 32 mM, 33 mM, 34 mM, 35 mM, 36 mM, 37 mM, 38 mM, 39 mM, 40 mM, 41 mM, 42 mM, 43 mM, 44 mM, 45 mM, 46 mM, 47 mM, 48 mM, 49 mM, 50 mM, 60 mM, 70 mM, 80 mM, 90 mM, or 100 mM.

[00340] The method can further involve maintaining the pH of the formulation. For example, maintaining the pH of the reaction medium while the peptidomimetic macrocycle is being added and/or dissolved therein. The pH can be maintained by the addition of a pH adjusting agent. Any suitable pH adjusting agents as described above and throughout the disclosure can be used.

[00341] Non-limiting examples of suitable pH adjusting agents which can be included in the methods disclosed herein are hydrochloric acid, sodium hydroxide, citric acid, phosphoric acid, lactic acid, tartaric acid, succinic

acid, or mixtures thereof. In one embodiment, the pH adjusting agent is hydrochloric acid. In one embodiment, the pH adjusting agent is sodium hydroxide. In one embodiment, the pH adjusting agent is phosphoric acid. In one embodiment, the pH adjusting agent is lactic acid. In one embodiment, the pH adjusting agent is tartaric acid. In one embodiment, the pH adjusting agent is tartaric acid. In one embodiment, the pH adjusting agent is succinic acid. In one embodiment, the buffering agent is a phosphate buffer and the pH adjusting agent in sodium hydroxide. For example, the buffering agent can be NaH_2PO_4 and the pH adjusting agent can be sodium hydroxide, or the buffering agent can be Na_2HPO_4 and the pH adjusting agent can be sodium hydroxide, other buffering agent can be a mixture of NaH_2PO_4 and Na_2HPO_4 and the pH adjusting agent can be sodium hydroxide, or buffering agent can be KH_2PO_4 and the pH adjusting agent can be sodium hydroxide, or the buffering agent can be K_2HPO_4 and the pH adjusting agent can be sodium hydroxide, or the buffering agent can be a mixture of KH_2PO_4 and K_2HPO_4 and the pH adjusting agent can be sodium hydroxide.

[00342] In some embodiments the amount of the pH adjusting agent added to the aqueous pharmaceutical formulation is in the range of about 0.001-1% w/v. For example, in some embodiments, the amount of the pH adjusting agent present is in the range of 0.01-0.1 % w/v, 0.1-1 % w/v, 0.005-1 % w/v, 0.05-1 % w/v, 0.5-1 % w/v, 0.001-.5 % w/v, 0.01-0.5 % w/v, 0.1-0.5 % w/v, 0.001-0.1 % w/v, or 0.01-0.1 vv. In some embodiments, the amount of the pH adjusting agent present in the formulation is in the range of about 0.01-0.1% w/v. In some embodiments, the amount of the pH adjusting agent present in the formulation is at least 0.01% w/v, 0.02% w/v, 0.03% w/v, 0.04 %w/v, 0.05% w/v, 0.06% w/v, 0.07% w/v, 0.08% w/v, 0.09% w/v, or 0.1% w/v. In some embodiments, the amount of the pH adjusting agent present in the formulation is at most 0.1% w/v, 0.09% w/v, 0.08% w/v, 0.07% w/v, 0.06% w/v, 0.05% w/v, 0.04% w/v, 0.03% w/v, 0.02 % w/v, 0.01% w/v.

[00343] In some embodiments the amount of the pH adjusting agent added to the aqueous pharmaceutical formulation is in the range of about 0.01-100 mg/mL. For example, in some embodiments, the amount of the pH adjusting agent present is in the range of 0.01-50 mg/mL, 0.01-10 mg/mL, 0.1-100 mg/mL, 0.1-50 mg/mL, 0.1-10 mg/mL, 1-100 mg/mL, 1-50 mg/mL, or 1-10 mg/mL. In some embodiments, the amount of the pH adjusting agent present in the formulation is in the range of about 1-10 mg/mL. In some embodiments, the amount of the pH adjusting agent present in the formulation is at least 1 mg/mL, 2 mg/mL, 3 mg/mL, 4 mg/mL, 5 mg/mL, 6 mg/mL, 7 mg/mL, 8 mg/mL, 9 mg/mL, or 10 mg/mL. In some embodiments, the amount of the pH adjusting agent present in the formulation is at most 10 mg/mL, 9 mg/mL, 8 mg/mL, 7 mg/mL, 6 mg/mL, 5 mg/mL, 4 mg/mL, 3 mg/mL, 2 mg/mL, 1 mg/mL. In some embodiments, the amount of the pH adjusting agent present in the formulation is about 1 mg/mL, about 1.5 mg/mL, about 2 mg/mL, about 2.5 mg/mL, about 3 mg/mL, about 3.5 mg/mL, about 4 mg/mL, about 4.5 mg/mL, about 5 mg/mL, about 6 mg/mL, about 7 mg/mL, about 8 mg/mL, about 9 mg/mL, about 10 mg/mL, about 12 mg/mL, about 14 mg/mL, about 16 mg/mL, about 18 mg/mL, or about 20 mg/mL. In some embodiments, the amount of the pH adjusting agent present in the formulation is of the pH adjusting agent is present in about 5 mg/mL of the formulation.

[00344] In some embodiments, the aqueous solution comprises a stabilizing agent. In such embodiments, the method of making the aqueous pharmaceutical formulations disclosed herein comprises dissolving at least one stabilizing agent in at least an aqueous diluent, and adding at least one peptidomimetic macrocycle or a pharmaceutically acceptable salt thereof. In some embodiments, the peptidomimetic macrocycle is added at once. In some embodiments, the peptidomimetic macrocycle is added slowly over a period of time as described above. As described above, the method can further comprise of stirring the peptide mixture for some additional time.

[00345] In amount of the stabilizing agent in the formulations can be in the range of about 0.001-1% w/v. For example, in the range of about 0.001-.01%, about 0.001-0.1% w/v, about 0.001-0.5% w/v, about 0.01-0.1% w/v, about 0.01-0.5% w/v, about 0.01-0.1% w/v, about 0.1-0.5% w/v or about 0.5-1% w/v. In some embodiments, the amount of the stabilizing agent in the formulation is about 0.01-0.1% w/v. In some embodiments, the amount of the stabilizing agent is at least about 0.01% w/v, about 0.02% w/v, about 0.03% w/v, about 0.04 %w/v, about 0.05% w/v, about 0.06% w/v, about 0.07% w/v, about 0.08% w/v, about 0.09% w/v, or about 0.1% w/v. In some embodiments, the amount of the stabilizing agent is at most about 0.1% w/v, about 0.09% w/v, about 0.08% w/v, about 0.07% w/v, about 0.06% w/v, about 0.05% w/v, about 0.04% w/v, about 0.03% w/v, about 0.02 % w/v, about 0.01% w/v. In some embodiments, the amount of the stabilizing agent in the formulation is about 0.01% w/v, about 0.02% w/v, about 0.03% w/v, about 0.04% w/v, about 0.05% w/v, about 0.06% w/v, about 0.07% w/v, about 0.08% w/v, about 0.09% w/v, or about 0.1% w/v. In some embodiments, the amount of the stabilizing agent in the formulation is about 0.01% w/v. In some embodiments, the amount of the stabilizing agent in the formulation is about 0.02% w/v. In some embodiments, the amount of the stabilizing agent in the formulation is about 0.03% w/v. In some embodiments, the amount of the stabilizing agent in the formulation is about 0.04% w/v. In some embodiments, the amount of the stabilizing agent in the formulation is about 0.05% w/v.

[00346] In some embodiments the amount of the stabilizing agent is about 0.01-10 mg/mL. For example, in some embodiments, the amount of the stabilizing agent is about 0.01-5 mg/mL, about 0.01-1 mg/mL, about 0.01-0.5 mg/mL, about 0.01-0.1 mg/mL, about 0.1-10 mg/mL, about 0.1-5 mg/mL, about 0.1-1 mg/mL, about 0.1-0.5 mg/mL, about 1-10 mg/mL, or about 1-5 mg/mL. In some embodiments, the amount of the stabilizing agent in the formulation is in the range of about 0.01-1.0 mg/mL.

[00347] In some embodiments, the amount of the stabilizing agent is at least about 0.1 mg/mL, about 0.2 mg/mL, about 0.3 mg/mL, about 0.4 mg/mL, about 0.5 mg/mL, about 0.6 mg/mL, about 0.7 mg/mL, about 0.8% mg/mL, about 0.9 mg/mL, or about 1 mg/mL. In some embodiments, the amount of the stabilizing agent is at most about 1 mg/mL, about 0.9 mg/mL, about 0.8 mg/mL, about 0.7 mg/mL, about 0. 6 mg/mL, about 0.5 mg/mL, about 0. 4 mg/mL, about 0.3 mg/mL, about 0.2 mg/mL, or about 0.1 mg/mL.

[00348] In some embodiments, the amount of the stabilizing agent is about 0.1 mg/mL, about 0. 2 mg/mL, about 0.3 mg/mL, about 0.4 mg/mL, about 0.5 mg/mL, about 0.6 mg/mL, about 0.7 mg/mL, about 0.8 mg/mL, about 0.9 mg/mL, or about 1 mg/mL. In some embodiments, the amount of the stabilizing agent in the formulation is about 0.1 mg/mL. In some embodiments, the amount of the stabilizing agent in the formulation is about 0.2 mg/mL. In

some embodiments, the amount of the stabilizing agent in the formulation is about 0.3 mg/mL. In some embodiments, the amount of the stabilizing agent in the formulation is about 0.4 mg/mL. In some embodiments, the amount of the stabilizing agent in the formulation is about 0.5 mg/mL.

[00349] In some embodiments, the aqueous solution comprises both a buffering agent and stabilizing agent. In such embodiments, the method of making the aqueous pharmaceutical formulations disclosed herein comprises dissolving at least one stabilizing agent and at least one buffering agent in an aqueous diluent, and adding at least one peptidomimetic macrocycle or a pharmaceutically acceptable salt thereof. In some embodiments, the peptidomimetic macrocycle is added at once. In some embodiments, the peptidomimetic macrocycle is added slowly over a period of time as described above. As described above, the method can further comprise of stirring the peptide mixture for some additional time.

[00350] In some examples, the method of making the aqueous pharmaceutical formulations disclosed herein comprises dissolving at least one buffering agent, at least one tonicity adjusting agent and at least one stabilizing agent in at least one aqueous diluent, and adding at least one peptidomimetic macrocycle or a pharmaceutically acceptable salt thereof. In some embodiments, the buffering agent, the tonicity adjusting agent and the stabilizing agents are dissolved in the aqueous diluent in this order. In some embodiments, the peptidomimetic macrocycle is added at once. In some embodiments, the peptidomimetic macrocycle is added slowly over a period of time as described above.

[00351] The amount of the tonicity adjusting agent in the aqueous pharmaceutical formulations disclosed herein can be in the range of about 0.001-50 % w/v, for example about 0.001-0.1% w/v , about 0.001-1.0% w/v, about 0.001-10% w/v, about 1-10% w/v, about 1-20% w/v, about 1-30% w/v, about 1-40% w/v, about 1-50% w/v, about 5-10% w/v, about 5-20% w/v, about 5-30% w/v, about 5-40% w/v, about 5-50% w/v, about 10-20% w/v, about 10-30% w/v, about 10-40% w/v, about 10-50% w/v, about 15-20% w/v, about 15-30% w/v, about 15-40% w/v, about 15-50% w/v, about 20-30% w/v, about 20-40% w/v, about 20-50% w/v, about 25-30% w/v, about 25-40% w/v, about 25-50% w/v, about 30-40% w/v, about 30-50,% w/v, about 35-40% w/v, about 35-50% w/v, about 40-50% w/v, or about 45-50% w/v. In some embodiments, the amount of the tonicity adjusting agent is about 1% w/v, about 2% w/v, about 3% w/v, about 4% w/v, about 5% w/v, about 6% w/v, about 7% w/v, about 8% w/v, about 9% w/v, or about 10% w/v. In some embodiments, the amount of the tonicity adjusting agent is about 7% w/v. In some embodiments, the amount of the tonicity adjusting agent is about 8% w/v. In some embodiments, the amount of the tonicity adjusting agent is about 9% w/v. In some embodiments, the amount of the tonicity adjusting agent is about 10% w/v.

[00352] The concentration of the tonicity adjusting agent can vary in the range of about 1-500 mg/mL. For example, the concentration of the tonicity adjusting agent in the aqueous pharmaceutical formulations disclosed herein can be in the range of about 1-400 mg/mL, 1-300 mg/mL, 1-200 mg/mL, 1-100 mg/mL, 10-500 mg/mL, 10-400 mg/mL, 10-300 mg/mL, 10-200 mg/mL, 10-100 mg/mL, 20-500 mg/mL, 20-400 mg/mL, 20-300 mg/mL, 20-200 mg/mL, 20-100 mg/mL, 30-500 mg/mL, 30-400 mg/mL, 30-300 mg/mL, 30-200 mg/mL, 30-100 mg/mL,

40-500 mg/mL, 40-400 mg/mL, 40-300 mg/mL , 40-200 mg/mL , 40-100, mg, 50-500 mg/mL, 50-400 mg/mL, 50-300 mg/mL, 50-200 mg/mL, 50-100 mg/mL, 60-500 mg/mL, 60-400 mg/mL, 60-30 mg/mL, 60-200 mg/mL, 60-100 mg/mL, 70-500 mg/mL, 70-400 mg/mL, 70-300 mg/mL, 70-200 mg/mL, 70-100 mg/mL, 80-500 mg/mL, 80-400 mg/mL, 80-300 mg/mL, 80-200 mg/mL, 80-200 mg/mL, 90-500 mg/mL, 90-400 mg/mL, 90-300 mg/mL, 90-200 mg/mL, 90-100 mg/mL, 100-500 mg/mL, 100-400 mg/mL, 100-300 mg/mL, 100-200 mg/mL, 200-500 mg/mL, 200-400 mg/mL, 200-300 mg/mL, 300-500 mg/mL, 300-400 mg/mL or 400-500 mg/mL. In some embodiments, the concentration of the tonicity adjusting agent is about 10 mg/mL, about 20 mg/mL, about 30 mg/mL, about 40 mg/mL, about 50 mg/mL, about 60 mg/mL, about 70 mg/mL, about 80 mg/mL, about 90 mg/mL, or about 100 mg/mL. In some embodiments, the concentration of the tonicity adjusting agent is about 50 mg/mL. In some embodiments, the concentration of the tonicity adjusting agent is about 80 mg/mL. In some embodiments, the concentration of the tonicity adjusting agent is about 100 mg/mL. In some embodiments, the tonicity adjusting agent is trehalose (for example, D- trehalose) and the concentration is about 80 mg/mL.

[00353] In some embodiments, the concentration of the tonicity adjusting agent is between about 100-500 mM. For example the concentration of the tonicity adjusting agent in the aqueous pharmaceutical formulations disclosed herein can be 100-400 mM, 100-300 mM, 100-200 mM, 200-500 mM, 200-400 mM, 200-300 mM, 300-500 mM, 300-400 mM or 400-500 mM. In some embodiments, the concentration of the tonicity adjusting agent is between about 200-300 mM, for example 210-300 mM, 220-300 mM, 230-300 mM, 240-300 mM, 250-300 mM, 260-300 mM, 270-300 mM, 280-300 mM, 290-300 mM, 200-290 mM, 210-290 mM, 220-290 mM, 230-290 mM, 240-290 mM, 250-290 mM, 260-290 mM, 270-290 mM, 280-290 mM, 200-280 mM, 210-280 mM, 220-280 mM, 230-280 mM, 240-280 mM, 250-280 mM, 260-280 mM, 270-280 mM, 200-270 mM, 210-270 mM, 220-270 mM, 230-270 mM, 240-270 mM, 250-270 mM, 260-270 mM, 200-260 mM, 210-260 mM, 220-260 mM, 230-260 mM, 240-260 mM, 250-260 mM, 200-250 mM, 210-250 mM, 220-250 mM, 230-250 mM, 240-250 mM, 200-240 mM, 210-240 mM, 220-240 mM, 230-240 mM, 200-230 mM, 210-230 mM, 220-230 mM, 200-220 mM, 210-220 mM, or 210-220 mM. In some embodiments, the concentration of the tonicity adjusting agent is between about 220-260 mM. For example, about 220 mM, 230 mM, 240 mM, 250 mM, or 260 mM.

[00354] The methods described herein can additionally comprise addition of one or more optional excipients and/or ingredients. For example addition of one or more antioxidants, antimicrobial agent, surfactants, lubricants, thickening agents, preservatives, chelating agents.

[00355] In some embodiments the amount of antioxidants used is in the range of about 0.001-5% w/v, for example about 0.001-4.5%, 0.001-4%, 0.001-3%, 0.001-2%, 0.002-1%, 0.001-.5%, or 0.001-.05% w/v. In some embodiments the amount of antioxidants used is in the range of about 0.001-about 0.5%, about 0.1-about 0.5%, about 0.2-about 0.5%, about 0.3-about 0.5%, about 0.4-about 0.5%, about 0.01-about 0.4%, about 0.1-about 0.4%, about 0.2-about 0.4%, about 0.3-about 0.4%, about 0.01-about 0.3%, about 0.1- about 0.3%, about 0.2-about 0.3%, about 0.01-about 0.2%, about 0.1-about 0.2%, or about 0.01-about 0.1% w/v .

[00356] Such antimicrobial agents can be employed at a level of from about 0.005-0.5% w/v, for example about 0.001- 0.01% w/v, about 0.01-0.1% w/v, about 0.1-0.5% w/v or about 0.01-0.05% w/v.

[00357] The methods described herein can additionally comprise prefiltering and/or clarifying the peptidomimetic formulation by a suitable process, for example by centrifugation or by filtration. Filtration can be by any suitable means, for example by depth filter media or by membrane filters. In some embodiments, filtration can be by means of a 0.22 micrometer filters.

[00358] The method can optionally involve sterilization of the aqueous pharmaceutical formulations. Sterilization can be performed by any suitable technique. For example, a suitable sterilization method can include one or more of sterile filtration, chemical, irradiation heat filtration, and addition of a chemical disinfectant to the aqueous pharmaceutical formulation. In some examples, the formulations are sterilized by moist heat sterilization. In some examples, the formulations are sterilized by dry heat sterilization. In some examples, the formulations are sterilized by chemical cold sterilization. In some examples, the formulations are sterilized by radiation sterilization. In some examples, the formulations are sterilized by filtration. In some examples, the formulations are sterilized by filtration using an appropriate micron sterilizing grade filters. The filtration can be carried out by any suitable means, e.g. cellulose-based filters, cellulosic esters (MCE), polyvinylidene fluoride (PVDF), polytetrafluoroethylene (PTFE), or polyethersulfone (PES) filters. In some embodiments PVDF filters are used. Filters of any appropriate micron size can be used. In some embodiments, the filter size can be .001-0.5 micrometer, for example .001-.01 micrometer, 0.01-0.1 micrometer, 0.1-0.2 micrometer, 0.2-0.3 micrometer, 0.3-0.4 3 micrometer or 0.4-0.5 micrometer. In some embodiments 0.22 micrometer filters are used. In some embodiments 0.22 micrometer PVDF filters are used.

[00359] The aqueous pharmaceutical formulations can be in a form that is suitable for direct administration or can be in a concentrated form that requires dilution relative to what is administered to the patient. For example, aqueous pharmaceutical formulations, described in this disclosure, can be in a form that is suitable for direct administration without any further dilution or reconstitution. The formulations can be diluted or reconstituted prior to administration with a suitable aqueous diluent(s) to obtain a finished concentration. The diluent can be an injection or infusion fluid. Examples of injection or infusion fluid include, but are not limited to, WFI (Bacteriostatic Water For Injection), SWFI (Sterile Water For Injection), D5W (Dextrose 5% in Water), DlOW (Dextrose 10% in Water), D5LR (Dextrose in Lactate Ringer's Solution), D5 ¼S (Dextrose 5% in 1/4 Strength Saline (5% Dextrose and 0.22% Sodium Chloride Injection)), D5½S (Dextrose 5% in 1/2 Strength Saline (5% Dextrose and 0.45 % Sodium Chloride Injection)), D5NS (Dextrose 5% in Normal Saline (5% Dextrose and 0.9% Sodium Chloride Injection)), D5R (Dextrose 5% in Ringer's Injection), DIONS (Dextrose 10% in Normal Saline (10% Dextrose and 0.9% Sodium Chloride Injection)), ISlOW (Invert Sugar 10% in Saline (10% Invert Sugar in 0.9% Sodium Chloride Injection)), LR (Lactated Ringer's Injection), Pr (Protein Hydrolysate Injection), R (Ringer's Injection), NS Sodium Chloride 0.9% (Normal Saline), SOD CL 5 (Sodium Chloride 5% (5% Sodium Chloride Injection), and Sod Lac (Sodium Lactate, 1/6 Molar (M/6 Sodium Lactate Injection)). In some examples,

the formulations can be diluted with 0.9% sodium chloride, 5% dextrose in water (D5W), 5% dextrose in normal saline (D5NS), 5 dextrose in half amount of normal saline (D5 1/2NS), lactated ringer's injection or a mixture thereof. Dilution/reconstitution can be performed immediately prior to the administration. In some cases, dilution/reconstitution can be performed shortly before the administration. In some cases, the dilution is performed at most 1 min, 5 min, 15 min, 30 min, 45 min, 60 min, 90 min, 2 h, 3 h, 4 h, 5 h, 6 h, 7 h, 8 h, 9 h, 10 h, 11 h, 12 h, 13 h, 14 h, 15 h, 16 h, 17 h, 18 h, 19 h, 20 h, 21 h, 22 h, 23 h, or 24 h before the administration to the subject. In some examples the reconstituted and diluted solutions is used within 1-10 hours, 2-8 hours, 3-7 hours, 4-6 hours reconstitution and/or dilution. In some examples, the formulations are diluted/reconstituted more than 1 day, 2 days, 3 days, 4 days, 5 days, 6 days, 1 week before administration.

[00360] **Figure 1** depicts the manufacturing process of an exemplary aqueous formulation according to the disclosure.

Purity, Stability and Degradation

[00361] The formulations of the disclosure can be characterized by low endotoxin concentration. In some embodiments, the formulations can have a concentration of endotoxin of less than about 100 EU/mL, for example, less than about 90 EU/mL, 80 EU/mL, 70 EU/mL, 60 EU/mL, 50 EU/mL, 40 EU/mL, 30 EU/mL, 20 EU/mL, 10 EU/mL, 5 EU/mL, 1 EU/mL, 0.5 EU/mL, 0.2 EU/mL, 0.1 EU/mL, 0.05 EU/mL, 0.01 EU/mL, 0.005 EU/mL, or 0.001 EU/mL. In some embodiments the concentration of the endotoxin is 0.1-10 EU/mL, for example about 0.1-1 EU/mL, 0.1-2 EU/mL,, 0.1-3 EU/mL, 0.1-4 EU/mL, 0.1-5 EU/mL, 0.1-6 EU/mL, 0.1-7 EU/mL, 0.1-8 EU/mL, 0.1-9 EU/mL, 1-2 EU/mL, 1-3 EU/mL, 1-4 EU/mL, 1-5 EU/mL, 1-6, 1-7, 1-8, 1-9, 1-10, 2-3 EU/mL, 2-4 EU/mL, 2-5 EU/mL, 2-6, 2-7, 2-8, 2-9, 2-10, 3-4 EU/mL, 3-5 EU/mL, 3-6 EU/mL, 3-7 EU/mL, 3-8 EU/mL, 3-9 EU/mL, 3-10 EU/mL, 4-5 EU/mL, 4-6 EU/mL, 4-7 EU/mL, 4-8 EU/mL, 4-9 EU/mL, 4-10 EU/mL, 5-6 EU/mL, 5-7 EU/mL, 5-8 EU/mL, 5-9 EU/mL, 5-10 EU/mL, 6-7 EU/mL, 6-8 EU/mL, 6-9 EU/mL, 6-10 EU/mL, 7-8 EU/mL, 7-9 EU/mL, 7-10 EU/mL, 8-9 EU/mL, 8-10 EU/mL, or 9-10 EU/mL.

[00362] In some embodiments the formulations of the disclosure are essentially particulate-free solutions. In some embodiments, the formulation is essentially free of particles of size greater than about 1 μm, 2 μm, 3 μm, 4 μm, 5 μm, 6 μm, 7 μm, 8 μm, 9 μm, 10 μm, 11 μm, 12 μm, 13 μm, 14 μm, 15 μm, 16 μm, 17 μm, 18 μm, 19 μm, 20 μm, 21 μm, 22 μm, 23 μm, 24 μm, 25 μm, 26 μm, 27 μm, 28 μm, 29 μm, 30 μm, 35 μm, 40 μm, 45 μm, 50 μm, or more.

[00363] In some embodiments, the formulation comprise at most about 1, about 2, about 3, about 4, about 5, about 6, about 7, about 8, about 9, about 10, about 11, about 12, about 13, about 14, about 15, about 16, about 17, about 18, about 19, about 20, about 21, about 22, about 23, about 24, about 25, about 26, about 27, about 28, about 29, about 30, about 50, about 100, about 200, about 300, about 400, about 500, about 600, about 700, about 800, about 900, about 1,000, about 1,100, about 1,200, about 1,300, about 1,400, about 1,500, about 1,600, about 1,700, about 1,800, about 1,900, about 2,000, about 2,200, about 2,400, about 2,600, about 2,800, about 3,000,

about 3,500, about 4,000, about 4,500, about 5,000, about 5,500, about 6,000, about 6,500, about 7,000, about 8,000, about 8,500, about 9,000, about 9,500, or about 10,000 particles of size greater than or equal to 10 μm per 1mL or 5 mL of formulation. In some embodiments the formulations of the disclosure are essentially free of particles of size greater than or equal to 10 μm. In some embodiments the formulations of the disclosure less than 500 particles of size greater than or equal to 10 μm in per 1 mL or 5 mL of formulation. In some embodiments the formulations of the disclosure less than 1000 particles of size greater than or equal to 10 μm in per 1 mL or 5 mL of formulation. In some embodiments the formulations of the disclosure less than 1200 particles of size greater than or equal to 10 μm in per 1 mL or 5 mL of formulation. In some embodiments the formulations of the disclosure less than 1,000-1,200 particles of size greater than or equal to 10 μm in per 1 mL or 5 mL of formulation.

[00364] In some embodiments, the formulation comprise at most about 1, about 2, about 3, about 4, about 5, about 6, about 7, about 8, about 9, about 10, about 11, about 12, about 13, about 14, about 15, about 16, about 17, about 18, about 19, about 20, about 21, about 22, about 23, about 24, about 25, about 26, about 27, about 28, about 29, about 30, about 50, about 60, about 70, about 80, about 90, about 100, about 110, about 120, about 130, about 140, about 150, about 200, about 300, about 400, about 500, about 600, about 700, about 800, about 900, about 1,000, about 1,100, about 1,200, about 1,300, about 1,400, about 1,500, about 1,600, about 1,700, about 1,800, about 1,900, about 2,000, about 2,500, about 3,000, about 3,500, about 4,000, about 4,500, about 5,000, about 5,500, or about 6,000 particles of size greater than or equal to 25 μm per 1 mL or 5 mL of formulation. In some embodiments the formulations of the disclosure are essentially free of particles of size greater than or equal to 25 μm. In some embodiments the formulations comprise at most 50 particles of size greater than or equal to 25 μm per 1 mL or 5 mL of formulation. In some embodiments the formulations comprise at most 100 particles of size greater than or equal to 25 μm per 1 mL or 5 mL of formulation. In some embodiments the formulations comprise at most 120 particles of size greater than or equal to 25 μm in per 1 mL or 5mL of formulation. In some embodiments the formulations comprise about 100-120 particles of size greater than or equal to 25 μm per 1 mL or 5 mL of formulation.

[00365] In some embodiments the formulations of the disclosure are essentially free of particles of size greater than or equal to 50 μm. In some embodiments the formulations comprise at most 1 particles of size greater than or equal to 50 μm per 1 mL or 5 mL of formulation. In some embodiments the formulations comprise at most 2 particles of size greater than or equal to 50 μm per 1 mL or 5 mL of formulation. In some embodiments the formulations comprise at most 3 particles of size greater than or equal to 50 μm in per 1 mL or 5 mL of formulation. In some embodiments the formulations comprise about 1-5 particles of size greater than or equal to 50 μm per 1 mL or 5 mL of formulation. In some embodiments the formulations of the disclosure are essentially free of particles of size greater than or equal to 50 μm. In some embodiments the formulations comprise at most 1 particles of size greater than or equal to 50 μm per container. In some embodiments the formulations comprise at most 2 particles of size greater than or equal to 50 μm per container. In some embodiments the formulations

comprise at most 3 particles of size greater than or equal to 50 μm in per container. In some embodiments the formulations comprise about 1-5 particles of size greater than or equal to 25 μm container.

[00366] In some embodiments, the formulations comprise 0-10000, 100-10,000, 500-10,000, 1,000-10,000, 1,500-10,000, 2,000-10,000, 2,500-10,000, 3,000-10,000, 3,500-10,000, 4,000-10,000, 4,500-10,000, 5,000-10,000, 5,500-10,000, 6,000-10,000, 6,500-10,000, 7,000-10,000, 7,500-10,000, 8,000-10,000, 8,500-10,000, 9,000-10,000, or 9,500-10,000 particles of size greater than or equal to 10 μm per mL of formulation.

[00367] In some embodiments, the formulations comprise 0-10000, 100-10,000, 500-10,000, 1,000-10,000, 1,500-10,000, 2,000-10,000, 2,500-10,000, 3,000-10,000, 3,500-10,000, 4,000-10,000, 4,500-10,000, 5,000-10,000, 5,500-10,000, 6,000-10,000, 6,500-10,000, 7,000-10,000, 7,500-10,000, 8,000-10,000, 8,500-10,000, 9,000-10,000, or 9,500-10,000 particles of size greater than or equal to 10 μm per 5 mL of formulation.

[00368] In some embodiments, the formulations comprise 0-10000, 100-10,000, 500-10,000, 1,000-10,000, 1,500-10,000, 2,000-10,000, 2,500-10,000, 3,000-10,000, 3,500-10,000, 4,000-10,000, 4,500-10,000, 5,000-10,000, 5,500-10,000, 6,000-10,000, 6,500-10,000, 7,000-10,000, 7,500-10,000, 8,000-10,000, 8,500-10,000, 9,000-10,000, or 9,500-10,000 particles of size greater than or equal to 25 μm per mL of formulation.

[00369] In some embodiments, the formulations comprise 0-10000, 100-10,000, 500-10,000, 1,000-10,000, 1,500-10,000, 2,000-10,000, 2,500-10,000, 3,000-10,000, 3,500-10,000, 4,000-10,000, 4,500-10,000, 5,000-10,000, 5,500-10,000, 6,000-10,000, 6,500-10,000, 7,000-10,000, 7,500-10,000, 8,000-10,000, 8,500-10,000, 9,000-10,000, or 9,500-10,000 particles of size greater than or equal to 25 μm per 5 mL of formulation.

[00370] In some embodiments, the formulations comprise 0-10000, 100-10,000, 500-10,000, 1,000-10,000, 1,500-10,000, 2,000-10,000, 2,500-10,000, 3,000-10,000, 3,500-10,000, 4,000-10,000, 4,500-10,000, 5,000-10,000, 5,500-10,000, 6,000-10,000, 6,500-10,000, 7,000-10,000, 7,500-10,000, 8,000-10,000, 8,500-10,000, 9,000-10,000, or 9,500-10,000 particles of size greater than or equal to 50 μm per 1 mL of formulation

[00371] In some embodiments, the formulations comprise 0-10000, 100-10,000, 500-10,000, 1,000-10,000, 1,500-10,000, 2,000-10,000, 2,500-10,000, 3,000-10,000, 3,500-10,000, 4,000-10,000, 4,500-10,000, 5,000-10,000, 5,500-10,000, 6,000-10,000, 6,500-10,000, 7,000-10,000, 7,500-10,000, 8,000-10,000, 8,500-10,000, 9,000-10,000, or 9,500-10,000 particles of size greater than or equal to 50 μm per 5 mL of formulation.

[00372] In some embodiments, the formulations of the present disclosure can remain stable after exposure to a single or multiple freeze-thaw events. Formulations of the present disclosure can also remain stable after exposure to physical agitation, such as one would expect to encounter upon shipping product from one location to another. Stability can be measured by any one of a number of different ways, including visual inspection for precipitate formation, analysis of percent peptidomimetic macrocycle remaining in solution after exposure to stress conditions (e.g., by size-exclusion HPLC), or analysis of the formation of chemical variants and/or decomposition products of the peptidomimetic macrocycle (e.g., by anion exchange or reverse phase HPLC analysis). In some embodiments of the present disclosure, no precipitate visible to the naked eye is formed in the formulation after at least one freeze thaw event. In some embodiments the formulation remains stable after at least three freeze thaw

events. In some embodiments the formulation remains stable after at least six freeze thaw events. In some embodiments, at least 80, 85, 90%, 95%, 96%, 975, 98%, or 99% of the peptidomimetic macrocycle remains in the formulation after at least one freeze thaw event.

[00373] In some embodiments, the total peptidomimetic degradation products formed in the formulations of the present disclosure is less than 1.0% when stored at a temperature of 40 °C for a period of one month. In some further embodiments, the total degradation products of the compound of Formula 1 formed is less than about 0.9%, about 0.8%, about 0.7%, about 0.6%, about 0.5%, about 0.4%, about 0.3%, about 0.2%, or about 0.1% when stored at a temperature of 40 °C for a period of one month.

[00374] In some embodiments, the total peptidomimetic degradation products formed in the formulations of the present disclosure is less than 1.0% when stored at a temperature of 40 °C for a period of about two months, about three months, about four months, about five months about six months.

[00375] In some further embodiments, the amount of any single impurity in the formulation at any storage temperature is less than .001%, 0.01%, 0.1%, 0.5%, 1.0%, 1.5%, 2.0%, 2.5%, 3.0%, 3.5%, 4.0%, 4.5%, 5.0%, 5.5%, 6.0%, 6.5%, 7.0%, 7.5%, 8.0%, 8.5%, 9.0%, 9,5%, or 10%. In some further embodiments, the amount of any single impurity in the formulation at any storage temperature is less than 1.0%. In some further embodiments, the amount of any single impurity in the formulation at any storage temperature is less than 2.0%. In some further embodiments, the amount of any single impurity in the formulation at any storage temperature is less than 3.0%. In some further embodiments, the amount of any single impurity in the formulation at any storage temperature is less than 4.0%. In some further embodiments, the amount of any single impurity in the formulation at any storage temperature is less than 5.0%.

[00376] In some further embodiments, the amount of any single impurity in the formulation at any storage temperature is less than .5% when stored at a temperature of -20 °C for a period of 0 months, 0.5 months, 1.0 months, 1.5 months, 2.0 months, 2.5 months, 3.0 months, 3.5 months, 4.0 months, 4.5 months, 5.0 months, 5.5 months, 6.0 months, 8 months, 10 months, 12 months, or more months. In some further embodiments, the amount of any single impurity in the formulation at any storage temperature is less than 1% when stored at a temperature of -20 °C for a period of 0 months, 0.5 months, 1.0 months, 1.5 months, 2.0 months, 2.5 months, 3.0 months, 3.5 months, 4.0 months, 4.5 months, 5.0 months, 5.5 months, 6.0 months, 8 months, 10 months, 12 months, or more months. In some further embodiments, the amount of any single impurity in the formulation at any storage temperature is less than 1.5% when stored at a temperature of -20 °C for a period of 0 months, 0.5 months, 1.0 months, 1.5 months, 2.0 months, 2.5 months, 3.0 months, 3.5 months, 4.0 months, 4.5 months, 5.0 months, 5.5 months, 6.0 months, 8 months, 10 months, 12 months, or more months. In some further embodiments, the amount of any single impurity in the formulation at any storage temperature is less than 2.0% when stored at a temperature of -20 °C for a period of 0 months, 0.5 months, 1.0 months, 1.5 months, 2.0 months, 2.5 months, 3.0 months, 3.5 months, 4.0 months, 4.5 months, 5.0 months, 5.5 months, 6.0 months, 8 months, 10 months, 12 months, or more months. In some further embodiments, the amount of any single impurity in the formulation at

any storage temperature is less than 2.5% when stored at a temperature of -20 °C for a period of 0 months, 0.5 months, 1.0 months, 1.5 months, 2.0 months, 2.5 months, 3.0 months, 3.5 months, 4.0 months, 4.5 months, 5.0 months, 5.5 months, 6.0 months, 8 months, 10 months, 12 months, or more months. In some further embodiments, the amount of any single impurity in the formulation at any storage temperature is less than 3.0% when stored at a temperature of -20 °C for a period of 0 months, 0.5 months, 1.0 months, 1.5 months, 2.0 months, 2.5 months, 3.0 months, 3.5 months, 4.0 months, 4.5 months, 5.0 months, 5.5 months, 6.0 months, 8 months, 10 months, 12 months, or more months. In some further embodiments, the amount of any single impurity in the formulation at any storage temperature is less than 5.0% when stored at a temperature of -20 °C for a period of 0 months, 0.5 months, 1.0 months, 1.5 months, 2.0 months, 2.5 months, 3.0 months, 3.5 months, 4.0 months, 4.5 months, 5.0 months, 5.5 months, 6.0 months, 8 months, 10 months, 12 months, or more months.

[00377] In some further embodiments, the amount of any single impurity in the formulation at any storage temperature is less than .5% when stored at a temperature of 5 °C for a period of 0 months, 0.5 months, 1.0 months, 1.5 months, 2.0 months, 2.5 months, 3.0 months, 3.5 months, 4.0 months, 4.5 months, 5.0 months, 5.5 months, 6.0 months, 8 months, 10 months, 12 months, or more months. In some further embodiments, the amount of any single impurity in the formulation at any storage temperature is less than 1% when stored at a temperature of 5 °C for a period of 0 months, 0.5 months, 1.0 months, 1.5 months, 2.0 months, 2.5 months, 3.0 months, 3.5 months, 4.0 months, 4.5 months, 5.0 months, 5.5 months, 6.0 months, 8 months, 10 months, 12 months, or more months. In some further embodiments, the amount of any single impurity in the formulation at any storage temperature is less than 1.5% when stored at a temperature of 5 °C for a period of 0 months, 0.5 months, 1.0 months, 1.5 months, 2.0 months, 2.5 months, 3.0 months, 3.5 months, 4.0 months, 4.5 months, 5.0 months, 5.5 months, 6.0 months, 8 months, 10 months, 12 months, or more months. In some further embodiments, the amount of any single impurity in the formulation at any storage temperature is less than 2.0% when stored at a temperature of 5 °C for a period of 0 months, 0.5 months, 1.0 months, 1.5 months, 2.0 months, 2.5 months, 3.0 months, 3.5 months, 4.0 months, 4.5 months, 5.0 months, 5.5 months, 6.0 months, 8 months, 10 months, 12 months, or more months. In some further embodiments, the amount of any single impurity in the formulation at any storage temperature is less than 2.5% when stored at a temperature of 5 °C for a period of 0 months, 0.5 months, 1.0 months, 1.5 months, 2.0 months, 2.5 months, 3.0 months, 3.5 months, 4.0 months, 4.5 months, 5.0 months, 5.5 months, 6.0 months, 8 months, 10 months, 12 months, or more months. In some further embodiments, the amount of any single impurity in the formulation at any storage temperature is less than 3.0% when stored at a temperature of 5 °C for a period of 0 months, 0.5 months, 1.0 months, 1.5 months, 2.0 months, 2.5 months, 3.0 months, 3.5 months, 4.0 months, 4.5 months, 5.0 months, 5.5 months, 6.0 months, 8 months, 10 months, 12 months, or more months. In some further embodiments, the amount of any single impurity in the formulation at any storage temperature is less than 5.0% when stored at a temperature of 5 °C for a period of 0 months, 0.5 months, 1.0 months, 1.5 months, 2.0 months, 2.5 months, 3.0 months, 3.5 months, 4.0 months, 4.5 months, 5.0 months, 5.5 months, 6.0 months, 8 months, 10 months, 12 months, or more months.

[00378] In some further embodiments, the amount of any single impurity in the formulation at any storage temperature is less than .5% when stored at a temperature of 25 °C for a period of 0 months, 0.5 months, 1.0 months, 1.5 months, 2.0 months, 2.5 months, 3.0 months, 3.5 months, 4.0 months, 4.5 months, 5.0 months, 5.5 months, 6.0 months, 8 months, 10 months, 12 months, or more months. In some further embodiments, the amount of any single impurity in the formulation at any storage temperature is less than 1% when stored at a temperature of 25 °C for a period of 0 months, 0.5 months, 1.0 months, 1.5 months, 2.0 months, 2.5 months, 3.0 months, 3.5 months, 4.0 months, 4.5 months, 5.0 months, 5.5 months, 6.0 months, 8 months, 10 months, 12 months, or more months. In some further embodiments, the amount of any single impurity in the formulation at any storage temperature is less than 1.5% when stored at a temperature of 25 °C for a period of 0 months, 0.5 months, 1.0 months, 1.5 months, 2.0 months, 2.5 months, 3.0 months, 3.5 months, 4.0 months, 4.5 months, 5.0 months, 5.5 months, 6.0 months, 8 months, 10 months, 12 months, or more months. In some further embodiments, the amount of any single impurity in the formulation at any storage temperature is less than 2.0% when stored at a temperature of 25 °C for a period of 0 months, 0.5 months, 1.0 months, 1.5 months, 2.0 months, 2.5 months, 3.0 months, 3.5 months, 4.0 months, 4.5 months, 5.0 months, 5.5 months, 6.0 months, 8 months, 10 months, 12 months, or more months. In some further embodiments, the amount of any single impurity in the formulation at any storage temperature is less than 2.5% when stored at a temperature of 25 °C for a period of 0 months, 0.5 months, 1.0 months, 1.5 months, 2.0 months, 2.5 months, 3.0 months, 3.5 months, 4.0 months, 4.5 months, 5.0 months, 5.5 months, 6.0 months, 8 months, 10 months, 12 months, or more months. In some further embodiments, the amount of any single impurity in the formulation at any storage temperature is less than 3.0% when stored at a temperature of 25 °C for a period of 0 months, 0.5 months, 1.0 months, 1.5 months, 2.0 months, 2.5 months, 3.0 months, 3.5 months, 4.0 months, 4.5 months, 5.0 months, 5.5 months, 6.0 months, 8 months, 10 months, 12 months, or more months. In some further embodiments, the amount of any single impurity in the formulation at any storage temperature is less than 5.0% when stored at a temperature of 25 °C for a period of 0 months, 0.5 months, 1.0 months, 1.5 months, 2.0 months, 2.5 months, 3.0 months, 3.5 months, 4.0 months, 4.5 months, 5.0 months, 5.5 months, 6.0 months, 8 months, 10 months, 12 months, or more months.

[00379] In some further embodiments, the amount of any single impurity in the formulation at any storage temperature is less than .5% when stored at a temperature of 40 °C for a period of 0 months, 0.5 months, 1.0 months, 1.5 months, 2.0 months, 2.5 months, 3.0 months, 3.5 months, 4.0 months, 4.5 months, 5.0 months, 5.5 months, 6.0 months, 8 months, 10 months, 12 months, or more months. In some further embodiments, the amount of any single impurity in the formulation at any storage temperature is less than 1% when stored at a temperature of 40 °C for a period of 0 months, 0.5 months, 1.0 months, 1.5 months, 2.0 months, 2.5 months, 3.0 months, 3.5 months, 4.0 months, 4.5 months, 5.0 months, 5.5 months, 6.0 months, 8 months, 10 months, 12 months, or more months. In some further embodiments, the amount of any single impurity in the formulation at any storage temperature is less than 1.5% when stored at a temperature of 40 °C for a period of 0 months, 0.5 months, 1.0 months, 1.5 months, 2.0 months, 2.5 months, 3.0 months, 3.5 months, 4.0 months, 4.5 months, 5.0 months, 5.5

months, 6.0 months, 8 months, 10 months, 12 months, or more months. In some further embodiments, the amount of any single impurity in the formulation at any storage temperature is less than 2.0% when stored at a temperature of 40 °C for a period of 0 months, 0.5 months, 1.0 months, 1.5 months, 2.0 months, 2.5 months, 3.0 months, 3.5 months, 4.0 months, 4.5 months, 5.0 months, 5.5 months, 6.0 months, 8 months, 10 months, 12 months, or more months. In some further embodiments, the amount of any single impurity in the formulation at any storage temperature is less than 2.5% when stored at a temperature of 40 °C for a period of 0 months, 0.5 months, 1.0 months, 1.5 months, 2.0 months, 2.5 months, 3.0 months, 3.5 months, 4.0 months, 4.5 months, 5.0 months, 5.5 months, 6.0 months, 8 months, 10 months, 12 months, or more months. In some further embodiments, the amount of any single impurity in the formulation at any storage temperature is less than 3.0% when stored at a temperature of 40 °C for a period of 0 months, 0.5 months, 1.0 months, 1.5 months, 2.0 months, 2.5 months, 3.0 months, 3.5 months, 4.0 months, 4.5 months, 5.0 months, 5.5 months, 6.0 months, 8 months, 10 months, 12 months, or more months. In some further embodiments, the amount of any single impurity in the formulation at any storage temperature is less than 5.0% when stored at a temperature of 40 °C for a period of 0 months, 0.5 months, 1.0 months, 1.5 months, 2.0 months, 2.5 months, 3.0 months, 3.5 months, 4.0 months, 4.5 months, 5.0 months, 5.5 months, 6.0 months, 8 months, 10 months, 12 months, or more months.

[00380] In some cases the pharmaceutically acceptable formulation expires in about 1-5 years. In some cases the formulation expires in about 1, 2, 3 or 4 years. In some cases the formulation expires in more than 5 years. In some cases the formulation expires in less than a year. In some cases the formulation expires in 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, or 11 months.

[00381] In some cases the total amount of peptidomimetic degradation products at the time of product expiration are in the range of above 0.1-10%. In some cases the total degradation product at the time of expiration is in the range of about 0.01-1, about 0.01-2, about 0.01-3, about 0.01-4, about 0.01-5, about 0.01-6, about 0.01-7, about 0.01-8, or about 0.01-9, about 1-2, about 1-3, about 1-4, about 1-5, about 1-6, about 1-7, about 1-8, about 1-9, about 2-3, about 3-4, about 2-5, about 2-6, about 2-7, about 2-8, about 2-9, about 3-4, about 3-5, about 3-6, about 3-7, about 3-8, about 3-9, about 3-10, about 4-5, about 4-6, about 4-7, about 4-8, about 4-9, about 4-10, about 5-6, about 5-7, about 5-8, about 5-9, about 5-10, about 6-7, about 6-8, about 6-9, about 6-10, about 7-8, about 7-9, about 7-10, about 8-9, about 8-10 or about 9-10%. In some embodiments the amount of total degradation product at the time of expiration is about 1%, about 2%, about 3%, about 4%, about 5%, about 6%, about 7%, about 8%, about 9%, about 10%. In some embodiments the amount of total degradation product at the time of expiration is about 0.01%, about 0.05%, about 0.1%, about 0.15%, about 0.2%, about 0.25%, about 0.3%, about 0.35%, about 0.40%, about 0.45%, about 0.50%, about 0.55%, about 0.60%, about 0.65%, about 0.70%, about 0.75%, about 0.80%, about 0.85%, about 0.90%, about 0.95%, or about 1.0%.

In some cases aqueous pharmaceutical formulations of the instant disclosure are stored at -40 to 65 °C, for example from -5 to 40 °C. In some cases the formulations can be stored at about -40 °C, about -30 °C, -20 °C, -10 °C, -5 °C, 0 °C, about 5 °C, about 10 °C, about 15 °C, about 20 °C, about 25 °C, about 30 °C, about 35 °C, about

40 °C, about 45 °C, about 50 °C, about 55 °C, about 60 °C, or about 65 °C. In some embodiments, the formulations are stored at or below ambient temperature. In some embodiments, the formulations are stored above ambient temperature.

Sparging

[00382] In some embodiments the stability of the peptidomimetic macrocycles in the formulations of the disclosure can be improved by sparging the formulation with an inert gas. A variety of inert gases can be used as a sparging material including but not limited to nitrogen, argon, helium, or a combination thereof. In some embodiments the inert gas is nitrogen. The sparging is generally carried out till the oxygen is reduced or completely removed from the formulations peptidomimetic macrocycles. The time period for sparging depends in several factors including the amount of formulation, the effectiveness of agitation and the flow rate of the inert gas. In some embodiments, sparging is done by bubbling the inert gas through the formulations for a period of about 1 min-12 h. In some embodiments the formulations are sparged for a period of about 1 min- about 11 h, about 1 min- about 10 h, about 1 min-9 h, about 1 min-8 h, about 1 min-7 h, about 1 min-6 h, about 1 min-5 h, about 1 min-4 h, about 1 min-3 h, about 1 min-2 h, about 1 min-1 h, about 1 min-45 min, about 1 min - about 30 min, about 1 min-15 min, about 1 min-10 min, about 1 min- about 9 min, about 1 min-8 min, about 1 min- about 7 min, about 1 min-6 min, about 1 min- about 5 min, about 1 min- about 4 min, about 1 min- about 3 min, about 1 min- about 2 min. In some embodiments, sparging is performed for less than about 1 minute.

Methods of Use

Methods

[00383] In one aspect, provided herein are aqueous pharmaceutical formulations that are useful in competitive binding assays to identify agents which bind to the natural ligand(s) of the proteins or peptides upon which the peptidomimetic macrocycles are modeled. For example, in the p53/MDMX system, labeled peptidomimetic macrocycles based on p53 can be used in a MDMX binding assay along with small molecules that competitively bind to MDMX. Competitive binding studies allow for rapid *in vitro* evaluation and determination of drug candidates specific for the p53/MDMX system. Such binding studies can be performed with any of the peptidomimetic macrocycles disclosed herein and their binding partners.

[00384] Further provided are methods for the generation of antibodies against the peptidomimetic macrocycles. In some embodiments, these antibodies specifically bind both the peptidomimetic macrocycle and the precursor peptides, such as p53, to which the peptidomimetic macrocycles are related. Such antibodies, for example, disrupt the native protein-protein interaction, for example, binding between p53 and MDMX.

[00385] In other aspects, provided herein are both prophylactic and therapeutic methods of treating a subject at risk of (or susceptible to) a disorder or having a disorder associated with aberrant (*e.g.*, insufficient or excessive) expression or activity of the molecules including p53, MDM2 or MDMX.

[00386] In another embodiment, a disorder is caused, at least in part, by an abnormal level of p53 or MDM2 or MDMX, (*e.g.*, over or under expression), or by the presence of p53 or MDM2 or MDMX exhibiting abnormal activity. As such, the reduction in the level and/or activity of p53 or MDM2 or MDMX, or the enhancement of the level and/or activity of p53 or MDM2 or MDMX, by peptidomimetic macrocycles derived from p53, is used, for example, to ameliorate or reduce the adverse symptoms of the disorder.

In another aspect, provided herein are methods for treating or preventing a disease including hyperproliferative disease and inflammatory disorder by interfering with the interaction or binding between binding partners, for example, between p53 and MDM2 or p53 and MDMX. These methods comprise administering an effective amount of a compound to a warm blooded animal, including a human. In some embodiments, the administration of one or more compounds disclosed herein induces cell growth arrest or apoptosis.

As used herein, the term "treatment" is defined as the application or administration of a therapeutic agent to a patient, or application or administration of a therapeutic agent to an isolated tissue or cell line from a patient, who has a disease, a symptom of disease or a predisposition toward a disease, with the purpose to cure, heal, alleviate, relieve, alter, remedy, ameliorate, improve or affect the disease, the symptoms of disease or the predisposition toward disease.

Disease and Disorders

[00387] In some embodiments, the pharmaceutical formulations can be used to treat, prevent, and/or diagnose cancers and neoplastic conditions. As used herein, the terms "cancer", "hyperproliferative" and "neoplastic" refer to cells having the capacity for autonomous growth, *i.e.*, an abnormal state or condition characterized by rapidly proliferating cell growth. Hyperproliferative and neoplastic disease states can be categorized as pathologic, *i.e.*, characterizing or constituting a disease state, or can be categorized as non-pathologic, *i.e.*, a deviation from normal but not associated with a disease state. The term is meant to include all types of cancerous growths or oncogenic processes, metastatic tissues or malignantly transformed cells, tissues, or organs, irrespective of histopathology type or stage of invasiveness. A metastatic tumor can arise from a multitude of primary tumor types, including but not limited to those of breast, lung, liver, colon and ovarian origin. "Pathologic hyperproliferative" cells occur in disease states characterized by malignant tumor growth. Examples of non-pathologic hyperproliferative cells include proliferation of cells associated with wound repair. Examples of cellular proliferative and/or differentiative disorders include cancer, *e.g.*, carcinoma, sarcoma, or metastatic disorders. In some embodiments, the pharmaceutical formulations can be used for controlling/treating breast cancer, ovarian cancer, colon cancer, lung cancer, metastasis of such cancers and the like.

[00388] Examples of cancers or neoplastic conditions include, but are not limited to, a fibrosarcoma, myosarcoma, liposarcoma, chondrosarcoma, osteogenic sarcoma, chordoma, angiosarcoma, endotheliosarcoma, lymphangiosarcoma, lymphangioendotheliosarcoma, synovioma, mesothelioma, Ewing's tumor, leiomyosarcoma, rhabdomyosarcoma, gastric cancer, esophageal cancer, rectal cancer, pancreatic cancer, ovarian cancer, prostate

cancer, uterine cancer, cancer of the head and neck, skin cancer, brain cancer, squamous cell carcinoma, sebaceous gland carcinoma, papillary carcinoma, papillary adenocarcinoma, cystadenocarcinoma, medullary carcinoma, bronchogenic carcinoma, renal cell carcinoma, hepatoma, bile duct carcinoma, choriocarcinoma, seminoma, embryonal carcinoma, Wilm's tumor, cervical cancer, testicular cancer, small cell lung carcinoma, non-small cell lung carcinoma, bladder carcinoma, epithelial carcinoma, glioma, astrocytoma, medulloblastoma, craniopharyngioma, ependymoma, pinealoma, hemangioblastoma, acoustic neuroma, oligodendroglioma, meningioma, melanoma, neuroblastoma, retinoblastoma, leukemia, lymphoma, Kaposi sarcoma, or glioblastoma multiforme.

[00389] In some embodiments, the cancer is head and neck cancer, melanoma, lung cancer, breast cancer, or glioma.

[00390] In some examples, the cancer is pancreatic cancer, bladder cancer, colon cancer, liver cancer, colorectal cancer (colon cancer or rectal cancer), breast cancer, prostate cancer, renal cancer, hepatocellular cancer, lung cancer, ovarian cancer, cervical cancer, gastric cancer, esophageal cancer, head and neck cancer, melanoma, neuroendocrine cancers, CNS cancers, brain tumors, bone cancer, skin cancer, ocular tumor, choriocarcinoma (tumor of the placenta), sarcoma or soft tissue cancer.

[00391] In some examples, cancer is bladder cancer, bone cancer, breast cancer, cervical cancer, CNS cancer, colon cancer, ocular tumor, renal cancer, liver cancer, lung cancer, pancreatic cancer, choriocarcinoma (tumor of the placenta), prostate cancer, sarcoma, skin cancer, soft tissue cancer or gastric cancer.

[00392] In some examples, the cancer is breast cancer. Non limiting examples of breast cancer that can be treated by the instant pharmaceutical formulations include ductal carcinoma in situ (DCIS or intraductal carcinoma), lobular carcinoma in situ (LCIS), invasive (or infiltrating) ductal carcinoma, invasive (or infiltrating) lobular carcinoma, inflammatory breast cancer, triple-negative breast cancer, paget disease of the nipple, phyllodes tumor (phylloides tumor or cystosarcoma phyllodes), angiosarcoma, adenoid cystic (or adenocystic) carcinoma, low-grade adenosquamous carcinoma, medullary carcinoma, papillary carcinoma, tubular carcinoma, metaplastic carcinoma, micropapillary carcinoma, and mixed carcinoma.

[00393] In some examples, the cancer is bone cancer. Non limiting examples of bone cancer that can be treated by the instant pharmaceutical formulations include osteosarcoma, chondrosarcoma, the Ewing Sarcoma Family of Tumors (ESFTs).

[00394] In some examples, the cancer is skin cancer. Non limiting examples of skin cancer that can be treated by the instant pharmaceutical formulations include melanoma, basal cell skin cancer, and squamous cell skin cancer.

[00395] In some examples, the cancer is ocular tumor. Non limiting examples of ocular tumor that can be treated by the pharmaceutical formulations of the instant disclosure include ocular tumor is choroidal nevus, choroidal melanoma, choroidal metastasis, choroidal hemangioma, choroidal osteoma, iris melanoma, uveal melanoma, melanocytoma, metastasis retinal capillary hemangiomas, congenital hypertrophy of the RPE, RPE adenoma or retinoblastoma.

[00396] Examples of proliferative disorders include hematopoietic neoplastic disorders. As used herein, the term "hematopoietic neoplastic disorders" includes diseases involving hyperplastic/neoplastic cells of hematopoietic origin, *e.g.*, arising from myeloid, lymphoid or erythroid lineages, or precursor cells thereof. The diseases can arise from poorly differentiated acute leukemias, *e.g.*, erythroblastic leukemia and acute megakaryoblastic leukemia. Additional exemplary myeloid disorders include, but are not limited to, acute promyeloid leukemia (APML), acute myelogenous leukemia (AML) and chronic myelogenous leukemia (CML) (reviewed in Vaickus (1991), *Crit Rev. Oncol./Hemotol.* 11:267-97); lymphoid malignancies include, but are not limited to acute lymphoblastic leukemia (ALL) which includes B-lineage ALL and T-lineage ALL, chronic lymphocytic leukemia (CLL), prolymphocytic leukemia (PLL), hairy cell leukemia (HLL) and Waldenstrom's macroglobulinemia (WM). Additional forms of malignant lymphomas include, but are not limited to non-Hodgkin lymphoma and variants thereof, peripheral T cell lymphomas, adult T cell leukemia/lymphoma (ATL), cutaneous T-cell lymphoma (CTCL), large granular lymphocytic leukemia (LGF), Hodgkin's disease and Reed-Stemberg disease.

[00397] Examples of cellular proliferative and/or differentiative disorders of the breast include, but are not limited to, proliferative breast disease including, *e.g.*, epithelial hyperplasia, sclerosing adenosis, and small duct papillomas; tumors, *e.g.*, stromal tumors such as fibroadenoma, phyllodes tumor, and sarcomas, and epithelial tumors such as large duct papilloma; carcinoma of the breast including in situ (noninvasive) carcinoma that includes ductal carcinoma in situ (including Paget's disease) and lobular carcinoma in situ, and invasive (infiltrating) carcinoma including, but not limited to, invasive ductal carcinoma, invasive lobular carcinoma, medullary carcinoma, colloid (mucinous) carcinoma, tubular carcinoma, and invasive papillary carcinoma, and miscellaneous malignant neoplasms. Disorders in the male breast include, but are not limited to, gynecomastia and carcinoma.

[00398] Examples of cellular proliferative and/or differentiative disorders of the skin include, but are not limited to proliferative skin disease such as melanomas, including mucosal melanoma, superficial spreading melanoma, nodular melanoma, lentigo (e.g. lentigo maligna, lentigo maligna melanoma, or acral lentiginous melanoma), amelanotic melanoma, desmoplastic melanoma, melanoma with features of a Spitz nevus, melanoma with small nevus-like cells, polypoid melanoma, and soft-tissue melanoma; basal cell carcinomas including micronodular basal cell carcinoma, superficial basal cell carcinoma, nodular basal cell carcinoma (rodent ulcer), cystic basal cell carcinoma, cicatricial basal cell carcinoma, pigmented basal cell carcinoma, aberrant basal cell carcinoma, infiltrative basal cell carcinoma, nevoid basal cell carcinoma syndrome, polypoid basal cell carcinoma, pore-like basal cell carcinoma, and fibroepithelioma of Pinkus; squamus cell carcinomas including acanthoma (large cell acanthoma), adenoid squamous cell carcinoma, basaloid squamous cell carcinoma, clear cell squamous cell carcinoma, signet-ring cell squamous cell carcinoma, spindle cell squamous cell carcinoma, Marjolin's ulcer, erythroplasia of Queyrat, and Bowen's disease; or other skin or subcutaneous tumors.

[00399] Examples of cellular proliferative and/or differentiative disorders of the lung include, but are not limited to, bronchogenic carcinoma, including paraneoplastic syndromes, bronchioloalveolar carcinoma, neuroendocrine

tumors, such as bronchial carcinoid, miscellaneous tumors, and metastatic tumors; pathologies of the pleura, including inflammatory pleural effusions, noninflammatory pleural effusions, pneumothorax, and pleural tumors, including solitary fibrous tumors (pleural fibroma) and malignant mesothelioma.

[00400] Examples of cellular proliferative and/or differentiative disorders of the colon include, but are not limited to, non-neoplastic polyps, adenomas, familial syndromes, colorectal carcinogenesis, colorectal carcinoma, and carcinoid tumors.

[00401] Examples of cellular proliferative and/or differentiative disorders of the liver include, but are not limited to, nodular hyperplasias, adenomas, and malignant tumors, including primary carcinoma of the liver and metastatic tumors. Examples of cellular proliferative and/or differentiative disorders of the ovary include, but are not limited to, ovarian tumors such as, tumors of coelomic epithelium, serous tumors, mucinous tumors, endometrioid tumors, clear cell adenocarcinoma, cystadenofibroma, Brenner tumor, surface epithelial tumors; germ cell tumors such as mature (benign) teratomas, monodermal teratomas, immature malignant teratomas, dysgerminoma, endodermal sinus tumor, choriocarcinoma; sex cord-stomal tumors such as, granulosa-theca cell tumors, thecomafibromas, androblastomas, hill cell tumors, and gonadoblastoma; and metastatic tumors such as Krukenberg tumors.

[00402] In one aspect, the present invention provides novel peptidomimetic macrocycles that are useful in competitive binding assays to identify agents which bind to the natural ligand(s) of the proteins or peptides upon which the peptidomimetic macrocycles are modeled. For example, in the BH3/BCL-X_L anti-apoptotic system labeled peptidomimetic macrocycles based on BH3 can be used in a BCL-X_L binding assay along with small molecules that competitively bind to BCL-X_L. Competitive binding studies allow for rapid *in vitro* evaluation and determination of drug candidates specific for the BH3/BCL-X_L system. The invention further provides for the generation of antibodies against the peptidomimetic macrocycles. In some embodiments, these antibodies specifically bind both the peptidomimetic macrocycle and the BH3 peptidomimetic precursors upon which the peptidomimetic macrocycles are derived. Such antibodies, for example, disrupt the BH3/BCL-XL systems, respectively.

[00403] In other aspects, the present invention provides for both prophylactic and therapeutic methods of treating a subject at risk of (or susceptible to) a disorder or having a disorder associated with aberrant (*e.g.*, insufficient or excessive) BCL-2 family member expression or activity (*e.g.*, extrinsic or intrinsic apoptotic pathway abnormalities). It is believed that some BCL-2 type disorders are caused, at least in part, by an abnormal level of one or more BCL-2 family members (*e.g.*, over or under expression), or by the presence of one or more BCL-2 family members exhibiting abnormal activity. As such, the reduction in the level and/or activity of the BCL-2 family member or the enhancement of the level and/or activity of the BCL-2 family member, is used, for example, to ameliorate or reduce the adverse symptoms of the disorder.

[00404] In one embodiment, the compounds of the invention are used to treat disorders associated with expression or overexpression of Mcl-1. Mcl-1 has been shown to be expressed in many tissues and neoplastic cell lines and is

thought to participate in the development of malignancies (Thallinger et al. (2004) Clin. Cancer Res. 10:4185-4191). The peptidomimetic macrocycles of the invention can be used for the treatment of such malignancies.

[00405] In one embodiment, the disorder being treated (*e.g.* cancer) is differentially responsive to the peptidomimetic macrocycles of the invention. In some embodiments, the cancer is treated with a BIM peptidomimetic macrocycle and is at least 2-fold less sensitive to treatment using a BID polypeptide (such as a BID peptidomimetic macrocycle or uncrosslinked polypeptide) as measured in an *in vitro* cell viability assay. In other embodiments, the cancer is at least 5-fold less sensitive to treatment using a BID polypeptide as measured in an *in vitro* cell viability assay. In yet other embodiments, the cancer is at least 8-fold less sensitive to treatment using a BID polypeptide as measured in an *in vitro* cell viability assay. In other embodiments, the cancer is treated with a BID peptidomimetic macrocycle and is at least 2-fold less sensitive to treatment using a BIM polypeptide (such as a BIM peptidomimetic macrocycle or uncrosslinked polypeptide) as measured in an *in vitro* cell viability assay. In other embodiments, the cancer is at least 5-fold less sensitive to treatment using a BIM polypeptide as measured in an *in vitro* cell viability assay. In yet other embodiments, the cancer is at least 8-fold less sensitive to treatment using a BIM polypeptide as measured in an *in vitro* cell viability assay.

[00406] In another embodiment, a method of treating a human patient is provided comprising performing an assay to evaluate the levels of a BCL-family protein and administering to the patient a peptidomimetic macrocycle if an aberrant or irregular level of expression of the BCL-family protein is detected. BCL-family proteins include, for example, BCL-2, BCL-X_L, MCL-1, Bfl1/A1, BOO/DIVA, NRH/NR13, BAX, BAD, BAK, BOK, BIK, PUMA, BIM, BMF, BLK, BNIP3, HRK, NIX, SPIKE, and Noxa. In one embodiment, a method of treating a human patient is provided comprising performing an assay to evaluate the levels of BCL-2 in the patient and administering to the patient a peptidomimetic macrocycle if an aberrant or irregular level of expression of BCL-2 is detected. In another embodiment, a method of treating a human patient is provided comprising performing an assay to evaluate the levels of BCL-X_L in the patient and administering to the patient a peptidomimetic macrocycle if an aberrant or irregular level of expression of BCL-X_L is detected. In another embodiment, a method of treating a human patient is provided comprising performing an assay to evaluate the levels of MCL-1 in the patient and administering to the patient a peptidomimetic macrocycle if an aberrant or irregular level of expression of MCL-1 is detected. In another embodiment, a method of treating a human patient is provided comprising performing an assay to evaluate the levels of BAX in the patient and administering to the patient a peptidomimetic macrocycle if an aberrant or irregular level of expression of BAX is detected. In another embodiment, a method of treating a human patient is provided comprising performing an assay to evaluate the levels of BAD in the patient and administering to the patient a peptidomimetic macrocycle if an aberrant or irregular level of expression of BAD is detected. In another embodiment, a method of treating a human patient is provided comprising performing an assay to evaluate the levels of BAK in the patient and administering to the patient a peptidomimetic macrocycle if an aberrant or irregular level of expression of BAK is detected. In another embodiment, a method of treating a human patient is provided comprising performing an assay to evaluate the

levels of PUMA in the patient and administering to the patient a peptidomimetic macrocycle if an aberrant or irregular level of expression of PUMA is detected. In another embodiment, a method of treating a human patient is provided comprising performing an assay to evaluate the levels of Noxa in the patient and administering to the patient a peptidomimetic macrocycle if an aberrant or irregular level of expression of Noxa is detected. In another embodiment, a method of treating a human patient is provided comprising performing an assay to evaluate the levels of Noxa in the patient and administering to the patient a peptidomimetic macrocycle if an aberrant or irregular level of expression of Noxa is detected. In another embodiment, a method of treating a human patient is provided comprising performing an assay to evaluate the levels of Bfl1/A1 in the patient and administering to the patient a peptidomimetic macrocycle if an aberrant or irregular level of expression of Bfl1/A1 is detected. In another embodiment, a method of treating a human patient is provided comprising performing an assay to evaluate the levels of BOO/DIVA in the patient and administering to the patient a peptidomimetic macrocycle if an aberrant or irregular level of expression of BOO/DIVA is detected. In another embodiment, a method of treating a human patient is provided comprising performing an assay to evaluate the levels of NRH/NR13 in the patient and administering to the patient a peptidomimetic macrocycle if an aberrant or irregular level of expression of NRH/NR13 is detected. In another embodiment, a method of treating a human patient is provided comprising performing an assay to evaluate the levels of BOK in the patient and administering to the patient a peptidomimetic macrocycle if an aberrant or irregular level of expression of BOK is detected. In another embodiment, a method of treating a human patient is provided comprising performing an assay to evaluate the levels of BIK in the patient and administering to the patient a peptidomimetic macrocycle if an aberrant or irregular level of expression of BIK is detected. In another embodiment, a method of treating a human patient is provided comprising performing an assay to evaluate the levels of BMF in the patient and administering to the patient a peptidomimetic macrocycle if an aberrant or irregular level of expression of BMF is detected. In another embodiment, a method of treating a human patient is provided comprising performing an assay to evaluate the levels of BLK in the patient and administering to the patient a peptidomimetic macrocycle if an aberrant or irregular level of expression of BLK is detected. In another embodiment, a method of treating a human patient is provided comprising performing an assay to evaluate the levels of BNIP3 in the patient and administering to the patient a peptidomimetic macrocycle if an aberrant or irregular level of expression of BNIP3 is detected. In another embodiment, a method of treating a human patient is provided comprising performing an assay to evaluate the levels of HRK in the patient and administering to the patient a peptidomimetic macrocycle if an aberrant or irregular level of expression of HRK is detected. In another embodiment, a method of treating a human patient is provided comprising performing an assay to evaluate the levels of Nix in the patient and administering to the patient a peptidomimetic macrocycle if an aberrant or irregular level of expression of Nix is detected. In another embodiment, a method of treating a human patient is provided comprising performing an assay to evaluate the levels of SPIKE in the patient and administering to the patient a peptidomimetic macrocycle if an aberrant or irregular level of expression of SPIKE is detected.

[00407] In one aspect, the invention provides methods of treating breast cancer by administering the peptidomimetic macrocycles of the invention. Breast cancer includes invasive breast carcinomas, such as invasive ductal carcinoma, invasive lobular carcinoma, tubular carcinoma, invasive cribriform carcinoma, medullary carcinoma, mucinous carcinoma and other tumours with abundant mucin, cystadenocarcinoma, columnar cell mucinous carcinoma, signet ring cell carcinoma, neuroendocrine tumours (including solid neuroendocrine carcinoma, atypical carcinoid tumour, small cell/oat cell carcinoma, or large cell neuroendocrine carcioma), invasive papillary carcinoma, invasive micropapillary carcinoma, apocrine carcinoma, metaplastic carcinomas, pure epithelial metaplastic carciomas, mixed epithelial/mesenchymal metaplastic carcinomas, lipid-rich carcinoma, secretory carcinoma, oncocytic carcinoma, adenoid cystic carcinoma, acinic cell carcinoma, glycogen-rich clear cell carcinoma, sebaceous carcinoma, inflammatory carcinoma or bilateral breast carcinoma; mesenchymal tumors such as haemangioma, angiomatosis, haemangiopericytoma, pseudoangiomatous stromal hyperplasia, myofibroblastoma, fibromatosis (aggressive), inflammatory myofibroblastic tumour, lipoma, angiolipoma, granular cell tumour, neurofibroma, schwannoma, angiosarcoma, liposarcoma, rhabdomyosarcoma, osteosarcoma, leiomyoma, or leiomysarcoma; myoepithelial lesions such as myoepitheliosis, adenomyoepithelial adenosis, adenomyoepithelioma, or malignant myoepithelioma; fibroepithelial tumours such as fibroadenoma, phyllodes tumour, low grade periductal stromal sarcoma, or mammary hamartoma; and tumours of the nipple such as nipple adenoma, syringomatous adenoma, or Paget's disease of the nipple.

[00408] Treatment of breast cancer can be effected in conjunction with any additional therapy, such as a therapy that is part of the standard of care. A surgical technique such as lumpectomy or mastectomy can be performed prior to, during, or following treatment with the peptidomimetic macrocycles of the invention. Alternatively, radiation therapy can be used for the treatment of breast cancer in conjunction with the peptidomimetic macrocycles of the invention. In other cases, the peptidomimetic macrocycles of the invention are administered in combination with a second therapeutic agent. Such an agent can be a chemotherapeutic agent such as an individual drug or combination of drugs and therapies. For example, the chemotherapeutic agent can be an adjuvant chemotherapeutic treatment such as CMF (cyclophosphamide, methotrexate, and 5-fluorouracil); FAC or CAF (5-fluorouracil, doxorubicin, cyclophosphamide); AC or CA (doxorubicin and cyclophosphamide); AC-Taxol (AC followed by paclitaxel); TAC (docetaxel, doxorubicin, and cyclophosphamide); FEC (5-fluorouracil, epirubicin and cyclophosphamide); FECD (FEC followed by docetaxel); TC (docetaxel and cyclophosphamide). In addition to chemotherapy, trastuzumab can also be added to the regimen depending on the tumor characteristics (i.e. HER2/neu status) and risk of relapse. Hormonal therapy can also be appropriate before, during or following chemotherapeutic treatment. For example, tamoxifen can be administered or a compound in the category of aromatase inhibitors including, but not limited to aminogluthetimide, anastrozole, exemestane, formestane, letrozole, or vorozole. In other embodiments, an antiangiogenic agent can be used in combination therapy for the treatment of breast cancer. The antiangiogenic agent can be an anti-VEGF agent including, but not limited to bevacizumab.

[00409] In another aspect, the peptidomimetic macrocycles of the invention can be used to treat ovarian cancer. Ovarian cancers include ovarian tumors such as, tumors of coelomic epithelium, serous tumors, mucinous tumors, endometrioid tumors, clear cell adenocarcinoma, cystadenofibroma, Brenner tumor, surface epithelial tumors; germ cell tumors such as mature (benign) teratomas, monodermal teratomas, immature malignant teratomas, dysgerminoma, endodermal sinus tumor, choriocarcinoma; sex cord-stomal tumors such as, granulosa-theca cell tumors, thecomafibromas, androblastomas, hill cell tumors, and gonadoblastoma; and metastatic tumors such as Krukenberg tumors.

[00410] The peptidomimetic macrocycles of the invention can be administered in conjunction with a second therapy such as a therapy that is part of the standard of care. Surgery, immunotherapy, chemotherapy, hormone therapy, radiation therapy, or a combination thereof, are some possible treatments available for ovarian cancer. Some possible surgical procedures include debulking, and a unilateral or bilateral oophorectomy and/or a unilateral or bilateral salpigectomy.

[00411] Anti-cancer drugs that can be used include cyclophosphamide, etoposide, altretamine, and ifosfamide. Hormone therapy with the drug tamoxifen can be used to shrink ovarian tumors. Radiation therapy can be external beam radiation therapy and/or brachytherapy.

[00412] In another aspect, the peptidomimetic macrocycles of the invention can be used to treat prostate cancer. Prostate cancers include adenocarcinomas and metastasized adenocarcinomas. The peptidomimetic macrocycles of the invention can be administered in conjunction with a second therapy such as a therapy that is part of the standard of care. Treatment for prostate cancer can involve surgery, radiation therapy, High Intensity Focused Ultrasound (HIFU), chemotherapy, cryosurgery, hormonal therapy, or any combination thereof. Surgery can involve prostatectomy, radical perineal prostatectomy, laparoscopic radical prostatectomy, transurethral resection of the prostate or orchiectomy. Radiation therapy can include external beam radiation therapy and/or brachytherapy. Hormonal therapy can include orchiectomy; administration of antiandrogens such as flutamide, bicalutamide, nilutamide, or cyproterone acetate; medications which inhibit the production of adrenal androgens such as DHEA, such as ketoconazole and aminoglutethimide; and GnRH antagonists or agonists such as Abarelix (Plenaxis®), Cetrorelix (Cetrotide®), Ganirelix (Antagon®), leuprolide, goserelin, triptorelin, or buserelin. Treatment with an anti-androgen agent, which blocks androgen activity in the body, is another available therapy. Such agents include flutamide, bicalutamide, and nilutamide. This therapy is typically combined with LHRH analog administration or an orchiectomy, which is termed a combined androgen blockade (CAB). Chemotherapy includes, but is not limited to, administration of docetaxel, for example with a corticosteroid such as prednisone. Anti-cancer drugs such as doxorubicin, estramustine, etoposide, mitoxantrone, vinblastine, paclitaxel, carboplatin can also be administered to slow the growth of prostate cancer, reduce symptoms and improve the quality of life. Additional compounds such as bisphosphonate drugs can also be administered.

[00413] In another aspect, the peptidomimetic macrocycles of the invention can be used to treat renal cancer. Renal cancers include, but are not limited to, renal cell carcinomas, metastases from extra-renal primary

neoplasms, renal lymphomas, squamous cell carcinomas, juxtaglomerular tumors (reninomas), transitional cell carcinomas, angiomyolipomas, oncocytomas and Wilm's tumors. The peptidomimetic macrocycles of the invention can be administered in conjunction with a second therapy such as a therapy that is part of the standard of care. Treatment for renal cancer can involve surgery, percutaneous therapies, radiation therapies, chemotherapy, vaccines, or other medication. Surgical techniques useful for treatment of renal cancer in combination with the peptidomimetic macrocycles of the invention include nephrectomy, which can include removal of the adrenal gland, retroperitoneal lymph nodes, and any other surrounding tissues affected by the invasion of the tumor. Percutaneous therapies include, for example, image-guided therapies which can involve imaging of a tumor followed by its targeted destruction by radiofrequency ablation or cryotherapy. In some cases, other chemotherapeutic or other medications useful in treating renal cancer can be α-interferon, interleukin-2, bevacizumab, sorafenib, sunitib, temsirolimus or other kinase inhibitors.

[00414] In other aspects, the invention provides methods of treating pancreatic cancer by administering peptidomimetic macrocycles of the invention, such as a pancreatic cancer selected from the following: an epitheliod carcinoma in the pancreatic duct tissue and an adenocarcinoma in a pancreatic duct. The most common type of pancreatic cancer is an adenocarcinoma, which occurs in the lining of the pancreatic duct. Possible treatments available for pancreatic cancer include surgery, immunotherapy, radiation therapy, and chemotherapy. Possible surgical treatment options include a distal or total pancreatectomy and a pancreaticoduodenectomy (Whipple procedure). Radiation therapy can be an option for pancreatic cancer patients, specifically external beam radiation where radiation is focused on the tumor by a machine outside the body. Another option is intraoperative electron beam radiation administered during an operation. Chemotherapy can also be used to treat pancreatic cancer patients. Suitable anti-cancer drugs include, but are not limited to, 5-fluorouracil (5-FU), mitomycin, ifosfamide, doxorubicin, streptozocin, chlorozotocin, and combinations thereof. The methods provided by the invention can provide a beneficial effect for pancreatic cancer patients, by administration of a polypeptide of the invention or a combination of administration of a peptidomimetic macrocycle and surgery, radiation therapy, or chemotherapy.

[00415] In one aspect, peptidomimetic macrocycles of the invention can be used for the treatment of colon cancer, including but not limited to non-neoplastic polyps, adenomas, familial syndromes, colorectal carcinogenesis, colorectal carcinoma, and carcinoid tumors. Possible treatments available for colon cancer that can be used in conjunction with the peptidomimetic macrocycles of the invention include surgery, chemotherapy, radiation therapy or targeted drug therapy.

[00416] Radiation therapy can include external beam radiation therapy and/or brachytherapy. Chemotherapy can be used to reduce the likelihood of metastasis developing, shrink tumor size, or slow tumor growth. Chemotherapy is often applied after surgery (adjuvant), before surgery (neo-adjuvant), or as the primary therapy if surgery is not indicated (palliative). For example, exemplary regimens for adjuvant chemotherapy involve the combination of infusional 5-fluorouracil, leucovorin, and oxaliplatin (FOLFOX). First line chemotherapy

regimens can involve the combination of infusional 5-fluorouracil, leucovorin, and oxaliplatin (FOLFOX) with a targeted drug such as bevacizumab, cetuximab or panitumumab or infusional 5-fluorouracil, leucovorin, and irinotecan (FOLFIRI) with targeted drug such as bevacizumab, cetuximab or panitumumab. Other chemotherapeutic agents that can be useful in the treatment or prevention of colon cancer in combination with the peptidomimetic macrocycles of the invention are Bortezomib (Velcade®), Oblimersen (Genasense®, G3139), Gefitinib and Erlotinib (Tarceva®) and Topotecan (Hycamtin®).

[00417] Some embodiments provide methods for the treatment of lung cancer using the peptidomimetic macrocycles of the invention. Examples of cellular proliferative and/or differentiative disorders of the lung include, but are not limited to, bronchogenic carcinoma, including paraneoplastic syndromes, bronchioloalveolar carcinoma, neuroendocrine tumors, such as bronchial carcinoid, miscellaneous tumors, and metastatic tumors; pathologies of the pleura, including inflammatory pleural effusions, noninflammatory pleural effusions, pneumothorax, and pleural tumors, including solitary fibrous tumors (pleural fibroma) and malignant mesothelioma.

[00418] The most common type of lung cancer is non-small cell lung cancer (NSCLC), which accounts for approximately 80-85% of lung cancers and is divided into squamous cell carcinomas, adenocarcinomas, and large cell undifferentiated carcinomas. Small cell lung cancer, *e.g.* small cell lung carcinomas, accounts for 15-20% of lung cancers. Treatment options for lung cancer include surgery, immunotherapy, radiation therapy, chemotherapy, photodynamic therapy, or a combination thereof. Some possible surgical options for treatment of lung cancer are a segmental or wedge resection, a lobectomy, or a pneumonectomy. Radiation therapy can be external beam radiation therapy or brachytherapy. Some anti-cancer drugs that can be used in chemotherapy to treat lung cancer in combination with the peptidomimetic macrocycles of the invention include cisplatin, carboplatin, paclitaxel, docetaxel, gemcitabine, vinorelbine, irinotecan, etoposide, vinblastine, gefitinib, ifosfamide, methotrexate, or a combination thereof. Photodynamic therapy (PDT) can be used to treat lung cancer patients. The methods described herein can provide a beneficial effect for lung cancer patients, by administration of a peptidomimetic macrocycle or a combination of administration of a peptidomimetic macrocycle and surgery, radiation therapy, chemotherapy, photodynamic therapy, or a combination thereof.

[00419] Examples of cellular proliferative and/or differentiative disorders of the liver include, but are not limited to, nodular hyperplasias, adenomas, and malignant tumors, including primary carcinoma of the liver and metastatic tumors.

[00420] Immunoproliferative disorders (also known as "immunoproliferative diseases" or "immunoproliferative neoplasms") are disorders of the immune system that are characterized by the abnormal proliferation of the primary cells of the immune system, which includes B cells, T cells and Natural Killer (NK) cells, or by the excessive production of immunoglobulins (also known as antibodies). Such disorders include the general categories of lymphoproliferative disorders, hypergammaglobulinemias, and paraproteinemias. Examples of such disorders include, but are not limited to, X-linked lymphoproliferative disorder, autosomal lymphoproliferative

disorder, Hyper-IgM syndrome, heavy chain disease, and cryoglobulinemia. Other immunoproliferative disorders can be graft versus host disease (GVHD); psoriasis; immune disorders associated with graft transplantation rejection; T cell lymphoma; T cell acute lymphoblastic leukemia; testicular angiocentric T cell lymphoma; benign lymphocytic angiitis; and autoimmune diseases such as lupus erythematosus, Hashimoto's thyroiditis, primary myxedema, Graves' disease, pernicious anemia, autoimmune atrophic gastritis, Addison's disease, insulin dependent diabetes mellitis, good pasture's syndrome, myasthenia gravis, pemphigus, Crohn's disease, sympathetic ophthalmia, autoimmune uveitis, multiple sclerosis, autoimmune hemolytic anemia, idiopathic thrombocytopenia, primary biliary cirrhosis, chronic action hepatitis, ulceratis colitis, Sjogren's syndrome, rheumatoid arthritis, polymyositis, scleroderma, and mixed connective tissue disease.

[00421] Combination Treatments

[00422] In one embodiment, peptidomimetic macrocycles of the invention can be used for the treatment of cancer in conjunction with alkylating and alkylating-like agents. Such agents include, for example, nitrogen mustards such as chlorambucil, chlormethine, cyclophosphamide, ifosfamide, and melphalan; nitrosoureas such as carmustine, fotemustine, lomustine, and streptozocin; platinum therapeutic agents such as carboplatin, cisplatin, oxaliplatin, BBR3464, and satraplatin; or other agents, including but not limited to busulfan, dacarbazine, procarbazine, temozolomide, thiotepa, treosulfan, or uramustine.

[00423] In another embodiment, peptidomimetic macrocycles of the invention can be used in conjunction with an antineoplastic agent which is an antimetabolite. For example, such an antineoplastic agent can be a folic acid such as aminopterin, methotrexate, pemetrexed, or raltitrexed. Alternatively, the antineoplastic agent can be a purine, including but not limited to cladribine, clofarabine, fludarabine, mercaptopurine, pentostatin, thioguanine. In further embodiments, the antineoplastic agent can be a pyrimidine such as capecitabine, cytarabine, fluorouracil, floxuridine, and gemcitabine.

[00424] In still other embodiments, peptidomimetic macrocycles of the invention can be used in conjunction with an antineoplastic agent which is an spindle poison/mitotic inhibitor. Agents in this category include taxanes, for example docetaxel and paclitaxel; and vinca alkaloids such as vinblastine, vincristine, vindesine, and vinorelbine. In yet other embodiments, peptidomimetic macrocycles of the invention can be used in combination with an antineoplastic agent which is a cytotoxic/antitumor antibiotic from the anthracycline family such as daunorubicin, doxorubicin, epirubicin, idarubicin, mitoxantrone, pixantrone, or valrubicin; an antibiotic from the streptomyces family such as actinomycin, bleomycin, mitomycin, or plicamycin; or hydroxyurea. Alternatively, agents used for combination therapy can be topoisomerase inhibitors including, but not limited to camptothecin, topotecan, irinotecan, etoposide, or teniposide.

[00425] Alternatively, the antineoplastic agent can be an antibody or antibody-derived agent. For example, a receptor tyrosine kinase-targeted antibody such as cetuximab, panitumumab, or trastuzumab can be used. Alternatively, the antibody can be an anti-CD20 antibody such as rituximab or tositumomab, or any other suitable antibody including but not limited to alemtuzumab, bevacizumab, and gemtuzumab. In other embodiments, the

antineoplastic agent is a photosensitizer such as aminolevulinic acid, methyl aminolevulinate, porfimer sodium, or verteporfin. In still other embodiments, the antineoplastic agent is a tyrosine kinase inhibitor such as dediranib, dasatinib, erlotinib, gefitinib, imatinib, lapatinib, nilotinib, sorafenib, sunitinib, or vandetanib. Other neoplastic agents suitable in the use of the invention include, for example, alitretinoin, tretinoin, altretamine, amsacrine, anagrelide, arsenic trioxide, asparaginase (pegaspargase), bexarotene, bortezomib, denileukin diftitox, estramustine, ixabepilone, masoprocol, or mitotane.

[00426] In other or further embodiments, the peptidomimetics macrocycles described herein are used to treat, prevent or diagnose conditions characterized by overactive cell death or cellular death due to physiologic insult, etc. Some examples of conditions characterized by premature or unwanted cell death are or alternatively unwanted or excessive cellular proliferation include, but are not limited to hypocellular/hypoplastic, acellular/aplastic, or hypercellular/hyperplastic conditions. Some examples include hematologic disorders including but not limited to fanconi anemia, aplastic anemia, thalaessemia, congenital neutropenia, myelodysplasia

[00427] In other or further embodiments, the peptidomimetics macrocycles of the invention that act to decrease apoptosis are used to treat disorders associated with an undesirable level of cell death. Thus, in some embodiments, the anti-apoptotic peptidomimetics macrocycles of the invention are used to treat disorders such as those that lead to cell death associated with viral infection, *e.g.*, infection associated with infection with human immunodeficiency virus (HIV). A wide variety of neurological diseases are characterized by the gradual loss of specific sets of neurons, and the anti-apoptotic peptidomimetics macrocycles of the invention are used, in some embodiments, in the treatment of these disorders. Such disorders include Alzheimer's disease, Parkinson's disease, amyotrophic lateral sclerosis (ALS) retinitis pigmentosa, spinal muscular atrophy, and various forms of cerebellar degeneration. The cell loss in these diseases does not induce an inflammatory response, and apoptosis appears to be the mechanism of cell death. In addition, a number of hematologic diseases are associated with a decreased production of blood cells. These disorders include anemia associated with chronic disease, aplastic anemia, chronic neutropenia, and the myelodysplastic syndromes. Disorders of blood cell production, such as myelodysplastic syndrome and some forms of aplastic anemia, are associated with increased apoptotic cell death within the bone marrow. These disorders could result from the activation of genes that promote apoptosis, acquired deficiencies in stromal cells or hematopoietic survival factors, or the direct effects of toxins and mediators of immune responses. Two common disorders associated with cell death are myocardial infarctions and stroke. In both disorders, cells within the central area of ischemia, which is produced in the event of acute loss of blood flow, appear to die rapidly as a result of necrosis. However, outside the central ischemic zone, cells die over a more protracted time period and morphologically appear to die by apoptosis.

[00428] In other or further embodiments, the anti-apoptotic peptidomimetics macrocycles of the invention are used to treat all such disorders associated with undesirable cell death.

[00429] Some examples of immunologic disorders that are treated with the peptidomimetics macrocycles described herein include but are not limited to organ transplant rejection, arthritis, lupus, IBD, Crohn's disease, asthma, multiple sclerosis, diabetes, etc.

[00430] Some examples of neurologic disorders that are treated with the peptidomimetics macrocycles described herein include but are not limited to Alzheimer's Disease, Down's Syndrome, Dutch Type Hereditary Cerebral Hemorrhage Amyloidosis, Reactive Amyloidosis, Familial Amyloid Nephropathy with Urticaria and Deafness, Muckle-Wells Syndrome, Idiopathic Myeloma; Macroglobulinemia-Associated Myeloma, Familial Amyloid Polyneuropathy, Familial Amyloid Cardiomyopathy, Isolated Cardiac Amyloid, Systemic Senile Amyloidosis, Adult Onset Diabetes, Insulinoma, Isolated Atrial Amyloid, Medullary Carcinoma of the Thyroid, Familial Amyloidosis, Hereditary Cerebral Hemorrhage With Amyloidosis, Familial Amyloidotic Polyneuropathy, Scrapie, Creutzfeldt-Jacob Disease, Gerstmann Straussler-Scheinker Syndrome, Bovine Spongiform Encephalitis, a prion-mediated disease, and Huntington's Disease.

[00431] Some examples of endocrinologic disorders that are treated with the peptidomimetics macrocycles described herein include but are not limited to diabetes, hypothyroidism, hypopituitarism, hypoparathyroidism, hypogonadism, etc.

[00432] Examples of cardiovascular disorders (*e.g.*, inflammatory disorders) that are treated or prevented with the peptidomimetics macrocycles of the invention include, but are not limited to, atherosclerosis, myocardial infarction, stroke, thrombosis, aneurism, heart failure, ischemic heart disease, angina pectoris, sudden cardiac death, hypertensive heart disease; non-coronary vessel disease, such as arteriolosclerosis, small vessel disease, nephropathy, hypertriglyceridemia, hypercholesterolemia, hyperlipidemia, xanthomatosis, asthma, hypertension, emphysema and chronic pulmonary disease; or a cardiovascular condition associated with interventional procedures ("procedural vascular trauma"), such as restenosis following angioplasty, placement of a shunt, stent, synthetic or natural excision grafts, indwelling catheter, valve or other implantable devices. Preferred cardiovascular disorders include atherosclerosis, myocardial infarction, aneurism, and stroke.

[00433] In some embodiments, the peptidomimetic macrocycles are useful in the treatment of viral disorders. For example, in the PB1/PA system, labeled peptidomimetic macrocycles based on PB1 can be used in a PA binding assay along with small molecules that competitively bind to PA. Competitive binding studies allow for rapid *in vitro* evaluation and determination of drug candidates specific for the PB1/PA system. Such binding studies can be performed with any of the peptidomimetic macrocycles disclosed herein and their binding partners. Antibodies can also be developed which disrupt the binding between PA and PD1.

[00434] For example, peptidomimetic macrocycles derived from the PB1 helix sequence, or peptidomimetic macrocycles that bind selectively to the PB1 peptide binding site of the PA protein, can selectively inhibit influenza RNA-dependent RNA polymerases. Peptidomimetic macrocycles derived from the PB2 helix sequence, or peptidomimetic macrocycles that bind selectively to the PB2 peptide binding site of the PB1 protein, can selectively inhibit influenza RNA-dependent RNA polymerases. When administered within a therapeutic window

after infection, such peptidomimetic macrocycles can reduce the severity or duration of an influenza infection. When administered prophylactically, such peptidomimetic macrocycles can prevent infection by influenza viruses and thereby decrease the spread of influenza and reduce large-scale epidemics.

[00435] In one aspect, the present invention provides novel peptidomimetic macrocycles that are useful in competitive binding assays to identify agents which bind to the natural ligand(s) of the proteins or peptides upon which the peptidomimetic macrocycles are modeled. For example, in the PB1/PA system, labeled peptidomimetic macrocycles based on PB1 can be used in a PA binding assay along with small molecules that competitively bind to PA. Competitive binding studies allow for rapid *in vitro* evaluation and determination of drug candidates specific for the PB1/PA system. Such binding studies can be performed with any of the peptidomimetic macrocycles disclosed herein and their binding partners.

[00436] In other aspects, the present invention provides for both prophylactic and therapeutic methods of treating a subject infected with, at risk of, or susceptible to an influenza virus. These methods comprise administering an effective amount of a compound to a warm blooded animal, including a human. In some embodiments, the administration of the compounds of the present invention prevents the proliferation or transmission of an influenza virus.

[00437] In some embodiments, peptidomimetic macrocycles are used to treat diseases induced by influenza viruses. Like other viruses, the replication of influenza virus involves six phases; transmission, entry, replication, biosynthesis, assembly, and exit. Entry occurs by endocytosis, replication and vRNP assembly takes place in the nucleus, and the virus buds from the plasma membrane. In the infected patient, the virus targets airway epithelial cells.

[00438] The methods described herein are also useful for development and/or identification of agents for the treatment of infections caused by viruses such as Abelson leukemia virus, Abelson murine leukemia virus, Abelson's virus, Acute laryngotracheobronchitis virus, Adelaide River virus, Adeno associated virus group, Adenovirus, African horse sickness virus, African swine fever virus, AIDS virus, Aleutian mink disease parvovirus, Alpharetrovirus, Alphavirus, ALV related virus, Amapari virus, Aphthovirus, Aquareovirus, Arbovirus, Arbovirus C, arbovirus group A, arbovirus group B, Arenavirus group, Argentine hemorrhagic fever virus, Argentine hemorrhagic fever virus, Arterivirus, Astrovirus, Ateline herpesvirus group, Aujezky's disease virus, Aura virus, Ausduk disease virus, Australian bat lyssavirus, Aviadenovirus, avian erythroblastosis virus, avian infectious bronchitis virus , avian leukemia virus, avian leukosis virus, avian lymphomatosis virus, avian myeloblastosis virus, avian paramyxovirus, avian pneumoencephalitis virus, avian reticuloendotheliosis virus, avian sarcoma virus, avian type C retrovirus group, Avihepadnavirus, Avipoxvirus, B virus, B19 virus, Babanki virus, baboon herpesvirus, baculovirus, Barmah Forest virus, Bebaru virus, Berrimah virus, Betaretrovirus, Birnavirus, Bittner virus, BK virus, Black Creek Canal virus, bluetongue virus, Bolivian hemorrhagic fever virus, Boma disease virus, border disease of sheep virus, borna virus, bovine alphaherpesvirus 1, bovine alphaherpesvirus 2, bovine coronavirus, bovine ephemeral fever virus, bovine immunodeficiency virus, bovine

leukemia virus, bovine leukosis virus, bovine mammillitis virus, bovine papillomavirus, bovine papular stomatitis virus, bovine parvovirus, bovine syncytial virus, bovine type C oncovirus, bovine viral diarrhea virus, Buggy Creek virus, bullet shaped virus group, Bunyamwera virus supergroup, Bunyavirus, Burkitt's lymphoma virus, Bwamba Fever, CA virus, Calicivirus, California encephalitis virus, camelpox virus, canarypox virus, canid herpesvirus, canine coronavirus, canine distemper virus, canine herpesvirus , canine minute virus, canine parvovirus, Cano Delgadito virus, caprine arthritis virus, caprine encephalitis virus, Caprine Herpes Virus, Capripox virus, Cardiovirus, caviid herpesvirus 1, Cercopithecid herpesvirus 1, cercopithecine herpesvirus 1, Cercopithecine herpesvirus 2, Chandipura virus, Changuinola virus, channel catfish virus, Charleville virus, chickenpox virus, Chikungunya virus, chimpanzee herpesvirus, chub reovirus, chum salmon virus, Cocal virus, Coho salmon reovirus, coital exanthema virus, Colorado tick fever virus, Coltivirus, Columbia SK virus, common cold virus, contagious ecthyma virus, contagious pustular dermatitis virus, Coronavirus, Corriparta virus, coryza virus, cowpox virus, coxsackie virus, CPV (cytoplasmic polyhedrosis virus), cricket paralysis virus, Crimean-Congo hemorrhagic fever virus, croup associated virus, Cryptovirus, Cypovirus, Cytomegalovirus, cytomegalovirus group, cytoplasmic polyhedrosis virus, deer papillomavirus, deltaretrovirus, dengue virus, Densovirus, Dependovirus, Dhori virus, diplorna virus, Drosophila C virus, duck hepatitis B virus, duck hepatitis virus 1, duck hepatitis virus 2, duovirus, Duvenhage virus, Deformed wing virus DWV, eastern equine encephalitis virus, eastern equine encephalomyelitis virus, EB virus, Ebola virus, Ebola-like virus, echo virus, echovirus, echovirus 10, echovirus 28, echovirus 9, ectromelia virus, EEE virus, EIA virus, EIA virus, encephalitis virus, encephalomyocarditis group virus, encephalomyocarditis virus, Enterovirus, enzyme elevating virus, enzyme elevating virus (LDH), epidemic hemorrhagic fever virus, epizootic hemorrhagic disease virus, Epstein-Barr virus, equid alphaherpesvirus 1, equid alphaherpesvirus 4, equid herpesvirus 2, equine abortion virus, equine arteritis virus, equine encephalosis virus, equine infectious anemia virus, equine morbillivirus, equine rhinopneumonitis virus, equine rhinovirus, Eubenangu virus, European elk papillomavirus, European swine fever virus, Everglades virus, Eyach virus, felid herpesvirus 1, feline calicivirus, feline fibrosarcoma virus, feline herpesvirus, feline immunodeficiency virus, feline infectious peritonitis virus, feline leukemia /sarcoma virus, feline leukemia virus, feline panleukopenia virus, feline parvovirus, feline sarcoma virus, feline syncytial virus, Filovirus, Flanders virus, Flavivirus, foot and mouth disease virus, Fort Morgan virus, Four Corners hantavirus, fowl adenovirus 1, fowlpox virus, Friend virus, Gammaretrovirus, GB hepatitis virus, GB virus, German measles virus, Getah virus, gibbon ape leukemia virus, glandular fever virus, goatpox virus, golden shinner virus, Gonometa virus, goose parvovirus, granulosis virus, Gross' virus, ground squirrel hepatitis B virus, group A arbovirus, Guanarito virus, guinea pig cytomegalovirus, guinea pig type C virus, Hantaan virus, Hantavirus, hard clam reovirus, hare fibroma virus, HCMV (human cytomegalovirus), hemadsorption virus 2, hemagglutinating virus of Japan, hemorrhagic fever virus, hendra virus, Henipaviruses, Hepadnavirus, hepatitis A virus, hepatitis B virus group, hepatitis C virus, hepatitis D virus, hepatitis delta virus, hepatitis E virus, hepatitis F virus, hepatitis G virus, hepatitis nonA nonB virus, hepatitis virus, hepatitis virus (nonhuman),

hepatoencephalomyelitis reovirus 3, Hepatovirus, heron hepatitis B virus, herpes B virus, herpes simplex virus, herpes simplex virus 1, herpes simplex virus 2, herpesvirus, herpesvirus 7, Herpesvirus ateles, Herpesvirus hominis, Herpesvirus infection, Herpesvirus saimiri, Herpesvirus suis, Herpesvirus varicellae, Highlands J virus, Hirame rhabdovirus, hog cholera virus, human adenovirus 2, human alphaherpesvirus 1, human alphaherpesvirus 2, human alphaherpesvirus 3, human B lymphotropic virus, human betaherpesvirus 5, human coronavirus, human cytomegalovirus group, human foamy virus, human gammaherpesvirus 4, human gammaherpesvirus 6, human hepatitis A virus, human herpesvirus 1 group, human herpesvirus 2 group, human herpesvirus 3 group, human herpesvirus 4 group, human herpesvirus 6, human herpesvirus 8, human immunodeficiency virus, human immunodeficiency virus 1, human immunodeficiency virus 2, human papillomavirus, human T cell leukemia virus, human T cell leukemia virus I, human T cell leukemia virus II, human T cell leukemia virus III, human T cell lymphoma virus I, human T cell lymphoma virus II, human T cell lymphotropic virus type 1, human T cell lymphotropic virus type 2, human T lymphotropic virus I, human T lymphotropic virus II, human T lymphotropic virus III, Ichnovirus, infantile gastroenteritis virus, infectious bovine rhinotracheitis virus, infectious haematopoietic necrosis virus, infectious pancreatic necrosis virus, influenza virus A, influenza virus B, influenza virus C, influenza virus D, influenza virus pr8, insect iridescent virus, insect virus, iridovirus, Japanese B virus , Japanese encephalitis virus, JC virus, Junin virus, Kaposi's sarcoma-associated herpesvirus, Kemerovo virus, Kilham's rat virus, Klamath virus, Kolongo virus, Korean hemorrhagic fever virus, kumba virus, Kysanur forest disease virus, Kyzylagach virus, La Crosse virus, lactic dehydrogenase elevating virus, lactic dehydrogenase virus, Lagos bat virus, Langur virus, lapine parvovirus, Lassa fever virus, Lassa virus, latent rat virus, LCM virus, Leaky virus, Lentivirus, Leporipoxvirus, leukemia virus, leukovirus, lumpy skin disease virus, lymphadenopathy associated virus, Lymphocryptovirus, lymphocytic choriomeningitis virus, lymphoproliferative virus group, Machupo virus, mad itch virus, mammalian type B oncovirus group, mammalian type B retroviruses, mammalian type C retrovirus group, mammalian type D retroviruses, mammary tumor virus, Mapuera virus, Marburg virus, Marburg-like virus, Mason Pfizer monkey virus, Mastadenovirus, Canaro virus, ME virus, measles virus, Menangle virus, Mengo virus, Mengovirus, Middelburg virus, milkers nodule virus, mink enteritis virus, minute virus of mice, MLV related virus, MM virus, Mokola virus, Molluscipoxvirus, Molluscum contagiosum virus, monkey B virus, monkeypox virus, Mononegavirales, Morbillivirus, Mount Elgon bat virus, mouse cytomegalovirus, mouse encephalomyelitis virus, mouse hepatitis virus, mouse K virus, mouse leukemia virus, mouse mammary tumor virus, mouse minute virus, mouse pneumonia virus, mouse poliomyelitis virus, mouse polyomavirus, mouse sarcoma virus, mousepox virus, Mozambique virus, Mucambo virus, mucosal disease virus, mumps virus, murid betaherpesvirus 1, murid cytomegalovirus 2, murine cytomegalovirus group, murine encephalomyelitis virus, murine hepatitis virus, murine leukemia virus, murine nodule inducing virus, murine polyomavirus, murine sarcoma virus, Muromegalovirus, Murray Valley encephalitis virus, myxoma virus, Myxovirus, Myxovirus multiforme, Myxovirus parotitidis, Nairobi sheep disease virus, Nairovirus, Nanirnavirus, Nariva virus, Ndumo virus, Neethling virus, Nelson Bay virus, neurotropic virus, New World Arenavirus,

newborn pneumonitis virus, Newcastle disease virus, Nipah virus, noncytopathogenic virus, Norwalk virus, nuclear polyhedrosis virus (NPV), nipple neck virus, O'nyong'nyong virus, Ockelbo virus, oncogenic virus, oncogenic viruslike particle, oncornavirus, Orbivirus, Orf virus, Oropouche virus, Orthohepadnavirus, Orthomyxovirus, Orthopoxvirus, Orthoreovirus, Orungo, ovine papillomavirus, ovine catarrhal fever virus, owl monkey herpesvirus, Palyam virus, Papillomavirus, Papillomavirus sylvilagi, Papovavirus, parainfluenza virus, parainfluenza virus type 1, parainfluenza virus type 2, parainfluenza virus type 3, parainfluenza virus type 4, Paramyxovirus, Parapoxvirus, paravaccinia virus, Parvovirus, Parvovirus B19, parvovirus group, Pestivirus, Phlebovirus, phocine distemper virus, Picodnavirus, Picornavirus, pig cytomegalovirus, pigeonpox virus, Piry virus, Pixuna virus, pneumonia virus of mice, Pneumovirus, poliomyelitis virus, poliovirus, Polydnavirus, polyhedral virus, polyoma virus, Polyomavirus, Polyomavirus bovis, Polyomavirus cercopitheci, Polyomavirus hominis 2, Polyomavirus maccacae 1, Polyomavirus muris 1, Polyomavirus muris 2, Polyomavirus papionis 1, Polyomavirus papionis 2, Polyomavirus sylvilagi, Pongine herpesvirus 1, porcine epidemic diarrhea virus, porcine hemagglutinating encephalomyelitis virus, porcine parvovirus, porcine transmissible gastroenteritis virus, porcine type C virus, pox virus, poxvirus, poxvirus variolae, Prospect Hill virus, Provirus, pseudocowpox virus, pseudorabies virus, psittacinepox virus, quailpox virus, rabbit fibroma virus, rabbit kidney vaculolating virus, rabbit papillomavirus, rabies virus, raccoon parvovirus, raccoonpox virus, Ranikhet virus, rat cytomegalovirus, rat parvovirus, rat virus, Rauscher's virus, recombinant vaccinia virus, recombinant virus, reovirus, reovirus 1, reovirus 2, reovirus 3, reptilian type C virus, respiratory infection virus, respiratory syncytial virus, respiratory virus, reticuloendotheliosis virus, Rhabdovirus, Rhabdovirus carpia, Rhadinovirus, Rhinovirus, Rhizidiovirus, Rift Valley fever virus, Riley's virus, rinderpest virus, RNA tumor virus, Ross River virus, Rotavirus, rougeole virus, Rous sarcoma virus, rubella virus, rubeola virus, Rubivirus, Russian autumn encephalitis virus, SA 11 simian virus, SA2 virus, Sabia virus, Sagiyama virus, Saimirine herpesvirus 1, salivary gland virus, sandfly fever virus group, Sandjimba virus, SARS virus, SDAV (sialodacryoadenitis virus), sealpox virus, Semliki Forest Virus, Seoul virus, sheeppox virus, Shope fibroma virus, Shope papilloma virus, simian foamy virus, simian hepatitis A virus, simian human immunodeficiency virus, simian immunodeficiency virus, simian parainfluenza virus, simian T cell lymphotrophic virus, simian virus, simian virus 40, Simplexvirus, Sin Nombre virus, Sindbis virus, smallpox virus, South American hemorrhagic fever viruses, sparrowpox virus, Spumavirus, squirrel fibroma virus, squirrel monkey retrovirus, SSV 1 virus group, STLV (simian T lymphotropic virus) type I, STLV (simian T lymphotropic virus) type II, STLV (simian T lymphotropic virus) type III, stomatitis papulosa virus, submaxillary virus, suid alphaherpesvirus 1, suid herpesvirus 2, Suipoxvirus, swamp fever virus, swinepox virus, Swiss mouse leukemia virus, TAC virus, Tacaribe complex virus, Tacaribe virus, Tanapox virus, Taterapox virus, Tench reovirus, Theiler's encephalomyelitis virus, Theiler's virus, Thogoto virus, Thottapalayam virus, Tick borne encephalitis virus, Tioman virus, Togavirus, Torovirus, tumor virus, Tupaia virus, turkey rhinotracheitis virus, turkeypox virus, type C retroviruses, type D oncovirus, type D retrovirus group, ulcerative disease rhabdovirus, Una virus, Uukuniemi virus group, vaccinia virus, vacuolating virus, varicella zoster virus,

Varicellovirus, Varicola virus, variola major virus, variola virus, Vasin Gishu disease virus, VEE virus, Venezuelan equine encephalitis virus, Venezuelan equine encephalomyelitis virus, Venezuelan hemorrhagic fever virus, vesicular stomatitis virus, Vesiculovirus, Vilyuisk virus, viper retrovirus, viral haemorrhagic septicemia virus, Visna Maedi virus, Visna virus, volepox virus, VSV (vesicular stomatitis virus), Wallal virus, Warrego virus, wart virus, WEE virus, West Nile virus, western equine encephalitis virus, western equine encephalomyelitis virus, Whataroa virus, Winter Vomiting Virus, woodchuck hepatitis B virus, woolly monkey sarcoma virus, wound tumor virus, WRSV virus, Yaba monkey tumor virus, Yaba virus, Yatapoxvirus, yellow fever virus, and the Yug Bogdanovac virus. In one embodiment an infectome will be produced for each virus that includes an inventory of the host cellular genes involved in virus infection during a specific phase of viral infection, such cellular entry or the replication cycle.

[00439] For some viruses a great deal of progress has been made in the elucidation of the steps involved during infection of host cells, and any of these steps can be targeted using peptidomimetic macrocycles. For example, experiments initiated in the early 1980s showed that influenza virus follows a stepwise, endocytic entry program with elements shared with other viruses such as alpha-and rhabdoviruses (Marsh and Helenius 1989; Whittaker 2006). The steps include: 1) Initial attachment to sialic acid containing glycoconjugates receptors on the cell surface; 2) signaling induced by the virus particle; 3) endocytosis by clathrin-dependent and clathrin-independent cellular mechanism; 4) acid-induced, hemaglutinin (HA)-mediated penetration from late endosomes; 5) acid-activated, M2 and matrix protein (M1) dependent uncoating of the capsid; and, 6) intra-cytosolic transport and nuclear import of vRNPs. These steps depend on assistance from the host cell in the form of sorting receptors, vesicle formation machinery, kinase-mediated regulation, organelle acidification, and, most likely, activities of the cytoskeleton.

[00440] Influenza attachment to the cells surface occurs via binding of the HA1 subunit to cell surface glycoproteins and glycolipids that carry oligosaccharide moieties with terminal sialic acid residues (Skehel and Wiley 2000). The linkage by which the sialic acid is connected to the next saccharide contributes to species specificity. Avian strains including H5N1 prefer an a-(2,3)-link and human strains a-(2,6)-link (Matrosovich 2006). In epithelial cells, binding occurs preferentially to microvilli on the apical surface, and endocytosis occurs at base of these extensions (Matlin 1982). Whether receptor binding induces signals that prepare the cell for the invasion is not yet known, but it is likely because activation of protein kinase C and synthesis of phopshatidylinositol-3-phosphate (PI3P) are required for efficient entry (Sieczkarski et al. 2003; Whittaker 2006).

[00441] Endocytic internalization occurs within a few minutes after binding (Matlin 1982; Yoshimura and Ohnishi 1984). In tissue culture cells influenza virus makes use of three different types of cellular processes; 1) preexisting clathrin coated pits, 2) virus-induced clathrin coated pits, and 3) endocytosis in vesicles without visible coat (Matlin 1982; Sieczkarski and Whittaker 2002; Rust et al. 2004). Video microscopy using fluorescent viruses showed the virus particles undergoing actin-mediated rapid motion in the cell periphery followed by minus end-directed, microtubule-mediated transport to the perinuclear area of the cell. Live cell imaging indicated

that the virus particles first entered a subpopulation of mobile, peripheral early endosomes that carry them deeper into the cytoplasm before penetration takes place (Lakadamyali et al. 2003; Rust et al. 2004). The endocytotic process is regulated by protein and lipid kinases, the proteasome, as well as by Rabs and ubiquitin-dependent sorting factors (Khor et al. 2003; Whittaker 2006).

[00442] The membrane penetration step is mediated by low pH-mediated activation of the trimeric, metastable HA, and the conversion of this Type I viral fusion protein to a membrane fusion competent conformation (Maeda et al. 1981; White et al. 1982). This occurs about 16 min after internalization, and the pH threshold varies between strains in the 5.0-5.6 range. The target membrane is the limiting membrane of intermediate or late endosomes. The mechanism of fusion has been extensively studied (Kielian and Rey 2006). Further it was observed that fusion itself does not seem to require any host cell components except a lipid bilayer membrane and a functional acidification system (Maeda et al. 1981; White et al. 1982). The penetration step is inhibited by agents such as lysosomotropic weak bases, carboxylic ionophores, and proton pump inhibitors (Matlin 1982; Whittaker 2006).

[00443] To allow nuclear import of the incoming vRNPs, the capsid has to be disassembled. This step involves acidification of the viral interior through the amantadine-sensitive M2-channels causes dissociation of M1 from the vRNPs (Bukrinskaya et al. 1982; Martin and Helenius 1991; Pinto et al. 1992). Transport of the individual vRNPs to the nuclear pore complexes and transfer into the nucleus depends on cellular nuclear transport receptors (O'Neill et al. 1995; Cros et al. 2005). Replication of the viral RNAs (synthesis of positive and negative strands), and transcription occurs in complexes tightly associated with the chromatin in the nucleus. It is evident that, although many of the steps are catalyzed by the viral polymerase, cellular factors are involved including RNA polymerase activating factors, a chaperone HSP90, hCLE, and a human splicing factor UAP56. Viral gene expression is subject to complex cellular control at the transcriptional level, a control system dependent on cellular kinases (Whittaker 2006).

[00444] The final assembly of an influenza particle occurs during a budding process at the plasma membrane. In epithelial cells, budding occurs at the apical membrane domain only (Rodriguez-Boulan 1983). First, the progeny vRNPs are transported within the nucleoplasm to the nuclear envelope, then from the nucleus to the cytoplasm, and finally they accumulate in the cell periphery. Exit from the nucleus is dependent on viral protein NEP and M1, and a variety of cellular proteins including CRM1 (a nuclear export receptor), caspases, and possibly some nuclear protein chaperones. Phosphorylation plays a role in nuclear export by regulating M1 and NEP synthesis, and also through the MAPK/ERK system (Bui et al. 1996; Ludwig 2006). G protein and protein kinase signaling is involved in influenza virus budding from infected host cells (Hui E. and Nayak D, 2002).

[00445] The three membrane proteins of the virus are synthesized, folded and assembled into oligomers in the ER (Doms et al. 1993). They pass through the Golgi complex; undergo maturation through modification of their carbohydrate moieties and proteolytic cleavage. After reaching the plasma membrane they associate with M1 and the vRNPs in a budding process that result in the inclusion of all eight vRNPs and exclusion of most host cell components except lipids.

[00446] Influenza infection is associated with activation of several signaling cascades including the MAPK pathway (ERK, JNK, p38 and BMK-1/ERK5), the κB/NF-κB signaling module, the Raf/MEK/ERK cascade, and programmed cell death (Ludwig 2006). These result in a variety of effects that limit the progress of infection such as transcriptional activation of IFN-β, apoptotic cell death, and a block in virus escape of from late endosomes (Ludwig 2006).

Administration

[00447] The aqueous pharmaceutical formulations of the present disclosure can draw upon many suitable parenteral modes of administration route. The formulations can be, for example, administered intravenously, intraarterially, intrathecally, or subcutaneously. If combinations of agents are administered as separate formulations, they can be administered by the same route or by different routes.

[00448] In some embodiments, the aqueous pharmaceutical formulation is administered in a single dose. A single dose of the aqueous pharmaceutical formulation can also be used when it is co-administered with another substance (e.g., an analgesic) for treatment of an acute condition.

[00449] In some embodiments, the aqueous pharmaceutical formulation (by itself or in combination with other drugs) is administered in multiple doses. Dosing can be about once, twice, three times, four times, five times, six times, seven times, eight times, nine times, ten times or more than ten times per day. Dosing can be about once a year, twice a year, every six months, every 4 months, every 3 months, every 60 days, once a month, once every two weeks, once a week, or once every other day. In another embodiment the aqueous pharmaceutical formulation alone or in combination with another therapeutic substance is administered together about once per day to about 10 times per day. In another embodiment the administration of the aqueous pharmaceutical formulation alone or in combination with another therapeutic substance continues for less than about 7 days. In yet another embodiment the administration continues for more than about 6, 10, 14, 28 days, two months, six months, or one year.

[00450] Administration of the formulations of the disclosure can continue as long as necessary. In some embodiments, a aqueous pharmaceutical formulation of the disclosure is administered for more than 1, 2, 3, 4, 5, 6, 7, 14, 28, 35, 42, 49, 56, 63, 70, 77, 84, 91, 98, 105, 112, 119, 126, 133, or 140 days. In some embodiments, a aqueous pharmaceutical formulation of the disclosure is administered for less than 140, 133, 126, 119, 112, 105, 98, 91, 84, 77, 70, 63, 56, 49, 42, 35, 28, 14, 7, 6, 5, 4, 3, 2, or 1 day. In some embodiments, an aqueous pharmaceutical formulation of the disclosure is administered for more than 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, or 12 days. In some embodiments, a aqueous pharmaceutical formulation of the disclosure is administered for less than 12, 11, 10, 9, 8, 7, 6, 5, 4, 3, 2, or 1 months. In some embodiments, an aqueous pharmaceutical formulation of the disclosure is administered for more than 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, or 12 years. In some embodiments, a aqueous pharmaceutical formulation of the disclosure is administered for less than 12, 11, 10, 9, 8, 7, 6, 5, 4, 3, 2,

or 1 years. In some embodiments, a aqueous pharmaceutical formulation of the disclosure is administered chronically on an ongoing basis.

[00451] Dosing for the aqueous pharmaceutical formulation formulations of the disclosure can be found by routine experimentation. The daily dose can range from about 1x 10^{-8} g to 5000 mg. Daily dose range can depend on the form of the aqueous pharmaceutical formulation e.g., the peptidomimetic macrocycle used, and/or route of administration, as described herein. For example, daily dose can be in the range of about 0.1-5000 mg, about 0.1-3000 mg, about 0.1-2000 mg, about 0.1-1000 mg, about 01.-500 mg, about 0.1-100 mg, 1-5000 mg, about 1-3000 mg, about 1-2000 mg, about 1-1000 mg, about 1-500 mg, or about 1-100 mg, about 10-5000 mg, about 10-3000 mg, about 10-2000 mg, about 10-1000 mg, about 10-500 mg, about 10-200 mg, about 10-100 mg, about 20-2000 mg, about 20-1500 mg, about 20-1000 mg, about 20-500 mg, about 20-100 mg, about 50-5000 mg, about 50-4000 mg, about 50-3000 mg, about 50-2000 mg, about 50-1000 mg, about 50-500 mg, about 50-100 mg, about 100-5000 mg, about 100-4000 mg, about 100-3000 mg, about 100-2000 mg, about 100-1000 mg, about 100-500 mg. In some embodiments, the daily dose of the aqueous pharmaceutical formulation is about 0.01, 0.1, 1, 10, 20, 30, 40, 50, 60, 70, 80, 90, 100, 200, 300, 400, 500, 600, 700, 800, 900, or 1000 mg. In some embodiments, the daily dose of the aqueous pharmaceutical formulation is 0.01 mg. In some embodiments, the daily dose of the aqueous pharmaceutical formulation is 0.1 mg. In some embodiments, the daily dose of the aqueous pharmaceutical formulation is 1 mg. In some embodiments, the daily dose of the aqueous pharmaceutical formulation is up to 10 mg. In some embodiments, the daily dose of the aqueous pharmaceutical formulation is up to 20 mg. In some embodiments, the daily dose of the aqueous pharmaceutical formulation is 50 mg. In some embodiments, the daily dose of the aqueous pharmaceutical formulation is 100 mg.

III. Kits

[00452] For use in the therapeutic methods of use described herein, the formulations of the disclosure can be available as a kit. Such kits can include a carrier, package, or container that is optionally compartmentalized to receive one or more doses of the aqueous pharmaceutical formulations for use in a method described herein. The kits provided herein can contain packaging materials. Packaging materials for use in packaging pharmaceutical products include, but are not limited to those described in e.g., U.S. Patent No. 5,323,907. Examples of pharmaceutical packaging materials include, but are not limited to, blister packs, bottles, tubes, bags, containers, bottles, and any packaging material suitable for a selected formulation and intended mode of administration and treatment.

[00453] The aqueous pharmaceutical formulations of the disclosure can be packaged in multidose form or in single dose form. In some cases, the formulations are packaged in multidose forms. In some embodiments the formulations are packaged as single dose units. In some embodiments of the disclosure single dose packaging of the formulations can offer several advantages over multi dose packaging including dosage control, increased patient compliance, improved product labeling, and reduced counterfeiting. In various embodiments single dosage

packaging of the formulations of the disclosure can be in form of vials, ampoules, tubes, bottles, pouches, packettes, syringes or blister packs. In some embodiments the single dose containers can be grouped together and placed into additional containers. In some embodiments the secondary container is a pouch.

[00454] In some examples, the formulations of the disclosure can be packed in a bottle or a vial. In some examples, the formulations can be packed in glass serum vial. In some examples, the formulations can be packed in serum vials composed of borosilicate glass. In some examples, the formulations are packed in a 1 mL, a 2 mL, a 3 mL, a 4 mL, a 5 mL, a 10 mL, a 20 mL, a 30 mL, or a 50 mL glass vial. In some examples, the formulations are packed in a 5 mL glass vial. In some examples, the formulations are packed in a 10 mL glass vial. In some examples, the formulations are packed in a 15 mL glass vial. In some examples, the formulations are packed in a 20 mL glass vial. In some embodiments, the vials comprise a 5 mm, a 10 mm, a 15 mm, 20 mm, 30 mm, or 50 mm orifice. In some embodiments, the formulations are packed in a 5 mL borosilicate glass vial with a 20 mm orifice. In some embodiments, the formulations are packed in a 10 mL borosilicate glass vial with a 20 mm orifice. The containers, bottles and/or vials can be equipped with suitable caps or stoppers. In some embodiments, the vials are equipped with a vinyl stopper. In some embodiments the formulations are packed in a 10 mL glass vial, with a 20 mm orifice, equipped with vinyl stoppers. The stoppers can be coated with FluroTek®. The containers, bottles and/or can also be equipped with a seal, for example, crimped-on flip-off caps. The seal can be aluminum and/or plastic. The container can be a glass ampoule.

[00455] In some embodiments, the containers, including the vials and the bottles, can be inspected for visible particulates, glass defects, and/or stopper/cap integrity before packaging the formulations therein. In some embodiments, the containers, including the vials and the bottles, can be inspected for visible particulates, glass defects, and/or stopper/cap integrity after packaging the formulations therein. In some embodiments, the containers, including the vials and the bottles, can be inspected for visible particulates, glass defects, and/or stopper/cap integrity before and/or after packaging the formulations therein. The containers, including the vials and the bottles, can also be additionally inspected for fill height after packaging the formulations therein. The inspection can be visual inspections and can be carried out under any convenient condition, for example in front of a black and white background.

[00456] A kit can also include labels listing contents and/or instructions for use, and package inserts with instructions for use. A set of instructions will also typically be included. In one embodiment, a label is on or associated with the container. In one embodiment, a label is on a container when letters, numbers or other characters forming the label are attached, molded or etched into the container itself; a label is associated with a container when it is present within a receptacle or carrier that also holds the container, e.g., as a package insert. In one embodiment, a label is used to indicate that the contents are to be used for a specific therapeutic application. The label also indicates directions for use of the contents, such as in the methods described herein. The labels can optionally indicate one or more items selected from a group comprising the date of manufacturing of the formulation, the recommended storage conditions, intended mode of administration for the formulation, the

amount of formulation enclosed and/or the concentration of the peptidomimetic macrocycle. The labels can further include any applicable warnings and/or possible side effects.

[00457] In certain embodiments, the pharmaceutical formulations are presented in a pack or dispenser device which contains one or more unit dosage forms containing a formulation provided herein. The pack, for example, contains metal or plastic foil, such as a blister pack. In one embodiment, the pack or dispenser device is accompanied by instructions for administration. In one embodiment, the pack or dispenser is also accompanied with a notice associated with the container in form prescribed by a governmental agency regulating the manufacture, use, or sale of pharmaceuticals, which notice is reflective of approval by the agency of the form of the drug for human or veterinary administration. Such notice, for example, is the labeling approved by the U.S. Food and Drug Administration for prescription drugs, or the approved product insert. In one embodiment, formulations containing a compound provided herein formulated in a compatible pharmaceutical carrier are also prepared, placed in an appropriate container, and labeled for treatment of an indicated condition.

Examples

Example 1: Peptidomimetic macrocycles

[00458] Peptidomimetic macrocycles were synthesized, purified and analyzed as previously described and as described below (Schafmeister et al., J. Am. Chem. Soc. 122:5891-5892 (2000); Schafmeister & Verdine, J. Am. Chem. Soc. 122:5891 (2005); Walensky et al., Science 305:1466-1470 (2004); and US Patent No. 7,192,713). Peptidomimetic macrocycles were designed by replacing two or more naturally occurring amino acids with the corresponding synthetic amino acids. Substitutions were made at i and i+4, and i and i+7 positions. Peptide synthesis was performed either manually or on an automated peptide synthesizer (Applied Biosystems, model 433A), using solid phase conditions, rink amide AM resin (Novabiochem), and Fmoc main-chain protecting group chemistry. For the coupling of natural Fmoc-protected amino acids (Novabiochem), 10 equivalents of amino acid and a 1:1:2 molar ratio of coupling reagents HBTU/HOBt (Novabiochem)/DIEA were employed. Non-natural amino acids (4 equiv) were coupled with a 1:1:2 molar ratio of HATU (Applied Biosystems)/HOBt/DIEA. The N-termini of the synthetic peptides were acetylated, while the C-termini were amidated.

[00459] Purification of cross-linked compounds was achieved by high performance liquid chromatography (HPLC) (Varian ProStar) on a reverse phase C18 column (Varian) to yield the pure compounds. Chemical composition of the pure products was confirmed by LC/MS mass spectrometry (Micromass LCT interfaced with Agilent 1100 HPLC system) and amino acid analysis (Applied Biosystems, model 420A).

[00460] The following protocol was used in the synthesis of dialkyne-crosslinked peptidomimetic macrocycles, including SP662, SP663 and SP664. Fully protected resin-bound peptides were synthesized on a PEG-PS resin (loading 0.45 mmol/g) on a 0.2 mmol scale. Deprotection of the temporary Fmoc group was achieved by 3 × 10 min treatments of the resin bound peptide with 20% (v/v) piperidine in DMF. After washing with NMP (3x),

dichloromethane (3x) and NMP (3x), coupling of each successive amino acid was achieved with 1 × 60 min incubation with the appropriate preactivated Fmoc-amino acid derivative. All protected amino acids (0.4 mmol) were dissolved in NMP and activated with HCTU (0.4 mmol) and DIEA (0.8 mmol) prior to transfer of the coupling solution to the deprotected resin-bound peptide. After coupling was completed, the resin was washed in preparation for the next deprotection/coupling cycle. Acetylation of the amino terminus was carried out in the presence of acetic anhydride/DIEA in NMP. The LC-MS analysis of a cleaved and deprotected sample obtained from an aliquot of the fully assembled resin-bound peptide was accomplished in order to verifying the completion of each coupling. In a typical example, tetrahydrofuran (4ml) and triethylamine (2ml) were added to the peptide resin (0.2 mmol) in a 40ml glass vial and shaken for 10 minutes. $Pd(PPh_3)_2Cl_2$ (0.014g, 0.02 mmol) and copper iodide (0.008g, 0.04 mmol) were then added and the resulting reaction mixture was mechanically shaken 16 hours while open to atmosphere. The diyne-cyclized resin-bound peptides were deprotected and cleaved from the solid support by treatment with TFA/H_2O/TIS (95/5/5 v/v) for 2.5 h at room temperature. After filtration of the resin the TFA solution was precipitated in cold diethyl ether and centrifuged to yield the desired product as a solid. The crude product was purified by preparative HPLC.

[00461] The following protocol was used in the synthesis of single alkyne-crosslinked peptidomimetic macrocycles, including SP665. Fully protected resin-bound peptides were synthesized on a Rink amide MBHA resin (loading 0.62 mmol/g) on a 0.1 mmol scale. Deprotection of the temporary Fmoc group was achieved by 2 × 20 min treatments of the resin bound peptide with 25% (v/v) piperidine in NMP. After extensive flow washing with NMP and dichloromethane, coupling of each successive amino acid was achieved with 1 × 60 min incubation with the appropriate preactivated Fmoc-amino acid derivative. All protected amino acids (1 mmol) were dissolved in NMP and activated with HCTU (1 mmol) and DIEA (1 mmol) prior to transfer of the coupling solution to the deprotected resin-bound peptide. After coupling was completed, the resin was extensively flow washed in preparation for the next deprotection/coupling cycle. Acetylation of the amino terminus was carried out in the presence of acetic anhydride/DIEA in NMP /NMM. The LC-MS analysis of a cleaved and deprotected sample obtained from an aliquot of the fully assembled resin-bound peptide was accomplished in order to verifying the completion of each coupling. In a typical example, the peptide resin (0.1 mmol) was washed with DCM. Resin was loaded into a microwave vial. The vessel was evacuated and purged with nitrogen. Molybdenumhexacarbonyl (0.01 eq, Sigma Aldrich 199959) was added. Anhydrous chlorobenzene was added to the reaction vessel. Then 2-fluorophenol (1eq, Sigma Aldrich F12804) was added. The reaction was then loaded into the microwave and held at 130°C for 10 minutes. Reaction can need to be pushed a subsequent time for completion. The alkyne metathesized resin-bound peptides were deprotected and cleaved from the solid support by treatment with TFA/H_2O/TIS (94/3/3 v/v) for 3 h at room temperature. After filtration of the resin the TFA solution was precipitated in cold diethyl ether and centrifuged to yield the desired product as a solid. The crude product was purified by preparative HPLC.

[00462] **Table** 1 shows a list of peptidomimetic macrocycles that were prepared. **Table 1a**, **Table 1b**, **Table 1c** and **Table 1d** shows a selection of peptidomimetic macrocycles. In some embodiments, peptidomimetic macrocycles exclude peptidomimetic macrocycles shown in **Table 2a**. In some embodiments, peptidomimetic macrocycles do not comprise a peptidomimetic macrocycle structure as shown in **Table 2a**. In other embodiments, peptidomimetic macrocycles exclude peptidomimetic macrocycles shown in **Table 2b**. In some embodiments, the peptidomimetic macrocycles disclosed herein do not comprise a peptidomimetic macrocycle structure as shown in **Table 2b**.

Example 2: Preparation of a pharmaceutical formulation 1-Liter peptidomimetic formulation Batch

[00463] Aileron peptide 1 is formulated as a pharmaceutical formulation. Aileron peptide 1 is an alpha helical hydrocarbon cross-linked polypeptide macrocycle, with an amino acid sequence less than 20 amino acids long that is derived from the transactivation domain of wild type human P53 protein and that contains a phenylalanine , a tryptophan and a leucine amino acid in the same positions relative to each other as in the transactivation domain of wild type human P53 protein. Aileron peptide 1 has a single cross link spanning amino acids in the i to the i+7 position of the amino acid sequence and has more than three amino acids between the i+7 position and the carboxyl terminus. Aileron peptide 1 binds to human MDM2 and MDM4 and has an observed mass of 950-975 m/e as measured by electrospray ionization-mass spectrometry.

[00464] For each liter of formulated Aileron peptide 1the peptides is sequentially dissolve in 900 mL of water for injection 182 mg monosodium phosphate, monohydrate, 2,968 mg disodium phosphate, anhydrous, and 82.2 g of D-trehalose. Add 3.0 mL of a 10% (w/w) aqueous solution of Polysorbate 20. Slowly add 15,000 mg Aileron peptide 1 divided by peptide content divided by peptide purity to the solution under stirring. E.g., if the peptide content is 94.3% and the peptide purity is 98.2%, 15,000/94.3*100/98./100 or 16,215 mg of bulk- Aileron peptide 1 would have to be added. While the peptide is dissolving the pH of the solution is kept between 7.5 and 7.7 by the addition of 0.1 N sodium hydroxide.

[00465] After all peptide is dissolved, adjust pH of the solution to 7.5 ± 0.1 with sodium hydroxide and subsequently q.s. with WFI to 1,000 mL. Stir solution for 5 minutes and then clarify solution by passing it through a 0.22-µm PVDF-membrane filter.

[00466] ***Example 3:*** Sterile filtration and fill.

[00329] The formulated product is filtered through two serial sterilization 0.22 µm PVDF membrane filters into a sterile container that is equipped with the fill needle. The filling process starts after both filters have passed the post filtration filter integrity test. If one or both filters do not pass the post filtration integrity test, the tandem sterile filtration process is repeated until both filters pass the test.

[00330] All vials are inspected for visible particulates, glass faults, fill high and stopper/cap integrity in front of a white and black background. Approximately 180 vial containers are then filled per 1-liter batch to a level of 5.2

mL to 5.7 mL each, with a fill target of 5.5 mL (the label claim is 5.0 mL). Fill volume accuracy is verified throughout the fill process. The filling machine loaded with vials and stoppers immediately stoppers each vial after it is filled. Capping occurs in line with filling and stopping or can occur separately under ISO Class 5 supply air. Weight check of the contents of the filled vials is performed throughout the filling process to assure that the vials receive the specified fill volume. Any rejected vials are discarded.

[00331] Example 4: Stability Analysis

[00332] To render the stability study more challenging 2 mL vials with 13 mm Ø stoppers and a fill volume of 1.0 mL were selected. The smaller vial size provided a greater surface to volume ratio which would amplify any container/closure effects on product stability. To assure that all surfaces of vial were challenged, the vials were stored in an inverted position. The tested storage conditions on inverted vials are: -20°C, +5°C, +25°C, and +40°C RH.

[00333] The results of this study are depicted in **Table** 5. There is no appreciable purity loss at storage temperatures between between -20°C and +25°C over the 6-month test period and only about a 1.8% purity loss of the sample that is stored at 40°C over the same period. The observed small but continuous increase of RRT values between 0.22 and 0.81 in the 40°C samples attests to both, the excellent detecting power and stability-indicating capability of the RP-HPLC (TFA) method. The peptidomimetic macrocycle concentration stayed within an acceptable ± 4% range over the 6-month period for all samples independent of the storage temperature.

[00334] Table 5: Product stability results of Aileron peptide 1 formulated at 15 mg/mL in 20 mM sodium phosphate, 240 mM trehalose, 300 ppm Polysorbate 20 buffer in a 5-fold scaled-down, inverted container/closure configuration to amplify any potential product degrading effects by the container/closure surface.

	Time Points																
	Initial	1 Month				2 Months				3 Months				6 Months			
Storage	-20°C	-20°C	5°C	25°C	40°C	-20°C	5°C	25°C	40°C	-20°C	5°C	25°C	40°C	-20°C	5°C	25°C	40°C
Assay [%]		100%	97%	96%	99%	103%	104%	101%	102%	99%	99%	99%	97%	100%	99%	99%	96%
Purity [%]	95.5%	95.9%	95.8%	96.1%	96.0%	95.8%	96.2%	96.1%	95.6%	95.9%	95.8%	96.0%	95.2%	95.7%	95.5%	95.7%	93.9%
Individual Impurities > 0.1%																	
~RRT 0.22									0.08%				0.08%				0.16%
~RRT 0.32									0.09%				0.14%				0.33%
~RRT 0.47									0.08%				0.14%				0.25%
~RRT 0.81									0.08%				0.12%				0.25%
~RRT 0.84	0.11%				0.06%				0.13%				0.14%				0.25%
~RRT 0.88	0.17%	0.12%	0.12%	0.13%	0.13%	0.14%		0.14%	0.14%			0.13%	0.13%	0.14%	0.17%	0.09%	0.18%
~RRT 0.90	0.22%	0.16%	0.19%	0.18%	0.18%	0.16%	0.15%	0.20%	0.20%	0.18%	0.17%	0.21%	0.21%	0.19%	0.21%	0.20%	0.23%
~RRT 0.93	0.54%	0.47%	0.50%			0.51%	0.44%			0.50%	0.51%			0.55%	0.54%	0.49%	0.52%
~RRT 1.03	2.24%	2.21%	2.22%	2.20%	2.20%	2.18%	2.13%	2.27%	2.27%	2.23%	2.24%	2.40%	2.40%	2.15%	2.24%	2.21%	2.30%
~RRT 1.04	0.17%	0.11%	0.12%	0.17%	0.17%	0.15%	0.13%	ND	ND	0.14%	0.14%			0.19%	0.15%	0.12%	0.16%

~RRT 1.06				0.10%	0.10%			0.14%	0.14%	0.00%	0.00%	0.16%	0.16%	0.09%	0.09%	0.13%	0.13%
~RRT 1.07	0.12%	0.13%	0.15%	0.16%	0.16%	0.11%	0.07%	0.14%	0.14%	0.15%	0.15%	0.17%	0.17%	0.12%	0.18%	0.12%	0.16%
~RRT 1.10	0.95%	0.95%	0.93%	0.93%	0.99%	0.98%	0.89%	1.00%	1.06%	0.95%	0.96%	0.99%	1.08%	0.92%	0.97%	0.99%	1.20%
Particulate Matter [Number of particles per container)																	
< 10 µm	<1					<1	<1	<1	<1	<2	<1	<1	~8				
≥ 10 µm	140					38	23	28	31	190	17	47	83				
≥ 25 µm	33					7	6	5	3	20	2	7	14				
≥ 50 µm	4					2	3	2	0	2	2	0	6				

RRT = relative retention time.

[00335] Example 5: Comparative data for TRIS and phosphate buffers

[00336] **Composition of formulations**

[00337] Two formulations, F1 and F2 were formulated. **Table 6** shows the compositions of the two formulations. Formulations were filled into 6 mL, ∅ 20 mm, colorless vials. The vials were equipped with teflon serum-stoppers D777-1, ∅ 20mm and aluminum caps without PP-cap, ∅ 20 mm. 6 vials of each formulation were prepared. The vials were stored at 2-8 °C. Exposure to direct sunlight was avoided.

[00338] Table 6: Composition of formulations F1 and F2:

Peptidomimetic Macrocycle	Formulation Code	Buffer system	Excipient	Surfactant %	Peptide (mg/ml)
Aileron peptide 1	F1	20mM Na-Phosphate pH 7.5	240 mM Trehalose	0.03	15
	F2	20mM Tris pH 7.5		0.03	

[00339] Two placebo formulations P1 (with 20 mM Na-phosphate buffer) and P2 (with 20 mM Tris buffer), without the peptidomimetic macrocycle, were also prepared.

[00340] Every filled 6ml vial was visually inspected using Seidenader. The results of this observation are summarized in **Table 7**. The observation images are shown in **Figure 2**.

[00341] Table 7: Comparative visual inspection of F1, F2, P1 and P2 indicate that the resulting formulations were comparable and yielded minimal visible particles.

Form. Code	total filled / inspected	no. of vials with particles				notes
		0	1-5	6-10	>10	
F1	6	4	2			1x faster 1x particle

F2	6	6				
P1	6	5	1			1x faster
P2	6	6				

[00342] Example 6: Shelf life of the peptidomimetic macrocycles of the invention

[00343] A pharmaceutical formulation of Aileron peptide 1, was formulated as described above and stored at varying temperatures (-20 °C, 2-8 °C, 25 °C 60% humidity and 40 °C 75% humidity. The purity of the samples was analyzed at regular time intervals. The results of these experiments for Aileron peptide 1 are summarized in **Figure 4**. These experiments support a greater than 2 year shelf life at -20 °C and 2-8 °C.

[00344] Example 7: Stability testing of Aileron peptide 1 was performed on a pharmaceutical formulation formulated as described above and stored at varying temperatures (-20 °C, 2-8 °C, 25 °C 60% humidity and 40 °C 75% humidity. The purity of the samples was analyzed at regular time intervals. The results of these experiments for Aileron peptide 1 are summarized in **Tables 8**, **9**, **10**, and **11**.

[00345] Table 8:

	Storage: -20 °C						
	Initial	**1 Month**	**2 Months**	**3 Months**	**6 Months**	**9 Months**	**12 Months**
Appearance[1]	Conforms	Conforms	Conforms	Conforms	Conforms	Conforms	Conforms
pH[2]	7.6	7.6	7.6	7.6	7.6	7.6*	7.6
Assay [mg/mL]	15.6	15.6	15.9	15.6	15.4	15.5	15.6
Purity [%][3]	99.0	99.0	98.9	98.9	98.9	99.0	99.0
Impurities [%][4]	0.4% @ 0.89	0.4% @ 0.89	0.4% @ 0.89	0.4% @ 0.89	0.4% @ 0.89	0.4% @ 0.88	0.4% @ 0.88
	0.4% @ 0.91	0.4% @ 0.91	0.5% @ 0.91	0.5% @ 0.91	0.5% @ 0.91	0.4% @ 0.91	0.4% @ 0.91
	0.2% @ 1.02	0.2% @ 1.02	0.2% @ 1.02	0.2% @ 1.02	0.2% @ 1.02	0.2% @ 1.02	0.2% @ 1.02
Particulate Matter[5]	184				18		557
CCIT[6]	63				0		8

Endotoxin[7]	conforms						conforms
	<1.8 EU/mL						<1.6 EU/mL

[00346] Table 9:

	Storage: +5 °C						
	Initial	**1 Month**	**2 Months**	**3 Months**	**6 Months**	**9 Months**	**12 Months**
Appearance[1]	Conforms	Conforms	Conforms	Conforms	Conforms	Conforms	Conforms
pH[2]	7.6	7.6	7.6	7.7	7.7	7.6	7.6
Assay [mg/mL]	15.6	15.7	15.8	15.8	15.5	15.6	15.6
Purity [%][3]	99.0	99.0	99.0	99.0	98.9	99.0	99.0
Impurities [%][4]	0.4% @ 0.89	0.4% @ 0.89	0.4% @ 0.89	0.4% @ 0.89	0.4% @ 0.89	0.4% @ 0.89	0.4% @ 0.89
	0.4% @ 0.91	0.4% @ 0.91	0.4% @ 0.91	0.4% @ 0.91	0.5% @ 0.91	0.4% @ 0.91	0.4% @ 0.91
	0.2% @ 1.02	0.2% @ 1.02	0.2% @ 1.02	0.2% @ 1.02	0.2% @ 1.02	0.2% @ 1.02	0.2% @ 1.02
Particulate Matter[5]	184				37		171
CCIT[6]	63				4		11
Endotoxin[7]	conforms						conforms
	<1.8 EU/mL						<1.6 EU/mL

[00347] Table 10:

	Storage: +25 °C/60% RH						
	Initial	1 Month	2 Months	**3 Months**	**6 Months**	**9 Months**	**12 Months**
Appearance[1]	Conforms	Conforms	Conforms	Conforms	Conforms	Conforms	Conforms
pH[2]	7.6	7.65	7.6	7.6	7.7	7.6	7.6
Assay [mg/mL]	15.6	15.6	15.8	15.4	15.2	15.1	15.0
Purity [%][3]	99.0	99.0	98.9	98.7	98.4	98.4	97.9
				0.2%	0.3% @	0.4% @	0.5% @

				@0.23	0.23	0.23	0.23
Impurities [%][4]							0.2% @ 0.32
				0.1% @ 0.82			0.4 @ 0.82
	0.4% @ 0.89	0.4% @ 0.89	0.4% @ 0.89	0.4% @ 0.89	0.4% @ 0.89	0.4% @ 0.89	0.4% @ 0.88
	0.4% @ 0.91	0.4% @ 0.91	0.4% @ 0.91	0.4% @ 0.91	0.4% @ 0.91	0.4% @ 0.91	0.4% @ 0.91
	0.2% @ 1.02	0.2% @ 1.02	0.2% @ 1.02	0.2% @ 1.02	0.2% @ 1.02	0.2% @ 1.02	0.2% @ 1.02
Particulate Matter[5]	184				5		185
CCIT[6]	63				1		8
Endotoxin[7]	conforms						conforms
	<1.8 EU/mL						<1.6 EU/mL

[1]Visual appearance Specification: Upon thawing, clear, colorless, particulate-free solution

[2]pH Specification: 7.3 to 7.7

[3]Purity by RP-HPLC(TFA) Specification: ≥ 95%; no single impurity > 3%

[4]>0.1% Impurities listed by RRT

[5]USP <788> (light obstruction) Specification: ≤ 6,000 particles ≥ 10 μm and ≤ 600 particles ≥ 25 μm per vial (upper cell: ≥ 10 μm particles; lower cells: ≥ 25 μm particles

[6]CCIT Specification: No dye intrusion

[7]Endotoxin: ≤ 4.4 EU/mL (based upon maximum patient dose of 17 mg ALRN-6924 per Kg of patient weight)

[00348] Table 11:

	Storage: +40 °C/75% RH						
	Initial	**1 Month**	**2 Months**	**3 Months**	**6 Months**	**9 Months**	**12 Months**
Appearance[1]	conforms	conforms	conforms	OOS*	OOS**	OOS**	OOS**
pH[2]	7.6	7.64	7.6	7.6	7.6	7.5	7.5
Assay [mg/mL]	15.6	15.6	15.4	15.1	14.6	14.4	14.1
Purity [%][3]	99.0	98.8	98.6	98.1	97.2	96.2	95.9

Impurities: [%][4]					0.3 @ 01.9	0.3 @ 01.9	0.3 @ 01.9
						0.2 @ 020	0.2 @ 020
	n.d.	0.2% @ 0.23	0.2% @ 0.23	0.2% @ 0.23	0.4% @ 0.23	0.3% @ 0.23	0.3% @ 0.23
						0.3% @ 0.24	0.3% @ 024
						0.2% @ 0.29	0.2% @ 0.29
			0.2% @ 0.34	0.2% @ 0.34	0.2% @ 0.34	0.3% @ 0.33	0.3% @ 0.32
							0.2% @ 0.36
					0.2% @ 0.48	0.2% @ 0.47	0.2% @ 0.47
						0.2% @ 0.74	0.2% @ 0.74
				0.2% @ 0.83	0.3% @ 0.83	0.3% @ 0.82	0.4% @ 0.82
	0.4% @ 0.89	0.4% @ 0.89	0.4% @ 0.89	0.4% @ 0.89	0.4% @ 0.89	0.4% @ 0.88	0.4% @ 0.88
	0.4% @ 0.91	0.4% @ 0.91	0.4% @ 0.91	0.4% @ 0.91	0.4% @ 0.91	0.4% @ 0.91	0.4% @ 0.91
	0.2% @ 1.02	0.2% @ 1.02	0.2% @ 1.02	0.3% @ 1.02	0.4% @ 1.04	0.5% @ 1.02	
				0.2% @ 1.10	0.4% @ 1.10	0.4% @ 1.10	0.5% @ 1.11

OOS*: Solution turned yellow

OOS**: Solution turned yellow (nonconformance confirmed)

[00349] Example 8: Stability testing of Aileron peptide 1

[00350] Aileron peptide 1 was performed on a pharmaceutical formulation formulated at a concentration of 15 mg/mL (20 mM sodium phosphate, 240 mM D-Trehalose, 330 ppm polysorbate 20, pH 7.5). 5 mL of this formulation was stored in a 10 mL clear serum vial (20 mm FluroTec®-coated stopper; 20 mm Flip-off™ seal).

The formulation was stored at -15 °C and was tested at regular intervals. The results of this analysis are summarized in **Table 12**.

[00351] Table 12:

Attribute	Test	Specification	Results
	Appearance	Upon thawing: Clear, colorless, particulate-free solution	Conforms
Identity	pH	7.5 ±0.2	7.6
	Osmolality	220 to 400 mOsmol/Kg	327
	RP-HPLC (TFA)	Co-elutes with ALRN-6924 reference standard	Conforms
Potency	qRP-HPLC (TFA)	15± 1.5 mg/mL	15.6
Purity	RP-HPLC(TFA)	Purity ≥ 95% by area integration	99.0%
		no single impurity > 3%[1]	RRT 0.88: 0.4% RRT 0.91: 0.4% RRT 1.02: 0.2%
Safety	Particulate matter USP <788>	≥ 10 µm: ≤ 6,000 particulates/vial ≥ 25 µm: ≤ 600 particulates/vial	≥ 10 µm: 557 ≥ 25 µm: 8
	Endotoxin, USP <85>	≤ 4.4 EU/mL[2]	< 1.6 EU/mL
	Container/Closure Integrity	No dye intrusion	Conforms
	Sterility; USP <71> (Membrane Filtration)	No growth	No growth

[1]Impurities> 0.1% are listed based on their relative retention time (RRT) with respect to the Aileron peptide 1peptide peak.

[2]Based on a maximum patient dose of 17 mg Aileron peptide 1 per Kg of patient weight.

[00352] Example 9: Stability testing of multiple batches of Aileron peptide 1 under varying storage conditions

[00353] Samples 1-7 of Aileron peptide 1 were formulated at a concentration of 15 mg/mL (20 mM sodium phosphate, 240 mM D-Trehalose, 330 ppm polysorbate 20, pH 7.5). These samples were stored under different storage conditions as described in **Table 13**. The formulations were tested for appearances and purity. The results are summarized in **Tables 14-16** below.

[00354] Table 13:

Sample Number	Sample Description
Sample 1	Aileron peptide 1 Drug product configuration Upright 15 mg/mL 12 month -20 °C (/- 5 °C)
Sample 2	Aileron peptide 1 Drug product configuration Upright Storage Only/Return 15 mg/mL 12 month -20 °C (+/- 5 °C)

Sample 3	Aileron peptide 1 Drug product configuration Inverted Storage Only/Return 15 mg/mL 12 month 25 °C/60% RH (+/- 2 °C/ +/- 5%RH)
Sample 4	Aileron peptide 1Drug product configuration Inverted 15 mg/mL 12 month 25 °C/60% RH (+/- 2 °C/ +/- 5%RH)
Sample 5	Aileron peptide 1Drug product configuration Inverted Storage Only/Return 15 mg/mL 12 month 5 °C (+/- 3 °C)
Sample 6	Aileron peptide 1Drug product configuration Inverted 15 mg/mL 12 month 5 °C (+/- 3 °C)
Sample 7	Aileron peptide 1Drug product configuration Inverted 15 mg/mL 12 month 40 °C/75%RH (+/- 2 °C/ +/-5%RH)

[00355] Table 14: Results of analysis of sample 1.

Test	Acceptance Criteria	Test Result(s)
Appearance	Upon thawing: Clear, colorless, particulate-free solution	Clear, colorless, particulate-free solution. Meets acceptance criteria.
pH	7.3 to 7.7	7.63 Meets acceptance criteria.
RP_HPLC (TFA) for Aileron peptide-1Concentration	≥ 13.5 mg/mL; ≤ 16.5 mg/mL	Injection #1 = 15.58 mg/mL Injection #2 = 15.54 mg/mL Mean = 15.6 mg/mL Meets acceptance criteria.
RP_HPLC (TFA) Purity by Area Integration	≥ 95% for ALRN-6924 peak	Injection #1 = 98.6% Injection #2 = 98.6% Mean = 98.6% Meets acceptance criteria.
RP_HPLC (TFA) Purity by Area Integration for: Largest Impurity (RRT 0.91)	No single impurity > 3%	Injection #1 = 0.41% Injection #2 = 0.42% Mean = 0.41% Meets acceptance criteria.
RP_HPLC (TFA) Purity by Area Integration for: Impurity (RRT 0.87)	Report Result ≥ 0.1%	Injection #1 = 0.07% Injection #2 = 0.07% Mean = 0.07%

RP_HPLC (TFA) Purity by Area Integration for: Impurity (RRT 0.88)	Report Result ≥ 0.1%	Injection #1 = 0.39% Injection #2 = 0.39% Mean = 0.39%
RP_HPLC (TFA) Purity by Area Integration for: Impurity (RRT 0.94)	Report Result ≥ 0.1%	Injection #1 = 0.11% Injection #2 = 0.10% Mean = 0.11%
RP_HPLC (TFA) Purity by Area Integration for: Impurity (RRT 1.02)	Report Result ≥ 0.1%	Injection #1 = 0.16% Injection #2 = 0.14% Mean = 0.15%
RP_HPLC (TFA) Purity by Area Integration for: Impurity (RRT 1.04)	Report Result ≥ 0.1%	Injection #1 = 0.09% Injection #2 = 0.09% Mean = 0.09%
RP_HPLC (TFA) Purity by Area Integration for: Impurity (RRT 1.10)	Report Result ≥ 0.1%	Injection #1 = 0.07% Injection #2 = 0.07% Mean = 0.07%
Total Impurities	Information	1.3%

[00356] Table 15: Results of analysis of sample 4.

Test	Acceptance Criteria	Test Result(s)
Appearance	Upon thawing: Clear, colorless, particulate-free solution	Clear, colorless, particulate-free solution. Meets acceptance criteria.
pH	7.3 to 7.7	7.64 Meets acceptance criteria.
RP_HPLC (TFA) for: Aileron peptide-1TEConcentration	≥ 13.5 mg/mL; ≤ 16.5 mg/mL	Injection #1 = 14.98 mg/mL Injection #2 = 15.00 mg/mL Mean = 15.0 mg/mL Meets acceptance criteria.
RP_HPLC (TFA) Purity by Area Integration	≥ 95% for Aileron peptide-1 peak	Injection #1 = 96.3% Injection #2 = 96.3% Mean = 96.3% Meets acceptance criteria.
RP_HPLC (TFA) Purity by Area Integration for: Largest Impurity (RRT 0.23)	No single impurity > 3%	Injection #1 = 0.47% Injection #2 = 0.47% Mean = 0.47% Meets acceptance criteria.
RP_HPLC (TFA) Purity by Area Integration for: Impurity (RRT 0.16)	Report Result ≥ 0.1%	Injection #1 = 0.11% Injection #2 = 0.11% Mean = 0.11%
RP_HPLC (TFA) Purity by Area Integration for: Impurity (RRT 0.19)	Report Result ≥ 0.1%	Injection #1 = 0.13% Injection #2 = 0.13% Mean = 0.13%
RP_HPLC (TFA) Purity by Area Integration for: Impurity (RRT 0.22)	Report Result ≥ 0.1%	Injection #1 = 0.07% Injection #2 = 0.07% Mean = 0.07%
RP_HPLC (TFA) Purity by Area Integration for: Impurity (RRT	Report Result ≥ 0.1%	Injection #1 = 0.10% Injection #2 = 0.10%

0.24)		Mean = 0.10%
RP_HPLC (TFA) Purity by Area Integration for: Impurity (RRT 0.25A)	Report Result ≥ 0.1%	Injection #1 = 0.07% Injection #2 = 0.06% Mean = 0.06%
RP_HPLC (TFA) Purity by Area Integration for: Impurity (RRT 0.25B)	Report Result ≥ 0.1%	Injection #1 = 0.06% Injection #2 = 0.05% Mean = 0.06%
RP_HPLC (TFA) Purity by Area Integration for: Impurity (RRT 0.28)	Report Result ≥ 0.1%	Injection #1 = 0.15% Injection #2 = 0.11% Mean = 0.13%
RP_HPLC (TFA) Purity by Area Integration for: Impurity (RRT 0.29)	Report Result ≥ 0.1%	Injection #1 = 0.11% Injection #2 = 0.09% Mean = 0.10%
RP_HPLC (TFA) Purity by Area Integration for: Impurity (RRT 0.31)	Report Result ≥ 0.1%	Injection #1 = 0.07% Injection #2 = 0.06% Mean = 0.06%
RP_HPLC (TFA) Purity by Area Integration for: Impurity (RRT 0.32)	Report Result ≥ 0.1%	Injection #1 = 0.21% Injection #2 = 0.20% Mean = 0.20%
RP_HPLC (TFA) Purity by Area Integration for: Impurity (RRT 0.36)	Report Result ≥ 0.1%	Injection #1 = 0.14% Injection #2 = 0.13% Mean = 0.13%
RP_HPLC (TFA) Purity by Area Integration for: Impurity (RRT 0.39)	Report Result ≥ 0.1%	Injection #1 = 0.07% Injection #2 = 0.08% Mean = 0.08%
RP_HPLC (TFA) Purity by Area Integration for: Impurity (RRT 0.41)	Report Result ≥ 0.1%	Injection #1 = 0.13% Injection #2 = 0.14% Mean = 0.14%
RP_HPLC (TFA) Purity by Area Integration for: Impurity (RRT 0.47)	Report Result ≥ 0.1%	Injection #1 = 0.12% Injection #2 = 0.14% Mean = 0.13%
RP_HPLC (TFA) Purity by Area Integration for: Impurity (RRT 0.82)	Report Result ≥ 0.1%	Injection #1 = 0.35% Injection #2 = 0.37% Mean = 0.36%
RP_HPLC (TFA) Purity by Area Integration for: Impurity (RRT 0.87)	Report Result ≥ 0.1%	Injection #1 = 0.07% Injection #2 = 0.07% Mean = 0.07%
RP_HPLC (TFA) Purity by Area Integration for: Impurity (RRT 0.88)	Report Result ≥ 0.1%	Injection #1 = 0.37% Injection #2 = 0.35% Mean = 0.36%
RP_HPLC (TFA) Purity by Area Integration for: Impurity (RRT 0.91)	Report Result ≥ 0.1%	Injection #1 = 0.36% Injection #2 = 0.35% Mean = 0.36%
RP_HPLC (TFA) Purity by Area Integration for: Impurity (RRT 1.02)	Report Result ≥ 0.1%	Injection #1 = 0.21% Injection #2 = 0.22% Mean = 0.22%
RP_HPLC (TFA) Purity by Area Integration for: Impurity (RRT 1.04)	Report Result ≥ 0.1%	Injection #1 = 0.10% Injection #2 = 0.10% Mean = 0.10%
RP_HPLC (TFA) Purity by Area Integration for: Impurity (RRT	Report Result ≥ 0.1%	Injection #1 = 0.08% Injection #2 = 0.09%

1.10)		Mean = 0.09%
RP_HPLC (TFA) Purity by Area Integration for: Impurity (RRT 1.11)	Report Result ≥ 0.1%	Injection #1 = 0.07% Injection #2 = 0.08% Mean = 0.07%
Total Impurities	Information	3.6%

[00357] Table 16: Results of analysis of sample 6.

Test	**Acceptance Criteria**	**Test Result(s)**
Appearance	Upon thawing: Clear, colorless, particulate-free solution	Clear, colorless, particulate-free solution. Meets acceptance criteria.
pH	7.3 to 7.7	7.64 Meets acceptance criteria.
RP_HPLC (TFA) for Aileron peptide-1 Concentration	≥ 13.5 mg/mL; ≤ 16.5 mg/mL	Injection #1 = 15.61 mg/mL Injection #2 = 15.62 mg/mL Mean = 15.6 mg/mL Meets acceptance criteria.
RP_HPLC (TFA) Purity by Area Integration	≥ 95% for Aileron peptide-1 peak	Injection #1 = 98.6% Injection #2 = 98.6% Mean = 98.6% Meets acceptance criteria.
RP_HPLC (TFA) Purity by Area Integration for: Largest Impurity (RRT 0.91)	No single impurity > 3%	Injection #1 = 0.43% Injection #2 = 0.41% Mean = 0.42% Meets acceptance criteria.
RP_HPLC (TFA) Purity by Area Integration for: Largest Impurity (RRT 0.82)	Report Result ≥ 0.1%	Injection #1 = 0.10% Injection #2 = 0.10% Mean = 0.10%
RP_HPLC (TFA) Purity by Area Integration for: Largest Impurity (RRT 0.87)	Report Result ≥ 0.1%	Injection #1 = 0.08% Injection #2 = 0.06% Mean = 0.07%
RP_HPLC (TFA) Purity by Area Integration for: Largest Impurity (RRT 0.88)	Report Result ≥ 0.1%	Injection #1 = 0.39% Injection #2 = 0.40% Mean = 0.40%
RP_HPLC (TFA) Purity by Area Integration for: Largest Impurity (RRT 0.94)	Report Result ≥ 0.1%	Injection #1 = 0.08% Injection #2 = 0.11% Mean = 0.10%
RP_HPLC (TFA) Purity by Area Integration for: Largest Impurity (RRT 1.02)	Report Result ≥ 0.1%	Injection #1 = 0.15% Injection #2 = 0.14% Mean = 0.14%
RP_HPLC (TFA) Purity by Area Integration for: Largest Impurity (RRT 1.04)	Report Result ≥ 0.1%	Injection #1 = 0.06% Injection #2 = 0.09% Mean = 0.07%
RP_HPLC (TFA) Purity by Area Integration for: Largest Impurity (RRT 1.10)	Report Result ≥ 0.1%	Injection #1 = 0.07% Injection #2 = 0.08% Mean = 0.08%
Total Impurities	Information	1.4%

[00358] Table 17: Results of analysis of sample 7.

Test	Acceptance Criteria	Test Result(s)
Appearance	Upon thawing: Clear, colorless, particulate-free solution	Clear, yellow, particulate-free solution. Does not meet acceptance criteria.
pH	7.3 to 7.7	7.45 Meets acceptance criteria.
RP_HPLC (TFA) for Aileron peptide-1 Concentration	≥ 13.5 mg/mL; ≤ 16.5 mg/mL	Injection #1 = 14.09 mg/mL Injection #2 = 14.05 mg/mL Mean = 14.1 mg/mL Meets acceptance criteria.
RP_HPLC (TFA) Purity by Area Integration	≥ 95% for Aileron peptide-1 peak	Injection #1 = 94.3% Injection #2 = 94.3% Mean = 94.3% Does not meet acceptance criteria.
RP_HPLC (TFA) Purity by Area Integration for: Largest Impurity (RRT 1.02)	No single impurity > 3%	Injection #1 = 0.58% Injection #2 = 0.59% Mean = 0.59% Meets acceptance criteria.
RP_HPLC (TFA) Purity by Area Integration for: Largest Impurity (RRT 0.11)	Report Results ≥ 0.1%	Injection #1 = 0.07% Injection #2 = 0.07% Mean = 0.07%
RP_HPLC (TFA) Purity by Area Integration for: Largest Impurity (RRT 0.12)	Report Results ≥ 0.1%	Injection #1 = 0.07% Injection #2 = 0.07% Mean = 0.07%
RP_HPLC (TFA) Purity by Area Integration for: Largest Impurity (RRT 0.16)	Report Results ≥ 0.1%	Injection #1 = 0.08% Injection #2 = 0.08% Mean = 0.08%
RP_HPLC (TFA) Purity by Area Integration for: Largest Impurity (RRT 0.19A)	Report Results ≥ 0.1%	Injection #1 = 0.39% Injection #2 = 0.39% Mean = 0.39%
RP_HPLC (TFA) Purity by Area Integration for: Largest Impurity (RRT 0.19B)	Report Results ≥ 0.1%	Injection #1 = 0.12% Injection #2 = 0.12% Mean = 0.12%
RP_HPLC (TFA) Purity by Area Integration for: Largest Impurity (RRT 0.20)	Report Results ≥ 0.1%	Injection #1 = 0.15% Injection #2 = 0.15% Mean = 0.15%
RP_HPLC (TFA) Purity by Area Integration for: Largest Impurity (RRT 0.23)	Report Results ≥ 0.1%	Injection #1 = 0.26% Injection #2 = 0.26% Mean = 0.26%
RP_HPLC (TFA) Purity by Area Integration for: Largest Impurity (RRT 0.24)	Report Results ≥ 0.1%	Injection #1 = 0.27% Injection #2 = 0.27% Mean = 0.27%
RP_HPLC (TFA) Purity by Area Integration for: Largest Impurity (RRT 0.25)	Report Results ≥ 0.1%	Injection #1 = 0.15% Injection #2 = 0.14% Mean = 0.14%

RP_HPLC (TFA) Purity by Area Integration for: Largest Impurity (RRT 0.28)	Report Results ≥ 0.1%	Injection #1 = 0.10% Injection #2 = 0.09% Mean = 0.09%
RP_HPLC (TFA) Purity by Area Integration for: Largest Impurity (RRT 0.29)	Report Results ≥ 0.1%	Injection #1 = 0.17% Injection #2 = 0.18% Mean = 0.17%
RP_HPLC (TFA) Purity by Area Integration for: Largest Impurity (RRT 0.32)	Report Results ≥ 0.1%	Injection #1 = 0.30% Injection #2 = 0.30% Mean = 0.30%
RP_HPLC (TFA) Purity by Area Integration for: Largest Impurity (RRT 0.36)	Report Results ≥ 0.1%	Injection #1 = 0.16% Injection #2 = 0.15% Mean = 0.16%
RP_HPLC (TFA) Purity by Area Integration for: Largest Impurity (RRT 0.41)	Report Results ≥ 0.1%	Injection #1 = 0.14% Injection #2 = 0.14% Mean = 0.14%
RP_HPLC (TFA) Purity by Area Integration for: Largest Impurity (RRT 0.43)	Report Results ≥ 0.1%	Injection #1 = 0.06% Injection #2 = 0.06% Mean = 0.06%
RP_HPLC (TFA) Purity by Area Integration for: Largest Impurity (RRT 0.47)	Report Results ≥ 0.1%	Injection #1 = 0.19% Injection #2 = 0.18% Mean = 0.18%
RP_HPLC (TFA) Purity by Area Integration for: Largest Impurity (RRT 0.74)	Report Results ≥ 0.1%	Injection #1 = 0.23% Injection #2 = 0.23% Mean = 0.23%
RP_HPLC (TFA) Purity by Area Integration for: Largest Impurity (RRT 0.82)	Report Results ≥ 0.1%	Injection #1 = 0.35% Injection #2 = 0.36% Mean = 0.35%
RP_HPLC (TFA) Purity by Area Integration for: Largest Impurity (RRT 0.83)	Report Results ≥ 0.1%	Injection #1 = 0.09% Injection #2 = 0.09% Mean = 0.09%
RP_HPLC (TFA) Purity by Area Integration for: Largest Impurity (RRT 0.87)	Report Results ≥ 0.1%	Injection #1 = 0.07% Injection #2 = 0.06% Mean = 0.07%
RP_HPLC (TFA) Purity by Area Integration for: Largest Impurity (RRT 0.88)	Report Results ≥ 0.1%	Injection #1 = 0.41% Injection #2 = 0.41% Mean = 0.41%
RP_HPLC (TFA) Purity by Area Integration for: Largest Impurity (RRT 0.91)	Report Results ≥ 0.1%	Injection #1 = 0.43% Injection #2 = 0.43% Mean = 0.43%
RP_HPLC (TFA) Purity by Area Integration for: Largest Impurity (RRT 0.96)	Report Results ≥ 0.1%	Injection #1 = 0.06% Injection #2 = 0.06% Mean = 0.06%
RP_HPLC (TFA) Purity by Area Integration for: Largest Impurity (RRT 1.04)	Report Results ≥ 0.1%	Injection #1 = 0.07% Injection #2 = 0.08% Mean = 0.07%
RP_HPLC (TFA) Purity by Area Integration for: Largest Impurity (RRT 0.96)	Report Results ≥ 0.1%	Injection #1 = 0.12% Injection #2 = 0.12% Mean = 0.12%
RP_HPLC (TFA) Purity by Area Integration for: Largest Impurity (RRT 1.11)	Report Results ≥ 0.1%	Injection #1 = 0.49% Injection #2 = 0.49% Mean = 0.49%

Total Impurities	Information	5.6%

[00359] Example 10: von Heijne (VH) value calculation

[00360] von Heijne values were calculated using a method adapted from Hessa et al., Recognition of transmembrane helices by the endoplasmic reticulum translocon, *Nature*: 433, 377-381 (*2005*). Briefly, each amino acid is assigned a fixed value, regardless of location along the polypeptide chain, according to the **Table 18** below:

[00361] **Table 18:** von Heijne Score of various amino acids

Amino Acid	von Heijne Score
I	-0.6
L	-0.5
Nle	-0.5
$	-0.5
St	-0.5
$e	-0.5
$r8	-0.5
$r5	-0.5
$s8	-0.5
$s5	-0.5
$er8	-0.5
F	-0.3
V	-0.3
Aib	-0.1
M	-0.1
C	-0.1
Abu	-0.1
Ac-	0
$-NH_2$	0
A	0.1
a	0.1
W	0.3
T	0.5
Y	0.6
G	0.6
S	0.8
N	2
H	2
P	2.2
Q	2.2
E	2.5
R	2.5
K	2.5
D	3.5

[00362] The von Heijne value (VH) for the polypeptide is then calculated as the sum total of values for all amino acids in the polypeptide. For example, a pentapeptide of the sequence Ac-AAAAA-NH_2 would have a VH score of 5*(0.1) = 0.5.

[00363] Example 11: Reverse-Phase HPLC retention time determination

[00364] Peptides were analyzed by reverse-phase HPLC on a 100 x 2.1 mm Phenomenex 2.6 micron, 100 Angstrom C18 column using the following mobile phase gradient at room temperature:

Time (min)	Flow rate (mL/min)	% A (0.1% TFA in water)	% B (0.1% TFA in acetonitrile)
0	0.6	80	20
20.0	0.6	20	80
20.1	0.6	5	95
21.0	0.6	5	95
21.1	0.6	80	20
21.2	0.6	5	95
21.5	0.6	5	95
21.8	0.6	80	20
23.5	0.6	80	20

[00365] In some embodiments, the retention time (RT) was then normalized to a 0-100 scale by the following equation: RT = [RT_raw (from above)* 3.317 - 0.534] * 3.3333. In some embodiments, the retention times were not normalizd.

CLAIMS

WHAT IS CLAIMED IS:

1. An aqueous pharmaceutical formulation comprising a peptidomimetic macrocycle that binds to MDM2 and/or MDMX proteins or a pharmaceutically acceptable salt thereof, a buffering agent, a tonicity agent, and a stabilizing agent wherein the amount of the peptidomimetic macrocycle in the aqueous pharmaceutical formulation is equal to or greater than15 mg/mL and wherein the aqueous pharmaceutical formulation comprises less than 2 % w/v of any micelle forming agent.
2. An aqueous pharmaceutical formulation comprising:
   (i) a peptidomimetic macrocycle or a pharmaceutically acceptable salt thereof, wherein the amount of the peptidomimetic macrocycle in the aqueous pharmaceutical formulation is equal to or greater than15 mg/mL;
   (ii) a buffering agent;
   (iii) a stabilizing agent; and
   (iv) a tonicity agent
   wherein the molar ratio of the peptidomimetic macrocycle to the buffering agent is in the range of 0.01-2.5.
3. An aqueous pharmaceutical formulation comprising a peptidomimetic macrocycle that binds to a target protein with a K_D value of $1x10^{-7}$ M or less, or a pharmaceutically acceptable salt thereof, a buffering agent, a tonicity agent, and a stabilizing agent wherein the amount of the peptidomimetic macrocycle in the aqueous pharmaceutical formulation is equal to or greater than15 mg/mL and wherein the aqueous pharmaceutical formulation comprises less than 2 % w/v of any micelle forming agent, wherein the peptidomimetic macrocycle or pharmaceutically acceptable salt thereof has
   a. a length value of from 10 to 24 amino acids,
   b. a von Heijne value of from 2 to 10,
   c. a net charge of from -4 to +2,
   d. a per cent alanine content of from 15% to 50%,
   e. or any combination of (a)-(d).
4. The aqueous pharmaceutical formulation of any of claims 1-3, wherein the peptidomimetic macrocycle or pharmaceutically acceptable salt thereof is not precipitated in the formulation.
5. The aqueous pharmaceutical formulation of claim 4, wherein an aqueous solubility of the peptidomimetic macrocycle is determined by evaluating the turbidity of a solution comprising the peptidomimetic macrocycle.
6. The aqueous pharmaceutical formulation of any of claims 1-5, wherein the peptidomimetic macrocycle or pharmaceutically acceptable salt thereof has an amphipathicity that falls in a range that is optimal for cell permeability.

7. The aqueous pharmaceutical formulation of any of claims 1-6, wherein the peptidomimetic macrocycle or pharmaceutically acceptable salt thereof has a length value of from 14 to 20 amino acids.
8. The aqueous pharmaceutical formulation of any of claims 1-7, wherein the peptidomimetic macrocycle or pharmaceutically acceptable salt thereof has a von Heijne value of from 2 to 9.
9. The aqueous pharmaceutical formulation of any of claims 1-8, wherein the peptidomimetic macrocycle or pharmaceutically acceptable salt thereof has a von Heijne value of from 3 to 8.
10. The aqueous pharmaceutical formulation of any of claims 1-9, wherein the peptidomimetic macrocycle or pharmaceutically acceptable salt thereof has a von Heijne value of from 4 to 7.
11. The aqueous pharmaceutical formulation of any of claims 1-10, wherein the peptidomimetic macrocycle or pharmaceutically acceptable salt thereof has a net charge of from -2 to 0.
12. The aqueous pharmaceutical formulation of any of claims 1-11, wherein the peptidomimetic macrocycle or pharmaceutically acceptable salt thereof has a per cent alanine content of from 15% to 40%.
13. The aqueous pharmaceutical formulation of any of claims 1-12, wherein the peptidomimetic macrocycle or pharmaceutically acceptable salt thereof has a per cent alanine content of from 20% to 40%.
14. The aqueous pharmaceutical formulation of any of claims 1-13, wherein the peptidomimetic macrocycle or pharmaceutically acceptable salt thereof has a per cent alanine content of from 25% to 40%.
15. The aqueous pharmaceutical formulation of any of claims 1-14, wherein the peptidomimetic macrocycle or pharmaceutically acceptable salt thereof has a length value of from 14 to 20 amino acids, a von Heijne value of from 4 to 7, a net charge of from -2 to 0, and a per cent alanine content of from 25% to 40%.
16. The aqueous pharmaceutical formulation of any of claims 1-15, wherein the peptidomimetic macrocycle or pharmaceutically acceptable salt thereof is soluble, does not have off-target effects, or a combination thereof.
17. The aqueous pharmaceutical formulation of any of claims 1-16, wherein the peptidomimetic macrocycle or pharmaceutically acceptable salt thereof comprises a first C-terminal amino acid that is hydrophobic.
18. The aqueous pharmaceutical formulation of any of claims 1-17, wherein the peptidomimetic macrocycle or pharmaceutically acceptable salt thereof comprises a second C-terminal amino acid that is hydrophobic.
19. The aqueous pharmaceutical formulation of any of claims 1-18, wherein the peptidomimetic macrocycle or pharmaceutically acceptable salt thereof comprises a third C-terminal amino acid that is hydrophobic.
20. The aqueous pharmaceutical formulation of any of claims 1-19, wherein the peptidomimetic macrocycle or pharmaceutically acceptable salt thereof comprises a fourth C-terminal amino acid that is hydrophobic.
21. The aqueous pharmaceutical formulation of any of claims 1-20, wherein the peptidomimetic macrocycle or pharmaceutically acceptable salt thereof comprises a fifth C-terminal amino acid that is hydrophobic.
22. The aqueous pharmaceutical formulation of any of claims 1-21, wherein the peptidomimetic macrocycle or pharmaceutically acceptable salt thereof comprises a sixth C-terminal amino acid that is hydrophobic.
23. The aqueous pharmaceutical formulation of any of claims 1-22,wherein the first amino acid connected to the crosslinker is N-terminal to the second amino acid connected to the crosslinker. and wherein the

peptidomimetic macrocycle or pharmaceutically acceptable salt thereof comprises 1, 2, 3, 4, 5, 6, 7, or 8 amino acids that are C-terminal to the second amino acid connected to the crosslinker.

24. The aqueous pharmaceutical formulation of any of claims 1-23, wherein the first amino acid connected to the crosslinker is N-terminal to the second amino acid connected to the crosslinker, and wherein the peptidomimetic macrocycle or pharmaceutically acceptable salt thereof comprises 1, 2, 3, 4, 5, or 6 hydrophobic amino acids that are C-terminal to the second amino acid connected to the crosslinker.
25. The aqueous pharmaceutical formulation of any of claims 1-24, wherein the first amino acid connected to the crosslinker is N-terminal to the second amino acid connected to the crosslinker, and wherein the peptidomimetic macrocycle or pharmaceutically acceptable salt thereof comprises 1, 2, or 3 glutamines that are C-terminal to the second amino acid connected to the crosslinker.
26. The aqueous pharmaceutical formulation of any of claims 1-25, wherein the amino acid that is hydrophobic is a small hydrophobic amino acid.
27. The aqueous pharmaceutical formulation of any of claims 1-26, wherein the amino acid that is hydrophobic is an alanine, a D-alanine, or an Aib.
28. The aqueous pharmaceutical formulation of any of claims 1-27, wherein the peptidomimetic macrocycle or pharmaceutically acceptable salt thereof is a helical polypeptide.
29. The aqueous pharmaceutical formulation of any of claims 1-28, wherein the peptidomimetic macrocycle or pharmaceutically acceptable salt thereof comprises an α-helix.
30. The aqueous pharmaceutical formulation of any of claims 1-29, wherein the peptidomimetic macrocycle or pharmaceutically acceptable salt thereof comprises an amphipathic α-helix.
31. The aqueous pharmaceutical formulation of any of claims 1-30, wherein the first amino acid connected to the crosslinker or the second amino acid connected to the crosslinker is an α,α-disubstituted amino acid.
32. The aqueous pharmaceutical formulation of any of claims 1-31, wherein the first amino acid connected to the crosslinker and the second amino acid connected to the crosslinker are α,α-disubstituted amino acids.
33. The aqueous pharmaceutical formulation of any of claims 1-32, wherein the first amino acid connected to the crosslinker and the second amino acid connected to the crosslinker are separated by two amino acids.
34. The aqueous pharmaceutical formulation of any of claims 1-32, wherein the first amino acid connected to the crosslinker and the second amino acid connected to the crosslinker are separated by three amino acids.
35. The aqueous pharmaceutical formulation of any of claims 1-32, wherein the first amino acid connected to the crosslinker and the second amino acid connected to the crosslinker are separated by six amino acids.
36. The aqueous pharmaceutical formulation of any of claims 1-35, wherein the crosslinker spans 1 turn of an α-helix of the peptidomimetic macrocycle.
37. The aqueous pharmaceutical formulation of any of claims 1-36, wherein the crosslinker spans 2 turns of an α-helix of the peptidomimetic macrocycle

38. The aqueous pharmaceutical formulation of any of claims 1-37, wherein the length of the crosslinker is from about 5 Å to about 9 Å per turn of an α-helix of the peptidomimetic macrocycle.
39. The aqueous pharmaceutical formulation of any of claims 1-38, wherein the peptidomimetic macrocycle or pharmaceutically acceptable salt thereof provides a therapeutic effect.
40. The aqueous pharmaceutical formulation of any of claims 1-39, wherein an ability of the peptidomimetic macrocycle or pharmaceutically acceptable salt thereof to penetrate cell membranes by an energy-dependent process is improved relative to a corresponding uncrosslinked peptidomimetic macrocycle.
41. The aqueous pharmaceutical formulation of any of claims 1-40, wherein an ability of the peptidomimetic macrocycle or pharmaceutically acceptable salt thereof to penetrate cell membranes by an energy-independent process is improved relative to a corresponding uncrosslinked peptidomimetic macrocycle.
42. The aqueous pharmaceutical formulation of claim 40 or 41, wherein the energy-dependent process is primary active transport, secondary transport, endocytosis, or a combination thereof.
43. The aqueous pharmaceutical formulation of any of claims 40-42, wherein the energy-dependent process is active transport.
44. The aqueous pharmaceutical formulation of any of claims 41-43, wherein the energy-independent process is passive diffusion, facilitated diffusion, filtration, or a combination thereof.
45. The aqueous pharmaceutical formulation of any of claims 41-44, wherein the energy-independent process is passive transport.
46. The aqueous pharmaceutical formulation of any of claims 1-45, wherein the peptidomimetic macrocycle or pharmaceutically acceptable salt thereof binds to MDM2 with a K_D value of $1x10^{-7}$ M or less.
47. The aqueous pharmaceutical formulation of any of claims 1-45, wherein the peptidomimetic macrocycle or pharmaceutically acceptable salt thereof binds to MDM2 or MDMX with a K_D value of $1x10^{-7}$ M or less.
48. The aqueous pharmaceutical formulation of any of claims 1-45, wherein the peptidomimetic macrocycle or pharmaceutically acceptable salt thereof binds to MDMX with a K_D value of $1x10^{-7}$ M or less.
49. The aqueous pharmaceutical formulation of any of claims 1-45, wherein the peptidomimetic macrocycle or pharmaceutically acceptable salt thereof binds to a PB1 peptide binding site of a PA protein with a K_D value of $1x10^{-7}$ M or less.
50. The aqueous pharmaceutical formulation of any of claims 1-45, wherein the peptidomimetic macrocycle or pharmaceutically acceptable salt thereof binds to a PB2 peptide binding site of a PB1 protein with a K_D value of $1x10^{-7}$ M or less.
51. The aqueous pharmaceutical formulation of any of claims 2-45, wherein the peptidomimetic macrocycle or pharmaceutically acceptable salt thereof binds to viral polymerase, for example, a RNA-dependent RNA polymerase with a K_D value of $1x10^{-7}$ M or less.
52. The aqueous pharmaceutical formulation of any of claim 49-51, wherein the peptidomimetic macrocycle or pharmaceutically acceptable salt thereof inhibits an influenza RNA-dependent RNA polymerase.

53. The peptidomimetic macrocycle of claim 51 or 52, wherein the virus is influenza virus.
54. The peptidomimetic macrocycle of any one of claims 51-53, wherein, wherein the peptidomimetic macrocycle is capable of competing with the binding of a peptide of the sequence MDVNPTLLFLKVPAQ or MERIKELRNLM to the viral RNA-dependent RNA polymerase.
55. The aqueous pharmaceutical formulation of any of claims 1-45, wherein the peptidomimetic macrocycle or pharmaceutically acceptable salt thereof binds to MCL-1, BCL-X_L, BCL-2, or a combination thereof with a K_D value of $1x10^{-7}$ M or less.
56. The aqueous pharmaceutical formulation of any of claims 1-45, wherein the peptidomimetic macrocycle or pharmaceutically acceptable salt thereof binds to MCL-1 with a K_D value of $1x10^{-7}$ M or less.
57. The aqueous pharmaceutical formulation of any of claims 1-45, wherein the peptidomimetic macrocycle or pharmaceutically acceptable salt thereof binds to BCL-X_L with a K_D value of $1x10^{-7}$ M or less.
58. The aqueous pharmaceutical formulation of any of claims 1-45, wherein the peptidomimetic macrocycle or pharmaceutically acceptable salt thereof binds to BCL-2 with a K_D value of $1x10^{-7}$ M or less.
59. The aqueous pharmaceutical formulation of any of claims 1-58, wherein the peptidomimetic macrocycle or pharmaceutically acceptable salt thereof has an IC_{50} value of 100 nM or less to a target protein.
60. The aqueous pharmaceutical formulation of any of claims 1-59, wherein the peptidomimetic macrocycle or pharmaceutically acceptable salt thereof has an EC_{50} value of 100 μM or less.
61. The aqueous pharmaceutical formulation of any of claims 1-60, wherein the peptidomimetic macrocycle or pharmaceutically acceptable salt thereof has an IC_{50} value of 10 nM or less to a target protein.
62. The aqueous pharmaceutical formulation of any of claims 1-61, wherein the peptidomimetic macrocycle or pharmaceutically acceptable salt thereof has an EC_{50} value of 10 μM or less.
63. The aqueous pharmaceutical formulation of any of claims 1-62, wherein the peptidomimetic macrocycle or pharmaceutically acceptable salt thereof has an IC_{50} value of 1 nM or less to a target protein.
64. The aqueous pharmaceutical formulation of any of claims 1-63, wherein the peptidomimetic macrocycle or pharmaceutically acceptable salt thereof has an EC_{50} value of 1 μM or less.
65. The aqueous pharmaceutical formulation of any of claims 1-64, wherein the peptidomimetic macrocycle or pharmaceutically acceptable salt thereof has a penetration efficiency value of 100 or less.
66. The aqueous pharmaceutical formulation of any of claims 1-65, wherein the peptidomimetic macrocycle or pharmaceutically acceptable salt thereof has a penetration efficiency value of 10 or less.
67. The aqueous pharmaceutical formulation of any of claims 1-66, wherein the peptidomimetic macrocycle or pharmaceutically acceptable salt thereof has a penetration efficiency value of 1 or less.
68. The aqueous pharmaceutical formulation of any of claims 1-67, wherein the peptidomimetic macrocycle penetrates cell membranes by an energy-dependent process and binds to an intracellular target with a K_D value of $1x10^{-7}$ M or less.

69. The aqueous pharmaceutical formulation of claim 68, wherein the energy-dependent process comprises primary active transport, secondary transport, or endocytosis.
70. The aqueous pharmaceutical formulation of claim 68 or 69, wherein the energy-dependent process comprises active transport.
71. The aqueous pharmaceutical formulation of any of claims 1-67, wherein the peptidomimetic macrocycle penetrates cell membranes by an energy-independent process and binds to an intracellular target with a K_D value of $1x10^{-7}$ M or less.
72. The aqueous pharmaceutical formulation of claim 71, wherein the energy-independent process comprises passive diffusion, facilitated diffusion, or filtration.
73. The aqueous pharmaceutical formulation of claim 71 or 72, wherein the energy-independent process comprises passive transport.
74. The aqueous pharmaceutical formulation of any one of claim 1to 73, wherein:
    (i) the amount of the buffering agent in the aqueous pharmaceutical formulation is 0.001-10% w/v;
    (ii) the amount of the stabilizing agent in the aqueous pharmaceutical formulation is 0.001-10% w/v; and
    (iii) the amount of the tonicity agent in the aqueous pharmaceutical formulation 1.0-10% w/v.
75. The aqueous pharmaceutical formulation of any one of the preceding claims, wherein the pharmaceutically acceptable salt of the peptidomimetic macrocycle is a sodium salt.
76. The aqueous pharmaceutical formulation of any one of claims 1-74, wherein the pharmaceutically acceptable salt of the peptidomimetic macrocycle is a potassium, lithium, calcium, zinc or magnesium salt.
77. The aqueous pharmaceutical formulation any one of the preceding claims, wherein the amount of the peptidomimetic macrocycle present in the aqueous pharmaceutical formulation is from about 0.1-10% w/v.
78. The aqueous pharmaceutical formulation of any one of the preceding claims, wherein the amount of the peptidomimetic macrocycle present in the aqueous pharmaceutical formulation is about 1% w/v, 1.5% w/v, or 2% w/v.
79. The aqueous pharmaceutical formulation of any one of the preceding claims, wherein the concentration of the peptidomimetic macrocycle present in the aqueous pharmaceutical formulation is about 15-100 mg/mL.
80. The aqueous pharmaceutical formulation of any one of the preceding claims, wherein the concentration of the peptidomimetic macrocycle present in the aqueous pharmaceutical formulation is about 15-50 mg/mL.
81. The aqueous pharmaceutical formulation of any one of the preceding claims, wherein the concentration of the peptidomimetic macrocycle present in the aqueous pharmaceutical formulation is about 15, 20, 25, or 50 mg/mL.

82. The aqueous pharmaceutical formulation of any one of the preceding claims, wherein the buffering agent is a phosphate buffer.
83. The aqueous pharmaceutical formulation of any one of the preceding claims, wherein the buffering agent is selected from a group consisting of ammonia solution, calcium carbonate, tribasic calcium phosphate, citric acid dihydrate, citric acid monohydrate, dibasic sodium phosphate, diethanolamine, malic acid, monobasic sodium phosphate, monoethanolamine, monosodium glutamate, phosphoric acid, phosphate-citrate buffer (dibasic sodium phosphate and citric acid), potassium citrate, sodium acetate, sodium bicarbonate, sodium borate, sodium citrate dehydrate, sodium hydroxide, sodium lactate, sodium carbonate, and triethanolamine (tris(hydroxymethyl)aminomethane).
84. The aqueous pharmaceutical formulation of any one of the preceding claims, wherein the buffering agent is selected from a group consisting of phosphoric acid, dibasic sodium phosphate, monobasic sodium phosphate or a mixture thereof.
85. The aqueous pharmaceutical formulation of any one of the preceding claims, wherein the buffering agent is 20 mM phosphate buffer
86. The aqueous pharmaceutical formulation of any one of the preceding claims, wherein the amount of the buffering agent is from about 0.001-10% w/v.
87. The aqueous pharmaceutical formulation of any one of the preceding claims, wherein the amount of the buffering agent present in the aqueous pharmaceutical formulation is from about 0.01-10% w/v.
88. The aqueous pharmaceutical formulation of any one of the preceding claims, wherein the amount of the buffering agent present in the aqueous pharmaceutical formulation is from about 0.01-5% w/v.
89. The aqueous pharmaceutical formulation of any one of the preceding claims, wherein the amount of the buffering agent present in the aqueous pharmaceutical formulation is from about 0.01-1% w/v.
90. The aqueous pharmaceutical formulation of any one of the preceding claims, wherein the amount of the buffering agent present in the aqueous pharmaceutical formulation is about 0.2% w/v.
91. The aqueous pharmaceutical formulation of any one of the claims 1-90, wherein the stabilizing agent is a non-ionic stabilizing agent.
92. The aqueous pharmaceutical formulation of any one of the claims 1-90, wherein the stabilizing agent is a fatty acid ester.
93. The aqueous pharmaceutical formulation of any one of the claims 1-90, wherein the stabilizing agent is a surfactant.
94. The aqueous pharmaceutical formulation of any one of the claims 1-90, wherein the stabilizing agent is a non-ionic surfactant.
95. The aqueous pharmaceutical formulation of any one of the claims 1-90, wherein the stabilizing agent is an anti-oxidant.

96. The aqueous pharmaceutical formulation of any one of the claims 1-90, wherein the stabilizing agent is selected from a group consisting of polyoxyethylene glycol alkyl ethers, polyoxypropylene glycol alkyl ethers, glucoside alkyl ethers, polyoxyethylene glycol octylphenol ethers, polyoxyethylene glycol alkylphenol ethers, glycerol alkyl esters, polyoxyethylene glycol sorbitan alkyl esters, sorbitan alkyl esters, cocamide MEA, cocamide DEA, dodecyldimethylamine oxide, block copolymers of polyethylene glycol and polypropylene glycol, and polyethoxylated tallow amine.
97. The aqueous pharmaceutical formulation of any one of the claims 1-90, wherein the stabilizing agent is a polyoxyethylene sorbitan fatty acid ester
98. The aqueous pharmaceutical formulation of any one of the claims 1-90, wherein the stabilizing agent is polysorbate 20, polysorbate 21, polysorbate 40, polysorbate 60, polysorbate 61, polysorbate 65, polysorbate 80, polysorbate 81, polysorbate 85 or polysorbate 120.
99. The aqueous pharmaceutical formulation of any one of the claims 1-90, wherein the stabilizing agent is polysorbate 20.
100. The aqueous pharmaceutical formulation of any one of the preceding claims, wherein the amount of the stabilizing agent present in the aqueous pharmaceutical formulation is from about 0.001-10 % w/v.
101. The aqueous pharmaceutical formulation of any one of the preceding claims, wherein the amount of the stabilizing agent present in the aqueous pharmaceutical formulation is from about 0.01-.05% w/v.
102. The aqueous pharmaceutical formulation of any one of the preceding claims, wherein the amount of the stabilizing agent present in the aqueous pharmaceutical formulation is about 0.03% w/v.
103. The aqueous pharmaceutical formulation of any one of the preceding claims, wherein the aqueous pharmaceutical formulation comprises 250-350 ppm polysorbate 20.
104. The aqueous pharmaceutical formulation of any one of the preceding claims, wherein the aqueous pharmaceutical formulation is a solution.
105. The aqueous pharmaceutical formulation of any one of the preceding claims, wherein the aqueous pharmaceutical formulation is sterile.
106. The aqueous pharmaceutical formulation of any one of the preceding claims, wherein the aqueous pharmaceutical formulation is colorless.
107. The aqueous pharmaceutical formulation of any one of the preceding claims, wherein the aqueous pharmaceutical formulation is particulate-free.
108. The aqueous pharmaceutical formulation of any one of the preceding claims, wherein the aqueous pharmaceutical formulation comprises less than about 6,000 particles of size $\geq$ 10 μm in about 5 mL of the aqueous formulation.
109. The aqueous pharmaceutical formulation of any one of the preceding claims, wherein the aqueous pharmaceutical formulation comprises less than about 600 particles of size $\geq$ 25 μm in about 5 mL of the aqueous formulation.

110. The aqueous pharmaceutical formulation of any one of the preceding claims, wherein the aqueous pharmaceutical formulation is a frozen solution.

111. The aqueous pharmaceutical formulation of any one of the preceding claims, wherein the aqueous pharmaceutical formulation is a refrigerated solution.

112. The aqueous pharmaceutical formulation of any one of the preceding claims, wherein the aqueous pharmaceutical formulation is a refrigerated solution.

113. The aqueous pharmaceutical formulation of any one of the preceding claims, wherein the aqueous pharmaceutical formulation is dissolved into a diluent prior to administration into a subject.

114. The aqueous pharmaceutical formulation of claim 113, wherein the diluent is water for injection.

115. The aqueous pharmaceutical formulation of claim 113, wherein the diluent is a solution of dextrose in water.

116. The aqueous pharmaceutical formulation of claim 113, wherein the amount of the diluent is from about 50-99% w/v.

117. The aqueous pharmaceutical formulation of claim 113, wherein the amount of the diluent is about 90% w/v.

118. The aqueous pharmaceutical formulation of any one of the claims 1-117, wherein the tonicity agent is a non-ionic tonicity agent.

119. The aqueous pharmaceutical formulation of any one of the claims 1-117, wherein the tonicity agent is a sugar or a sugar alcohol.

120. The aqueous pharmaceutical formulation of any one of the claims 1-117, wherein the tonicity agent is a mono- or a disaccharide.

121. The aqueous pharmaceutical formulation of any one of the claims 1-117, wherein the tonicity agent is selected from a groups consisting of glucose, fructose, galactose, sucrose, lactose, maltose, trehalose, and mixtures thereof.

122. The aqueous pharmaceutical formulation of any one of the preceding claims, wherein the tonicity agent is mannitol, glycerin, or a combination thereof.

123. The aqueous pharmaceutical formulation of any one of the claims 1-117, wherein the tonicity agent is D-trehalose.

124. The aqueous pharmaceutical formulation of any one of the preceding claims, wherein the amount of the tonicity agent present in the aqueous pharmaceutical formulation is from about 1-15% w/v.

125. The aqueous pharmaceutical formulation any one of the preceding claims, wherein the amount of the tonicity agent present in the aqueous pharmaceutical formulation is about 8% w/v.

126. The aqueous pharmaceutical formulation of any one of the preceding claims, wherein the concentration of the tonicity agent is from about 200-300 mM.

127. The aqueous pharmaceutical formulation of any one of the preceding claims, wherein the concentration of the tonicity agent is 240 mM.

128. The aqueous pharmaceutical formulation of any one of the preceding claims1, wherein the pH of the aqueous pharmaceutical formulation is from about 4.0-9.0.

129. The aqueous pharmaceutical formulation of any one of the preceding claims, wherein the pH of the aqueous pharmaceutical formulation is from about 4.5-8.5.

130. The aqueous pharmaceutical formulation of any one of the preceding claims, wherein the pH of the aqueous pharmaceutical formulation is from about 5.0-8.0.

131. The aqueous pharmaceutical formulation of any one of the preceding claims, wherein the pH of the aqueous pharmaceutical formulation is from about 5.5-7.5.

132. The aqueous pharmaceutical formulation of any one of the preceding claims, wherein the pH of the aqueous pharmaceutical formulation is about 7.0-7.5.

133. The aqueous pharmaceutical formulation of any one of claims 1-132, wherein the aqueous pharmaceutical formulation is stable for at least two years at a temperature of about -20 °C-25 °C.

134. The aqueous pharmaceutical formulation of any one of claims 1-132, wherein the aqueous pharmaceutical formulation is stable for at least one years at a temperature of about -20 °C-25 °C.

135. The aqueous pharmaceutical formulation of any one of claims 1-132, wherein the aqueous pharmaceutical formulation is stable for at least 6 months at a temperature of about -20 °C-25 °C.

136. The aqueous pharmaceutical formulation of any one of claims 1-132, wherein the aqueous pharmaceutical formulation is stable for at least 3 months at a temperature of about -20 °C-25 °C.

137. The aqueous pharmaceutical formulation of any one of claims 1-132, wherein the aqueous pharmaceutical formulation is stable for at least 3 months at a temperature of about 45 °C.

138. The aqueous pharmaceutical formulation of any one of claims 1-132, wherein the aqueous pharmaceutical formulation is stable for at least 6 months at a temperature of about 45 °C.

139. The aqueous pharmaceutical formulation of any one of claims 1-132, wherein the aqueous pharmaceutical formulation is stable for at least 3 weeks at a temperature of about 75 °C.

140. The aqueous pharmaceutical formulation of any one of claims 1-132, wherein the aqueous pharmaceutical formulation is stable for at least 1.5 weeks at a temperature of about 75 °C.

141. The aqueous pharmaceutical formulation of any one of claims 1-140, wherein the aqueous pharmaceutical formulation upon storage for 24 months at from about 2 °C- 8 °C comprises at least 95% of the initial amount of the peptidomimetic macrocycle.

142. The aqueous pharmaceutical formulation of any one of claims 1-140, wherein the aqueous pharmaceutical formulation upon storage for 12 months at from about 2 °C- 8 °C comprises at least 95% of the initial amount of the peptidomimetic macrocycle.

143. The aqueous pharmaceutical formulation of any one of claims 1-140, wherein the aqueous pharmaceutical formulation upon storage for 6 months at from about 2 °C- 8 °C comprises at least 95% of the initial amount of the peptidomimetic macrocycle.

144. The aqueous pharmaceutical formulation of any one of claims 1-140, wherein the aqueous pharmaceutical formulation upon storage for 3 months at from about 2 °C- 8 °C comprises at least 95% of the initial amount of the peptidomimetic macrocycle.

145. The aqueous pharmaceutical formulation of any one of the preceding claims, wherein the osmolality of the aqueous pharmaceutical formulation is from about 100-600 milliosmoles per kilogram, for example from about 220-400 milliosmoles per kilogram.

146. The aqueous pharmaceutical formulation of any one of the preceding claims, wherein the endotoxin level of the aqueous pharmaceutical formulation is at most 2.0, 4.0, 6.0, 8.0 or 10 EU/mL^2.The aqueous pharmaceutical formulation of any one of the preceding claims, wherein the endotoxin level of the aqueous pharmaceutical formulation is at most 4.5 EU/mL^2.

147. The aqueous pharmaceutical formulation of any one of the preceding claims, wherein the aqueous pharmaceutical formulation is contained in a container.

148. The aqueous pharmaceutical formulation of claim 147, wherein the container is a single use container.

149. The aqueous pharmaceutical formulation of claim 147, wherein the container is a multi-use container.

150. The aqueous pharmaceutical formulation of any one of claims 147-149, wherein the container is a glass vial.

151. The aqueous pharmaceutical formulation of any one of claims 147-149, wherein the container is a pre-filled syringe to be used alone or in an injection device.

152. The aqueous pharmaceutical formulation of any one of claims 147-149, wherein the container is a cartridge for a pen injection system.

153. The aqueous pharmaceutical formulation of any one of claims 147-149, wherein the container is a glass ampoule.

154. The aqueous pharmaceutical formulation of claim 150, wherein the glass vial is a 20 mL, 10 mL, or a 5 mL glass serum vial.

155. The aqueous pharmaceutical formulation of claim 150, wherein the glass vial comprises borosilicate glass or polycarbonate.

156. The aqueous pharmaceutical formulation of any one of claims 147-155, wherein the container comprises stopper and/or cap.

157. The aqueous pharmaceutical formulation of claim 156, wherein the stopper is a rubber stopper.

158. The aqueous pharmaceutical formulation of any one of claims 147-155, wherein the container comprises a seal.

159. The aqueous pharmaceutical formulation of claim 158, wherein seal is an aluminum seal.

160. The aqueous pharmaceutical formulation any one of the preceding claims, wherein aqueous pharmaceutical formulation is prepared by adding the peptidomimetic macrocycle or a pharmaceutically acceptable salt thereof to water or an aqueous solution, wherein the peptidomimetic macrocycle is capable of binding to the MDM2 and/or MDMX proteins.

161. The method of claim 160, wherein the pharmaceutically acceptable salt is a sodium salt, potassium salt or calcium salt.

162. The method of claim 160 or 161, wherein the aqueous pharmaceutical formulation is prepared by dissolving a sodium salt of the peptidomimetic macrocycle in water.

163. The method of any one of claim 160 or 161, wherein the aqueous solution comprises a buffering agent and a stabilizing agent.

164. The aqueous pharmaceutical formulation of any one claims 1-163, wherein the aqueous pharmaceutical formulation is suitable for administration to a subject without reconstitution or dilution.

165. The aqueous pharmaceutical formulation of any one claims 1-163, wherein the aqueous pharmaceutical formulation requires reconstitution prior to administration to a subject.

166. The aqueous pharmaceutical formulation of claim 165, wherein reconstitution involves dilution with an aqueous solution.

167. The aqueous pharmaceutical formulation of claim 166, wherein the aqueous solution is a solution of dextrose in water.

168. The aqueous pharmaceutical formulation of any one of the preceding claims, wherein the micelle forming agent in solutol-HS-15.

169. The aqueous pharmaceutical formulation of any one of the preceding claims, wherein the peptidomimetic macrocycle forms a micelle in absence of a surfactant.

170. The aqueous pharmaceutical formulation of any one of the preceding claims, wherein the aqueous pharmaceutical formulation does not form micelle.

171. The aqueous pharmaceutical formulation of any one of the preceding claims, wherein the aqueous pharmaceutical formulation further comprises a preservative.

172. The aqueous pharmaceutical formulation of claim 171, wherein the preservative is selected from a group consisting of benzalkonium chloride, EDTA and combination thereof.

173. The aqueous pharmaceutical formulation of claim 171, wherein the preservative is selected from a group consisting of phenol, meta-cresol and combination thereof.

174. The aqueous pharmaceutical formulation of any one of the preceding claims, wherein the aqueous pharmaceutical formulation further comprises a co-solvent.

175. The aqueous pharmaceutical formulation of claim 174, wherein the co-solvent is selected from a group consisting of dimethyl sulfoxide (DMSO), N-methylpyrrolidone (NMP), dimethylacetamide (DMA) and combinations thereof.

176. The aqueous pharmaceutical formulation of any one of the preceding claims, wherein the molecular weight of the peptidomimetic macrocycle is in the range of 1800-2000 D.

177. The aqueous pharmaceutical formulation of any one of the preceding claims, wherein the peptidomimetic macrocycle has an observed mass (m/e) in the range of 900-1000 D.

178. An aqueous pharmaceutical formulation comprising a peptidomimetic macrocycle that binds to MDM2 and/or MDMX proteins or a pharmaceutically acceptable salt thereof, phosphate buffering agent, D-trehalose, and polysorbate 20, wherein the peptidomimetic macrocycle comprises an amino acid sequence which is at least about 60%, 65%, 70%, 75%, 80%, 85%, 90%, 95% identical to an amino acid sequence in any of **Table 1**, **Table 1a**, **Table 1b**, and **Table 1c**.

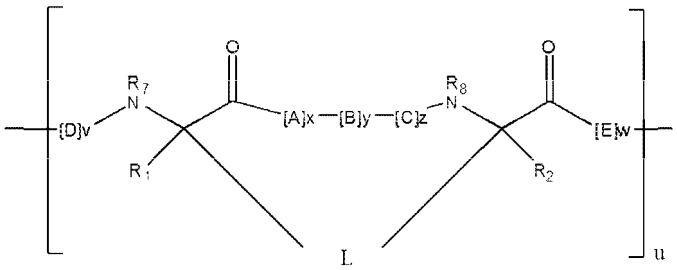
179. The aqueous pharmaceutical formulation of claim 178, wherein the amount of the peptidomimetic macrocycle in the aqueous pharmaceutical formulation is equal to or greater than15 mg/mL.

180. The aqueous pharmaceutical formulation of any one of claims 178-179, wherein the amount of D-trehalose in the aqueous pharmaceutical formulation is about 8% w/v.

181. The aqueous pharmaceutical formulation of any one of claims 178-180, wherein the amount of polysorbate 20 in the aqueous pharmaceutical formulation is about 0.03% w/v.

182. The aqueous pharmaceutical formulation of any one of claims 178-181, wherein the aqueous pharmaceutical formulation comprises less than 2 % w/v of any micelle forming agent.

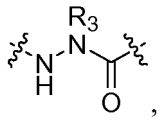
183. The aqueous pharmaceutical formulation of any one of the preceding claims, wherein the peptidomimetic macrocycle comprises an amino acid sequence which is at least about 60%, 65%, 70%, 75%, 80%, 85%, 90%, 95% identical to an amino acid sequence in any of Table 1, Table 1a, Table 1b, and Table 1c, and wherein the peptidomimetic macrocycle has the formula:



Formula (I)

wherein:

each A, C, D and E is independently an amino acid;

each B is independently an amino acid, , [–NH–L_3–CO–], [–NH–L_3–SO_2–], or [–NH–L_3–];

each R_1 and R_2 is independently –H, alkyl, alkenyl, alkynyl, arylalkyl, cycloalkyl, cycloalkylalkyl, heteroalkyl, or heterocycloalkyl, unsubstituted or substituted with halo; or forms a macrocycle–forming linker L' connected to the alpha position of one of said D or E amino acids;

each R_3 independently is hydrogen, alkyl, alkenyl, alkynyl, arylalkyl, heteroalkyl, cycloalkyl, heterocycloalkyl, cycloalkylalkyl, cycloaryl, or heterocycloaryl, optionally substituted with R_5;

each L and L' is independently a macrocycle–forming linker;

each L^3 is independently alkylene, alkenylene, alkynylene, heteroalkylene, cycloalkylene, heterocycloalkylene, arylene, heteroarylene, or $[-R^4\text{-}K\text{-}R^4-]_n$, each being optionally substituted with R^5;

each R^4 is independently alkylene, alkenylene, alkynylene, heteroalkylene, cycloalkylene, heterocycloalkylene, arylene, or heteroarylene, each being optionally substituted with R^5;

each K is independently O, S, SO, SO_2, CO, CO_2, or $CONR^3$;

each R_5 is independently halogen, alkyl, $–OR_6$, $–N(R_6)_2$, $–SR_6$, $–SOR_6$, $–SO_2R_6$, $–CO_2R_6$, a fluorescent moiety, a radioisotope or a therapeutic agent;

each R_6 is independently –H, alkyl, alkenyl, alkynyl, arylalkyl, cycloalkylalkyl, heterocycloalkyl, a fluorescent moiety, a radioisotope or a therapeutic agent;

each R_7 is independently –H, alkyl, alkenyl, alkynyl, arylalkyl, cycloalkyl, heteroalkyl, cycloalkylalkyl, heterocycloalkyl, cycloaryl, or heterocycloaryl, optionally substituted with R_5, or part of a cyclic structure with a D residue;

each R_8 is independently –H, alkyl, alkenyl, alkynyl, arylalkyl, cycloalkyl, heteroalkyl, cycloalkylalkyl, heterocycloalkyl, cycloaryl, or heterocycloaryl, optionally substituted with R_5, or part of a cyclic structure with an E residue;

each v is independently an integer from 1–1000;

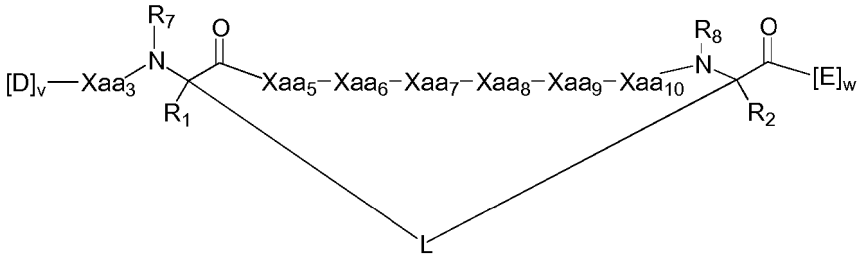
each w is independently an integer from 3–1000;

u is an integer from 1–10;

each x, y and z is independently an integer from 0–10; and

each n is independently an integer from 1–5.

184. The aqueous pharmaceutical formulation of any one of the preceding claims, wherein the peptidomimetic macrocycle has formula:



wherein:

each of Xaa_3, Xaa_5, Xaa_6, Xaa_7, Xaa_8, Xaa_9, and Xaa_{10} is individually an amino acid, wherein at least three of Xaa_3, Xaa_5, Xaa_6, Xaa_7, Xaa_8, Xaa_9, and Xaa_{10} are the same amino acid as the amino acid at the corresponding position of the sequence Phe_3-X_4-His_5-Tyr_6-Trp_7-Ala_8-Gln_9-Leu_{10}-X_{11}-Ser_{12} or Phe_3-X_4-Glu_5-Tyr_6-Trp_7-Ala_8-Gln_9-Leu_{10}/Cba_{10}-X_{11}-Ala_{12}, where each X is an amino acid;

each D and E is independently an amino acid;

each R_1 and R_2 are independently –H, alkyl, alkenyl, alkynyl, arylalkyl, cycloalkyl, cycloalkylalkyl, heteroalkyl, or heterocycloalkyl, unsubstituted or substituted with halo–; or at least one of R_1 and R_2 forms a macrocycle-forming linker L' connected to the alpha position of one of said D or E amino acids;

each L or L' is independently a macrocycle-forming linker;

each R_5 is independently halogen, alkyl, $-OR_6$, $-N(R_6)_2$, $-SR_6$, $-SOR_6$, $-SO_2R_6$, $-CO_2R_6$, a fluorescent moiety, a radioisotope or a therapeutic agent;

each R_6 is independently –H, alkyl, alkenyl, alkynyl, arylalkyl, cycloalkylalkyl, heterocycloalkyl, a fluorescent moiety, a radioisotope or a therapeutic agent;

R_7 is –H, alkyl, alkenyl, alkynyl, arylalkyl, cycloalkyl, heteroalkyl, cycloalkylalkyl, heterocycloalkyl, cycloaryl, or heterocycloaryl, optionally substituted with R_5, or part of a cyclic structure with a D residue;

R_8 is –H, alkyl, alkenyl, alkynyl, arylalkyl, cycloalkyl, heteroalkyl, cycloalkylalkyl, heterocycloalkyl, cycloaryl, or heterocycloaryl, optionally substituted with R_5, or part of a cyclic structure with an E residue;

v is an integer from 1-1000; and

w is an integer from 0-1000.

185. The aqueous pharmaceutical formulation of claim 183 or 184, wherein at least one of the macrocycle-forming linker has a formula $–L_1–L_2–$, wherein

L_1 and L_2 are independently alkylene, alkenylene, alkynylene, heteroalkylene, cycloalkylene, heterocycloalkylene, cycloarylene, heterocycloarylene, or $[-R_4-K-R_4-]_n$, each being optionally substituted with R_5;

each R_4 is independently alkylene, alkenylene, alkynylene, heteroalkylene, cycloalkylene, heterocycloalkylene, arylene, or heteroarylene;

each K is independently O, S, SO, SO_2, CO, CO_2, or $CONR_3$; and
each R_3 independently is hydrogen, alkyl, alkenyl, alkynyl, arylalkyl, heteroalkyl, cycloalkyl, heterocycloalkyl, cycloalkylalkyl, cycloaryl, or heterocycloaryl, optionally substituted with R_5;
n is an integer from 1-5.

186. The aqueous pharmaceutical formulation of claim 184, wherein w is an integer from 3-1000, for example 3-500, 3-200, 3-100, 3-50, 3-30, 3-20, or 3-10.

187. The aqueous pharmaceutical formulation of claim 184, wherein Xaa_5 is Glu or an amino acid analog thereof.

188. The aqueous pharmaceutical formulation of claim 183 or 184, wherein each E is independently an amino acid selected from Ala (alanine), D-Ala (D-alanine), Aib (α–aminoisobutyric acid), Sar (N-methyl glycine), and Ser (serine).

189. The aqueous pharmaceutical formulation of claim 183 or 184, wherein $[D]_v$ is $–Leu_1\text{-}Thr_2$.

190. The aqueous pharmaceutical formulation of claim 183 or 184, wherein w is 1, 2, 3, 4, 5, 6, 7, 8, 9, or 10

191. The aqueous pharmaceutical formulation of claim 183 or 184, wherein w is 3-10.

192. The aqueous pharmaceutical formulation of claim 183 or 184, wherein w is 3-6.

193. The aqueous pharmaceutical formulation of claim 183 or 184, wherein w is 6-10.

194. The aqueous pharmaceutical formulation of claim 183 or 184, wherein w is 6.

195. The aqueous pharmaceutical formulation of claim 183 or 184, wherein v is 1-10.

196. The aqueous pharmaceutical formulation of claim 183or 184, wherein v is 2-10.

197. The aqueous pharmaceutical formulation of claim 183 or 184, wherein v is 2-5.

198. The aqueous pharmaceutical formulation of claim 183 or 184, wherein v is 2.

199. The aqueous pharmaceutical formulation of claim 185, wherein L_1 and L_2 are independently alkylene, alkenylene, alkynylene, heteroalkylene, cycloalkylene, heterocycloalkylene, cycloarylene, or heterocycloarylene, each being optionally substituted with R_5.

200. The aqueous pharmaceutical formulation of claim 185, wherein L_1 and L_2 are independently alkylene or alkenylene.

201. The aqueous pharmaceutical formulation of claim 183 or 184, wherein L is alkylene, alkenylene, or alkynylene.

202. The aqueous pharmaceutical formulation of claim 183 or 184, wherein L is alkylene.

203. The aqueous pharmaceutical formulation of claim 183 or 184, wherein L is C_3-C_{16} alkylene.

204. The aqueous pharmaceutical formulation of claim 183 or 184, wherein L is C_{10}-C_{14} alkylene.

205. The aqueous pharmaceutical formulation of claim 183 or 184, wherein R_1 and R_2 are independently –H, alkyl, alkenyl, alkynyl, arylalkyl, cycloalkyl, cycloalkylalkyl, heteroalkyl, or heterocycloalkyl, unsubstituted or substituted with halo–.

206. The aqueous pharmaceutical formulation of claim 183 or 184, wherein R_1 and R_2 are H.

207. The aqueous pharmaceutical formulation of claim 183 or 184, wherein R_1 and R_2 are independently alkyl.

208. The aqueous pharmaceutical formulation of claim 183 or 184, wherein R_1 and R_2 are methyl.

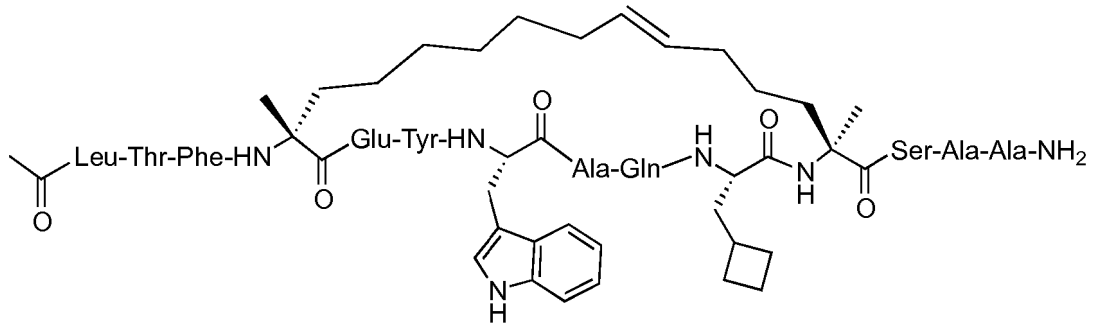
209. The aqueous pharmaceutical formulation of claim 183, wherein x+y+z = 6.

210. The aqueous pharmaceutical formulation of claim 183, wherein u is 1.

211. The aqueous pharmaceutical formulation of claim 183 or 184, wherein each E is Ser or Ala or an analog thereof.

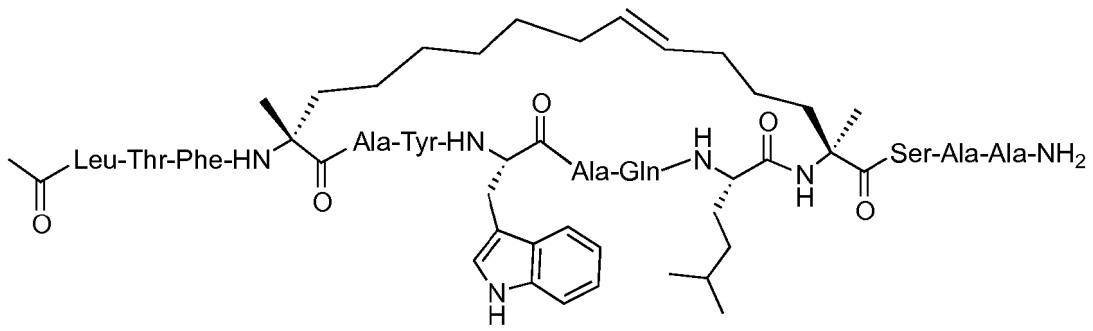
212. The aqueous pharmaceutical formulation of claim 183 or 184, comprising at least one amino acid which is an amino acid analog.

213. The aqueous pharmaceutical formulation of any one of claims 178, 183 and 184, wherein the peptidomimetic macrocycle has a formula of:



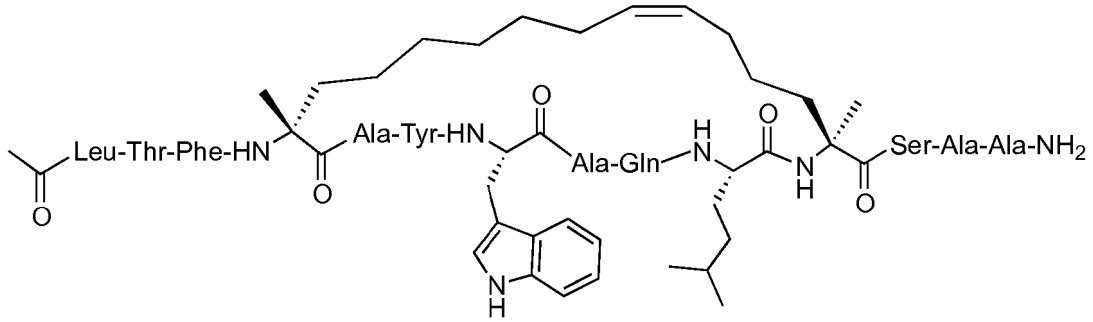
or a pharmaceutically acceptable salt thereof.

214. The aqueous pharmaceutical formulation of any one of claims 178, 183 and 184, wherein the peptidomimetic macrocycle has a formula of:



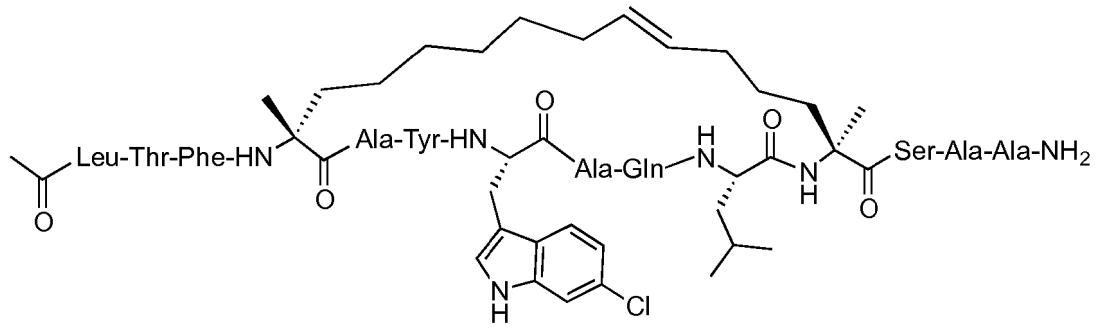
or a pharmaceutically acceptable salt thereof.

215. The aqueous pharmaceutical formulation of any one of claims 178, 183 and 184, wherein the peptidomimetic macrocycle has a formula of:



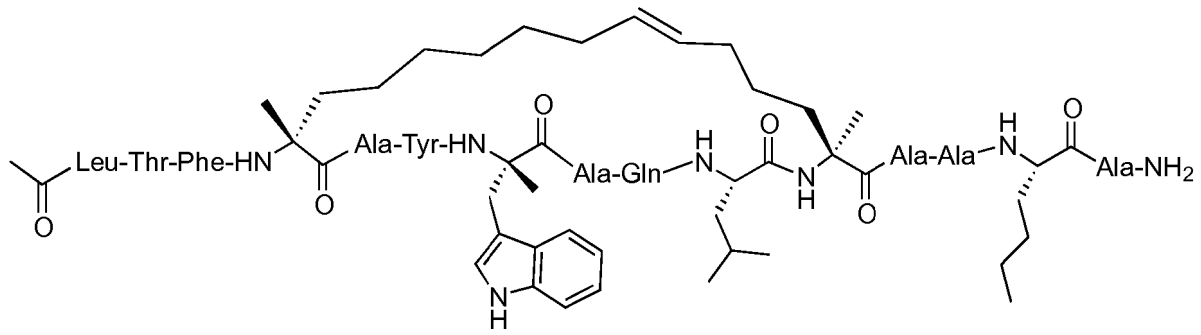
or a pharmaceutically acceptable salt thereof.

216. The aqueous pharmaceutical formulation of any one of claims 178, 183 and 184, wherein the peptidomimetic macrocycle has a formula of:



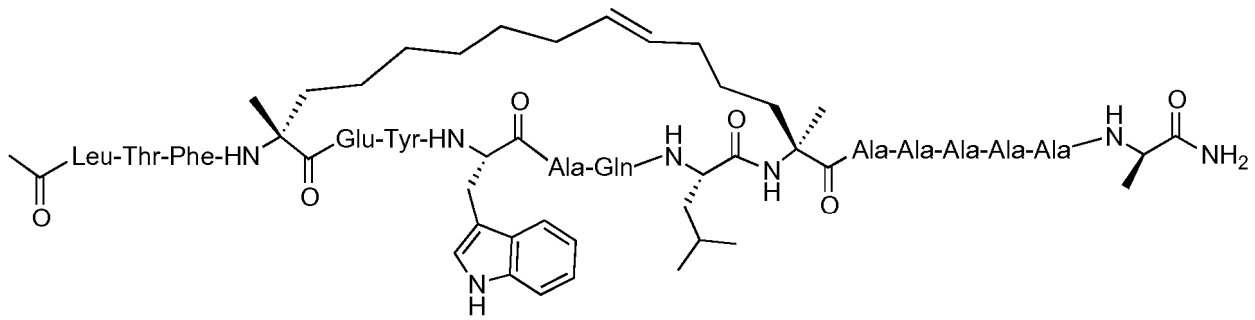
or a pharmaceutically acceptable salt thereof.

217. The aqueous pharmaceutical formulation of any one of claims 178, 183 and 184, wherein the peptidomimetic macrocycle has a formula of



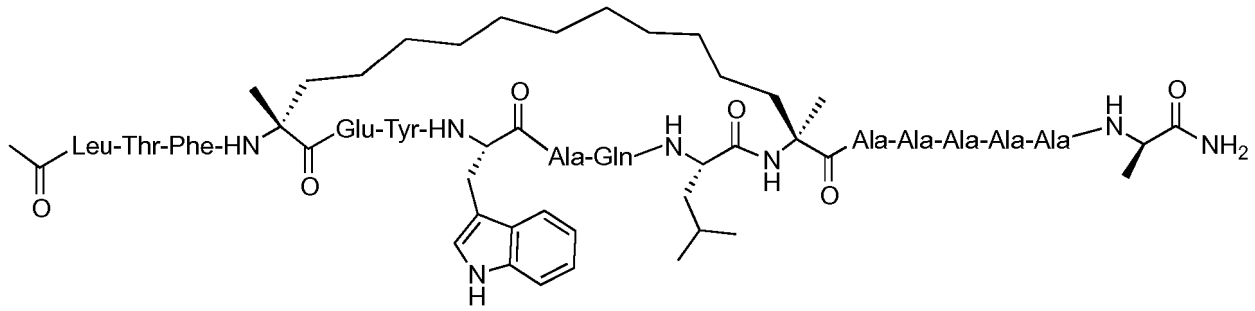
or a pharmaceutically acceptable salt thereof.

218. The aqueous pharmaceutical formulation of any one of claims 178, 183 and 184, wherein the peptidomimetic macrocycle has a formula of:



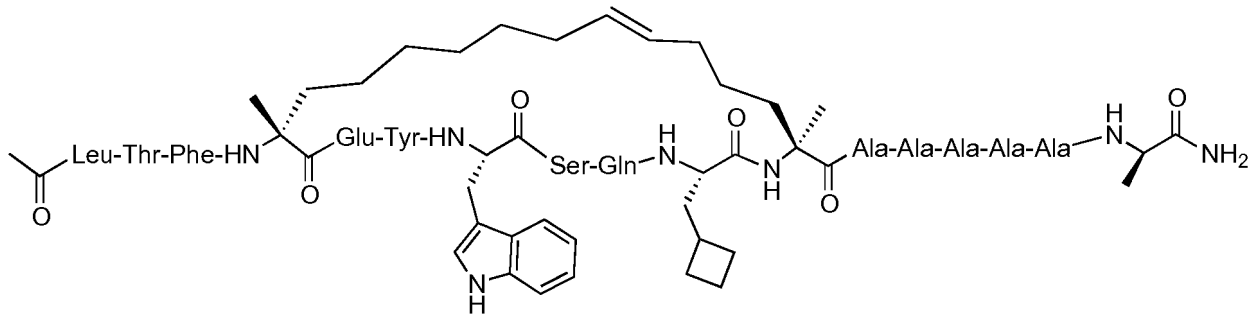
or a pharmaceutically acceptable salt thereof.

219. The aqueous pharmaceutical formulation of any one of claims 178, 183 and 184, wherein the peptidomimetic macrocycle has a formula of:



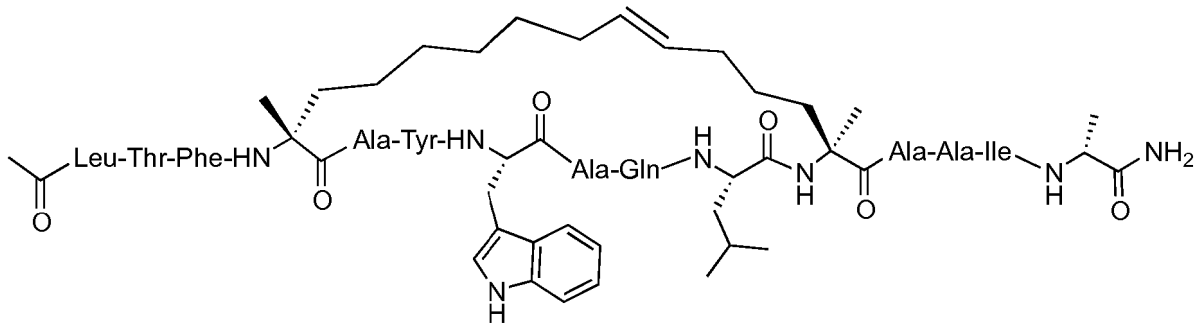
or a pharmaceutically acceptable salt thereof.

220. The aqueous pharmaceutical formulation of any one of claims 178, 183 and 184, wherein the peptidomimetic macrocycle has a formula of:



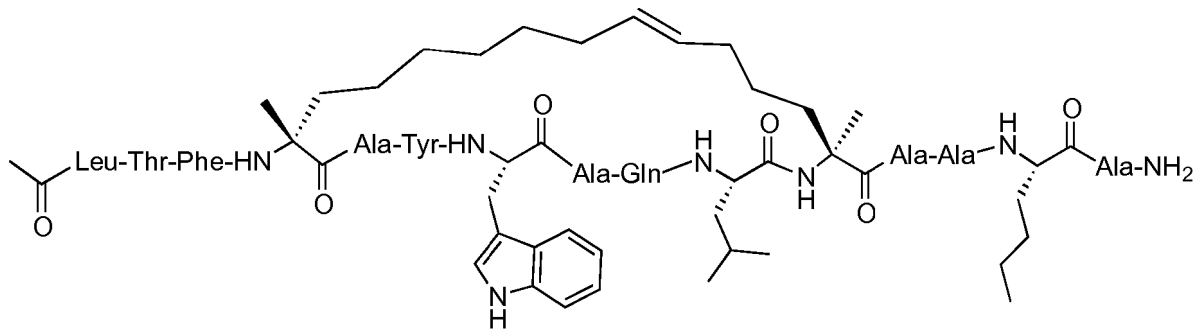
or a pharmaceutically acceptable salt thereof.

221. The aqueous pharmaceutical formulation of any one of claims 178, 183 and 184, wherein the peptidomimetic macrocycle has a formula of a:



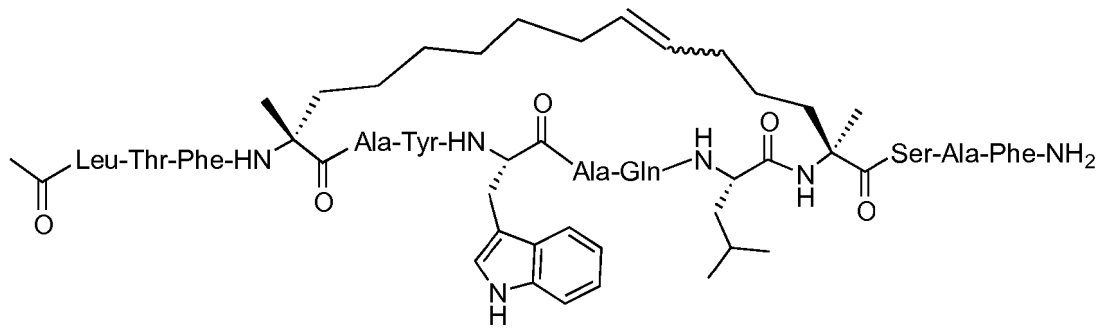
or a pharmaceutically acceptable salt thereof.

222. The aqueous pharmaceutical formulation of any one of claims 178, 183 and 184, wherein the peptidomimetic macrocycle has a formula of:



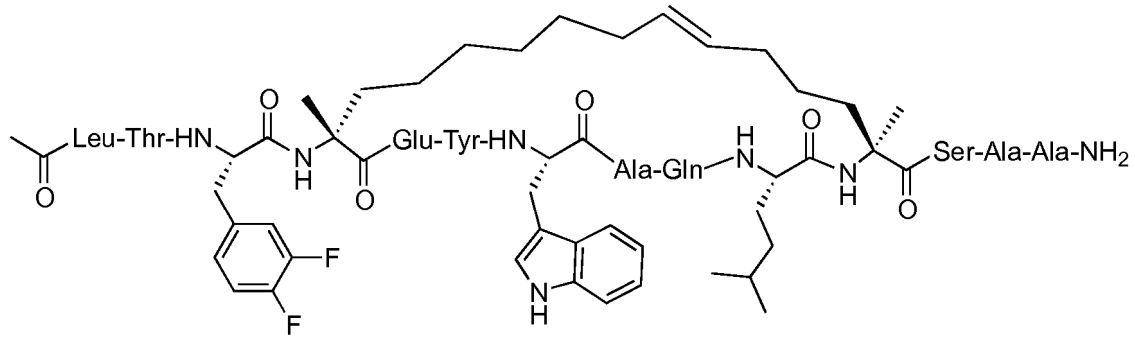
or a pharmaceutically acceptable salt thereof.

223. The aqueous pharmaceutical formulation of any one of claims 178, 183 and 184, wherein the peptidomimetic macrocycle has a formula of :



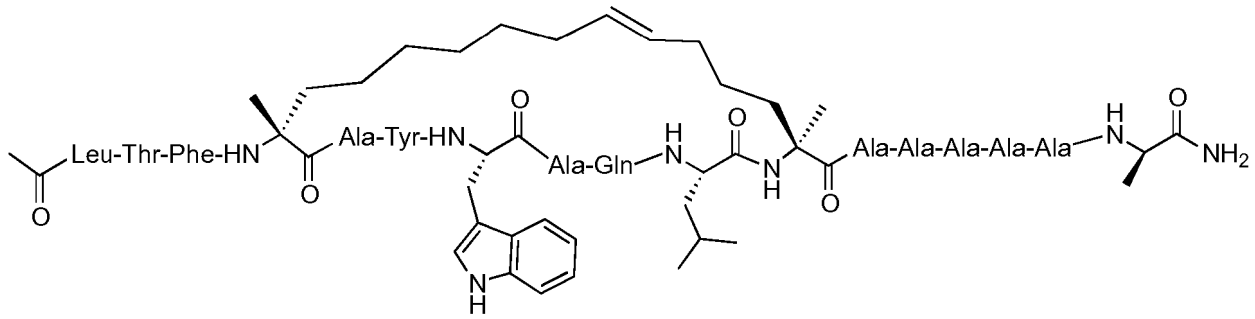
or a pharmaceutically acceptable salt thereof.

224. The aqueous pharmaceutical formulation of any one of claims 178, 183 and 184, wherein the peptidomimetic macrocyclea:



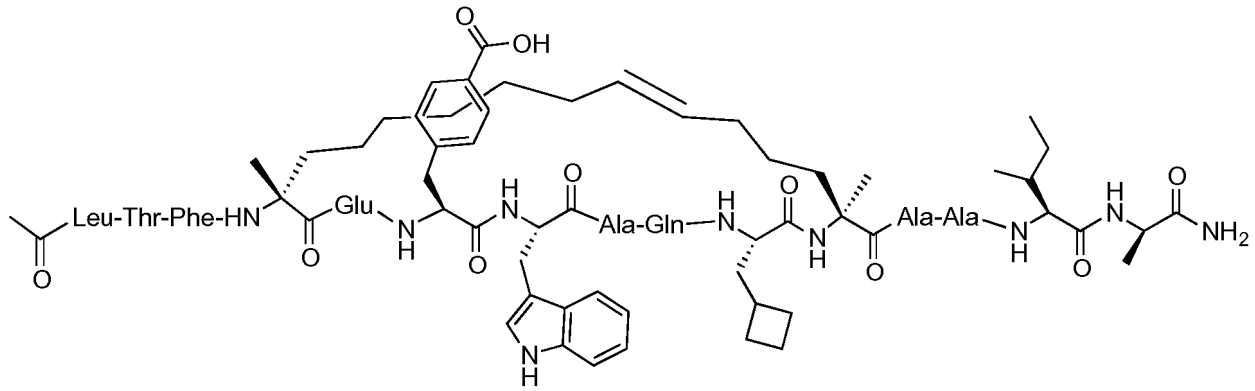
or a pharmaceutically acceptable salt thereof.

225. The aqueous pharmaceutical formulation of any one of claims 178, 183 and 184, wherein the peptidomimetic macrocycle has a formula 0f:



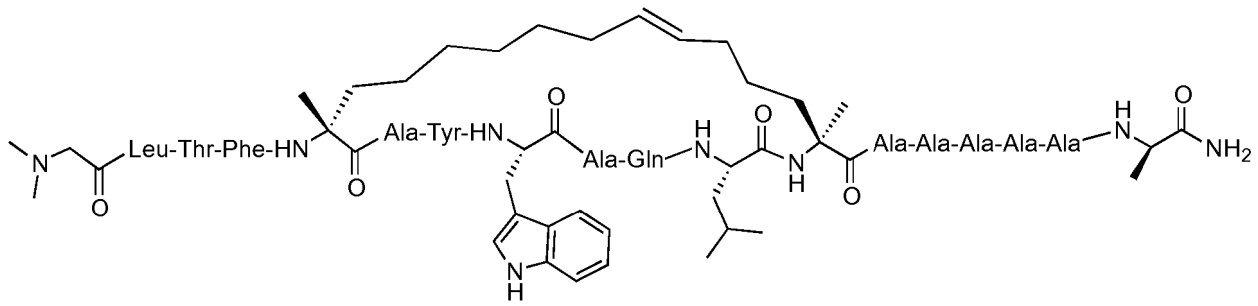
or a pharmaceutically acceptable salt thereof.

226. The aqueous pharmaceutical formulation of any one of claims 178, 183 and 184, wherein the peptidomimetic macrocycle has a formula of:



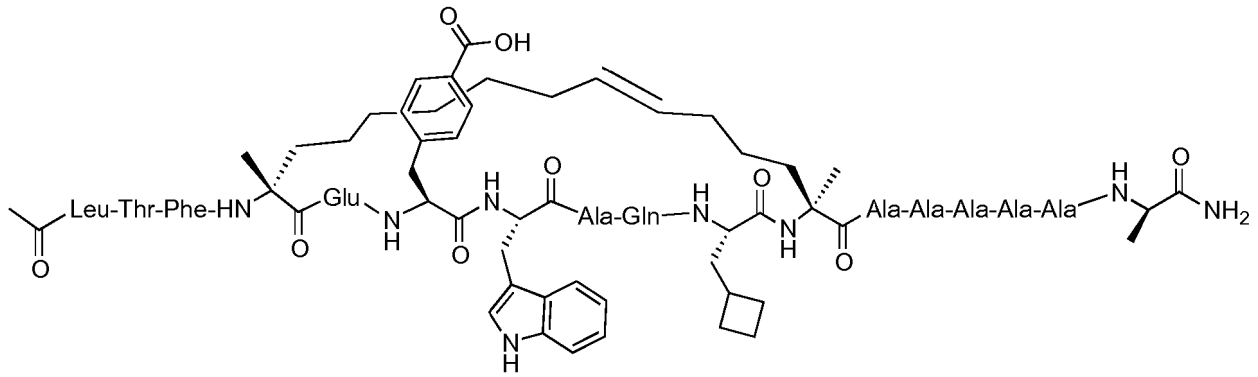
or a pharmaceutically acceptable salt thereof.

227. The aqueous pharmaceutical formulation of any one of claims 178, 183 and 184, wherein the peptidomimetic macrocycle a formula of:



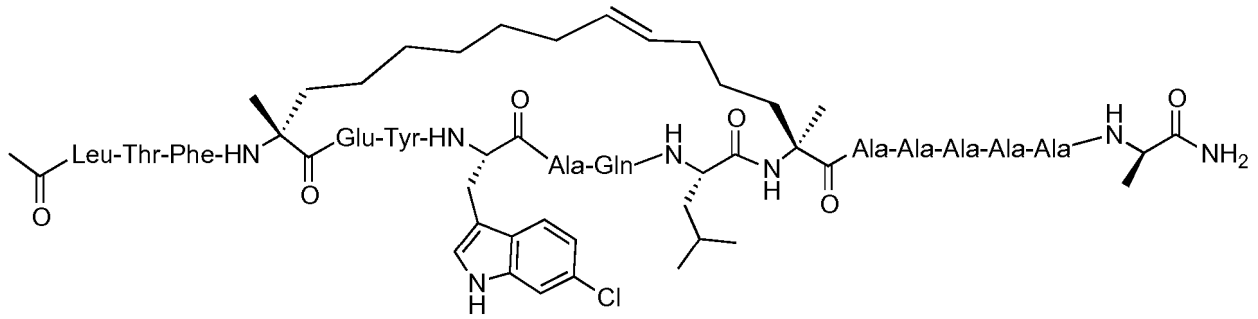
or a pharmaceutically acceptable salt thereof.

228. The aqueous pharmaceutical formulation of any one of claims 178, 183 and 184, wherein the peptidomimetic macrocycle has a formula of:



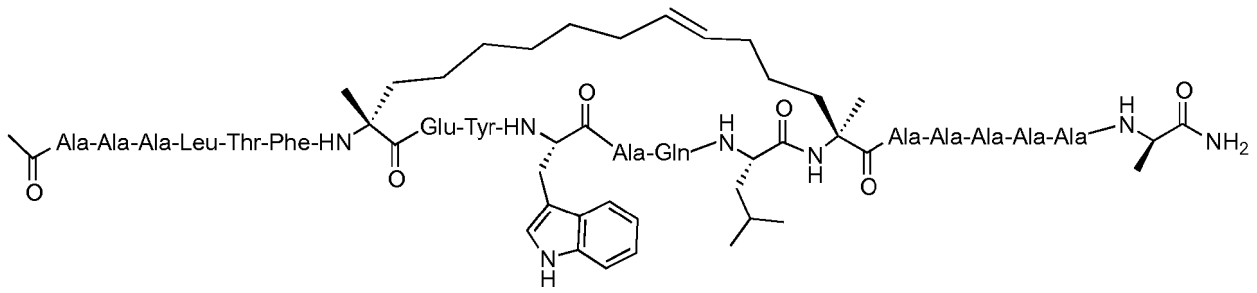
or a pharmaceutically acceptable salt thereof.

229. The aqueous pharmaceutical formulation of any one of claims 178, 183 and 184, wherein the peptidomimetic macrocycle has a formula of:



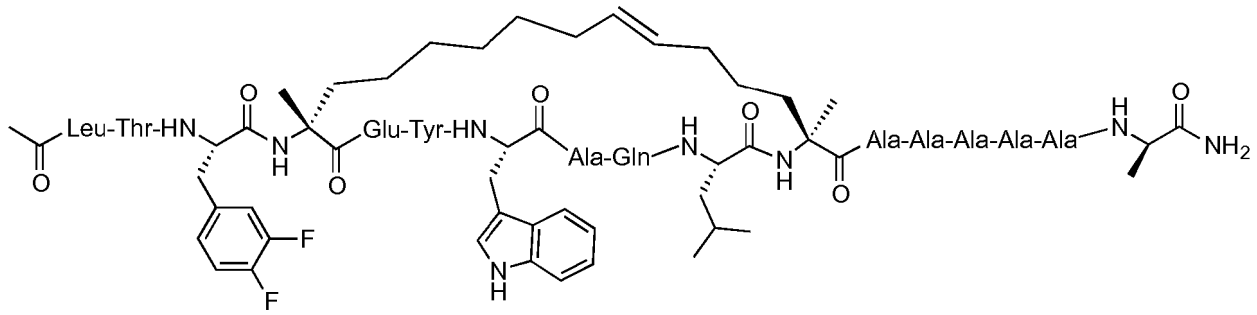
or a pharmaceutically acceptable salt thereof.

230. The aqueous pharmaceutical formulation of any one of claims 178, 183 and 184, wherein the peptidomimetic macrocycle has a formula of



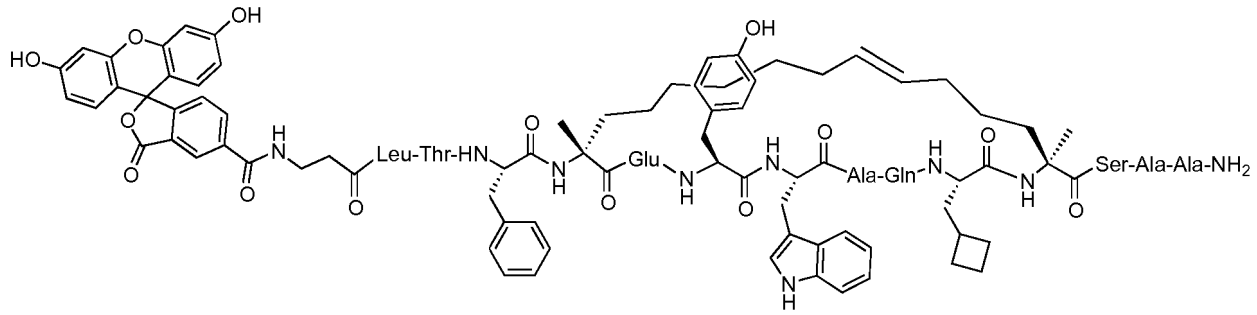
or a pharmaceutically acceptable salt thereof.

231. The aqueous pharmaceutical formulation of any one of claims 178, 183 and 184, wherein the peptidomimetic macrocycle has a formula of:



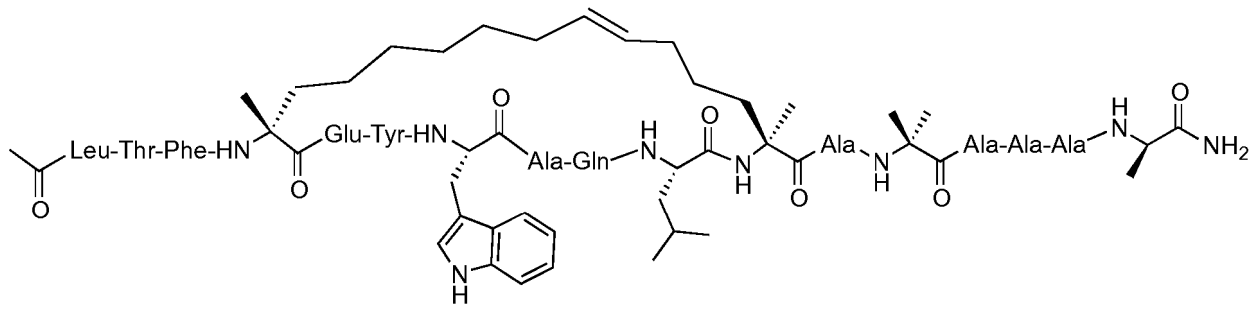
or a pharmaceutically acceptable salt thereof.

232. The aqueous pharmaceutical formulation of any one of claims 178, 183 and 184, wherein the peptidomimetic macrocycle has a formula of:



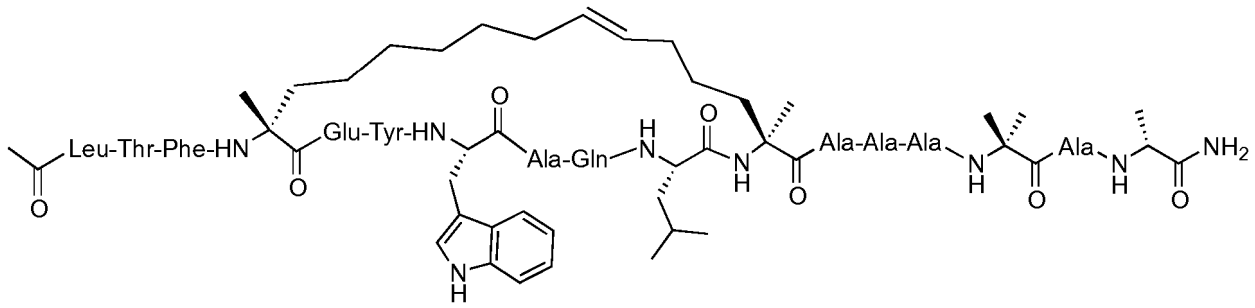
or a pharmaceutically acceptable salt thereof.

233. The aqueous pharmaceutical formulation of any one of claims 178, 183 and 184, wherein the peptidomimetic macrocycle has a formula of:



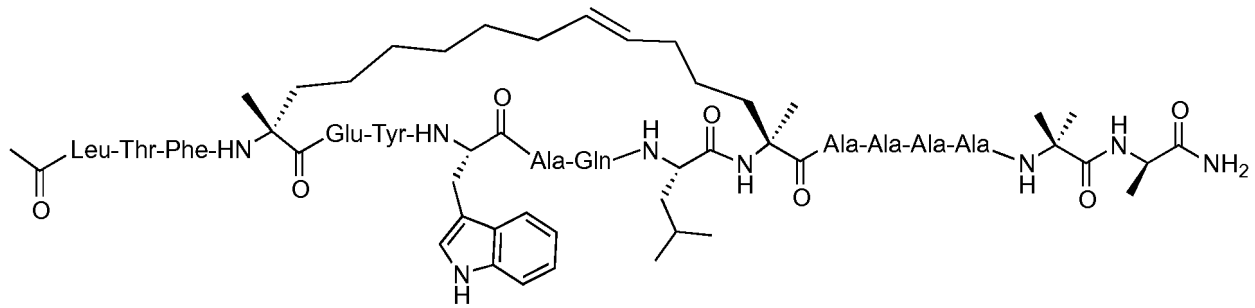
or a pharmaceutically acceptable salt thereof.

234. The aqueous pharmaceutical formulation of any one of claims 178, 183 and 184, wherein the peptidomimetic macrocycle has a formula of:



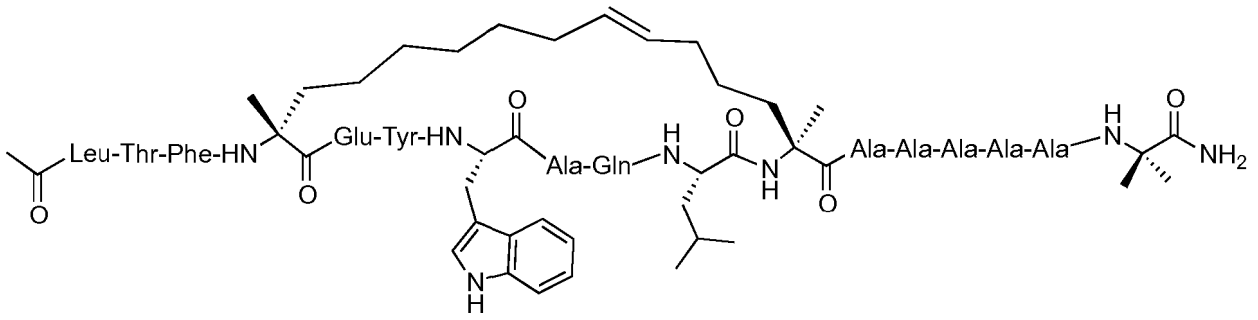
or a pharmaceutically acceptable salt thereof.

235. The aqueous pharmaceutical formulation of any one of claims 178, 183 and 184, wherein the peptidomimetic macrocycle has a formula of:



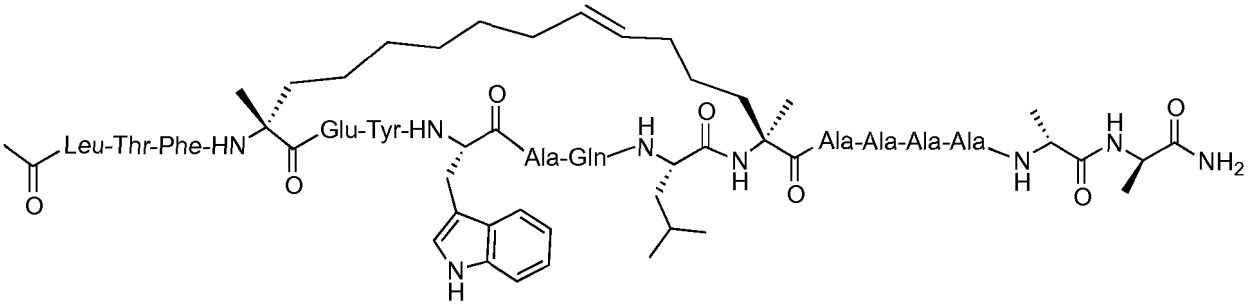
or a pharmaceutically acceptable salt thereof.

236. The aqueous pharmaceutical formulation of any one of claims 178, 183 and 184, wherein the peptidomimetic macrocycle has a formula of:



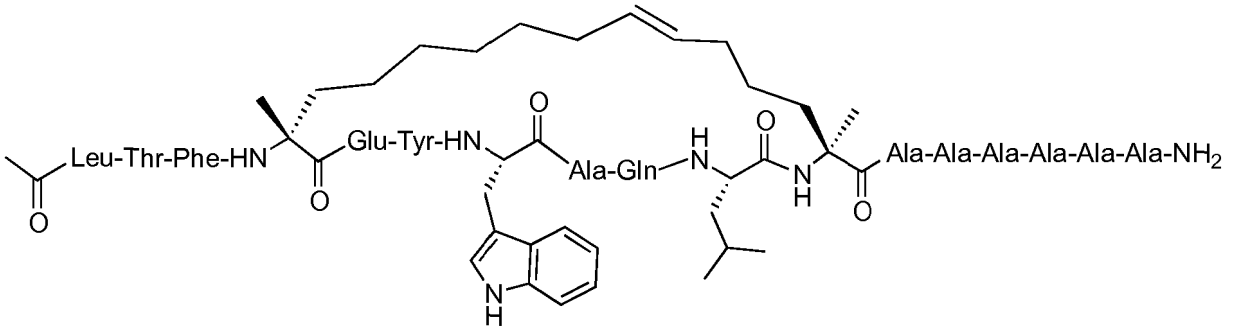
or a pharmaceutically acceptable salt thereof.

237. The aqueous pharmaceutical formulation of any one of claims 178, 183 and 184, wherein the peptidomimetic macrocycle has a formula of:



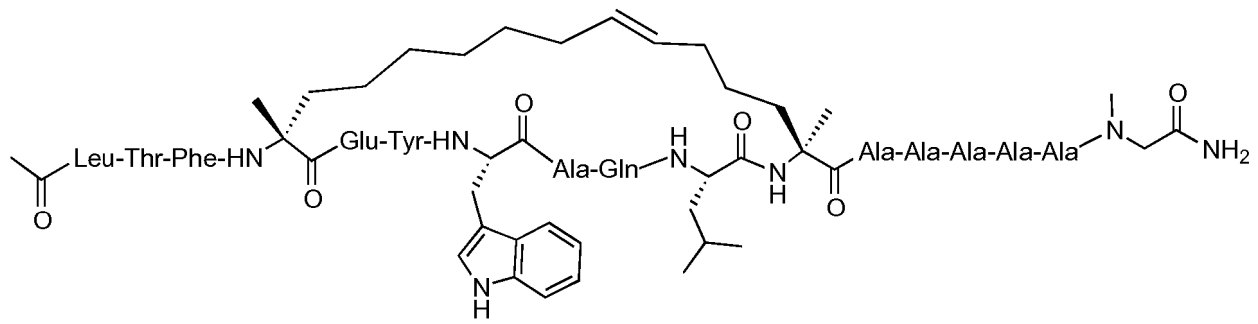
or a pharmaceutically acceptable salt thereof.

238. The aqueous pharmaceutical formulation of any one of claims 178, 183 and 184, wherein the peptidomimetic macrocycle has a formula of:



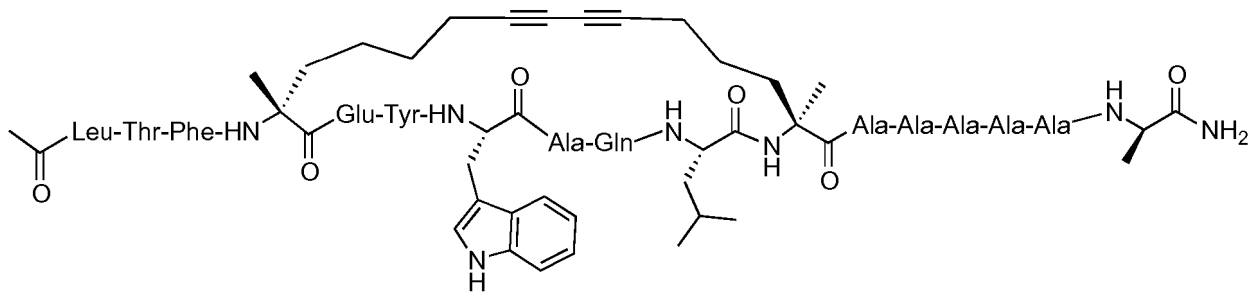
or a pharmaceutically acceptable salt thereof.

239. The aqueous pharmaceutical formulation of any one of claims 178, 183 and 184, wherein the peptidomimetic macrocycle has a formula of:



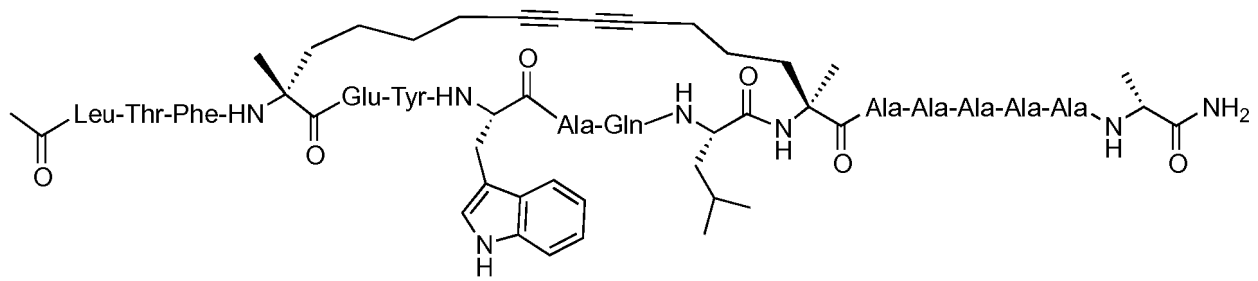
or a pharmaceutically acceptable salt thereof.

240. The aqueous pharmaceutical formulation of any one of claims 178, 183 and 184, wherein the peptidomimetic macrocycle has a formula of:



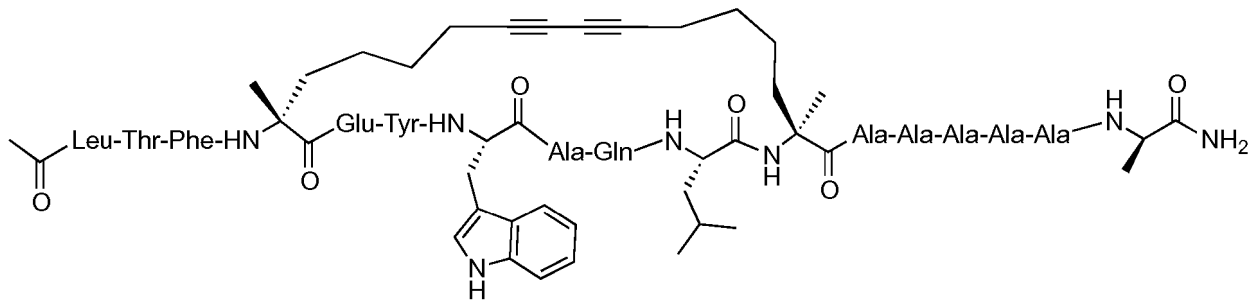
or a pharmaceutically acceptable salt thereof.

241. The aqueous pharmaceutical formulation of any one of claims 178, 183 and 184, wherein the peptidomimetic macrocycle has a formula of:



or a pharmaceutically acceptable salt thereof.

242. The aqueous pharmaceutical formulation of any one of claims 178, 183 and 184, wherein the peptidomimetic macrocycle has a formula of:



or a pharmaceutically acceptable salt thereof.

243. A method of treating cancer in a subject comprising administering to the subject a therapeutically effective amount of the aqueous pharmaceutical formulation of any one of the preceding claims.

244. A method of treating cancer in a subject comprising administering to the subject a stable aqueous pharmaceutical formulation a peptidomimetic macrocycle peptidomimetic macrocycle that is capable of binding to the MDM2 and/or MDMX proteins and wherein the amount of the peptidomimetic macrocycle in the aqueous pharmaceutical formulation is greater than15 mg/mL and wherein the aqueous pharmaceutical formulation contains less than 2% w/v of any micelle forming agent.

245. The method of claim 244, wherein the aqueous pharmaceutical formulation further comprises a buffering agent.

246. The method of claim 244, wherein the aqueous pharmaceutical formulation further comprises a stabilizing agent.

247. The method of any one of claims 244, wherein the aqueous pharmaceutical formulation further comprises a tonicity agent.

248. The method of any one of claims 243-247, wherein the cancer is selected from a group consisting of bladder cancer, bone cancer, breast cancer, cervical cancer, CNS cancer, colon cancer, ocular tumor, renal cancer, liver cancer, lung cancer, pancreatic cancer, choriocarcinoma (tumor of the placenta), prostate cancer, sarcoma, skin cancer, soft tissue cancer, gastric cancer, gall bladder cancer, biliary cancer, renal cancer, neoblastoma, or neuroendocrine cancer.

249. A method modulating the activity of p53 and/or MDM2 and/or MDMX in a subject comprising administering to the subject a stable aqueous pharmaceutical formulation comprising a peptidomimetic macrocycle capable of binding to the MDM2 and/or MDMX proteins, wherein the amount of the peptidomimetic macrocycle in the aqueous pharmaceutical formulation is greater than15 mg/mL and wherein the aqueous pharmaceutical formulation contains less than 2% w/v of any micelle forming agent.

250. The method of claim 249, wherein the aqueous pharmaceutical formulation further comprises a buffering agent.

251. The method of claim 249, wherein the aqueous pharmaceutical formulation further comprises a tonicity agent.

252. The method of any one of claims 249, wherein the aqueous pharmaceutical formulation further comprises a stabilizing agent.

253. A method of antagonizing the interaction between p53 and MDM2 and/or between p53 and MDMX proteins in a subject comprising administering to the subject a aqueous pharmaceutical formulation comprising a peptidomimetic macrocycle capable of binding to the MDM2 and/or MDMX proteins, wherein the amount of the peptidomimetic macrocycle in the aqueous pharmaceutical formulation is greater than15 mg/mL and wherein the aqueous pharmaceutical formulation contains less than 2% w/v of any micelle forming agent.

254. The method of claim 253, wherein the aqueous pharmaceutical formulation further comprises a buffering agent.

255. The method of claim 253, wherein the aqueous pharmaceutical formulation further comprises a stabilizing agent.

256. The method of any one of claims 253, wherein the aqueous pharmaceutical formulation further comprises a tonicity agent.

257. A method of making an aqueous pharmaceutical formulation comprising adding greater than 15 mg/mL of a peptidomimetic macrocycle or a pharmaceutically acceptable salt thereof to water or an aqueous solution, wherein the aqueous pharmaceutical formulation comprises less than 2% w/v of any micelle forming agent.

258. The method of claim 257, wherein the peptidomimetic macrocycle is capable of binding to the MDM2 and/or MDMX proteins.

259. The method of claim 257 or 258, comprising adding a sodium salt of the peptidomimetic macrocycle to water or an aqueous solution.

260. The method of any one of claims 257-259, wherein the aqueous solution comprises a buffering agent.

261. The method of any one of claims 257-260, wherein the aqueous solution comprises a tonicity agent.

262. The method of any one of claims 257-261, wherein the aqueous solution further comprises a stabilizing agent.

263. The method of any one of claims 257-262, further comprising adjusting the pH of the solution comprising the buffering agent and the stabilizing agent during the addition of the peptidomimetic macrocycle.

264. The method of claim 263, where in the pH is adjusted by addition of a pH adjusting agent.

265. The method of claim 263 or 264, where in the pH is adjusted to be in the range of from about 6.0-8.0.

266. The method of claim 263, wherein the amount of the pH adjusting agent added is from about 0.01-10% w/v.

267. The method of claim 263, wherein the amount of the pH adjusting agent added is about 0.09% w/v.

268. The method of claim 263, where in the pH adjusting agent comprises an acid.

269. The method of claim 263, where in the pH adjusting agent comprises a base.

270. The method of claim 263, where in the pH adjusting agent comprises phosphoric acid.

271. The method of claim 263, where in the pH adjusting agent comprises sodium hydroxide, for example 0.1 N NaOH.

272. The method of any one of claims 257-271, further comprising filtration of the aqueous pharmaceutical formulation obtained after the addition of the peptidomimetic macrocycle to the aqueous solution.

273. The method of claim 272, wherein the filtration is performed under vacuum.

274. The method of claim 272, wherein the filtration is performed under pressure.

275. The method of claim 272, wherein the filtration comprises sterilizing filtration.

276. The method of claim 272, wherein the filtration comprises use of membrane filter.

277. The method of claim 276, wherein the membrane filter comprises cellulose or cellulose derivative.

278. The method of claim 276, wherein the membrane filter comprises cellulosic ester (MCE).

279. The method of claim 276, wherein the membrane filter comprise polytetrafluoroethylene (PTFE).

280. The method of claim 276, wherein the membrane filter comprise polyvinylidene.

281. The method of claim 276, wherein the membrane filter comprise polyvinylidene chloride.

282. The method of claim 276, wherein the membrane filter comprise polyvinylidene fluoride.

283. The method of claim 276, wherein the membrane filter has a pore size in the range from about 10 nm – 10 μm.

284. The method of claim 272, wherein the filtration results in clarification of the aqueous formulation.

285. The method of claim 284, wherein the membrane filter has a pore size of about 0.2 μm.

286. The method of claim 272, wherein the filtering involves passing the aqueous pharmaceutical formulation through one or more membrane filters.

287. The method of any one of claims 257-286, wherein the method is used for commercial manufacturing of the aqueous pharmaceutical formulation.

288. The method of claim 257, wherein the amount of aqueous pharmaceutical formulation made is about 1 liter to about 100 liters.

289. The method of claim 257, wherein the amount of aqueous pharmaceutical formulation made is about 10 litres to about 100 litres.

290. The method of claim 257, wherein the amount of aqueous pharmaceutical formulation made is about 10 litres to about 50 litres.

291. A kit comprising, in suitable container means, an aqueous pharmaceutical formulation comprising a peptidomimetic macrocycle and instructions for administration of the aqueous pharmaceutical formulation to a human subject, wherein the peptidomimetic macrocycle is capable of binding to MDM2 and/or MDMX proteins and wherein the amount of the peptidomimetic macrocycle in the aqueous pharmaceutical formulation is greater than15 mg/mL and the aqueous pharmaceutical formulation comprises less than 2% w/v of any micelle forming agent.

292. The kit of claim 291, wherein the instructions are for intravenous administration of the aqueous formulation.

293. A kit for formulating an aqueous pharmaceutical formulation comprising, in suitable container means, a peptidomimetic macrocycle capable of binding to the MDM2 and/or MDMX proteins or a pharmaceutically acceptable salt thereof, wherein the amount of the peptidomimetic macrocycle in the aqueous pharmaceutical formulation is greater than15 mg/mL and the aqueous pharmaceutical formulation comprises less than 2% w/v of any micelle forming agent.