PEPTIDOMIMETIC MACROCYCLES AND USES THEREOF

CROSS-REFERENCE

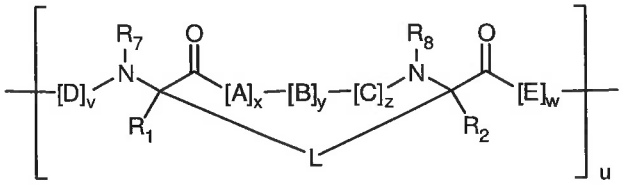
[0001] This application claims priority to U.S. Provisional Application No. 62/214,142, filed September 3, 2015; U.S. Provisional Application No. 62/310,254, filed March 18, 2016; U.S. Provisional Application No. 62/344,651, filed June 2, 2016; and U.S. Provisional Application No. 62/344,791, filed June 2, 2016, which are incorporated herein by reference in their entirety.

BACKGROUND OF THE INVENTION

[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) 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 (MDM4) 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. 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 p53 (F19, W23, and L26) are essential for binding to MDM2 and MDMX. There remains a considerable need for compounds capable of binding to and modulating the activity of p53, MDM2 and/or MDMX. Provided herein are p53-based peptidomimetic macrocycles that modulate an activity of p53. Also provided herein are p53-based peptidomimetic macrocycles that inhibit the interactions between p53, MDM2 and/or MDMX proteins. Further, provided herein are p53-based peptidomimetic macrocycles that can be used for treating diseases including but not limited to cancer and other hyperproliferative diseases.

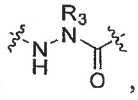
SUMMARY OF THE INVENTION

[0003] In one aspect, there is provided use of a therapeutically-effective amount of a peptidomimetic macrocycle or a pharmaceutically acceptable salt thereof and at least one additional pharmaceutically active agent in the manufacture of a medicament to treat hyperproliferative disease, cancers and neoplastic conditions characterized by aberrant activity of MDM2 and MDMX in a subject, wherein the peptidomimetic macrocycle is to be administered simultaneously or sequentially in combination with the at least one additional pharmaceutically active agent, wherein the peptidomimetic macrocycle comprises 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, and wherein the peptidomimetic macrocycle has the formula:



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 hydrogen, 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 and 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, arylene, heteroarylene, 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 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;

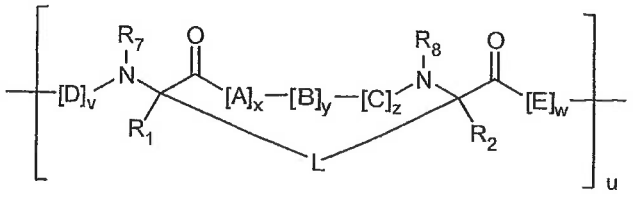
each w is independently an integer from 1–1000;

u is an integer from 1–10;

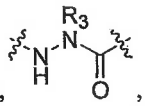
each x, y and z is independently an integer from 0–10; and

each n is independently an integer from 1–5;

wherein the peptidomimetic macrocycle is not a peptidomimetic macrocycle of Tables 2a or 2b, wherein the at least one additional pharmaceutically active agent is fulvestrant, everolimus, romidepsin, palbociclib, trametinib, rituximab, dabrafenib, vemurafenib, azacitidine, decitabine, midostaurin, vincristine, cyclophosphamide or cytarabine. In one example, the disclosure provides a method of treating cancer in a subject in need thereof, the method comprising administering to the subject a therapeutically effectiveamount of a peptidomimetic macrocycle and at least one additional pharmaceutically active agent, wherein the peptidomimetic macrocycle has a Formula:



wherein:

- each A, C, D, and E is independently a natural or non-natural amino acid or an amino acid analog, and each terminal D and E independently optionally includes a capping group;
- each B is independently a natural or non-natural amino acid, an 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–; 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 is independently –H, 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, 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 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 and w is independently an integer from 1-1000, for example 1-500, 1-200, 1-100, 1-50, 1-30, 1-20, or 1-10;
- u is an integer from 1-10, for example 1-5, 1-3 or 1-2;
- each x, y and z is independently an integer from 0-10, for example the sum of x+y+z is 2, 3, or 6; and
- n is an integer from 1-5.

[0004] In some examples, w>2 and each of the first two amino acid represented by E comprises an uncharged side chain or a negatively charged side chain.

[0005] In some examples, the first C-terminal amino acid and/or the second C-terminal amino acid represented by E comprise a hydrophobic side chain. For example, the first C-terminal amino acid and/or the

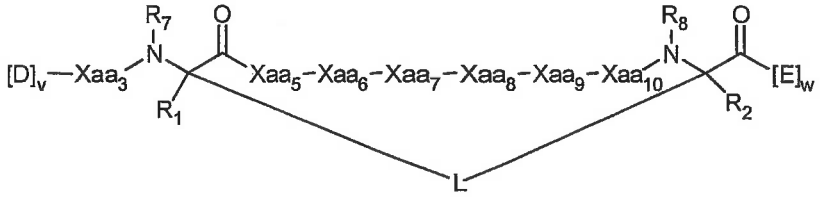
second C-terminal amino acid represented by E comprises a hydrophobic side chain, for example a large hydrophobic side chain.

[0006] In some examples, w is between 3 and 1000. For example, the third amino acid represented by E comprises a large hydrophobic side chain.

[0007] In other examples, the peptidomimetic macrocycle excludes the sequence of: Ac-RTQATF$r8NQWAibANle$TNAibTR-NH_2, Ac-RTQATF$r8NQWAibANle$TNAibTR-NH_2, Ac-$r8SQQTFS$LWRLLAibQN-NH_2, Ac-QSQ$r8TFSNLW$LLAibQN-NH_2, Ac-QS$r5QTFStNLW$LLAibQN-NH_2, or Ac-QSQQ$r8FSNLWR$LAibQN-NH_2.

[0008] In other examples, the peptidomimetic macrocycle excludes the sequence of: Ac-Q$r8QQTFSN$WRLLAibQN-NH_2.

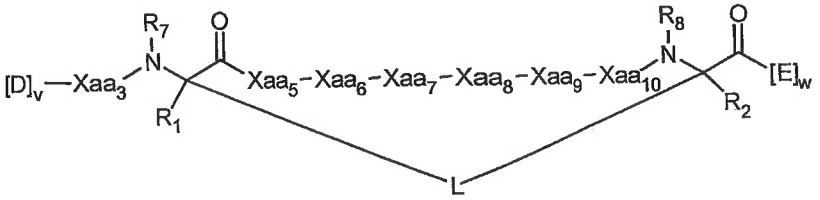
[0009] In another example, the disclosure provides a method of treating cancer in a subject in need thereof, the method comprising administering to the subject a therapeutically effective amount of a peptidomimetic macrocycle and at least one additional pharmaceutically active agent, wherein the peptidomimetic macrocycle has a formula:



- 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}, wherein each X is an amino acid;
- each D and E is independently an amino acid;
- 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 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, arylene, heteroarylene, 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;

- R_7 is –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;
- R_8 is –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;
- 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
- n is an integer from 1-5.

[0010] In another example, the disclosure provides a method of treating cancer in a subject in need thereof, the method comprising administering to the subject a therapeutically effective amount of a peptidomimetic macrocycle and at least one additional pharmaceutically active agent, wherein the peptidomimetic macrocycle has a Formula:

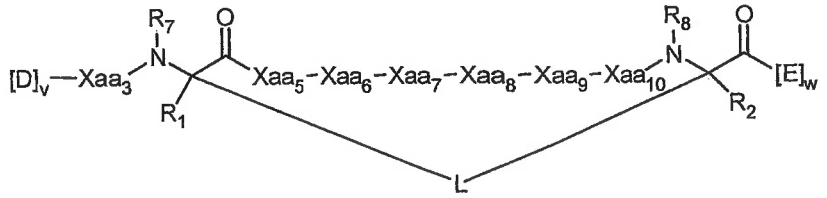


wherein:

- 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-Glu_5-Tyr_6-Trp_7-Ala_8-Gln_9-Leu_{10}/Cba_{10}-X_{11}-Ala_{12}, wherein 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);
- 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 and L' is independently a macrocycle-forming linker of the formula $–L_1–L_2–$;
- each L_1 and L_2 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_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, aryl, or heteroaryl, 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, 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
- n is an integer from 1-5.

[0011] In another example, the disclosure provides a method of treating cancer in a subject in need thereof, the method comprising administering to the subject a therapeutically effective amount of a peptidomimetic macrocycle and at least one additional pharmaceutically active agent, wherein the peptidomimetic macrocycle has a Formula:



[0012] In some examples of any of the Formulas described herein, $[D]_v$ is $-Leu_1-Thr_2$. In other examplesof the Formulas described herein, each E other than the third amino acid represented by E is an amino acid selected from Ala (alanine), D-Ala (D-alanine), Aib (α-aminoisobutyric acid), Sar (N-methyl glycine), and Ser (serine).

[0013] In some examples, w is an integer from 3-10, for example 3-6, 3-8, 6-8, or 6-10. In some examples, w is 3. In other examples, w is 6. In some examples, v is an integer from 1-10, for example 2-5. In some examples, v is 2.

[0014] In some examples, peptides disclosed herein bind a binding site defined at least in part by the MDMX amino acid side chains of L17, V46, M50, Y96 (forming the rim of the pocket) and L99. Without being bound by theory, binding to such a binding site improves one or more properties such as binding affinity, induction of apoptosis, *in vitro* or *in vivo* anti-tumor efficacy, or reduced ratio of binding affinities to MDMX versus MDM2.

[0015] *In some examples, the peptidomimetic macrocycle has improved binding affinity to MDM2 or MDMX* relative to a corresponding peptidomimetic macrocycle wherein w is 0, 1 or 2. In other instances, the peptidomimetic macrocycle 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 still other instances, the peptidomimetic macrocycle has improved *in vitro* anti-tumor efficacy against p53 positive tumor cell lines relative to a corresponding peptidomimetic macrocycle wherein w is 0, 1 or 2. In some examples, the peptidomimetic macrocycle shows improved *in vitro* induction of apoptosis in p53 positive tumor cell lines relative to a corresponding peptidomimetic macrocycle wherein w is 0, 1 or 2. In other instances, the peptidomimetic macrocycle of claim 1, wherein the peptidomimetic macrocycle has an improved *in vitro* anti-tumor efficacy

ratio for p53 positive versus p53 negative or mutant tumor cell lines relative to a corresponding peptidomimetic macrocycle wherein w is 0, 1 or 2. In some instances the improved efficacy ratio *in vitro*, is 1-29, ≥30-49, or ≥50. In still other instances, the peptidomimetic macrocycle has improved *in vivo* anti-tumor efficacy against p53 positive tumors relative to a corresponding peptidomimetic macrocycle wherein w is 0, 1 or 2. In some instances the improved efficacy ratio *in vivo* is -29, ≥30-49, or ≥50. In yet other instances, the peptidomimetic macrocycle has improved *in vivo* induction of apoptosis in p53 positive tumors relative to a corresponding peptidomimetic macrocycle wherein w is 0, 1 or 2. In some examples, the peptidomimetic macrocycle has improved cell permeability relative to a corresponding peptidomimetic macrocycle wherein w is 0, 1 or 2. In other cases, the peptidomimetic macrocycle has improved solubility relative to a corresponding peptidomimetic macrocycle wherein w is 0, 1 or 2. Exemplary cell lines include of MCF-7, HCT-116, MV4-11, DOHH2, MEL-HO, MEL-JUSO, SK-MEL-5, HT1080, MES-SA, SR, MDA-MB-134-VI, ZR-75-1, A427, A549, MOLM-13, SJSA-1, U2OS, RKO, A498, Caki-2, 22RV1, MSTO-211H, C3A, AGS, SNU-1, RMG-1, HEC-151, HEC-265, MOLT-3 and A375 cell lines.

[0016] In some examples, Xaa_5 is Glu or an amino acid analog thereof. In some examples, Xaa_5 is Glu or an amino acid analog thereof and wherein the peptidomimetic macrocycle has an improved property, such as improved binding affinity, improved solubility, improved cellular efficacy, improved cell permeability, improved *in vivo* or *in vitro* anti-tumor efficacy, or improved induction of apoptosis relative to a corresponding peptidomimetic macrocycle wherein Xaa_5 is Ala.

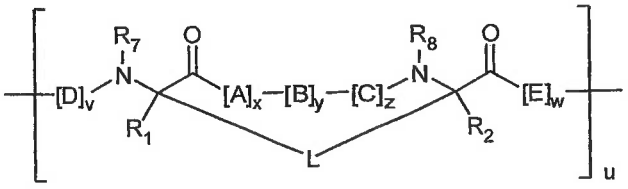
[0017] In some examples, the peptidomimetic macrocycle has improved binding affinity to MDM2 or MDMX relative to a corresponding peptidomimetic macrocycle wherein Xaa_5 is Ala. In other examples, the peptidomimetic macrocycle has a reduced ratio of binding affinities to MDMX vs MDM2 relative to a corresponding peptidomimetic macrocycle wherein Xaa_5 is Ala. In some examples, the peptidomimetic macrocycle has improved solubility relative to a corresponding peptidomimetic macrocycle wherein Xaa_5 is Ala, or the peptidomimetic macrocycle has improved cellular efficacy relative to a corresponding peptidomimetic macrocycle wherein Xaa_5 is Ala.

[0018] In some examples, Xaa_5 is Glu or an amino acid analog thereof and wherein the peptidomimetic macrocycle has improved biological activity, such as improved binding affinity, improved solubility, improved cellular efficacy, improved helicity, improved cell permeability, improved *in vivo* or *in vitro* anti-tumor efficacy, or improved induction of apoptosis relative to a corresponding peptidomimetic macrocycle wherein Xaa_5 is Ala.

[0019] In some examples, the peptidomimetic macrocycle has an activity against a p53+/+ cell line which is at least 2-fold, 3-fold, 5-fold, 10-fold, 20-fold, 30-fold, 50-fold, 70-fold, or 100-fold greater than its binding affinity against a p53-/- cell line. In some examples, the peptidomimetic macrocycle has an activity against a p53+/+ cell line which is between 1 and 29-fold, between 30 and 49-fold, or ≥50-fold greater than its binding affinity against a p53-/- cell line. Activity can be measured, for example, as an IC50 value. For example, the p53+/+ cell line is SJSA-1, RKO, HCT-116, or MCF-7 and the p53-/- cell line is RKO-E6 or SW-480. In some examples, the peptide has an IC50 against the p53+/+ cell line of less than 1 μM.

[0020] In some examples, Xaa_5 is Glu or an amino acid analog thereof and the peptidomimetic macrocycle has an activity against a p53+/+ cell line which is at least 10-fold greater than its binding affinity against a p53-/- cell line.

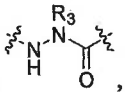
[0021] In another example, the disclosure provides a method of modulating the activity of p53 and/or MDM2 and/or MDMX in a subject in need thereof comprising administering to the subject a therapeutically-effective amount of a peptidomimetic macrocycle and at least one additional pharmaceutically active agent, wherein the peptidomimetic macrocycle comprises 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)

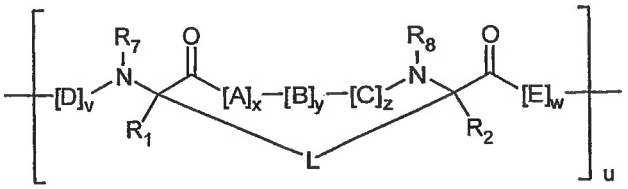
or pharmaceutically acceptable salt thereof,

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 hydrogen, 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 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, arylene, heteroarylene, 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 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; and
- each n is independently an integer from 1–5.

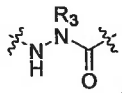
[0022] In another example, the disclosure provides a method of antagonizing an interaction between p53 and MDM2 proteins and/or between p53 and MDMX proteins in a subject in need thereof comprising administering to the subject a therapeutically-effective amount of a peptidomimetic macrocycle and at least one additional pharmaceutically active agent, wherein the peptidomimetic macrocycle comprises 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 and wherein the peptidomimetic macrocycle has the formula:



Formula (I)

or pharmaceutically acceptable salt thereof,

wherein:

- each A, C, D, and E is independently a natural or non-natural amino acid or an amino acid analog, and each terminal D and E independently optionally includes a capping group;
- each B is independently a natural or non-natural amino acid, an 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–; 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 and 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, arylene, heteroarylene, 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 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; and
- each n is independently an integer from 1–5.

[0023] In some examples, the cancer is selected from the group consisting of head and neck cancer, melanoma, lung cancer, breast cancer, colon cancer, ovarian cancer, NSCLC, stomach cancer, prostate cancer, leukemia, lymphoma, mesothelioma, renal cancer, non-Hodgkin lymphoma (NHL), and glioma.

[0024] In some examples, the at least one additional pharmaceutically active agent is a nucleoside metabolic inhibitor, a microtubule inhibitor, a platinum-based drug, a hypomethylating agent, a protein kinase inhibitor, a bruton's tyrosine kinase inhibitor, a CDK4 and/or CDK6 inhibitor, a B-raf inhibitor, a K-ras inhibitor, a MEK-1 and/or MEK-2 inhibitor, an estrogen receptor antagonist, an HDAC inhibitor, an anti-CD20 monoclonal antibody, an anti-PD-1 monoclonal antibody, a hormonal antagonist, an agent the alleviates CDK2NA deletion, an agent that alleviates CDK9 abnormality, an AMT regulator, an agent that alleviates AKT activation, an agent that alleviates PTEN deletion, an agent that alleviates Wip-1Alpha overexpression, an agent that upregulates BIM, or an aromatase inhibitor.

[0025] In some examples, the at least one additional pharmaceutically active agent binds to or modulates B-raf. In some examples, the at least one additional pharmaceutically active agent is a B-raf inhibitor. In some examples, the B-raf inhibitor is vemurafenib, dabrafenib, trametinib, sorafenib, C-1, or NVP-LGX818. In some examples, the B-raf inhibitor is vemurafenib or dabrafenib and the cancer is melanoma.

[0026] In some examples, the at least one additional pharmaceutically active agent is a nucleoside metabolic regulator or modulator. In some examples, the at least one additional pharmaceutically active

agent is a nucleoside metabolic inhibitor. In some examples, the nucleoside metabolic inhibitor is capecitabine, gemcitabine or cytarabine. In some examples, the nucleoside metabolic inhibitor is capecitabine and the cancer is colon or breast cancer. In some examples, the nucleoside metabolic inhibitor is gemcitabine and the cancer is ovarian, NSCLC, or breast cancer. In some examples, the nucleoside metabolic inhibitor is cytarabine and the cancer is Leukemia or Lymphoma.

[0027] In some examples, the at least one additional pharmaceutically active agent is an estrogen receptor antagonist. In some examples, the estrogen receptor antagonist is fulvestrant. In some embodiments, the cancer is breast cancer. In some examples, the cancer is an estrogen receptor positive breast cancer. In some examples, the cancer is a Her2 negative positive breast cancer.

[0028] In some examples, the at least one additional pharmaceutically active agent is a microtubule regulator or modulator. In some examples, the at least one additional pharmaceutically active agent is a microtubule inhibitor. In some examples, the microtubule inhibitor is paclitaxel, abraxane or docetaxel. In some examples, the microtubule inhibitor is paclitaxel and the cancer is ovarian cancer. In some examples, the microtubule inhibitor is abraxane and the cancer is ovarian cancer. In some examples, the microtubule inhibitor is docetaxel and the cancer is NSCLC, breast cancer, prostate cancer or stomach cancer.

[0029] In some examples, the at least one additional pharmaceutically active agent is a platinum-based drug. In some examples, the platinum-based drug is carboplatin or cisplatin. In some examples, the platinum-based drug is carboplatin and the cancer is NSCLC or ovarian cancer. In some examples, the platinum-based drug is cisplatin and the cancer is NSCLC, mesothelioma or ovarian cancer.

[0030] In some examples, the at least one additional pharmaceutically active agent is a hypomethylating agent. In some examples, the hypomethylating agent is azacitidine or dacogen. In some examples, the hypomethylating agent is azacitidine or dacogen and the cancer is myelodysplastic syndrome.

[0031] In some examples, the at least one additional pharmaceutically active agent binds to or modulates a protein kinase. In some examples, the additional pharmaceutically active is a protein kinase inhibitor. In some examples, the protein kinase inhibitor is sorafenib, midostaurin (PKC412), or quizartinib. In some examples, the protein kinase inhibitor is sorafenib and the cancer is kidney or liver cancer.

[0032] In some examples, the at least one additional pharmaceutically active agent binds to or modulates a bruton's tyrosine kinase. In some examples, the at least one additional pharmaceutically active agent is a bruton's tyrosine kinase inhibitor. In some examples, the bruton's tyrosine kinase inhibitor is ibrutinib. In some examples, the bruton's tyrosine kinase inhibitor is ibrutinib and the cancer is non-Hodgkin lymphoma (NHL).

[0033] In someexamples, the bruton's tyrosine kinase inhibitor is ibrutinib and the cancer is non-Hodgkin lymphoma (NHL). In some examples, the at least one additional pharmaceutically active agent binds to or modulates CDK4 and/or CDK6. In some examples, the at least one additional pharmaceutically active agent is a CDK4 and/or CDK6 inhibitor. In some examples, the CDK4 and/or CDK6 inhibitor is palbociclib. In someexamples, the CDK4 and/or CDK6 inhibitor is palbociclib and the cancer is breast cancer. In some

examples, the cancer is breast cancer. In some examples, the cancer is an estrogen receptor positive breast cancer. In some examples, the cancer is a Her2 negative positive breast cancer.

[0034] In some examples, the at least one additional pharmaceutically active agent binds to or modulates MEK-1 and/or MEK-2. In some examples, the at least one additional pharmaceutically active agent is a MEK-1 and/or MEK-2 inhibitor. In some examples, the MEK-1 and/or MEK-2 inhibitor is trametinib, pimasertib, or PD0325901. In some examples, the MEK-1 and/or MEK-2 inhibitor is trametinib and the cancer is melanoma. In some examples, the MEK-1 and/or MEK-2 inhibitor is pimasertib. In some examples, the MEK-1 and/or MEK-2 inhibitor is pimasertib and the cancer is NSCLC. In some examples, the MEK-1 and/or MEK-2 inhibitor is PD0325901.

[0035] In some examples, the at least one additional pharmaceutically active agent is an anti-CD20 monoclonal antibody. In some examples, the anti-CD20 monoclonal antibody is rituximab or obinutuzumab. In some examples, the cancer is NHL or a B-cell lymphoma.

[0036] In some examples, the at least one additional pharmaceutically active agent is an anti-PD-1 monoclonal antibody. In some examples, the anti-PD-1 monoclonal antibody is pembrolizumab or nivolumab. In some examples, the anti-PD-1 monoclonal antibody is pembrolizumab or nivolumab and the cancer is melanoma or NSCLC.

[0037] In some examples, the at least one additional pharmaceutically active agent is an aromatase inhibitor. In some examples, the aromatase inhibitor is letrozole or exemestane. In some embodiments, the aromatase inhibitor is letrozole or exemestane and the cancer is breast cancer.

[0038] In some examples, the at least one additional pharmaceutically active agent binds to or modulates topoisomerase I or II. In some examples, the at least one additional pharmaceutically active agent is an inhibitor of topoisomerase I or II. In some examples, the at least one additional pharmaceutically active agent is topotecan, rinotecan, idarubicin, teniposide or epirubicin. In some examples, the at least one additional pharmaceutically active agent is topotecan, rinotecan or epirubicin.

[0039] In some examples, the at least one additional pharmaceutically active agent binds to or modulates BCR-ABL kinase or BCR-ABL and Src family tyrosine kinase. In some examples, the at least one additional pharmaceutically active agent is an inhibitor of BCR-ABL kinase or BCR-ABL and Src family tyrosine kinase. In some examples, the at least one additional pharmaceutically active agent is nilotinib, bosutinib, dasatinib or imatinib.

[0040] In some examples, the at least one additional pharmaceutically active agent binds to or modulates PI3K. In someexamples, the at least one additional pharmaceutically active agent is a PI3K inhibitor. In some examples, the at least one additional pharmaceutically active agent is GDC-0941 or AMG511.

[0041] In some examples, the at least one additional pharmaceutically active agent is a hormone antagonist. In some examples, the at least one additional pharmaceutically active agent is letrozole or casodex. In some examples, the at least one additional pharmaceutically active agent is fluoroucil. In some examples, the at least one additional pharmaceutically active agent is a purine analog.

[0042] In some examples, the at least one additional pharmaceutically active agent binds to or modulates mTOR. In some examples, the at least one additional pharmaceutically active agent is an mTOR inhibitor. In some examples, the at least one additional pharmaceutically active agent is AD8005. In some examples, the at least one additional pharmaceutically active agent is everolimus. In some examples, the cancer is breast cancer. In some examples, the cancer is an estrogen receptor positive breast cancer. In some examples, the cancer is a Her2 negative positive breast cancer. In some examples, the at least one additional pharmaceutically active agent binds to or modulates both PI3K/mTOR kinase. In some examples, the at least one additional pharmaceutically active agent is a dual PI3K/mTOR kinase inhibitor. In some examples, the at least one additional pharmaceutically active agent is BEZ235.

[0043] In some examples, the at least one additional pharmaceutically active agent binds to or modulates both BCL-2 and/or BCL-XL. In some examples, the at least one additional pharmaceutically active agent is BCL-2 and/or BCL-XL inhibitor. In some examples, the at least one additional pharmaceutically active agent is venetoclax (ABT-199) or ABT-263. In some examples, the at least one additional pharmaceutically active agent is a purine analog. In some examples, the at least one additional pharmaceutically active agent is fludarabine.

[0044] In some examples, the at least one additional pharmaceutically active agent binds to or modulates wild type or mutant K-ras.

[0045] In some examples, the at least one additional pharmaceutically active agent is radiation.

[0046] In some examples, the at least one additional pharmaceutically active agent is a multi-targeted tyrosine kinase modulator or binder. In some examples, the at least one additional pharmaceutically active agent is multi-targeted tyrosine kinase inhibitor. In some examples, the at least one additional pharmaceutically active agent is ponatinib.

[0047] In some examples, the at least one additional pharmaceutically active agent is a pan-histone deacetylase (HDAC) modulator or binder. In some examples, the at least one additional pharmaceutically active agent is a pan-histone deacetylase (HDAC) inhibitor. In some examples, the at least one additional pharmaceutically active agent is romidepsin. In some examples, the at least one additional pharmaceutically active agent is panobinostat. In some examples, the cancer is adult T cell leukemia/lymphoma (ATL), cutaneous T-cell lymphoma (CTCL), or peripheral T-cell lymphoma (PTCL).

[0048] In some examples, the at least one additional pharmaceutically active agent binds to or modulates AKT kinase. In some examples, the at least one additional pharmaceutically active agent is an AKT kinase inhibitor. In some examples, the at least one additional pharmaceutically active agent is a MK-2206.

[0049] In some examples, the at least one additional pharmaceutically active agent alleviates CDKN2A (cyclin-dependent kinase inhibitor 2A) deletion. In some examples, the at least one additional pharmaceutically active agent alleviates CDK9 (cyclin-dependent kinase 9) abnormality. In some examples, the at least one additional pharmaceutically active agent alleviates ATM deficiency. In some examples, the at least one additional pharmaceutically active agent alleviates AKT activation. In some

examples, the at least one additional pharmaceutically active agent alleviates PTEN deletion. In some examples, the at least one additional pharmaceutically active agent alleviates Wip-1Alpha over expression.

[0050] In some examples, the at least one additional pharmaceutically active agent upregulates BIM or is a BIM mimetic. In some examples, the at least one additional pharmaceutically active agent is pegylated IFN2a, vinblastine, dexamethasone, or asparaginase. In some examples, the at least one additional pharmaceutically active agent is dexamethasone. In some examples, the cancer is a B-cell lymphoma.

[0051] In some examples, the peptidomimetic macrocycle and the additional pharmaceutically active agent are present in a single formulation. In some examples, the peptidomimetic macrocycle and the additional pharmaceutically active agent are present in two different formulations. In some examples, the two different formulations are administered simultaneously. In some examples, the two different formulations are administered sequentially. In some examples, a sub-therapeutic amount of the additional therapeutic agent is administered. In some examples, a therapeutically effective amount of the additional therapeutic agent is administered.

[0052] In some examples, the subject comprises cancer cells that overexpress PD-L1. In some examples, the subject comprises cancer cells that overexpress PD-1. In some examples, the subject comprises cancer cells that overexpress miR-34. In some examples, the at least one additional pharmaceutically active agent is a PD-1 antagonist. In some examples, the at least one additional pharmaceutically active agent is a PD-L1 antagonist. In some examples, the at least one additional pharmaceutically active agent is an agent that blocks the binding of PD-L1 to PD-1. In some examples, the at least one additional pharmaceutically active agent specifically binds to PD-1. In some examples, the at least one additional pharmaceutically active agent specifically binds to PD-L1. In some examples, PD-L1 expression is downregulated. In some examples, PD-1 expression is downregulated.

[0053] In some examples, the at least one additional pharmaceutically active agent is selected from the group consisting of venetoclax (ABT-199), clofarabine, cyclophosphamide, cytarabine, doxorubicin, imatinib mesylate, methotrexate, prednisone, vincristine, azacitadine, cyclophosphamide, cytarabine, dabrafenib, decitabine, doxorubicin, etoposide, vincristine, doxorubicin, methotrexate, capecitabine, cyclophosphamide, docetaxel, doxorubicin, eribulin mesylate, everolimus, exemestane, fluorouracil, fluorouracil, fulvestrant, gemcitabine, goserelin acetate, letrozole, megestrol acetate, methotrexate, paclitaxel, palbociclib, pertuzumab, tamoxifen citrate, trastuzumab, capecitabine, cetuximab, fluorouracil, irinotecan, ramucirumab, carboplatin, cisplatin, doxorubicin, megestrol acetate, paclitaxel, docetaxel, doxorubicin, fluorouracil, ramucirumab, trastuzumab, axitinib, everolimus, pazopanib, sorafenib tosylate, sorafenib tosylate, dacarbazine, paclitaxel, trametinib, vemurafenib, cisplatin, pemetrexed, bendamustine, bortezomib, brentuximab vedotin, chlorambucil, cyclophosphamide, dexamethasone, doxorubicin, ibrutinib, lenalidomide, methotrexate, prednisone, rituximab, vincristine, afatinib dimaleate, carboplatin, cisplatin, crizotinib, docetaxel, erlotinib, gemcitabine, methotrexate, paclitaxel, pemetrexed, ramucirumab, carboplatin, cisplatin, cyclophosphamide, gemcitabine, olaparib, paclitaxel, topotecan, abiraterone, cabazitaxel, docetaxel, enzalutamide, goserelin

acetate, prednisone, doxorubicin, imatinib mesylate, romidepsin, obinutuzumab, pazopanib, and combinations thereof.

[0054] In some examples, the at least one additional pharmaceutically active agent inhibits S-phase. In some examples, the at least one additional pharmaceutically active agent inhibits M-phase.

[0055] In some examples, the peptidomimetic macrocycle antagonizes an interaction between p53 and MDM2 proteins. In some examples, the peptidomimetic macrocycle antagonizes an interaction between p53 and MDMX proteins. In some examples, the peptidomimetic macrocycle antagonizes an interaction between p53 and MDM2 proteins and p53 and MDMX proteins. In some examples, the peptidomimetic macrocycle antagonizes an interaction between p53 and MDM2 proteins and p53 and MDMX proteins.

[0056] In one aspect, provided herein is a method of selecting a peptidomimetic macrocycle that reduces PD-L1 expression, comprising: contacting a cancer cell line expressing a first level of PD-L1 with a peptidomimetic macrocycle comprising a polypeptide with a crosslinker connecting a first amino acid and a second amino acid; incubating the cancer cell line for an incubation period; measuring a second level of PD-L1 expression after the incubation period; selecting the peptidomimetic macrocycle as a peptidomimetic macrocycle that reduces PD-L1 expression when the second level of PD-L1 expression is at least 1.1, 1.5, 2, 3, 4, 5, 6, 7, 8, 9, 10, 25, 50, or 100 fold lower than the first level of PD-L1 expression.

[0057] In some examples, the measuring comprises flow cytometry. In some examples, the cancer cell line is selected from the group consisting of MCF-7, HCT-116, MV4-11, DOHH2, and A375. In some examples, the method further comprises measuring a level of p53 expression before (a), after (b), or both. In some examples, the method further comprises measuring a level of p21 expression before (a), after (b), or both. In some examples, the method further comprises measuring a level of miR-34 expression before (a), after (b), or both. In some examples, the miR-34 is miR-34a, miR-34b, miR-34c, or a combination thereof. In some examples, the first level of PD-L1 expression in the cancer cell line is high. In some examples, the first level of PD-L1 expression in the cancer cell line is low. In some examples, the cancer cell line is p53 wild-type. In some examples, the incubation period is about 24, 48, or 72 hours after the contacting. In some examples, the incubation period is at least 6, 12, 24, 36, 48, 60, or 72 hours after the contacting. In some examples, the method further comprises measuring a level apoptosis after the incubation period.

INCORPORATION BY REFERENCE

[0058] 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

[0059] 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:

[0060] **Figure 1A** depicts western blots demonstrating Aileron peptide 1 activates the p53-pathway in AML cell lines treated with increasing amounts of Aileron peptide 1.

[0061] **Figure 1B** depicts a western blot demonstrating Aileron peptide 1 activates the p53-pathway in AML cell lines treated with the indicated amounts of Aileron peptide 1.

[0062] **Figure 1C** depicts a western blot demonstrating Aileron peptide 1 activates the p53-pathway in primary AML cells lines treated with the indicated amounts of Aileron peptide 1.

[0063] **Figure 2** depicts graphs of relative mRNA expression normalized to GAPDH in AML cell lines treated with increasing amounts of Aileron peptide 1.

[0064] **Figure 3A** depicts a western blot demonstrating that p53 is stabilized in response to Aileron peptide 1 treatment in a dose-dependent manner.

[0065] **Figure 3B** depicts a western blot demonstrating that p53 is stabilized in response to Aileron peptide 1 treatment in a time-dependent manner.

[0066] **Figure 4A** depicts a western blot of immunoprecipitations demonstrating Aileron peptide 1 is an inhibitor of the p53-MDMX interaction.

[0067] **Figure 4B** depicts a western blot of immunoprecipitations demonstrating Aileron peptide 1 is a dual inhibitor of the p53-MDM2 and p53-MDMX interaction.

[0068] **Figure 4C** depicts a western blot of immunoprecipitations demonstrating Aileron peptide 1 is an inhibitor of the p53-MDM2 interaction.

[0069] **Figure 5A** depicts a graph demonstrating inhibition of cellular proliferation of AML cell lines treated with the indicated amount of Aileron peptide 1 (AP1).

[0070] **Figure 5B** depicts a graph demonstrating inhibition of cellular proliferation of AML cell lines treated with the indicated amount of AP1.

[0071] **Figure 5C** depicts a graph demonstrating inhibition of cellular proliferation of AML cell lines treated with the indicated amount of AP1.

[0072] **Figure 5D** depicts a graph demonstrating inhibition of cellular proliferation of AML cell lines treated with the indicated amount of AP1.

[0073] **Figure 6** depicts a graph demonstrating inhibition of clonogenic capacity of AML cell lines treated with the indicated amount of AP1.

[0074] **Figure 7A** depicts a graph demonstrating inhibition of cellular proliferation of AML cell lines treated with the indicated amount of AP1.

[0075] **Figure 7B** depicts a graph demonstrating inhibition of cellular proliferation of AML cell lines treated with the indicated amount of AP1.

[0076] **Figure 8A** depicts a graph (left) and corresponding FACS data (right) demonstrating Aileron peptide 1 induces apoptotic cell death in a p53 wild type AML cell line.

[0077] **Figure 8B** depicts a graph (left) and corresponding FACS data (right) demonstrating Aileron peptide 1 induces apoptotic cell death in a p53 wild type AML cell line.

[0078] **Figure 8C** depicts a graph (left) and corresponding FACS data (right) demonstrating Aileron peptide 1 does not induce apoptotic cell death in a p53 null AML cell line.

[0079] **Figure 8D** depicts a graph (left) and corresponding FACS data (right) demonstrating Aileron peptide 1 induces apoptotic cell death in a p53 wild type AML cell line.

[0080] **Figure 8E** depicts a graph (left) and corresponding FACS data (right) demonstrating Aileron peptide 1 induces apoptotic cell death in a p53 wild type AML cell line.

[0081] **Figure 9A** depicts a graph demonstrating cytarabine (Ara-C) treatment inhibits proliferation of AML cell lines.

[0082] **Figure 9B** depicts a graph demonstrating Ara-C synergizes with AP1 to inhibit proliferation of AML cell lines.

[0083] **Figure 9C** depicts a graph demonstrating Ara-C synergizes with AP1 to inhibit proliferation of AML cell lines.

[0084] **Figure 10A** depicts a graph demonstrating inhibition of cellular proliferation of primary AML cells treated with the indicated amount of AP1.

[0085] **Figure 10B** depicts a graph demonstrating inhibition of cellular proliferation of primary AML cells treated with the indicated amount of AP1.

[0086] **Figure 10C** depicts a graph demonstrating inhibition of cellular proliferation of primary AML cells treated with the indicated amount of AP1.

[0087] **Figure 10D** depicts a graph demonstrating inhibition of cellular proliferation of primary AML cells treated with the indicated amount of AP1.

[0088] **Figure 11A** depicts a graph demonstrating inhibition of clonogenic capacity of primary AML cells treated with the indicated amount of AP1.

[0089] **Figure 11B** depicts a graph demonstrating inhibition of clonogenic capacity of primary AML cells treated with the indicated amount of AP1.

[0090] **Figure 12** depicts a graph (top) and corresponding FACS data (bottom) demonstrating AP1 induces apoptotic cell death in primary AML cells.

[0091] **Figure 13** shows a structure of peptidomimetic macrocycle 46 (Table 2b), a p53 peptidomimetic macrocycle, complexed with MDMX (Primary SwissProt accession number Q7ZUW7; Entry MDM4_DANRE).

[0092] **Figure 14** shows overlaid structures of p53 peptidomimetic macrocycles 142 (Table 2b) and SP43 bound to MDMX (Primary SwissProt accession number Q7ZUW7; Entry MDM4_DANRE).

[0093] **Figure 15** shows the effect of SP154, a peptidomimetic macrocycle, on tumor growth in a mouse MCF-7 xenograft model.

[0094] **Figure 16** shows the effect of SP249, a peptidomimetic macrocycle, on tumor growth in a mouse MCF-7 xenograft model.

[0095] **Figure 17** shows the effect of SP315, a peptidomimetic macrocycle, on tumor growth in a mouse MCF-7 xenograft model.

[0096] **Figure 18** shows the effect of SP252, a point mutation of SP154, on tumor growth in a mouse MCF-7 xenograft model.

[0097] **Figure 19** shows a plot of solubility for peptidomimetic macrocycles with varying C-terminal extensions.

[0098] **Figure 20** shows that the peptidomimetic macrocycles of the disclosure show synergy with Zelboraf (Vemurafenib, a.k.a. PLX4032) in B-Raf-mutant Melanoma Cell Line A375.

[0099] **Figure 21** shows that the peptidomimetic macrocycles of the disclosure show synergy with Zelboraf in B-Raf-mutant melanoma cell line Mel-Ho but not in B-Raf-WT Mel-Juso.

[00100] **Figure 22** shows that the peptidomimetic macrocycles of the disclosure can reduce expression levels of PD-L1 in HCT116 p53+/+ cells.

[00101] **Figure 23** shows a graph of MCF-7 cell proliferation determined using a WST-1 assay measured at the indicated time points after different numbers of MCF-7 cells were grown at 37 °C for a 24 hour growth period.

[00102] **Figure 24A** shows a bar graph of MCF-7 breast cancer cell proliferation when treated with the indicated concentrations of Aileron peptide 1. Cells were evaluated for viability by MTT assay 5 days after beginning treatment. Treatment with Aileron peptide 1 supresses MCF-7 breast cancer cell growth.

[00103] **Figure 24B** shows a bar graph of MOLT-3 cell proliferation when treated with the indicated concentrations of Aileron peptide 1. Cells were evaluated for viability by a WST-1 assay 72 hours after beginning treatment. Treatment with Aileron peptide 1 supresses MOLT-3 cell growth.

[00104] **Figure 25A** shows a graph of MCF-7 breast cancer cell proliferation when treated with the indicated amounts of Aileron petide 1 (log μM), Aileron peptide 1 + 400 nM everolimus, or Aileron peptide 1 + 10 nM fulvestrant. Cells were evaluated for viability by MTT assay 5 days after beginning treatment. Aileron peptide 1 in combination with fulvestrant and everolimus yields enhanced inhibition of cancer cell proliferation.

[00105] **Figure 25B** shows a graph of MCF-7 breast cancer cell proliferation inhibition (fraction of control) when treated with the indicated amounts of AP1 (μM), AP1+ 400 nM everolimus, or AP1+ 10 nM fulvestrant. Cells were evaluated for viability by MTT assay 5 days after beginning treatment. AP1 in combination with fulvestrant and everolimus yields enhanced inhibition of cancer cell proliferation.

[00106] **Figure 26** shows a bar graph of MCF-7 cell proliferation when treated with the indicated concentrations of fulvestrant. Cells were evaluated for viability by a WST-1 assay 5 days after beginning treatment. Fulvestrant treatment inhibited MCF-7 breast cancer cell proliferation with limited cell killing as a single agent.

[00107] **Figure 27A** shows a graph of MCF-7 breast cancer cell proliferation when treated with the indicated amounts of Aileron petide 1, Aileron peptide 1 + 3 nM fulvestrant, Aileron peptide 1 + 10 nM fulvestrant, or Aileron peptide 1 + 30 nM fulvestrant. Cells were evaluated for viability by MTT assay 5 days after beginning treatment. Combination with fulvestrant enhances Aileron peptide 1 inhibition of cancer cell proliferation and cell killing.

[00108] Figure 27B shows a graph of MCF-7 breast cancer cell proliferation when treated with the indicated amounts of fulvestrant, fulvestrant + 0.13 μM Aileron peptide 1, fulvestrant + 0.4 μM Aileron peptide 1, or fulvestrant + 1.2 μM Aileron peptide 1. Cells were evaluated for viability by MTT assay 5 days after beginning treatment. Combination with Aileron peptide 1 enhances fulvestrant inhibition of cancer cell proliferation and cell killing.

[00109] Figure 28A shows a graph of MCF-7 breast cancer cell proliferation when treated with the indicated fixed amounts of Aileron petide 1 (AP1) in combination with the indicated fixed amounts of fulvestrant (FU). Cells were evaluated for viability by MTT assay 5 days after beginning treatment. Combination with Aileron peptide 1 enhances fulvestrant inhibition of cancer cell proliferation and cell killing.

[00110] Figure 28B shows a graph of MCF-7 breast cancer cell proliferation when treated with 0.1 μM Aileron petide 1, 3 nM fulvestrant, or 0.1 μM Aileron petide 1 and 3 nM fulvestrant. Cells were evaluated for viability by MTT assay 5 days after beginning treatment. Combination with Aileron peptide 1 enhances fulvestrant inhibition of cancer cell proliferation and cell killing.

[00111] Figure 29 shows a bar graph of MCF-7 cell proliferation when treated with the indicated concentrations of everolimus. Cells were evaluated for viability by a WST-1 assay 5 days after beginning treatment. Everolimus treatment inhibited MCF-7 breast cancer cell proliferation with limited cell killing as a single agent.

[00112] Figure 30A shows a graph of MCF-7 breast cancer cell proliferation when treated with the indicated amounts of Aileron petide 1, Aileron peptide 1 + 1 nM everolimus, Aileron peptide 1 + 3 nM everolimus, Aileron peptide 1 + 10 nM everolimus, or Aileron peptide 1 + 100 nM everolimus. Cells were evaluated for viability by MTT assay 5 days after beginning treatment. Combination with everolimus enhances Aileron peptide 1 inhibition of cancer cell proliferation and cell killing.

[00113] Figure 30B shows a graph of MCF-7 breast cancer cell proliferation when treated with the indicated amounts of everolimus, everolimus + 0.13 μM Aileron peptide 1, everolimus + 0.4 μM Aileron peptide 1, or everolimus + 1.2 μM Aileron peptide 1. Cells were evaluated for viability by MTT assay 5 days after beginning treatment. Combination with Aileron peptide 1 enhances everolimus inhibition of cancer cell proliferation and cell killing.

[00114] Figure 31A shows a graph of MCF-7 breast cancer cell proliferation when treated with the indicated fixed amounts of Aileron petide 1 (AP1) in combination with the indicated fixed amounts of everolimus (EV). Cells were evaluated for viability by MTT assay 5 days after beginning treatment. Combination with Aileron peptide 1 enhances everolimus inhibition of cancer cell proliferation and cell killing.

[00115] Figure 31B shows a graph of MCF-7 breast cancer cell proliferation when treated with 0.1 μM Aileron petide 1, 3 nM everolimus, or 0.1 μM Aileron petide 1 and 3 nM everolimus. Cells were evaluated for viability by MTT assay 5 days after beginning treatment. Combination with Aileron peptide 1 enhances everolimus inhibition of cancer cell proliferation and cell killing.

[00116] Figure 32 shows a bar graph of MOLT-3 cell proliferation when treated with the indicated concentrations of romidepsin. Cells were evaluated for viability by a WST-1 assay 72 hours after beginning treatment. Romidepsin treatment inhibited MOLT-3 cell proliferation.

[00117] Figure 33A shows a graph of MOLT-3 cell proliferation when treated with the indicated amounts of Aileron petide 1, Aileron peptide 1 + 0.5 nM romidepsin, Aileron peptide 1 + 1.5 nM romidepsin, or Aileron peptide 1 + 3 nM romidepsin. Cells were evaluated for viability by MTT assay 72 hours after beginning treatment. Combination with romidepsin enhances Aileron peptide 1 inhibition of cancer cell proliferation and cell killing.

[00118] Figure 33B shows a graph of MOLT-3 cell proliferation when treated with the indicated amounts of romidepsin, romidepsin + 0.05 μM Aileron peptide 1, romidepsin + 0.2 μM Aileron peptide 1, or romidepsin + 0.8 μM Aileron peptide 1. Cells were evaluated for viability by a WST-1 assay 72 hours after beginning treatment. MOLT-3 cells were pretreated with Aileron peptide 1 for 2 hours before adding romedepsin. Combination with Aileron peptide 1 enhances romidepsin inhibition of cancer cell proliferation and cell killing.

[00119] Figure 34A shows a graph of MOLT-3 cell proliferation when treated with the indicated fixed amounts of Aileron petide 1 (AP1) in combination with the indicated fixed amounts of romidepsin (RO). Cells were evaluated for viability by a WST-1 assay 72 hours after beginning treatment. MOLT-3 cells were pretreated with Aileron peptide 1 for 2 hours before adding romedepsin. Aileron peptide 1 and romidepsin suppressed MOLT-3 cell growth. Combination with romidepsin enhances Aileron peptide 1 inhibition of cancer cell proliferation and cell killing.

[00120] Figure 34B shows a graph of MOLT-3 cell proliferation when treated with the indicated fixed amounts of Aileron petide 1 (AP1) in combination with the indicated fixed amounts of romidepsin (RO). Cells were evaluated for viability by MTT assay 72 hours after beginning treatment. MOLT-3 cells were pretreated with Aileron peptide 1 for 2 hours before adding romedepsin. Aileron peptide 1 and romidepsin suppressed MOLT-3 cell growth. Combination with romidepsin enhances Aileron peptide 1 inhibition of cancer cell proliferation and cell killing.

[00121] Figure 34C shows a graph of MOLT-3 cell proliferation when treated with 0.1 μM Aileron petide 1, 1.5 nM romidepsin, or 0.1 μM Aileron petide 1 and 1.5 nM romidepsin. Cells were evaluated for viability by MTT assay 72 hours after beginning treatment. MOLT-3 cells were pretreated with Aileron peptide 1 for 2 hours before adding romedepsin. Aileron peptide 1 and romidepsin suppressed MOLT-3 cell growth. Combination with romidepsin enhances Aileron peptide 1 inhibition of cancer cell proliferation and cell killing.

[00122] Figure 35 shows a bar graph of MCF-7 cell proliferation when treated with the indicated concentrations of palbociclib. Cells were evaluated for viability by a WST-1 assay 5 days after beginning treatment. Palbociclib treatment inhibited MCF-7 breast cancer cell proliferation with limited cell killing as a single agent.

[00123] Figure 36A shows a graph of MCF-7 breast cancer cell viability when treated with the indicated amounts of Aileron petide 1, Aileron peptide 1 + 0.3 μM palbociclib, Aileron peptide 1 + 1 μM palbociclib, Aileron peptide 1 + 3 μM palbociclib, or Aileron peptide 1 + 10 μM palbociclib. Cells were evaluated for viability by MTT assay 5 days after beginning treatment. Palbociclib has anti-proliferative effects when dosed with Aileron peptide 1. Aileron peptide 1 and palbociclib combination studies show complementary *in vitro* anticancer activity. Combination with palbociclib enhances Aileron peptide 1 inhibition of cancer cell proliferation and cell killing.

[00124] Figure 36B shows a graph of MCF-7 breast cancer cell proliferation when treated with the indicated amounts of palbociclib, palbociclib + 0.13 μM Aileron peptide 1, palbociclib + 0.4 μM Aileron peptide 1, or palbociclib + 1.2 μM Aileron peptide 1. Cells were evaluated for viability by MTT assay 5 days after beginning treatment. Combination with Aileron peptide 1 enhances palbociclib inhibition of cancer cell proliferation and cell killing.

[00125] Figure 37A shows a graph of MCF-7 breast cancer cell proliferation when treated with the indicated fixed amounts of Aileron petide 1 (AP1) in combination with the indicated fixed amounts of palbociclib (PO). Cells were evaluated for viability by MTT assay 5 days after beginning treatment.

[00126] Figure 37B shows a graph of MCF-7 breast cancer cell viability when treated with 0.3 μM palbociclib or 0.3 μM Aileron petide 1 and 0.3 μM palbociclib. Cells were evaluated for viability by MTT assay 5 days after beginning treatment. Aileron peptide 1 kills cancer cells when dosed with palbociclib.

[00127] Figure 38A shows MV4-11 cell proliferation when treated with the indicated concentrations of Ara-C.

[00128] Figure 38B shows MV4-11 cell viability when treated with varying concentrations of AP1 and Ara-C. Combination with Ara-C enhanced AP1 inhibition of cancer cell proliferation and cell killing.

[00129] Figure 38C shows a combination index profile of treatment with AP1and Ara-C.

[00130] Figure 39A shows MV4-11 cell proliferation when treated with the indicated concentrations of azacitidine.

[00131] Figure 39B shows MV4-11 cell viability when treated with varying concentrations of AP1 and azacitidine. Combination with azacitidine enhanced AP1 inhibition of cancer cell proliferation and cell killing.

[00132] Figure 39C shows a combination index profile of treatment with AP1and azacitidine.

[00133] Figure 40A shows MV4-11 cell proliferation when treated with the indicated concentrations of decitabine.

[00134] Figure 40B shows MV4-11 cell viability when treated with varying concentrations of AP1 and decitabine. Combination with decitabine enhanced AP1 inhibition of cancer cell proliferation and cell killing.

[00135] Figure 40C shows a combination index profile of treatment with AP1and decitabine.

[00136] Figure 41A shows MV4-11 cell proliferation when treated with the indicated concentrations of midostaurin.

[00137] Figure 41B shows MV4-11 cell viability when treated with varying concentrations of AP1 and midostaurin. Combination with midostaurin enhanced AP1 inhibition of cancer cell proliferation and cell killing.

[00138] Figure 41C shows a combination index profile of treatment with AP1and midostaurin.

[00139] Figure 42A shows DOHH-2 cell proliferation when treated with the indicated concentrations of vincristine (VCR).

[00140] Figure 42B shows DOHH-2 cell viability when treated with varying concentrations of AP1 and VCR. Combination with vincristine enhanced AP1 inhibition of cancer cell proliferation and cell killing.

[00141] Figure 42C shows a combination index profile of treatment with AP1 and vincristine.

[00142] Figure 43 shows DOHH-2 cell viability when treated with AP1 alone, vincristine alone, and AP1 in combination with vincristine.

[00143] Figure 44A shows DOHH-2 cell proliferation when treated with the indicated concentrations of AP1.

[00144] Figure 44B shows DOHH-2 cell viability when treated with varying concentrations of cyclophosphamide (CTX) and AP1. Combination with vincristine enhanced CTX inhibition of cancer cell proliferation and cell killing.

[00145] Figure 44C shows a combination index profile of treatment with AP1and CTX.

[00146] Figure 45 shows DOHH-2 cell viability when treated with AP1 alone, CTX alone, and AP1 in combination with CTX.

[00147] Figure 46 shows the order of addition effects on DOHH-2 cell viability using various concentrations of AP1 in combination with VCR.

[00148] Figure 47 shows DOHH-2 cell viability based on the order of addition when treated with varying concentrations of AP1 and VCR after pretreatment with AP1 for 24 hrs.

[00149] Figure 48 shows DOHH-2 cell viability based on the order of addition when treated with varying concentrations of AP1 and VCR after pretreatment with VCR for 24 hrs.

[00150] Figure 49 shows the order of addition effects on DOHH-2 cell viability using various concentrations of AP1 in combination with CTX.

[00151] Figure 50 shows DOHH-2 cell viability based on the order of addition when treated with varying concentrations of AP1 and CTX after pretreatment with AP1 for 24 hrs.

[00152] Figure 51 shows DOHH-2 cell viability based on the order of addition when treated with varying concentrations of AP1 and CTX after pretreatment with CTX for 24 hrs.

[00153] Figure 52 shows the order of addition effects on MV4-11 cell viability using various concentrations of AP1 and midostaurin.

[00154] Figure 53 shows MV4-11 cell viability based on the order of addition when treated with varying concentrations of AP1 and midostaurin after pretreatment with midostaurin for 24 hrs.

[00155] Figure 54 shows MV4-11 cell viability based on the order of addition when treated with varying concentrations of AP1 and midostaurin after pretreatment with AP1 for 24 hrs.

[00156] Figure 55 shows the order of addition effects on MV4-11 cell viability using various concentrations of AP1 in combination with decitabine.

[00157] Figure 56 shows MV4-11 cell viability based on the order of addition when treated with varying concentrations of AP1 and decitabine after pretreatment with decitabine for 24 hrs.

[00158] Figure 57 shows MV4-11 cell viability based on the order of addition when treated with varying concentrations of AP1 and decitabine after pretreatment with AP1 for 24 hrs.

[00159] Figure 58 shows the order of addition effects on MV4-11 cell viability using various concentrations of AP1 in combination with Ara-C.

[00160] Figure 59 shows MV4-11 cell viability based on the order of addition when treated with varying concentrations of AP1 and Ara-C after pretreatment with AP1 for 24 hrs.

[00161] Figure 60 shows MV4-11 cell viability based on the order of addition when treated with varying concentrations of AP1 and Ara-C after pretreatment with Ara-C for 24 hrs.

[00162] Figure 61 shows the order of addition effects on MV4-11 cell viability using various concentrations of AP1 in combination with azacitidine.

[00163] Figure 62 shows MV4-11 cell viability based on the order of addition when treated with varying concentrations of AP1 and azacitidine after 24 hrs pretreatment with AP1.

[00164] Figure 63 shows MV4-11 cell viability based on the order of addition when treated with varying concentrations of AP1 and azacitidine after pretreatment with azacitidine for 24 hrs.

[00165] Figure 64A shows MCF-7 cell proliferation when treated with the indicated concentrations of fulvestrant.

[00166] Figure 64B shows MCF-7 cell viability when treated with varying concentrations of AP1 and fulvestrant.

[00167] Figure 64A shows MCF-7 cell proliferation when treated with varying concentrations of AP1.

[00168] Figure 65B shows MCF-7 cell viability when treated with varying concentrations of AP1 and fulvestrant.

[00169] Figure 65C shows the IC_{50} values of AP1 alone and AP1 with varying concentrations of fulvestrant (FUL).

[00170] Figure 66A shows MCF-7 cell proliferation when treated with varying concentrations of everolimus.

[00171] Figure 66B shows MCF-7 cell viability when treated with varying concentrations of AP1 and everolimus.

[00172] Figure 67A shows MCF-7 cell proliferation when treated with varying concentrations of AP1. AP1 treatment suppressed MCF-7 breast cancer cell proliferation.

[00173] Figure 67B shows a graph of MCF-7 cell viability when treated with varying concentrations of AP1 and everolimus.

[00174] Figure 68A shows the effects of rituximab alone on DOHH-2 cell growth.

[00175] Figure 68B shows DOHH-2 cell viability when treated with varying concentrations of AP1 and rituximab.

[00176] Figure 69A shows the effects of AP1 alone on DOHH-2 cell growth.

[00177] Figure 69B shows DOHH-2 cell viability when treated with varying concentrations of AP1 and rituximab.

[00178] Figure 70 shows DOHH-2 cell viability when treated with AP1 alone, rituximab alone, and varying concentrations of AP1 in combination with rituximab.

[00179] Figure 71A shows the effects of AP1 alone on MOLT-3 cell growth.

[00180] Figure 71B shows MOLT-3 cell viability when treated with varying concentrations of AP1 and romidepsin.

[00181] Figure 72A shows the effects of romidepsin alone on MOLT-3 cell growth.

[00182] Figure 72B shows MOLT-3 cell viability when treated with varying concentrations of AP1 and romidepsin.

[00183] Figure 72C shows the IC_{50} values of AP1 alone and AP1 with varying concentrations of romidepsin.

[00184] Figure 73 shows MOLT-3 cell viability when treated with AP1 alone, romidepsin alone, and AP1 in combination with romidepsin.

[00185] Figure 74A shows MCF-7 cell proliferation when treated with varying concentrations of ribociclib.

[00186] Figure 74B shows MCF-7 cell viability when treated with varying concentrations of AP1 and ribociclib.

[00187] Figure 75A shows MCF-7 cell proliferation when treated with varying concentrations of AP1.

[00188] Figure 75B shows MCF-7 cell viability when treated with varying concentrations of AP1 and ribociclib.

[00189] Figure 76A shows MCF-7 cell proliferation when treated with varying concentrations of abemaciclib.

[00190] Figure 76B shows MCF-7 cell viability when treated with varying concentrations of AP1 and abemaciclib.

[00191] Figure 77A shows MCF-7 cell proliferation when treated with varying concentrations of AP1.

[00192] Figure 77B shows MCF-7 cell viability when treated with varying concentrations of AP1 and abemaciclib.

[00193] Figure 78A shows MCF-7 cell proliferation when treated with varying concentrations of palbociclib.

[00194] Figure 78B shows MCF-7 cell viability when treated with varying concentrations of AP1 and palbociclib.

[00195] Figure 79A shows MCF-7 cell proliferation when treated with varying concentrations of AP1.

[00196] Figure 79B shows MCF-7 cell viability when treated with varying concentrations of AP1 and palbociclib.

[00197] Figure 80 shows the order of addition effects of AP1 and palbociclib on MCF-7 cell growth.

[00198] Figure 81 shows MCF-7 cell viability based on the order of addition when treated with varying concentrations of AP1 and palbociclib after 24 hrs pretreatment with AP1.

[00199] Figure 82 shows MCF-7 cell viability when treated with varying concentrations of AP1 and palbociclib determined using CyQUANT.

[00200] Figure 83 shows MCF-7 cell viability based on the order of addition when treated with varying concentrations of AP1 and dexamethasone (Dex).

[00201] Figure 84A shows A375 cell viability when treated with varying concentrations of zelboraf.

[00202] Figure 84B shows A375 cell viability with treatment with varying concentrations of AP1 and zelboraf.

[00203] Figure 85A shows A375 cell viability when treated with varying concentrations of AP1.

[00204] Figure 85B shows A375 cell viability with treatment with varying concentrations of zelboraf and AP1.

[00205] Figure 86A shows A375 cell viability when treated with varying concentrations of tafinlar.

[00206] Figure 86B shows A375 cell viability with treatment with varying concentrations of AP1 and tafinlar.

[00207] Figure 87A shows A375 cell viability when treated with varying concentrations of AP1.

[00208] Figure 87B shows A375 cell viability with treatment with varying concentrations of tafinlar and AP1.

[00209] Figure 88A shows A375 cell viability when treated with varying concentrations of mekinist.

[00210] Figure 88B shows cancer cell viability with treatment with varying concentrations of AP1 and mekinist.

[00211] Figure 89A shows A375 cell viability when treated with varying concentrations of AP1.

[00212] Figure 89B shows A375 cell viability with treatment with varying concentrations of mekinist and AP1.

[00213] Figure 90A shows a combination index plot of fulvestrant in MCF-7 cells.

[00214] Figure 90B shows a combination index plot of everolimus in MCF-7 cells.

[00215] Figure 90C shows a combination index plot of palbociclib (WST-1) in MCF-7 cells

[00216] Figure 90D shows a combination index plot of palbociclib (CyQUANT) in MCF-7 cells.

[00217] Figure 90E shows a combination index plot of romidepsin in MCF-7 cells.

[00218] Figure 91A shows a combination index plot of Ara-C in MV4-11 cells.

[00219] Figure 91B shows a combination index plot of decitabine in MV4-11 cells.

[00220] Figure 91C shows a combination index plot of azacitidine in MV4-11 cells.

[00221] Figure 91D shows a combination index plot of midostuarin in MV4-11 cells.

[00222] Figure 92A shows a combination index plot of vincristine in DOHH-2 cells.

[00223] Figure 92B shows a combination index plot of cyclophosphamide in DOHH-2 cells.

[00224] Figure 92C shows a combination index plot ofrituximab in DOHH-2 cells.

[00225] Figure 93 shows a combination index plot of romidepsin in MOLT-3 cells.

[00226] Figure 94A shows a combination index plot of mekinist in A375 cells

[00227] Figure 94B shows a combination index plot of zelboraf in A375 cells.

[00228] Figure 94C shows a combination index plot of tafinlar in A375 cells.

DETAILED DESCRIPTION OF THE INVENTION

[00229] 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.

[00230] 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.

[00231] 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.

[00232] 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.

[00233] 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.

[00234] 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.

[00235] 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.

[00236] The term "β-amino acid" refers to a molecule containing both an amino group and a carboxyl group in a β configuration.

[00237] 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.

[00238] The following table shows a summary of the properties of natural amino acids:

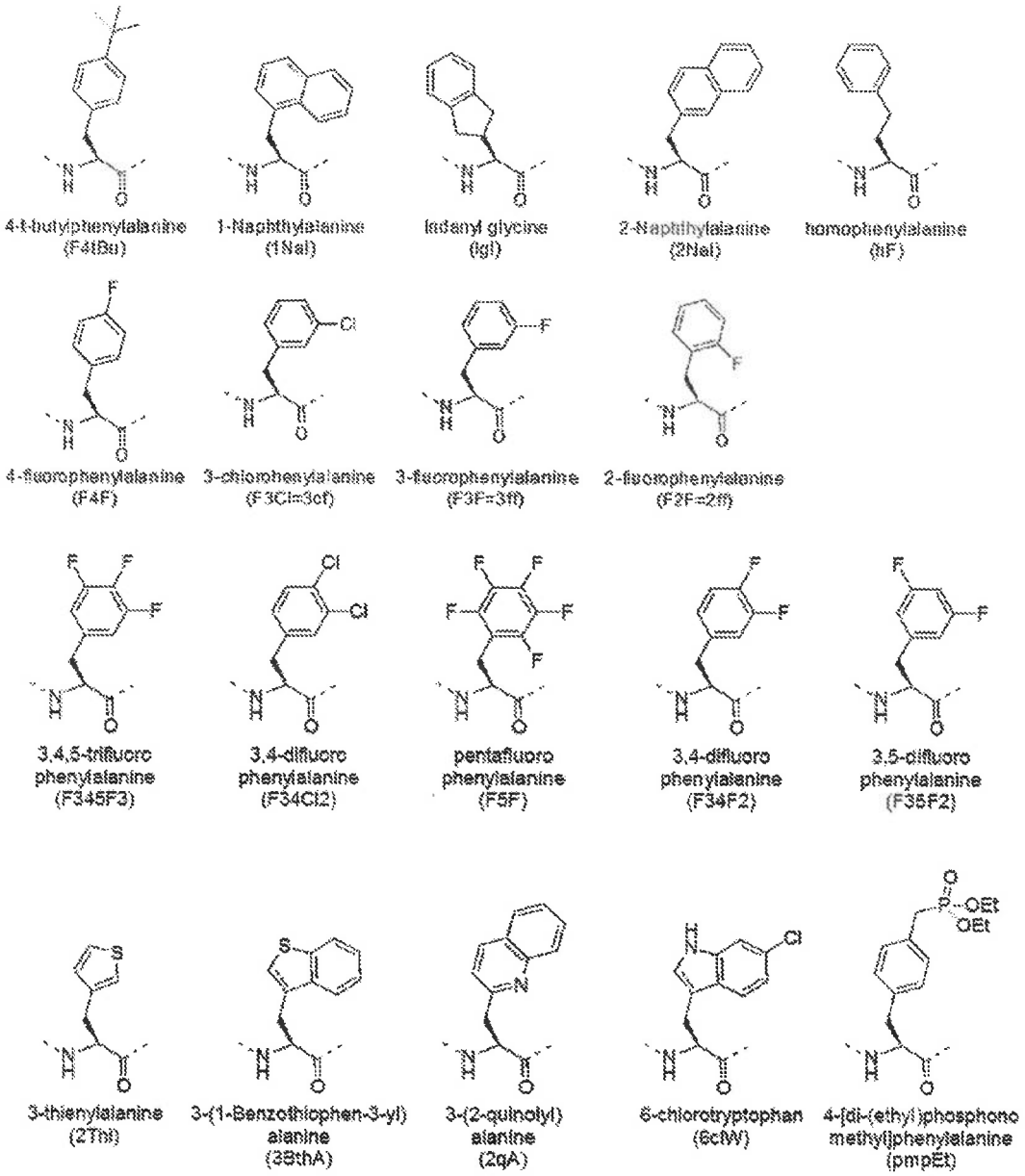
Amino Acid	3-Letter Code	1-Letter Code	Side-chain Polarity	Side-chain charge (pH 7.4)	Hydropathy Index
Alanine	Ala	A	nonpolar	neutral	1.8
Arginine	Arg	R	polar	positive	−4.5
Asparagine	Asn	N	polar	neutral	−3.5
Aspartic acid	Asp	D	polar	negative	−3.5
Cysteine	Cys	C	polar	neutral	2.5
Glutamic acid	Glu	E	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

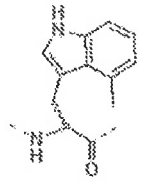
[00239] "Hydrophobic amino acids" include small hydrophobic amino acids and large hydrophobic amino acids. "Small hydrophobic amino acids" are glycine, alanine, proline, and analogs thereof. "Large hydrophobic amino acids" are valine, leucine, isoleucine, phenylalanine, methionine, tryptophan, and analogs 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.

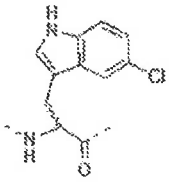
[00240] The term "amino acid analog" refers to a molecule which is structurally similar to an amino acid and which can be substituted for an amino acid in the formation of a peptidomimetic macrocycle. Amino acid analogs include, without limitation, β-amino acids and amino acids wherein the amino or carboxy 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).

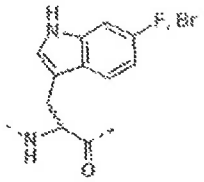
[00241] The term "non-natural amino acid" refers to an amino acid which is not one of the twenty amino acids commonly found in peptides synthesized in nature, and known by the one letter abbreviations A, R, N, C, D,

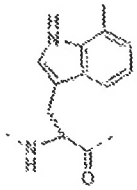
Q, E, G, H, I, L, K, M, F, P, S, T, W, Y and V. Non-natural amino acids or amino acid analogs include, without limitation, structures according to the following:

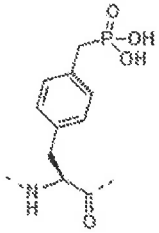


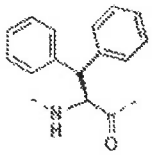

D- or L- 4-methyl tryptophan (dl4mW)

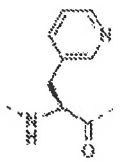

D- or L- 5-chloro tryptophan (dl5clW)

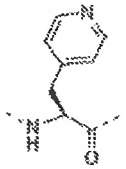

D/L-6-fluorotryptophan & D/L-6-bromotryptophan (dl6FW & dl6brW)

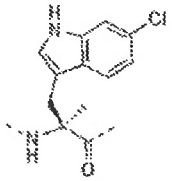

D/L-7-methyl tryptophan (dl7mW)

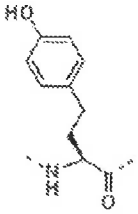

4-(phosphonomethyl) phenylalanine (Pmp)


3,3-diphenyl-alanine (Dip)

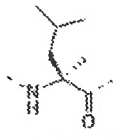

3-pyridyl-alanine (3Pal)

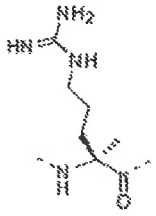

4-pyridyl-alanine (4Pal)

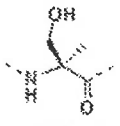

α-methyl-6-chloro tryptophan (Me6clW)

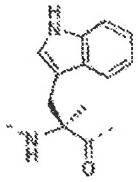

homotyrosine (hY)


α-methyl-phenylalaline (Amf)


α-methyl-leucine (Ami)

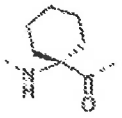

α-methyl-arginine (Amr)

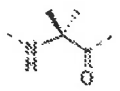

α-methyl-serine (Ams)


α-methyl-tryptophan (Amw)


1-amino-cyclopropane-1-carboxylic acid (Ac3c)

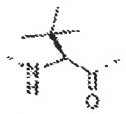

1-amino-cyclopentane-1-carboxylic acid (Ac5c)

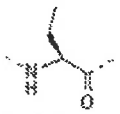

1-amino-cyclohexane-1-carboxylic acid (Ac6c)

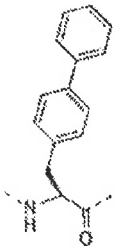

α-amino isobutyric acid (Aib)

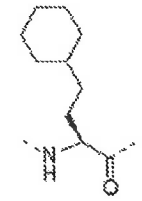

Norleucine (Nle)


Homoleucine (hL)

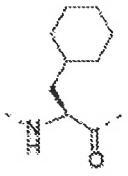

tert-Butyl glycine (Tle)


aminobutyric acid (Abu)

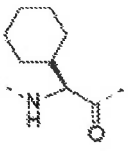

biphenylalanine (Bip)



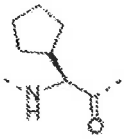
homocyclohexyl alanine (hCha)



cyclohexyl alanine (Cha)



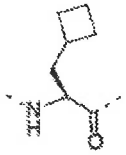
cyclohexyl glycine (Chg)



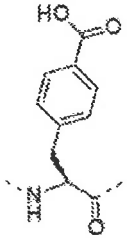
cyclopentyl glycine (Cpg)



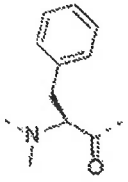
Adamantyl glycine (Adm)



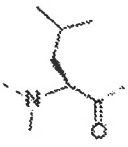
cyclobutyl alanine (Cba)



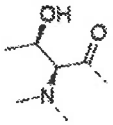
4-carboxyl phenylalanine (F4COOH)



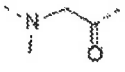
N-methyl phenylalanine (NmF)



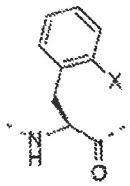
N-methyl leucine (NmL)



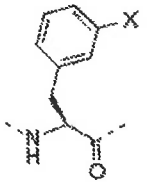
N-methyl threonine (NmT)



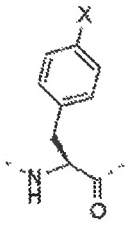
sarcosine (Ser)



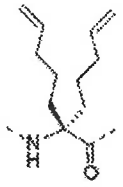
2-chlorophenylalanine (X=Cl), 2-bromophenylalanine (X=Br), 2-trimethylphenylalanine (X=CF3), 2-cyanophenylalanine (X=CN), 2-methylphenylalanine (X=Me), 2-nitrophenylalanine (X=NO2), (F2X, X=Cl,Br,CF3,CN,Me,NO2)



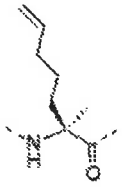
3-chlorophenylalanine (X=Cl), 3-bromophenylalanine (X=Br), 3-trimethylphenylalanine (X=CF3), 3-cyanophenylalanine (X=CN), 3-methylphenylalanine (X=Me), 3-nitrophenylalanine (X=NO2), (F3X, X=Cl,Br,CF3,CN,Me,NO2)



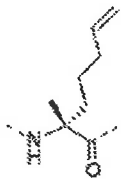
4-chlorophenylalanine (X=Cl), 4-bromophenylalanine (X=Br), 4-trimethylphenylalanine (X=CF3), 4-cyanophenylalanine (X=CN), 4-methylphenylalanine (X=Me), 4-nitrophenylalanine (X=NO2), (F4X, X=Cl,Br,CF3,CN,Me,NO2)



St/



S/



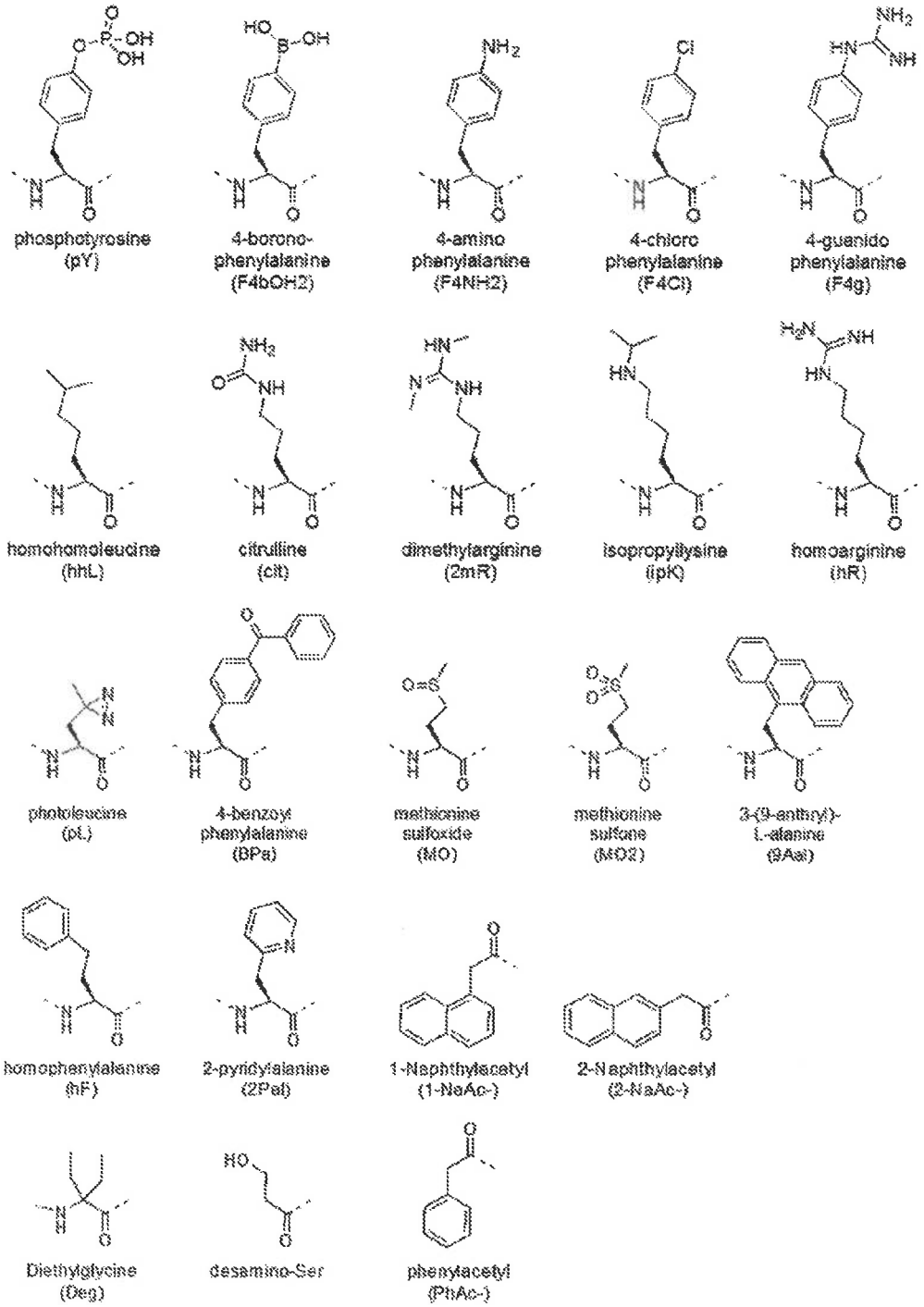
S/r5



S/s8



S/r8



[00242] 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.

[00243] 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-alanine; 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.

[00244] 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; $Lys(Me_3)$-OH chloride; Nω-nitro-D-arginine; and Nω-nitro-L-arginine.

[00245] 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.

[00246] 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.

[00247] 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.

[00248] 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.

[00249] 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.

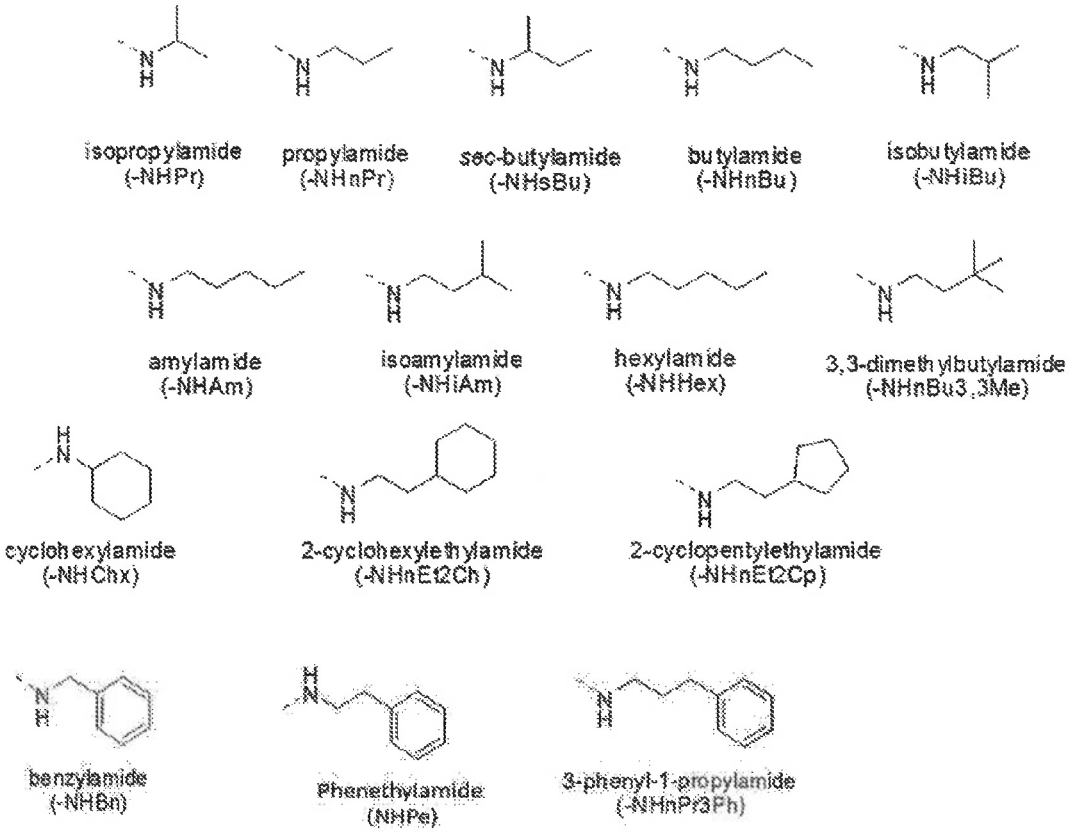
[00250] Amino acid analogs include analogs of tryptophan. Examples of amino acid analogs of tryptophan include, but are not limited to, the following: α-methyl-tryptophan; β-(3-benzothienyl)-D-alanine; β-(3-benzothienyl)-L-alanine; 1-methyl-tryptophan; 4-methyl-tryptophan; 5-benzyloxy-tryptophan; 5-bromo-tryptophan; 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.

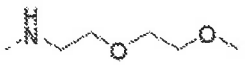
[00251] In some embodiments, amino acid analogs are racemic. In some embodiments, the D isomer of the amino acid analog is used. In some embodiments, the L isomer of the amino acid analog is used. In other embodiments, the amino acid analog comprises chiral centers that are in the R or S configuration. 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.

[00252] 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 abolishing 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.

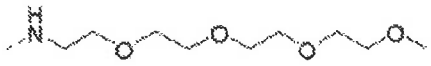
[00253] A "conservative amino acid substitution" is one in which the amino acid residue is replaced with an amino acid residue having a similar side chain. Families of amino acid residues having similar side chains have been defined in the art. These families include amino acids with basic side chains (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, e.g., 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).

[00254] 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 (i.e. –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, secondary, and tertiary amines, including pegylated secondary amines. Representative secondary amine capping groups for the C-terminus include:



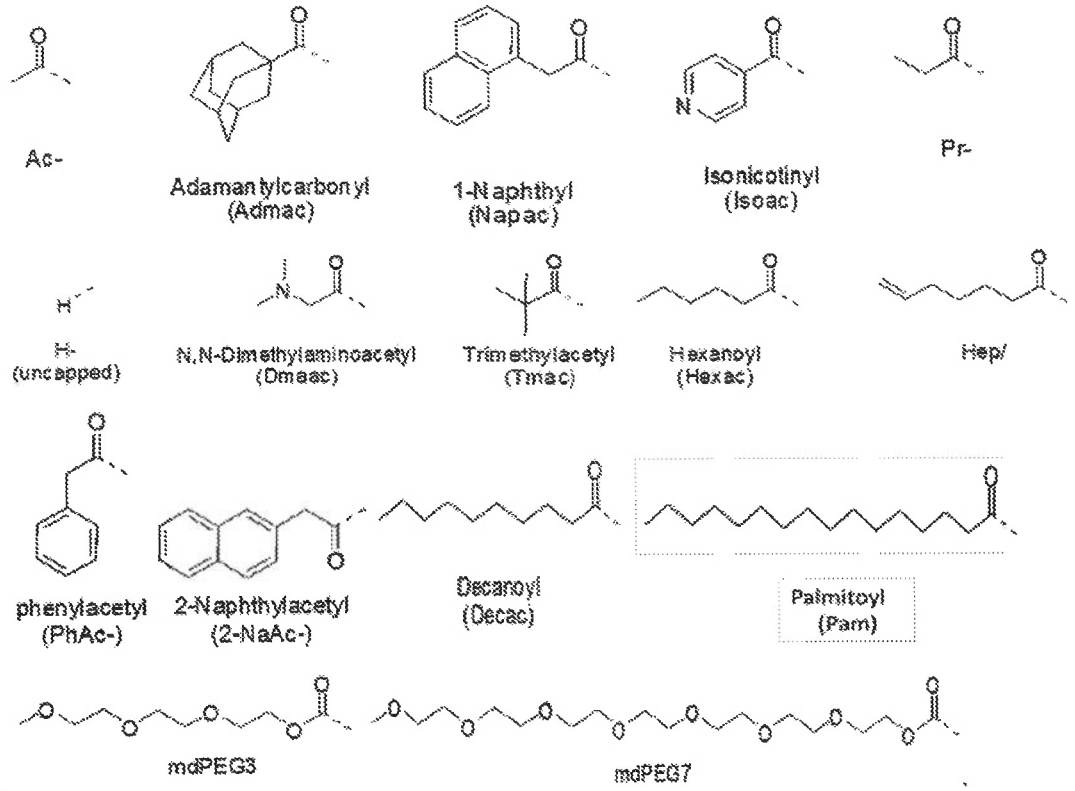


n-dPeg2-amide
(-NHmdPeg2)



n-dPeg4-amide
(-NHmdPeg4)

[00255] The capping group of an amino terminus includes an unmodified amine (*i.e.* $-NH_2$) 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:



[00256]

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.

[00257] The symbol "$\diagup\!\!\!\diagup$" when used as part of a molecular structure refers to a single bond or a *trans* or *cis* double bond.

[00258] 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).

[00259] 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.

[00260] 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).

[00261] 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.

[00262] 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., 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.*, Nature 2011, 479, 88; and Peryshkov *et al.*, 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.

[00263] The term "halo" or "halogen" refers to fluorine, chlorine, bromine or iodine or a radical thereof.

[00264] 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.

[00265] The term "alkylene" refers to a divalent alkyl (*i.e.*, -R-).

[00266] 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.

[00267] 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.

[00268] 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.

[00269] "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.

[00270] "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-$C(O)NH_2$-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,

[00271] "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.

[00272] "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)-$CH{=}CH_2$.

[00273] "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, $-CH_2OH$, $-CH_2CH_2OH$, $-CH_2CH_2CH_2OH$, $-CH_2CH_2CH_2CH_2OH$, $-CH_2CH_2CH_2\ CH_2CH_2OH$, $-CH_2CH(OH)CH_3$, $-CH_2CH(OH)CH_2CH_3$, $-CH(OH)CH_3$ and $-C(CH_3)_2CH_2OH$.

[00274] "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 $-C(CH_3)_2CH_2COOH$.

[00275] 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.

[00276] 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.

[00277] 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.

[00278] 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.

[00279] 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.

[00280] 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.

[00281] 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 invention 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.

[00282] 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%.

[00283] 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.

[00284] 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."

[00285] The term "on average" represents the mean value derived from performing at least three independent replicates for each data point.

[00286] 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.

[00287] 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.

[00288] 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.

[00289] 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.

[00290] The term "solid tumor" or "solid cancer" as used herein refers to tumors that usually do not contain cysts or liquid areas. Solid tumors as used herein include sarcomas, carcinomas and lymphomas. In various embodiments, leukemia (cancer of blood) is not solid tumor.

[00291] Solid tumor cancers that can be treated by the methods provided herein include, but are not limited to, sarcomas, carcinomas, and lymphomas. In specific embodiments, solid tumors that can be treated in accordance with the methods described include, but are not limited to, cancer of the breast, liver, neuroblastoma, head, neck, eye, mouth, throat, esophagus, esophagus, chest, bone, lung, kidney, colon, rectum or other gastrointestinal tract organs, stomach, spleen, skeletal muscle, subcutaneous tissue, prostate, breast, ovaries, testicles or other reproductive organs, skin, thyroid, blood, lymph nodes, kidney, liver, pancreas, and brain or central nervous system. Solid tumors that can be treated by the instant methods include tumors and/or metastasis (wherever located) other than lymphatic cancer, for example brain and other central nervous system tumors (including but not limited to tumors of the meninges, brain, spinal cord, cranial nerves and other parts of central nervous system, e.g. glioblastomas or medulla blastemas); head and/or neck cancer; breast tumors; circulatory system tumors (including but not limited to heart, mediastinum and pleura, and other intrathoracic organs, vascular tumors and tumor-associated vascular tissue); excretory system tumors (including but not limited to tumors of kidney, renal pelvis, ureter, bladder, other and unspecified urinary organs); gastrointestinal tract tumors (including but not limited to tumors of oesophagus, stomach, small intestine, colon, colorectal, rectosigmoid junction, rectum, anus and anal canal, tumors involving the liver and intrahepatic bile ducts, gall bladder, other and unspecified parts of biliary tract, pancreas, other and digestive organs); oral cavity tumors (including but not limited to tumors of lip, tongue, gum, floor of mouth, palate, and other parts of mouth, parotid gland, and other parts of the salivary glands, tonsil, oropharynx, nasopharynx, pyriform sinus, hypopharynx, and other sites in the lip, oral cavity and pharynx); reproductive system tumors (including but not limited to tumors of vulva, vagina, Cervix uteri, Corpus uteri, uterus, ovary, and other sites associated with female genital organs, placenta, penis, prostate, testis, and other sites associated with male genital organs); respiratory tract tumors (including but not limited to tumors of nasal cavity and middle ear, accessory sinuses, larynx, trachea, bronchus and lung, e.g. small cell lung cancer or non-small cell lung cancer); skeletal system tumors (including but not limited to tumors of bone and articular cartilage of limbs, bone articular cartilage and other sites); skin tumors (including but not limited to malignant melanoma of the skin, non-melanoma skin cancer, basal cell carcinoma of skin, squamous cell carcinoma of skin, mesothelioma, Kaposi's sarcoma); and tumors involving other tissues including peripheral nerves and autonomic nervous system, connective and soft tissue, retroperitoneum and peritoneum, eye and adnexa, thyroid, adrenal gland and other endocrine glands and related structures, secondary and unspecified malignant neoplasm of lymph nodes, secondary malignant neoplasm of respiratory and digestive systems and secondary malignant neoplasm of other sites.

[00292] In some examples, the solid tumor treated by the methods of the instant disclosure 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.

[00293] In some examples, the solid tumor to be treated by the methods of the instant disclosure is selected 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.

[00294] In some examples, the solid tumor treated by the methods of the instant disclosure is breast cancer. Non limiting examples of breast cancer that can be treated by the instant methods 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.

[00295] In some examples, the solid tumor treated by the methods of the instant disclosure is bone cancer. Non limiting examples of bone cancer that can be treated by the instant methods include osteosarcoma, chondrosarcoma, the Ewing Sarcoma Family of Tumors (ESFTs).

[00296] In some examples, the solid tumor treated by the methods of the instant disclosure is skin cancer. Non limiting examples of skin cancer that can be treated by the instant methods include melanoma, basal cell skin cancer, and squamous cell skin cancer.

[00297] In some examples, the solid tumor treated by the methods of the instant disclosure is ocular tumor. Non limiting examples of ocular tumor that can be treated by the methods of the instant disclosure include ocular tumor is choroidal nevus, choroidal melanoma, choroidal metastasis, choroidal hemangioma, choroidal osteoma, iris melanoma, uveal melanoma, intraocular lymphoma, melanocytoma, metastasis retinal capillary hemangiomas, congenital hypertrophy of the RPE, RPE adenoma or retinoblastoma.

[00298] In some embodiments solid tumors treated by the methods disclosed herein exclude cancers that are known to be associated with HPV (Human papillomavirus). The excluded group includes HPV positive cervical cancer, HPV positive anal cancer, and HPV head and neck cancers, such as oropharyngeal cancers.

[00299] The term "liquid cancer" as used herein refers to cancer cells that are present in body fluids, such as blood, lymph and bone marrow. Liquid cancers include leukemia, myeloma and liquid lymphomas. Liquid lymphomas include lymphomas that contain cysts or liquid areas. Liquid cancers as used herein do not include solid tumors, such as sarcomas and carcinomas or solid lymphomas that do not contain contain cysts or liquid areas.

[00300] Liquid cancer cancers that can be treated by the methods provided herein include, but are not limited to, leukemias, myelomas, and liquid lymphomas. In specific embodiments, liquid cancers that can be treated in accordance with the methods described include, but are not limited to, liquid lymphomas, lekemias, and myelomas. Exemplary liquid lymphomas and leukemias that can be treated in accordance with the methods described include, but are not limited to, chronic lymphocytic leukemia/small lymphocytic lymphoma, B-cell prolymphocytic leukemia, lymphoplasmacytic lymphoma (such as waldenström macroglobulinemia), splenic marginal zone lymphoma, plasma cell myeloma, plasmacytoma, monoclonal immunoglobulin deposition diseases, heavy chain diseases, extranodal marginal zone B cell lymphoma, also called malt lymphoma, nodal marginal zone B cell lymphoma (nmzl), follicular lymphoma, mantle cell lymphoma, diffuse large B cell lymphoma, mediastinal (thymic) large B cell lymphoma, intravascular large B cell lymphoma, primary effusion lymphoma, burkitt lymphoma/leukemia, T cell prolymphocytic leukemia, T cell large granular lymphocytic leukemia, aggressive NK cell leukemia, adult T cell leukemia/lymphoma, extranodal NK/T cell lymphoma, nasal type, enteropathy-type T cell lymphoma, hepatosplenic T cell lymphoma, blastic NK cell lymphoma, mycosis fungoides / sezary syndrome, primary cutaneous CD30-positive T cell lymphoproliferative disorders, primary cutaneous anaplastic large cell lymphoma, lymphomatoid papulosis, angioimmunoblastic T cell lymphoma, peripheral T cell lymphoma, unspecified, anaplastic large cell lymphoma, classical Hodgkin lymphomas (nodular sclerosis, mixed cellularity, lymphocyte-rich, lymphocyte depleted or not depleted), and nodular lymphocyte-predominant Hodgkin lymphoma.

[00301] Examples of liquid cancers include cancers involving hyperplastic/neoplastic cells of hematopoietic origin, *e.g.*, arising from myeloid, lymphoid or erythroid lineages, or precursor cells thereof. Exemplary disorders include: 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, L. (1991) Crit Rev. in 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), multiple mylenoma, hairy cell leukemia (HLL) and Waldenstrom's macroglobulinemia (WM). Additional forms of malignant liquid lymphomas include, but are not limited to non-Hodgkin lymphoma and variants thereof, adult T cell leukemia/lymphoma (ATL), cutaneous T-cell lymphoma (CTCL), periphieral T-cell lymphoma (PTCL), large granular lymphocytic leukemia (LGF), Hodgkin's disease and Reed-Sternberg disease. For example, liquid cancers include, but are not limited to, acute lymphocytic leukemia (ALL); T-cell acute lymphocytic leukemia (T-ALL); anaplastic large cell lymphoma (ALCL); chronic myelogenous leukemia (CML); acute myeloid leukemia (AML); chronic lymphocytic leukemia (CLL); B-cell chronic lymphocytic leukemia (B-CLL); diffuse large B-cell lymphomas (DLBCL); hyper eosinophilia / chronic eosinophilia; and Burkitt's lymphoma.

[00302] In embodiments, the cancer comprises an acute lymphoblastic leukemia; acute myeloid leukemia; AIDS-related cancers; AIDS-related lymphoma; chronic lymphocytic leukemia; chronic myelogenous leukemia; chronic myeloproliferative disorders; adult T cell leukemia/lymphoma (ATL), cutaneous T-cell

lymphoma (CTCL), periphieral T-cell lymphoma (PTCL); Hodgkin lymphoma; multiple myeloma; multiple myeloma/plasma cell neoplasm; Non-Hodgkin lymphoma; or primary central nervous system (CNS) lymphoma. In various embodiments, the liquid cancer can be B-cell chronic lymphocytic leukemia, B-cell lymphoma-DLBCL, B-cell lymphoma-DLBCL-germinal center-like, B-cell lymphoma-DLBCL-activated B-cell-like, or Burkitt's lymphoma.

[00303] In some embodiments, a subject treated in accordance with the methods provided herein is a human who has or is diagnosed with cancer lacking p53 deactivating mutation and/or expressing wild type p53. In some embodiments, a subject treated for cancer in accordance with the methods provided herein is a human predisposed or susceptible to cancer lacking p53 deactivating mutation and/or expressing wild type p53. In some embodiments, a subject treated for cancer in accordance with the methods provided herein is a human at risk of developing cancer lacking p53 deactivating mutation and/or expressing wild type p53. A p53 deactivating mutation in some example can be a mutation in DNA-binding domain of the p53 protein. In some examples the p53 deactivating mutation can be a missense mutation. In various examples, the cancer can be determined to lack one or more p53 deactivating mutations selected from mutations at one or more of residues R175, G245, R248, R249, R273, and R282. The lack of p53 deactivating mutation and/or the presence of wild type p53 in the cancer can be determined by any suitable method known in art, for example by sequencing, array based testing, RNA analysis and amplifications methods like PCR.

[00304] In certain embodiments, the human subject is refractory and/or intolerant to one or more other standard treatment of the cancer known in art. In some embodiments, the human subject has had at least one unsuccessful prior treatment and/or therapy of the cancer.

[00305] In some embodiments, a subject treated for tumor in accordance with the methods provided herein is a human, who has or is diagnosed with a tumor. In other embodiments, a subject treated for tumor in accordance with the methods provided herein is a human, predisposed or susceptible to a tumor. In some embodiments, a subject treated for tumor in accordance with the methods provided herein is a human, at risk of developing a tumor.

[00306] In some embodiments, a subject treated for tumor in accordance with the methods provided herein is a human, who has or is diagnosed with a tumor, determined to lack a p53 deactivating mutation and/or expressing wild type p53. In other embodiments, a subject treated for tumor in accordance with the methods provided herein is a human, predisposed or susceptible to a tumor, determined to lack a p53 deactivating mutation and/or expressing wild type p53. In some embodiments, a subject treated for tumor in accordance with the methods provided herein is a human, at risk of developing a tumor, determined to lack a p53 deactivating mutation and/or expressing wild type p53. A p53 deactivating mutation, as used herein is any mutation that leads to loss of (or a decrease in) the *in vitro* apoptotic activity of p53.

[00307] In some embodiments, the subject treated for tumor in accordance with the methods provided herein is a human, who has or is diagnosed with a tumor, determined to have a p53 gain of function mutation. In other embodiments, a subject treated for tumor in accordance with the methods provided herein is a human, predisposed or susceptible to a tumor, determined to have a p53 gain of function mutation. In some

embodiments, a subject treated for tumor in accordance with the methods provided herein is a human, at risk of developing a tumor, determined to have a p53 gain of function mutation. A p53 gain of function mutation, as used herein is any mutation such that the mutant p53 exerts oncogenic functions beyond their negative domination over the wild-type p53 tumor suppressor functions. The p53 gain of function mutant protein mat exhibit new activities that can contribute actively to various stages of tumor progression and to increased resistance to anticancer treatments. Accordingly, in some embodiments, a subject with a tumor in accordance with the composition as provided herein is a human who has or is diagnosed with a tumor that is determined to have a p53 gain of function mutation.

[00308] In some embodiments, the subject treated for tumor in accordance with the methods provided herein is a human, who has or is diagnosed with a tumor that is not p53 negative. In other embodiments, a subject treated for tumor in accordance with the methods provided herein is a human, predisposed or susceptible to a tumor that is not p53 negative. In some embodiments, a subject treated for tumor in accordance with the methods provided herein is a human, at risk of developing a tumor that is not p53 negative.

[00309] In some embodiments, the subject treated for tumor in accordance with the methods provided herein is a human, who has or is diagnosed with a tumor that expresses p53 with partial loss of function mutation. In other embodiments, a subject treated for tumor in accordance with the methods provided herein is a human, predisposed or susceptible to a tumor that expresses p53 with partial loss of function mutation. In some embodiments, a subject treated for tumor in accordance with the methods provided herein is a human, at risk of developing a tumor that expresses p53 with partial loss of function mutation. As used herein "a partial loss of p53 function" mutation means that the mutant p53 exhibits some level of function of normal p53, but to a lesser or slower extent. For example, a partial loss of p53 function can mean that the cells become arrested in cell division to a lesser or slower extent.

[00310] In some embodiments, the subject treated for tumor in accordance with the methods provided herein is a human, who has or is diagnosed with a tumor that expresses p53 with a copy loss mutation and a deactivating mutation. In other embodiments, a subject treated for tumor in accordance with the methods provided herein is a human, predisposed or susceptible to a tumor that expresses p53 with a copy loss mutation and a deactivating mutation. In some embodiments, a subject treated for tumor in accordance with the methods provided herein is a human, at risk of developing a tumor that expresses p53 with a copy loss mutation and a deactivating mutation. [

[00311] In some embodiments, the subject treated for tumor in accordance with the methods provided herein is a human, who has or is diagnosed with a tumor that expresses p53 with a copy loss mutation. In other embodiments, a subject treated for tumor in accordance with the methods provided herein is a human, predisposed or susceptible to a tumor that expresses p53 with a copy loss mutation. In some embodiments, a subject treated for tumor in accordance with the methods provided herein is a human, at risk of developing a tumor that expresses p53 with a copy loss mutation.

[00312] In some embodiments, the subject treated for tumor in accordance with the methods provided herein is a human, who has or is diagnosed with a tumor that expresses p53 with one or more silent mutations. In

other embodiments, a subject treated for tumor in accordance with the methods provided herein is a human, predisposed or susceptible to a tumor that expresses p53 with one or more silent mutations. In some embodiments, a subject treated for tumor in accordance with the methods provided herein is a human, at risk of developing a tumor that expresses p53 with one or more silent mutations. Silent mutations as used herein are mutations which cause no change in the encoded p53 amino acid sequence.

[00313] In some embodiments, a subject treated for tumor in accordance with the methods provided herein is a human, who has or is diagnosed with a tumor, determined to lack a dominant p53 deactivating mutation. Dominant p53 deactivating mutation or dominant negative mutation, as used herein, is a mutation wherein the mutated p53 inhibits or disrupt the activity of the wild-type p53 gene.

[00314] 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.

Pharmaceutically-acceptable salts

[00315] The invention provides the use of pharmaceutically-acceptable salts of any therapeutic compound described herein. Pharmaceutically-acceptable salts include, for example, acid-addition salts and base-addition salts. The acid that is added to the compound to form an acid-addition salt can be an organic acid or an inorganic acid. A base that is added to the compound to form a base-addition salt can be an organic base or an inorganic base. In some embodiments, a pharmaceutically-acceptable salt is a metal salt. In some embodiments, a pharmaceutically-acceptable salt is an ammonium salt.

[00316] Metal salts can arise from the addition of an inorganic base to a compound of the invention. The inorganic base consists of a metal cation paired with a basic counterion, such as, for example, hydroxide, carbonate, bicarbonate, or phosphate. The metal can be an alkali metal, alkaline earth metal, transition metal, or main group metal. In some embodiments, the metal is lithium, sodium, potassium, cesium, cerium, magnesium, manganese, iron, calcium, strontium, cobalt, titanium, aluminum, copper, cadmium, or zinc.

[00317] In some embodiments, a metal salt is a lithium salt, a sodium salt, a potassium salt, a cesium salt, a cerium salt, a magnesium salt, a manganese salt, an iron salt, a calcium salt, a strontium salt, a cobalt salt, a titanium salt, an aluminum salt, a copper salt, a cadmium salt, or a zinc salt.

[00318] Ammonium salts can arise from the addition of ammonia or an organic amine to a compound of the invention. In some embodiments, the organic amine is triethyl amine, diisopropyl amine, ethanol amine, diethanol amine, triethanol amine, morpholine, N-methylmorpholine, piperidine, N-methylpiperidine, N-ethylpiperidine, dibenzylamine, piperazine, pyridine, pyrrazole, pipyrrazole, imidazole, pyrazine, or pipyrazine.

[00319] In some embodiments, an ammonium salt is a triethyl amine salt, a diisopropyl amine salt, an ethanol amine salt, a diethanol amine salt, a triethanol amine salt, a morpholine salt, an N-methylmorpholine salt, a piperidine salt, an N-methylpiperidine salt, an N-ethylpiperidine salt, a dibenzylamine salt, a piperazine salt, a pyridine salt, a pyrrazole salt, a pipyrrazole salt, an imidazole salt, a pyrazine salt, or a pipyrazine salt.

[00320] Acid addition salts can arise from the addition of an acid to a compound of the invention. In some embodiments, the acid is organic. In some embodiments, the acid is inorganic. In some embodiments, the acid is hydrochloric acid, hydrobromic acid, hydroiodic acid, nitric acid, nitrous acid, sulfuric acid, sulfurous acid, a phosphoric acid, isonicotinic acid, lactic acid, salicylic acid, tartaric acid, ascorbic acid, gentisinic acid, gluconic acid, glucaronic acid, saccaric acid, formic acid, benzoic acid, glutamic acid, pantothenic acid, acetic acid, propionic acid, butyric acid, fumaric acid, succinic acid, methanesulfonic acid, ethanesulfonic acid, benzenesulfonic acid, p-toluenesulfonic acid, citric acid, oxalic acid, or maleic acid.

[00321] In some embodiments, the salt is a hydrochloride salt, a hydrobromide salt, a hydroiodide salt, a nitrate salt, a nitrite salt, a sulfate salt, a sulfite salt, a phosphate salt, isonicotinate salt, a lactate salt, a salicylate salt, a tartrate salt, an ascorbate salt, a gentisinate salt, a gluconate salt, a glucaronate salt, a saccarate salt, a formate salt, a benzoate salt, a glutamate salt, a pantothenate salt, an acetate salt, a propionate salt, a butyrate salt, a fumarate salt, a succinate salt, a methanesulfonate (mesylate) salt, an ethanesulfonate salt, a benzenesulfonate salt, a p-toluenesulfonate salt, a citrate salt, an oxalate salt , or a maleate salt.

Purity of Compounds of the Invention

[00322] Any compound herein can be purified. A compound herein can be 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.

Formulation and Administration

Mode of Administration

[00323] An effective amount of a peptidomimetic macrocycles of the disclosure can be administered in either single or multiple doses by any of the accepted modes of administration. In some embodiments, the peptidomimetic macrocycles of the disclosure are administered parenterally, for example, by subcutaneous, intramuscular, intrathecal, intravenous or epidural injection. For example, the peptidomimetic macrocycle is administered intravenously, intraarterially, subcutaneously or by infusion. In some examples, the peptidomimetic macrocycle is administered intravenously. In some examples, the peptidomimetic macrocycle is administered intraarterially.

[00324] Regardless of the route of administration selected, the peptidomimetic macrocycles of the present disclosure, and/or the pharmaceutical compositions of the present disclosure, are formulated into pharmaceutically-acceptable dosage forms. The peptidomimetic macrocycles according to the disclosure can be formulated for administration in any convenient way for use in human or veterinary medicine, by analogy with other pharmaceuticals.

[00325] In one aspect, the disclosure provides pharmaceutical formulation comprising a therapeutically-effective amount of one or more of the peptidomimetic macrocycles described above, formulated together with one or more pharmaceutically acceptable carriers (additives) and/or diluents. In one embodiment, one or more of the peptidomimetic macrocycles described herein are formulated for parenteral administration for parenteral administration, one or more peptidomimetic macrocycles disclosed herein can be formulated as aqueous or nonaqueous solutions, dispersions, suspensionsor emulsions or sterile powders which can be reconstituted into sterile injectable solutions or dispersions just prior to use. Such formulations can comprise sugars, alcohols, antioxidants, buffers, bacteriostats, solutes which render the formulation isotonic with the blood of the intended recipient or suspending or thickening agents. These compositions can also contain adjuvants such as preservatives, wetting agents, emulsifying agents and dispersing agents. Prevention of the action of microorganisms upon the subject compounds can be ensured by the inclusion of various antibacterial and antifungal agents, for example, paraben, chlorobutanol, phenol sorbic acid, and the like. It can also be desirable to include isotonic agents, such as sugars, sodium chloride, and the like into the compositions. In addition, prolonged absorption of the injectable pharmaceutical form can be brought about by the inclusion of agents which delay absorption such as aluminum monostearate and gelatin. If desired the formulation can be diluted prior to use with, for example, an isotonic saline solution or a dextrose solution. In some examples, the peptidomimetic macrocycle is formulated as an aqueous solution and is administered intravenously.

Amount and frequency of administration

[00326] Dosing can be determined using various techniques. The selected dosage level can depend upon a variety of factors including the activity of the particular peptidomimetic macrocycle employed, the route of administration, the time of administration, the rate of excretion or metabolism of the particular peptidomimetic macrocycle being employed, the duration of the treatment, other drugs, compounds and/or materials used in combination with the particular peptidomimetic macrocycle employed, the age, sex, weight, condition, general health and prior medical history of the patient being treated, and like factors well known in

the medical arts. The dosage values can also vary with the severity of the condition to be alleviated. For any particular subject, specific dosage regimens can be adjusted over time according to the individual need and the professional judgment of the person administering or supervising the administration of the compositions.

[00327] A physician or veterinarian can prescribe the effective amount of the pharmaceutical composition required. For example, the physician or veterinarian could start doses of the compounds of the disclosure employed in the pharmaceutical composition at levels lower than that required in order to achieve the desired therapeutic effect and gradually increase the dosage until the desired effect is achieved.

[00328] In some embodiments, a suitable daily dose of a peptidomimetic macrocycle of the disclosure can be that amount of the peptidomimetic macrocycle which is the lowest dose effective to produce a therapeutic effect. Such an effective dose will generally depend upon the factors described above. The precise time of administration and amount of any particular peptidomimetic macrocycle that will yield the most effective treatment in a given patient will depend upon the activity, pharmacokinetics, and bioavailability of a particular peptidomimetic macrocycle, physiological condition of the patient (including age, sex, disease type and stage, general physical condition, responsiveness to a given dosage and type of medication), route of administration, and the like.

[00329] Dosage can be based on the amount of the peptidomimetic macrocycle per kg body weight of the patient. Alternatively, the dosage of the subject disclosure can be determined by reference to the plasma concentrations of the peptidomimetic macrocycle. For example, the maximum plasma concentration (Cmax) and the area under the plasma concentration-time curve from time 0 to infinity (AUC) can be used.

[00330] In some embodiments, the subject is a human subject and the amount of the peptidomimetic macrocycle administered is 0.01-100 mg per kilogram body weight of the human subject. For example, in various examples, the amount of the peptidomimetic macrocycle administered is about .01-50 mg/kg, about 0.01-20 mg/kg, about 0.01-10 mg/kg, about 0.1-100 mg/kg, about 0.1-50 mg/kg, about 0.1-20 mg/kg, about 0.1-10 mg/kg, about 0.5-100 mg/kg, about 0.5-50 mg/kg, about 0.5-20 mg/kg, about 0.5-10 mg/kg, about 1-100 mg/kg, about 1-50 mg/kg, about 1-20 mg/kg, about 1-10 mg/kg body weight of the human subject. In one embodiment, about 0.5 mg-10 mg of the peptidomimetic macrocycle per kilogram body weight of the human subject is administered. In some examples the amount of the peptidomimetic macrocycle administered is about 0.16 mg, about 0.32 mg, about 0.64 mg, about 1.28 mg, about 3.56 mg, about 7.12 mg, about 14.24 mg, or about 20 mg per kilogram body weight of the human subject. In some examples the amount of the peptidomimetic macrocycle administered is about 0.16 mg, about 0.32 mg, about 0.64 mg, about 1.28 mg, about 3.56 mg, about 7.12 mg, or about 14.24 mg per kilogram body weight of the human subject. In some examples the amount of the peptidomimetic macrocycle administered is about 0.16 mg per kilogram body weight of the human subject. In some examples the amount of the peptidomimetic macrocycle administered is about 0.32 mg per kilogram body weight of the human subject. In some examples the amount of the peptidomimetic macrocycle administered is about 0.64 mg per kilogram body weight of the human subject. In some examples the amount of the peptidomimetic macrocycle administered is about 1.28 mg per kilogram body weight of the human subject. In some examples the amount of the peptidomimetic macrocycle

administered is about 3.56 mg per kilogram body weight of the human subject. In some examples the amount of the peptidomimetic macrocycle administered is about 7.12 mg per kilogram body weight of the human subject. In some examples the amount of the peptidomimetic macrocycle administered is about 14.24 mg per kilogram body weight of the human subject.

[00331] In some embodiments about 0.5- about 20 mg or about 0.5- about 10 mg of the peptidomimetic macrocycle per kilogram body weight of the human subject is administered two times a week. For example about 0.5- about 1 mg, about 0.5- about 5 mg, about 0.5- about 10 mg, about 0.5- about 15 mg, about 1- about 5 mg, about 1- about 10 mg, about 1- about 15 mg, about 1- about 20 mg, about 5- about 10 mg, about 1- about 15 mg, about 5- about 20 mg, about 10- about 15 mg, about 10- about 20 mg, or about 15- about 20 mg of the peptidomimetic macrocycle per kilogram body weight of the human subject is administered about twice a week. In some examples about 1 mg, about 1.25 mg, about 1.5 mg, about 1.75 mg, about 2 mg, about 2.25 mg, about 2.5 mg, about 2.75 mg, about 3 mg, about 3.25 mg, about 3.5 mg, about 3.75 mg, about 4 mg, about 4.25 mg, about 4.5 mg, about 4.75 mg, about 5 mg, about 5.25 mg, about 5.5 mg, about 5.75 mg, about 6 mg, about 6.25 mg, about 6.5 mg, about 6.75 mg, about 7 mg, about 7.25 mg, about 7.5 mg, about 7.75 mg, about 8 mg, about 8.25 mg, about 8.5 mg, about 8.75 mg, about 9 mg, about 9.25 mg, about 9.5 mg, about 9.75 mg, about 10 mg, about 10.25 mg, about 10.5 mg, about 10.75 mg, about 11 mg, about 11.25 mg, about 11.5 mg, about 11.75 mg, about 12 mg, about 12.25 mg, about 12.5 mg, about 12.75 mg, about 13 mg, about 13.25 mg, about 13.5 mg, about 13.75 mg, about 14 mg, about 14.25 mg, about 14.5 mg, about 14.75 mg, about 15 mg, about 15.25 mg, about 15.5 mg, about 15.75 mg, about 16 mg, about 16.5 mg, about 17 mg, about 17.5 mg, about 18 mg, about 18.5 mg, about 19 mg, about 19.5 mg, or about 20 mg of the peptidomimetic macrocycle per kilogram body weight of the human subject is administered two times a week. In some examples, the amount of the peptidomimetic macrocycle administered is about 1.25 mg, about 2.5 mg, about 5 mg, about 10 mg, or about 20 mg per kilogram body weight of the human subject and the peptidomimetic macrocycle is administered two times a week. In some examples, the amount of the peptidomimetic macrocycle administered is about 1.25 mg, about 2.5 mg, about 5 mg or about 10 mg per kilogram body weight of the human subject and the peptidomimetic macrocycle is administered two times a week.

[00332] In some embodiments about 0.5- about 20 mg or about 0.5- about 10 mg of the peptidomimetic macrocycle per kilogram body weight of the human subject is administered once a week. For example about 0.5- about 1 mg, about 0.5- about 5 mg, about 0.5- about 10 mg, about 0.5- about 15 mg, about 1- about 5 mg, about 1- about 10 mg, about 1- about 15 mg, about 1- about 20 mg, about 5- about 10 mg, about 1- about 15 mg, about 5- about 20 mg, about 10- about 15 mg, about 10- about 20 mg, or about 15- about 20 mg of the peptidomimetic macrocycle per kilogram body weight of the human subject is administered once a week. In some examples about 1 mg, about 1.25 mg, about 1.5 mg, about 1.75 mg, about 2 mg, about 2.25 mg, about 2.5 mg, about 2.75 mg, about 3 mg, about 3.25 mg, about 3.5 mg, about 3.75 mg, about 4 mg, about 4.25 mg, about 4.5 mg, about 4.75 mg, about 5 mg, about 5.25 mg, about 5.5 mg, about 5.75 mg, about 6 mg, about 6.25 mg, about 6.5 mg, about 6.75 mg, about 7 mg, about 7.25 mg, about 7.5 mg, about 7.75 mg, about 8 mg, about 8.25 mg, about 8.5 mg, about 8.75 mg, about 9 mg, about 9.25 mg, about 9.5 mg, about 9.75 mg, about

10 mg, about 10.25 mg, about 10.5 mg, about 10.75 mg, about 11 mg, about 11.25 mg, about 11.5 mg, about 11.75 mg, about 12 mg, about 12.25 mg, about 12.5 mg, about 12.75 mg, about 13 mg, about 13.25 mg, about 13.5 mg, about 13.75 mg, about 14 mg, about 14.25 mg, about 14.5 mg, about 14.75 mg, about 15 mg, about 15.25 mg, about 15.5 mg, about 15.75 mg, about 16 mg, about 16.5 mg, about 17 mg, about 17.5 mg, about 18 mg, about 18.5 mg, about 19 mg, about 19.5 mg, or about 20 mg of the peptidomimetic macrocycle per kilogram body weight of the human subject is administered once a week. In some examples, the amount of the peptidomimetic macrocycle administered is about 1.25 mg, about 2.5 mg, about 5 mg, about 10 mg, or about 20 mg per kilogram body weight of the human subject and the peptidomimetic macrocycle is administered once a week. In some examples, the amount of the peptidomimetic macrocycle administered is about 1.25 mg, about 2.5 mg, about 5 mg or about 10 mg per kilogram body weight of the human subject and the peptidomimetic macrocycle is administered once a week.

[00333] In some embodiments about 0.5- about 20 mg or about 0.5- about 10 mg of the peptidomimetic macrocycle per kilogram body weight of the human subject is administered 3, 4, 5, 6, or 7 times a week. For example, about 0.5- about 1 mg, about 0.5- about 5 mg, about 0.5- about 10 mg, about 0.5- about 15 mg, about 1- about 5 mg, about 1- about 10 mg, about 1- about 15 mg, about 1- about 20 mg, about 5- about 10 mg, about 1- about 15 mg, about 5- about 20 mg, about 10- about 15 mg, about 10- about 20 mg, or about 15- about 20 mg of the peptidomimetic macrocycle per kilogram body weight of the human subject is administered 3, 4, 5, 6, or 7 times a week. In some examples about 1 mg, about 1.25 mg, about 1.5 mg, about 1.75 mg, about 2 mg, about 2.25 mg, about 2.5 mg, about 2.75 mg, about 3 mg, about 3.25 mg, about 3.5 mg, about 3.75 mg, about 4 mg, about 4.25 mg, about 4.5 mg, about 4.75 mg, about 5 mg, about 5.25 mg, about 5.5 mg, about 5.75 mg, about 6 mg, about 6.25 mg, about 6.5 mg, about 6.75 mg, about 7 mg, about 7.25 mg, about 7.5 mg, about 7.75 mg, about 8 mg, about 8.25 mg, about 8.5 mg, about 8.75 mg, about 9 mg, about 9.25 mg, about 9.5 mg, about 9.75 mg, about 10 mg, about 10.25 mg, about 10.5 mg, about 10.75 mg, about 11 mg, about 11.25 mg, about 11.5 mg, about 11.75 mg, about 12 mg, about 12.25 mg, about 12.5 mg, about 12.75 mg, about 13 mg, about 13.25 mg, about 13.5 mg, about 13.75 mg, about 14 mg, about 14.25 mg, about 14.5 mg, about 14.75 mg, about 15 mg, about 15.25 mg, about 15.5 mg, about 15.75 mg, about 16 mg, about 16.5 mg, about 17 mg, about 17.5 mg, about 18 mg, about 18.5 mg, about 19 mg, about 19.5 mg, or about 20 mg of the peptidomimetic macrocycle per kilogram body weight of the human subject is administered 3, 4, 5, 6, or 7 times a week. In some examples, the amount of the peptidomimetic macrocycle administered is about 1.25 mg, about 2.5 mg, about 5 mg, about 10 mg, or about 20 mg per kilogram body weight of the human subject and the peptidomimetic macrocycle is administered 3, 4, 5, 6, or 7 times a week. In some examples, the amount of the peptidomimetic macrocycle administered is about 1.25 mg, about 2.5 mg, about 5 mg, or about 10 mg per kilogram body weight of the human subject and the peptidomimetic macrocycle is administered 3, 4, 5, 6, or 7 times a week.

[00334] In some embodiments, about 0.5- about 20 mg or about 0.5- about 10 mg of the peptidomimetic macrocycle per kilogram body weight of the human subject is administered once every 2, 3, or 4 weeks. For example, about 0.5- about 1 mg, about 0.5- about 5 mg, about 0.5- about 10 mg, about 0.5- about 15 mg,

about 1- about 5 mg, about 1- about 10 mg, about 1- about 15 mg, about 1- about 20 mg, about 5- about 10 mg, about 1- about 15 mg, about 5- about 20 mg, about 10- about 15 mg, about 10- about 20 mg, or about 15- about 20 mg of the peptidomimetic macrocycle per kilogram body weight of the human subject is administrated 3, 4, 5, 6, or 7 once every 2 or 3 week. In some examples about 1 mg, about 1.25 mg, about 1.5 mg, about 1.75 mg, about 2 mg, about 2.25 mg, about 2.5 mg, about 2.75 mg, about 3 mg, about 3.25 mg, about 3.5 mg, about 3.75 mg, about 4 mg, about 4.25 mg, about 4.5 mg, about 4.75 mg, about 5 mg, about 5.25 mg, about 5.5 mg, about 5.75 mg, about 6 mg, about 6.25 mg, about 6.5 mg, about 6.75 mg, about 7 mg, about 7.25 mg, about 7.5 mg, about 7.75 mg, about 8 mg, about 8.25 mg, about 8.5 mg, about 8.75 mg, about 9 mg, about 9.25 mg, about 9.5 mg, about 9.75 mg, about 10 mg, about 10.25 mg, about 10.5 mg, about 10.75 mg, about 11 mg, about 11.25 mg, about 11.5 mg, about 11.75 mg, about 12 mg, about 12.25 mg, about 12.5 mg, about 12.75 mg, about 13 mg, about 13.25 mg, about 13.5 mg, about 13.75 mg, about 14 mg, about 14.25 mg, about 14.5 mg, about 14.75 mg, about 15 mg, about 15.25 mg, about 15.5 mg, about 15.75 mg, about 16 mg, about 16.5 mg, about 17 mg, about 17.5 mg, about 18 mg, about 18.5 mg, about 19 mg, about 19.5 mg, or about 20 mg of the peptidomimetic macrocycle per kilogram body weight of the human subject is administered once every 2 or 3 weeks. In some examples, the amount of the peptidomimetic macrocycle administered is about 1.25 mg, about 2.5 mg, about 5 mg, about 10 mg, or about 20 mg per kilogram body weight of the human subject and the peptidomimetic macrocycle is administered once every 2 weeks. In some examples, the amount of the peptidomimetic macrocycle administered is about 1.25 mg, about 2.5 mg, about 5 mg or about 10 mg per kilogram body weight of the human subject and the peptidomimetic macrocycle is administered once every 2 weeks. In some examples, the amount of the peptidomimetic macrocycle administered is about 1.25 mg, about 2.5 mg, about 5 mg, about 10 mg, or about 20 mg per kilogram body weight of the human subject and the peptidomimetic macrocycle is administered once every 3 weeks. In some examples, the amount of the peptidomimetic macrocycle administered is about 1.25 mg, about 2.5 mg, about 5 mg, or about 10 mg per kilogram body weight of the human subject and the peptidomimetic macrocycle is administered once every 3 weeks.

[00335] In some embodiments, the peptidomimetic macrocycle is administered gradually over a period of time. A desired amount of peptidomimetic macrocycle can, for example can be administered gradually over a period of from about 0.1 h -24 h. In some cases a desired amount of peptidomimetic macrocycle is administered gradually over a period of 0.1 h, 0.5 h, 1 h, 1.5 h, 2 h, 2.5 h, 3 h, 3.5 h, 4 h, 4.5 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. In some examples, a desired amount of peptidomimetic macrocycle is administered gradually over a period of 0.25 -12 h, for example over a period of 0.25-1 h, 0.25-2 h, 0.25-3 h, 0.25-4 h, 0.25-6 h, 0.25-8 h, 0.25-10 h. In some examples, a desired amount of peptidomimetic macrocycle is administered gradually over a period of 0.25-2 h. In some examples, a desired amount of peptidomimetic macrocycle is administered gradually over a period of 0.25-1 h. In some examples, a desired amount of peptidomimetic macrocycle is administered gradually over a period of 0.25 h, 0.3 h, 0.4 h, 0.5 h, 0.6 h, 0.7 h, 0.8 h, 0.9 h, 1.0 h, 1.1 h, 1.2 h, 1.3 h, 1.4 h, 1.5 h, 1.6 h, 1.7 h, 1.8 h, 1.9 h, or 2.0 h. In some examples, a desired amount of peptidomimetic macrocycle is

administered gradually over a period of 1 h. In some examples, a desired amount of peptidomimetic macrocycle is administered gradually over a period of 2 h.

[00336] Administration of the peptidomimetic macrocycles can continue as long as necessary. In some embodiments, one or more peptidomimetic macrocycle of the disclosure is administered for more than 1 day, more than 1 week, more than 1 month, more than 2 months, more than 3 months, more than 4 months, more than 5 months, more than 6 months, more than 7 months, more than 8 months, more than 9 months, more than 10 months, more than 11 months, more than 12 months, more than 13 months, more than 14 months, more than 15 months, more than 16 months, more than 17 months, more than 18 months, more than 19 months, more than 20 months, more than 21 months, more than 22 months, more than 23 months, or more than 24 months. In some embodiments, one or more peptidomimetic macrocycle of the disclosure is administered for less than 1 week, less than 1 month, less than 2 months, less than 3 months, less than 4 months, less than 5 months, less than 6 months, less than 7 months, less than 8 months, less than 9 months, less than 10 months, less than 11 months, less than 12 months, less than 13 months, less than 14 months, less than 15 months, less than 16 months, less than 17 months, less than 18 months, less than 19 months, less than 20 months, less than 21 months, less than 22 months, less than 23 months, or less than 24 months.

[00337] In some embodiments, the peptidomimetic macrocycle is administered on day 1, 8, 15 and 28 of a 28 day cycle. In some embodiments, the peptidomimetic macrocycle is administered on day 1, 8, 15 and 28 of a 28 day cycle and administration is continued for two cycles. In some embodiments, the peptidomimetic macrocycle is administered on day 1, 8, 15 and 28 of a 28 day cycle and administration is continued for three cycles. In some embodiments, the peptidomimetic macrocycle is administered on day 1, 8, 15 and 28 of a 28 day cycle and administration is continued for 4, 5, 6, 7, 8, 9, 10, or more cycles.

[00338] In some embodiments, the peptidomimetic macrocycle is administered on day 1, 8, 11 and 21 of a 21-day cycle. In some embodiments, the peptidomimetic macrocycle is administered on day 1, 8, 11 and 21 of a 21-day cycle and administration is continued for two cycles. In some embodiments, the peptidomimetic macrocycle is administered on day 1, 8, 11 and 21 of a 21-day cycle and administration is continued for three cycles. In some embodiments, the peptidomimetic macrocycle is administered on day 1, 8, 11 and 21 of a 21-day cycle and administration is continued for 4, 5, 6, 7, 8, 9, 10, or more cycles.

[00339] In some embodiments, one or more peptidomimetic macrocycle of the disclosure is administered chronically on an ongoing basis. In some embodiments administration of one or more peptidomimetic macrocycle of the disclosure is continued until documentation of disease progression, unacceptable toxicity, or patient or physician decision to discontinue administration.

[00340] In some embodiments, the compounds of the invention can be used to treat one condition. In some embodiments, the compounds of the invention can be used to treat two conditions. In some embodiments, the compounds of the invention can be used to treat three conditions. In some embodiments, the compounds of the invention can be used to treat four conditions. In some embodiments, the compounds of the invention can be used to treat five conditions.

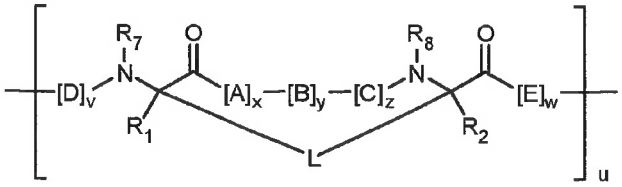
Sequence Homology

[00341] 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.

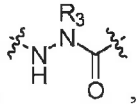
[00342] Various methods and software programs can be used to determine the homology between two or more peptides, such as NCBI BLAST, Clustal W, MAFFT, Clustal Omega, AlignMe, Praline, or another suitable method or algorithm.

Peptidomimetic Macrocycles

[00343] In some embodiments, a peptidomimetic macrocycle has the Formula (I):



wherein:

- each A, C, D, and E is independently a natural or non-natural amino acid or an amino acid analog, and each terminal D and E independently optionally includes a capping group;
- each B is independently a natural or non-natural amino acid, an 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–, 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 is independently hydrogen, alkyl, alkenyl, alkynyl, arylalkyl, heteroalkyl, cycloalkyl, heterocycloalkyl, cycloalkylalkyl, aryl, or heteroaryl, 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, 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 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 and w is independently an integer from 1-1000, for example 1-500, 1-200, 1-100, 1-50, 1-30, 1-20, or 1-10;
- u is an integer from 1-10, for example 1-5, 1-3 or 1-2;
- each x, y, and z is independently an integer from 0-10, for example the sum of x+y+z is 2, 3, or 6; and
- n is an integer from 1-5.

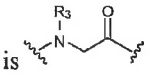
[00344] In some embodiments, v and w are integers from 1-30. In some embodiments, w is an integer from 3-1000, for example 3-500, 3-200, 3-100, 3-50, 3-30, 3-20, or 3-10. In some embodiments, the sum of x+y+z is 3 or 6. In some embodiments, the sum of x+y+z is 3. In other embodiments, the sum of x+y+z is 6.

[00345] 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 1-1000, for example 1-500, 1-200, 1-100, 1-50, 1-30, 1-20, or 1-10. In some embodiments, v is 2.

[00346] 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.

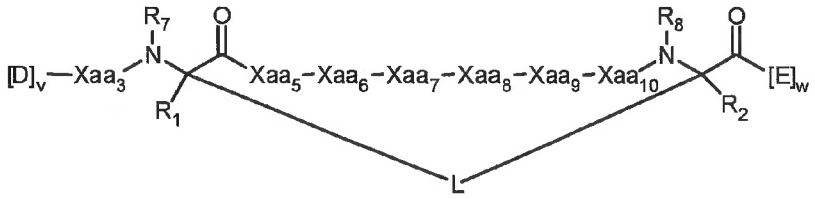
[00347] In one example, at least one of R_1 and R_2 is alkyl that is unsubstituted or substituted with halo-. In another example, both R_1 and R_2 are independently alkyl that is unsubstituted or substituted with halo–. In some embodiments, at least one of R_1 and R_2 is methyl. In other embodiments, R_1 and R_2 are methyl.

[00348] 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 wherein the amino acids are not identical, e.g. Gln–Asp–Ala as well as embodiments wherein 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.

[00349] In some embodiments, the peptidomimetic macrocycle comprises a secondary structure which is an α-helix and R_8 is –H, allowing for 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  .

[00350] 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.

[00351] In some embodiments, peptidomimetic macrocycles are also provided of the formula:



wherein:

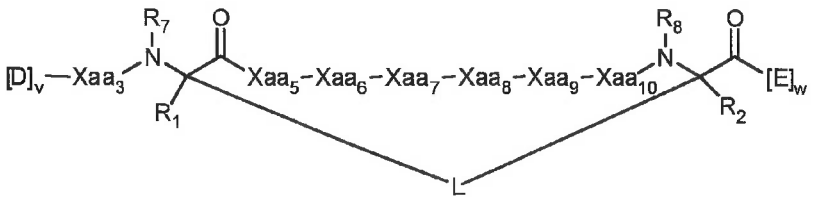
- each of Xaa_3, Xaa_5, Xaa_6, Xaa_7, Xaa_8, Xaa_9, and Xaa_{10} is individually an amino acid, wherein at least three of Xaa_3, Xaa_5, Xaa_6, Xaa_7, Xaa_8, Xaa_9, and Xaa_{10} are the same amino acid as the amino acid at the corresponding position of the sequence Phe_3-X_4-His_5-Tyr_6-Trp_7-Ala_8-Gln_9-Leu_{10}-X_{11}-Ser_{12}, wherein each X is an amino acid;
- each D and E is independently a natural or non-natural amino acid or an amino acid analog;
- 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 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, arylene, heteroarylene, 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;
- R_7 is –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;
- R_8 is –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;
- 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
- n is an integer from 1-5.

[00352] In some embodiments, v and w are integers from 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.

[00353] 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}.

[00354] In some embodiments, a peptidomimetic macrocycle has 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-Glu_5-Tyr_6-Trp_7-Ala_8-Gln_9-Leu_{10}/Cba_{10}-X_{11}-Ala_{12}, wherein each X is an amino acid;
- each D is independently a natural or non-natural amino acid or an amino acid analog;
- each E is independently a natural or non-natural amino acid or an amino acid analog, for example an amino acid selected from 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 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 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, arylene, heteroarylene, 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;
- R_7 is –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;
- R_8 is –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;
- 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
- n is an integer from 1-5.

[00355] 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}.

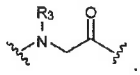
[00356] In some embodiments, w is an integer from 3-10, for example 3-6, 3-8, 6-8, or 6-10. In some embodiments, w is 3. In other embodiments, w is 6. In some embodiments, v is an integer from 1-10, for example 2-5. In some embodiments, v is 2.

[00357] 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.

[00358] 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.

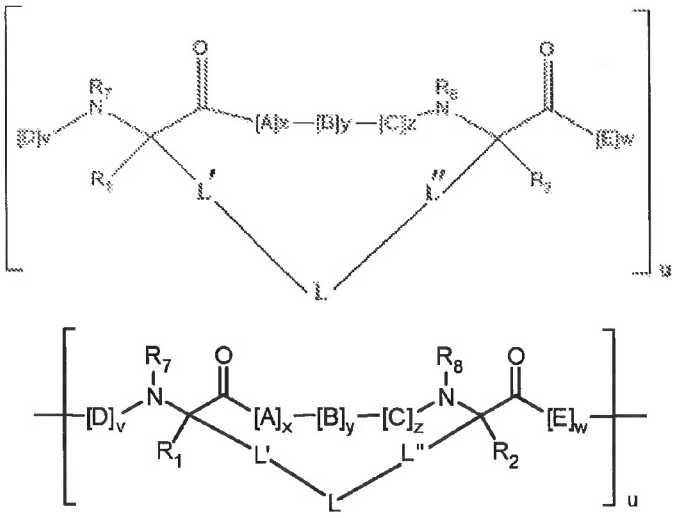
[00359] In some embodiments, x+y+z is at least 3. In other embodiments, x+y+z is 1, 2, 3, 4, 5, 6, 7, 8, 9 or 10. In some embodiments, the sum of x+y+z is 3 or 6. In some embodiments, the sum of x+y+z is 3. In other embodiments, the sum of x+y+z is 6. Each occurrence of A, B, C, D or E in a macrocycle or macrocycle precursor is independently selected. For example, a sequence represented by the formula $[A]_x$, when x is 3, encompasses embodiments wherein the amino acids are not identical, e.g. Gln–Asp–Ala as well as embodiments wherein 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.

[00360] 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



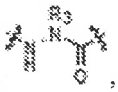
[00361] In other embodiments, the length of the macrocycle-forming linker L as measured from a first Cα to a second Cα is selected to stabilize a desired secondary peptide structure, such as an α-helix formed by residues of the peptidomimetic macrocycle including, but not necessarily limited to, those between the first Cα to a second Cα.

[00362] In some embodiments, a peptidomimetic macrocycle of Formula (I) has Formula (Ia):



Formula (Ia)

wherein:

- each A, C, D, and E is independently a natural or non-natural amino acid or an amino acid analog;
- 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-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 $CONR_3$;
- n is 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 x, y and z is independently an integer from 0-10, for example x+y+z is 2, 3, or 6; and
- u is an integer from 1-10, for example 1-5, 1-3, or 1-2.

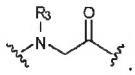
[00363] In some embodiments, L is a macrocycle-forming linker of the formula $–L_1–L_2–$. In some embodiments, each L_1 and L_2 is independently alkylene, alkenylene, alkynylene, heteroalkylene, cycloalkylene, heterocycloalkylene, arylene, heteroarylene, or $[-R_4-K-R_4-]_n$, each being optionally substituted with R_5; each R_4 is 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 n is an integer from 1-5.

[00364] 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.

[00365] In some 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 wherein 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 may encompass peptidomimetic macrocycles which are the same or different. For example, a compound may comprise peptidomimetic macrocycles comprising different linker lengths or chemical compositions.

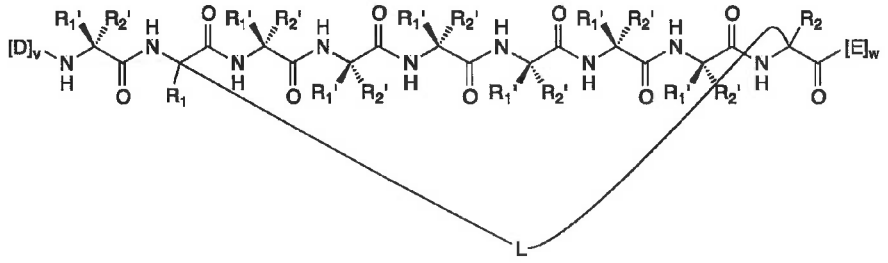
[00366] In some embodiments, the peptidomimetic macrocycle comprises a secondary structure which is a helix and R_8 is –H, allowing intrahelical hydrogen bonding. In some embodiments, at least one of A, B, C, D or E is an α,α-disubstituted amino acid. In one example, B is an α,α-disubstituted amino acid. 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



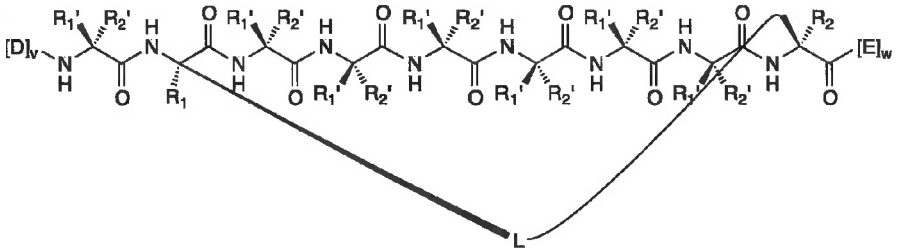
[00367] In other embodiments, the length of the macrocycle-forming linker L as measured from a first Cα to a second Cα is selected to stabilize a desired secondary peptide structure, such as a helix formed by residues of the peptidomimetic macrocycle including, but not necessarily limited to, those between the first Cα to a second Cα.

[00368] In one embodiment, the peptidomimetic macrocycle of Formula (I) is:



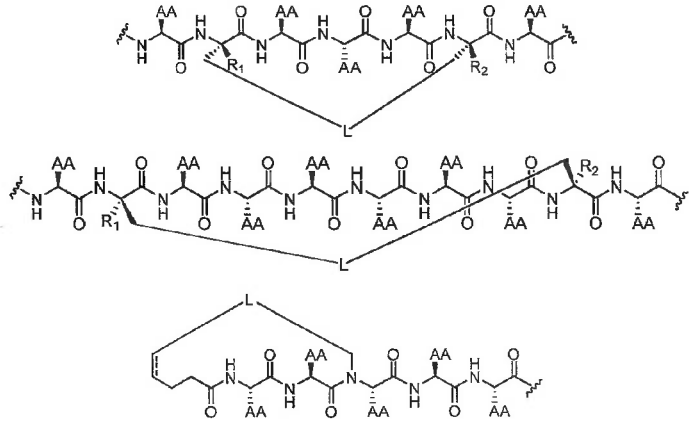
wherein each R_1 and R_2 is independently –H, alkyl, alkenyl, alkynyl, arylalkyl, cycloalkyl, cycloalkylalkyl, heteroalkyl, or heterocycloalkyl, unsubstituted or substituted with halo–.

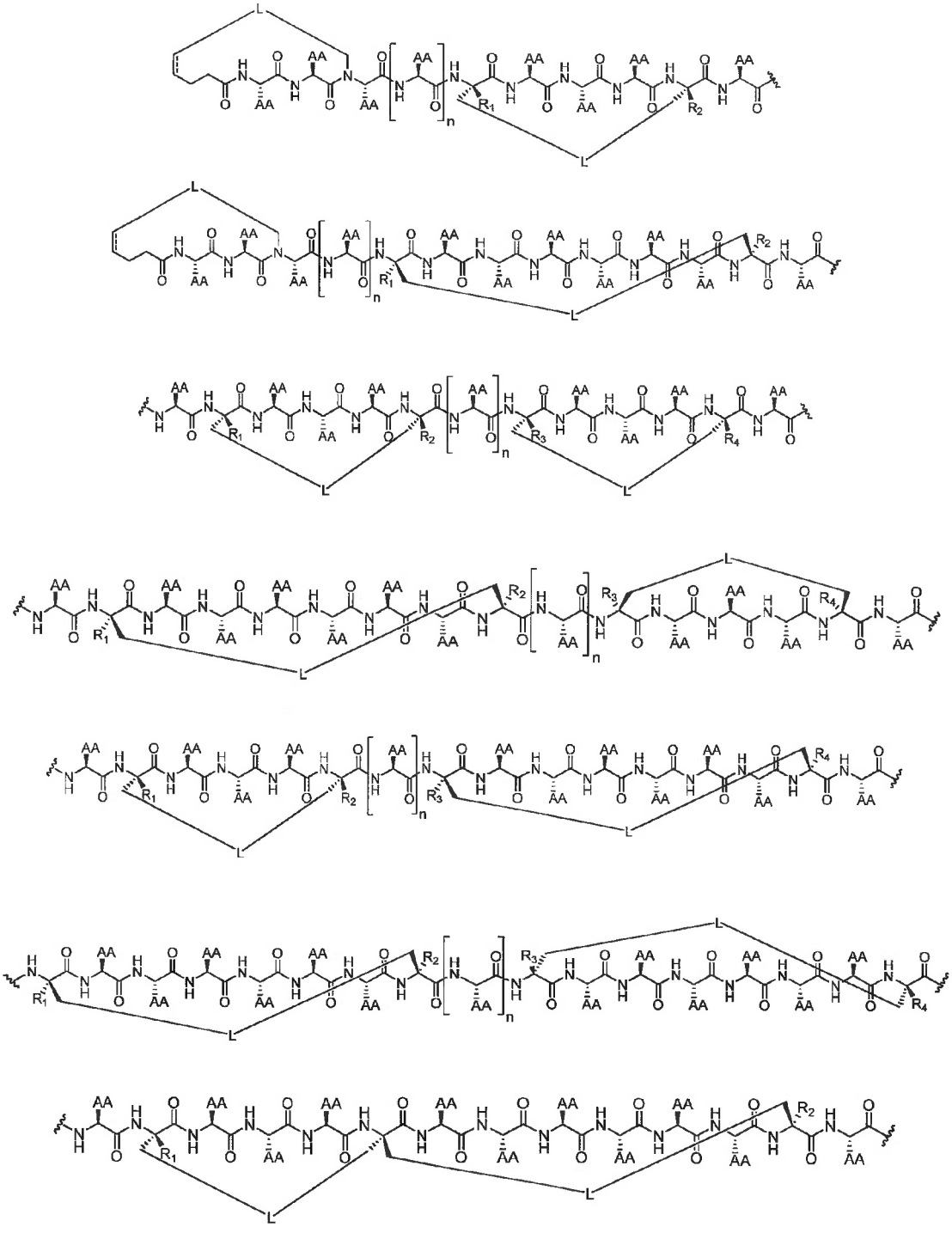
[00369] In related embodiments, the peptidomimetic macrocycle of Formula (I) is:

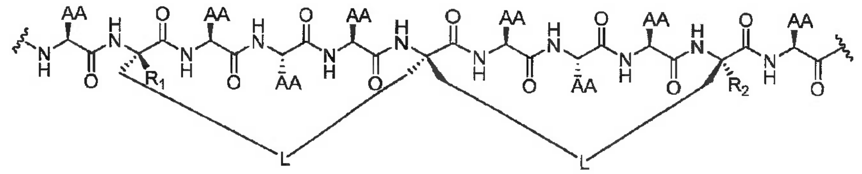


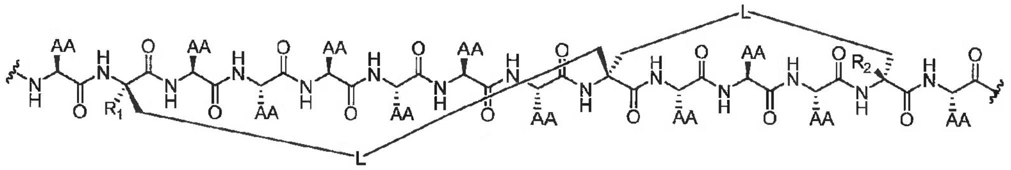
wherein each R_1' and R_2' is independently an amino acid.

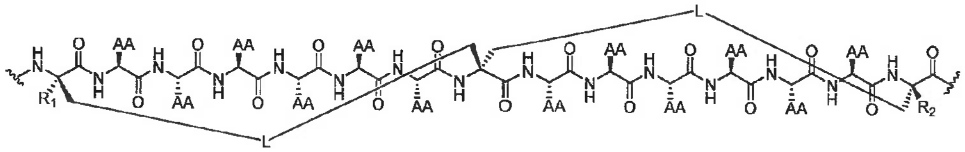
[00370] In other embodiments, the peptidomimetic macrocycle of Formula (I) is a compound of any of the formulas shown below:





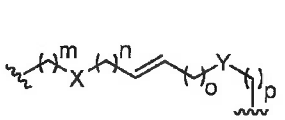




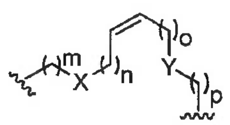


wherein "AA" represents any natural or non-natural amino acid side chain and " " is $[D]_v$, $[E]_w$ as defined above, and n is an integer between 0 and 20, 50, 100, 200, 300, 400 or 500. In some embodiments, n is 0. In other embodiments, n is less than 50.

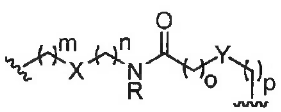
[00371] Exemplary embodiments of the macrocycle-forming linker L are shown below.



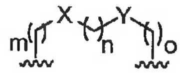
where X, Y = $-CH_2-$, O, S, or NH
m, n, o, p = 0-10



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



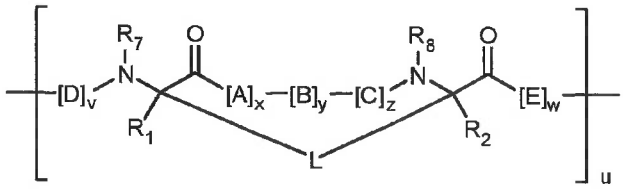
where X, Y = $-CH_2-$, O, S, or NH
m, n, o = 0-10

[00372] In other embodiments, D and/or E in the compound of Formula I are further modified 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.

[00373] 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

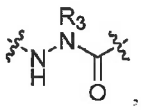
least two macrocycle-forming linkers. In a specific embodiment, a peptidomimetic macrocycle comprises two macrocycle-forming linkers. In an embodiment, u is 2.

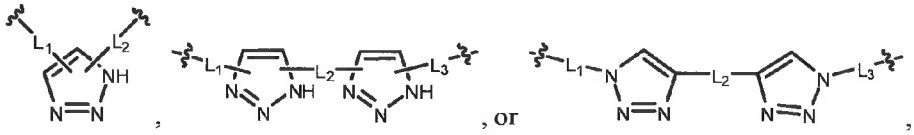
[00374] In some embodiments, the peptidomimetic macrocycles have the Formula (I):



Formula (I)

wherein:

- each A, C, D, and E is independently a natural or non-natural amino acid or an amino acid analog;
- 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–, 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 is independently hydrogen, alkyl, alkenyl, alkynyl, arylalkyl, heteroalkyl, cycloalkyl, heterocycloalkyl, cycloalkylalkyl, aryl, or heteroaryl, optionally substituted with R_5;
- each L and L' is independently macrocycle-forming linker of the formula



wherein 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 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 and w is independently an integer from 1-1000;
- each x, y and z is independently an integer from 0-10;
- us ia an integer from 1-10; and
- n is an integer from 1-5.

[00375] In one example, at least one of R_1 and R_2 is alkyl that is unsubstituted or substituted with halo–. In another example, both R_1 and R_2 are independently alkyl that are 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.

[00376] In some 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 wherein the amino acids are identical, e.g. Gln–Gln–Gln. This applies for any value of x, y, or z in the indicated ranges.

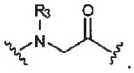
[00377] In some embodiments, each of the first two amino acid represented by E comprises an uncharged side chain or a negatively charged side chain. In some embodiments, each of the first three amino acid represented by E comprises an uncharged side chain or a negatively charged side chain. In some embodiments, each of the first four amino acid represented by E comprises an uncharged side chain or a negatively charged side chain. In some embodiments, one or more or each of the amino acid that is *i*+1, *i*+2, *i*+3, *i*+4, *i*+5, and/or *i*+6 with respect to Xaa_{13} represented by E comprises an uncharged side chain or a negatively charged side chain.

[00378] In some embodiments, the first C-terminal amino acid and/or the second C-terminal amino acid represented by E comprise a hydrophobic side chain. For example, the first C-terminal amino acid and/or the second C-terminal amino acid represented by E comprises a hydrophobic side chain, for example a small hydrophobic side chain. In some embodiments, the first C-terminal amino acid, the second C-terminal amino acid, and/or the third C-terminal amino acid represented by E comprise a hydrophobic side chain. For example, the first C-terminal amino acid, the second C-terminal amino acid, and/or the third C-terminal amino acid represented by E comprises a hydrophobic side chain, for example a small hydrophobic side chain. In some embodiments, one or more or each of the amino acid that is *i*+1, *i*+2, *i*+3, *i*+4, *i*+5, and/or *i*+6 with respect to Xaa_{13} represented by E comprises an uncharged side chain or a negatively charged side chain

[00379] In some embodiments, w is between 1 and 1000. For example, the first amino acid represented by E comprises a small hydrophobic side chain. In some embodiments, w is between 2 and 1000. For example, the second amino acid represented by E comprises a small hydrophobic side chain. In some embodiments, w is between 3 and 1000. For example, the third amino acid represented by E comprises a small hydrophobic side

chain. For example, the third amino acid represented by E comprises a small hydrophobic side chain. In some embodiments, w is between 4 and 1000. In some embodiments, w is between 5 and 1000. In some embodiments, w is between 6 and 1000. In some embodiments, w is between 7 and 1000. In some embodiments, w is between 8 and 1000.

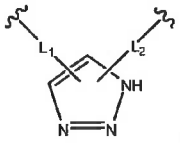
[00380] In some embodiments, the peptidomimetic macrocycle comprises a secondary structure which is a helix and R_8 is –H, allowing intrahelical hydrogen bonding. In some embodiments, at least one of A, B, C, D or E is an α,α-disubstituted amino acid. In one example, B is an α,α-disubstituted amino acid. 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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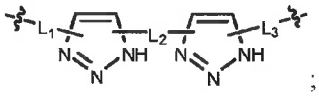
[00381] In other embodiments, the length of the macrocycle-forming linker L as measured from a first Cα to a second Cα is selected to stabilize a desired secondary peptide structure, such as a helix formed by residues of the peptidomimetic macrocycle including, but not necessarily limited to, those between the first Cα to a second Cα.

[00382] In some embodiments, L is a macrocycle-forming linker of the formula

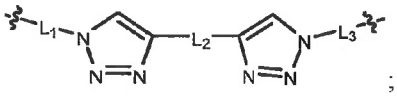


.

[00383] In some embodiments, L is a macrocycle-forming linker of the formula

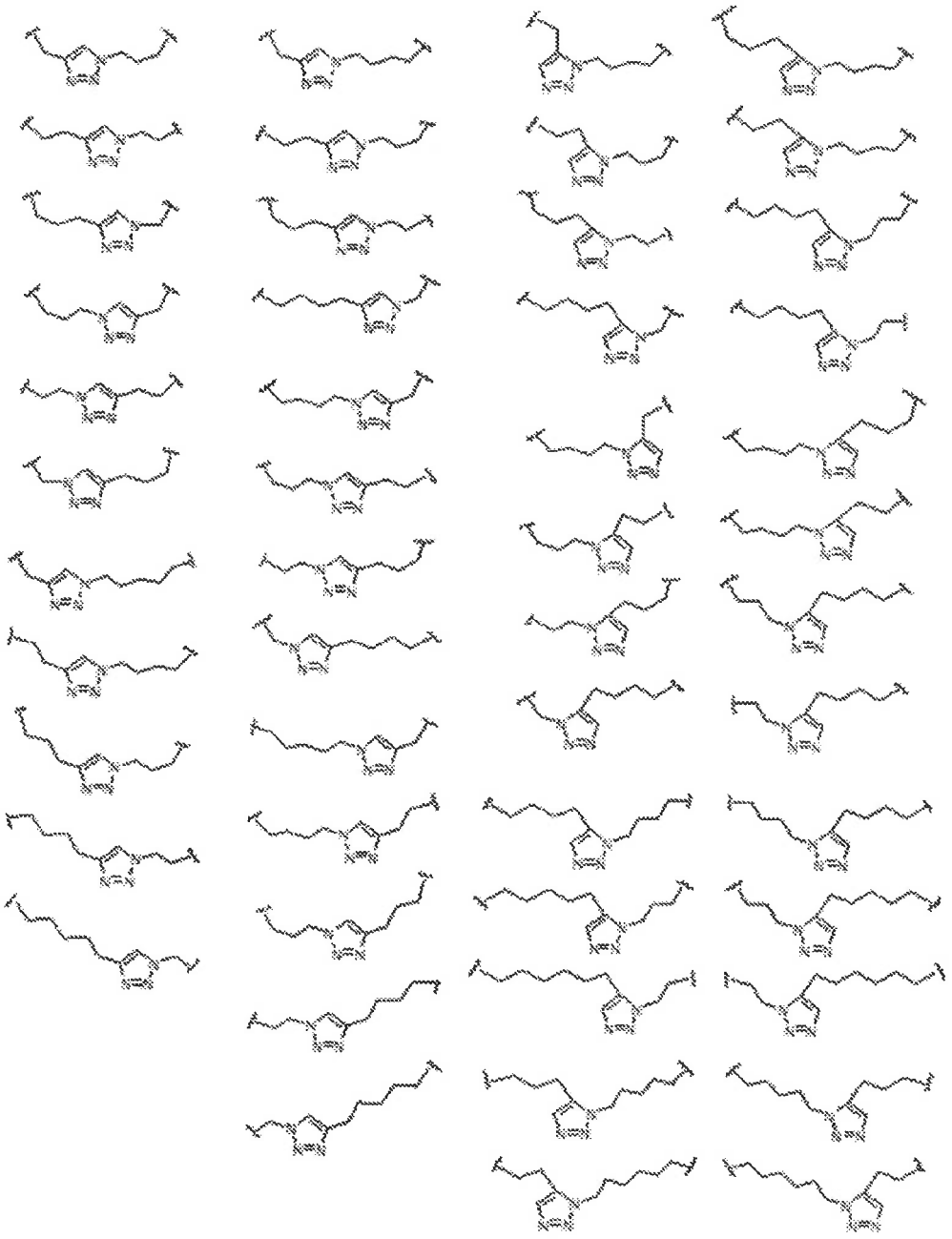


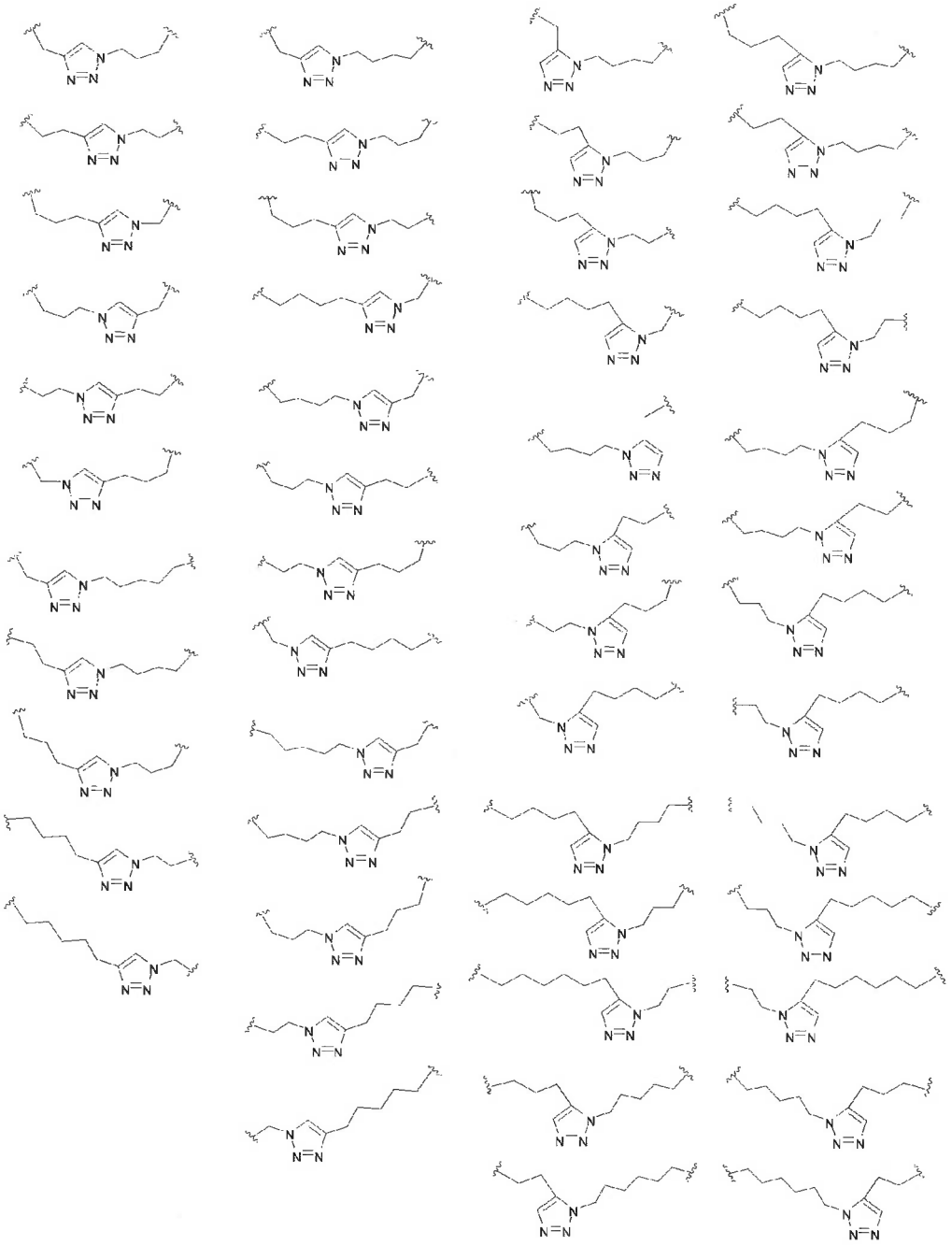
; or

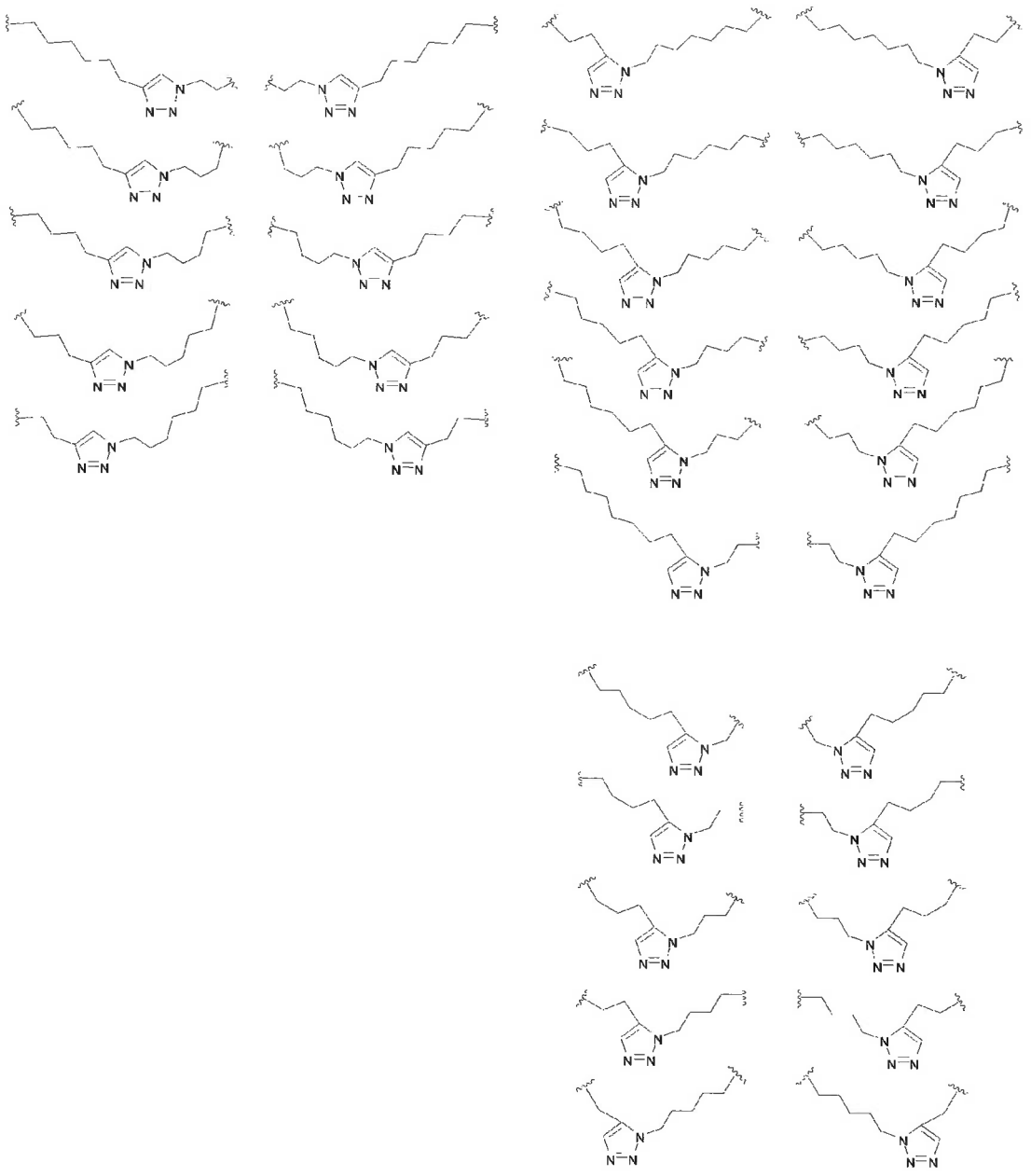


; or a tautomer thereof.

[00384] Exemplary embodiments of the macrocycle-forming linker L are shown below.







[00385] Amino acids which are used in the formation of triazole crosslinkers are represented according to the legend indicated below. Stereochemistry at the alpha position of each amino acid is S unless otherwise indicated. For azide amino acids, the number of carbon atoms indicated refers to the number of methylene units between the alpha carbon and the terminal azide. For alkyne amino acids, the number of carbon atoms indicated is the number of methylene units between the alpha position and the triazole moiety plus the two carbon atoms within the triazole group derived from the alkyne.

$5a5	Alpha-Me alkyne 1,5 triazole (5 carbon)
$5n3	Alpha-Me azide 1,5 triazole (3 carbon)
$4rn6	Alpha-Me R-azide 1,4 triazole (6 carbon)

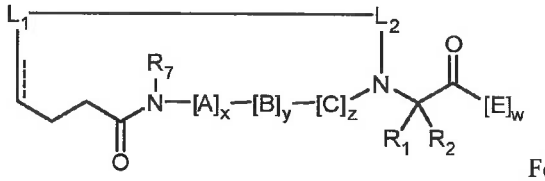
$4a5	Alpha-Me alkyne 1,4 triazole (5 carbon)

[00386] 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, or Table 1c and also with any of the R– substituents indicated herein.

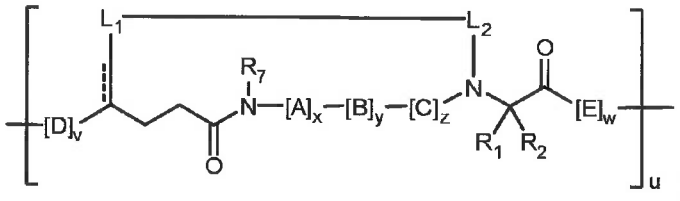
[00387] In some embodiments, the peptidomimetic macrocycle comprises at least one α-helix motif. For example, A, B and/or C in the compound of Formula I include one or more α-helices. As a general matter, α-helices include between 3 and 4 amino acid residues per turn. In some embodiments, the α-helix 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.

[00388] In other embodiments, provided are peptidomimetic macrocycles of Formula (II) or (IIa):

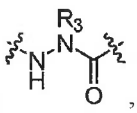


Formula (II)



Formula (IIa)

wherein:

- each A, C, D, and E is independently a natural or non-natural amino acid or an amino acid analog, 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 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 R_3 is independently hydrogen, alkyl, alkenyl, alkynyl, arylalkyl, heteroalkyl, cycloalkyl, heterocycloalkyl, cycloalkylalkyl, aryl, or heteroaryl, optionally substituted with R_5;
- each L and L' is 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, arylene, heteroarylene, 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, aryl, or heteroaryl, optionally substituted with R_5;
- each v and 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

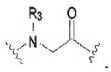
n is an integer from 1-5.

[00389] In one example, L_1 and L_2, either alone or in combination, do not form a triazole or a thioether.

[00390] 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.

[00391] 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 wherein the amino acids are not identical, e.g. Gln–Asp–Ala as well as embodiments wherein the amino acids are identical, e.g. Gln–Gln–Gln. This applies for any value of x, y, or z in the indicated ranges.

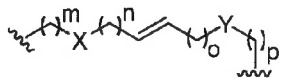
[00392] In some embodiments, the peptidomimetic macrocycle comprises a secondary structure which is an α-helix and R_8 is –H, allowing intrahelical hydrogen bonding. In some embodiments, at least one of A, B, C, D or E is an α,α-disubstituted amino acid. In one example, B is an α,α-disubstituted amino acid. For example, 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



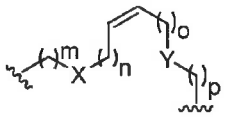
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[00393] In other embodiments, the length of the macrocycle-forming linker L as measured from a first Cα to a second Cα is selected to stabilize a desired secondary peptide structure, such as an α-helix formed by residues of the peptidomimetic macrocycle including, but not necessarily limited to, those between the first Cα to a second Cα.

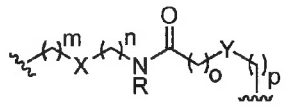
[00394] Exemplary embodiments of the macrocycle-forming linker $-L_1-L_2-$ are shown below.



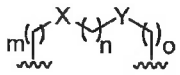
where X, Y = -CH_2-, O, S, or NH
m, n, o, p = 0-10



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

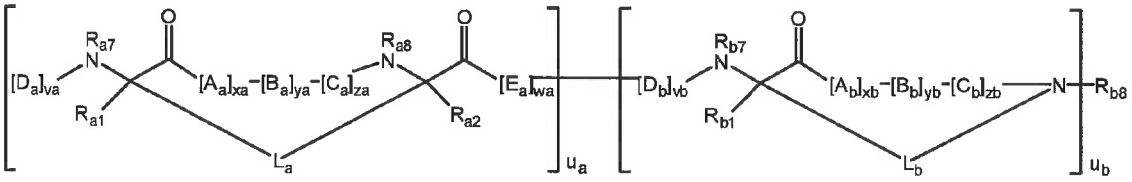


where X, Y = -CH_2-, O, S, or NH
m, n, o, p = 0-10
R = H, alkyl, other substituent



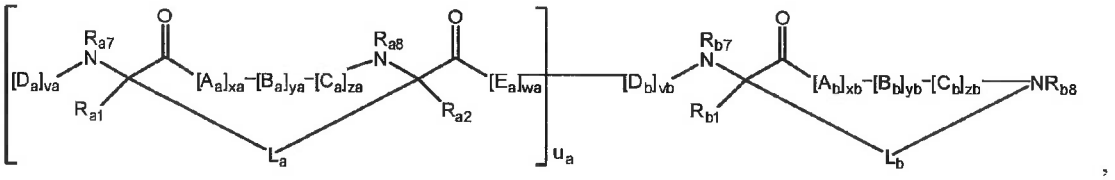
where X, Y = -CH_2-, O, S, or NH
m, n, o = 0-10

[00395] In some embodiments, the peptidomimetic macrocycle has the Formula (III) or Formula (IIIa):



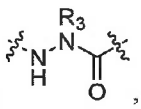
Formula (III)

or



Formula (IIIa)

wherein:

- each A_a, C_a, D_a, E_a, A_b, C_b, and D_b is independently a natural or non-natural amino acid or an amino acid analog;
- each B_a and B_b is independently a natural or non-natural amino acid, amino acid analog,  , [-NH-L_4-CO-], [-NH-L_4-SO_2-], or [-NH-L_4-];
- each R_{a1} is independently alkyl, alkenyl, alkynyl, arylalkyl, cycloalkyl, cycloalkylalkyl, heteroalkyl, or heterocycloalkyl, any of which is unsubstituted or substituted; or H; or R_{a1} forms a macrocycle-forming linker L' connected to the alpha position of one of the D_a or E_a amino acids; or together with L_a forms a ring that is unsubstituted or substituted;
- each R_{a2} is independently alkyl, alkenyl, alkynyl, arylalkyl, cycloalkyl, cycloalkylalkyl, heteroalkyl, or heterocycloalkyl, any of which is unsubstituted or substituted; or H; or R_{a2} forms a macrocycle-forming linker L' connected to the alpha position of one of the D_a or E_a amino acids; or together with L_a forms a

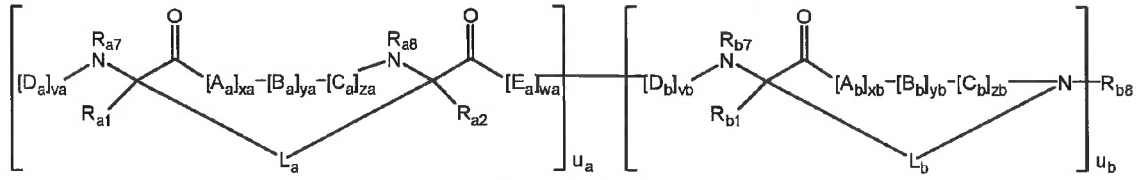
ring that is unsubstituted or substituted;

- each R_{b1} is independently alkyl, alkenyl, alkynyl, arylalkyl, cycloalkyl, cycloalkylalkyl, heteroalkyl, or heterocycloalkyl, any of which is unsubstituted or substituted; or H; or R_{b1} forms a macrocycle-forming linker L' connected to the alpha position of one of the D_b amino acids; or together with L_b forms a ring that is unsubstituted or substituted;
- each R_3 is independently alkyl, alkenyl, alkynyl, arylalkyl, heteroalkyl, cycloalkyl, heterocycloalkyl, cycloalkylalkyl, cycloaryl, or heterocycloaryl, any of which is unsubstituted or substituted, or H;
- each L_a is independently a macrocycle-forming linker, and optionally forms a ring with R_{a1} or R_{a2} that is unsubstituted or substituted;
- each L_b is independently a macrocycle-forming linker, and optionally forms a ring with R_{b1} that is unsubstituted or substituted;
- each L' is independently a macrocycle-forming linker;
- each L_4 is independently alkylene, alkenylene, alkynylene, heteroalkylene, cycloalkylene, heterocycloalkylene, cycloarylene, heterocycloarylene, or $[-R_4-K-R_4-]_n$, any of which is unsubstituted or substituted;
- each R_4 is independently alkylene, alkenylene, alkynylene, heteroalkylene, cycloalkylene, heterocycloalkylene, arylene, or heteroarylene, any of which is unsubstituted or substituted;
- each K is independently O, S, SO, SO_2, CO, CO_2, OCO_2, NR_3, $CONR_3$, $OCONR_3$, OSO_2NR_3, NR_{3q}, $CONR_{3q}$, $OCONR_{3q}$, or OSO_2NR_{3q}, wherein each R_{3q} is independently a point of attachment to R_{a1}, R_{a2}, or R_{b1};
- R_{a7} is alkyl, alkenyl, alkynyl, arylalkyl, cycloalkyl, heteroalkyl, cycloalkylalkyl, heterocycloalkyl, cycloaryl, or heterocycloaryl, any of which is unsubstituted or substituted; or H; or part of a cyclic structure with a D_a amino acid;
- R_{b7} is alkyl, alkenyl, alkynyl, arylalkyl, cycloalkyl, heteroalkyl, cycloalkylalkyl, heterocycloalkyl, cycloaryl, or heterocycloaryl, any of which is unsubstituted or substituted; or H; or part of a cyclic structure with a D_b amino acid;
- R_{a8} is alkyl, alkenyl, alkynyl, arylalkyl, cycloalkyl, heteroalkyl, cycloalkylalkyl, heterocycloalkyl, cycloaryl, or heterocycloaryl, any of which is unsubstituted or substituted; or H; or part of a cyclic structure with an E_a amino acid;
- R_{b8} is alkyl, alkenyl, alkynyl, arylalkyl, cycloalkyl, heteroalkyl, cycloalkylalkyl, heterocycloalkyl, cycloaryl, or heterocycloaryl, any of which is unsubstituted or substituted; or H; or an amino acid sequence of 1-1000 amino acid residues;
- each va and vb is independently an integer from 0-1000;
- each wa and wb is independently an integer from 0-1000;
- each ua and ub is independently 0, 1, 2, 3, 4, 5, 6, 7, 8, 9, or 10, wherein ua+ub is at least 1;
- each xa and xb is independently 0, 1, 2, 3, 4, 5, 6, 7, 8, 9, or 10;
- each ya and yb is independently 0, 1, 2, 3, 4, 5, 6, 7, 8, 9, or 10;

- each za and zb is independently 0, 1, 2, 3, 4, 5, 6, 7, 8, 9, or 10; and
- each n is independently 1, 2, 3, 4, or 5,

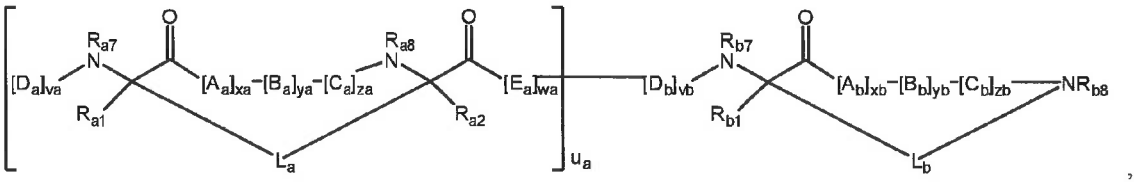
or a pharmaceutically-acceptable salt thereof.

[00396] In some embodiments, the peptidomimetic macrocycle has the Formula (III) or Formula (IIIa):



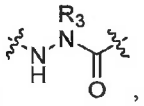
Formula (III)

or



Formula (IIIa)

wherein:

- each A_a, C_a, D_a, E_a, A_b, C_b, and D_b is independently a natural or non-natural amino acid or an amino acid analgo;
- each B_a and B_b is independently a natural or non-natural amino acid, amino acid analog,  , [-NH-L_4-CO-], [-NH-L_4-SO_2-], or [-NH-L_4-];
- each R_{a1} is independently alkyl, alkenyl, alkynyl, arylalkyl, cycloalkyl, cycloalkylalkyl, heteroalkyl, or heterocycloalkyl, any of which is unsubstituted or substituted; or H; or R_{a1} forms a macrocycle-forming linker L' connected to the alpha position of one of the D_a or E_a amino acids; or together with L_a forms a ring that is unsubstituted or substituted;
- each R_{a2} is independently alkyl, alkenyl, alkynyl, arylalkyl, cycloalkyl, cycloalkylalkyl, heteroalkyl, or heterocycloalkyl, any of which is unsubstituted or substituted; or H; or R_{a2} forms a macrocycle-forming linker L' connected to the alpha position of one of the D_a or E_a amino acids; or together with L_a forms a ring that is unsubstituted or substituted;
- each R_{b1} is independently alkyl, alkenyl, alkynyl, arylalkyl, cycloalkyl, cycloalkylalkyl, heteroalkyl, or heterocycloalkyl, any of which is unsubstituted or substituted; or H; or R_{b1} forms a macrocycle-forming linker L' connected to the alpha position of one of the D_b amino acids; or together with L_b forms a ring that is unsubstituted or substituted;
- each R_3 is independently alkyl, alkenyl, alkynyl, arylalkyl, heteroalkyl, cycloalkyl, heterocycloalkyl, cycloalkylalkyl, cycloaryl, or heterocycloaryl, any of which is unsubstituted or substituted with R_5, or H;
- each L_a is independently a macrocycle-forming linker, and optionally forms a ring with R_{a1} or R_{a2} that is

unsubstituted or substituted;

- each L_b is independently a macrocycle-forming linker, and optionally forms a ring with R_{b1} that is unsubstituted or substituted;
- each L' is independently a macrocycle-forming linker;
- each L_4 is independently alkylene, alkenylene, alkynylene, heteroalkylene, cycloalkylene, heterocycloalkylene, cycloarylene, heterocycloarylene, or $[-R_4-K-R_4-]_n$, any of which is unsubstituted or substituted with R_5;
- each R_4 is independently alkylene, alkenylene, alkynylene, heteroalkylene, cycloalkylene, heterocycloalkylene, arylene, or heteroarylene, any of which is unsubstituted or substituted with R_5;
- each K is independently O, S, SO, SO_2, CO, CO_2, OCO_2, NR_3, $CONR_3$, $OCONR_3$, OSO_2NR_3, NR_{3q}, $CONR_{3q}$, $OCONR_{3q}$, or OSO_2NR_{3q}, wherein each R_{3q} is independently a point of attachment to R_{a1}, R_{a2}, or R_{b1};
- 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_{a7} is independently alkyl, alkenyl, alkynyl, arylalkyl, cycloalkyl, heteroalkyl, cycloalkylalkyl, heterocycloalkyl, cycloaryl, or heterocycloaryl, any of which is unsubstituted or substituted with R_5; or H; or part of a cyclic structure with a D_a amino acid;
- R_{b7} is alkyl, alkenyl, alkynyl, arylalkyl, cycloalkyl, heteroalkyl, cycloalkylalkyl, heterocycloalkyl, cycloaryl, or heterocycloaryl, any of which is unsubstituted or substituted with R_5; or H; or part of a cyclic structure with a D_b amino acid;
- each R_{a8} is independently alkyl, alkenyl, alkynyl, arylalkyl, cycloalkyl, heteroalkyl, cycloalkylalkyl, heterocycloalkyl, cycloaryl, or heterocycloaryl, any of which is unsubstituted or substituted with R_5; or H; or part of a cyclic structure with an E_a amino acid;
- R_{b8} is alkyl, alkenyl, alkynyl, arylalkyl, cycloalkyl, heteroalkyl, cycloalkylalkyl, heterocycloalkyl, cycloaryl, or heterocycloaryl, any of which is unsubstituted or substituted with R_5; or H; or an amino acid sequence of 1-1000 amino acid residues;
- each va and vb is independently an integer from 0-1000;
- each wa and wb is independently an integer from 0-1000;
- each ua and ub is independently 0, 1, 2, 3, 4, 5, 6, 7, 8, 9, or 10, wherein ua+ub is at least 1;
- each xa and xb is independently 0, 1, 2, 3, 4, 5, 6, 7, 8, 9, or 10;
- each ya and yb is independently 0, 1, 2, 3, 4, 5, 6, 7, 8, 9, or 10;
- each za and zb is independently 0, 1, 2, 3, 4, 5, 6, 7, 8, 9, or 10; and
- each n is independently 1, 2, 3, 4, or 5,

or a pharmaceutically-acceptable salt thereof.

[00397] In some embodiments, the peptidomimetic macrocycle of the invention has the formula defined above, wherein:

- each L_a is independently a macrocycle-forming linker of the formula $-L_1-L_2-$, and optionally forms a ring with R_{a1} or R_{a2} that is unsubstituted or substituted;
- each L_b is independently a macrocycle-forming linker of the formula $-L_1-L_2-$, and optionally forms a ring with R_{b1} that is unsubstituted or substituted;
- each 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 $[-R_4-K-R_4-]_n$, any of which is unsubstituted or substituted with R_5;
- each R_4 is independently alkylene, alkenylene, alkynylene, heteroalkylene, cycloalkylene, heterocycloalkylene, arylene, or heteroarylene, any of which is unsubstituted or substituted with R_5;
- each K is independently O, S, SO, SO_2, CO, CO_2, OCO_2, NR_3, $CONR_3$, $OCONR_3$, OSO_2NR_3, NR_{3q}, $CONR_{3q}$, $OCONR_{3q}$, or OSO_2NR_{3q}, wherein each R_{3q} is independently a point of attachment to R_{a1}, R_{a2}, or R_{b1};
- 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; and
- each R_6 is independently H, alkyl, alkenyl, alkynyl, arylalkyl, cycloalkylalkyl, heterocycloalkyl, a fluorescent moiety, a radioisotope or a therapeutic agent,

or a pharmaceutically-acceptable salt thereof.

[00398] In some embodiments, the peptidomimetic macrocycle has the formula defined above wherein one of L_a and L_b is a bis-thioether-containing macrocycle-forming linker. In some embodiments, one of L_a and L_b is a macrocycle-forming linker of the formula $-L_1-S-L_2-S-L_3-$.

[00399] In some embodiments, the peptidomimetic macrocycle has the formula defined above wherein one of L_a and L_b is a bis-sulfone-containing macrocycle-forming linker. In some embodiments, one of L_a and L_b is a macrocycle-forming linker of the formula $-L_1-SO_2-L_2-SO_2-L_3-$.

[00400] In some embodiments, the peptidomimetic macrocycle has the formula defined above wherein one of L_a and L_b is a bis-sulfoxide-containing macrocycle-forming linker. In some embodiments, one of L_a and L_b is a macrocycle-forming linker of the formula $-L_1-S(O)-L_2-S(O)-L_3-$.

[00401] In some embodiments, a peptidomimetic macrocycle of the invention comprises one or more secondary structures. In some embodiments, the peptidomimetic macrocycle comprises a secondary structure that is an α-helix. In some embodiments, the peptidomimetic macrocycle comprises a secondary structure that is a β-hairpin turn.

[00402] In some embodiments, u_a is 0. In some embodiments, u_a is 0, and L_b is a macrocycle-forming linker that crosslinks an α-helical secondary structure. In some embodiments, u_a is 0, and L_b is a macrocycle-forming linker that crosslinks a β-hairpin secondary structure. In some embodiments, u_a is 0, and L_b is a hydrocarbon-containing macrocycle-forming linker that crosslinks an α-helical secondary structure. In some embodiments,

u_a is 0, and L_b is a hydrocarbon-containing macrocycle-forming linker that crosslinks a β-hairpin secondary structure.

[00403] In some embodiments, u_b is 0. In some embodiments, u_b is 0, and L_a is a macrocycle-forming linker that crosslinks an α-helical secondary structure. In some embodiments, u_b is 0, and L_a is a macrocycle-forming linker that crosslinks a β-hairpin secondary structure. In some embodiments, u_b is 0, and L_a is a hydrocarbon-containing macrocycle-forming linker that crosslinks an α-helical secondary structure. In some embodiments, u_b is 0, and L_a is a hydrocarbon-containing macrocycle-forming linker that crosslinks a β-hairpin secondary structure.

[00404] In some embodiments, the peptidomimetic macrocycle comprises only α-helical secondary structures. In other embodiments, the peptidomimetic macrocycle comprises only β-hairpin secondary structures.

[00405] In other embodiments, the peptidomimetic macrocycle comprises a combination of secondary structures, wherein the secondary structures are α-helical and β-hairpin structures. In some embodiments, L_a and L_b are a combination of hydrocarbon-, triazole, or sulfur-containing macrocycle-forming linkers. In some embodiments, the peptidomimetic macrocycle comprises L_a and L_b, wherein L_a is a hydrocarbon-containing macrocycle-forming linker that crosslinks a β-hairpin structure, and L_b is a triazole-containing macrocycle-forming linker that crosslinks an α-helical structure. In some embodiments, the peptidomimetic macrocycle comprises L_a and L_b, wherein L_a is a hydrocarbon-containing macrocycle-forming linker that crosslinks an α-helical structure, and L_b is a triazole-containing macrocycle-forming linker that crosslinks a β-hairpin structure. In some embodiments, the peptidomimetic macrocycle comprises L_a and L_b, wherein L_a is a triazole-containing macrocycle-forming linker that crosslinks an α-helical structure, and L_b is a hydrocarbon-containing macrocycle-forming linker that crosslinks a β-hairpin structure. In some embodiments, the peptidomimetic macrocycle comprises L_a and L_b, wherein L_a is a triazole-containing macrocycle-forming linker that crosslinks a β-hairpin structure, and L_b is a hydrocarbon-containing macrocycle-forming linker that crosslinks an α-helical structure.

[00406] In some embodiments, u_a+u_b is at least 1. In some embodiments, $u_a+u_b = 2$.

[00407] In some embodiments, u_a is 1, u_b is 1, L_a is a triazole-containing macrocycle-forming linker that crosslinks an α-helical secondary structure, and L_b is a hydrocarbon-containing macrocycle-forming linker that crosslinks an α-helical structure. In some embodiments, u_a is 1, u_b is 1, L_a is a triazole-containing macrocycle-forming linker that crosslinks an α-helical secondary structure, and L_b is a hydrocarbon-containing macrocycle-forming linker that crosslinks a β-hairpin structure. In some embodiments, u_a is 1, u_b is 1, L_a is a triazole-containing macrocycle-forming linker that crosslinks a β-hairpin secondary structure, and L_b is a hydrocarbon-containing macrocycle-forming linker that crosslinks an α-helical structure. In some embodiments, u_a is 1, u_b is 1, L_a is a triazole-containing macrocycle-forming linker that crosslinks a β-hairpin secondary structure, and L_b is a hydrocarbon-containing macrocycle-forming linker that crosslinks a β-hairpin structure.

[00408] In some embodiments, u_a is 1, u_b is 1, L_a is a hydrocarbon-containing macrocycle-forming linker that crosslinks an α-helical secondary structure, and L_b is a triazole-containing macrocycle-forming linker that

crosslinks an α-helical secondary structure. In some embodiments, u_a is 1, u_b is 1, L_a is a hydrocarbon-containing macrocycle-forming linker that crosslinks an α-helical secondary structure, and L_b is a triazole-containing macrocycle-forming linker that crosslinks a β-hairpin secondary structure. In some embodiments, u_a is 1, u_b is 1, L_a is a hydrocarbon-containing macrocycle-forming linker that crosslinks a β-hairpin secondary structure, and L_b is a triazole-containing macrocycle-forming linker that crosslinks an α-helical secondary structure. In some embodiments, u_a is 1, u_b is 1, L_a is a hydrocarbon-containing macrocycle-forming linker that crosslinks a β-hairpin secondary structure, and L_b is a triazole-containing macrocycle-forming linker that crosslinks a β-hairpin secondary structure.

[00409] In some embodiments, u_a is 1, u_b is 1, L_a is a hydrocarbon-containing macrocycle-forming linker with an α-helical secondary structure, and L_b is a sulfur-containing macrocycle-forming linker. In some embodiments, u_a is 1, u_b is 1, L_a is a hydrocarbon-containing macrocycle-forming linker with a β-hairpin secondary structure, and L_b is a sulfur-containing macrocycle-forming linker.

[00410] In some embodiments, u_a is 1, u_b is 1, L_a is a sulfur-containing macrocycle-forming linker, and L_b is a hydrocarbon-containing macrocycle-forming linker with an α-helical secondary structure. In some embodiments, u_a is 1, u_b is 1, L_a is a sulfur-containing macrocycle-forming linker, and L_b is a hydrocarbon-containing macrocycle-forming linker with a β-hairpin secondary structure.

[00411] In some embodiments, u_a is 1, u_b is 1, L_a is a hydrocarbon-containing macrocycle-forming linker that crosslinks an α-helical structure, and L_b is a hydrocarbon-containing macrocycle-forming linker that crosslinks an α-helical structure. In some embodiments, u_a is 1, u_b is 1, L_a is a hydrocarbon-containing macrocycle-forming linker that crosslinks an α-helical structure, and L_b is a hydrocarbon-containing macrocycle-forming linker that crosslinks a β-hairpin structure. In some embodiments, u_a is 1, u_b is 1, L_a is a hydrocarbon-containing macrocycle-forming linker that crosslinks a β-hairpin structure, and L_b is a hydrocarbon-containing macrocycle-forming linker that crosslinks an α-helical structure. In some embodiments, u_a is 1, u_b is 1, L_a is a hydrocarbon-containing macrocycle-forming linker that crosslinks a β-hairpin structure, and L_b is a hydrocarbon-containing macrocycle-forming linker that crosslinks a β-hairpin structure.

[00412] In some embodiments, R_{b1} is H.

[00413] 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 atom by deuterium or tritium, or the replacement of a carbon atom by ^{13}C- or ^{14}C are contemplated.

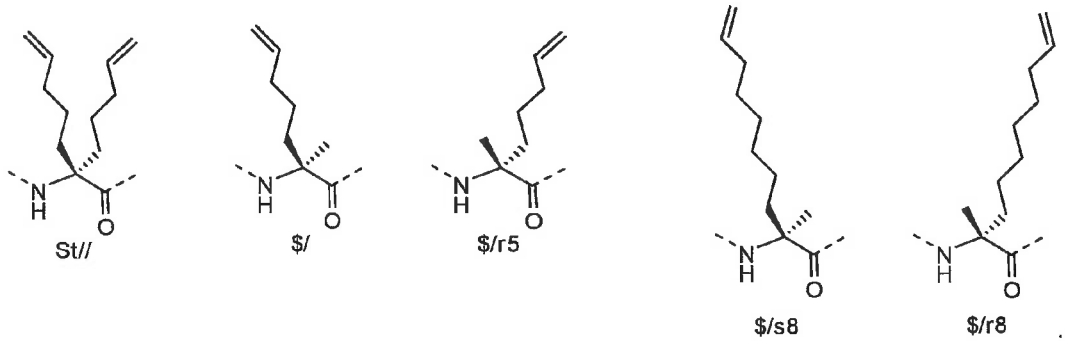
[00414] Unless otherwise stated, any compounds (including peptidomimetic macrocycles, macrocycle precursors, and other compositions) are also meant to encompass compounds which differ only in the presence of one or more isotopically enriched atoms. For example, compounds having the described structures 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 invention.

[00415] 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. All isotopic variations of the compounds disclosed herein, whether radioactive or not, are contemplated herein.

Preparation of Peptidomimetic Macrocycles

[00416] 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.

[00417] 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:



[00418] 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.

[00419] Additional methods of forming peptidomimetic macrocycles which are envisioned as suitable include those disclosed by Mustapa *et al.*, J. Org. Chem. (2003), 68, pp. 8193-8198; Yang *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

[00420] 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.

Biological Samples

[00421] As used in the present application, "biological sample" means any fluid or other material derived from the body of a normal or diseased subject, such as blood, serum, plasma, lymph, urine, saliva, tears, cerebrospinal fluid, milk, amniotic fluid, bile, ascites fluid, pus, and the like. Also included within the meaning of the term "biological sample" is an organ or tissue extract and culture fluid in which any cells or tissue preparation from a subject has been incubated. The biological samples can be any samples from which genetic material can be obtained. Biological samples can also include solid or liquid cancer cell samples or specimens. The cancer cell sample can be a cancer cell tissue sample. In some embodiments, the cancer cell tissue sample can obtained from surgically excised tissue. Exemplary sources of biological samples include fine needle aspiration, core needle biopsy, vacuum assisted biopsy, incisional biopsy, excisional biopsy, punch biopsy, shave biopsy or skin biopsy. In some cases, the biological samples comprise fine needle aspiration samples. In some embodiments, the biological samples comprise tissue samples, including, for example, excisional biopsy, incisional biopsy, or other biopsy. The biological samples can comprise a mixture of two or more sources; for example, fine needle aspirates and tissue samples. Tissue samples and cellular samples can also be obtained without invasive surgery, for example by punctuating the chest wall or the abdominal wall or from masses of breast, thyroid or other sites with a fine needle and withdrawing cellular material (fine needle aspiration biopsy). In some embodiments, a biological sample is a bone marrow aspirate sample. A biological sample can be obtained by methods known in the art such as the biopsy methods provided herein, swabbing, scraping, phlebotomy, or any other suitable method.

Methods of detecting wild type p53 and/or p53 mutations

[00422] In some embodiments, a subject lacking p53-deactivating mutations is a candidate for cancer treatment with a compound of the invention. Cancer cells from patient groups should be assayed in order to determine p53-deactivating mutations and/or expression of wild type p53 prior to treatment with a compound of the invention.

[00423] The activity of the p53 pathway can be determined by the mutational status of genes involved in the p53 pathways, including, for example, AKT1, AKT2, AKT3, ALK, BRAF, CDK4, CDKN2A, DDR2, EGFR, ERBB2 (HER2), FGFR1, FGFR3, GNA11, GNQ, GNAS, KDR, KIT, KRAS, MAP2K1 (MEK1), MET, HRAS, NOTCH1, NRAS, NTRK2, PIK3CA, NF1, PTEN, RAC1, RB1, NTRK3, STK11, PIK3R1, TSC1, TSC2, RET, TP53, and VHL. Genes that modulate the activity of p53 can also be assessed, including, for example, kinases: ABL1, JAK1, JAAK2, JAK3; receptor tyrosine kinases: FLT3 and KIT; receptors: CSF3R,

IL7R, MPL, and NOTCH1; transcription factors: BCOR, CEBPA, CREBBP, ETV6, GATA1, GATA2. MLL, KZF1, PAX5, RUNX1, STAT3, WT1, and TP53; epigenetic factors: ASXL1, DNMT3A, EZH2, KDM6A (UTX), SUZ12, TET2, PTPN11, SF3B1, SRSF2, U2AF35, ZRSR2; RAS proteins: HRAS, KRAS, and NRAS; adaptors CBL and CBL-B; FBXW7, IDH1, IDH2, and NPM1.

[00424] Cancer cell samples can be obtained, for example, from solid or liquid tumors via primary or metastatic tumor resection (e.g. pneumonectomy, lobetomy, wedge resection, and craniotomy) primary or metastatic disease biopsy (e.g. transbronchial or needle core), pleural or ascites fluid (e.g. FFPE cell pellet), bone marrow aspirate, bone marrow clot, and bone marrow biopsy, or macro-dissection of tumor rich areas (solid tumors).

[00425] To detect the p53 wild type gene and/or lack of p53 deactivation mutation in a tissue, cancerous tissue can be isolated from surrounding normal tissues. For example, the tissue can be isolated from paraffin or cryostat sections. Cancer cells can also be separated from normal cells by flow cytometry. If the cancer cells tissue is highly contaminated with normal cells, detection of mutations can be more difficult.

[00426] Various methods and assays for analyzing wild type p53 and/or p53 mutations are suitable for use in the invention. Non-limiting examples of assays include polymerase chain reaction (PCR), restriction fragment length polymorphism (RFLP), microarray, Southern Blot, Northern Blot, Western Blot, Eastern Blot, H&E staining, microscopic assessment of tumors, next-generation DNA sequencing (NGS) (e.g. extraction, purification, quantification, and amplification of DNA, library preparation) immunohistochemistry, and fluorescent *in situ* hybridization (FISH).

[00427] A microarray allows a researcher to investigate multiple DNA sequences attached to a surface, for example, a DNA chip made of glass or silicon, or a polymeric bead or resin. The DNA sequences are hybridized with fluorescent or luminescent probes. The microarray can indicate the presence of oligonucleotide sequences in a sample based on hybridization of sample sequences to the probes, followed by washing and subsequent detection of the probes. Quantification of the fluorescent or luminescent signal indicates the presence of known oligonucleotide sequences in the sample.

[00428] PCR allows amplification of DNA oligomers rapidly, and can be used to identify an oligonucleotide sequence in a sample. PCR experiments involve contacting an oligonucleotide sample with a PCR mixture containing primers complementary to a target sequence, one or more DNA polymerase enzymes, deoxnucleotide triphosphate (dNTP) building blocks, including dATP, dGTP, dTTP, and dCTP, and suitable buffers, salts, and additives. If a sample contains an oligonucleotide sequence complementary to a pair of primers, the experiment amplifies the sample sequence, which can be collected and identified.

[00429] In some embodiments, an assay comprises amplifying a biomolecule from the cancer sample. The biomolecule can be a nucleic acid molecule, such as DNA or RNA. In some embodiments, the assay comprises circularization of a nucleic acid molecule, followed by digestion of the circularized nucleic acid molecule.

[00430] In some embodiments, the assay comprises contacting an organism, or a biochemical sample collected from an organism, such as a nucleic acid sample, with a library of oligonucleotides, such as PCR primers. The

library can contain any number of oligonucleotide molecules. The oligonucleotide molecules can bind individual DNA or RNA motifs, or any combination of motifs described herein. The motifs can be any distance apart, and the distance can be known or unknown. In some embodiments, two or more oligonucleotides in the same library bind motifs a known distance apart in a parent nucleic acid sequence. Binding of the primers to the parent sequence can take place based on the complementarity of the primers to the parent sequence. Binding can take place, for example, under annealing, or under stringent conditions.

[00431] In some embodiments, the results of an assay are used to design a new oligonucleotide sequence for future use. In some embodiments, the results of an assay are used to design a new oligonucleotide library for future use. In some embodiments, the results of an assay are used to revise, refine, or update an existing oligonucleotide library for future use. For example, an assay can reveal that a previously-undocumented nucleic acid sequence is associated with the presence of a target material. This information can be used to design or redesign nucleic acid molecules and libraries.

[00432] In some embodiments, one or more nucleic acid molecules in a library comprise a barcode tag. In some embodiments, one or more of the nucleic acid molecules in a library comprise type I or type II restriction sites suitable for circularization and cutting an amplified sample nucleic acid sequence. Such primers can be used to circularize a PCR product and cut the PCR product to provide a product nucleic acid sequence with a sequence that is organized differently from the nucleic acid sequence native to the sample organism.

[00433] After a PCR experiment, the presence of an amplified sequence can be verified. Non-limiting examples of methods for finding an amplified sequence include DNA sequencing, whole transcriptome shotgun sequencing (WTSS, or RNA-seq), mass spectrometry (MS), microarray, pyrosequencing, column purification analysis, polyacrylamide gel electrophoresis, and index tag sequencing of a PCR product generated from an index-tagged primer.

[00434] In some embodiments, more than one nucleic acid sequence in the sample organism is amplified. Non-limiting examples of methods of separating different nucleic acid sequences in a PCR product mixture include column purification, high performance liquid chromatography (HPLC), HPLC/MS, polyacrylamide gel electrophoresis, size exclusion chromatography.

[00435] The amplified nucleic acid molecules can be identified by sequencing. Nucleic acid sequencing can be done on automated instrumentation. Sequencing experiments can be done in parallel to analyze tens, hundreds, or thousands of sequences simultaneously. Non-limiting examples of sequencing techniques follow.

[00436] In pyrosequencing, DNA is amplified within a water droplet containing a single DNA template bound to a primer-coated bead in an oil solution. Nucleotides are added to a growing sequence, and the addition of each base is evidenced by visual light.

[00437] Ion semiconductor sequencing detects the addition of a nucleic acid residue as an electrical signal associated with a hydrogen ion liberated during synthesis. A reaction well containing a template is flooded with the four types of nucleotide building blocks, one at a time. The timing of the electrical signal identifies which building block was added, and identifies the corresponding residue in the template.

[00438] DNA nanoball uses rolling circle replication to amplify DNA into nanoballs. Unchained sequencing by ligation of the nanoballs reveals the DNA sequence.

[00439] In a reversible dyes approach, nucleic acid molecules are annealed to primers on a slide and amplified. Four types of fluorescent dye residues, each complementary to a native nucleobase, are added, the residue complementary to the next base in the nucleic acid sequence is added, and unincorporated dyes are rinsed from the slide. Four types of reversible terminator bases (RT-bases) are added, and non-incorporated nucleotides are washed away. Fluorescence indicates the addition of a dye residue, thus identifying the complementary base in the template sequence. The dye residue is chemically removed, and the cycle repeats.

[00440] Detection of point mutations can be accomplished by molecular cloning of the p53 allele(s) present in the cancer cell tissue and sequencing that allele(s). Alternatively, the polymerase chain reaction can be used to amplify p53 gene sequences directly from a genomic DNA preparation from the cancer cell tissue. The DNA sequence of the amplified sequences can then be determined. See e.g., Saiki et al., *Science*, Vol. 239, p. 487, 1988; U.S. Pat. No. 4,683,202; and U.S. Pat. No. 4,683,195. Specific deletions of p53 genes can also be detected. For example, restriction fragment length polymorphism (RFLP) probes for the p53 gene or surrounding marker genes can be used to score loss of a p53 allele.

[00441] Loss of wild type p53 genes can also be detected on the basis of the loss of a wild type expression product of the p53 gene. Such expression products include both the mRNA as well as the p53 protein product itself. Point mutations can be detected by sequencing the mRNA directly or via molecular cloning of cDNA made from the mRNA. The sequence of the cloned cDNA can be determined using DNA sequencing techniques. The cDNA can also be sequenced via the polymerase chain reaction (PCR).

[00442] Alternatively, mismatch detection can be used to detect point mutations in the p53 gene or the mRNA product. The method can involve the use of a labeled riboprobe that is complementary to the human wild type p53 gene. The riboprobe and either mRNA or DNA isolated from the cancer cell tissue are annealed (hybridized) together and subsequently digested with the enzyme RNase A which is able to detect some mismatches in a duplex RNA structure. If a mismatch is detected by RNase A, the enzyme cleaves at the site of the mismatch. Thus, when the annealed RNA preparation is separated on an electrophoretic gel matrix, if a mismatch has been detected and cleaved by RNase A, an RNA product is seen that is smaller than the full-length duplex RNA for the riboprobe and the p53 mRNA or DNA. The riboprobe need not be the full length of the p53 mRNA or gene but can be a segment of either. If the riboprobe comprises only a segment of the p53 mRNA or gene it will be desirable to use a number of these probes to screen the whole mRNA sequence for mismatches.

[00443] In similar fashion, DNA probes can be used to detect mismatches, through enzymatic or chemical cleavage. See, e.g., Cotton *et al.*, *Proc. Natl. Acad. Sci. USA*, vol. 85, 4397, 1988; and Shenk *et al.*, *Proc. Natl. Acad. Sci. USA*, vol. 72, p. 989, 1975. Alternatively, mismatches can be detected by shifts in the electrophoretic mobility of mismatched duplexes relative to matched duplexes. See, e.g., Cariello, Human Genetics, vol. 42, p. 726, 1988. With either riboprobes or DNA probes, the cellular mRNA or DNA which might contain a mutation can be amplified using PCR (see below) before hybridization.

[00444] DNA sequences of the p53 gene from the cancer cell tissue which have been amplified by use of polymerase chain reaction can also be screened using allele-specific probes. These probes are nucleic acid oligomers, each of which contains a region of the p53 gene sequence harboring a known mutation. For example, one oligomer can be about 30 nucleotides in length, corresponding to a portion of the p53 gene sequence. At the position coding for the 175th codon of p53 gene the oligomer encodes an alanine, rather than the wild type codon valine. By use of a battery of such allele-specific probes, the PCR amplification products can be screened to identify the presence of a previously identified mutation in the p53 gene. Hybridization of allele-specific probes with amplified p53 sequences can be performed, for example, on a nylon filter. Hybridization to a particular probe indicates the presence of the same mutation in the cancer cell tissue as in the allele-specific probe.

[00445] The identification of p53 gene structural changes in cancer cells can be facilitated through the application of a diverse series of high resolution, high throughput microarray platforms. Essentially two types of array include those that carry PCR products from cloned nucleic acids (e.g. cDNA, BACs, cosmids) and those that use oligonucleotides. The methods can provide a way to survey genome wide DNA copy number abnormalities and expression levels to allow correlations between losses, gains and amplifications in cancer cells with genes that are over- and under- expressed in the same samples. The gene expression arrays that provide estimates of mRNA levels in cancer cells have given rise to exon-specific arrays that can identify both gene expression levels, alternative splicing events and mRNA processing alterations.

[00446] Oligonucleotide arrays can be used to interrogate single nucleotide polymorphisms (SNPs) throughout the genome for linkage and association studies and these have been adapted to quantify copy number abnormalities and loss of heterozygosity events. DNA sequencing arrays can allow resequencing of chromosome regions, exomes, and whole genomes.

[00447] SNP-based arrays or other gene arrays or chips can determine the presence of wild type p53 allele and the structure of mutations. A single nucleotide polymorphism (SNP), a variation at a single site in DNA, is the most frequent type of variation in the genome. For example, there are an estimated 5-10 million SNPs in the human genome. SNPs can be synonymous or nonsynonymous substitutions. Synonymous SNP substitutions do not result in a change of amino acid in the protein due to the degeneracy of the genetic code, but can affect function in other ways. For example, a seemingly silent mutation in a gene that codes for a membrane transport protein can slow down translation, allowing the peptide chain to misfold, and produce a less functional mutant membrane transport protein. Nonsynonymous SNP substitutions can be missense substitutions or nonsense substitutions. Missense substitutions occur when a single base change results in change in amino acid sequence of the protein and malfunction thereof leads to disease. Nonsense substitutions occur when a point mutation results in a premature stop codon, or a nonsense codon in the transcribed mRNA, which results in a truncated and usually, nonfunctional, protein product. As SNPs are highly conserved throughout evolution and within a population, the map of SNPs serves as an excellent genotypic marker for research. SNP array is a useful tool to study the whole genome.

[00448] In addition, SNP array can be used for studying the Loss Of Heterozygosity (LOH). LOH is a form of allelic imbalance that can result from the complete loss of an allele or from an increase in copy number of one allele relative to the other. While other chip-based methods (e.g., comparative genomic hybridization can detect only genomic gains or deletions), SNP array has the additional advantage of detecting copy number neutral LOH due to uniparental disomy (UPD). In UPD, one allele or whole chromosome from one parent are missing leading to reduplication of the other parental allele (uni-parental = from one parent, disomy = duplicated). In a disease setting this occurrence can be pathologic when the wild type allele (e.g., from the mother) is missing and instead two copies of the heterozygous allele (e.g., from the father) are present. This usage of SNP array has a huge potential in cancer diagnostics as LOH is a prominent characteristic of most human cancers. SNP array technology have shown that cancers (e.g. gastric cancer, liver cancer, etc.) and hematologic malignancies (ALL, MDS, CML etc) have a high rate of LOH due to genomic deletions or UPD and genomic gains. In the present disclosure, using high density SNP array to detect LOH allows identification of pattern of allelic imbalance to determine the presence of wild type p53 allele (Lips *et al.*, 2005; Lai *et al.*, 2007).

[00449] Examples of p53 gene sequence and single nucleotide polymorphism arrays include p53 Gene Chip (Affymetrix, Santa Clara, CA), Roche p53 Ampli-Chip (Roche Molecular Systems, Pleasanton, CA), GeneChip Mapping arrays (Affymetrix, Santa Clara, CA), SNP Array 6.0 (Affymetrix, Santa Clara, CA), BeadArrays (Illumina, San Diego, CA), etc.

[00450] Mutations of wild type p53 genes can also be detected on the basis of the mutation of a wild type expression product of the p53 gene. Such expression products include both the mRNA as well as the p53 protein product itself. Point mutations can be detected by sequencing the mRNA directly or via molecular cloning of cDNA made from the mRNA. The sequence of the cloned cDNA can be determined using DNA sequencing techniques. The cDNA can also be sequenced via the polymerase chain reaction (PCR). A panel of monoclonal antibodies could be used in which each of the epitopes involved in p53 functions are represented by a monoclonal antibody. Loss or perturbation of binding of a monoclonal antibody in the panel can indicate mutational alteration of the p53 protein and thus of the p53 gene itself. Mutant p53 genes or gene products can also be detected in body samples, including, for example, serum, stool, urine, and sputum. The same techniques discussed above for detection of mutant p53 genes or gene products in tissues can be applied to other body samples.

Loss of wild type p53 genes can also be detected by screening for loss of wild type p53 protein function. Although all of the functions which the p53 protein undoubtedly possesses have yet to be elucidated, at least two specific functions are known. Protein p53 binds to the SV40 large T antigen as well as to the adenovirus E1B antigen. Loss of the ability of the p53 protein to bind to either or both of these antigens indicates a mutational alteration in the protein which reflects a mutational alteration of the gene itself. Alternatively, a panel of monoclonal antibodies could be used in which each of the epitopes involved in p53 functions are represented by a monoclonal antibody. Loss or perturbation of binding of a monoclonal antibody in the panel

would indicate mutational alteration of the p53 protein and thus of the p53 gene itself. Any method for detecting an altered p53 protein can be used to detect loss of wild type p53 genes.

Assay to Determine α-helicity

[00451] 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)).

Assay to Determine Melting Temperature (Tm).

[00452] 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).

Protease Resistance Assay.

[00453] 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).

Ex Vivo Stability Assay.

[00454] 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.

In vitro Binding Assays.

[00455] 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).

[00456] 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.

In vitro Displacement Assays To Characterize Antagonists of Peptide-Protein Interactions.

[00457] 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.

[00458] 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).

[00459] 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

[00460] 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.

Assay for Protein-ligand Kd Titration Experiments.

[00461] 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 Annis, D. A.; Nazef, N.; Chuang, C. C.; Scott, M. P.; Nash, H. M. *J. Am. Chem. Soc.* 2004, *126*, 15495-15503; also in 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.

Assay for Competitive Binding Experiments by Affinity Selection-Mass Spectrometry

[00462] 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.

Binding Assays in Intact Cells.

[00463] 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 (50 mM 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.

Cellular Penetrability Assays.

[00464] 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.

Cellular Efficacy Assays.

[00465] 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.

In Vivo Stability Assay.

[00466] 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.

In vivo Efficacy in Animal Models.

[00467] 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.

Clinical Trials

[00468] To determine the suitability of the peptidomimetic macrocycles for treatment of humans, clinical trials are performed. For example, patients diagnosed with cancer 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.

Pharmaceutical Compositions and Routes of Administration

[00469] Pharmaceutical compositions disclosed herein include peptidomimetic macrocycles and pharmaceutically acceptable derivatives or prodrugs thereof. A "pharmaceutically acceptable derivative" means any pharmaceutically acceptable salt, ester, salt of an ester, pro-drug or other derivative of a compound disclosed herein which, upon administration to a recipient, is capable of providing (directly or indirectly) a compound disclosed herein. Particularly favored pharmaceutically acceptable derivatives are those that increase the bioavailability of the compounds when administered to a mammal (*e.g.*, by increasing absorption into the blood of an orally administered compound) or which increases delivery of the active compound to a biological compartment (*e.g.*, the brain or lymphatic system) relative to the parent species. Some pharmaceutically acceptable derivatives include a chemical group which increases aqueous solubility or active transport across the gastrointestinal mucosa.

[00470] In some embodiments, peptidomimetic macrocycles are modified by covalently or non-covalently joining appropriate functional groups to enhance selective biological properties. Such modifications include those which increase biological penetration into a given biological compartment (*e.g.*, blood, lymphatic

system, central nervous system), increase oral availability, increase solubility to allow administration by injection, alter metabolism, and alter rate of excretion.

[00471] Pharmaceutically acceptable salts of the compounds disclosed herein include those derived from pharmaceutically acceptable inorganic and organic acids and bases. Examples of suitable acid salts include acetate, adipate, benzoate, benzenesulfonate, butyrate, citrate, digluconate, dodecylsulfate, formate, fumarate, glycolate, hemisulfate, heptanoate, hexanoate, hydrochloride, hydrobromide, hydroiodide, lactate, maleate, malonate, methanesulfonate, 2-naphthalenesulfonate, nicotinate, nitrate, palmoate, phosphate, picrate, pivalate, propionate, salicylate, succinate, sulfate, tartrate, tosylate and undecanoate. Salts derived from appropriate bases include alkali metal (*e.g.*, sodium), alkaline earth metal (*e.g.*, magnesium), ammonium and N-(alkyl)$_4^+$ salts.

[00472] For preparing pharmaceutical compositions from the compounds disclosed herein, pharmaceutically acceptable carriers include either solid or liquid carriers. Solid form preparations include powders, tablets, pills, capsules, cachets, suppositories, and dispersible granules. A solid carrier can be one or more substances, which also acts as diluents, flavoring agents, binders, preservatives, tablet disintegrating agents, or an encapsulating material. Details on techniques for formulation and administration are well described in the scientific and patent literature, see, *e.g.*, the latest edition of Remington's Pharmaceutical Sciences, Maack Publishing Co, Easton PA.

[00473] In powders, the carrier is a finely divided solid, which is in a mixture with the finely divided active component. In tablets, the active component is mixed with the carrier having the necessary binding properties in suitable proportions and compacted in the shape and size desired.

[00474] Suitable solid excipients are carbohydrate or protein fillers include, but are not limited to sugars, including lactose, sucrose, mannitol, or sorbitol; starch from corn, wheat, rice, potato, or other plants; cellulose such as methyl cellulose, hydroxypropylmethyl-cellulose, or sodium carboxymethylcellulose; and gums including arabic and tragacanth; as well as proteins such as gelatin and collagen. If desired, disintegrating or solubilizing agents are added, such as the cross-linked polyvinyl pyrrolidone, agar, alginic acid, or a salt thereof, such as sodium alginate.

[00475] Liquid form preparations include solutions, suspensions, and emulsions, for example, water or water/propylene glycol solutions. For parenteral injection, liquid preparations can be formulated in solution in aqueous polyethylene glycol solution.

[00476] The pharmaceutical preparation can be in unit dosage form. In such form the preparation is subdivided into unit doses containing appropriate quantities of the active component. The unit dosage form can be a packaged preparation, the package containing discrete quantities of preparation, such as packeted tablets, capsules, and powders in vials or ampoules. Also, the unit dosage form can be a capsule, tablet, cachet, or lozenge itself, or it can be the appropriate number of any of these in packaged form.

When one or more compositions disclosed herein comprise a combination of a peptidomimetic macrocycle and one or more additional therapeutic or prophylactic agents, both the compound and the additional agent should be present at dosage levels of between about 1 to 100%, and more preferably between about 5 to 95%

of the dosage normally administered in a monotherapy regimen. In some embodiments, the additional agents are administered separately, as part of a multiple dose regimen, from one or more compounds disclosed herein. Alternatively, those agents are part of a single dosage form, mixed together with the compounds disclosed herein in a single composition.

Methods of Use

[00477] In one aspect, provided herein are 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 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. 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.

[00478] 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.

[00479] 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.

[00480] 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.

[00481] 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.

[00482] In some embodiments, the peptidomimetic macrocycles 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 histopathologic 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 differentiation disorders include cancer, *e.g.*, carcinoma, sarcoma, or metastatic disorders. In some embodiments, the peptidomimetic macrocycles are novel therapeutic agents for controlling breast cancer, ovarian cancer, colon cancer, lung cancer, metastasis of such cancers and the like.

[00483] 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, or Kaposi sarcoma.

[00484] In some embodiments, the cancer is head and neck cancer, melanoma, lung cancer, breast cancer, or glioma.

[00485] 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), periphieral T-cell lymphoma (PTCL), large granular lymphocytic leukemia (LGF), Hodgkin's disease and Reed-Stemberg disease.

[00486] Examples of cellular proliferative and/or differentiation 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.

[00487] 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.

[00488] Examples of cellular proliferative and/or differentiation 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.

[00489] 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.

[00490] 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.

[00491] 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.

Combination Treatment

[00492] The terms "combination therapy" or "combined treatment" or in "combination" as used herein denotes any form of concurrent or parallel treatment with at least two distinct therapeutic agents.

[00493] In some embodiments, the combination therapy can be particularly advantageous, since not only the therapeutic (for *e.g.* anti-cancerous) effect may be enhanced compared to the effect of each compound alone, the dosage of each agent in a combination therapy may also be reduced as compared to monotherapy with each agent, while still achieving an overall therapeutic (*e.g.* anti-tumor) effect. In addition, in some embodiments, the peptidomimetic macrocycles of the disclosure can exhibit synergistic effect with the additional pharmaceutical agents. In such cases, due to the synergistic effect, the total amount of drugs administered to a patient can advantageously be reduced, which may result in decreased side effects.

[00494] The present disclosure also provides methods for combination therapies in which the peptidomimetic macrocycles of the disclosure are used in combination with at least one additional pharmaceutically active agent. In various embodiments, the at least one additional pharmaceutically active agent may be capable of modulating the same or a different target as the peptidomimetic macrocycles of the disclosure. In some embodiments, the at least one additional pharmaceutically active agent may modulate the same target as the peptidomimetic macrocycles of the disclosure, or other components of the same pathway, or even overlapping sets of target enzymes. In some embodiments, the at least one additional pharmaceutically active agent may modulate a different target as the peptidomimetic macrocycles of the disclosure.

[00495] Combination therapy includes but is not limited to the combination of peptidomimetic macrocycles of this disclosure with chemotherapeutic agents, therapeutic antibodies, and radiation treatment, to provide a synergistic therapeutic effect.

[00496] Accordingly, in one aspect, the present disclosure provides a method for treating cancer, the method comprising administering to a subject in need thereof (a) an effective amount of a peptidomimetic macrocycle of the disclosure and (b) an effective amount of at least one additional pharmaceutically active agent to provide a combination therapy. In some embodiments, the combination therapy may have an enhanced therapeutic effect compared to the effect of the peptidomimetic macrocycle and the at least one additional pharmaceutically active agent each administered alone. According to certain exemplary embodiments, the combination therapy has a synergistic therapeutic effect. According to this embodiment, the combination therapy produces a significantly better therapeutic result (*e.g.*, anti-cancer, cell growth arrest, apoptosis,

induction of differentiation, cell death, etc.) than the additive effects achieved by each individual constituent when administered alone at a therapeutic dose.

[00497] In some embodiments, the peptidomimetic macrocycles of the disclosure are used in combination with one or more anti-cancer (antineoplastic or cytotoxic) chemotherapy drug. Suitable chemotherapeutic agents for use in the combinations of the present disclosure include, but are not limited to, alkylating agents, antibiotic agents, antimetabolic agents, hormonal agents, plant-derived agents, anti-angiogenic agents, differentiation inducing agents, cell growth arrest inducing agents, apoptosis inducing agents, cytotoxic agents, agents affecting cell bioenergetics, biologic agents, *e.g.*, monoclonal antibodies, kinase inhibitors and inhibitors of growth factors and their receptors, gene therapy agents, cell therapy, *e.g.*, stem cells, or any combination thereof.

[00498] In some embodiments, the peptidomimetic macrocycles of the disclosure are used in combination with an estrogen receptor antagonist. In one example, the peptidomimetic macrocycles of the disclosure are used in combination with the estrogen receptor antagonist fulvestrant (FASLODEX). Fulvestrant is a selective estrogen receptor degrader (SERD) and is indicated for the treatment of hormone receptor positive metastatic breast cancer in postmenopausal women with disease progression following anti-estrogen therapy. Fulvestrant is a complete estrogen receptor antagonist with little to no agonist effects and accelerates the proteasomal degradation of the estrogen receptor. Fulvestrant has poor oral bioavailability and is typically administered via intramuscular injection. Fulvestrant-induced expression of ErbB3 and ErbB4 receptors sensitizes oestrogen receptor-positive breast cancer cells to heregulin beta1 (*see*, e.g., Hutcheson et al., Breast cancer Research (2011) 13:R29).

[00499] In some embodiments, the peptidomimetic macrocycles of the disclosure are used in combination with an aromatase inhibitor. In one example, the peptidomimetic macrocycles of the disclosure are used in combination with exemestane.

[00500] In some embodiments, the peptidomimetic macrocycles of the disclosure are used in combination with a mTOR inhibitor. In one example, the peptidomimetic macrocycles of the disclosure are used in combination with everolimus (AFINITOR). Everolimus affects the mTORC1 protein complex and can lead to hyper-activation of the kinase AKT, which can lead to longer survival in some cell types. Everolimus binds to FKBP12, a protein receptor which directly interacts with mTORC1 and inhibits downstream signaling. mRNAs that codify proteins implicated in the cell cycle and in the glycolysis process are impaired or altered as a result, inhibiting tumor growth and proliferation. In some embodiments, the peptidomimetic macrocycles of the disclosure are used in combination with a mTOR inhibitor and an aromatase inhibitor. For example, the peptidomimetic macrocyclyes can be used in combination with everolimus and exemestane. Everolimus shows clinical efficacy in combination with tamoxifen, letrozole, or exemestane for the treatment of estrogen receptor-positive breast cancer (*see*, *e.g.*, Chen et al., Mol. Cancer Res. 11(10); 1269-78 (2013).

[00501] In some examples, the peptidomimetic macrocycles of the disclosure are used in combination with one or more antimetabolites, for example in combination with Capecitabine (XELODA), Gemcitabine

(GEMZAR) and Cytarabine (cytosine arabinoside also known as Ara-C (arabinofuranosyl cytidine; Cytosar-U)).

[00502] In some embodiments, the peptidomimetic macrocycles of the disclosure are used in combination with taxanes. Exemplary non-limiting taxanes that may be used in combination with the instant peptidomimetic macrocycles include paclitaxel (ABRAXANE or TAXOL) and docetaxel (TAXOTERE). In some embodiments the peptidomimetic macrocycles of the instant disclosure are used in combination with paclitaxel. In some embodiments the peptidomimetic macrocycles of the instant disclosure are used in combination with docetaxel.

[00503] In some embodiments, the peptidomimetic macrocycles of the disclosure are used in combination with therapeutic antibodies. Examples of therapeutic antibodies that can be combined with compounds of this disclosure include but are not limited to anti CD20 antibodies, for example rituximab (MABTHERA/ RITUXAN) or obinutuzumab (GAZYVA). Other antibodies that can be used in combination with the peptidomimetic macrocycles of the disclosure include antibodies against the programed cell death (PD-1) receptor, for example pembrolizumab (KEYTRUDA) or nivolumba (OPDIVO).

[00504] PD-1 antagonists useful in the any of the treatment method, medicaments and uses of the present invention include a monoclonal antibody (mAb), or antigen binding fragment thereof, which specifically binds to PD-1 or PD-L1, and preferably specifically binds to human PD-1 or human PD-L1. A PD-1 antagonist can be any chemical compound or biological molecule that blocks binding of PD-L1 expressed on a cancer cell to PD-1 expressed on an immune cell (T cell, B cell or NKT cell) and may also block binding of PD-L2 expressed on a cancer cell to the immune-cell expressed PD-1. Alternative names or synonyms for PD-1 and its ligands include: PDCD1, PD1, CD279 and SLEB2 for PD-1; PDCD1L1, PDL1, B7H1, B7-4, CD274 and B7-H for PD-L1; and PDCD1L2, PDL2, B7-DC, Btdc and CD273 for PD-L2. In any of the treatment method, medicaments and uses of the present invention in which a human individual is being treated, the PD-1 antagonist can block binding of human PD-L1 to human PD-1, and may block binding of both human PD-L1 and PD-L2 to human PD- 1.

[00505] Examples of mAbs that bind to human PD-1, and useful in the treatment method, medicaments and uses of the present invention, are described in US7521051, US8008449, and US8354509. Specific anti-human PD-1 mAbs useful as the PD-1 antagonist in the treatment method, medicaments and uses of the present invention include: MK-3475, a humanized IgG4 mAb with the structure described in WHO Drug Information, Vol. 27, No. 2, pages 161-162 (2013), nivolumab (BMS-936558), a human IgG4 mAb with the structure described in WHO Drug Information, Vol. 27, No. 1, pages 68-69 (2013); the humanized antibodies h409A11, h409A16 and h409A17, which are described in WO2008/156712, and AMP-514.

[00506] Other PD-1 antagonists useful in the any of the treatment method, medicaments and uses of the present invention include an immunoadhesin that specifically binds to PD-1 or PD-L1. Examples of immunoadhesion molecules that specifically bind to PD-1 are described in WO2010/027827 and WO2011/066342. Specific fusion proteins useful as thePD-1 antagonist in the treatment method, medicaments

and uses of the present invention include AMP-224 (also known as B7-DCIg), which is a PD-L2-FC fusion protein and binds to human PD-1.

[00507] Other antibodies that can be used in combination with the peptidomimetic macrocycles of the disclosure include antibodies against human PD-L1. Examples of antibodies that bind to human PD-L1 and useful in the treatment method, medicaments and uses of the present invention, are described in WO2013/019906, W02010/077634 Al and US8383796. Specific anti-human PD-L1 mAbs useful as the PD-1 antagonist in the treatment method, medicaments and uses of the present invention include MPDL3280A, BMS-936559, MEDI4736, MSB0010718C and an antibody which comprises the heavy chain and light chain variable regions of SEQ ID NO:24 and SEQ ID NO:21, respectively, of WO2013/019906. Exemplary useful antibodies targeting PD-1 receptors include Pidilizumab, BMS 936559, and MPDL328OA. An exemplary anti-PD-Ll antibody is human monoclonal antibody MDX-1105 which binds PD-L1 and blocks its binding to and activation of its receptor PD-1, which may enhance the T cell-mediated immune response to neoplasms and reverse T-cell inactivation in chronic infections disease. An exemplary anti-PD-1 antibody is human monoclonal antibody MDX-1106 which binds and blocks the activation of PD-1 by its ligands PD-L1 and PD-L2, resulting in the activation of T cells and cell-mediated immune responses against tumor cell

[00508] Several approaches have been described for quantifying PD-Ll protein expression in IHC assays of tumor tissue sections. See, e.g., Thompson, R. H., et al, PNAS 101 (49); 17174-17179 (2004); Thompson, R. H. et al, Cancer Res. 66:3381-3385 (2006); Gadiot, J., et al, Cancer 117:2192-2201 (2011); Taube, J. M. et al, Sci Transl Med 4, 127ra37 (2012); and Toplian, S. L. et al, New Eng. J Med. 366 (26): 2443-2454 (2012). One approach employs a simple binary end-point of positive or negative for PD- LI expression, with a positive result defined in terms of the percentage of tumor cells that exhibit histologic evidence of cell-surface membrane staining. A tumor tissue section is counted as positive for PD-Ll expression is at least 1%, and preferably 5% of total tumor cells. In another approach, PD-Ll expression in the tumor tissue section is quantified in the tumor cells as well as in infiltrating immune cells, which predominantly comprise lymphocytes. The percentage of tumor cells and infiltrating immune cells that exhibit membrane staining are separately quantified as < 5%, 5 to 9%, and then in 10% increments up to 100%. For tumor cells, PD-Ll expression is counted as negative if the score is < 5% score and positive if the score is > 5%. PD-Ll expression in the immune infiltrate is reported as a semi-quantitative measurement called the adjusted inflammation score (AIS), which is determined by multiplying the percent of membrane staining cells by the intensity of the infiltrate, which is graded as none (0), mild (score of 1, rare lymphocytes), moderate (score of 2, focal infiltration of tumor by lymphohistiocytic aggregates), or severe (score of 3, diffuse infiltration). A tumor tissue section is counted as positive for PD-Ll expression by immune infiltrates if the AIS is > 5. A tissue section from a tumor that has been stained by IHC with a diagnostic PD- LI antibody may also be scored for PD-Ll protein expression by assessing PD-Ll expression in both the tumor cells and infiltrating immune cells in the tissue section. This PD-L1 scoring process can comprise examining each tumor nest in the tissue section for staining, and assigning to the tissue section one or both of a modified H score (MHS) and a modified proportion score (MPS). To assign the MHS, four separate percentages are estimated across all of

the viable tumor cells and stained mononuclear inflammatory cells in all of the examined tumor nests: (a) cells that have no staining (intensity = 0), (b) weak staining (intensity =1+), (c) moderate staining (intensity =2+) and (d) strong staining (intensity =3+). A cell must have at least partial membrane staining to be included in the weak, moderate or strong staining percentages. The estimated percentages, the sum of which is 100%, are then input into the formula of 1 x (percent of weak staining cells) + 2 x (percent of moderate staining cells) + 3 x (percent of strong staining cells), and the result is assigned to the tissue section as the MHS. The MPS is assigned by estimating, across all of the viable tumor cells and stained mononuclear inflammatory cells in all of the examined tumor nests, the percentage of cells that have at least partial membrane staining of any intensity, and the resulting percentage is assigned to the tissue section as the MPS. In some embodiments, the tumor is designated as positive for PD-L1 expression if the MHS or the MPS is positive. The level of PD-L mRNA expression may be compared to the mRNA expression levels of one or more reference genes that are frequently used in quantitative RT-PCR, such as ubiquitin C. In some embodiments, a level of PD-L1 expression (protein and/or mRNA) by malignant cells and/or by infiltrating immune cells within a tumor is determined to be "overexpressed" or "elevated" based on comparison with the level of PD-L1 expression (protein and/ or mRNA) by an appropriate control. For example, a control PD-L1 protein or mRNA expression level may be the level quantified in nonmalignant cells of the same type or in a section from a matched normal tissue. In some preferred embodiments, PD-L1 expression in a tumor sample is determined to be elevated if PD-L1 protein (and/or PD-L1 mRNA) in the sample is at least 10%, 20%, or 30% greater than in the control.

[00509] In some embodiments, the peptidomimetic macrocycles of the disclosure are used in combination with antihormone therapy. Exemplary hormone antagonists that may be used in combination with the peptidomimetic macrocycles of the instant disclosure include letrozole (FEMARA) and casodex.

[00510] In some embodiments, the peptidomimetic macrocycles of the disclosure are used in in combination with hypomethylating agents or demethylating agents. Examples of such agents that may be used in combination with the peptidomimetic macrocycles of the disclosure include azacitidine (VIDAZA, AZADINE) and decitabine (Dacogen).

[00511] In some embodiments, the peptidomimetic macrocycles of the disclosure are used in in combination with an anti-inflammatory agent. In some embodiments, the peptidomimetic macrocycles of the disclosure are used in in combination with a corticosteroid. In some embodiments, the peptidomimetic macrocycles of the disclosure are used in in combination with a glucocorticosteroid. In one example, the peptidomimetic macrocycles of the disclosure are used in combination with dexamethasone.

[00512] In some embodiments, the peptidomimetic macrocycles of the disclosure are used in in combination with a histone deacetylase (HDAC) inhibitor. In some embodiments, the peptidomimetic macrocycles of the disclosure are used in in combination with a depsipeptide. In one example, the peptidomimetic macrocycles of the disclosure are used in combination with romidepsin (ISTODAX). Exemplary cancers for treatment with the peptidomimetic macrocycles of the disclosure and HDAC inhibitors, such as romidepsin, include T-cell lymphomas, for example, adult T cell leukemia/lymphoma (ATL), cutaneous T-cell lymphoma (CTCL), or

periphieral T-cell lymphoma (PTCL). HDAC inhibitors may interact synergistically with MDM2 inhibitors by mediating hyperacetylation of p53. Acetylation may be required for p53 activation. HDAC inhibitors may enhance the antitumor action of MDM2 inhibitors by diminishing MDM2 inhibitor-induced MDM2 expression. MDM2 is upregulated by p53 activation in a feedback loop that negatively controls p53 activity. MDM2 inhibitors may elicit cancer cell death by downregulating MDM4 expression. MDM4 is the second main negative regulator of p53, which is structurally homologues, but functionally not redundant to MDM2. Nutlin-3 and vorinostat cooperate in affecting cell viability and in inducing cell death and $\Delta\psi m$ loss in A549 cells and cooperate in inducing cell death, $\Delta\psi m$ loss and caspase-3 activity in A2780 cells (*see, e.g.*, J. Sonnemann et al., Invest New Drugs (2012) 30:25–36).

[00513] In some embodiments, the peptidomimetic macrocycles of the disclosure are used in in combination with platinum-based antineoplastic drugs (platinum drugs or platins). Examples of the platins that may be used in combination with the peptidomimetic macrocycles of the disclosure include cisplatin (also known as cisplatinum, platamin, neoplatin, cismaplat, cis-diamminedichloroplatinum(II), or CDDP; tradename PLATINOL) and carboplatin (also known as cis-diammine(1,1-cyclobutanedicarboxylato)platinum(II); tradenames PARAPLATIN and PARAPLATIN-AQ).

[00514] In some embodiments, the peptidomimetic macrocycles of the disclosure are used in in combination with a kinase inhibitor drug. The compounds described herein can be used in combination with MEK inhibitors. The compounds described herein can be used in combination with MEK1 inhibitors. The compounds described herein can be used in combination with MEK2 inhibitors. The compounds described herein can be used in combination with inhibitors of MEK1 and MEK2. In one example, he peptidomimetic macrocycles of the disclosure are used in in combination with trametinib (MEKINIST). The compounds described herein can be used in combination with BRAF inhibitors. The BRAF inhibitors used in combination with the peptidomimetic macrocycles of the disclosure may be inhibitor of either wild type or mutated BRAF. In some examples, the peptidomimetic macrocycles of the disclosure are used in combination with at least one additional pharmaceutically active agent that is an inhibitor of wild type BRAF. In some examples, the peptidomimetic macrocycles of the disclosure are used in combination with at least one additional pharmaceutically active agent that is an inhibitor of mutated BRAF. In some examples, the peptidomimetic macrocycles of the disclosure are used in combination with at least one additional pharmaceutically active agent that is an inhibitor of a V600E mutated BRAF. In some embodiments the compounds described herein can be used in combination with one or more BRAF inhibitors selected from vemurafenib (ZELBORAF a.k.a. PLX4032), dabrafenib (TAFINLAR), C-1, NVP-LGX818 and sorafenib (NEXAVAR). In some embodiments the compounds described herein can synergize with one or more BRAF inhibitors. In some embodiments one or more of the compounds described herein can synergize with all BRAF inhibitors.

[00515] The compounds described herein can be used in combination with KRAS inhibitors. The KRAS inhibitors used in combination with the peptidomimetic macrocycles of the disclosure may be inhibitor of either wild type or mutated KRAS. In some examples, the peptidomimetic macrocycles of the disclosure are used in combination with at least one additional pharmaceutically active agent that is an inhibitor of wild type

KRAS. In some examples, the peptidomimetic macrocycles of the disclosure are used in combination with at least one additional pharmaceutically active agent that is an inhibitor of mutated KRAS. In some embodiments the compounds described herein can synergize with one or more KRAS inhibitors. In some embodiments one or more of the compounds described herein can synergize with all KRAS inhibitors.

[00516] The peptidomimetic macrocycles of the disclosure may also be used in combination with Bruton's tyrosine kinase (BTK) inhibitor, for example in combination with ibrutinib (IMBRUVICA). In some embodiments the compounds described herein can synergize with one or more BTK inhibitor. In some embodiments one or more of the compounds described herein can synergize with all BTK inhibitors.

[00517] In some examples, the peptidomimetic macrocycles of the disclosure may also be used in combination with inhibitors of the cyclin-dependent kinases, for example with an inhibitor of CDK4 and/or CDK6. An example of such inhibitor that may be used in combination with the instant peptidomimetic macrocycle is palbociclib (IBRANCE) (*see*, *e.g.*, Clin. Cancer Res.; 2015, 21(13); 2905–10). In some examples, the peptidomimetic macrocycles of the disclosure may be used in combination with an inhibitor of CDK4 and/or CDK6 and with an agent that reinforces the cytostatic activity of CDK4/6 inhibitors and/or with an agent that converts reversible cytostasis into irreversible growth arrest or cell death. Exemplary cancer subtypes include NSCLC, melanoma, neuroblastoma, glioblastoma, liposarcoma, and mantle cell lymphoma.

[00518] In some embodiments, a method of treating cancer in a subject in need thereof can comprise administering to the subject a therapeutically effective amount of a p53 agent that inhibits the interaction between p53 and MDM2 and/or p53 and MDMX, and/or modulates the activity of p53 and/or MDM2 and/or MDMX; and at least one additional pharmaceutically active agent, wherein the at least one additional pharmaceutically active agent modulates the activity of CDK4 and/or CDK6, and/or inhibits CDK4 and/or CDK6. In some examples, the p53 agent antagonizes an interaction between p53 and MDM2 proteins and/or between p53 and MDMX proteins. In some examples, the at least one additional pharmaceutically active agent binds to CDK4 and/or CDK6. In some examples, the p53 agent is selected from the group consisting of a small organic or inorganic molecule; a saccharine; an oligosaccharide; a polysaccharide; a peptide, a protein, a peptide analog, a peptide derivative; an antibody, an antibody fragment, a peptidomimetic; a peptidomimetic macrocycle of any one of claims 1-56; a nucleic acid; a nucleic acid analog, a nucleic acid derivative; an extract made from biological materials; a naturally occurring or synthetic composition; and any combination thereof. In some examples, the p53 agent is selected from the group consisting of RG7388 (RO5503781, idasanutlin); RG7112 (RO5045337); nutlin3a; nutlin3b; nutlin3; nutlin2; spirooxindole containing small molecules; 1,4-diazepines; 1,4-benzodiazepine-2,5-dione compounds; WK23; WK298; SJ172550; RO2443; RO5963; RO5353; RO2468; MK8242 (SCH900242); MI888; MI773 (SAR405838); NVPCGM097; DS3032b; AM8553; AMG232; NSC207895 (XI006); JNJ26854165 (serdemetan); RITA (NSC652287); YH239EE; and any combination thereof. In some examples, the at least one additional pharmaceutically active agent is selected from the group consisting of a small organic or inorganic molecule; a saccharine; an oligosaccharide; a polysaccharide; a peptide, a protein, a peptide analog, a peptide derivative; an antibody, an antibody fragment, a peptidomimetic; a peptidomimetic macrocycle of any one of claims 1-56; a nucleic acid;

a nucleic acid analog, a nucleic acid derivative; an extract made from biological materials; a naturally occurring or synthetic composition; and any combination thereof. In some examples, the at least one additional pharmaceutically active agent is selected from the group consisting of palbociclib (PD0332991); abemaciclib (LY2835219); ribociclib (LEE 011); voruciclib (P1446A-05); fascaplysin; arcyriaflavin; 2-bromo-12,13-dihydro-5H-indolo[2,3-a]pyrrolo[3,4-c]carbazole-5,7(6H)-dione; 3-amino thioacridone (3-ATA), trans-4-((6-(ethylamino)-2-((1-(phenylmethyl)-1H-indol-5-yl)amino)-4-pyrimidinyl)amino)-cyclohexano (CINK4); 1,4-dimethoxyacridine-9(10H)-thione (NSC 625987); 2-methyl-5-(p-tolylamino)benzo[d]thiazole-4,7-dione (ryuvidine); and flavopiridol (alvocidib); and any combination thereof.

[00519] In some examples, the peptidomimetic macrocycles of the disclosure may also be used in combination with inhibitors of the cyclin-dependent kinases and an estrogen receptor antagonist. An example of such inhibitors that may be used in combination with the instant peptidomimetic macrocycle is palbociclib and fulvestrant. In some examples, the peptidomimetic macrocycles of the disclosure may also be used in combination with at least one additional pharmaceutically active agent that alleviates CDKN2A (cyclin-dependent kinase inhibitor 2A) deletion. In some example, the peptidomimetic macrocycles of the disclosure may also be used in combination with at least one additional pharmaceutically active agent that alleviates CDK9 (cyclin-dependent kinase 9) abnormality.

[00520] The peptidomimetic macrocycles of the disclosure may also be used in combination with one or more pharmaceutically active agent that regulates the ATM (upregulate or downregulate). In some embodiments the compounds described herein can synergize with one or more ATM regulators. In some embodiments one or more of the compounds described herein can synergize with all ATM regulators.

[00521] In some embodiments, the peptidomimetic macrocycles of the disclosure may be used in combination with one or more pharmaceutically active agent that inhibits the AKT (protein kinase B (PKB)). In some embodiments the compounds described herein can synergize with one or more AKT inhibitors.

[00522] In some examples, the peptidomimetic macrocycles of the disclosure may also be used in combination with at least one additional pharmaceutically active agent that alleviates PTEN (phosphatase and tensin homolog) deletion.

[00523] In some examples, the peptidomimetic macrocycles of the disclosure may also be used in combination with at least one additional pharmaceutically active agent that alleviates Wip-1Alpha over expression.

[00524] In some examples, the peptidomimetic macrocycles of the disclosure may be used in combination with at least one additional pharmaceutically active agent that is a Nucleoside metabolic inhibitor. Exemplary nucleoside metabolic inhibitors that may be used include capecitabine, gemcitabine and cytarabine (Arac).

[00525] The table below lists various suitable additional pharmaceutically active agents for use with the methods described herein.

Cancer Type	Drug name	Brand name	Drug works predominately in S or M phase
ALL	ABT-199	none	No
ALL	clofarabine	Clofarex	Yes; S phase

ALL	cyclophosphamide	Clafen, Cytoxan, Neosar	Yes: S phase
ALL	cytarabine	Cytosar-U, Tarabine PFS	Yes: S phase
ALL	doxorubicin	Adriamycin	Yes: S phase
ALL	imatinib mesylate	Gleevec	No
ALL	methotrexate	Abitrexate, Mexate, Folex	Yes: S phase
ALL	prednisone	Deltasone, Medicorten	No
ALL	romidepsin	Istodax	
ALL	vincristine	Vincasar	Yes: M phase
AML	ABT-199	none	No
AML	azacitadine	Vidaza	No
AML	cyclophosphamide	Clafen, Cytoxan, Neosar	Yes: S phase
AML	cytarabine	Cytosar-U, Tarabine PFS	Yes: S phase
AML	decitabine	Dacogen	No
AML	doxorubicin	Adriamycin	Yes: S phase
AML	etoposide	Etopophos, Vepesid	Yes: S and M phases
AML	vincristine	Vincasar	Yes: M phase
bone	doxorubicin	Adriamycin	Yes: S phase
bone	methotrexate	Abitrexate, Mexate, Folex	Yes: S phase
breast	capecitabine	Xeloda	Yes: S phase
breast	cyclophosphamide	Clafen, Cytoxan, Neosar	Yes: S phase
breast	docetaxel	Taxotere	Yes: M phase
breast	doxorubicin	Adriamycin	Yes: S phase
breast	eribulin mesylate	Haliben	Yes: M phase
breast	everolimus	Afinitor	No
breast	exemestane	Aromasin	No
breast	fluorouracil	Adrucil, Efudex	Yes: S phase
breast	fulvestrant	Faslofex	
breast	gemcitabine	Gemzar	Yes: S phase
breast	goserelin acetate	Zoladex	No
breast	letrozole	Femara	No
breast	megestrol acetate	Megace	No
breast	methotrexate	Abitrexate, Mexate, Folex	Yes: S phase
breast	paclitaxel	Abraxane, Taxol	Yes: M phase
breast	palbociclib	Ibrance	Might cause G1 arrest
breast	pertuzumab	Perjeta	No
breast	tamoxifen citrate	Nolvadex	No
breast	trastuzumab	Herceptin, Kadcyla	No
colon	capecitabine	Xeloda	Yes: S phase
colon	cetuximab	Erbitux	No
colon	fluorouracil	Adrucil, Efudex	Yes: S phase
colon	irinotecan	camptosar	Yes: S and M phases
colon	ramucirumab	Cyramza	No
endometrial	carboplatin	Paraplatin, Paraplat	Yes: S phase
endometrial	cisplatin	Platinol	Yes: S phase

endometrial	doxorubicin	Adriamycin	Yes: S phase
endometrial	megestrol acetate	Megace	No
endometrial	paclitaxel	Abraxane, Taxol	Yes: M phase
gastric	docetaxel	Taxotere	Yes: M phase
gastric	doxorubicin	Adriamycin	Yes: S phase
gastric	fluorouracil	Adrucil, Efudex	Yes: S phase
gastric	ramucirumab	Cyramza	No
gastric	trastuzumab	Herceptin	No
kidney	axitinib	Inlyta	No
kidney	everolimus	Afinitor	No
kidney	pazopanib	Votrient	No
kidney	sorafenib tosylate	Nexavar	No
liver	sorafenib tosylate	Nexavar	No
melanoma	dacarbazine	DTIC, DTIC-Dome	Yes: S phase
melanoma	paclitaxel	Abraxane, Taxol	Yes: M phase
melanoma	trametinib	Mekinist	No
melanoma	vemurafenib	Zelboraf	No
melanoma	dabrafenib	Taflinar	
mesothelioma	cisplatin	Platinol	Yes: S phase
mesothelioma	pemetrexed	Alimta	Yes: S phase
NHL	ABT-199	none	No
NHL	bendamustine	Treanda	Causes DNA crosslinking, but is also toxic to resting cells
NHL	bortezomib	Velcade	No
NHL	brentuximab vedotin	Adcetris	Yes: M phase
NHL	chlorambucil	Ambochlorin, Leukeran, Linfolizin	Yes: S phase
NHL	cyclophosphamide	Clafen, Cytoxan, Neosar	Yes: S phase
NHL	dexamethasone	Decadrone, Dexasone	No
NHL	doxorubicin	Adriamycin	Yes: S phase
NHL	Ibrutinib	Imbruvica	No
NHL	lenalidomide	Revlimid	No
NHL	methotrexate	Abitrexate, Mexate, Folex	Yes: S phase
NHL	obinutuzumab	Gazyva	No
NHL	prednisone	Deltasone, Medicorten	No
NHL	romidepsin	Istodax	
NHL	rituximab	Rituxan	No
NHL	vincristine	Vincasar	Yes: M phase
NSCLC	afatinib Dimaleate	Gilotrif	No
NSCLC	carboplatin	Paraplatin, Paraplat	Yes: S phase
NSCLC	cisplatin	Platinol	Yes: S phase
NSCLC	crizotinib	Xalkori	No
NSCLC	docetaxel	Taxotere	Yes: M phase
NSCLC	erlotinib	Tarceva	No
NSCLC	gemcitabine	Gemzar	Yes: S phase

NSCLC	methotrexate	Abitrexate, Mexate, Folex	Yes: S phase
NSCLC	paclitaxel	Abraxane, Taxol	Yes: M phase
NSCLC	palbociclib	Ibrance	Might cause G1 arrest
NSCLC	pemetrexed	Alimta	Yes: S phase
NSCLC	ramucirumab	Cyramza	No
ovarian	carboplatin	Paraplatin, Paraplat	Yes: S phase
ovarian	cisplatin	Platinol	Yes; S phase
ovarian	cyclophosphamide	Clafen, Cytoxan, Neosar	Yes: S phase
ovarian	gemcitabine	Gemzar	Yes: S phase
ovarian	olaparib	Lynparza	Yes: G2/M phase arrest
ovarian	paclitaxel	Abraxane, Taxol	Yes: M phase
ovarian	topotecan	Hycamtin	Yes: S phase
prostate	abiraterone	Zytiga	No
prostate	cabazitaxel	Jevtana	Yes: M phase
prostate	docetaxel	Taxotere	Yes: M phase
prostate	enzalutamide	Xtandi	No
prostate	goserelin acetate	Zoladex	No
prostate	prednisone	Deltasone, Medicorten	No
soft tissue sarcoma	doxorubicin	Adriamycin	Yes: S phase
soft tissue sarcoma	imatinib mesylate	Gleevec	No
soft tissue sarcoma	pazopanib	Votrient	No
T-cell lymphoma	romidepsin	Istodax	

[00526] The peptidomimetic macrocycles or a composition comprising same and the at least one additional pharmaceutically active agent or a composition comprising same can be administered simultaneously (*i.e.*, simultaneous administration) and/or sequentially (*i.e.*, sequential administration).

[00527] According to certain embodiments, the peptidomimetic macrocycles and the at least one additional pharmaceutically active agent are administered simultaneously, either in the same composition or in separate compositions. The term "simultaneous administration," as used herein, means that the peptidomimetic macrocycle and the at least one additional pharmaceutically active agent are administered with a time separation of no more than about 15 minutes, such as no more than about any of 10, 5, or 1 minutes. When the drugs are administered simultaneously, the peptidomimetic macrocycle and the at least one additional pharmaceutically active agent may be contained in the same composition (*e.g.*, a composition comprising both the peptidomimetic macrocycle and the at least additional pharmaceutically active agent) or in separate compositions (*e.g.*, the peptidomimetic macrocycle is contained in one composition and the at least additional pharmaceutically active agent is contained in another composition).

[00528] According to other embodiments, the peptidomimetic macrocycles and the at least one additional pharmaceutically active agent are administered sequentially, *i.e.*, the peptidomimetic macrocycle is administered either prior to or after the administration of the additional pharmaceutically active agent. The term "sequential administration" as used herein means that the peptidomimetic macrocycle and the additional pharmaceutically active agent are administered with a time separation of more than about 15 minutes, such as

more than about any of 20, 30, 40, 50, 60 or more minutes. Either the peptidomimetic macrocycle or the pharmaceutically active agent may be administered first. The peptidomimetic macrocycle and the additional pharmaceutically active agent are contained in separate compositions, which may be contained in the same or different packages.

[00529] In some embodiments, the administration of the peptidomimetic macrocycles and the additional pharmaceutically active agent are concurrent, *i.e.*, the administration period of the peptidomimetic macrocycles and that of the agent overlap with each other. In some embodiments, the administration of the peptidomimetic macrocycles and the additional pharmaceutically active agent are non-concurrent. For example, in some embodiments, the administration of the peptidomimetic macrocycles is terminated before the additional pharmaceutically active agent is administered. In some embodiments, the administration of the additional pharmaceutically active agent is terminated before the peptidomimetic macrocycle is administered. The time period between these two non-concurrent administrations can range from being days apart to being weeks apart.

[00530] The dosing frequency of the peptidomimetic macrocycle and the at least one additional pharmaceutically active agent may be adjusted over the course of the treatment, based on the judgment of the administering physician. When administered separately, the peptidomimetic macrocycle and the at least one additional pharmaceutically active agent can be administered at different dosing frequency or intervals. For example, the peptidomimetic macrocycle can be administered weekly, while the at least one additional pharmaceutically active agent can be administered more or less frequently. Or, the peptidomimetic macrocycle can be administered twice weekly, while the at least one additional pharmaceutically active agent can be administered more or less frequently. In addition, the peptidomimetic macrocycle and the at least one additional pharmaceutically active agent can be administered using the same route of administration or using different routes of administration.

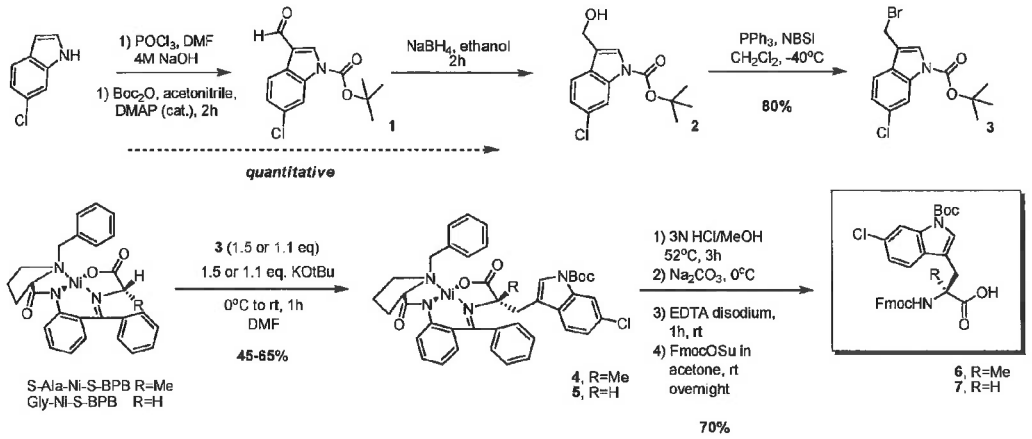
[00531] According to certain embodiments, the peptidomimetic macrocycles and the additional pharmaceutically active agent are administered within a single pharmaceutical composition. According to some embodiments, the pharmaceutical composition further comprises pharmaceutically acceptable diluents or carrier. According to certain embodiments, the peptidomimetic macrocycles and the additional pharmaceutically active agent are administered within different pharmaceutical composition.

[00532] According to certain embodiments, peptidomimetic macrocycles is administered in an amount of from 0 mg/kg body weight to 100 mg/kg body weight. According to other embodiments, the peptidomimetic macrocycle is administered at an amount of from 0.5 mg/kg body weight to 20 mg/kg body weight. According to additional embodiments, the peptidomimetic macrocycle is administered at an amount of from 1.0 mg/kg body weight to 10 mg/kg body weight. The at least one additional pharmaceutical agent is administered at the therapeutic amount known to be used for treating the specific type of cancer. According to other embodiments, the at least one additional pharmaceutical agent is administered in an amount lower than the therapeutic amount known to be used for treating the disease, *i.e.* a sub-therapeutic amount of the at least one additional pharmaceutical agent is administered.

[00533] 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 described herein can be employed in practicing the disclosure. It is intended that the following claims define the scope and that methods and structures within the scope of these claims and their equivalents be covered thereby.

Examples

Example 1: Synthesis of 6-chlorotryptophan Fmoc amino acids



[00534] Tert-butyl 6-chloro-3-formyl-1H-indole-1-carboxylate, 1. To a stirred solution of dry DMF (12 mL) was added dropwise $POCl_3$ (3.92 mL, 43 mmol, 1.3 equiv) at 0 °C under Argon. The solution was stirred at the same temperature for 20 min before a solution of 6-chloroindole (5.0 g, 33 mmol, 1 eq.) in dry DMF (30 mL) was added dropwise. The resulting mixture was allowed to warm to room temperature and stirred for an additional 2.5h. Water (50 mL) was added and the solution was neutralized with 4M aqueous NaOH (pH ~ 8). The resulting solid was filtered off, washed with water and dried under vacuum. This material was directly used in the next step without additional purification. To a stirred solution of the crude formyl indole (33 mmol, 1 eq.) in THF (150 mL) was added successively Boc_2O (7.91 g, 36.3 mmol, 1.1 equiv) and DMAP (0.4 g, 3.3 mmol, 0.1 equiv) at room temperature under N_2. The resulting mixture was stirred at room temperature for 1.5h and the solvent was evaporated under reduced pressure. The residue was taken up in EtOAc and washed with 1N HCl, dried and concentrated to give the formyl indole **1** (9 g, 98 % over 2 steps) as a white solid. ^1H NMR ($CDCl_3$) δ: 1.70 (s, Boc, 9H); 7.35 (dd, 1H); 8.21 (m, 3H); 10.07 (s, 1H).

[00535] Tert-butyl 6-chloro-3-(hydroxymethyl)-1H-indole-1-carboxylate, **2**. To a solution of compound **1** (8.86g, 32 mmol, 1 eq.) in ethanol (150 mL) was added $NaBH_4$ (2.4g, 63 mmol, 2 eq.). The reaction was stirred for 3 h at room temperature. The reaction mixture was concentrated and the residue was poured into diethyl ether and water. The organic layer was separated, dried over magnesium sulfate and concentrated to

give a white solid (8.7g, 98%). This material was directly used in the next step without additional purification. ^{1}H NMR ($CDCl_3$) δ: 1.65 (s, Boc, 9H); 4.80 (s, 2H, CH_2); 7.21 (dd, 1H); 7.53 (m, 2H); 8.16 (bs, 1H).

[00536] Tert-butyl 3-(bromomethyl)-6-chloro-1H-indole-1-carboxylate, **3**. To a solution of compound **2** (4.1g, 14.6 mmol, 1 eq.) in dichloromethane (50 mL) under argon was added a solution of triphenylphosphine (4.59g, 17.5 mmol, 1.2 eq.) in dichloromethane (50 mL) at -40°C. The reaction solution was stirred an additional 30 min at 40°C. Then NBS (3.38g, 19 mmol, 1.3 eq.) was added. The resulting mixture was allowed to warm to room temperature and stirred overnight. Dichloromethane was evaporated, Carbon Tetrachloride (100 mL) was added and the mixture was stirred for 1h and filtrated. The filtrate was concentrated, loaded in a silica plug and quickly eluted with 25% EtOAc in Hexanes. The solution was concentrated to give a white foam (3.84g, 77%). ^{1}H NMR ($CDCl_3$) δ: 1.66 (s, Boc, 9H); 4.63 (s, 2H, CH_2); 7.28 (dd, 1H); 7.57 (d, 1H); 7.64 (bs, 1H); 8.18 (bs, 1H).

[00537] αMe-6Cl-Trp(Boc)-Ni-S-BPB, **4**. To **S-Ala-Ni-S-BPB** (2.66g, 5.2 mmol, 1 eq.) and KO-*t*Bu (0.87g, 7.8 mmol, 1.5 eq.) was added 50 mL of DMF under argon. The bromide derivative compound **3** (2.68g, 7.8 mmol, 1.5 eq.) in solution of DMF (5.0 mL) was added via syringe. The reaction mixture was stirred at ambient temperature for 1h. The solution was then quenched with 5 % aqueous acetic acid and diluted with water. The desired product was extracted in dichloromethane, dried and concentrated. The oily product **4** was purified by flash chromatography (solid loading) on normal phase using EtOAc and Hexanes as eluents to give a red solid (1.78g, 45% yield). αMe-6Cl-Trp(Boc)-Ni-S-BPB, **4**: M+H calc. 775.21, M+H obs. 775.26; ^{1}H NMR ($CDCl_3$) δ: 1.23 (s, 3H, αMe); 1.56 (m, 11H, Boc + CH_2); 1.82-2.20 (m, 4H, $2CH_2$); 3.03 (m, 1H, CH_α); 3.24 (m, 2H, CH_2); 3.57 and 4.29 (AB system, 2H, CH_2 (benzyl), J= 12.8Hz); 6.62 (d, 2H); 6.98 (d, 1H); 7.14 (m, 2H); 7.23 (m, 1H); 7.32-7.36 (m, 5H); 7.50 (m, 2H); 7.67 (bs, 1H); 7.98 (d, 2H); 8.27 (m, 2H).

[00538] Fmoc-αMe-6Cl-Trp(Boc)-OH, **6**. To a solution of 3N HCl/MeOH (1/3, 15 mL) at 50°C was added a solution of compound **4** (1.75g, 2.3 mmol, 1 eq.) in MeOH (5 ml) dropwise. The starting material disappeared within 3-4 h. The acidic solution was then cooled to 0°C with an ice bath and quenched with an aqueous solution of Na_2CO_3 (1.21g, 11.5 mmol, 5 eq.). Methanol was removed and 8 more equivalents of Na_2CO_3 (1.95g, 18.4 mmol) were added to the suspension. The Nickel scavenging EDTA disodium salt dihydrate (1.68g, 4.5 mmol, 2 eq.) was then added and the suspension was stirred for 2h. A solution of Fmoc-OSu (0.84g, 2.5 mmol, 1.1 eq.) in acetone (50 mL) was added and the reaction was stirred overnight. Afterwards, the reaction was diluted with diethyl ether and 1N HCl. The organic layer was then dried over magnesium sulfate and concentrated in vacuo. The desired product **6** was purified on normal phase using acetone and dichloromethane as eluents to give a white foam (0.9g, 70% yield). Fmoc-αMe-6Cl-Trp(Boc)-OH, **6**: M+H calc. 575.19, M+H obs. 575.37; ^{1}H NMR ($CDCl_3$) 1.59 (s, 9H, Boc); 1.68 (s, 3H, Me); 3.48 (bs, 2H, CH_2); 4.22 (m, 1H, CH); 4.39 (bs, 2H, CH_2); 5.47 (s, 1H, NH); 7.10 (m, 1H); 7.18 (m, 2H); 7.27 (m, 2H); 7.39 (m, 2H); 7.50 (m, 2H); 7.75 (d, 2H); 8.12 (bs, 1H).

[00539] 6Cl-Trp(Boc)-Ni-S-BPB, **5**. To **Gly-Ni-S-BPB** (4.6g, 9.2 mmol, 1 eq.) and KO-*t*Bu (1.14g, 10.1 mmol, 1.1 eq.) was added 95 mL of DMF under argon. The bromide derivative compound **3** (3.5g, 4.6 mmol,

1.1 eq.) in solution of DMF (10 mL) was added via syringe. The reaction mixture was stirred at ambient temperature for 1h. The solution was then quenched with 5 % aqueous acetic acid and diluted with water. The desired product was extracted in dichloromethane, dried and concentrated. The oily product **5** was purified by flash chromatography (solid loading) on normal phase using EtOAc and Hexanes as eluents to give a red solid (5g, 71% yield). 6Cl-Trp(Boc)-Ni-S-BPB, **5**: M+H calc. 761.20, M+H obs. 761.34; ^{1}H NMR ($CDCl_3$) δ: 1.58 (m, 11H, Boc + CH_2); 1.84 (m, 1H); 1.96 (m, 1H); 2.24 (m, 2H, CH_2); 3.00 (m, 1H, CH_α); 3.22 (m, 2H, CH_2); 3.45 and 4.25 (AB system, 2H, CH_2 (benzyl), J= 12.8Hz); 4.27 (m, 1H, CH_α); 6.65 (d, 2H); 6.88 (d, 1H); 7.07 (m, 2H); 7.14 (m, 2H); 7.28 (m, 3H); 7.35-7.39 (m, 2H); 7.52 (m, 2H); 7.96 (d, 2H); 8.28 (m, 2H).

[00540] Fmoc-6Cl-Trp(Boc)-OH, **7**. To a solution of 3N HCl/MeOH (1/3, 44 mL) at 50°C was added a solution of compound **5** (5g, 6.6 mmol, 1 eq.) in MeOH (10 ml) dropwise. The starting material disappeared within 3-4 h. The acidic solution was then cooled to 0°C with an ice bath and quenched with an aqueous solution of Na_2CO_3 (3.48g, 33 mmol, 5 eq.). Methanol was removed and 8 more equivalents of Na_2CO_3 (5.57g, 52 mmol) were added to the suspension. The Nickel scavenging EDTA disodium salt dihydrate (4.89g, 13.1 mmol, 2 eq.) and the suspension was stirred for 2h. A solution of Fmoc-OSu (2.21g, 6.55 mmol, 1.1 eq.) in acetone (100 mL) was added and the reaction was stirred overnight. Afterwards, the reaction was diluted with diethyl ether and 1N HCl. The organic layer was then dried over magnesium sulfate and concentrated in vacuo. The desired product **7** was purified on normal phase using acetone and dichloromethane as eluents to give a white foam (2.6g, 69% yield). Fmoc-6Cl-Trp(Boc)-OH, **7**: M+H calc. 561.17, M+H obs. 561.37; ^{1}H NMR ($CDCl_3$) 1.63 (s, 9H, Boc); 3.26 (m, 2H, CH_2); 4.19 (m, 1H, CH); 4.39 (m, 2H, CH_2); 4.76 (m, 1H); 5.35 (d, 1H, NH); 7.18 (m, 2H); 7.28 (m, 2H); 7.39 (m, 3H); 7.50 (m, 2H); 7.75 (d, 2H); 8.14 (bs, 1H).

Example 2: Peptidomimetic macrocycles

[00541] 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.

[00542] 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).

[00543] 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.

[00544] 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 may 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.

[00545] Table 1 shows a list of peptidomimetic macrocycles prepared.

Table 1

SP	Sequence	Isomer	Exact Mass	Found Mass	Calc (M+1)/1	Calc (M+2)/2	Calc (M+3)/3
SP1	Ac-F$r8AYWEAc3cL$AAA-NH_2		1456.78	729.44	1457.79	729.4	486.6
SP2	Ac-F$r8AYWEAc3cL$AAibA-NH_2		1470.79	736.4	1471.8	736.4	491.27
SP3	Ac-LTF$r8AYWAQL$SANle-NH_2		1715.97	859.02	1716.98	858.99	573
SP4	Ac-LTF$r8AYWAQL$SAL-NH_2		1715.97	859.02	1716.98	858.99	573
SP5	Ac-LTF$r8AYWAQL$SAM-NH_2		1733.92	868.48	1734.93	867.97	578.98
SP6	Ac-LTF$r8AYWAQL$SAhL-NH_2		1729.98	865.98	1730.99	866	577.67
SP7	Ac-LTF$r8AYWAQL$SAF-NH_2		1749.95	876.36	1750.96	875.98	584.32
SP8	Ac-LTF$r8AYWAQL$SAI-NH_2		1715.97	859.02	1716.98	858.99	573
SP9	Ac-LTF$r8AYWAQL$SAChg-NH_2		1741.98	871.98	1742.99	872	581.67
SP10	Ac-LTF$r8AYWAQL$SAAib-NH_2		1687.93	845.36	1688.94	844.97	563.65
SP11	Ac-LTF$r8AYWAQL$SAA-NH_2		1673.92	838.01	1674.93	837.97	558.98
SP12	Ac-LTF$r8AYWA$LSNle-NH_2		1767.04	884.77	1768.05	884.53	590.02
SP13	Ac-LTF$r8AYWA$LSA-NH_2		1724.99	864.23	1726	863.5	576
SP14	Ac-F$r8AYWEAc3cL$AANle-NH_2		1498.82	750.46	1499.83	750.42	500.61
SP15	Ac-F$r8AYWEAc3cL$AAL-NH_2		1498.82	750.46	1499.83	750.42	500.61
SP16	Ac-F$r8AYWEAc3cL$AAM-NH_2		1516.78	759.41	1517.79	759.4	506.6
SP17	Ac-F$r8AYWEAc3cL$AAhL-NH_2		1512.84	757.49	1513.85	757.43	505.29
SP18	Ac-F$r8AYWEAc3cL$AAF-NH_2		1532.81	767.48	1533.82	767.41	511.94
SP19	Ac-F$r8AYWEAc3cL$AAI-NH_2		1498.82	750.39	1499.83	750.42	500.61
SP20	Ac-F$r8AYWEAc3cL$AAChg-NH_2		1524.84	763.48	1525.85	763.43	509.29
SP21	Ac-F$r8AYWEAc3cL$AACha-NH_2		1538.85	770.44	1539.86	770.43	513.96
SP22	Ac-F$r8AYWEAc3cL$AAAib-NH_2		1470.79	736.84	1471.8	736.4	491.27
SP23	Ac-LTF$r8AYWAQL$AAAibV-NH_2		1771.01	885.81	1772.02	886.51	591.34
SP24	Ac-LTF$r8AYWAQL$AAAibV-NH_2	iso2	1771.01	886.26	1772.02	886.51	591.34
SP25	Ac-LTF$r8AYWAQL$SAibAA-NH_2		1758.97	879.89	1759.98	880.49	587.33
SP26	Ac-LTF$r8AYWAQL$SAibAA-NH_2	iso2	1758.97	880.34	1759.98	880.49	587.33
SP27	Ac-HLTF$r8HHWHQL$AANleNle-NH_2		2056.15	1028.86	2057.16	1029.08	686.39
SP28	Ac-DLTF$r8HHWHQL$RRLV-NH_2		2190.23	731.15	2191.24	1096.12	731.08
SP29	Ac-HHTF$r8HHWHQL$AAML-NH_2		2098.08	700.43	2099.09	1050.05	700.37
SP30	Ac-F$r8HHWHQL$RRDCha-NH_2		1917.06	959.96	1918.07	959.54	640.03
SP31	Ac-F$r8HHWHQL$HRFV-NH_2		1876.02	938.65	1877.03	939.02	626.35
SP32	Ac-HLTF$r8HHWHQL$AAhLA-NH_2		2028.12	677.2	2029.13	1015.07	677.05
SP33	Ac-DLTF$r8HHWHQL$RRChgl-NH_2		2230.26	1115.89	2231.27	1116.14	744.43
SP34	Ac-DLTF$r8HHWHQL$RRChgl-NH_2	iso2	2230.26	1115.96	2231.27	1116.14	744.43
SP35	Ac-HHTF$r8HHWHQL$AAChav-NH_2		2106.14	1053.95	2107.15	1054.08	703.05
SP36	Ac-F$r8HHWHQL$RRDa-NH_2		1834.99	918.3	1836	918.5	612.67
SP37	Ac-F$r8HHWHQL$HRAibG-NH_2		1771.95	886.77	1772.96	886.98	591.66
SP38	Ac-F$r8AYWAQL$HHNleL-NH_2		1730.97	866.57	1731.98	866.49	578
SP39	Ac-F$r8AYWSAL$HQANle-NH_2		1638.89	820.54	1639.9	820.45	547.3
SP40	Ac-F$r8AYWVQL$QHChgl-NH_2		1776.01	889.44	1777.02	889.01	593.01

SP	Sequence	Isomer	Exact Mass	Found Mass	Calc (M+1)/1	Calc (M+2)/2	Calc (M+3)/3
SP41	Ac-F$r8AYWTAL$QQNlev-NH_2		1671.94	836.97	1672.95	836.98	558.32
SP42	Ac-F$r8AYWYQL$HAibAa-NH_2		1686.89	844.52	1687.9	844.45	563.3
SP43	Ac-LTF$r8AYWAQL$HHLa-NH_2		1903.05	952.27	1904.06	952.53	635.36
SP44	Ac-LTF$r8AYWAQL$HHLa-NH_2	iso2	1903.05	952.27	1904.06	952.53	635.36
SP45	Ac-LTF$r8AYWAQL$HQNlev-NH_2		1922.08	962.48	1923.09	962.05	641.7
SP46	Ac-LTF$r8AYWAQL$HQNlev-NH_2	iso2	1922.08	962.4	1923.09	962.05	641.7
SP47	Ac-LTF$r8AYWAQL$QQMl-NH_2		1945.05	973.95	1946.06	973.53	649.36
SP48	Ac-LTF$r8AYWAQL$QQMl-NH_2	iso2	1945.05	973.88	1946.06	973.53	649.36
SP49	Ac-LTF$r8AYWAQL$HAibhLV-NH_2		1893.09	948.31	1894.1	947.55	632.04
SP50	Ac-LTF$r8AYWAQL$AHFA-NH_2		1871.01	937.4	1872.02	936.51	624.68
SP51	Ac-HLTF$r8HHWHQL$AANlel-NH_2		2056.15	1028.79	2057.16	1029.08	686.39
SP52	Ac-DLTF$r8HHWHQL$RRLa-NH_2		2162.2	721.82	2163.21	1082.11	721.74
SP53	Ac-HHTF$r8HHWHQL$AAMv-NH_2		2084.07	1042.92	2085.08	1043.04	695.7
SP54	Ac-F$r8HHWHQL$RRDA-NH_2		1834.99	612.74	1836	918.5	612.67
SP55	Ac-F$r8HHWHQL$HRFCha-NH_2		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-NH_2		1771.01	885.81	1772.02	886.51	591.34
SP65	Ac-LTF$r8AYWAQL$AAIA-NH_2	iso2	1771.01	866.8	1772.02	886.51	591.34
SP66	Ac-LTF$r8AYWAAL$AAMA-NH_2		1731.94	867.08	1732.95	866.98	578.32
SP67	Ac-LTF$r8AYWAAL$AAMA-NH_2	iso2	1731.94	867.28	1732.95	866.98	578.32
SP68	Ac-LTF$r8AYWAQL$AANleA-NH_2		1771.01	867.1	1772.02	886.51	591.34
SP69	Ac-LTF$r8AYWAQL$AANleA-NH_2	iso2	1771.01	886.89	1772.02	886.51	591.34
SP70	Ac-LTF$r8AYWAQL$AAIa-NH_2		1771.01	886.8	1772.02	886.51	591.34
SP71	Ac-LTF$r8AYWAQL$AAIa-NH_2	iso2	1771.01	887.09	1772.02	886.51	591.34
SP72	Ac-LTF$r8AYWAAL$AAMa-NH_2		1731.94	867.17	1732.95	866.98	578.32
SP73	Ac-LTF$r8AYWAAL$AAMa-NH_2	iso2	1731.94	867.37	1732.95	866.98	578.32
SP74	Ac-LTF$r8AYWAQL$AANlea-NH_2		1771.01	887.08	1772.02	886.51	591.34
SP75	Ac-LTF$r8AYWAQL$AANlea-NH_2	iso2	1771.01	887.08	1772.02	886.51	591.34
SP76	Ac-LTF$r8AYWAAL$AAIv-NH_2		1742.02	872.37	1743.03	872.02	581.68
SP77	Ac-LTF$r8AYWAAL$AAIv-NH_2	iso2	1742.02	872.74	1743.03	872.02	581.68
SP78	Ac-LTF$r8AYWAQL$AAMv-NH_2		1817	910.02	1818.01	909.51	606.67
SP79	Ac-LTF$r8AYWAAL$AANlev-NH_2		1742.02	872.37	1743.03	872.02	581.68
SP80	Ac-LTF$r8AYWAAL$AANlev-NH_2	iso2	1742.02	872.28	1743.03	872.02	581.68
SP81	Ac-LTF$r8AYWAQL$AAIl-NH_2		1813.05	907.81	1814.06	907.53	605.36
SP82	Ac-LTF$r8AYWAQL$AAIl-NH_2	iso2	1813.05	907.81	1814.06	907.53	605.36
SP83	Ac-LTF$r8AYWAAL$AAMl-NH_2		1773.99	887.37	1775	888	592.34
SP84	Ac-LTF$r8AYWAQL$AANlel-NH_2		1813.05	907.61	1814.06	907.53	605.36
SP85	Ac-LTF$r8AYWAQL$AANlel-NH_2	iso2	1813.05	907.71	1814.06	907.53	605.36
SP86	Ac-F$r8AYWEAL$AAMA-NH_2		1575.82	789.02	1576.83	788.92	526.28
SP87	Ac-F$r8AYWEAL$AANleA-NH_2		1557.86	780.14	1558.87	779.94	520.29
SP88	Ac-F$r8AYWEAL$AAIa-NH_2		1557.86	780.33	1558.87	779.94	520.29
SP89	Ac-F$r8AYWEAL$AAMa-NH_2		1575.82	789.3	1576.83	788.92	526.28
SP90	Ac-F$r8AYWEAL$AANlea-NH_2		1557.86	779.4	1558.87	779.94	520.29
SP91	Ac-F$r8AYWEAL$AAIv-NH_2		1585.89	794.29	1586.9	793.95	529.64

SP	Sequence	Isomer	Exact Mass	Found Mass	Calc (M+1)/1	Calc (M+2)/2	Calc (M+3)/3
SP92	Ac-F$r8AYWEAL$AAMv-NH_2		1603.85	803.08	1604.86	802.93	535.62
SP93	Ac-F$r8AYWEAL$AANlev-NH_2		1585.89	793.46	1586.9	793.95	529.64
SP94	Ac-F$r8AYWEAL$AAIl-NH_2		1599.91	800.49	1600.92	800.96	534.31
SP95	Ac-F$r8AYWEAL$AAMl-NH_2		1617.86	809.44	1618.87	809.94	540.29
SP96	Ac-F$r8AYWEAL$AANlel-NH_2		1599.91	801.7	1600.92	800.96	534.31
SP97	Ac-F$r8AYWEAL$AANlel-NH_2	iso2	1599.91	801.42	1600.92	800.96	534.31
SP98	Ac-LTF$r8AY6clWAQL$SAA-NH_2		1707.88	855.72	1708.89	854.95	570.3
SP99	Ac-LTF$r8AY6clWAQL$SAA-NH_2	iso2	1707.88	855.35	1708.89	854.95	570.3
SP100	Ac-WTF$r8FYWSQL$AVAa-NH_2		1922.01	962.21	1923.02	962.01	641.68
SP101	Ac-WTF$r8FYWSQL$AVAa-NH_2	iso2	1922.01	962.49	1923.02	962.01	641.68
SP102	Ac-WTF$r8VYWSQL$AVA-NH_2		1802.98	902.72	1803.99	902.5	602
SP103	Ac-WTF$r8VYWSQL$AVA-NH_2	iso2	1802.98	903	1803.99	902.5	602
SP104	Ac-WTF$r8FYWSQL$SAAa-NH_2		1909.98	956.47	1910.99	956	637.67
SP105	Ac-WTF$r8FYWSQL$SAAa-NH_2	iso2	1909.98	956.47	1910.99	956	637.67
SP106	Ac-WTF$r8VYWSQL$AVAaa-NH_2		1945.05	974.15	1946.06	973.53	649.36
SP107	Ac-WTF$r8VYWSQL$AVAaa-NH_2	iso2	1945.05	973.78	1946.06	973.53	649.36
SP108	Ac-LTF$r8AYWAQL$AVG-NH_2		1671.94	837.52	1672.95	836.98	558.32
SP109	Ac-LTF$r8AYWAQL$AVG-NH_2	iso2	1671.94	837.21	1672.95	836.98	558.32
SP110	Ac-LTF$r8AYWAQL$AVQ-NH_2		1742.98	872.74	1743.99	872.5	582
SP111	Ac-LTF$r8AYWAQL$AVQ-NH_2	iso2	1742.98	872.74	1743.99	872.5	582
SP112	Ac-LTF$r8AYWAQL$SAa-NH_2		1673.92	838.23	1674.93	837.97	558.98
SP113	Ac-LTF$r8AYWAQL$SAa-NH_2	iso2	1673.92	838.32	1674.93	837.97	558.98
SP114	Ac-LTF$r8AYWAQhL$SAA-NH_2		1687.93	844.37	1688.94	844.97	563.65
SP115	Ac-LTF$r8AYWAQhL$SAA-NH_2	iso2	1687.93	844.81	1688.94	844.97	563.65
SP116	Ac-LTF$r8AYWEQLStSA$-NH_2		1826	905.27	1827.01	914.01	609.67
SP117	Ac-LTF$r8AYWAQL$SLA-NH_2		1715.97	858.48	1716.98	858.99	573
SP118	Ac-LTF$r8AYWAQL$SLA-NH_2	iso2	1715.97	858.87	1716.98	858.99	573
SP119	Ac-LTF$r8AYWAQL$SWA-NH_2		1788.96	895.21	1789.97	895.49	597.33
SP120	Ac-LTF$r8AYWAQL$SWA-NH_2	iso2	1788.96	895.28	1789.97	895.49	597.33
SP121	Ac-LTF$r8AYWAQL$SVS-NH_2		1717.94	859.84	1718.95	859.98	573.65
SP122	Ac-LTF$r8AYWAQL$SAS-NH_2		1689.91	845.85	1690.92	845.96	564.31
SP123	Ac-LTF$r8AYWAQL$SVG-NH_2		1687.93	844.81	1688.94	844.97	563.65
SP124	Ac-ETF$r8VYWAQL$SAa-NH_2		1717.91	859.76	1718.92	859.96	573.64
SP125	Ac-ETF$r8VYWAQL$SAA-NH_2		1717.91	859.84	1718.92	859.96	573.64
SP126	Ac-ETF$r8VYWAQL$SVA-NH_2		1745.94	873.82	1746.95	873.98	582.99
SP127	Ac-ETF$r8VYWAQL$SLA-NH_2		1759.96	880.85	1760.97	880.99	587.66
SP128	Ac-ETF$r8VYWAQL$SWA-NH_2		1832.95	917.34	1833.96	917.48	611.99
SP129	Ac-ETF$r8KYWAQL$SWA-NH_2		1861.98	931.92	1862.99	932	621.67
SP130	Ac-ETF$r8VYWAQL$SVS-NH_2		1761.93	881.89	1762.94	881.97	588.32
SP131	Ac-ETF$r8VYWAQL$SAS-NH_2		1733.9	867.83	1734.91	867.96	578.97
SP132	Ac-ETF$r8VYWAQL$SVG-NH_2		1731.92	866.87	1732.93	866.97	578.31
SP133	Ac-LTF$r8VYWAQL$SSa-NH_2		1717.94	859.47	1718.95	859.98	573.65
SP134	Ac-ETF$r8VYWAQL$SSa-NH_2		1733.9	867.83	1734.91	867.96	578.97
SP135	Ac-LTF$r8VYWAQL$SNa-NH_2		1744.96	873.38	1745.97	873.49	582.66
SP136	Ac-ETF$r8VYWAQL$SNa-NH_2		1760.91	881.3	1761.92	881.46	587.98
SP137	Ac-LTF$r8VYWAQL$SAa-NH_2		1701.95	851.84	1702.96	851.98	568.32
SP138	Ac-LTF$r8VYWAQL$SVA-NH_2		1729.98	865.53	1730.99	866	577.67
SP139	Ac-LTF$r8VYWAQL$SVA-NH_2	iso2	1729.98	865.9	1730.99	866	577.67
SP140	Ac-LTF$r8VYWAQL$SWA-NH_2		1816.99	909.42	1818	909.5	606.67
SP141	Ac-LTF$r8VYWAQL$SVS-NH_2		1745.98	873.9	1746.99	874	583
SP142	Ac-LTF$r8VYWAQL$SVS-NH_2	iso2	1745.98	873.9	1746.99	874	583

SP	Sequence	Isomer	Exact Mass	Found Mass	Calc (M+1)/1	Calc (M+2)/2	Calc (M+3)/3
SP143	Ac-LTF$r8VYWAQL$SAS-NH_2		1717.94	859.84	1718.95	859.98	573.65
SP144	Ac-LTF$r8VYWAQL$SAS-NH_2	iso2	1717.94	859.91	1718.95	859.98	573.65
SP145	Ac-LTF$r8VYWAQL$SVG-NH_2		1715.97	858.87	1716.98	858.99	573
SP146	Ac-LTF$r8VYWAQL$SVG-NH_2	iso2	1715.97	858.87	1716.98	858.99	573
SP147	Ac-LTF$r8EYWAQCha$SAA-NH_2		1771.96	886.85	1772.97	886.99	591.66
SP148	Ac-LTF$r8EYWAQCha$SAA-NH_2	iso2	1771.96	886.85	1772.97	886.99	591.66
SP149	Ac-LTF$r8EYWAQCpg$SAA-NH_2		1743.92	872.86	1744.93	872.97	582.31
SP150	Ac-LTF$r8EYWAQCpg$SAA-NH_2	iso2	1743.92	872.86	1744.93	872.97	582.31
SP151	Ac-LTF$r8EYWAQF$SAA-NH_2		1765.91	883.44	1766.92	883.96	589.64
SP152	Ac-LTF$r8EYWAQF$SAA-NH_2	iso2	1765.91	883.89	1766.92	883.96	589.64
SP153	Ac-LTF$r8EYWAQCba$SAA-NH_2		1743.92	872.42	1744.93	872.97	582.31
SP154	Ac-LTF$r8EYWAQCba$SAA-NH_2	iso2	1743.92	873.39	1744.93	872.97	582.31
SP155	Ac-LTF3Cl$r8EYWAQL$SAA-NH_2		1765.89	883.89	1766.9	883.95	589.64
SP156	Ac-LTF3Cl$r8EYWAQL$SAA-NH_2	iso2	1765.89	883.96	1766.9	883.95	589.64
SP157	Ac-LTF34F2$r8EYWAQL$SAA-NH_2		1767.91	884.48	1768.92	884.96	590.31
SP158	Ac-LTF34F2$r8EYWAQL$SAA-NH_2	iso2	1767.91	884.48	1768.92	884.96	590.31
SP159	Ac-LTF34F2$r8EYWAQhL$SAA-NH_2		1781.92	891.44	1782.93	891.97	594.98
SP160	Ac-LTF34F2$r8EYWAQhL$SAA-NH_2	iso2	1781.92	891.88	1782.93	891.97	594.98
SP161	Ac-ETF$r8EYWAQL$SAA-NH_2		1747.88	874.34	1748.89	874.95	583.63
SP162	Ac-LTF$r8AYWVQL$SAA-NH_2		1701.95	851.4	1702.96	851.98	568.32
SP163	Ac-LTF$r8AHWAQL$SAA-NH_2		1647.91	824.83	1648.92	824.96	550.31
SP164	Ac-LTF$r8AEWAQL$SAA-NH_2		1639.9	820.39	1640.91	820.96	547.64
SP165	Ac-LTF$r8ASWAQL$SAA-NH_2		1597.89	799.38	1598.9	799.95	533.64
SP166	Ac-LTF$r8AEWAQL$SAA-NH_2	iso2	1639.9	820.39	1640.91	820.96	547.64
SP167	Ac-LTF$r8ASWAQL$SAA-NH_2	iso2	1597.89	800.31	1598.9	799.95	533.64
SP168	Ac-LTF$r8AF4coohWAQL$SAA-NH_2		1701.91	851.4	1702.92	851.96	568.31
SP169	Ac-LTF$r8AF4coohWAQL$SAA-NH_2	iso2	1701.91	851.4	1702.92	851.96	568.31
SP170	Ac-LTF$r8AHWAQL$AAIa-NH_2		1745	874.13	1746.01	873.51	582.67
SP171	Ac-ITF$r8FYWAQL$AAIa-NH_2		1847.04	923.92	1848.05	924.53	616.69
SP172	Ac-ITF$r8EHWAQL$AAIa-NH_2		1803.01	903.17	1804.02	902.51	602.01
SP173	Ac-ITF$r8EHWAQL$AAIa-NH_2	iso2	1803.01	903.17	1804.02	902.51	602.01
SP174	Ac-ETF$r8EHWAQL$AAIa-NH_2		1818.97	910.76	1819.98	910.49	607.33
SP175	Ac-ETF$r8EHWAQL$AAIa-NH_2	iso2	1818.97	910.85	1819.98	910.49	607.33
SP176	Ac-LTF$r8AHWVQL$AAIa-NH_2		1773.03	888.09	1774.04	887.52	592.02
SP177	Ac-ITF$r8FYWVQL$AAIa-NH_2		1875.07	939.16	1876.08	938.54	626.03
SP178	Ac-ITF$r8EYWVQL$AAIa-NH_2		1857.04	929.83	1858.05	929.53	620.02
SP179	Ac-ITF$r8EHWVQL$AAIa-NH_2		1831.04	916.86	1832.05	916.53	611.35
SP180	Ac-LTF$r8AEWAQL$AAIa-NH_2		1736.99	869.87	1738	869.5	580
SP181	Ac-LTF$r8AF4coohWAQL$AAIa-NH_2		1799	900.17	1800.01	900.51	600.67
SP182	Ac-LTF$r8AF4coohWAQL$AAIa-NH_2	iso2	1799	900.24	1800.01	900.51	600.67
SP183	Ac-LTF$r8AHWAQL$AHFA-NH_2		1845.01	923.89	1846.02	923.51	616.01
SP184	Ac-ITF$r8FYWAQL$AHFA-NH_2		1947.05	975.05	1948.06	974.53	650.02
SP185	Ac-ITF$r8FYWAQL$AHFA-NH_2	iso2	1947.05	976.07	1948.06	974.53	650.02
SP186	Ac-ITF$r8FHWAQL$AEFA-NH_2		1913.02	958.12	1914.03	957.52	638.68
SP187	Ac-ITF$r8FHWAQL$AEFA-NH_2	iso2	1913.02	957.86	1914.03	957.52	638.68
SP188	Ac-ITF$r8EHWAQL$AHFA-NH_2		1903.01	952.94	1904.02	952.51	635.34
SP189	Ac-ITF$r8EHWAQL$AHFA-NH_2	iso2	1903.01	953.87	1904.02	952.51	635.34
SP190	Ac-LTF$r8AHWVQL$AHFA-NH_2		1873.04	937.86	1874.05	937.53	625.35
SP191	Ac-ITF$r8FYWVQL$AHFA-NH_2		1975.08	988.83	1976.09	988.55	659.37
SP192	Ac-ITF$r8EYWVQL$AHFA-NH_2		1957.05	979.35	1958.06	979.53	653.36
SP193	Ac-ITF$r8EHWVQL$AHFA-NH_2		1931.05	967	1932.06	966.53	644.69

SP	Sequence	Isomer	Exact Mass	Found Mass	Calc (M+1)/1	Calc (M+2)/2	Calc (M+3)/3
SP194	Ac-ITF$r8EHWVQL$AHFA-NH_2	iso2	1931.05	967.93	1932.06	966.53	644.69
SP195	Ac-ETF$r8EYWAAL$SAA-NH_2		1690.86	845.85	1691.87	846.44	564.63
SP196	Ac-LTF$r8AYWVAL$SAA-NH_2		1644.93	824.08	1645.94	823.47	549.32
SP197	Ac-LTF$r8AHWAAL$SAA-NH_2		1590.89	796.88	1591.9	796.45	531.3
SP198	Ac-LTF$r8AEWAAL$SAA-NH_2		1582.88	791.9	1583.89	792.45	528.63
SP199	Ac-LTF$r8AEWAAL$SAA-NH_2	iso2	1582.88	791.9	1583.89	792.45	528.63
SP200	Ac-LTF$r8ASWAAL$SAA-NH_2		1540.87	770.74	1541.88	771.44	514.63
SP201	Ac-LTF$r8ASWAAL$SAA-NH_2	iso2	1540.87	770.88	1541.88	771.44	514.63
SP202	Ac-LTF$r8AYWAAL$AAIa-NH_2		1713.99	857.39	1715	858	572.34
SP203	Ac-LTF$r8AYWAAL$AAIa-NH_2	iso2	1713.99	857.84	1715	858	572.34
SP204	Ac-LTF$r8AYWAAL$AHFA-NH_2		1813.99	907.86	1815	908	605.67
SP205	Ac-LTF$r8EHWAQL$AHIa-NH_2		1869.03	936.1	1870.04	935.52	624.02
SP206	Ac-LTF$r8EHWAQL$AHIa-NH_2	iso2	1869.03	937.03	1870.04	935.52	624.02
SP207	Ac-LTF$r8AHWAQL$AHIa-NH_2		1811.03	906.87	1812.04	906.52	604.68
SP208	Ac-LTF$r8EYWAQL$AHIa-NH_2		1895.04	949.15	1896.05	948.53	632.69
SP209	Ac-LTF$r8AYWAQL$AAFa-NH_2		1804.99	903.2	1806	903.5	602.67
SP210	Ac-LTF$r8AYWAQL$AAFa-NH_2	iso2	1804.99	903.28	1806	903.5	602.67
SP211	Ac-LTF$r8AYWAQL$AAWa-NH_2		1844	922.81	1845.01	923.01	615.67
SP212	Ac-LTF$r8AYWAQL$AAVa-NH_2		1756.99	878.86	1758	879.5	586.67
SP213	Ac-LTF$r8AYWAQL$AAVa-NH_2	iso2	1756.99	879.3	1758	879.5	586.67
SP214	Ac-LTF$r8AYWAQL$AALa-NH_2		1771.01	886.26	1772.02	886.51	591.34
SP215	Ac-LTF$r8AYWAQL$AALa-NH_2	iso2	1771.01	886.33	1772.02	886.51	591.34
SP216	Ac-LTF$r8EYWAQL$AAIa-NH_2		1829.01	914.89	1830.02	915.51	610.68
SP217	Ac-LTF$r8EYWAQL$AAIa-NH_2	iso2	1829.01	915.34	1830.02	915.51	610.68
SP218	Ac-LTF$r8EYWAQL$AAFa-NH_2		1863	932.87	1864.01	932.51	622.01
SP219	Ac-LTF$r8EYWAQL$AAFa-NH_2	iso2	1863	932.87	1864.01	932.51	622.01
SP220	Ac-LTF$r8EYWAQL$AAVa-NH_2		1815	908.23	1816.01	908.51	606.01
SP221	Ac-LTF$r8EYWAQL$AAVa-NH_2	iso2	1815	908.31	1816.01	908.51	606.01
SP222	Ac-LTF$r8EHWAQL$AAIa-NH_2		1803.01	903.17	1804.02	902.51	602.01
SP223	Ac-LTF$r8EHWAQL$AAIa-NH_2	iso2	1803.01	902.8	1804.02	902.51	602.01
SP224	Ac-LTF$r8EHWAQL$AAWa-NH_2		1876	939.34	1877.01	939.01	626.34
SP225	Ac-LTF$r8EHWAQL$AAWa-NH_2	iso2	1876	939.62	1877.01	939.01	626.34
SP226	Ac-LTF$r8EHWAQL$AALa-NH_2		1803.01	902.8	1804.02	902.51	602.01
SP227	Ac-LTF$r8EHWAQL$AALa-NH_2	iso2	1803.01	902.9	1804.02	902.51	602.01
SP228	Ac-ETF$r8EHWVQL$AALa-NH_2		1847	924.82	1848.01	924.51	616.67
SP229	Ac-LTF$r8AYWAQL$AAAa-NH_2		1728.96	865.89	1729.97	865.49	577.33
SP230	Ac-LTF$r8AYWAQL$AAAa-NH_2	iso2	1728.96	865.89	1729.97	865.49	577.33
SP231	Ac-LTF$r8AYWAQL$AAAibA-NH_2		1742.98	872.83	1743.99	872.5	582
SP232	Ac-LTF$r8AYWAQL$AAAibA-NH_2	iso2	1742.98	872.92	1743.99	872.5	582
SP233	Ac-LTF$r8AYWAQL$AAAAa-NH_2		1800	901.42	1801.01	901.01	601.01
SP234	Ac-LTF$r5AYWAQL$s8AAIa-NH_2		1771.01	887.17	1772.02	886.51	591.34
SP235	Ac-LTF$r5AYWAQL$s8SAA-NH_2		1673.92	838.33	1674.93	837.97	558.98
SP236	Ac-LTF$r8AYWAQCba$AANleA-NH_2		1783.01	892.64	1784.02	892.51	595.34
SP237	Ac-ETF$r8AYWAQCba$AANleA-NH_2		1798.97	900.59	1799.98	900.49	600.66
SP238	Ac-LTF$r8EYWAQCba$AANleA-NH_2		1841.01	922.05	1842.02	921.51	614.68
SP239	Ac-LTF$r8AYWAQCba$AWNleA-NH_2		1898.05	950.46	1899.06	950.03	633.69
SP240	Ac-ETF$r8AYWAQCba$AWNleA-NH_2		1914.01	958.11	1915.02	958.01	639.01
SP241	Ac-LTF$r8EYWAQCba$AWNleA-NH_2		1956.06	950.62	1957.07	979.04	653.03
SP242	Ac-LTF$r8EYWAQCba$SAFA-NH_2		1890.99	946.55	1892	946.5	631.34
SP243	Ac-LTF34F2$r8EYWAQCba$SANleA-NH_2		1892.99	947.57	1894	947.5	632

SP	Sequence	Isomer	Exact Mass	Found Mass	Calc (M+1)/1	Calc (M+2)/2	Calc (M+3)/3
SP244	Ac-LTF$r8EF4coohWAQCba$SANleA-NH_2		1885	943.59	1886.01	943.51	629.34
SP245	Ac-LTF$r8EYWSQCba$SANleA-NH_2		1873	937.58	1874.01	937.51	625.34
SP246	Ac-LTF$r8EYWWQCba$SANleA-NH_2		1972.05	987.61	1973.06	987.03	658.36
SP247	Ac-LTF$r8EYWAQCba$AAIa-NH_2		1841.01	922.05	1842.02	921.51	614.68
SP248	Ac-LTF34F2$r8EYWAQCba$AAIa-NH_2		1876.99	939.99	1878	939.5	626.67
SP249	Ac-LTF$r8EF4coohWAQCba$AAIa-NH_2		1869.01	935.64	1870.02	935.51	624.01
SP250	Pam-ETF$r8EYWAQCba$SAA-NH_2		1956.1	979.57	1957.11	979.06	653.04
SP251	Ac-LThF$r8EFWAQCba$SAA-NH_2		1741.94	872.11	1742.95	871.98	581.65
SP252	Ac-LTA$r8EYWAQCba$SAA-NH_2		1667.89	835.4	1668.9	834.95	556.97
SP253	Ac-LTF$r8EYAAQCba$SAA-NH_2		1628.88	815.61	1629.89	815.45	543.97
SP254	Ac-LTF$r8EY2NalAQCba$SAA-NH_2		1754.93	879.04	1755.94	878.47	585.98
SP255	Ac-LTF$r8AYWAQCba$SAA-NH_2		1685.92	844.71	1686.93	843.97	562.98
SP256	Ac-LTF$r8EYWAQCba$SAF-NH_2		1819.96	911.41	1820.97	910.99	607.66
SP257	Ac-LTF$r8EYWAQCba$SAFa-NH_2		1890.99	947.41	1892	946.5	631.34
SP258	Ac-LTF$r8AYWAQCba$SAF-NH_2		1761.95	882.73	1762.96	881.98	588.32
SP259	Ac-LTF34F2$r8AYWAQCba$SAF-NH_2		1797.93	900.87	1798.94	899.97	600.32
SP260	Ac-LTF$r8AF4coohWAQCba$SAF-NH_2		1789.94	896.43	1790.95	895.98	597.65
SP261	Ac-LTF$r8EY6clWAQCba$SAF-NH_2		1853.92	929.27	1854.93	927.97	618.98
SP262	Ac-LTF$r8AYWSQCba$SAF-NH_2		1777.94	890.87	1778.95	889.98	593.65
SP263	Ac-LTF$r8AYWWQCba$SAF-NH_2		1876.99	939.91	1878	939.5	626.67
SP264	Ac-LTF$r8AYWAQCba$AAIa-NH_2		1783.01	893.19	1784.02	892.51	595.34
SP265	Ac-LTF34F2$r8AYWAQCba$AAIa-NH_2		1818.99	911.23	1820	910.5	607.34
SP266	Ac-LTF$r8AY6clWAQCba$AAIa-NH_2		1816.97	909.84	1817.98	909.49	606.66
SP267	Ac-LTF$r8AF4coohWAQCba$AAIa-NH_2		1811	906.88	1812.01	906.51	604.67
SP268	Ac-LTF$r8EYWAQCba$AAFa-NH_2		1875	938.6	1876.01	938.51	626.01
SP269	Ac-LTF$r8EYWAQCba$AAFa-NH_2	iso2	1875	938.6	1876.01	938.51	626.01
SP270	Ac-ETF$r8AYWAQCba$AWNlea-NH_2		1914.01	958.42	1915.02	958.01	639.01
SP271	Ac-LTF$r8EYWAQCba$AWNlea-NH_2		1956.06	979.42	1957.07	979.04	653.03
SP272	Ac-ETF$r8EYWAQCba$AWNlea-NH_2		1972.01	987.06	1973.02	987.01	658.34
SP273	Ac-ETF$r8EYWAQCba$AWNlea-NH_2	iso2	1972.01	987.06	1973.02	987.01	658.34
SP274	Ac-LTF$r8AYWAQCba$SAFa-NH_2		1832.99	917.89	1834	917.5	612
SP275	Ac-LTF$r8AYWAQCba$SAFa-NH_2	iso2	1832.99	918.07	1834	917.5	612
SP276	Ac-ETF$r8AYWAQL$AWNlea-NH_2		1902.01	952.22	1903.02	952.01	635.01
SP277	Ac-LTF$r8EYWAQL$AWNlea-NH_2		1944.06	973.5	1945.07	973.04	649.03
SP278	Ac-ETF$r8EYWAQL$AWNlea-NH_2		1960.01	981.46	1961.02	981.01	654.34
SP279	Dmaac-LTF$r8EYWAQhL$SAA-NH_2		1788.98	896.06	1789.99	895.5	597.33
SP280	Hexac-LTF$r8EYWAQhL$SAA-NH_2		1802	902.9	1803.01	902.01	601.67
SP281	Napac-LTF$r8EYWAQhL$SAA-NH_2		1871.99	937.58	1873	937	625
SP282	Decac-LTF$r8EYWAQhL$SAA-NH_2		1858.06	930.55	1859.07	930.04	620.36
SP283	Admac-LTF$r8EYWAQhL$SAA-NH_2		1866.03	934.07	1867.04	934.02	623.02
SP284	Tmac-LTF$r8EYWAQhL$SAA-NH_2		1787.99	895.41	1789	895	597
SP285	Pam-LTF$r8EYWAQhL$SAA-NH_2		1942.16	972.08	1943.17	972.09	648.39
SP286	Ac-LTF$r8AYWAQCba$AANleA-NH_2	iso2	1783.01	892.64	1784.02	892.51	595.34
SP287	Ac-LTF34F2$r8EYWAQCba$AAIa-NH_2	iso2	1876.99	939.62	1878	939.5	626.67
SP288	Ac-LTF34F2$r8EYWAQCba$SAA-NH_2		1779.91	892.07	1780.92	890.96	594.31
SP289	Ac-LTF34F2$r8EYWAQCba$SAA-NH_2	iso2	1779.91	891.61	1780.92	890.96	594.31
SP290	Ac-LTF$r8EF4coohWAQCba$SAA-NH_2		1771.92	887.54	1772.93	886.97	591.65
SP291	Ac-LTF$r8EF4coohWAQCba$SAA-NH_2	iso2	1771.92	887.63	1772.93	886.97	591.65
SP292	Ac-LTF$r8EYWSQCba$SAA-NH_2		1759.92	881.9	1760.93	880.97	587.65
SP293	Ac-LTF$r8EYWSQCba$SAA-NH_2	iso2	1759.92	881.9	1760.93	880.97	587.65

SP	Sequence	Isomer	Exact Mass	Found Mass	Calc (M+1)/1	Calc (M+2)/2	Calc (M+3)/3
SP294	Ac-LTF$r8EYWAQhL$SAA-NH_2		1745.94	875.05	1746.95	873.98	582.99
SP295	Ac-LTF$r8AYWAQhL$SAF-NH_2		1763.97	884.02	1764.98	882.99	589
SP296	Ac-LTF$r8AYWAQhL$SAF-NH_2	iso2	1763.97	883.56	1764.98	882.99	589
SP297	Ac-LTF34F2$r8AYWAQhL$SAA-NH_2		1723.92	863.67	1724.93	862.97	575.65
SP298	Ac-LTF34F2$r8AYWAQhL$SAA-NH_2	iso2	1723.92	864.04	1724.93	862.97	575.65
SP299	Ac-LTF$r8AF4coohWAQhL$SAA-NH_2		1715.93	859.44	1716.94	858.97	572.98
SP300	Ac-LTF$r8AF4coohWAQhL$SAA-NH_2	iso2	1715.93	859.6	1716.94	858.97	572.98
SP301	Ac-LTF$r8AYWSQhL$SAA-NH_2		1703.93	853.96	1704.94	852.97	568.98
SP302	Ac-LTF$r8AYWSQhL$SAA-NH_2	iso2	1703.93	853.59	1704.94	852.97	568.98
SP303	Ac-LTF$r8EYWAQL$AANleA-NH_2		1829.01	915.45	1830.02	915.51	610.68
SP304	Ac-LTF34F2$r8AYWAQL$AANleA-NH_2		1806.99	904.58	1808	904.5	603.34
SP305	Ac-LTF$r8AF4coohWAQL$AANleA-NH_2		1799	901.6	1800.01	900.51	600.67
SP306	Ac-LTF$r8AYWSQL$AANleA-NH_2		1787	894.75	1788.01	894.51	596.67
SP307	Ac-LTF34F2$r8AYWAQhL$AANleA-NH_2		1821	911.79	1822.01	911.51	608.01
SP308	Ac-LTF34F2$r8AYWAQhL$AANleA-NH_2	iso2	1821	912.61	1822.01	911.51	608.01
SP309	Ac-LTF$r8AF4coohWAQhL$AANleA-NH_2		1813.02	907.95	1814.03	907.52	605.35
SP310	Ac-LTF$r8AF4coohWAQhL$AANleA-NH_2	iso2	1813.02	908.54	1814.03	907.52	605.35
SP311	Ac-LTF$r8AYWSQhL$AANleA-NH_2		1801.02	901.84	1802.03	901.52	601.35
SP312	Ac-LTF$r8AYWSQhL$AANleA-NH_2	iso2	1801.02	902.62	1802.03	901.52	601.35
SP313	Ac-LTF$r8AYWAQhL$AAAAa-NH_2		1814.01	908.63	1815.02	908.01	605.68
SP314	Ac-LTF$r8AYWAQhL$AAAAa-NH_2	iso2	1814.01	908.34	1815.02	908.01	605.68
SP315	Ac-LTF$r8AYWAQL$AAAAAa-NH_2		1871.04	936.94	1872.05	936.53	624.69
SP316	Ac-LTF$r8AYWAQL$AAAAAAa-NH_2	iso2	1942.07	972.5	1943.08	972.04	648.37
SP317	Ac-LTF$r8AYWAQL$AAAAAAa-NH_2	iso1	1942.07	972.5	1943.08	972.04	648.37
SP318	Ac-LTF$r8EYWAQhL$AANleA-NH_2		1843.03	922.54	1844.04	922.52	615.35
SP319	Ac-AATF$r8AYWAQL$AANleA-NH_2		1800	901.39	1801.01	901.01	601.01
SP320	Ac-LTF$r8AYWAQL$AANleAA-NH_2		1842.04	922.45	1843.05	922.03	615.02
SP321	Ac-ALTF$r8AYWAQL$AANleAA-NH_2		1913.08	957.94	1914.09	957.55	638.7
SP322	Ac-LTF$r8AYWAQCba$AANleAA-NH_2		1854.04	928.43	1855.05	928.03	619.02
SP323	Ac-LTF$r8AYWAQhL$AANleAA-NH_2		1856.06	929.4	1857.07	929.04	619.69
SP324	Ac-LTF$r8EYWAQCba$SAAA-NH_2		1814.96	909.37	1815.97	908.49	605.99
SP325	Ac-LTF$r8EYWAQCba$SAAA-NH_2	iso2	1814.96	909.37	1815.97	908.49	605.99
SP326	Ac-LTF$r8EYWAQCba$SAAAA-NH_2		1886	944.61	1887.01	944.01	629.67
SP327	Ac-LTF$r8EYWAQCba$SAAAA-NH_2	iso2	1886	944.61	1887.01	944.01	629.67
SP328	Ac-ALTF$r8EYWAQCba$SAA-NH_2		1814.96	909.09	1815.97	908.49	605.99
SP329	Ac-ALTF$r8EYWAQCba$SAAA-NH_2		1886	944.61	1887.01	944.01	629.67
SP330	Ac-ALTF$r8EYWAQCba$SAA-NH_2	iso2	1814.96	909.09	1815.97	908.49	605.99
SP331	Ac-LTF$r8EYWAQL$AAAAAa-NH_2	iso2	1929.04	966.08	1930.05	965.53	644.02
SP332	Ac-LTF$r8EY6clWAQCba$SAA-NH_2		1777.89	890.78	1778.9	889.95	593.64
SP333	Ac-LTF$r8EF4cooh6clWAQCba$SANleA-NH_2		1918.96	961.27	1919.97	960.49	640.66
SP334	Ac-LTF$r8EF4cooh6clWAQCba$SANleA-NH_2	iso2	1918.96	961.27	1919.97	960.49	640.66
SP335	Ac-LTF$r8EF4cooh6clWAQCba$AAIa-NH_2		1902.97	953.03	1903.98	952.49	635.33
SP336	Ac-LTF$r8EF4cooh6clWAQCba$AAIa-NH_2	iso2	1902.97	953.13	1903.98	952.49	635.33

SP	Sequence	Isomer	Exact Mass	Found Mass	Calc (M+1)/1	Calc (M+2)/2	Calc (M+3)/3
SP337	Ac-LTF$r8AY6clWAQL$AAAAAa-NH_2		1905	954.61	1906.01	953.51	636.01
SP338	Ac-LTF$r8AY6clWAQL$AAAAAa-NH_2	iso2	1905	954.9	1906.01	953.51	636.01
SP339	Ac-F$r8AY6clWEAL$AAAAAAa-NH_2		1762.89	883.01	1763.9	882.45	588.64
SP340	Ac-ETF$r8EYWAQL$AAAAAa-NH_2		1945	974.31	1946.01	973.51	649.34
SP341	Ac-ETF$r8EYWAQL$AAAAAa-NH_2	iso2	1945	974.49	1946.01	973.51	649.34
SP342	Ac-LTF$r8EYWAQL$AAAAAAa-NH_2		2000.08	1001.6	2001.09	1001.05	667.7
SP343	Ac-LTF$r8EYWAQL$AAAAAAa-NH_2	iso2	2000.08	1001.6	2001.09	1001.05	667.7
SP344	Ac-LTF$r8AYWAQL$AANleAAa-NH_2		1913.08	958.58	1914.09	957.55	638.7
SP345	Ac-LTF$r8AYWAQL$AANleAAa-NH_2	iso2	1913.08	958.58	1914.09	957.55	638.7
SP346	Ac-LTF$r8EYWAQCba$AAAAAa-NH_2		1941.04	972.55	1942.05	971.53	648.02
SP347	Ac-LTF$r8EYWAQCba$AAAAAa-NH_2	iso2	1941.04	972.55	1942.05	971.53	648.02
SP348	Ac-LTF$r8EF4coohWAQCba$AAAAAa-NH_2		1969.04	986.33	1970.05	985.53	657.35
SP349	Ac-LTF$r8EF4coohWAQCba$AAAAAa-NH_2	iso2	1969.04	986.06	1970.05	985.53	657.35
SP350	Ac-LTF$r8EYWSQCba$AAAAAa-NH_2		1957.04	980.04	1958.05	979.53	653.35
SP351	Ac-LTF$r8EYWSQCba$AAAAAa-NH_2	iso2	1957.04	980.04	1958.05	979.53	653.35
SP352	Ac-LTF$r8EYWAQCba$SAAa-NH_2		1814.96	909	1815.97	908.49	605.99
SP353	Ac-LTF$r8EYWAQCba$SAAa-NH_2	iso2	1814.96	909	1815.97	908.49	605.99
SP354	Ac-ALTF$r8EYWAQCba$SAAa-NH_2		1886	944.52	1887.01	944.01	629.67
SP355	Ac-ALTF$r8EYWAQCba$SAAa-NH_2	iso2	1886	944.98	1887.01	944.01	629.67
SP356	Ac-ALTF$r8EYWAQCba$SAAAa-NH_2		1957.04	980.04	1958.05	979.53	653.35
SP357	Ac-ALTF$r8EYWAQCba$SAAAa-NH_2	iso2	1957.04	980.04	1958.05	979.53	653.35
SP358	Ac-AALTF$r8EYWAQCba$SAAAa-NH_2		2028.07	1016.1	2029.08	1015.04	677.03
SP359	Ac-AALTF$r8EYWAQCba$SAAAa-NH_2	iso2	2028.07	1015.57	2029.08	1015.04	677.03
SP360	Ac-RTF$r8EYWAQCba$SAA-NH_2		1786.94	895.03	1787.95	894.48	596.65
SP361	Ac-LRF$r8EYWAQCba$SAA-NH_2		1798.98	901.51	1799.99	900.5	600.67
SP362	Ac-LTF$r8EYWRQCba$SAA-NH_2		1828.99	916.4	1830	915.5	610.67
SP363	Ac-LTF$r8EYWARCba$SAA-NH_2		1771.97	887.63	1772.98	886.99	591.66
SP364	Ac-LTF$r8EYWAQCba$RAA-NH_2		1812.99	908.08	1814	907.5	605.34
SP365	Ac-LTF$r8EYWAQCba$SRA-NH_2		1828.99	916.12	1830	915.5	610.67
SP366	Ac-LTF$r8EYWAQCba$SAR-NH_2		1828.99	916.12	1830	915.5	610.67
SP367	5-FAM-BaLTF$r8EYWAQCba$SAA-NH_2		2131	1067.09	2132.01	1066.51	711.34
SP368	5-FAM-BaLTF$r8AYWAQL$AANleA-NH_2		2158.08	1080.6	2159.09	1080.05	720.37
SP369	Ac-LAF$r8EYWAQL$AANleA-NH_2		1799	901.05	1800.01	900.51	600.67
SP370	Ac-ATF$r8EYWAQL$AANleA-NH_2		1786.97	895.03	1787.98	894.49	596.66
SP371	Ac-AAF$r8EYWAQL$AANleA-NH_2		1756.96	880.05	1757.97	879.49	586.66
SP372	Ac-AAAF$r8EYWAQL$AANleA-NH_2		1827.99	915.57	1829	915	610.34
SP373	Ac-AAAAF$r8EYWAQL$AANleA-NH_2		1899.03	951.09	1900.04	950.52	634.02
SP374	Ac-AATF$r8EYWAQL$AANleA-NH_2		1858	930.92	1859.01	930.01	620.34
SP375	Ac-AALTF$r8EYWAQL$AANleA-NH_2		1971.09	987.17	1972.1	986.55	658.04
SP376	Ac-AAALTF$r8EYWAQL$AANleA-NH_2		2042.12	1023.15	2043.13	1022.07	681.71
SP377	Ac-LTF$r8EYWAQL$AANleAA-NH_2		1900.05	952.02	1901.06	951.03	634.36
SP378	Ac-ALTF$r8EYWAQL$AANleAA-NH_2		1971.09	987.63	1972.1	986.55	658.04
SP379	Ac-AALTF$r8EYWAQL$AANleAA-NH_2		2042.12	1022.69	2043.13	1022.07	681.71
SP380	Ac-LTF$r8EYWAQCba$AANleAA-NH_2		1912.05	958.03	1913.06	957.03	638.36
SP381	Ac-LTF$r8EYWAQhL$AANleAA-NH_2		1914.07	958.68	1915.08	958.04	639.03
SP382	Ac-ALTF$r8EYWAQhL$AANleAA-NH_2		1985.1	994.1	1986.11	993.56	662.71
SP383	Ac-LTF$r8ANmYWAQL$AANleA-NH_2		1785.02	894.11	1786.03	893.52	596.01
SP384	Ac-LTF$r8ANmYWAQL$AANleA-NH_2	iso2	1785.02	894.11	1786.03	893.52	596.01
SP385	Ac-LTF$r8AYNmWAQL$AANleA-NH_2		1785.02	894.11	1786.03	893.52	596.01

SP	Sequence	Isomer	Exact Mass	Found Mass	Calc (M+1)/1	Calc (M+2)/2	Calc (M+3)/3
SP386	Ac-LTF$r8AYNmWAQL$AANleA-NH_2	iso2	1785.02	894.11	1786.03	893.52	596.01
SP387	Ac-LTF$r8AYAmwAQL$AANleA-NH_2		1785.02	894.01	1786.03	893.52	596.01
SP388	Ac-LTF$r8AYAmwAQL$AANleA-NH_2	iso2	1785.02	894.01	1786.03	893.52	596.01
SP389	Ac-LTF$r8AYWAibQL$AANleA-NH_2		1785.02	894.01	1786.03	893.52	596.01
SP390	Ac-LTF$r8AYWAibQL$AANleA-NH_2	iso2	1785.02	894.01	1786.03	893.52	596.01
SP391	Ac-LTF$r8AYWAQL$AAibNleA-NH_2		1785.02	894.38	1786.03	893.52	596.01
SP392	Ac-LTF$r8AYWAQL$AAibNleA-NH_2	iso2	1785.02	894.38	1786.03	893.52	596.01
SP393	Ac-LTF$r8AYWAQL$AaNleA-NH_2		1771.01	887.54	1772.02	886.51	591.34
SP394	Ac-LTF$r8AYWAQL$AaNleA-NH_2	iso2	1771.01	887.54	1772.02	886.51	591.34
SP395	Ac-LTF$r8AYWAQL$ASarNleA-NH_2		1771.01	887.35	1772.02	886.51	591.34
SP396	Ac-LTF$r8AYWAQL$ASarNleA-NH_2	iso2	1771.01	887.35	1772.02	886.51	591.34
SP397	Ac-LTF$r8AYWAQL$AANleAib-NH_2		1785.02	894.75	1786.03	893.52	596.01
SP398	Ac-LTF$r8AYWAQL$AANleAib-NH_2	iso2	1785.02	894.75	1786.03	893.52	596.01
SP399	Ac-LTF$r8AYWAQL$AANleNmA-NH_2		1785.02	894.6	1786.03	893.52	596.01
SP400	Ac-LTF$r8AYWAQL$AANleNmA-NH_2	iso2	1785.02	894.6	1786.03	893.52	596.01
SP401	Ac-LTF$r8AYWAQL$AANleSar-NH_2		1771.01	886.98	1772.02	886.51	591.34
SP402	Ac-LTF$r8AYWAQL$AANleSar-NH_2	iso2	1771.01	886.98	1772.02	886.51	591.34
SP403	Ac-LTF$r8AYWAQL$AANleAAib-NH_2		1856.06		1857.07	929.04	619.69
SP404	Ac-LTF$r8AYWAQL$AANleAAib-NH_2	iso2	1856.06		1857.07	929.04	619.69
SP405	Ac-LTF$r8AYWAQL$AANleANmA-NH_2		1856.06	930.37	1857.07	929.04	619.69
SP406	Ac-LTF$r8AYWAQL$AANleANmA-NH_2	iso2	1856.06	930.37	1857.07	929.04	619.69
SP407	Ac-LTF$r8AYWAQL$AANleAa-NH_2		1842.04	922.69	1843.05	922.03	615.02
SP408	Ac-LTF$r8AYWAQL$AANleAa-NH_2	iso2	1842.04	922.69	1843.05	922.03	615.02
SP409	Ac-LTF$r8AYWAQL$AANleASar-NH_2		1842.04	922.6	1843.05	922.03	615.02
SP410	Ac-LTF$r8AYWAQL$AANleASar-NH_2	iso2	1842.04	922.6	1843.05	922.03	615.02
SP411	Ac-LTF$/r8AYWAQL$/AANleA-NH_2		1799.04	901.14	1800.05	900.53	600.69
SP412	Ac-LTFAibAYWAQLAibAANleA-NH_2		1648.9	826.02	1649.91	825.46	550.64
SP413	Ac-LTF$r8Cou4YWAQL$AANleA-NH_2		1975.05	989.11	1976.06	988.53	659.36
SP414	Ac-LTF$r8Cou4YWAQL$AANleA-NH_2	iso2	1975.05	989.11	1976.06	988.53	659.36
SP415	Ac-LTF$r8AYWCou4QL$AANleA-NH_2		1975.05	989.11	1976.06	988.53	659.36
SP416	Ac-LTF$r8AYWAQL$Cou4ANleA-NH_2		1975.05	989.57	1976.06	988.53	659.36
SP417	Ac-LTF$r8AYWAQL$Cou4ANleA-NH_2	iso2	1975.05	989.57	1976.06	988.53	659.36
SP418	Ac-LTF$r8AYWAQL$ACou4NleA-NH_2		1975.05	989.57	1976.06	988.53	659.36
SP419	Ac-LTF$r8AYWAQL$ACou4NleA-NH_2	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-NH_2		1694.98	849.33	1695.99	848.5	566
SP429	Ac-LThL$r8AYWAQL$AANleA-NH_2		1751.04	877.09	1752.05	876.53	584.69
SP430	Ac-LTF$r8AYAAQL$AANleA-NH_2		1655.97	829.54	1656.98	828.99	553
SP431	Ac-LTF$r8AY2NalAQL$AANleA-NH_2		1782.01	892.63	1783.02	892.01	595.01
SP432	Ac-LTF$r8EYWCou4QCba$SAA-NH_2		1947.97	975.8	1948.98	974.99	650.33
SP433	Ac-LTF$r8EYWCou7QCba$SAA-NH_2		16.03	974.9	17.04	9.02	6.35
SP434	Ac-LTF%r8EYWAQCba%SAA-NH_2		1745.94	874.8	1746.95	873.98	582.99

SP	Sequence	Isomer	Exact Mass	Found Mass	Calc (M+1)/1	Calc (M+2)/2	Calc (M+3)/3
SP435	Dmaac-LTF$r8EYWAQCba$SAA-NH_2		1786.97	894.8	1787.98	894.49	596.66
SP436	Dmaac-LTF$r8AYWAQL$AAAAAa-NH_2		1914.08	958.2	1915.09	958.05	639.03
SP437	Dmaac-LTF$r8AYWAQL$AAAAAa-NH_2	iso2	1914.08	958.2	1915.09	958.05	639.03
SP438	Dmaac-LTF$r8EYWAQL$AAAAAa-NH_2		1972.08	987.3	1973.09	987.05	658.37
SP439	Dmaac-LTF$r8EYWAQL$AAAAAa-NH_2	iso2	1972.08	987.3	1973.09	987.05	658.37
SP440	Dmaac-LTF$r8EF4coohWAQCba$AAIa-NH_2		1912.05	957.4	1913.06	957.03	638.36
SP441	Dmaac-LTF$r8EF4coohWAQCba$AAIa-NH_2	iso2	1912.05	957.4	1913.06	957.03	638.36
SP442	Dmaac-LTF$r8AYWAQL$AANleA-NH_2		1814.05	908.3	1815.06	908.03	605.69
SP443	Dmaac-LTF$r8AYWAQL$AANleA-NH_2	iso2	1814.05	908.3	1815.06	908.03	605.69
SP444	Ac-LTF%r8AYWAQL%AANleA-NH_2		1773.02	888.37	1774.03	887.52	592.01
SP445	Ac-LTF%r8EYWAQL%AAAAAa-NH_2		1931.06	966.4	1932.07	966.54	644.69
SP446	Cou6BaLTF$r8EYWAQhL$SAA-NH_2		2018.05	1009.9	2019.06	1010.03	673.69
SP447	Cou8BaLTF$r8EYWAQhL$SAA-NH_2		1962.96	982.34	1963.97	982.49	655.32
SP448	Ac-LTF4I$r8EYWAQL$AAAAAa-NH_2		2054.93	1028.68	2055.94	1028.47	685.98
SP449	Ac-LTF$r8EYWAQL$AAAAAa-NH_2		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-NH_2		1930.02	966.82	1931.03	966.02	644.35
SP553	Ac-LTF$r8EYWAEL$AAAAAa-NH_2	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-NH_2		1963	983.28	1964.01	982.51	655.34
SP556	Ac-LTF$r8EF4bOH2WAQL$AAAAAa-NH_2		1957.05	980.04	1958.06	979.53	653.36
SP557	Ac-AAALTF$r8EYWAQL$AAAAAa-NH_2		2142.15	1072.83	2143.16	1072.08	715.06
SP558	Ac-LTF34F2$r8EYWAQL$AAAAAa-NH_2		1965.02	984.3	1966.03	983.52	656.01
SP559	Ac-RTF$r8EYWAQL$AAAAAa-NH_2		1972.06	987.81	1973.07	987.04	658.36
SP560	Ac-LTA$r8EYWAQL$AAAAAa-NH_2		1853.01	928.33	1854.02	927.51	618.68
SP561	Ac-LTF$r8EYWAibQL$AAAAAa-NH_2		1943.06	973.48	1944.07	972.54	648.69
SP562	Ac-LTF$r8EYWAQL$AAibAAAa-NH_2		1943.06	973.11	1944.07	972.54	648.69
SP563	Ac-LTF$r8EYWAQL$AAAibAAa-NH_2		1943.06	973.48	1944.07	972.54	648.69
SP564	Ac-LTF$r8EYWAQL$AAAAibAa-NH_2		1943.06	973.48	1944.07	972.54	648.69
SP565	Ac-LTF$r8EYWAQL$AAAAAiba-NH_2		1943.06	973.38	1944.07	972.54	648.69
SP566	Ac-LTF$r8EYWAQL$AAAAAiba-NH_2	iso2	1943.06	973.38	1944.07	972.54	648.69
SP567	Ac-LTF$r8EYWAQL$AAAAAAib-NH_2		1943.06	973.01	1944.07	972.54	648.69
SP568	Ac-LTF$r8EYWAQL$AaAAAa-NH_2		1929.04	966.54	1930.05	965.53	644.02
SP569	Ac-LTF$r8EYWAQL$AAaAAa-NH_2		1929.04	966.35	1930.05	965.53	644.02
SP570	Ac-LTF$r8EYWAQL$AAAaAa-NH_2		1929.04	966.54	1930.05	965.53	644.02
SP571	Ac-LTF$r8EYWAQL$AAAaAa-NH_2	iso2	1929.04	966.35	1930.05	965.53	644.02
SP572	Ac-LTF$r8EYWAQL$AAAAAa-NH_2		1929.04	966.35	1930.05	965.53	644.02
SP573	Ac-LTF$r8EYWAQL$AAAAAA-NH_2		1929.04	966.35	1930.05	965.53	644.02
SP574	Ac-LTF$r8EYWAQL$ASarAAAa-NH_2		1929.04	966.54	1930.05	965.53	644.02
SP575	Ac-LTF$r8EYWAQL$AASarAAa-NH_2		1929.04	966.35	1930.05	965.53	644.02
SP576	Ac-LTF$r8EYWAQL$AAASarAa-NH_2		1929.04	966.35	1930.05	965.53	644.02
SP577	Ac-LTF$r8EYWAQL$AAAASara-NH_2		1929.04	966.35	1930.05	965.53	644.02
SP578	Ac-LTF$r8EYWAQL$AAAAASar-NH_2		1929.04	966.08	1930.05	965.53	644.02
SP579	Ac-7LTF$r8EYWAQL$AAAAAa-NH_2		1918.07	951.99	1919.08	960.04	640.37
SP581	Ac-TF$r8EYWAQL$AAAAAa-NH_2		1815.96	929.85	1816.97	908.99	606.33
SP582	Ac-F$r8EYWAQL$AAAAAa-NH_2		1714.91	930.92	1715.92	858.46	572.64
SP583	Ac-LVF$r8EYWAQL$AAAAAa-NH_2		1927.06	895.12	1928.07	964.54	643.36
SP584	Ac-AAF$r8EYWAQL$AAAAAa-NH_2		1856.98	859.51	1857.99	929.5	620

SP	Sequence	Isomer	Exact Mass	Found Mass	Calc (M+1)/1	Calc (M+2)/2	Calc (M+3)/3
SP585	Ac-LTF$r8EYWAQL$AAAAa-NH_2		1858	824.08	1859.01	930.01	620.34
SP586	Ac-LTF$r8EYWAQL$AAAa-NH_2		1786.97	788.56	1787.98	894.49	596.66
SP587	Ac-LTF$r8EYWAQL$AAa-NH_2		1715.93	1138.57	1716.94	858.97	572.98
SP588	Ac-LTF$r8EYWAQL$Aa-NH_2		1644.89	1144.98	1645.9	823.45	549.3
SP589	Ac-LTF$r8EYWAQL$a-NH_2		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-NH_2		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-NH_2		1601.85	979.58	1602.86	801.93	534.96
SP596	4-FBzl-LTF$r8EYWAQL$AAAAAa-NH_2		2009.05	970.52	2010.06	1005.53	670.69
SP597	4-FBzl-LTF$r8EYWAQCba$SAA-NH_2		1823.93	965.8	1824.94	912.97	608.98
SP598	Ac-LTF$r8RYWAQL$AAAAAa-NH_2		1956.1	988.28	1957.11	979.06	653.04
SP599	Ac-LTF$r8HYWAQL$AAAAAa-NH_2		1937.06	1003.54	1938.07	969.54	646.69
SP600	Ac-LTF$r8QYWAQL$AAAAAa-NH_2		1928.06	993.92	1929.07	965.04	643.69
SP601	Ac-LTF$r8CitYWAQL$AAAAAa-NH_2		1957.08	987	1958.09	979.55	653.37
SP602	Ac-LTF$r8GlaYWAQL$AAAAAa-NH_2		1973.03	983	1974.04	987.52	658.68
SP603	Ac-LTF$r8F4gYWAQL$AAAAAa-NH_2		2004.1	937.86	2005.11	1003.06	669.04
SP604	Ac-LTF$r82mRYWAQL$AAAAAa-NH_2		1984.13	958.58	1985.14	993.07	662.38
SP605	Ac-LTF$r8ipKYWAQL$AAAAAa-NH_2		1970.14	944.52	1971.15	986.08	657.72
SP606	Ac-LTF$r8F4$NH_2$YWAQL$AAAAAa-NH_2		1962.08	946	1963.09	982.05	655.03
SP607	Ac-LTF$r8EYWAAL$AAAAAa-NH_2		1872.02	959.32	1873.03	937.02	625.01
SP608	Ac-LTF$r8EYWALL$AAAAAa-NH_2		1914.07	980.88	1915.08	958.04	639.03
SP609	Ac-LTF$r8EYWAAibL$AAAAAa-NH_2		1886.03	970.61	1887.04	944.02	629.68
SP610	Ac-LTF$r8EYWASL$AAAAAa-NH_2		1888.01	980.51	1889.02	945.01	630.34
SP611	Ac-LTF$r8EYWANL$AAAAAa-NH_2		1915.02	1006.41	1916.03	958.52	639.35
SP612	Ac-LTF$r8EYWACitL$AAAAAa-NH_2		1958.07		1959.08	980.04	653.7
SP613	Ac-LTF$r8EYWAHL$AAAAAa-NH_2		1938.04	966.24	1939.05	970.03	647.02
SP614	Ac-LTF$r8EYWARL$AAAAAa-NH_2		1957.08		1958.09	979.55	653.37
SP615	Ac-LTF$r8EpYWAQL$AAAAAa-NH_2		2009.01		2010.02	1005.51	670.68
SP616	Cbm-LTF$r8EYWAQCba$SAA-NH_2		1590.85		1591.86	796.43	531.29
SP617	Cbm-LTF$r8EYWAQL$AAAAAa-NH_2		1930.04		1931.05	966.03	644.35
SP618	Ac-LTF$r8EYWAQL$SAAAAa-NH_2		1945.04	1005.11	1946.05	973.53	649.35
SP619	Ac-LTF$r8EYWAQL$AAAASa-NH_2		1945.04	986.52	1946.05	973.53	649.35
SP620	Ac-LTF$r8EYWAQL$SAAASa-NH_2		1961.03	993.27	1962.04	981.52	654.68
SP621	Ac-LTF$r8EYWAQTba$AAAAAa-NH_2		1943.06	983.1	1944.07	972.54	648.69
SP622	Ac-LTF$r8EYWAQAdm$AAAAAa-NH_2		2007.09	990.31	2008.1	1004.55	670.04
SP623	Ac-LTF$r8EYWAQCha$AAAAAa-NH_2		1969.07	987.17	1970.08	985.54	657.36
SP624	Ac-LTF$r8EYWAQhCha$AAAAAa-NH_2		1983.09	1026.11	1984.1	992.55	662.04
SP625	Ac-LTF$r8EYWAQF$AAAAAa-NH_2		1963.02	957.01	1964.03	982.52	655.35
SP626	Ac-LTF$r8EYWAQhF$AAAAAa-NH_2		1977.04	1087.81	1978.05	989.53	660.02
SP627	Ac-LTF$r8EYWAQL$AANleAAa-NH_2		1971.09	933.45	1972.1	986.55	658.04
SP628	Ac-LTF$r8EYWAQAdm$AANleAAa-NH_2		2049.13	1017.97	2050.14	1025.57	684.05
SP629	4-FBz-BaLTF$r8EYWAQL$AAAAAa-NH_2		2080.08		2081.09	1041.05	694.37
SP630	4-FBz-BaLTF$r8EYWAQCba$SAA-NH_2		1894.97		1895.98	948.49	632.66
SP631	Ac-LTF$r5EYWAQL$s8AAAAAa-NH_2		1929.04	1072.68	1930.05	965.53	644.02
SP632	Ac-LTF$r5EYWAQCba$s8SAA-NH_2		1743.92	1107.79	1744.93	872.97	582.31
SP633	Ac-LTF$r8EYWAQL$AAhhLAAa-NH_2		1999.12		2000.13	1000.57	667.38
SP634	Ac-LTF$r8EYWAQL$AAAAAAAa-NH_2		2071.11		2072.12	1036.56	691.38
SP635	Ac-LTF$r8EYWAQL$AAAAAAAAa-NH_2		2142.15	778.1	2143.16	1072.08	715.06

SP	Sequence	Isomer	Exact Mass	Found Mass	Calc (M+1)/1	Calc (M+2)/2	Calc (M+3)/3
SP636	Ac-LTF$r8EYWAQL$AAAAAAAAAa-NH_2		2213.19	870.53	2214.2	1107.6	738.74
SP637	Ac-LTA$r8EYAAQCba$SAA-NH_2		1552.85		1553.86	777.43	518.62
SP638	Ac-LTA$r8EYAAQL$AAAAAa-NH_2		1737.97	779.45	1738.98	869.99	580.33
SP639	Ac-LTF$r8EPmpWAQL$AAAAAa-NH_2		2007.03	779.54	2008.04	1004.52	670.02
SP640	Ac-LTF$r8EPmpWAQCba$SAA-NH_2		1821.91	838.04	1822.92	911.96	608.31
SP641	Ac-ATF$r8HYWAQL$S-NH_2		1555.82	867.83	1556.83	778.92	519.61
SP642	Ac-LTF$r8HAWAQL$S-NH_2		1505.84	877.91	1506.85	753.93	502.95
SP643	Ac-LTF$r8HYWAQA$S-NH_2		1555.82	852.52	1556.83	778.92	519.61
SP644	Ac-LTF$r8EYWAQCba$SA-NH_2		1672.89	887.18	1673.9	837.45	558.64
SP645	Ac-LTF$r8EYWAQL$SAA-NH_2		1731.92	873.32	1732.93	866.97	578.31
SP646	Ac-LTF$r8HYWAQCba$SAA-NH_2		1751.94	873.05	1752.95	876.98	584.99
SP647	Ac-LTF$r8SYWAQCba$SAA-NH_2		1701.91	844.88	1702.92	851.96	568.31
SP648	Ac-LTF$r8RYWAQCba$SAA-NH_2		1770.98	865.58	1771.99	886.5	591.33
SP649	Ac-LTF$r8KYWAQCba$SAA-NH_2		1742.98	936.57	1743.99	872.5	582
SP650	Ac-LTF$r8QYWAQCba$SAA-NH_2		1742.94	930.93	1743.95	872.48	581.99
SP651	Ac-LTF$r8EYWAACba$SAA-NH_2		1686.9	1032.45	1687.91	844.46	563.31
SP652	Ac-LTF$r8EYWAQCba$AAA-NH_2		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-NH_2						
SP657	Ac-LTF$r8AF4bOH2WAAL$AAAAAa-NH_2						
SP658	Ac-LTF$r8EF4bOH2WAQCba$SAA-NH_2						
SP659	Ac-LTF$r8ApYWAQL$AAAAAa-NH_2						
SP660	Ac-LTF$r8ApYWAAL$AAAAAa-NH_2						
SP661	Ac-LTF$r8EpYWAQCba$SAA-NH_2						
SP662	Ac-LTF$rda6AYWAQL$da5AAAAAa-NH_2		1974.06	934.44			
SP663	Ac-LTF$rda6EYWAQCba$da5SAA-NH_2		1846.95	870.52		869.94	
SP664	Ac-LTF$rda6EYWAQL$da5AAAAAa-NH_2						
SP665	Ac-LTF$ra9EYWAQL$a6AAAAAa-NH_2			936.57		935.51	
SP666	Ac-LTF$ra9EYWAQL$a6AAAAAa-NH_2						
SP667	Ac-LTF$ra9EYWAQCba$a6SAA-NH_2						
SP668	Ac-LTA$ra9EYWAQCba$a6SAA-NH_2						
SP669	5-FAM-BaLTF$ra9EYWAQCba$a6SAA-NH_2						
SP670	5-FAM-BaLTF$r8EYWAQL$AAAAAa-NH_2		2316.11				
SP671	5-FAM-BaLTF$/r8EYWAQL$/AAAAAa-NH_2		2344.15				
SP672	5-FAM-BaLTA$r8EYWAQL$AAAAAa-NH_2		2240.08				
SP673	5-FAM-BaLTF$r8AYWAQL$AAAAAa-NH_2		2258.11				
SP674	5-FAM-BaATF$r8EYWAQL$AAAAAa-NH_2		2274.07				
SP675	5-FAM-BaLAF$r8EYWAQL$AAAAAa-NH_2		2286.1				
SP676	5-FAM-BaLTF$r8EAWAQL$AAAAAa-NH_2		2224.09				
SP677	5-FAM-BaLTF$r8EYAAQL$AAAAAa-NH_2		2201.07				
SP678	5-FAM-BaLTA$r8EYAAQL$AAAAAa-NH_2		2125.04				
SP679	5-FAM-BaLTF$r8EYWAAL$AAAAAa-NH_2		2259.09				
SP680	5-FAM-BaLTF$r8EYWAQA$AAAAAa-NH_2		2274.07				
SP681	5-FAM-BaLTF$/r8EYWAQCba$/SAA-NH_2		2159.03				
SP682	5-FAM-BaLTA$r8EYWAQCba$SAA-NH_2		2054.97				
SP683	5-FAM-BaLTF$r8EYAAQCba$SAA-NH_2		2015.96				

SP	Sequence	Isomer	Exact Mass	Found Mass	Calc (M+1)/1	Calc (M+2)/2	Calc (M+3)/3
SP684	5-FAM-BaLTA$r8EYAAQCba$SAA-NH_2		1939.92				
SP685	5-FAM-BaQSQQTF$r8NLWRLL$QN-NH_2		2495.23				
SP686	5-TAMRA-BaLTF$r8EYWAQCba$SAA-NH_2		2186.1				
SP687	5-TAMRA-BaLTA$r8EYWAQCba$SAA-NH_2		2110.07				
SP688	5-TAMRA-BaLTF$r8EYAAQCba$SAA-NH_2		2071.06				
SP689	5-TAMRA-BaLTA$r8EYAAQCba$SAA-NH_2		1995.03				
SP690	5-TAMRA-BaLTF$/r8EYWAQCba$/SAA-NH_2		2214.13				
SP691	5-TAMRA-BaLTF$r8EYWAQL$AAAAAa-NH_2		2371.22				
SP692	5-TAMRA-BaLTA$r8EYWAQL$AAAAAa-NH_2		2295.19				
SP693	5-TAMRA-BaLTF$/r8EYWAQL$/AAAAAa-NH_2		2399.25				
SP694	Ac-LTF$r8EYWCou7QCba$SAA-OH		1947.93				
SP695	Ac-LTF$r8EYWCou7QCba$S-OH		1805.86				
SP696	Ac-LTA$r8EYWCou7QCba$SAA-NH_2		1870.91				
SP697	Ac-LTF$r8EYACou7QCba$SAA-NH_2		1831.9				
SP698	Ac-LTA$r8EYACou7QCba$SAA-NH_2		1755.87				
SP699	Ac-LTF$/r8EYWCou7QCba$/SAA-NH_2		1974.98				
SP700	Ac-LTF$r8EYWCou7QL$AAAAAa-NH_2		2132.06				
SP701	Ac-LTF$/r8EYWCou7QL$/AAAAAa-NH_2		2160.09				
SP702	Ac-LTF$r8EYWCou7QL$AAAAA-OH		2062.01				
SP703	Ac-LTF$r8EYWCou7QL$AAAA-OH		1990.97				
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-NH_2	iso2		974.4		973.53	
SP708	Ac-LTF$r8AYWAAL$AAAAAa-NH_2	iso2	1814.01	908.82	1815.02	908.01	605.68
SP709	Biotin-BaLTF$r8EYWAQL$AAAAAa-NH_2		2184.14	1093.64	2185.15	1093.08	729.05
SP710	Ac-LTF$r8HAWAQL$S-NH_2	iso2	1505.84	754.43	1506.85	753.93	502.95
SP711	Ac-LTF$r8EYWAQCba$SA-NH_2	iso2	1672.89	838.05	1673.9	837.45	558.64
SP712	Ac-LTF$r8HYWAQCba$SAA-NH_2	iso2	1751.94	877.55	1752.95	876.98	584.99
SP713	Ac-LTF$r8SYWAQCba$SAA-NH_2	iso2	1701.91	852.48	1702.92	851.96	568.31
SP714	Ac-LTF$r8RYWAQCba$SAA-NH_2	iso2	1770.98	887.45	1771.99	886.5	591.33
SP715	Ac-LTF$r8KYWAQCba$SAA-NH_2	iso2	1742.98	872.92	1743.99	872.5	582
SP716	Ac-LTF$r8EYWAQCba$AAA-NH_2	iso2	1727.93	865.71	1728.94	864.97	576.98
SP717	Ac-LTF$r8EYWAQL$AAAAAaBaC-NH_2		2103.09	1053.12	2104.1	1052.55	702.04
SP718	Ac-LTF$r8EYWAQL$AAAAAadPeg4C-NH_2		2279.19	1141.46	2280.2	1140.6	760.74
SP719	Ac-LTA$r8AYWAAL$AAAAAa-NH_2		1737.98	870.43	1738.99	870	580.33
SP720	Ac-LTF$r8AYAAAL$AAAAAa-NH_2		1698.97	851	1699.98	850.49	567.33
SP721	5-FAM-BaLTF$r8AYWAAL$AAAAAa-NH_2		2201.09	1101.87	2202.1	1101.55	734.7
SP722	Ac-LTA$r8AYWAQL$AAAAAa-NH_2		1795	898.92	1796.01	898.51	599.34
SP723	Ac-LTF$r8AYAAQL$AAAAAa-NH_2		1755.99	879.49	1757	879	586.34
SP724	Ac-LTF$rda6AYWAAL$da5AAAAAa-NH_2		1807.97		1808.98	904.99	603.66

SP	Sequence	Isomer	Exact Mass	Found Mass	Calc (M+1)/1	Calc (M+2)/2	Calc (M+3)/3
SP725	FITC-BaLTF$r8EYWAQL$AAAAAa-NH_2		2347.1	1174.49	2348.11	1174.56	783.37
SP726	FITC-BaLTF$r8EYWAQCba$SAA-NH_2		2161.99	1082.35	2163	1082	721.67
SP733	Ac-LTF$r8EYWAQL$EAAAAa-NH_2		1987.05	995.03	1988.06	994.53	663.36
SP734	Ac-LTF$r8AYWAQL$EAAAAa-NH_2		1929.04	966.35	1930.05	965.53	644.02
SP735	Ac-LTF$r8EYWAQL$AAAAAaBaKbio-NH_2		2354.25	1178.47	2355.26	1178.13	785.76
SP736	Ac-LTF$r8AYWAAL$AAAAAa-NH_2		1814.01	908.45	1815.02	908.01	605.68
SP737	Ac-LTF$r8AYAAAL$AAAAAa-NH_2	iso2	1698.97	850.91	1699.98	850.49	567.33
SP738	Ac-LTF$r8AYAAQL$AAAAAa-NH_2	iso2	1755.99	879.4	1757	879	586.34
SP739	Ac-LTF$r8EYWAQL$EAAAAa-NH_2	iso2	1987.05	995.21	1988.06	994.53	663.36
SP740	Ac-LTF$r8AYWAQL$EAAAAa-NH_2	iso2	1929.04	966.08	1930.05	965.53	644.02
SP741	Ac-LTF$r8EYWAQCba$SAAAAa-NH_2		1957.04	980.04	1958.05	979.53	653.35
SP742	Ac-LTF$r8EYWAQLStAAA$r5AA-NH_2		2023.12	1012.83	2024.13	1012.57	675.38
SP743	Ac-LTF$r8EYWAQL$AAAAA-NH_2		2108.17	1055.44	2109.18	1055.09	703.73
SP744	Ac-LTF$r8EYWAQL$AAAAAA-NH_2		2179.21	1090.77	2180.22	1090.61	727.41
SP745	Ac-LTF$r8EYWAQL$AAAAAAA-NH_2		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-NH_2		1929.04	965.85	1930.05	965.53	644.02
SP748	Ac-AAAALTF$r8EYWAQL$AAA-NH_2		2000.08	1001.4	2001.09	1001.05	667.7
SP749	Ac-AAAAALTF$r8EYWAQL$AAA-NH_2		2071.11	1037.13	2072.12	1036.56	691.38
SP750	Ac-AAAAAALTF$r8EYWAQL$AAA-NH_2		2142.15		2143.16	1072.08	715.06
SP751	Ac-LTF$rda6EYWAQCba$da6SAA-NH_2	iso2	1751.89	877.36	1752.9	876.95	584.97
SP752	Ac-t$r5wya$r5f4CF3ekllr-NH_2			844.25			
SP753	Ac-tawy$r5nf4CF3e$r5llr-NH_2			837.03			
SP754	Ac-tawya$r5f4CF3ek$r5lr-NH_2			822.97			
SP755	Ac-tawyanf4CF3e$r5llr$r5a-NH_2			908.35			
SP756	Ac-t$s8wyanf4CF3e$r5llr-NH_2			858.03			
SP757	Ac-tawy$s8nf4CF3ekll$r5a-NH_2			879.86			
SP758	Ac-tawya$s8f4CF3ekllr$r5a-NH_2			936.38			
SP759	Ac-tawy$s8naekll$r5a-NH_2			844.25			
SP760	5-FAM-Batawy$s8nf4CF3ekll$r5a-NH_2						
SP761	5-FAM-Batawy$s8naekll$r5a-NH_2						
SP762	Ac-tawy$s8nf4CF3eall$r5a-NH_2						
SP763	Ac-tawy$s8nf4CF3ekll$r5aaaaa-NH_2						
SP764	Ac-tawy$s8nf4CF3eall$r5aaaaa-NH_2						

[00546] Table 1a shows a selection of peptidomimetic macrocycles.

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-NH_2		1885	943.59	1886.01	943.51	629.34
SP331	Ac-LTF$r8EYWAQL$AAAAAa-NH_2	iso2	1929.04	966.08	1930.05	965.53	644.02
SP555	Ac-LTF$r8EY6clWAQL$AAAAAa-NH_2		1963	983.28	1964.01	982.51	655.34
SP557	Ac-AAALTF$r8EYWAQL$AAAAAa-NH_2		2142.15	1072.83	2143.16	1072.08	715.06
SP558	Ac-LTF34F2$r8EYWAQL$AAAAAa-NH_2		1965.02	984.3	1966.03	983.52	656.01
SP562	Ac-LTF$r8EYWAQL$AAibAAAa-NH_2		1943.06	973.11	1944.07	972.54	648.69

SP564	Ac-LTF$r8EYWAQL$AAAAibAa-NH_2		1943.06	973.48	1944.07	972.54	648.69
SP566	Ac-LTF$r8EYWAQL$AAAAAiba-NH_2	iso2	1943.06	973.38	1944.07	972.54	648.69
SP567	Ac-LTF$r8EYWAQL$AAAAAAib-NH_2		1943.06	973.01	1944.07	972.54	648.69
SP572	Ac-LTF$r8EYWAQL$AAAAaa-NH_2		1929.04	966.35	1930.05	965.53	644.02
SP573	Ac-LTF$r8EYWAQL$AAAAAA-NH_2		1929.04	966.35	1930.05	965.53	644.02
SP578	Ac-LTF$r8EYWAQL$AAAAASar-NH_2		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-NH_2		1974.06	934.44		933.49	
SP367	5-FAM-BaLTF$r8EYWAQCba$SAA-NH_2		2131	1067.09	2132.01	1066.51	711.34
SP349	Ac-LTF$r8EF4coohWAQCba$AAAAAa-NH_2	iso2	1969.04	986.06	1970.05	985.53	657.35
SP347	Ac-LTF$r8EYWAQCba$AAAAAa-NH_2	iso2	1941.04	972.55	1942.05	971.53	648.02

[00547] Table 1b shows a further selection of peptidomimetic macrocycles.

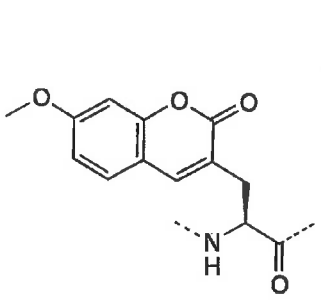
Table 1b

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

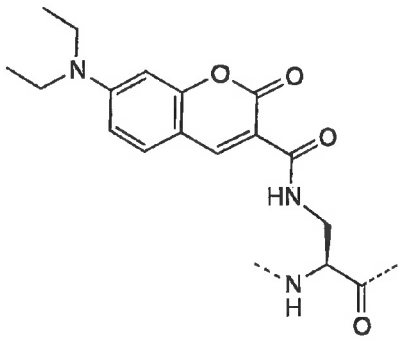
[00548] In the sequences shown above and elsewhere, the following abbreviations are used: "Nle" represents norleucine, "Aib" represents 2-aminoisobutyric acid, "Ac" represents acetyl, and "Pr" represents propionyl. Amino acids represented as "$" are alpha-Me S5-pentenyl-alanine olefin amino acids connected by an all-carbon crosslinker comprising one double bond. Amino acids represented as "$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.

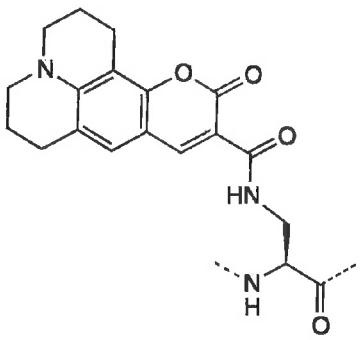
[00549] Amino acids designated as "Cit" represent citrulline. Amino acids designated as "Cou4", "Cou6", "Cou7" and "Cou8", respectively, represent the following structures:



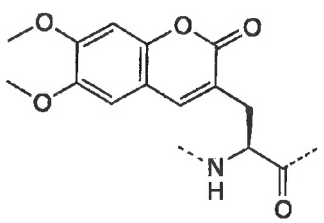
Cou



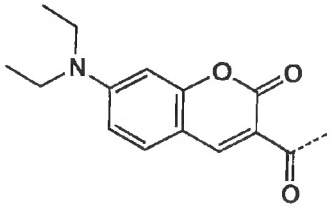
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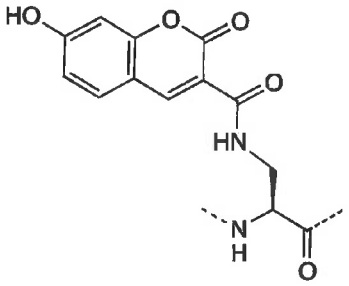
Cou3



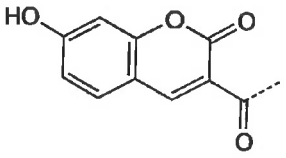
Cou4



Cou6



Cou7

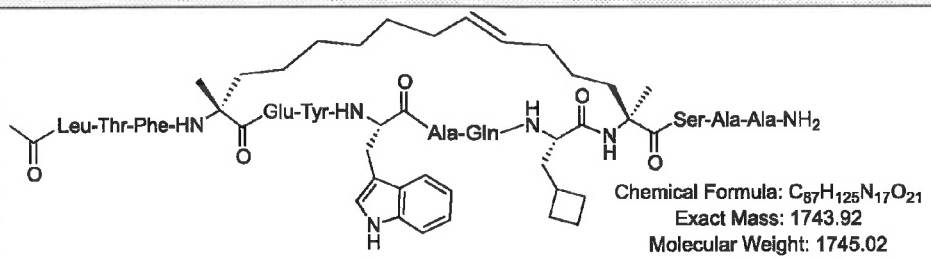
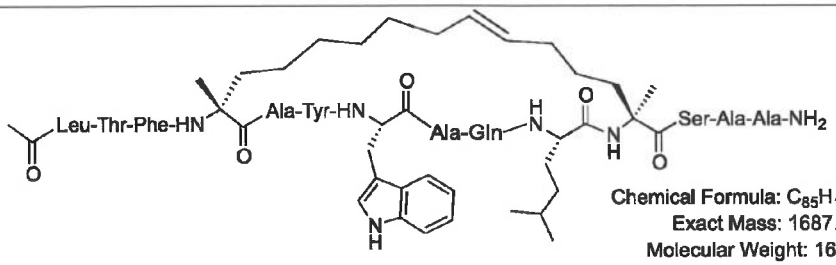
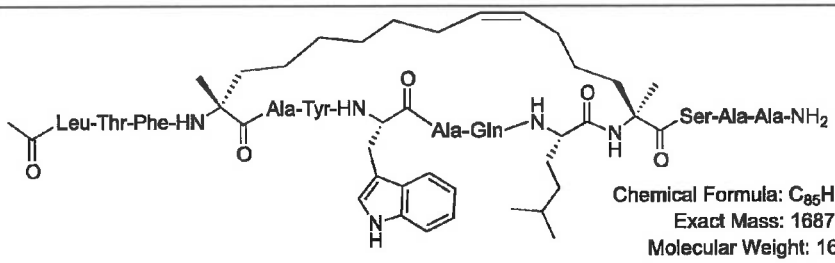
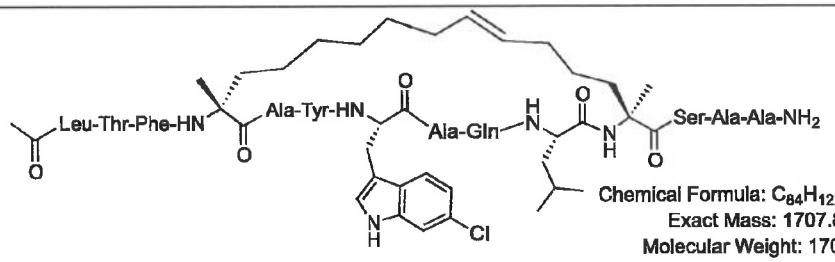
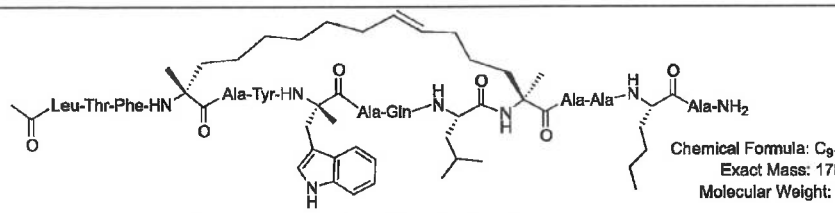


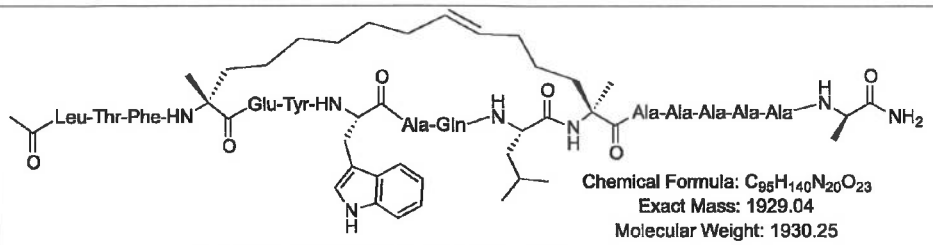
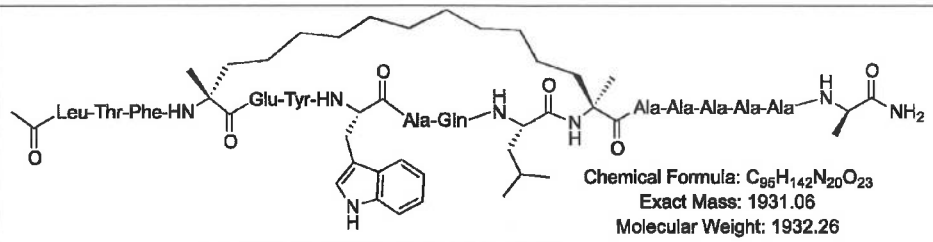
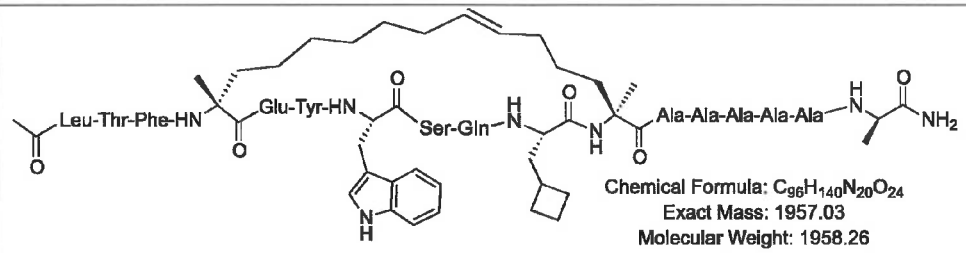
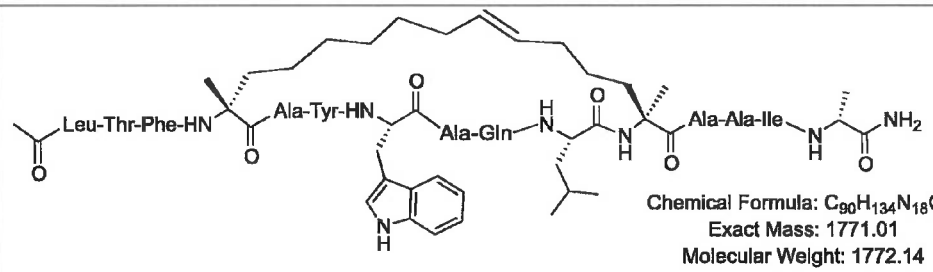
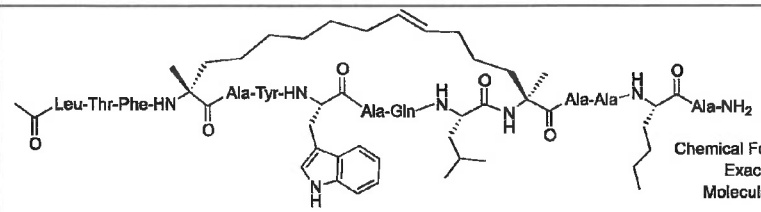
Cou8

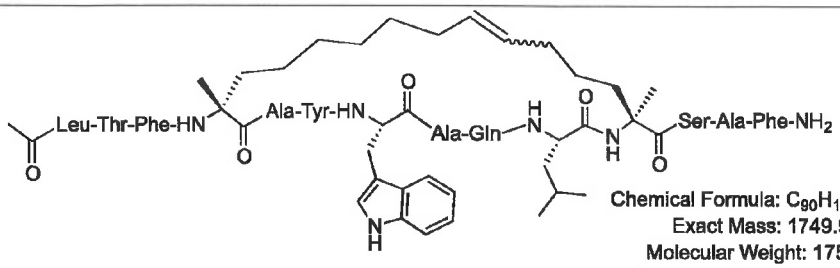
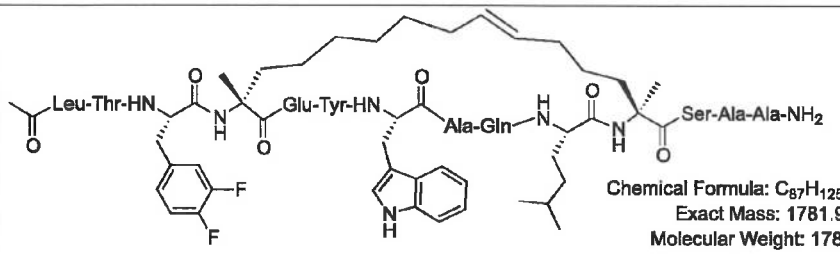
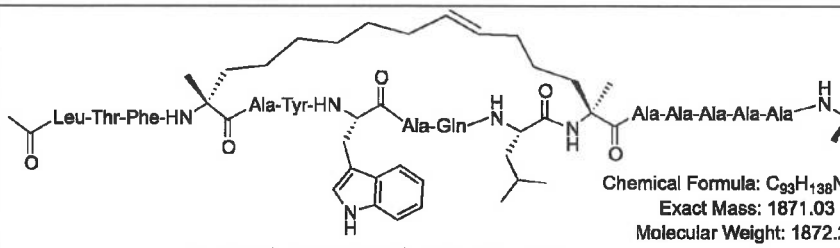
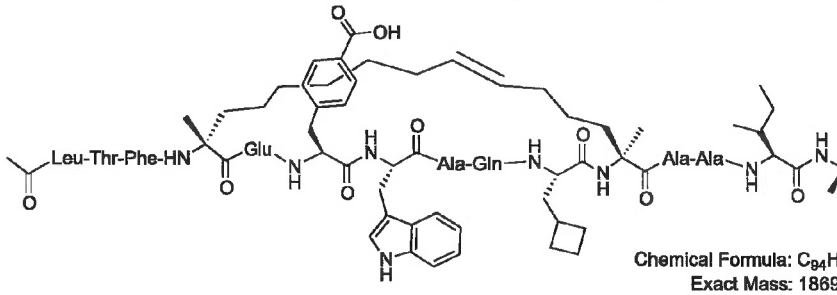
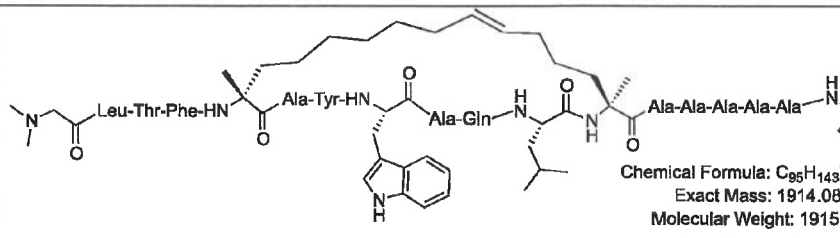
[00550] In some embodiments, a peptidomimetic macrocycle is obtained in more than one isomer, for example due to the configuration of a double bond within the structure of the crosslinker (*E* vs *Z*). Such isomers can or cannot be separable by conventional chromatographic methods. In some embodiments, one isomer has improved biological properties relative to the other isomer. In one embodiment, an *E* crosslinker 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* crosslinker 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.

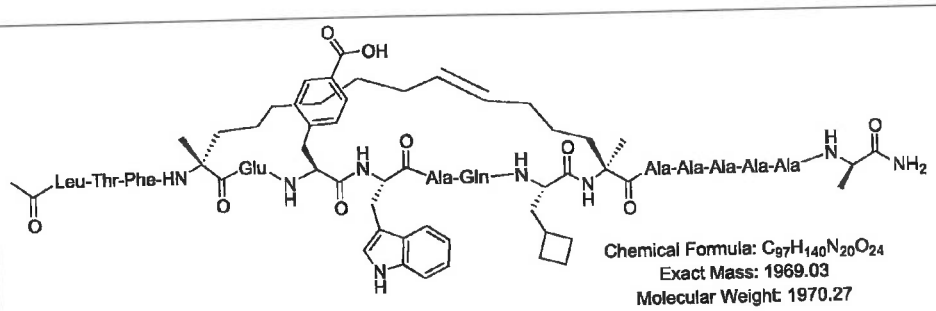
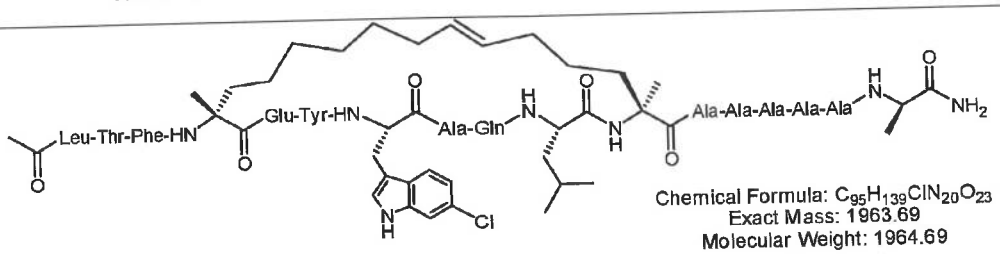
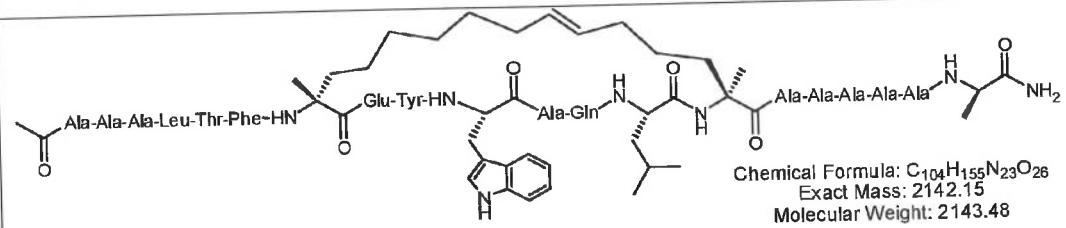
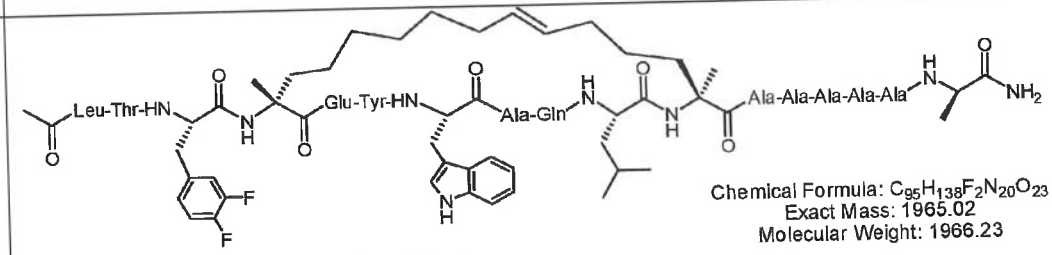
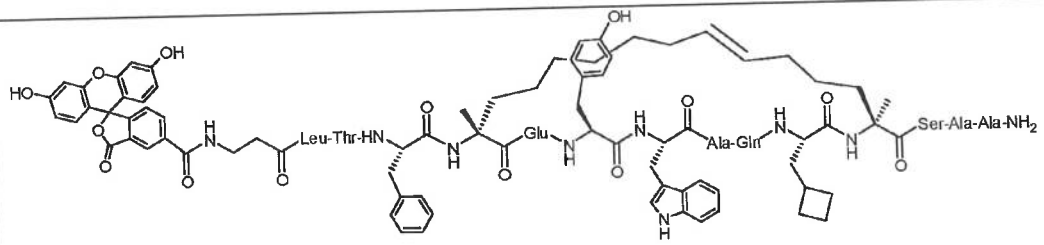
[00551] Table 1c shows exemplary peptidomimetic macrocycles:

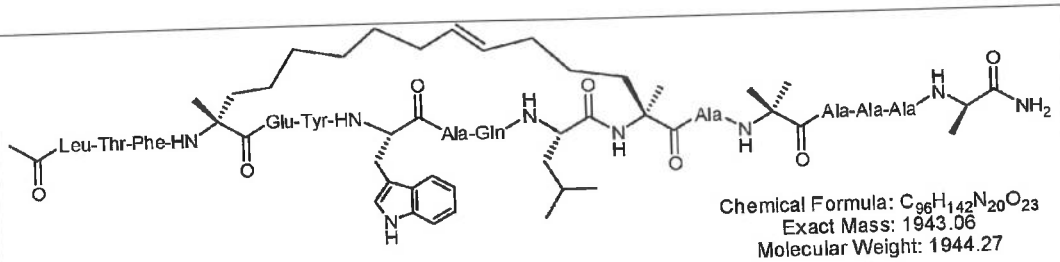
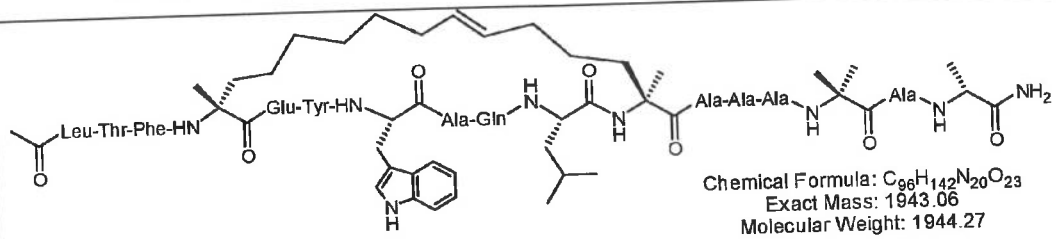
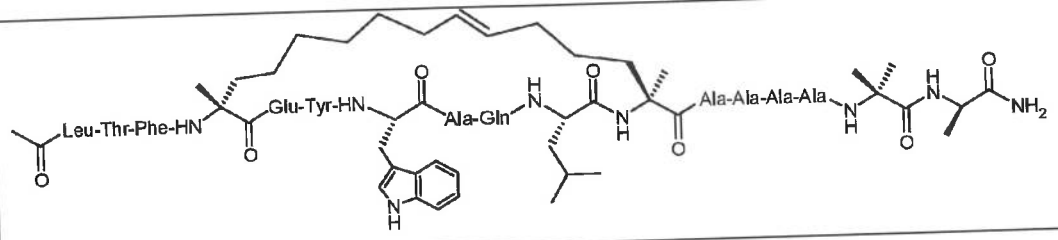
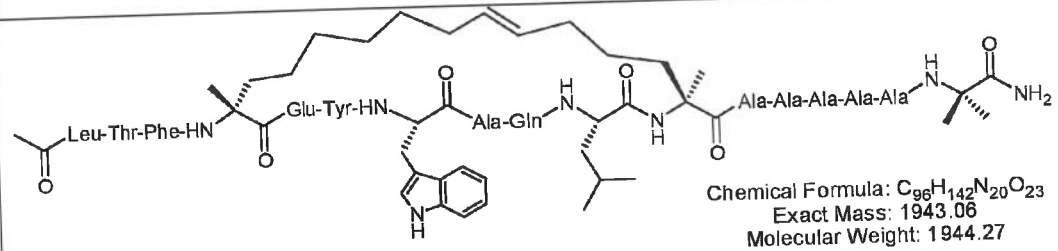
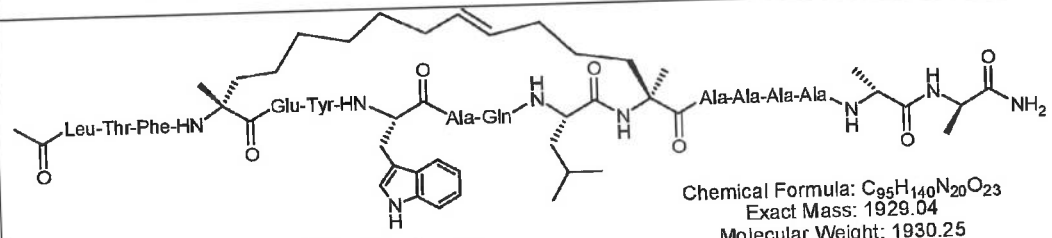
Table 1c

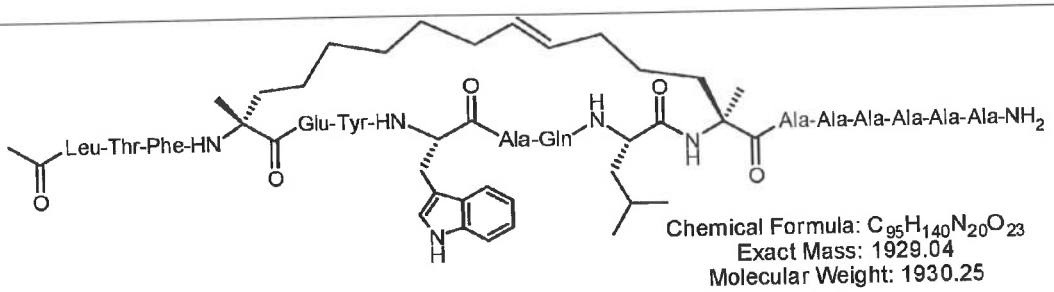
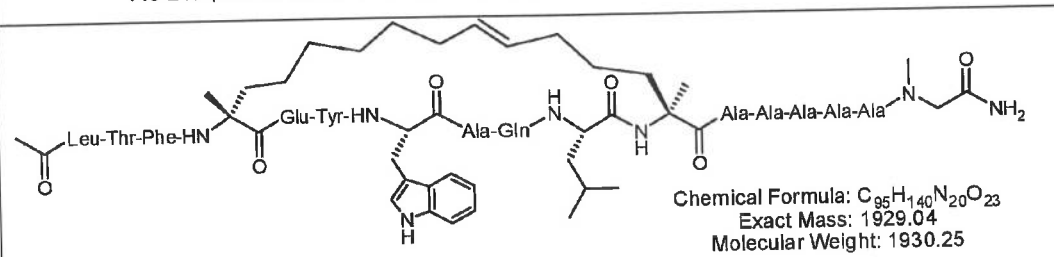
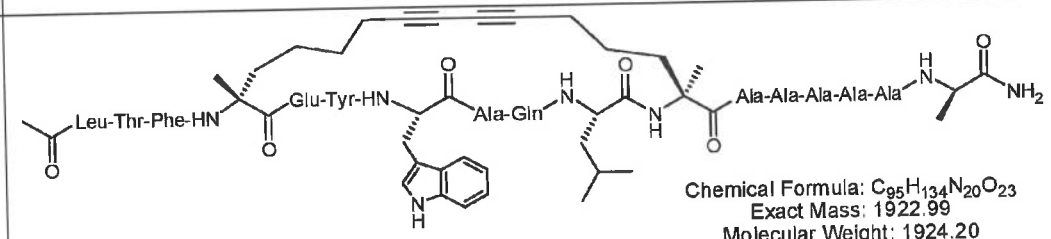
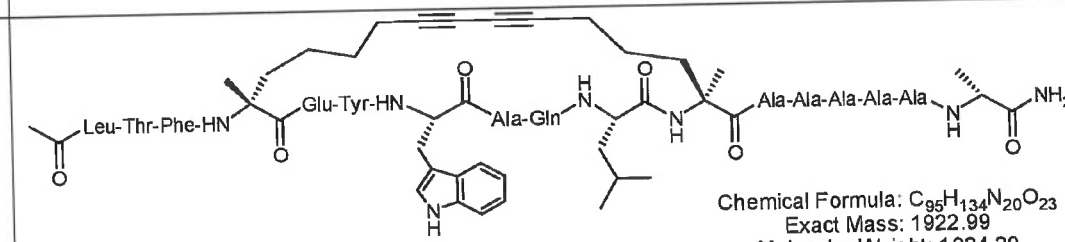
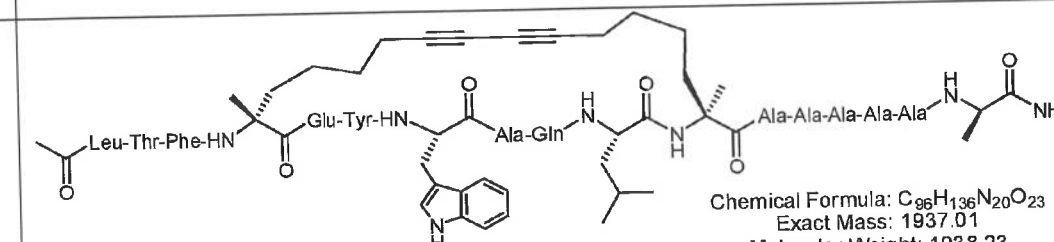
SP#	Structure
SP154	 Chemical Formula: $C_{87}H_{125}N_{17}O_{21}$ Exact Mass: 1743.92 Molecular Weight: 1745.02 Ac-L T F $er8 E Y W A Q Cba $e S A A -NH2
SP115	 Chemical Formula: $C_{85}H_{125}N_{17}O_{19}$ Exact Mass: 1687.93 Molecular Weight: 1689.00 Ac-L T F $er8 A Y W A Q hL $e S A A -NH2
SP114	 Chemical Formula: $C_{85}H_{125}N_{17}O_{19}$ Exact Mass: 1687.93 Molecular Weight: 1689.00 Ac-L T F $zr8 A Y W A Q hL $z S A A -NH2
SP99	 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 A Q L $e S A A -NH2
SP388	 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 A Q L $e A A Nle A -NH2

SP331	 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
SP445	 Chemical Formula: $C_{96}H_{142}N_{20}O_{23}$ Exact Mass: 1931.06 Molecular Weight: 1932.26 Ac-L T F %r8 E Y W A Q L % A A A A A a -NH2
SP351	 Chemical Formula: $C_{96}H_{140}N_{20}O_{24}$ Exact Mass: 1957.03 Molecular Weight: 1958.26 Ac-L T F $er8 E Y W S Q Cba $e A A A A A a -NH2
SP71	 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 A A I a -NH2
SP69	 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 A A Nle A -NH2

SP7	 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 $ S A F -NH2
SP160	 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 S A A -NH2
SP315	 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 A A A A A a -NH2
SP249	 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 A Q Cba $e A A-I-a -NH2
SP437	 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 A Q L $e A A A A A a -NH2

SP349	 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 WAQCba $e AAAAA a-NH2
SP555	 Chemical Formula: $C_{95}H_{139}ClN_{20}O_{23}$ Exact Mass: 1963.69 Molecular Weight: 1964.69 Ac-LTF$er8EY6clWAQL$eAAAAAa-NH2
SP557	 Chemical Formula: $C_{104}H_{155}N_{23}O_{26}$ Exact Mass: 2142.15 Molecular Weight: 2143.48 Ac-AAALTF$er8EYWAQL$eAAAAAa-NH2
SP558	 Chemical Formula: $C_{95}H_{138}F_2N_{20}O_{23}$ Exact Mass: 1965.02 Molecular Weight: 1966.23 Ac-LTF34F2$er8EYWAQL$eAAAAAa-NH2
SP367	 5-FAM-BaLTF$er8EYWAQCba$eSAA-NH2

SP562	 Ac-LTF$er8EYWAQL$eAAibAAAa-NH2 Chemical Formula: $C_{96}H_{142}N_{20}O_{23}$ Exact Mass: 1943.06 Molecular Weight: 1944.27
SP564	 Ac-LTF$er8EYWAQL$eAAAAibAa-NH2 Chemical Formula: $C_{96}H_{142}N_{20}O_{23}$ Exact Mass: 1943.06 Molecular Weight: 1944.27
SP566	
SP567	 Ac-LTF$er8EYWAQL$eAAAAAAib-NH2 Chemical Formula: $C_{96}H_{142}N_{20}O_{23}$ Exact Mass: 1943.06 Molecular Weight: 1944.27
SP572	 Ac-LTF$er8EYWAQL$eAAAAaa-NH2 Chemical Formula: $C_{95}H_{140}N_{20}O_{23}$ Exact Mass: 1929.04 Molecular Weight: 1930.25

SP573	 Chemical Formula: $C_{95}H_{140}N_{20}O_{23}$ Exact Mass: 1929.04 Molecular Weight: 1930.25 Ac-LTF$er8EYWAQL$eAAAAAA-NH2
SP578	 Chemical Formula: $C_{95}H_{140}N_{20}O_{23}$ Exact Mass: 1929.04 Molecular Weight: 1930.25 Ac-LTF$er8EYWAQL$eAAAAASar-NH2
SP664	 Chemical Formula: $C_{95}H_{134}N_{20}O_{23}$ Exact Mass: 1922.99 Molecular Weight: 1924.20 Ac-LTF$rda6EYWAQL$da5AAAAAa-NH2
SP662	 Chemical Formula: $C_{95}H_{134}N_{20}O_{23}$ Exact Mass: 1922.99 Molecular Weight: 1924.20 Ac-LTF$rda6EYWAQL$da5AAAAAa-NH2
	 Chemical Formula: $C_{96}H_{136}N_{20}O_{23}$ Exact Mass: 1937.01 Molecular Weight: 1938.23

[00552] In some embodiments, peptidomimetic macrocycles exclude peptidomimetic macrocycles shown in Table 2a:

Table 2a

Sequence
L$r5QETFSD$s8WKLLPEN
LSQ$r5TFSDLW$s8LLPEN
LSQE$r5FSDLWK$s8LPEN
LSQET$r5SDLWKL$s8PEN
LSQETF$r5DLWKLL$s8EN
LXQETFS$r5LWKLLP$s8N
LSQETFSD$r5WKLLPE$s8
LSQQTF$r5DLWKLL$s8EN
LSQETF$r5DLWKLL$s8QN
LSQQTF$r5DLWKLL$s8QN
LSQETF$r5NLWKLL$s8QN
LSQQTF$r5NLWKLL$s8QN
LSQQTF$r5NLWRLL$s8QN
QSQQTF$r5NLWKLL$s8QN
QSQQTF$r5NLWRLL$s8QN
QSQQTA$r5NLWRLL$s8QN
L$r8QETFSD$WKLLPEN
LSQ$r8TFSDLW$LLPEN
LSQE$r8FSDLWK$LPEN
LSQET$r8SDLWKL$PEN
LSQETF$r8DLWKLL$EN
LXQETFS$r8LWKLLP$N
LSQETFSD$r8WKLLPE$
LSQQTF$r8DLWKLL$EN
LSQETF$r8DLWKLL$QN
LSQQTF$r8DLWKLL$QN
LSQETF$r8NLWKLL$QN
LSQQTF$r8NLWKLL$QN
LSQQTF$r8NLWRLL$QN
QSQQTF$r8NLWKLL$QN
QSQQTF$r8NLWRLL$QN
QSQQTA$r8NLWRLL$QN
QSQQTF$r8NLWRKK$QN
QQTF$r8DLWRLL$EN
QQTF$r8DLWRLL$

LSQQTFDLWLL
QQTFDLWLL
QQTA$r8DLWRLL$EN
QSQQTF$r5NLWRLL$s8QN (dihydroxylated olefin)
QSQQTA$r5NLWRLL$s8QN (dihydroxylated olefin)
QSQQTF$r8DLWRLL$QN
QTF$r8NLWRLL$
QSQQTFNLWLLPQN
QSQTFNLWRLLPQN
TFSLWKLL
ETFDLWLL
QTFNLWLL
SQEFSNLWKLL

[00553] 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.

[00554] In some embodiments, peptidomimetic macrocycles do not comprise a peptidomimetic macrocycle structure as shown in Table 2a.

[00555] In some embodiments, peptidomimetic macrocycles exclude those shown in Table 2b:

Table 2b

Number	Sequence	Exact Mass	M+2	Observed mass (m/e)
1	Ac-LSQETF$r8DLWKLL$EN-NH_2	2068.13	1035.07	1035.36
2	Ac-LSQETF$r8NLWKLL$QN-NH_2	2066.16	1034.08	1034.31
3	Ac-LSQQTF$r8NLWRLL$QN-NH_2	2093.18	1047.59	1047.73
4	Ac-QSQQTF$r8NLWKLL$QN-NH_2	2080.15	1041.08	1041.31
5	Ac-QSQQTF$r8NLWRLL$QN-NH_2	2108.15	1055.08	1055.32
6	Ac-QSQQTA$r8NLWRLL$QN-NH_2	2032.12	1017.06	1017.24
7	Ac-QAibQQTF$r8NLWRLL$QN-NH_2	2106.17	1054.09	1054.34
8	Ac-QSQQTFSNLWRLLPQN-NH_2	2000.02	1001.01	1001.26
9	Ac-QSQQTF$/r8NLWRLL$/QN-NH_2	2136.18	1069.09	1069.37
10	Ac-QSQAibTF$r8NLWRLL$QN-NH_2	2065.15	1033.58	1033.71
11	Ac-QSQQTF$r8NLWRLL$AN-NH_2	2051.13	1026.57	1026.70
12	Ac-ASQQTF$r8NLWRLL$QN-NH_2	2051.13	1026.57	1026.90
13	Ac-QSQQTF$r8ALWRLL$QN-NH_2	2065.15	1033.58	1033.41
14	Ac-QSQETF$r8NLWRLL$QN-NH_2	2109.14	1055.57	1055.70
15	Ac-RSQQTF$r8NLWRLL$QN-NH_2	2136.20	1069.10	1069.17
16	Ac-RSQQTF$r8NLWRLL$EN-NH_2	2137.18	1069.59	1069.75

17	Ac-LSQETFSDLWKLLPEN-NH_2	1959.99	981.00	981.24
18	Ac-QSQTFSLWRLLPQN-NH_2	2008.09	1005.05	1004.97
19	Ac-QSQQFSNWRLLPQN-NH_2	2036.06	1019.03	1018.86
20	Ac-QSQQTSNLRLLPQN-NH_2	1917.04	959.52	959.32
21	Ac-QSQQTFNLWLLPQN-NH_2	2007.06	1004.53	1004.97
22	Ac-RTQATF$r8NQWAibANle$TNAibTR-NH_2	2310.26	1156.13	1156.52
23	Ac-QSQQTF$r8NLWRLL$RN-NH_2	2136.20	1069.10	1068.94
24	Ac-QSQRTF$r8NLWRLL$QN-NH_2	2136.20	1069.10	1068.94
25	Ac-QSQQTF$r8NNleWRLL$QN-NH_2	2108.15	1055.08	1055.44
26	Ac-QSQQTF$r8NLWRNleL$QN-NH_2	2108.15	1055.08	1055.84
27	Ac-QSQQTF$r8NLWRLNle$QN-NH_2	2108.15	1055.08	1055.12
28	Ac-QSQQTY$r8NLWRLL$QN-NH_2	2124.15	1063.08	1062.92
29	Ac-RAibQQTF$r8NLWRLL$QN-NH_2	2134.22	1068.11	1068.65
30	Ac-MPRFMDYWEGLN-NH_2	1598.70	800.35	800.45
31	Ac-RSQQRF$r8NLWRLL$QN-NH_2	2191.25	1096.63	1096.83
32	Ac-QSQQRF$r8NLWRLL$QN-NH_2	2163.21	1082.61	1082.87
33	Ac-RAibQQRF$r8NLWRLL$QN-NH_2	2189.27	1095.64	1096.37
34	Ac-RSQQRF$r8NFWRLL$QN-NH_2	2225.23	1113.62	1114.37
35	Ac-RSQQRF$r8NYWRLL$QN-NH_2	2241.23	1121.62	1122.37
36	Ac-RSQQTF$r8NLWQLL$QN-NH_2	2108.15	1055.08	1055.29
37	Ac-QSQQTF$r8NLWQAmlL$QN-NH_2	2094.13	1048.07	1048.32
38	Ac-QSQQTF$r8NAmlWRLL$QN-NH_2	2122.17	1062.09	1062.35
39	Ac-NlePRF$r8DYWEGL$QN-NH_2	1869.98	935.99	936.20
40	Ac-NlePRF$r8NYWRLL$QN-NH_2	1952.12	977.06	977.35
41	Ac-RF$r8NLWRLL$Q-NH_2	1577.96	789.98	790.18
42	Ac-QSQQTF$r8N2ffWRLL$QN-NH_2	2160.13	1081.07	1081.40
43	Ac-QSQQTF$r8N3ffWRLL$QN-NH_2	2160.13	1081.07	1081.34
44	Ac-QSQQTF#r8NLWRLL#QN-NH_2	2080.12	1041.06	1041.34
45	Ac-RSQQTA$r8NLWRLL$QN-NH_2	2060.16	1031.08	1031.38
46	Ac-QSQQTF%r8NLWRLL%QN-NH_2	2110.17	1056.09	1056.55
47	HepQSQ$TFSNLWRLLPQN-$NH_2$	2051.10	1026.55	1026.82
48	HepQSQTFr8NLWRLL$QN-$NH_2$	2159.23	1080.62	1080.89
49	Ac-QSQQTF$r8NL6clWRLL$QN-NH_2	2142.11	1072.06	1072.35
50	Ac-QSQQTF$r8NLMe6clwRLL$QN-NH_2	2156.13	1079.07	1079.27
51	Ac-LTFEHYWAQLTS-NH_2	1535.74	768.87	768.91
52	Ac-LTFHYWQLTS-NH_2	1585.83	793.92	794.17
53	Ac-LTFEYWALTS-NH_2	1520.79	761.40	761.67
54	Ac-LTF$zr8HYWAQL$zS-NH_2	1597.87	799.94	800.06
55	Ac-LTF$r8HYWRQL$S-NH_2	1682.93	842.47	842.72
56	Ac-QS$QTFStNLWRLL$s8QN-NH_2	2145.21	1073.61	1073.90
57	Ac-QSQQTASNLWRLLPQN-NH_2	1923.99	963.00	963.26
58	Ac-QSQQTA$/r8NLWRLL$/QN-NH_2	2060.15	1031.08	1031.24
59	Ac-ASQQTF$/r8NLWRLL$/QN-NH_2	2079.16	1040.58	1040.89
60	Ac-SQQFSNLWRLLAibQN-NH_2	2009.09	1005.55	1005.86
61	Ac-QSQTFNLWRLLAibQN-NH_2	2023.10	1012.55	1012.79
62	Ac-QSQQFSNWRLLAibQN-NH_2	2024.06	1013.03	1013.31
63	Ac-QSQQTFNLWLLAibQN-NH_2	1995.06	998.53	998.87
64	Ac-QSQQTFSLWRLAibQN-NH_2	2011.06	1006.53	1006.83
65	Ac-QSQQTFSNLWLLAN-NH_2	1940.02	971.01	971.29

66	Ac-$/SQQ$/FSNLWRLLAibQN-NH_2	2037.12	1019.56	1019.78
67	Ac-QS$/QTF$/NLWRLLAibQN-NH_2	2051.13	1026.57	1026.90
68	Ac-QSQQ$/FSN$/WRLLAibQN-NH_2	2052.09	1027.05	1027.36
69	Ac-QSQQTF$/NLW$/LLAibQN-NH_2	2023.09	1012.55	1013.82
70	Ac-QSQTFSLWRLLAibQN-NH_2	1996.09	999.05	999.39
71	Ac-QSQ$/TFS$/LWRLLAibQN-NH_2	2024.12	1013.06	1013.37
72	Ac-QS$/QTFSt//NLWRLL$/s8QN-NH_2	2201.27	1101.64	1102.00
73	Ac-$r8SQQTFS$LWRLLAibQN-NH_2	2038.14	1020.07	1020.23
74	Ac-QSQ$r8TFSNLW$LLAibQN-NH_2	1996.08	999.04	999.32
75	Ac-QSQQTFS$r8LWRLLA$N-NH_2	2024.12	1013.06	1013.37
76	Ac-QS$r5QTFStNLW$LLAibQN-NH_2	2032.12	1017.06	1017.39
77	Ac-$/r8SQQTFS$/LWRLLAibQN-NH_2	2066.17	1034.09	1034.80
78	Ac-QSQ$/r8TFSNLW$/LLAibQN-NH_2	2024.11	1013.06	1014.34
79	Ac-QSQQTFS$/r8LWRLLA$/N-NH_2	2052.15	1027.08	1027.16
80	Ac-QS$/r5QTFSt//NLW$/LLAibQN-NH_2	2088.18	1045.09	1047.10
81	Ac-QSQQTFSNLWRLLAibQN-NH_2	1988.02	995.01	995.31
82	Hep/QSQ$/TF$/r8NLWRLL$/QN-$NH_2$	2215.29	1108.65	1108.93
83	Ac-ASQQTF$r8NLRWLL$QN-NH_2	2051.13	1026.57	1026.90
84	Ac-QSQQTF$/r8NLWRLL$/Q-NH_2	2022.14	1012.07	1012.66
85	Ac-QSQQTF$r8NLWRLL$Q-NH_2	1994.11	998.06	998.42
86	Ac-AAARAA$r8AAARAA$AA-NH_2	1515.90	758.95	759.21
87	Ac-LTFEHYWAQLTSA-NH_2	1606.78	804.39	804.59
88	Ac-LTF$r8HYWAQL$SA-NH_2	1668.90	835.45	835.67
89	Ac-ASQQTFSNLWRLLPQN-NH_2	1943.00	972.50	973.27
90	Ac-QS$QTFStNLW$r5LLAibQN-NH_2	2032.12	1017.06	1017.30
91	Ac-QSQQTFAibNLWRLLAibQN-NH_2	1986.04	994.02	994.19
92	Ac-QSQQTFNleNLWRLLNleQN-NH_2	2042.11	1022.06	1022.23
93	Ac-QSQQTF$/r8NLWRLLAibQN-$NH_2$	2082.14	1042.07	1042.23
94	Ac-QSQQTF$/r8NLWRLLNleQN-$NH_2$	2110.17	1056.09	1056.29
95	Ac-QSQQTFAibNLWRLL$/QN-$NH_2$	2040.09	1021.05	1021.25
96	Ac-QSQQTFNleNLWRLL$/QN-$NH_2$	2068.12	1035.06	1035.31
97	Ac-QSQQTF%r8NL6clWRNleL%QN-NH_2	2144.13	1073.07	1073.32
98	Ac-QSQQTF%r8NLMe6clWRLL%QN-NH_2	2158.15	1080.08	1080.31
101	Ac-FNleYWEL-NH_2	1160.63	-	1161.70
102	Ac-F$r8AYWELL$A-NH_2	1344.75	-	1345.90
103	Ac-F$r8AYWQLL$A-NH_2	1343.76	-	1344.83
104	Ac-NlePRF$r8NYWELL$QN-NH_2	1925.06	963.53	963.69
105	Ac-NlePRF$r8DYWRLL$QN-NH_2	1953.10	977.55	977.68
106	Ac-NlePRF$r8NYWRLL$Q-NH_2	1838.07	920.04	920.18
107	Ac-NlePRF$r8NYWRLL$-NH_2	1710.01	856.01	856.13
108	Ac-QSQQTF$r8DLWRLL$QN-NH_2	2109.14	1055.57	1055.64
109	Ac-QSQQTF$r8NLWRLL$EN-NH_2	2109.14	1055.57	1055.70
110	Ac-QSQQTF$r8NLWRLL$QD-NH_2	2109.14	1055.57	1055.64
111	Ac-QSQQTF$r8NLWRLL$S-NH_2	1953.08	977.54	977.60
112	Ac-ESQQTF$r8NLWRLL$QN-NH_2	2109.14	1055.57	1055.70
113	Ac-LTF$r8NLWRNleL$Q-NH_2	1635.99	819.00	819.10
114	Ac-LRF$r8NLWRNleL$Q-NH_2	1691.04	846.52	846.68
115	Ac-QSQQTF$r8NWWRNleL$QN-NH_2	2181.15	1091.58	1091.64
116	Ac-QSQQTF$r8NLWRNleL$Q-NH_2	1994.11	998.06	998.07

117	Ac-QTF$r8NLWRNleL$QN-NH_2	1765.00	883.50	883.59
118	Ac-NlePRF$r8NWWRLL$QN-NH_2	1975.13	988.57	988.75
119	Ac-NlePRF$r8NWWRLL$A-NH_2	1804.07	903.04	903.08
120	Ac-TSFAEYWNLLNH_2	1467.70	734.85	734.90
121	Ac-QTF$r8HWWSQL$S-NH_2	1651.85	826.93	827.12
122	Ac-FMYWEL-NH_2	1178.58	-	1179.64
123	Ac-QTFEHWWSQLLS-NH_2	1601.76	801.88	801.94
124	Ac-QSQQTF$r8NLAmwRLNle$QN-NH_2	2122.17	1062.09	1062.24
125	Ac-FMAibY6clWEAc3cL-NH_2	1130.47	-	1131.53
126	Ac-FNle$Y6clWE$L-NH_2	1194.59	-	1195.64
127	Ac-F$zr8AY6clWEAc3cL$z-NH_2	1277.63	639.82	1278.71
128	Ac-F$r8AY6clWEAc3cL$A-NH_2	1348.66	-	1350.72
129	Ac-NlePRF$r8NY6clWRLL$QN-NH_2	1986.08	994.04	994.64
130	Ac-AF$r8AAWALA$A-NH_2	1223.71	-	1224.71
131	Ac-TF$r8AAWRLA$Q-NH_2	1395.80	698.90	399.04
132	Pr-TF$r8AAWRLA$Q-NH_2	1409.82	705.91	706.04
133	Ac-QSQQTF%r8NLWRNleL%QN-NH_2	2110.17	1056.09	1056.22
134	Ac-LTF%r8HYWAQL%SA-NH_2	1670.92	836.46	836.58
135	Ac-NlePRF%r8NYWRLL%QN-NH_2	1954.13	978.07	978.19
136	Ac-NlePRF%r8NY6clWRLL%QN-NH_2	1988.09	995.05	995.68
137	Ac-LTF%r8HY6clWAQL%S-NH_2	1633.84	817.92	817.93
138	Ac-QS%QTF%StNLWRLL%s8QN-NH_2	2149.24	1075.62	1075.65
139	Ac-LTF%r8HY6clWRQL%S-NH_2	1718.91	860.46	860.54
140	Ac-QSQQTF%r8NL6clWRLL%QN-NH_2	2144.13	1073.07	1073.64
141	Ac-%r8SQQTFS%LWRLLAibQN-NH_2	2040.15	1021.08	1021.13
142	Ac-LTF%r8HYWAQL%S-NH_2	1599.88	800.94	801.09
143	Ac-TSF%r8QYWNLL%P-NH_2	1602.88	802.44	802.58
147	Ac-LTFEHYWAQLTS-NH_2	1535.74	768.87	769.5
152	Ac-F$er8AY6clWEAc3cL$e-NH_2	1277.63	639.82	1278.71
153	Ac-AF$r8AAWALA$A-NH_2	1277.63	639.82	1277.84
154	Ac-TF$r8AAWRLA$Q-NH_2	1395.80	698.90	699.04
155	Pr-TF$r8AAWRLA$Q-NH_2	1409.82	705.91	706.04
156	Ac-LTF$er8HYWAQL$eS-NH_2	1597.87	799.94	800.44
159	Ac-CCPGCCBaQSQQTF$r8NLWRLL$QN-NH_2	2745.30	1373.65	1372.99
160	Ac-CCPGCCBaQSQQTA$r8NLWRLL$QN-NH_2	2669.27	1335.64	1336.09
161	Ac-CCPGCCBaNlePRF$r8NYWRLL$QN-NH_2	2589.26	1295.63	1296.2
162	Ac-LTF$/r8HYWAQL$/S-NH_2	1625.90	813.95	814.18
163	Ac-F%r8HY6clWRAc3cL%-NH_2	1372.72	687.36	687.59
164	Ac-QTF%r8HWWSQL%S-NH_2	1653.87	827.94	827.94
165	Ac-LTA$r8HYWRQL$S-NH_2	1606.90	804.45	804.66
166	Ac-Q$r8QQTFSN$WRLLAibQN-NH_2	2080.12	1041.06	1041.61
167	Ac-QSQQ$r8FSNLWR$LAibQN-NH_2	2066.11	1034.06	1034.58
168	Ac-F$r8AYWEAc3cL$A-NH_2	1314.70	658.35	1315.88
169	Ac-F$r8AYWEAc3cL$S-NH_2	1330.70	666.35	1331.87
170	Ac-F$r8AYWEAc3cL$Q-NH_2	1371.72	686.86	1372.72
171	Ac-F$r8AYWEAibL$S-NH_2	1332.71	667.36	1334.83
172	Ac-F$r8AYWEAL$S-NH_2	1318.70	660.35	1319.73
173	Ac-F$r8AYWEQL$S-NH_2	1375.72	688.86	1377.53
174	Ac-F$r8HYWEQL$S-NH_2	1441.74	721.87	1443.48

175	Ac-F$r8HYWAQL$S-NH_2	1383.73	692.87	1385.38
176	Ac-F$r8HYWAAc3cL$S-NH_2	1338.71	670.36	1340.82
177	Ac-F$r8HYWRAc3cL$S-NH_2	1423.78	712.89	713.04
178	Ac-F$r8AYWEAc3cL#A-$NH_2$	1300.69	651.35	1302.78
179	Ac-NlePTF%r8NYWRLL%QN-NH_2	1899.08	950.54	950.56
180	Ac-TF$r8AAWRAL$Q-NH_2	1395.80	698.90	699.13
181	Ac-TSF%r8HYWAQL%S-NH_2	1573.83	787.92	787.98
184	Ac-F%r8AY6clWEAc3cL%A-NH_2	1350.68	676.34	676.91
185	Ac-LTF$r8HYWAQI$S-NH_2	1597.87	799.94	800.07
186	Ac-LTF$r8HYWAQNle$S-NH_2	1597.87	799.94	800.07
187	Ac-LTF$r8HYWAQL$A-NH_2	1581.87	791.94	792.45
188	Ac-LTF$r8HYWAQL$Abu-NH_2	1595.89	798.95	799.03
189	Ac-LTF$r8HYWAbuQL$S-NH_2	1611.88	806.94	807.47
190	Ac-LTF$er8AYWAQL$eS-NH_2	1531.84	766.92	766.96
191	Ac-LAF$r8HYWAQL$S-NH_2	1567.86	784.93	785.49
192	Ac-LAF$r8AYWAQL$S-NH_2	1501.83	751.92	752.01
193	Ac-LTF$er8AYWAQL$eA-NH_2	1515.85	758.93	758.97
194	Ac-LAF$r8AYWAQL$A-NH_2	1485.84	743.92	744.05
195	Ac-LTF$r8NLWANleL$Q-NH_2	1550.92	776.46	776.61
196	Ac-LTF$r8NLWANleL$A-NH_2	1493.90	747.95	1495.6
197	Ac-LTF$r8ALWANleL$Q-NH_2	1507.92	754.96	755
198	Ac-LAF$r8NLWANleL$Q-NH_2	1520.91	761.46	761.96
199	Ac-LAF$r8ALWANleL$A-NH_2	1420.89	711.45	1421.74
200	Ac-A$r8AYWEAc3cL$A-NH_2	1238.67	620.34	1239.65
201	Ac-F$r8AYWEAc3cL$AA-NH_2	1385.74	693.87	1386.64
202	Ac-F$r8AYWEAc3cL$Abu-NH_2	1328.72	665.36	1330.17
203	Ac-F$r8AYWEAc3cL$Nle-NH_2	1356.75	679.38	1358.22
204	Ac-F$r5AYWEAc3cL$s8A-NH_2	1314.70	658.35	1315.51
205	Ac-F$AYWEAc3cL$r8A-NH_2	1314.70	658.35	1315.66
206	Ac-F$r8AYWEAc3cI$A-NH_2	1314.70	658.35	1316.18
207	Ac-F$r8AYWEAc3cNle$A-NH_2	1314.70	658.35	1315.66
208	Ac-F$r8AYWEAmIL$A-NH_2	1358.76	680.38	1360.21
209	Ac-F$r8AYWENleL$A-NH_2	1344.75	673.38	1345.71
210	Ac-F$r8AYWQAc3cL$A-NH_2	1313.72	657.86	1314.7
211	Ac-F$r8AYWAAc3cL$A-NH_2	1256.70	629.35	1257.56
212	Ac-F$r8AYWAbuAc3cL$A-NH_2	1270.71	636.36	1272.14
213	Ac-F$r8AYWNleAc3cL$A-NH_2	1298.74	650.37	1299.67
214	Ac-F$r8AbuYWEAc3cL$A-NH_2	1328.72	665.36	1329.65
215	Ac-F$r8NleYWEAc3cL$A-NH_2	1356.75	679.38	1358.66
216	5-FAM-BaLTFEHYWAQLTS-NH_2	1922.82	962.41	962.87
217	5-FAM-BaLTF%r8HYWAQL%S-NH_2	1986.96	994.48	994.97
218	Ac-LTF$r8HYWAQhL$S-NH_2	1611.88	806.94	807
219	Ac-LTF$r8HYWAQTle$S-NH_2	1597.87	799.94	799.97
220	Ac-LTF$r8HYWAQAdm$S-NH_2	1675.91	838.96	839.09
221	Ac-LTF$r8HYWAQhCha$S-NH_2	1651.91	826.96	826.98
222	Ac-LTF$r8HYWAQCha$S-NH_2	1637.90	819.95	820.02
223	Ac-LTF$r8HYWAc6cQL$S-NH_2	1651.91	826.96	826.98
224	Ac-LTF$r8HYWAc5cQL$S-NH_2	1637.90	819.95	820.02
225	Ac-LThF$r8HYWAQL$S-NH_2	1611.88	806.94	807

226	Ac-LTIgl$r8HYWAQL$S-NH_2	1625.90	813.95	812.99
227	Ac-LTF$r8HYWAQChg$S-NH_2	1623.88	812.94	812.99
228	Ac-LTF$r8HYWAQF$S-NH_2	1631.85	816.93	816.99
229	Ac-LTF$r8HYWAQIgl$S-NH_2	1659.88	830.94	829.94
230	Ac-LTF$r8HYWAQCba$S-NH_2	1609.87	805.94	805.96
231	Ac-LTF$r8HYWAQCpg$S-NH_2	1609.87	805.94	805.96
232	Ac-LTF$r8HhYWAQL$S-NH_2	1611.88	806.94	807
233	Ac-F$r8AYWEAc3chL$A-NH_2	1328.72	665.36	665.43
234	Ac-F$r8AYWEAc3cTle$A-NH_2	1314.70	658.35	1315.62
235	Ac-F$r8AYWEAc3cAdm$A-NH_2	1392.75	697.38	697.47
236	Ac-F$r8AYWEAc3chCha$A-NH_2	1368.75	685.38	685.34
237	Ac-F$r8AYWEAc3cCha$A-NH_2	1354.73	678.37	678.38
238	Ac-F$r8AYWEAc6cL$A-NH_2	1356.75	679.38	679.42
239	Ac-F$r8AYWEAc5cL$A-NH_2	1342.73	672.37	672.46
240	Ac-hF$r8AYWEAc3cL$A-NH_2	1328.72	665.36	665.43
241	Ac-Igl$r8AYWEAc3cL$A-NH_2	1342.73	672.37	671.5
243	Ac-F$r8AYWEAc3cF$A-NH_2	1348.69	675.35	675.35
244	Ac-F$r8AYWEAc3cIgl$A-NH_2	1376.72	689.36	688.37
245	Ac-F$r8AYWEAc3cCba$A-NH_2	1326.70	664.35	664.47
246	Ac-F$r8AYWEAc3cCpg$A-NH_2	1326.70	664.35	664.39
247	Ac-F$r8AhYWEAc3cL$A-NH_2	1328.72	665.36	665.43
248	Ac-F$r8AYWEAc3cL$Q-NH_2	1371.72	686.86	1372.87
249	Ac-F$r8AYWEAibL$A-NH_2	1316.72	659.36	1318.18
250	Ac-F$r8AYWEAL$A-NH_2	1302.70	652.35	1303.75
251	Ac-LAF$r8AYWAAL$A-NH_2	1428.82	715.41	715.49
252	Ac-LTF$r8HYWAAc3cL$S-NH_2	1552.84	777.42	777.5
253	Ac-NleTF$r8HYWAQL$S-NH_2	1597.87	799.94	800.04
254	Ac-VTF$r8HYWAQL$S-NH_2	1583.85	792.93	793.04
255	Ac-FTF$r8HYWAQL$S-NH_2	1631.85	816.93	817.02
256	Ac-WTF$r8HYWAQL$S-NH_2	1670.86	836.43	836.85
257	Ac-RTF$r8HYWAQL$S-NH_2	1640.88	821.44	821.9
258	Ac-KTF$r8HYWAQL$S-NH_2	1612.88	807.44	807.91
259	Ac-LNleF$r8HYWAQL$S-NH_2	1609.90	805.95	806.43
260	Ac-LVF$r8HYWAQL$S-NH_2	1595.89	798.95	798.93
261	Ac-LFF$r8HYWAQL$S-NH_2	1643.89	822.95	823.38
262	Ac-LWF$r8HYWAQL$S-NH_2	1682.90	842.45	842.55
263	Ac-LRF$r8HYWAQL$S-NH_2	1652.92	827.46	827.52
264	Ac-LKF$r8HYWAQL$S-NH_2	1624.91	813.46	813.51
265	Ac-LTF$r8NleYWAQL$S-NH_2	1573.89	787.95	788.05
266	Ac-LTF$r8VYWAQL$S-NH_2	1559.88	780.94	780.98
267	Ac-LTF$r8FYWAQL$S-NH_2	1607.88	804.94	805.32
268	Ac-LTF$r8WYWAQL$S-NH_2	1646.89	824.45	824.86
269	Ac-LTF$r8RYWAQL$S-NH_2	1616.91	809.46	809.51
270	Ac-LTF$r8KYWAQL$S-NH_2	1588.90	795.45	795.48
271	Ac-LTF$r8HNleWAQL$S-NH_2	1547.89	774.95	774.98
272	Ac-LTF$r8HVWAQL$S-NH_2	1533.87	767.94	767.95
273	Ac-LTF$r8HFWAQL$S-NH_2	1581.87	791.94	792.3
274	Ac-LTF$r8HWWAQL$S-NH_2	1620.88	811.44	811.54
275	Ac-LTF$r8HRWAQL$S-NH_2	1590.90	796.45	796.52

276	Ac-LTF$r8HKWAQL$S-NH_2	1562.90	782.45	782.53
277	Ac-LTF$r8HYWNleQL$S-NH_2	1639.91	820.96	820.98
278	Ac-LTF$r8HYWVQL$S-NH_2	1625.90	813.95	814.03
279	Ac-LTF$r8HYWFQL$S-NH_2	1673.90	837.95	838.03
280	Ac-LTF$r8HYWWQL$S-NH_2	1712.91	857.46	857.5
281	Ac-LTF$r8HYWKQL$S-NH_2	1654.92	828.46	828.49
282	Ac-LTF$r8HYWANleL$S-NH_2	1582.89	792.45	792.52
283	Ac-LTF$r8HYWAVL$S-NH_2	1568.88	785.44	785.49
284	Ac-LTF$r8HYWAFL$S-NH_2	1616.88	809.44	809.47
285	Ac-LTF$r8HYWAWL$S-NH_2	1655.89	828.95	829
286	Ac-LTF$r8HYWARL$S-NH_2	1625.91	813.96	813.98
287	Ac-LTF$r8HYWAQL$Nle-NH_2	1623.92	812.96	813.39
288	Ac-LTF$r8HYWAQL$V-NH_2	1609.90	805.95	805.99
289	Ac-LTF$r8HYWAQL$F-NH_2	1657.90	829.95	830.26
290	Ac-LTF$r8HYWAQL$W-NH_2	1696.91	849.46	849.5
291	Ac-LTF$r8HYWAQL$R-NH_2	1666.94	834.47	834.56
292	Ac-LTF$r8HYWAQL$K-NH_2	1638.93	820.47	820.49
293	Ac-Q$r8QQTFSN$WRLLAibQN-NH_2	2080.12	1041.06	1041.54
294	Ac-QSQQ$r8FSNLWR$LAibQN-NH_2	2066.11	1034.06	1034.58
295	Ac-LT2Pal$r8HYWAQL$S-NH_2	1598.86	800.43	800.49
296	Ac-LT3Pal$r8HYWAQL$S-NH_2	1598.86	800.43	800.49
297	Ac-LT4Pal$r8HYWAQL$S-NH_2	1598.86	800.43	800.49
298	Ac-LTF2CF3$r8HYWAQL$S-NH_2	1665.85	833.93	834.01
299	Ac-LTF2CN$r8HYWAQL$S-NH_2	1622.86	812.43	812.47
300	Ac-LTF2Me$r8HYWAQL$S-NH_2	1611.88	806.94	807
301	Ac-LTF3Cl$r8HYWAQL$S-NH_2	1631.83	816.92	816.99
302	Ac-LTF4CF3$r8HYWAQL$S-NH_2	1665.85	833.93	833.94
303	Ac-LTF4tBu$r8HYWAQL$S-NH_2	1653.93	827.97	828.02
304	Ac-LTF5F$r8HYWAQL$S-NH_2	1687.82	844.91	844.96
305	Ac-LTF$r8HY3BthAAQL$S-NH_2	1614.83	808.42	808.48
306	Ac-LTF2Br$r8HYWAQL$S-NH_2	1675.78	838.89	838.97
307	Ac-LTF4Br$r8HYWAQL$S-NH_2	1675.78	838.89	839.86
308	Ac-LTF2Cl$r8HYWAQL$S-NH_2	1631.83	816.92	816.99
309	Ac-LTF4Cl$r8HYWAQL$S-NH_2	1631.83	816.92	817.36
310	Ac-LTF3CN$r8HYWAQL$S-NH_2	1622.86	812.43	812.47
311	Ac-LTF4CN$r8HYWAQL$S-NH_2	1622.86	812.43	812.47
312	Ac-LTF34Cl2$r8HYWAQL$S-NH_2	1665.79	833.90	833.94
313	Ac-LTF34F2$r8HYWAQL$S-NH_2	1633.85	817.93	817.95
314	Ac-LTF35F2$r8HYWAQL$S-NH_2	1633.85	817.93	817.95
315	Ac-LTDip$r8HYWAQL$S-NH_2	1673.90	837.95	838.01
316	Ac-LTF2F$r8HYWAQL$S-NH_2	1615.86	808.93	809
317	Ac-LTF3F$r8HYWAQL$S-NH_2	1615.86	808.93	809
318	Ac-LTF4F$r8HYWAQL$S-NH_2	1615.86	808.93	809
319	Ac-LTF4I$r8HYWAQL$S-NH_2	1723.76	862.88	862.94
320	Ac-LTF3Me$r8HYWAQL$S-NH_2	1611.88	806.94	807.07
321	Ac-LTF4Me$r8HYWAQL$S-NH_2	1611.88	806.94	807
322	Ac-LT1Nal$r8HYWAQL$S-NH_2	1647.88	824.94	824.98
323	Ac-LT2Nal$r8HYWAQL$S-NH_2	1647.88	824.94	825.06
324	Ac-LTF3CF3$r8HYWAQL$S-NH_2	1665.85	833.93	834.01

325	Ac-LTF4NO2$r8HYWAQL$S-NH_2	1642.85	822.43	822.46
326	Ac-LTF3NO2$r8HYWAQL$S-NH_2	1642.85	822.43	822.46
327	Ac-LTF$r82ThiYWAQL$S-NH_2	1613.83	807.92	807.96
328	Ac-LTF$r8HBipWAQL$S-NH_2	1657.90	829.95	830.01
329	Ac-LTF$r8HF4tBuWAQL$S-NH_2	1637.93	819.97	820.02
330	Ac-LTF$r8HF4CF3WAQL$S-NH_2	1649.86	825.93	826.02
331	Ac-LTF$r8HF4ClWAQL$S-NH_2	1615.83	808.92	809.37
332	Ac-LTF$r8HF4MeWAQL$S-NH_2	1595.89	798.95	799.01
333	Ac-LTF$r8HF4BrWAQL$S-NH_2	1659.78	830.89	830.98
334	Ac-LTF$r8HF4CNWAQL$S-NH_2	1606.87	804.44	804.56
335	Ac-LTF$r8HF4NO2WAQL$S-NH_2	1626.86	814.43	814.55
336	Ac-LTF$r8H1NalWAQL$S-NH_2	1631.89	816.95	817.06
337	Ac-LTF$r8H2NalWAQL$S-NH_2	1631.89	816.95	816.99
338	Ac-LTF$r8HWAQL$S-NH_2	1434.80	718.40	718.49
339	Ac-LTF$r8HY1NalAQL$S-NH_2	1608.87	805.44	805.52
340	Ac-LTF$r8HY2NalAQL$S-NH_2	1608.87	805.44	805.52
341	Ac-LTF$r8HYWAQI$S-NH_2	1597.87	799.94	800.07
342	Ac-LTF$r8HYWAQNle$S-NH_2	1597.87	799.94	800.44
343	Ac-LTF$er8HYWAQL$eA-NH_2	1581.87	791.94	791.98
344	Ac-LTF$r8HYWAQL$Abu-NH_2	1595.89	798.95	799.03
345	Ac-LTF$r8HYWAbuQL$S-NH_2	1611.88	806.94	804.47
346	Ac-LAF$r8HYWAQL$S-NH_2	1567.86	784.93	785.49
347	Ac-LTF$r8NLWANleL$Q-NH_2	1550.92	776.46	777.5
348	Ac-LTF$r8ALWANleL$Q-NH_2	1507.92	754.96	755.52
349	Ac-LAF$r8NLWANleL$Q-NH_2	1520.91	761.46	762.48
350	Ac-F$r8AYWAAc3cL$A-NH_2	1256.70	629.35	1257.56
351	Ac-LTF$r8AYWAAL$S-NH_2	1474.82	738.41	738.55
352	Ac-LVF$r8AYWAQL$S-NH_2	1529.87	765.94	766
353	Ac-LTF$r8AYWAbuQL$S-NH_2	1545.86	773.93	773.92
354	Ac-LTF$r8AYWNleQL$S-NH_2	1573.89	787.95	788.17
355	Ac-LTF$r8AbuYWAQL$S-NH_2	1545.86	773.93	773.99
356	Ac-LTF$r8AYWHQL$S-NH_2	1597.87	799.94	799.97
357	Ac-LTF$r8AYWKQL$S-NH_2	1588.90	795.45	795.53
358	Ac-LTF$r8AYWOQL$S-NH_2	1574.89	788.45	788.5
359	Ac-LTF$r8AYWRQL$S-NH_2	1616.91	809.46	809.51
360	Ac-LTF$r8AYWSQL$S-NH_2	1547.84	774.92	774.96
361	Ac-LTF$r8AYWRAL$S-NH_2	1559.89	780.95	780.95
362	Ac-LTF$r8AYWRQL$A-NH_2	1600.91	801.46	801.52
363	Ac-LTF$r8AYWRAL$A-NH_2	1543.89	772.95	773.03
364	Ac-LTF$r5HYWAQL$s8S-NH_2	1597.87	799.94	799.97
365	Ac-LTF$HYWAQL$r8S-NH_2	1597.87	799.94	799.97
366	Ac-LTF$r8HYWAAL$S-NH_2	1540.84	771.42	771.48
367	Ac-LTF$r8HYWAAbuL$S-NH_2	1554.86	778.43	778.51
368	Ac-LTF$r8HYWALL$S-NH_2	1582.89	792.45	792.49
369	Ac-F$r8AYWHAL$A-NH_2	1310.72	656.36	656.4
370	Ac-F$r8AYWAAL$A-NH_2	1244.70	623.35	1245.61
371	Ac-F$r8AYWSAL$A-NH_2	1260.69	631.35	1261.6
372	Ac-F$r8AYWRAL$A-NH_2	1329.76	665.88	1330.72
373	Ac-F$r8AYWKAL$A-NH_2	1301.75	651.88	1302.67

374	Ac-F$r8AYWOAL$A-NH_2	1287.74	644.87	1289.13
375	Ac-F$r8VYWEAc3cL$A-NH_2	1342.73	672.37	1343.67
376	Ac-F$r8FYWEAc3cL$A-NH_2	1390.73	696.37	1392.14
377	Ac-F$r8WYWEAc3cL$A-NH_2	1429.74	715.87	1431.44
378	Ac-F$r8RYWEAc3cL$A-NH_2	1399.77	700.89	700.95
379	Ac-F$r8KYWEAc3cL$A-NH_2	1371.76	686.88	686.97
380	Ac-F$r8ANleWEAc3cL$A-NH_2	1264.72	633.36	1265.59
381	Ac-F$r8AVWEAc3cL$A-NH_2	1250.71	626.36	1252.2
382	Ac-F$r8AFWEAc3cL$A-NH_2	1298.71	650.36	1299.64
383	Ac-F$r8AWWEAc3cL$A-NH_2	1337.72	669.86	1338.64
384	Ac-F$r8ARWEAc3cL$A-NH_2	1307.74	654.87	655
385	Ac-F$r8AKWEAc3cL$A-NH_2	1279.73	640.87	641.01
386	Ac-F$r8AYWVAc3cL$A-NH_2	1284.73	643.37	643.38
387	Ac-F$r8AYWFAc3cL$A-NH_2	1332.73	667.37	667.43
388	Ac-F$r8AYWWAc3cL$A-NH_2	1371.74	686.87	686.97
389	Ac-F$r8AYWRAc3cL$A-NH_2	1341.76	671.88	671.94
390	Ac-F$r8AYWKAc3cL$A-NH_2	1313.75	657.88	657.88
391	Ac-F$r8AYWEVL$A-NH_2	1330.73	666.37	666.47
392	Ac-F$r8AYWEFL$A-NH_2	1378.73	690.37	690.44
393	Ac-F$r8AYWEWL$A-NH_2	1417.74	709.87	709.91
394	Ac-F$r8AYWERL$A-NH_2	1387.77	694.89	1388.66
395	Ac-F$r8AYWEKL$A-NH_2	1359.76	680.88	1361.21
396	Ac-F$r8AYWEAc3cL$V-NH_2	1342.73	672.37	1343.59
397	Ac-F$r8AYWEAc3cL$F-NH_2	1390.73	696.37	1392.58
398	Ac-F$r8AYWEAc3cL$W-NH_2	1429.74	715.87	1431.29
399	Ac-F$r8AYWEAc3cL$R-NH_2	1399.77	700.89	700.95
400	Ac-F$r8AYWEAc3cL$K-NH_2	1371.76	686.88	686.97
401	Ac-F$r8AYWEAc3cL$AV-NH_2	1413.77	707.89	707.91
402	Ac-F$r8AYWEAc3cL$AF-NH_2	1461.77	731.89	731.96
403	Ac-F$r8AYWEAc3cL$AW-NH_2	1500.78	751.39	751.5
404	Ac-F$r8AYWEAc3cL$AR-NH_2	1470.80	736.40	736.47
405	Ac-F$r8AYWEAc3cL$AK-NH_2	1442.80	722.40	722.41
406	Ac-F$r8AYWEAc3cL$AH-NH_2	1451.76	726.88	726.93
407	Ac-LTF2NO2$r8HYWAQL$S-NH_2	1642.85	822.43	822.54
408	Ac-LTA$r8HYAAQL$S-NH_2	1406.79	704.40	704.5
409	Ac-LTF$r8HYAAQL$S-NH_2	1482.82	742.41	742.47
410	Ac-QSQQTF$r8NLWALL$AN-NH_2	1966.07	984.04	984.38
411	Ac-QAibQQTF$r8NLWALL$AN-NH_2	1964.09	983.05	983.42
412	Ac-QAibQQTF$r8ALWALL$AN-NH_2	1921.08	961.54	961.59
413	Ac-AAAATF$r8AAWAAL$AA-NH_2	1608.90	805.45	805.52
414	Ac-F$r8AAWRAL$Q-NH_2	1294.76	648.38	648.48
415	Ac-TF$r8AAWAAL$Q-NH_2	1310.74	656.37	1311.62
416	Ac-TF$r8AAWRAL$A-NH_2	1338.78	670.39	670.46
417	Ac-VF$r8AAWRAL$Q-NH_2	1393.82	697.91	697.99
418	Ac-AF$r8AAWAAL$A-NH_2	1223.71	612.86	1224.67
420	Ac-TF$r8AAWKAL$Q-NH_2	1367.80	684.90	684.97
421	Ac-TF$r8AAWOAL$Q-NH_2	1353.78	677.89	678.01
422	Ac-TF$r8AAWSAL$Q-NH_2	1326.73	664.37	664.47
423	Ac-LTF$r8AAWRAL$Q-NH_2	1508.89	755.45	755.49

424	Ac-F$r8AYWAQL$A-NH_2	1301.72	651.86	651.96
425	Ac-F$r8AWWAAL$A-NH_2	1267.71	634.86	634.87
426	Ac-F$r8AWWAQL$A-NH_2	1324.73	663.37	663.43
427	Ac-F$r8AYWEAL$-NH_2	1231.66	616.83	1232.93
428	Ac-F$r8AYWAAL$-NH_2	1173.66	587.83	1175.09
429	Ac-F$r8AYWKAL$-NH_2	1230.72	616.36	616.44
430	Ac-F$r8AYWOAL$-NH_2	1216.70	609.35	609.48
431	Ac-F$r8AYWQAL$-NH_2	1230.68	616.34	616.44
432	Ac-F$r8AYWAQL$-NH_2	1230.68	616.34	616.37
433	Ac-F$r8HYWDQL$S-NH_2	1427.72	714.86	714.86
434	Ac-F$r8HFWEQL$S-NH_2	1425.74	713.87	713.98
435	Ac-F$r8AYWHQL$S-NH_2	1383.73	692.87	692.96
436	Ac-F$r8AYWKQL$S-NH_2	1374.77	688.39	688.45
437	Ac-F$r8AYWOQL$S-NH_2	1360.75	681.38	681.49
438	Ac-F$r8HYWSQL$S-NH_2	1399.73	700.87	700.95
439	Ac-F$r8HWWEQL$S-NH_2	1464.76	733.38	733.44
440	Ac-F$r8HWWAQL$S-NH_2	1406.75	704.38	704.43
441	Ac-F$r8AWWHQL$S-NH_2	1406.75	704.38	704.43
442	Ac-F$r8AWWKQL$S-NH_2	1397.79	699.90	699.92
443	Ac-F$r8AWWOQL$S-NH_2	1383.77	692.89	692.96
444	Ac-F$r8HWWSQL$S-NH_2	1422.75	712.38	712.42
445	Ac-LTF$r8NYWANleL$Q-NH_2	1600.90	801.45	801.52
446	Ac-LTF$r8NLWAQL$Q-NH_2	1565.90	783.95	784.06
447	Ac-LTF$r8NYWANleL$A-NH_2	1543.88	772.94	773.03
448	Ac-LTF$r8NLWAQL$A-NH_2	1508.88	755.44	755.49
449	Ac-LTF$r8AYWANleL$Q-NH_2	1557.90	779.95	780.06
450	Ac-LTF$r8ALWAQL$Q-NH_2	1522.89	762.45	762.45
451	Ac-LAF$r8NYWANleL$Q-NH_2	1570.89	786.45	786.5
452	Ac-LAF$r8NLWAQL$Q-NH_2	1535.89	768.95	769.03
453	Ac-LAF$r8AYWANleL$A-NH_2	1470.86	736.43	736.47
454	Ac-LAF$r8ALWAQL$A-NH_2	1435.86	718.93	719.01
455	Ac-LAF$r8AYWAAL$A-NH_2	1428.82	715.41	715.41
456	Ac-F$r8AYWEAc3cL$AAib-NH_2	1399.75	700.88	700.95
457	Ac-F$r8AYWAQL$AA-NH_2	1372.75	687.38	687.78
458	Ac-F$r8AYWAAc3cL$AA-NH_2	1327.73	664.87	664.84
459	Ac-F$r8AYWSAc3cL$AA-NH_2	1343.73	672.87	672.9
460	Ac-F$r8AYWEAc3cL$AS-NH_2	1401.73	701.87	701.84
461	Ac-F$r8AYWEAc3cL$AT-NH_2	1415.75	708.88	708.87
462	Ac-F$r8AYWEAc3cL$AL-NH_2	1427.79	714.90	714.94
463	Ac-F$r8AYWEAc3cL$AQ-NH_2	1442.76	722.38	722.41
464	Ac-F$r8AFWEAc3cL$AA-NH_2	1369.74	685.87	685.93
465	Ac-F$r8AWWEAc3cL$AA-NH_2	1408.75	705.38	705.39
466	Ac-F$r8AYWEAc3cL$SA-NH_2	1401.73	701.87	701.99
467	Ac-F$r8AYWEAL$AA-NH_2	1373.74	687.87	687.93
468	Ac-F$r8AYWENleL$AA-NH_2	1415.79	708.90	708.94
469	Ac-F$r8AYWEAc3cL$AbuA-NH_2	1399.75	700.88	700.95
470	Ac-F$r8AYWEAc3cL$NleA-NH_2	1427.79	714.90	714.86
471	Ac-F$r8AYWEAibL$NleA-NH_2	1429.80	715.90	715.97
472	Ac-F$r8AYWEAL$NleA-NH_2	1415.79	708.90	708.94

473	Ac-F$r8AYWENleL$NleA-NH_2	1457.83	729.92	729.96
474	Ac-F$r8AYWEAibL$Abu-NH_2	1330.73	666.37	666.39
475	Ac-F$r8AYWENleL$Abu-NH_2	1358.76	680.38	680.39
476	Ac-F$r8AYWEAL$Abu-NH_2	1316.72	659.36	659.36
477	Ac-LTF$r8AFWAQL$S-NH_2	1515.85	758.93	759.12
478	Ac-LTF$r8AWWAQL$S-NH_2	1554.86	778.43	778.51
479	Ac-LTF$r8AYWAQI$S-NH_2	1531.84	766.92	766.96
480	Ac-LTF$r8AYWAQNle$S-NH_2	1531.84	766.92	766.96
481	Ac-LTF$r8AYWAQL$SA-NH_2	1602.88	802.44	802.48
482	Ac-LTF$r8AWWAQL$A-NH_2	1538.87	770.44	770.89
483	Ac-LTF$r8AYWAQI$A-NH_2	1515.85	758.93	759.42
484	Ac-LTF$r8AYWAQNle$A-NH_2	1515.85	758.93	759.42
485	Ac-LTF$r8AYWAQL$AA-NH_2	1586.89	794.45	794.94
486	Ac-LTF$r8HWWAQL$S-NH_2	1620.88	811.44	811.47
487	Ac-LTF$r8HRWAQL$S-NH_2	1590.90	796.45	796.52
488	Ac-LTF$r8HKWAQL$S-NH_2	1562.90	782.45	782.53
489	Ac-LTF$r8HYWAQL$W-NH_2	1696.91	849.46	849.5
491	Ac-F$r8AYWAbuAL$A-NH_2	1258.71	630.36	630.5
492	Ac-F$r8AbuYWEAL$A-NH_2	1316.72	659.36	659.51
493	Ac-NlePRF%r8NYWRLL%QN-NH_2	1954.13	978.07	978.54
494	Ac-TSF%r8HYWAQL%S-NH_2	1573.83	787.92	787.98
495	Ac-LTF%r8AYWAQL%S-NH_2	1533.86	767.93	768
496	Ac-HTF$r8HYWAQL$S-NH_2	1621.84	811.92	811.96
497	Ac-LHF$r8HYWAQL$S-NH_2	1633.88	817.94	818.02
498	Ac-LTF$r8HHWAQL$S-NH_2	1571.86	786.93	786.94
499	Ac-LTF$r8HYWHQL$S-NH_2	1663.89	832.95	832.38
500	Ac-LTF$r8HYWAHL$S-NH_2	1606.87	804.44	804.48
501	Ac-LTF$r8HYWAQL$H-NH_2	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-NH_2	1547.80	774.90	774.96
509	Ac-STF$r8AYWAQL$S-NH_2	1505.79	753.90	753.94
510	Ac-LEF$r8AYWAQL$S-NH_2	1559.84	780.92	781.25
511	Ac-LSF$r8AYWAQL$S-NH_2	1517.83	759.92	759.93
512	Ac-LTF$r8EYWAQL$S-NH_2	1589.85	795.93	795.97
513	Ac-LTF$r8SYWAQL$S-NH_2	1547.84	774.92	774.96
514	Ac-LTF$r8AYWEQL$S-NH_2	1589.85	795.93	795.9
515	Ac-LTF$r8AYWAEL$S-NH_2	1532.83	767.42	766.96
516	Ac-LTF$r8AYWASL$S-NH_2	1490.82	746.41	746.46
517	Ac-LTF$r8AYWAQL$E-NH_2	1573.85	787.93	787.98
518	Ac-LTF2CN$r8HYWAQL$S-NH_2	1622.86	812.43	812.47
519	Ac-LTF3Cl$r8HYWAQL$S-NH_2	1631.83	816.92	816.99
520	Ac-LTDip$r8HYWAQL$S-NH_2	1673.90	837.95	838.01
521	Ac-LTF$r8HYWAQTle$S-NH_2	1597.87	799.94	800.04
522	Ac-F$r8AY6clWEAL$A-NH_2	1336.66	669.33	1338.56

523	Ac-F$r8AYdl6brWEAL$A-NH_2	1380.61	691.31	692.2
524	Ac-F$r8AYdl6fWEAL$A-NH_2	1320.69	661.35	1321.61
525	Ac-F$r8AYdl4mWEAL$A-NH_2	1316.72	659.36	659.36
526	Ac-F$r8AYdl5clWEAL$A-NH_2	1336.66	669.33	669.35
527	Ac-F$r8AYdl7mWEAL$A-NH_2	1316.72	659.36	659.36
528	Ac-LTF%r8HYWAQL%A-NH_2	1583.89	792.95	793.01
529	Ac-LTF$r8HCouWAQL$S-NH_2	1679.87	840.94	841.38
530	Ac-LTFEHCouWAQLTS-NH_2	1617.75	809.88	809.96
531	Ac-LTA$r8HCouWAQL$S-NH_2	1603.84	802.92	803.36
532	Ac-F$r8AYWEAL$AbuA-NH_2	1387.75	694.88	694.88
533	Ac-F$r8AYWEAl$AA-NH_2	1373.74	687.87	687.93
534	Ac-F$r8AYWEANle$AA-NH_2	1373.74	687.87	687.93
535	Ac-F$r8AYWEAmIL$AA-NH_2	1429.80	715.90	715.97
536	Ac-F$r8AYWQAL$AA-NH_2	1372.75	687.38	687.48
537	Ac-F$r8AYWAAL$AA-NH_2	1315.73	658.87	658.92
538	Ac-F$r8AYWAbuAL$AA-NH_2	1329.75	665.88	665.95
539	Ac-F$r8AYWNleAL$AA-NH_2	1357.78	679.89	679.94
540	Ac-F$r8AbuYWEAL$AA-NH_2	1387.75	694.88	694.96
541	Ac-F$r8NleYWEAL$AA-NH_2	1415.79	708.90	708.94
542	Ac-F$r8FYWEAL$AA-NH_2	1449.77	725.89	725.97
543	Ac-LTF$r8HYWAQhL$S-NH_2	1611.88	806.94	807
544	Ac-LTF$r8HYWAQAdm$S-NH_2	1675.91	838.96	839.04
545	Ac-LTF$r8HYWAQIgl$S-NH_2	1659.88	830.94	829.94
546	Ac-F$r8AYWAQL$AA-NH_2	1372.75	687.38	687.48
547	Ac-LTF$r8ALWAQL$Q-NH_2	1522.89	762.45	762.52
548	Ac-F$r8AYWEAL$AA-NH_2	1373.74	687.87	687.93
549	Ac-F$r8AYWENleL$AA-NH_2	1415.79	708.90	708.94
550	Ac-F$r8AYWEAibL$Abu-NH_2	1330.73	666.37	666.39
551	Ac-F$r8AYWENleL$Abu-NH_2	1358.76	680.38	680.38
552	Ac-F$r8AYWEAL$Abu-NH_2	1316.72	659.36	659.36
553	Ac-F$r8AYWEAc3cL$AbuA-NH_2	1399.75	700.88	700.95
554	Ac-F$r8AYWEAc3cL$NleA-NH_2	1427.79	714.90	715.01
555	H-LTF$r8AYWAQL$S-NH_2	1489.83	745.92	745.95
556	mdPEG3-LTF$r8AYWAQL$S-NH_2	1679.92	840.96	840.97
557	mdPEG7-LTF$r8AYWAQL$S-NH_2	1856.02	929.01	929.03
558	Ac-F$r8ApmpEt6clWEAL$A-NH_2	1470.71	736.36	788.17
559	Ac-LTF3Cl$r8AYWAQL$S-NH_2	1565.81	783.91	809.18
560	Ac-LTF3Cl$r8HYWAQL$A-NH_2	1615.83	808.92	875.24
561	Ac-LTF3Cl$r8HYWWQL$S-NH_2	1746.87	874.44	841.65
562	Ac-LTF3Cl$r8AYWWQL$S-NH_2	1680.85	841.43	824.63
563	Ac-LTF$r8AYWWQL$S-NH_2	1646.89	824.45	849.98
564	Ac-LTF$r8HYWWQL$A-NH_2	1696.91	849.46	816.67
565	Ac-LTF$r8AYWWQL$A-NH_2	1630.89	816.45	776.15
566	Ac-LTF4F$r8AYWAQL$S-NH_2	1549.83	775.92	776.15
567	Ac-LTF2F$r8AYWAQL$S-NH_2	1549.83	775.92	776.15
568	Ac-LTF3F$r8AYWAQL$S-NH_2	1549.83	775.92	785.12
569	Ac-LTF34F2$r8AYWAQL$S-NH_2	1567.83	784.92	785.12
570	Ac-LTF35F2$r8AYWAQL$S-NH_2	1567.83	784.92	1338.74
571	Ac-F3Cl$r8AYWEAL$A-NH_2	1336.66	669.33	705.28

572	Ac-F3Cl$r8AYWEAL$AA-NH_2	1407.70	704.85	680.11
573	Ac-F$r8AY6clWEAL$AA-NH_2	1407.70	704.85	736.83
574	Ac-F$r8AY6clWEAL$-NH_2	1265.63	633.82	784.1
575	Ac-LTF$r8HYWAQLSt/S-$NH_2$	16.03	9.02	826.98
576	Ac-LTF$r8HYWAQL$S-NHsBu	1653.93	827.97	828.02
577	Ac-STF$r8AYWAQL$S-NH_2	1505.79	753.90	753.94
578	Ac-LTF$r8AYWAEL$S-NH_2	1532.83	767.42	767.41
579	Ac-LTF$r8AYWAQL$E-NH_2	1573.85	787.93	787.98
580	mdPEG3-LTF$r8AYWAQL$S-NH_2	1679.92	840.96	840.97
581	Ac-LTF$r8AYWAQhL$S-NH_2	1545.86	773.93	774.31
583	Ac-LTF$r8AYWAQCha$S-NH_2	1571.88	786.94	787.3
584	Ac-LTF$r8AYWAQChg$S-NH_2	1557.86	779.93	780.4
585	Ac-LTF$r8AYWAQCba$S-NH_2	1543.84	772.92	780.13
586	Ac-LTF$r8AYWAQF$S-NH_2	1565.83	783.92	784.2
587	Ac-LTF4F$r8HYWAQhL$S-NH_2	1629.87	815.94	815.36
588	Ac-LTF4F$r8HYWAQCha$S-NH_2	1655.89	828.95	828.39
589	Ac-LTF4F$r8HYWAQChg$S-NH_2	1641.87	821.94	821.35
590	Ac-LTF4F$r8HYWAQCba$S-NH_2	1627.86	814.93	814.32
591	Ac-LTF4F$r8AYWAQhL$S-NH_2	1563.85	782.93	782.36
592	Ac-LTF4F$r8AYWAQCha$S-NH_2	1589.87	795.94	795.38
593	Ac-LTF4F$r8AYWAQChg$S-NH_2	1575.85	788.93	788.35
594	Ac-LTF4F$r8AYWAQCba$S-NH_2	1561.83	781.92	781.39
595	Ac-LTF3Cl$r8AYWAQhL$S-NH_2	1579.82	790.91	790.35
596	Ac-LTF3Cl$r8AYWAQCha$S-NH_2	1605.84	803.92	803.67
597	Ac-LTF3Cl$r8AYWAQChg$S-NH_2	1591.82	796.91	796.34
598	Ac-LTF3Cl$r8AYWAQCba$S-NH_2	1577.81	789.91	789.39
599	Ac-LTF$r8AYWAQhF$S-NH_2	1579.84	790.92	791.14
600	Ac-LTF$r8AYWAQF3CF3$S-NH_2	1633.82	817.91	818.15
601	Ac-LTF$r8AYWAQF3Me$S-NH_2	1581.86	791.93	791.32
602	Ac-LTF$r8AYWAQ1Nal$S-NH_2	1615.84	808.92	809.18
603	Ac-LTF$r8AYWAQBip$S-NH_2	1641.86	821.93	822.13
604	Ac-LTF$r8FYWAQL$A-NH_2	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-NH_2	1316.72	659.36	659.44
617	Ac-F$r8AYdl5clWEAL$A-NH_2	1336.66	669.33	669.43
618	Ac-LThF$r8AYWAQL$S-NH_2	1545.86	773.93	774.11
619	Ac-LT2Nal$r8AYWAQL$S-NH_2	1581.86	791.93	792.43
620	Ac-LTA$r8AYWAQL$S-NH_2	1455.81	728.91	729.15
621	Ac-LTF$r8AYWVQL$S-NH_2	1559.88	780.94	781.24
622	Ac-LTF$r8HYWAAL$A-NH_2	1524.85	763.43	763.86

623	Ac-LTF$r8VYWAQL$A-NH_2	1543.88	772.94	773.37
624	Ac-LTF$r8IYWAQL$S-NH_2	1573.89	787.95	788.17
625	Ac-FTF$r8VYWSQL$S-NH_2	1609.85	805.93	806.22
626	Ac-ITF$r8FYWAQL$S-NH_2	1607.88	804.94	805.2
627	Ac-2NalTF$r8VYWSQL$S-NH_2	1659.87	830.94	831.2
628	Ac-ITF$r8LYWSQL$S-NH_2	1589.89	795.95	796.13
629	Ac-FTF$r8FYWAQL$S-NH_2	1641.86	821.93	822.13
630	Ac-WTF$r8VYWAQL$S-NH_2	1632.87	817.44	817.69
631	Ac-WTF$r8WYWAQL$S-NH_2	1719.88	860.94	861.36
632	Ac-VTF$r8AYWSQL$S-NH_2	1533.82	767.91	768.19
633	Ac-WTF$r8FYWSQL$S-NH_2	1696.87	849.44	849.7
634	Ac-FTF$r8IYWAQL$S-NH_2	1607.88	804.94	805.2
635	Ac-WTF$r8VYWSQL$S-NH_2	1648.87	825.44	824.8
636	Ac-FTF$r8LYWSQL$S-NH_2	1623.87	812.94	812.8
637	Ac-YTF$r8FYWSQL$S-NH_2	1673.85	837.93	837.8
638	Ac-LTF$r8AY6clWEAL$A-NH_2	1550.79	776.40	776.14
639	Ac-LTF$r8AY6clWSQL$S-NH_2	1581.80	791.90	791.68
640	Ac-F$r8AY6clWSAL$A-NH_2	1294.65	648.33	647.67
641	Ac-F$r8AY6clWQAL$AA-NH_2	1406.72	704.36	703.84
642	Ac-LHF$r8AYWAQL$S-NH_2	1567.86	784.93	785.21
643	Ac-LTF$r8AYWAQL$S-NH_2	1531.84	766.92	767.17
644	Ac-LTF$r8AHWAQL$S-NH_2	1505.84	753.92	754.13
645	Ac-LTF$r8AYWAHL$S-NH_2	1540.84	771.42	771.61
646	Ac-LTF$r8AYWAQL$H-NH_2	1581.87	791.94	792.15
647	H-LTF$r8AYWAQL$A-NH_2	1473.84	737.92	737.29
648	Ac-HHF$r8AYWAQL$S-NH_2	1591.83	796.92	797.35
649	Ac-aAibWTF$r8VYWSQL$S-NH_2	1804.96	903.48	903.64
650	Ac-AibWTF$r8HYWAQL$S-NH_2	1755.91	878.96	879.4
651	Ac-AibAWTF$r8HYWAQL$S-NH_2	1826.95	914.48	914.7
652	Ac-fWTF$r8HYWAQL$S-NH_2	1817.93	909.97	910.1
653	Ac-AibWWTF$r8HYWAQL$S-NH_2	1941.99	972.00	972.2
654	Ac-WTF$r8LYWSQL$S-NH_2	1662.88	832.44	832.8
655	Ac-WTF$r8NleYWSQL$S-NH_2	1662.88	832.44	832.6
656	Ac-LTF$r8AYWSQL$a-NH_2	1531.84	766.92	767.2
657	Ac-LTF$r8EYWARL$A-NH_2	1601.90	801.95	802.1
658	Ac-LTF$r8EYWAHL$A-NH_2	1582.86	792.43	792.6
659	Ac-aTF$r8AYWAQL$S-NH_2	1489.80	745.90	746.08
660	Ac-AibTF$r8AYWAQL$S-NH_2	1503.81	752.91	753.11
661	Ac-AmfTF$r8AYWAQL$S-NH_2	1579.84	790.92	791.14
662	Ac-AmwTF$r8AYWAQL$S-NH_2	1618.86	810.43	810.66
663	Ac-NmLTF$r8AYWAQL$S-NH_2	1545.86	773.93	774.11
664	Ac-LNmTF$r8AYWAQL$S-NH_2	1545.86	773.93	774.11
665	Ac-LSarF$r8AYWAQL$S-NH_2	1501.83	751.92	752.18
667	Ac-LGF$r8AYWAQL$S-NH_2	1487.82	744.91	745.15
668	Ac-LTNmF$r8AYWAQL$S-NH_2	1545.86	773.93	774.2
669	Ac-TF$r8AYWAQL$S-NH_2	1418.76	710.38	710.64
670	Ac-ETF$r8AYWAQL$A-NH_2	1531.81	766.91	767.2
671	Ac-LTF$r8EYWAQL$A-NH_2	1573.85	787.93	788.1
672	Ac-LT2Nal$r8AYWSQL$S-NH_2	1597.85	799.93	800.4

673	Ac-LTF$r8AYWAAL$S-NH_2	1474.82	738.41	738.68
674	Ac-LTF$r8AYWAQhCha$S-NH_2	1585.89	793.95	794.19
675	Ac-LTF$r8AYWAQChg$S-NH_2	1557.86	779.93	780.97
676	Ac-LTF$r8AYWAQCba$S-NH_2	1543.84	772.92	773.19
677	Ac-LTF$r8AYWAQF3CF3$S-NH_2	1633.82	817.91	818.15
678	Ac-LTF$r8AYWAQ1Nal$S-NH_2	1615.84	808.92	809.18
679	Ac-LTF$r8AYWAQBip$S-NH_2	1641.86	821.93	822.32
680	Ac-LT2Nal$r8AYWAQL$S-NH_2	1581.86	791.93	792.15
681	Ac-LTF$r8AYWVQL$S-NH_2	1559.88	780.94	781.62
682	Ac-LTF$r8AWWAQL$S-NH_2	1554.86	778.43	778.65
683	Ac-FTF$r8VYWSQL$S-NH_2	1609.85	805.93	806.12
684	Ac-ITF$r8FYWAQL$S-NH_2	1607.88	804.94	805.2
685	Ac-ITF$r8LYWSQL$S-NH_2	1589.89	795.95	796.22
686	Ac-FTF$r8FYWAQL$S-NH_2	1641.86	821.93	822.41
687	Ac-VTF$r8AYWSQL$S-NH_2	1533.82	767.91	768.19
688	Ac-LTF$r8AHWAQL$S-NH_2	1505.84	753.92	754.31
689	Ac-LTF$r8AYWAQL$H-NH_2	1581.87	791.94	791.94
690	Ac-LTF$r8AYWAHL$S-NH_2	1540.84	771.42	771.61
691	Ac-aAibWTF$r8VYWSQL$S-NH_2	1804.96	903.48	903.9
692	Ac-AibWTF$r8HYWAQL$S-NH_2	1755.91	878.96	879.5
693	Ac-AibAWTF$r8HYWAQL$S-NH_2	1826.95	914.48	914.7
694	Ac-fWTF$r8HYWAQL$S-NH_2	1817.93	909.97	910.2
695	Ac-AibWWTF$r8HYWAQL$S-NH_2	1941.99	972.00	972.7
696	Ac-WTF$r8LYWSQL$S-NH_2	1662.88	832.44	832.7
697	Ac-WTF$r8NleYWSQL$S-NH_2	1662.88	832.44	832.7
698	Ac-LTF$r8AYWSQL$a-NH_2	1531.84	766.92	767.2
699	Ac-LTF$r8EYWARL$A-NH_2	1601.90	801.95	802.2
700	Ac-LTF$r8EYWAHL$A-NH_2	1582.86	792.43	792.6
701	Ac-aTF$r8AYWAQL$S-NH_2	1489.80	745.90	746.1
702	Ac-AibTF$r8AYWAQL$S-NH_2	1503.81	752.91	753.2
703	Ac-AmfTF$r8AYWAQL$S-NH_2	1579.84	790.92	791.2
704	Ac-AmwTF$r8AYWAQL$S-NH_2	1618.86	810.43	810.7
705	Ac-NmLTF$r8AYWAQL$S-NH_2	1545.86	773.93	774.1
706	Ac-LNmTF$r8AYWAQL$S-NH_2	1545.86	773.93	774.4
707	Ac-LSarF$r8AYWAQL$S-NH_2	1501.83	751.92	752.1
708	Ac-TF$r8AYWAQL$S-NH_2	1418.76	710.38	710.8
709	Ac-ETF$r8AYWAQL$A-NH_2	1531.81	766.91	767.4
710	Ac-LTF$r8EYWAQL$A-NH_2	1573.85	787.93	788.2
711	Ac-WTF$r8VYWSQL$S-NH_2	1648.87	825.44	825.2
713	Ac-YTF$r8FYWSQL$S-NH_2	1673.85	837.93	837.3
714	Ac-F$r8AY6clWSAL$A-NH_2	1294.65	648.33	647.74
715	Ac-ETF$r8EYWVQL$S-NH_2	1633.84	817.92	817.36
716	Ac-ETF$r8EHWAQL$A-NH_2	1563.81	782.91	782.36
717	Ac-ITF$r8EYWAQL$S-NH_2	1589.85	795.93	795.38
718	Ac-ITF$r8EHWVQL$A-NH_2	1575.88	788.94	788.42
719	Ac-ITF$r8EHWAQL$S-NH_2	1563.85	782.93	782.43
720	Ac-LTF4F$r8AYWAQCba$S-NH_2	1561.83	781.92	781.32
721	Ac-LTF3Cl$r8AYWAQhL$S-NH_2	1579.82	790.91	790.64
722	Ac-LTF3Cl$r8AYWAQCha$S-NH_2	1605.84	803.92	803.37

723	Ac-LTF3Cl$r8AYWAQChg$S-NH_2	1591.82	796.91	796.27
724	Ac-LTF3Cl$r8AYWAQCba$S-NH_2	1577.81	789.91	789.83
725	Ac-LTF$r8AY6clWSQL$S-NH_2	1581.80	791.90	791.75
726	Ac-LTF4F$r8HYWAQhL$S-NH_2	1629.87	815.94	815.36
727	Ac-LTF4F$r8HYWAQCba$S-NH_2	1627.86	814.93	814.32
728	Ac-LTF4F$r8AYWAQhL$S-NH_2	1563.85	782.93	782.36
729	Ac-LTF4F$r8AYWAQChg$S-NH_2	1575.85	788.93	788.35
730	Ac-ETF$r8EYWVAL$S-NH_2	1576.82	789.41	788.79
731	Ac-ETF$r8EHWAAL$A-NH_2	1506.79	754.40	754.8
732	Ac-ITF$r8EYWAAL$S-NH_2	1532.83	767.42	767.75
733	Ac-ITF$r8EHWVAL$A-NH_2	1518.86	760.43	760.81
734	Ac-ITF$r8EHWAAL$S-NH_2	1506.82	754.41	754.8
735	Pam-LTF$r8EYWAQL$S-NH_2	1786.07	894.04	894.48
736	Pam-ETF$r8EYWAQL$S-NH_2	1802.03	902.02	902.34
737	Ac-LTF$r8AYWLQL$S-NH_2	1573.89	787.95	787.39
738	Ac-LTF$r8EYWLQL$S-NH_2	1631.90	816.95	817.33
739	Ac-LTF$r8EHWLQL$S-NH_2	1605.89	803.95	804.29
740	Ac-LTF$r8VYWAQL$S-NH_2	1559.88	780.94	781.34
741	Ac-LTF$r8AYWSQL$S-NH_2	1547.84	774.92	775.33
742	Ac-ETF$r8AYWAQL$S-NH_2	1547.80	774.90	775.7
743	Ac-LTF$r8EYWAQL$S-NH_2	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-NH_2	1474.82	738.41	738.79
755	Ac-LTF$r8AYWCouQL$S-NH_2	1705.88	853.94	854.61
756	Ac-LTF$r8CouYWAQL$S-NH_2	1705.88	853.94	854.7
757	Ac-CouTF$r8AYWAQL$S-NH_2	1663.83	832.92	833.33
758	H-LTF$r8AYWAQL$A-NH_2	1473.84	737.92	737.29
759	Ac-HHF$r8AYWAQL$S-NH_2	1591.83	796.92	797.72
760	Ac-LT2Nal$r8AYWSQL$S-NH_2	1597.85	799.93	800.68
761	Ac-LTF$r8HCouWAQL$S-NH_2	1679.87	840.94	841.38
762	Ac-LTF$r8AYWCou2QL$S-NH_2	1789.94	895.97	896.51
763	Ac-LTF$r8Cou2YWAQL$S-NH_2	1789.94	895.97	896.5
764	Ac-Cou2TF$r8AYWAQL$S-NH_2	1747.90	874.95	875.42
765	Ac-LTF$r8ACou2WAQL$S-NH_2	1697.92	849.96	850.82
766	Dmaac-LTF$r8AYWAQL$S-NH_2	1574.89	788.45	788.82
767	Hexac-LTF$r8AYWAQL$S-NH_2	1587.91	794.96	795.11
768	Napac-LTF$r8AYWAQL$S-NH_2	1657.89	829.95	830.36
769	Pam-LTF$r8AYWAQL$S-NH_2	1728.06	865.03	865.45
770	Ac-LT2Nal$r8HYAAQL$S-NH_2	1532.84	767.42	767.61
771	Ac-LT2Nal$/r8HYWAQL$/S-NH_2	1675.91	838.96	839.1

772	Ac-LT2Nal$r8HYFAQL$S-NH_2	1608.87	805.44	805.9
773	Ac-LT2Nal$r8HWAAQL$S-NH_2	1555.86	778.93	779.08
774	Ac-LT2Nal$r8HYAWQL$S-NH_2	1647.88	824.94	825.04
775	Ac-LT2Nal$r8HYAAQW$S-NH_2	1605.83	803.92	804.05
776	Ac-LTW$r8HYWAQL$S-NH_2	1636.88	819.44	819.95
777	Ac-LT1Nal$r8HYWAQL$S-NH_2	1647.88	824.94	825.41

[00556] In some embodiments, a peptidomimetic macrocycles disclosed herein does not comprise a peptidomimetic macrocycle structure as shown in Table 2b.

[00557] 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
SP765	Ac-tawyanfekllr-NH_2			777.46			
SP766	Ac-tawyanf4CF3ekllr-NH_2			811.41			

Example 3: X-ray co-crystallography of peptidomimetic macrocycles in complex with MDMX

[00558] For co-crystallization with peptide 46 (Table 2b), a stoichiometric amount of compound from a 100 mM stock solution in DMSO was added to the zebrafish MDMX protein solution and allowed to sit overnight at 4°C before setting up crystallization experiments. Procedures were similar to those described by Popowicz et al. with some variations, as noted below. Protein (residues 15-129, L46V/V95L) was obtained from an *E. coli* BL21(DE3) expression system using the pET15b vector. Cells were grown at 37°C and induced with 1 mM IPTG at an OD_{600} of 0.7. Cells were allowed to grow an additional 18 hr at 23°C. Protein was purified using Ni-NT Agarose followed by Superdex 75 buffered with 50 mM $NaPO_4$, pH 8.0, 150 mM NaCl, 2 mM TCEP and then concentrated to 24 mg/ml. The buffer was exchanged to 20 mM Tris, pH 8.0, 50 mM NaCl, 2 mM DTT for crystallization experiments. Initial crystals were obtained with the Nextal (Qiagen) AMS screen #94 and the final optimized reservoir was 2.6 M AMS, 75 mM Hepes, pH 7.5. Crystals grew routinely as thin plates at 4°C and were cryo-protected by pulling them through a solution containing concentrated (3.4 M) malonate followed by flash cooling, storage, and shipment in liquid nitrogen.

[00559] Data collection was performed at the APS at beamline 31-ID (SGX-CAT) at 100°K and wavelength 0.97929Å. The beamline was equipped with a Rayonix 225-HE detector. For data collection, crystals were rotated through 180° in 1° increments using 0.8 second exposure times. Data were processed and reduced using Mosflm/scala (CCP4; see The CCP4 Suite: Programs for Protein Crystallography. Acta Crystallogr. D50, 760-763 (1994); P.R. Evans. Joint CCP4 and ESF-EACBM Newsletter **33**, 22-24 (1997)) in space group C2 (unit cell: a = 109.2786, b = 81.0836, c = 30.9058Å, $\alpha = 90$, $\beta = 89.8577$, $\gamma = 90°$). Molecular replacement with program Molrep (CCP4; see A.Vagin & A. Teplyakov. J. Appl. Cryst. **30**, 1022-1025 (1997)) was performed with the MDMX component of the structure determined by Popowicz et al. (2Z5S; see G.M. Popowicz, A. Czarna, U. Rothweiler, A. Szwagierczak, M. Krajewski, L. Weber & T.A. Holak. Cell Cycle **6**, 2386-2392 (2007)) and identified two molecules in the asymmetric unit. Initial refinement of just the two

molecules of the zebrafish MDMX with program Refmac (CCP4; see G.N. Murshudov, A.A. Vagin & E.J. Dodson. Acta Crystallogr. D53, 240-255 (1997)) resulted in an R-factor of 0.3424 (R_{free} = 0.3712) and rmsd values for bonds (0.018 Å) and angles (1.698°). The electron density for the stapled peptide components, starting with Gln^{19} and including all of the aliphatic staple, was very clear. Further refinement with CNX (Accelrys) using data to 2.3 Å resolution resulted in a model (comprised of 1448 atoms from MDMX, 272 atoms from the stapled peptides and 46 water molecules) that is well refined (R_f = 0.2601, R_{free} = 0.3162, rmsd bonds = 0.007 Å and rmsd angles = 0.916°).

[00560] Results from this Example are shown in **Figures 13 and 14**.

Example 4: Circular Dichroism (CD) analysis of alpha-helicity

[00561] Peptide solutions were analyzed by CD spectroscopy using a Jasco J-815 spectropolarimeter (Jasco Inc., Easton, MD) with the Jasco Spectra Manager Ver.2 system software. A Peltier temperature controller was used to maintain temperature control of the optical cell. Results are expressed as mean molar ellipticity [0] (deg cm^2 $dmol^{-1}$) as calculated from the equation [0]=0obs·MRW/10*l*c where 0obs is the observed ellipticity in millidegrees, MRW is the mean residue weight of the peptide (peptide molecular weight/number of residues), l is the optical path length of the cell in centimeters, and c is the peptide concentration in mg/ml. Peptide concentrations were determined by amino acid analysis. Stock solutions of peptides were prepared in benign CD buffer (20 mM phosphoric acid, pH 2). The stocks were used to prepare peptide solutions of 0.05 mg/ml in either benign CD buffer or CD buffer with 50% trifluoroethanol (TFE) for analyses in a 10 mm pathlength cell. Variable wavelength measurements of peptide solutions were scanned at 4 °C from 195 to 250 nm, in 0.2 nm increments, and a scan rate 50 nm per minute. The average of six scans was reported.

[00562] Table 3 shows circular dichroism data for selected peptidomimetic macrocycles:

Table 3

SP#	Molar Ellipticity Benign (222 in 0%TFE)	Molar Ellipticity 50%TFE (222 in 50%TFE)	Molar Ellipticity TFE - Molar Ellipticity Benign	% Helix 50% TFE compared to 50%TFE parent (CD)	% Helix benign compared to 50%TFE parent (CD)
7	124	-19921.4	-20045.4	137.3	-0.9
11	-398.2	-16623.4	16225.2	106.1	2.5
41	-909	-21319.4	20410.4	136	5.8
43	-15334.5	-18247.4	2912.9	116.4	97.8
69	-102.6	-21509.7	-21407.1	148.2	0.7
71	-121.2	-17957	-17835.9	123.7	0.8
154	-916.2	-30965.1	-30048.9	213.4	6.3
230	-213.2	-17974	-17760.8	123.9	1.5
233	-477.9	-19032.6	-18554.7	131.2	3.3

Example 5: Direct binding assay MDM2 with Fluorescence polarization (FP)

[00563] The assay was performed according to the following general protocol:

1. Dilute MDM2 (In-house, 41kD) into FP buffer (High salt buffer-200 mM Nacl,5 mM CHAPS, pH 7.5) to make 10 μM working stock solution.

2. Add 30 µl of 10 µM of protein stock solution into A1 and B1 well of 96-well black HE microplate (Molecular Devices).

3. Fill in 30 µl of FP buffer into column A2 to A12, B2 to B12, C1 to C12, and D1 to D12.

4. 2 or 3 fold series dilution of protein stock from A1, B1 into A2, B2; A2, B2 to A3, B3; … to reach the single digit nM concentration at the last dilution point.

5. Dilute 1mM (in 100% DMSO) of FAM labeled linear peptide with DMSO to 100 µM (dilution 1: 10). Then, dilute from 100 µM to 10 µM with water (dilution 1:10) and then dilute with FP buffer from 10 µM to 40 nM (dilution 1:250). This is the working solution which will be a 10 nM concentration in well (dilution 1:4). Keep the diluted FAM labeled peptide in the dark until use.

6. Add 10 µl of 10 nM of FAM labeled peptide into each well and incubate, and read at different time points. K_D with 5-FAM-BaLTFEHYWAQLTS-NH_2 is ~13.38 nM.

Example 6: Competitive Fluorescence polarization assay for MDM2

[00564] The assay was performed according to the following general protocol:

1. Dilute MDM2 (In-house, 41kD) into FP buffer (High salt buffer-200 mM Nacl,5 mM CHAPS, pH 7.5) to make 84 nM (2X) working stock solution.

2. Add 20µl of 84 nM (2X) of protein stock solution into each well of 96-well black HE microplate (Molecular Devices)

3. Dilute 1 mM (in 100% DMSO) of FAM labeled linear peptide with DMSO to 100 µM (dilution 1: 10). Then, dilute from 100 µM to 10 µM with water (dilution 1:10) and then dilute with FP buffer from 10 µM to 40 nM (dilution 1:250). This is the working solution which will be a 10 nM concentration in well (dilution 1:4). Keep the diluted FAM labeled peptide in the dark until use.

4. Make unlabeled peptide dose plate with FP buffer starting with 1 µM (final) of peptide and making 5 fold serial dilutions for 6 points using following dilution scheme. Dilute 10mM (in 100% DMSO) with DMSO to 5mM (dilution 1: 2). Then, dilute from 5mM to 500 µM with H_2O (dilution 1:10) and then dilute with FP buffer from 500 µM to 20 µM (dilution 1:25). Making 5 fold serial dilutions from 4 µM (4X) for 6 points.

5. Transfer 10 µl of serial diluted unlabeled peptides to each well which is filled with 20µl of 84nM of protein.

6. Add 10 µl of 10 nM (4X) of FAM labeled peptide into each well and incubate for 3hr to read.

Example 7: Direct binding assay MDMX with Fluorescence polarization (FP)

[00565] The assay was performed according to the following general protocol:

1. Dilute MDMX (In-house, 40kD) into FP buffer (High salt buffer-200 mM Nacl,5 mM CHAPS, pH 7.5) to make 10 µM working stock solution.

2. Add 30 µl of 10 µM of protein stock solution into A1 and B1 well of 96-well black HE microplate (Molecular Devices).

3. Fill in 30 µl of FP buffer into column A2 to A12, B2 to B12, C1 to C12, and D1 to D12.

4. 2 or 3 fold series dilution of protein stock from A1, B1 into A2, B2; A2, B2 to A3, B3; ... to reach the single digit nM concentration at the last dilution point.

5. Dilute 1mM (in 100% DMSO) of FAM labeled linear peptide with DMSO to 100 μM (dilution 1: 10). Then, dilute from 100 μM to 10 μM with water (dilution 1:10) and then dilute with FP buffer from 10 μM to 40 nM (dilution 1:250). This is the working solution which will be a 10nM concentration in well (dilution 1:4). Keep the diluted FAM labeled peptide in the dark until use.

6. Add 10 μl of 10 nM of FAM labeled peptide into each well and incubate, and read at different time points. K_D with 5-FAM-BaLTFEHYWAQLTS-NH_2 is ~51 nM.

Example 8: Competitive Fluorescence polarization assay for MDMX

[00566] The assay was performed according to the following general protocol:

1. Dilute MDMX (In-house, 40kD) into FP buffer (High salt buffer-200 mM NaCl, 5 mM CHAPS, pH 7.5.) to make 300 nM (2X) working stock solution.

2. Add 20 μl of 300 nM (2X) of protein stock solution into each well of 96-well black HE microplate (Molecular Devices)

3. Dilute 1mM (in 100% DMSO) of FAM labeled linear peptide with DMSO to 100 μM (dilution 1: 10). Then, dilute from 100 μM to 10 μM with water (dilution 1:10) and then dilute with FP buffer from 10 μM to 40 nM (dilution 1:250). This is the working solution which will be a 10 nM concentration in well (dilution 1:4). Keep the diluted FAM labeled peptide in the dark until use.

4. Make unlabeled peptide dose plate with FP buffer starting with 5 μM (final) of peptide and making 5 fold serial dilutions for 6 points using following dilution scheme.

5. Dilute 10 mM (in 100% DMSO) with DMSO to 5 mM (dilution 1: 2). Then, dilute from 5 mM to 500 μM with H_2O (dilution 1:10) and then dilute with FP buffer from 500 μM to 20 μM (dilution 1:25). Making 5 fold serial dilutions from 20 μM (4X) for 6 points.

6. Transfer 10 μl of serial diluted unlabeled peptides to each well which is filled with 20 μl of 300 nM of protein.

7. Add 10μl of 10nM (4X) of FAM labeled peptide into each well and incubate for 3hr to read.

Results from Examples 5-8 are shown in Table 4. The following scale is used: "+" represents a value greater than 1000 nM, "++" represents a value greater than 100 and less than or equal to 1000 nM, "+++" represents a value greater than 10 nM and less than or equal to 100 nM, and "++++" represents a value of less than or equal to 10 nM.

Table 4

SP#	IC_{50} (MDM2)	IC_{50} (MDMX)	Ki (MDM2)	Ki (MDMX)
3	++	++	+++	+++
4	+++	++	++++	+++
5	+++	++	++++	+++
6	++	++	+++	+++
7	+++	+++	++++	+++
8	++	++	+++	+++

9	++	++	+++	+++
10	++	++	+++	+++
11	+++	++	++++	+++
12	+	+	+++	++
13	++	++	+++	++
14	+++	+++	++++	++++
15	+++	++	+++	+++
16	+++	+++	++++	+++
17	+++	+++	++++	+++
18	+++	+++	++++	++++
19	++	+++	+++	+++
20	++	++	+++	+++
21	++	+++	+++	+++
22	+++	+++	++++	+++
23	++	++	+++	+++
24	+++	++	++++	+++
26	+++	++	++++	+++
28	+++	+++	++++	+++
30	++	++	+++	+++
32	+++	++	++++	+++
38	+	++	++	+++
39	+	++	++	++
40	++	++	++	+++
41	++	+++	+++	+++
42	++	++	+++	++
43	+++	+++	++++	+++
45	+++	+++	++++	++++
46	+++	+++	++++	+++
47	++	++	+++	+++
48	++	++	+++	+++
49	++	++	+++	+++
50	+++	++	++++	+++
52	+++	+++	++++	++++
54	++	++	+++	+++
55	+	+	++	++
65	+++	++	++++	+++
68	++	++	+++	+++
69	+++	++	++++	+++
70	++	++	++++	+++
71	+++	++	++++	+++
75	+++	++	++++	+++
77	+++	++	++++	+++
80	+++	++	++++	+++
81	++	++	+++	+++
82	++	++	+++	+++
85	+++	++	++++	+++
99	++++	++	++++	+++
100	++	++	++++	+++
101	+++	++	++++	+++
102	++	++	++++	+++
103	++	++	++++	+++
104	+++	++	++++	+++
105	+++	++	++++	+++

106	++	++	+++	+++
107	++	++	+++	+++
108	+++	++	++++	+++
109	+++	++	++++	+++
110	++	++	++++	+++
111	++	++	++++	+++
112	++	++	+++	+++
113	++	++	+++	+++
114	+++	++	++++	+++
115	++++	++	++++	+++
116	+	+	++	++
118	++++	++	++++	+++
120	+++	++	++++	+++
121	++++	++	++++	+++
122	++++	++	++++	+++
123	++++	++	++++	+++
124	++++	++	++++	+++
125	++++	++	++++	+++
126	++++	++	++++	+++
127	++++	++	++++	+++
128	++++	++	++++	+++
129	++++	++	++++	+++
130	++++	++	++++	+++
133	++++	++	++++	+++
134	++++	++	++++	+++
135	++++	++	++++	+++
136	++++	++	++++	+++
137	++++	++	++++	+++
139	++++	++	++++	+++
142	++++	+++	++++	+++
144	++++	++	++++	+++
146	++++	++	++++	+++
148	++++	++	++++	+++
150	++++	++	++++	+++
153	++++	+++	++++	+++
154	++++	+++	++++	++++
156	++++	++	++++	+++
158	++++	++	++++	+++
160	++++	++	++++	+++
161	++++	++	++++	+++
166	++++	++	++++	+++
167	+++	++	++++	++
169	++++	+++	++++	+++
170	++++	++	++++	+++
173	++++	++	++++	+++
175	++++	++	++++	+++
177	+++	++	++++	+++
180	+++	++	++++	+++
182	++++	++	++++	+++
185	+++	+	++++	++
186	+++	++	++++	+++
189	+++	++	++++	+++
192	+++	++	++++	+++

194	+++	++	++++	++
196	+++	++	++++	+++
197	++++	++	++++	+++
199	+++	++	++++	++
201	+++	++	++++	++
203	+++	++	++++	+++
204	+++	++	++++	+++
206	+++	++	++++	+++
207	++++	++	++++	+++
210	++++	++	++++	+++
211	++++	++	++++	+++
213	++++	++	++++	+++
215	+++	++	++++	+++
217	++++	++	++++	+++
218	++++	++	++++	+++
221	++++	+++	++++	+++
227	++++	++	++++	+++
230	++++	+++	++++	++++
232	++++	++	++++	+++
233	++++	+++	++++	+++
236	+++	++	++++	+++
237	+++	++	++++	+++
238	+++	+++	++++	+++
239	+++	++	+++	+++
240	+++	++	++++	+++
241	+++	++	++++	+++
242	+++	++	++++	+++
243	+++	+++	++++	+++
244	+++	+++	++++	++++
245	+++	+++	++++	+++
246	+++	++	++++	+++
247	+++	+++	++++	+++
248	+++	+++	++++	+++
249	+++	+++	++++	++++
250	++	+	++	+
252	++	+	++	+
254	+++	++	++++	+++
255	+++	+++	++++	+++
256	+++	+++	++++	+++
257	+++	+++	++++	+++
258	+++	++	++++	+++
259	+++	+++	++++	+++
260	+++	+++	++++	+++
261	+++	++	++++	+++
262	+++	++	++++	+++
263	+++	++	++++	+++
264	+++	+++	++++	+++
266	+++	++	++++	+++
267	+++	+++	++++	++++
270	++++	+++	++++	+++
271	++++	+++	++++	++++
272	++++	+++	++++	++++
276	+++	+++	++++	++++

277	+++	+++	++++	++++
278	+++	+++	++++	++++
279	++++	+++	++++	+++
280	+++	++	++++	+++
281	+++	+	+++	++
282	++	+	+++	+
283	+++	++	+++	++
284	+++	++	++++	+++
289	+++	+++	++++	+++
291	+++	+++	++++	++++
293	++++	+++	++++	+++
306	++++	++	++++	+++
308	++	++	+++	+++
310	+++	+++	++++	+++
312	+++	++	+++	+++
313	++++	++	++++	+++
314	++++	+++	++++	++++
315	+++	+++	++++	+++
316	++++	++	++++	+++
317	+++	++	+++	+++
318	+++	++	+++	+++
319	+++	++	+++	++
320	+++	++	+++	++
321	+++	++	++++	+++
322	+++	++	+++	++
323	+++	+	+++	++
328	+++	+++	++++	+++
329	+++	+++	++++	+++
331	++++	+++	++++	++++
332	++++	+++	++++	++++
334	++++	+++	++++	++++
336	++++	+++	++++	++++
339	++++	++	++++	+++
341	+++	+++	++++	++++
343	+++	+++	++++	++++
347	+++	+++	++++	+++
349	++++	+++	++++	++++
351	++++	+++	++++	++++
353	++++	+++	++++	++++
355	++++	+++	++++	++++
357	++++	+++	++++	++++
359	++++	+++	++++	+++
360	++++	++++	++++	++++
363	+++	+++	++++	++++
364	+++	+++	++++	++++
365	+++	+++	++++	++++
366	+++	+++	++++	+++
369	++	++	+++	+++
370	+++	+++	++++	+++
371	++	++	+++	+++
372	++	++	+++	+++
373	+++	+++	+++	+++
374	+++	+++	++++	++++

375	+++	+++	++++	++++
376	+++	+++	++++	++++
377	+++	+++	++++	+++
378	+++	+++	++++	+++
379	+++	+++	++++	+++
380	+++	+++	++++	+++
381	+++	+++	++++	+++
382	+++	+++	++++	++++
384	++	+	++	+
386	++	+	++	+
388	++	+++	+++	++++
390	+++	+++	++++	+++
392	+++	+++	++++	++++
394	++++	+++	++++	++++
396	++++	++++	++++	++++
398	+++	+++	++++	+++
402	++++	++++	++++	++++
404	+++	+++	++++	++++
408	+++	+++	++++	+++
410	++++	++++	++++	++++
411	++	+	++	+
412	++++	+++	++++	++++
415	++++	++++	++++	++++
416	+++	+++	++++	+++
417	+++	+++	++++	+++
418	++++	+++	++++	++++
419	+++	+++	+++	++++
421	++++	++++	++++	++++
423	+++	+++	++++	+++
425	+++	+++	+++	+++
427	++	++	+++	+++
432	++++	+++	++++	++++
434	+++	+++	++++	+++
435	++++	+++	++++	++++
437	+++	+++	++++	+++
439	++++	+++	++++	++++
441	++++	++++	++++	++++
443	+++	+++	++++	+++
445	+++	++	++++	+++
446	+++	+	++++	+
447	++	+	++	+
551	N/A	N/A	++++	+++
555	N/A	N/A	++++	+++
556	N/A	N/A	++++	+++
557	N/A	N/A	+++	+++
558	N/A	N/A	+++	+++
559	N/A	N/A	+++	+++
560	N/A	N/A	+	+
561	N/A	N/A	++++	+++
562	N/A	N/A	+++	+++
563	N/A	N/A	+++	+++
564	N/A	N/A	++++	+++
565	N/A	N/A	+++	+++

566	N/A	N/A	++++	+++
567	N/A	N/A	++++	+++
568	N/A	N/A	++++	++++
569	N/A	N/A	++++	+++
570	N/A	N/A	++++	+++
571	N/A	N/A	++++	+++
572	N/A	N/A	+++	+++
573	N/A	N/A	+++	+++
574	N/A	N/A	++++	+++
575	N/A	N/A	++++	+++
576	N/A	N/A	++++	+++
577	N/A	N/A	++++	+++
578	N/A	N/A	++++	+++
585	N/A	N/A	+++	+++
586	N/A	N/A	++++	+++
587	N/A	N/A	++++	++++
589	N/A	N/A	++++	
594	N/A	N/A	++++	++++
596	N/A	N/A	++++	+++
597	N/A	N/A	++++	+++
598	N/A	N/A	++++	+++
600	N/A	N/A	++++	++++
602	N/A	N/A	++++	++++
603	N/A	N/A	++++	++++
604	N/A	N/A	+++	+++
608	N/A	N/A	++++	+++
609	N/A	N/A	++++	+++
610	N/A	N/A	++++	+++
611	N/A	N/A	++++	+++
612	N/A	N/A	++++	+++
613	N/A	N/A	++++	+++
615	N/A	N/A	++++	++++
433	N/A	N/A	++++	+++
686	N/A	N/A	++++	+++
687	N/A	N/A	++	++
595	N/A	N/A	+	N/A
665	N/A	N/A	+++	N/A
708	N/A	N/A	+++	+++
710	N/A	N/A	+++	+++
711	N/A	N/A	+++	++
712	N/A	N/A	++++	++++
713	N/A	N/A	++++	++++
716	N/A	N/A	++++	++++
765	+	+		
766	+++	+		
752	++	+		
753	+++	+		
754	++	+		
755	++++	+		
756	+++	+		
757	++++	+		
758	+++	+		

Example 9: Competition Binding ELISA (MDM2 & MDMX)

[00567] p53-His6 protein (30 nM/well) is coated overnight at room temperature in the wells of a 96-well Immulon plates. On the day of the experiment, plates are washed with 1X PBS-Tween 20 (0.05%) using an automated ELISA plate washer, blocked with ELISA Micro well Blocking for 30 minutes at room temperature; excess blocking agent is washed off by washing plates with 1X PBS-Tween 20 (0.05%). Peptides are diluted from 10 mM DMSO stocks to 500 µM working stocks in sterile water, further dilutions made in 0.5% DMSO to keep the concentration of DMSO constant across the samples. The peptides are added to wells at 2X desired concentrations in 50 µL volumes, followed by addition of diluted GST-MDM2 or GST-HMDX protein (final concentration: 10nM). Samples are incubated at room temperature for 2h, plates are washed with PBS-Tween 20 (0.05%) prior to adding 100 µL of HRP-conjugated anti-GST antibody [Hypromatrix, INC] diluted to 0.5 µg/ml in HRP-stabilizing buffer. Post 30 min incubation with detection antibody, plates are washed and incubated with 100 µL per well of TMB-E Substrate solution up to 30 minutes; reactions are stopped using 1M HCL and absorbance measured at 450 nm on micro plate reader. Data is analyzed using Graph Pad PRISM software.

Example 10: Cell Viability assay

[00568] The assay was performed according to the following general protocol:

Cell Plating: Trypsinize, count and seed cells at the pre-determined densities in 96-well plates a day prior to assay. Following cell densities are used for each cell line in use:

- SJSA-1: 7500 cells/ well
- RKO: 5000 cells/well
- RKO-E6: 5000 cells/well
- HCT-116: 5000 cells/well
- SW-480: 2000 cells/well
- MCF-7: 5000 cells/well

[00569] On the day of study, replace media with fresh media with 11% FBS (assay media) at room temperature. Add 180µL of the assay media per well. Control wells with no cells, receive 200 µL media.

[00570] Peptide dilution: all dilutions are made at room temperature and added to cells at room temperature.

- Prepare 10 mM stocks of the peptides in DMSO. Serially dilute the stock using 1:3 dilution scheme to get 10, 3.3, 1.1, 0.33, 0.11, 0.03, 0.01mM solutions using DMSO as diluents. Dilute the serially DMSO-diluted peptides 33.3 times using sterile water. This gives range of 10X working stocks. Also prepare DMSO/sterile water (3% DMSO) mix for control wells.
- Thus the working stocks concentration range µM will be 300, 100, 30, 10, 3, 1, 0.3 and 0 µM. Mix well at each dilution step using multichannel.
- Row H has controls. H1- H3 will receive 20 µL of assay media. H4-H9 will receive 20 µL of 3% DMSO-water vehicle. H10-H12 will have media alone control with no cells.

- Positive control: MDM2 small molecule inhibitor,Nutlin-3a (10 mM) is used as positive control. Nutlin was diluted using the same dilution scheme as peptides.

[00571] Addition of working stocks to cells:

- Add 20 µL of 10X desired concentration to appropriate well to achieve the final concentrations in total 200 µL volume in well. (20 µL of 300 µM peptide + 180 µL of cells in media = 30 µM final concentration in 200 µL volume in wells). Mix gently a few times using pipette. Thus final concentration range used will be 30, 10, 3, 1, 0.3, 0.1, 0.03 & 0 µM (for potent peptides further dilutions are included).
- Controls include wells that get no peptides but contain the same concentration of DMSO as the wells containing the peptides, and wells containing NO CELLS.
- Incubate for 72 hours at 37°C in humidified 5% CO_2 atmosphere.
- The viability of cells is determined using MTT reagent from Promega. Viability of SJSA-1, RKO, RKO-E6, HCT-116 cells is determined on day 3, MCF-7 cells on day 5 and SW-480 cells on day 6. At the end of designated incubation time, allow the plates to come to room temperature. Remove 80 µL of assay media from each well. Add 15 µL of thawed MTT reagent to each well.
- Allow plate to incubate for 2h at 37°C in humidified 5% CO_2 atmosphere and add 100 µL solubilization reagent as per manufacturer's protocol. Incubate with agitation for 1h at room temperature and read on Synergy Biotek multiplate reader for absorbance at 570nM.
- Analyze the cell viability against the DMSO controls using GraphPad PRISM analysis tools.

[00572] Reagents:

- Invitrogen cell culture Media
- Falcon 96-well clear cell culture treated plates (Nunc 353072)
- DMSO (Sigma D 2650)
- RPMI 1640 (Invitrogen 72400)
- MTT (Promega G4000)

[00573] **Instruments:** Multiplate Reader for Absorbance readout (Synergy 2).

[00574] Results from cell viability assays are shown in Tables 5 and 6. The following scale is used: "+" represents a value greater than 30 µM, "++" represents a value greater than 15 µM and less than or equal to 30 µM, "+++" represents a value greater than 5 µM and less than or equal to 15 µM, and "++++" represents a value of less than or equal to 5 µM. "IC50 ratio" represents the ratio of average IC50 in p53+/+ cells relative to average IC50 in p53-/- cells.

Table 5

SP#	SJSA-1 EC50 (72h)	SP#	SJSA-1 EC50 (72h)	SP#	SJSA-1 EC50 (72h)	SP#	SJSA-1 EC50 (72h)
3	+++	170	++++	295	+++	443	++++
4	+++	171	++	296	++++	444	+++
5	++++	173	+++	297	+++	445	++++
6	++	174	++++	298	++++	449	++++

SP#	SJSA-1 EC50 (72h)	SP#	SJSA-1 EC50 (72h)	SP#	SJSA-1 EC50 (72h)	SP#	SJSA-1 EC50 (72h)
7	++++	175	+++	300	++++	551	++++
8	+++	176	+++	301	++++	552	++++
9	+++	177	++++	302	++++	554	+
10	+++	179	+++	303	++++	555	++++
11	++++	180	+++	304	++++	586	++++
12	++	181	+++	305	++++	587	++++
13	+++	182	++++	306	++++	588	++++
14	+	183	++++	307	+++	589	+++
15	++	184	+++	308	++++	432	++++
16	+	185	+++	309	+++	672	+
17	+	186	++	310	++++	673	++
18	+	188	++	312	++++	682	+
19	++	190	++++	313	++++	686	+
20	+	192	+++	314	++++	557	++++
21	+	193	++	315	++++	558	++++
22	+	194	+	316	++++	560	+
24	+++	195	++++	317	++++	561	++++
26	++++	196	++++	318	++++	562	++++
28	+	197	++++	319	++++	563	++++
29	+	198	++	320	++++	564	++++
30	+	199	+++	321	++++	566	++++
32	++	200	+++	322	++++	567	++++
38	+	201	++++	323	++++	568	+++
39	+	202	+++	324	++++	569	++++
40	+	203	++++	326	++++	571	++++
41	+	204	++++	327	++++	572	++++
42	+	205	++	328	++++	573	++++
43	++	206	++	329	++++	574	++++
45	+	207	+++	330	++++	575	++++
46	+	208	+++	331	++++	576	++++
47	+	209	++++	332	++++	577	++++
48	+	210	+++	333	++	578	++++
49	+++	211	++++	334	+++	585	++++
50	++++	213	++++	335	++++	687	+
52	+	214	++++	336	++++	662	++++
54	+	215	++++	337	++++	663	++++
55	+	216	++++	338	++++	553	+++
65	++++	217	++++	339	++++	559	++++
68	++++	218	++++	340	++++	579	++++
69	++++	219	++++	341	++++	581	++++
70	++++	220	+++	342	++++	582	++
71	++++	221	++++	343	++++	582	++++
72	++++	222	+++	344	++++	584	+++
74	++++	223	++++	345	++++	675	++++
75	++++	224	++	346	++++	676	++++
77	++++	225	+++	347	++++	677	+
78	++	226	++	348	++++	679	++++
80	++++	227	+++	349	++++	700	+++
81	+++	228	++++	350	++++	704	+++
82	+++	229	++++	351	++++	591	+
83	+++	230	++++	352	++++	706	++

SP#	SJSA-1 EC50 (72h)	SP#	SJSA-1 EC50 (72h)	SP#	SJSA-1 EC50 (72h)	SP#	SJSA-1 EC50 (72h)
84	+	231	++++	353	++++	695	++
85	+++	232	++++	355	++++	595	++++
99	++++	233	++++	357	++++	596	++++
102	+++	234	++++	358	++++	597	+++
103	+++	235	++++	359	++++	598	+++
104	+++	236	++++	360	++++	599	++++
105	+++	237	++++	361	+++	600	++++
108	+++	238	++++	362	++++	601	+++
109	+++	239	+++	363	++++	602	+++
110	+++	240	++	364	++++	603	+++
111	++	241	+++	365	+++	604	+++
114	++++	242	++++	366	++++	606	++++
115	++++	243	++++	367	++++	607	++++
118	++++	244	++++	368	+	608	++++
120	++++	245	++++	369	++++	610	++++
121	++++	246	+++	370	++++	611	++++
122	++++	247	++++	371	++++	612	++++
123	++++	248	++++	372	+++	613	+++
124	+++	249	++++	373	+++	614	+++
125	++++	250	++	374	++++	615	++++
126	++++	251	+	375	++++	618	++++
127	++++	252	+	376	++++	619	++++
128	+++	253	+	377	++++	707	++++
129	++	254	+++	378	++++	620	++++
130	++++	255	+++	379	++++	621	++++
131	+++	256	++	380	++++	622	++++
132	++++	257	+++	381	++++	623	++++
133	+++	258	+++	382	++++	624	++++
134	+++	259	++	386	+++	625	++++
135	+++	260	++	388	++	626	+++
136	++	261	++	390	++++	631	++++
137	+++	262	+++	392	+++	633	++++
139	++++	263	++	394	+++	634	++++
142	+++	264	++++	396	+++	635	+++
144	++++	266	+++	398	+++	636	+++
147	++++	267	++++	402	+++	638	+
148	++++	270	++	404	+++	641	+++
149	++++	271	++	408	++++	665	++++
150	++++	272	++	410	+++	708	++++
152	+++	276	++	411	+++	709	+++
153	++++	277	++	412	+	710	+
154	++++	278	++	421	+++	711	++++
155	++	279	++++	423	++++	712	++++
156	+++	280	+++	425	++++	713	++++
157	+++	281	++	427	++++	714	+++
158	+++	282	++	434	+++	715	+++
160	++++	283	++	435	++++	716	++++
161	++++	284	++++	436	++++	765	+
162	+++	289	++++	437	++++	753	+
163	+++	290	+++	438	++++	754	+
166	++	291	++++	439	++++	755	+

SP#	SJSA-1 EC50 (72h)	SP#	SJSA-1 EC50 (72h)	SP#	SJSA-1 EC50 (72h)	SP#	SJSA-1 EC50 (72h)
167	+++	292	++++	440	++++	756	+
168	++	293	++++	441	++++	757	++++
169	++++	294	++++	442	++++	758	+++

Table 6

SP#	HCT-116 EC50 (72h)	RKO EC_{50} (72h)	RKO-E6 EC_{50} (72h)	SW480 EC50 (6days)	IC_{50} Ratio
4	++++	++++	+++	++++	
5	++++	++++	+++	++++	
7	++++	++++	+++	++++	
10	++++	+++	+++	+++	
11	++++	++++	++	+++	
50	++++	++++	++	+++	
65	+++	+++	+++	+++	
69	++++	++++	+	++++	
70	++++	++++	++	+++	
71	++++	++++	+++	+++	
81	+++	+++	+++	+++	
99	++++	++++	+++	++++	
109	++++	++++	++	+++	
114		+++	+	+++	
115		+++	+	+++	1-29
118	+++	++++	+	++++	
120	++++	++++	+	++++	
121	++++	++++	+	++++	
122		+++	+	+++	1-29
125	+++	+++	+	+	
126	+	+	+	+	
148		++	+	+	
150		++	+	+	
153	+++		+		
154	+++	+++	+	+	30-49
158	+	+	+	+	
160	+++	+	+	+	1-29
161	+++	+	+	+	
175	+	+	+	+	
196	++++	++++	+++	++++	
219	++++	+++	+	+	1-29
233	++++				
237	++++		+	+	
238	++++		+	+	
243	++++		+	+	
244	++++		+	+	≥50
245	++++		+	+	
247	++++		+	+	
249	++++	++++	+	+	≥50
255	++++		+		
291			+		
293	+++		+		
303	+++		+		1-29
305			+		

SP#	HCT-116 EC50 (72h)	RKO EC_{50} (72h)	RKO-E6 EC_{50} (72h)	SW480 EC50 (6days)	IC_{50} Ratio
306	++++		+		
310	++++		+		
312	++++				
313	++++		++		
314			+		
315	++++	++++	++	++++	≥50
316	++++	++++	+	+++	≥50
317	+++		+	++	
321	++++		+		
324	+++		+		
325	+++				
326	+++		+		
327	+++		+		
328	+++		++		
329	++++		+		
330			+		
331	++++	++++	+	+	≥50
338	++++	++++	++	+++	
341	+++	++	+	+	
343	+++		+	+	
346	++++		+	+	
347	+++		+	+	
349	++++	+++	+	+	30-49
350	++++		+	+	
351	++++	+++	+	+	30-49
353	++	++	+	+	
355	++++	++	+	+	1-29
357	++++	++++	+	+	
358	++++	++	+	+	
359	++++	++	+	+	
367	++++		+	+	30-49
386	++++	++++	++++	++++	
388	++	++	+	+++	1-29
390	++++	++++	+++	++++	
435	+++	++	+		
436	++++	++++	++		
437	++++	++++	++	++++	30-49
440	++	++	+		
442	++++	++++	++		
444	++++	++++	+++		
445	++++	+++	+	+	≥50
555					≥50
557					≥50
558					30-49
562					30-49
564					30-49
566					30-49
567					≥50
572					≥50
573					30-49
578					30-49
662					≥50

SP#	HCT-116 EC50 (72h)	RKO EC_{50} (72h)	RKO-E6 EC_{50} (72h)	SW480 EC50 (6days)	IC_{50} Ratio
379					1-29
375					1-29
559					≥50
561					1-29
563					1-29
568					1-29
569					1-29
571					1-29
574					1-29
575					1-29
576					1-29
577					30-49
433					1-29
551					30-49
553					1-29
710				+	
711				+	
712				++	
713				++	
714				+++	
715				+++	
716				+	

Example 11: p21 ELISA assay

[00575] The assay was performed according to the following general protocol:

Cell Plating:

- Trypsinize, count and seed SJSA1 cells at the density of 7500 cells/ 100 µL/well in 96-well plates a day prior to assay.
- On the day of study, replace media with fresh RPMI-11% FBS (assay media). Add 90µL of the assay media per well. Control wells with no cells, receive 100 µL media.

[00576] Peptide dilution:

- Prepare 10 mM stocks of the peptides in DMSO. Serially dilute the stock using 1:3 dilution scheme to get 10, 3.3, 1.1, 0.33, 0.11, 0.03, 0.01mM solutions using DMSO as diluents. Dilute the serially DMSO-diluted peptides 33.3 times using sterile water This gives range of 10X working stocks. Also prepare DMSO/sterile water (3% DMSO) mix for control wells.
- Thus the working stocks concentration range µM will be 300, 100, 30, 10, 3, 1, 0.3 and 0 µM. Mix well at each dilution step using multichannel.
- Row H has controls. H1- H3 will receive 10 µL of assay media. H4-H9 will receive 10 µL of 3% DMSO-water vehicle. H10-H12 will have media alone control with no cells.
- Positive control: MDM2 small molecule inhibitor,Nutlin-3a (10 mM) is used as positive control. Nutlin was diluted using the same dilution scheme as peptides.

[00577] Addition of working stocks to cells:

- Add 10 µL of 10X desired concentration to appropriate well to achieve the final concentrations in total 100 µL volume in well. (10 µL of 300 µM peptide + 90 µL of cells in media = 30 µM final concentration in 100 µL volume in wells). Thus final concentration range used will be 30, 10, 3, 1, 0.3& 0 µM.
- Controls will include wells that get no peptides but contain the same concentration of DMSO as the wells containing the peptides, and wells containing NO CELLS.
- 20h-post incubation, aspirate the media; wash cells with 1X PBS (without Ca^{++}/Mg^{++}) and lyse in 60 µL of 1X Cell lysis buffer (Cell Signaling technologies 10X buffer diluted to 1X and supplemented with protease inhibitors and Phosphatase inhibitors) on ice for 30 min.
- Centrifuge plates in at 5000 rpm speed in at 4^0C for 8 min; collect clear supernatants and freeze at -80 ^{0}C till further use.

[00578] Protein Estimation:

- Total protein content of the lysates is measured using BCA protein detection kit and BSA standards from Thermofisher. Typically about 6-7 µg protein is expected per well.
- Use 50 µL of the lysate per well to set up p21 ELISA.

[00579] **Human Total p21 ELISA:** The ELISA assay protocol is followed as per the manufacturer's instructions. 50 µL lysate is used for each well, and each well is set up in triplicate.

[00580] Reagents:

- -Cell-Based Assay (-)-Nutlin-3 (10 mM): Cayman Chemicals, catalog # 600034
- - OptiMEM, Invitrogen catalog # 51985
- -Cell Signaling Lysis Buffer (10X), Cell signaling technology, Catalog # 9803
- -Protease inhibitor Cocktail tablets(mini), Roche Chemicals, catalog # 04693124001
- -Phosphatase inhibitor Cocktail tablet, Roche Chemicals, catalog # 04906837001
- -Human total p21 ELISA kit, R&D Systems, DYC1047-5
- -STOP Solution (1M HCL), Cell Signaling Technologies, Catalog # 7002

[00581] Instruments: Micro centrifuge- Eppendorf 5415D and Multiplate Reader for Absorbance readout (Synergy 2).

Example 12: Caspase 3 Detection assay:

[00582] The assay was performed according to the following general protocol:

Cell Plating: Trypsinize, count and seed SJSA1 cells at the density of 7500 cells/ 100 µL/well in 96-well plates a day prior to assay. On the day of study, replace media with fresh RPMI-11% FBS (assay media). Add 180µL of the assay media per well. Control wells with no cells, receive 200 µL media.

[00583] Peptide dilution:

- Prepare 10 mM stocks of the peptides in DMSO. Serially dilute the stock using 1:3 dilution scheme to get 10, 3.3, 1.1, 0.33, 0.11, 0.03, 0.01mM solutions using DMSO as diluents. Dilute the

serially DMSO-diluted peptides 33.3 times using sterile water This gives range of 10X working stocks. Also prepare DMSO/sterile water (3% DMSO) mix for control wells.

- Thus the working stocks concentration range μM will be 300, 100, 30, 10, 3, 1, 0.3 and 0 μM. Mix well at each dilution step using multichannel. Add 20 μL of 10X working stocks to appropriate wells.
- Row H has controls. H1- H3 will receive 20 μL of assay media. H4-H9 will receive 20 μL of 3% DMSO-water vehicle. H10-H12 will have media alone control with no cells.
- Positive control: MDM2 small molecule inhibitor,Nutlin-3a (10 mM) is used as positive control. Nutlin was diluted using the same dilution scheme as peptides.

[00584] Addition of working stocks to cells:

- Add 10 μL of 10X desired concentration to appropriate well to achieve the final concentrations in total 100 μL volume in well. (10 μL of 300 μM peptide + 90 μL of cells in media = 30 μM final concentration in 100 μL volume in wells). Thus final concentration range used will be 30, 10, 3, 1, 0.3& 0 μM.
- Controls will include wells that get no peptides but contain the same concentration of DMSO as the wells containing the peptides, and wells containing NO CELLS.
- 48 h-post incubation, aspirate 80 μL media from each well; add 100 μL Caspase3/7Glo assay reagent (Promega Caspase 3/7 glo assay system, G8092)per well, incubate with gentle shaking for 1h at room temperature.
- read on Synergy Biotek multiplate reader for luminescence.
- Data is analyzed as Caspase 3 activation over DMSO-treated cells.

[00585] Results from Examples 11 and 12 are shown in Table 7:

Table 7

SP#	caspase 0.3μM	caspase 1 μM	caspase 3μM	caspase 10μM	caspase 30μM	p21 0.3μM	p21 1μM	p21 3μM	p21 10μM	p21 30μM
4			9	37	35			317	3049	3257
7	0.93	1.4	5.08	21.7	23.96		18	368	1687	2306
8			1	19	25			34	972	2857
10	1		1	17	32		10	89	970	2250
11	1		5	23	33.5		140	350	2075.5	3154
26	1		1	3	14					
50			8	29	29		44	646	1923	1818
65	1		6	28	34	-69	-24	122	843	1472
69	4.34	9.51	16.39	26.59	26.11	272	458.72	1281.39	2138.88	1447.22
70			1	9	26		-19	68	828	1871
71	0.95	1.02	3.68	14.72	23.52		95	101	1204	2075
72	1		1	4	10	-19	57	282	772	1045
77	1		2	19	23					
80	1		2	13	20					
81	1		1	6	21		0	0	417	1649
99	1		7	31	33	-19	117	370	996	1398
109			4	16	25		161	445	1221	1680

SP#	caspase 0.3μM	caspase 1 μM	caspase 3μM	caspase 10μM	caspase 30μM	p21 0.3μM	p21 1μM	p21 3μM	p21 10μM	p21 30μM
114	1		6	28	34	-21	11	116	742	910
115	1		10	26	32	-10	36	315	832	1020
118	1		2	18	27	-76	-62	-11	581	1270
120	2		11	20	30	-4	30	164	756	1349
121	1		5	19	30	9	33	81	626	1251
122	1		2	15	30	-39	-18	59	554	1289
123	1		1	6	14					
125	1		3	9	29	50	104	196	353	1222
126	1		1	6	30	-47	-10	90	397	1443
127	1		1	4	13					
130	1		2	6	17					
139	1		2	9	18					
142	1		2	15	20					
144	1		4	10	16					
148	1		11	23	31	-23	55	295	666	820
149	1		2	4	10	35	331	601	1164	1540
150	2		11	19	35	-37	24	294	895	906
153	2		10	15	20					
154	2.68	4	13.93	19.86	30.14	414.04	837.45	1622.42	2149.51	2156.98
158	1		1.67	5	16.33	-1.5	95	209.5	654	1665.5
160	2		10	16	31	-43	46	373	814	1334
161	2		8	14	22	13	128	331	619	1078
170	1		1	16	20					
175	1		5	12	21	-65	1	149	543	1107
177	1		1	8	20					
183	1		1	4	8	-132	-119	-14	1002	818
196	1		4	33	26	-49	-1	214	1715	687
197	1		1	10	20					
203	1		3	12	10	77	329	534	1805	380
204	1		4	10	10	3	337	928	1435	269
218	1		2	8	18					
219	1		5	17	34	28	53	289	884	1435
221	1		3	6	12	127	339	923	1694	1701
223	1		1	5	18					
230	1		2	3	11	245.5	392	882	1549	2086
233	6	8	17	22	23	2000	2489	3528	3689	2481
237	1		5	9	15	0	0	2	284	421
238	1		2	4	21	0	149	128	825	2066
242	1		4	5	18	0	0	35	577	595
243	1		2	5	23	0	0	0	456	615
244	1		2	7	17	0	178	190	708	1112
245	1		3	9	16	0	0	0	368	536
247	1		3	11	24	0	0	49	492	699
248						0	50	22	174	1919
249	2		5	11	23	0	0	100	907	1076
251						0	0	0	0	0
252						0	0	0	0	0
253						0	0	0	0	0
254	1	3	7	14	22	118	896	1774	3042	3035
286	1	4	11	20	22	481	1351	2882	3383	2479
287	1	1	3	11	23	97	398	986	2828	3410

SP#	caspase 0.3μM	caspase 1 μM	caspase 3μM	caspase 10μM	caspase 30μM	p21 0.3μM	p21 1μM	p21 3μM	p21 10μM	p21 30μM
315	11	14.5	25.5	32	34	2110	2209	2626	2965	2635
316	6.5	10.5	21	32	32.5	1319	1718	2848	2918	2540
317	3	4	9	26	35	551	624	776	1367	1076
331	4.5	8	11	14.5	30.5	1510	1649	2027	2319	2509
338	1	5	23	20	29	660.37	1625.38	3365.87	2897.62	2727
341	3	8	11	14	21	1325.62	1873	2039.75	2360.75	2574
343	1	1	2	5	29	262	281	450	570	1199
346						235.86	339.82	620.36	829.32	1695.78
347	2	3	5	8	29	374	622	659	905	1567
349	1	8	11	16	24	1039.5	1598.88	1983.75	2191.25	2576.38
351	3	9	13	15	24	1350.67	1710.67	2030.92	2190.67	2668.54
353	1	2	5	7	30	390	490	709	931	1483
355	1	4	11	13	30	191	688	1122	1223	1519
357	2	7	11	15	23	539	777	1080	1362	1177
358	1	2	3	6	24	252	321	434	609	1192
359	3	9	11	13	23	1163.29	1508.79	1780.29	2067.67	2479.29
416						33.74	39.82	56.57	86.78	1275.28
417						0	0	101.13	639.04	2016.58
419						58.28	97.36	221.65	1520.69	2187.94
432						54.86	68.86	105.11	440.28	1594.4

Example 13. Cell Lysis by Peptidomimetic Macrocycles

[00586] SJSA-1 cells were plated out one day in advance in clear flat-bottom plates (Costar, catalog number 353072) at 7500cells/well with 100ul/well of growth media, leaving row H columns 10-12 empty for media alone. On the day of the assay, media was exchanged with RPMI 1% FBS media, 90uL of media per well.

[00587] 10 mM stock solutions of the peptidomimetic macrocycles were prepared in 100% DMSO. Peptidomimetic macrocycles were then diluted serially in 100% DMSO, and then further diluted 20-fold in sterile water to prepare working stock solutions in 5% DMSO/water of each peptidomimetic macrocycle at concentrations ranging from 500 μM to 62.5 μM.

[00588] 10 μL of each compound was added to the 90 uL of SJSA-1 cells to yield final concentrations of 50 μM to 6.25 μM in 0.5% DMSO-containing media. The negative control (non-lytic) sample was 0.5% DMSO alone and positive control (lytic) samples include 10 μM Melittin and 1% Triton X-100.

[00589] Cell plates were incubated for 1 hour at 37 °C. After the 1 hour incubation, the morphology of the cells is examined by microscope and then the plates were centrifuged at 1200 rpm for 5 minutes at room temperature. 40 μL of supernatant for each peptidomimetic macrocycle and control sample is transferred to clear assay plates. LDH release is measured using the LDH cytotoxicity assay kit from Caymen, catalog# 1000882. Results are shown in Table 8:

Table 8

SP#	6.25 μM % Lysed cells (1h LDH)	12.5 μM % Lysed cells (1h LDH)	25 μM % Lysed cells (1h LDH)	50 μM % Lysed cells (1h LDH)
3	1	0	1	3
4	-2	1	1	2
6	1	1	1	1
7	0	0	0	0

SP#	6.25 μM % Lysed cells (1h LDH)	12.5 μM % Lysed cells (1h LDH)	25 μM % Lysed cells (1h LDH)	50 μM % Lysed cells (1h LDH)
8	-1	0	1	1
9	-3	0	0	2
11	-2	1	2	3
15	1	2	2	5
18	0	1	2	4
19	2	2	3	21
22	0	-1	0	0
26	2	5	-1	0
32	0	0	2	0
39	0	-1	0	3
43	0	0	-1	-1
55	1	5	9	13
65	0	0	0	2
69	1	0.5	-0.5	5
71	0	0	0	0
72	2	1	0	3
75	-1	3	1	1
77	-2	-2	1	-1
80	0	1	1	5
81	1	1	0	0
82	0	0	0	1
99	1.5	3	2	3.5
108	0	0	0	1
114	3	-1	4	9
115	0	1	-1	6
118	4	2	2	4
120	0	-1	0	6
121	1	0	1	7
122	1	3	0	6
123	-2	2	5	3
125	0	1	0	2
126	1	2	1	1
130	1	3	0	-1
139	-2	-3	-1	-1
142	1	0	1	3
144	1	2	-1	2
147	8	9	16	55
148	0	1	-1	0
149	6	7	7	21
150	-1	-2	0	2
153	4	3	2	3
154	-1	-1.5	-1	-1
158	0	-6	-2	
160	-1	0	-1	1
161	1	1	-1	0
169	2	3	3	7
170	2	2	1	-1
174	5	3	2	5
175	3	2	1	0
177	-1	-1	0	1
182	0	2	3	6

SP#	6.25 μM % Lysed cells (1h LDH)	12.5 μM % Lysed cells (1h LDH)	25 μM % Lysed cells (1h LDH)	50 μM % Lysed cells (1h LDH)
183	2	1	0	3
190	-1	-1	0	1
196	0	-2	0	3
197	1	-4	-1	-2
203	0	-1	2	2
204	4	3	2	0
211	5	4	3	1
217	2	1	1	2
218	0	-3	-4	1
219	0	0	-1	2
221	3	3	3	11
223	-2	-2	-4	-1
230	0.5	-0.5	0	3
232	6	6	5	5
233	2.5	4.5	3.5	6
237	0	3	7	55
243	4	23	39	64
244	0	1	0	4
245	1	14	11	56
247	0	0	0	4
249	0	0	0	0
254	11	34	60	75
279	6	4	5	6
280	5	4	6	18
284	5	4	5	6
286	0	0	0	0
287	0	6	11	56
316	0	1	0	1
317	0	1	0	0
331	0	0	0	0
335	0	0	0	1
336	0	0	0	0
338	0	0	0	1
340	0	2	0	0
341	0	0	0	0
343	0	1	0	0
347	0	0	0	0
349	0	0	0	0
351	0	0	0	0
353	0	0	0	0
355	0	0	0	0
357	0	0	0	0
359	0	0	0	0
413	5	3	3	3
414	3	3	2	2
415	4	4	2	2

Example 14: p53 GRIP assay

[00590] Thermo Scientific* BioImage p53-MDM2 Redistribution Assay monitors the protein interaction with MDM2 and cellular translocation of GFP-tagged p53 in response to drug compounds or other stimuli.

Recombinant CHO-hIR cells stably express human p53 (1-312) fused to the C-terminus of enhanced green fluorescent protein (EGFP) and PDE4A4-MDM2 (1-124), a fusion protein between PDE4A4 and MDM2 (1-124). They provide a ready-to-use assay system for measuring the effects of experimental conditions on the interaction of p53 and MDM2. Imaging and analysis is performed with a HCS platform.

[00591] CHO-hIR cells are regularly maintained in Ham's F12 media supplemented with 1% Penicillin-Streptomycin, 0.5 mg/ml Geneticin, 1 mg/ml Zeocin and 10% FBS. Cells seeded into 96-well plates at the density of 7000 cells/ 100 µL per well 18-24 hours prior to running the assay using culture media. The next day, media is refreshed and PD-177 is added to cells to the final concentration of 3µM to activate foci formation. Control wells are kept without PD-177 solution. 24h post stimulation with PD-177, cells are washed once with Opti-MEM Media and 50 µL of the Opti-MEM Media supplemented with PD-177 (6 µM) is added to cells. Peptides are diluted from 10 mM DMSO stocks to 500 µM working stocks in sterile water, further dilutions made in 0.5% DMSO to keep the concentration of DMSO constant across the samples. Final highest DMSO concentration is 0.5% and is used as the negative control. Cayman Chemicals Cell-Based Assay (-)-Nutlin-3 (10 mM) is used as positive control. Nutlin was diluted using the same dilution scheme as peptides.50 µL of 2X desired concentrations is added to the appropriate well to achieve the final desired concentrations. Cells are then incubated with peptides for 6 h at 37 °C in humidified 5% CO2 atmosphere. Post-incubation period, cells are fixed by gently aspirating out the media and adding 150 µL of fixing solution per well for 20 minutes at room temperature. Fixed cells are washed 4 times with 200 µL PBS per well each time. At the end of last wash, 100 µL of 1µM Hoechst staining solution is added. Sealed plates incubated for at least 30 min in dark, washed with PBS to remove excess stain and PBS is added to each well. Plates can be stored at 4 °C in dark up to 3 days. The translocation of p53/MDM2 is imaged using Molecular translocation module on Cellomics Arrayscan instrument using 10x objective, XF-100 filter sets for Hoechst and GFP. The output parameters were Mean- CircRINGAvgIntenRatio (the ratio of average fluorescence intensities of nucleus and cytoplasm (well average)). The minimally acceptable number of cells per well used for image analysis was set to 500 cells.

Example 15: MCF-7 Breast Cancer Study using SP315, SP249 and SP154

[00592] A xenograft study was performed to test the efficacy of SP315, SP249 and SP154 in inhibiting tumor growth in athymic mice in the MCF-7 breast cancer xenograft model. A negative control stapled peptide. SP252, a point mutation of SP154 (F to A at position 19) was also tested in one group; this peptide had shown no activity in the SJSA-1 *in vitro* viability assay. Slow release 90 day 0.72 mg 17β-estradiol pellets (Innovative Research, Sarasota, FL) were implanted subcutaneously (sc) on the nape of the neck one day prior to tumor cell implantation (Day -1). On Day 0, MCF-7 tumor cells were implanted sc in the flank of female nude (Crl:NU-Foxn1nu) mice. On Day 18, the resultant sc tumors were measured using calipers to determine their length and width and the mice were weighed. The tumor sizes were calculated using the formula (length x width^2)/2 and expressed as cubic millimeters (mm^3). Mice with tumors smaller than 85.3 mm^3 or larger than 417.4 mm^3 were excluded from the subsequent group formation. Thirteen groups of mice, 10 mice per group,

were formed by randomization such that the group mean tumor sizes were essentially equivalent (mean of groups ± standard deviation of groups = 180.7 ± 17.5 mm^3).

[00593] SP315, SP249, SP154 and SP252 dosing solutions were prepared from peptides formulated in a vehicle containing MPEG(2K)-DSPE at 50 mg/mL concentration in a 10 mM Histidine buffered saline at pH 7. This formulation was prepared once for the duration of the study. This vehicle was used as the vehicle control in the subsequent study.

[00594] Each group was assigned to a different treatment regimen. Group 1, as the vehicle negative control group, received the vehicle administered at 8 mL/kg body weight intravenously (iv) three times per week from Days 18-39. Groups 2 and 3 received SP154 as an iv injection at 30 mg/kg three times per week or 40 mg/kg twice a week, respectively. Group 4 received 6.7 mg/kg SP249 as an iv injection three times per week. Groups 5, 6, 7 and 8 received SP315 as an iv injection of 26.7 mg/kg three times per week, 20 mg/kg twice per week, 30 mg/kg twice per week, or 40 mg/kg twice per week, respectively. Group 9 received 30 mg/kg SP252 as an iv injection three times per week.

[00595] During the dosing period the mice were weighed and tumors measured 1-2 times per week. Results in terms of tumor volume are shown in **Figures 15-18** and tumor growth inhibition compared with the vehicle group, body weight change and number of mice with ≥20% body weight loss or death is shown in Table 9. Tumor growth inhibition (TGI) was calculated as $\%TGI=100-[(TuVol^{Treated\text{-}day\ x}-TuVol^{Treated\text{-}day18})/(TuVol^{Vehicle\ negative\ control\text{-}day\ x}-TuVol^{Vehicle\ negative\ control-day18})*100$, where x= day that effect of treatment is being assessed. Group 1, the vehicle negative control group, showed good tumor growth rate for this tumor model.

[00596] For SP154, in the group dosed with 40 mg/kg twice a week 2 mice died during treatment, indicating that this dosing regimen was not tolerable. The dosing regimen of 30 mg/kg of SP154 three times per week was well-tolerated and yielded a TGI of 84%.

[00597] For SP249, the group dosed with 6.7 mg/kg three times per week 4 mice died during treatment, indicating that this dosing regimen was not tolerable.

[00598] All dosing regimens used for SP315 showed good tolerability, with no body weight loss or deaths noted. Dosing with 40 mg/kg of SP315 twice per week produced the highest TGI (92%). The dosing regimens of SP315 of 26.7 mg/kg three times per week, 20 mg/kg twice per week, 30 mg/kg twice per week produced TGI of 86, 82, and 85%, respectively.

[00599] For SP252, the point mutation of SP154 which shows no appreciable activity in *in vitro* assays, dosing with 30 mg/kg three times per week was well-tolerated with no body weight loss or deaths noted. While TGI of 88% was noted by Day 32, that TGI was reduced to 41% by Day 39.

[00600] Results from this Example are shown in **Figures 15-18** and are summarized in Table 9.

Table 9

Group Number	Treatment Group	% BW Change	No. with ≥ 10% BW Loss	No. with ≥ 20% BW Loss or death	% TGI
1	Vehicle	+8.6	0/10	0/10	-

2	SP154 30 mg/kg 3x/wk iv	+5.7	0/10	0/10	*84
3	SP154 40 mg/kg 2x/wk iv	N/A	0/10	2/10 (2 deaths)	Regimen not tolerated
4	SP249 6.7 mg/kg 3x/wk iv	N/A	6/10	4/10	Regimen not tolerated
5	SP315 26.7 mg/kg 3x/wk iv	+3.7	0/10	0/10	*86
6	SP315 20 mg/kg 2x/wk iv	+3.9	0/10	0/10	*82
7	SP315 30 mg/kg 2x/wk iv	+8.0	0/10	0/10	*85
8	SP315 40 mg/kg 2x/wk iv	+2.1	0/10	0/10	*92
9	SP252 30 mg/kg 3x/wk iv	+3.3	0/10	0/10	*41

***p ≤ 0.05 Vs Vehicle Control**

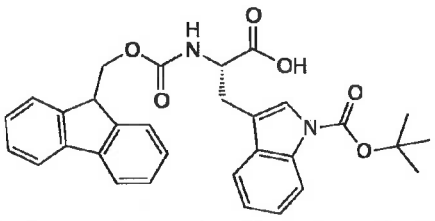
Example 16: Solubility Determination for Peptidomimetic Macrocycles

[00601] Peptidomimetic macrocycles are first dissolved in neat N, N-dimethylacetamide (DMA, Sigma-Aldrich, 38840-1L-F) to make 20X stock solutions over a concentration range of 20-140 mg/mL. The DMA stock solutions are diluted 20-fold in an aqueous vehicle containing 2% Solutol-HS-15, 25 mM histidine, 45 mg/mL mannitol to obtain final concentrations of 1-7 mg/ml of the peptidomimetic macrocycles in 5% DMA, 2% Solutol-HS-15, 25 mM histidine, 45 mg/mL mannitol. The final solutions are mixed gently by repeat pipetting or light vortexing, and then the final solutions are sonicated for 10 min at room temperature in an ultrasonic water bath. Careful visual observation is then performed under hood light using a 7x visual amplifier to determine if precipitate exists on the bottom or as a suspension. Additional concentration ranges are tested as needed to determine the maximum solubility limit for each peptidomimetic macrocycle.

[00602] Results from this Example are shown in **Figure 19**.

Example 17: Preparation of Peptidomimetic Macrocycles using a Boc-protected amino acid.

[00603] Peptidomimetic macrocycle precursors were prepared as described in Example 2 comprising an R8 amino acid at position "i" and an S5 amino acid at position "i+7". The amino acid at position "i+3" was a Boc-protected tryptophan which was incorporated during solid-phase synthesis. Specifically, the Boc-protected tryptophan amino acid shown below (and commercially available, for example, from Novabiochem) was using during solid phase synthesis:



[00604] Metathesis was performed using a ruthenium catalyst prior to the cleavage and deprotection steps. The composition obtained following cyclization was determined by HPLC analysis to contain primarily peptidomimetic macrocycles having a crosslinker comprising a trans olefin ("iso2", comprising the double

bond in an E configuration). Unexpectedly, a ratio of 90:10 was observed for the *trans* and *cis* products, respectively.

Example 18: Testing of peptidomimetic macrocycles for ability to reduce immune checkpoint protein expression or inhibit immune checkpoint protein activity

[00605] HCT-116 cells that are $p53^{WT}$ (but not p53 null) upregulate p53 and down-regulate PD-L1 in response to dosing with Nutlin3. p53 effects on PD-L1 are mediated by transcription of miR-34a, -b and –c. The peptidomimetic macrocycles described herein can increase p53 levels in cancer cells. p53 expression is inversely correlated with PD-L1 in patients with NSCLC and PD-L1 expression is higher in patients with mutant p53 compared to $p53^{WT}$. Patients with low PD-L1 expression and high p53 expression have better survival compared to patients with high PD-L1 expression and low p53 expression. p53 regulates PD-L1 and the miR-34 family downregulates PD-L1 expression by directly repressing PD-L1. Furthermore, therapeutic delivery of miR-34a represses PD-L1 *in vivo* and therapeutic delivery of miR-34a alone or in combination with XRT increases CD8+ T cells. Therapeutic delivery of miR-34a also increases IFN-γ promoting tumor growth delay. miR-34a is directly transactivated by p53 to regulate several pathways in cancer, including tumor immune evasion.

[00606] Assays were performed to determine whether the peptidomimetic macrocycles can diminish PD-L1 activity or expression. Briefly, HCT-116 $p53^{+/+}$ cells and HCT-116 $p53^{-/-}$ cells were treated with DMSO or 10μM SP or 20μM SP as indicated in **Figure 22**. As shown in **Figure 22**, SP treatment led to decreased PD-L1 expression in HCT-116 $p53^{+/+}$ cells, but not HCT-116 $p53^{-/-}$ cells. Similar assays will be performed in cell lines that express higher levels of PD-L1, such as A549 cells, H460 cells, and syngeneic mouse cell lines.

[00607] Assays will be performed to determine whether the peptidomimetic macrocycles can diminish PD-L1 activity or expression via miR-34a to enhance immune response against tumors. Assays will be performed to determine whether the peptidomimetic macrocycles of the invention mimic the immune-enhancing effects of anti-PD-1 and/or anti-PD-L1 agents (with added benefit of cell cycle arrest and apoptosis). Briefly, cancer cells from different lineages MCF-7 (breast), HCT-116 (large intestine), MV4-11 (leukemia), DOHH2, and A375 (melanoma) will be dosed with peptidomimetic macrocycles. These cell lines and others will be chosen to include cell lines that have high levels of PD-L1 expression and others that have low levels of PD-L1 expression. Changes in protein and mRNA levels of PD-1, PD-L1 and miR-34a (and p53 and p21 as controls) will be measured, for example, using flow cytometry. RT-PCR assays will be conducted to quantify miR-34a, miR-34b, and/or miR-34c levels in samples taken by FlowMetric in parallel with flow cytometry measurements. Full dose-response curves will be taken 24, 48, and 72 hours after dosing. Additionally, apoptosis measurements will be taken in parallel.

Example 19: WST-1 Cell Proliferation Assays

[00608] The human tumor cell lines MCF-7 and MOLT-3 were obtained from American Type Culture Collection (ATCC) and grown in EMEM and RPMI1640, respectively. All media were supplemented with 10% (v/v) fetal calf serum, 100 units penicillin and 100 μg/ml streptomycin at 37 °C and 5% CO_2. Prior to dosing, MCF-7 cells were switched to serum free medium and grown at 37 °C overnight.

[00609] One day prior to assaying, cells were trypsinized, counted and seeded at pre-determined densities in 96-well plates as follows: MCF-7, 5000 cells/well/200 µl; MOLT-3, 30,000 cells/well/200 µl.
Cells were dosed with Aileron peptide 1, palbociclib, everolimus, fulvestrant, or romidepsin alone or in combination with Aileron peptide 1 and incubated for three to five days. The WST-1 variant of the MTT assay was used to measure cell viability according to the manufacturer's protocol. WST-1 is a cell-impermeable, sulfonated tetrazolium salt that can be used to examine cell viability without killing the cells. Results can be seen in **Figure 23** (MCF-7 cells, no treatment), **Figure 24** (MCF-7 or MOLT-3 cells, Aileron peptide 1), **Figure 25** (fulvestrant or everolimus), **Figures 26-28** (fulvestrant), **Figures 29-31** (everolimus), **Figures 32-34** (romidepsin), and **Figures 35-37** (palbociclib).

Example 20: Synergism between PLX4032 and the peptidomimetic macrocycles of the disclosure in B-Raf-mutant melanoma cell line A375 and Mel-Ho (V600E) but not in Mel-Juso (H- & N-Ras mutations, COSMIC)

[00610] The combination of a representative peptidomimetic macrocycle of the disclosure (a p53 hydrocarbon cross-linked polypeptide macrocycle with an observed mass of 950-975 m/e) and commercially available targeted agent PLX4032 BRAF inhibitor was tested at various drug doses. The EC_{50} of Aileron peptide 1 on A375 cells was determined to be 70 nM. As seen in **Figure 20**, the peptidomimetic macrocycle displayed synergy with PLX4032 in B-Raf-mutant melanoma cell line A375. As seen in **Figure 21**, the peptidomimetic macrocycle also displayed synergy with PLX4032 in Mel-Ho (V600E) but not in Mel-Juso (H- & N-Ras mutations, COSMIC).

Example 21: Synergism between fluvestant and the peptidomimetic macrocycles of the disclosure in the MCF-7 breast cancer cell line

[00611] The combination of a representative peptidomimetic macrocycle of the disclosure (a p53 hydrocarbon cross-linked polypeptide macrocycle with an observed mass of 950-975 m/e) and commercially available targeted agent fluvestrant was tested at various drug doses. Initially, various MCF-7 cell numbers were plated and evaluated 3-7 days later to determine the optimal number of cells to be plated and treatment duration **(Figure 23)**. Next, the optimal number of cells were plated and treated with various concentrations of Aileron peptide 1 or with various concentrations of fluvestrant alone. Cells were evaluated for viability by WST-1 assay or MTT assay 3-7 days after beginning treatment **(Figures 24A** and **26)**. A number of concentrations around the IC_{50} of the peptidomimetic macrocycle and a number of concentrations around the IC_{50} of fluvestrant were then determined.

	IC_{50} (nM)
FUL	0.768
FUL+0.13 µM Aileron peptide 1	0.4428
FUL+0.4 µM Aileron peptide 1	0.2609

FUL+1.2 μM Aileron peptide 1	0.2621

[00612] The EC_{50} of Aileron peptide 1 on MCF-7 cells was determined to be 410 nM. These chosen concentrations were tested on MCF-7 cells for Aileron peptide 1 in combination with fluvestrant. The optimal number of MCF-7 cells was plated and treated with Aileron peptide 1 and fluvestrant in combination. Aileron peptide 1 was added to the cells simultaneously with the fluvestrant. Cells were evaluated for viability by WST-1 assay or MTT assay 3-7 days after beginning the simultaneous treatments (**Figures 25, 27 and 28**). As seen in **Figure 26**, fulvestrant inhibited MCF-7 breast cancer cell proliferation with limited cell killing as a single agent. However, as seen in **Figures 25, 27 and 28**, Aileron peptide 1 displayed synergy with fluvestant in the MCF-7 breast cancer cell line. Combination index (CI) values were calculated using the CompuSyn software. The data were expressed as log(CI). CI values: 0–0.1, very strong synergism; 0.1–0.3, strong synergism; 0.3–0.7, synergism; 0.7–0.85, moderate synergism; 0.85–0.90, slight synergism; 0.90–1.10, nearly additive; 1.10–1.20, slight antagonism; 1.20–1.45, moderate antagonism; 1.45–3.3, antagonism; 3.3–10, strong antagonism; 10, very strong antagonism.

[00613] Exemplary cooperativity index calculations are shown in the table below:

Dose Aileron peptide 1 (μM)	Dose fulvestrant (nM)	Effect	CI
0.001	3.0	0.323	0.14159
0.003	3.0	0.402	0.09317
0.01	3.0	0.418	0.10712
0.03	3.0	0.482	0.12223
0.1	3.0	0.588	0.17027
0.3	3.0	0.644	0.34356
1.0	3.0	0.709	0.77439
3.0	3.0	0.755	1.74401
10.0	3.0	0.901	1.62697
30.0	3.0	0.92	3.70727
0.001	10.0	0.429	0.23789
0.003	10.0	0.414	0.26661
0.01	10.0	0.466	0.21426
0.03	10.0	0.519	0.19805
0.1	10.0	0.594	0.22753
0.3	10.0	0.701	0.28387
1.0	10.0	0.737	0.68105
3.0	10.0	0.786	1.43567

10.0	10.0	0.911	1.42122
30.0	10.0	0.946	2.26507
0.001	30.0	0.43	0.70343
0.003	30.0	0.418	0.76190
0.01	30.0	0.443	0.67686
0.03	30.0	0.478	0.60025
0.1	30.0	0.586	0.42426
0.3	30.0	0.6	0.66109
1.0	30.0	0.718	0.84264
3.0	30.0	0.758	1.79040
10.0	30.0	0.897	1.73116
30.0	30.0	0.917	3.89829
0.13	0.03	0.269	0.90978
0.13	0.1	0.321	0.68139
0.13	0.3	0.486	0.30536
0.13	1.0	0.552	0.23162
0.13	3.0	0.63	0.17212
0.13	10.0	0.61	0.24727
0.13	30.0	0.611	0.40656
0.13	100.0	0.594	1.07046
0.13	300.0	0.58	3.09815
0.13	900.0	0.627	6.70074
0.4	0.03	0.492	0.89889
0.4	0.1	0.524	0.77451
0.4	0.3	0.58	0.59564
0.4	1.0	0.666	0.39101
0.4	3.0	0.675	0.38341
0.4	10.0	0.693	0.38057
0.4	30.0	0.685	0.49815
0.4	100.0	0.66	0.98770
0.4	300.0	0.679	1.92173
0.4	900.0	0.667	5.45686

Example 22: Synergism between everolimus and the peptidomimetic macrocycles of the disclosure in the MCF-7 breast cancer cell line

[00614] The combination of a representative peptidomimetic macrocycle of the disclosure (a p53 hydrocarbon cross-linked polypeptide macrocycle with an observed mass of 950-975 m/e) and commercially available targeted agent everolimus was tested at various drug doses. Initially, various MCF-7 cell numbers were plated and evaluated 3-7 days later to determine the optimal number of cells to be plated and treatment duration **(Figure 23)**. Next, the optimal number of cells were plated and treated with various concentrations of Aileron peptide 1 or with various concentrations of everolimus alone. Cells were evaluated for viability by WST-1 assay or MTT assay 3-7 days after beginning treatment **(Figures 24A and 29)**. A number of concentrations around the IC_{50} of the peptidomimetic macrocycle and a number of concentrations around the IC_{50} of everolimus were then determined. The EC_{50} of Aileron peptide 1 on MCF-7 cells was determined to be 410 nM. These chosen concentrations were tested on MCF-7 cells for Aileron peptide 1 in combination with everolimus. The optimal number of MCF-7 cells was plated and treated with Aileron peptide 1 and everolimus in combination. Aileron peptide 1 was added to the cells simultaneously with the everolimus. Cells were evaluated for viability by WST-1 assay or MTT assay 3-7 days after beginning the simultaneous treatments **(Figures 25, 30 and 31)**. As seen in **Figure 29**, everolimus inhibited MCF-7 breast cancer cell proliferation with limited cell killing as a single agent. However, as seen in **Figures 25, 30 and 31**, Aileron peptide 1 displayed synergy with everolimus in the MCF-7 breast cancer cell line.

[00615] Exemplary cooperativity index calculations are shown in the table below:

Dose Aileron peptide 1 (μM)	Dose everolimus (μM)	Effect	CI
0.001	0.001	0.363	0.46998
0.003	0.001	0.365	0.45978
0.01	0.001	0.406	0.23282
0.03	0.001	0.429	0.21862
0.1	0.001	0.516	0.22558
0.3	0.001	0.703	0.23698
1.0	0.001	0.811	0.39235
3.0	0.001	0.864	0.74302
10.0	0.001	0.952	0.65211
30.0	0.001	0.964	1.37599
0.001	0.003	0.469	0.18255
0.003	0.003	0.495	0.11727
0.01	0.003	0.508	0.10758
0.03	0.003	0.557	0.08415
0.1	0.003	0.609	0.14138
0.3	0.003	0.722	0.21318

1.0	0.003	0.819	0.36874
3.0	0.003	0.871	0.69183
10.0	0.003	0.945	0.77158
30.0	0.003	0.952	1.95633
0.001	0.01	0.524	0.21623
0.003	0.01	0.537	0.17334
0.01	0.01	0.525	0.22955
0.03	0.01	0.554	0.17216
0.1	0.01	0.623	0.15213
0.3	0.01	0.716	0.22398
1.0	0.01	0.799	0.42963
3.0	0.01	0.854	0.81864
10.0	0.01	0.933	0.98709
30.0	0.01	0.953	1.90630
0.001	0.1	0.515	2.53851
0.003	0.1	0.541	1.56244
0.01	0.1	0.522	2.24431
0.03	0.1	0.563	1.07533
0.1	0.1	0.645	0.31323
0.3	0.1	0.735	0.22476
1.0	0.1	0.783	0.48900
3.0	0.1	0.844	0.89820
10.0	0.1	0.909	1.45716
30.0	0.1	0.925	3.41419
0.13	0.0001	0.477	0.31844
0.13	0.0003	0.548	0.22849
0.13	0.001	0.567	0.21454
0.13	0.003	0.626	0.16282
0.13	0.01	0.673	0.13216
0.13	0.03	0.699	0.12434
0.13	0.1	0.717	0.13805
0.13	0.3	0.743	0.15137
0.13	1.0	0.762	0.21739
0.13	3.0	0.789	0.27115

0.4	0.0001	0.633	0.45701
0.4	0.0003	0.664	0.38983
0.4	0.001	0.673	0.37246
0.4	0.003	0.723	0.28218
0.4	0.01	0.74	0.25644
0.4	0.03	0.746	0.25127
0.4	0.1	0.76	0.23938
0.4	0.3	0.8	0.18580
0.4	1.0	0.804	0.21110
0.4	3.0	0.828	0.20196
1.2	0.0001	0.703	0.94557
1.2	0.0003	0.746	0.73428
1.2	0.001	0.768	0.63825
1.2	0.003	0.783	0.57706
1.2	0.01	0.798	0.51924
1.2	0.03	0.798	0.52033
1.2	0.1	0.816	0.45611
1.2	0.3	0.832	0.40364
1.2	1.0	0.814	0.49378
1.2	3.0	0.845	0.39182

[00616] Analysis was performed according to Chou *et al.*, Advances in Enzyme Regulation, 22:27-55 (1984) and Zhang *et al.*, Am J Cancer Res., 6:97-104 (2016). Combination index (CI) values were calculated using the CompuSyn software. The data were expressed as log(CI). CI values: 0–0.1, very strong synergism; 0.1–0.3, strong synergism; 0.3–0.7, synergism; 0.7–0.85, moderate synergism; 0.85–0.90, slight synergism; 0.90–1.10, nearly additive; 1.10–1.20, slight antagonism; 1.20–1.45, moderate antagonism; 1.45–3.3, antagonism; 3.3–10, strong antagonism; 10, very strong antagonism.

Example 23: Treatment with romidepsin and the peptidomimetic macrocycles of the disclosure in the human MOLT-3 T-lymphoid cell line

[00617] The combination of Aileron peptide 1 and commercially available targeted agent romidepsin was tested at various drug doses. Initially, various MOLT-3 cell numbers were plated and evaluated 3-7 days later to determine the optimal number of cells to be plated and treatment duration. Next, the optimal number of cells were plated and treated with various concentrations of Aileron peptide 1 or with various concentrations of romidepsin alone. Cells were evaluated for viability by WST-1 assay or MTT assay 3-7 days after beginning treatment (**Figures 24B** and **32**). A number of concentrations around the IC_{50} of the peptidomimetic macrocycle and a number of concentrations around the IC_{50} of romidepsin were then determined.

	IC_{50} (μM)
Aileron peptide 1	0.088
Aileron peptide 1+0.5 nM Romidepsin	0.1014
Aileron peptide 1+1.5 nM Romidepsin	0.038
Aileron peptide 1+3 nM Romidepsin	0.028

[00618] The EC_{50} of Aileron peptide 1 on MOLT-3 cells was determined to be 210 nM. These chosen concentrations were tested on MOLT-3 cells for the peptidomimetic macrocycle in combination with romidepsin. The optimal number of MOLT-3 cells was plated and treated with Aileron peptide 1 and romidepsin in combination. Aileron peptide 1 was added to the cells 2 hours prior to addition of the romidepsin. Cells were evaluated for viability by WST-1 assay or MTT assay 3-7 days after beginning the sequential treatment (**Figures 33** and **34**).

Example 24: Treatment with palbociclib and the peptidomimetic macrocycles of the disclosure in the MCF-7 breast cancer cell line

[00619] The combination of Aileron peptide 1 and commercially available targeted agent palbociclib was tested at various drug doses. Initially, various MCF-7 cell numbers were plated and evaluated 3-7 days later to determine the optimal number of cells to be plated and treatment duration (**Figure 23**). Next, the optimal number of cells were plated and treated with various concentrations of Aileron peptide 1 or with various concentrations of palbociclib alone. Cells were evaluated for viability by WST-1 assay or MTT assay 3-7 days or 120 hrs after beginning treatment (**Figures 24A** and **35**). A number of concentrations around the IC_{50} of the peptidomimetic macrocycle and a number of concentrations around the IC_{50} of palbociclib were then determined. The EC_{50} of Aileron peptide 1 on MCF-7 cells was determined to be 410 nM. These chosen concentrations were tested on MCF-7 cells for Aileron peptide 1 in combination with palbociclib. The optimal number of MCF-7 cells was plated and treated with Aileron peptide 1 and palbociclib in combination. Aileron peptide 1 was added to the cells simultaneously with the palbociclib. Cells were evaluated for viability by WST-1 assay or MTT assay 3-7 days after beginning the simultaneous treatments (**Figures 36** and **37**).

[00620] Exemplary cooperativity index calculations are shown in the table below:

Dose Aileron peptide 1 (μM)	Dose palbociclib (μM)	Effect	CI
0.001	0.3	0.178	0.59570
0.003	0.3	0.184	0.59898
0.01	0.3	0.223	0.54530
0.03	0.3	0.25	0.62998
0.1	0.3	0.325	0.79278
0.3	0.3	0.532	0.68885

1.0	0.3	0.65	1.13080
3.0	0.3	0.743	1.92593
10.0	0.3	0.924	1.17267
30.0	0.3	0.945	2.32597
0.4	0.001	0.585	0.57898
0.4	0.003	0.553	0.67550
0.4	0.01	0.55	0.68802
0.4	0.03	0.545	0.71276
0.4	0.1	0.556	0.70459
0.4	0.3	0.608	0.61579
0.4	1.0	0.592	0.90805
0.4	3.0	0.614	1.46501
0.4	10.0	0.698	2.61449
0.4	30.0	0.999	0.02893

[00621] Cells were also evaluated for viability using the CyQUANT method after beginning treatment (**Figures 78A and 79A**). Cells were evaluated for viability using the CyQUANT method after beginning the simultaneous treatments (**Figures 78B and 79B**). Analysis was performed according to Chou *et al.*, Advances in Enzyme Regulation, 22:27-55 (1984) and Zhang *et al.*, Am J Cancer Res., 6:97-104 (2016). Combination index (CI) values were calculated using the CompuSyn software. The data were expressed as log(CI). CI values: 0–0.1, very strong synergism; 0.1–0.3, strong synergism; 0.3–0.7, synergism; 0.7–0.85, moderate synergism; 0.85–0.90, slight synergism; 0.90–1.10, nearly additive; 1.10–1.20, slight antagonism; 1.20–1.45, moderate antagonism; 1.45–3.3, antagonism; 3.3–10, strong antagonism; 10, very strong antagonism.

Example 25: Treatment with dexamethasone and the peptidomimetic macrocycles of the disclosure in the DOHH-2 human lymphoma B-cell line

[00622] The combination of one or more representative peptidomimetic macrocycles of the disclosure and commercially available targeted agent dexamethasone are tested at various drug doses. Initially, various DOHH-2 cell numbers are plated and evaluated 3-7 days later to determine the optimal number of cells to be plated and treatment duration. Next, the optimal number of cells are plated and treated with various concentrations of a representative peptidomimetic macrocycle of the disclosure or with various concentrations of dexamethasone alone. Cells are evaluated for viability by WST-1 assay or MTT assay 3-7 days after beginning treatment. A number of concentrations around the IC_{50} of the peptidomimetic macrocycle and a number of concentrations around the IC_{50} of dexamethasone are then determined. The EC_{50} of Aileron peptide 1 on DOHH-2 cells was determined to be 60 nM. These chosen concentrations are tested on DOHH-2 cells for the peptidomimetic macrocycle in combination with dexamethasone. The optimal number of DOHH-2 cells are plated and treated with the representative peptidomimetic macrocycle of the disclosure and dexamethasone in combination. In some cases, the peptidomimetic macrocycle are added to the cells simultaneously with the

dexamethasone. In some cases, the peptidomimetic macrocycle are added to the cells prior to addition of the dexamethasone. In some cases, the peptidomimetic macrocycle are added to the cells after addition of the dexamethasone. Cells are evaluated for viability by WST-1 assay or MTT assay 3-7 days after beginning the simultaneous or sequential treatments.

Example 26: Treatment with trametinib and the peptidomimetic macrocycles of the disclosure in the A375 human melanoma cell line

[00623] The combination of one or more representative peptidomimetic macrocycles of the disclosure and commercially available targeted agent trametinib are tested at various drug doses. Initially, various A375 cell numbers are plated and evaluated 3-7 days later to determine the optimal number of cells to be plated and treatment duration. Next, the optimal number of cells are plated and treated with various concentrations of a representative peptidomimetic macrocycle of the disclosure or with various concentrations of trametinib alone. Cells are evaluated for viability by WST-1 assay or MTT assay 3-7 days after beginning treatment. A number of concentrations around the IC_{50} of the peptidomimetic macrocycle and a number of concentrations around the IC_{50} of trametinib are then determined. The EC_{50} of Aileron peptide 1 on A375 cells was determined to be 70 nM. These chosen concentrations are tested on A375 cells for the peptidomimetic macrocycle in combination with trametinib. The optimal number of A375 cells are plated and treated with the representative peptidomimetic macrocycle of the disclosure and trametinib in combination. In some cases, the peptidomimetic macrocycle are added to the cells simultaneously with the trametinib. In some cases, the peptidomimetic macrocycle are added to the cells prior to addition of the trametinib. In some cases, the peptidomimetic macrocycle are added to the cells after addition of the trametinib. Cells are evaluated for viability by WST-1 assay or MTT assay 3-7 days after beginning the simultaneous or sequential treatments.

Example 27: Treatment with rituximab and the peptidomimetic macrocycles of the disclosure in the DOHH-2 human lymphoma B-cell line

[00624] The combination of one or more representative peptidomimetic macrocycles of the disclosure and commercially available targeted agent rituximab were tested at various drug doses. Initially, various DOHH-2 cell numbers were plated and evaluated 3-7 days later to determine the optimal number of cells to be plated and treatment duration. Next, the optimal number of cells were plated and treated with various concentrations of a representative peptidomimetic macrocycle of the disclosure or with various concentrations of rituximab alone. Cells were evaluated for viability by WST-1 assay or MTT assay 3-7 days after beginning treatment. A number of concentrations around the IC_{50} of the peptidomimetic macrocycle and a number of concentrations around the IC_{50} of rituximab were then determined. The EC_{50} of Aileron peptide 1 on DOHH-2 cells was determined to be 60 nM. These chosen concentrations were tested on DOHH-2 cells for the peptidomimetic macrocycle in combination with rituximab. The optimal number of DOHH-2 cells were plated and treated with the representative peptidomimetic macrocycle of the disclosure and rituximab in combination. In some cases, the peptidomimetic macrocycle were added to the cells simultaneously with the rituximab. In some cases, the peptidomimetic macrocycle were added to the cells prior to addition of the rituximab. In some cases, the peptidomimetic macrocycle were added to the cells after addition of the rituximab. Cells were

evaluated for viability by WST-1 assay or MTT assay 3-7 days after beginning the simultaneous or sequential treatments.

Example 28: Treatment with obinutuzumab and the peptidomimetic macrocycles of the disclosure in the DOHH-2 human lymphoma B-cell line

[00625] The combination of one or more representative peptidomimetic macrocycles of the disclosure and commercially available targeted agent obinutuzumab are tested at various drug doses. Initially, various DOHH-2 cell numbers are plated and evaluated 3-7 days later to determine the optimal number of cells to be plated and treatment duration. Next, the optimal number of cells are plated and treated with various concentrations of a representative peptidomimetic macrocycle of the disclosure or with various concentrations of obinutuzumab alone. Cells are evaluated for viability by WST-1 assay or MTT assay 3-7 days after beginning treatment. A number of concentrations around the IC_{50} of the peptidomimetic macrocycle and a number of concentrations around the IC_{50} of obinutuzumab are then determined. The EC_{50} of Aileron peptide 1 on DOHH-2 cells was determined to be 60 nM. These chosen concentrations are tested on DOHH-2 cells for the peptidomimetic macrocycle in combination with obinutuzumab. The optimal number of DOHH-2 cells are plated and treated with the representative peptidomimetic macrocycle of the disclosure and obinutuzumab in combination. In some cases, the peptidomimetic macrocycle are added to the cells simultaneously with the obinutuzumab. In some cases, the peptidomimetic macrocycle are added to the cells prior to addition of the obinutuzumab. In some cases, the peptidomimetic macrocycle are added to the cells after addition of the obinutuzumab. Cells are evaluated for viability by WST-1 assay or MTT assay 3-7 days after beginning the simultaneous or sequential treatments.

Example 29: Treatment with dabrafenib and the peptidomimetic macrocycles of the disclosure in the A375 human melanoma cell line

[00626] The combination of one or more representative peptidomimetic macrocycles of the disclosure and commercially available targeted agent dabrafenib are tested at various drug doses. Initially, various A375 cell numbers are plated and evaluated 3-7 days later to determine the optimal number of cells to be plated and treatment duration. Next, the optimal number of cells are plated and treated with various concentrations of a representative peptidomimetic macrocycle of the disclosure or with various concentrations of dabrafenib alone. Cells are evaluated for viability by WST-1 assay or MTT assay 3-7 days after beginning treatment. A number of concentrations around the IC_{50} of the peptidomimetic macrocycle and a number of concentrations around the IC_{50} of dabrafenib are then determined. The EC_{50} of Aileron peptide 1 on A375 cells was determined to be 70 nM. These chosen concentrations are tested on A375 cells for the peptidomimetic macrocycle in combination with dabrafenib. The optimal number of A375 cells are plated and treated with the representative peptidomimetic macrocycle of the disclosure and dabrafenib in combination. In some cases, the peptidomimetic macrocycle are added to the cells simultaneously with the dabrafenib. In some cases, the peptidomimetic macrocycle are added to the cells prior to addition of the dabrafenib. In some cases, the peptidomimetic macrocycle are added to the cells after addition of the dabrafenib. Cells are evaluated for viability by WST-1 assay or MTT assay 3-7 days after beginning the simultaneous or sequential treatments.

Example 30: Treatment with vemurafenib and the peptidomimetic macrocycles of the disclosure in the A375 human melanoma cell line

[00627] The combination of one or more representative peptidomimetic macrocycles of the disclosure and commercially available targeted agent vemurafenib are tested at various drug doses. Initially, various A375 cell numbers are plated and evaluated 3-7 days later to determine the optimal number of cells to be plated and treatment duration. Next, the optimal number of cells are plated and treated with various concentrations of a representative peptidomimetic macrocycle of the disclosure or with various concentrations of vemurafenib alone. Cells are evaluated for viability by WST-1 assay or MTT assay 3-7 days after beginning treatment. A number of concentrations around the IC_{50} of the peptidomimetic macrocycle and a number of concentrations around the IC_{50} of vemurafenib are then determined. The EC_{50} of Aileron peptide 1 on A375 cells was determined to be 70 nM. These chosen concentrations are tested on A375 cells for the peptidomimetic macrocycle in combination with vemurafenib. The optimal number of A375 cells are plated and treated with the representative peptidomimetic macrocycle of the disclosure and vemurafenib in combination. In some cases, the peptidomimetic macrocycle are added to the cells simultaneously with the vemurafenib. In some cases, the peptidomimetic macrocycle are added to the cells prior to addition of the vemurafenib. In some cases, the peptidomimetic macrocycle are added to the cells after addition of the vemurafenib. Cells are evaluated for viability by WST-1 assay or MTT assay 3-7 days after beginning the simultaneous or sequential treatments.

Example 31: Treatment with dabrafenib, vemurafenib and the peptidomimetic macrocycles of the disclosure in the A375 human melanoma cell line

[00628] The combination of one or more representative peptidomimetic macrocycles of the disclosure and commercially available targeted agents dabrafenib and vemurafenib are tested at various drug doses. Initially, various A375 cell numbers are plated and evaluated 3-7 days later to determine the optimal number of cells plated and treatment duration. Next, the optimal number of cells are plated and treated with various concentrations of a representative peptidomimetic macrocycle of the disclosure or with various concentrations of vemurafenib alone or with various concentrations of dabrafenib alone. Cells are evaluated for viability by WST-1 assay or MTT assay 3-7 days after beginning treatment. A number of concentrations around the IC_{50} of the peptidomimetic macrocycle and a number of concentrations around the IC_{50} of dabrafenib and vemurafenib are then determined. The EC_{50} of Aileron peptide 1 on A375 cells is determined to be 70 nM. These chosen concentrations are tested on A375 cells for the peptidomimetic macrocycle in combination with dabrafenib and vemurafenib. The optimal number of A375 cells are plated and treated with the representative peptidomimetic macrocycle of the disclosure and dabrafenib and vemurafenib in combination. In some cases, the peptidomimetic macrocycle are added to the cells simultaneously with the dabrafenib and vemurafenib. In some cases, the peptidomimetic macrocycle are added to the cells prior to addition of the dabrafenib and vemurafenib. In some cases, the peptidomimetic macrocycle are added to the cells after addition of the dabrafenib and vemurafenib. Cells are evaluated for viability by WST-1 assay or MTT assay 3-7 days after beginning the simultaneous or sequential treatments.

Example 32: Treatment with cytarabine (Ara-C), azacitidine, decitabine, and midostaurin with the peptidomimetic macrocycles of the disclosure in the MV4-11 leukemia cancer cell line.

[00629] The combinations of Aileron peptide 1 (AP1) and commercially available Ara-C (**Figure 38A**), azacitidine (**Figure 39A**), decitabine (**Figure 40A**), and midostaurin (**Figure 41A**) were tested at various drug doses. Initially, various MV4-11 cell numbers were plated and evaluated 3-7 days later to determine the optimal number of cells to be plated and treatment duration.

[00630] Next, the optimal number of cells were plated and treated with various concentrations of AP1 or with various concentrations of Ara-C, azacitidine, decitabine, or midostaurin alone. Cells were evaluated for viability by WST-1 assay or MTT assay 3-7 days after beginning treatment. AP1 in combination with Ara-C (**Figure 38B**), azacitidine (**Figure 39B**), decitabine (**Figure 40B**), or midostaurin (**Figure 41B**). All showed complementary *in vitro* anticancer activity. Combination with Ara-C, azacitidine, decitabine, or midostaurin enhanced AP1 inhibition of cancer cell proliferation and cell killing.

[00631] A drug combination index plot was used to assess the synergistic, additive, or antagonistic properties of each combination treatment. The anti-proliferative effect of the Ara-C and AP1 combination was mostly additive with some degree of synergy (**Figure 38C**). The anti-proliferative effect of the azacitidine and AP1 combination was mostly additive with some synergy (**Figure 39C**). The anti-proliferative effect of the decitabine and AP1 combination was mostly additive (**Figure 40C**). The anti-proliferative effect of the midostaurin and AP1 combination was mostly synergistic (**Figure 41C**). Combination index (CI) values were calculated using the CompuSyn software. The data were expressed as log(CI). CI values: 0–0.1, very strong synergism; 0.1–0.3, strong synergism; 0.3–0.7, synergism; 0.7–0.85, moderate synergism; 0.85–0.90, slight synergism; 0.90–1.10, nearly additive; 1.10–1.20, slight antagonism; 1.20–1.45, moderate antagonism; 1.45–3.3, antagonism; 3.3–10, strong antagonism; 10, very strong antagonism.

Example 33: Treatment with vincristine (VCR) and cyclophosphamide (CTX) with the peptidomimetic macrocycles of the disclosure in the DOHH-2 lymphoma B-cell cancer cell line.

[00632] The combinations of AP1 and commercially available VCR (**Figure 42A**) and CTX (**Figure 44A**) were tested at various drug doses. Initially, various DOHH-2 cell numbers were plated and evaluated 3-7 days later to determine the optimal number of cells to be plated and treatment duration.

[00633] Next, the optimal number of cells were plated and treated with various concentrations of AP1 or with various concentrations of VCR or CTX alone. Cells were evaluated for viability by WST-1 assay or MTT assay 72 hours after beginning treatment with VCR (**Figure 42B**) or CTX (**Figure 44B**). AP1 in combination with VCR showed complementary *in vitro* anticancer activity (**Figure 43**). AP1 in combination with CTX showed complementary *in vitro* anticancer activity (**Figure 45**).

[00634] A drug combination index plot was used to assess the synergistic, additive, or antagonistic properties of each combination treatment. The anti-proliferative effect of the VCR and AP1 combination was mostly synergistic (**Figure 42C**). The anti-proliferative effect of the CTX and AP1 combination was synergistic (**Figure 44C**). Combination index (CI) values were calculated using the CompuSyn software. The data were expressed as log(CI). CI values: 0–0.1, very strong synergism; 0.1–0.3, strong synergism; 0.3–0.7, synergism;

0.7–0.85, moderate synergism; 0.85–0.90, slight synergism; 0.90–1.10, nearly additive; 1.10–1.20, slight antagonism; 1.20–1.45, moderate antagonism; 1.45–3.3, antagonism; 3.3–10, strong antagonism; 10, very strong antagonism.

[00635] A number of concentrations around the IC_{50} of the peptidomimetic macrocycle and a number of concentrations around the IC_{50} of VCR were then determined.

	IC_{50} (μM)
AP1	0.3095
AP1 + 0.3 nM VCR	0.2520
AP1 + 3 nM VCR	0.092

[00636] A number of concentrations around the IC_{50} of the peptidomimetic macrocycle and a number of concentrations around the IC_{50} of CTX were then determined.

	IC_{50} (mM)
CTX	1.981
CTX + 0.07 μM AP1	0.4109
CTX + 0.2 μM AP1	0.1718
CTX + 0.6 μM AP1	0.2579

Example 34: The order of addition effects on DOHH-2 cell viability using various concentrations of AP1 in combination with VCR.

[00637] The anticancer activity of the combination treatment was assessed based on the order of addition of the drugs. DOHH-2 cells were sequentially treated by varying concentrations of AP1 and VCR for 72 hrs (**Figure 46**). AP1 suppressed DOHH-2 cell growth with or without VCR (**Figure 47**). Similiarly, VCR suppressed DOHH-2 cell growth with or without AP1 (**Figure 48**).

Example 35: The order of addition effects on DOHH-2 cell viability using various concentrations of AP1 in combination with CTX.

[00638] The anticancer activity of the combination treatment was assessed based on the order of addition of the drugs. DOHH-2 cells were sequentially treated by varying concentrations of AP1 and CTX for 72 hrs (**Figure 49**). AP1 suppressed DOHH-2 cell growth with or without CTX (**Figure 50**). Similiarly, CTX suppressed DOHH-2 cell growth with or without AP1 (**Figure 51**).

Example 36: The order of addition effects on MV4-11 cell viability using various concentrations of AP1 in combination with midostaurin.

[00639] The anticancer activity of the combination treatment was assessed based on the order of addition of the drugs. MV4-11 cells were sequentially treated by varying concentrations of AP1 and midostaurin for 72 hrs (**Figure 52**). AP1 suppressed MV4-11 cell growth with or without midostaurin (**Figure 53**). Similiarly, midostaurin suppressed MV4-11 cell growth with or without AP1 (**Figure 54**).

Example 37: The order of addition effects on MV4-11 cell viability using various concentrations of AP1 in combination with decitabine.

[00640] The anticancer activity of the combination treatment was assessed based on the order of addition of the drugs. MV4-11 cells were sequentially treated by varying concentrations of AP1 and decitabine for 72 hrs **(Figure 55)**. AP1 suppressed MV4-11 cell growth with or without decitabine **(Figure 56)**. Similiarly, decitabine suppressed MV4-11 cell growth with or without AP1 **(Figure 57)**.

Example 38: The order of addition effects on MV4-11 cell viability using various concentrations of AP1 in combination with Ara-C.

[00641] The anticancer activity of the combination treatment was assessed based on the order of addition of the drugs. MV4-11 cells were sequentially treated by varying concentrations of AP1 and Ara-C for 72 hrs **(Figure 58)**. AP1 suppressed MV4-11 cell growth with or without Ara-C **(Figure 59)**. Similiarly, Ara-C suppressed MV4-11 cell growth with or without AP1 **(Figure 60)**.

Example 39: The order of addition effects on MV4-11 cell viability using various concentrations of AP1 in combination with azacitidine.

[00642] The anticancer activity of the combination treatment was assessed based on the order of addition of the drugs. MV4-11 cells were sequentially treated by varying concentrations of AP1 and azacitidine for 72 hrs **(Figure 61)**. AP1 suppressed MV4-11 cell growth with or without azacitidine **(Figure 62)**. Similiarly, azacitidine suppressed MV4-11 cell growth with or without AP1 **(Figure 63)**.

Example 40: Treatment with fulvestrant (FUL) and everolimus with the peptidomimetic macrocycles of the disclosure in the MCF-7 breast cancer cell line.

[00643] The combinations of AP1 and commercially available fulvestrant **(Figures 64A and 65A)** and everolimus **(Figures 66A and 67A)** were tested at various drug doses. Initially, various MCF-7 cell numbers were plated and evaluated 3-7 days later to determine the optimal number of cells to be plated and treatment duration.

[00644] Next, the optimal number of cells were plated and treated with various concentrations of AP1 or with various concentrations of fulvestrant or everolimus alone. Cells were evaluated for viability by WST-1 assay or MTT assay 120 hours after beginning treatment. AP1 suppressed MCF-7 cell growth with or without fulvestrant **(Figures 64B and 65B)**. AP1 suppressed MCF-7 cell growth with or without everolimus **(Figures 66B and 67B)**.

[00645] A number of concentrations around the IC_{50} of the peptidomimetic macrocycle and a number of concentrations around the IC_{50} of FUL were then determined.

	IC_{50} (nM)
FUL	0.768
FUL + 0.13 μM AP1	0.4428
FUL + 0.4 μM AP1	0.2609
FUL + 1.2 μM AP1	0.2621

Example 41: Treatment with rituximab and romidepsin with the peptidomimetic macrocycles of the disclosure in the MOLT-3 T-lymphoid cancer cell line.

[00646] The combinations of AP1 and commercially available rituximab **(Figures 68A and 69A)** and romidepsin **(Figures 71A and 72A)** were tested at various drug doses. Initially, various MOLT-3 cell numbers were plated and evaluated 3-7 days later to determine the optimal number of cells to be plated and treatment duration.

[00647] Next, the optimal number of cells were plated and treated with various concentrations of AP1 or with various concentrations of rituximab or romidepsin alone. Cells were evaluated for viability by WST-1 assay or MTT assay 3-7 days after beginning treatment with rituximab **(Figures 68B and 69B)** or romidepsin **(Figure 71A and 72B)**. AP1 in combination with rituximab showed complementary *in vitro* anticancer activity **(Figure 70)**. AP1 in combination with romidepsin showed complementary *in vitro* anticancer activity **(Figure 73)**.

Example 42: Treatment with rituximab and romidepsin with the peptidomimetic macrocycles of the disclosure in the MCF-7 breast cancer cell line.

[00648] The combinations of AP1 and commercially available ribociclib **(Figures 74A and 75A)** and abemaciclib **(Figures 76A and 77A)** were tested at various drug doses. Initially, various MCF-7 cell numbers were plated and evaluated 3-7 days later to determine the optimal number of cells to be plated and treatment duration.

[00649] Next, the optimal number of cells were plated and treated with various concentrations of AP1 or with various concentrations of ribociclib or abemaciclib alone. Cells were evaluated for viability by WST-1 assay or MTT assay 72 or 120 hours after beginning treatment with rituximab **(Figures 74B and 75B)** or romidepsin **(Figure 76A and 77B)**.

Example 43: The order of addition effects on MCF-7 cell viability using various concentrations of AP1 in combination with palbociclib using the CyQUANT method.

[00650] The anticancer activity of the combination treatment was assessed based on the order of addition of the drugs. MCF-7 cells were sequentially treated by varying concentrations of AP1 and palbociclib for 72 hrs **(Figure 80)**. AP1 suppressed MCF-7 cell growth with or without palbociclib **(Figure 81)**. Similiarly, palbociclib suppressed MCF-7 cell growth with or without AP1 **(Figure 82)**.

Example 44: Treatment with dexamethasone with the peptidomimetic macrocycles of the disclosure in the MCF-7 breast cancer cell line.

[00651] The combination of AP1 and commercially available dexamethasone was tested at various drug doses for 120 hrs. Cells were evaluated for viability by WST-1 assay. AP1 suppressed MCF-7 cell growth with or without dexamethasone **(Figure 83)**.

Example 45: Treatment with zelboraf, tafinlar, and mekinist with the peptidomimetic macrocycles of the disclosure in the A375 melanoma cancer cell line.

[00652] The combinations of AP1 and commercially available zelboraf **(Figures 84A and 85A)**, tafinlar **(Figures 86A and 87A)**, and mekinist **(Figures 88A and 89A)** were tested at various drug doses. Initially, various A375 cell numbers were plated and evaluated 3-7 days later to determine the optimal number of cells to be plated and treatment duration.

[00653] Next, the optimal number of cells were plated and treated with various concentrations of AP1 or with various concentrations of zelboraf or tafinlar alone. Cells were evaluated for viability by WST-1 assay or MTT assay 72 hours after beginning treatment with zelboraf **(Figures 84B and 85B)**, tafinlar **(Figure 86A and 87B)**, or mekinist **(Figures 88B and 89B)**.

Example 46: Combination index plots of fulvestrant, everolimus, palbociclib (WST-1), palbociclib (WST-1), and romidepsin in MCF-7 cells.

[00654] The combination index plots suggest additive or better complimentarity for AP1 in MCF-7 cells using fulvestrant **(Figure 90A)**, everolimus **(Figure 90B)**, palbociclib via WST-1 **(Figure 90C)**, palbociclib via CyQUANT **(Figure 90D)**, and romidepsin **(Figures 90E)**. Combination index (CI) values were calculated using the CompuSyn software. The data were expressed as log(CI). CI values: 0–0.1, very strong synergism; 0.1–0.3, strong synergism; 0.3–0.7, synergism; 0.7–0.85, moderate synergism; 0.85–0.90, slight synergism; 0.90–1.10, nearly additive; 1.10–1.20, slight antagonism; 1.20–1.45, moderate antagonism; 1.45–3.3, antagonism; 3.3–10, strong antagonism; 10, very strong antagonism.

Example 47: Combination index plots of Ara-C, decitabine, azacitidine, and midostaurin in MV4-11 cells

[00655] The combination index plots suggest additive or better complimentarity for AP1 in MV4-11 cells using Ara-C **(Figure 91A)**, decitabine **(Figure 91B)**, azacitidine **(Figure 91C)**, and midostaurin **(Figure 91D)**. Combination index (CI) values were calculated using the CompuSyn software. The data were expressed as log(CI). CI values: 0–0.1, very strong synergism; 0.1–0.3, strong synergism; 0.3–0.7, synergism; 0.7–0.85, moderate synergism; 0.85–0.90, slight synergism; 0.90–1.10, nearly additive; 1.10–1.20, slight antagonism; 1.20–1.45, moderate antagonism; 1.45–3.3, antagonism; 3.3–10, strong antagonism; 10, very strong antagonism

Example 48: Combination index plots of vincristine, cyclophosphamide, and rituximab in DOHH-2 cells.

[00656] The combination index plots suggest additive or better complimentarity for AP1 in DOHH-2 cells using vincristine **(Figure 92A)**, cyclophosphamide **(Figure 92B)**, and rituximab **(Figure 92C)**. Combination index (CI) values were calculated using the CompuSyn software. The data were expressed as log(CI). CI values: 0–0.1, very strong synergism; 0.1–0.3, strong synergism; 0.3–0.7, synergism; 0.7–0.85, moderate synergism; 0.85–0.90, slight synergism; 0.90–1.10, nearly additive; 1.10–1.20, slight antagonism; 1.20–1.45, moderate antagonism; 1.45–3.3, antagonism; 3.3–10, strong antagonism; 10, very strong antagonism

Example 49: Combination index plot of romidepsin in MOLT-3 cells.

[00657] The combination index plots suggest mostly additive complimentarity for AP1 in MOLT-3 cells using romidepsin **(Figure 93)**. Combination index (CI) values were calculated using the CompuSyn software. The data were expressed as log(CI). CI values: 0–0.1, very strong synergism; 0.1–0.3, strong synergism; 0.3–0.7, synergism; 0.7–0.85, moderate synergism; 0.85–0.90, slight synergism; 0.90–1.10, nearly additive; 1.10–1.20, slight antagonism; 1.20–1.45, moderate antagonism; 1.45–3.3, antagonism; 3.3–10, strong antagonism; 10, very strong antagonism

Example 50: Combination index plots of vincristine, cyclophosphamide, and rituximab in A375 cells.

[00658] The combination index plots suggest additive or better complimentarity for AP1 in A375 cells using mekinist (**Figure 94A**), zelboraf (**Figure 94B**), and tafinlar (**Figure 94C**). Combination index (CI) values were calculated using the CompuSyn software. The data were expressed as log(CI). CI values: 0–0.1, very strong synergism; 0.1–0.3, strong synergism; 0.3–0.7, synergism; 0.7–0.85, moderate synergism; 0.85–0.90, slight synergism; 0.90–1.10, nearly additive; 1.10–1.20, slight antagonism; 1.20–1.45, moderate antagonism; 1.45–3.3, antagonism; 3.3–10, strong antagonism; 10, very strong antagonism

Example 51: Aileron peptide 1 activation of the p53-pathway in AML cell lines

[00659] The Molm13 cell line was treated with increasing amounts of Aileron peptide 1 (0.1 μM, 0.2 μM, 0.4 μM, 0.5 μM, 1.0 μM, 2.5 μM, 5.0 μM, or 10.0 μM) (**Figure 1A**). Lysates were subjected to SDS-PAGE and probed by Western blotting with antibodies specific to MDM2, p53, p21, and β-Actin. The results demonstrate that Aileron peptide 1 activates the p53-pathway in the Molm13 cell line.

[00660] The OCI/AML3 cell line was treated with increasing amounts of Aileron peptide 1 (0.1 μM, 0.2 μM, 0.4 μM, 0.5 μM, 1.0 μM, 2.5 μM, 5.0 μM, or 10.0 μM) (**Figure 1B**). Lysates were subjected to SDS-PAGE and probed by Western blotting with antibodies specific to MDM2, p53, p21, and β-Actin. The results demonstrate that Aileron peptide 1 activates the p53-pathway in the OCI/AML3 cell line.

[00661] The HL60 cell line was treated with increasing amounts of Aileron peptide 1 (0.1 μM, 0.2 μM, 0.4 μM, 0.5 μM, 1.0 μM, 2.5 μM, 5.0 μM, or 10.0 μM) (**Figure 1C**). Lysates were subjected to SDS-PAGE and probed by Western blotting with antibodies specific to MDM2, p53, p21, and β-Actin. The results demonstrate that Aileron peptide 1 does not activate the p53-pathway in the p53 null HL60 cell line.

[00662] The Molm13, OCI/AML3, Molm14 and ML2 cell lines were treated with vehicle or 1.0 μM Aileron peptide (**Figure 1B**). Lysates were subjected to SDS-PAGE and probed by Western blotting with antibodies specific to MDM2, p53, p21, and β-Actin. The results demonstrate that Aileron peptide 1 activates the p53-pathway in these cell lines.

[00663] mRNA expression of p21, MDM2, Puma, Bax, and Gadd45a was also determined in Molm13 and Oci/AML3 cells lines folloing treatment with ncreasing amounts of Aileron peptide 1 (0.1 μM, 0.2 μM, 0.4 μM, 0.5 μM, 1.0 μM, 2.5 μM, 5.0 μM, or 10.0 μM) (**Figure 2**). Expression levels were normalized to GAPDH mRNA expression levels.The results demonstrate that Aileron peptide 1 activates the p53-pathway in these cell lines.

Example 52: Aileron peptide 1 activation of the p53-pathway in primary AML cells

[00664] Two primary AML cell lines were treated with with vehicle or 1.0 μM Aileron peptide 1 or 5.0 μM Aileron peptide 1 (**Figure 1C**). Lysates were subjected to SDS-PAGE and probed by Western blotting with antibodies specific to MDM2, p53, p21, and β-Actin. The results demonstrate that Aileron peptide 1 activates the p53-pathway in primary AML cells.

Example 53: Aileron peptide 1 stabilizes p53 in AML cells

[00665] The Molm13, OCI/AML3, Molm14, HL60 and ML2 cell lines were treated with vehicle or increasing amounts of Aileron peptide 1 (0.1 μM, 0.2 μM, 0.4 μM, 0.5 μM, 1.0 μM, 2.5 μM, 5.0 μM, or 10.0 μM) (**Figures 3A and 3B**) for 24 hrs, 48 hrs or 72 hrs. Lysates were subjected to SDS-PAGE and probed by

Western blotting with antibodies specific to MDM2, p53, p21, and β-Actin. The results demonstrate that Aileron peptide 1 stabilizes p53 in a time and dose dependant manner the AML p53 wild type cell lines tested.

Example 54: Immunoprecipitation Assays in AML Cells

[00666] AML p53 wild type cell lines were treated with vehicle or 10.0 μM Aileron peptide (**Figures 4A, 4B, and 4C**). Lysates were subjected to immunoprecipitation with a MDMX specific antibody (**Figure 4A**), a p53 specific antibody (**Figure 4B**), or a MDM2 specific antibody (**Figure 4C**). Immunoprecipitates were washed and subjected to SDS-PAGE and probed by Western blotting with antibodies specific to MDM2, MDMX, p53, and/or β-Actin. The results demonstrate that Aileron peptide 1 inhibits the p53-MDMX and the p53-MDM2 interaction.

Example 55: Cellular Proliferation Assays of AML Cells

[00667] The Molm13, OCI/AML3, Molm14, HL60 and ML2 cell lines were plated at a known density (cells/mL) and treated with vehicle or increasing amounts of Aileron peptide 1 (0.1 μM, 0.2 μM, 0.4 μM, 0.5 μM, 1.0 μM, 2.5 μM, 5.0 μM, or 10.0 μM) (**Figures 5A-5D**). Cell proliferation was measured over time by counting the number of live cells/mL at various time points and plotted. All p53 wild type cell lines treated with Aileron peptide 1 demonstrated reduced levels of cellular proliferation over time compared to vehicle alone.

Example 56: Clonogenicity Assay on AML Cell Lines

[00668] The Molm13, OCI/AML3, Molm14, HL60 and ML2 cell lines were treated with vehicle or 1.0 μM Aileron peptide 1. A clonogenicity assay was then performed and the number of clonies was counted (**Figure 6**). The results demonstrated that Aileron peptide 1 treatment in the p53 wild type cell lines tested inhibited their clonogenic capacity.

Example 57: Cellular Proliferation Assays of AML Cell Lines

[00669] The OCI/AML3, HL60 and Kasumi-1 cell lines were plated at a known density (cells/mL) and treated with vehicle or 10.0 μM Aileron peptide 1 (**Figures 7A and 7B**). Cell proliferation was measured over time by counting the number of live cells/mL at various time points and plotted. The p53 wild type OCI/AML3, but not the p53 null HL60 or the p53R248Q Kasumi-1 cell lines treated with Aileron peptide 1 demonstrated reduced levels of cellular proliferation over time compared to vehicle alone.

Example 58: Apoptosis Assays of AML Cell Lines

[00670] The Molm13, OCI/AML3, Molm14, HL60 and ML2 cell lines were treated with vehicle or increasing amounts of Aileron peptide 1 (1.0 μM, 5.0 μM, or 10.0 μM) (**Figures 8A-8E**). Cells were probed with DAPI and a FITC-labeled anti-Annexin-V antibody. FACS analysis was performed to determine the number of viable cells and the number of cells in early apoptosis, late apoptosis and undergoing necrosis and the results were plotted. The results demonstrate that Aileron peptide 1 induces apoptotic cell death in p53 wild type AML cell lines tested.

Example 59: Cellular Proliferation in AML Cells Treated with Ara-C

[00671] AML cell lines were plated at a known density (cells/mL) and were treated with vehicle or increasing amounts of Ara-C alone (**Figure 9A**); with vehicle, Aileron peptide 1 alone, or with Ara-C and Aileron

peptide 1 **(Figure 9B)**; or with vehicle, Ara-C alone, or with Ara-C and increasing amounts of Aileron peptide 1. Cell proliferation was measured over time by counting the number of live cells/mL at various time points and plotted. The results demonstrate that cytarabine (Ara-C) treatment inhibits proliferation of AML cell lines and that Ara-C synergizes with AP1 to inhibit proliferation of AML cell lines.

Example 60: Cellular Proliferation Assays and Clonogenicity Assays of Primary AML Cells

[00672] Primary AML cell lines were plated at a known density (cells/mL) and treated with vehicle or or increasing amounts of Aileron peptide 1 (1.0 μM, 5.0 μM, or 10.0 μM) **(Figures 10A-10D)**. Cell proliferation was measured over time by counting the number of live cells/mL at various time points and plotted. The primary AML cell lines treated with Aileron peptide 1 demonstrated reduced levels of cellular proliferation over time compared to vehicle alone.

Example 61: Clonogenicity Assay on Primary AML Cell Lines

[00673] A primary AML cell line and a primary AML cell line from a patient in remission were treated with vehicle or increasing amounts of Aileron peptide 1 (0.1 μM, 0.25 μM, 0.5 μM, or 1.0 μM) **(Figure 11A and 11B)**. A clonogenicity assay was then performed and the number of clonies was counted. The results demonstrated that Aileron peptide 1 treatment in the primary AMl cell line tested inhibited its clonogenic capacity to a higher extent than the primary AML cell line from the patient in remission and cells from a healthy donor.

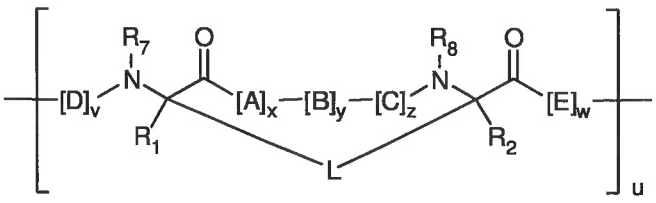
Example 62: Apoptosis Assays on Primary AML Cell Lines

[00674] A primary AML cell line was treated with vehicle or increasing amounts of Aileron peptide 1 (1.0 μM, 5.0 μM, or 10.0 μM) **(Figure 12)**. Cells were probed with DAPI and a FITC-labeled anti-Annexin-V antibody. FACS analysis was performed to determine the number of viable cells and the number of cells in early apoptosis, late apoptosis and undergoing necrosis and the results were plotted. The results demonstrate that Aileron peptide 1 induces apoptotic cell death in primary AML cells.

CLAIMS

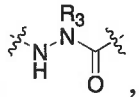
WHAT IS CLAIMED IS:

1. Use of a therapeutically-effective amount of a peptidomimetic macrocycle or a pharmaceutically acceptable salt thereof and at least one additional pharmaceutically active agent in the manufacture of a medicament to treat hyperproliferative disease, cancers and neoplastic conditions characterized by aberrant activity of MDM2 and MDMX in a subject, wherein the peptidomimetic macrocycle is to be administered simultaneously or sequentially in combination with the at least one additional pharmaceutically active agent, wherein the peptidomimetic macrocycle comprises 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, and wherein the peptidomimetic macrocycle has the formula:



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 hydrogen, 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 and 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, arylene, heteroarylene, 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 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;

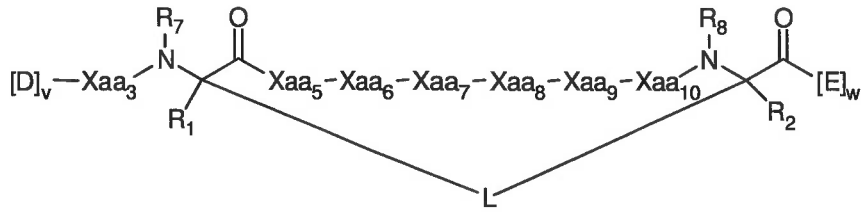
u is an integer from 1–10;

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

each n is independently an integer from 1–5;

wherein the peptidomimetic macrocycle is not a peptidomimetic macrocycle of Tables 2a or 2b, wherein the at least one additional pharmaceutically active agent is fulvestrant, everolimus, romidepsin, palbociclib, trametinib, rituximab, dabrafenib, vemurafenib, azacitidine, decitabine, midostaurin, vincristine, cyclophosphamide or cytarabine.

2. The use of claim 1, wherein the peptidomimetic macrocycle has a 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} wherein each X_4 and X_{11} is independently an amino acid;

each D and E is independently an amino acid;

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 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, arylene, heteroarylene, 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;

R_7 is –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;

R_8 is –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;

v is an integer from 1-1000;

w is an integer from 3-1000; and

n is an integer from 1-5.

3. The use of claim 1, wherein w is more than 2.

4. The use of claim 3, wherein each of the first two amino acid represented by E comprises an uncharged side chain or a negatively charged side chain.

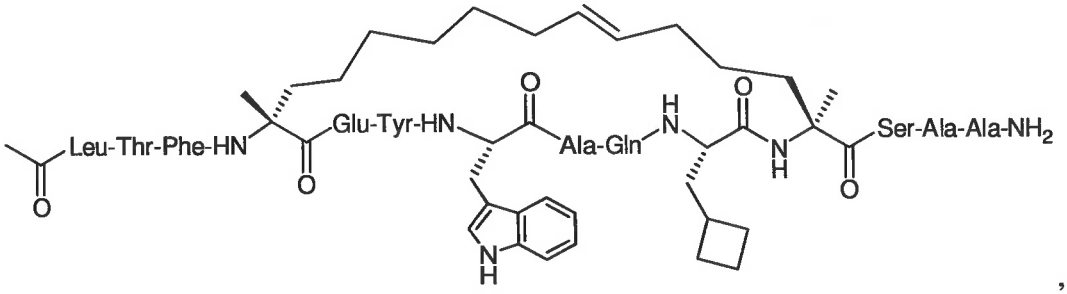
5. The use of claim 4, wherein each E is independently an amino acid selected from Ala (alanine), D-Ala (D-alanine), Aib (α-aminoisobutyric acid), Sar (N-methyl glycine), and Ser (serine).

6. The use of claim 1, wherein the at least one additional pharmaceutically active agent is palbociclib.

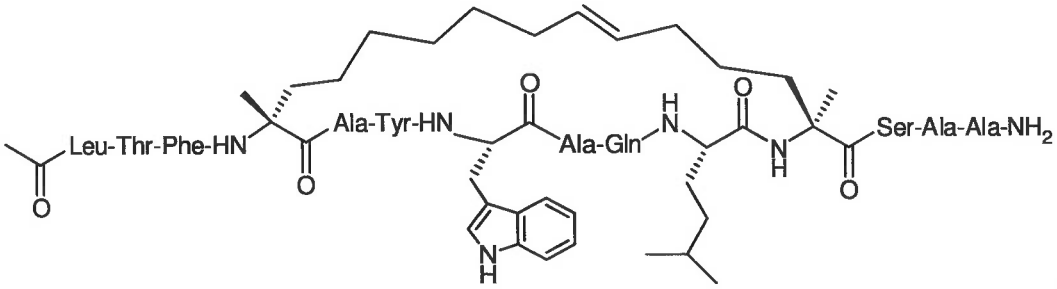
7. The use of claim 1, wherein the cancer is selected from the group consisting of head and neck cancer, melanoma, lung cancer, breast cancer, colon cancer, ovarian cancer, NSCLC, stomach cancer, prostate cancer, leukemia, lymphoma, mesothelioma, renal cancer, non-Hodgkin lymphoma (NHL), and glioma.

8. The use of claim 1, wherein the subject comprises cancer cells that overexpress PD-L1, PD-1, miR-34, or any combination thereof.

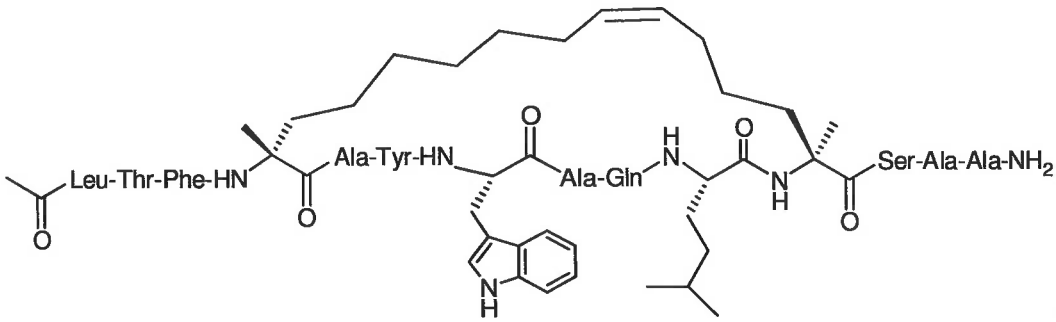
9. The use of claim 1, wherein the peptidomimetic macrocycle is selected from the group consisting of:


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Glu-Tyr-HN
Ala-Gln
Ser-Ala-Ala-NH2

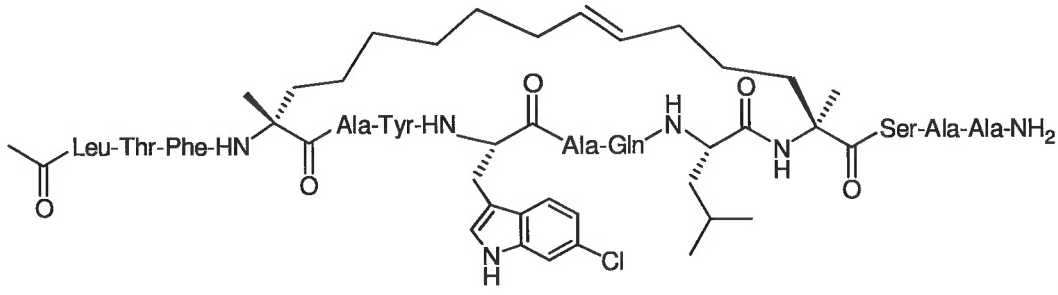
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Ala-Gln
Ser-Ala-Ala-NH2

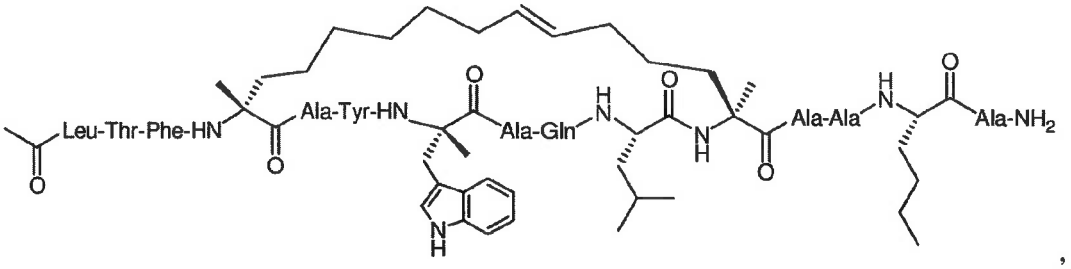
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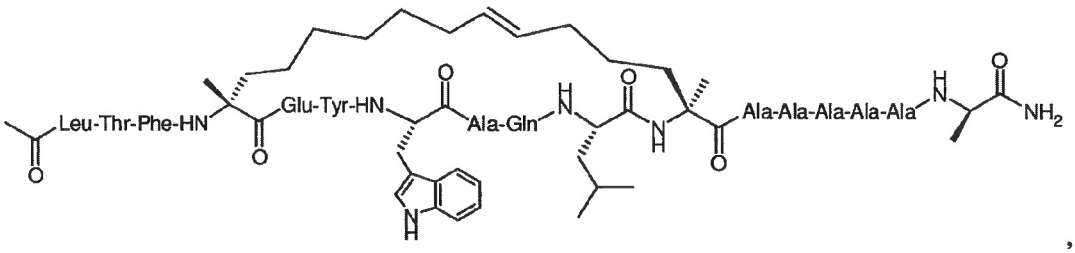
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Cl

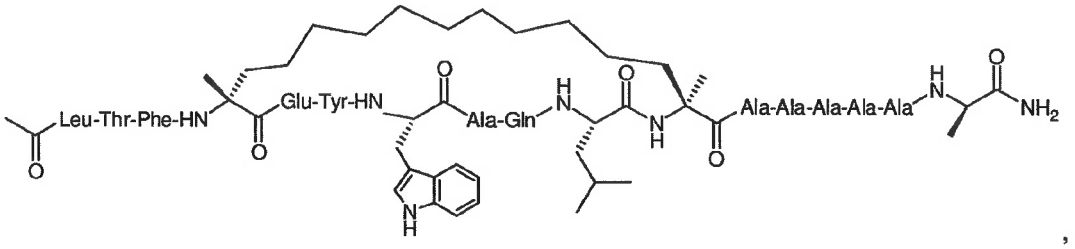
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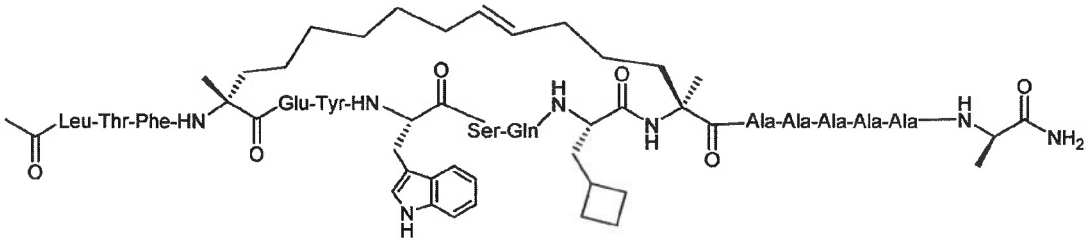
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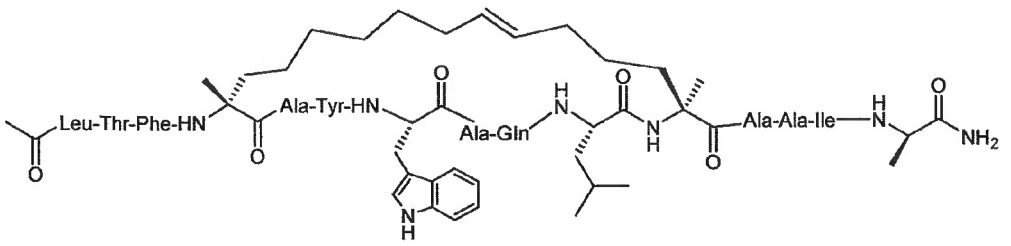

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NH2

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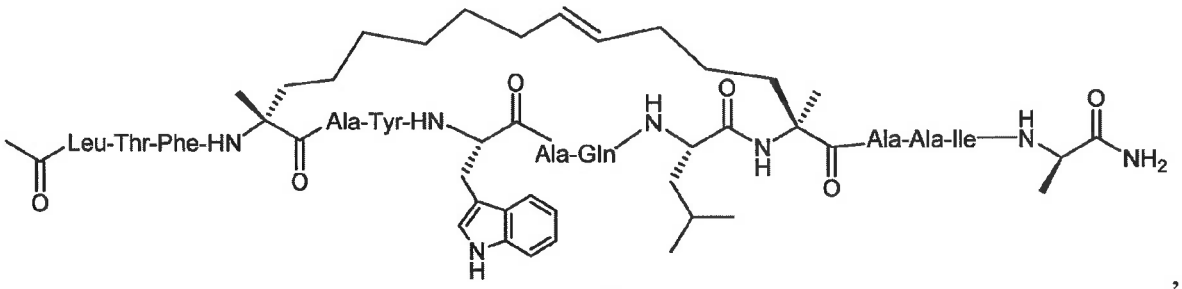

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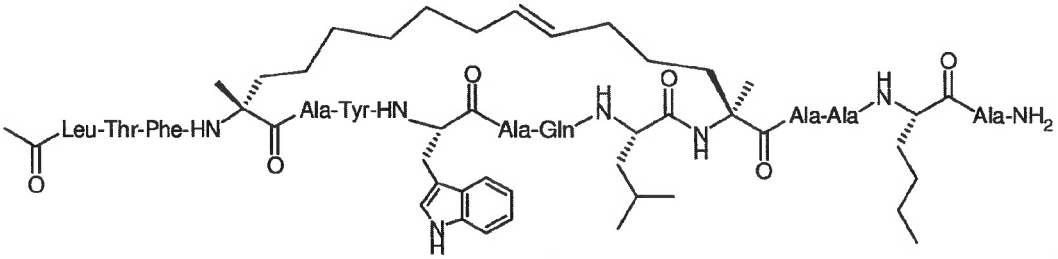

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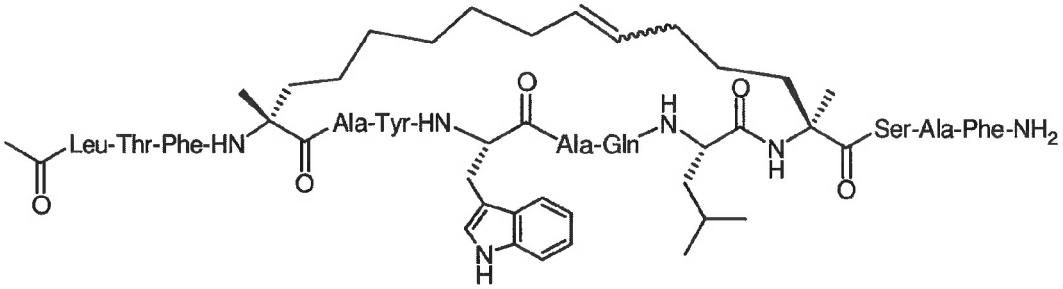
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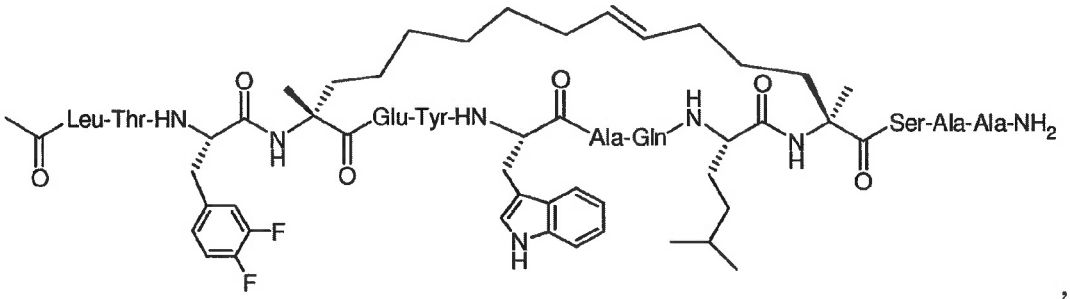
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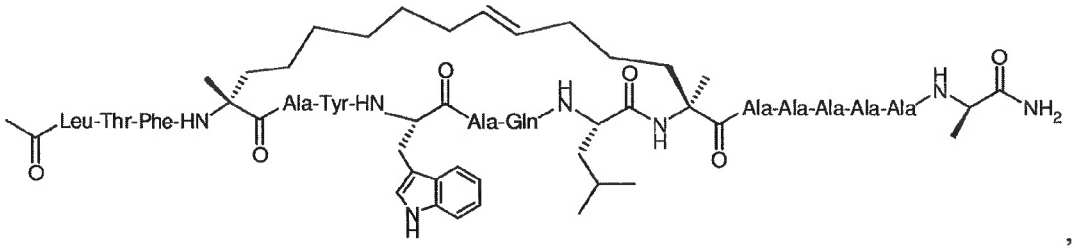
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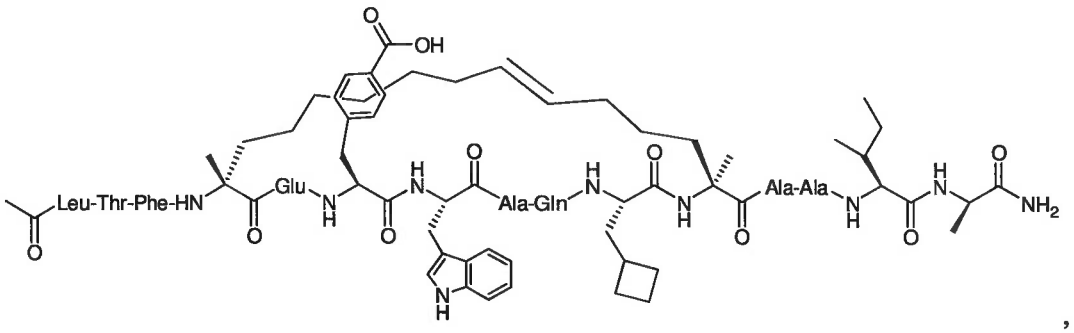
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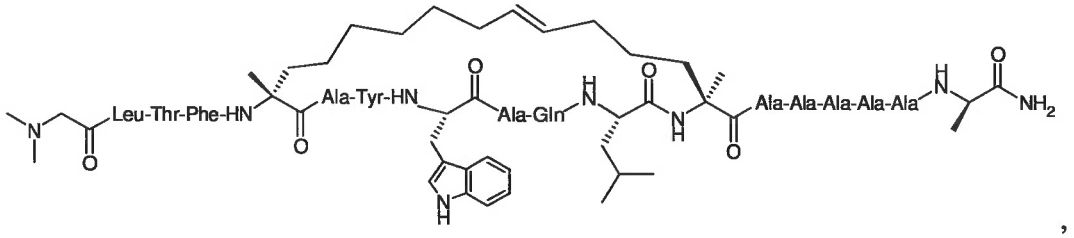
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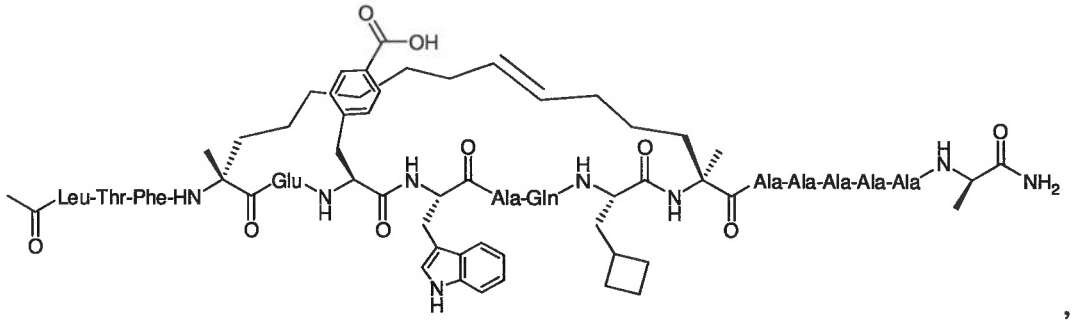
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Glu
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Ala-Ala
NH2

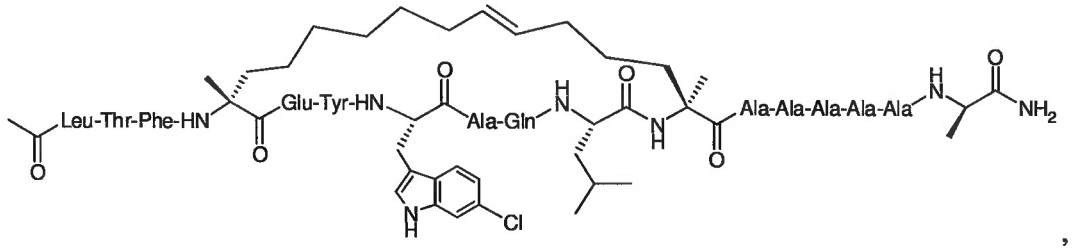
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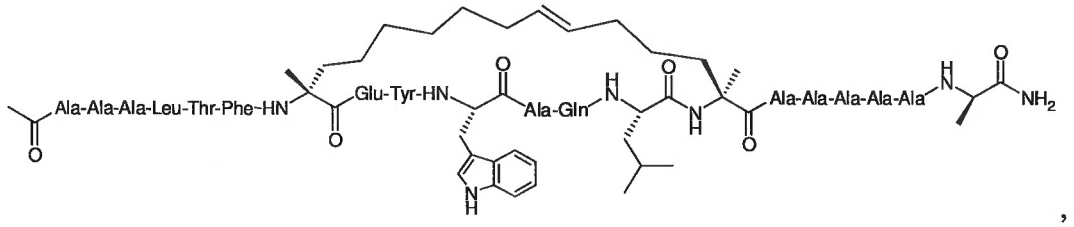
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Ala-Ala-Ala-Ala-Ala
NH2

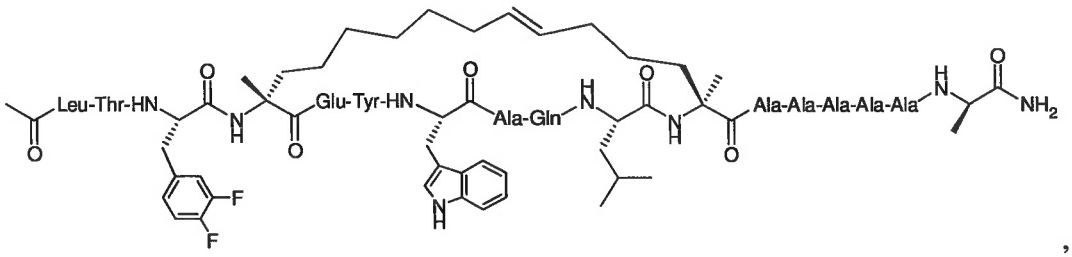
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Leu-Thr-Phe-HN
Glu-Tyr-HN
Ala-Gln
Ala-Ala-Ala-Ala-Ala
NH2
Cl

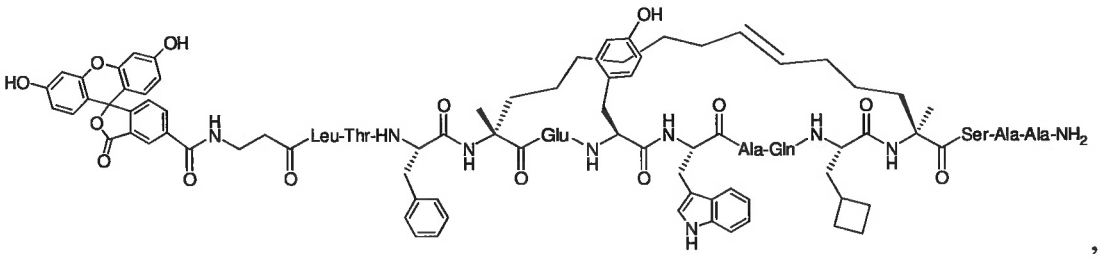
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Ala-Ala-Ala-Leu-Thr-Phe-HN
Glu-Tyr-HN
Ala-Gln
Ala-Ala-Ala-Ala-Ala
NH2

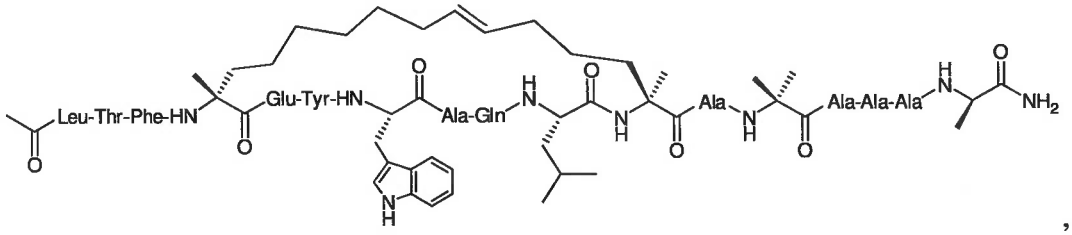
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Leu-Thr-HN
Glu-Tyr-HN
Ala-Gln
Ala-Ala-Ala-Ala-Ala
NH2
F
F

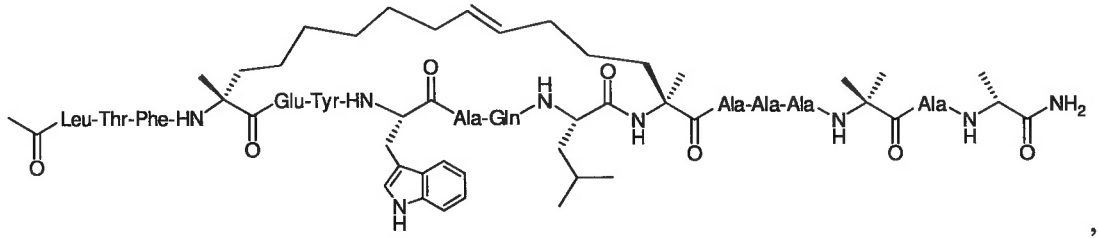
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HO
OH
OH
Leu-Thr-HN
Glu
Ala-Gln
Ser-Ala-Ala-NH2

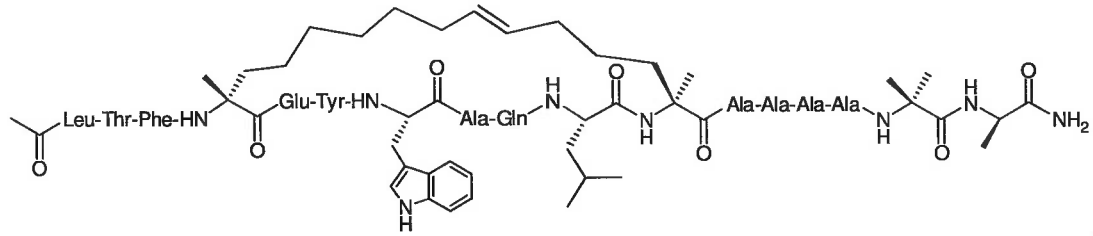
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Leu-Thr-Phe-HN
Glu-Tyr-HN
Ala-Gln
Ala
Ala-Ala-Ala
NH2

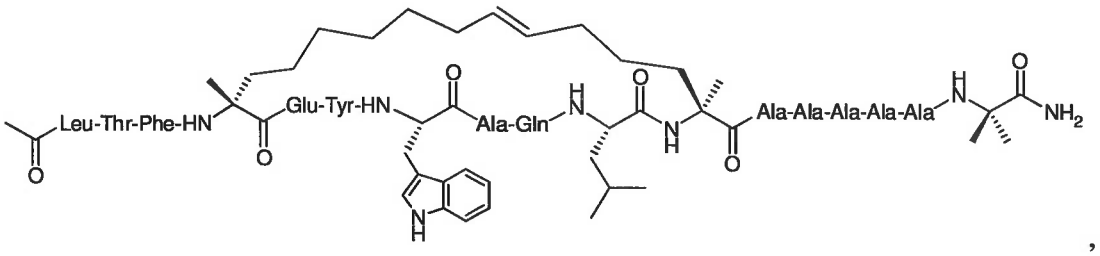
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Leu-Thr-Phe-HN
Glu-Tyr-HN
Ala-Gln
Ala-Ala-Ala
Ala
NH2

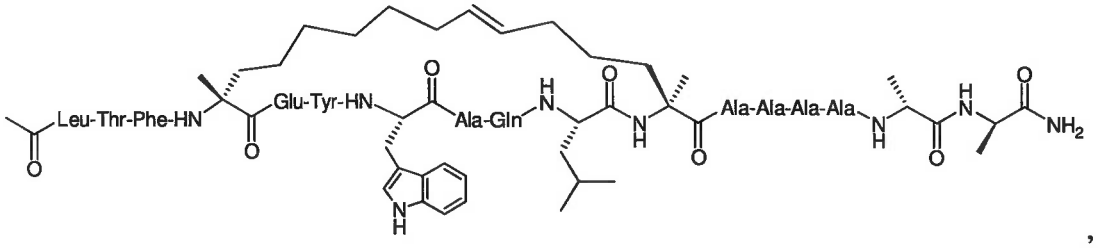
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Leu-Thr-Phe-HN
Glu-Tyr-HN
Ala-Gln
Ala-Ala-Ala-Ala
NH2

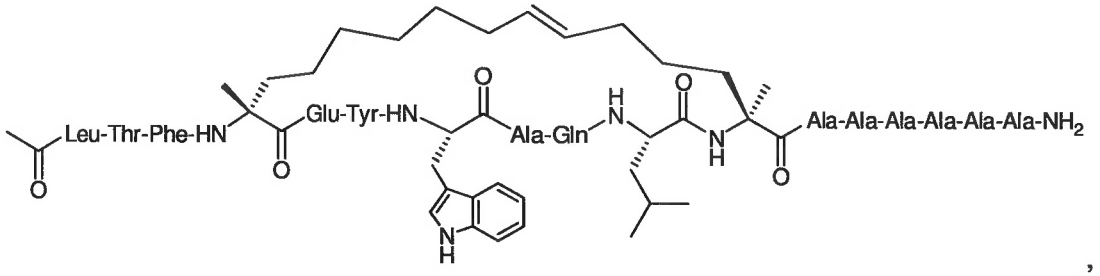
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Leu-Thr-Phe-HN
Glu-Tyr-HN
Ala-Gln
Ala-Ala-Ala-Ala-Ala
NH2

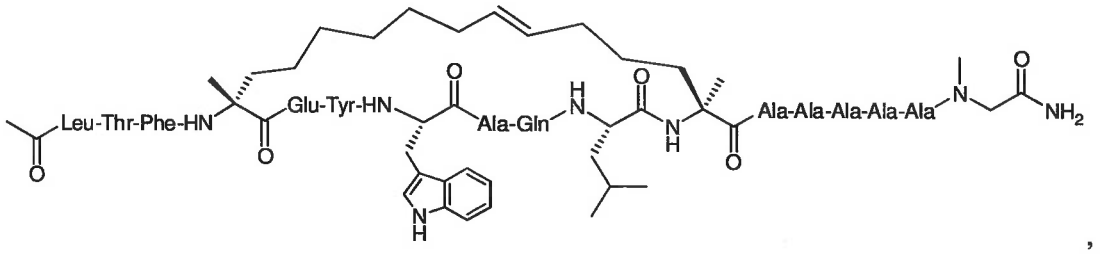
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Leu-Thr-Phe-HN
Glu-Tyr-HN
Ala-Gln
Ala-Ala-Ala-Ala
NH2

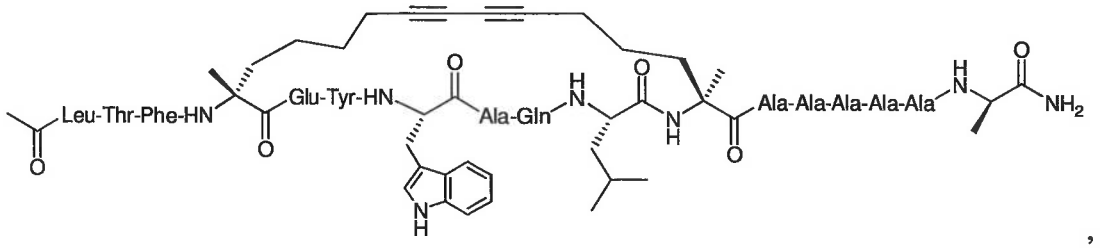
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Leu-Thr-Phe-HN
Glu-Tyr-HN
Ala-Gln
Ala-Ala-Ala-Ala-Ala-Ala-NH2

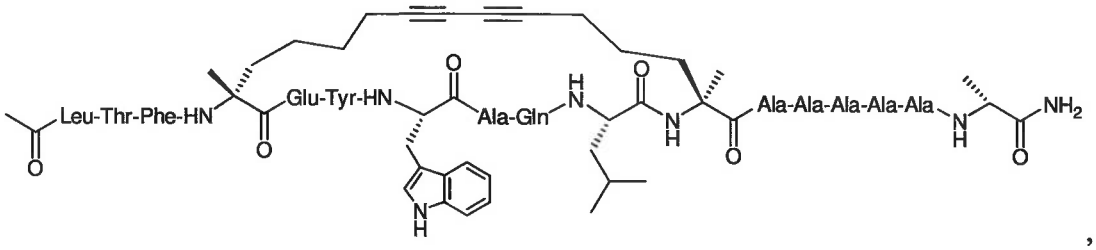
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Leu-Thr-Phe-HN
Glu-Tyr-HN
Ala-Gln
Ala-Ala-Ala-Ala-Ala
NH2

,

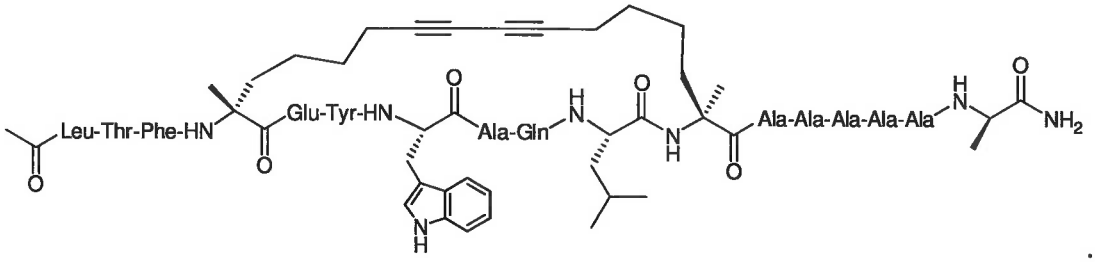

Leu-Thr-Phe-HN
Glu-Tyr-HN
Ala-Gln
Ala-Ala-Ala-Ala-Ala
NH2

,



,

and



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10. The use of claim 1, wherein the peptidomimetic macrocycle comprises an amino acid sequence Xaa_3-Xaa_4-Xaa_5-Xaa_6-Xaa_7-Xaa_8-Xaa_9-Xaa_{10}-Xaa_{11}-Xaa_{12}, wherein:

Xaa_3 is Phe or an analog thereof;

Xaa_4 and Xaa_{11} are independently a cross-linking amino acid;

Xaa_5 is Glu, His, or an analog thereof;

Xaa_6 is Tyr, or an analog thereof;

Xaa_7 is Trp, or an analog thereof;

Xaa_8 is Ala, or an analog thereof;

Xaa_9 is Gln, or an analog thereof;

Xaa_{10} is Leu, Cba, or an analog thereof; and

Xaa_{12} is Ser, Ala or an analog thereof.

11. The use of claim 1, wherein the cancer is AML.

12. The use of claim 1, wherein the cancer is myelodysplastic syndrome.

13. The use of claim 1, wherein the cancer is peripheral T cell lymphoma.

14. The use of claim 1, wherein the cancer is breast cancer.

15. The use of claim 1, wherein the cancer is sarcoma, liposarcoma, osteosarcoma, chondrosarcoma, leiomyosarcoma, rhabdomyosarcoma, fibrosarcoma, chordoma, synovioma, angiosarcoma, glioblastoma, medulla blastema, mesothelioma, epithelial carcinoma, embryonal carcinoma, bladder carcinoma, non-small-cell lung carcinoma (NSCLC), testicular cancer, invasive (or infiltrating) ductal carcinoma, invasive (or infiltrating) lobular carcinoma, esophageal cancer, diffuse large B-cell lymphoma, hepatocellular cancer, prostate cancer, stomach cancer, squamous cell carcinoma, cystadenocarcinoma, renal cell carcinoma, colon cancer, papillary carcinoma, pancreatic cancer, uterine cancer, uveal melanoma, or tumors involving other tissues including peripheral nerves and autonomic nervous system, connective and soft tissue, retroperitoneum and peritoneum, eye and adnexa, thyroid, adrenal gland and other endocrine glands and related structures, secondary and unspecified malignant neoplasm of lymph nodes, secondary malignant neoplasm of respiratory and digestive systems and secondary malignant neoplasm of other sites.

16. The use of claim 1, wherein the at least one additional pharmaceutically active agent is a cytarabine.

17. The use of claim 1, wherein the cancer is AML and the at least one additional pharmaceutically active agent is cytarabine.

18. The use of claim 1, wherein the combination of the peptidomimetic macrocycle or a pharmaceutically acceptable salt thereof and the at least one additional pharmaceutically active agent is synergistic.

19. The use of claim 18, wherein the at least one additional pharmaceutically active agent is midostaurin, vemurafenib, fluvestant, everolimus, cytarabine, azacitidine, vincristine, or cyclophosphamide.