PEPTIDOMIMETIC MACROCYCLES AND USES THEREOF

CROSS-REFERENCE

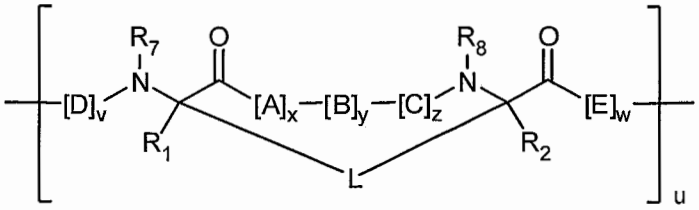
[0001] This application claims priority to U.S. Provisional Application No. 62/214,142, filed September 3, 2015; U.S. Provisional Application No. 62/310,254, filed March 18, 2016; U.S. Provisional Application No. 62/344,651, filed June 2, 2016; and U.S. Provisional Application No. 62/344,791, filed June 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.

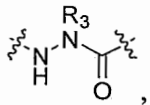
SUMMARY OF THE INVENTION

[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 for modulating the activity of p53 and/or MDM2 and/or MDMX in a subject with cancer, 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;

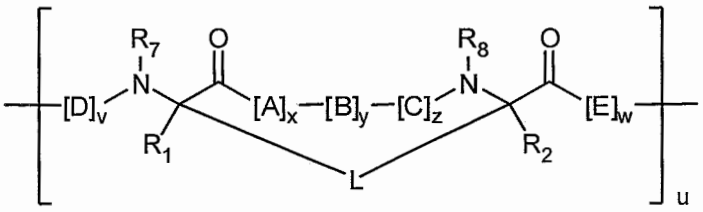
u is an integer from 1–10;

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

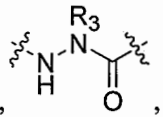
each n is independently an integer from 1–5;

wherein the peptidomimetic macrocycle is not a peptidomimetic macrocycle of Tables 2a or 2b, wherein the at least one additional pharmaceutically active agent is 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. 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

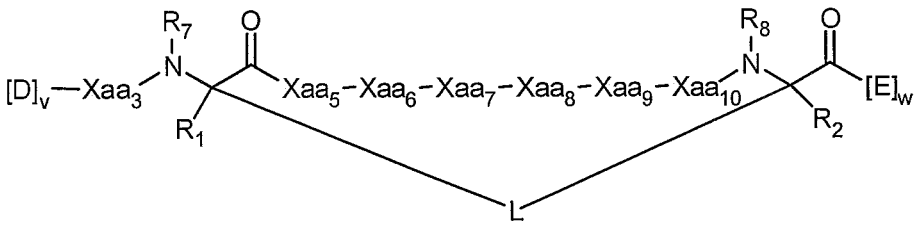
second C-terminal amino acid represented by E comprises a hydrophobic side chain, for example a large hydrophobic side chain.

[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.

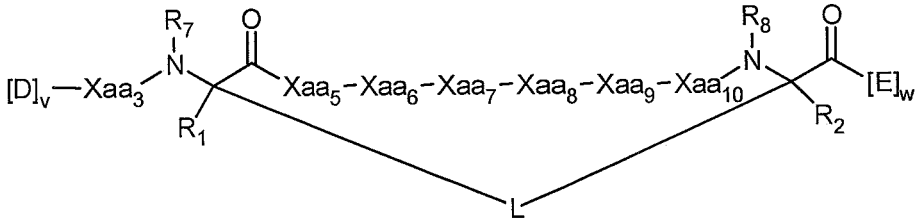
[0009] In another example, the disclosure provides a method of treating cancer in a subject in need thereof, the method comprising administering to the subject a therapeutically effective amount of a peptidomimetic macrocycle and at least one additional pharmaceutically active agent, wherein the peptidomimetic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

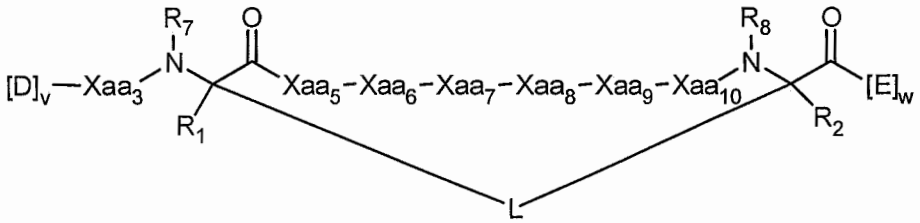


wherein:

- 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 $[-R_4\text{-}K\text{-}R_4-]_n$, each being optionally substituted with R_5;
- each R_4 is independently alkylene, alkenylene, alkynylene, heteroalkylene, cycloalkylene, heterocycloalkylene, arylene, or heteroarylene;
- each K is independently O, S, SO, SO_2, CO, CO_2, or $CONR_3$;
- each R_5 is independently halogen, alkyl, $-OR_6$, $-N(R_6)_2$, $-SR_6$, $-SOR_6$, $-SO_2R_6$, $-CO_2R_6$, a fluorescent moiety, a radioisotope or a therapeutic agent;
- each R_6 is independently –H, alkyl, alkenyl, alkynyl, arylalkyl, cycloalkylalkyl, heterocycloalkyl, a fluorescent moiety, a radioisotope or a therapeutic agent;

- 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 $–Leu_1\text{-}Thr_2$. 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.

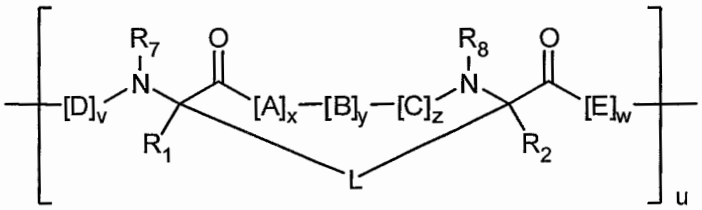
[0017] In some examples, the peptidomimetic macrocycle has improved binding affinity to MDM2 or MDMX relative to a corresponding peptidomimetic macrocycle wherein Xaa_5 is Ala. In other examples, the peptidomimetic macrocycle has a reduced ratio of binding affinities to MDMX vs MDM2 relative to a corresponding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

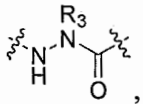
[0021] In another example, the disclosure provides a method of modulating the activity of p53 and/or MDM2 and/or MDMX in a subject in need thereof comprising administering to the subject a therapeutically-effective amount of a peptidomimetic macrocycle and at least one additional pharmaceutically active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

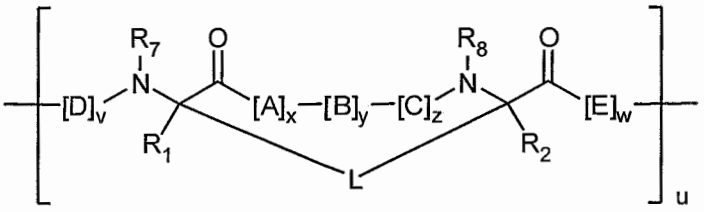
or pharmaceutically acceptable salt thereof,

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.

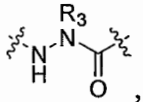
[0022] In another example, the disclosure provides a method of antagonizing an interaction between p53 and MDM2 proteins and/or between p53 and MDMX proteins in a subject in need thereof comprising administering to the subject a therapeutically-effective amount of a peptidomimetic macrocycle and at least 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.

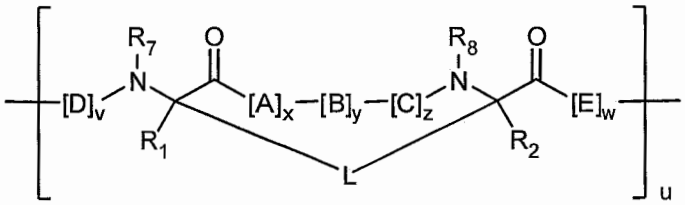
BRIEF DESCRIPTION OF THE DRAWINGS

[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:

CLAIMS

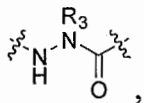
WHAT IS CLAIMED IS:

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 for modulating the activity of p53 and/or MDM2 and/or MDMX in a subject with cancer, 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;

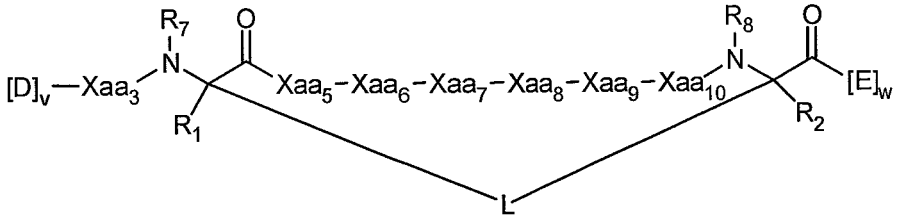
u is an integer from 1–10;

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 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.

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 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, selumetinib, midostaurin (PKC412), venetoclax and combinations thereof.

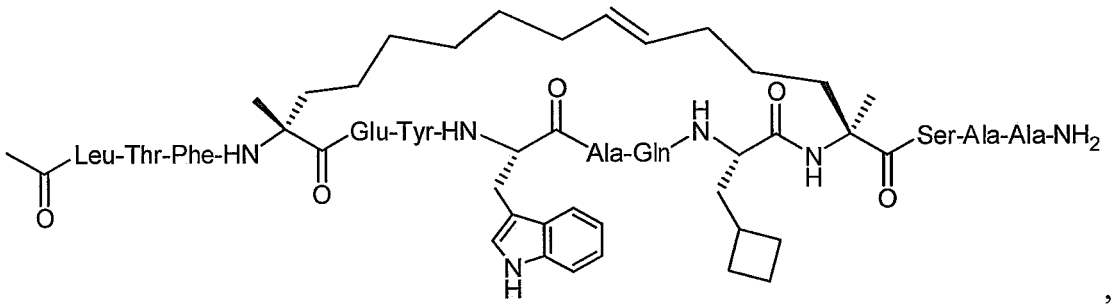
7. The use of claim 1, wherein the at least one additional pharmaceutically active agent is a PD-1 antagonist or a PD-L1 antagonist.

8. The use of claim 1, wherein the at least one additional pharmaceutically active agent modulates the activity of CDK4 and/or CDK6, and/or inhibits CDK4 and/or CDK6.

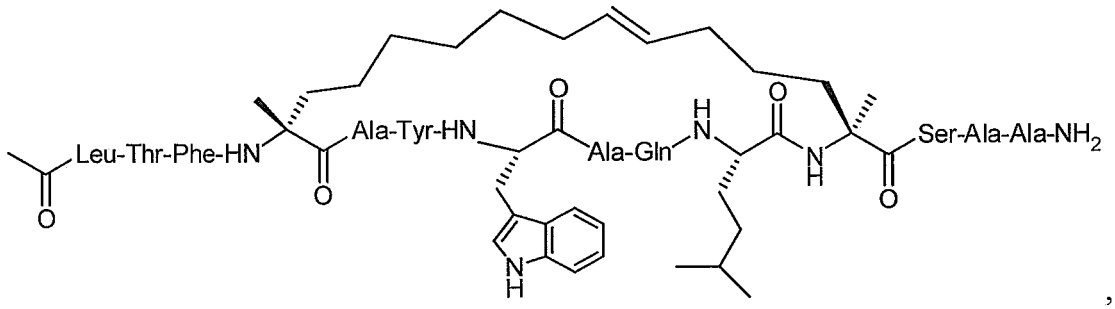
9. The use of claim 1, wherein the cancer is selected from the group consisting of head and neck cancer, melanoma, lung cancer, breast cancer, colon cancer, ovarian cancer, NSCLC, stomach cancer, prostate cancer, leukemia, lymphoma, mesothelioma, renal cancer, non-Hodgkin lymphoma (NHL), and glioma.

10. The use of claim 1, wherein the subject comprises cancer cells that overexpress PD-L1, PD-1, miR-34, or any combination thereof.

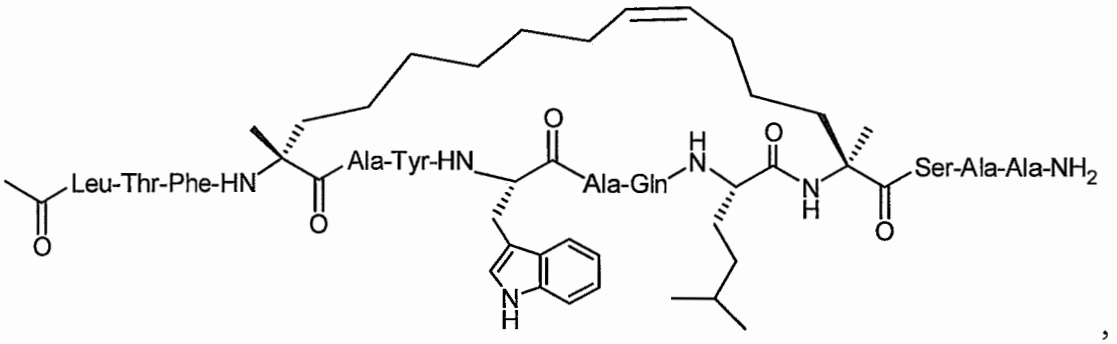
11. The use of claim 1, wherein the peptidomimetic macrocycle is selected from the group consisting of:



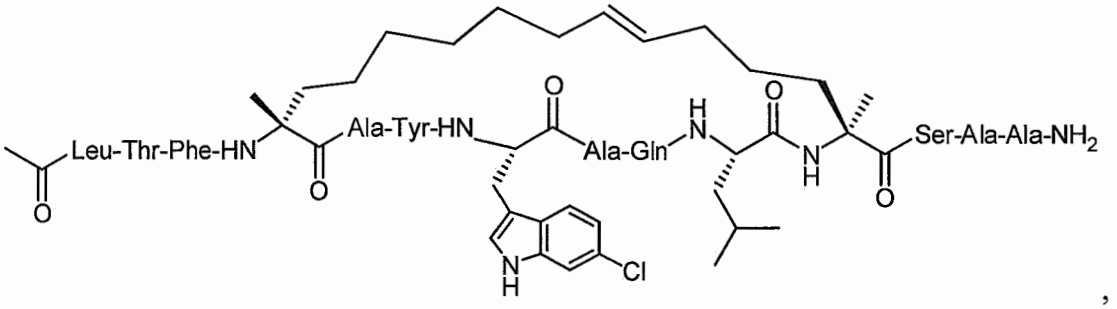
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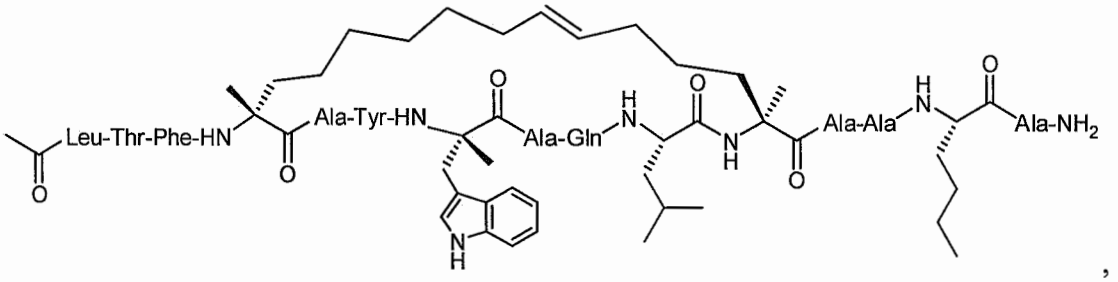
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Leu-Thr-Phe-HN
Ala-Tyr-HN
Ala-Gln
Ser-Ala-Ala-NH2

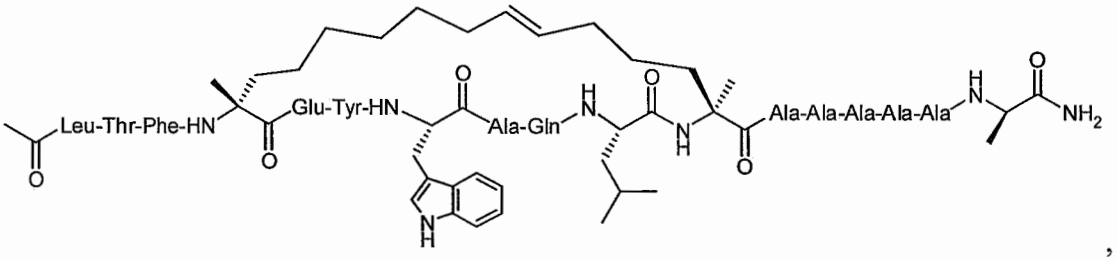
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Cl

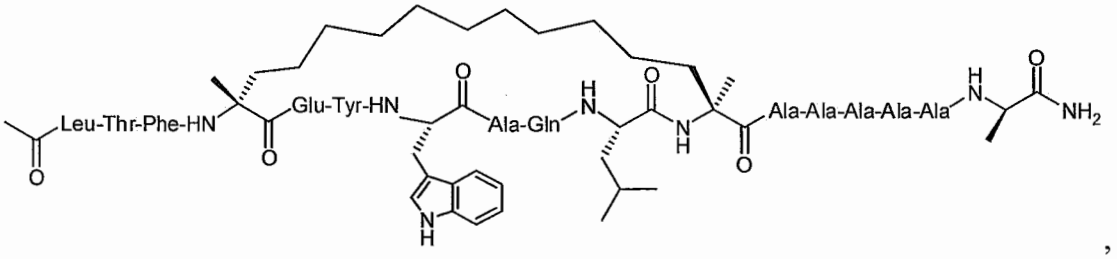
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Ala-NH2

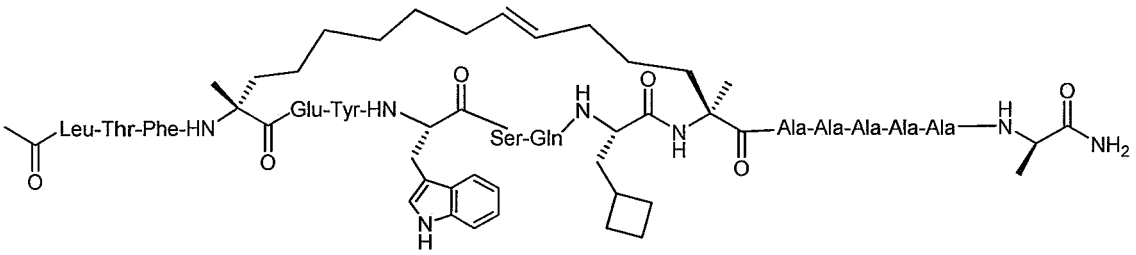
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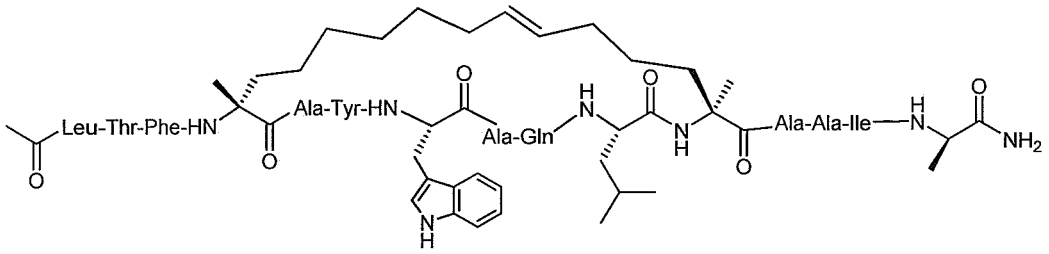

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Glu-Tyr-HN
Ala-Gln
Ala-Ala-Ala-Ala-Ala
NH2

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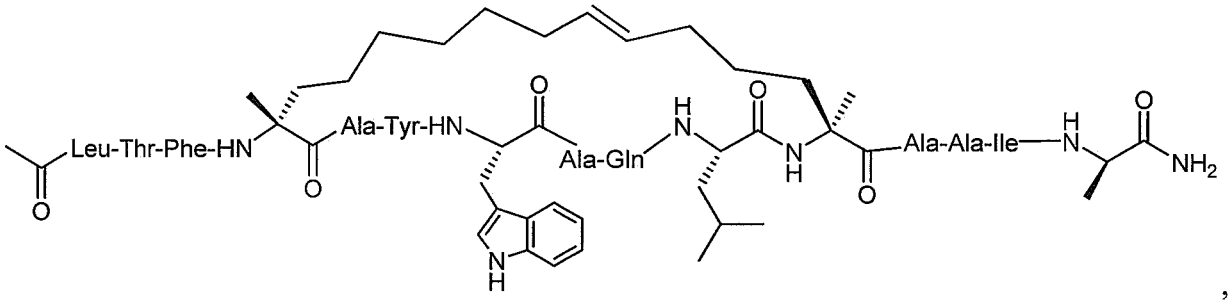

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Ala-Gln
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NH2

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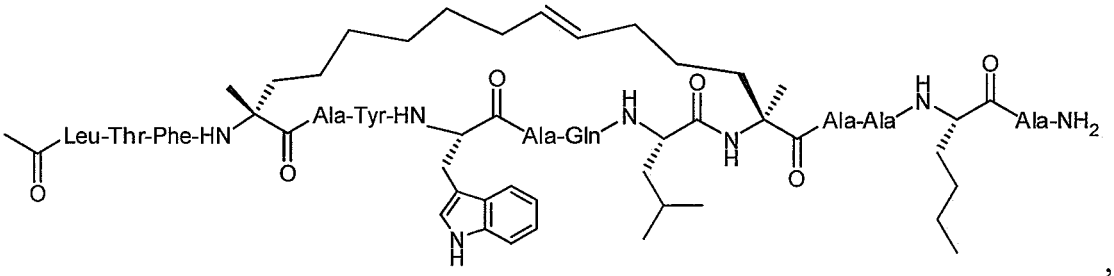

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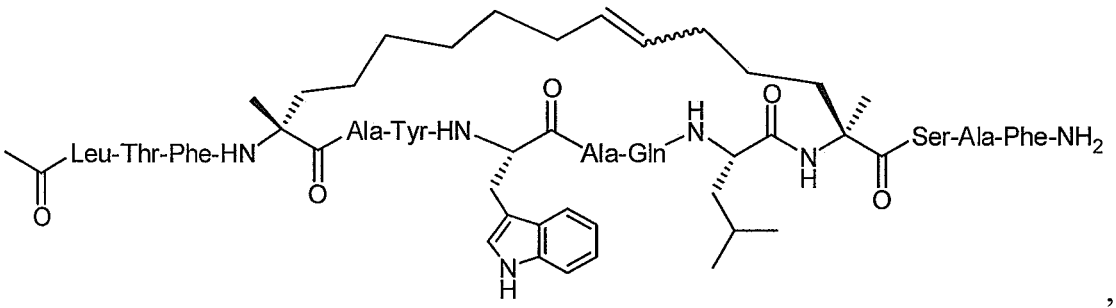
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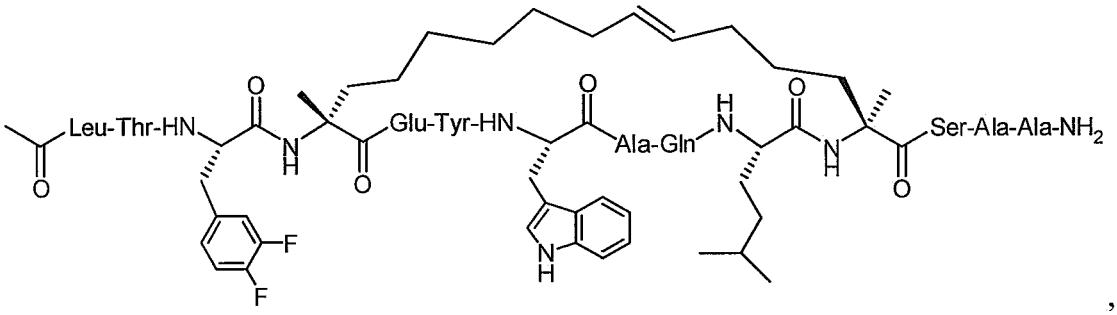
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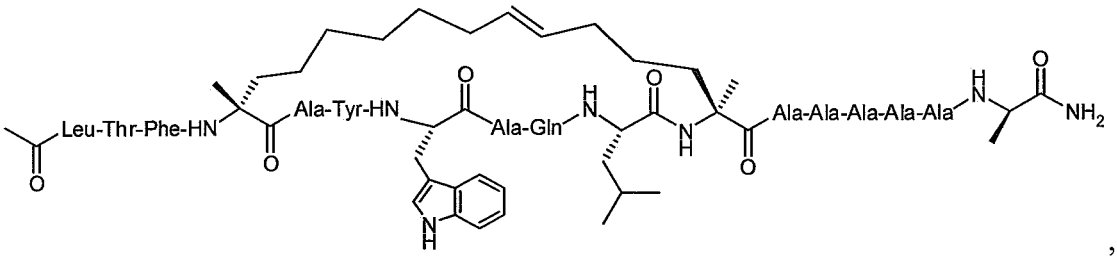
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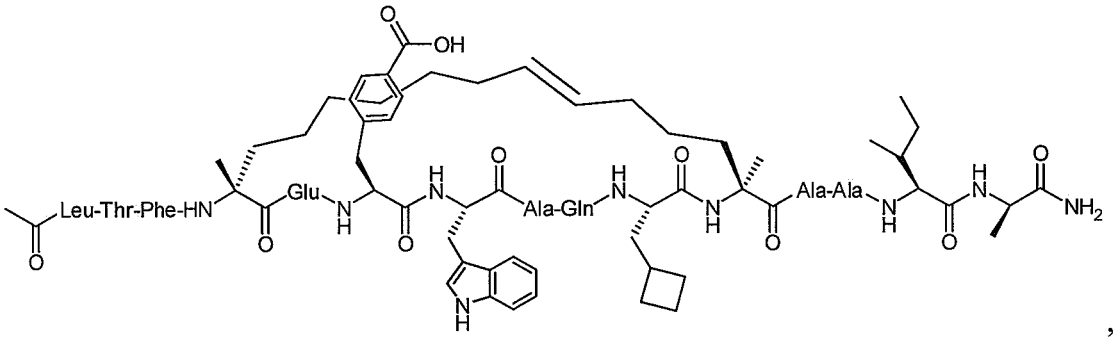
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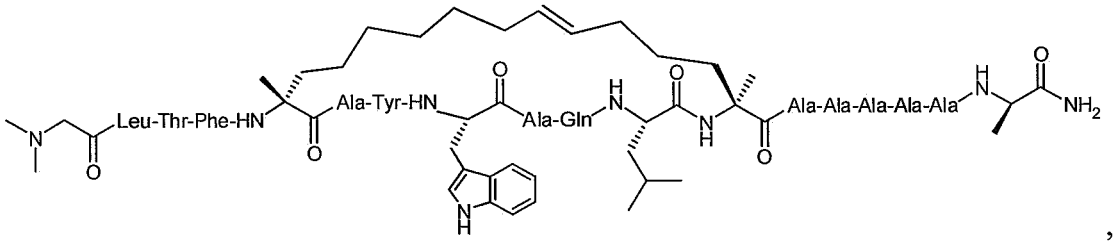
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NH2

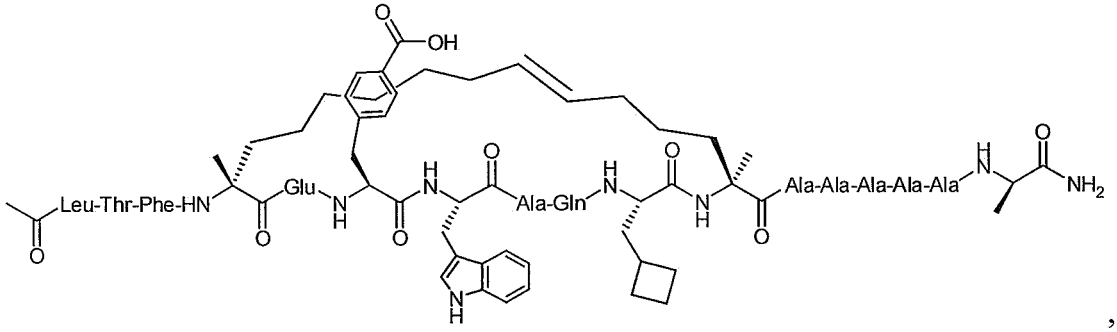
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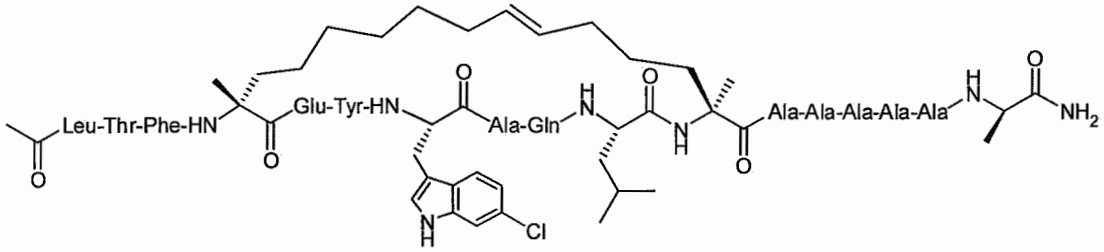
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Ala-Gln
Ala-Ala-Ala-Ala-Ala
NH2

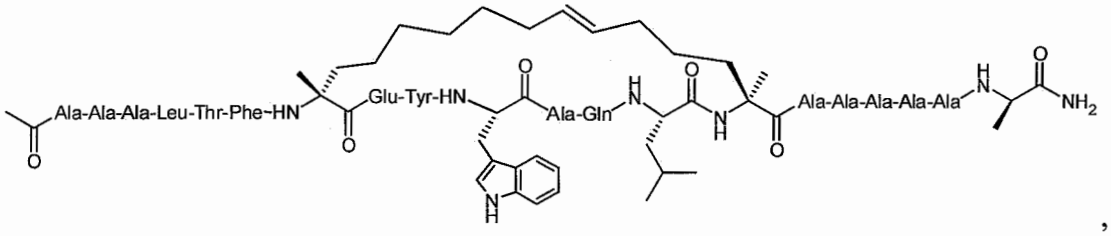
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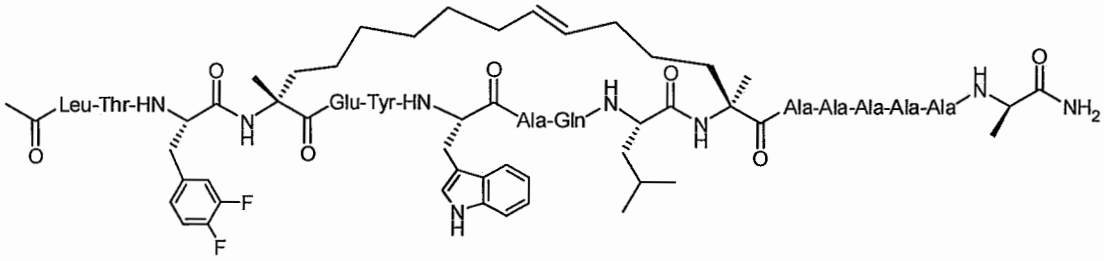
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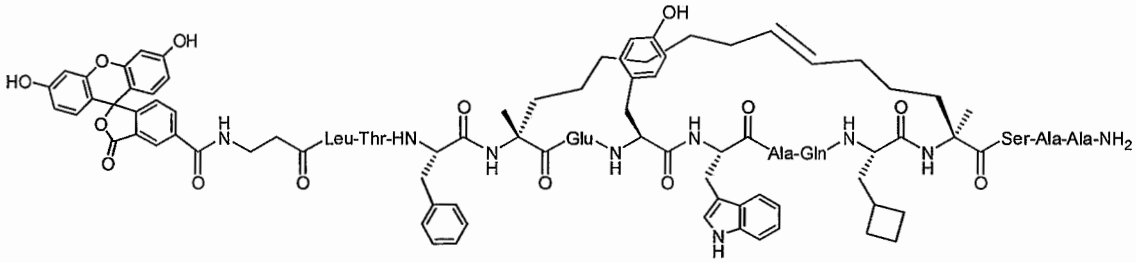
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Glu-Tyr-HN
Ala-Gln
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NH2

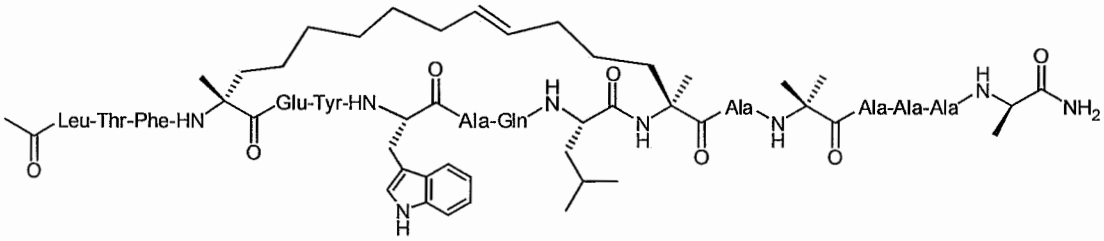
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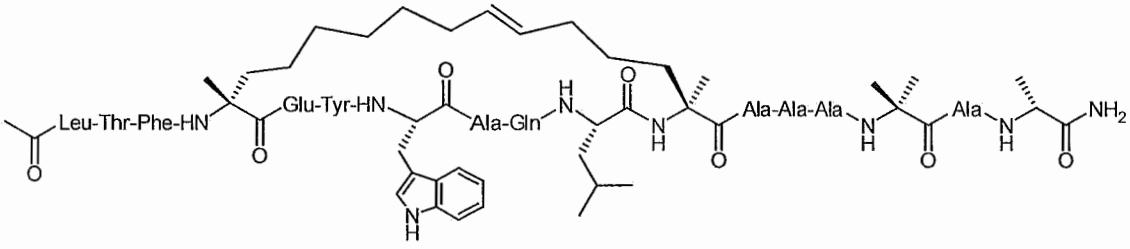
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OH
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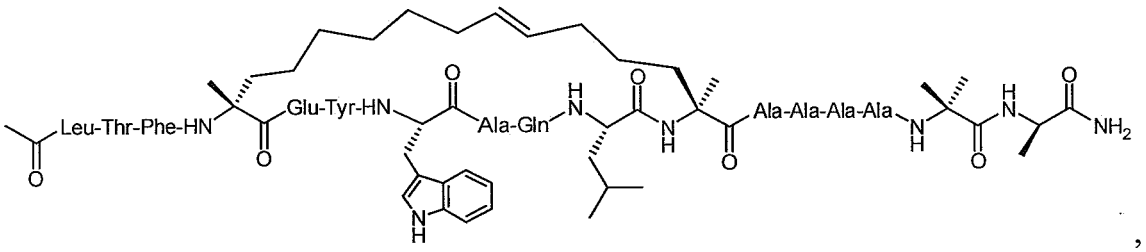
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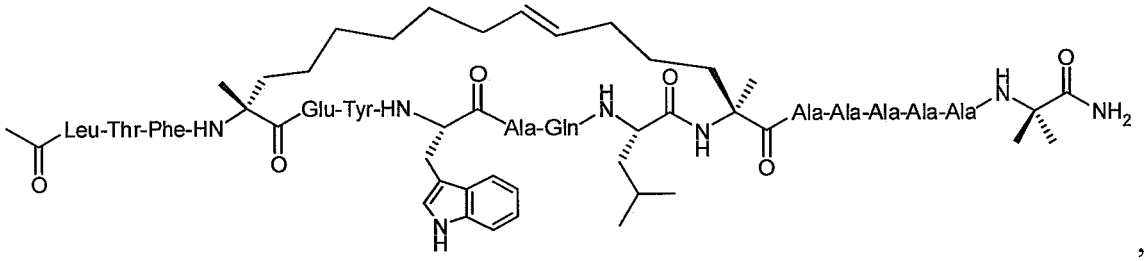
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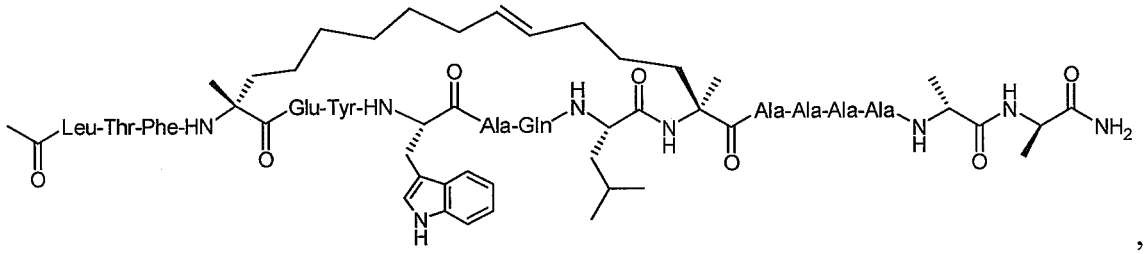
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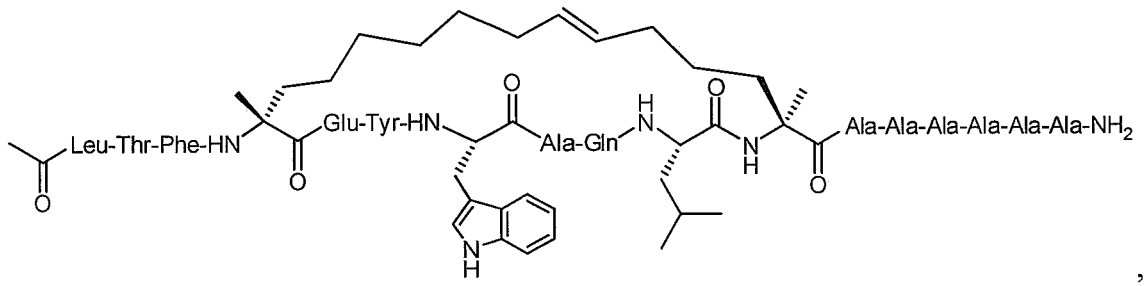
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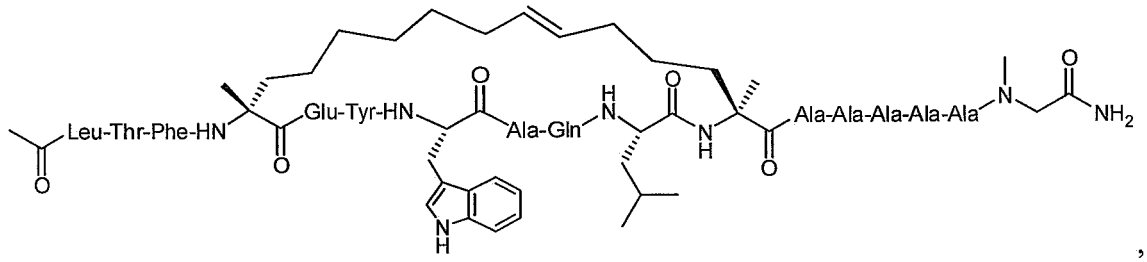
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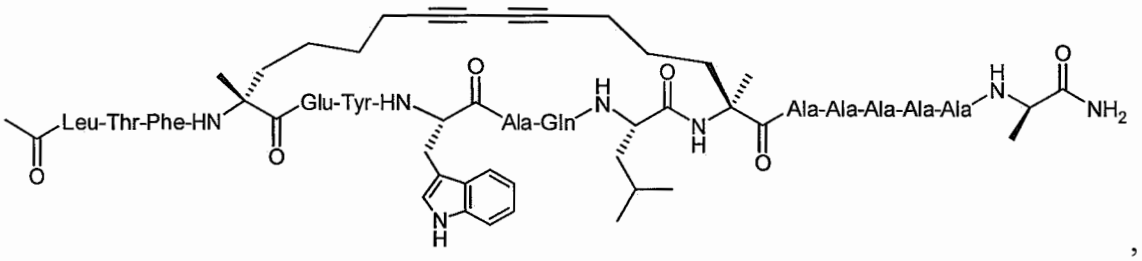
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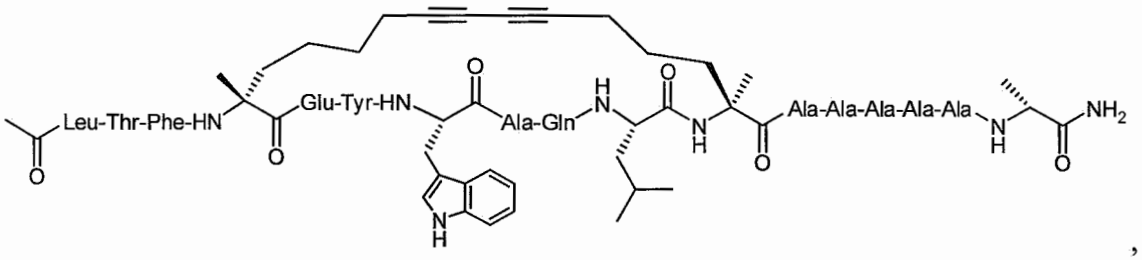
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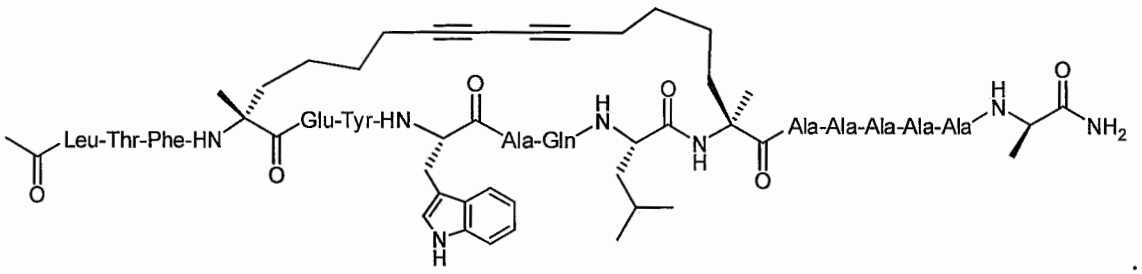


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and



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12. 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.

13. The use of claim 1, wherein the cancer is AML.

14. The use of claim 1, wherein the cancer is myelodysplastic syndrome.

15. The use of claim 1, wherein the cancer is peripheral T cell lymphoma.

16. The use of claim 1, wherein the cancer is breast cancer.

17. The use of claim 1, wherein the at least one additional pharmaceutically active agent is a microtubule inhibitor.

18. The use of claim 1, wherein the at least one additional pharmaceutically active agent is paclitaxel.

19. The use of claim 1, wherein the at least one additional pharmaceutically active agent is eribulin.

20. The use of claim 1, wherein the at least one additional pharmaceutically active agent is a nucleoside metabolic inhibitor.

21. The use of claim 1, wherein the at least one additional pharmaceutically active agent is a cytarabine.

22. The use of claim 1, wherein the cancer is AML and the at least one additional pharmaceutically active agent is a nucleoside metabolic inhibitor.

23. The use of claim 1, wherein the cancer is AML and the at least one additional pharmaceutically active agent is cytarabine.

24. 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.

25. The use of claim 24, wherein the at least one additional pharmaceutically active agent is midostaurin, PLX4032, fluvestant, everolimus, cytarabine, azacitidine, vincristine, or cyclophosphamide.

26. A method of selecting a peptidomimetic macrocycle that reduces PD-L1 expression, comprising:

(a) 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;

(b) incubating the cancer cell line for an incubation period;

(c) measuring a second level of PD-L1 expression after the incubation period;

(d) 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.