v is an integer from 1-1000;

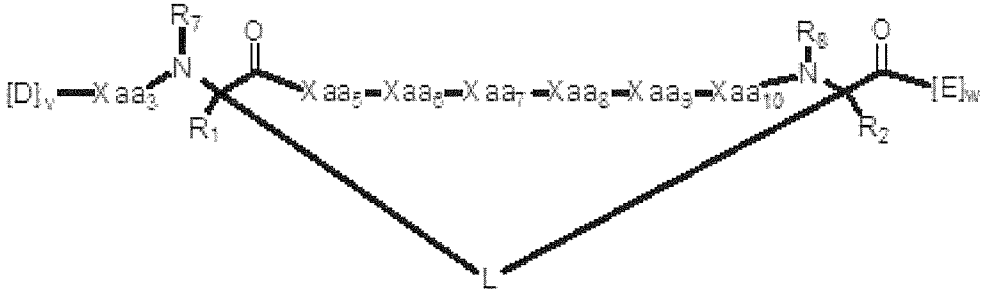
w is an integer from 3-1000;

n is an integer from 1-5; and

Xaa_7 is Boc-protected tryptophan.

[0037] In some embodiments, the peptidomimetic macrocycle of Formula (I) comprises an α-helix.

[0037a] In one embodiment, there is provided a peptidomimetic macrocycle of Formula:



or a pharmaceutically-acceptable salt thereof

wherein:

each of Xaa_3, Xaa_5, Xaa_6, Xaa_7, Xaa_8, Xaa_9, and Xaa_{10} is independently 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} (SEQ ID NO: 9), where each of X_4 and X_{11} is independently an amino acid;

each D is independently an amino acid;

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);

R_1 and R_2 are 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 of the formula $–L_1–L_2–$;

each L_1 and L_2 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_3 is independently hydrogen, alkyl, alkenyl, alkynyl, arylalkyl, heteroalkyl, cycloalkyl, heterocycloalkyl, cycloalkylalkyl, cycloaryl, or heterocycloaryl, 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;

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;

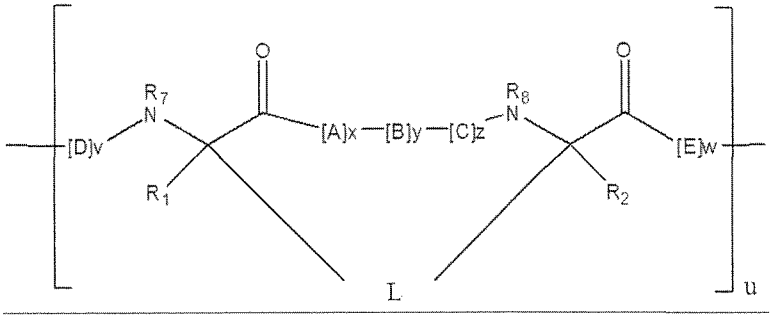
R_8 is –H, alkyl, alkenyl, alkynyl, arylalkyl, cycloalkyl, heteroalkyl, cycloalkylalkyl, heterocycloalkyl, cycloaryl, or heterocycloaryl, optionally substituted with R_5, or part of a cyclic structure with an E residue;

v is an integer from 1–1000;

w is an integer from 3–1000; and

n is an integer from 1–5.

[0037b] In one embodiment, there is provided a peptidomimetic macrocycle comprising an amino acid sequence which is at least about 60% identical to an amino acid sequence in any of Table 1, Table 1a, Table 1b, and Table 1c, wherein the peptidomimetic macrocycle has the formula:

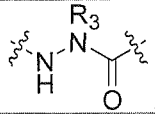


Formula (I)

or a pharmaceutically-acceptable salt thereof,

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 of the formula –L_1–L_2–;

each L_1 and L_2 and 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;

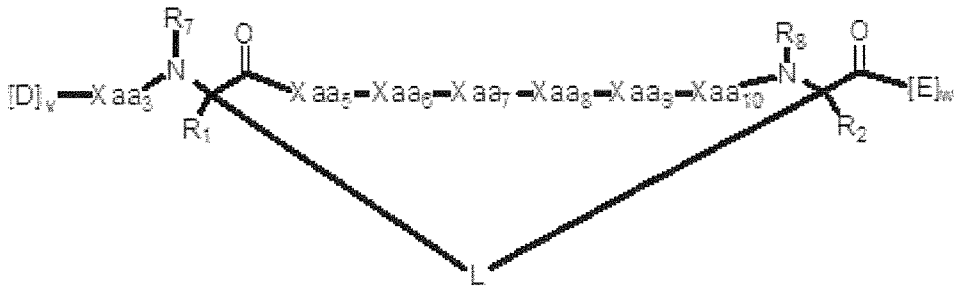
each w is independently an integer from 3–1000;

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.

[0037c] In one embodiment, there is provided a peptidomimetic macrocycle of Formula:



or pharmaceutically-acceptable salt thereof

wherein:

each of Xaa_3, Xaa_5, Xaa_6, Xaa_7, Xaa_8, Xaa_9, and Xaa_{10} is independently 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 acids 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} (SEQ ID NO: 8) or Phe_3–X_4–Glu_5–Tyr_6–Trp_7–Ala_8–Gln_9–Leu_{10}/Cba_{10}–X_{11}–Ala_{12} (SEQ ID NO: 9), wherein each X_4 and X_{11} is independently an amino acid;

each D is independently an amino acid;

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);

R_1 and R_2 are 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 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;

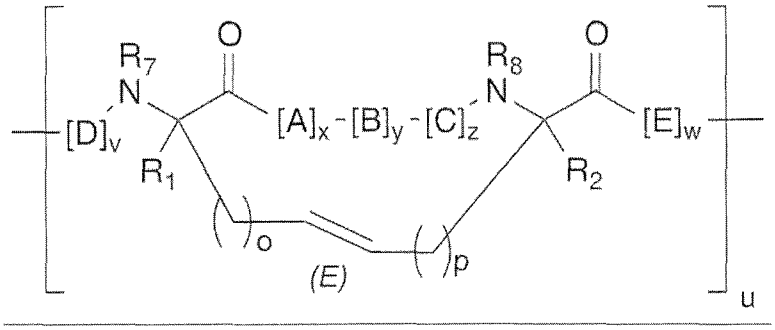
R_7 is –H, alkyl, alkenyl, alkynyl, arylalkyl, cycloalkyl, heteroalkyl, cycloalkylalkyl, heterocycloalkyl, cycloaryl, or heterocycloaryl, optionally substituted with R_5, or part of a cyclic structure with a D residue;

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 3–1000.

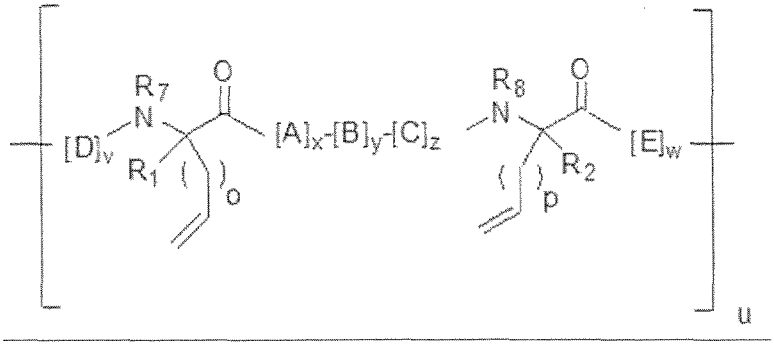
[0037d] In one embodiment, there is provided a method method of preparing a composition comprising a peptidomimetic macrocycle of Formula (Ia):



Formula (Ia),

or pharmaceutically-acceptable salt thereof,

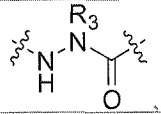
comprising an amino acid sequence which is about 60% to about 100% identical to an amino acid sequence in any of Table 1, Table 1a, Table 1b, and Table 1c, the method comprising treating a compound of Formula (II) or pharmaceutically-acceptable salt thereof



Formula (II),

with a catalyst to result in the compound of Formula (Ia) or pharmaceutically-acceptable salt thereof, wherein in the compound of Formula (Ia) or pharmaceutically-acceptable salt thereof and in the compound of Formula (II) or pharmaceutically-acceptable salt thereof

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 hydrogen, alkyl, alkenyl, alkynyl, arylalkyl, cycloalkyl, cycloalkylalkyl, heteroalkyl, or heterocycloalkyl, unsubstituted or substituted with halogen; or forms a macrocycle–forming linker L' connected to the alpha position of one of the 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' is independently a macrocycle–forming linker of the formula $–L_1–L_2–$;

each L_1, L_2 and 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 and $R_{4'}$ 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 hydrogen, alkyl, alkenyl, alkynyl, arylalkyl, cycloalkylalkyl, heterocycloalkyl, a fluorescent moiety, a radioisotope or a therapeutic agent;

each R_7 is independently hydrogen, 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 hydrogen, 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;

each n is independently an integer from 1–5;

each o is independently an integer from 1 to 15;

each p is independently an integer from 1 to 15;

(E) indicates a trans double bond or an *E*-double bond; and

one or more of A, B, and C has a side chain bearing a protecting group.

[0037e] In one embodiment, there is provided a peptidomimetic macrocycle or pharmaceutically-acceptable salt thereof comprising an amino acid sequence with at least about 60% sequence identity to an amino acid sequence selected from the group consisting of SEQ ID NO: 108, SEQ ID NO: 123, SEQ ID NO: 124, SEQ ID NO: 163, SEQ ID NO: 169, SEQ ID NO: 324, SEQ ID NO: 340, SEQ ID NO: 358, SEQ ID NO: 360, SEQ ID NO: 376, SEQ ID NO: 454, SEQ ID NO: 446, SEQ ID NO: 464, SEQ ID NO: 466, SEQ ID NO: 467, SEQ ID NO: 471, SEQ ID NO: 473, SEQ ID NO: 475, SEQ ID NO: 476, SEQ ID NO: 481, SEQ ID NO: 482, SEQ ID NO: 487, SEQ ID NO: 572, and SEQ ID NO: 1500.

[0037f] In one embodiment, there is provided a peptidomimetic macrocycle or pharmaceutically-acceptable salt thereof comprising an amino acid sequence with at least about 80% sequence identity to an amino acid sequence selected from the group consisting of SEQ ID NO: 108, SEQ ID NO: 123, SEQ ID NO: 124, SEQ ID NO: 163, SEQ ID NO: 169, SEQ ID NO: 324, SEQ ID NO: 340, SEQ ID NO: 358, SEQ ID NO: 360, SEQ ID NO: 376, SEQ ID NO: 446, SEQ

ID NO: 454, SEQ ID NO: 464, SEQ ID NO: 466, SEQ ID NO: 467, SEQ ID NO: 471, SEQ ID NO: 473, SEQ ID NO: 475, SEQ ID NO: 476, SEQ ID NO: 481, SEQ ID NO: 482, SEQ ID NO: 487, SEQ ID NO: 572, and SEQ ID NO: 1500.

[0037g] In one embodiment, there is provided a peptidomimetic macrocycle or pharmaceutically-acceptable salt thereof comprising an amino acid sequence with at least about 90% sequence identity to an amino acid sequence selected from the group consisting of SEQ ID NO: 108, SEQ ID NO: 123, SEQ ID NO: 124, SEQ ID NO: 163, SEQ ID NO: 169, SEQ ID NO: 324, SEQ ID NO: 340, SEQ ID NO: 358, SEQ ID NO: 360, SEQ ID NO: 376, SEQ ID NO: 446, SEQ ID NO: 454, SEQ ID NO: 464, SEQ ID NO: 466, SEQ ID NO: 467, SEQ ID NO: 471, SEQ ID NO: 473, SEQ ID NO: 475, SEQ ID NO: 476, SEQ ID NO: 481, SEQ ID NO: 482, SEQ ID NO: 487, SEQ ID NO: 572, and SEQ ID NO: 1500.

[0037h] In one embodiment, there is provided a peptidomimetic macrocycle or pharmaceutically-acceptable salt thereof comprising an amino acid sequence with at least about 95% sequence identity to an amino acid sequence selected from the group consisting of SEQ ID NO: 108, SEQ ID NO: 123, SEQ ID NO: 124, SEQ ID NO: 163, SEQ ID NO: 169, SEQ ID NO: 324, SEQ ID NO: 340, SEQ ID NO: 358, SEQ ID NO: 360, SEQ ID NO: 376, SEQ ID NO: 446, SEQ ID NO: 454, SEQ ID NO: 464, SEQ ID NO: 466, SEQ ID NO: 467, SEQ ID NO: 471, SEQ ID NO: 473, SEQ ID NO: 475, SEQ ID NO: 476, SEQ ID NO: 481, SEQ ID NO: 482, SEQ ID NO: 487, SEQ ID NO: 572, and SEQ ID NO: 1500.

[0037i] In one embodiment, there is provided a peptidomimetic macrocycle or pharmaceutically-acceptable salt thereof comprising an amino acid sequence selected from the group consisting of SEQ ID NO: 108, SEQ ID NO: 123, SEQ ID NO: 124, SEQ ID NO: 163, SEQ ID NO: 169, SEQ ID NO: 324, SEQ ID NO: 340, SEQ ID NO: 358, SEQ ID NO: 360, SEQ ID NO: 376, SEQ ID NO: 446, SEQ ID NO: 454, SEQ ID NO: 464, SEQ ID NO: 466, SEQ ID NO: 467, SEQ ID NO: 471, SEQ ID NO: 473, SEQ ID NO: 475, SEQ ID NO: 476, SEQ ID NO: 481, SEQ ID NO: 482, SEQ ID NO: 487, SEQ ID NO: 572, and SEQ ID NO: 1500.

BRIEF DESCRIPTION OF THE DRAWINGS

[0038] The novel features of the invention are set forth with particularity in the appended claims. A better understanding of the features and advantages of the present invention will be obtained by reference to the following detailed description that sets forth illustrative embodiments, in which the principles of the invention are utilized, and the accompanying drawings of which:

[0039] **Figure 1** shows a structure of peptidomimetic macrocycle 46 (Table 2b), a p53 peptidomimetic macrocycle, complexed with MDMX (Primary SwissProt accession number Q7ZUW7; Entry MDM4_DANRE).

[0040] **Figure 2** shows overlaid structures of p53 peptidomimetic macrocycles 142 (Table 2b) and SP43 bound to MDMX (Primary SwissProt accession number Q7ZUW7; Entry MDM4_DANRE).

[0041] **Figure 3** shows the effect of SP154, a peptidomimetic macrocycle, on tumor growth in a mouse MCF-7 xenograft model.

[0042] **Figure 4** shows the effect of SP249, a peptidomimetic macrocycle, on tumor growth in a mouse MCF-7 xenograft model.

[0043] **Figure 5** shows the effect of SP315, a peptidomimetic macrocycle, on tumor growth in a mouse MCF-7 xenograft model.

[0044] **Figure 6** shows the effect of SP252, a point mutation of SP154, on tumor growth in a mouse MCF-7 xenograft model.

[0045] **Figure 7** shows a plot of solubility for peptidomimetic macrocycles with varying C-terminal extensions.

DETAILED DESCRIPTION OF THE INVENTION

[0046] 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.

[0047] 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.

[0048] As used herein, the term "stability" refers 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.

[0049] As used herein, the term "helical stability" refers to the maintenance of α helical structure by a peptidomimetic macrocycle as measured by circular dichroism or NMR. For example, in some embodiments, a peptidomimetic macrocycle exhibits at least a 1.25, 1.5, 1.75 or 2-fold increase in α-helicity as determined by circular dichroism compared to a corresponding uncrosslinked macrocycle.

[0050] 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.

[0051] 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.

[0052] The term "β-amino acid" refers to a molecule containing both an amino group and a carboxyl group in a β configuration.

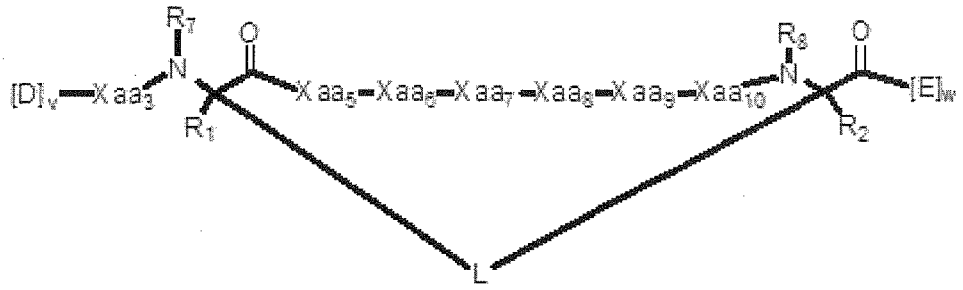
[0053] The term "naturally occurring amino acid" refers to any one of the twenty amino acids commonly found in peptides synthesized in nature, and known by the one letter abbreviations A, R, N, C, D, Q, E, G, H, I, L, K, M, F, P, S, T, W, Y and V.

[0054] 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

WHAT IS CLAIMED IS:

1. A peptidomimetic macrocycle of Formula:



or a pharmaceutically-acceptable salt thereof

wherein:

each of Xaa_3, Xaa_5, Xaa_6, Xaa_7, Xaa_8, Xaa_9, and Xaa_{10} is independently 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} (SEQ ID NO: 9), where each of X_4 and X_{11} is independently an amino acid;

each D is independently an amino acid;

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);

R_1 and R_2 are 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 of the formula $–L_1–L_2–$;

each L_1 and L_2 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_3 is independently hydrogen, alkyl, alkenyl, alkynyl, arylalkyl, heteroalkyl,

cycloalkyl, heterocycloalkyl, cycloalkylalkyl, cycloaryl, or heterocycloaryl, 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;

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;

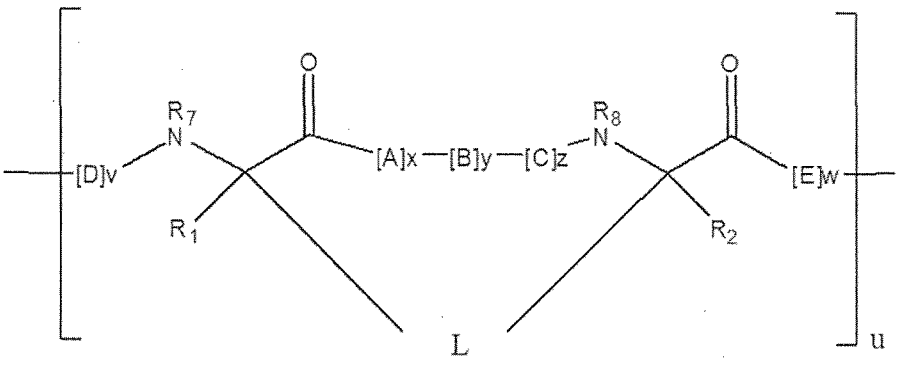
R_8 is –H, alkyl, alkenyl, alkynyl, arylalkyl, cycloalkyl, heteroalkyl, cycloalkylalkyl, heterocycloalkyl, cycloaryl, or heterocycloaryl, optionally substituted with R_5, or part of a cyclic structure with an E residue;

v is an integer from 1–1000;

w is an integer from 3–1000; and

n is an integer from 1–5.

2. A peptidomimetic macrocycle comprising an amino acid sequence which is at least about 60% identical to an amino acid sequence in any of Table 1, Table 1a, Table 1b, and Table 1c, wherein the peptidomimetic macrocycle has the formula:

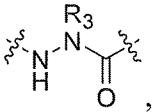


Formula (I)

or a pharmaceutically-acceptable salt thereof,

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 of the formula –L_1–L_2–;

each L_1 and L_2 and 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;

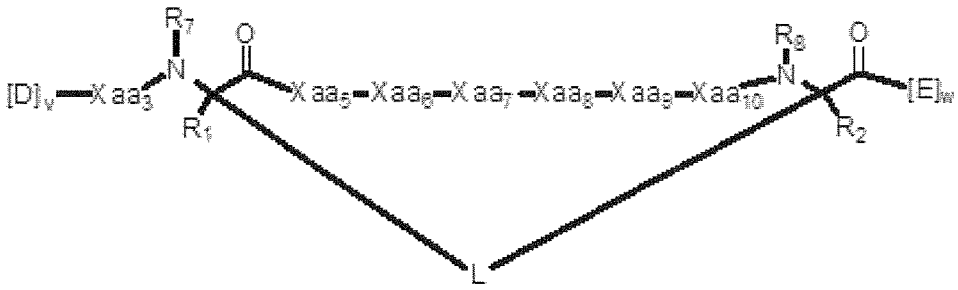
each w is independently an integer from 3–1000;

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.

3. A peptidomimetic macrocycle of Formula:



or pharmaceutically-acceptable salt thereof

wherein:

each of Xaa_3, Xaa_5, Xaa_6, Xaa_7, Xaa_8, Xaa_9, and Xaa_{10} is independently 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 acids 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} (SEQ ID NO: 8) or Phe_3–X_4–Glu_5–Tyr_6–Trp_7–Ala_8–Gln_9–Leu_{10}/Cba_{10}–X_{11}–Ala_{12} (SEQ ID NO: 9), wherein each X_4 and X_{11} is independently an amino acid;

each D is independently an amino acid;

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);

R_1 and R_2 are 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 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 3–1000.

4. The peptidomimetic macrocycle or pharmaceutically-acceptable salt thereof of any one of claims 1, 2, and 3, wherein the peptidomimetic macrocycle or pharmaceutically-acceptable salt thereof has an improved binding affinity to MDM2 or MDMX relative to a corresponding peptidomimetic macrocycle, wherein w is 0, 1 or 2 in the corresponding peptidomimetic macrocycle.

5. The peptidomimetic macrocycle or pharmaceutically-acceptable salt thereof of any one of claims 1, 2, and 3, wherein the peptidomimetic macrocycle or pharmaceutically-acceptable

salt thereof has a reduced ratio of binding affinities to MDMX versus MDM2 relative to a corresponding peptidomimetic macrocycle, wherein w is 0, 1 or 2 in the corresponding peptidomimetic macrocycle.

6. The peptidomimetic macrocycle or pharmaceutically-acceptable salt thereof of any one of claims 1, 2, and 3, wherein the peptidomimetic macrocycle or pharmaceutically-acceptable salt thereof has an improved *in vitro* anti–tumor efficacy against a p53 positive tumor cell line relative to a corresponding peptidomimetic macrocycle, wherein w is 0, 1 or 2 in the corresponding peptidomimetic macrocycle.

7. The peptidomimetic macrocycle or pharmaceutically-acceptable salt thereof of any one of claims 1, 2, and 3, wherein the peptidomimetic macrocycle or pharmaceutically-acceptable salt thereof has an improved *in vitro* induction of apoptosis in a p53 positive tumor cell line relative to a corresponding peptidomimetic macrocycle, wherein w is 0, 1 or 2 in the corresponding peptidomimetic macrocycle.

8. The peptidomimetic macrocycle or pharmaceutically-acceptable salt thereof of any one of claims 1, 2, and 3, wherein the peptidomimetic macrocycle or pharmaceutically-acceptable salt thereof has an improved *in vitro* anti-tumor efficacy ratio for a p53 positive versus a p53 negative or a p53 mutant tumor cell line relative to a corresponding peptidomimetic macrocycle, wherein w is 0, 1 or 2 in the corresponding peptidomimetic macrocycle.

9. The peptidomimetic macrocycle or pharmaceutically-acceptable salt thereof of any one of claims 1, 2, and 3, wherein the peptidomimetic macrocycle or pharmaceutically-acceptable salt thereof has an improved *in vivo* anti-tumor efficacy against a p53 positive tumor relative to a corresponding peptidomimetic macrocycle, wherein w is 0, 1 or 2 in the corresponding peptidomimetic macrocycle.

10. The peptidomimetic macrocycle or pharmaceutically-acceptable salt thereof of any one of claims 1, 2, and 3, wherein the peptidomimetic macrocycle or pharmaceutically-acceptable salt thereof has an improved *in vivo* induction of apoptosis in a p53 positive tumor relative to a corresponding peptidomimetic macrocycle, wherein w is 0, 1 or 2 in the corresponding peptidomimetic macrocycle.

11. The peptidomimetic macrocycle or pharmaceutically-acceptable salt thereof of any one of claims 1, 2, and 3, wherein the peptidomimetic macrocycle or pharmaceutically-acceptable

salt thereof has an improved cell permeability relative to a corresponding peptidomimetic macrocycle, wherein w is 0, 1 or 2 in the corresponding peptidomimetic macrocycle.

12. The peptidomimetic macrocycle or pharmaceutically-acceptable salt thereof of any one of claims 1, 2, and 3, wherein the peptidomimetic macrocycle or pharmaceutically-acceptable salt thereof has an improved solubility relative to a corresponding peptidomimetic macrocycle, wherein w is 0, 1 or 2 in the corresponding peptidomimetic macrocycle.

13. The peptidomimetic macrocycle or pharmaceutically-acceptable salt thereof of claim 1 or 3, wherein Xaa_5 is Glu.

14. The peptidomimetic macrocycle or pharmaceutically-acceptable salt thereof of claim 13, wherein the peptidomimetic macrocycle or pharmaceutically-acceptable salt thereof has an improved property relative to a corresponding peptidomimetic macrocycle, wherein the improved property is selected from the group consisting of improved binding affinity, improved solubility, improved cellular efficacy, improved helicity, improved cell permeability, improved *in vivo* or *in vitro* anti–tumor efficacy, and improved induction of apoptosis, wherein Xaa_5 is Ala in the corresponding peptidomimetic macrocycle.

15. The peptidomimetic macrocycle or pharmaceutically-acceptable salt thereof of claim 1, wherein $[D]_v$ is $–Leu_1–Thr_2$.

16. The peptidomimetic macrocycle or pharmaceutically-acceptable salt thereof of any one of claims 1, 2, and 3, wherein w is 3–10.

17. The peptidomimetic macrocycle or pharmaceutically-acceptable salt thereof of claim 16, wherein w is 3–6.

18. The peptidomimetic macrocycle or pharmaceutically-acceptable salt thereof of claim 16, wherein w is 6–10.

19. The peptidomimetic macrocycle or pharmaceutically-acceptable salt thereof of claim 16, wherein w is 6.

20. The peptidomimetic macrocycle or pharmaceutically-acceptable salt thereof of claim 1 or 3, wherein v is 1–10.

21. The peptidomimetic macrocycle or pharmaceutically-acceptable salt thereof of claim 20, wherein v is 2–10.

22. The peptidomimetic macrocycle or pharmaceutically-acceptable salt thereof of claim 20, wherein v is 2–5.

23. The peptidomimetic macrocycle or pharmaceutically-acceptable salt thereof of claim 20, wherein v is 2.

24. The peptidomimetic macrocycle or pharmaceutically-acceptable salt thereof of claim 2, wherein $[D]_v$ is Leu_1–Thr_2.

25. The peptidomimetic macrocycle or pharmaceutically-acceptable salt thereof of claim 1, wherein each L_1 and L_2 is independently alkylene, alkenylene, alkynylene, heteroalkylene, cycloalkylene, heterocycloalkylene, cycloarylene, or heterocycloarylene, each being optionally substituted with R_5.

26. The peptidomimetic macrocycle or pharmaceutically-acceptable salt thereof of claim 1, wherein each L_1 and L_2 is independently alkylene or alkenylene.

27. The peptidomimetic macrocycle or pharmaceutically-acceptable salt thereof of claim 1, wherein L is alkylene, alkenylene, or alkynylene.

28. The peptidomimetic macrocycle or pharmaceutically-acceptable salt thereof of any one of claims 2, 27, and 3 wherein L is alkenylene.

29. The peptidomimetic macrocycle or pharmaceutically-acceptable salt thereof of claim 28, wherein L is C_3–C_{16} alkenylene.

30. The peptidomimetic macrocycle or pharmaceutically-acceptable salt thereof of claim 29, wherein L is C_{10}–C_{14} alkenylene.

31. The peptidomimetic macrocycle or pharmaceutically-acceptable salt thereof of claim 1, wherein R_1 and R_2 are independently –H, alkyl, alkenyl, alkynyl, arylalkyl, cycloalkyl, cycloalkylalkyl, heteroalkyl, or heterocycloalkyl, unsubstituted or substituted with halo–.

32. The peptidomimetic macrocycle or pharmaceutically-acceptable salt thereof of claim 1, wherein R_1 and R_2 are H.

33. The peptidomimetic macrocycle or pharmaceutically-acceptable salt thereof of claim 1, wherein R_1 and R_2 are independently alkyl.

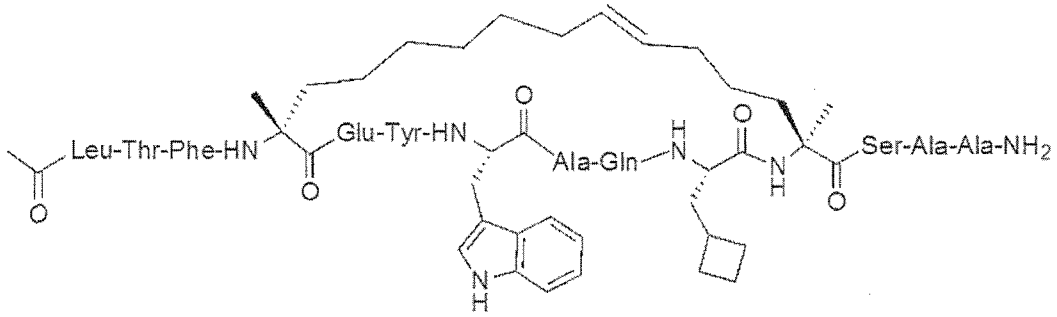
34. The peptidomimetic macrocycle or pharmaceutically-acceptable salt thereof of claim 33, wherein R_1 and R_2 are methyl.

35. The peptidomimetic macrocycle or pharmaceutically-acceptable salt thereof of claim 2, wherein x+y+z = 6.

36. The peptidomimetic macrocycle or pharmaceutically-acceptable salt thereof of claim 2, wherein u is 1.

37. The peptidomimetic macrocycle or pharmaceutically-acceptable salt thereof of any one of claims 1, 2, and 3, wherein each E is independently Ser or Ala.

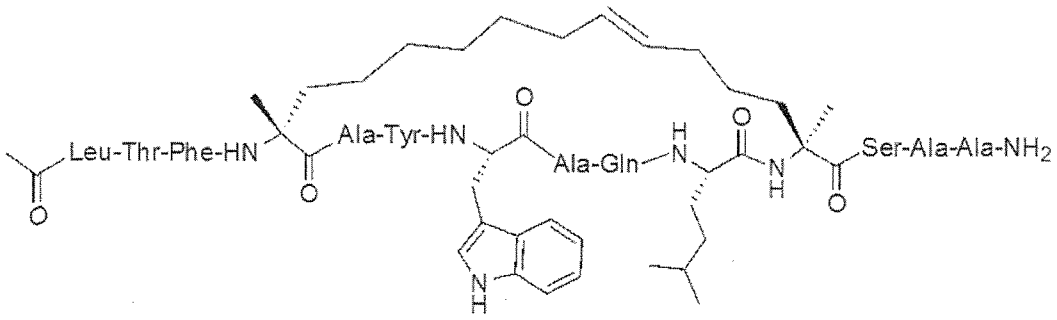
38. The peptidomimetic macrocycle of claim 1, having formula:



(SEQ ID NO: 163)

or a pharmaceutically acceptable salt thereof.

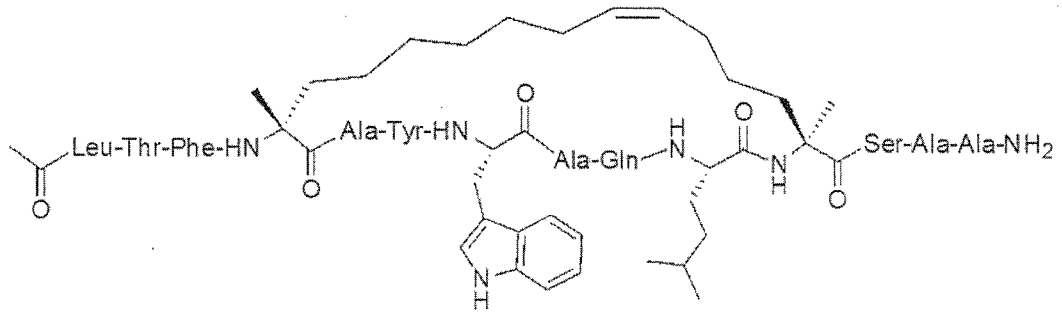
39. The peptidomimetic macrocycle of claim 1, having formula:



(SEQ ID NO: 124)

or a pharmaceutically acceptable salt thereof.

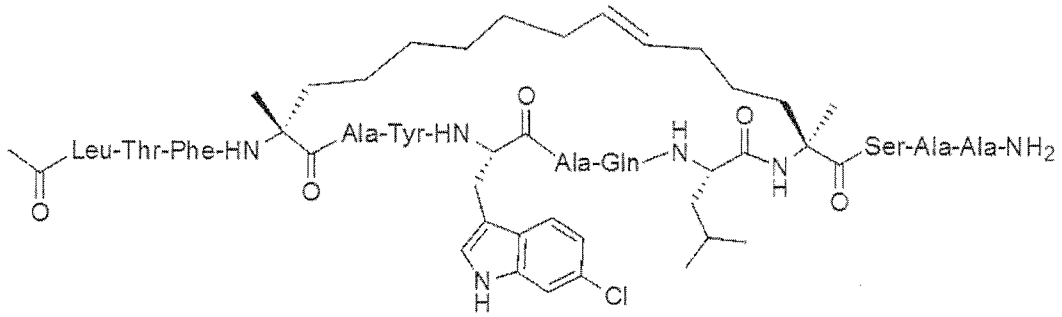
40. The peptidomimetic macrocycle of claim 1, having formula:



(SEQ ID NO: 123)

or a pharmaceutically acceptable salt thereof.

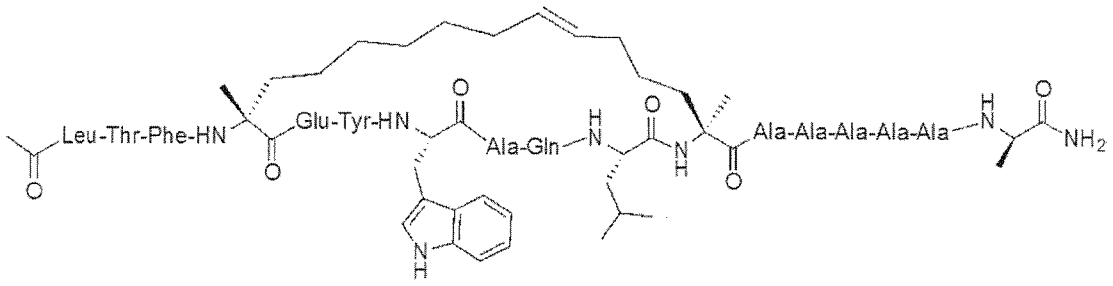
41. The peptidomimetic macrocycle of claim 1, having formula:



(SEQ ID NO: 108)

or a pharmaceutically acceptable salt thereof.

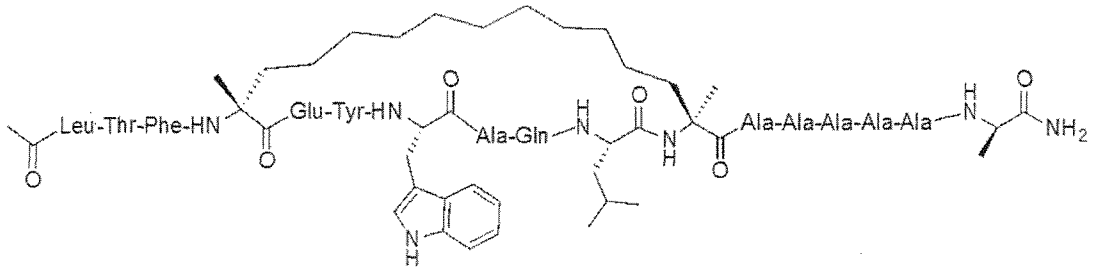
42. The peptidomimetic macrocycle of claim 1, having formula:



(SEQ ID NO: 340)

or a pharmaceutically acceptable salt thereof.

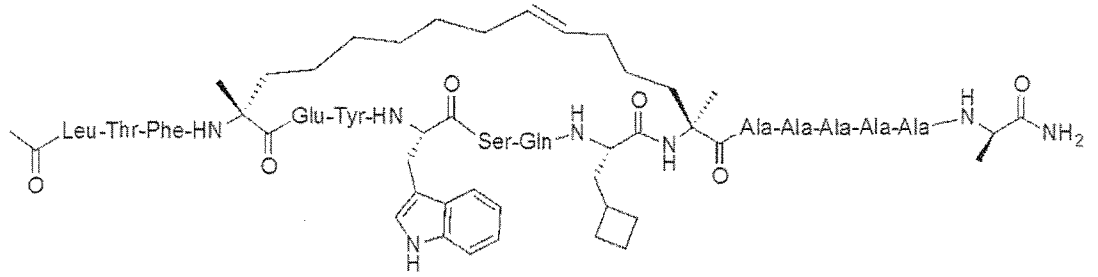
43. The peptidomimetic macrocycle of claim 1, having formula:



(SEQ ID NO: 454)

or a pharmaceutically acceptable salt thereof.

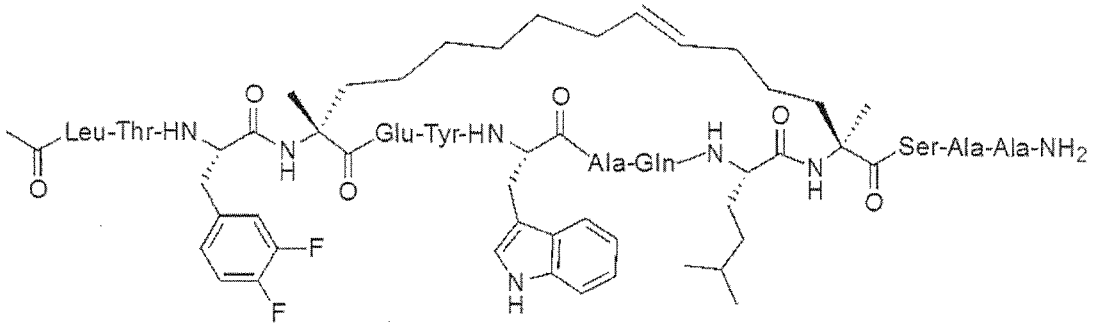
44. The peptidomimetic macrocycle of claim 1, having formula:



(SEQ ID NO: 360)

or a pharmaceutically acceptable salt thereof.

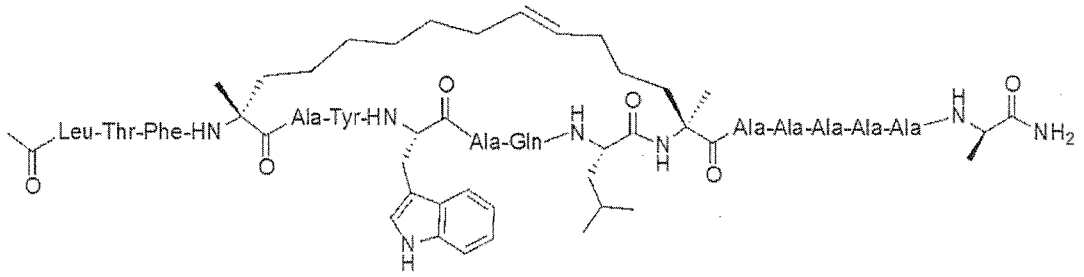
45. The peptidomimetic macrocycle of claim 1, having formula:



(SEQ ID NO: 169)

or a pharmaceutically acceptable salt thereof.

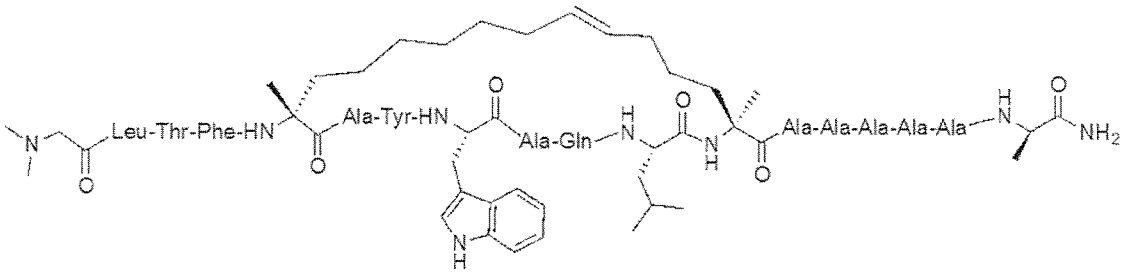
46. The peptidomimetic macrocycle of claim 1, having formula:



(SEQ ID NO: 324)

or a pharmaceutically acceptable salt thereof.

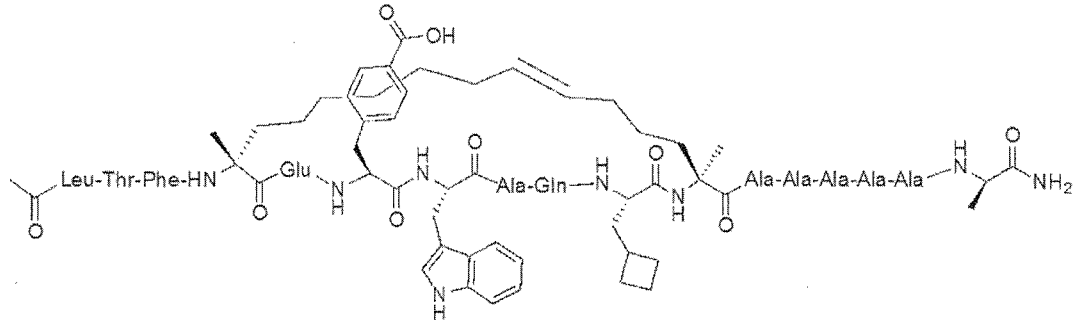
47. The peptidomimetic macrocycle of claim 1, having formula:



(SEQ ID NO: 446)

or a pharmaceutically acceptable salt thereof.

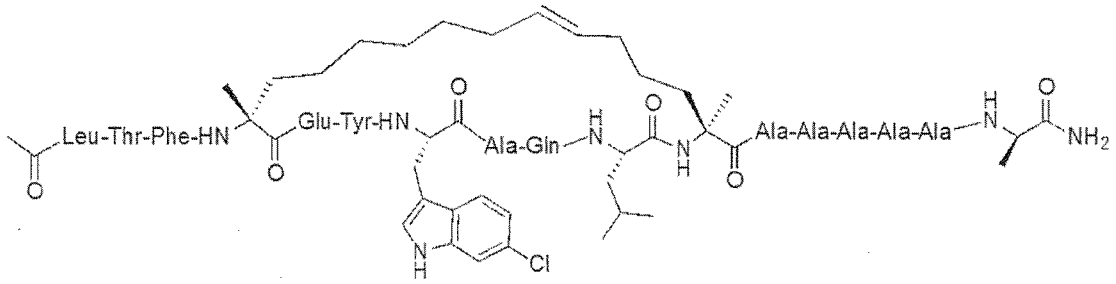
48. The peptidomimetic macrocycle of claim 1, having formula:



(SEQ ID NO: 358)

or a pharmaceutically acceptable salt thereof.

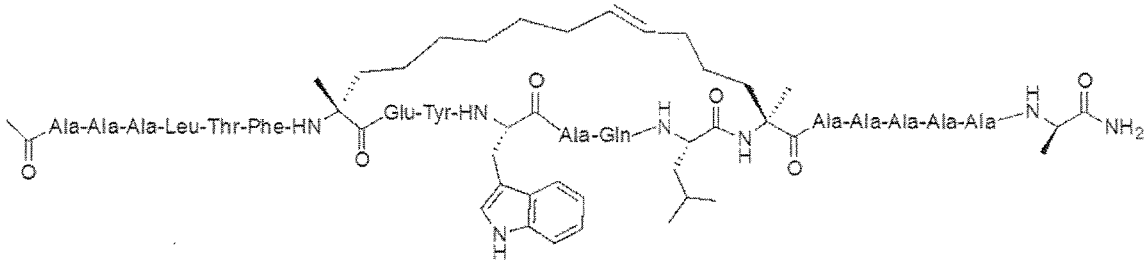
49. The peptidomimetic macrocycle of claim 1, having formula:



(SEQ ID NO: 464)

or a pharmaceutically acceptable salt thereof.

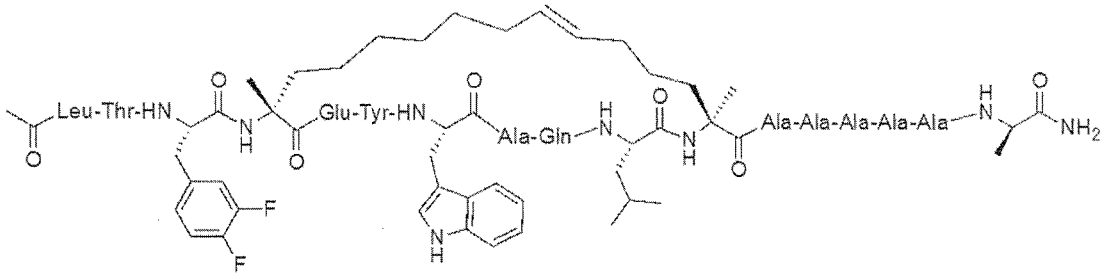
50. The peptidomimetic macrocycle of claim 1, having formula:



(SEQ ID NO: 466)

or a pharmaceutically acceptable salt thereof.

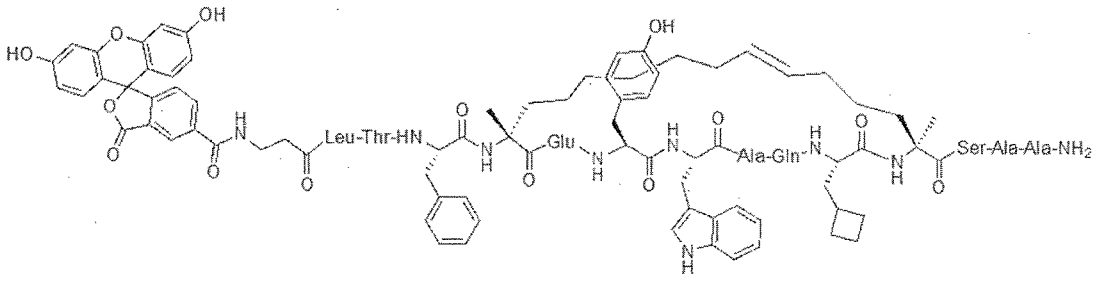
51. The peptidomimetic macrocycle of claim 1, having formula:



(SEQ ID NO: 467)

or a pharmaceutically acceptable salt thereof.

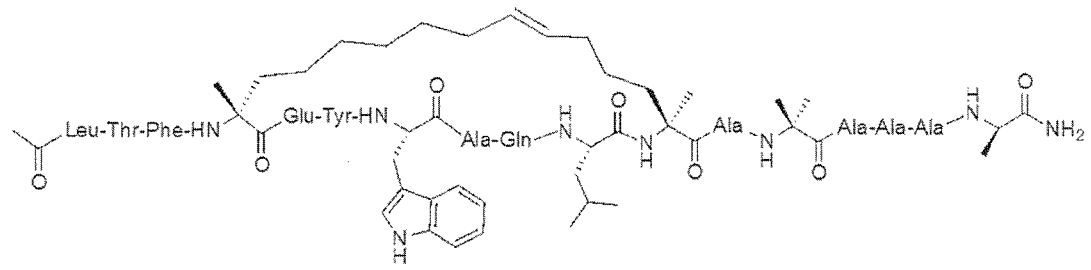
52. The peptidomimetic macrocycle of claim 1, having formula:



(SEQ ID NO: 376)

or a pharmaceutically acceptable salt thereof.

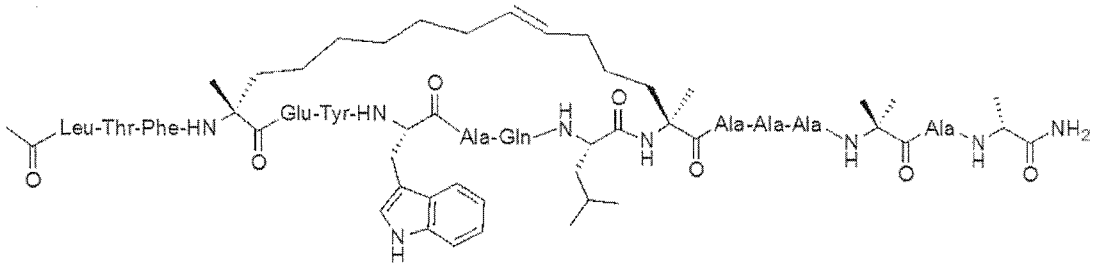
53. The peptidomimetic macrocycle of claim 1, having formula:



(SEQ ID NO: 471)

or a pharmaceutically acceptable salt thereof.

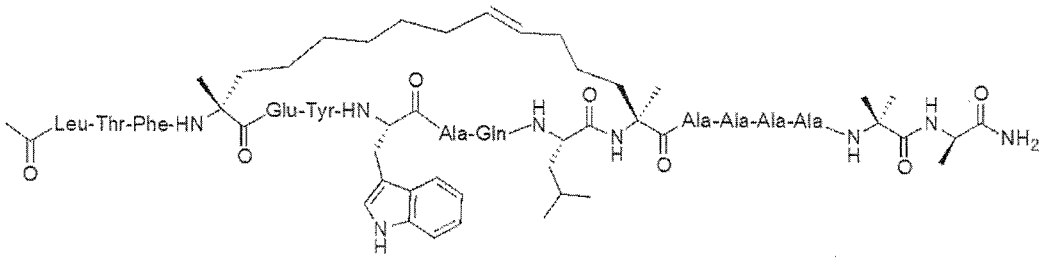
54. The peptidomimetic macrocycle of claim 1, having formula:



(SEQ ID NO: 473)

or a pharmaceutically acceptable salt thereof.

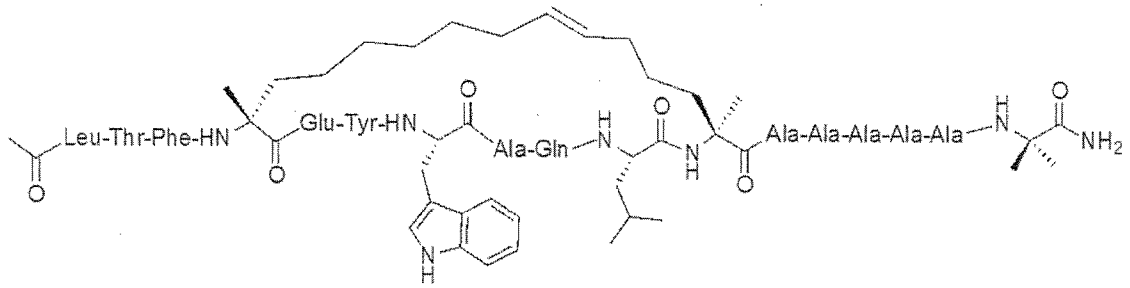
55. The peptidomimetic macrocycle of claim 1, having formula:



(SEQ ID NO: 475)

or a pharmaceutically acceptable salt thereof.

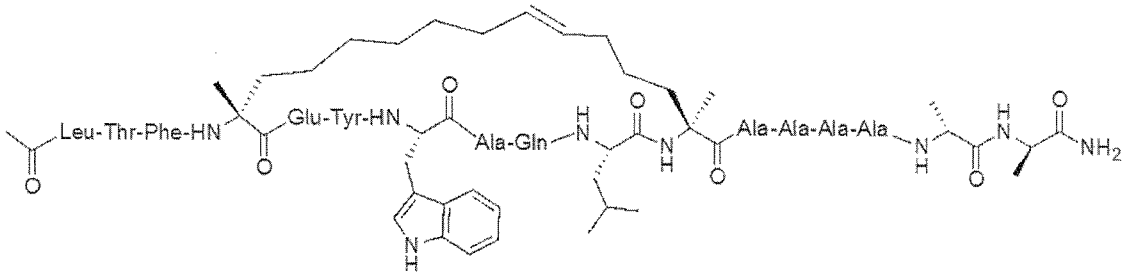
56. The peptidomimetic macrocycle of claim 1, having formula:



(SEQ ID NO: 476)

or a pharmaceutically acceptable salt thereof.

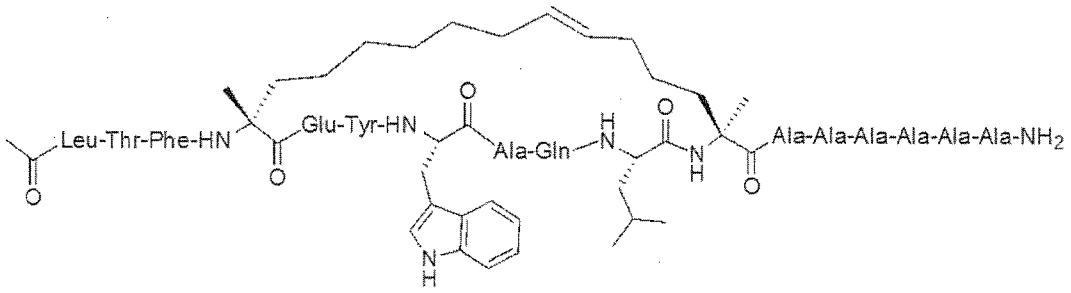
57. The peptidomimetic macrocycle of claim 1, having formula:



(SEQ ID NO: 481)

or a pharmaceutically acceptable salt thereof.

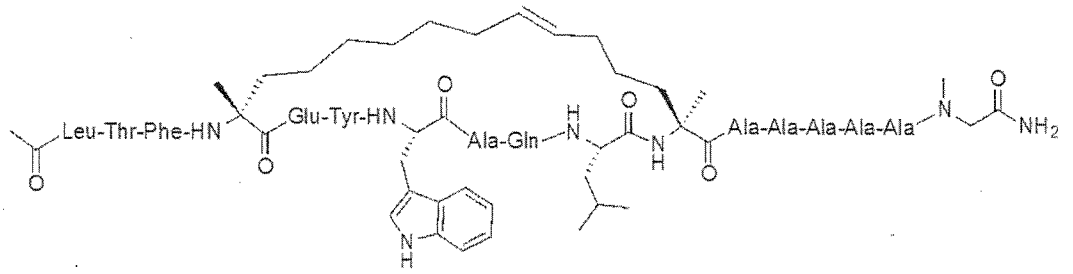
58. The peptidomimetic macrocycle of claim 1, having formula:



(SEQ ID NO: 482)

or a pharmaceutically acceptable salt thereof.

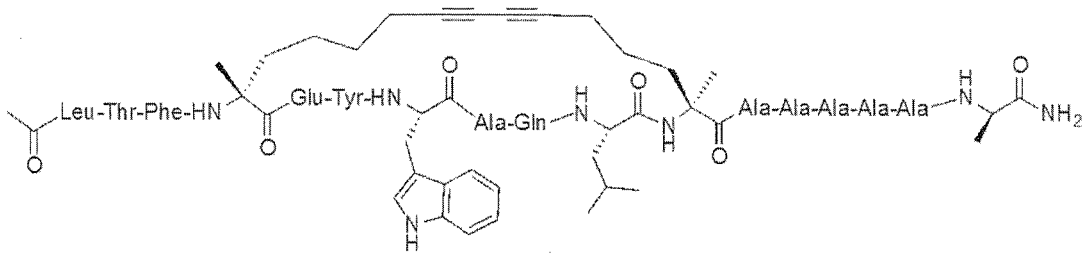
59. The peptidomimetic macrocycle of claim 1, having formula:



(SEQ ID NO: 487)

or a pharmaceutically acceptable salt thereof.

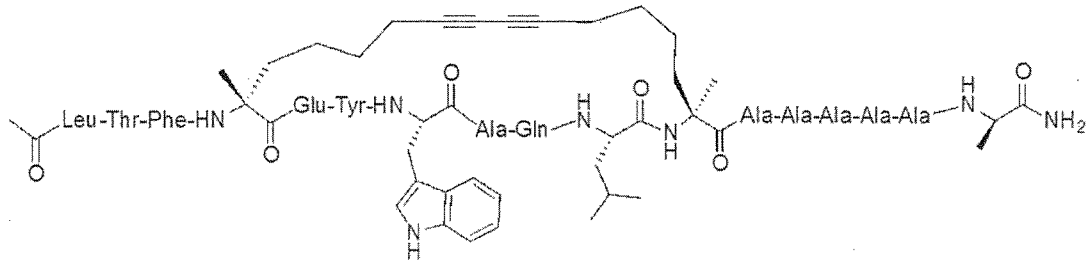
60. The peptidomimetic macrocycle of claim 1, having formula:



(SEQ ID NO: 572)

or a pharmaceutically acceptable salt thereof.

61. The peptidomimetic macrocycle of claim 1, having formula:



(SEQ ID NO: 1500)

or a pharmaceutically acceptable salt thereof.

62. The peptidomimetic macrocycle or pharmaceutically-acceptable salt thereof of claim 16, wherein w is 3.

63. The peptidomimetic macrocycle or pharmaceutically-acceptable salt thereof of claim 2, wherein v is 1–10.

64. The peptidomimetic macrocycle or pharmaceutically-acceptable salt thereof of claim 2, wherein v is 3–10.

65. The peptidomimetic macrocycle or pharmaceutically-acceptable salt thereof of claim 2, wherein v is 3–5.

66. The peptidomimetic macrocycle or pharmaceutically-acceptable salt thereof of claim 2, wherein v is 3.

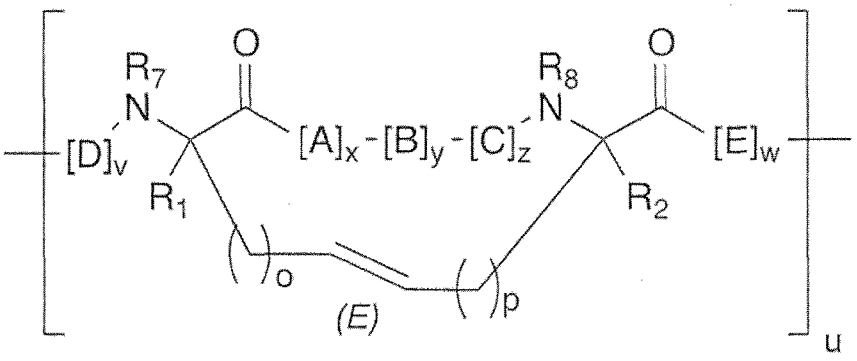
67. The peptidomimetic macrocycle or pharmaceutically-acceptable salt thereof of claim 2, wherein the peptidomimetic macrocycle or pharmaceutically-acceptable salt thereof comprises an amino acid sequence which is at least about 80% identical to an amino acid sequence in any of Table 1, Table 1a, Table 1b, and Table 1c.

68. The peptidomimetic macrocycle or pharmaceutically-acceptable salt thereof of claim 67, wherein the peptidomimetic macrocycle or pharmaceutically-acceptable salt thereof comprises an amino acid sequence which is at least about 90% identical to an amino acid sequence in any of Table 1, Table 1a, Table 1b, and Table 1c.

69. The peptidomimetic macrocycle or pharmaceutically-acceptable salt thereof of claim 68, wherein the peptidomimetic macrocycle or pharmaceutically-acceptable salt thereof

comprises an amino acid sequence which is at least about 95% identical to an amino acid sequence in any of Table 1, Table 1a, Table 1b, and Table 1c.

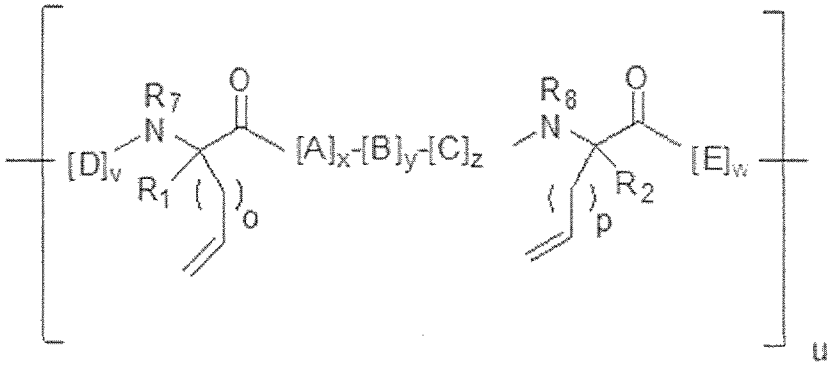
70. A method of preparing a composition comprising a peptidomimetic macrocycle of Formula (Ia):



Formula (Ia),

or pharmaceutically-acceptable salt thereof,

comprising an amino acid sequence which is about 60% to about 100% identical to an amino acid sequence in any of Table 1, Table 1a, Table 1b, and Table 1c, the method comprising treating a compound of Formula (II) or pharmaceutically-acceptable salt thereof

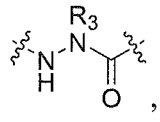


Formula (II),

with a catalyst to result in the compound of Formula (Ia) or pharmaceutically-acceptable salt thereof,

wherein in the compound of Formula (Ia) or pharmaceutically-acceptable salt thereof and in the compound of Formula (II) or pharmaceutically-acceptable salt thereof

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 hydrogen, alkyl, alkenyl, alkynyl, arylalkyl, cycloalkyl, cycloalkylalkyl, heteroalkyl, or heterocycloalkyl, unsubstituted or substituted with halogen; or forms a macrocycle–forming linker L' connected to the alpha position of one of the 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' is independently a macrocycle–forming linker of the formula –L_1–L_2–;

each L_1, L_2 and 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 and $R_{4'}$ 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 hydrogen, alkyl, alkenyl, alkynyl, arylalkyl, cycloalkylalkyl, heterocycloalkyl, a fluorescent moiety, a radioisotope or a therapeutic agent;

each R_7 is independently hydrogen, 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 hydrogen, 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;

each n is independently an integer from 1–5;

each o is independently an integer from 1 to 15;

each p is independently an integer from 1 to 15;

(E) indicates a trans double bond or an *E*-double bond; and

one or more of A, B, and C has a side chain bearing a protecting group.

71. The method of claim 70, wherein the protecting group is a nitrogen atom protecting group.

72. The method of claim 70, wherein the protecting group is a Boc group.

73. The method of claim 71, wherein the side chain bearing the protecting group comprises a protected indole.

74. The method of claim 73, wherein the protecting group is borne on the side chain of a tryptophan (W).

75. The method of claim 74, wherein the protecting group is a Boc group.

76. The method of claim 70, wherein after the step of treating the compound of Formula (II) or pharmaceutically-acceptable salt thereof with the catalyst, the compound of Formula (Ia) or pharmaceutically-acceptable salt thereof is obtained in an amount equal or higher than an amount obtained of a corresponding compound which is a Z isomer.

77. The method of claim 76, wherein after the step of treating the compound of Formula (II) or pharmaceutically-acceptable salt thereof with the catalyst, the compound of Formula (Ia) or pharmaceutically-acceptable salt thereof is obtained in an amount that is 2, 3, 4, 5, 6, 7, 8, 9,

or 10–fold higher than an amount obtained of the corresponding compound which is the Z isomer.

78. The method of claim 70, wherein the catalyst is a ruthenium catalyst.

79. The method of claim 70, further comprising the step of treating the compound of Formula (Ia) or pharmaceutically-acceptable salt thereof with a reducing agent or an oxidizing agent.

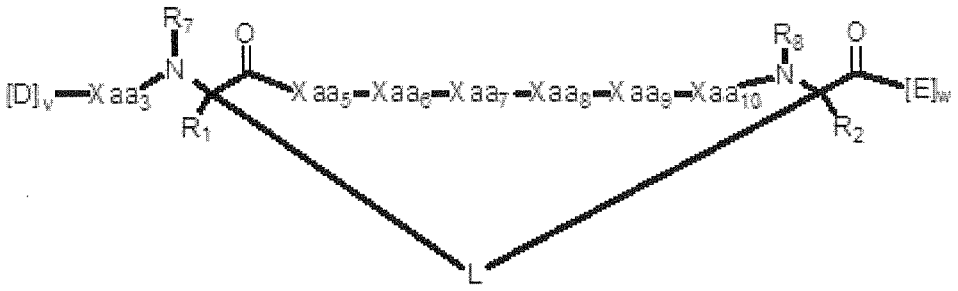
80. The method of claim 70, wherein the compound of Formula (II) or pharmaceutically-acceptable salt thereof is further attached to a solid support.

81. The method of claim 70, wherein the compound of Formula (II) or pharmaceutically-acceptable salt thereof is not attached to a solid support.

82. The method of claim 70, further comprising removing the protecting group from the compound of Formula (Ia) or pharmaceutically-acceptable salt thereof.

83. The method of claim 70, wherein the treating is conducted at a temperature ranging from about 20 °C to about 80 °C.

84. The method of claim 70, wherein the peptidomimetic macrocycle of Formula (Ia) has the Formula:



or pharmaceutically-acceptable salt thereof,

wherein:

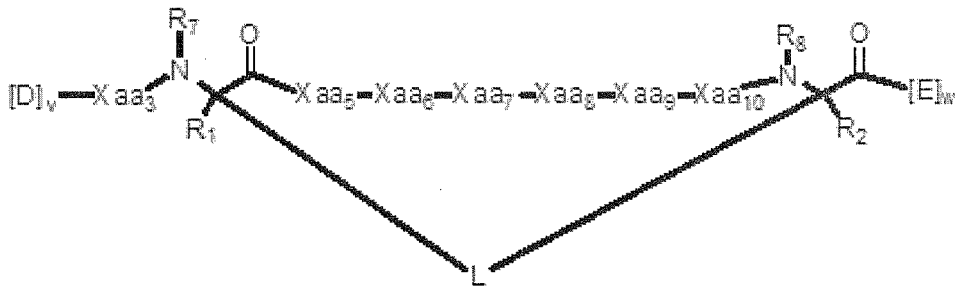
each of Xaa_3, Xaa_5, Xaa_6, Xaa_7, Xaa_8, Xaa_9, and Xaa_{10} is independently an amino acid, wherein at least two of Xaa_3, Xaa_5, Xaa_6, Xaa_8, Xaa_9, and Xaa_{10} are the same amino acid as the amino acid at the corresponding position of the sequence Phe_3–X_4–His_5–Tyr_6–Trp_7–Ala_8–Gln_9–Leu_{10}–X_{11}–Ser_{12} (SEQ ID NO: 8), wherein each of X_4 and X_{11} is independently an amino acid;

L comprises a double bond in the E configuration;

v is an integer from 1–500; and

Xaa_7 is Boc–protected tryptophan.

85. The method of claim 70, wherein the peptidomimetic macrocycle of Formula (Ia) has the Formula:



or pharmaceutically-acceptable salt thereof,

wherein:

each of Xaa_3, Xaa_5, Xaa_6, Xaa_7, Xaa_8, Xaa_9, and Xaa_{10} is independently an amino acid, wherein at least two of Xaa_3, Xaa_5, Xaa_6, 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} (SEQ ID NO: 9), wherein each of X_4 and X_{11} is independently an amino acid;

L comprises a double bond in the E configuration;

v is an integer from 1–500; and

Xaa_7 is Boc–protected tryptophan.

86. The method of claim 70, wherein the peptidomimetic macrocycle of Formula (Ia) or pharmaceutically-acceptable salt thereof comprises an α–helix.

87. The method of claims 73 or 74, wherein L is C_3–C_{16} alkenylene.

88. The method of claim 87, wherein L is C_{10}–C_{14} alkenylene.

89. The method of claim 70, wherein w is 3–10.

90. The method of claim 70, wherein w is 3–6.

91. The method of claim 70, wherein w is 3.

92. The method of claim 70, wherein v is 1–10.

93. The method of claim 70, wherein v is 3–10.

94. The method of claim 70, wherein v is 3–5.

95. The method of claim 70, wherein v is 3.

96. The method of claim 70, wherein x+y+z = 6 in the peptidomimetic macrocycle of Formula (Ia) or pharmaceutically-acceptable salt thereof.

97. The method of claim 70, wherein u is 1.

98. The method of claim 70, wherein each E is independently an amino acid selected from the group consisting of Ser and Ala.

99. The method of claim 70, wherein the peptidomimetic macrocycle of Formula (Ia) or pharmaceutically-acceptable salt thereof comprises an amino acid sequence which is about 80% to about 100% identical to an amino acid sequence in any of Table 1, Table 1a, Table 1b, and Table 1c.

100. The method of claim 99, wherein the peptidomimetic macrocycle of Formula (Ia) or pharmaceutically-acceptable salt thereof comprises an amino acid sequence which is about 90% to about 100% identical to an amino acid sequence in any of Table 1, Table 1a, Table 1b, and Table 1c.

101. The method of claim 100, wherein the peptidomimetic macrocycle of Formula (Ia) or pharmaceutically-acceptable salt thereof comprises an amino acid sequence which is about 95% to about 100% identical to an amino acid sequence in any of Table 1, Table 1a, Table 1b, and Table 1c.

102. The peptidomimetic macrocycle or pharmaceutically-acceptable salt thereof of claim 3, wherein at least three of Xaa_3, Xaa_5, Xaa_6, Xaa_7, Xaa_8, Xaa_9, and Xaa_{10} are the same amino acids 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} (SEQ ID NO: 8).

103. The peptidomimetic macrocycle or pharmaceutically-acceptable salt thereof of claim 3, wherein at least three of Xaa_3, Xaa_5, Xaa_6, Xaa_7, Xaa_8, Xaa_9, and Xaa_{10} are the same amino

acids 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} (SEQ ID NO: 9).

104. A peptidomimetic macrocycle or pharmaceutically-acceptable salt thereof comprising an amino acid sequence with at least about 60% sequence identity to an amino acid sequence selected from the group consisting of SEQ ID NO: 108, SEQ ID NO: 123, SEQ ID NO: 124, SEQ ID NO: 163, SEQ ID NO: 169, SEQ ID NO: 324, SEQ ID NO: 340, SEQ ID NO: 358, SEQ ID NO: 360, SEQ ID NO: 376, SEQ ID NO: 454, SEQ ID NO: 446, SEQ ID NO: 464, SEQ ID NO: 466, SEQ ID NO: 467, SEQ ID NO: 471, SEQ ID NO: 473, SEQ ID NO: 475, SEQ ID NO: 476, SEQ ID NO: 481, SEQ ID NO: 482, SEQ ID NO: 487, SEQ ID NO: 572, and SEQ ID NO: 1500.

105. A peptidomimetic macrocycle or pharmaceutically-acceptable salt thereof comprising an amino acid sequence with at least about 80% sequence identity to an amino acid sequence selected from the group consisting of SEQ ID NO: 108, SEQ ID NO: 123, SEQ ID NO: 124, SEQ ID NO: 163, SEQ ID NO: 169, SEQ ID NO: 324, SEQ ID NO: 340, SEQ ID NO: 358, SEQ ID NO: 360, SEQ ID NO: 376, SEQ ID NO: 446, SEQ ID NO: 454, SEQ ID NO: 464, SEQ ID NO: 466, SEQ ID NO: 467, SEQ ID NO: 471, SEQ ID NO: 473, SEQ ID NO: 475, SEQ ID NO: 476, SEQ ID NO: 481, SEQ ID NO: 482, SEQ ID NO: 487, SEQ ID NO: 572, and SEQ ID NO: 1500.

106. A peptidomimetic macrocycle or pharmaceutically-acceptable salt thereof comprising an amino acid sequence with at least about 90% sequence identity to an amino acid sequence selected from the group consisting of SEQ ID NO: 108, SEQ ID NO: 123, SEQ ID NO: 124, SEQ ID NO: 163, SEQ ID NO: 169, SEQ ID NO: 324, SEQ ID NO: 340, SEQ ID NO: 358, SEQ ID NO: 360, SEQ ID NO: 376, SEQ ID NO: 446, SEQ ID NO: 454, SEQ ID NO: 464, SEQ ID NO: 466, SEQ ID NO: 467, SEQ ID NO: 471, SEQ ID NO: 473, SEQ ID NO: 475, SEQ ID NO: 476, SEQ ID NO: 481, SEQ ID NO: 482, SEQ ID NO: 487, SEQ ID NO: 572, and SEQ ID NO: 1500.

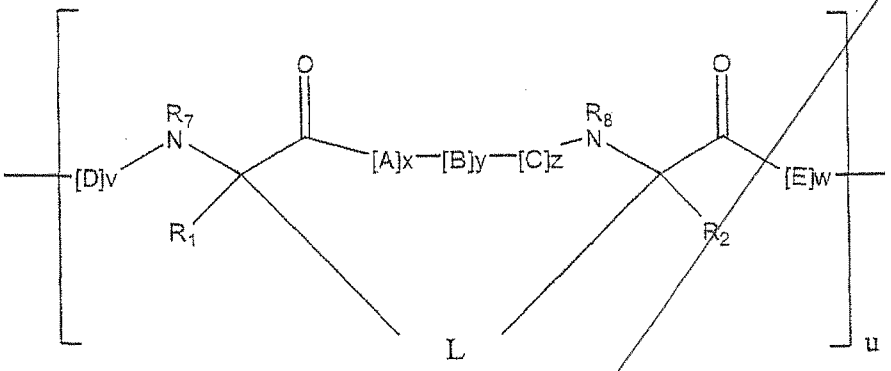
107. A peptidomimetic macrocycle or pharmaceutically-acceptable salt thereof comprising an amino acid sequence with at least about 95% sequence identity to an amino acid sequence selected from the group consisting of SEQ ID NO: 108, SEQ ID NO: 123, SEQ ID NO: 124, SEQ ID NO: 163, SEQ ID NO: 169, SEQ ID NO: 324, SEQ ID NO: 340, SEQ ID NO: 358,

SEQ ID NO: 360, SEQ ID NO: 376, SEQ ID NO: 446, SEQ ID NO: 454, SEQ ID NO: 464, SEQ ID NO: 466, SEQ ID NO: 467, SEQ ID NO: 471, SEQ ID NO: 473, SEQ ID NO: 475, SEQ ID NO: 476, SEQ ID NO: 481, SEQ ID NO: 482, SEQ ID NO: 487, SEQ ID NO: 572, and SEQ ID NO: 1500.

108. A peptidomimetic macrocycle or pharmaceutically-acceptable salt thereof comprising an amino acid sequence selected from the group consisting of SEQ ID NO: 108, SEQ ID NO: 123, SEQ ID NO: 124, SEQ ID NO: 163, SEQ ID NO: 169, SEQ ID NO: 324, SEQ ID NO: 340, SEQ ID NO: 358, SEQ ID NO: 360, SEQ ID NO: 376, SEQ ID NO: 446, SEQ ID NO: 454, SEQ ID NO: 464, SEQ ID NO: 466, SEQ ID NO: 467, SEQ ID NO: 471, SEQ ID NO: 473, SEQ ID NO: 475, SEQ ID NO: 476, SEQ ID NO: 481, SEQ ID NO: 482, SEQ ID NO: 487, SEQ ID NO: 572, and SEQ ID NO: 1500.

WHAT IS CLAIMED IS:

1. A peptidomimetic macrocycle comprising an amino acid sequence which is at least about 60% identical to an amino acid sequence chosen from the group consisting of the amino acid sequences in Table 1, Table 1a, Table 1b, or Table 1c, wherein the peptidomimetic macrocycle has the formula:

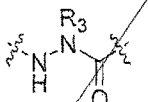


Formula (I)

or a pharmaceutically acceptable salt thereof,

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

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

each L_1 and L_2 and L_3 is independently alkylene, alkenylene, alkynylene, heteroalkylene, cycloalkylene, heterocycloalkylene, arylene, heteroarylene, or $[-R_4-K-R_4-]_m$, 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, 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 is independently an integer from 1-1000;

each w is independently an integer from 1-1000;

u is an integer from 1-10;

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

each n is independently an integer from 1-5;

wherein a first C–terminal amino acid represented by E comprises a hydrophobic side chain, or when a w>1 a first or a second C–terminal amino acid represented by E comprises a hydrophobic side chain; and

wherein the peptidomimetic macrocycle or pharmaceutically acceptable salt thereof is not a peptidomimetic macrocycle of Tables 2a or 2b or pharmaceutically acceptable salt thereof.

2. The peptidomimetic macrocycle or pharmaceutically acceptable salt thereof of claim 1, 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).

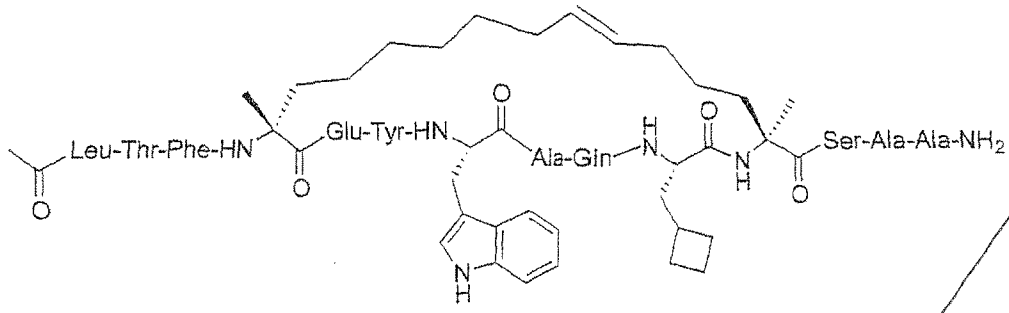
3. The peptidomimetic macrocycle or pharmaceutically acceptable salt thereof of claim 1, wherein x+y+z = 6.

4. The peptidomimetic macrocycle or pharmaceutically acceptable salt thereof of claim 1, wherein u is 1.

5. The peptidomimetic macrocycle or pharmaceutically acceptable salt thereof of claim 1, wherein w is 3-1000.

6. The peptidomimetic macrocycle or pharmaceutically acceptable salt thereof of claim 1, wherein w is 3-1000 and 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).

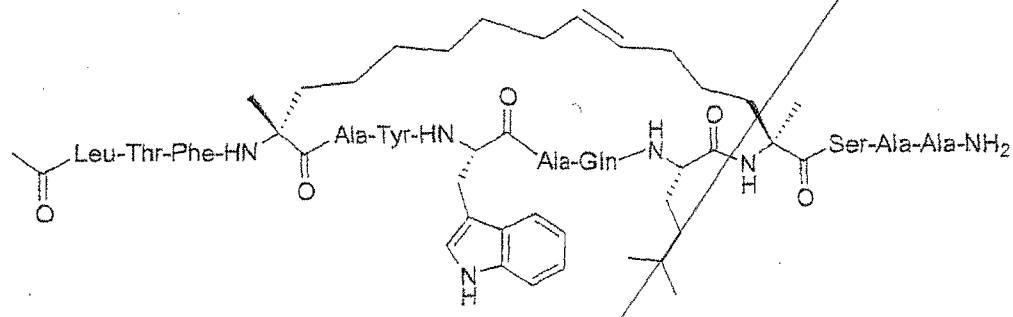
7. The peptidomimetic macrocycle of claim 1, having formula:



(SEQ ID NO: 163)

or a pharmaceutically acceptable salt thereof.

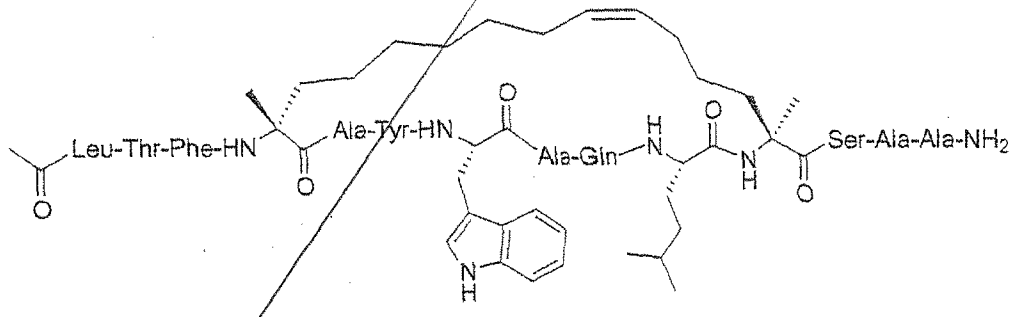
8. The peptidomimetic macrocycle of claim 1, having formula:



(SEQ ID NO: 124)

or a pharmaceutically acceptable salt thereof.

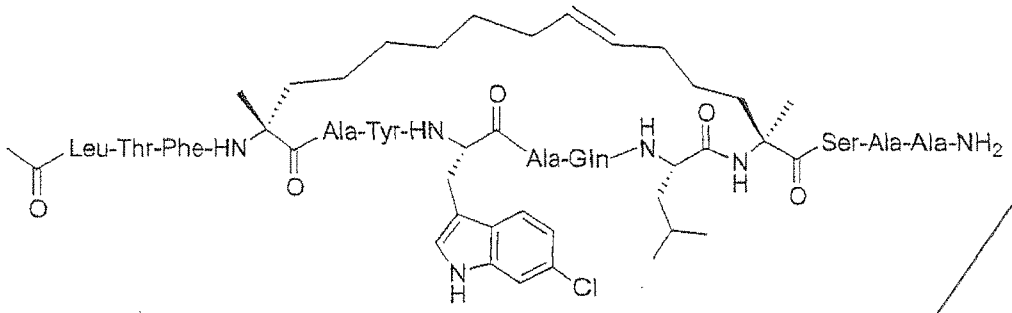
9. The peptidomimetic macrocycle of claim 1, having formula:



(SEQ ID NO: 123)

or a pharmaceutically acceptable salt thereof.

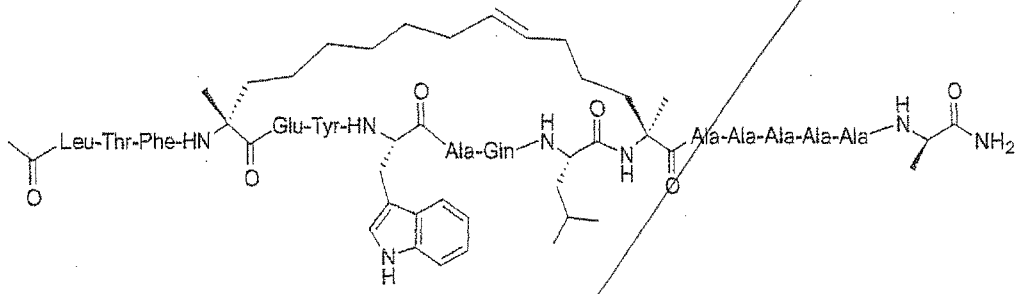
10. The peptidomimetic macrocycle of claim 1, having formula:



(SEQ ID NO: 108)

or a pharmaceutically acceptable salt thereof.

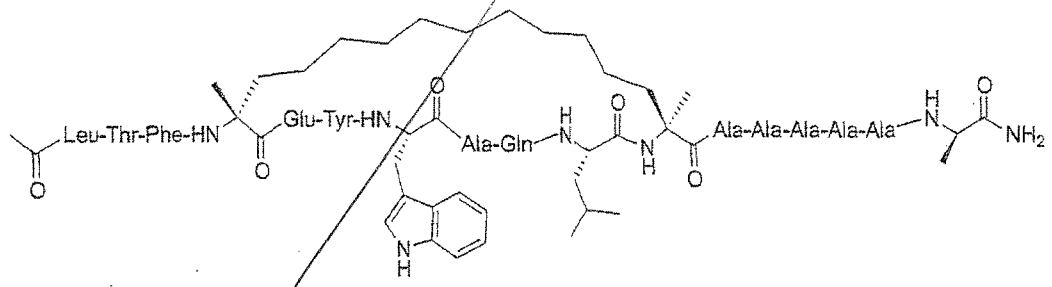
11. The peptidomimetic macrocycle of claim 1, having formula:



(SEQ ID NO: 340)

or a pharmaceutically acceptable salt thereof.

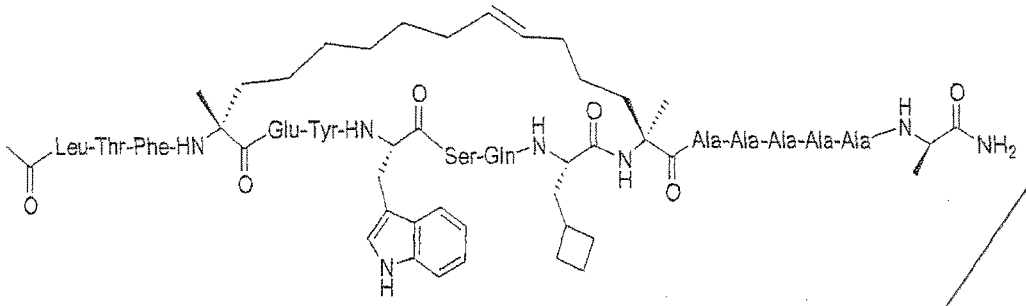
12. The peptidomimetic macrocycle of claim 1, having formula:



(SEQ ID NO: 454)

or a pharmaceutically acceptable salt thereof.

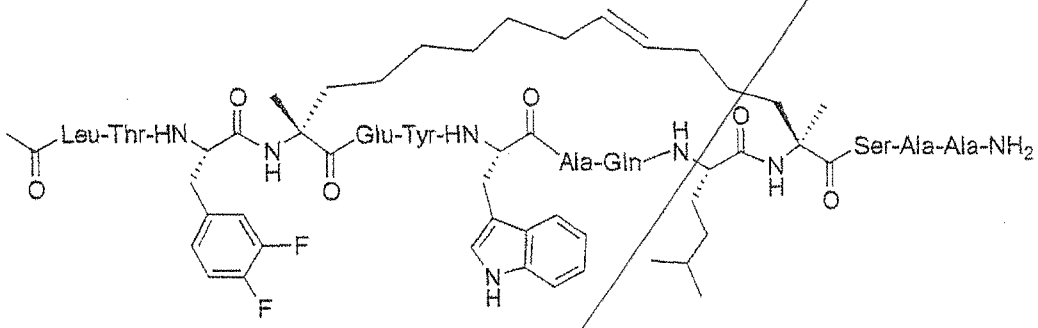
13. The peptidomimetic macrocycle of claim 1, having formula:



(SEQ ID NO: 360)

or a pharmaceutically acceptable salt thereof.

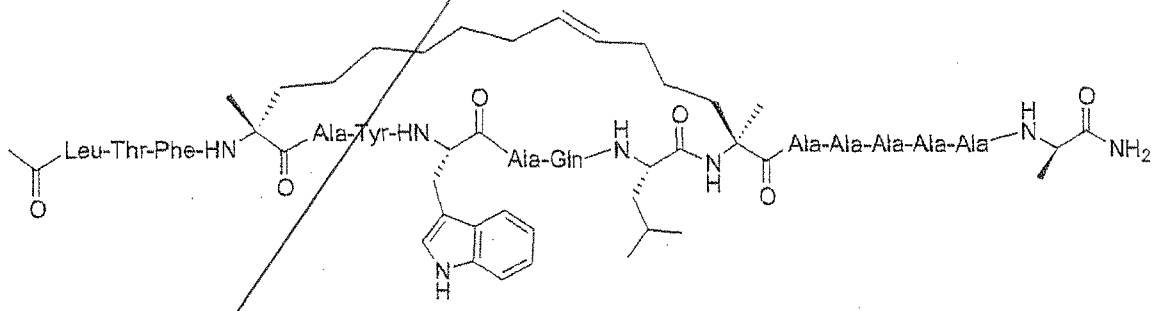
14. The peptidomimetic macrocycle of claim 1, having formula:



(SEQ ID NO: 169)

or a pharmaceutically acceptable salt thereof.

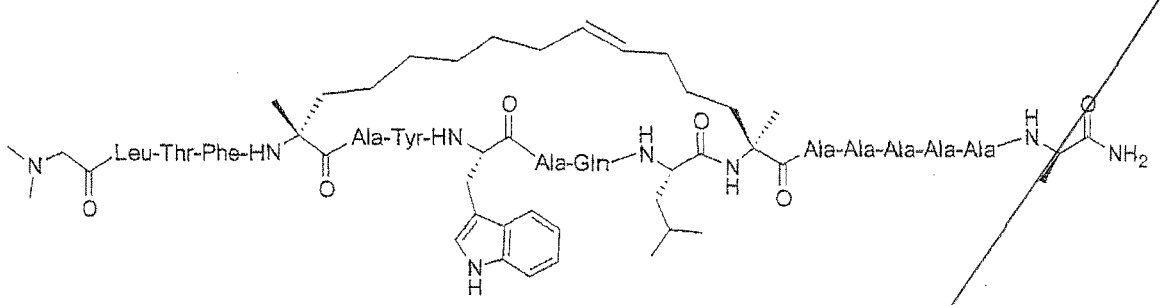
15. The peptidomimetic macrocycle of claim 1, having formula:



(SEQ ID NO: 324)

or a pharmaceutically acceptable salt thereof.

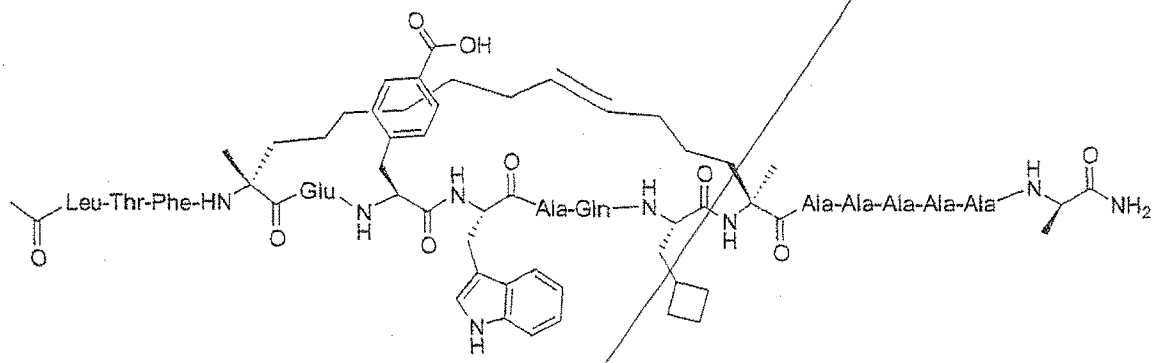
16. The peptidomimetic macrocycle of claim 1, having formula:



(SEQ ID NO: 446)

or a pharmaceutically acceptable salt thereof.

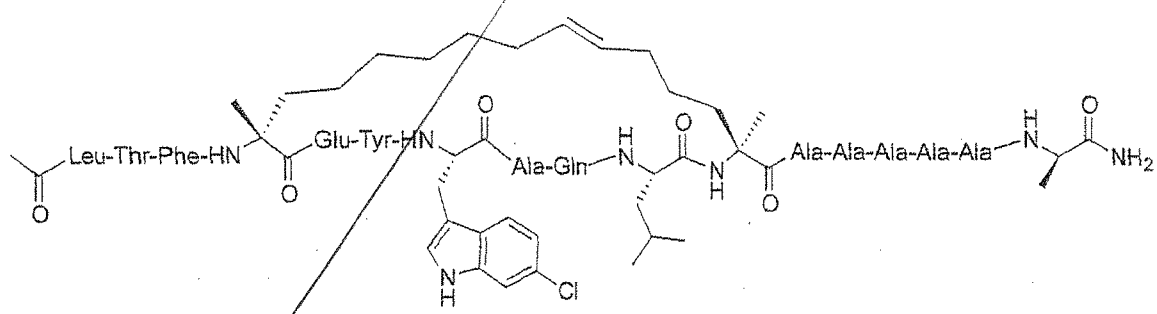
17. The peptidomimetic macrocycle of claim 1, having formula:



(SEQ ID NO: 358)

or a pharmaceutically acceptable salt thereof.

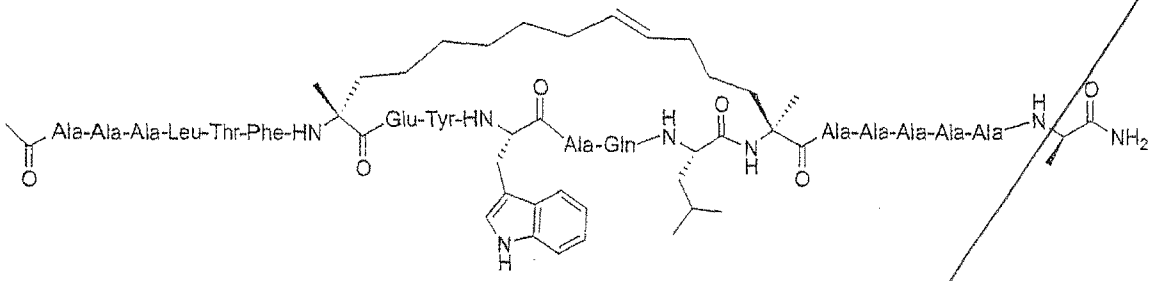
18. The peptidomimetic macrocycle of claim 1, having formula:



(SEQ ID NO: 464)

or a pharmaceutically acceptable salt thereof.

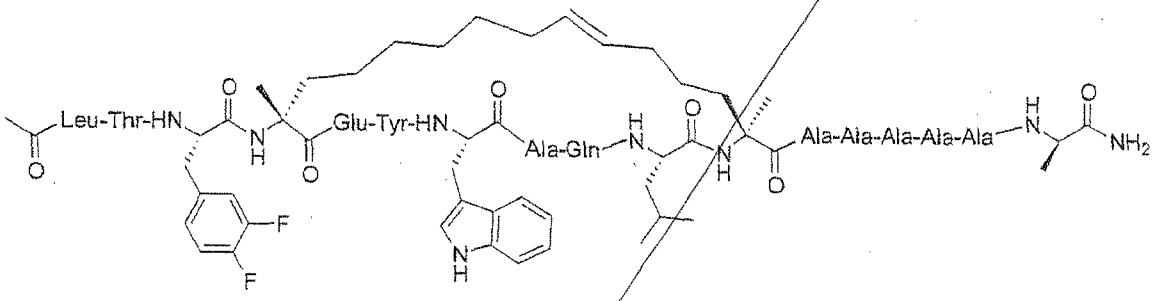
19. The peptidomimetic macrocycle of claim 1, having formula:



(SEQ ID NO: 466)

or a pharmaceutically acceptable salt thereof.

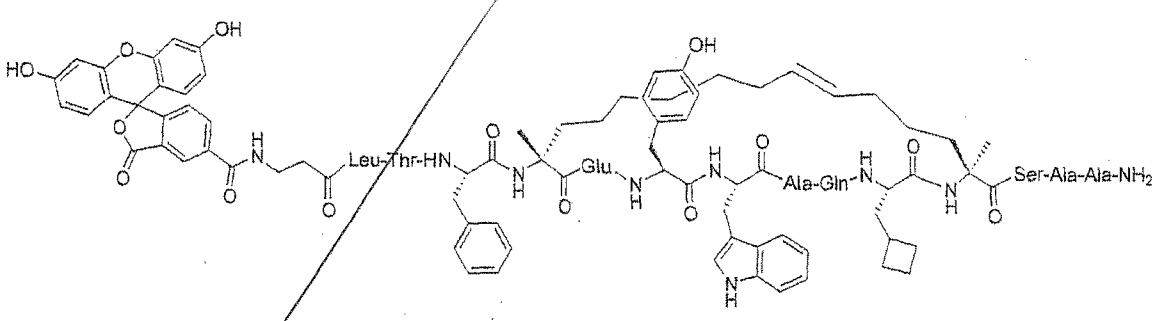
20. The peptidomimetic macrocycle of claim 1, having formula:



(SEQ ID NO: 467)

or a pharmaceutically acceptable salt thereof.

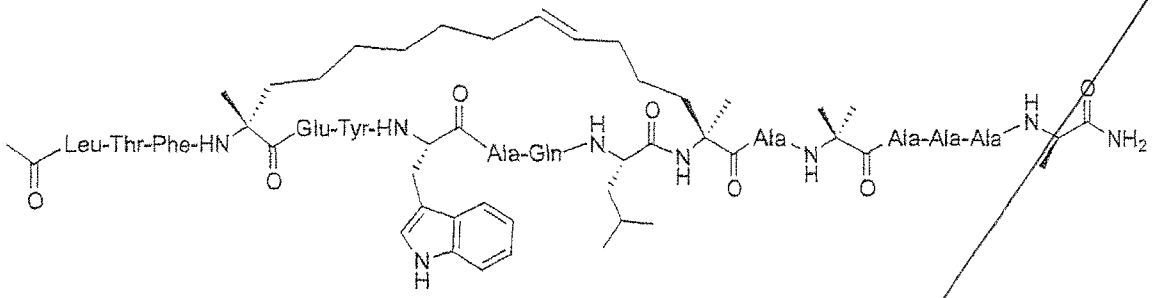
21. The peptidomimetic macrocycle of claim 1, having formula:



(SEQ ID NO: 376)

or a pharmaceutically acceptable salt thereof.

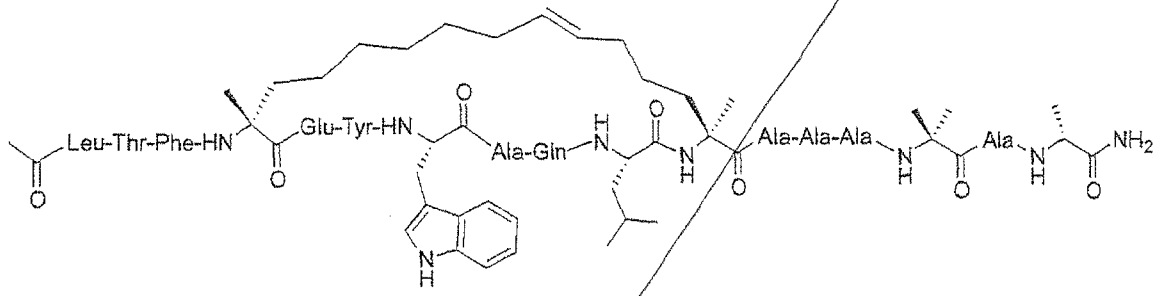
22. The peptidomimetic macrocycle of claim 1, having formula:



(SEQ ID NO: 471)

or a pharmaceutically acceptable salt thereof.

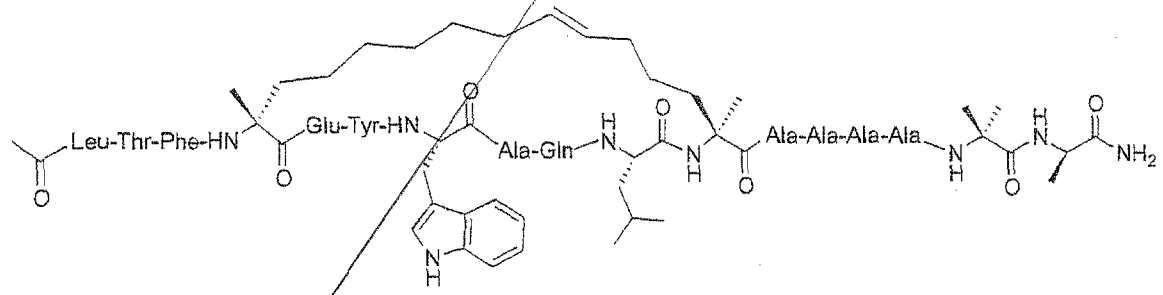
23. The peptidomimetic macrocycle of claim 1, having formula:



(SEQ ID NO: 473)

or a pharmaceutically acceptable salt thereof.

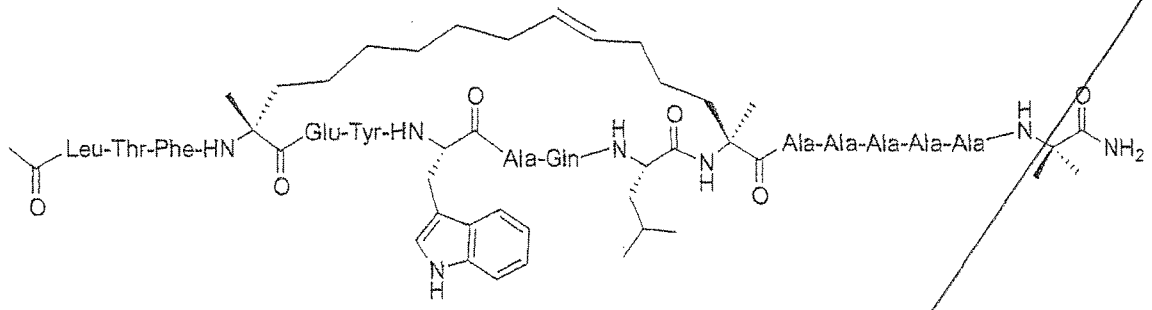
24. The peptidomimetic macrocycle of claim 1, having formula:



(SEQ ID NO: 475)

or a pharmaceutically acceptable salt thereof.

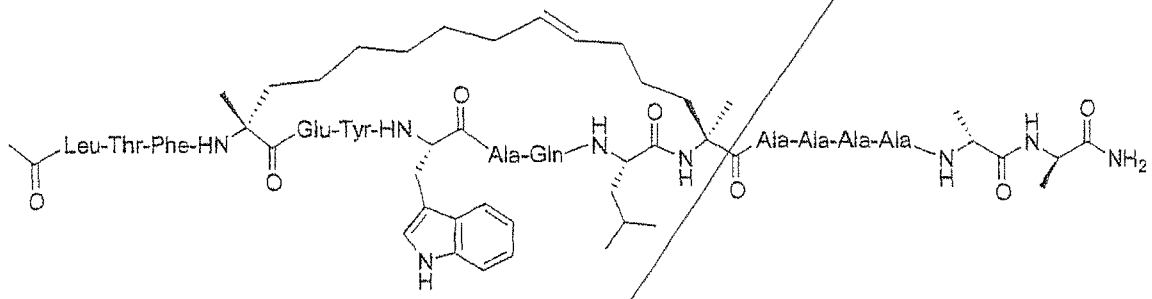
25. The peptidomimetic macrocycle of claim 1, having formula:



(SEQ ID NO: 476)

or a pharmaceutically acceptable salt thereof.

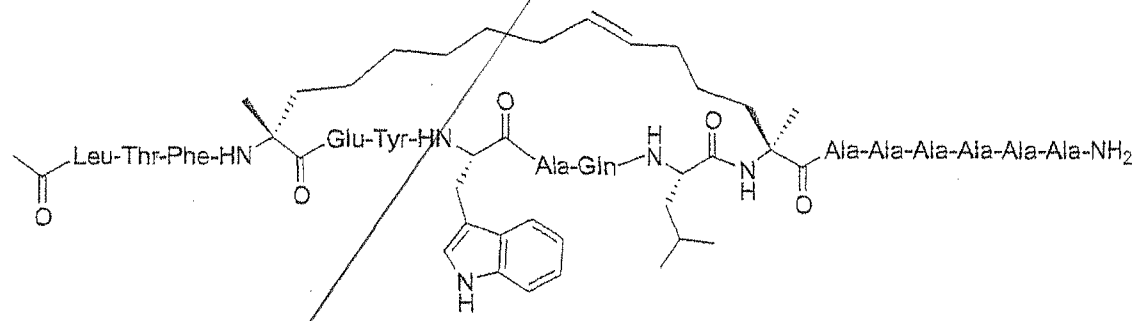
26. The peptidomimetic macrocycle of claim 1, having formula:



(SEQ ID NO: 481)

or a pharmaceutically acceptable salt thereof.

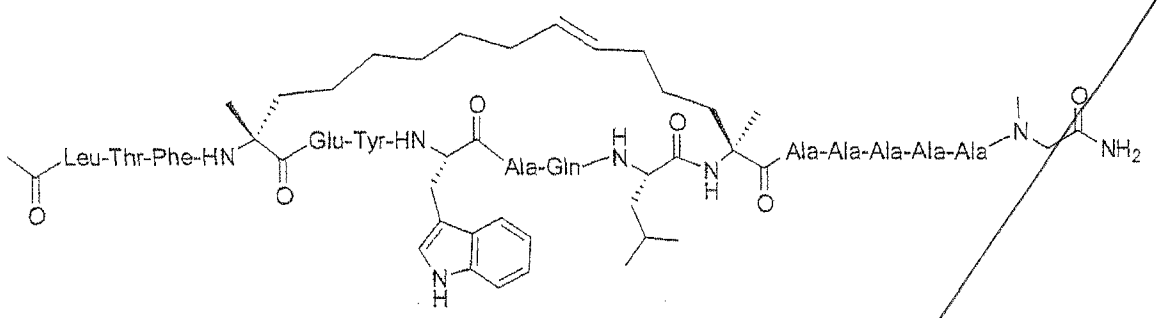
27. The peptidomimetic macrocycle of claim 1, having formula:



(SEQ ID NO: 482)

or a pharmaceutically acceptable salt thereof.

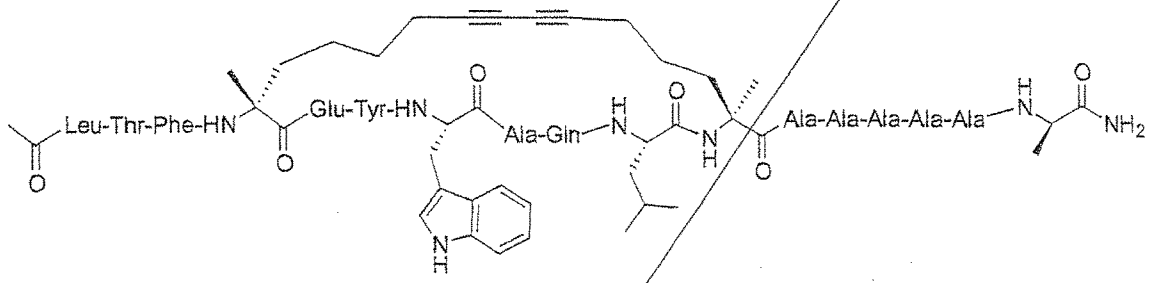
28. The peptidomimetic macrocycle of claim 1, having formula:



(SEQ ID NO: 487)

or a pharmaceutically acceptable salt thereof.

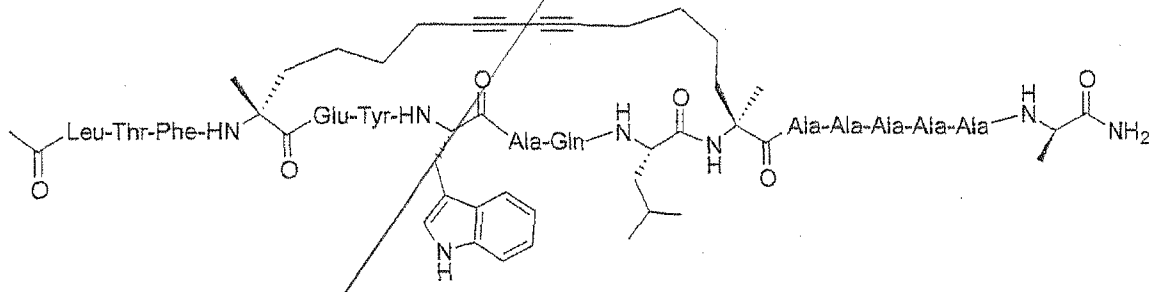
29. The peptidomimetic macrocycle of claim 1, having formula:



(SEQ ID NO: 572)

or a pharmaceutically acceptable salt thereof.

30. The peptidomimetic macrocycle of claim 1, having formula:



(SEQ ID NO: 1500)

or a pharmaceutically acceptable salt thereof.

31. The peptidomimetic macrocycle or pharmaceutically acceptable salt thereof of claim 1, wherein a first C–terminal amino acid represented by E comprises a hydrophobic side chain.

32. The peptidomimetic macrocycle or pharmaceutically acceptable salt thereof of claim 1, wherein w>1.

33. The peptidomimetic macrocycle or pharmaceutically acceptable salt thereof of claim 1, wherein a second C–terminal amino acid represented by E comprises a hydrophobic side chain.

34. The peptidomimetic macrocycle or pharmaceutically acceptable salt thereof of claim 1, wherein each of a two first amino acids represented by E is independently an amino acid comprising an uncharged side chain or an amino acid comprising a negatively charged side chain.

35. The peptidomimetic macrocycle or pharmaceutically acceptable salt thereof of claim 31, wherein the hydrophobic side chain is a small hydrophobic side chain.

36. The peptidomimetic macrocycle or pharmaceutically acceptable salt thereof of claim 1, wherein the peptidomimetic macrocycle or pharmaceutically acceptable salt thereof comprises an amino acid sequence which is at least about 80% identical to an amino acid sequence in any of Table 1, Table 1a, Table 1b, and Table 1c.

37. The peptidomimetic macrocycle or pharmaceutically acceptable salt thereof of claim 1, wherein the peptidomimetic macrocycle or pharmaceutically acceptable salt thereof comprises an amino acid sequence which is at least about 90% identical to an amino acid sequence in any of Table 1, Table 1a, Table 1b, and Table 1c.

38. The peptidomimetic macrocycle or pharmaceutically acceptable salt thereof of claim 1, wherein the peptidomimetic macrocycle or pharmaceutically acceptable salt thereof comprises an amino acid sequence which is at least about 95% identical to an amino acid sequence in any of Table 1, Table 1a, Table 1b, and Table 1c.

39. The peptidomimetic macrocycle or pharmaceutically acceptable salt thereof of claim 1, wherein each L_1 and L_2 and L_3 is independently alkylene, alkenylene, alkynylene, heteroalkylene, cycloalkylene, heterocycloalkylene, arylene, or heteroarylene, each being optionally substituted with R_5.

40. The peptidomimetic macrocycle or pharmaceutically acceptable salt thereof of claim 1, wherein each L_1 and L_2 and L_3 is independently alkylene or alkenylene.

41. The peptidomimetic macrocycle or pharmaceutically acceptable salt thereof of claim 1, wherein each L is independently alkylene, alkenylene, or alkynylene.

42. The peptidomimetic macrocycle or pharmaceutically acceptable salt thereof of claim 1, wherein each L is independently C_3–C_{16} alkylene, alkenylene, or alkynylene.

43. The peptidomimetic macrocycle or pharmaceutically acceptable salt thereof of claim 1, wherein L is C_{10}–C_{14} alkylene, alkenylene, or alkynylene.

4. The peptidomimetic macrocycle or pharmaceutically acceptable salt thereof of claim 1, wherein v ; 3.

5. The peptidomimetic macrocycle or pharmaceutically acceptable salt thereof of claim 1, wherein +y+z = 6, v is an integer from 1-10, w is an integer from 3-10, and u is 1.

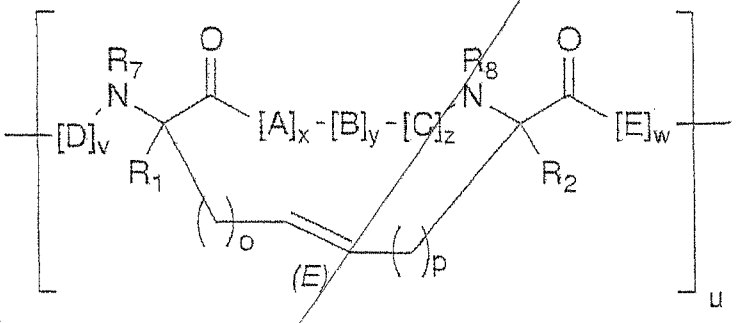
6. A pharmaceutical composition comprising the peptidomimetic macrocycle or pharmaceutically cceptable salt thereof of any one of claims 1-45, and a pharmaceutically acceptable carrier therefore.

7. Use of a peptidomimetic macrocycle of any one of claims 1-45, in the manufacture of a ıedicament for treating disease in a subject.

8. Use of a peptidomimetic macrocycle of any one of claims 1-45, in the manufacture of a ıedicament for modulating the activity of p53 and/or MDM2 and/or MDMX in a subject.

9. Use of a peptidomimetic macrocycle of any one of claims 1-45, in the manufacture of a ıedicament for antagonizing the interaction between p53 and MDM2 and/or between p53 and MDMX roteins.

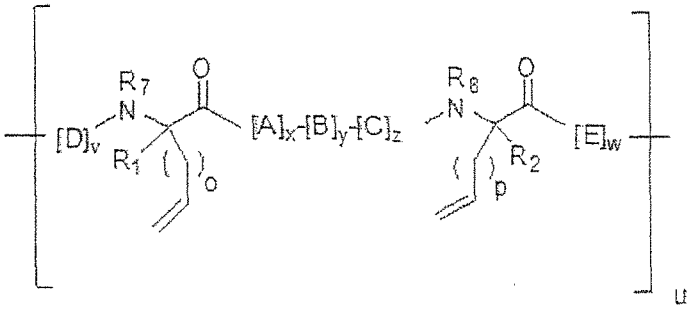
0. A method of preparing a composition comprising a peptidomimetic macrocycle of Formula (Ia):



Formula (Ia),

or a pharmaceutically acceptable salt thereof,

comprising an amino acid sequence which is about 60% to about 100% identical to an amino acid sequence in any of Table 1, Table 1a, Table 1b, and Table 1c, the method comprising treating a compound of Formula (II):



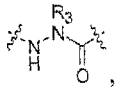
Formula (II),

or a pharmaceutically acceptable salt thereof,

with a catalyst to result in the compound of Formula (Ia) or pharmaceutically acceptable salt thereof;

wherein in the compound of Formula (Ia) or pharmaceutically acceptable salt thereof and in the compound of Formula (II) or pharmaceutically acceptable salt thereof:

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 hydrogen, alkyl, alkenyl, alkynyl, arylalkyl, cycloalkyl, cycloalkylalkyl, heteroalkyl, or heterocycloalkyl, unsubstituted or substituted with halogen; or forms a macrocycle–forming linker L' connected to the alpha position of one of the D or E amino acids;

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 $–L_1–L_2–$;

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

each R_4 and 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 hydrogen, alkyl, alkenyl, alkynyl, arylalkyl, cycloalkylalkyl, heterocycloalkyl, a fluorescent moiety, a radioisotope or a therapeutic agent;

each R_7 is independently hydrogen, 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 hydrogen, 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 is independently an integer from 1–1000;

each w is independently an integer from 1–1000;

u is an integer from 1–10;

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

each n is independently an integer from 1–5;

each o is independently an integer from 1 to 15;

each p is independently an integer from 1 to 15;

(E) represents a trans double bond or an *E*-double bond; and

one or more of A, B, and C has a side chain bearing a protecting group;

wherein a first C–terminal amino acid represented by E comprises a hydrophobic side chain, or when a w>1 a first or a second C–terminal amino acid represented by E comprises a hydrophobic side chain; and

wherein the peptidomimetic macrocycle or pharmaceutically acceptable salt thereof is not a peptidomimetic macrocycle of Tables 2a or 2b or pharmaceutically acceptable salt thereof.

51. The peptidomimetic macrocycle of claim 1, having an amino acid sequence of SEQ ID NO:570.