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(54) Title: PEPTIDOMIMETIC MACROCYCLES AND USES THEREOF

(57) Abstract: Methods for treating liquid cancer, determined to lack a p53 deactivation mutation, in a subject are provided. Also provided are peptidomimetic macrocycles for use in treatment of a liquid cancer, determined to lack a p53 deactivation mutation, in a subject.

PEPTIDOMIMETIC MACROCYCLES AND USES THEREOF

CROSS REFERENCE

[0001] This application claims the benefit of U.S. Provisional Patent Application No. 62/136,357, filed on March 20, 2015, and U.S. Provisional Patent Application No. 62/232,275, filed on September 24, 2015, the entirety of each of which is incorporated herein by reference.

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

[0003] Provided herein are compounds capable of binding to and modulating the activity of p53, MDM2 and/or MDMX. Also provided herein are pharmaceutical formulations comprising p53-based peptidomimetic macrocycles that modulate an activity of p53. Also provided herein are pharmaceutical formulations comprising p53-based peptidomimetic macrocycles that inhibit the interactions between p53, MDM2 and/or MDMX proteins.

Further, provided herein are methods for treating diseases including but not limited to liquid cancers and other hyperproliferative diseases.

SUMMARY OF THE INVENTION

[0004] Described herein are methods of treating a liquid tumor determined to lack a p53 deactivating mutation, in a human subject in need thereof where the method comprises administering to the human subject a pharmaceutical composition comprising a therapeutically effective amount of a peptidomimetic macrocycle or a pharmaceutically acceptable salt thereof, wherein the peptidomimetic macrocycle binds to MDM2 and/or MDMX proteins.

[0005] Further disclosed herein are methods of treating a liquid tumor that lacks a p53 deactivating mutation, in a human subject in need thereof where the method comprises administering to the human subject a pharmaceutical composition comprising a therapeutically effective amount of a peptidomimetic macrocycle or a pharmaceutically acceptable salt thereof, wherein the peptidomimetic macrocycle binds to MDM2 and/or MDMX proteins.

[0006] Further disclosed herein are methods of treating a liquid tumor that has a p53 deactivating mutation in a p53 gene, in a human subject in need thereof where the method comprises administering to the human subject a pharmaceutical composition comprising a therapeutically effective amount of a peptidomimetic macrocycle or a pharmaceutically acceptable salt thereof, wherein the peptidomimetic macrocycle binds to MDM2 and/or MDMX proteins.

[0007] Further disclosed herein are methods of treating a liquid tumor in a human subject in need thereof, where the method comprises administering to the human subject a pharmaceutical composition comprising a therapeutically effective amount of a peptidomimetic macrocycle or a pharmaceutically acceptable salt thereof, where the peptidomimetic macrocycle binds to MDM2 and/or MDMX proteins and where the liquid tumor is not negative for p53 protein expression (such as liquid tumors that express wild-type p53 protein or mutated p53 protein with partial functionality).

[0008] Further disclosed herein are methods of treating a liquid tumor in a human subject in need thereof, where the method comprises administering to the human subject a pharmaceutical composition comprising a therapeutically effective amount of a peptidomimetic macrocycle or a pharmaceutically acceptable salt thereof, wherein the peptidomimetic macrocycle binds to MDM2 and/or MDMX proteins and wherein the liquid

tumor expresses a p53 protein with a gain of function mutation (such as a super apoptotic p53).

[0009] Further disclosed herein are methods of treating a liquid tumor in a human subject in need thereof, wherein the method comprises administering to the human subject a pharmaceutical composition comprising a therapeutically effective amount of a peptidomimetic macrocycle or a therapeutically equivalent amount of a pharmaceutically acceptable salt thereof, where the peptidomimetic macrocycle binds to MDM2 and/or MDMX proteins and wherein the liquid tumor express a p53 protein with a mutation that causes a partial loss of function.

[0010] Further disclosed herein are methods of treating a liquid tumor a human subject in need thereof, wherein the method comprises administering to the human subject a pharmaceutical composition comprising a therapeutically effective amount of a peptidomimetic macrocycle or a pharmaceutically acceptable salt thereof, wherein the peptidomimetic macrocycle binds to MDM2 and/or MDMX proteins and wherein cells in the liquid tumor express p53 from only a single genomic copy of the p53 gene (for example where the cells have a copy loss mutation, e.g., are haploinsufficient).

[0011] Further disclosed herein are methods of treating a liquid tumor a human subject in need thereof wherein the method comprises administering to the human subject a pharmaceutical composition comprising a therapeutically effective amount of a peptidomimetic macrocycle or a pharmaceutically acceptable salt thereof, where the peptidomimetic macrocycle binds to MDM2 and/or MDMX proteins and wherein the liquid tumor express a p53 protein with one or more silent mutations.

[0012] Further disclosed herein are methods of treating a liquid tumor a human subject in need thereof wherein the method comprises administering to the human subject a pharmaceutical composition comprising a therapeutically effective amount of a peptidomimetic macrocycle or a therapeutically equivalent amount of a pharmaceutically acceptable salt thereof, wherein the peptidomimetic macrocycle binds to MDM2 and/or MDMX proteins and where cells in the liquid tumor are negative for p53 expression.

[0013] In some embodiments, the cells in the liquid tumor have the p53 deactivating mutation in one copy of the p53 gene. In another embodiment, the cells in the liquid tumor have a second p53 deactivating mutation in a second copy of a p53 gene. In another embodiment, the p53 deactivating mutation in one copy of the p53 gene is the same as the second p53 deactivating mutation in the second copy of a p53 gene. In another embodiment, the p53 deactivating mutation in one copy of the p53 gene is different from the second p53

deactivating mutation in the second copy of a p53 gene. In another embodiment, the p53 deactivating mutation in the p53 gene results in the lack of p53 protein expression from the p53 gene or in expression of partial a p53 protein with partial loss of function. In another embodiment, the second p53 deactivating mutation in the second copy of a p53 gene results in the lack of p53 protein expression from the p53 gene or in expression of partial a p53 protein with partial loss of function.

[0014] In some embodiments, the cells of the liquid tumor have at least one mutation in a copy of a p53 gene, where the mutation eliminates or reduces the activity of a p53 protein expressed from the copy of the p53 gene, as compared to wild type p53 expressed from a copy of a non-mutated p53 gene. In another embodiment, the at least one mutation in a copy of a p53 gene is a non-synonymous mutation. In another embodiment, the at least one mutation in a copy of a p53 gene is a synonymous mutation. In another embodiment, the at least one mutation in a copy of a p53 gene is a synonymous mutation, where the synonymous mutation does not change amino acid sequence of a p53 protein expressed from the copy of the p53 gene. In another embodiment, the at least one mutation in a copy of a p53 gene is a synonymous mutation, where the synonymous mutation increases or decreases binding of a micro-RNA to a mRNA. In another embodiment, the at least one mutation in a copy of a p53 gene is a synonymous mutation, where the synonymous mutation alters (*e.g.*, increases or decreases) the half-life of mRNA.

[0015] Further disclosed herein are methods of treating a liquid tumor in a human subject in need thereof where the method comprises administering to the human subject a pharmaceutical composition comprising a therapeutically effective amount of a peptidomimetic macrocycle or a therapeutically equivalent amount of a pharmaceutically acceptable salt thereof, where the peptidomimetic macrocycle binds to MDM2 and/or MDMX proteins.

[0016] In some embodiments, the peptidomimetic macrocycle disrupts the interaction between p53 and MDM2 and MDMX.

[0017] In some embodiments, the method comprises determining the lack of the p53 deactivating mutation in the liquid tumor prior to the administration of the pharmaceutical composition. In another embodiment, determining the lack of the p53 deactivating mutation comprises confirming the presence of wild type p53 in the liquid tumor. In another embodiment, the method comprises determining a presence of a p53 gain of function mutation in the liquid tumor. In another embodiment, the method comprises determining a presence of a deactivating mutation of p53 in the liquid tumor. In another embodiment, the

method comprises determining a presence of a copy loss mutation of p53 in the liquid tumor. In another embodiment, the method comprises determining a presence of a partial loss of function mutation of P53 in the liquid tumor. In another embodiment, the method comprises confirming the lack of the p53 deactivating mutation in the liquid tumor prior to the administration of the pharmaceutical composition. In another embodiment, the confirming the lack of the p53 deactivating mutation comprises confirming the presence of wild type p53 in the liquid tumor. In another embodiment, the method comprises confirming a presence of a p53 gain of function mutation in the liquid tumor. In another embodiment, the method comprises confirming a presence of a deactivating mutation of p53 in the liquid tumor. In another embodiment, the method comprises confirming a presence of a copy loss mutation of p53 in the liquid tumor. In another embodiment, the method comprises comprising confirming a presence of a partial loss of function mutation of P53 in the liquid tumor.

[0018] In some embodiments, the determining or the confirming is performed within 1-15 months prior to the administration of the pharmaceutical composition. In another embodiment, the determining or the confirming is performed within 1-12 months prior to the administration of the pharmaceutical composition. In another embodiment, the determining or the confirming is performed within 1-3 months prior to the administration of the pharmaceutical composition. In another embodiment, the determining or the confirming is performed within 1 month prior to the administration of the pharmaceutical composition. In another embodiment, the determining or the confirming is performed within 21 days prior to the administration of the pharmaceutical composition. In another embodiment, the determining or the confirming is performed up to about 1 year prior to the administration of the pharmaceutical composition. In another embodiment, the determining or the confirming is performed up to about 2 years prior to the administration of the pharmaceutical composition. In another embodiment, the determining or the confirming is performed up to about 3 years prior to the administration of the pharmaceutical composition.

[0019] In some embodiments,the treatment results in re-activation of the p53 pathway, decreased liquid cancer cell proliferation, increased p53 protein, increased p21, and/or increased apoptosis in the human subject.

[0020] In some embodiments, the pharmaceutical composition is administered two or three times a week. In another embodiment, the pharmaceutical composition is administered two times a week. In another embodiment, the pharmaceutical composition is administered once every 2 or 3 weeks. In another embodiment, the pharmaceutical composition is administered once every 1 or 2 weeks. In another embodiment, the pharmaceutical composition is

administered on days 1, 4, 8, and 11 of a 21-day cycle. In another embodiment, the pharmaceutical composition is administered on days 1, 8, and 15 of a 28-day cycle.

[0021] In some embodiments, the amount of the compound administered is about 0.5-30 mg per kilogram body weight of the human subject. In another embodiment, the amount of the compound administered is about 0.5-20 mg per kilogram body weight of the human subject. In another embodiment, the amount of the compound administered is about 0.5-10 mg per kilogram body weight of the human subject. In another embodiment, the amount of the compound administered is about 0.04 mg, about 0.08 mg, about 0.16 mg, about 0.32 mg, about 0.64 mg, about 1.25 mg, about 1.28 mg, about 1.92 mg, about 2.5 mg, about 3.56 mg, about 3.75 mg, about 5.0 mg, about 7.12 mg, about 7.5 mg, about 10 mg, about 14.24 mg, about 15 mg, about 20 mg, or about 30 mg per kilogram body weight of the human subject. In another embodiment, the amount of the compound administered is about 1.92 mg, about 3.75 mg, about 7.5 mg, about 15.0 mg, or about 30.0 mg per kilogram body weight of the human subject and the compound is administered two times a week. In another embodiment, the amount of the compound administered is about 1.28 mg, about 2.56 mg, about 5.0 mg, about 10 mg, or about 20 mg per kilogram body weight of the human subject and the compound is administered two times a week. In another embodiment, the amount of the compound administered is about 1.92 mg, about 3.75 mg, about 7.5 mg, about 15.0 mg, or about 30.0 mg per kilogram body weight of the human subject and the compound is administered once a week. In another embodiment, the amount of the compound administered is about 1.28 mg, about 2.56 mg, about 5.0 mg, about 10 mg, or about 20 mg per kilogram body weight of the human subject and the compound is administered once a week. In another embodiment, the amount of the compound administered is about about 1.92 mg, about 3.75 mg, about 7.5 mg, about 15.0 mg, or about 30.0 mg mg per kilogram body weight of the human subject and the compound is administered once a day three, five or seven times in a seven day period. In another embodiment, the compound is administered intravenously once a day, seven times in a seven day period. In another embodiment, the amount of the compound administered is about 1.28 mg, about 2.56 mg, about 5.0 mg, about 10 mg, or about 20 mg per kilogram body weight of the human subject and the compound is administered once a day three, five or seven times in a seven day period. In another embodiment, the compound is administered intravenously once a day, seven times in a seven day period.

[0022] In some embodiments, the compound is administered over a period of 0.25 h, 0.5 h, 1 h, 2 h, 3 h, 4 h, 5 h, 6 h, 7 h, 8 h, 9 h, 10 h, 11 h, or 12 h. In another embodiment, the

compound is administered over a period of 0.25-2 h. In another embodiment, the compound is gradually administered over a period of 1 h. In another embodiment, the compound is gradually administered over a period of 2 h.

[0023] In some embodiments, the treatment results in about 95%, about 90%, about 85%, about 80%, about 75%, about 70%, about 65%, about 60%, about 55%, about 50%, about 45%, about 40%, about 35%, about 30%, about 25%, about 20%, about 15% , about 10%, or about 5% reduction in the number of liquid cancer cells within a period of 1 month after treatment initiation. In another embodiment, the treatment results in at least about 60%, at least about 65%, at least about 70%, at least about 75%, at least about 80%, at least about 85%, at least about 90%, or at least about 95% reduction in the number of liquid cancer cells within a period of 1 month after treatment initiation. In another embodiment, the treatment results in about 95%, about 90%, about 85%, about 80%, about 75%, about 70%, about 65%, about 60%, about 55%, about 50%, about 45%, about 40%, about 35%, about 30%, about 25%, about 20%, about 15% , about 10%, or about 5% reduction in the number of liquid cancer cells within a period of 1 year after treatment initiation. In another embodiment, the treatment results in at least about 60%, at least about 65%, at least about 70%, at least about 75%, at least about 80%, at least about 85%, at least about 90%, or at least about 95% reduction in the number of liquid cancer cells within a period of 1 year after treatment initiation. In another embodiment, the treatment results in about 95%, about 90%, about 85%, about 80%, about 75%, about 70%, about 65%, about 60%, about 55%, about 50%, about 45%, about 40%, about 35%, about 30%, about 25%, about 20%, about 15% , about 10%, or about 5% reduction the number of liquid cancer cells within a period of 6 months after treatment initiation. In another embodiment, the treatment results in at least about 60%, at least about 65%, at least about 70%, at least about 75%, at least about 80%, at least about 85%, at least about 90%, or at least about 95% reduction in the number of liquid cancer cells within a period of 6 months after treatment initiation. In another embodiment, the treatment results in about 95%, about 90%, about 85%, about 80%, about 75%, about 70%, about 65%, about 60%, about 55%, about 50%, about 45%, about 40%, about 35%, about 30%, about 25%, about 20%, about 15% , about 10%, or about 5% reduction in the number of liquid cancer cells within a period of 3 months after treatment initiation. In another embodiment, the treatment results in at least about 60%, at least about 65%, at least about 70%, at least about 75%, at least about 80%, at least about 85%, at least about 90%, or at least about 95% reduction in the number of liquid cancer cells within a period of 3 months after treatment initiation.

[0024] In some embodiments, the liquid cancer is a stable disease.

[0025] In some embodiments, the treatment results in an increased survival time of the human subject as compared to the expected survival time of the human subject if the human subject was not treated with the compound. In another embodiment, the increase in the survival time of the human subject is at least 30 days. In another embodiment, the increase in the survival time of the human subject is at least 3 months. In another embodiment, the increase in the survival time of the human subject is at least 6 months. In another embodiment, the increase in the survival time of the human subject is at least 1 year.

[0026] In some embodiments, the in vivo circulating half-life of the compound is about 1 h, 2 h, 3 h, 4 h, 5 h, 6 h, 7 h, 8 h, 9 h, 10 h or 12 h. In another embodiment, the in vivo circulating half-life of the compound is about 4 h. In another embodiment, in vivo circulating the half-life of the compound is about 6 h.

[0027] In some embodiments, the biological tissue half-life of the compound is about 1 h, 2 h, 3 h, 4 h, 5 h, 6 h, 7 h, 8 h, 9 h, 10 h or 12 h. In another embodiment, the biological tissue half-life of the compound is about 10 h.

[0028] In some embodiments, the human subject is refractory and/or intolerant to one or more other treatment of the liquid cancer. In another embodiment, the human subject has had at least one unsuccessful prior treatment and/or therapy of the liquid cancer.

[0029] In some embodiments, the liquid cancer expresses wild-type p53 protein.

[0030] In some embodiments, the liquid cancer is selected from a group consisting of liquid lymphoma, leukemia, and myeloma. In another embodiment, the liquid cancer is a liquid lymphoma. In another embodiment, the liquid cancer is a leukemia. In another embodiment, the liquid cancer is an acute leukemia. In another embodiment, the acute leukemia is an acute myeloid leukemia (AML). In another embodiment, the acute leukemia is an acute lymphoid leukemia (ALL). In another embodiment, the liquid cancer is a myeloma. In another embodiment, the liquid cancer is not a HPV positive cancer. In another embodiment, the liquid cancer is not HPV positive cervical cancer, HPV positive anal cancer or HPV positive head and neck cancer, such as oropharyngeal cancers.

[0031] In some embodiments, the compound is administered intravenously.

[0032] In some embodiments, the method further comprises administering in addition to the compound, a therapeutically effective amount of at least one additional therapeutic agent and/or therapeutic procedure to the human subject.

[0033] In some embodiments, the human subject exhibits a complete response to the treatment. In another embodiment, the human subject exhibits a partial response to the treatment.

[0034] In some embodiments, the liquid cancer is a progressive disease. In another embodiment, the liquid cancer is a stable disease.

[0035] In some embodiments, the method further comprises determining clinical activity of the administered compound. In another embodiment, the clinical activity is determined by an imaging method selected from a group consisting of computed tomography (CT), magnetic resonance imaging (MRI), bone scanning, and positron emission tomography (PET) scan. In another embodiment, the PET scan uses one or more tracers. In another embodiment, the one or more tracers comprises ^{18}F-fluorodeoxyglucose (FDG), ^{64}Cu diacetyl-bis(N^4-methylthiosemicarbazone) (ATSM), ^{18}F-fluoride, 3'-deoxy-3'-[^{18}F]fluorothymidine (FLT), ^{18}F-fluoromisonidazole (FMISO), Gallium, Technetium-99m, or Thallium.

[0036] In another embodiment, the method further comprises obtaining a biological sample from the human subject at one or more specific time-points and analyzing the biological sample with an analytical procedure. In another embodiment, the analytical procedure is selected from a group comprising blood chemistry analysis, chromosomal translocation analysis, needle biopsy, tissue biopsy, fluorescence in situ hybridization, laboratory biomarker analysis, immunohistochemistry staining method, flow cytometry, or a combination thereof. In another embodiment, the method comprises tabulating and/or plotting results of the analytical procedure. In another embodiment, the one or more specific time-points comprise a time-point before the administration of the compound to the human subject. In another embodiment, the one or more specific time-points comprise a time-point after the administration of the compound to the human subject. In another embodiment, the one or more specific time-points comprise a time-point before and a time-point after the administration of the compound to the human subject. In another embodiment, the method further comprises comparing the biological samples collected before and after the administration of the compound to the human subject. In another embodiment, the one or more specific time-points comprise multiple time-points before and after the administration of the compound to the human subject. In another embodiment, the method further comprises comparing the biological samples collected at the multiple time-points. In another embodiment, the biological sample is used for biomarker assessment. In another embodiment, the biological sample is used for pharmacokinetic assessment. In another embodiment, the pharmacokinetic assessment comprises studying the level of the peptidomimetic macrocycle

and/or its metabolites in the biological sample at the specific time-points. In another embodiment, the biological sample is a blood sample or a bone marrow sample. In another embodiment, the biological sample is used for pharmacodynamic assessment. In another embodiment, the pharmacodynamic assessment comprises studying the level of p53, MDM2, MDMX, p21 and/or caspase in the biological sample at the specific time-points. In another embodiment, the biological sample is a liquid cancer cell specimen. In another embodiment, the biological sample is used for immunogenicity assays.

[0037] In some embodiments, the method further comprises selecting and/or identifying at least one circulating tumor cells (CTC) or a mononuclear blood cells (MNBC) in the human subject prior to the administration of the compound to the human subject. In another embodiment, the method further comprises measuring the number of circulating tumor cells (CTCs) or mononuclear blood cells (MNBCs) at one or more specific time-points, where the number of circulating tumor cells (CTCs) or mononuclear blood cells (MNBCs) is the total number of at least one circulating tumor cells (CTC) or a mononuclear blood cells (MNBC) at the specific time-point. In another embodiment, the method further comprises measuring a baseline sum diameter, where the baseline sum diameter is a sum of the diameters of the at least one circulating tumor cells (CTC) or a mononuclear blood cells (MNBC) prior to the administration of the compound to the human subject. In another embodiment, the treatment results in disappearance of the least one circulating tumor cells (CTC) or a mononuclear blood cells (MNBC). In another embodiment, the treatment the number of CTCs and/or MNBCs is reduced. In another embodiment, the one or more specific time-points, comprise a time-point after the treatment. In another embodiment, the number of CTCs and/or MNBCs at the time-point after the treatment is at least 30% less than the baseline number of CTCs and/or MNBCs. In another embodiment, the treatment results in neither sufficient increase nor a sufficient decrease in the number of CTCs and/or MNBCs at the one or more specific time-points, taking as reference the baseline number of CTCs and/or MNBCs.

[0038] In some embodiments, the peptidomimetic macrocycle is not an inhibitor of cytochrome P450 isoforms.

[0039] In some embodiments, the treatment results in essentially no dose-limiting thrombocytopenia. In another embodiment, the treatment causes essentially no adverse effects in a normal-hematopoietic organ and/or tissue. In another embodiment, the treatment results in essentially no adverse event in the human subject that is possibly, probably, or definitely related to the administration of the compound. In another embodiment, the

treatment results in essentially no serious adverse event in the human subject that is probably, probably, or definitely related to the administration of the compound.

[0040] In some embodiments, the lack of p53 deactivation mutation in the liquid cancer is determined by DNA sequencing of the nucleic acid encoding the p53 protein. In another embodiment, the lack of p53 deactivation mutation in the liquid cancer is determined by RNA array based testing. In another embodiment, the lack of p53 deactivation mutation in the liquid cancer is determined by RNA analysis. In another embodiment, the lack of p53 deactivation mutation in the liquid cancer is determined by polymerase chain reaction (PCR). In another embodiment, the p53 deactivating mutation comprises mutations in DNA-binding domain of the protein. In another embodiment, the p53 deactivating mutation comprises missense mutation. In another embodiment, the p53 deactivating mutation is a dominant deactivating mutation. In another embodiment, the p53 deactivating mutation comprises one or more mutations selected from a groups consisting of V173L, R175H, G245C, R248W, R249S and R273H. In another embodiment, the p53 deactivating mutation comprises one or more of mutations shown in Table 1.

[0041] Also disclosed herein are methods of treating liquid cancer in a human subject determined to lack a p53 deactivating mutation, where the method comprises administering to the human subject 0.5-20 mg of a peptidomimetic macrocycle per kilogram body weight of the human subject or a pharmaceutically acceptable salt thereof on days 1, 8 and 15 of a 28-day cycle.

[0042] In some embodiments, the peptidomimetic macrocycle per kilogram body weight of the human subject or a pharmaceutically acceptable salt thereof is administered to the human subject.

[0043] In some embodiments, the amount of the peptidomimetic macrocycle entered on day 8 and/or day 15 is greater than the amount of the peptidomimetic macrocycle entered on day 1. In another embodiment, the amount of the peptidomimetic macrocycle entered on day 8 and/or day 15 is equal than the amount of the peptidomimetic macrocycle entered on day 1. In another embodiment, the amount of the peptidomimetic macrocycle entered on day 1 and/or day 8 is greater than the amount of the peptidomimetic macrocycle entered on day 15. In another embodiment, equal amounts of the peptidomimetic macrocycle are administered on days 1, 8 and 15.

[0044] In some embodiments, the 28-day cycle is repeated 2 or 3 times.

[0045] Also disclosed herein are methods of treating liquid cancer in a human subject determined to lack a p53 deactivating mutation, where the method comprises administering to

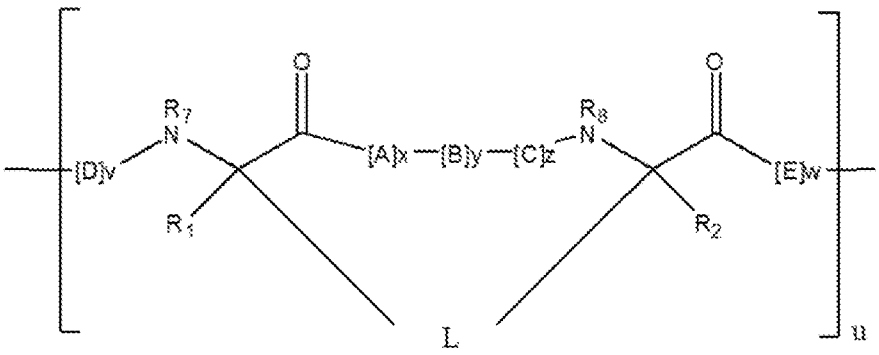
the human subject 0.25-10 mg of a peptidomimetic macrocycle per kilogram body weight of the human subject or a pharmaceutically acceptable salt thereof on days 1, 4, 8 and 11 of a 21-day cycle.

[0046] In some embodiments, 0.25-5 mg of the peptidomimetic macrocycle per kilogram body weight of the human subject or a pharmaceutically acceptable salt thereof is administered to the human subject.

[0047] In some embodiments, the amount of the peptidomimetic macrocycle entered on day 4, 8, and/or day 11 is greater than the amount of the peptidomimetic macrocycle entered on day 1. In another embodiment, the amount of the peptidomimetic macrocycle entered on day 4, 8, and/or day 11 is equal than the amount of the peptidomimetic macrocycle entered on day 1. In another embodiment, the amount of the peptidomimetic macrocycle entered on day 1, 4, and/or day 8 is greater than the amount of the peptidomimetic macrocycle entered on day 11. In another embodiment, equal amounts of the peptidomimetic macrocycle is administered on days 1, 4, 8, and 151.

[0048] In some embodiments, the 21-day cycle is repeated 2 or 3 times.

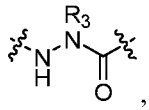
[0049] In some embodiments, the peptidomimetic macrocycle comprises an amino acid sequence which is at least about 60%, at least about 70%, at least about 80%, at least about 90%, or at least about 95% identical to an amino acid sequence in any of Table 3, Table 3a, Table 3b, and Table 3c, where the peptidomimetic macrocycle has the formula:



Formula (I)

wherein:

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

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

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

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

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

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

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

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

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

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

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

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

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

each v is independently an integer from 0–1000;

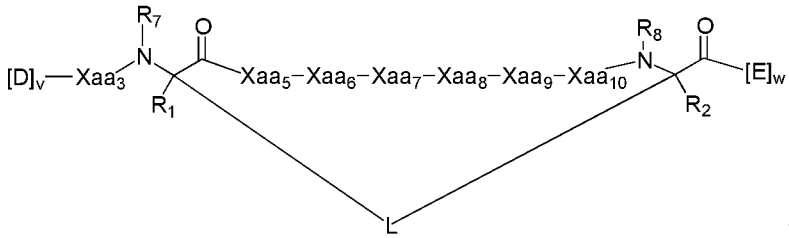
each w is independently an integer from 0–1000, for example, 0-500, 0-200, 0-100, 0-50, 0-30, 0-20, 0-10, 0-5, 1-1000, 1-500, 1-200, 1-100, 1-50, 1-30, 1-20, 1-10, 1-5, 3-1000, 3-500, 3-200, 3-100, 3-50, 3-30, 3-20, 3-10, 0, 1, 2, 3, 4, 5, 6, 7, 8, 9, or 10;

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.

[0050] In some embodiments, the peptidomimetic macrocycle has formula:



wherein:

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

each D is independently an amino acid;

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

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

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

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

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

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

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

v is an integer from 1-1000; and

w is an integer from 0-1000.

[0051] In some embodiments, at least one of the macrocycle-forming linker has a formula –L_1–L_2–, where L_1 and L_2 are independently alkylene, alkenylene, alkynylene, heteroalkylene, cycloalkylene, heterocycloalkylene, cycloarylene, heterocycloarylene, or $[-R_4\text{-}K\text{-}R_4-]_n$, each being optionally substituted with R_5; each R_4 is independently alkylene, alkenylene, alkynylene, heteroalkylene, cycloalkylene, heterocycloalkylene, arylene, or heteroarylene; each K is independently O, S, SO, SO_2, CO, CO_2, or $CONR_3$; each R_3 is independently hydrogen, alkyl, alkenyl, alkynyl, arylalkyl, heteroalkyl, cycloalkyl, heterocycloalkyl, cycloalkylalkyl, cycloaryl, or heterocycloaryl, optionally substituted with R_5; and n is an integer from 1-5.

[0052] In some embodiments, w is an integer from 0–1000, for example, 0-500, 0-200, 0-100, 0-50, 0-30, 0-20, 0-10, 0-5, 1-1000, 1-500, 1-200, 1-100, 1-50, 1-30, 1-20, 1-10, 1-5, 3-1000, 3-500, 3-200, 3-100, 3-50, 3-30, 3-20, 3-10, 0, 1, 2, 3, 4, 5, 6, 7, 8, 9, or 10.

[0053] In some embodiments, Xaa_5 is Glu or an amino acid analog thereof. In another embodiment, each E is independently Ala (alanine), Ser (serine) or an analog thereof. In another embodiment, $[D]_v$ is $–Leu_1\text{-}Thr_2$.

[0054] In some embodiments, w is 3-10. In another embodiment, w is 3-6. In another embodiment, w is 6-10. In another embodiment, w is 6.

[0055] In some embodiments, v is 1-10. In another embodiment, v is 2-10. In another embodiment, v is 2-5. In another embodiment, v is 2.

[0056] In some embodiments, L_1 and L_2 are independently alkylene, alkenylene, alkynylene, heteroalkylene, cycloalkylene, heterocycloalkylene, cycloarylene, or heterocycloarylene, each being optionally substituted with R_5. In another embodiment, L_1 and L_2 are independently alkylene or alkenylene. In another embodiment, L is alkylene, alkenylene, or alkynylene. In another embodiment, L is alkylene. In another embodiment, L is C_3-C_{16} alkylene. In another embodiment, L is C_{10}-C_{14} alkylene.

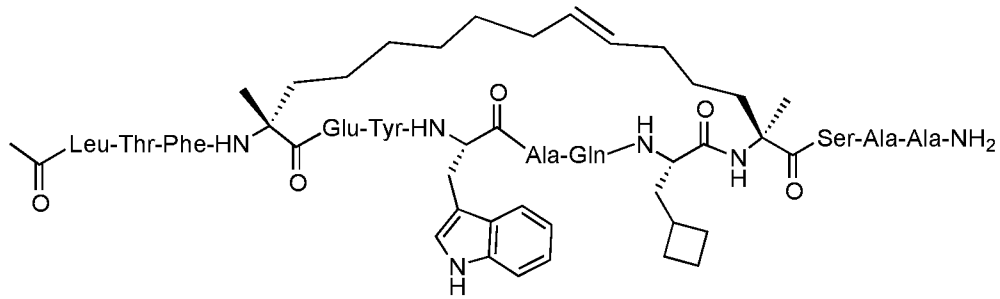
[0057] In some embodiments, R_1 and R_2 are independently –H, alkyl, alkenyl, alkynyl, arylalkyl, cycloalkyl, cycloalkylalkyl, heteroalkyl, or heterocycloalkyl, unsubstituted or substituted with halo–. In another embodiment, R_1 and R_2 are H. In another embodiment, R_1 and R_2 are independently alkyl. In another embodiment, R_1 and R_2 are methyl.

[0058] In some embodiments, x+y+z = 6.

[0059] In some embodiments, u is 1.

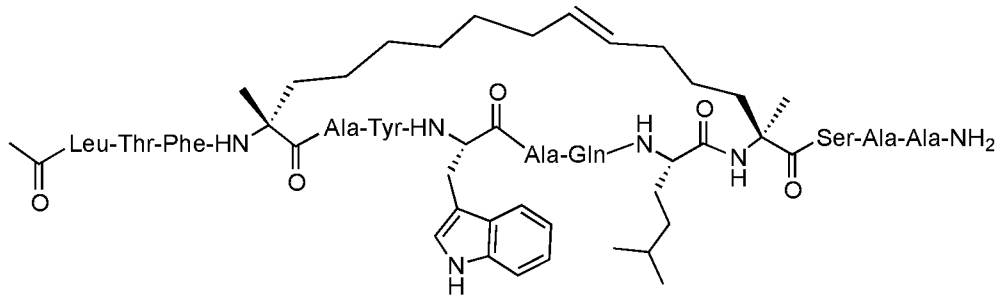
[0060] In some embodiments, the peptidomimetic macrocycle comprises at least one amino acid which is an amino acid analog.

[0061] In some embodiments, the peptidomimetic macrocycle has formula:



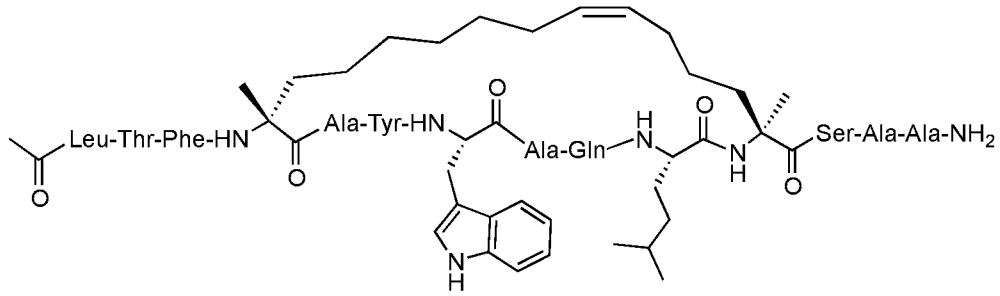
or a pharmaceutically acceptable salt thereof.

[0062] In some embodiments, the peptidomimetic macrocycle has formula:



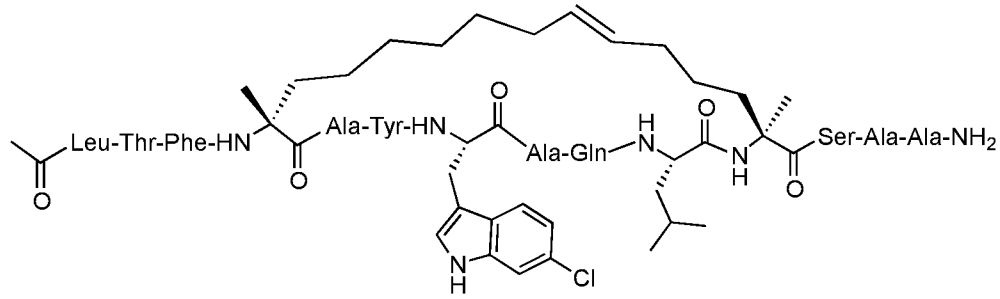
or a pharmaceutically acceptable salt thereof.

[0063] In some embodiments, the peptidomimetic macrocycle has formula:



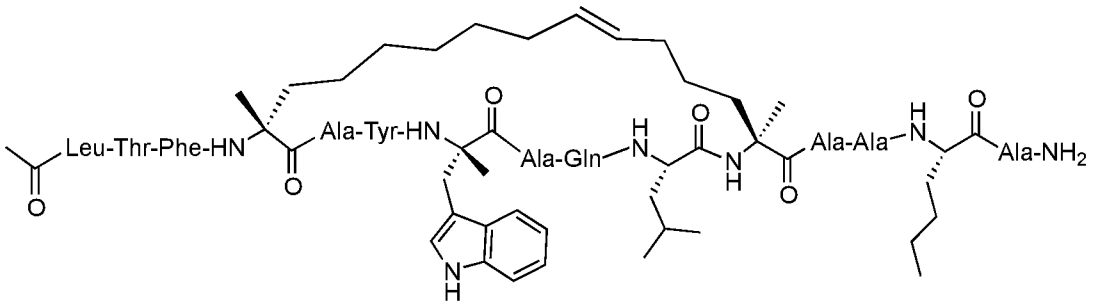
or a pharmaceutically acceptable salt thereof.

[0064] In some embodiments, the peptidomimetic macrocycle has formula:



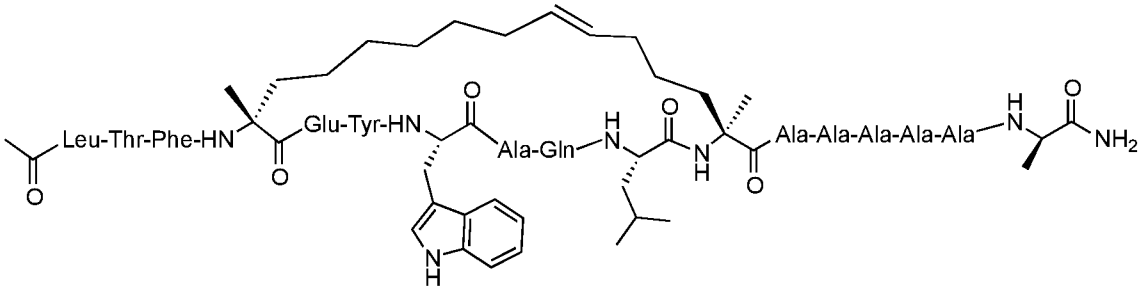
or a pharmaceutically acceptable salt thereof.

[0065] In some embodiments, the peptidomimetic macrocycle has formula:



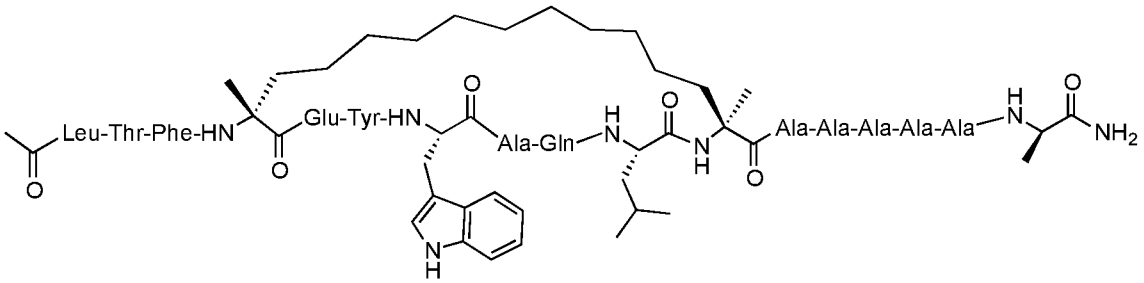
or a pharmaceutically acceptable salt thereof.

[0066] In some embodiments, the peptidomimetic macrocycle has formula:



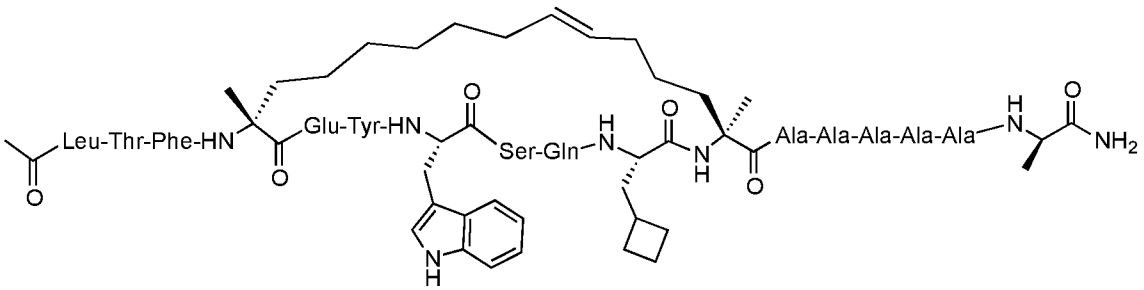
or a pharmaceutically acceptable salt thereof.

[0067] In some embodiments, the peptidomimetic macrocycle has formula:



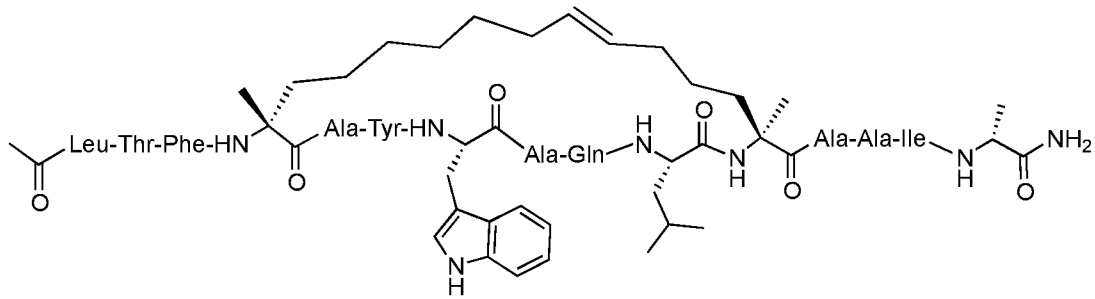
or a pharmaceutically acceptable salt thereof.

[0068] In some embodiments, the peptidomimetic macrocycle has formula:



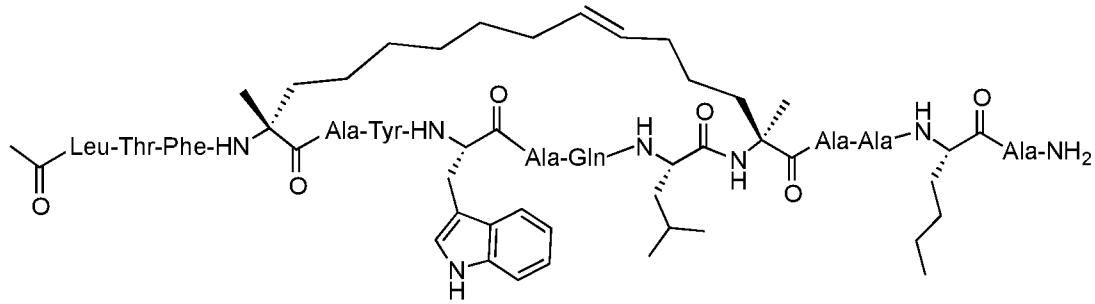
or a pharmaceutically acceptable salt thereof.

[0069] In some embodiments, the peptidomimetic macrocycle has formula:



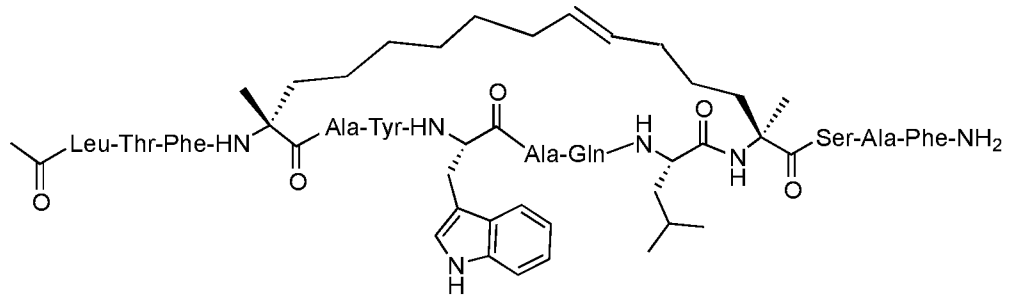
or a pharmaceutically acceptable salt thereof.

[0070] In some embodiments, the peptidomimetic macrocycle has formula:



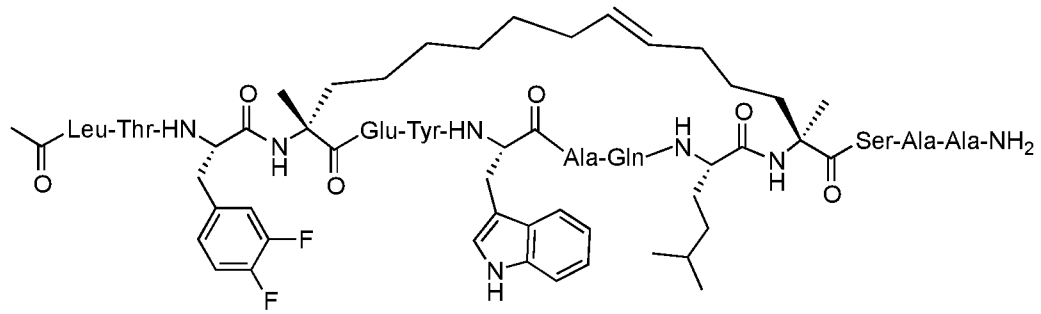
or a pharmaceutically acceptable salt thereof.

[0071] In some embodiments, the peptidomimetic macrocycle has formula:



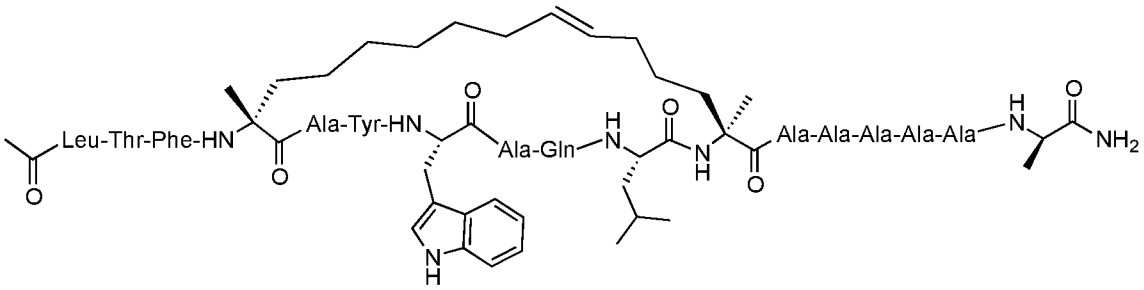
or a pharmaceutically acceptable salt thereof.

[0072] In some embodiments, the peptidomimetic macrocycle has formula:



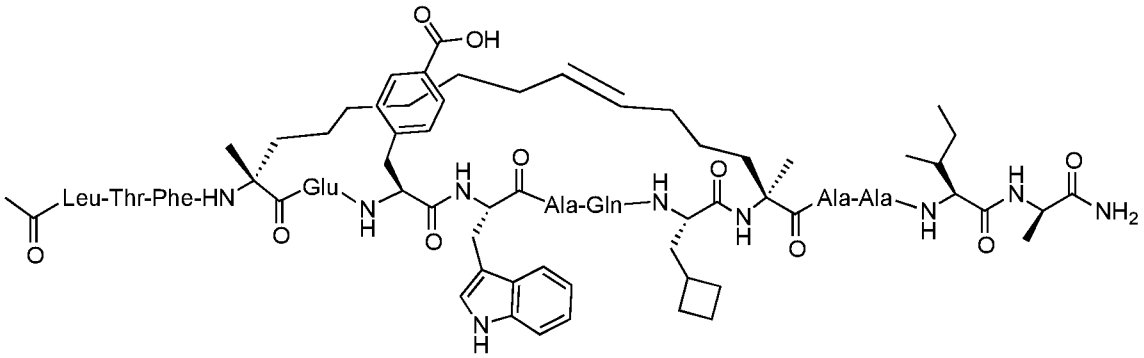
or a pharmaceutically acceptable salt thereof.

[0073] In some embodiments, the peptidomimetic macrocycle has formula:



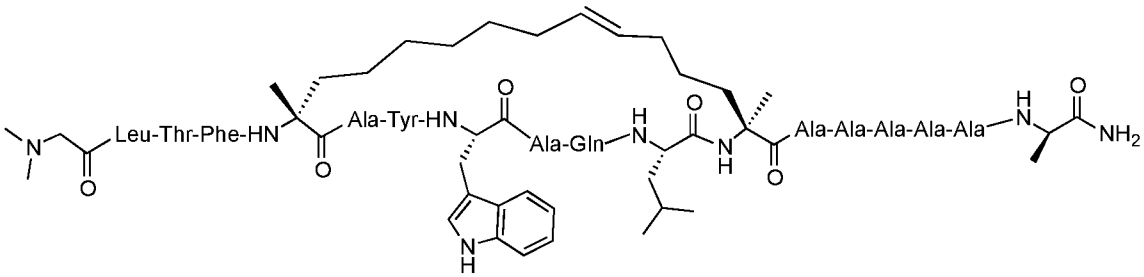
or a pharmaceutically acceptable salt thereof.

[0074] In some embodiments, the peptidomimetic macrocycle has formula:



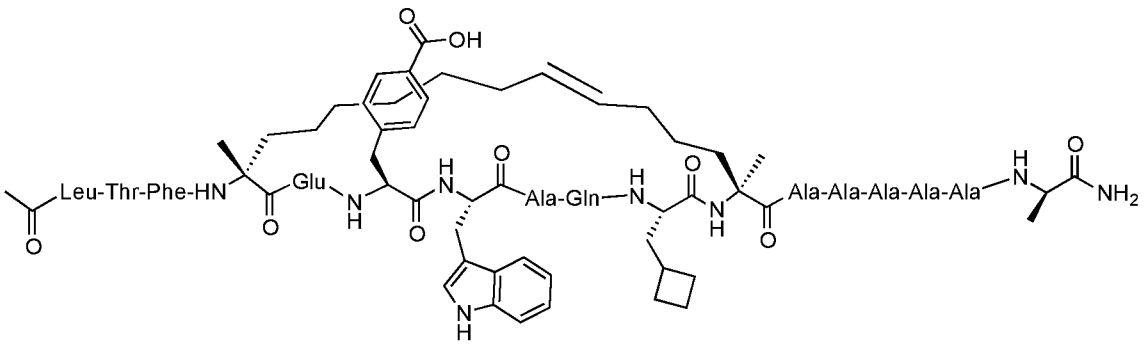
or a pharmaceutically acceptable salt thereof.

[0075] In some embodiments, the peptidomimetic macrocycle has formula:



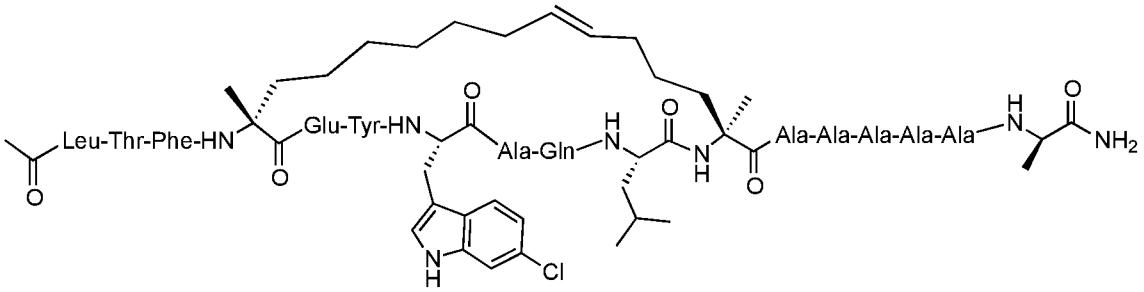
or a pharmaceutically acceptable salt thereof.

[0076] In some embodiments, the peptidomimetic macrocycle has formula:



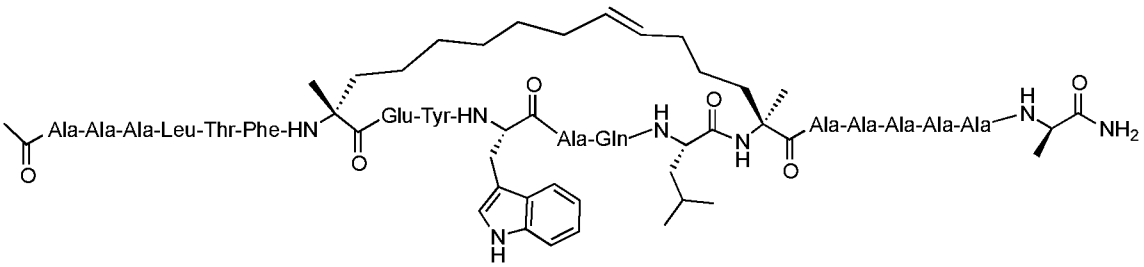
or a pharmaceutically acceptable salt thereof.

[0077] In some embodiments, the peptidomimetic macrocycle has formula:



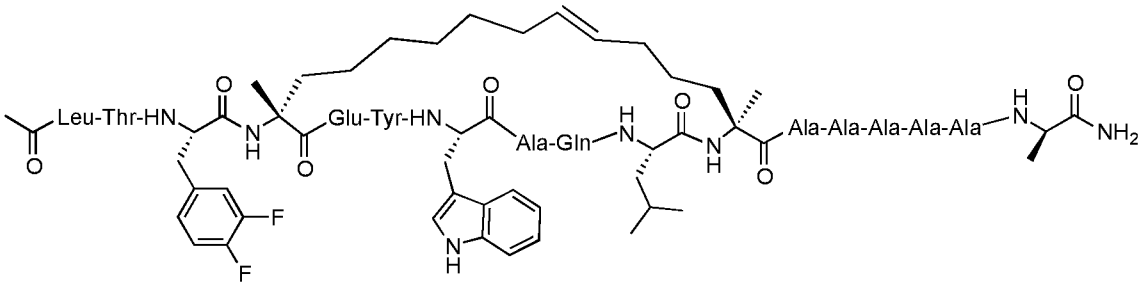
or a pharmaceutically acceptable salt thereof.

[0078] In some embodiments, the peptidomimetic macrocycle has formula:



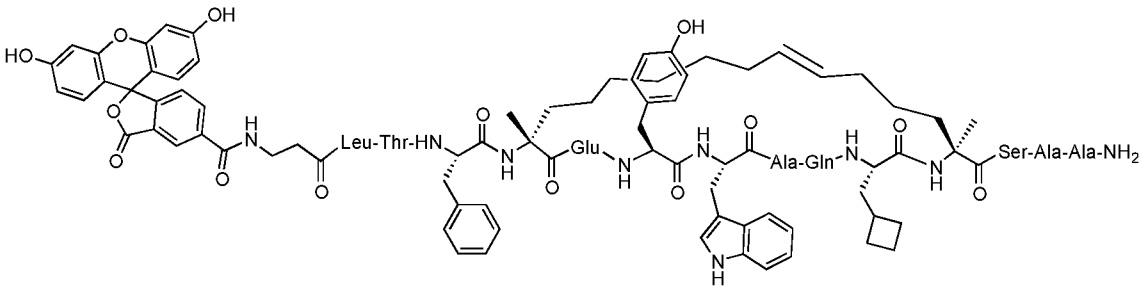
or a pharmaceutically acceptable salt thereof.

[0079] In some embodiments, the peptidomimetic macrocycle has formula:



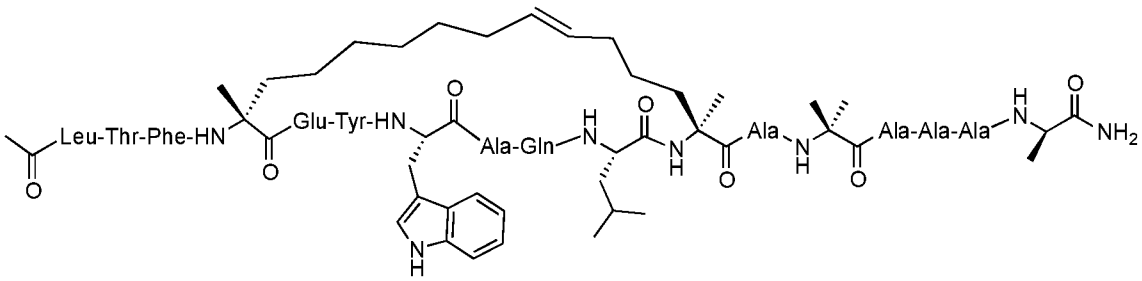
or a pharmaceutically acceptable salt thereof.

[0080] In some embodiments, the peptidomimetic macrocycle has formula:



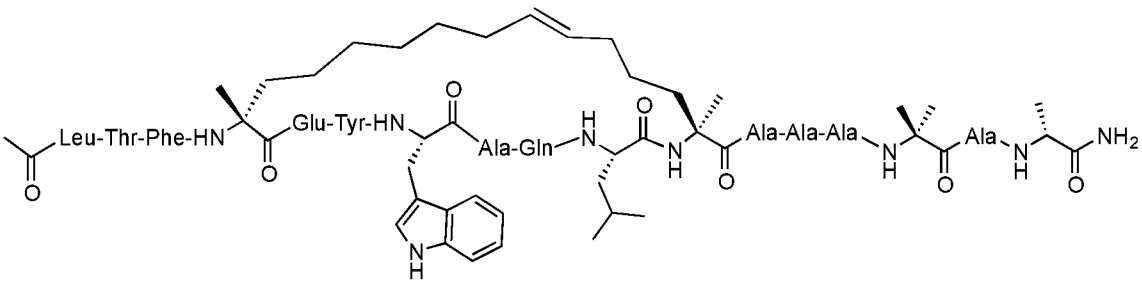
or a pharmaceutically acceptable salt thereof.

[0081] In some embodiments, the peptidomimetic macrocycle has formula:



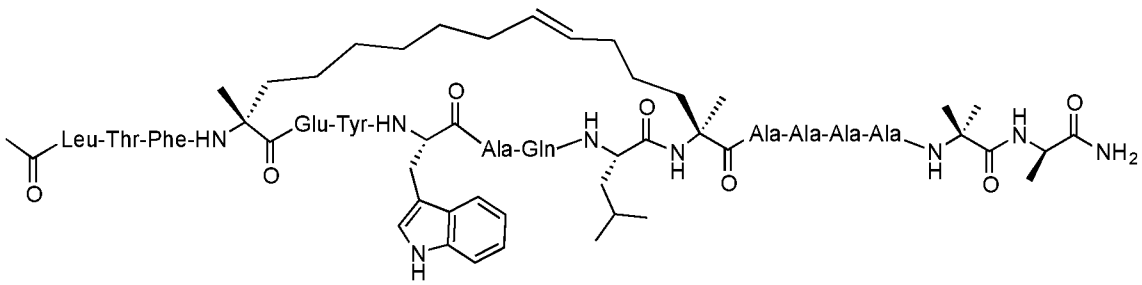
or a pharmaceutically acceptable salt thereof.

[0082] In some embodiments, the peptidomimetic macrocycle has formula:



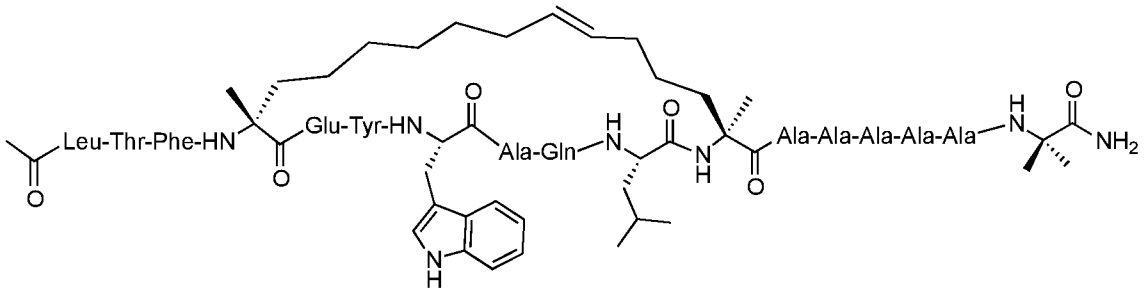
or a pharmaceutically acceptable salt thereof.

[0083] In some embodiments, the peptidomimetic macrocycle has formula:



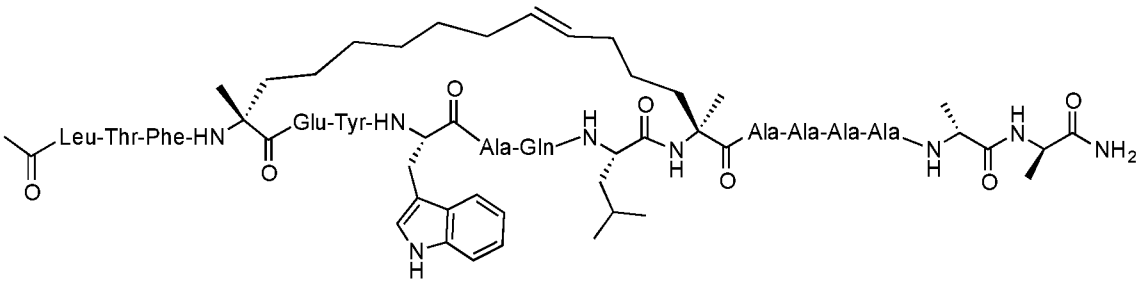
or a pharmaceutically acceptable salt thereof.

[0084] In some embodiments, the peptidomimetic macrocycle has formula:



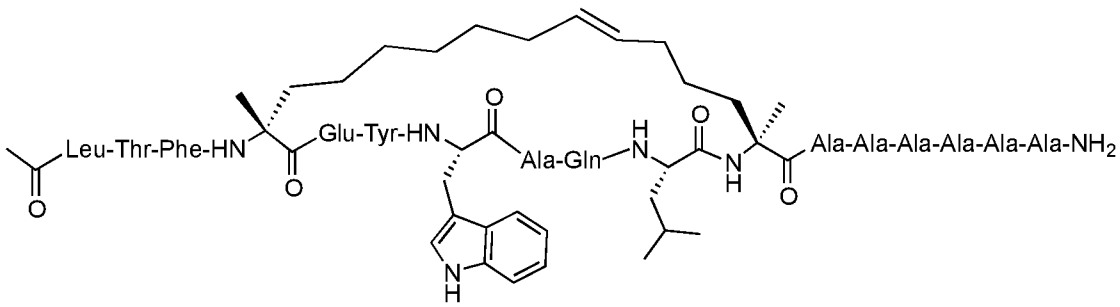
or a pharmaceutically acceptable salt thereof.

[0085] In some embodiments, the peptidomimetic macrocycle has formula:



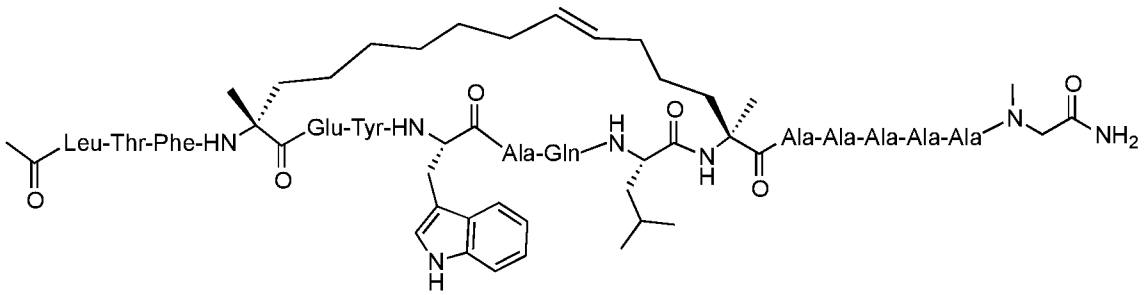
or a pharmaceutically acceptable salt thereof.

[0086] In some embodiments, the peptidomimetic macrocycle has formula:



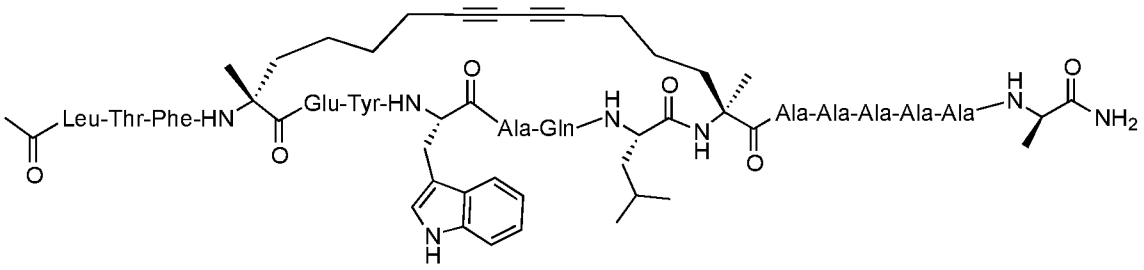
or a pharmaceutically acceptable salt thereof.

[0087] In some embodiments, the peptidomimetic macrocycle has formula:



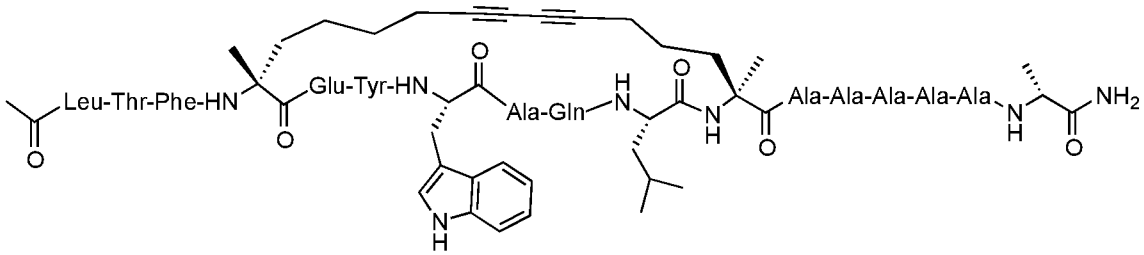
or a pharmaceutically acceptable salt thereof.

[0088] In some embodiments, the peptidomimetic macrocycle has formula:



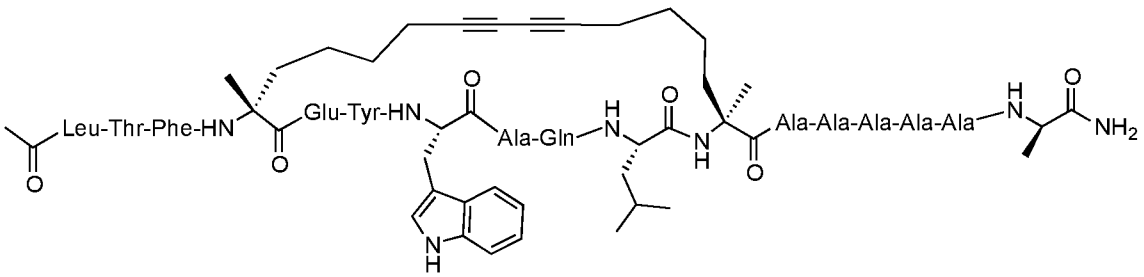
or a pharmaceutically acceptable salt thereof.

[0089] In some embodiments, the peptidomimetic macrocycle has formula:



or a pharmaceutically acceptable salt thereof.

[0090] In some embodiments, the peptidomimetic macrocycle has formula:



or a pharmaceutically acceptable salt thereof.

[0091] Also disclosed herein are methods of identifying one or more liquid cancer biomarkers in a human subject lacking a p53 deactivating mutation, comprising administering to the human subject a therapeutically effective amount of a peptidomimetic macrocycle.

[0092] In some embodiments, the biomarkers are p53 status, MDM2 expression level or MDMX expression level.

INCORPORATION BY REFERENCE

[0093] 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

[0094] 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:

[0095] Figure 1 shows human wild type P53 coding and protein sequence.

[0096] Figure 2 shows peptide 1 yielded robust apoptotic responses in p53 wild-type hematopoietic cell lines.

[0097] Figure 3 shows peptide 1 yielded on-mechanism p21 pharmacodynamic responses in p53 wild-type hematopoietic cell lines.

[0098] Figure 4 shows peptide 1 selectively killed p53 wild-type cancer cells in a representative hematopoietic cell line panel.

[0099] Figure 5 shows survival of animals after dosing of peptide 1 in AML xenograft model.

[00100] **Figure 6** shows the dose-dependant platelet response of peptide 1 in 4-week monkey GLP toxicity study.

DETAILED DESCRIPTION OF THE INVENTION

[00101] While preferred embodiments of the present disclosure have been shown and described herein, it will be obvious to those skilled in the art that such embodiments are provided by way of example only. Numerous variations, changes, and substitutions will now occur to those skilled in the art without departing from the disclosure. It should be understood that various alternatives to the embodiments of the disclosure described herein can be employed in practicing the disclosure. It is intended that the following claims define the scope of the disclosure and that methods and structures within the scope of these claims and their equivalents be covered thereby.

DEFINITIONS

[00102] 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.

[00103] 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.

[00104] As used herein, the term "laboratory TLS" refers to a 25% increase in the levels of serum uric acid, potassium, or phosphorus or a 25% decrease in calcium levels.

[00105] 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.

[00106] 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.

[00107] 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.

[00108] The term "β-amino acid" refers to a molecule containing both an amino group and a carboxyl group in a β configuration.

[00109] 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.

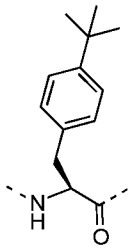
[00110] The following table shows a summary of the properties of natural amino acids:

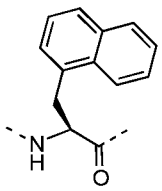
Amino Acid	3-Letter Code	1-Letter Code	Side-chain Polarity	Side-chain charge (pH 7.4)	Hydropathy Index
Alanine	Ala	A	nonpolar	neutral	1.8
Arginine	Arg	R	polar	positive	−4.5
Asparagine	Asn	N	polar	neutral	−3.5
Aspartic acid	Asp	D	polar	negative	−3.5
Cysteine	Cys	C	polar	neutral	2.5
Glutamic acid	Glu	E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

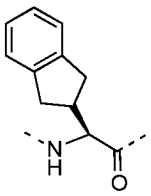
[00111] "Hydrophobic amino acids" include small hydrophobic amino acids and large hydrophobic amino acids. "Small hydrophobic amino acid" are glycine, alanine, proline, and analogs thereof. "Large hydrophobic amino acids" are valine, leucine, isoleucine, phenylalanine, methionine, tryptophan, and analogs thereof. "Polar amino acids" are serine, threonine, asparagine, glutamine, cysteine, tyrosine, and analogs thereof. "Charged amino acids" are lysine, arginine, histidine, aspartate, glutamate, and analogs thereof.

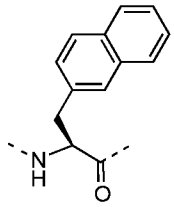
[00112] The term "amino acid analog" refers to a molecule which is structurally similar to an amino acid and which can be substituted for an amino acid in the formation of a peptidomimetic macrocycle. Amino acid analogs include, without limitation, β-amino acids and amino acids where the amino or carboxy group is substituted by a similarly reactive group (*e.g.*, substitution of the primary amine with a secondary or tertiary amine, or substitution of the carboxy group with an ester).

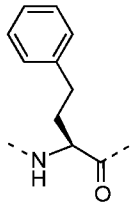
[00113] The term "non-natural amino acid" refers to an amino acid which is not one of the twenty amino acids commonly found in peptides synthesized in nature, and known by the one letter abbreviations A, R, N, C, D, Q, E, G, H, I, L, K, M, F, P, S, T, W, Y and V. Non-natural amino acids or amino acid analogs include, without limitation, structures according to the following:

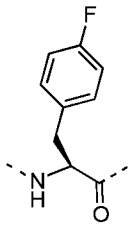

4-t-butylphenylalanine (F4tBu)

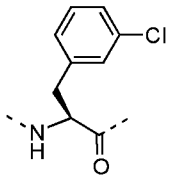

1-Naphthylalanine (1Nal)

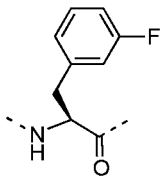

Indanyl glycine (Igl)

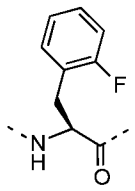

2-Naphthylalanine (2Nal)

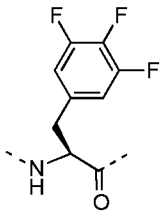

homophenylalanine (hF)

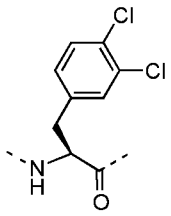

4-fluorophenylalanine (F4F)

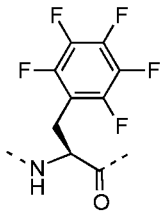

3-chlorohenylalanine (F3Cl=3cf)

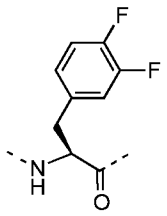

3-fluorophenylalanine (F3F=3ff)

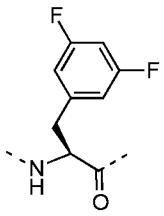

2-fluorophenylalanine (F2F=2ff)

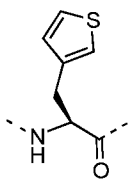

3,4,5-trifluoro phenylalanine (F345F3)

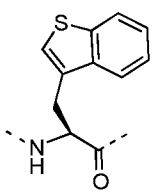

3,4-difluoro phenylalanine (F34Cl2)

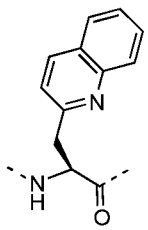

pentafluoro phenylalanine (F5F)

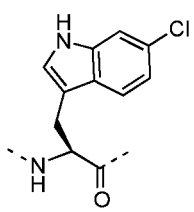

3,4-difluoro phenylalanine (F34F2)

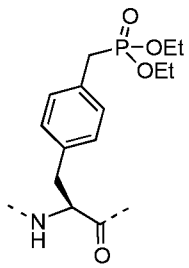

3,5-difluoro phenylalanine (F35F2)

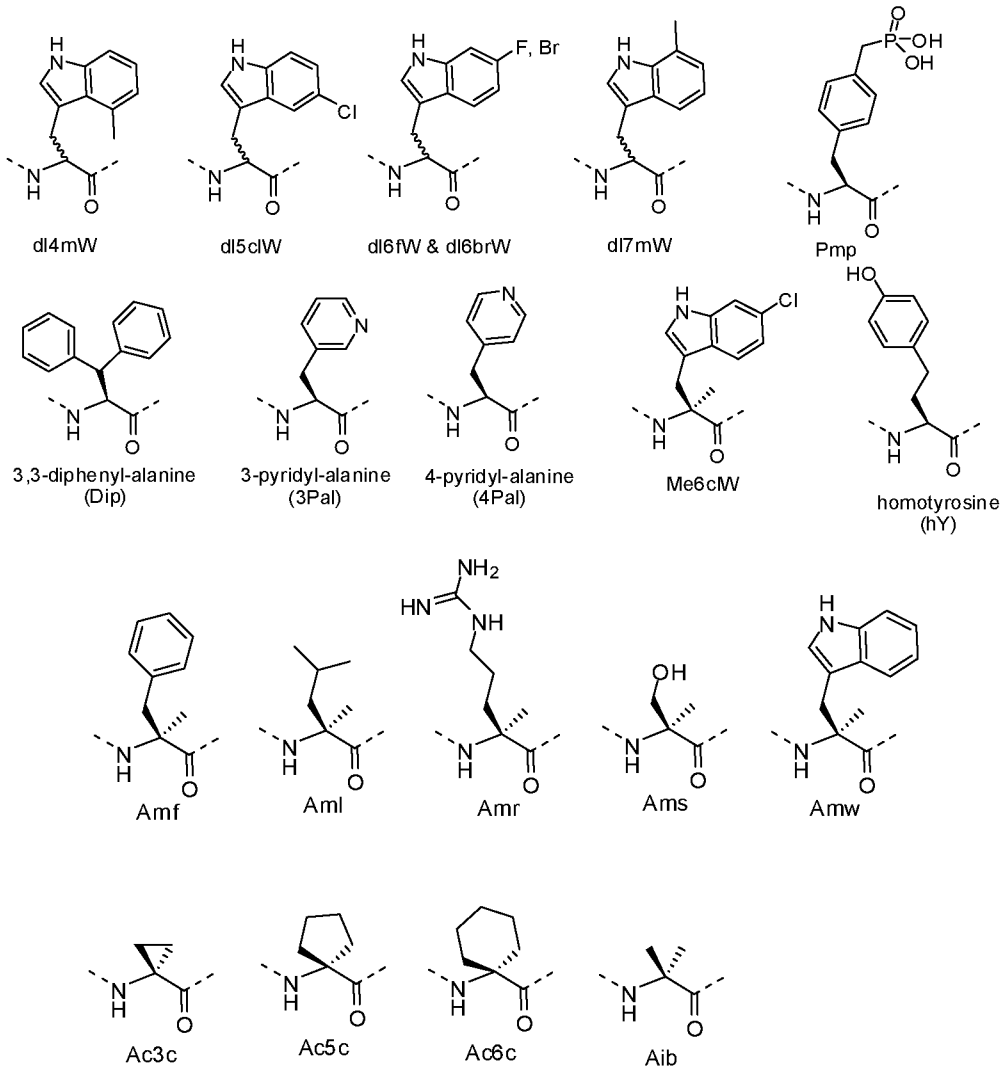

3-thienylalanine (2Thi)

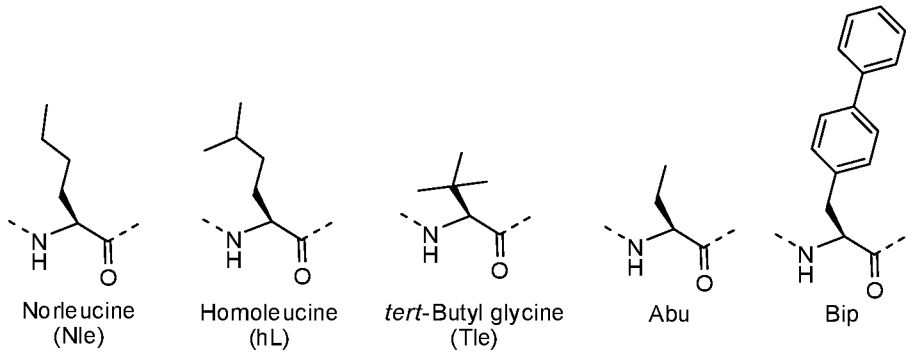

3-(1-Benzothiophen-3-yl) alanine (3BthA)


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

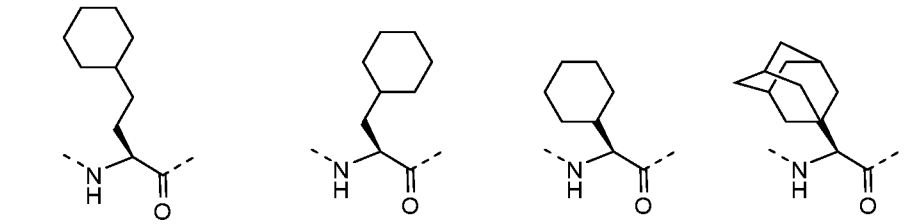

6-chlorotryptophan (6clW)


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

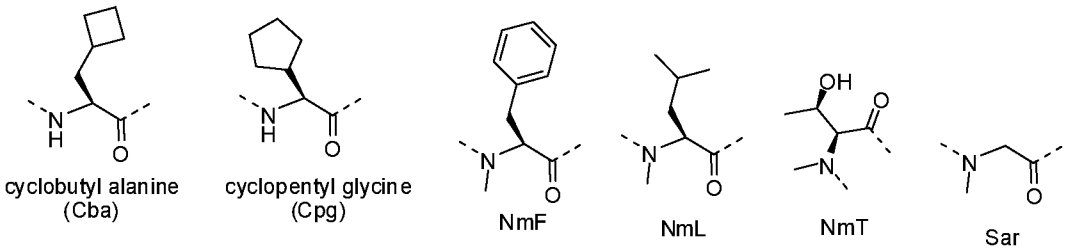

dl4mW
dl5clW
dl6fW & dl6brW
F, Br
dl7mW
Pmp
3,3-diphenyl-alanine
(Dip)
3-pyridyl-alanine
(3Pal)
4-pyridyl-alanine
(4Pal)
Me6clW
homotyrosine
(hY)
Amf
Aml
Amr
Ams
Amw
Ac3c
Ac5c
Ac6c
Aib



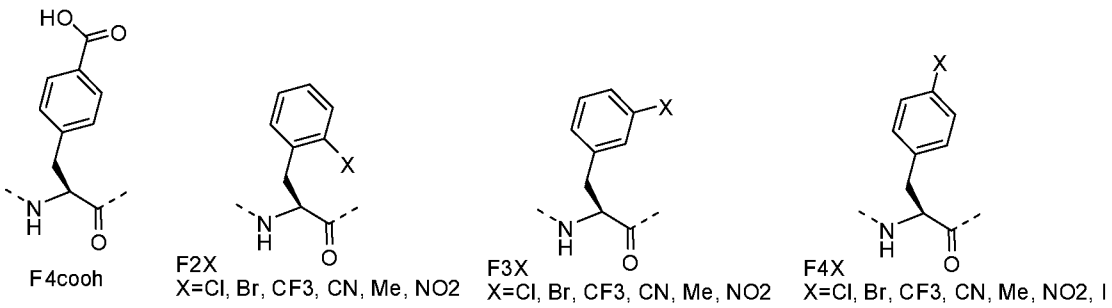
Norleucine (Nle) | Homoleucine (hL) | *tert*-Butyl glycine (Tle) | Abu | Bip



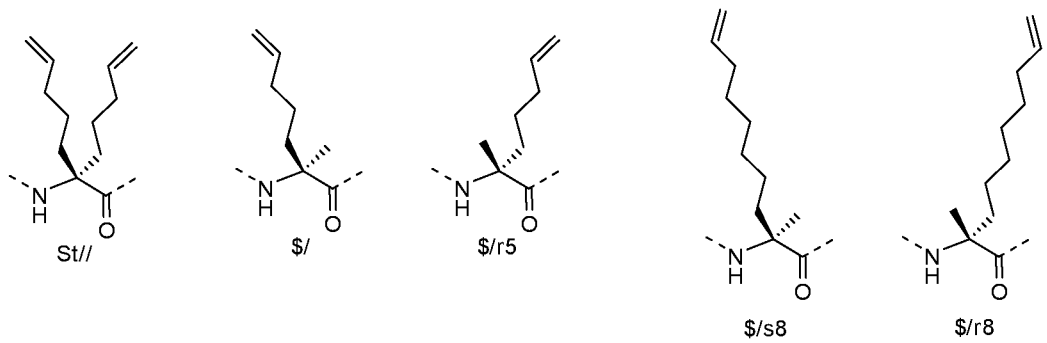
homocyclohexyl alanine (hCha) | cyclohexyl alanine (Cha) | cyclohexyl glycine (Chg) | Adamantyl glycine (Adm)



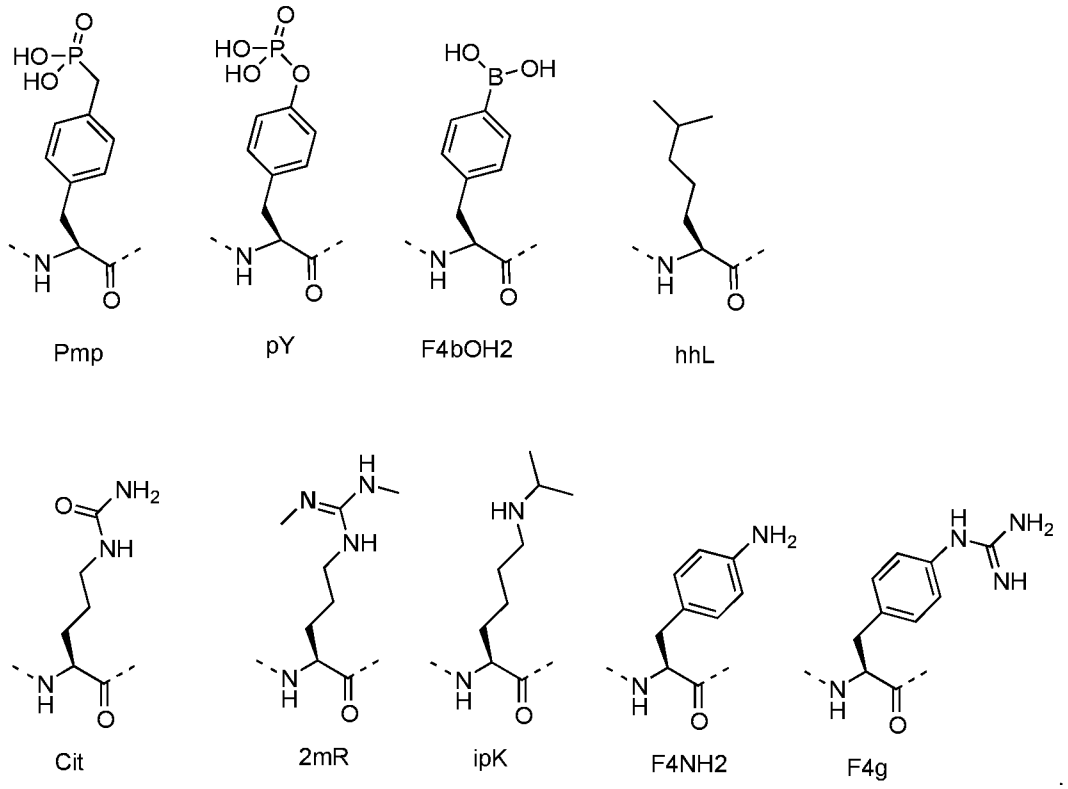
cyclobutyl alanine (Cba) | cyclopentyl glycine (Cpg) | NmF | NmL | NmT | Sar



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



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



[00114] 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.

[00115] Amino acid analogs include analogs of alanine, valine, glycine or leucine. Examples of amino acid analogs of alanine, valine, glycine, and leucine include, but are not limited to, the following: α – methoxyglycine; α - allyl - L – alanine; α - aminoisobutyric acid; α - methyl – leucine; β - (1 - naphthyl) - D – alanine; β - (1 - naphthyl) - L – alanine; β - (2 - naphthyl) - D – alanine; β - (2 - naphthyl) - L – alanine; β - (2 - pyridyl) - D – alanine; β - (2 - pyridyl) - L – alanine; β - (2 - thienyl) - D – alanine; β - (2 - thienyl) - L – alanine; β - (3 - benzothienyl) - D – alanine; β - (3 - benzothienyl) - L – alanine; β - (3 - pyridyl) - D – alanine; β - (3 - pyridyl) - L – alanine; β - (4 - pyridyl) - D – alanine; β - (4 - pyridyl) - L – alanine; β - chloro - L – alanine; β - cyano - L – alanin; β - cyclohexyl - D – alanine; β - cyclohexyl - L – alanine; β - cyclopenten - 1 - yl - alanine; β - cyclopentyl – alanine; β - cyclopropyl - L - Ala – OH • dicyclohexylammonium salt; β - t - butyl - D – alanine; β - t - butyl - L – alanine; γ - aminobutyric acid; L - α,β - diaminopropionic acid; 2,4 - dinitro – phenylglycine; 2,5 - dihydro - D – phenylglycine; 2 - amino - 4,4,4 - trifluorobutyric acid; 2 - fluoro – phenylglycine; 3 - amino - 4,4,4 - trifluoro - butyric acid; 3 - fluoro – valine; 4,4,4 - trifluoro – valine; 4,5 - dehydro - L - leu – OH • dicyclohexylammonium salt; 4 - fluoro - D – phenylglycine; 4 - fluoro - L – phenylglycine; 4 - hydroxy - D – phenylglycine; 5,5,5 - trifluoro – leucine; 6 - aminohexanoic acid; cyclopentyl - D - Gly – OH • dicyclohexylammonium salt; cyclopentyl - Gly – OH • dicyclohexylammonium salt; D - α,β - diaminopropionic acid; D - α - aminobutyric acid; D - α - t – butylglycine; D - (2 - thienyl)glycine; D - (3 - thienyl)glycine; D - 2 - aminocaproic acid; D - 2 – indanylglycine; D – allylglycine•dicyclohexylammonium salt; D – cyclohexylglycine; D – norvaline; D – phenylglycine; β - aminobutyric acid; β - aminoisobutyric acid; (2 - bromophenyl)glycine; (2 - methoxyphenyl)glycine; (2 - methylphenyl)glycine; (2 - thiazoyl)glycine; (2 - thienyl)glycine; 2 - amino - 3 - (dimethylamino) - propionic acid; L - α,β - diaminopropionic acid; L - α - aminobutyric acid; L - α - t – butylglycine; L - (3 - thienyl)glycine; L - 2 - amino

- 3 - (dimethylamino) - propionic acid; L - 2 - aminocaproic acid dicyclohexyl - ammonium salt; L - 2 – indanylglycine; L - allylglycine•dicyclohexyl ammonium salt; L – cyclohexylglycine; L – phenylglycine; L – propargylglycine; L – norvaline; N - α - aminomethyl - L – alanine; D - α,γ - diaminobutyric acid; L - α,γ - diaminobutyric acid; β - cyclopropyl - L – alanine; (N - β - (2,4 - dinitrophenyl)) - L - α,β - diaminopropionic acid; (N - β - 1 - (4,4 - dimethyl - 2,6 - dioxocyclohex - 1 - ylidene)ethyl) - D - α,β - diaminopropionic acid; (N - β - 1 - (4,4 - dimethyl - 2,6 - dioxocyclohex - 1 - ylidene)ethyl) - L - α,β - diaminopropionic acid; (N - β - 4 - methyltrityl) - L - α,β - diaminopropionic acid; (N - β - allyloxycarbonyl) - L - α,β - diaminopropionic acid; (N - γ - 1 - (4,4 - dimethyl - 2,6 - dioxocyclohex - 1 - ylidene)ethyl) - D - α,γ - diaminobutyric acid; (N - γ - 1 - (4,4 - dimethyl - 2,6 - dioxocyclohex - 1 - ylidene)ethyl) - L - α,γ - diaminobutyric acid; (N - γ - 4 - methyltrityl) - D - α,γ - diaminobutyric acid; (N - γ - 4 - methyltrityl) - L - α,γ - diaminobutyric acid; (N - γ - allyloxycarbonyl) - L - α,γ - diaminobutyric acid; D - α,γ - diaminobutyric acid; 4,5 - dehydro - L – leucine; cyclopentyl - D - Gly – OH; cyclopentyl - Gly – OH; D – allylglycine; D – homocyclohexylalanine; L - 1 – pyrenylalanine; L - 2 - aminocaproic acid; L – allylglycine; L – homocyclohexylalanine; and N - (2 - hydroxy - 4 - methoxy - Bzl) - Gly – OH.

[00116] Amino acid analogs include analogs of arginine or lysine. Examples of amino acid analogs of arginine and lysine include, but are not limited to, the following: citrulline; L - 2 - amino - 3 - guanidinopropionic acid; L - 2 - amino - 3 - ureidopropionic acid; L – citrulline; $Lys(Me)_2$ – OH; $Lys(N_3)$ – OH; Nδ - benzyloxycarbonyl - L – ornithine; Nω - nitro - D – arginine; Nω - nitro - L – arginine; α - methyl – ornithine; 2,6 - diaminoheptanedioic acid; L – ornithine; (Nδ - 1 - (4,4 - dimethyl - 2,6 - dioxo - cyclohex - 1 - ylidene)ethyl) - D – ornithine; (Nδ - 1 - (4,4 - dimethyl - 2,6 - dioxo - cyclohex - 1 - ylidene)ethyl) - L – ornithine; (Nδ - 4 - methyltrityl) - D – ornithine; (Nδ - 4 - methyltrityl) - L – ornithine; D – ornithine; L – ornithine; Arg(Me)(Pbf) – OH; $Arg(Me)_2$ – OH (asymmetrical); Arg(Me)2 - OH (symmetrical); Lys(ivDde) – OH; Lys(Me)2 - OH • HCl; Lys(Me3) - OH chloride; Nω - nitro - D – arginine; and Nω - nitro - L – arginine.

[00117] 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.

[00118] 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.

[00119] 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.

[00120] 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.

[00121] 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.

[00122] 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.

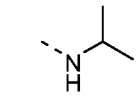
[00123] In some embodiments, amino acid analogs are racemic. In some embodiments, the D isomer of the amino acid analog is used. In some embodiments, the L isomer of the amino acid analog is used. In other embodiments, the amino acid analog comprises chiral centers that are in the R or S configuration. 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.

[00124] A "non-essential" amino acid residue is a residue that can be altered from the wild-type sequence of a polypeptide without abolishing or substantially altering its essential biological or biochemical activity (*e.g.*, receptor binding or activation). An "essential" amino acid residue is a residue that, when altered from the wild-type sequence of the polypeptide, results in abolishing or substantially abolishing the polypeptide's essential biological or biochemical activity.

[00125] A "conservative amino acid substitution" is one in which the amino acid residue is replaced with an amino acid residue having a similar side chain. Families of amino acid residues having similar side chains have been defined in the art. These families include amino acids with basic side chains (*e.g.*, K, R, H), acidic side chains (*e.g.*, D, E), uncharged polar side chains (*e.g.*, G, N, Q, S, T, Y, C), nonpolar side chains (*e.g.*, A, V, L, I, P, F, M, W), beta-branched side chains (*e.g.*, T, V, I) and aromatic side chains (*e.g.*, Y, F, W, H). Thus, a predicted nonessential amino acid residue in a polypeptide, for example, is replaced with another amino acid residue from the same side chain family. Other examples of acceptable substitutions are substitutions based on isosteric considerations (e.g. norleucine for methionine) or other properties (e.g. 2-thienylalanine for phenylalanine, or 6-Cl-tryptophan for tryptophan).

[00126] 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 and secondary amines, including pegylated

secondary amines. Representative secondary amine capping groups for the C-terminus include: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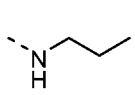
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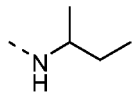
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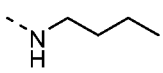
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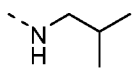
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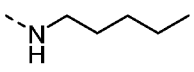
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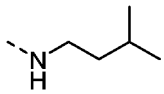
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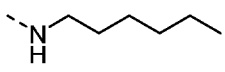
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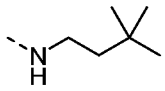
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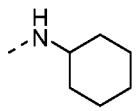
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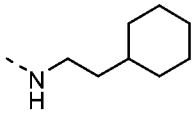
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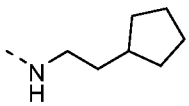
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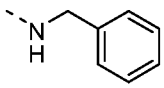
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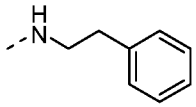
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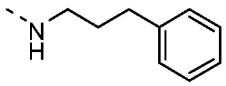
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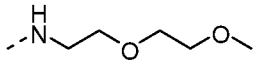
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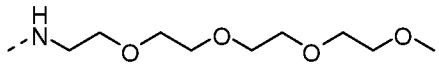
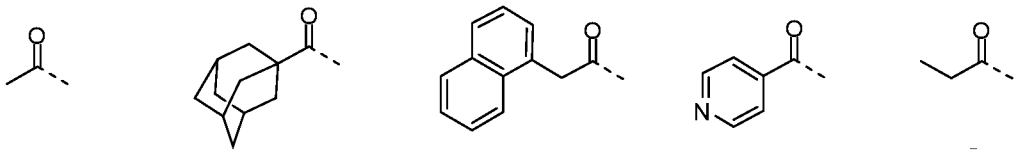
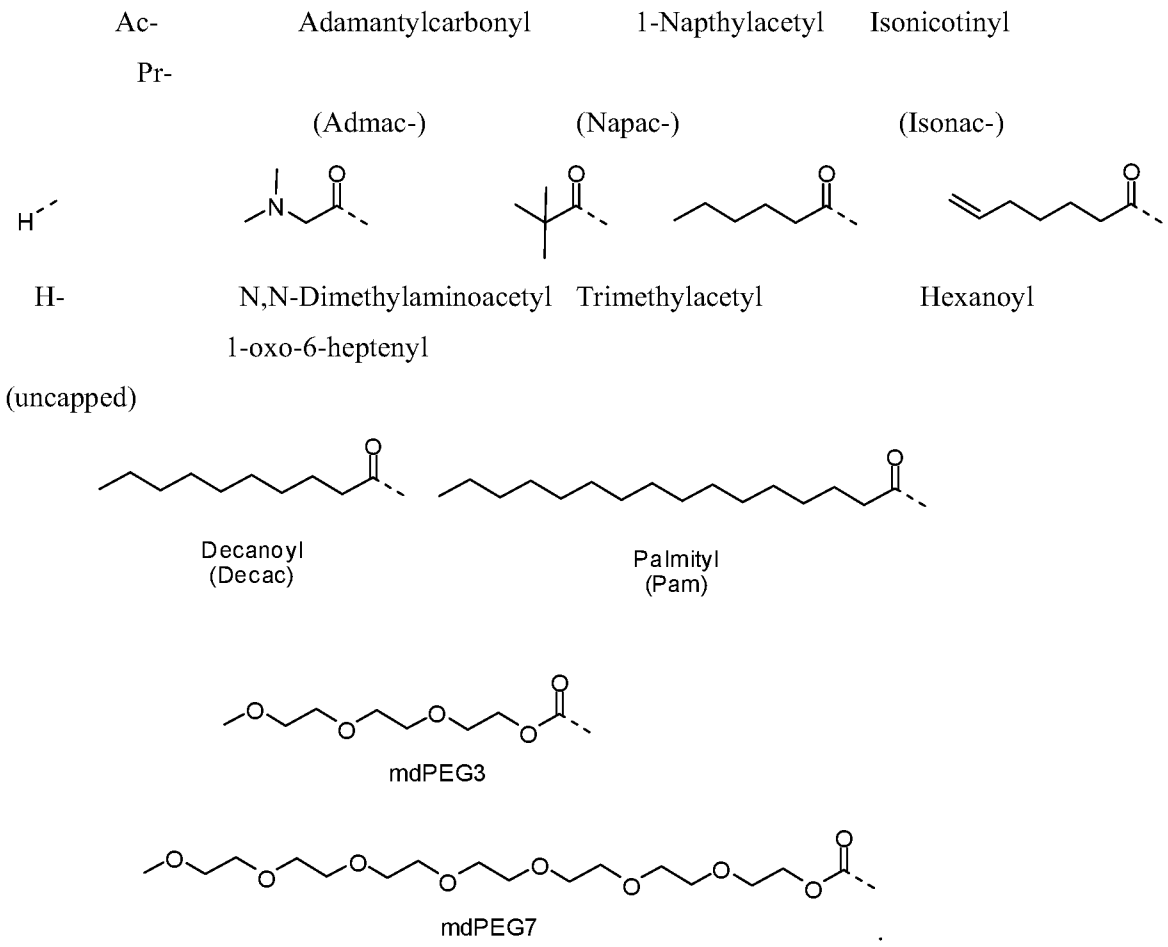

n-diPeg4-amide
(-NHmdPeg4)

[00127] The capping group of an amino terminus includes an unmodified amine (ie – NH_2) or an amine with a substituent. For example, the amino terminus can be substituted with an acyl group to yield a carboxamide at the N-terminus. Various substituents include but are not limited to substituted acyl groups, including C_1-C_6 carbonyls, C_7-C_{30} carbonyls, and pegylated carbamates. Representative capping groups for the N-terminus include, but are not limited to, 4-FBzl (4-fluoro-benzyl) and the following:





[00128] 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.

[00129] The symbol "$\diagup\!\!\!\diagup$" when used as part of a molecular structure refers to a single bond or a *trans* or *cis* double bond.

[00130] 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).

[00131] 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.

[00132] 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).

[00133] 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.

[00134] The term "macrocyclization reagent" or "macrocycle-forming reagent" as used herein refers to any reagent which can be used to prepare a peptidomimetic macrocycle by mediating the reaction between two reactive groups. Reactive groups can be, for example, an azide and alkyne, in which case macrocyclization reagents include, without limitation, Cu reagents such as reagents which provide a reactive Cu(I) species, such as CuBr, CuI or CuOTf, as well as Cu(II) salts such as $Cu(CO_2CH_3)_2$, $CuSO_4$, and $CuCl_2$ that can be converted in situ to an active Cu(I) reagent by the addition of a reducing agent such as ascorbic acid or sodium ascorbate. Macrocyclization reagents can additionally include, for example, Ru reagents known in the art such as $Cp^*RuCl(PPh_3)_2$, $[Cp^*RuCl]_4$ or other Ru reagents which can provide a reactive Ru(II) species. In other cases, the reactive groups are terminal olefins. In such embodiments, the macrocyclization reagents or macrocycle-forming reagents are metathesis catalysts including, but not limited to, stabilized, late transition metal carbene complex catalysts such as Group VIII transition metal carbene catalysts. For example, such catalysts are Ru and Os metal centers having a +2 oxidation state, an electron count of 16 and pentacoordinated. In other examples, catalysts have W or Mo centers. Various catalysts are disclosed in Grubbs et al., "Ring Closing Metathesis and Related Processes in Organic Synthesis" Acc. Chem. Res. 1995, 28, 446-452, U.S. Pat. No. 5,811,515; U.S. Pat. No. 7,932,397; U.S. Application No. 2011/0065915; U.S. Application No. 2011/0245477; Yu et al., "Synthesis of Macrocyclic Natural Products by Catalyst-Controlled Stereoselective Ring-Closing Metathesis," Nature 2011, 479, 88; and Peryshkov et al., "Z-Selective Olefin Metathesis Reactions Promoted by Tungsten Oxo Alkylidene

Complexes," J. Am. Chem. Soc. 2011, 133, 20754. In yet other cases, the reactive groups are thiol groups. In such embodiments, the macrocyclization reagent is, for example, a linker functionalized with two thiol-reactive groups such as halogen groups. In some examples, the macrocyclization reagent include palladium reagents, for example $Pd(PPh_3)_4$, $Pd(PPh_3)_2Cl_2$, Pd(dppe)Cl, $Pd(dppp)Cl_2$, and $Pd(dppf)Cl_2$.

[00135] The term "halo" or "halogen" refers to fluorine, chlorine, bromine or iodine or a radical thereof.

[00136] 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.

[00137] The term "alkylene" refers to a divalent alkyl (*i.e.*, -R-).

[00138] 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.

[00139] 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.

[00140] 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.

[00141] "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.

[00142] "Arylamido" refers to an aryl group, as defined above, wherein one of the aryl group's hydrogen atoms has been replaced with one or more -C(O)NH_2 groups. Representative examples of an arylamido group include 2-C(O)NH2-phenyl, 3-C(O)NH_2-phenyl, 4-C(O)NH_2-phenyl, 2-C(O)NH_2-pyridyl, 3-C(O)NH_2-pyridyl, and 4-C(O)NH_2-pyridyl.

[00143] "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.

[00144] "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=$CH_2$.

[00145] "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 -$C(CH_3)_2CH_2OH$.

[00146] "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 -$C(CH_3)_2CH_2COOH$.

[00147] 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.

[00148] 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.

[00149] 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.

[00150] 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.

[00151] 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.

[00152] 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.

[00153] In some embodiments, the compounds disclosed herein contain one or more asymmetric centers and thus occur as racemates and racemic mixtures, single enantiomers, individual diastereomers and diastereomeric mixtures. All such isomeric forms of these compounds are included unless expressly provided otherwise. In some embodiments, the compounds disclosed herein are also represented in multiple tautomeric forms, in such

instances, the compounds include all tautomeric forms of the compounds described herein (*e.g.*, if alkylation of a ring system results in alkylation at multiple sites, the disclosure includes all such reaction products). All such isomeric forms of such compounds are included unless expressly provided otherwise. All crystal forms of the compounds described herein are included unless expressly provided otherwise.

[00154] 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%.

[00155] 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.

[00156] 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."

[00157] The term "on average" represents the mean value derived from performing at least three independent replicates for each data point.

[00158] 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.

[00159] 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.

[00160] 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.

[00161] 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.

[00162] 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, myelodysplastic syndrome (MDS), and liquid lymphomas. For example, liquid cancer can be acute myeloid leukemia (AML). 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 cysts or liquid areas.

[00163] The term "adverse event" (AE) as used herein includes any noxious, pathological, or unintended change in anatomical, physiological, or metabolic functions as indicated by physical signs, symptoms, and/or laboratory changes occurring in any phase of the clinical study whether or not temporally associated with the administration of study medication and whether or not considered related to the study medication. This definition includes an exacerbation of pre-existing medical conditions or events, intercurrent illnesses, hypersensitivity reactions, drug interactions, or clinically significant laboratory findings. An AE does not include the following: (i) medical or surgical procedures, e.g., tooth extraction, transfusion, surgery (The medical condition that leads to the procedure is to be recorded as an AE); (ii) pre-existing conditions or procedures present or detected at the start of the study that do not worsen; (iii) hospitalization for elective surgeries or for other situations in which an untoward medical event has not occurred; (iv) abnormal laboratory value, unless it is clinically significant according to the Investigator, requires intervention, or results in a delay, discontinuation or change in the dose of study drug ; (v) overdose of study drug or concomitant medication unaccompanied by signs/symptoms; if sign/symptoms occur, the final diagnosis should be recorded as an AE; (vi) pregnancy by itself, unless a complication occurs during pregnancy leading to hospitalization; in this case, the medical condition that leads to the hospitalization is to be recorded as the AE; and (vii) significant worsening of the

disease under investigation which is captured as an efficacy parameter in this study and, thus, is not recorded as an AE.

[00164] The term serious adverse event (SAE) as used herein refers to an adverse event that results in any of the following outcomes:(i) death; (ii) life-threatening adverse experience (i.e., immediate risk of death from the event as it occurred; this does not include an adverse event that, had it occurred in a more serious form, might have caused death); (iii) persistent or significant disability/incapacitation; (iv) hospitalization or prolongation of existing hospitalization; and (v) congenital anomaly/birth defect.Important medical events that can not result in death, be life-threatening, or require hospitalization can be considered serious when, based on medical judgment, they can jeopardize the patient or can require medical or surgical intervention to prevent one of the outcomes listed in this definition. Hospitalizations due to the underlying disease will not be reported as an SAE unless there is reason to suspect a causal relationship with the study drug.

[00165] An AE or suspected adverse reaction is considered "unexpected" (referred to as Unexpected Adverse Event (UAE) if it is not listed in the peptidomimetic macrocycle Investigator's Brochure or is not listed at the specificity or severity that has been observed; or, is not consistent with the risk information described in the protocol or elsewhere. For example, under this definition, hepatic necrosis would be unexpected (by virtue of greater severity) if the Investigator's Brochure referred only to elevated hepatic enzymes or hepatitis. Similarly, cerebral thromboembolism and cerebral vasculitis would be unexpected (by virtue of greater specificity) if the Investigator's Brochure listed only cerebral vascular accidents. "Unexpected," as used in this definition, also refers to AEs or suspected adverse reactions that are mentioned in the Investigator's Brochure as occurring with a class of drugs or as anticipated from the pharmacological properties of the peptidomimetic macrocycle but are not specifically mentioned as occurring with the peptidomimetic macrocycle.

[00166] A "Dose-Limiting Toxicity" (DLT) as used herein is defined as any non hematologic Grade ≥3 AE that is considered to be possibly, probably, or definitely related to the study drug, with the following exceptions: (1) for fatigue, nausea, emesis, diarrhea or mucositis, all Grade 4 and any Grade 3 AE requiring total parenteral nutrition (TPN) or hospitalization will be considered DLT; (2) for electrolyte imbalances, only Grade ≥3 AE that do not respond to correction within 24 hours will be considered DLT; (3) for infusion reactions, only a Grade 3 reaction which caused hospitalization or Grade 4 will be considered DLT; (4) any grade alopecia; (5) any event that can clearly be determined to be unrelated to the study drug (e.g., solely related to disease progression). DLT also includes: i) ANC fails to

recover to >0.5 Gi/L within 42 days from the start of therapy in the absence of active leukemia or myelodysplasia; and ii) Platelet count fails to recover to >20,000 or associated with clinically significant bleeding that requires transfusion of red cells or platelets within 42 days from the start of therapy in the absence of active leukemia or myelodysplasia. In addition, specific hematologic DLTs are defined as:

(i) Thrombocytopenia – Grade 4 of any duration, Grade 3 for ≥7 days, or Grade 3 associated with clinically significant bleeding;

(ii) Neutropenia – Grade 4 for ≥3 days, or any Grade ≥3 febrile neutropenia.

[00167] The above criteria can be used to make individual patient determinations regarding dose reductions, interruptions or discontinuation throughout the course of the trial, but DLTs occurring during Cycle 1 will be used to inform safety and tolerability assessments for dose escalation decisions. The DLT-evaluable population will include all patients in Phase 1 Dose Escalation who experience a DLT during the first cycle of treatment.

[00168] The "Maximum Tolerated Dose" (MTD) as used herein is defined as the dose at which ≤1 of 6 patients experiences a treatment-related toxicity that qualifies as a DLT, with the next higher dose having ≥2 of up to 6 patients experiencing a DLT. The MTD can not be established until all patients enrolled in the cohort have completed Cycle 1, discontinued treatment or had a dose reduction. Previously established tolerability of a dose level will be reevaluated if DLTs are observed in later cycles.

[00169] The term "subject" or "patient" encompasses mammals and non-mammals. Examples of mammals include, but are not limited to, humans; non-human primates such as chimpanzees, and other apes and monkey species; farm animals such as cattle, horses, sheep, goats, swine; domestic animals such as rabbits, dogs, and cats; laboratory animals including rodents, such as rats, mice and guinea pigs, and the like. Examples of non-mammals include, but are not limited to, birds, fish and the like. In one embodiment of the methods and compositions provided herein, the mammal is a human.

[00170] 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.

OVERVIEW

[00171] In one aspect, the disclosure provides a method of treating liquid cancer, determined to lack a p53 deactivating mutation, in a subject. The method comprises

administering to the subject a therapeutically effective amount of a peptidomimetic macrocycle or a pharmaceutically acceptable salt thereof, wherein the peptidomimetic macrocycle binds to MDM2 and/or MDMX proteins. In some embodiments, the peptidomimetic macrocycle disrupts the interaction between p53 and MDM2 and MDMX.

[00172] In another aspect, the disclosure provides a method of treating liquid cancer in a subject expressing wild type p53. The method comprises administering to the subject a therapeutically effective amount of a peptidomimetic macrocycle or a pharmaceutically acceptable salt thereof, wherein the peptidomimetic macrocycle binds to MDM2 and/or MDMX proteins. In some embodiments, the peptidomimetic macrocycle disrupts the interaction between p53 and MDM2 and MDMX.

[00173] In some embodiments, a subject treated in accordance with the methods provided herein is a human who has or is diagnosed with liquid cancer lacking p53 deactivating mutation and/or expressing wild type p53. In some embodiments, a subject treated for liquid cancer in accordance with the methods provided herein is a human predisposed or susceptible to liquid cancer lacking p53 deactivating mutation and/or expressing wild type p53. In some embodiments, a subject treated for liquid cancer in accordance with the methods provided herein is a human at risk of developing liquid 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 liquid 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 liquid 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.

[00174] In certain embodiments, the human subject is refractory and/or intolerant to one or more other standard treatment of the liquid cancer known in art. In some embodiments, the human subject has had at least one unsuccessful prior treatment and/or therapy of the liquid cancer.

[00175] In some embodiments, the methods for treating liquid cancer provided herein inhibit, reduce, diminish, arrest, or stabilize a liquid cancer cell associated with the liquid cancer. In some embodiments, the methods for treating liquid cancer provided herein inhibit, reduce, diminish, arrest, or stabilize the blood flow, metabolism, or edema in a liquid cancer cell associated with the liquid cancer or one or more symptoms thereof. In some

embodiments, the methods for treating liquid cancer provided herein cause the regression of the number od liquid cancer cells, or liquid cancer cell metabolism, and/or one or more symptoms associated with the liquid cancer. In some embodiments, the methods for treating liquid cancer provided herein maintain the number of CTCs and/or MNBCs so that the number of CTCs and/orMNBCs does not increase, or increases by less than the increase of the number of CTCs and/or MNBCs after administration of a standard therapy as measured by conventional methods available to one of skill in the art, such as ultrasound, CT Scan, MRI, dynamic contrast-enhanced MRI, or PET Scan. In specific embodiments, the methods for treating liquid cancer provided herein decrease liquid cancer cell number. In some embodiments, the methods for treating liquid cancer provided herein reduce the formation of CTCs and/or MNBCs. In certain embodiments, the methods for treating liquid cancer provided herein eradicate, remove, or control primary, regional and/or metastatic liquid cancer cells associated with the liquid cancer. In some embodiments, the methods for treating liquid cancer provided herein decrease the number or size of metastases associated with the liquid cancer. In some embodiments, the methods for treating liquid cancer provided herein result in complete response to the treatment. In some embodiments, the methods for treating liquid cancer provided herein result in partial response to the treatment. In some embodiments, the liquid cancer treated by the methods disclosed herein is a stable disease. In some embodiments, the liquid cancer treated by the methods disclosed herein is a progressive disease.

[00176] 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, acute myelogenous leukemia (AML), myelodysplastic syndromes (MDS), 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.

[00177] In one aspect, myelodysplastic syndromes (MDS) is a heterogenous group of clonal, hematopoietic stem cell disorders characterized by distinct morphological bone marrow changes, abnormal blood counts, common cytogenetic abnormalities, and recurrent mutations. MDS can predominantly occur in the elderly. Treatment of MDS can be based on risk stratification, with the International Prognostic Scoring System (IPSS) or revised IPSS (IPSS-R) being the most common classification systems. Low-risk MDS patients can receive supportive care or hematopoietic growth factors. A subset of patients with 5q deletions can be treated with lenalidomide. High-risk patients can be treated with hypomethylating agents (e.g., azacitidine, decitabine), intensive chemotherapy, and/or allogeneic stem cell transplantation. In some cases, MDS patients can be transformed to AML. Some MDS patients can develop progressive bone marrow failure and/or die of complications related to neutropenia (e.g., infection) or thrombocytopenia (e.g., bleeding). Initial management of MDS can be based on risk stratification. The newer IPSS-R can place patients into 5 categories: very good, good, intermediate, high, and very-high risk groups. Patients in the very good, good, and select intermediate-risk patients can be categorized as "low-risk," whereas high, very high, and certain intermediate-risk patients can be categorized as the "high-risk" group. Azacitidine (5'-azacytidine) and decitabine (5'-aza-2'-deoxycytidine), which both are cytosine analogues, can lead to inhibition of DNA-methyltransferases (DNMTs) and can act as hypomethylating agents.

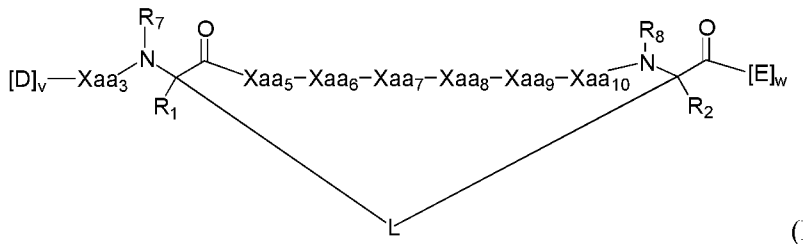
[00178] In another aspect, acute myeloid leukemia (AML) is characterized by the proliferation and accumulation of myeloid cells with accompanying hematopoietic failure. AML can be caused by chemical exposure, prior chemotherapy and radiation, or other environmental toxins.

[00179] Examples of liquid cancers includes 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, peripheral T cell lymphomas, adult T cell leukemia/lymphoma (ATL), cutaneous T-cell lymphoma (CTCL), large granular lymphocytic leukemia (LGF), Hodgkin's disease and Reed-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.

[00180] 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; cutaneous T-cell lymphoma; Hodgkin lymphoma; multiple myeloma; multiple myeloma/plasma cell neoplasm; Non-Hodgkin lymphoma; primary central nervous system (CNS) lymphoma; or T-cell 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.

[00181] The peptidomimetic macrocycle can be any cross-linked peptide, i.e. any peptide that comprises at least one macrocycle-forming linker which forms a macrocycle between a first amino acid residue (or analog) and a second amino acid residue. For example, the peptidomimetic macrocycle can be a peptidomimetic macrocycle capable of binding to the MDM2 and/or MDMX proteins. In some embodiments, the peptidomimetic macrocycles can be a peptidomimetic macrocycle of Formula I:



(Formula I)

wherein:

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

each D and E is independently an amino acid;

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

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

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

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

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

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

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

w is an integer from 0-1000.

[00182] Administration of the peptidomimetic macrocycle can be achieved by any suitable means. For example the peptidomimetic macrocycle can be administered parenterally. For example, administration can be intravenous, intra-arterial, intraosseous

infusion, intra-muscular, intracerebral, intracerebroventricular, intrathecal, or subcutaneous. In some embodiments administration is performed intravenously.

[00183] In some embodiments, the methods disclosed herein additionally or optionally comprise evaluating the safety and/or tolerability of the peptidomimetic macrocycles of the disclosure in subjects with liquid cancers determined to lack a p53 deactivating mutation or with liquid cancers expressing wild-type (WT) p53 protein.

[00184] Also provided here in are methods to determine the dose limiting toxicities (DLT) and the maximum tolerated dose (MTD or OBD) or the optimal biological dose (OBD) of the peptidomimetic macrocycles disclosed herein in subjects with liquid cancers determined to lack a p53 deactivating mutation or with liquid cancers expressing wild-type (WT) p53 protein.

[00185] In some embodiments, the methods disclosed herein additionally or optionally comprise the pharmacokinetic (PK) analysis of the peptidomimetic macrocycles and/or its metabolites in blood following single and/or multiple administration of the peptidomimetic macrocycles to the subject.

[00186] In some embodiments, the methods disclosed herein additionally or optionally comprise studying the effect of the peptidomimetic macrocycles on pharmacodynamic (PD) biomarkers in liquid cancer samples (including bone marrow aspirates), (e.g., p21, caspase, MDM2) and blood samples (e.g., macrophage inhibitory cytokine-1 [MIC-1]), and assessing possible correlation between these biomarkers and clinical response.

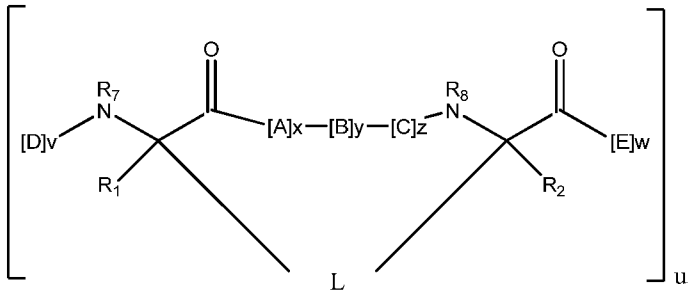
[00187] In some embodiments, the methods disclosed herein additionally or optionally include steps to assess potential patient biomarkers (e.g., p53 status, MDM2 and MDMX expression levels), the effect of the peptidomimetic macrocycles treatment on these biomarkers, and possible correlation between these biomarkers and clinical response of the peptidomimetic macrocycles.

[00188] Also provided herein are methods to evaluate clinical activity of the peptidomimetic macrocycles in subjects with specific liquid cancer types lacking a p53 deactivating mutation and/or expressing WT p53 in the dose expansion phase.

COMPOUND AND COMPOSITIONS

Peptidomimetic macrocycles

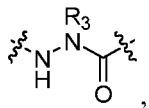
[00189] In some embodiments, a peptidomimetic macrocycle has the Formula (I):



Formula I

wherein:

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

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

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

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

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

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

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

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

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

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

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

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

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

each v is independently an integer from 0–1000, for example, 0-500, 0-200, 0-100, 0-50, 0-30, 0-20, 0-10, 0-5, 1-1000, 1-500, 1-200, 1-100, 1-50, 1-30, 1-20, 1-10, 1-5, 3-1000, 3-500, 3-200, 3-100, 3-50, 3-30, 3-20, 3-10, 0, 1, 2, 3, 4, 5, 6, 7, 8, 9, or 10;

each w is independently an integer from 0–1000, for example, 0-500, 0-200, 0-100, 0-50, 0-30, 0-20, 0-10, 0-5, 1-1000, 1-500, 1-200, 1-100, 1-50, 1-30, 1-20, 1-10, 1-5, 3-1000, 3-500, 3-200, 3-100, 3-50, 3-30, 3-20, 3-10, 0, 1, 2, 3, 4, 5, 6, 7, 8, 9, or 10;

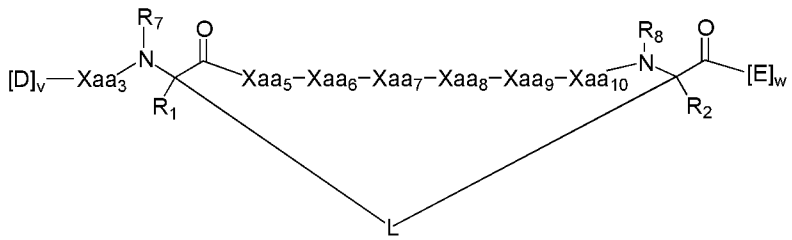
u is an integer from 1–10;

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

each n is independently an integer from 1–5.

[00190] In some embodiments, each v and w is independently integers between 1-30. In some embodiments, w or v 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.

[00191] In some embodiments, peptidomimetic macrocycles are also provided of the formula:



wherein:

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

each D and E is independently an amino acid;

each R_1 and R_2 is independently –H, alkyl, alkenyl, alkynyl, arylalkyl, cycloalkyl, cycloalkylalkyl, heteroalkyl, or heterocycloalkyl, unsubstituted or substituted with halo–; or at least one of R_1 and R_2 forms a macrocycle-forming linker L' connected to the alpha position of one of said D or E amino acids or Xaa_3;

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

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

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

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

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

v is an integer from 0–1000, for example, 0-500, 0-200, 0-100, 0-50, 0-30, 0-20, 0-10, 0-5, 1-1000, 1-500, 1-200, 1-100, 1-50, 1-30, 1-20, 1-10, 1-5, 3-1000, 3-500, 3-200, 3-100, 3-50, 3-30, 3-20, 3-10, 0, 1, 2, 3, 4, 5, 6, 7, 8, 9, or 10; and

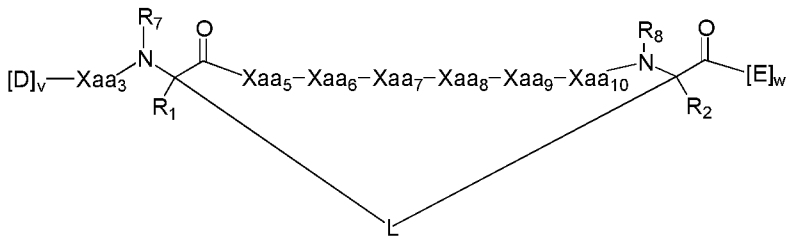
w is an integer from 0–1000, for example, 0-500, 0-200, 0-100, 0-50, 0-30, 0-20, 0-10, 0-5, 1-1000, 1-500, 1-200, 1-100, 1-50, 1-30, 1-20, 1-10, 1-5, 3-1000, 3-500, 3-200, 3-100, 3-50, 3-30, 3-20, 3-10, 0, 1, 2, 3, 4, 5, 6, 7, 8, 9, or 10.

[00192] In some embodiments, each v and w is independently an integer between 1-30. In some embodiments, w or v 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.

[00193] 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}.

[00194] 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 an amino acid;

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

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

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

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

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

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

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

v is an integer from 0–1000, for example, 0-500, 0-200, 0-100, 0-50, 0-30, 0-20, 0-10, 0-5, 1-1000, 1-500, 1-200, 1-100, 1-50, 1-30, 1-20, 1-10, 1-5, 3-1000, 3-500, 3-200, 3-100, 3-50, 3-30, 3-20, 3-10, 0, 1, 2, 3, 4, 5, 6, 7, 8, 9, or 10; and

w is an integer from 0–1000, for example, 0-500, 0-200, 0-100, 0-50, 0-30, 0-20, 0-10, 0-5, 1-1000, 1-500, 1-200, 1-100, 1-50, 1-30, 1-20, 1-10, 1-5, 3-1000, 3-500, 3-200, 3-100, 3-50, 3-30, 3-20, 3-10, 0, 1, 2, 3, 4, 5, 6, 7, 8, 9, or 10.

[00195] 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}.

[00196] 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.

[00197] In an embodiment of any of the Formulas described herein, of the macrocycle-forming linker (L) has a formula $–L_1–L_2–$, wherein

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

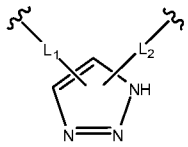
each R_4 is independently alkylene, alkenylene, alkynylene, heteroalkylene, cycloalkylene, heterocycloalkylene, arylene, or heteroarylene;

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

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

n is an integer from 1-5.

[00198] In some embodiments in the Formulas described herein, L (or L') is a macrocycle-forming linker of the formula



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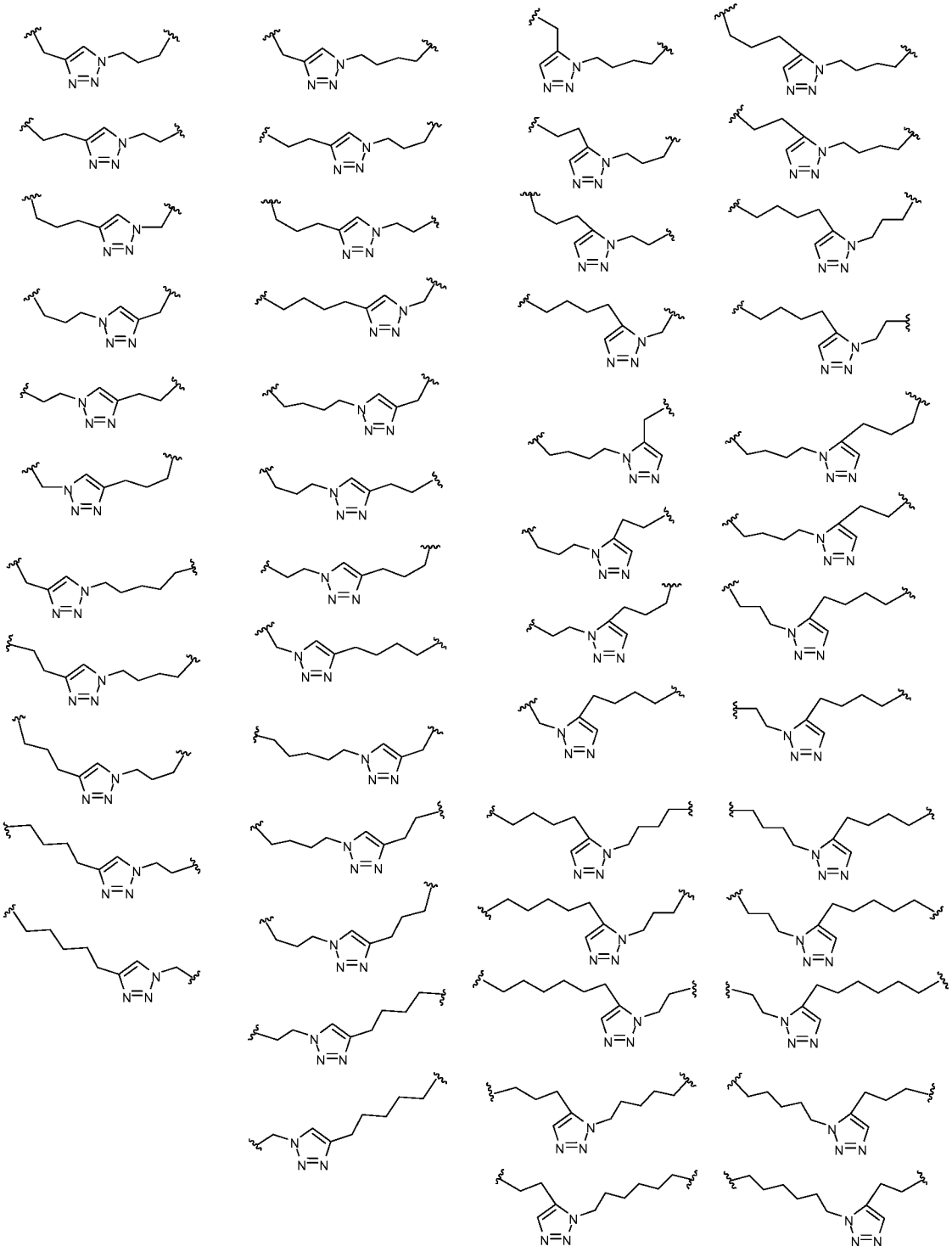
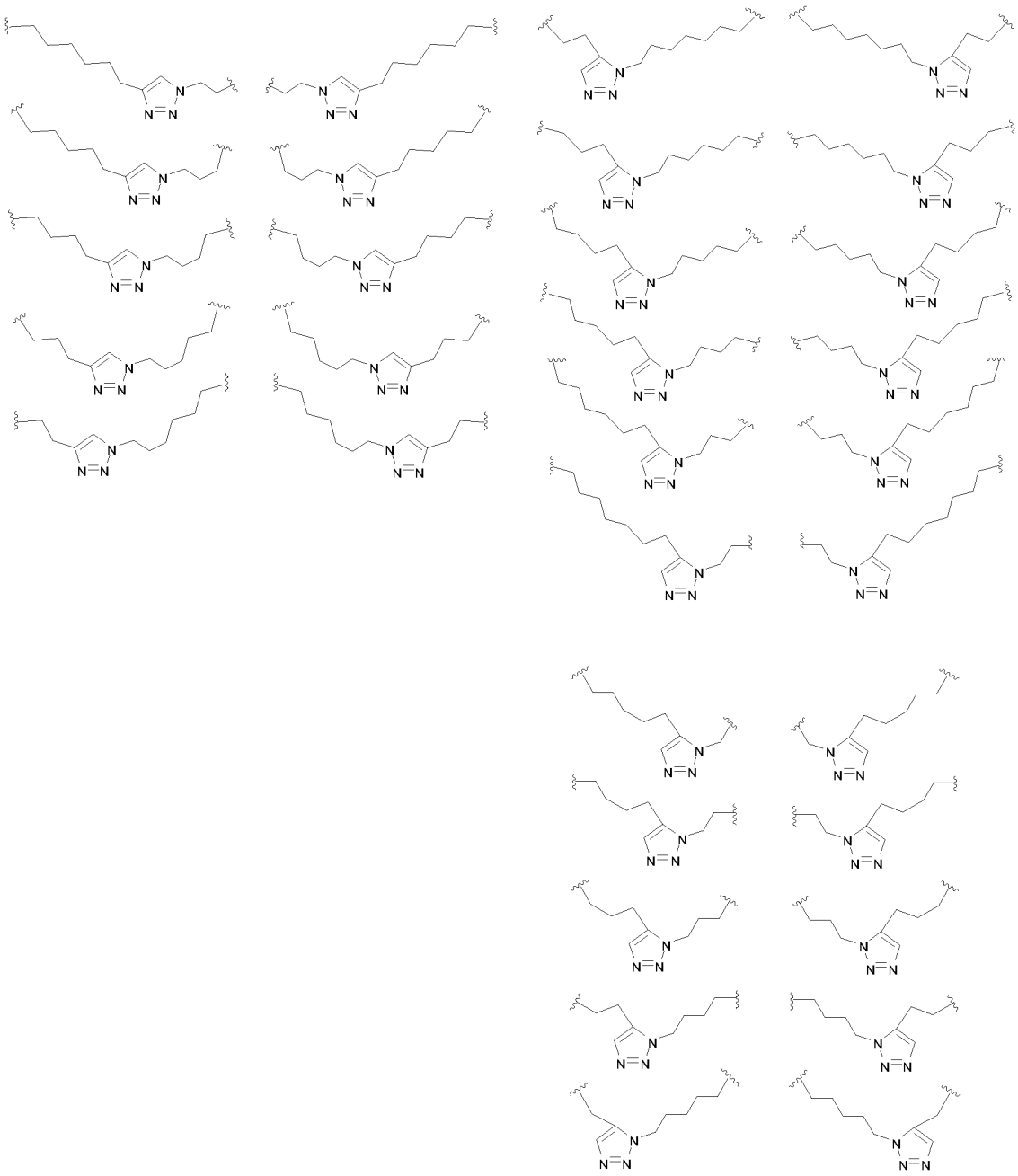
[00199] Exemplary embodiments of such macrocycle-forming linkers L are shown below.





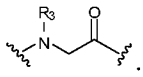
[00200] In an embodiment of any of the Formulas described herein, L_1 and L_2, either alone or in combination, form a triazole or a thioether.

[00201] 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.

[00202] 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

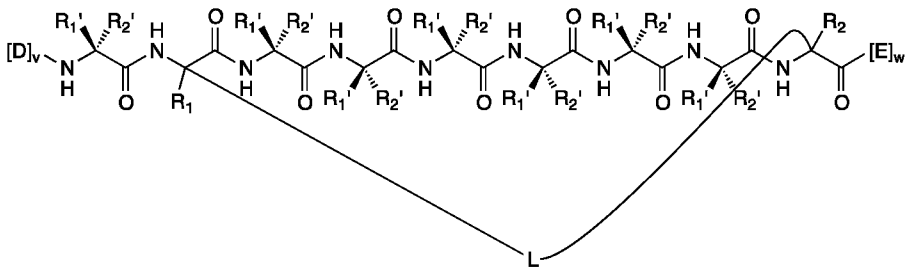
substituted with halo–. In some embodiments, at least one of R_1 and R_2 is methyl. In other embodiments, R_1 and R_2 are methyl.

[00203] In some embodiments, x+y+z is at least 3. In other embodiments, x+y+z is 1, 2, 3, 4, 5, 6, 7, 8, 9 or 10. In some embodiments, the sum of x+y+z is 3 or 6. In some embodiments, the sum of x+y+z is 3. In other embodiments, the sum of x+y+z is 6. Each occurrence of A, B, C, D or E in a macrocycle or macrocycle precursor is independently selected. For example, a sequence represented by the formula $[A]_x$, when x is 3, encompasses embodiments where the amino acids are not identical, e.g. Gln–Asp–Ala as well as embodiments where the amino acids are identical, e.g. Gln–Gln–Gln. This applies for any value of x, y, or z in the indicated ranges. Similarly, when u is greater than 1, each compound can encompass peptidomimetic macrocycles which are the same or different. For example, a compound can comprise peptidomimetic macrocycles comprising different linker lengths or chemical compositions.

[00204] 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  .

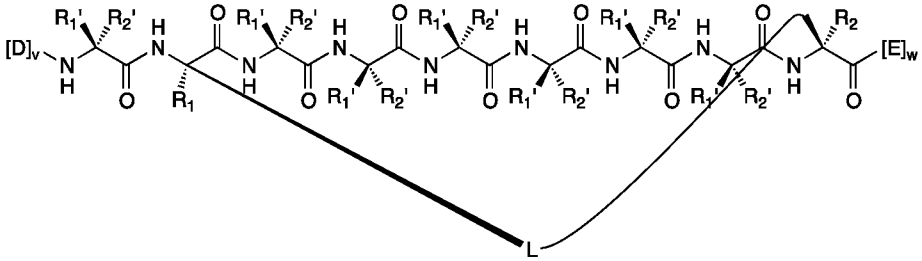
[00205] In other embodiments, the length of the macrocycle-forming linker L as measured from a first Cα to a second Cα is selected to stabilize a desired secondary peptide structure, such as an α-helix formed by residues of the peptidomimetic macrocycle including, but not necessarily limited to, those between the first Cα to a second Cα.

[00206] In one embodiment, the peptidomimetic macrocycle of Formula (I) is:



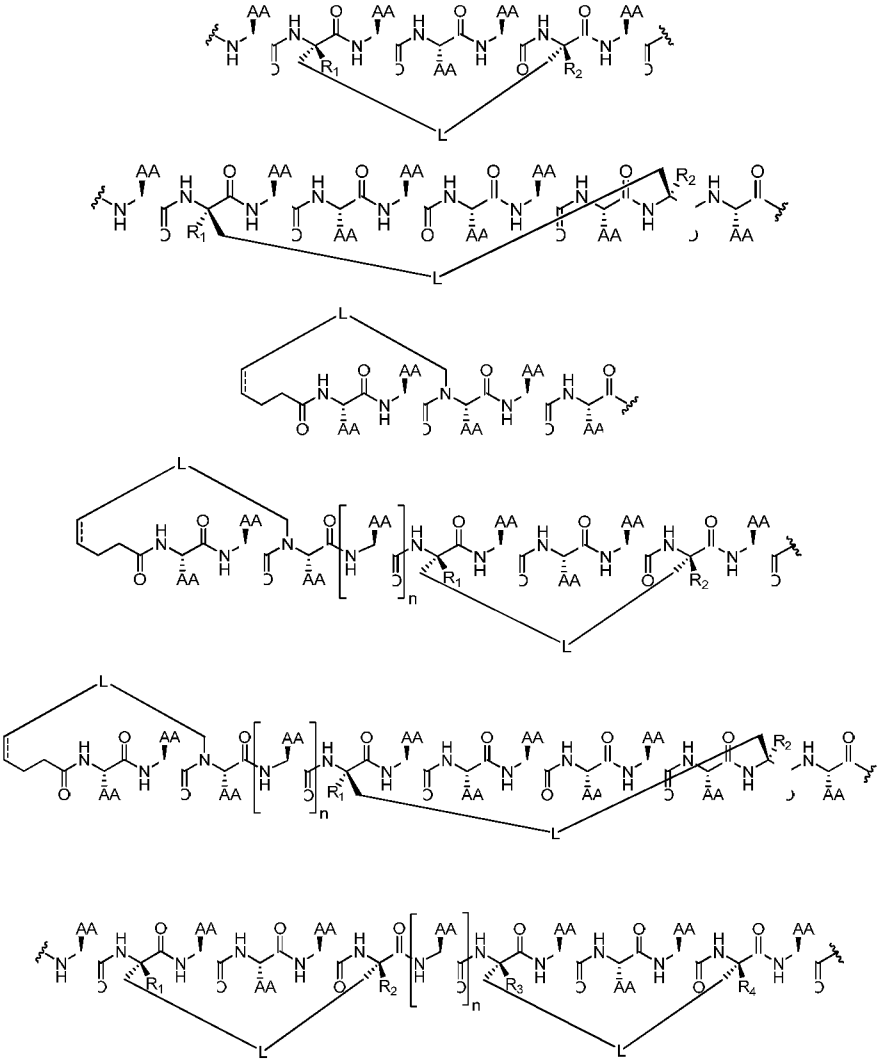
wherein each R_1 and R_2 is independently independently –H, alkyl, alkenyl, alkynyl, arylalkyl, cycloalkyl, cycloalkylalkyl, heteroalkyl, or heterocycloalkyl, unsubstituted or substituted with halo–.

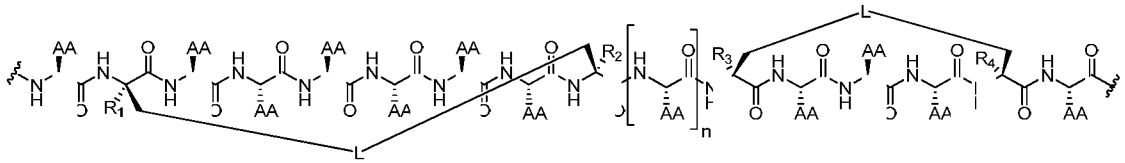
[00207] In related embodiments, the peptidomimetic macrocycle of Formula (I) is:

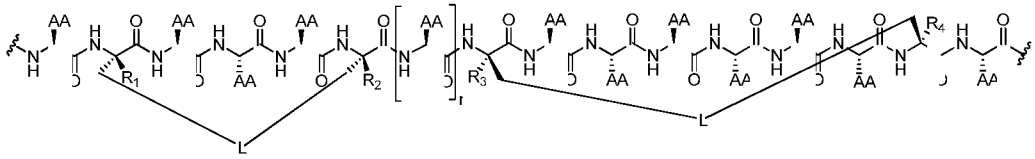


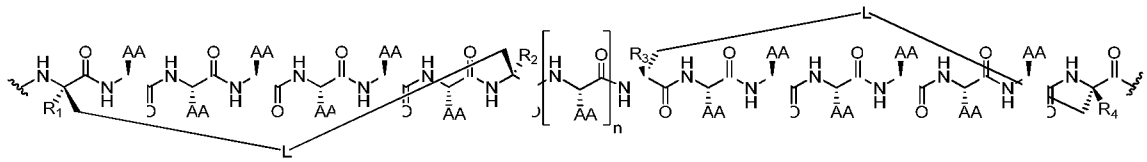
wherein each R_1' and R_2' is independently an amino acid.

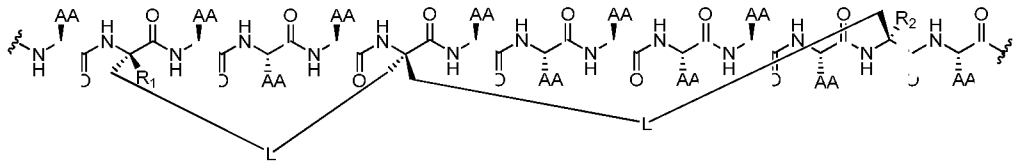
[00208] In other embodiments, the peptidomimetic macrocycle of Formula (I) is a compound of any of the formulas shown below:

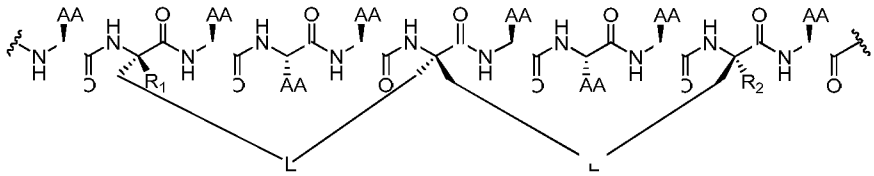


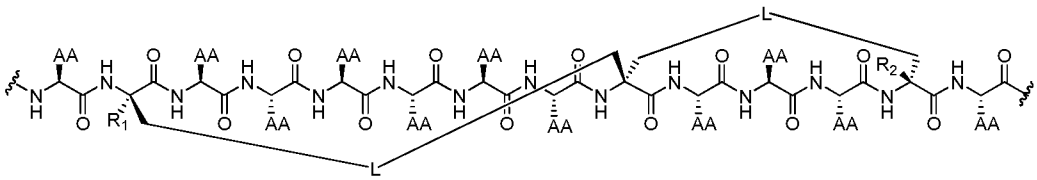


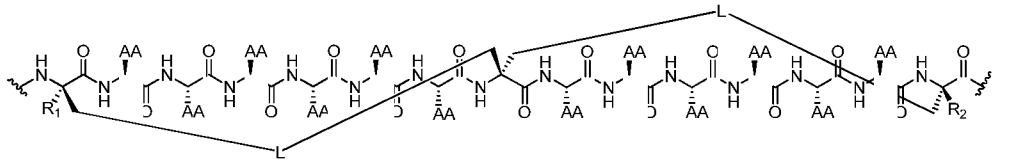






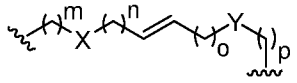




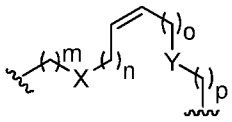


wherein "AA" represents any natural or non-natural amino acid side chain and "$\overset{\S}{\S}$" is $[D]_v$, $[E]_w$ as defined above, and n is an integer between 0 and 20, 50, 100, 200, 300, 400 or 500. In some embodiments, n is 0. In other embodiments, n is less than 50.

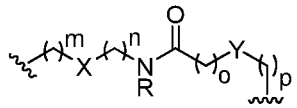
[00209] Exemplary embodiments of the macrocycle-forming linker L are shown below.



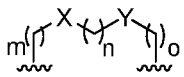
where X, Y = $-CH_2-$, O, S, or NH
m, n, o, p = 0-10



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

[00210] In other embodiments, D and/or E in the compound of Formula I are further modified in order to facilitate cellular uptake. In some embodiments, lipidating or PEGylating a peptidomimetic macrocycle facilitates cellular uptake, increases bioavailability, increases blood circulation, alters pharmacokinetics, decreases immunogenicity and/or decreases the needed frequency of administration.

[00211] 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.

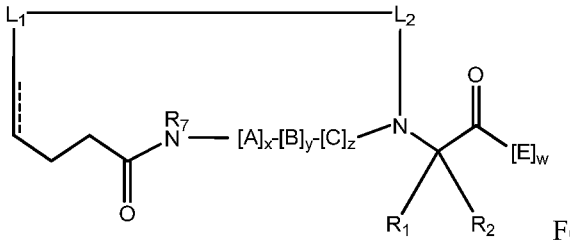
[00212] In some embodiments, any of the macrocycle-forming linkers described herein can be used in any combination with any of the sequences shown in Table 3, Table 3a, Table 3b, or Table 3c and also with any of the R– substituents indicated herein.

[00213] 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

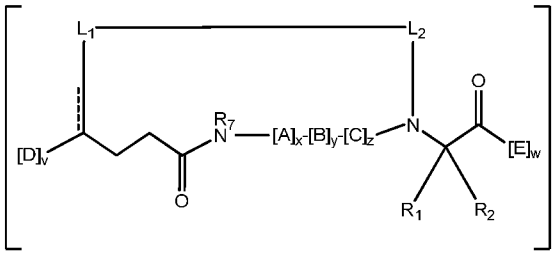
turns and, therefore, 3 to 20 amino acid residues. In specific embodiments, the α-helix includes 1 turn, 2 turns, 3 turns, 4 turns, or 5 turns. In some embodiments, the macrocycle-forming linker stabilizes an α-helix motif included within the peptidomimetic macrocycle. Thus, in some embodiments, the 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.

[00214] In other embodiments, provided are peptidomimetic macrocycles of Formula (IV) or (IVa):



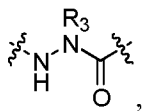
Formula (IV)



Formula (IVa)

wherein:

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

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

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;

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

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

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

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

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

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

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

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

v and w are independently integers from 1-1000;

u is an integer from 1-10;

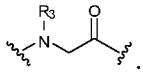
x, y and z are independently integers from 0-10; and

n is an integer from 1-5.

[00215] In one example, L_1 and L_2, either alone or in combination, do not form a triazole or a thioether.

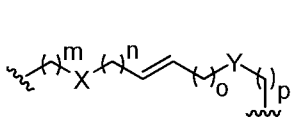
[00216] In one example, at least one of R_1 and R_2 is alkyl, unsubstituted or substituted with halo–. In another example, both R_1 and R_2 are independently alkyl, unsubstituted or substituted with halo–. In some embodiments, at least one of R_1 and R_2 is methyl. In other embodiments, R_1 and R_2 are methyl.

[00217] In some embodiments, x+y+z is at least 1. In other embodiments, x+y+z is at least 2. In other embodiments, x+y+z is 1, 2, 3, 4, 5, 6, 7, 8, 9 or 10. Each occurrence of A, B, C, D or E in a macrocycle or macrocycle precursor is independently selected. For example, a sequence represented by the formula $[A]_x$, when x is 3, encompasses embodiments where the amino acids are not identical, e.g. Gln–Asp–Ala as well as embodiments where the amino acids are identical, e.g. Gln–Gln–Gln. This applies for any value of x, y, or z in the indicated ranges.

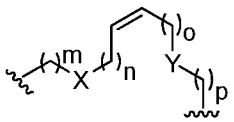
[00218] In some embodiments, the peptidomimetic macrocycle comprises a secondary structure which is an α-helix and R_8 is –H, allowing intrahelical hydrogen bonding. In some embodiments, at least one of A, B, C, D or E is an α,α-disubstituted amino acid. In one example, B is an α,α-disubstituted amino 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  .

[00219] 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.

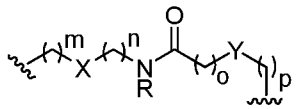
[00220] Exemplary embodiments of the macrocycle-forming linker $-L_1-L_2-$ are shown below.



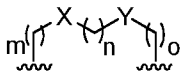
where X, Y = $-CH_2-$, O, S, or NH
m, n, o, p = 0-10



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

[00221] Unless otherwise stated, any compounds (including peptidomimetic macrocycles, macrocycle precursors, and other compositions) are also meant to encompass compounds which differ only in the presence of one or more isotopically enriched atoms. For example, compounds having the described structures except for the replacement of a

hydrogen by a deuterium or tritium, or the replacement of a carbon by ^{13}C- or ^{14}C-enriched carbon are within the scope of this disclosure.

[00222] 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.

[00223] The circulating half-life of the peptidomimetic macrocycles in human blood can be about 1-24 h. For example the circulating half-life of the peptidomimetic macrocycles in human blood can me about 2-24 h, 4-24 h, 6-24 h, 8-24 h, 10- 24 h, 12- 24 h, 14-24 h, 16-24 h, 18-24 h, 20-24 h, 22-24 h, 1- 20 h, 4-20 h, 6-20 h, 8-20 h, 10- 20 h, 12- 20 h, 14-20 h, 16-20 h, 18-20 h, 1- 16 h, 4-16 h, 6-16 h, 8-16 h, 10- 16 h, 12-16 h, 14-16 h, 1- 12 h, 4-12 h, 6-12 h, 8-12 h, 10- 12 h, 1- 8 h, 4-8 h, 6-8 h, or 1-4 h. In some examples, the circulating half-life of the peptidomimetic macrocycles in human blood can be bout 1-12 h, for example about 1 h, 2 h, 3 h, 4 h, 5 h, 6 h, 7 h, 8 h, 9 h, 10 h, 11 h, or 12 h. In some examples, the circulating half-life of the peptidomimetic macrocycles in human blood is about 2 h. In some examples, the circulating half-life of the peptidomimetic macrocycles in human blood is about 4 h. In some examples, the circulating half-life of the peptidomimetic macrocycles in human blood is about 6 h. In some examples, the circulating half-life of the peptidomimetic macrocycles in human blood is about 8 h. In some examples, the circulating half-life of the peptidomimetic macrocycles in human blood is about 10 h.

[00224] The half-life of the peptidomimetic macrocycles in biological tissue can be about 1-24 h. For example the circulating half-life of the peptidomimetic macrocycles in human blood can me about 1-24 h, 5-24 h, 10-24 h, 15-24 h, 20- 24 h, 1-22 h, 5-22 h, 10-22 h, 15-22 h, 20- 22 h, 1- 20 h, 5-20 h, 15-20 h, 1- 18 h, 5-18 h, 10-18 h, 15-18 h, 1- 16 h, 5-16 h, 10-16 h, 15-16 h, 1- 14 h, 5-14 h, 10-14 h, 1- 12 h, 5-12 h, 10-12 h, 1-10 h, 5-10h, 1-8 h, 5-8 h, 1-6 h, 5-6h, or 1-4 h. In some examples, the circulating half-life of the peptidomimetic macrocycles in human blood can be bout 5-20 h, for example about 5 h, 6 h, 7 h, 8 h, 9 h, 10 h, 11 h, 12 h, 13 h, 14 h, 15 h, 16 h, 17 h, 18 h, 19 h or 20 h. In some examples, the circulating half-life of the peptidomimetic macrocycles in human blood is about 2 h. In some examples, the circulating half-life of the peptidomimetic macrocycles in human blood is about 4 h. In some examples, the circulating half-life of the peptidomimetic macrocycles in human blood is about 6 h. In some examples, the circulating half-life of the peptidomimetic

macrocycles in human blood is about 8 h. In some examples, the circulating half-life of the peptidomimetic macrocycles in human blood is about 10 h.

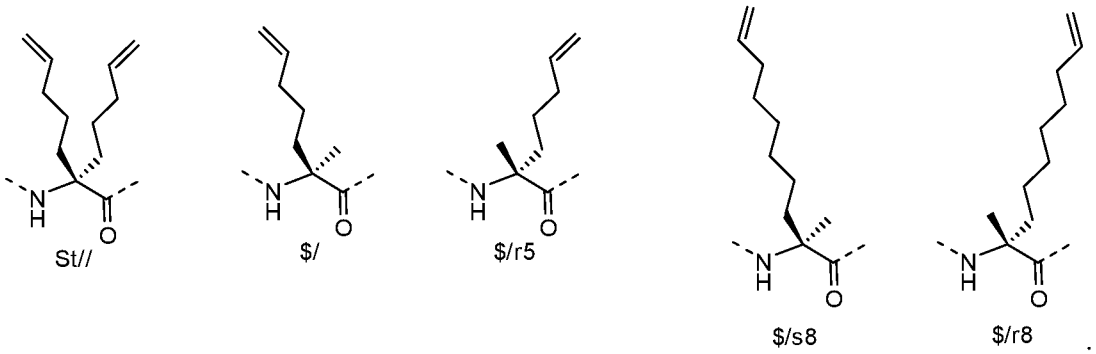
[00225] The circulating half-life of the peptidomimetic macrocycles in human blood can be greater than, equal to, or less than the half-life of the peptidomimetic macrocycles in biological tissue. In some examples, the circulating half-life of the peptidomimetic macrocycles in human blood can be greater than the half-life of the peptidomimetic macrocycles in biological tissue. In some examples, the circulating half-life of the peptidomimetic macrocycles in human blood can be equal to the half-life of the peptidomimetic macrocycles in biological tissue. In some examples, the half-life of the peptidomimetic macrocycles in biological tissue is greater than the circulating half-life of the peptidomimetic macrocycles in human blood. This can facilitate administration of the peptidomimetic macrocycles at a lower dose and/or at lower frequency. In some embodiments, the half-life of the peptidomimetic macrocycles in biological tissue is at least 1 h, at least 2 h, at least 3 h, at least 4 h, at least 5 h , at least 6 h, at least 7 h, at least 8 h, at least 9 h, at least 10 h, at least 11 h, or at least 12 h greater than the than the circulating half-life of the peptidomimetic macrocycles in human blood. In some examples, the circulating half-life of the peptidomimetic macrocycles in human blood is about 4 h and the half -life of the in biological tissue is about 10 h. In some examples, the circulating half-life of the peptidomimetic macrocycles in human blood is about 6 h and the half -life of the in biological tissue is about 10 h.

Preparation of Peptidomimetic Macrocycles

[00226] 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 3, Table 3a, Table 3b, or Table 3c 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.

[00227] 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:



[00228] 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.

[00229] Additional methods of forming peptidomimetic macrocycles which are envisioned as suitable include those disclosed by Mustapa, M. Firouz Mohd et al., J. Org. Chem (2003), 68, pp. 8193-8198; Yang, Bin et al. Bioorg Med. Chem. Lett. (2004), 14, pp. 1403-1406; U.S. Patent No. 5,364,851; U.S. Patent No. 5,446,128; U.S. Patent No. 5,824,483; U.S. Patent No. 6,713,280; and U.S. Patent No. 7,202,332. In such embodiments, amino acid precursors are used containing an additional substituent R- at the alpha position. Such amino acids are incorporated into the macrocycle precursor at the desired positions, which can be at the positions where the crosslinker is substituted or, alternatively, elsewhere in the sequence of the macrocycle precursor. Cyclization of the precursor is then effected according to the indicated method.

Assays

[00230] 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.

Assay to Determine α-helicity

[00231] 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)

[00232] 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

[00233] 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

[00234] 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

[00235] 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).

[00236] 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

[00237] 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.

[00238] 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).

[00239] 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

[00240] 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

[00241] To assess the binding and affinity of test compounds for proteins, a protein-ligand Kd titration experiment is performed, for example. Protein-ligand K_d titrations experiments are conducted as follows: 2 μL DMSO aliquots of a serially diluted stock solution of titrant peptidomimetic macrocycle (5, 2.5, ..., 0.098 mM) are prepared then dissolved in 38 μL of PBS. The resulting solutions are mixed by repeated pipetting and clarified by centrifugation at 10 000g for 10 min. To 4.0 μL aliquots of the resulting supernatants is added 4.0 μL of 10 μM hMDM2 in PBS. Each 8.0 μL experimental sample thus contains 40 pmol (1.5 μg) of protein at 5.0 μM concentration in PBS, varying concentrations (125, 62.5, ..., 0.24 μM) of the titrant peptide, and 2.5% DMSO. Duplicate samples thus prepared for each concentration point are incubated at room temperature for 30 min, then chilled to 4 °C prior to SEC-LC-MS analysis of 2.0 μL injections. The $(M + H)^{1+}$, $(M + 2H)^{2+}$, $(M + 3H)^{3+}$, and/or $(M + Na)^{1+}$ ion is observed by ESI-MS; extracted ion chromatograms are quantified, then fit to equations to derive the binding affinity K_d as described in "*A General Technique to Rank Protein-Ligand Binding Affinities and Determine Allosteric vs. Direct Binding Site Competition in Compound Mixtures*." Annis, D. A.; Nazef, N.; Chuang, C. C.; Scott, M. P.; Nash, H. M. *J. Am. Chem. Soc.* **2004**, *126*, 15495-15503; also in "*ALIS: An Affinity Selection-Mass Spectrometry System for the Discovery and*

Characterization of Protein-Ligand Interactions" D. A. Annis, C.-C. Chuang, and N. Nazef. In Mass Spectrometry in Medicinal Chemistry. Edited by Wanner K, Höfner G: Wiley-VCH; **2007**:121-184. Mannhold R, Kubinyi H, Folkers G (Series Editors): Methods and Principles in Medicinal Chemistry.

Assay for Competitive Binding Experiments by Affinity Selection-Mass Spectrometry

[00242] 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

[00243] It is possible to measure binding of peptides or peptidomimetic macrocycles to their natural acceptors in intact cells by immunoprecipitation experiments. For example, intact cells are incubated with fluoresceinated (FITC-labeled) compounds for 4 hrs in the absence of serum, followed by serum replacement and further incubation that ranges from 4-18 hrs. Cells are then pelleted and incubated in lysis buffer (50mM Tris [pH 7.6], 150 mM NaCl, 1% CHAPS and protease inhibitor cocktail) for 10 minutes at 4 °C. Extracts are

centrifuged at 14,000 rpm for 15 minutes and supernatants collected and incubated with 10 µl goat anti-FITC antibody for 2 hrs, rotating at 4 °C followed by further 2 hrs incubation at 4 °C with protein A/G Sepharose (50 µl of 50% bead slurry). After quick centrifugation, the pellets are washed in lysis buffer containing increasing salt concentration (*e.g.*, 150, 300, 500 mM). The beads are then re-equilibrated at 150 mM NaCl before addition of SDS-containing sample buffer and boiling. After centrifugation, the supernatants are optionally electrophoresed using 4%-12% gradient Bis-Tris gels followed by transfer into Immobilon-P membranes. After blocking, blots are optionally incubated with an antibody that detects FITC and also with one or more antibodies that detect proteins that bind to the peptidomimetic macrocycle.

Cellular Penetrability Assays

[00244] 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

[00245] 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

[00246] 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

[00247] 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

[00248] To determine the suitability of the peptidomimetic macrocycles for treatment of humans, clinical trials are performed. For example, patients diagnosed with liquid 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.

FORMULATION AND ADMINISTRATION

Mode of Administration

[00249] 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.

[00250] 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.

[00251] 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

[00252] 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.

[00253] A physician or veterinarian can prescribe the effective amount of the compound required. For example, the physician or veterinarian could start doses of the compounds of the disclosure employed in the compound 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.

[00254] 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.

[00255] 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.

[00256] In some embodiments, the subject is a human subject and the amount of the compound administered is 0.01-100 mg per kilogram body weight of the human subject. For example, in various examples, the amount of the compound 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 compound 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 compound 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 compound administered is about 0.16 mg per kilogram body weight of the human subject. In some examples the amount of the compound administered is about 0.32 mg per kilogram body weight of the human subject. In some examples the amount of the compound administered is about 0.64 mg per kilogram body weight of the human subject. In some examples the amount of the compound administered is about 1.28 mg per kilogram body weight of the human subject. In some examples the amount of the compound administered is about 3.56 mg per kilogram body weight of the human subject. In some examples the amount of the compound administered is about 7.12 mg per kilogram body weight of the human subject. In some examples the amount of the compound administered is about 14.24 mg per kilogram body weight of the human subject.

[00257] In some embodiments about 0.5- about 20 mg or about 0.5- about 10 mg of the compound 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 compound 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 compound per kilogram body weight of the human subject is administered two times a week. In some examples, the amount of the compound 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 compound is administered two times a week. In some examples, the amount of the compound 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 compound is administered two times a week.

[00258] In some embodiments about 0.5- about 20 mg or about 0.5- about 10 mg of the compound 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 compound 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 compound per kilogram body weight of the human subject is administered once a week. In some examples, the amount of the compound 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 compound is administered once a week. In some examples, the amount of the compound 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 compound is administered once a week

[00259] In some embodiments about 0.5- about 20 mg or about 0.5- about 10 mg of the compound 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 compound 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 compound 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 compound 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 compound is administered 3, 4, 5, 6, or 7 times a week. In some examples, the amount of the compound 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 compound is administered 3, 4, 5, 6, or 7 times a week.

[00260] In some embodiments, about 0.5- about 20 mg or about 0.5- about 10 mg of the compound 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 compound 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 compound per kilogram body weight of the human subject is administered once every 2 or 3 weeks. In some examples, the amount of the compound 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 compound is administered once every 2 weeks. In some examples, the amount of the compound 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 compound is administered once every 2 weeks. In some examples, the amount of the compound 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 compound is administered once every 3 weeks. In some examples, the amount of the compound 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 compound is administered once every 3 weeks.

[00261] In some embodiments, the compound is administered gradually over a period of time. A desired amount of compound 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 compound 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 compound 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 compound is administered gradually over a period of 0.25-2 h. In some examples, a desired amount of compound is administered gradually over a period of 0.25-1 h. In some examples, a desired amount of compound 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 compound is administered gradually over a period of 1 h. In some examples, a desired amount of compound is administered gradually over a period of 2 h.

[00262] Administration of the compound can continue as long as necessary. In some embodiments, one or more compound 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 compound 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.

[00263] In some embodiments, the compound is administered on day 1, 8, 15 and 28 of a 28 day cycle. In some embodiments, the compound 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 compound 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 compound 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.

[00264] In some embodiments, the compound is administered on day 1, 8, 11 and 21 of a 21 day cycle. In some embodiments, the compound 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 compound is administered on day 1, 8, 11 and 21of a 21 day cycle and administration is continued for three cycles. In some embodiments, the compound 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.

[00265] In some embodiments, one or more compound of the disclosure is administered chronically on an ongoing basis. In some embodiments administration of one or more compound of the disclosure is continued until documentation of disease progression, unacceptable toxicity, or patient or physician decision to discontinue administration.

METHOD AND USES

[00266] In one aspect, the disclosure provides a method of treating liquid cancer in a subject, the method comprising administering to the subject a therapeutically effective amount of a peptidomimetic macrocycle or a pharmaceutically acceptable salt thereof, wherein the peptidomimetic macrocycle binds to MDM2 and/or MDMX proteins. In some embodiments, the peptidomimetic macrocycle can disrupt the interaction between p53 and MDM2 and MDMX. In some embodiments, treatment according to the method disclosed herein can result in re-activation of the p53 pathway, decreased liquid cancer cell proliferation, increased p53 protein, increased p21, and/or increased apoptosis in the human subject.

[00267] In one aspect, the disclosure provides a method of treating liquid cancer, determined to lack a p53 deactivating mutation, in a subject the method comprising administering to the subject a therapeutically effective amount of a peptidomimetic macrocycle or a pharmaceutically acceptable salt thereof, wherein the peptidomimetic macrocycle binds to MDM2 and/or MDMX proteins. In some embodiments, the peptidomimetic macrocycle can disrupt the interaction between p53 and MDM2 and MDMX. The method further can comprise confirming the lack of the p53 deactivating mutation in the

subject prior to the administration of the peptidomimetic macrocycle. In some embodiments, treatment according to the method disclosed herein can result in re-activation of the p53 pathway, decreased liquid cancer cell proliferation, increased p53 protein, increased p21, and/or increased apoptosis in the human subject.

[00268] In one aspect, the disclosure provides a method of treating liquid cancer in a subject expressing wild type p53, the method comprising administering to the subject a therapeutically effective amount of a peptidomimetic macrocycle or a pharmaceutically acceptable salt thereof, wherein the peptidomimetic macrocycle binds to MDM2 and/or MDMX proteins. In some embodiments, the peptidomimetic macrocycle can disrupt the interaction between p53 and MDM2 and MDMX. The method further can comprise confirming the wild type p53 status of the subject prior to the administration of the peptidomimetic macrocycle. In some embodiments, treatment according to the method disclosed herein can result in re-activation of the p53 pathway, decreased liquid cancer cell proliferation, increased p53 protein, increased p21, and/or increased apoptosis in the human subject.

[00269] In some embodiments, the methods for treating liquid cancer provided herein inhibit, reduce, diminish, arrest, or stabilize a liquid cancer cell, such as a CTC or an MNBC, associated with the liquid cancer. In other embodiments, the methods for treating liquid cancer provided herein inhibit, reduce, diminish, arrest, or stabilize the symptoms associated with the liquid cancer or two or more symptoms thereof. In some examples, the methods for treating liquid cancer provided herein cause the reduction in the number of liquid cancer cells and/or one or more symptoms associated with the liquid cancer. In other examples, the methods for treating liquid cancer provided herein maintain the number of liquid cancer cells so that they donot increase, or so that the number of liquid cancer cells increases by less than the increase of a number of liquid cancer cells after administration of a standard therapy as measured by, for example, conventional methods available to one of skill in the art, such as ultrasound, CT Scan, MRI, dynamic contrast-enhanced MRI, or PET Scan. In some examples, the methods for treating liquid cancer provided herein decrease the number of liquid cancer cells. In some examples, the methods for treating liquid cancer provided herein reduce the formation of liquid cancer cells. In some examples, the methods for treating liquid cancer provided herein eradicate, remove, or control primary, regional and/or metastatic liquid cancer cells associated with the liquid cancer. In some examples, the methods for treating liquid cancer provided herein decrease the number or size of metastases associated with the liquid cancer. In some examples, the methods for treating liquid cancer provided

herein reduce the number of liquid cancer cells in a subject by an amount in the range of about 5- about 10%, about 5- about 20%, about 10- about 20%, about 15- about 20%, about 10- about 30%, about 20- about 30%, about 20- about 40%, about 30- about 40%, about 10- about 50%, about 20- about 50%, about 30- about 50%, about 40- about 50%, about 10- about 60%, about 20- about 60%, about 30- about 60%, about 40- about 60%, about 50- about 60%, about 10- about 70%, about 20- about 70%, about 30- about 70%, about 40- about 70%, about 50- about 70%, about 60- about 70%, about 10- about 80%, about 20- about 80%, about 30- about 80%, about 40- about 80%, about 50- about 80%, about 60- about 80%, about 70- about 80%, about 10- about 90%, about 20- about 90%, about 30- about 90%, about 40- about 90%, about 50- about 90%, about 60- about 90%, about 70- about 90%, about 80- about 90%, about 10- about 100%, about 20% - about 100%, about 30- about 100%, about 40- about 100%, about 50- about 100%, about 60- about 100%, about 70- about 100%, about 80- about 100%, about 90- about 100%, about 95- about 100%, or any range in between, relative to the number of liquid cancer cells in a subject prior to administration of the peptidomimetic macrocycles as assessed by, for example, CT Scan, MRI, DCE-MRI, or PET Scan. In certain embodiments, the methods herein reduce the number of liquid cancer cells in a subject by at least about 5%, at least about 10%, at least about 15%, at least about 20%, at least about 25%, at least about 30%, at least about 35%, at least about 40%, at least about 45%, at least about 50%, at least about 55%, at least about 60%, at least about 65%, at least about 70%, at least about 75%, at least about 80%, at least about 85%, at least about 90%, at least about 95%, at least about 99%, or about 100%, relative to the number of liquid cancer cells prior to administration of the peptidomimetic macrocycle as assessed by, for example, CT Scan, MRI, DCE-MRI, or PET Scan.

[00270] In some embodiments, the methods provided herein reduce the liquid cancer cell perfusion in a subject by an amount in the range of about 5- about 10%, about 5- about 20%, about 10- about 20%, about 15- about 20%, about 10- about 30%, about 20- about 30%, about 20- about 40%, about 30- about 40%, about 10- about 50%, about 20- about 50%, about 30- about 50%, about 40- about 50%, about 10- about 60%, about 20- about 60%, about 30- about 60%, about 40- about 60%, about 50- about 60%, about 10- about 70%, about 20- about 70%, about 30- about 70%, about 40- about 70%, about 50- about 70%, about 60- about 70%, about 10- about 80%, about 20- about 80%, about 30- about 80%, about 40- about 80%, about 50- about 80%, about 60- about 80%, about 70- about 80%, about 10- about 90%, about 20- about 90%, about 30- about 90%, about 40- about 90%, about 50- about 90%, about 60- about 90%, about 70- about 90%, about 80- about 90%,

about 10- about 100%, about 20% - about 100%, about 30- about 100%, about 40- about 100%, about 50- about 100%, about 60- about 100%, about 70- about 100%, about 80- about 100%, about 90- about 100%, about 95- about 100%, or any range in between, relative to liquid cancer cell perfusion prior to administration of the peptidomimetic macrocycle, as assessed by, for example, MRI, DCE-MRI, or PET Scan. In certain embodiments, the methods provided herein reduce the liquid cancer cell perfusion in a subject by at least about 5%, about 10%, about 15%, about 20%, about 25%, about 30%, about 35%, about 40%, about 45%, about 50%, about 55%, about 60%, about 65%, about 70%, about 75%, about 80%, about 85%, about 90%, about 95%, about 99%, or about 100%, relative to liquid cancer cell perfusion prior to administration of the peptidomimetic macrocycle as assessed by, for example, MRI, DCE-MRI, or PET Scan.

[00271] In some embodiments, the methods provided herein inhibit or decrease liquid cancer cell metabolism in a subject in the range of about 5- about 10%, about 5- about 20%, about 10- about 20%, about 15- about 20%, about 10- about 30%, about 20- about 30%, about 20- about 40%, about 30- about 40%, about 10- about 50%, about 20- about 50%, about 30- about 50%, about 40- about 50%, about 10- about 60%, about 20- about 60%, about 30- about 60%, about 40- about 60%, about 50- about 60%, about 10- about 70%, about 20- about 70%, about 30- about 70%, about 40- about 70%, about 50- about 70%, about 60- about 70%, about 10- about 80%, about 20- about 80%, about 30- about 80%, about 40- about 80%, about 50- about 80%, about 60- about 80%, about 70- about 80%, about 10- about 90%, about 20- about 90%, about 30- about 90%, about 40- about 90%, about 50- about 90%, about 60- about 90%, about 70- about 90%, about 80- about 90%, about 10- about 100%, about 20% - about 100%, about 30- about 100%, about 40- about 100%, about 50- about 100%, about 60- about 100%, about 70- about 100%, about 80- about 100%, about 90- about 100%, about 95- about 100%, or any range in between, relative to liquid cancer cell metabolism prior to administration of the peptidomimetic macrocycle, as assessed by, for example, MRI, DCE-MRI, or PET Scan. In certain embodiments, the methods provided herein inhibit or decrease liquid cancer cell metabolism in a subject as assessed by, for example,PET scanning. In specific embodiments, the methods provided herein inhibit or decrease liquid cancer cell metabolism in a subject by at least about 5%, at least about 10%, at least about 15%, at least about 20%, at least about 25%, at least about 30%, at least about 35%, at least about 40%, at least about 45%, at least about 50%, at least about 55%, at least about 60%, at least about 65%, at least about 70%, at least about 75%, at least about 80%, at least about 85%, at least about 90%, at least about 95%, or about 100%,

relative to liquid cancer cell metabolism prior to administration of the peptidomimetic macrocycle.

[00272] In other aspect, the disclosure provides a method for increasing the survival time of a subject with liquid cancer determined to lack a p53 deactivating mutation and/or with liquid cancer expressing wild type p53, the method comprising administering to the subject a therapeutically effective amount of a peptidomimetic macrocycle or a pharmaceutically acceptable salt thereof, wherein the peptidomimetic macrocycle binds to MDM2 and/or MDMX proteins. In some examples, the survival time of the subject is at least 30 days longer than the expected survival time of the subject if the subject was not treated according to the methods provided herein. In some examples, the survival time of the subject is at 1 month – about 5 years longer than the expected survival time of the subject if the subject was not treated according to the methods provided herein. For example, the survival time of the subject is at least 3 months, at least 6 months, at least 9 months, at least 12 months, at least 15 months, at least 18 months, at least 21 months, or at least 24 months longer than the expected survival time of the subject if the subject was not treated according to the methods disclosed herein disclosure.

[00273] In one aspect, the disclosure provides a method to assessed presence, absence or amount of the biomarker in a subject suffering with liquid cancer. In some examples, the biomarkers include patient biomarkers, for example, the p53 status of the subject and the MDM2 and MDMX expression levels in the subject.

[00274] The method of the disclosure can also optionally include studying and/or evaluating the safety and/or tolerability of the peptidomimetic macrocycles disclosed herein in the subject.

[00275] Also provided herein is a method to re-activate the p53 pathway in a subject with a liquid cancer lacking a p53 deactivating mutation and/or expressing wild type p53, the method comprising administering to the subject a therapeutically effective amount of a peptidomimetic macrocycle or a pharmaceutically acceptable salt thereof, wherein the peptidomimetic macrocycle binds to MDM2 and/or MDMX proteins.

[00276] Also provided herein is a method to decrease liquid cancer cell proliferation in a human subject with a liquid cancer lacking a p53 deactivating mutation and/or expressing wild type p53, the method comprising administering to the subject a therapeutically effective amount of a peptidomimetic macrocycle or a pharmaceutically acceptable salt thereof, wherein the peptidomimetic macrocycle binds to MDM2 and/or MDMX proteins.

[00277] Also provided herein is a method to increased p53 protein in a subject with a liquid cancer lacking a p53 deactivating mutation and/or expressing wild type p53, the method comprising administering to the subject a therapeutically effective amount of a peptidomimetic macrocycle or a pharmaceutically acceptable salt thereof, wherein the peptidomimetic macrocycle binds to MDM2 and/or MDMX proteins.

[00278] Also provided herein is a method to increased p21 in a subject with a liquid cancer lacking a p53 deactivating mutation and/or expressing wild type p53, the method comprising administering to the subject a therapeutically effective amount of a peptidomimetic macrocycle or a pharmaceutically acceptable salt thereof, wherein the peptidomimetic macrocycle binds to MDM2 and/or MDMX proteins.

[00279] Also provided herein is a method to increased apoptosis in a subject with a liquid cancer lacking a p53 deactivating mutation and/or expressing wild type p53, the method comprising administering to the subject a therapeutically effective amount of a peptidomimetic macrocycle or a pharmaceutically acceptable salt thereof, wherein the peptidomimetic macrocycle binds to MDM2 and/or MDMX proteins.

[00280] In some embodiments, the disclosure also provides a method to determine the dose limiting toxicities (DLTs) and /or maximum tolerated dose (MTD or OBD) or the optimal biological dose (OBD) of the peptidomimetic macrocycles disclosed herein in subject with a liquid cancer (e.g., a liquid lymphoma) lacking a p53 deactivating mutation and/or expressing wild type p53.

[00281] The methods of the disclosure can optionally include pharmacokinetic analysis of the peptidomimetic macrocycles disclosed herein. Accordingly, the methods can further comprise collecting one or more biological sample from the subject at one or more specific time point and analyzing the one or more biological sample for levels of the peptidomimetic macrocycles and/or it metabolites. The biological sample can be a blood sample from the subject, for example, a blood sample from a human subject. The one or more specific time point can include time points before, after and/or during the administration of the peptidomimetic macrocycle to the subject. In some embodiments one or more biological sample includes biological samples collected before and after each administration of the peptidomimetic macrocycle to the subject. In some embodiments a biological sample for pharmacokinetic analysis is collected before the first administration of the peptidomimetic macrocycle to the subject and at one or more time points after each administration of the peptidomimetic macrocycles to the subject. The biological sample collected before the administration of the peptidomimetic macrocycle to the subject can be done within 0-24 hour

before the start of administration of the peptidomimetic macrocycle to the subject. For example, the biological sample can be collected within 24 h, within 23 h, within 22 h, within 21 h, within 20 h, within 19 h, within 18 h, within 17 h, within 16 h, within 15 h, within 14 h, within 13 h, within 12 h, within 11 h, within 10 h, within 9 h, within 8 h, within 7 h, within 6 h, within 5 h, within 4 h, within 3 h, within 2 h, within 1 h, within 30 min, within 15 min, or immediately before the administration of the peptidomimetic macrocycle to the subject. One or more biological samples collected after the administration of the peptidomimetic macrocycle to the subject can be collected, for example after 0 min, 5 min, 10 min, 20 min, 30 min, 45 min, 60 min, 1.25 h, 1.5 h, 1.75 h, 2.0 h, 2.25 h, 2.5 h, 2.75 h, 3.0 h, 3.25 h, 3.5 h, 3.75 h, 4.0 h, 4.25 h, 4.5 h, 4.75 h, 5.0 h, 5.25 h, 5.5 h, 5.75 h, 6.0 h, 6.25 h, 6.5 h, 6.75 h, 7.0 h, 7.25 h, 7.5 h, 7.75 h, 8.0 h, 8.25 h, 8.5 h, 8.75 h, , 9.0 h, 9.25 h, 9.5 h, 9.75 h, 10.0 h, 10.25 h, 10.5 h, 10.75 h, 11.0 h, 11.25 h, 11.5 h, 11.75 h, 12.0 h, 20 h, 24 h, 28 h, 32 h, 36 h, 40 h, 44 h, 48 h, 52 h, 56 h, 60 h, 64 h, 68 h, 72 h, or 0-72 h after the administration of the peptidomimetic macrocycle to the subject. In some embodiments, the peptidomimetic macrocycle is administered on day 1, day 8, day 15 of a 28 day cycle and biological sample is collected before administration on day 1, after the administration on day 1 (multiple biological samples can be collected, for example after about 0 min, about 30 min, about 1 h, about 2 h, about 4 h, about 8 h, about 24 h, and 48 hour after administration), before administration on day 8, after administration on day 8 (multiple biological samples can be collected, for example after about 0 min, about 30 min, about 1 h, about 2 h, and about 4 h after administration), before administration on day 15 and after administration on day 15(multiple biological samples can be collected, for example after about 0 min, about 30 min, about 1 h, about 2 h, about 4 h, about 8 h, and about 24 h after administration). In some embodiments, the peptidomimetic macrocycle is administered on day 1, day 8, day 11 of a 21 day cycle and biological sample is collected before administration on day 1, after the administration on day 1 (multiple biological samples can be collected, for example after about 0 min, about 30 min, about 1 h, about 2 h, about 4 h, about 8 h, about 24 h, and 48 hour after administration), before administration on day 8, after administration on day 8 (multiple biological samples can be collected, for example after about 0 min, about 30 min, about 1 h, about 2 h, and about 4 h after administration), before administration on day 11 and after administration on day 11 (multiple biological samples can be collected, for example after about 0 min, about 30 min, about 1 h, about 2 h, about 4 h, about 8 h, and about 24 h after administration).

[00282] The method of the disclosure can optionally include pharmacodynamic analysis of the peptidomimetic macrocycles disclosed herein. Accordingly, the methods can comprise collecting one or more biological samples from the subject at one or more specific time points for pharmacodynamic analysis. Pharmacodynamic analysis can include analyzing the levels of biomarkers including MIC-1, p53, MDM2, MDMX, p21 and/or cases in the biological sample. Detection of biomarkers in a biological sample can be performed by, for example, direct measurement, immunohistochemistry, immunoblotting, immunoflourescense, immunoabsorbence, immunoprecipitations, protein array, flourescence in situ hybridization, FACS analysis, hybridization, in situ hybridization, Northern blots, Southern blots, Western blots, ELISA, radioimmunoassay, gene array/chip, PCR, RT-PCR, or cytogenetic analysis. The biological sample for pharmacodynamic analysis can be a blood sample or a liquid cancer cell specimen from the subject, for example, a biological sample for pharmacodynamic analysis can be a blood sample or a liquid cancer cell specimen from the human subject. The biological samples for pharmacodynamic analysis of the peptidomimetic macrocycles can be collected any time before, during, or after the administration of the peptidomimetic macrocycle to the subject. In some embodiments a blood sample for pharmacokinetic analysis is collected before the first administration of the peptidomimetic macrocycle to the subject and at one or more time points after each administration of the peptidomimetic macrocycles to the subject. The blood sample collected before the administration of the peptidomimetic macrocycle to the subject can be done within 0-24 hour before the start of administration of the peptidomimetic macrocycle to the subject. For example, the biological sample can be collected within 24 h, within 23 h, within 22 h, within 21 h, within 20 h, within 19 h, within 18 h, within 17 h, within 16 h, within 15 h, within 14 h, within 13 h, within 12 h, within 11 h, within 10 h, within 9 h, within 8 h, within 7 h, within 6 h, within 5 h, within 4 h, within 3 h, within 2 h, within 1 h, within 30 min, within 15 min of, or immediately before the administration of the peptidomimetic macrocycle to the subject. One or more blood samples for pharmacodynamic analysis collected after the administration of the peptidomimetic macrocycle to the subject can be collected from 0-about 72 h, for example after about 12 h, after about 24 h, after about 36 h or after about 48 h after the administration of the peptidomimetic macrocycle to the subject. In some embodiments, the peptidomimetic macrocycle is administered on day 1, day 8, day 15 of a 28 day cycle and blood samples for pharmacodynamic analysis are collected before administration on day 1, after the administration on day 1 (multiple samples can be collected, for example after about 24 h and 48 hour after administration), before administration on day 8, after administration on

day 8 (multiple samples can be collected, for example with about 1 h administration), before administration on day 15 and after administration on day 15 (multiple samples can be collected, for example with about 1 h and about 48 h after administration), and day 22. Biological samples for pharmacodynamic analysis can be collected at any time before, after or during the administration of the peptidomimetic macrocycle to the subject. For example the peptidomimetic macrocycle can be administered on day 1, day 8, day 15 of a 28 day cycle and liquid cancer cell samples for pharmacodynamic analysis are collected before administration on day 1 and between day 14-day 18, for example of day 16. In some embodiments, the peptidomimetic macrocycle is administered on day 1, day 8, day 11, of a 21 day cycle and blood samples for pharmacodynamic analysis are collected before administration on day 1, after the administration on day 1 (multiple samples can be collected, for example after about 24 h and 48 hour after administration), before administration on day 8, after administration on day 8 (multiple samples can be collected, for example with about 1 h administration), before administration on day 11 and after administration on day 11 (multiple samples can be collected, for example with about 1 h and about 48 h after administration), and day 22. Biological samples for pharmacodynamic analysis can be collected at any time before, after or during the administration of the peptidomimetic macrocycle to the subject. For example the peptidomimetic macrocycle can be administered on day 1, day 8, day 11 of a 21 day cycle and liquid cancer cell samples for pharmacodynamic analysis are collected before administration on day 1 and between day 10-day 14, for example of day 12.

[00283] The method of the disclosure can optionally include clinical activity analysis of the peptidomimetic macrocycles disclosed herein. Accordingly, the methods can comprise analyzing one or more biological samples collected from the subject at one or more specific time points. Any appropriate analytical procedure can be used for the analysis of the biological samples. For example, imaging techniques like radiographs, ultrasound, CT scan, PET scan, MRI scan, chest x-ray, laparoscopy, complete blood count (CBC) test, bone scanning and fecal occult blood test can be used. Further analytical procedures that can be used include blood chemistry analysis, chromosomal translocation analysis, needle biopsy, tissue biopsy, fluorescence in situ hybridization, laboratory biomarker analysis, immunohistochemistry staining method, flow cytometry, or a combination thereof. The method can further comprise tabulating and/or plotting results of the analytical procedure.

[00284] For example, pharmacodynamics can be assessed by laboratory-based evaluation of several biomarkers of p53 activation, including levels of p21, caspase and

MDM2 in liquid cancer cell tissue, and where available in CTC, as well as MIC-1 in blood, before and after treatment with the peptidomimetic macrocycles.

[00285] Results available from previous genetic and biomarker tests, and additional tests of the blood and t liquid cancer cell samples for biomarkers relevant to the safety and efficacy of the peptidomimetic macrocycles can be investigated for possible correlation with patient outcome.

[00286] For example, clinical activity or response can be evaluated by standard imaging assessments, such as computed tomography (CT), magnetic resonance imaging (MRI), and bone scans. In addition, [^{18}F]-fluorodeoxyglucose and [^{18}F]-fluorothymidine positron emission tomography (FDG-PET and FLT-PET, respectively), or other techniques considered clinically appropriate for the patient's specific disease type can be used. CT-imaging can be performed, for example, at the end of Cycle 2, and every 2 cycles (e.g., Cycles 4 and 6) thereafter for DR-A and after the last infusion in Cycle 3 and every 3 cycles (e.g., Cycles 6 and 9) thereafter in DR-B. Anti- liquid cancer cell activity can be assessed using IWG (2014) (Appendix H) criteria for patients with liquid lymphomas. Additionally, for patients with an FDG-avid liquid lymphoma, FDG-PET imaging can be performed at baseline and post-baseline as outlined in IWG 2014. FLT-PET imaging can be performed at baseline for patients with liquid cancer cell commonly showing sufficient uptake of FLT tracer, e.g., patients with liquid lymphoma. For example, DR-A assigned patients who demonstrate a standard uptake value (SUV) of ≥ 5 at baseline can have a repeat FLT image one day after their last infusion of study medication in Cycle 1, i.e., Day 16. For example, DR-B patients who demonstrate a standard uptake value (SUV) of ≥ 5 at baseline can have a repeat FLT image one day after their last infusion of study medication in Cycle 1, i.e., Day 12.

Biological Samples

[00287] 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. Biological samples also include liquid cancer cell samples or specimens. Liquid cancer cell sample can be a liquid cancer cell tissue sample. In some embodiments, the liquid cancer cell tissue sample can obtained from surgically excised tissue. 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.

[00288] The biological samples obtained can be used in fresh, frozen, or fixed (e.g., paraffin-embedded) form, depending on the nature of the sample, the assay used, and the convenience of the practitioner. Although fresh, frozen and fixed materials are suitable for various RNA and protein assays, generally, fresh tissues can be preferred for ex vivo measurements of activity.

[00289] Fixed tissue samples can also be employed. Tissue obtained by biopsy is often fixed, usually by formalin, formaldehyde, or gluteraldehyde, for example, or by alcohol immersion. Fixed biological samples are often dehydrated and embedded in paraffin or other solid supports. See the reference Plenat et al., 2001, *Ann. Pathol.* 21:29-47. Non-embedded, fixed tissue, as well as fixed and embedded tissue, can be used in the present methods. Solid supports for embedding fixed tissue can be removed with organic solvents to enable subsequent rehydration of preserved tissue.

[00290] In some cases, the assay includes a step of cell or tissue culture. For example, cells from a biopsy can be disaggregated using enzymes (such as collagenase and hyaluronidase) and or physical disruption (e.g., repeated passage through a 25-gauge needle) to dissociate the cells, collected by centrifugation, and resuspended in desired buffer or culture medium for culture, immediate analysis, or further processing.

Subject/Patient population

[00291] In some embodiments, a subject treated for liquid cancer in accordance with the methods provided herein is a human, who has or is diagnosed with a liquid cancer. In other embodiments, a subject treated for liquid cancer in accordance with the methods provided herein is a human, predisposed or susceptible to a liquid cancer. In some embodiments, a subject treated for liquid cancer in accordance with the methods provided herein is a human, at risk of developing a liquid cancer.

[00292] In some embodiments, a subject treated for liquid cancer in accordance with the methods provided herein is a human, who has or is diagnosed with a liquid cancer, determined to lack a p53 deactivating mutation and/or expressing wild type p53. In other embodiments, a subject treated for liquid cancer in accordance with the methods provided herein is a human, predisposed or susceptible to a liquid cancer, determined to lack a p53

deactivating mutation and/or expressing wild type p53. In some embodiments, a subject treated for liquid cancer in accordance with the methods provided herein is a human, at risk of developing a liquid cancer, 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. Non limiting examples of p53 deactivating mutations are included in Table 1. Accordingly, in some embodiments, a subject with a liquid cancer in accordance with the composition as provided herein is a human who has or is diagnosed with a liquid cancer that is determined to lack a p53 deactivation mutation, such as those shown in Table 1.

[00293] In some embodiments, a subject treated for liquid cancer in accordance with the methods provided herein is a human, who has or is diagnosed with a liquid cancer, 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.

Table 1: Examples of p53 deactivating mutations

Mutation at position	Amino acid change
62	E62_W91del
122	V122X
135	C135S
143	V143A
144	Q144P
146	W146X
157	V157F
158	R158H
163	Y163N
168	H168Y
173	V173L
175	R175H
175	R175P
175	R175Q
175	R175S
219	P219H
234	Y234C
234	Y234H
237	M237I
240	S240R
245	G245C
245	G245S
246	M246I
248	R248Q
248	R248W
249	R249S
272	V272M

273	R273H
274	V274F
279	G279E
280	R280K
281	D281H
282	R282W
306	R306P
308	P300_L308del
327	P300_Y327del
332	D324_I332del
337	R337C
344	L344P

Table 1 refers to the sequence of the wild-type human TP53 tumor protein p53 shown in Figure 1. Amino acid changes are reported as: the amino acid being substituted followed by the position of the amino acid being substituted in the wild type p53 sequence, followed by the amino acid used for substitution. For example L344P, indicates that the leucine residue (L) at the 344 position in the wild type sequence is replaced by a proline residue (P).

[00294] In some embodiments, a subject treated for liquid cancer in accordance with the methods provided herein is a refractory patient. In a certain embodiment, a refractory patient is a patient refractory to a standard therapy (e.g., surgery, radiation, anti-androgen therapy and/or drug therapy such as chemotherapy). In certain embodiments, a patient with the liquid cancer is refractory to a therapy when the liquid cancer has not significantly been eradicated and/or the one or more symptoms have not been significantly alleviated. The determination of whether a patient is refractory can be made either in vivo or in vitro by any method known in the art for assaying the effectiveness of a treatment of liquid cancer. In various embodiments, a patient with liquid cancer is refractory when the number of CTCs or MNBCs associated with the liquid cancer have not decreased or have increased. In various embodiments, a patient with liquid cancer is refractory when one or more liquid cancer cells metastasize and/or spread to another organ.

[00295] In some embodiments, a subject treated for liquid cancer accordance with the methods provided herein is a human that has proven refractory to therapies other than treatment with the peptidomimetic macrocycles of the disclosure, but is no longer on these therapies. In certain embodiments, a subject treated for liquid cancer in accordance with the methods provided herein is a human already receiving one or more conventional anti-cancer therapies, such as surgery, drug therapy such as chemotherapy, anti-androgen therapy or radiation. Among these patients are refractory patients, patients who are too young for conventional therapies, and patients with recurring liquid cancer cells despite treatment with existing therapies.

[00296] In some embodiments, the subject is a human who has had at least one unsuccessful prior treatment and/or therapy of the liquid cancer.

Methods of detecting wild type p53 and/or p53 mutations

[00297] The liquid cancer cell samples from a subject can be assayed in order to determine the lack of a p53 deactivating mutation and/or expression of wild type p53.

[00298] In order to detect the p53 wild-type gene and/or lack of p53 deactivation mutation in a tissue, it can be helpful to isolate the tissue free 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 liquid cancer cells tissue is highly contaminated with normal cells, detection of mutations can be more difficult.

[00299] Detection of point mutations can be accomplished by molecular cloning of the p53 allele (or alleles) present in the liquid 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 liquid 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.

[00300] 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.

[00301] 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).

[00302] Alternatively, mismatch detection can be used to detect point mutations in the p53 gene or its mRNA product. The method can involve the use of a labeled riboprobe which is complementary to the human wild-type p53 gene. The riboprobe and either mRNA or DNA isolated from the liquid 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, it 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 will be seen which 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.

[00303] 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.

[00304] DNA sequences of the p53 gene from the liquid 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 liquid cancer cell tissue as in the allele-specific probe.

[00305] The identification of p53 gene structural changes in liquid cancer cells can be facilitated through the application of a diverse series of high resolution, high throughput microarray platforms. Essentially there are two types of array; 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 liquid 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 liquid cancer cells have given rise to exon-specific arrays that can identify both gene expression levels, alternative splicing events and mRNA processing alterations. Oligonucleotide arrays are also being 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 and whole genomes.

[00306] SNP -based arrays or other gene arrays or chips are also contemplated to 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. 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.

[00307] 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 not only liquid cancers (e.g. gastric cancer, liver cancer etc) but also 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 ah, 2005; Lai et al, 2007).

[00308] Examples for current 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.

[00309] 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, such as, serum, stool, or other body fluids, such as 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.

[00310] 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 means for detecting an altered p53 protein can be used to detect loss of wild-type p53 genes.

[00311] Mutant p53 genes or gene products can also be detected in body samples, such as, serum, stool, or other body fluids, such as 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.

[00312] Determination of the lack of p53 deactivating mutation and/or expression of wild type p53 in the subject with liquid cancer can be performedd any time before, during or after the administration of the peptidomimetic macrocycles. In some embodiments, the determination of the lack of a p53 deactivating mutation and/or expression of wild type p53 is performed before the first administration of the peptidomimetic macrocycle to the subject, for example about 5 years – about 1 month, about 4 years – about 1month, about 3 years – 1 month, about 2 years- about 1 month, about 1 years – about 1 month, about 5 years – about 1 week, about 4 years – about 1 week, about 3 years – about 1 month, about 2 years- about 1 week, about 1 year – about 1 week, about 5 years – about 1 day, about 4 years – about 1 day, about 3 years – about 1 day, about 2 years- about 1day, about 1 year – about 1 day, about 15

months- about 1 month, about 15 months- about 1 week, about 15 months - about 1 day, about 12 months- about 1 month, about 12 months- about 1 week, about 12 months- about 1 day, about 6 months-1 about month, about 6 months- about 1 week, about 6 months- about 1 day, about 3 months-1 about month, about 3 months- about 1 week, or about 3 months- about 1 day prior to the first administration of the peptidomimetic macrocycle to the subject. In some examples, the confirmation of the lack of the p53 deactivating mutation and/or expression of wild type p53 is performed up to 6 years, 5 years, 4 years, 3 years, 24 months, 23 months, 22 months, 21 months, 20 months, 19 months, 18 months, 17 months, 16 months, 15 months, 14 months, 13 months, 12 months, 11 months, 10 months, 9 months, 8 months, 7 months, 6 months, 5 months, 4 months, 3 months, 2 months, 1 months, 4 weeks (28 days), 3 weeks (21 days), 2 weeks (14 days), 1 week (7days), 6 days, 5 days, 4 days, 3 days, 2 days or 1 day before the first administration of the peptidomimetic macrocycle to the subject. In some examples the confirmation of the lack of the p53 deactivating mutation is performed within 1 month of the first administration of the peptidomimetic macrocycle to the subject. In some examples the confirmation of the lack of the p53 deactivating mutation is performed within 21 days of the first administration of the peptidomimetic macrocycle to the subject.

Liquid cancers

[00313] Liquid cancers that can be treated by the instant methods include, but are not limited to, liquid lymphomas, lekemias, and myelomas. Examples of 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.

[00314] Examples of liquid cancers that can be treated by the methods of the disclosure include cancers involving hyperplastic/neoplastic cells of hematopoietic origin, *e.g.*, arising from myeloid, lymphoid or erythroid lineages, or precursor cells thereof. Examples of 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 lymphomas include, but are not limited to non-Hodgkin lymphoma and variants thereof, peripheral T cell lymphomas, adult T cell leukemia/lymphoma (ATL), cutaneous T-cell lymphoma (CTCL), large granular lymphocytic leukemia (LGF), Hodgkin's disease and Reed-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.

[00315] In some embodiments, the liquid cancer treated by the methods of the disclosure is an acute lymphoblastic leukemia; acute myeloid leukemia; AIDS-related cancers; AIDS-related lymphoma; chronic lymphocytic leukemia; chronic myelogenous leukemia; chronic myeloproliferative disorders; cutaneous T-cell lymphoma; Hodgkin lymphoma; multiple myeloma; multiple myeloma/plasma cell neoplasm; Non-Hodgkin lymphoma; primary central nervous system (CNS) lymphoma; or T-cell 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.

[00316] In some embodiments liquid cancers treated by the methods disclosed herein exclude cancers that are known to be associated with HPV (Human papillomavirus).

[00317] The effectiveness and/or response of cancer treatment by the methods disclosed herein can be determined by any suitable method. The response can be a complete response, and which can be an objective response, a clinical response, or a pathological response to treatment. For example, the response can be determined based upon the techniques for evaluating response to treatment of liquid cancers as described in or by Revised International Working Group Response Criteria for liquid lymphoma patients (IWG 2014), which is hereby incorporated by reference in its entirety. The response can be a duration of survival (or probability of such duration) or progression-free interval. The timing or duration of such events can be determined from about the time of diagnosis, or from about the time treatment is initiated or from about the time treatment is finished (like the final administration of the peptidomimetic macrocycle). Alternatively, the response can be based upon a reduction in the number of liquid cancer cells, the number of liquid cancer cells per unit volume, or liquid cancer cell metabolism, or based upon overall liquid cancer cell burden, or based upon levels of serum markers especially where elevated in the disease state.

[00318] The response in individual patients can be characterized as a complete response, a partial response, stable disease, and progressive disease. In some embodiments, the response is complete response (CR). Complete response can be defined as disappearance of all circulating tumor cells (CTC) or a mononuclear blood cells (MNBC) i.e. any pathological lymph nodes (whether target or non-target) must have reduction in short axis to < 10 mm. In some examples (*e.g.*, AML), complete response can be defined as the following: bone marrow blasts < 5%; absence of blasts with Auer rods; absence of extramedullary disease; absolute neutrophil count > 1.0 x 109/L (1000/μL); platelet count >100 x 109/L (100 000/μL); and independence of red cell transfusions. In certain embodiments, the response is a CR with Incomplete Recovery (CRi). CR with Incomplete Recovery, in some examples (*e.g.*, AML), can be defined to include all CR criteria except for residual neutropenia (< 1.0 x 109/L [1000/μL]) or thrombocytopenia (<100 x 109/L [100 000/μL]). In certain embodiments, the response is a morphologic leukemia free state. Morphologic leukemia free state, in some examples (*e.g.*, AML), can be defined to include bone marrow blasts < 5%; absence of blasts with Auer rods; absence of extramedullary disease; and no hematologic recovery required. In certain embodiments, the response is a partial response (PR). Partial response can be defined to mean at least 30% decrease in the sum of diameters of circulating tumor cells (CTC) or a mononuclear blood cells (MNBC), taking as reference the baseline

sum diameters. In some examples (*e.g.*, AML), partial response can be defined to include all hematologic criteria of CR; decrease of bone marrow blast percentage to 5% to 25%; and decrease of pretreatment bone marrow blast percentage by at least 50%. In certain embodiments, the response is a morphologic leukemia free state. Morphologic leukemia free state, in some examples (*e.g.*, AML), can be defined to include bone marrow blasts < 5%; absence of blasts with Auer rods; absence of extramedullary disease; and no hematologic recovery required. In certain embodiments, the response is a relapse. Relapse, in some examples (*e.g.*, AML), can be defined to include bone marrow blasts < 5%; absence of blasts with Auer rods; absence of extramedullary disease; and no hematologic recovery required. In some embodiments, the response is progressive disease (PD). Progressive disease can be defined as at least a 20% increase in the number of circulating tumor cells (CTC) or a mononuclear blood cells (MNBC), taking as reference the smallest number on study (this includes the baseline number if that is the smallest) and an absolute increase of at least 1, at least 2, at least 3, at least 4, at least 5, at least 6, at least 7, at least 8, at least 9, at least 10, at least 11, at least 12, at least 13, at least 14, at least 15, at least 16, at least 17, at least 18, at least 19, at least 20, at least 30, at least 40, at least 50, or at least 100 or more circulating tumor cells (CTC) or a mononuclear blood cells (MNBC). The appearance of one or more new lesions can also be considered as progression. In some embodiments, the disease can be stable disease (SD). Stable disease can be characterized by neither sufficient decrease in liquid cancer cell number to qualify for PR nor sufficient increase to qualify for PD, taking as reference the smallest number of CTCs and/or MNBCs while on study. In certain embodiments, the response is a pathological complete response. A pathological complete response, e.g., as determined by a pathologist following examination of tissue removed at the time of surgery or biopsy, generally refers to an absence of histological evidence of invasiveand/or non-invasive liquid cancer cells in the surgical specimen.

COMBINATION TREATMENT

[00319] Also provided herein are combination therapies for the treatment of a liquid cancer which involve the administration of the peptidomimetic macrocycles disclosed herein in combination with one or more additional therapies to a subject with liquid cancer determined to lack a p53 deactivating mutation and/or express wild type p53. In a specific embodiment, presented herein are combination therapies for the treatment of liquid cancer which involve the administration of an effective amount of the peptidomimetic macrocycles in combination with an effective amount of another therapy to a subject with a liquid cancer

determined to lack a p53 deactivating mutation and/or with a liquid cancer expressing wild type p53.

[00320] As used herein, the term "in combination," refers, in the context of the administration of the peptidomimetic macrocycles, to the administration of the peptidomimetic macrocycles prior to, concurrently with, or subsequent to the administration of one or more additional therapies (e.g., agents, surgery, or radiation) for use in treating liquid cancer. The use of the term "in combination" does not restrict the order in which the peptidomimetic macrocycles and one or more additional therapies are administered to a subject. In specific embodiments, the interval of time between the administration of the peptidomimetic macrocycles and the administration of one or more additional therapies can be about 1- about 5 minutes, about 1- about 30 minutes, about 30 minutes to about 60 minutes, about 1 hour, about 1- about 2 hours, about 2- about 6 hours, about 2- about 12 hours, about 12- about 24 hours, about 1- about 2 days, about 2 days, about 3 days, about 4 days, about 5 days, about 6 days, about 7 days, about 1 week, about 2 weeks, about 3 weeks, about 4 weeks, about 5 weeks, about 6 weeks, about 7 weeks, about 8 weeks, about 9 weeks, about 10 weeks, about 15 weeks, about 20 weeks, about 26 weeks, about 52 weeks, about 11- about 15 weeks, about 15- about 20 weeks, about 20- about 30 weeks, about 30- about 40 weeks, about 40- about 50 weeks, about 1 month, about 2 months, about 3 months, about 4 months, about 5 months, about 6 months, about 7 months, about 8 months, about 9 months, about 10 months, about 11 months, about 12 months, about 1 year, about 2 years, or any period of time in between. In certain embodiments, the peptidomimetic macrocycles and one or more additional therapies are administered less than 1 day, less than 1 week, less than 2 weeks, less than 3 weeks, less than 4 weeks, less than one month, less than 2 months, less than 3 months, less than 6 months, less than 1 year, less than 2 years, or less than 5 years apart.

[00321] In some embodiments, the combination therapies provided herein involve administering of the peptidomimetic macrocycles 1-2 times a week, once every week, once every 2 weeks, once every 3 weeks, once every 4 weeks, once every 5 weeks, once every 6 weeks, once every 7 weeks or once every 8 weeks and administering one or more additional therapies once a week, once every 2 weeks, once every 3 weeks, once every 4 weeks, once every month, once every 2 months (e.g., approximately 8 weeks), once every 3 months (e.g., approximately 12 weeks), or once every 4 months (e.g., approximately 16 weeks). In certain embodiments, the peptidomimetic macrocycles and one or more additional therapies are cyclically administered to a subject. Cycling therapy involves the administration of the

peptidomimetic macrocycles compounds for a period of time, followed by the administration of one or more additional therapies for a period of time, and repeating this sequential administration. In certain embodiments, cycling therapy can also include a period of rest where the peptidomimetic macrocycles or the additional therapy is not administered for a period of time (e.g., 2 days, 3 days, 4 days, 5 days, 6 days, 7 days, 1 week, 2 weeks, 3 weeks, 4 weeks, 5 weeks, 10 weeks, 20 weeks, 1 month, 2 months, 3 months, 4 months, 5 months, 6 months, 7 months, 8 months, 9 months, 10 months, 11 months, 12 months, 2 years, or 3 years). In an embodiment, the number of cycles administered is from 1 to 12 cycles, from 2 to 10 cycles, or from 2 to 8 cycles.

[00322] In some embodiments, the methods for treating liquid cancer provided herein comprise administering the peptidomimetic macrocycles as a single agent for a period of time prior to administering the peptidomimetic macrocycles in combination with an additional therapy. In certain embodiments, the methods for treating cancer provided herein comprise administering an additional therapy alone for a period of time prior to administering the peptidomimetic macrocycles in combination with the additional therapy.

[00323] In some embodiments, the administration of the peptidomimetic macrocycles and one or more additional therapies in accordance with the methods presented herein have an additive effect relative the administration of the peptidomimetic macrocycles or said one or more additional therapies alone. In some embodiments, the administration of the peptidomimetic macrocycles and one or more additional therapies in accordance with the methods presented herein have a synergistic effect relative to the administration of the peptidomimetic macrocycles or said one or more additional therapies alone.

[00324] As used herein, the term "synergistic," refers to the effect of the administration of the peptidomimetic macrocycles in combination with one or more additional therapies (e.g., agents), which combination is more effective than the additive effects of any two or more single therapies (e.g., agents). In a specific embodiment, a synergistic effect of a combination therapy permits the use of lower dosages (e.g., sub-optimal doses) of the peptidomimetic macrocycles or an additional therapy and/or less frequent administration of the peptidomimetic macrocycles or an additional therapy to a subject. In certain embodiments, the ability to utilize lower dosages of the peptidomimetic macrocycles or of an additional therapy and/or to administer the peptidomimetic macrocycles or said additional therapy less frequently reduces the toxicity associated with the administration of the peptidomimetic macrocycles or of said additional therapy, respectively, to a subject without reducing the efficacy of the peptidomimetic macrocycles or of said additional therapy,

respectively, in the treatment of liquid cancer. In some embodiments, a synergistic effect results in improved efficacy of the peptidomimetic macrocycles and each of said additional therapies in treating cancer. In some embodiments, a synergistic effect of a combination of the peptidomimetic macrocycles and one or more additional therapies avoids or reduces adverse or unwanted side effects associated with the use of any single therapy.

[00325] The combination of the peptidomimetic macrocycles and one or more additional therapies can be administered to a subject in the same pharmaceutical composition. Alternatively, the peptidomimetic macrocycles and one or more additional therapies can be administered concurrently to a subject in separate pharmaceutical compositions. The peptidomimetic macrocycles and one or more additional therapies can be administered sequentially to a subject in separate pharmaceutical compositions. The peptidomimetic macrocycles compounds and one or more additional therapies can also be administered to a subject by the same or different routes of administration.

[00326] The combination therapies provided herein involve administering to a subject to in need thereof the peptidomimetic macrocycles in combination with conventional, or known, therapies for treating cancer. Other therapies for cancer or a condition associated therewith are aimed at controlling or relieving one or more symptoms. Accordingly, in some embodiments, the combination therapies provided herein involve administering to a subject to in need thereof a pain reliever, or other therapies aimed at alleviating or controlling one or more symptoms associated with or a condition associated therewith.

[00327] Non-limiting specific examples of anti-cancer agents that can be used in combination with the peptidomimetic macrocycles include: a hormonal agent (e.g., aromatase inhibitor, selective estrogen receptor modulator (SERM), and estrogen receptor antagonist), chemotherapeutic agent (e.g., microtubule disassembly blocker, antimetabolite, topoisomerase inhibitor, and DNA crosslinker or damaging agent), anti-antigenic agent (e.g., VEGF antagonist, receptor antagonist, integrin antagonist, vascular targeting agent (VTA)/vascular disrupting agent (VDA)), radiation therapy, and conventional surgery.

[00328] Non-limiting examples of hormonal agents that can be used in combination with the peptidomimetic macrocycles include aromatase inhibitors, SERMs, and estrogen receptor antagonists. Hormonal agents that are aromatase inhibitors can be steroidal or no steroidal. Non-limiting examples of no steroidal hormonal agents include letrozole, anastrozole, aminoglutethimide, fadrozole, and vorozole. Non-limiting examples of steroidal hormonal agents include aromasin (exemestane), formestane, and testolactone. Non-limiting examples of hormonal agents that are SERMs include tamoxifen (branded/marketed as

Nolvadex®), afimoxifene, arzoxifene, bazedoxifene, clomifene, femarelle, lasofoxifene, ormeloxifene, raloxifene, and toremifene. Non-limiting examples of hormonal agents that are estrogen receptor antagonists include fulvestrant. Other hormonal agents include but are not limited to abiraterone and lonaprisan.

[00329] Non-limiting examples of chemotherapeutic agents that can be used in combination with of peptidomimetic macrocycles include microtubule disassembly blocker, antimetabolite, topoisomerase inhibitor, and DNA crosslinker or damaging agent. Chemotherapeutic agents that are microtubule disassembly blockers include, but are not limited to, taxanes (e.g., paclitaxel (branded/marketed as TAXOL®), docetaxel, abraxane, larotaxel, ortataxel, and tesetaxel); epothilones (e.g., ixabepilone); and vinca alkaloids (e.g., vinorelbine, vinblastine, vindesine, and vincristine (branded/marketed as ONCOVIN®)).

[00330] Chemotherapeutic agents that are antimetabolites include, but are not limited to, folate anitmetabolites (e.g., methotrexate, aminopterin, pemetrexed, raltitrexed); purine antimetabolites (e.g., cladribine, clofarabine, fludarabine, mercaptopurine, pentostatin, thioguanine); pyrimidine antimetabolites (e.g., 5-fluorouracil, capcitabine, gemcitabine (GEMZAR®), cytarabine, decitabine, floxuridine, tegafur); and deoxyribonucleotide antimetabolites (e.g., hydroxyurea).

[00331] Chemotherapeutic agents that are topoisomerase inhibitors include, but are not limited to, class I (camptotheca) topoisomerase inhibitors (e.g., topotecan (branded/marketed as HYCAMTIN®) irinotecan, rubitecan, and belotecan); class II (podophyllum) topoisomerase inhibitors (e.g., etoposide or VP-16, and teniposide); anthracyclines (e.g., doxorubicin, epirubicin, Doxil, aclarubicin, amrubicin, daunorubicin, idarubicin, pirarubicin, valrubicin, and zorubicin); and anthracenediones (e.g., mitoxantrone, and pixantrone).

[00332] Chemotherapeutic agents that are DNA crosslinkers (or DNA damaging agents) include, but are not limited to, alkylating agents (e.g., cyclophosphamide, mechlorethamine, ifosfamide (branded/marketed as IFEX®), trofosfamide, chlorambucil, melphalan, prednimustine, bendamustine, uramustine, estramustine, carmustine (branded/marketed as BiCNU®), lomustine, semustine, fotemustine, nimustine, ranimustine, streptozocin, busulfan, mannosulfan, treosulfan, carboquone, N,N′N′-triethylenethiophosphoramide, triaziquone, triethylenemelamine); alkylating-like agents (e.g., carboplatin (branded/marketed as PARAPLATIN®), cisplatin, oxaliplatin, nedaplatin, triplatin tetranitrate, satraplatin, picoplatin); nonclassical DNA crosslinkers (e.g., procarbazine, dacarbazine, temozolomide (branded/marketed as TEMODAR®), altretamine,

mitobronitol); and intercalating agents (e.g., actinomycin, bleomycin, mitomycin, and plicamycin).

[00333] Non-limiting examples of other therapies that can be administered to a subject in combination with the peptidomimetic macrocycles include: (1) a statin such as lovostatin (e.g., branded/marketed as MEVACOR®); (2) an mTOR inhibitor such as sirolimus which is also known as Rapamycin (e.g., branded/marketed as RAPAMUNE®), temsirolimus (e.g., branded/marketed as TORISEL®), evorolimus (e.g., branded/marketed as AFINITOR®), and deforolimus; (3) a farnesyltransferase inhibitor agent such as tipifarnib; (4) an antifibrotic agent such as pirfenidone; (5) a pegylated interferon such as PEG-interferon alfa-2b; (6) a CNS stimulant such as methylphenidate (branded/marketed as RITALIN®); (7) a HER-2 antagonist such as anti-HER-2 antibody (e.g., trastuzumab) and kinase inhibitor (e.g., lapatinib); (8) an IGF-1 antagonist such as an anti-IGF-1 antibody (e.g., AVE1642 and IMC-A11) or an IGF-1 kinase inhibitor; (9) EGFR/HER-1 antagonist such as an anti-EGFR antibody (e.g., cetuximab, panitumamab) or EGFR kinase inhibitor (e.g., erlotinib; gefitinib); (10) SRC antagonist such as bosutinib; (11) cyclin dependent kinase (CDK) inhibitor such as seliciclib; (12) Janus kinase 2 inhibitor such as lestaurtinib; (13) proteasome inhibitor such as bortezomib; (14) phosphodiesterase inhibitor such as anagrelide; (15) inosine monophosphate dehydrogenase inhibitor such as tiazofurine; (16) lipoxygenase inhibitor such as masoprocol; (17) endothelin antagonist; (18) retinoid receptor antagonist such as tretinoin or alitretinoin; (19) immune modulator such as lenalidomide, pomalidomide, or thalidomide; (20) kinase (e.g., tyrosine kinase) inhibitor such as imatinib, dasatinib, erlotinib, nilotinib, gefitinib, sorafenib, sunitinib, lapatinib, or TG100801; (21) non-steroidal anti-inflammatory agent such as celecoxib (branded/marketed as CELEBREX®); (22) human granulocyte colony-stimulating factor (G-CSF) such as filgrastim (branded/marketed as NEUPOGEN®); (23) folinic acid or leucovorin calcium; (24) integrin antagonist such as an integrin $\alpha5\beta1$-antagonist (e.g., JSM6427); (25) nuclear factor kappa beta (NF-$\kappa\beta$) antagonist such as OT-551, which is also an anti-oxidant. (26) hedgehog inhibitor such as CUR61414, cyclopamine, GDC-0449, and anti-hedgehog antibody; (27) histone deacetylase (HDAC) inhibitor such as SAHA (also known as vorinostat (branded/marketed as ZOLINZA)), PCI-24781, SB939, CHR-3996, CRA-024781, ITF2357, JNJ-26481585, or PCI-24781; (28) retinoid such as isotretinoin (e.g., branded/marketed as ACCUTANE®); (29) hepatocyte growth factor/scatter factor (HGF/SF) antagonist such as HGF/SF monoclonal antibody (e.g., AMG 102); (30) synthetic chemical such as antineoplaston; (31) anti-diabetic such as rosaiglitazone (e.g., branded/marketed as AVANDIA®); (32) antimalarial and amebicidal drug such as

chloroquine (e.g., branded/marketed as ARALEN®); (33) synthetic bradykinin such as RMP-7; (34) platelet-derived growth factor receptor inhibitor such as SU-101; (35) receptor tyrosine kinase inhibitorsof Flk-1/KDR/VEGFR2, FGFR1 and PDGFR beta such as SU5416 and SU6668; (36) anti-inflammatory agent such as sulfasalazine (e.g., branded/marketed as AZULFIDINE®); and (37) TGF-beta antisense therapy.

[00334] In some embodiments the peptidomimetic macrocycles disclosed herein can inhibit one or more transporter enzymes (e.g., OATP1B1, OATP1B3, BSEP) at concentrations that can be clinically relevant. Therefore the peptidomimetic macrocycles disclosed herein can interact with medications that are predominantly cleared by hepatobiliary transporters. In particular, methotrexate and statins (e.g., atorvastatin, fluvastatin lovastatin, pitavastatin pravastatin, rosuvastatin and simvastatin) can not be dosed within 48 h, 36 h, 24 h, or 12 h ((for example within 24 h) of the administration of the peptidomimetic macrocycles disclosed herein. Examples of medications that can be affected by co-administration with peptidomimetic macrocycles disclosed herein are listed below. In various embodiments one or more of the medications selected from Table 1 is not dosed within 48 h, 36 h, 24 h, or 12 h (for example within 24 h) of the administration of the peptidomimetic macrocycles disclosed herein.

[00335] **Table 2***:* Exemple medications that can be affected by co-administration with peptidomimetic macrocycles disclosed herein.

Medication	Therapeutic Area
Irinotecan	Oncology
Bosentan	Pulmonary artery hypertension
Caspofungin	Antifungal
Methotrexate	Oncology & rheumatology
Repaglinide	Diabetes mellitus
Atorvastatin	Hypercholesterolemia
Cerivastatin	Hypercholesterolemia
Fluvastatin	Hypercholesterolemia
Lovastatin	Hypercholesterolemia
Pitavastatin	Hypercholesterolemia
Pravastatin	Hypercholesterolemia
Rosuvastatin	Hypercholesterolemia

Simvastatin	Hypercholesterolemia

Biological Samples

[00336] 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 biopsy methods provided herein, swabbing, scraping, phlebotomy, or any other suitable method.

Methods of detecting wild type p53 and/or p53 mutations

[00337] 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.

[00338] 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.

[00339] 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).

[00340] 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.

[00341] 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).

[00342] 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.

[00343] 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.

[00344] 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.

[00345] 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.

[00346] 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.

[00347] 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.

[00348] 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.

[00349] 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.

[00350] 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.

[00351] 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.

[00352] 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.

[00353] DNA nanoball uses rolling circle replication to amplify DNA into nanoballs. Unchained sequencing by ligation of the nanoballs reveals the DNA sequence.

[00354] 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.

[00355] 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.

[00356] 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).

[00357] 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.

[00358] 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.

[00359] 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.

[00360] 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.

[00361] 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.

[00362] 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 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.

[00363] 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).

[00364] 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.

[00365] 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.

[00366] 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.

EXAMPLES

Example 1: Peptidomimetic macrocycles

[00367] 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.

[00368] 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).

[00369] 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.

[00370] The following protocol was used in the synthesis of single alkyne-crosslinked peptidomimetic macrocycles, including SP665. Fully protected resin-bound peptides were synthesized on a Rink amide MBHA resin (loading 0.62 mmol/g) on a 0.1 mmol scale. Deprotection of the temporary Fmoc group was achieved by 2 × 20 min treatments of the resin bound peptide with 25% (v/v) piperidine in NMP. After extensive flow washing with NMP and dichloromethane, coupling of each successive amino acid was achieved with 1 × 60 min incubation with the appropriate preactivated Fmoc-amino acid derivative. All protected amino acids (1 mmol) were dissolved in NMP and activated with HCTU (1 mmol) and DIEA (1 mmol) prior to transfer of the coupling solution to the deprotected resin-bound peptide.

After coupling was completed, the resin was extensively flow washed in preparation for the next deprotection/coupling cycle. Acetylation of the amino terminus was carried out in the presence of acetic anhydride/DIEA in NMP /NMM. The LC-MS analysis of a cleaved and deprotected sample obtained from an aliquot of the fully assembled resin-bound peptide was accomplished in order to verifying the completion of each coupling. In a typical example, the peptide resin (0.1 mmol) was washed with DCM. Resin was loaded into a microwave vial. The vessel was evacuated and purged with nitrogen. Molybdenumhexacarbonyl (0.01 eq, Sigma Aldrich 199959) was added. Anhydrous chlorobenzene was added to the reaction vessel. Then 2-fluorophenol (1eq, Sigma Aldrich F12804) was added. The reaction was then loaded into the microwave and held at 130°C for 10 minutes. Reaction can need to be pushed a subsequent time for completion. The alkyne metathesized resin-bound peptides were deprotected and cleaved from the solid support by treatment with TFA/H_2O/TIS (94/3/3 v/v) for 3 h at room temperature. After filtration of the resin the TFA solution was precipitated in cold diethyl ether and centrifuged to yield the desired product as a solid. The crude product was purified by preparative HPLC.

[00371] Table 3 shows a list of peptidomimetic macrocycles prepared.

Table 3

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

SP	Sequence	Isomer	Exact Mass	Found Mass	Calc (M+1)/1	Calc (M+2)/2	Calc (M+3)/3
SP28	Ac-DLTF$r8HHWHQL$RRLV-NH2		2190.23	731.15	2191.24	1096.12	731.08
SP29	Ac-HHTF$r8HHWHQL$AAML-NH2		2098.08	700.43	2099.09	1050.05	700.37
SP30	Ac-F$r8HHWHQL$RRDCha-NH2		1917.06	959.96	1918.07	959.54	640.03
SP31	Ac-F$r8HHWHQL$HRFV-NH2		1876.02	938.65	1877.03	939.02	626.35
SP32	Ac-HLTF$r8HHWHQL$AAhLA-NH2		2028.12	677.2	2029.13	1015.07	677.05
SP33	Ac-DLTF$r8HHWHQL$RRChgl-NH2		2230.26	1115.89	2231.27	1116.14	744.43
SP34	Ac-DLTF$r8HHWHQL$RRChgl-NH2	iso2	2230.26	1115.96	2231.27	1116.14	744.43
SP35	Ac-HHTF$r8HHWHQL$AAChav-NH2		2106.14	1053.95	2107.15	1054.08	703.05
SP36	Ac-F$r8HHWHQL$RRDa-NH2		1834.99	918.3	1836	918.5	612.67
SP37	Ac-F$r8HHWHQL$HRAibG-NH2		1771.95	886.77	1772.96	886.98	591.66
SP38	Ac-F$r8AYWAQL$HHNleL-NH2		1730.97	866.57	1731.98	866.49	578
SP39	Ac-F$r8AYWSAL$HQANle-NH2		1638.89	820.54	1639.9	820.45	547.3
SP40	Ac-F$r8AYWVQL$QHChgl-NH2		1776.01	889.44	1777.02	889.01	593.01
SP41	Ac-F$r8AYWTAL$QQNlev-NH2		1671.94	836.97	1672.95	836.98	558.32
SP42	Ac-F$r8AYWYQL$HAibAa-NH2		1686.89	844.52	1687.9	844.45	563.3
SP43	Ac-LTF$r8AYWAQL$HHLa-NH2		1903.05	952.27	1904.06	952.53	635.36
SP44	Ac-LTF$r8AYWAQL$HHLa-NH2	iso2	1903.05	952.27	1904.06	952.53	635.36
SP45	Ac-LTF$r8AYWAQL$HQNlev-NH2		1922.08	962.48	1923.09	962.05	641.7
SP46	Ac-LTF$r8AYWAQL$HQNlev-NH2	iso2	1922.08	962.4	1923.09	962.05	641.7
SP47	Ac-LTF$r8AYWAQL$QQMl-NH2		1945.05	973.95	1946.06	973.53	649.36
SP48	Ac-LTF$r8AYWAQL$QQMl-NH2	iso2	1945.05	973.88	1946.06	973.53	649.36
SP49	Ac-LTF$r8AYWAQL$HAibhLV-NH2		1893.09	948.31	1894.1	947.55	632.04
SP50	Ac-LTF$r8AYWAQL$AHFA-NH2		1871.01	937.4	1872.02	936.51	624.68
SP51	Ac-HLTF$r8HHWHQL$AANlel-NH2		2056.15	1028.79	2057.16	1029.08	686.39
SP52	Ac-DLTF$r8HHWHQL$RRLa-NH2		2162.2	721.82	2163.21	1082.11	721.74
SP53	Ac-HHTF$r8HHWHQL$AAMv-NH2		2084.07	1042.92	2085.08	1043.04	695.7
SP54	Ac-F$r8HHWHQL$RRDA-NH2		1834.99	612.74	1836	918.5	612.67
SP55	Ac-F$r8HHWHQL$HRFCha-NH2		1930.06	966.47	1931.07	966.04	644.36
SP56	Ac-F$r8AYWEAL$AA-NHAm		1443.82	1445.71	1444.83	722.92	482.28
SP57	Ac-F$r8AYWEAL$AA-NHiAm		1443.82	723.13	1444.83	722.92	482.28
SP58	Ac-F$r8AYWEAL$AA-NHnPr3Ph		1491.82	747.3	1492.83	746.92	498.28
SP59	Ac-F$r8AYWEAL$AA-NHnBu33Me		1457.83	1458.94	1458.84	729.92	486.95
SP60	Ac-F$r8AYWEAL$AA-NHnPr		1415.79	709.28	1416.8	708.9	472.94
SP61	Ac-F$r8AYWEAL$AA-NHnEt2Ch		1483.85	1485.77	1484.86	742.93	495.62
SP62	Ac-F$r8AYWEAL$AA-NHnEt2Cp		1469.83	1470.78	1470.84	735.92	490.95
SP63	Ac-F$r8AYWEAL$AA-NHHex		1457.83	730.19	1458.84	729.92	486.95
SP64	Ac-LTF$r8AYWAQL$AAIA-NH2		1771.01	885.81	1772.02	886.51	591.34
SP65	Ac-LTF$r8AYWAQL$AAIA-NH2	iso2	1771.01	866.8	1772.02	886.51	591.34
SP66	Ac-LTF$r8AYWAAL$AAMA-NH2		1731.94	867.08	1732.95	866.98	578.32
SP67	Ac-LTF$r8AYWAAL$AAMA-NH2	iso2	1731.94	867.28	1732.95	866.98	578.32
SP68	Ac-LTF$r8AYWAQL$AANleA-NH2		1771.01	867.1	1772.02	886.51	591.34
SP69	Ac-LTF$r8AYWAQL$AANleA-NH2	iso2	1771.01	886.89	1772.02	886.51	591.34
SP70	Ac-LTF$r8AYWAQL$AAIa-NH2		1771.01	886.8	1772.02	886.51	591.34
SP71	Ac-LTF$r8AYWAQL$AAIa-NH2	iso2	1771.01	887.09	1772.02	886.51	591.34
SP72	Ac-LTF$r8AYWAAL$AAMa-NH2		1731.94	867.17	1732.95	866.98	578.32
SP73	Ac-LTF$r8AYWAAL$AAMa-NH2	iso2	1731.94	867.37	1732.95	866.98	578.32
SP74	Ac-LTF$r8AYWAQL$AANlea-NH2		1771.01	887.08	1772.02	886.51	591.34
SP75	Ac-LTF$r8AYWAQL$AANlea-NH2	iso2	1771.01	887.08	1772.02	886.51	591.34
SP76	Ac-LTF$r8AYWAAL$AAIv-NH2		1742.02	872.37	1743.03	872.02	581.68
SP77	Ac-LTF$r8AYWAAL$AAIv-NH2	iso2	1742.02	872.74	1743.03	872.02	581.68
SP78	Ac-LTF$r8AYWAQL$AAMv-NH2		1817	910.02	1818.01	909.51	606.67
SP79	Ac-LTF$r8AYWAAL$AANlev-NH2		1742.02	872.37	1743.03	872.02	581.68
SP80	Ac-LTF$r8AYWAAL$AANlev-NH2	iso2	1742.02	872.28	1743.03	872.02	581.68
SP81	Ac-LTF$r8AYWAQL$AAIl-NH2		1813.05	907.81	1814.06	907.53	605.36
SP82	Ac-LTF$r8AYWAQL$AAIl-NH2	iso2	1813.05	907.81	1814.06	907.53	605.36
SP83	Ac-LTF$r8AYWAAL$AAMl-NH2		1773.99	887.37	1775	888	592.34

SP	Sequence	Isomer	Exact Mass	Found Mass	Calc (M+1)/1	Calc (M+2)/2	Calc (M+3)/3
SP84	Ac-LTF$r8AYWAQL$AANlel-NH2		1813.05	907.61	1814.06	907.53	605.36
SP85	Ac-LTF$r8AYWAQL$AANlel-NH2	iso2	1813.05	907.71	1814.06	907.53	605.36
SP86	Ac-F$r8AYWEAL$AAMA-NH2		1575.82	789.02	1576.83	788.92	526.28
SP87	Ac-F$r8AYWEAL$AANleA-NH2		1557.86	780.14	1558.87	779.94	520.29
SP88	Ac-F$r8AYWEAL$AAIa-NH2		1557.86	780.33	1558.87	779.94	520.29
SP89	Ac-F$r8AYWEAL$AAMa-NH2		1575.82	789.3	1576.83	788.92	526.28
SP90	Ac-F$r8AYWEAL$AANlea-NH2		1557.86	779.4	1558.87	779.94	520.29
SP91	Ac-F$r8AYWEAL$AAIv-NH2		1585.89	794.29	1586.9	793.95	529.64
SP92	Ac-F$r8AYWEAL$AAMv-NH2		1603.85	803.08	1604.86	802.93	535.62
SP93	Ac-F$r8AYWEAL$AANlev-NH2		1585.89	793.46	1586.9	793.95	529.64
SP94	Ac-F$r8AYWEAL$AAIl-NH2		1599.91	800.49	1600.92	800.96	534.31
SP95	Ac-F$r8AYWEAL$AAMl-NH2		1617.86	809.44	1618.87	809.94	540.29
SP96	Ac-F$r8AYWEAL$AANlel-NH2		1599.91	801.7	1600.92	800.96	534.31
SP97	Ac-F$r8AYWEAL$AANlel-NH2	iso2	1599.91	801.42	1600.92	800.96	534.31
SP98	Ac-LTF$r8AY6clWAQL$SAA-NH2		1707.88	855.72	1708.89	854.95	570.3
SP99	Ac-LTF$r8AY6clWAQL$SAA-NH2	iso2	1707.88	855.35	1708.89	854.95	570.3
SP100	Ac-WTF$r8FYWSQL$AVAa-NH2		1922.01	962.21	1923.02	962.01	641.68
SP101	Ac-WTF$r8FYWSQL$AVAa-NH2	iso2	1922.01	962.49	1923.02	962.01	641.68
SP102	Ac-WTF$r8VYWSQL$AVA-NH2		1802.98	902.72	1803.99	902.5	602
SP103	Ac-WTF$r8VYWSQL$AVA-NH2	iso2	1802.98	903	1803.99	902.5	602
SP104	Ac-WTF$r8FYWSQL$SAAa-NH2		1909.98	956.47	1910.99	956	637.67
SP105	Ac-WTF$r8FYWSQL$SAAa-NH2	iso2	1909.98	956.47	1910.99	956	637.67
SP106	Ac-WTF$r8VYWSQL$AVAaa-NH2		1945.05	974.15	1946.06	973.53	649.36
SP107	Ac-WTF$r8VYWSQL$AVAaa-NH2	iso2	1945.05	973.78	1946.06	973.53	649.36
SP108	Ac-LTF$r8AYWAQL$AVG-NH2		1671.94	837.52	1672.95	836.98	558.32
SP109	Ac-LTF$r8AYWAQL$AVG-NH2	iso2	1671.94	837.21	1672.95	836.98	558.32
SP110	Ac-LTF$r8AYWAQL$AVQ-NH2		1742.98	872.74	1743.99	872.5	582
SP111	Ac-LTF$r8AYWAQL$AVQ-NH2	iso2	1742.98	872.74	1743.99	872.5	582
SP112	Ac-LTF$r8AYWAQL$SAa-NH2		1673.92	838.23	1674.93	837.97	558.98
SP113	Ac-LTF$r8AYWAQL$SAa-NH2	iso2	1673.92	838.32	1674.93	837.97	558.98
SP114	Ac-LTF$r8AYWAQhL$SAA-NH2		1687.93	844.37	1688.94	844.97	563.65
SP115	Ac-LTF$r8AYWAQhL$SAA-NH2	iso2	1687.93	844.81	1688.94	844.97	563.65
SP116	Ac-LTF$r8AYWEQLStSA$-NH2		1826	905.27	1827.01	914.01	609.67
SP117	Ac-LTF$r8AYWAQL$SLA-NH2		1715.97	858.48	1716.98	858.99	573
SP118	Ac-LTF$r8AYWAQL$SLA-NH2	iso2	1715.97	858.87	1716.98	858.99	573
SP119	Ac-LTF$r8AYWAQL$SWA-NH2		1788.96	895.21	1789.97	895.49	597.33
SP120	Ac-LTF$r8AYWAQL$SWA-NH2	iso2	1788.96	895.28	1789.97	895.49	597.33
SP121	Ac-LTF$r8AYWAQL$SVS-NH2		1717.94	859.84	1718.95	859.98	573.65
SP122	Ac-LTF$r8AYWAQL$SAS-NH2		1689.91	845.85	1690.92	845.96	564.31
SP123	Ac-LTF$r8AYWAQL$SVG-NH2		1687.93	844.81	1688.94	844.97	563.65
SP124	Ac-ETF$r8VYWAQL$SAa-NH2		1717.91	859.76	1718.92	859.96	573.64
SP125	Ac-ETF$r8VYWAQL$SAA-NH2		1717.91	859.84	1718.92	859.96	573.64
SP126	Ac-ETF$r8VYWAQL$SVA-NH2		1745.94	873.82	1746.95	873.98	582.99
SP127	Ac-ETF$r8VYWAQL$SLA-NH2		1759.96	880.85	1760.97	880.99	587.66
SP128	Ac-ETF$r8VYWAQL$SWA-NH2		1832.95	917.34	1833.96	917.48	611.99
SP129	Ac-ETF$r8KYWAQL$SWA-NH2		1861.98	931.92	1862.99	932	621.67
SP130	Ac-ETF$r8VYWAQL$SVS-NH2		1761.93	881.89	1762.94	881.97	588.32
SP131	Ac-ETF$r8VYWAQL$SAS-NH2		1733.9	867.83	1734.91	867.96	578.97
SP132	Ac-ETF$r8VYWAQL$SVG-NH2		1731.92	866.87	1732.93	866.97	578.31
SP133	Ac-LTF$r8VYWAQL$SSa-NH2		1717.94	859.47	1718.95	859.98	573.65
SP134	Ac-ETF$r8VYWAQL$SSa-NH2		1733.9	867.83	1734.91	867.96	578.97
SP135	Ac-LTF$r8VYWAQL$SNa-NH2		1744.96	873.38	1745.97	873.49	582.66
SP136	Ac-ETF$r8VYWAQL$SNa-NH2		1760.91	881.3	1761.92	881.46	587.98
SP137	Ac-LTF$r8VYWAQL$SAa-NH2		1701.95	851.84	1702.96	851.98	568.32
SP138	Ac-LTF$r8VYWAQL$SVA-NH2		1729.98	865.53	1730.99	866	577.67
SP139	Ac-LTF$r8VYWAQL$SVA-NH2	iso2	1729.98	865.9	1730.99	866	577.67

SP	Sequence	Isomer	Exact Mass	Found Mass	Calc (M+1)/1	Calc (M+2)/2	Calc (M+3)/3
SP140	Ac-LTF$r8VYWAQL$SWA-NH2		1816.99	909.42	1818	909.5	606.67
SP141	Ac-LTF$r8VYWAQL$SVS-NH2		1745.98	873.9	1746.99	874	583
SP142	Ac-LTF$r8VYWAQL$SVS-NH2	iso2	1745.98	873.9	1746.99	874	583
SP143	Ac-LTF$r8VYWAQL$SAS-NH2		1717.94	859.84	1718.95	859.98	573.65
SP144	Ac-LTF$r8VYWAQL$SAS-NH2	iso2	1717.94	859.91	1718.95	859.98	573.65
SP145	Ac-LTF$r8VYWAQL$SVG-NH2		1715.97	858.87	1716.98	858.99	573
SP146	Ac-LTF$r8VYWAQL$SVG-NH2	iso2	1715.97	858.87	1716.98	858.99	573
SP147	Ac-LTF$r8EYWAQCha$SAA-NH2		1771.96	886.85	1772.97	886.99	591.66
SP148	Ac-LTF$r8EYWAQCha$SAA-NH2	iso2	1771.96	886.85	1772.97	886.99	591.66
SP149	Ac-LTF$r8EYWAQCpg$SAA-NH2		1743.92	872.86	1744.93	872.97	582.31
SP150	Ac-LTF$r8EYWAQCpg$SAA-NH2	iso2	1743.92	872.86	1744.93	872.97	582.31
SP151	Ac-LTF$r8EYWAQF$SAA-NH2		1765.91	883.44	1766.92	883.96	589.64
SP152	Ac-LTF$r8EYWAQF$SAA-NH2	iso2	1765.91	883.89	1766.92	883.96	589.64
SP153	Ac-LTF$r8EYWAQCba$SAA-NH2		1743.92	872.42	1744.93	872.97	582.31
SP154	Ac-LTF$r8EYWAQCba$SAA-NH2	iso2	1743.92	873.39	1744.93	872.97	582.31
SP155	Ac-LTF3Cl$r8EYWAQL$SAA-NH2		1765.89	883.89	1766.9	883.95	589.64
SP156	Ac-LTF3Cl$r8EYWAQL$SAA-NH2	iso2	1765.89	883.96	1766.9	883.95	589.64
SP157	Ac-LTF34F2$r8EYWAQL$SAA-NH2		1767.91	884.48	1768.92	884.96	590.31
SP158	Ac-LTF34F2$r8EYWAQL$SAA-NH2	iso2	1767.91	884.48	1768.92	884.96	590.31
SP159	Ac-LTF34F2$r8EYWAQhL$SAA-NH2		1781.92	891.44	1782.93	891.97	594.98
SP160	Ac-LTF34F2$r8EYWAQhL$SAA-NH2	iso2	1781.92	891.88	1782.93	891.97	594.98
SP161	Ac-ETF$r8EYWAQL$SAA-NH2		1747.88	874.34	1748.89	874.95	583.63
SP162	Ac-LTF$r8AYWVQL$SAA-NH2		1701.95	851.4	1702.96	851.98	568.32
SP163	Ac-LTF$r8AHWAQL$SAA-NH2		1647.91	824.83	1648.92	824.96	550.31
SP164	Ac-LTF$r8AEWAQL$SAA-NH2		1639.9	820.39	1640.91	820.96	547.64
SP165	Ac-LTF$r8ASWAQL$SAA-NH2		1597.89	799.38	1598.9	799.95	533.64
SP166	Ac-LTF$r8AEWAQL$SAA-NH2	iso2	1639.9	820.39	1640.91	820.96	547.64
SP167	Ac-LTF$r8ASWAQL$SAA-NH2	iso2	1597.89	800.31	1598.9	799.95	533.64
SP168	Ac-LTF$r8AF4coohWAQL$SAA-NH2		1701.91	851.4	1702.92	851.96	568.31
SP169	Ac-LTF$r8AF4coohWAQL$SAA-NH2	iso2	1701.91	851.4	1702.92	851.96	568.31
SP170	Ac-LTF$r8AHWAQL$AAIa-NH2		1745	874.13	1746.01	873.51	582.67
SP171	Ac-ITF$r8FYWAQL$AAIa-NH2		1847.04	923.92	1848.05	924.53	616.69
SP172	Ac-ITF$r8EHWAQL$AAIa-NH2		1803.01	903.17	1804.02	902.51	602.01
SP173	Ac-ITF$r8EHWAQL$AAIa-NH2	iso2	1803.01	903.17	1804.02	902.51	602.01
SP174	Ac-ETF$r8EHWAQL$AAIa-NH2		1818.97	910.76	1819.98	910.49	607.33
SP175	Ac-ETF$r8EHWAQL$AAIa-NH2	iso2	1818.97	910.85	1819.98	910.49	607.33
SP176	Ac-LTF$r8AHWVQL$AAIa-NH2		1773.03	888.09	1774.04	887.52	592.02
SP177	Ac-ITF$r8FYWVQL$AAIa-NH2		1875.07	939.16	1876.08	938.54	626.03
SP178	Ac-ITF$r8EYWVQL$AAIa-NH2		1857.04	929.83	1858.05	929.53	620.02
SP179	Ac-ITF$r8EHWVQL$AAIa-NH2		1831.04	916.86	1832.05	916.53	611.35
SP180	Ac-LTF$r8AEWAQL$AAIa-NH2		1736.99	869.87	1738	869.5	580
SP181	Ac-LTF$r8AF4coohWAQL$AAIa-NH2		1799	900.17	1800.01	900.51	600.67
SP182	Ac-LTF$r8AF4coohWAQL$AAIa-NH2	iso2	1799	900.24	1800.01	900.51	600.67
SP183	Ac-LTF$r8AHWAQL$AHFA-NH2		1845.01	923.89	1846.02	923.51	616.01
SP184	Ac-ITF$r8FYWAQL$AHFA-NH2		1947.05	975.05	1948.06	974.53	650.02
SP185	Ac-ITF$r8FYWAQL$AHFA-NH2	iso2	1947.05	976.07	1948.06	974.53	650.02
SP186	Ac-ITF$r8FHWAQL$AEFA-NH2		1913.02	958.12	1914.03	957.52	638.68
SP187	Ac-ITF$r8FHWAQL$AEFA-NH2	iso2	1913.02	957.86	1914.03	957.52	638.68
SP188	Ac-ITF$r8EHWAQL$AHFA-NH2		1903.01	952.94	1904.02	952.51	635.34
SP189	Ac-ITF$r8EHWAQL$AHFA-NH2	iso2	1903.01	953.87	1904.02	952.51	635.34
SP190	Ac-LTF$r8AHWVQL$AHFA-NH2		1873.04	937.86	1874.05	937.53	625.35
SP191	Ac-ITF$r8FYWVQL$AHFA-NH2		1975.08	988.83	1976.09	988.55	659.37
SP192	Ac-ITF$r8EYWVQL$AHFA-NH2		1957.05	979.35	1958.06	979.53	653.36
SP193	Ac-ITF$r8EHWVQL$AHFA-NH2		1931.05	967	1932.06	966.53	644.69
SP194	Ac-ITF$r8EHWVQL$AHFA-NH2	iso2	1931.05	967.93	1932.06	966.53	644.69
SP195	Ac-ETF$r8EYWAAL$SAA-NH2		1690.86	845.85	1691.87	846.44	564.63

SP	Sequence	Isomer	Exact Mass	Found Mass	Calc (M+1)/1	Calc (M+2)/2	Calc (M+3)/3
SP196	Ac-LTF$r8AYWVAL$SAA-NH2		1644.93	824.08	1645.94	823.47	549.32
SP197	Ac-LTF$r8AHWAAL$SAA-NH2		1590.89	796.88	1591.9	796.45	531.3
SP198	Ac-LTF$r8AEWAAL$SAA-NH2		1582.88	791.9	1583.89	792.45	528.63
SP199	Ac-LTF$r8AEWAAL$SAA-NH2	iso2	1582.88	791.9	1583.89	792.45	528.63
SP200	Ac-LTF$r8ASWAAL$SAA-NH2		1540.87	770.74	1541.88	771.44	514.63
SP201	Ac-LTF$r8ASWAAL$SAA-NH2	iso2	1540.87	770.88	1541.88	771.44	514.63
SP202	Ac-LTF$r8AYWAAL$AAIa-NH2		1713.99	857.39	1715	858	572.34
SP203	Ac-LTF$r8AYWAAL$AAIa-NH2	iso2	1713.99	857.84	1715	858	572.34
SP204	Ac-LTF$r8AYWAAL$AHFA-NH2		1813.99	907.86	1815	908	605.67
SP205	Ac-LTF$r8EHWAQL$AHIa-NH2		1869.03	936.1	1870.04	935.52	624.02
SP206	Ac-LTF$r8EHWAQL$AHIa-NH2	iso2	1869.03	937.03	1870.04	935.52	624.02
SP207	Ac-LTF$r8AHWAQL$AHIa-NH2		1811.03	906.87	1812.04	906.52	604.68
SP208	Ac-LTF$r8EYWAQL$AHIa-NH2		1895.04	949.15	1896.05	948.53	632.69
SP209	Ac-LTF$r8AYWAQL$AAFa-NH2		1804.99	903.2	1806	903.5	602.67
SP210	Ac-LTF$r8AYWAQL$AAFa-NH2	iso2	1804.99	903.28	1806	903.5	602.67
SP211	Ac-LTF$r8AYWAQL$AAWa-NH2		1844	922.81	1845.01	923.01	615.67
SP212	Ac-LTF$r8AYWAQL$AAVa-NH2		1756.99	878.86	1758	879.5	586.67
SP213	Ac-LTF$r8AYWAQL$AAVa-NH2	iso2	1756.99	879.3	1758	879.5	586.67
SP214	Ac-LTF$r8AYWAQL$AALa-NH2		1771.01	886.26	1772.02	886.51	591.34
SP215	Ac-LTF$r8AYWAQL$AALa-NH2	iso2	1771.01	886.33	1772.02	886.51	591.34
SP216	Ac-LTF$r8EYWAQL$AAIa-NH2		1829.01	914.89	1830.02	915.51	610.68
SP217	Ac-LTF$r8EYWAQL$AAIa-NH2	iso2	1829.01	915.34	1830.02	915.51	610.68
SP218	Ac-LTF$r8EYWAQL$AAFa-NH2		1863	932.87	1864.01	932.51	622.01
SP219	Ac-LTF$r8EYWAQL$AAFa-NH2	iso2	1863	932.87	1864.01	932.51	622.01
SP220	Ac-LTF$r8EYWAQL$AAVa-NH2		1815	908.23	1816.01	908.51	606.01
SP221	Ac-LTF$r8EYWAQL$AAVa-NH2	iso2	1815	908.31	1816.01	908.51	606.01
SP222	Ac-LTF$r8EHWAQL$AAIa-NH2		1803.01	903.17	1804.02	902.51	602.01
SP223	Ac-LTF$r8EHWAQL$AAIa-NH2	iso2	1803.01	902.8	1804.02	902.51	602.01
SP224	Ac-LTF$r8EHWAQL$AAWa-NH2		1876	939.34	1877.01	939.01	626.34
SP225	Ac-LTF$r8EHWAQL$AAWa-NH2	iso2	1876	939.62	1877.01	939.01	626.34
SP226	Ac-LTF$r8EHWAQL$AALa-NH2		1803.01	902.8	1804.02	902.51	602.01
SP227	Ac-LTF$r8EHWAQL$AALa-NH2	iso2	1803.01	902.9	1804.02	902.51	602.01
SP228	Ac-ETF$r8EHWVQL$AALa-NH2		1847	924.82	1848.01	924.51	616.67
SP229	Ac-LTF$r8AYWAQL$AAAa-NH2		1728.96	865.89	1729.97	865.49	577.33
SP230	Ac-LTF$r8AYWAQL$AAAa-NH2	iso2	1728.96	865.89	1729.97	865.49	577.33
SP231	Ac-LTF$r8AYWAQL$AAAibA-NH2		1742.98	872.83	1743.99	872.5	582
SP232	Ac-LTF$r8AYWAQL$AAAibA-NH2	iso2	1742.98	872.92	1743.99	872.5	582
SP233	Ac-LTF$r8AYWAQL$AAAAa-NH2		1800	901.42	1801.01	901.01	601.01
SP234	Ac-LTF$r5AYWAQL$s8AAIa-NH2		1771.01	887.17	1772.02	886.51	591.34
SP235	Ac-LTF$r5AYWAQL$s8SAA-NH2		1673.92	838.33	1674.93	837.97	558.98
SP236	Ac-LTF$r8AYWAQCba$AANleA-NH2		1783.01	892.64	1784.02	892.51	595.34
SP237	Ac-ETF$r8AYWAQCba$AANleA-NH2		1798.97	900.59	1799.98	900.49	600.66
SP238	Ac-LTF$r8EYWAQCba$AANleA-NH2		1841.01	922.05	1842.02	921.51	614.68
SP239	Ac-LTF$r8AYWAQCba$AWNleA-NH2		1898.05	950.46	1899.06	950.03	633.69
SP240	Ac-ETF$r8AYWAQCba$AWNleA-NH2		1914.01	958.11	1915.02	958.01	639.01
SP241	Ac-LTF$r8EYWAQCba$AWNleA-NH2		1956.06	950.62	1957.07	979.04	653.03
SP242	Ac-LTF$r8EYWAQCba$SAFA-NH2		1890.99	946.55	1892	946.5	631.34
SP243	Ac-LTF34F2$r8EYWAQCba$SANleA-NH2		1892.99	947.57	1894	947.5	632
SP244	Ac-LTF$r8EF4coohWAQCba$SANleA-NH2		1885	943.59	1886.01	943.51	629.34
SP245	Ac-LTF$r8EYWSQCba$SANleA-NH2		1873	937.58	1874.01	937.51	625.34
SP246	Ac-LTF$r8EYWWQCba$SANleA-NH2		1972.05	987.61	1973.06	987.03	658.36
SP247	Ac-LTF$r8EYWAQCba$AAIa-NH2		1841.01	922.05	1842.02	921.51	614.68
SP248	Ac-LTF34F2$r8EYWAQCba$AAIa-NH2		1876.99	939.99	1878	939.5	626.67
SP249	Ac-LTF$r8EF4coohWAQCba$AAIa-NH2		1869.01	935.64	1870.02	935.51	624.01
SP250	Pam-ETF$r8EYWAQCba$SAA-NH2		1956.1	979.57	1957.11	979.06	653.04
SP251	Ac-LThF$r8EFWAQCba$SAA-NH2		1741.94	872.11	1742.95	871.98	581.65

SP	Sequence	Isomer	Exact Mass	Found Mass	Calc (M+1)/1	Calc (M+2)/2	Calc (M+3)/3
SP252	Ac-LTA$r8EYWAQCba$SAA-NH2		1667.89	835.4	1668.9	834.95	556.97
SP253	Ac-LTF$r8EYAAQCba$SAA-NH2		1628.88	815.61	1629.89	815.45	543.97
SP254	Ac-LTF$r8EY2NalAQCba$SAA-NH2		1754.93	879.04	1755.94	878.47	585.98
SP255	Ac-LTF$r8AYWAQCba$SAA-NH2		1685.92	844.71	1686.93	843.97	562.98
SP256	Ac-LTF$r8EYWAQCba$SAF-NH2		1819.96	911.41	1820.97	910.99	607.66
SP257	Ac-LTF$r8EYWAQCba$SAFa-NH2		1890.99	947.41	1892	946.5	631.34
SP258	Ac-LTF$r8AYWAQCba$SAF-NH2		1761.95	882.73	1762.96	881.98	588.32
SP259	Ac-LTF34F2$r8AYWAQCba$SAF-NH2		1797.93	900.87	1798.94	899.97	600.32
SP260	Ac-LTF$r8AF4coohWAQCba$SAF-NH2		1789.94	896.43	1790.95	895.98	597.65
SP261	Ac-LTF$r8EY6clWAQCba$SAF-NH2		1853.92	929.27	1854.93	927.97	618.98
SP262	Ac-LTF$r8AYWSQCba$SAF-NH2		1777.94	890.87	1778.95	889.98	593.65
SP263	Ac-LTF$r8AYWWQCba$SAF-NH2		1876.99	939.91	1878	939.5	626.67
SP264	Ac-LTF$r8AYWAQCba$AAIa-NH2		1783.01	893.19	1784.02	892.51	595.34
SP265	Ac-LTF34F2$r8AYWAQCba$AAIa-NH2		1818.99	911.23	1820	910.5	607.34
SP266	Ac-LTF$r8AY6clWAQCba$AAIa-NH2		1816.97	909.84	1817.98	909.49	606.66
SP267	Ac-LTF$r8AF4coohWAQCba$AAIa-NH2		1811	906.88	1812.01	906.51	604.67
SP268	Ac-LTF$r8EYWAQCba$AAFa-NH2		1875	938.6	1876.01	938.51	626.01
SP269	Ac-LTF$r8EYWAQCba$AAFa-NH2	iso2	1875	938.6	1876.01	938.51	626.01
SP270	Ac-ETF$r8AYWAQCba$AWNlea-NH2		1914.01	958.42	1915.02	958.01	639.01
SP271	Ac-LTF$r8EYWAQCba$AWNlea-NH2		1956.06	979.42	1957.07	979.04	653.03
SP272	Ac-ETF$r8EYWAQCba$AWNlea-NH2		1972.01	987.06	1973.02	987.01	658.34
SP273	Ac-ETF$r8EYWAQCba$AWNlea-NH2	iso2	1972.01	987.06	1973.02	987.01	658.34
SP274	Ac-LTF$r8AYWAQCba$SAFa-NH2		1832.99	917.89	1834	917.5	612
SP275	Ac-LTF$r8AYWAQCba$SAFa-NH2	iso2	1832.99	918.07	1834	917.5	612
SP276	Ac-ETF$r8AYWAQL$AWNlea-NH2		1902.01	952.22	1903.02	952.01	635.01
SP277	Ac-LTF$r8EYWAQL$AWNlea-NH2		1944.06	973.5	1945.07	973.04	649.03
SP278	Ac-ETF$r8EYWAQL$AWNlea-NH2		1960.01	981.46	1961.02	981.01	654.34
SP279	Dmaac-LTF$r8EYWAQhL$SAA-NH2		1788.98	896.06	1789.99	895.5	597.33
SP280	Hexac-LTF$r8EYWAQhL$SAA-NH2		1802	902.9	1803.01	902.01	601.67
SP281	Napac-LTF$r8EYWAQhL$SAA-NH2		1871.99	937.58	1873	937	625
SP282	Decac-LTF$r8EYWAQhL$SAA-NH2		1858.06	930.55	1859.07	930.04	620.36
SP283	Admac-LTF$r8EYWAQhL$SAA-NH2		1866.03	934.07	1867.04	934.02	623.02
SP284	Tmac-LTF$r8EYWAQhL$SAA-NH2		1787.99	895.41	1789	895	597
SP285	Pam-LTF$r8EYWAQhL$SAA-NH2		1942.16	972.08	1943.17	972.09	648.39
SP286	Ac-LTF$r8AYWAQCba$AANleA-NH2	iso2	1783.01	892.64	1784.02	892.51	595.34
SP287	Ac-LTF34F2$r8EYWAQCba$AAIa-NH2	iso2	1876.99	939.62	1878	939.5	626.67
SP288	Ac-LTF34F2$r8EYWAQCba$SAA-NH2		1779.91	892.07	1780.92	890.96	594.31
SP289	Ac-LTF34F2$r8EYWAQCba$SAA-NH2	iso2	1779.91	891.61	1780.92	890.96	594.31
SP290	Ac-LTF$r8EF4coohWAQCba$SAA-NH2		1771.92	887.54	1772.93	886.97	591.65
SP291	Ac-LTF$r8EF4coohWAQCba$SAA-NH2	iso2	1771.92	887.63	1772.93	886.97	591.65
SP292	Ac-LTF$r8EYWSQCba$SAA-NH2		1759.92	881.9	1760.93	880.97	587.65
SP293	Ac-LTF$r8EYWSQCba$SAA-NH2	iso2	1759.92	881.9	1760.93	880.97	587.65
SP294	Ac-LTF$r8EYWAQhL$SAA-NH2		1745.94	875.05	1746.95	873.98	582.99
SP295	Ac-LTF$r8AYWAQhL$SAF-NH2		1763.97	884.02	1764.98	882.99	589
SP296	Ac-LTF$r8AYWAQhL$SAF-NH2	iso2	1763.97	883.56	1764.98	882.99	589
SP297	Ac-LTF34F2$r8AYWAQhL$SAA-NH2		1723.92	863.67	1724.93	862.97	575.65
SP298	Ac-LTF34F2$r8AYWAQhL$SAA-NH2	iso2	1723.92	864.04	1724.93	862.97	575.65
SP299	Ac-LTF$r8AF4coohWAQhL$SAA-NH2		1715.93	859.44	1716.94	858.97	572.98
SP300	Ac-LTF$r8AF4coohWAQhL$SAA-NH2	iso2	1715.93	859.6	1716.94	858.97	572.98
SP301	Ac-LTF$r8AYWSQhL$SAA-NH2		1703.93	853.96	1704.94	852.97	568.98
SP302	Ac-LTF$r8AYWSQhL$SAA-NH2	iso2	1703.93	853.59	1704.94	852.97	568.98
SP303	Ac-LTF$r8EYWAQL$AANleA-NH2		1829.01	915.45	1830.02	915.51	610.68
SP304	Ac-LTF34F2$r8AYWAQL$AANleA-NH2		1806.99	904.58	1808	904.5	603.34
SP305	Ac-LTF$r8AF4coohWAQL$AANleA-NH2		1799	901.6	1800.01	900.51	600.67
SP306	Ac-LTF$r8AYWSQL$AANleA-NH2		1787	894.75	1788.01	894.51	596.67
SP307	Ac-LTF34F2$r8AYWAQhL$AANleA-NH2		1821	911.79	1822.01	911.51	608.01

SP	Sequence	Isomer	Exact Mass	Found Mass	Calc (M+1)/1	Calc (M+2)/2	Calc (M+3)/3
SP308	Ac-LTF34F2$r8AYWAQhL$AANleA-NH2	iso2	1821	912.61	1822.01	911.51	608.01
SP309	Ac-LTF$r8AF4coohWAQhL$AANleA-NH2		1813.02	907.95	1814.03	907.52	605.35
SP310	Ac-LTF$r8AF4coohWAQhL$AANleA-NH2	iso2	1813.02	908.54	1814.03	907.52	605.35
SP311	Ac-LTF$r8AYWSQhL$AANleA-NH2		1801.02	901.84	1802.03	901.52	601.35
SP312	Ac-LTF$r8AYWSQhL$AANleA-NH2	iso2	1801.02	902.62	1802.03	901.52	601.35
SP313	Ac-LTF$r8AYWAQhL$AAAAa-NH2		1814.01	908.63	1815.02	908.01	605.68
SP314	Ac-LTF$r8AYWAQhL$AAAAa-NH2	iso2	1814.01	908.34	1815.02	908.01	605.68
SP315	Ac-LTF$r8AYWAQL$AAAAAa-NH2		1871.04	936.94	1872.05	936.53	624.69
SP316	Ac-LTF$r8AYWAQL$AAAAAAa-NH2	iso2	1942.07	972.5	1943.08	972.04	648.37
SP317	Ac-LTF$r8AYWAQL$AAAAAAa-NH2	iso1	1942.07	972.5	1943.08	972.04	648.37
SP318	Ac-LTF$r8EYWAQhL$AANleA-NH2		1843.03	922.54	1844.04	922.52	615.35
SP319	Ac-AATF$r8AYWAQL$AANleA-NH2		1800	901.39	1801.01	901.01	601.01
SP320	Ac-LTF$r8AYWAQL$AANleAA-NH2		1842.04	922.45	1843.05	922.03	615.02
SP321	Ac-ALTF$r8AYWAQL$AANleAA-NH2		1913.08	957.94	1914.09	957.55	638.7
SP322	Ac-LTF$r8AYWAQCba$AANleAA-NH2		1854.04	928.43	1855.05	928.03	619.02
SP323	Ac-LTF$r8AYWAQhL$AANleAA-NH2		1856.06	929.4	1857.07	929.04	619.69
SP324	Ac-LTF$r8EYWAQCba$SAAA-NH2		1814.96	909.37	1815.97	908.49	605.99
SP325	Ac-LTF$r8EYWAQCba$SAAA-NH2	iso2	1814.96	909.37	1815.97	908.49	605.99
SP326	Ac-LTF$r8EYWAQCba$SAAAA-NH2		1886	944.61	1887.01	944.01	629.67
SP327	Ac-LTF$r8EYWAQCba$SAAAA-NH2	iso2	1886	944.61	1887.01	944.01	629.67
SP328	Ac-ALTF$r8EYWAQCba$SAA-NH2		1814.96	909.09	1815.97	908.49	605.99
SP329	Ac-ALTF$r8EYWAQCba$SAAA-NH2		1886	944.61	1887.01	944.01	629.67
SP330	Ac-ALTF$r8EYWAQCba$SAA-NH2	iso2	1814.96	909.09	1815.97	908.49	605.99
SP331	Ac-LTF$r8EYWAQL$AAAAAa-NH2	iso2	1929.04	966.08	1930.05	965.53	644.02
SP332	Ac-LTF$r8EY6clWAQCba$SAA-NH2		1777.89	890.78	1778.9	889.95	593.64
SP333	Ac-LTF$r8EF4cooh6clWAQCba$SANleA-NH2		1918.96	961.27	1919.97	960.49	640.66
SP334	Ac-LTF$r8EF4cooh6clWAQCba$SANleA-NH2	iso2	1918.96	961.27	1919.97	960.49	640.66
SP335	Ac-LTF$r8EF4cooh6clWAQCba$AAIa-NH2		1902.97	953.03	1903.98	952.49	635.33
SP336	Ac-LTF$r8EF4cooh6clWAQCba$AAIa-NH2	iso2	1902.97	953.13	1903.98	952.49	635.33
SP337	Ac-LTF$r8AY6clWAQL$AAAAAa-NH2		1905	954.61	1906.01	953.51	636.01
SP338	Ac-LTF$r8AY6clWAQL$AAAAAa-NH2	iso2	1905	954.9	1906.01	953.51	636.01
SP339	Ac-F$r8AY6clWEAL$AAAAAAa-NH2		1762.89	883.01	1763.9	882.45	588.64
SP340	Ac-ETF$r8EYWAQL$AAAAAa-NH2		1945	974.31	1946.01	973.51	649.34
SP341	Ac-ETF$r8EYWAQL$AAAAAa-NH2	iso2	1945	974.49	1946.01	973.51	649.34
SP342	Ac-LTF$r8EYWAQL$AAAAAAa-NH2		2000.08	1001.6	2001.09	1001.05	667.7
SP343	Ac-LTF$r8EYWAQL$AAAAAAa-NH2	iso2	2000.08	1001.6	2001.09	1001.05	667.7
SP344	Ac-LTF$r8AYWAQL$AANleAAa-NH2		1913.08	958.58	1914.09	957.55	638.7
SP345	Ac-LTF$r8AYWAQL$AANleAAa-NH2	iso2	1913.08	958.58	1914.09	957.55	638.7
SP346	Ac-LTF$r8EYWAQCba$AAAAAa-NH2		1941.04	972.55	1942.05	971.53	648.02
SP347	Ac-LTF$r8EYWAQCba$AAAAAa-NH2	iso2	1941.04	972.55	1942.05	971.53	648.02
SP348	Ac-LTF$r8EF4coohWAQCba$AAAAAa-NH2		1969.04	986.33	1970.05	985.53	657.35
SP349	Ac-LTF$r8EF4coohWAQCba$AAAAAa-NH2	iso2	1969.04	986.06	1970.05	985.53	657.35
SP350	Ac-LTF$r8EYWSQCba$AAAAAa-NH2		1957.04	980.04	1958.05	979.53	653.35
SP351	Ac-LTF$r8EYWSQCba$AAAAAa-NH2	iso2	1957.04	980.04	1958.05	979.53	653.35
SP352	Ac-LTF$r8EYWAQCba$SAAa-NH2		1814.96	909	1815.97	908.49	605.99
SP353	Ac-LTF$r8EYWAQCba$SAAa-NH2	iso2	1814.96	909	1815.97	908.49	605.99
SP354	Ac-ALTF$r8EYWAQCba$SAAa-NH2		1886	944.52	1887.01	944.01	629.67
SP355	Ac-ALTF$r8EYWAQCba$SAAa-NH2	iso2	1886	944.98	1887.01	944.01	629.67
SP356	Ac-ALTF$r8EYWAQCba$SAAAa-NH2		1957.04	980.04	1958.05	979.53	653.35
SP357	Ac-ALTF$r8EYWAQCba$SAAAa-NH2	iso2	1957.04	980.04	1958.05	979.53	653.35
SP358	Ac-AALTF$r8EYWAQCba$SAAAa-NH2		2028.07	1016.1	2029.08	1015.04	677.03
SP359	Ac-AALTF$r8EYWAQCba$SAAAa-NH2	iso2	2028.07	1015.57	2029.08	1015.04	677.03
SP360	Ac-RTF$r8EYWAQCba$SAA-NH2		1786.94	895.03	1787.95	894.48	596.65
SP361	Ac-LRF$r8EYWAQCba$SAA-NH2		1798.98	901.51	1799.99	900.5	600.67

SP	Sequence	Isomer	Exact Mass	Found Mass	Calc (M+1)/1	Calc (M+2)/2	Calc (M+3)/3
SP362	Ac-LTF$r8EYWRQCba$SAA-NH2		1828.99	916.4	1830	915.5	610.67
SP363	Ac-LTF$r8EYWARCba$SAA-NH2		1771.97	887.63	1772.98	886.99	591.66
SP364	Ac-LTF$r8EYWAQCba$RAA-NH2		1812.99	908.08	1814	907.5	605.34
SP365	Ac-LTF$r8EYWAQCba$SRA-NH2		1828.99	916.12	1830	915.5	610.67
SP366	Ac-LTF$r8EYWAQCba$SAR-NH2		1828.99	916.12	1830	915.5	610.67
SP367	5-FAM-BaLTF$r8EYWAQCba$SAA-NH2		2131	1067.09	2132.01	1066.51	711.34
SP368	5-FAM-BaLTF$r8AYWAQL$AANleA-NH2		2158.08	1080.6	2159.09	1080.05	720.37
SP369	Ac-LAF$r8EYWAQL$AANleA-NH2		1799	901.05	1800.01	900.51	600.67
SP370	Ac-ATF$r8EYWAQL$AANleA-NH2		1786.97	895.03	1787.98	894.49	596.66
SP371	Ac-AAF$r8EYWAQL$AANleA-NH2		1756.96	880.05	1757.97	879.49	586.66
SP372	Ac-AAAF$r8EYWAQL$AANleA-NH2		1827.99	915.57	1829	915	610.34
SP373	Ac-AAAAF$r8EYWAQL$AANleA-NH2		1899.03	951.09	1900.04	950.52	634.02
SP374	Ac-AATF$r8EYWAQL$AANleA-NH2		1858	930.92	1859.01	930.01	620.34
SP375	Ac-AALTF$r8EYWAQL$AANleA-NH2		1971.09	987.17	1972.1	986.55	658.04
SP376	Ac-AAALTF$r8EYWAQL$AANleA-NH2		2042.12	1023.15	2043.13	1022.07	681.71
SP377	Ac-LTF$r8EYWAQL$AANleAA-NH2		1900.05	952.02	1901.06	951.03	634.36
SP378	Ac-ALTF$r8EYWAQL$AANleAA-NH2		1971.09	987.63	1972.1	986.55	658.04
SP379	Ac-AALTF$r8EYWAQL$AANleAA-NH2		2042.12	1022.69	2043.13	1022.07	681.71
SP380	Ac-LTF$r8EYWAQCba$AANleAA-NH2		1912.05	958.03	1913.06	957.03	638.36
SP381	Ac-LTF$r8EYWAQhL$AANleAA-NH2		1914.07	958.68	1915.08	958.04	639.03
SP382	Ac-ALTF$r8EYWAQhL$AANleAA-NH2		1985.1	994.1	1986.11	993.56	662.71
SP383	Ac-LTF$r8ANmYWAQL$AANleA-NH2		1785.02	894.11	1786.03	893.52	596.01
SP384	Ac-LTF$r8ANmYWAQL$AANleA-NH2	iso2	1785.02	894.11	1786.03	893.52	596.01
SP385	Ac-LTF$r8AYNmWAQL$AANleA-NH2		1785.02	894.11	1786.03	893.52	596.01
SP386	Ac-LTF$r8AYNmWAQL$AANleA-NH2	iso2	1785.02	894.11	1786.03	893.52	596.01
SP387	Ac-LTF$r8AYAmwAQL$AANleA-NH2		1785.02	894.01	1786.03	893.52	596.01
SP388	Ac-LTF$r8AYAmwAQL$AANleA-NH2	iso2	1785.02	894.01	1786.03	893.52	596.01
SP389	Ac-LTF$r8AYWAibQL$AANleA-NH2		1785.02	894.01	1786.03	893.52	596.01
SP390	Ac-LTF$r8AYWAibQL$AANleA-NH2	iso2	1785.02	894.01	1786.03	893.52	596.01
SP391	Ac-LTF$r8AYWAQL$AAibNleA-NH2		1785.02	894.38	1786.03	893.52	596.01
SP392	Ac-LTF$r8AYWAQL$AAibNleA-NH2	iso2	1785.02	894.38	1786.03	893.52	596.01
SP393	Ac-LTF$r8AYWAQL$AaNleA-NH2		1771.01	887.54	1772.02	886.51	591.34
SP394	Ac-LTF$r8AYWAQL$AaNleA-NH2	iso2	1771.01	887.54	1772.02	886.51	591.34
SP395	Ac-LTF$r8AYWAQL$ASarNleA-NH2		1771.01	887.35	1772.02	886.51	591.34
SP396	Ac-LTF$r8AYWAQL$ASarNleA-NH2	iso2	1771.01	887.35	1772.02	886.51	591.34
SP397	Ac-LTF$r8AYWAQL$AANleAib-NH2		1785.02	894.75	1786.03	893.52	596.01
SP398	Ac-LTF$r8AYWAQL$AANleAib-NH2	iso2	1785.02	894.75	1786.03	893.52	596.01
SP399	Ac-LTF$r8AYWAQL$AANleNmA-NH2		1785.02	894.6	1786.03	893.52	596.01
SP400	Ac-LTF$r8AYWAQL$AANleNmA-NH2	iso2	1785.02	894.6	1786.03	893.52	596.01
SP401	Ac-LTF$r8AYWAQL$AANleSar-NH2		1771.01	886.98	1772.02	886.51	591.34
SP402	Ac-LTF$r8AYWAQL$AANleSar-NH2	iso2	1771.01	886.98	1772.02	886.51	591.34
SP403	Ac-LTF$r8AYWAQL$AANleAAib-NH2		1856.06		1857.07	929.04	619.69
SP404	Ac-LTF$r8AYWAQL$AANleAAib-NH2	iso2	1856.06		1857.07	929.04	619.69
SP405	Ac-LTF$r8AYWAQL$AANleANmA-NH2		1856.06	930.37	1857.07	929.04	619.69
SP406	Ac-LTF$r8AYWAQL$AANleANmA-NH2	iso2	1856.06	930.37	1857.07	929.04	619.69
SP407	Ac-LTF$r8AYWAQL$AANleAa-NH2		1842.04	922.69	1843.05	922.03	615.02
SP408	Ac-LTF$r8AYWAQL$AANleAa-NH2	iso2	1842.04	922.69	1843.05	922.03	615.02
SP409	Ac-LTF$r8AYWAQL$AANleASar-NH2		1842.04	922.6	1843.05	922.03	615.02
SP410	Ac-LTF$r8AYWAQL$AANleASar-NH2	iso2	1842.04	922.6	1843.05	922.03	615.02
SP411	Ac-LTF$/r8AYWAQL$/AANleA-NH2		1799.04	901.14	1800.05	900.53	600.69
SP412	Ac-LTFAibAYWAQLAibAANleA-NH2		1648.9	826.02	1649.91	825.46	550.64
SP413	Ac-LTF$r8Cou4YWAQL$AANleA-NH2		1975.05	989.11	1976.06	988.53	659.36
SP414	Ac-LTF$r8Cou4YWAQL$AANleA-NH2	iso2	1975.05	989.11	1976.06	988.53	659.36
SP415	Ac-LTF$r8AYWCou4QL$AANleA-NH2		1975.05	989.11	1976.06	988.53	659.36
SP416	Ac-LTF$r8AYWAQL$Cou4ANleA-NH2		1975.05	989.57	1976.06	988.53	659.36
SP417	Ac-LTF$r8AYWAQL$Cou4ANleA-NH2	iso2	1975.05	989.57	1976.06	988.53	659.36

SP	Sequence	Isomer	Exact Mass	Found Mass	Calc (M+1)/1	Calc (M+2)/2	Calc (M+3)/3
SP418	Ac-LTF$r8AYWAQL$ACou4NleA-NH2		1975.05	989.57	1976.06	988.53	659.36
SP419	Ac-LTF$r8AYWAQL$ACou4NleA-NH2	iso2	1975.05	989.57	1976.06	988.53	659.36
SP420	Ac-LTF$r8AYWAQL$AANleA-OH		1771.99	887.63	1773	887	591.67
SP421	Ac-LTF$r8AYWAQL$AANleA-OH	iso2	1771.99	887.63	1773	887	591.67
SP422	Ac-LTF$r8AYWAQL$AANleA-NHnPr		1813.05	908.08	1814.06	907.53	605.36
SP423	Ac-LTF$r8AYWAQL$AANleA-NHnPr	iso2	1813.05	908.08	1814.06	907.53	605.36
SP424	Ac-LTF$r8AYWAQL$AANleA-NHnBu33Me		1855.1	929.17	1856.11	928.56	619.37
SP425	Ac-LTF$r8AYWAQL$AANleA-NHnBu33Me	iso2	1855.1	929.17	1856.11	928.56	619.37
SP426	Ac-LTF$r8AYWAQL$AANleA-NHHex		1855.1	929.17	1856.11	928.56	619.37
SP427	Ac-LTF$r8AYWAQL$AANleA-NHHex	iso2	1855.1	929.17	1856.11	928.56	619.37
SP428	Ac-LTA$r8AYWAQL$AANleA-NH2		1694.98	849.33	1695.99	848.5	566
SP429	Ac-LThL$r8AYWAQL$AANleA-NH2		1751.04	877.09	1752.05	876.53	584.69
SP430	Ac-LTF$r8AYAAQL$AANleA-NH2		1655.97	829.54	1656.98	828.99	553
SP431	Ac-LTF$r8AY2NalAQL$AANleA-NH2		1782.01	892.63	1783.02	892.01	595.01
SP432	Ac-LTF$r8EYWCou4QCba$SAA-NH2		1947.97	975.8	1948.98	974.99	650.33
SP433	Ac-LTF$r8EYWCou7QCba$SAA-NH2		16.03	974.9	17.04	9.02	6.35
SP434	Ac-LTF%r8EYWAQCba%SAA-NH2		1745.94	874.8	1746.95	873.98	582.99
SP435	Dmaac-LTF$r8EYWAQCba$SAA-NH2		1786.97	894.8	1787.98	894.49	596.66
SP436	Dmaac-LTF$r8AYWAQL$AAAAAa-NH2		1914.08	958.2	1915.09	958.05	639.03
SP437	Dmaac-LTF$r8AYWAQL$AAAAAa-NH2	iso2	1914.08	958.2	1915.09	958.05	639.03
SP438	Dmaac-LTF$r8EYWAQL$AAAAAa-NH2		1972.08	987.3	1973.09	987.05	658.37
SP439	Dmaac-LTF$r8EYWAQL$AAAAAa-NH2	iso2	1972.08	987.3	1973.09	987.05	658.37
SP440	Dmaac-LTF$r8EF4coohWAQCba$AAIa-NH2		1912.05	957.4	1913.06	957.03	638.36
SP441	Dmaac-LTF$r8EF4coohWAQCba$AAIa-NH2	iso2	1912.05	957.4	1913.06	957.03	638.36
SP442	Dmaac-LTF$r8AYWAQL$AANleA-NH2		1814.05	908.3	1815.06	908.03	605.69
SP443	Dmaac-LTF$r8AYWAQL$AANleA-NH2	iso2	1814.05	908.3	1815.06	908.03	605.69
SP444	Ac-LTF%r8AYWAQL%AANleA-NH2		1773.02	888.37	1774.03	887.52	592.01
SP445	Ac-LTF%r8EYWAQL%AAAAAa-NH2		1931.06	966.4	1932.07	966.54	644.69
SP446	Cou6BaLTF$r8EYWAQhL$SAA-NH2		2018.05	1009.9	2019.06	1010.03	673.69
SP447	Cou8BaLTF$r8EYWAQhL$SAA-NH2		1962.96	982.34	1963.97	982.49	655.32
SP448	Ac-LTF4I$r8EYWAQL$AAAAAa-NH2		2054.93	1028.68	2055.94	1028.47	685.98
SP449	Ac-LTF$r8EYWAQL$AAAAAa-NH2		1929.04	966.17	1930.05	965.53	644.02
SP550	Ac-LTF$r8EYWAQL$AAAAAa-OH		1930.02	966.54	1931.03	966.02	644.35
SP551	Ac-LTF$r8EYWAQL$AAAAAa-OH	iso2	1930.02	965.89	1931.03	966.02	644.35
SP552	Ac-LTF$r8EYWAEL$AAAAAa-NH2		1930.02	966.82	1931.03	966.02	644.35
SP553	Ac-LTF$r8EYWAEL$AAAAAa-NH2	iso2	1930.02	966.91	1931.03	966.02	644.35
SP554	Ac-LTF$r8EYWAEL$AAAAAa-OH		1931.01	967.28	1932.02	966.51	644.68
SP555	Ac-LTF$r8EY6clWAQL$AAAAAa-NH2		1963	983.28	1964.01	982.51	655.34
SP556	Ac-LTF$r8EF4bOH2WAQL$AAAAAa-NH2		1957.05	980.04	1958.06	979.53	653.36
SP557	Ac-AAALTF$r8EYWAQL$AAAAAa-NH2		2142.15	1072.83	2143.16	1072.08	715.06
SP558	Ac-LTF34F2$r8EYWAQL$AAAAAa-NH2		1965.02	984.3	1966.03	983.52	656.01
SP559	Ac-RTF$r8EYWAQL$AAAAAa-NH2		1972.06	987.81	1973.07	987.04	658.36
SP560	Ac-LTA$r8EYWAQL$AAAAAa-NH2		1853.01	928.33	1854.02	927.51	618.68
SP561	Ac-LTF$r8EYWAibQL$AAAAAa-NH2		1943.06	973.48	1944.07	972.54	648.69
SP562	Ac-LTF$r8EYWAQL$AAibAAAa-NH2		1943.06	973.11	1944.07	972.54	648.69
SP563	Ac-LTF$r8EYWAQL$AAAibAAa-NH2		1943.06	973.48	1944.07	972.54	648.69
SP564	Ac-LTF$r8EYWAQL$AAAAibAa-NH2		1943.06	973.48	1944.07	972.54	648.69
SP565	Ac-LTF$r8EYWAQL$AAAAAiba-NH2		1943.06	973.38	1944.07	972.54	648.69
SP566	Ac-LTF$r8EYWAQL$AAAAAiba-NH2	iso2	1943.06	973.38	1944.07	972.54	648.69
SP567	Ac-LTF$r8EYWAQL$AAAAAAib-NH2		1943.06	973.01	1944.07	972.54	648.69
SP568	Ac-LTF$r8EYWAQL$AaAAAa-NH2		1929.04	966.54	1930.05	965.53	644.02
SP569	Ac-LTF$r8EYWAQL$AAaAAa-NH2		1929.04	966.35	1930.05	965.53	644.02
SP570	Ac-LTF$r8EYWAQL$AAAaAa-NH2		1929.04	966.54	1930.05	965.53	644.02
SP571	Ac-LTF$r8EYWAQL$AAAaAa-NH2	iso2	1929.04	966.35	1930.05	965.53	644.02
SP572	Ac-LTF$r8EYWAQL$AAAAaa-NH2		1929.04	966.35	1930.05	965.53	644.02
SP573	Ac-LTF$r8EYWAQL$AAAAAA-NH2		1929.04	966.35	1930.05	965.53	644.02

SP	Sequence	Isomer	Exact Mass	Found Mass	Calc (M+1)/1	Calc (M+2)/2	Calc (M+3)/3
SP574	Ac-LTF$r8EYWAQL$ASarAAAa-NH2		1929.04	966.54	1930.05	965.53	644.02
SP575	Ac-LTF$r8EYWAQL$AASarAAa-NH2		1929.04	966.35	1930.05	965.53	644.02
SP576	Ac-LTF$r8EYWAQL$AAASarAa-NH2		1929.04	966.35	1930.05	965.53	644.02
SP577	Ac-LTF$r8EYWAQL$AAAASara-NH2		1929.04	966.35	1930.05	965.53	644.02
SP578	Ac-LTF$r8EYWAQL$AAAAASar-NH2		1929.04	966.08	1930.05	965.53	644.02
SP579	Ac-7LTF$r8EYWAQL$AAAAAa-NH2		1918.07	951.99	1919.08	960.04	640.37
SP581	Ac-TF$r8EYWAQL$AAAAAa-NH2		1815.96	929.85	1816.97	908.99	606.33
SP582	Ac-F$r8EYWAQL$AAAAAa-NH2		1714.91	930.92	1715.92	858.46	572.64
SP583	Ac-LVF$r8EYWAQL$AAAAAa-NH2		1927.06	895.12	1928.07	964.54	643.36
SP584	Ac-AAF$r8EYWAQL$AAAAAa-NH2		1856.98	859.51	1857.99	929.5	620
SP585	Ac-LTF$r8EYWAQL$AAAAa-NH2		1858	824.08	1859.01	930.01	620.34
SP586	Ac-LTF$r8EYWAQL$AAAa-NH2		1786.97	788.56	1787.98	894.49	596.66
SP587	Ac-LTF$r8EYWAQL$AAa-NH2		1715.93	1138.57	1716.94	858.97	572.98
SP588	Ac-LTF$r8EYWAQL$Aa-NH2		1644.89	1144.98	1645.9	823.45	549.3
SP589	Ac-LTF$r8EYWAQL$a-NH2		1573.85	1113.71	1574.86	787.93	525.62
SP590	Ac-LTF$r8EYWAQL$AAA-OH		1716.91	859.55	1717.92	859.46	573.31
SP591	Ac-LTF$r8EYWAQL$A-OH		1574.84	975.14	1575.85	788.43	525.95
SP592	Ac-LTF$r8EYWAQL$AAA-NH2		1715.93	904.75	1716.94	858.97	572.98
SP593	Ac-LTF$r8EYWAQCba$SAA-OH		1744.91	802.49	1745.92	873.46	582.64
SP594	Ac-LTF$r8EYWAQCba$S-OH		1602.83	913.53	1603.84	802.42	535.28
SP595	Ac-LTF$r8EYWAQCba$S-NH2		1601.85	979.58	1602.86	801.93	534.96
SP596	4-FBzl-LTF$r8EYWAQL$AAAAAa-NH2		2009.05	970.52	2010.06	1005.53	670.69
SP597	4-FBzl-LTF$r8EYWAQCba$SAA-NH2		1823.93	965.8	1824.94	912.97	608.98
SP598	Ac-LTF$r8RYWAQL$AAAAAa-NH2		1956.1	988.28	1957.11	979.06	653.04
SP599	Ac-LTF$r8HYWAQL$AAAAAa-NH2		1937.06	1003.54	1938.07	969.54	646.69
SP600	Ac-LTF$r8QYWAQL$AAAAAa-NH2		1928.06	993.92	1929.07	965.04	643.69
SP601	Ac-LTF$r8CitYWAQL$AAAAAa-NH2		1957.08	987	1958.09	979.55	653.37
SP602	Ac-LTF$r8GlaYWAQL$AAAAAa-NH2		1973.03	983	1974.04	987.52	658.68
SP603	Ac-LTF$r8F4gYWAQL$AAAAAa-NH2		2004.1	937.86	2005.11	1003.06	669.04
SP604	Ac-LTF$r82mRYWAQL$AAAAAa-NH2		1984.13	958.58	1985.14	993.07	662.38
SP605	Ac-LTF$r8ipKYWAQL$AAAAAa-NH2		1970.14	944.52	1971.15	986.08	657.72
SP606	Ac-LTF$r8F4NH2YWAQL$AAAAAa-NH2		1962.08	946	1963.09	982.05	655.03
SP607	Ac-LTF$r8EYWAAL$AAAAAa-NH2		1872.02	959.32	1873.03	937.02	625.01
SP608	Ac-LTF$r8EYWALL$AAAAAa-NH2		1914.07	980.88	1915.08	958.04	639.03
SP609	Ac-LTF$r8EYWAAibL$AAAAAa-NH2		1886.03	970.61	1887.04	944.02	629.68
SP610	Ac-LTF$r8EYWASL$AAAAAa-NH2		1888.01	980.51	1889.02	945.01	630.34
SP611	Ac-LTF$r8EYWANL$AAAAAa-NH2		1915.02	1006.41	1916.03	958.52	639.35
SP612	Ac-LTF$r8EYWACitL$AAAAAa-NH2		1958.07		1959.08	980.04	653.7
SP613	Ac-LTF$r8EYWAHL$AAAAAa-NH2		1938.04	966.24	1939.05	970.03	647.02
SP614	Ac-LTF$r8EYWARL$AAAAAa-NH2		1957.08		1958.09	979.55	653.37
SP615	Ac-LTF$r8EpYWAQL$AAAAAa-NH2		2009.01		2010.02	1005.51	670.68
SP616	Cbm-LTF$r8EYWAQCba$SAA-NH2		1590.85		1591.86	796.43	531.29
SP617	Cbm-LTF$r8EYWAQL$AAAAAa-NH2		1930.04		1931.05	966.03	644.35
SP618	Ac-LTF$r8EYWAQL$SAAAAa-NH2		1945.04	1005.11	1946.05	973.53	649.35
SP619	Ac-LTF$r8EYWAQL$AAAASa-NH2		1945.04	986.52	1946.05	973.53	649.35
SP620	Ac-LTF$r8EYWAQL$SAAASa-NH2		1961.03	993.27	1962.04	981.52	654.68
SP621	Ac-LTF$r8EYWAQTba$AAAAAa-NH2		1943.06	983.1	1944.07	972.54	648.69
SP622	Ac-LTF$r8EYWAQAdm$AAAAAa-NH2		2007.09	990.31	2008.1	1004.55	670.04
SP623	Ac-LTF$r8EYWAQCha$AAAAAa-NH2		1969.07	987.17	1970.08	985.54	657.36
SP624	Ac-LTF$r8EYWAQhCha$AAAAAa-NH2		1983.09	1026.11	1984.1	992.55	662.04
SP625	Ac-LTF$r8EYWAQF$AAAAAa-NH2		1963.02	957.01	1964.03	982.52	655.35
SP626	Ac-LTF$r8EYWAQhF$AAAAAa-NH2		1977.04	1087.81	1978.05	989.53	660.02
SP627	Ac-LTF$r8EYWAQL$AANleAAa-NH2		1971.09	933.45	1972.1	986.55	658.04
SP628	Ac-LTF$r8EYWAQAdm$AANleAAa-NH2		2049.13	1017.97	2050.14	1025.57	684.05
SP629	4-FBz-BaLTF$r8EYWAQL$AAAAAa-NH2		2080.08		2081.09	1041.05	694.37
SP630	4-FBz-BaLTF$r8EYWAQCba$SAA-NH2		1894.97		1895.98	948.49	632.66

SP	Sequence	Isomer	Exact Mass	Found Mass	Calc (M+1)/1	Calc (M+2)/2	Calc (M+3)/3
SP631	Ac-LTF$r5EYWAQL$s8AAAAAa-NH2		1929.04	1072.68	1930.05	965.53	644.02
SP632	Ac-LTF$r5EYWAQCba$s8SAA-NH2		1743.92	1107.79	1744.93	872.97	582.31
SP633	Ac-LTF$r8EYWAQL$AAhhLAAa-NH2		1999.12		2000.13	1000.57	667.38
SP634	Ac-LTF$r8EYWAQL$AAAAAAAa-NH2		2071.11		2072.12	1036.56	691.38
SP635	Ac-LTF$r8EYWAQL$AAAAAAAAa-NH2		2142.15	778.1	2143.16	1072.08	715.06
SP636	Ac-LTF$r8EYWAQL$AAAAAAAAAa-NH2		2213.19	870.53	2214.2	1107.6	738.74
SP637	Ac-LTA$r8EYAAQCba$SAA-NH2		1552.85		1553.86	777.43	518.62
SP638	Ac-LTA$r8EYAAQL$AAAAAa-NH2		1737.97	779.45	1738.98	869.99	580.33
SP639	Ac-LTF$r8EPmpWAQL$AAAAAa-NH2		2007.03	779.54	2008.04	1004.52	670.02
SP640	Ac-LTF$r8EPmpWAQCba$SAA-NH2		1821.91	838.04	1822.92	911.96	608.31
SP641	Ac-ATF$r8HYWAQL$S-NH2		1555.82	867.83	1556.83	778.92	519.61
SP642	Ac-LTF$r8HAWAQL$S-NH2		1505.84	877.91	1506.85	753.93	502.95
SP643	Ac-LTF$r8HYWAQA$S-NH2		1555.82	852.52	1556.83	778.92	519.61
SP644	Ac-LTF$r8EYWAQCba$SA-NH2		1672.89	887.18	1673.9	837.45	558.64
SP645	Ac-LTF$r8EYWAQL$SAA-NH2		1731.92	873.32	1732.93	866.97	578.31
SP646	Ac-LTF$r8HYWAQCba$SAA-NH2		1751.94	873.05	1752.95	876.98	584.99
SP647	Ac-LTF$r8SYWAQCba$SAA-NH2		1701.91	844.88	1702.92	851.96	568.31
SP648	Ac-LTF$r8RYWAQCba$SAA-NH2		1770.98	865.58	1771.99	886.5	591.33
SP649	Ac-LTF$r8KYWAQCba$SAA-NH2		1742.98	936.57	1743.99	872.5	582
SP650	Ac-LTF$r8QYWAQCba$SAA-NH2		1742.94	930.93	1743.95	872.48	581.99
SP651	Ac-LTF$r8EYWAACba$SAA-NH2		1686.9	1032.45	1687.91	844.46	563.31
SP652	Ac-LTF$r8EYWAQCba$AAA-NH2		1727.93	895.46	1728.94	864.97	576.98
SP653	Ac-LTF$r8EYWAQL$AAAAA-OH		1858.99	824.54	1860	930.5	620.67
SP654	Ac-LTF$r8EYWAQL$AAAA-OH		1787.95	894.48	1788.96	894.98	596.99
SP655	Ac-LTF$r8EYWAQL$AA-OH		1645.88	856	1646.89	823.95	549.63
SP656	Ac-LTF$r8AF4bOH2WAQL$AAAAAa-NH2						
SP657	Ac-LTF$r8AF4bOH2WAAL$AAAAAa-NH2						
SP658	Ac-LTF$r8EF4bOH2WAQCba$SAA-NH2						
SP659	Ac-LTF$r8ApYWAQL$AAAAAa-NH2						
SP660	Ac-LTF$r8ApYWAAL$AAAAAa-NH2						
SP661	Ac-LTF$r8EpYWAQCba$SAA-NH2						
SP662	Ac-LTF$rda6AYWAQL$da5AAAAAa-NH2		1974.06	934.44			
SP663	Ac-LTF$rda6EYWAQCba$da5SAA-NH2		1846.95	870.52		869.94	
SP664	Ac-LTF$rda6EYWAQL$da5AAAAAa-NH2						
SP665	Ac-LTF$ra9EYWAQL$a6AAAAAa-NH2			936.57		935.51	
SP666	Ac-LTF$ra9EYWAQL$a6AAAAAa-NH2						
SP667	Ac-LTF$ra9EYWAQCba$a6SAA-NH2						
SP668	Ac-LTA$ra9EYWAQCba$a6SAA-NH2						
SP669	5-FAM-BaLTF$ra9EYWAQCba$a6SAA-NH2						
SP670	5-FAM-BaLTF$r8EYWAQL$AAAAAa-NH2		2316.11				
SP671	5-FAM-BaLTF$/r8EYWAQL$/AAAAAa-NH2		2344.15				
SP672	5-FAM-BaLTA$r8EYWAQL$AAAAAa-NH2		2240.08				
SP673	5-FAM-BaLTF$r8AYWAQL$AAAAAa-NH2		2258.11				
SP674	5-FAM-BaATF$r8EYWAQL$AAAAAa-NH2		2274.07				
SP675	5-FAM-BaLAF$r8EYWAQL$AAAAAa-NH2		2286.1				
SP676	5-FAM-BaLTF$r8EAWAQL$AAAAAa-NH2		2224.09				
SP677	5-FAM-BaLTF$r8EYAAQL$AAAAAa-NH2		2201.07				
SP678	5-FAM-BaLTA$r8EYAAQL$AAAAAa-NH2		2125.04				
SP679	5-FAM-BaLTF$r8EYWAAL$AAAAAa-NH2		2259.09				
SP680	5-FAM-BaLTF$r8EYWAQA$AAAAAa-NH2		2274.07				
SP681	5-FAM-BaLTF$/r8EYWAQCba$/SAA-NH2		2159.03				
SP682	5-FAM-BaLTA$r8EYWAQCba$SAA-NH2		2054.97				
SP683	5-FAM-BaLTF$r8EYAAQCba$SAA-NH2		2015.96				
SP684	5-FAM-BaLTA$r8EYAAQCba$SAA-NH2		1939.92				
SP685	5-FAM-BaQSQQTF$r8NLWRLL$QN-NH2		2495.23				

SP	Sequence	Isomer	Exact Mass	Found Mass	Calc (M+1)/1	Calc (M+2)/2	Calc (M+3)/3
SP686	5-TAMRA-BaLTF$r8EYWAQCba$SAA-NH2		2186.1				
SP687	5-TAMRA-BaLTA$r8EYWAQCba$SAA-NH2		2110.07				
SP688	5-TAMRA-BaLTF$r8EYAAQCba$SAA-NH2		2071.06				
SP689	5-TAMRA-BaLTA$r8EYAAQCba$SAA-NH2		1995.03				
SP690	5-TAMRA-BaLTF$/r8EYWAQCba$/SAA-NH2		2214.13				
SP691	5-TAMRA-BaLTF$r8EYWAQL$AAAAAa-NH2		2371.22				
SP692	5-TAMRA-BaLTA$r8EYWAQL$AAAAAa-NH2		2295.19				
SP693	5-TAMRA-BaLTF$/r8EYWAQL$/AAAAAa-NH2		2399.25				
SP694	Ac-LTF$r8EYWCou7QCba$SAA-OH		1947.93				
SP695	Ac-LTF$r8EYWCou7QCba$S-OH		1805.86				
SP696	Ac-LTA$r8EYWCou7QCba$SAA-NH2		1870.91				
SP697	Ac-LTF$r8EYACou7QCba$SAA-NH2		1831.9				
SP698	Ac-LTA$r8EYACou7QCba$SAA-NH2		1755.87				
SP699	Ac-LTF$/r8EYWCou7QCba$/SAA-NH2		1974.98				
SP700	Ac-LTF$r8EYWCou7QL$AAAAAa-NH2		2132.06				
SP701	Ac-LTF$/r8EYWCou7QL$/AAAAAa-NH2		2160.09				
SP702	Ac-LTF$r8EYWCou7QL$AAAAA-OH		2062.01				
SP703	Ac-LTF$r8EYWCou7QL$AAAA-OH		1990.97				
SP704	Ac-LTF$r8EYWCou7QL$AAA-OH		1919.94				
SP705	Ac-LTF$r8EYWCou7QL$AA-OH		1848.9				
SP706	Ac-LTF$r8EYWCou7QL$A-OH		1777.86				
SP707	Ac-LTF$r8EYWAQL$AAAASa-NH2	iso2		974.4		973.53	
SP708	Ac-LTF$r8AYWAAL$AAAAAa-NH2	iso2	1814.01	908.82	1815.02	908.01	605.68
SP709	Biotin-BaLTF$r8EYWAQL$AAAAAa-NH2		2184.14	1093.64	2185.15	1093.08	729.05
SP710	Ac-LTF$r8HAWAQL$S-NH2	iso2	1505.84	754.43	1506.85	753.93	502.95
SP711	Ac-LTF$r8EYWAQCba$SA-NH2	iso2	1672.89	838.05	1673.9	837.45	558.64
SP712	Ac-LTF$r8HYWAQCba$SAA-NH2	iso2	1751.94	877.55	1752.95	876.98	584.99
SP713	Ac-LTF$r8SYWAQCba$SAA-NH2	iso2	1701.91	852.48	1702.92	851.96	568.31
SP714	Ac-LTF$r8RYWAQCba$SAA-NH2	iso2	1770.98	887.45	1771.99	886.5	591.33
SP715	Ac-LTF$r8KYWAQCba$SAA-NH2	iso2	1742.98	872.92	1743.99	872.5	582
SP716	Ac-LTF$r8EYWAQCba$AAA-NH2	iso2	1727.93	865.71	1728.94	864.97	576.98
SP717	Ac-LTF$r8EYWAQL$AAAAAaBaC-NH2		2103.09	1053.12	2104.1	1052.55	702.04
SP718	Ac-LTF$r8EYWAQL$AAAAAadPeg4C-NH2		2279.19	1141.46	2280.2	1140.6	760.74
SP719	Ac-LTA$r8AYWAAL$AAAAAa-NH2		1737.98	870.43	1738.99	870	580.33
SP720	Ac-LTF$r8AYAAAL$AAAAAa-NH2		1698.97	851	1699.98	850.49	567.33
SP721	5-FAM-BaLTF$r8AYWAAL$AAAAAa-NH2		2201.09	1101.87	2202.1	1101.55	734.7
SP722	Ac-LTA$r8AYWAQL$AAAAAa-NH2		1795	898.92	1796.01	898.51	599.34
SP723	Ac-LTF$r8AYAAQL$AAAAAa-NH2		1755.99	879.49	1757	879	586.34
SP724	Ac-LTF$rda6AYWAAL$da5AAAAAa-NH2		1807.97		1808.98	904.99	603.66
SP725	FITC-BaLTF$r8EYWAQL$AAAAAa-NH2		2347.1	1174.49	2348.11	1174.56	783.37
SP726	FITC-BaLTF$r8EYWAQCba$SAA-NH2		2161.99	1082.35	2163	1082	721.67
SP733	Ac-LTF$r8EYWAQL$EAAAAa-NH2		1987.05	995.03	1988.06	994.53	663.36
SP734	Ac-LTF$r8AYWAQL$EAAAAa-NH2		1929.04	966.35	1930.05	965.53	644.02
SP735	Ac-LTF$r8EYWAQL$AAAAAaBaKbio-NH2		2354.25	1178.47	2355.26	1178.13	785.76
SP736	Ac-LTF$r8AYWAAL$AAAAAa-NH2		1814.01	908.45	1815.02	908.01	605.68
SP737	Ac-LTF$r8AYAAAL$AAAAAa-NH2	iso2	1698.97	850.91	1699.98	850.49	567.33
SP738	Ac-LTF$r8AYAAQL$AAAAAa-NH2	iso2	1755.99	879.4	1757	879	586.34
SP739	Ac-LTF$r8EYWAQL$EAAAAa-NH2	iso2	1987.05	995.21	1988.06	994.53	663.36
SP740	Ac-LTF$r8AYWAQL$EAAAAa-NH2	iso2	1929.04	966.08	1930.05	965.53	644.02
SP741	Ac-LTF$r8EYWAQCba$SAAAAa-NH2		1957.04	980.04	1958.05	979.53	653.35
SP742	Ac-LTF$r8EYWAQLStAAA$r5AA-NH2		2023.12	1012.83	2024.13	1012.57	675.38

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

[00372] Table 3a shows a selection of peptidomimetic macrocycles.

Table 3a

SP	Sequence	Isomer	Exact Mass	Found Mass	Calc (M+1)/1	Calc (M+2)/2	Calc (M+3)/3
SP244	Ac-LTF$r8EF4coohWAQCba$SANleA-NH2		1885	943.59	1886.01	943.51	629.34
SP331	Ac-LTF$r8EYWAQL$AAAAAa-NH2	iso2	1929.04	966.08	1930.05	965.53	644.02
SP555	Ac-LTF$r8EY6clWAQL$AAAAAa-NH2		1963	983.28	1964.01	982.51	655.34
SP557	Ac-AAALTF$r8EYWAQL$AAAAAa-NH2		2142.15	1072.83	2143.16	1072.08	715.06
SP558	Ac-LTF34F2$r8EYWAQL$AAAAAa-NH2		1965.02	984.3	1966.03	983.52	656.01
SP562	Ac-LTF$r8EYWAQL$AAibAAAa-NH2		1943.06	973.11	1944.07	972.54	648.69
SP564	Ac-LTF$r8EYWAQL$AAAAibAa-NH2		1943.06	973.48	1944.07	972.54	648.69
SP566	Ac-LTF$r8EYWAQL$AAAAAiba-NH2	iso2	1943.06	973.38	1944.07	972.54	648.69
SP567	Ac-LTF$r8EYWAQL$AAAAAAib-NH2		1943.06	973.01	1944.07	972.54	648.69
SP572	Ac-LTF$r8EYWAQL$AAAAaa-NH2		1929.04	966.35	1930.05	965.53	644.02
SP573	Ac-LTF$r8EYWAQL$AAAAAA-NH2		1929.04	966.35	1930.05	965.53	644.02
SP578	Ac-LTF$r8EYWAQL$AAAAASar-NH2		1929.04	966.08	1930.05	965.53	644.02
SP551	Ac-LTF$r8EYWAQL$AAAAAa-OH	iso2	1930.02	965.89	1931.03	966.02	644.35
SP662	Ac-LTF$rda6AYWAQL$da5AAAAAa-NH2		1974.06	934.44		933.49	
SP367	5-FAM-BaLTF$r8EYWAQCba$SAA-NH2		2131	1067.09	2132.01	1066.51	711.34
SP349	Ac-LTF$r8EF4coohWAQCba$AAAAAa-NH2	iso2	1969.04	986.06	1970.05	985.53	657.35
SP347	Ac-LTF$r8EYWAQCba$AAAAAa-NH2	iso2	1941.04	972.55	1942.05	971.53	648.02

[00373] Table 3b shows a further selection of peptidomimetic macrocycles.

Table 3b

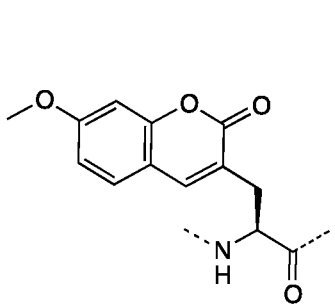
SP	Sequence	Isomer	Exact Mass	Found Mass	Calc (M+1)/1	Calc (M+2)/2	Calc (M+3)/3
SP581	Ac-TF$r8EYWAQL$AAAAAa-NH2		1815.96	929.85	1816.97	908.99	606.33
SP582	Ac-F$r8EYWAQL$AAAAAa-NH2		1714.91	930.92	1715.92	858.46	572.64
SP583	Ac-LVF$r8EYWAQL$AAAAAa-NH2		1927.06	895.12	1928.07	964.54	643.36

SP584	Ac-AAF$r8EYWAQL$AAAAAa-NH2		1856.98	859.51	1857.99	929.5	620
SP585	Ac-LTF$r8EYWAQL$AAAAa-NH2		1858	824.08	1859.01	930.01	620.34
SP586	Ac-LTF$r8EYWAQL$AAAa-NH2		1786.97	788.56	1787.98	894.49	596.66
SP587	Ac-LTF$r8EYWAQL$AAa-NH2		1715.93	1138.57	1716.94	858.97	572.98
SP588	Ac-LTF$r8EYWAQL$Aa-NH2		1644.89	1144.98	1645.9	823.45	549.3
SP589	Ac-LTF$r8EYWAQL$a-NH2		1573.85	1113.71	1574.86	787.93	525.62

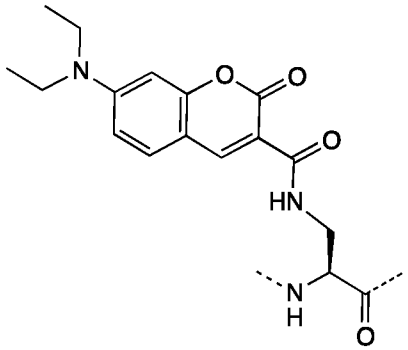
[00374] In the sequences shown above and elsewhere, the following abbreviations are used: "Nle" represents norleucine, "Aib" represents 2-aminoisobutyric acid, "Ac" represents acetyl, and "Pr" represents propionyl. Amino acids represented as "$" are alpha-Me S5-pentenyl-alanine olefin amino acids connected by an all-carbon crosslinker comprising one double bond. Amino acids represented as "$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.

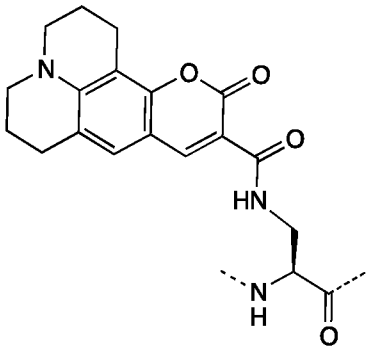
[00375] Amino acids designated as "Cit" represent citrulline. Amino acids designated as "Cou4", "Cou6", "Cou7" and "Cou8", respectively, represent the following structures:



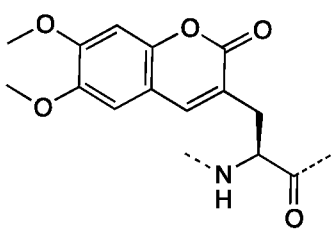
Cou



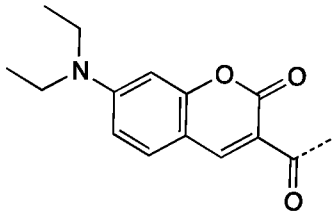
Cou2



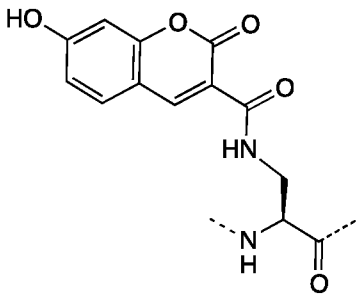
Cou3



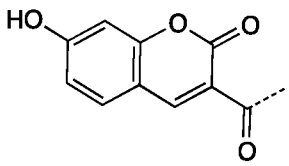
Cou4



Cou6



Cou7



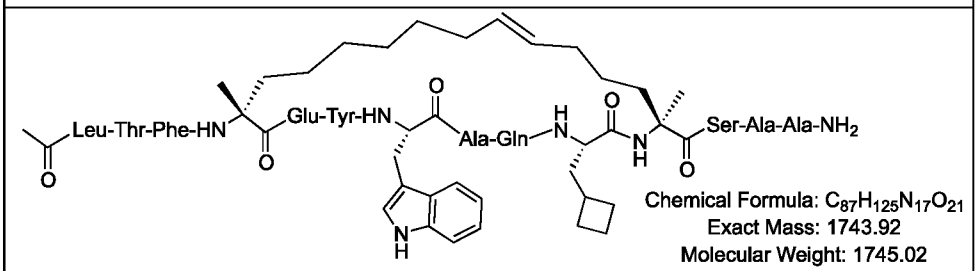
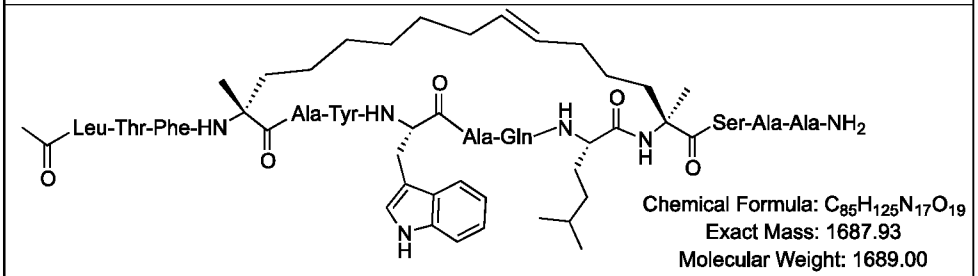
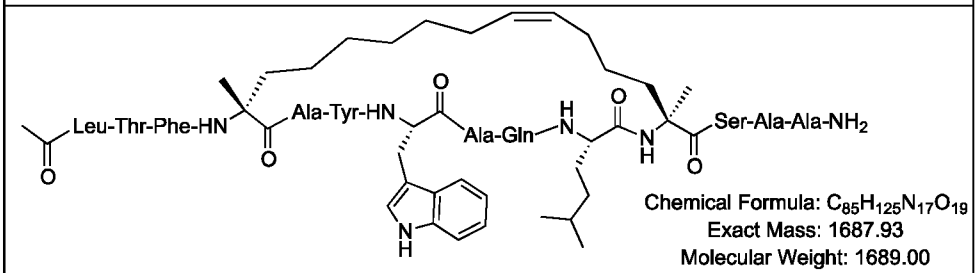
Cou8

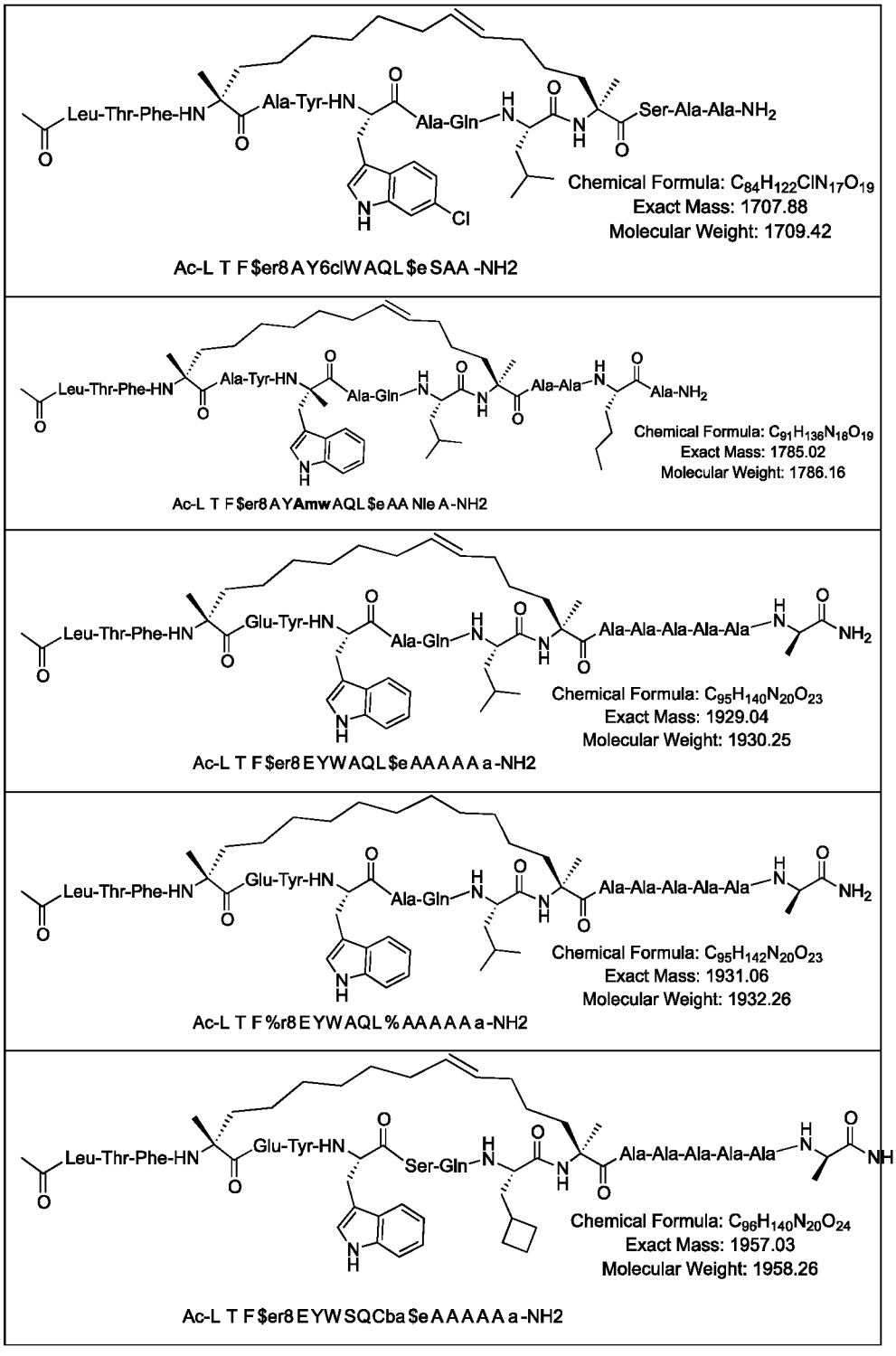
[00376] In some embodiments, a peptidomimetic macrocycle is obtained in more than one isomer, for example due to the configuration of a double bond within the structure of the

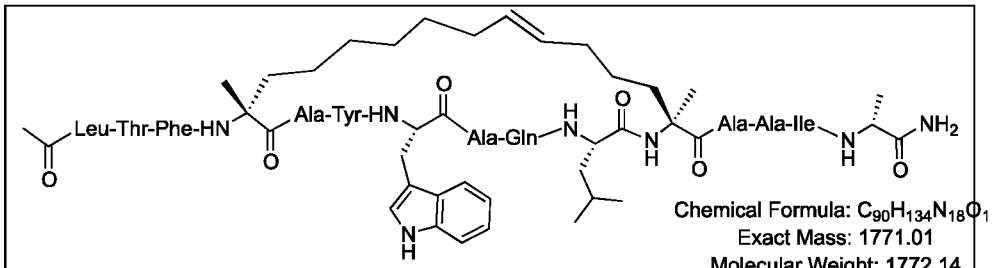
crosslinker (*E* vs *Z*). In some embodiments, such isomers can or cannot be separated by conventional chromatographic methods. In some embodiments, one isomer has improved biological properties relative to the other isomer. In one embodiment, an *E* crosslinker olefin isomer of a peptidomimetic macrocycle 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.

[00377] Table 3c shows exemple peptidomimetic macrocycles:

Table 3c

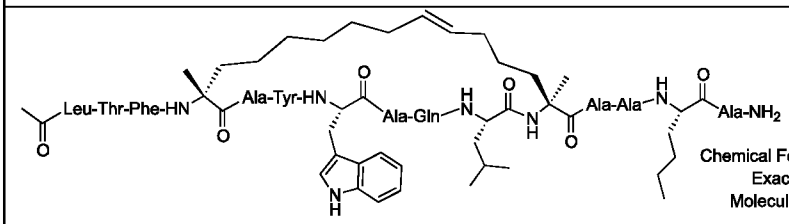
Structure
 Ac-L T F $er8 E Y W A Q Cba $e S A A -NH2
 Ac-L T F $er8 A Y W A Q hL $e S A A -NH2
 Ac-L T F $zr8 A Y W A Q hL $z S A A -NH2


Leu-Thr-Phe-HN
Ala-Tyr-HN
Ala-Gln
Ser-Ala-Ala-NH2
Cl
Chemical Formula: C84H122ClN17O19
Exact Mass: 1707.88
Molecular Weight: 1709.42
Ac-L T F $er8 A Y6cl W A Q L $e S A A -NH2
Leu-Thr-Phe-HN
Ala-Tyr-HN
Ala-Gln
Ala-Ala
Ala-NH2
Chemical Formula: C91H136N18O19
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
Leu-Thr-Phe-HN
Glu-Tyr-HN
Ala-Gln
Ala-Ala-Ala-Ala-Ala
NH2
Chemical Formula: C95H140N20O23
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
Leu-Thr-Phe-HN
Glu-Tyr-HN
Ala-Gln
Ala-Ala-Ala-Ala-Ala
NH2
Chemical Formula: C95H142N20O23
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
Leu-Thr-Phe-HN
Glu-Tyr-HN
Ser-Gln
Ala-Ala-Ala-Ala-Ala
NH
Chemical Formula: C96H140N20O24
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



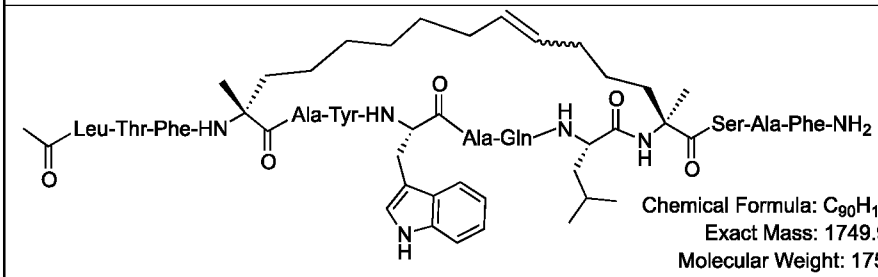
Chemical Formula: $C_{90}H_{134}N_{18}O_{1}$
Exact Mass: 1771.01
Molecular Weight: 1772.14

Ac-L T F$er8AYWAQL$eAA I a-NH2



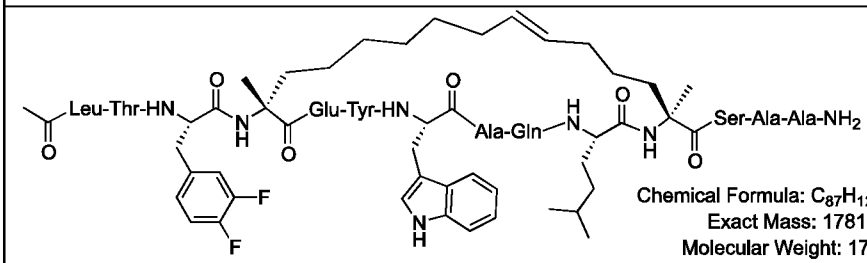
Chemical Formula: $C_{90}H_{134}N_{18}O_{19}$
Exact Mass: 1771.01
Molecular Weight: 1772.14

Ac-L T F$er8AYWAQL$eAA Nle A-NH2



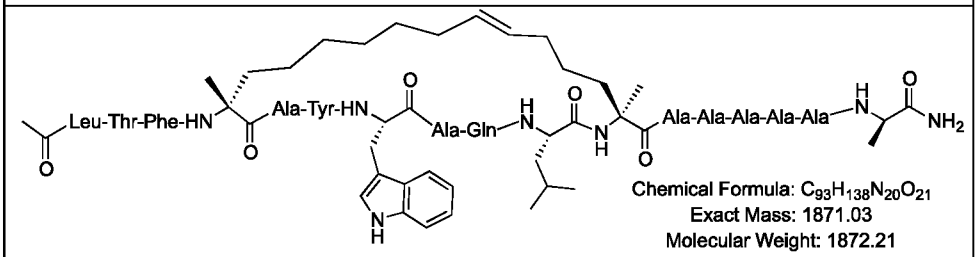
Chemical Formula: $C_{90}H_{127}N_{17}O_{19}$
Exact Mass: 1749.95
Molecular Weight: 1751.07

Ac-L T F$r8AYWAQL$SA F-NH2



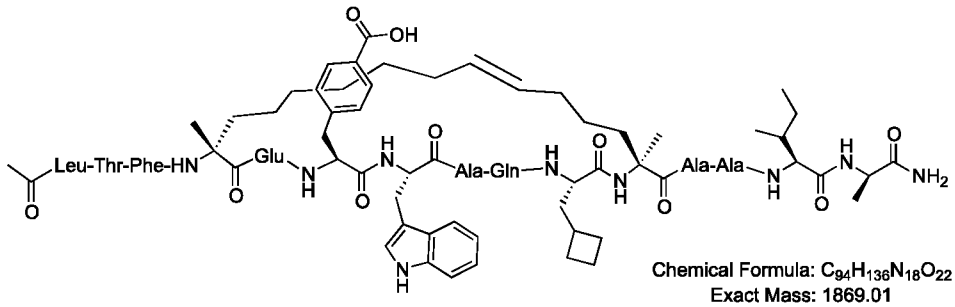
Chemical Formula: $C_{87}H_{125}F_{2}N_{17}O_{21}$
Exact Mass: 1781.92
Molecular Weight: 1783.02

Ac-L T F34F2$er8EYWAQhL$eSAA -NH2



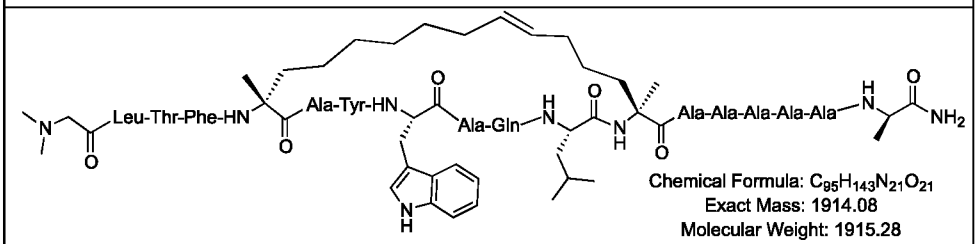
Chemical Formula: $C_{93}H_{138}N_{20}O_{21}$
Exact Mass: 1871.03
Molecular Weight: 1872.21

Ac-L T F$er8AYWAQL$eAAAAA a-NH2



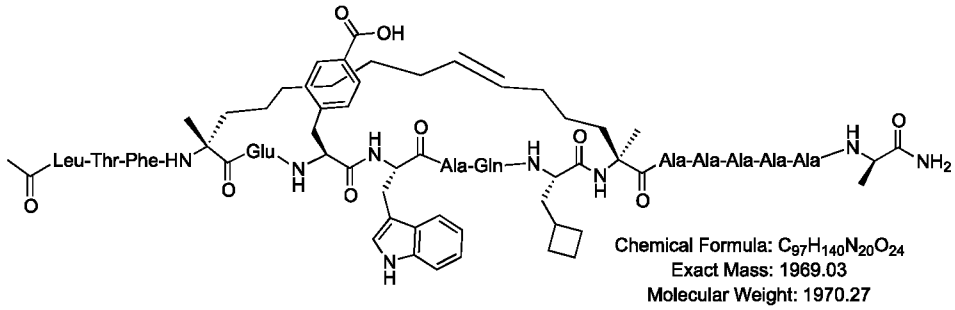
Chemical Formula: $C_{94}H_{136}N_{18}O_{22}$
Exact Mass: 1869.01
Molecular Weight: 1870.19

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



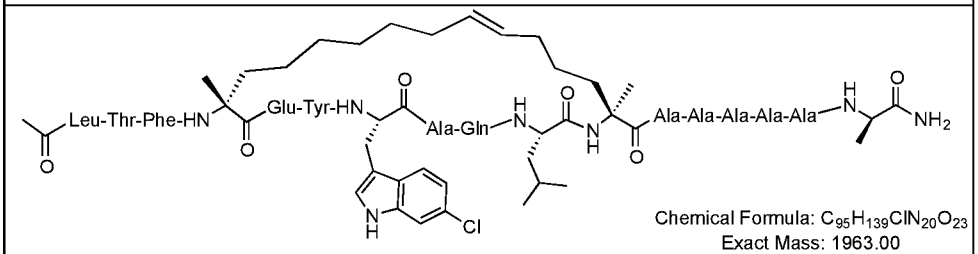
Chemical Formula: $C_{95}H_{143}N_{21}O_{21}$
Exact Mass: 1914.08
Molecular Weight: 1915.28

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



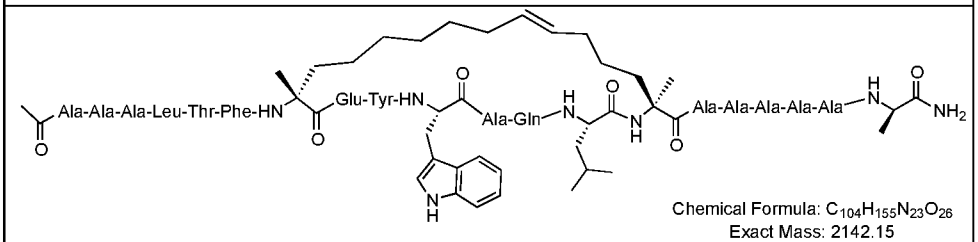
Chemical Formula: $C_{97}H_{140}N_{20}O_{24}$
Exact Mass: 1969.03
Molecular Weight: 1970.27

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



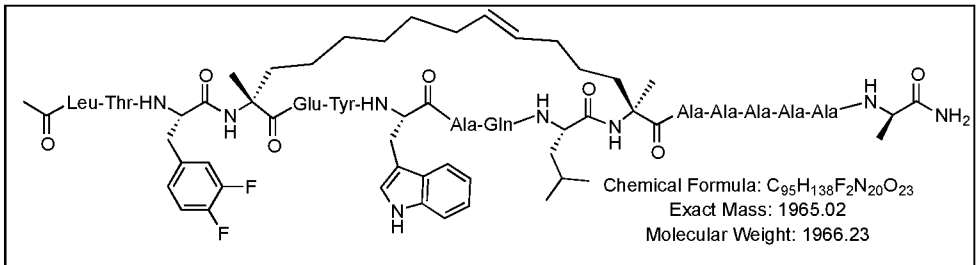
Chemical Formula: $C_{95}H_{139}ClN_{20}O_{23}$
Exact Mass: 1963.00
Molecular Weight: 1964.69

Ac-L T F $er8 E Y6cl W AQ L $e A A A A A a-NH2



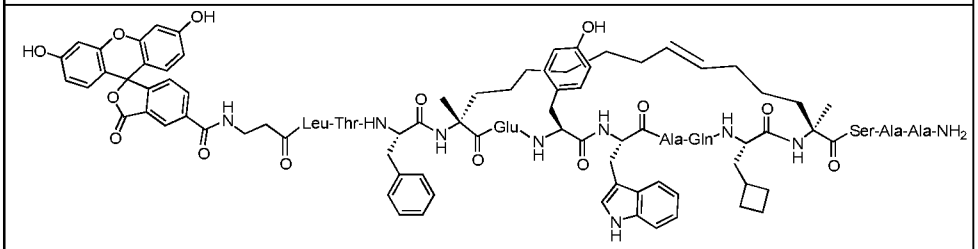
Chemical Formula: $C_{104}H_{155}N_{23}O_{26}$
Exact Mass: 2142.15
Molecular Weight: 2143.48

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

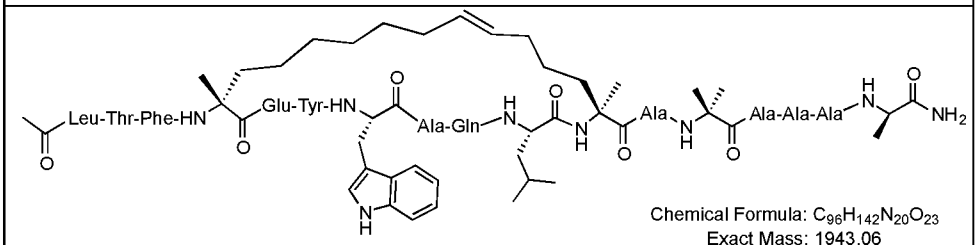


Chemical Formula: $C_{95}H_{138}F_2N_{20}O_{23}$
Exact Mass: 1965.02
Molecular Weight: 1966.23

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

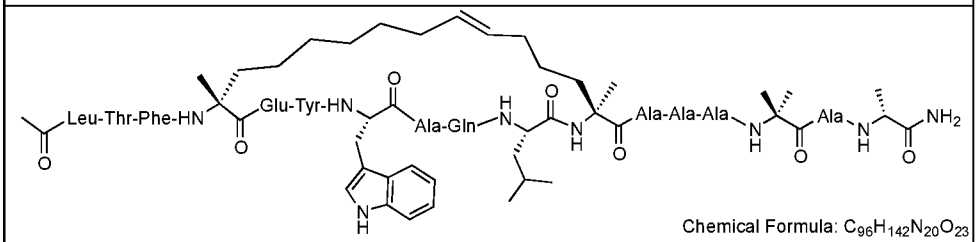


5-FAM- Ba L T F $er8 E YWAQ Cba $e SAA -NH2



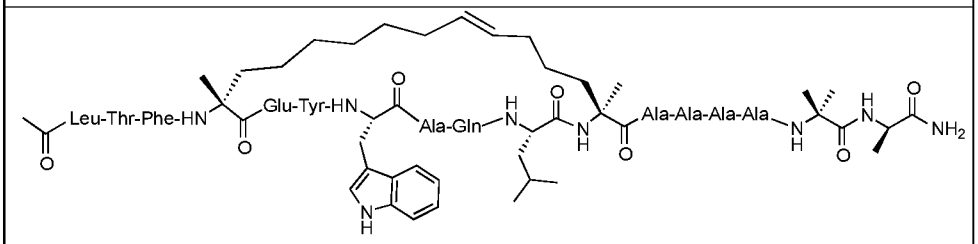
Chemical Formula: $C_{96}H_{142}N_{20}O_{23}$
Exact Mass: 1943.06
Molecular Weight: 1944.27

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

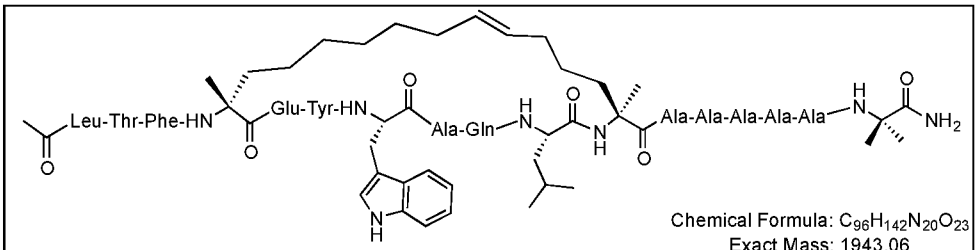


Chemical Formula: $C_{96}H_{142}N_{20}O_{23}$
Exact Mass: 1943.06
Molecular Weight: 1944.27

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

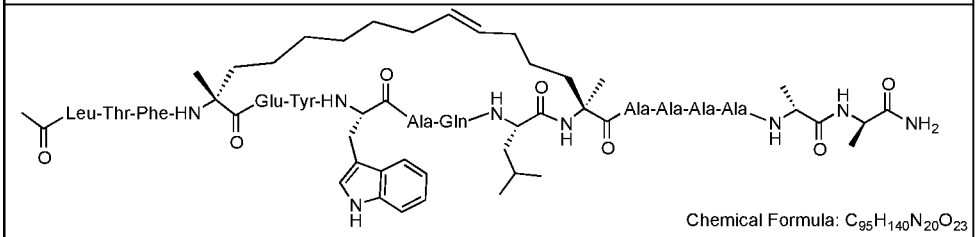


Ac-LTF$er8EYWAQL$eAAAA Aib a-NH2



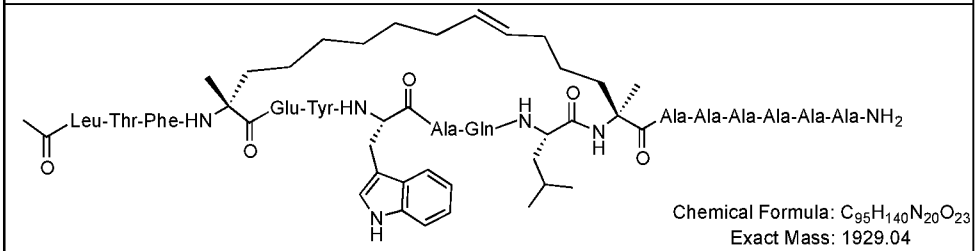
Chemical Formula: $C_{96}H_{142}N_{20}O_{23}$
Exact Mass: 1943.06
Molecular Weight: 1944.27

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



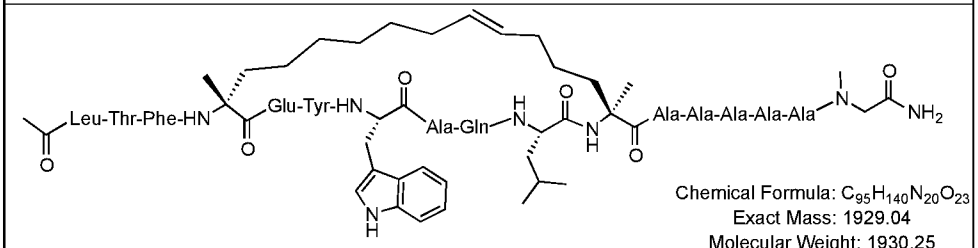
Chemical Formula: $C_{95}H_{140}N_{20}O_{23}$
Exact Mass: 1929.04
Molecular Weight: 1930.25

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



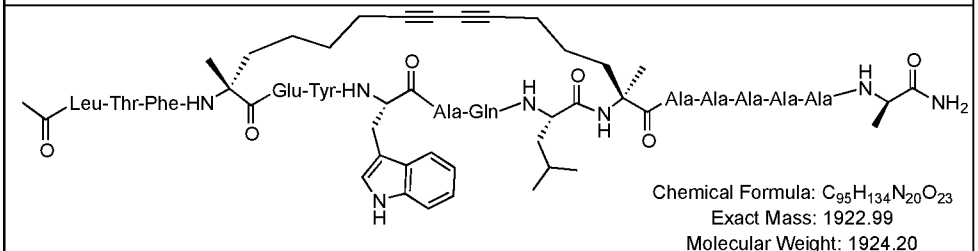
Chemical Formula: $C_{95}H_{140}N_{20}O_{23}$
Exact Mass: 1929.04
Molecular Weight: 1930.25

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



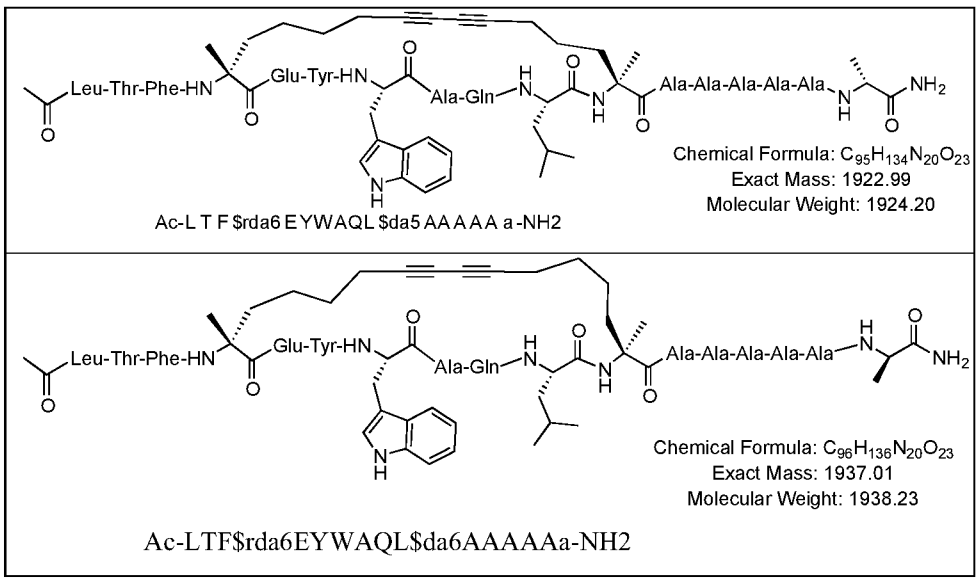
Chemical Formula: $C_{95}H_{140}N_{20}O_{23}$
Exact Mass: 1929.04
Molecular Weight: 1930.25

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



Chemical Formula: $C_{95}H_{134}N_{20}O_{23}$
Exact Mass: 1922.99
Molecular Weight: 1924.20

Ac-LTF$rda6EYWAQL$da5AAAAAa-NH2



[00378] In some embodiments, peptidomimetic macrocycles exclude one or more of the peptidomimetic macrocycles shown in Table 4a:

Table 4a

Number	Sequence
1	L$r5QETFSD$s8WKLLPEN
2	LSQ$r5TFSDLW$s8LLPEN
3	LSQE$r5FSDLWK$s8LPEN
4	LSQET$r5SDLWKL$s8PEN
5	LSQETF$r5DLWKLL$s8EN
6	LXQETFS$r5LWKLLP$s8N
7	LSQETFSD$r5WKLLPE$s8
8	LSQQTF$r5DLWKLL$s8EN
9	LSQETF$r5DLWKLL$s8QN
10	LSQQTF$r5DLWKLL$s8QN
11	LSQETF$r5NLWKLL$s8QN
12	LSQQTF$r5NLWKLL$s8QN
13	LSQQTF$r5NLWRLL$s8QN
14	QSQQTF$r5NLWKLL$s8QN
15	QSQQTF$r5NLWRLL$s8QN
16	QSQQTA$r5NLWRLL$s8QN
17	L$r8QETFSD$WKLLPEN
18	LSQ$r8TFSDLW$LLPEN
19	LSQE$r8FSDLWK$LPEN
20	LSQET$r8SDLWKL$PEN
21	LSQETF$r8DLWKLL$EN
22	LXQETFS$r8LWKLLP$N
23	LSQETFSD$r8WKLLPE$
24	LSQQTF$r8DLWKLL$EN
25	LSQETF$r8DLWKLL$QN
26	LSQQTF$r8DLWKLL$QN
27	LSQETF$r8NLWKLL$QN
28	LSQQTF$r8NLWKLL$QN
29	LSQQTF$r8NLWRLL$QN

30	QSQQTF$r8NLWKLL$QN
31	QSQQTF$r8NLWRLL$QN
32	QSQQTA$r8NLWRLL$QN
33	QSQQTF$r8NLWRKK$QN
34	QQTF$r8DLWRLL$EN
35	QQTF$r8DLWRLL$
36	LSQQTFDLWLL
37	QQTFDLWLL
38	QQTA$r8DLWRLL$EN
39	QSQQTF$r5NLWRLL$s8QN (dihydroxylated alkylene crosslink)
40	QSQQTA$r5NLWRLL$s8QN (dihydroxylated alkylene crosslink)
41	QSQQTF$r8DLWRLL$QN
42	QTF$r8NLWRLL$
43	QSQQTFNLWLLPQN
44	QSQTFNLWRLLPQN
45	TFSLWKLL
46	ETFDLWLL
47	QTFNLWLL
48	SQEFSNLWKLL

In Table 4a, 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.

[00379] In some embodiments, peptidomimetic macrocycles do not comprise a peptidomimetic macrocycle structure as shown in Table 4a.

[00380] In other embodiments, peptidomimetic macrocycles exclude one or more of the peptidomimetic macrocycles shown in Table 4b:

Table 4b

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

16	Ac-RSQQTF$r8NLWRLL$EN-NH2	2137.18	1069.59	1069.75
17	Ac-LSQETFSDLWKLLPEN-NH2	1959.99	981.00	981.24
18	Ac-QSQTFSLWRLLPQN-NH2	2008.09	1005.05	1004.97
19	Ac-QSQQFSNWRLLPQN-NH2	2036.06	1019.03	1018.86
20	Ac-QSQQTSNLRLLPQN-NH2	1917.04	959.52	959.32
21	Ac-QSQQTFNLWLLPQN-NH2	2007.06	1004.53	1004.97
22	Ac-RTQATF$r8NQWAibANle$TNAibTR-NH2	2310.26	1156.13	1156.52
23	Ac-QSQQTF$r8NLWRLL$RN-NH2	2136.20	1069.10	1068.94
24	Ac-QSQRTF$r8NLWRLL$QN-NH2	2136.20	1069.10	1068.94
25	Ac-QSQQTF$r8NNleWRLL$QN-NH2	2108.15	1055.08	1055.44
26	Ac-QSQQTF$r8NLWRNleL$QN-NH2	2108.15	1055.08	1055.84
27	Ac-QSQQTF$r8NLWRLNle$QN-NH2	2108.15	1055.08	1055.12
28	Ac-QSQQTY$r8NLWRLL$QN-NH2	2124.15	1063.08	1062.92
29	Ac-RAibQQTF$r8NLWRLL$QN-NH2	2134.22	1068.11	1068.65
30	Ac-MPRFMDYWEGLN-NH2	1598.70	800.35	800.45
31	Ac-RSQQRF$r8NLWRLL$QN-NH2	2191.25	1096.63	1096.83
32	Ac-QSQQRF$r8NLWRLL$QN-NH2	2163.21	1082.61	1082.87
33	Ac-RAibQQRF$r8NLWRLL$QN-NH2	2189.27	1095.64	1096.37
34	Ac-RSQQRF$r8NFWRLL$QN-NH2	2225.23	1113.62	1114.37
35	Ac-RSQQRF$r8NYWRLL$QN-NH2	2241.23	1121.62	1122.37
36	Ac-RSQQTF$r8NLWQLL$QN-NH2	2108.15	1055.08	1055.29
37	Ac-QSQQTF$r8NLWQAmlL$QN-NH2	2094.13	1048.07	1048.32
38	Ac-QSQQTF$r8NAmlWRLL$QN-NH2	2122.17	1062.09	1062.35
39	Ac-NlePRF$r8DYWEGL$QN-NH2	1869.98	935.99	936.20
40	Ac-NlePRF$r8NYWRLL$QN-NH2	1952.12	977.06	977.35
41	Ac-RF$r8NLWRLL$Q-NH2	1577.96	789.98	790.18
42	Ac-QSQQTF$r8N2ffWRLL$QN-NH2	2160.13	1081.07	1081.40
43	Ac-QSQQTF$r8N3ffWRLL$QN-NH2	2160.13	1081.07	1081.34
44	Ac-QSQQTF#r8NLWRLL#QN-NH2	2080.12	1041.06	1041.34
45	Ac-RSQQTA$r8NLWRLL$QN-NH2	2060.16	1031.08	1031.38
46	Ac-QSQQTF%r8NLWRLL%QN-NH2	2110.17	1056.09	1056.55
47	HepQSQ$TFSNLWRLLPQN-NH2	2051.10	1026.55	1026.82
48	HepQSQTFr8NLWRLL$QN-NH2	2159.23	1080.62	1080.89
49	Ac-QSQQTF$r8NL6clWRLL$QN-NH2	2142.11	1072.06	1072.35
50	Ac-QSQQTF$r8NLMe6clwRLL$QN-NH2	2156.13	1079.07	1079.27
51	Ac-LTFEHYWAQLTS-NH2	1535.74	768.87	768.91
52	Ac-LTFHYWQLTS-NH2	1585.83	793.92	794.17
53	Ac-LTFEYWALTS-NH2	1520.79	761.40	761.67
54	Ac-LTF$zr8HYWAQL$zS-NH2	1597.87	799.94	800.06
55	Ac-LTF$r8HYWRQL$S-NH2	1682.93	842.47	842.72
56	Ac-QS$QTFStNLWRLL$s8QN-NH2	2145.21	1073.61	1073.90
57	Ac-QSQQTASNLWRLLPQN-NH2	1923.99	963.00	963.26
58	Ac-QSQQTA$/r8NLWRLL$/QN-NH2	2060.15	1031.08	1031.24
59	Ac-ASQQTF$/r8NLWRLL$/QN-NH2	2079.16	1040.58	1040.89
60	Ac-SQQFSNLWRLLAibQN-NH2	2009.09	1005.55	1005.86
61	Ac-QSQTFNLWRLLAibQN-NH2	2023.10	1012.55	1012.79
62	Ac-QSQQFSNWRLLAibQN-NH2	2024.06	1013.03	1013.31
63	Ac-QSQQTFNLWLLAibQN-NH2	1995.06	998.53	998.87
64	Ac-QSQQTFSLWRLAibQN-NH2	2011.06	1006.53	1006.83
65	Ac-QSQQTFSNLWLLAN-NH2	1940.02	971.01	971.29
66	Ac-$/SQQ$/FSNLWRLLAibQN-NH2	2037.12	1019.56	1019.78

67	Ac-QS$/QTF$/NLWRLLAibQN-NH2	2051.13	1026.57	1026.90
68	Ac-QSQQ$/FSN$/WRLLAibQN-NH2	2052.09	1027.05	1027.36
69	Ac-QSQQTF$/NLW$/LLAibQN-NH2	2023.09	1012.55	1013.82
70	Ac-QSQTFSLWRLLAibQN-NH2	1996.09	999.05	999.39
71	Ac-QSQ$/TFS$/LWRLLAibQN-NH2	2024.12	1013.06	1013.37
72	Ac-QS$/QTFSt//NLWRLL$/s8QN-NH2	2201.27	1101.64	1102.00
73	Ac-$r8SQQTFS$LWRLLAibQN-NH2	2038.14	1020.07	1020.23
74	Ac-QSQ$r8TFSNLW$LLAibQN-NH2	1996.08	999.04	999.32
75	Ac-QSQQTFS$r8LWRLLA$N-NH2	2024.12	1013.06	1013.37
76	Ac-QS$r5QTFStNLW$LLAibQN-NH2	2032.12	1017.06	1017.39
77	Ac-$/r8SQQTFS$/LWRLLAibQN-NH2	2066.17	1034.09	1034.80
78	Ac-QSQ$/r8TFSNLW$/LLAibQN-NH2	2024.11	1013.06	1014.34
79	Ac-QSQQTFS$/r8LWRLLA$/N-NH2	2052.15	1027.08	1027.16
80	Ac-QS$/r5QTFSt//NLW$/LLAibQN-NH2	2088.18	1045.09	1047.10
81	Ac-QSQQTFSNLWRLLAibQN-NH2	1988.02	995.01	995.31
82	Hep/QSQ$/TF$/r8NLWRLL$/QN-NH2	2215.29	1108.65	1108.93
83	Ac-ASQQTF$r8NLRWLL$QN-NH2	2051.13	1026.57	1026.90
84	Ac-QSQQTF$/r8NLWRLL$/Q-NH2	2022.14	1012.07	1012.66
85	Ac-QSQQTF$r8NLWRLL$Q-NH2	1994.11	998.06	998.42
86	Ac-AAARAA$r8AAARAA$AA-NH2	1515.90	758.95	759.21
87	Ac-LTFEHYWAQLTSA-NH2	1606.78	804.39	804.59
88	Ac-LTF$r8HYWAQL$SA-NH2	1668.90	835.45	835.67
89	Ac-ASQQTFSNLWRLLPQN-NH2	1943.00	972.50	973.27
90	Ac-QS$QTFStNLW$r5LLAibQN-NH2	2032.12	1017.06	1017.30
91	Ac-QSQQTFAibNLWRLLAibQN-NH2	1986.04	994.02	994.19
92	Ac-QSQQTFNleNLWRLLNleQN-NH2	2042.11	1022.06	1022.23
93	Ac-QSQQTF$/r8NLWRLLAibQN-NH2	2082.14	1042.07	1042.23
94	Ac-QSQQTF$/r8NLWRLLNleQN-NH2	2110.17	1056.09	1056.29
95	Ac-QSQQTFAibNLWRLL$/QN-NH2	2040.09	1021.05	1021.25
96	Ac-QSQQTFNleNLWRLL$/QN-NH2	2068.12	1035.06	1035.31
97	Ac-QSQQTF%r8NL6clWRNleL%QN-NH2	2144.13	1073.07	1073.32
98	Ac-QSQQTF%r8NLMe6clWRLL%QN-NH2	2158.15	1080.08	1080.31
101	Ac-FNleYWEL-NH2	1160.63	-	1161.70
102	Ac-F$r8AYWELL$A-NH2	1344.75	-	1345.90
103	Ac-F$r8AYWQLL$A-NH2	1343.76	-	1344.83
104	Ac-NlePRF$r8NYWELL$QN-NH2	1925.06	963.53	963.69
105	Ac-NlePRF$r8DYWRLL$QN-NH2	1953.10	977.55	977.68
106	Ac-NlePRF$r8NYWRLL$Q-NH2	1838.07	920.04	920.18
107	Ac-NlePRF$r8NYWRLL$-NH2	1710.01	856.01	856.13
108	Ac-QSQQTF$r8DLWRLL$QN-NH2	2109.14	1055.57	1055.64
109	Ac-QSQQTF$r8NLWRLL$EN-NH2	2109.14	1055.57	1055.70
110	Ac-QSQQTF$r8NLWRLL$QD-NH2	2109.14	1055.57	1055.64
111	Ac-QSQQTF$r8NLWRLL$S-NH2	1953.08	977.54	977.60
112	Ac-ESQQTF$r8NLWRLL$QN-NH2	2109.14	1055.57	1055.70
113	Ac-LTF$r8NLWRNleL$Q-NH2	1635.99	819.00	819.10
114	Ac-LRF$r8NLWRNleL$Q-NH2	1691.04	846.52	846.68
115	Ac-QSQQTF$r8NWWRNleL$QN-NH2	2181.15	1091.58	1091.64
116	Ac-QSQQTF$r8NLWRNleL$Q-NH2	1994.11	998.06	998.07
117	Ac-QTF$r8NLWRNleL$QN-NH2	1765.00	883.50	883.59
118	Ac-NlePRF$r8NWWRLL$QN-NH2	1975.13	988.57	988.75
119	Ac-NlePRF$r8NWWRLL$A-NH2	1804.07	903.04	903.08

120	Ac-TSFAEYWNLLNH2	1467.70	734.85	734.90
121	Ac-QTF$r8HWWSQL$S-NH2	1651.85	826.93	827.12
122	Ac-FMYWEL-NH2	1178.58	-	1179.64
123	Ac-QTFEHWWSQLLS-NH2	1601.76	801.88	801.94
124	Ac-QSQQTF$r8NLAmwRLNle$QN-NH2	2122.17	1062.09	1062.24
125	Ac-FMAibY6clWEAc3cL-NH2	1130.47	-	1131.53
126	Ac-FNle$Y6clWE$L-NH2	1194.59	-	1195.64
127	Ac-F$zr8AY6clWEAc3cL$z-NH2	1277.63	639.82	1278.71
128	Ac-F$r8AY6clWEAc3cL$A-NH2	1348.66	-	1350.72
129	Ac-NlePRF$r8NY6clWRLL$QN-NH2	1986.08	994.04	994.64
130	Ac-AF$r8AAWALA$A-NH2	1223.71	-	1224.71
131	Ac-TF$r8AAWRLA$Q-NH2	1395.80	698.90	399.04
132	Pr-TF$r8AAWRLA$Q-NH2	1409.82	705.91	706.04
133	Ac-QSQQTF%r8NLWRNleL%QN-NH2	2110.17	1056.09	1056.22
134	Ac-LTF%r8HYWAQL%SA-NH2	1670.92	836.46	836.58
135	Ac-NlePRF%r8NYWRLL%QN-NH2	1954.13	978.07	978.19
136	Ac-NlePRF%r8NY6clWRLL%QN-NH2	1988.09	995.05	995.68
137	Ac-LTF%r8HY6clWAQL%S-NH2	1633.84	817.92	817.93
138	Ac-QS%QTF%StNLWRLL%s8QN-NH2	2149.24	1075.62	1075.65
139	Ac-LTF%r8HY6clWRQL%S-NH2	1718.91	860.46	860.54
140	Ac-QSQQTF%r8NL6clWRLL%QN-NH2	2144.13	1073.07	1073.64
141	Ac-%r8SQQTFS%LWRLLAibQN-NH2	2040.15	1021.08	1021.13
142	Ac-LTF%r8HYWAQL%S-NH2	1599.88	800.94	801.09
143	Ac-TSF%r8QYWNLL%P-NH2	1602.88	802.44	802.58
147	Ac-LTFEHYWAQLTS-NH2	1535.74	768.87	769.5
152	Ac-F$er8AY6clWEAc3cL$e-NH2	1277.63	639.82	1278.71
153	Ac-AF$r8AAWALA$A-NH2	1277.63	639.82	1277.84
154	Ac-TF$r8AAWRLA$Q-NH2	1395.80	698.90	699.04
155	Pr-TF$r8AAWRLA$Q-NH2	1409.82	705.91	706.04
156	Ac-LTF$er8HYWAQL$eS-NH2	1597.87	799.94	800.44
159	Ac-CCPGCCBaQSQQTF$r8NLWRLL$QN-NH2	2745.30	1373.65	1372.99
160	Ac-CCPGCCBaQSQQTA$r8NLWRLL$QN-NH2	2669.27	1335.64	1336.09
161	Ac-CCPGCCBaNlePRF$r8NYWRLL$QN-NH2	2589.26	1295.63	1296.2
162	Ac-LTF$/r8HYWAQL$/S-NH2	1625.90	813.95	814.18
163	Ac-F%r8HY6clWRAc3cL%-NH2	1372.72	687.36	687.59
164	Ac-QTF%r8HWWSQL%S-NH2	1653.87	827.94	827.94
165	Ac-LTA$r8HYWRQL$S-NH2	1606.90	804.45	804.66
166	Ac-Q$r8QQTFSN$WRLLAibQN-NH2	2080.12	1041.06	1041.61
167	Ac-QSQQ$r8FSNLWR$LAibQN-NH2	2066.11	1034.06	1034.58
168	Ac-F$r8AYWEAc3cL$A-NH2	1314.70	658.35	1315.88
169	Ac-F$r8AYWEAc3cL$S-NH2	1330.70	666.35	1331.87
170	Ac-F$r8AYWEAc3cL$Q-NH2	1371.72	686.86	1372.72
171	Ac-F$r8AYWEAibL$S-NH2	1332.71	667.36	1334.83
172	Ac-F$r8AYWEAL$S-NH2	1318.70	660.35	1319.73
173	Ac-F$r8AYWEQL$S-NH2	1375.72	688.86	1377.53
174	Ac-F$r8HYWEQL$S-NH2	1441.74	721.87	1443.48
175	Ac-F$r8HYWAQL$S-NH2	1383.73	692.87	1385.38
176	Ac-F$r8HYWAAc3cL$S-NH2	1338.71	670.36	1340.82
177	Ac-F$r8HYWRAc3cL$S-NH2	1423.78	712.89	713.04
178	Ac-F$r8AYWEAc3cL#A-NH2	1300.69	651.35	1302.78

179	Ac-NlePTF%r8NYWRLL%QN-NH2	1899.08	950.54	950.56
180	Ac-TF$r8AAWRAL$Q-NH2	1395.80	698.90	699.13
181	Ac-TSF%r8HYWAQL%S-NH2	1573.83	787.92	787.98
184	Ac-F%r8AY6clWEAc3cL%A-NH2	1350.68	676.34	676.91
185	Ac-LTF$r8HYWAQI$S-NH2	1597.87	799.94	800.07
186	Ac-LTF$r8HYWAQNle$S-NH2	1597.87	799.94	800.07
187	Ac-LTF$r8HYWAQL$A-NH2	1581.87	791.94	792.45
188	Ac-LTF$r8HYWAQL$Abu-NH2	1595.89	798.95	799.03
189	Ac-LTF$r8HYWAbuQL$S-NH2	1611.88	806.94	807.47
190	Ac-LTF$er8AYWAQL$eS-NH2	1531.84	766.92	766.96
191	Ac-LAF$r8HYWAQL$S-NH2	1567.86	784.93	785.49
192	Ac-LAF$r8AYWAQL$S-NH2	1501.83	751.92	752.01
193	Ac-LTF$er8AYWAQL$eA-NH2	1515.85	758.93	758.97
194	Ac-LAF$r8AYWAQL$A-NH2	1485.84	743.92	744.05
195	Ac-LTF$r8NLWANleL$Q-NH2	1550.92	776.46	776.61
196	Ac-LTF$r8NLWANleL$A-NH2	1493.90	747.95	1495.6
197	Ac-LTF$r8ALWANleL$Q-NH2	1507.92	754.96	755
198	Ac-LAF$r8NLWANleL$Q-NH2	1520.91	761.46	761.96
199	Ac-LAF$r8ALWANleL$A-NH2	1420.89	711.45	1421.74
200	Ac-A$r8AYWEAc3cL$A-NH2	1238.67	620.34	1239.65
201	Ac-F$r8AYWEAc3cL$AA-NH2	1385.74	693.87	1386.64
202	Ac-F$r8AYWEAc3cL$Abu-NH2	1328.72	665.36	1330.17
203	Ac-F$r8AYWEAc3cL$Nle-NH2	1356.75	679.38	1358.22
204	Ac-F$r5AYWEAc3cL$s8A-NH2	1314.70	658.35	1315.51
205	Ac-F$AYWEAc3cL$r8A-NH2	1314.70	658.35	1315.66
206	Ac-F$r8AYWEAc3cI$A-NH2	1314.70	658.35	1316.18
207	Ac-F$r8AYWEAc3cNle$A-NH2	1314.70	658.35	1315.66
208	Ac-F$r8AYWEAmlL$A-NH2	1358.76	680.38	1360.21
209	Ac-F$r8AYWENleL$A-NH2	1344.75	673.38	1345.71
210	Ac-F$r8AYWQAc3cL$A-NH2	1313.72	657.86	1314.7
211	Ac-F$r8AYWAAc3cL$A-NH2	1256.70	629.35	1257.56
212	Ac-F$r8AYWAbuAc3cL$A-NH2	1270.71	636.36	1272.14
213	Ac-F$r8AYWNleAc3cL$A-NH2	1298.74	650.37	1299.67
214	Ac-F$r8AbuYWEAc3cL$A-NH2	1328.72	665.36	1329.65
215	Ac-F$r8NleYWEAc3cL$A-NH2	1356.75	679.38	1358.66
216	5-FAM-BaLTFEHYWAQLTS-NH2	1922.82	962.41	962.87
217	5-FAM-BaLTF%r8HYWAQL%S-NH2	1986.96	994.48	994.97
218	Ac-LTF$r8HYWAQhL$S-NH2	1611.88	806.94	807
219	Ac-LTF$r8HYWAQTle$S-NH2	1597.87	799.94	799.97
220	Ac-LTF$r8HYWAQAdm$S-NH2	1675.91	838.96	839.09
221	Ac-LTF$r8HYWAQhCha$S-NH2	1651.91	826.96	826.98
222	Ac-LTF$r8HYWAQCha$S-NH2	1637.90	819.95	820.02
223	Ac-LTF$r8HYWAc6cQL$S-NH2	1651.91	826.96	826.98
224	Ac-LTF$r8HYWAc5cQL$S-NH2	1637.90	819.95	820.02
225	Ac-LThF$r8HYWAQL$S-NH2	1611.88	806.94	807
226	Ac-LTIgl$r8HYWAQL$S-NH2	1625.90	813.95	812.99
227	Ac-LTF$r8HYWAQChg$S-NH2	1623.88	812.94	812.99
228	Ac-LTF$r8HYWAQF$S-NH2	1631.85	816.93	816.99
229	Ac-LTF$r8HYWAQIgl$S-NH2	1659.88	830.94	829.94
230	Ac-LTF$r8HYWAQCba$S-NH2	1609.87	805.94	805.96
231	Ac-LTF$r8HYWAQCpg$S-NH2	1609.87	805.94	805.96

232	Ac-LTF$r8HhYWAQL$S-NH2	1611.88	806.94	807
233	Ac-F$r8AYWEAc3chL$A-NH2	1328.72	665.36	665.43
234	Ac-F$r8AYWEAc3cTle$A-NH2	1314.70	658.35	1315.62
235	Ac-F$r8AYWEAc3cAdm$A-NH2	1392.75	697.38	697.47
236	Ac-F$r8AYWEAc3chCha$A-NH2	1368.75	685.38	685.34
237	Ac-F$r8AYWEAc3cCha$A-NH2	1354.73	678.37	678.38
238	Ac-F$r8AYWEAc6cL$A-NH2	1356.75	679.38	679.42
239	Ac-F$r8AYWEAc5cL$A-NH2	1342.73	672.37	672.46
240	Ac-hF$r8AYWEAc3cL$A-NH2	1328.72	665.36	665.43
241	Ac-Igl$r8AYWEAc3cL$A-NH2	1342.73	672.37	671.5
243	Ac-F$r8AYWEAc3cF$A-NH2	1348.69	675.35	675.35
244	Ac-F$r8AYWEAc3cIgl$A-NH2	1376.72	689.36	688.37
245	Ac-F$r8AYWEAc3cCba$A-NH2	1326.70	664.35	664.47
246	Ac-F$r8AYWEAc3cCpg$A-NH2	1326.70	664.35	664.39
247	Ac-F$r8AhYWEAc3cL$A-NH2	1328.72	665.36	665.43
248	Ac-F$r8AYWEAc3cL$Q-NH2	1371.72	686.86	1372.87
249	Ac-F$r8AYWEAibL$A-NH2	1316.72	659.36	1318.18
250	Ac-F$r8AYWEAL$A-NH2	1302.70	652.35	1303.75
251	Ac-LAF$r8AYWAAL$A-NH2	1428.82	715.41	715.49
252	Ac-LTF$r8HYWAAc3cL$S-NH2	1552.84	777.42	777.5
253	Ac-NleTF$r8HYWAQL$S-NH2	1597.87	799.94	800.04
254	Ac-VTF$r8HYWAQL$S-NH2	1583.85	792.93	793.04
255	Ac-FTF$r8HYWAQL$S-NH2	1631.85	816.93	817.02
256	Ac-WTF$r8HYWAQL$S-NH2	1670.86	836.43	836.85
257	Ac-RTF$r8HYWAQL$S-NH2	1640.88	821.44	821.9
258	Ac-KTF$r8HYWAQL$S-NH2	1612.88	807.44	807.91
259	Ac-LNleF$r8HYWAQL$S-NH2	1609.90	805.95	806.43
260	Ac-LVF$r8HYWAQL$S-NH2	1595.89	798.95	798.93
261	Ac-LFF$r8HYWAQL$S-NH2	1643.89	822.95	823.38
262	Ac-LWF$r8HYWAQL$S-NH2	1682.90	842.45	842.55
263	Ac-LRF$r8HYWAQL$S-NH2	1652.92	827.46	827.52
264	Ac-LKF$r8HYWAQL$S-NH2	1624.91	813.46	813.51
265	Ac-LTF$r8NleYWAQL$S-NH2	1573.89	787.95	788.05
266	Ac-LTF$r8VYWAQL$S-NH2	1559.88	780.94	780.98
267	Ac-LTF$r8FYWAQL$S-NH2	1607.88	804.94	805.32
268	Ac-LTF$r8WYWAQL$S-NH2	1646.89	824.45	824.86
269	Ac-LTF$r8RYWAQL$S-NH2	1616.91	809.46	809.51
270	Ac-LTF$r8KYWAQL$S-NH2	1588.90	795.45	795.48
271	Ac-LTF$r8HNleWAQL$S-NH2	1547.89	774.95	774.98
272	Ac-LTF$r8HVWAQL$S-NH2	1533.87	767.94	767.95
273	Ac-LTF$r8HFWAQL$S-NH2	1581.87	791.94	792.3
274	Ac-LTF$r8HWWAQL$S-NH2	1620.88	811.44	811.54
275	Ac-LTF$r8HRWAQL$S-NH2	1590.90	796.45	796.52
276	Ac-LTF$r8HKWAQL$S-NH2	1562.90	782.45	782.53
277	Ac-LTF$r8HYWNleQL$S-NH2	1639.91	820.96	820.98
278	Ac-LTF$r8HYWVQL$S-NH2	1625.90	813.95	814.03
279	Ac-LTF$r8HYWFQL$S-NH2	1673.90	837.95	838.03
280	Ac-LTF$r8HYWWQL$S-NH2	1712.91	857.46	857.5
281	Ac-LTF$r8HYWKQL$S-NH2	1654.92	828.46	828.49
282	Ac-LTF$r8HYWANleL$S-NH2	1582.89	792.45	792.52
283	Ac-LTF$r8HYWAVL$S-NH2	1568.88	785.44	785.49

284	Ac-LTF$r8HYWAFL$S-NH2	1616.88	809.44	809.47
285	Ac-LTF$r8HYWAWL$S-NH2	1655.89	828.95	829
286	Ac-LTF$r8HYWARL$S-NH2	1625.91	813.96	813.98
287	Ac-LTF$r8HYWAQL$Nle-NH2	1623.92	812.96	813.39
288	Ac-LTF$r8HYWAQL$V-NH2	1609.90	805.95	805.99
289	Ac-LTF$r8HYWAQL$F-NH2	1657.90	829.95	830.26
290	Ac-LTF$r8HYWAQL$W-NH2	1696.91	849.46	849.5
291	Ac-LTF$r8HYWAQL$R-NH2	1666.94	834.47	834.56
292	Ac-LTF$r8HYWAQL$K-NH2	1638.93	820.47	820.49
293	Ac-Q$r8QQTFSN$WRLLAibQN-NH2	2080.12	1041.06	1041.54
294	Ac-QSQQ$r8FSNLWR$LAibQN-NH2	2066.11	1034.06	1034.58
295	Ac-LT2Pal$r8HYWAQL$S-NH2	1598.86	800.43	800.49
296	Ac-LT3Pal$r8HYWAQL$S-NH2	1598.86	800.43	800.49
297	Ac-LT4Pal$r8HYWAQL$S-NH2	1598.86	800.43	800.49
298	Ac-LTF2CF3$r8HYWAQL$S-NH2	1665.85	833.93	834.01
299	Ac-LTF2CN$r8HYWAQL$S-NH2	1622.86	812.43	812.47
300	Ac-LTF2Me$r8HYWAQL$S-NH2	1611.88	806.94	807
301	Ac-LTF3Cl$r8HYWAQL$S-NH2	1631.83	816.92	816.99
302	Ac-LTF4CF3$r8HYWAQL$S-NH2	1665.85	833.93	833.94
303	Ac-LTF4tBu$r8HYWAQL$S-NH2	1653.93	827.97	828.02
304	Ac-LTF5F$r8HYWAQL$S-NH2	1687.82	844.91	844.96
305	Ac-LTF$r8HY3BthAAQL$S-NH2	1614.83	808.42	808.48
306	Ac-LTF2Br$r8HYWAQL$S-NH2	1675.78	838.89	838.97
307	Ac-LTF4Br$r8HYWAQL$S-NH2	1675.78	838.89	839.86
308	Ac-LTF2Cl$r8HYWAQL$S-NH2	1631.83	816.92	816.99
309	Ac-LTF4Cl$r8HYWAQL$S-NH2	1631.83	816.92	817.36
310	Ac-LTF3CN$r8HYWAQL$S-NH2	1622.86	812.43	812.47
311	Ac-LTF4CN$r8HYWAQL$S-NH2	1622.86	812.43	812.47
312	Ac-LTF34Cl2$r8HYWAQL$S-NH2	1665.79	833.90	833.94
313	Ac-LTF34F2$r8HYWAQL$S-NH2	1633.85	817.93	817.95
314	Ac-LTF35F2$r8HYWAQL$S-NH2	1633.85	817.93	817.95
315	Ac-LTDip$r8HYWAQL$S-NH2	1673.90	837.95	838.01
316	Ac-LTF2F$r8HYWAQL$S-NH2	1615.86	808.93	809
317	Ac-LTF3F$r8HYWAQL$S-NH2	1615.86	808.93	809
318	Ac-LTF4F$r8HYWAQL$S-NH2	1615.86	808.93	809
319	Ac-LTF4I$r8HYWAQL$S-NH2	1723.76	862.88	862.94
320	Ac-LTF3Me$r8HYWAQL$S-NH2	1611.88	806.94	807.07
321	Ac-LTF4Me$r8HYWAQL$S-NH2	1611.88	806.94	807
322	Ac-LT1Nal$r8HYWAQL$S-NH2	1647.88	824.94	824.98
323	Ac-LT2Nal$r8HYWAQL$S-NH2	1647.88	824.94	825.06
324	Ac-LTF3CF3$r8HYWAQL$S-NH2	1665.85	833.93	834.01
325	Ac-LTF4NO2$r8HYWAQL$S-NH2	1642.85	822.43	822.46
326	Ac-LTF3NO2$r8HYWAQL$S-NH2	1642.85	822.43	822.46
327	Ac-LTF$r82ThiYWAQL$S-NH2	1613.83	807.92	807.96
328	Ac-LTF$r8HBipWAQL$S-NH2	1657.90	829.95	830.01
329	Ac-LTF$r8HF4tBuWAQL$S-NH2	1637.93	819.97	820.02
330	Ac-LTF$r8HF4CF3WAQL$S-NH2	1649.86	825.93	826.02
331	Ac-LTF$r8HF4ClWAQL$S-NH2	1615.83	808.92	809.37
332	Ac-LTF$r8HF4MeWAQL$S-NH2	1595.89	798.95	799.01
333	Ac-LTF$r8HF4BrWAQL$S-NH2	1659.78	830.89	830.98
334	Ac-LTF$r8HF4CNWAQL$S-NH2	1606.87	804.44	804.56

335	Ac-LTF$r8HF4NO2WAQL$S-NH2	1626.86	814.43	814.55
336	Ac-LTF$r8H1NalWAQL$S-NH2	1631.89	816.95	817.06
337	Ac-LTF$r8H2NalWAQL$S-NH2	1631.89	816.95	816.99
338	Ac-LTF$r8HWAQL$S-NH2	1434.80	718.40	718.49
339	Ac-LTF$r8HY1NalAQL$S-NH2	1608.87	805.44	805.52
340	Ac-LTF$r8HY2NalAQL$S-NH2	1608.87	805.44	805.52
341	Ac-LTF$r8HYWAQI$S-NH2	1597.87	799.94	800.07
342	Ac-LTF$r8HYWAQNle$S-NH2	1597.87	799.94	800.44
343	Ac-LTF$er8HYWAQL$eA-NH2	1581.87	791.94	791.98
344	Ac-LTF$r8HYWAQL$Abu-NH2	1595.89	798.95	799.03
345	Ac-LTF$r8HYWAbuQL$S-NH2	1611.88	806.94	804.47
346	Ac-LAF$r8HYWAQL$S-NH2	1567.86	784.93	785.49
347	Ac-LTF$r8NLWANleL$Q-NH2	1550.92	776.46	777.5
348	Ac-LTF$r8ALWANleL$Q-NH2	1507.92	754.96	755.52
349	Ac-LAF$r8NLWANleL$Q-NH2	1520.91	761.46	762.48
350	Ac-F$r8AYWAAc3cL$A-NH2	1256.70	629.35	1257.56
351	Ac-LTF$r8AYWAAL$S-NH2	1474.82	738.41	738.55
352	Ac-LVF$r8AYWAQL$S-NH2	1529.87	765.94	766
353	Ac-LTF$r8AYWAbuQL$S-NH2	1545.86	773.93	773.92
354	Ac-LTF$r8AYWNleQL$S-NH2	1573.89	787.95	788.17
355	Ac-LTF$r8AbuYWAQL$S-NH2	1545.86	773.93	773.99
356	Ac-LTF$r8AYWHQL$S-NH2	1597.87	799.94	799.97
357	Ac-LTF$r8AYWKQL$S-NH2	1588.90	795.45	795.53
358	Ac-LTF$r8AYWOQL$S-NH2	1574.89	788.45	788.5
359	Ac-LTF$r8AYWRQL$S-NH2	1616.91	809.46	809.51
360	Ac-LTF$r8AYWSQL$S-NH2	1547.84	774.92	774.96
361	Ac-LTF$r8AYWRAL$S-NH2	1559.89	780.95	780.95
362	Ac-LTF$r8AYWRQL$A-NH2	1600.91	801.46	801.52
363	Ac-LTF$r8AYWRAL$A-NH2	1543.89	772.95	773.03
364	Ac-LTF$r5HYWAQL$s8S-NH2	1597.87	799.94	799.97
365	Ac-LTF$HYWAQL$r8S-NH2	1597.87	799.94	799.97
366	Ac-LTF$r8HYWAAL$S-NH2	1540.84	771.42	771.48
367	Ac-LTF$r8HYWAAbuL$S-NH2	1554.86	778.43	778.51
368	Ac-LTF$r8HYWALL$S-NH2	1582.89	792.45	792.49
369	Ac-F$r8AYWHAL$A-NH2	1310.72	656.36	656.4
370	Ac-F$r8AYWAAL$A-NH2	1244.70	623.35	1245.61
371	Ac-F$r8AYWSAL$A-NH2	1260.69	631.35	1261.6
372	Ac-F$r8AYWRAL$A-NH2	1329.76	665.88	1330.72
373	Ac-F$r8AYWKAL$A-NH2	1301.75	651.88	1302.67
374	Ac-F$r8AYWOAL$A-NH2	1287.74	644.87	1289.13
375	Ac-F$r8VYWEAc3cL$A-NH2	1342.73	672.37	1343.67
376	Ac-F$r8FYWEAc3cL$A-NH2	1390.73	696.37	1392.14
377	Ac-F$r8WYWEAc3cL$A-NH2	1429.74	715.87	1431.44
378	Ac-F$r8RYWEAc3cL$A-NH2	1399.77	700.89	700.95
379	Ac-F$r8KYWEAc3cL$A-NH2	1371.76	686.88	686.97
380	Ac-F$r8ANleWEAc3cL$A-NH2	1264.72	633.36	1265.59
381	Ac-F$r8AVWEAc3cL$A-NH2	1250.71	626.36	1252.2
382	Ac-F$r8AFWEAc3cL$A-NH2	1298.71	650.36	1299.64
383	Ac-F$r8AWWEAc3cL$A-NH2	1337.72	669.86	1338.64
384	Ac-F$r8ARWEAc3cL$A-NH2	1307.74	654.87	655
385	Ac-F$r8AKWEAc3cL$A-NH2	1279.73	640.87	641.01

386	Ac-F$r8AYWVAc3cL$A-NH2	1284.73	643.37	643.38
387	Ac-F$r8AYWFAc3cL$A-NH2	1332.73	667.37	667.43
388	Ac-F$r8AYWWAc3cL$A-NH2	1371.74	686.87	686.97
389	Ac-F$r8AYWRAc3cL$A-NH2	1341.76	671.88	671.94
390	Ac-F$r8AYWKAc3cL$A-NH2	1313.75	657.88	657.88
391	Ac-F$r8AYWEVL$A-NH2	1330.73	666.37	666.47
392	Ac-F$r8AYWEFL$A-NH2	1378.73	690.37	690.44
393	Ac-F$r8AYWEWL$A-NH2	1417.74	709.87	709.91
394	Ac-F$r8AYWERL$A-NH2	1387.77	694.89	1388.66
395	Ac-F$r8AYWEKL$A-NH2	1359.76	680.88	1361.21
396	Ac-F$r8AYWEAc3cL$V-NH2	1342.73	672.37	1343.59
397	Ac-F$r8AYWEAc3cL$F-NH2	1390.73	696.37	1392.58
398	Ac-F$r8AYWEAc3cL$W-NH2	1429.74	715.87	1431.29
399	Ac-F$r8AYWEAc3cL$R-NH2	1399.77	700.89	700.95
400	Ac-F$r8AYWEAc3cL$K-NH2	1371.76	686.88	686.97
401	Ac-F$r8AYWEAc3cL$AV-NH2	1413.77	707.89	707.91
402	Ac-F$r8AYWEAc3cL$AF-NH2	1461.77	731.89	731.96
403	Ac-F$r8AYWEAc3cL$AW-NH2	1500.78	751.39	751.5
404	Ac-F$r8AYWEAc3cL$AR-NH2	1470.80	736.40	736.47
405	Ac-F$r8AYWEAc3cL$AK-NH2	1442.80	722.40	722.41
406	Ac-F$r8AYWEAc3cL$AH-NH2	1451.76	726.88	726.93
407	Ac-LTF2NO2$r8HYWAQL$S-NH2	1642.85	822.43	822.54
408	Ac-LTA$r8HYAAQL$S-NH2	1406.79	704.40	704.5
409	Ac-LTF$r8HYAAQL$S-NH2	1482.82	742.41	742.47
410	Ac-QSQQTF$r8NLWALL$AN-NH2	1966.07	984.04	984.38
411	Ac-QAibQQTF$r8NLWALL$AN-NH2	1964.09	983.05	983.42
412	Ac-QAibQQTF$r8ALWALL$AN-NH2	1921.08	961.54	961.59
413	Ac-AAAATF$r8AAWAAL$AA-NH2	1608.90	805.45	805.52
414	Ac-F$r8AAWRAL$Q-NH2	1294.76	648.38	648.48
415	Ac-TF$r8AAWAAL$Q-NH2	1310.74	656.37	1311.62
416	Ac-TF$r8AAWRAL$A-NH2	1338.78	670.39	670.46
417	Ac-VF$r8AAWRAL$Q-NH2	1393.82	697.91	697.99
418	Ac-AF$r8AAWAAL$A-NH2	1223.71	612.86	1224.67
420	Ac-TF$r8AAWKAL$Q-NH2	1367.80	684.90	684.97
421	Ac-TF$r8AAWOAL$Q-NH2	1353.78	677.89	678.01
422	Ac-TF$r8AAWSAL$Q-NH2	1326.73	664.37	664.47
423	Ac-LTF$r8AAWRAL$Q-NH2	1508.89	755.45	755.49
424	Ac-F$r8AYWAQL$A-NH2	1301.72	651.86	651.96
425	Ac-F$r8AWWAAL$A-NH2	1267.71	634.86	634.87
426	Ac-F$r8AWWAQL$A-NH2	1324.73	663.37	663.43
427	Ac-F$r8AYWEAL$-NH2	1231.66	616.83	1232.93
428	Ac-F$r8AYWAAL$-NH2	1173.66	587.83	1175.09
429	Ac-F$r8AYWKAL$-NH2	1230.72	616.36	616.44
430	Ac-F$r8AYWOAL$-NH2	1216.70	609.35	609.48
431	Ac-F$r8AYWQAL$-NH2	1230.68	616.34	616.44
432	Ac-F$r8AYWAQL$-NH2	1230.68	616.34	616.37
433	Ac-F$r8HYWDQL$S-NH2	1427.72	714.86	714.86
434	Ac-F$r8HFWEQL$S-NH2	1425.74	713.87	713.98
435	Ac-F$r8AYWHQL$S-NH2	1383.73	692.87	692.96
436	Ac-F$r8AYWKQL$S-NH2	1374.77	688.39	688.45
437	Ac-F$r8AYWOQL$S-NH2	1360.75	681.38	681.49

438	Ac-F$r8HYWSQL$S-NH2	1399.73	700.87	700.95
439	Ac-F$r8HWWEQL$S-NH2	1464.76	733.38	733.44
440	Ac-F$r8HWWAQL$S-NH2	1406.75	704.38	704.43
441	Ac-F$r8AWWHQL$S-NH2	1406.75	704.38	704.43
442	Ac-F$r8AWWKQL$S-NH2	1397.79	699.90	699.92
443	Ac-F$r8AWWOQL$S-NH2	1383.77	692.89	692.96
444	Ac-F$r8HWWSQL$S-NH2	1422.75	712.38	712.42
445	Ac-LTF$r8NYWANleL$Q-NH2	1600.90	801.45	801.52
446	Ac-LTF$r8NLWAQL$Q-NH2	1565.90	783.95	784.06
447	Ac-LTF$r8NYWANleL$A-NH2	1543.88	772.94	773.03
448	Ac-LTF$r8NLWAQL$A-NH2	1508.88	755.44	755.49
449	Ac-LTF$r8AYWANleL$Q-NH2	1557.90	779.95	780.06
450	Ac-LTF$r8ALWAQL$Q-NH2	1522.89	762.45	762.45
451	Ac-LAF$r8NYWANleL$Q-NH2	1570.89	786.45	786.5
452	Ac-LAF$r8NLWAQL$Q-NH2	1535.89	768.95	769.03
453	Ac-LAF$r8AYWANleL$A-NH2	1470.86	736.43	736.47
454	Ac-LAF$r8ALWAQL$A-NH2	1435.86	718.93	719.01
455	Ac-LAF$r8AYWAAL$A-NH2	1428.82	715.41	715.41
456	Ac-F$r8AYWEAc3cL$AAib-NH2	1399.75	700.88	700.95
457	Ac-F$r8AYWAQL$AA-NH2	1372.75	687.38	687.78
458	Ac-F$r8AYWAAc3cL$AA-NH2	1327.73	664.87	664.84
459	Ac-F$r8AYWSAc3cL$AA-NH2	1343.73	672.87	672.9
460	Ac-F$r8AYWEAc3cL$AS-NH2	1401.73	701.87	701.84
461	Ac-F$r8AYWEAc3cL$AT-NH2	1415.75	708.88	708.87
462	Ac-F$r8AYWEAc3cL$AL-NH2	1427.79	714.90	714.94
463	Ac-F$r8AYWEAc3cL$AQ-NH2	1442.76	722.38	722.41
464	Ac-F$r8AFWEAc3cL$AA-NH2	1369.74	685.87	685.93
465	Ac-F$r8AWWEAc3cL$AA-NH2	1408.75	705.38	705.39
466	Ac-F$r8AYWEAc3cL$SA-NH2	1401.73	701.87	701.99
467	Ac-F$r8AYWEAL$AA-NH2	1373.74	687.87	687.93
468	Ac-F$r8AYWENleL$AA-NH2	1415.79	708.90	708.94
469	Ac-F$r8AYWEAc3cL$AbuA-NH2	1399.75	700.88	700.95
470	Ac-F$r8AYWEAc3cL$NleA-NH2	1427.79	714.90	714.86
471	Ac-F$r8AYWEAibL$NleA-NH2	1429.80	715.90	715.97
472	Ac-F$r8AYWEAL$NleA-NH2	1415.79	708.90	708.94
473	Ac-F$r8AYWENleL$NleA-NH2	1457.83	729.92	729.96
474	Ac-F$r8AYWEAibL$Abu-NH2	1330.73	666.37	666.39
475	Ac-F$r8AYWENleL$Abu-NH2	1358.76	680.38	680.39
476	Ac-F$r8AYWEAL$Abu-NH2	1316.72	659.36	659.36
477	Ac-LTF$r8AFWAQL$S-NH2	1515.85	758.93	759.12
478	Ac-LTF$r8AWWAQL$S-NH2	1554.86	778.43	778.51
479	Ac-LTF$r8AYWAQI$S-NH2	1531.84	766.92	766.96
480	Ac-LTF$r8AYWAQNle$S-NH2	1531.84	766.92	766.96
481	Ac-LTF$r8AYWAQL$SA-NH2	1602.88	802.44	802.48
482	Ac-LTF$r8AWWAQL$A-NH2	1538.87	770.44	770.89
483	Ac-LTF$r8AYWAQI$A-NH2	1515.85	758.93	759.42
484	Ac-LTF$r8AYWAQNle$A-NH2	1515.85	758.93	759.42
485	Ac-LTF$r8AYWAQL$AA-NH2	1586.89	794.45	794.94
486	Ac-LTF$r8HWWAQL$S-NH2	1620.88	811.44	811.47
487	Ac-LTF$r8HRWAQL$S-NH2	1590.90	796.45	796.52
488	Ac-LTF$r8HKWAQL$S-NH2	1562.90	782.45	782.53

489	Ac-LTF$r8HYWAQL$W-NH2	1696.91	849.46	849.5
491	Ac-F$r8AYWAbuAL$A-NH2	1258.71	630.36	630.5
492	Ac-F$r8AbuYWEAL$A-NH2	1316.72	659.36	659.51
493	Ac-NlePRF%r8NYWRLL%QN-NH2	1954.13	978.07	978.54
494	Ac-TSF%r8HYWAQL%S-NH2	1573.83	787.92	787.98
495	Ac-LTF%r8AYWAQL%S-NH2	1533.86	767.93	768
496	Ac-HTF$r8HYWAQL$S-NH2	1621.84	811.92	811.96
497	Ac-LHF$r8HYWAQL$S-NH2	1633.88	817.94	818.02
498	Ac-LTF$r8HHWAQL$S-NH2	1571.86	786.93	786.94
499	Ac-LTF$r8HYWHQL$S-NH2	1663.89	832.95	832.38
500	Ac-LTF$r8HYWAHL$S-NH2	1606.87	804.44	804.48
501	Ac-LTF$r8HYWAQL$H-NH2	1647.89	824.95	824.98
502	Ac-LTF$r8HYWAQL$S-NHPr	1639.91	820.96	820.98
503	Ac-LTF$r8HYWAQL$S-NHsBu	1653.93	827.97	828.02
504	Ac-LTF$r8HYWAQL$S-NHiBu	1653.93	827.97	828.02
505	Ac-LTF$r8HYWAQL$S-NHBn	1687.91	844.96	844.44
506	Ac-LTF$r8HYWAQL$S-NHPe	1700.92	851.46	851.99
507	Ac-LTF$r8HYWAQL$S-NHChx	1679.94	840.97	841.04
508	Ac-ETF$r8AYWAQL$S-NH2	1547.80	774.90	774.96
509	Ac-STF$r8AYWAQL$S-NH2	1505.79	753.90	753.94
510	Ac-LEF$r8AYWAQL$S-NH2	1559.84	780.92	781.25
511	Ac-LSF$r8AYWAQL$S-NH2	1517.83	759.92	759.93
512	Ac-LTF$r8EYWAQL$S-NH2	1589.85	795.93	795.97
513	Ac-LTF$r8SYWAQL$S-NH2	1547.84	774.92	774.96
514	Ac-LTF$r8AYWEQL$S-NH2	1589.85	795.93	795.9
515	Ac-LTF$r8AYWAEL$S-NH2	1532.83	767.42	766.96
516	Ac-LTF$r8AYWASL$S-NH2	1490.82	746.41	746.46
517	Ac-LTF$r8AYWAQL$E-NH2	1573.85	787.93	787.98
518	Ac-LTF2CN$r8HYWAQL$S-NH2	1622.86	812.43	812.47
519	Ac-LTF3Cl$r8HYWAQL$S-NH2	1631.83	816.92	816.99
520	Ac-LTDip$r8HYWAQL$S-NH2	1673.90	837.95	838.01
521	Ac-LTF$r8HYWAQTle$S-NH2	1597.87	799.94	800.04
522	Ac-F$r8AY6clWEAL$A-NH2	1336.66	669.33	1338.56
523	Ac-F$r8AYdl6brWEAL$A-NH2	1380.61	691.31	692.2
524	Ac-F$r8AYdl6fWEAL$A-NH2	1320.69	661.35	1321.61
525	Ac-F$r8AYdl4mWEAL$A-NH2	1316.72	659.36	659.36
526	Ac-F$r8AYdl5clWEAL$A-NH2	1336.66	669.33	669.35
527	Ac-F$r8AYdl7mWEAL$A-NH2	1316.72	659.36	659.36
528	Ac-LTF%r8HYWAQL%A-NH2	1583.89	792.95	793.01
529	Ac-LTF$r8HCouWAQL$S-NH2	1679.87	840.94	841.38
530	Ac-LTFEHCouWAQLTS-NH2	1617.75	809.88	809.96
531	Ac-LTA$r8HCouWAQL$S-NH2	1603.84	802.92	803.36
532	Ac-F$r8AYWEAL$AbuA-NH2	1387.75	694.88	694.88
533	Ac-F$r8AYWEAI$AA-NH2	1373.74	687.87	687.93
534	Ac-F$r8AYWEANle$AA-NH2	1373.74	687.87	687.93
535	Ac-F$r8AYWEAmlL$AA-NH2	1429.80	715.90	715.97
536	Ac-F$r8AYWQAL$AA-NH2	1372.75	687.38	687.48
537	Ac-F$r8AYWAAL$AA-NH2	1315.73	658.87	658.92
538	Ac-F$r8AYWAbuAL$AA-NH2	1329.75	665.88	665.95
539	Ac-F$r8AYWNleAL$AA-NH2	1357.78	679.89	679.94
540	Ac-F$r8AbuYWEAL$AA-NH2	1387.75	694.88	694.96

541	Ac-F$r8NleYWEAL$AA-NH2	1415.79	708.90	708.94
542	Ac-F$r8FYWEAL$AA-NH2	1449.77	725.89	725.97
543	Ac-LTF$r8HYWAQhL$S-NH2	1611.88	806.94	807
544	Ac-LTF$r8HYWAQAdm$S-NH2	1675.91	838.96	839.04
545	Ac-LTF$r8HYWAQIgl$S-NH2	1659.88	830.94	829.94
546	Ac-F$r8AYWAQL$AA-NH2	1372.75	687.38	687.48
547	Ac-LTF$r8ALWAQL$Q-NH2	1522.89	762.45	762.52
548	Ac-F$r8AYWEAL$AA-NH2	1373.74	687.87	687.93
549	Ac-F$r8AYWENleL$AA-NH2	1415.79	708.90	708.94
550	Ac-F$r8AYWEAibL$Abu-NH2	1330.73	666.37	666.39
551	Ac-F$r8AYWENleL$Abu-NH2	1358.76	680.38	680.38
552	Ac-F$r8AYWEAL$Abu-NH2	1316.72	659.36	659.36
553	Ac-F$r8AYWEAc3cL$AbuA-NH2	1399.75	700.88	700.95
554	Ac-F$r8AYWEAc3cL$NleA-NH2	1427.79	714.90	715.01
555	H-LTF$r8AYWAQL$S-NH2	1489.83	745.92	745.95
556	mdPEG3-LTF$r8AYWAQL$S-NH2	1679.92	840.96	840.97
557	mdPEG7-LTF$r8AYWAQL$S-NH2	1856.02	929.01	929.03
558	Ac-F$r8ApmpEt6clWEAL$A-NH2	1470.71	736.36	788.17
559	Ac-LTF3Cl$r8AYWAQL$S-NH2	1565.81	783.91	809.18
560	Ac-LTF3Cl$r8HYWAQL$A-NH2	1615.83	808.92	875.24
561	Ac-LTF3Cl$r8HYWWQL$S-NH2	1746.87	874.44	841.65
562	Ac-LTF3Cl$r8AYWWQL$S-NH2	1680.85	841.43	824.63
563	Ac-LTF$r8AYWWQL$S-NH2	1646.89	824.45	849.98
564	Ac-LTF$r8HYWWQL$A-NH2	1696.91	849.46	816.67
565	Ac-LTF$r8AYWWQL$A-NH2	1630.89	816.45	776.15
566	Ac-LTF4F$r8AYWAQL$S-NH2	1549.83	775.92	776.15
567	Ac-LTF2F$r8AYWAQL$S-NH2	1549.83	775.92	776.15
568	Ac-LTF3F$r8AYWAQL$S-NH2	1549.83	775.92	785.12
569	Ac-LTF34F2$r8AYWAQL$S-NH2	1567.83	784.92	785.12
570	Ac-LTF35F2$r8AYWAQL$S-NH2	1567.83	784.92	1338.74
571	Ac-F3Cl$r8AYWEAL$A-NH2	1336.66	669.33	705.28
572	Ac-F3Cl$r8AYWEAL$AA-NH2	1407.70	704.85	680.11
573	Ac-F$r8AY6clWEAL$AA-NH2	1407.70	704.85	736.83
574	Ac-F$r8AY6clWEAL$-NH2	1265.63	633.82	784.1
575	Ac-LTF$r8HYWAQLSt/S-NH2	16.03	9.02	826.98
576	Ac-LTF$r8HYWAQL$S-NHsBu	1653.93	827.97	828.02
577	Ac-STF$r8AYWAQL$S-NH2	1505.79	753.90	753.94
578	Ac-LTF$r8AYWAEL$S-NH2	1532.83	767.42	767.41
579	Ac-LTF$r8AYWAQL$E-NH2	1573.85	787.93	787.98
580	mdPEG3-LTF$r8AYWAQL$S-NH2	1679.92	840.96	840.97
581	Ac-LTF$r8AYWAQhL$S-NH2	1545.86	773.93	774.31
583	Ac-LTF$r8AYWAQCha$S-NH2	1571.88	786.94	787.3
584	Ac-LTF$r8AYWAQChg$S-NH2	1557.86	779.93	780.4
585	Ac-LTF$r8AYWAQCba$S-NH2	1543.84	772.92	780.13
586	Ac-LTF$r8AYWAQF$S-NH2	1565.83	783.92	784.2
587	Ac-LTF4F$r8HYWAQhL$S-NH2	1629.87	815.94	815.36
588	Ac-LTF4F$r8HYWAQCha$S-NH2	1655.89	828.95	828.39
589	Ac-LTF4F$r8HYWAQChg$S-NH2	1641.87	821.94	821.35
590	Ac-LTF4F$r8HYWAQCba$S-NH2	1627.86	814.93	814.32
591	Ac-LTF4F$r8AYWAQhL$S-NH2	1563.85	782.93	782.36
592	Ac-LTF4F$r8AYWAQCha$S-NH2	1589.87	795.94	795.38

593	Ac-LTF4F$r8AYWAQChg$S-NH2	1575.85	788.93	788.35
594	Ac-LTF4F$r8AYWAQCba$S-NH2	1561.83	781.92	781.39
595	Ac-LTF3Cl$r8AYWAQhL$S-NH2	1579.82	790.91	790.35
596	Ac-LTF3Cl$r8AYWAQCha$S-NH2	1605.84	803.92	803.67
597	Ac-LTF3Cl$r8AYWAQChg$S-NH2	1591.82	796.91	796.34
598	Ac-LTF3Cl$r8AYWAQCba$S-NH2	1577.81	789.91	789.39
599	Ac-LTF$r8AYWAQhF$S-NH2	1579.84	790.92	791.14
600	Ac-LTF$r8AYWAQF3CF3$S-NH2	1633.82	817.91	818.15
601	Ac-LTF$r8AYWAQF3Me$S-NH2	1581.86	791.93	791.32
602	Ac-LTF$r8AYWAQ1Nal$S-NH2	1615.84	808.92	809.18
603	Ac-LTF$r8AYWAQBip$S-NH2	1641.86	821.93	822.13
604	Ac-LTF$r8FYWAQL$A-NH2	1591.88	796.94	797.33
605	Ac-LTF$r8HYWAQL$S-NHAm	1667.94	834.97	835.92
606	Ac-LTF$r8HYWAQL$S-NHiAm	1667.94	834.97	835.55
607	Ac-LTF$r8HYWAQL$S-NHnPr3Ph	1715.94	858.97	859.79
608	Ac-LTF$r8HYWAQL$S-NHnBu3,3Me	1681.96	841.98	842.49
610	Ac-LTF$r8HYWAQL$S-NHnPr	1639.91	820.96	821.58
611	Ac-LTF$r8HYWAQL$S-NHnEt2Ch	1707.98	854.99	855.35
612	Ac-LTF$r8HYWAQL$S-NHHex	1681.96	841.98	842.4
613	Ac-LTF$r8AYWAQL$S-NHmdPeg2	1633.91	817.96	818.35
614	Ac-LTF$r8AYWAQL$A-NHmdPeg2	1617.92	809.96	810.3
615	Ac-LTF$r8AYWAQL$A-NHmdPeg4	1705.97	853.99	854.33
616	Ac-F$r8AYdl4mWEAL$A-NH2	1316.72	659.36	659.44
617	Ac-F$r8AYdl5clWEAL$A-NH2	1336.66	669.33	669.43
618	Ac-LThF$r8AYWAQL$S-NH2	1545.86	773.93	774.11
619	Ac-LT2Nal$r8AYWAQL$S-NH2	1581.86	791.93	792.43
620	Ac-LTA$r8AYWAQL$S-NH2	1455.81	728.91	729.15
621	Ac-LTF$r8AYWVQL$S-NH2	1559.88	780.94	781.24
622	Ac-LTF$r8HYWAAL$A-NH2	1524.85	763.43	763.86
623	Ac-LTF$r8VYWAQL$A-NH2	1543.88	772.94	773.37
624	Ac-LTF$r8IYWAQL$S-NH2	1573.89	787.95	788.17
625	Ac-FTF$r8VYWSQL$S-NH2	1609.85	805.93	806.22
626	Ac-ITF$r8FYWAQL$S-NH2	1607.88	804.94	805.2
627	Ac-2NalTF$r8VYWSQL$S-NH2	1659.87	830.94	831.2
628	Ac-ITF$r8LYWSQL$S-NH2	1589.89	795.95	796.13
629	Ac-FTF$r8FYWAQL$S-NH2	1641.86	821.93	822.13
630	Ac-WTF$r8VYWAQL$S-NH2	1632.87	817.44	817.69
631	Ac-WTF$r8WYWAQL$S-NH2	1719.88	860.94	861.36
632	Ac-VTF$r8AYWSQL$S-NH2	1533.82	767.91	768.19
633	Ac-WTF$r8FYWSQL$S-NH2	1696.87	849.44	849.7
634	Ac-FTF$r8IYWAQL$S-NH2	1607.88	804.94	805.2
635	Ac-WTF$r8VYWSQL$S-NH2	1648.87	825.44	824.8
636	Ac-FTF$r8LYWSQL$S-NH2	1623.87	812.94	812.8
637	Ac-YTF$r8FYWSQL$S-NH2	1673.85	837.93	837.8
638	Ac-LTF$r8AY6clWEAL$A-NH2	1550.79	776.40	776.14
639	Ac-LTF$r8AY6clWSQL$S-NH2	1581.80	791.90	791.68
640	Ac-F$r8AY6clWSAL$A-NH2	1294.65	648.33	647.67
641	Ac-F$r8AY6clWQAL$AA-NH2	1406.72	704.36	703.84
642	Ac-LHF$r8AYWAQL$S-NH2	1567.86	784.93	785.21
643	Ac-LTF$r8AYWAQL$S-NH2	1531.84	766.92	767.17
644	Ac-LTF$r8AHWAQL$S-NH2	1505.84	753.92	754.13

645	Ac-LTF$r8AYWAHL$S-NH2	1540.84	771.42	771.61
646	Ac-LTF$r8AYWAQL$H-NH2	1581.87	791.94	792.15
647	H-LTF$r8AYWAQL$A-NH2	1473.84	737.92	737.29
648	Ac-HHF$r8AYWAQL$S-NH2	1591.83	796.92	797.35
649	Ac-aAibWTF$r8VYWSQL$S-NH2	1804.96	903.48	903.64
650	Ac-AibWTF$r8HYWAQL$S-NH2	1755.91	878.96	879.4
651	Ac-AibAWTF$r8HYWAQL$S-NH2	1826.95	914.48	914.7
652	Ac-fWTF$r8HYWAQL$S-NH2	1817.93	909.97	910.1
653	Ac-AibWWTF$r8HYWAQL$S-NH2	1941.99	972.00	972.2
654	Ac-WTF$r8LYWSQL$S-NH2	1662.88	832.44	832.8
655	Ac-WTF$r8NleYWSQL$S-NH2	1662.88	832.44	832.6
656	Ac-LTF$r8AYWSQL$a-NH2	1531.84	766.92	767.2
657	Ac-LTF$r8EYWARL$A-NH2	1601.90	801.95	802.1
658	Ac-LTF$r8EYWAHL$A-NH2	1582.86	792.43	792.6
659	Ac-aTF$r8AYWAQL$S-NH2	1489.80	745.90	746.08
660	Ac-AibTF$r8AYWAQL$S-NH2	1503.81	752.91	753.11
661	Ac-AmfTF$r8AYWAQL$S-NH2	1579.84	790.92	791.14
662	Ac-AmwTF$r8AYWAQL$S-NH2	1618.86	810.43	810.66
663	Ac-NmLTF$r8AYWAQL$S-NH2	1545.86	773.93	774.11
664	Ac-LNmTF$r8AYWAQL$S-NH2	1545.86	773.93	774.11
665	Ac-LSarF$r8AYWAQL$S-NH2	1501.83	751.92	752.18
667	Ac-LGF$r8AYWAQL$S-NH2	1487.82	744.91	745.15
668	Ac-LTNmF$r8AYWAQL$S-NH2	1545.86	773.93	774.2
669	Ac-TF$r8AYWAQL$S-NH2	1418.76	710.38	710.64
670	Ac-ETF$r8AYWAQL$A-NH2	1531.81	766.91	767.2
671	Ac-LTF$r8EYWAQL$A-NH2	1573.85	787.93	788.1
672	Ac-LT2Nal$r8AYWSQL$S-NH2	1597.85	799.93	800.4
673	Ac-LTF$r8AYWAAL$S-NH2	1474.82	738.41	738.68
674	Ac-LTF$r8AYWAQhCha$S-NH2	1585.89	793.95	794.19
675	Ac-LTF$r8AYWAQChg$S-NH2	1557.86	779.93	780.97
676	Ac-LTF$r8AYWAQCba$S-NH2	1543.84	772.92	773.19
677	Ac-LTF$r8AYWAQF3CF3$S-NH2	1633.82	817.91	818.15
678	Ac-LTF$r8AYWAQ1Nal$S-NH2	1615.84	808.92	809.18
679	Ac-LTF$r8AYWAQBip$S-NH2	1641.86	821.93	822.32
680	Ac-LT2Nal$r8AYWAQL$S-NH2	1581.86	791.93	792.15
681	Ac-LTF$r8AYWVQL$S-NH2	1559.88	780.94	781.62
682	Ac-LTF$r8AWWAQL$S-NH2	1554.86	778.43	778.65
683	Ac-FTF$r8VYWSQL$S-NH2	1609.85	805.93	806.12
684	Ac-ITF$r8FYWAQL$S-NH2	1607.88	804.94	805.2
685	Ac-ITF$r8LYWSQL$S-NH2	1589.89	795.95	796.22
686	Ac-FTF$r8FYWAQL$S-NH2	1641.86	821.93	822.41
687	Ac-VTF$r8AYWSQL$S-NH2	1533.82	767.91	768.19
688	Ac-LTF$r8AHWAQL$S-NH2	1505.84	753.92	754.31
689	Ac-LTF$r8AYWAQL$H-NH2	1581.87	791.94	791.94
690	Ac-LTF$r8AYWAHL$S-NH2	1540.84	771.42	771.61
691	Ac-aAibWTF$r8VYWSQL$S-NH2	1804.96	903.48	903.9
692	Ac-AibWTF$r8HYWAQL$S-NH2	1755.91	878.96	879.5
693	Ac-AibAWTF$r8HYWAQL$S-NH2	1826.95	914.48	914.7
694	Ac-fWTF$r8HYWAQL$S-NH2	1817.93	909.97	910.2
695	Ac-AibWWTF$r8HYWAQL$S-NH2	1941.99	972.00	972.7
696	Ac-WTF$r8LYWSQL$S-NH2	1662.88	832.44	832.7

697	Ac-WTF$r8NleYWSQL$S-NH2	1662.88	832.44	832.7
698	Ac-LTF$r8AYWSQL$a-NH2	1531.84	766.92	767.2
699	Ac-LTF$r8EYWARL$A-NH2	1601.90	801.95	802.2
700	Ac-LTF$r8EYWAHL$A-NH2	1582.86	792.43	792.6
701	Ac-aTF$r8AYWAQL$S-NH2	1489.80	745.90	746.1
702	Ac-AibTF$r8AYWAQL$S-NH2	1503.81	752.91	753.2
703	Ac-AmfTF$r8AYWAQL$S-NH2	1579.84	790.92	791.2
704	Ac-AmwTF$r8AYWAQL$S-NH2	1618.86	810.43	810.7
705	Ac-NmLTF$r8AYWAQL$S-NH2	1545.86	773.93	774.1
706	Ac-LNmTF$r8AYWAQL$S-NH2	1545.86	773.93	774.4
707	Ac-LSarF$r8AYWAQL$S-NH2	1501.83	751.92	752.1
708	Ac-TF$r8AYWAQL$S-NH2	1418.76	710.38	710.8
709	Ac-ETF$r8AYWAQL$A-NH2	1531.81	766.91	767.4
710	Ac-LTF$r8EYWAQL$A-NH2	1573.85	787.93	788.2
711	Ac-WTF$r8VYWSQL$S-NH2	1648.87	825.44	825.2
713	Ac-YTF$r8FYWSQL$S-NH2	1673.85	837.93	837.3
714	Ac-F$r8AY6clWSAL$A-NH2	1294.65	648.33	647.74
715	Ac-ETF$r8EYWVQL$S-NH2	1633.84	817.92	817.36
716	Ac-ETF$r8EHWAQL$A-NH2	1563.81	782.91	782.36
717	Ac-ITF$r8EYWAQL$S-NH2	1589.85	795.93	795.38
718	Ac-ITF$r8EHWVQL$A-NH2	1575.88	788.94	788.42
719	Ac-ITF$r8EHWAQL$S-NH2	1563.85	782.93	782.43
720	Ac-LTF4F$r8AYWAQCba$S-NH2	1561.83	781.92	781.32
721	Ac-LTF3Cl$r8AYWAQhL$S-NH2	1579.82	790.91	790.64
722	Ac-LTF3Cl$r8AYWAQCha$S-NH2	1605.84	803.92	803.37
723	Ac-LTF3Cl$r8AYWAQChg$S-NH2	1591.82	796.91	796.27
724	Ac-LTF3Cl$r8AYWAQCba$S-NH2	1577.81	789.91	789.83
725	Ac-LTF$r8AY6clWSQL$S-NH2	1581.80	791.90	791.75
726	Ac-LTF4F$r8HYWAQhL$S-NH2	1629.87	815.94	815.36
727	Ac-LTF4F$r8HYWAQCba$S-NH2	1627.86	814.93	814.32
728	Ac-LTF4F$r8AYWAQhL$S-NH2	1563.85	782.93	782.36
729	Ac-LTF4F$r8AYWAQChg$S-NH2	1575.85	788.93	788.35
730	Ac-ETF$r8EYWVAL$S-NH2	1576.82	789.41	788.79
731	Ac-ETF$r8EHWAAL$A-NH2	1506.79	754.40	754.8
732	Ac-ITF$r8EYWAAL$S-NH2	1532.83	767.42	767.75
733	Ac-ITF$r8EHWVAL$A-NH2	1518.86	760.43	760.81
734	Ac-ITF$r8EHWAAL$S-NH2	1506.82	754.41	754.8
735	Pam-LTF$r8EYWAQL$S-NH2	1786.07	894.04	894.48
736	Pam-ETF$r8EYWAQL$S-NH2	1802.03	902.02	902.34
737	Ac-LTF$r8AYWLQL$S-NH2	1573.89	787.95	787.39
738	Ac-LTF$r8EYWLQL$S-NH2	1631.90	816.95	817.33
739	Ac-LTF$r8EHWLQL$S-NH2	1605.89	803.95	804.29
740	Ac-LTF$r8VYWAQL$S-NH2	1559.88	780.94	781.34
741	Ac-LTF$r8AYWSQL$S-NH2	1547.84	774.92	775.33
742	Ac-ETF$r8AYWAQL$S-NH2	1547.80	774.90	775.7
743	Ac-LTF$r8EYWAQL$S-NH2	1589.85	795.93	796.33
744	Ac-LTF$r8HYWAQL$S-NHAm	1667.94	834.97	835.37
745	Ac-LTF$r8HYWAQL$S-NHiAm	1667.94	834.97	835.27
746	Ac-LTF$r8HYWAQL$S-NHnPr3Ph	1715.94	858.97	859.42
747	Ac-LTF$r8HYWAQL$S-NHnBu3,3Me	1681.96	841.98	842.67
748	Ac-LTF$r8HYWAQL$S-NHnBu	1653.93	827.97	828.24

749	Ac-LTF$r8HYWAQL$S-NHnPr	1639.91	820.96	821.31
750	Ac-LTF$r8HYWAQL$S-NHnEt2Ch	1707.98	854.99	855.35
751	Ac-LTF$r8HYWAQL$S-NHHex	1681.96	841.98	842.4
752	Ac-LTF$r8AYWAQL$S-NHmdPeg2	1633.91	817.96	855.35
753	Ac-LTF$r8AYWAQL$A-NHmdPeg2	1617.92	809.96	810.58
754	Ac-LTF$r5AYWAAL$s8S-NH2	1474.82	738.41	738.79
755	Ac-LTF$r8AYWCouQL$S-NH2	1705.88	853.94	854.61
756	Ac-LTF$r8CouYWAQL$S-NH2	1705.88	853.94	854.7
757	Ac-CouTF$r8AYWAQL$S-NH2	1663.83	832.92	833.33
758	H-LTF$r8AYWAQL$A-NH2	1473.84	737.92	737.29
759	Ac-HHF$r8AYWAQL$S-NH2	1591.83	796.92	797.72
760	Ac-LT2Nal$r8AYWSQL$S-NH2	1597.85	799.93	800.68
761	Ac-LTF$r8HCouWAQL$S-NH2	1679.87	840.94	841.38
762	Ac-LTF$r8AYWCou2QL$S-NH2	1789.94	895.97	896.51
763	Ac-LTF$r8Cou2YWAQL$S-NH2	1789.94	895.97	896.5
764	Ac-Cou2TF$r8AYWAQL$S-NH2	1747.90	874.95	875.42
765	Ac-LTF$r8ACou2WAQL$S-NH2	1697.92	849.96	850.82
766	Dmaac-LTF$r8AYWAQL$S-NH2	1574.89	788.45	788.82
767	Hexac-LTF$r8AYWAQL$S-NH2	1587.91	794.96	795.11
768	Napac-LTF$r8AYWAQL$S-NH2	1657.89	829.95	830.36
769	Pam-LTF$r8AYWAQL$S-NH2	1728.06	865.03	865.45
770	Ac-LT2Nal$r8HYAAQL$S-NH2	1532.84	767.42	767.61
771	Ac-LT2Nal$/r8HYWAQL$/S-NH2	1675.91	838.96	839.1
772	Ac-LT2Nal$r8HYFAQL$S-NH2	1608.87	805.44	805.9
773	Ac-LT2Nal$r8HWAAQL$S-NH2	1555.86	778.93	779.08
774	Ac-LT2Nal$r8HYAWQL$S-NH2	1647.88	824.94	825.04
775	Ac-LT2Nal$r8HYAAQW$S-NH2	1605.83	803.92	804.05
776	Ac-LTW$r8HYWAQL$S-NH2	1636.88	819.44	819.95
777	Ac-LT1Nal$r8HYWAQL$S-NH2	1647.88	824.94	825.41

[00381] In some embodiments, a peptidomimetic macrocycles disclosed herein do not comprise a peptidomimetic macrocycle structure as shown in Table 4b.

[00382] Table 4c shows examples of non-crosslinked polypeptides comprising D-amino acids.

Table 4c

SP	Sequence	Isomer	Exact Mass	Found Mass	Calc (M+1)/1	Calc (M+2)/2	Calc (M+3)/3
SP765	Ac-tawyanfekllr-NH2			777.46			
SP766	Ac-tawyanf4CF3ekllr-NH2			811.41			

Example 2: Safety and/or tolerability study

STUDY OBJECTIVES

[00383] This study is designed to (i) evaluate the safety and/or tolerability of peptide 1, which is peptide of this disclosure, administered by IV infusion once weekly for three consecutive weeks of a 21 or a 28-day cycle, and (ii) determine the DLTs and the MTD or OBD of peptide 1 in patients with advanced liquid cancers expressing WT p53 protein.

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. 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. 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.

INVESTIGATIONAL PLAN

Study Design

[00384] This study comprises a dose-escalation, 2-arm study designed to evaluate the safety, tolerability, PK, PD, and anti-liquid cancer cell effects of peptide 1 administered by IV infusion using 2 different dosing regimens of a 28- or 21-day cycle, in patients with advanced liquid cancer (e.g. leukemia, myeloma, and liquid lymphoma) expressing WT p53 protein (see p53 Status Determination below). For example, peptide 1 can be used in patients with relapsed/refractory acute myeloid leukemia (AML) and/or acute lymphoid leukemia (ALL). Patients receive peptide 1 either once weekly for three consecutive weeks for a 28-day cycle or twice weekly for two consecutive weeks for a 21-day cycle. Many patients with a liquid lymphoma present circulating tumor cells (CTC) in peripheral blood, which can be detected and analyzed using flow cytometry. Thus, detection of study drug-specific target engagement in these cells is possible.

[00385] The study consists of a Dose Escalation Phase (DEP) and an Expansion Phase (EXP). The DEP is a "3+3" dose escalation design to establish the MTD or OBD of peptide-1. The EXP enrolls up to 2 distinct groups of patients with specific liquid cancers at the MTD or OBD to further investigate the clinical safety profile and potential efficacy of the dose level. The selection of patients for the EXP is finalized based on results of the DEP, as well as data from additional nonclinical pharmacology studies. The later includes the investigation of multiple liquid cancer cell lines (e.g., leukemia, liquid lymphoma, myeloma) that facilitate the comparison of cell line sensitivity to peptide-1 across and within liquid cancer types.

[00386] Treatment of patients in the dose escalation and the dose expansion phases of the study continues until documentation of disease progression, unacceptable toxicity, or patient or physician decision to discontinue therapy.

[00387] p53 Status Determination and Tumor Sampling Requirement prior to Enrollment:

[00388] A central laboratory tests both archived tissue samples or fresh biopsy samples from all patients enrolled in the study for p53 status using Next-Generation Sequencing (NGS).

[00389] For the First 3 Dose Levels of Stage 1:

Patients can be enrolled irrespective of p53 status. Nevertheless, patients are still tested for p53 status at the central laboratory. To this end, archived tissue can be used (e.g., sample must not be older than 3 years), or alternatively, a fresh biopsy can be considered, unless the biopsy poses a significant risk to the patient.

[00390] Starting at Dose Level 4 of Stage 1 (and for patients enrolled in Stage 2 of the DEP):

[00391] Only patients with liquid cancer cells expressing WT p53 protein are enrolled. This key inclusion criterion is based on the proposed mechanism of action of peptide 1, which requires WT p53 protein to be pharmacologically active. The inclusion criterion is also supported by results of *in vitro* liquid cancer cell growth assays, in which peptide 1 demonstrates activity in liquid cancer cells expressing WT p53 protein, but not in cells with mutations of p53. Patients can meet the p53 requirement through one of the following scenarios:

- Patients can be eligible based on a previous p53 gene test result done at a local lab. These patients are still tested for p53 status using NGS at the central laboratory. To this end, archived tissue can be used (sample must not be older than 3 years), or alternatively, a fresh biopsy should be considered, unless the biopsy poses a significant risk to the patient. Patients who do not have archived tissue and for whom a biopsy poses a significant risk are not enrolled.
- Patients can be eligible based on archived tissue tested for p53 (sample must not be older than 3 years) at the central lab, or alternatively, a fresh biopsy can be considered, unless the biopsy poses a significant risk to the patient. Patients who do not have archived tissue and for whom a biopsy poses a significant risk, are not enrolled.

[00392] For patients enrolling into the EXP:

- Only patients with liquid cancer cells expressing p53 WT are enrolled, and all patients must be tested for p53 status using NGS at the central laboratory PRIOR to

enrollment. Archived tissue can be used (sample must not be older than 1 year), or alternatively, a fresh biopsy can be considered, unless the biopsy poses a significant risk to the patient. Patients who do not have archived tissue and for whom a biopsy poses a significant risk, are not enrolled.

[00393] Only patients with liquid cancer cells expressing WT p53 protein are enrolled. The determination of p53 status is performed on liquid cancer cell samples obtained during the screening period. The assay can be performed by study sites with required capabilities; otherwise it can be performed at a central laboratory. Results from archival tissue samples, if available, can be used to determine patient eligibility in the DEP. The total number of patients enrolled in the study depends on the number of dose levels and the number of patients in each cohort before MTD or OBD is established. Approximately 45 patients, exclusive of replacements for patients who discontinue for non-safety reasons, are enrolled in the DEP, and a total of up to approximately 60 additional patients for each of the up to two patient groups (total of 60) are enrolled in the EXP cohorts. Enrollment of a total of up to 100 patients is planned for the study. Approximately 6 clinical sites in the US are planned. The expected accrual phase is approximately 15 months. The expected follow-up phase is approximately 8 months after the last patient is enrolled, for a total study duration of approximately 23 months.

[00394] Patients who satisfy all inclusion and exclusion criteria, including documentation of WT p53 status, are enrolled in cohorts of 3 to 6 patients to receive peptide 1. Peptide 1 is administered by IV infusion in Dose Regimen A over 1 hour (±5 min) on Days 1, 8 and 15 of a 28-day cycle or in Dose Regimen B also over 1 hour (± 5 min), starting at Dose Level 3, on Days 1, 4, 8, 11 of a 21-day cycle.

[00395] Treatment continues until disease progression, unacceptable toxicity or patient or physician withdrawal of consent. After the MTD or OBD is established, additional patients can be enrolled in up to two separate expansion cohorts (approximately 30 patients per expansion cohort to gain further experience at this dose level and in particular patient or liquid cancer cell types. Selection of patient or liquid cancer cell types is determined in part on the basis of observations made in the dose escalation portion of the study.

[00396] Safety is evaluated based on the incidence, severity, duration, causality, seriousness, and type of AE, and changes in the patient's physical examination, vital signs and clinical laboratory results. Investigators use the NCI CTCAE version 4.0 to assess the severity of AEs.

[00397] Because the primary objectives of this study are based on safety and PK, statistical analyses are descriptive in nature and accounts for all doses studied and all observed responses, including patients who achieve a complete response (CR) or partial response (PR) or who maintain stable disease (SD) based on IWG (2014) criteria. Patients who receive at least one dose of peptide 1 constitute the safety population and are included in all safety analyses. Patients who complete at least one cycle of peptide 1 and undergo a post-treatment objective disease assessment constitute the efficacy-evaluable patient population.

PATIENT POPULATION

Inclusion criteria

[00398] All AML patients are required to have relapsed or refractory acute myeloid leukemia according to WHO criteria. Patients with acute promyelocytic leukemia are excluded. All MDS patients are required to have: (i) Diagnosis of MDS confirmed within 8 weeks prior to study entry; (ii) Not responsive to or intolerant to hypomethylating agents (azacytidine or decitabine); (iii) IPSS-R intermediate/high/very high-risk MDS patients (applying IPSS-R criteria at screening); or, if IPSS-R status cannot be determined (e.g., if cytogenetics are not available due to dry tap), FAB classification: RAEB-1 (5% to 9% BM blasts), RAEB-2 (10% to 19% BM blasts), CMML (10% to 20% BM blasts) and WBC < 13,000/μL, RAEB-t (20% to 30% BM blasts); (iv) MDS patients must also meet at least one of the following: a. Progression (according to 2006 IWG criteria) at any time after initiation of azacitidine or decitabine treatment; b. Failure to achieve complete or partial response or hematological improvement (according to 2006 IWG) after at least six 4-week cycles of azacitidine or decitabine; c. Relapse after initial complete or partial response or hematological improvement (according to 2006 IWG criteria) observed after at least four 4-week cycles of azacitidine or decitabine; d. Intolerance to azacitidine or decitabine defined by drug-related ≥Grade 3 liver or renal toxicity leading to treatment discontinuation.

[00399] All patients are required to meet the following inclusion criterias: (i) Male or female patients age 18 years and older, inclusive, at the time of informed consent (ii) Histologically- or cytologically-confirmed liquid cancers. Standard curative measures do not exist or are no longer effective; (iii) WT p53 status for the relapsing or treatment-refractory liquid neoplasm is mandatory for patients enrolling at Dose Level 4 and higher in Stage 1 of the DEP, as well as for all patients enrolled in Stage 2 of the DEP or in the EXP; (iv) at least one target lesion that is measurable by Revised International Working Group Response Criteria (IWG (2014)) in liquid lymphoma patients (v) ECOG performance status 0-1; (vi)

predicted life expectancy of ≥3 months; (vii) adequate hematologic function, measured within 7 days prior to the first dose of peptide 1 (defined as: ANC $\geq 1.5 \times 10^9$/L, Hemoglobin ≥9.0 g/d, and Platelets $\geq 100 \times 10^9$/L); (viii) adequate hepatic function, measured within 7 days prior to the first dose of peptide 1 (defined as: in the absence of disease involvement in the liver:bilirubin ≤1.5 times institutional ULN: AST and ALT ≤2.5 times ULN; in the presence of disease involvement in the liver:bilirubin ≤2 times ULN: AST and ALT ≤5 times ULN, (ix) adequate renal function, measured within 7 days prior to the first dose of peptide 1, (defined as: urinalysis with no evidence of +2 or higher proteinuria, serum creatinine ≤1.5 times institutional ULN or calculated creatinine clearance ≥50 mL/min (Cockcroft-Gault formula)); (x) acceptable coagulation profile, measured within 7 days prior to the first dose of peptide 1 (defined as: PT or INR ≤1.5 times ULN; aPTT ≤1.5 times ULN); (Xi) at least 4 weeks since prior chemotherapy or biologic therapy, radiotherapy or surgery (intra-thoracic, intra-abdominal or intra-pelvic) with recovery to Grade 1 or baseline of significant toxicities, excluding alopecia, from previous therapies. Palliative radiotherapy for bone lesions ≤2 weeks prior to the first dose of peptide 1 is acceptable if acute toxicity has resolved; (xii) negative serum pregnancy test within 14 days prior to the first dose of peptide 1 for women of child-bearing potential, defined as a sexually mature woman who has not undergone a hysterectomy or who has not been naturally postmenopausal for ≥24 consecutive months (i.e., who has had menses any time in the preceding 24 consecutive months); (xiii) all patients (males and females) of child-bearing potential agree to use an effective method of birth control (i.e., latex condom, diaphragm, cervical cap, IUD, birth control pill, etc.) beginning two weeks before the first dose of peptide 1 and for 30 days after the last dose of peptide 1; (xiv) ability to understand and willingness to sign a written informed consent document; and patients with prostate cancer must continue androgen deprivation therapy, unless such therapy was discontinued 6 months prior to first dose of peptide 1. In a study of using peptide 1 for acute myeloid leukemia (AML) or acute lymphoid leukemia (ALL), patients with pathological confirmation of AML or ALL, such as B-cell acute lymphoid leukemia (B-ALL) and T-cell acute lymphocytic leukemia (T-ALL), are included. In such study, patients who are relapsed, refractory or intolerant to standard chemotherapy are included.

Exclusion criterias

[00400] Patients who meet any of the following criteria at screening or Day -1 are excluded: (i) previous treatment with investigational agents that affect MDM2 or MDMX activity; known hypersensitivity to any study drug component; (iii) known and untreated

brain metastases. Patients with brain metastases that have been treated and demonstrated to be clinically stable for ≥30 days can be enrolled onto the dose escalation portion of the study; (iv) history of coagulopathy, platelet disorder or history of non-drug induced thrombocytopenia; (v) history of pulmonary embolism within 6 months prior to the first dose of peptide 1 or untreated DVT; (vi) required concurrent use of anti-coagulants or anti-platelet medication, with the exception of aspirin doses ≤ 81 mg/day, low-dose SC heparin or SC low-molecular-weight heparin for DVT prophylaxis, or heparin flushes to maintain IV catheter patency; (vii) patients with pre-existing history of or known cardiovascular risk (for example: history of acute coronary syndromes including myocardial infarction, unstable angina, coronary artery bypass graft, angioplasty, or stenting within 6 months prior to the first dose of peptide 1; uncontrolled hypertension defined as a systolic BP ≥160 mmHg and/or diastolic BP ≥100 mmHg; pre-existing cardiac failure (New York Heart Association class III-IV); atrial fibrillation on anti-coagulants; clinically significant uncontrolled arrhythmias or arrhythmia requiring treatment, with the exceptions of atrial fibrillation and paroxysmal supraventricular tachycardia; severe valvulopathy; corrected QTc interval on screening ECG ≥450 msec for males and ≥470 msec for females); (viii) clinically significant gastrointestinal bleeding within 6 months prior to the first dose of peptide 1; (ix) clinically significant third-space fluid accumulation (e.g., ascites requiring tapping despite the use of diuretics, or pleural effusion that requires tapping or is associated with shortness of breath); (x) pregnant or lactating females; (xi) evidence of serious and/or unstable pre-existing medical, psychiatric or other condition (including laboratory abnormalities) that could interfere with patient safety or provision of informed consent to participate in this study; (xii) active uncontrolled infection, a history of HIV/AIDS, or a history of hepatitis B or C in the absence of hepatocellular carcinoma. Patients with primary liver cancer that have positive hepatitis serology but are not demonstrating active viral hepatitis can be considered for enrollment if they meet all other inclusion and no other exclusion criteria; (xiii) starting at dose level 4 and higher in Stage 1 of the DEP (as well as for all patients enrolling in Stage 2 of the DEP or in the EXP): Cancers with known Human Papilloma Virus (HPV)-association such as HPV-positive cervical cancers, HPV-positive oropharyngeal cancers or HPV-positive anal cancers; (xiv)known history of another primary malignancy that has not been in remission for ≥2 years. Non-melanoma skin cancer and cervical carcinoma *in situ* or squamous intraepithelial lesions (e.g., CIN or PIN) are allowed; (xv) any psychological, sociological, or geographical condition that could potentially interfere with compliance with the study protocol and follow-up schedule; (xvi) the required use of any concomitant medications that are predominantly

cleared by hepatobiliary transporters (e.g., OATP members OATP1B1 and OATP1B3) within 24 hours of peptide 1 infusion; (xvii) the use of any investigational agents within 4 weeks or 5 circulating half-lives prior to the first dose of peptide 1. In a study of using peptide 1 for acute myeloid leukemia (AML) or acute lymphoid leukemia (ALL), patients with acute undifferentiated or biphenotypic leukemia are excluded. Patients with a leukemic blast count of more than 50,000/uL are excluded. Patients with deletion of chromosome 17, or del(17p) are excluded.

Patient removal/replacement from study therapy

[00401] A patient can be removed from the study therapy for a variety of reasons, including: (i) disease progression; (ii) unacceptable adverse event(s); (iii) intercurrent illness that prevents further participation; (iv) clinically significant toxicity despite a 2-week dosing delay or after two dose reductions; (v) patient refusal to continue treatment through the study and/or consent withdrawal for study participation; (vi) patient unable or unwilling to comply with study requirements; (vii) pregnancy or failure to use adequate birth control; (viii) general or specific changes in the patient's condition that render the patient unacceptable for further treatment in this study in the judgment of the investigator

[00402] Any patient who completes screening and does not receive a dose of peptide 1 is replaced. A patient in the dose escalation portion of the study who discontinues the study prior to completion of the first cycle for reasons other than safety is replaced. A patient in the dose expansion portion of the study who discontinues study participation prior to the completion of the first cycle of treatment for any reason can be replaced.

TREATMENT PLAN

Study drug administration

[00403] The study drug is the investigational agent peptide 1. This investigational agent is distributed to clinical sites. Patients begin treatment with peptide 1 within 21 days following the start of screening. Peptide 1 drug is a frozen liquid product supplied in single-use glass vials. The peptidomimetic macrocycle for injection is stored frozen at $\leq$ -15°C. Peptide 1 is introduced into an IV infusion bag containing D5W; this is known as peptide 1 dosing solution and is provided by the site pharmacy for administration to the patient. Peptide 1 dosing solution is labeled with a patient identification number. An investigative staff confirms this information and its relevancy to the intended patient. Peptide 1 is administered by IV infusion in D5W over 1 hour (±5 min) on Days 1, 8 and 15 of a 28-day

cycle for DR-A or Days 1, 4, 8, 11 for DR-B of a 21 day treatment cycle. The pre-defined dose is calculated for each patient based on body weight at the start of each cycle.

[00404] Peptide 1 is not administered outside of the planned schedule for Dose Regimens A and B in Cycle 1, i.e., there are no planned windows for dose days. Follow-up visits on non-dosing days have a window of $\pm$ 1 day in DR-A on Days 22 and 29 and in DR-B on Days 18 and 21. Deviations are noted on the eCRF. Treatment of patients in the dose escalation and the dose expansion phases of the study continue until documentation of disease progression, unacceptable toxicity, or patient or physician decision to discontinue therapy.

[00405] In case of infusion-related reactions, peptide 1 infusion is temporarily discontinued. Pharmacologic agents and other therapeutic interventions can be administered per institutional guidelines. The decision to re-start peptide 1 infusion is made after a careful assessment of the patient.

Starting dose, dose escalation and dose reduction

[00406] Starting at Dose Level (DL) 3, patients are sequentially assigned to one of two treatment arms: Dose Regimen (DR) A continues testing administration of peptide 1 once per week, or Dose Regimen (DR) B testing administration of peptide 1 twice per week. For Dose Level 3, DR- A is enrolled first, DR-B is enrolled second. The starting dose (DL-1) in DEP, based on results from nonclinical toxicology assessments, is 0.16 mg/kg. During the first 2 dose levels, patients receive peptide 1 on Days 1, 8, and 15 of a 28-day cycle. Starting with DL 3, patients in DR- A continues being treated once a week on Days 1, 8, and 15 of a 28-day cycle, whereas patients in DR- B are treated twice a week, on Days 1 and 4, 8 and 11 of a 21-day cycle.

Dose Levels for the Dose Escalation Portion of Study

[00407] In the Dose Escalation portion of the study, increasing dose levels of peptide 1 are evaluated in cohorts of 3-6 patients. Peptide 1 is administered by IV infusion using 2 different dosing regimens of a 28- or 21-day cycle, in patients with advanced liquid lymphomas expressing WT p53 protein. Patients receive peptide 1 either once weekly for three consecutive weeks for a 28-day cycle or twice weekly for two consecutive weeks for a 21-day cycle. Many patients with a liquid lymphoma present circulating tumor cells (CTC) in peripheral blood, which can be detected and analyzed using flow cytometry. This analysis allows detection of study drug-specific target engagement in these cells. Based on allometric

scaling, the projected AUC in humans at 0.16 mg/kg (50 μg•hr/mL) is approximately 9% of the rat AUC at STD_{10} and approximately 6% of the AUC at the monkey HNSTD.

[00408] In the absence of DLT in ≥33% of patients in either DR, subsequent cohorts of 3 to 6 patients will receive escalated doses until the MTD or an OBD is established for each dose regimen.

[00409] A 2-stage dose escalation design is employed. During the initial Stage 1 Escalation Phase (Table 5), 100% dose increments are utilized until ≥1 of 3 patients in a cohort experiences any Grade ≥2 AE that is at least possibly related to study drug. Subsequent dose escalation will continue using 3-patient cohorts and the modified Fibonacci sequence (i.e., Stage 2 Escalation Phase; Table 6), until the MTD or OBD is established.

Table 5: Dose Level and Dose Regimen Schematic

Dose Escalation Phase (DES)							Dose Expansion Phase
Dose Level 1	**Dose Level 2**	**Dose Level 3A**	**Dose Level 4A**	**Dose Level 5A**	**Dose Level 6A**	**Dose Level 7A**	Dose(s) & Regimen(s) to be Determined
		Per Dose, mg/Kg					
0.16 mg/Kg	0.32 mg/Kg	0.64 mg/Kg	1.25 mg/Kg	2.5 mg/Kg	5.0 mg/Kg	10.0 mg/Kg	**P53 WT Pre-Dose 1** Fresh Sample
Only Dose Regimen A		**DR-A: 1x/wk for 3 wks, 28 day Cycle** **Liquid Cancer** **DR-B: 2x/wk for 2 wks, 21 Day Cycle**					
		0.32 mg/Kg	0.64 mg/Kg	1.25 mg/Kg	2.5 mg/Kg	5.0 mg/Kg	
		Per Dose, mg/Kg					
		Dose Level 3B	**Dose Level 4B**	**Dose Level 5B**	**Dose Level 6B**	**Dose Level 7B**	
p53 WT Not Necessary Archive Sample Used if Available		**p53 WT Pre-Dose 1 Necessary** From Archive or Fresh Sample					

Dosing Overview

Clinical Screen Day -21 to Day -1	**Dose Regimen A Clinic Visits – 28 Day Cycle**								**Begin Next Cycle**
	Dose: Day 1	Day 2	Day 3	Dose: Day 8		Dose: Day 15	Day 16	Day 22	Day 29
	Dose Regimen B Clinic Visits - 21 Day Cycle								**Begin Next Cycle**
	Dose: Day 1	Day 2	Day 3	Dose: Day 4	Dose: Day 8	Dose: Day 11	Day 12	Day 18	Day 22

Peptide 1 Administration for each Dose Level (DL) and Dose Regimen

Dose Regimen A	Dose- Day 1 mg/Kg	Dose- Day 8 mg/Kg	Dose- Day 15 mg/Kg		Total Dose per Cycle mg/Kg	
Dose Level 3	0.64	0.64	0.64	**28-Day Cycle**	DL 3- 1.92	
DL 4	1.25	1.25	1.25		DL 4- 3.75	
DL 5	2.5	2.5	2.5		DL 5- 7.5	
DL 6	5.0	5.0	5.0		DL 6- 15.0	
DL 7	10.0	10.0	10.0		DL 7- 30.0	
Dose Regimen B	**Dose- Day 1** mg/Kg	**Dose- Day 4** mg/Kg	**Dose- Day 8** mg/Kg	**Dose- Day 11** mg/Kg		**Total Dose per Cycle** mg/Kg
Dose Level 3	0.32	0.32	0.32	0.32	**21-Day Cycle**	DL 3- 1.28
DL 4	0.64	0.64	0.64	0.64		DL 4- 2.56
DL 5	1.25	1.25	1.25	1.25		DL 5- 5.0
DL 6	2.5	2.5	2.5	2.5		DL 6- 10.0
DL 7	5.0	5.0	5.0	5.0		DL 7- 20.0

[00410] The escalation scheme can be switched to the Stage 2 Escalation Schedule at any point that the Investigators, Sponsor's Medical Monitor and Safety Physician representative agree on a more conservative progression.

[00411] The observation of DLT(s) is used to make individual patient determinations regarding dose reductions, interruptions or discontinuation throughout the course of the trial, but DLTs occurring during Cycle 1 is used to inform safety and tolerability assessments for dose escalation decisions.

[00412] If DLTs are observed in the first cohort, the dose is de-escalated to Dose Level -1. If DLTs are observed at Dose Level -1, the dose is de-escalated to Dose Level -2. If DLTs are observed at Dose Level -2, other dose levels can be considered and implemented after discussions among the Investigators, Sponsor's Medical Monitor and Safety Physician representative.

[00413] Within each Dose Regimen:

[00414] If no DLT is observed in a cohort, the subsequent patient group is enrolled at the next planned dose level of that dose regimen.

[00415] If DLT is observed in ≥2 of 3 patients at any dose level no further dose escalation occurs in that DR, and the current dose is defined as the MAD.

[00416] If DLT is observed in 1 of 3 patients at any dose level, then up to 3 additional patients are enrolled in the same DR at that same dose level. If DLT is observed in ≥2 patients in the expanded cohort, then no further dose escalation occurs, and the current dose is defined as the MAD.

[00417] After the MAD is defined, either the previously administered lower dose is expanded to a total of 6 patients, or an intermediate (between the MAD and the next lower dose level) is investigated in up to six patients. The highest dose tolerated without DLT in at

least 5 of 6 patients in a cohort from one treatment arm is defined as the MTD or OBD for that treatment arm.

[00418] The selection of dose regimen and dose level for up to 2 EXP cohorts is based on the MTD determination in Cycle 1, as well as the cumulative safety, efficacy and PK/PD profile of peptide 1 in subsequent treatment cycles in DEP.

[00419] Dose levels are be increased between cycles within each cohort, and patients are assigned only one dose level (i.e., no intra-patient dose escalation).

Dose Level for the Expansion Portion of Study

[00420] After the MTD or OBD is defined, approximately 30 additional patients can be enrolled in up to two expansion cohorts of the study to gain further experience at this dose level and investigate the effect of peptide 1 in specific patient or liquid cancer cell types. There can be up to two expansion cohorts, for which two disease types can be selected for evaluation. The dose and dosing schedule of peptide 1 administered to patients in the expansion cohort is derived from evaluation of available safety and other information from patients from both dose regimens in the dose escalation portion of the study.

Intra-Patient Dose Escalation

[00421] Intra-patient dose escalation is not be permitted.

Dose and Schedule Adjustments for Toxicity

[00422] Toxicity that occurs during a cycle must recover as outlined below for treatment to continue. Hemoglobin ≥8.5 g/dL; ANC ≥1.0 10^9/L; platelet count ≥75 $\times 10^9$/L; liver function tests back to grade prior to previous cycle (includes PT/INR); other toxicities must return to Grade ≤1 or to baseline level if Grade >1 was acceptable for inclusion in the trial as described in the criteria listed in Section 4.

[00423] In the event a Grade 4 AE considered related to peptide 1 is observed, peptide 1 must be discontinued permanently. Exceptions include Grade 4 neutropenia lasting <3 days, and emesis, diarrhea or electrolyte abnormalities that resolve within 2 days on optimum treatment. For these exceptions, treatment can be delayed for up to 2 weeks to allow resolution of the toxicity (i.e., return to Grade ≤1 or baseline), followed by re-treatment at a reduced dose. Two dose reductions are permitted. A third dose reduction requires evidence of clinical benefit and approval by the Medical Monitor.

[00424] In the event a Grade 3 AE considered related to peptide 1 is observed (exceptions are Grade 3 nausea, emesis, diarrhea or clinically insignificant electrolyte abnormalities that resolve within 2 days on optimum treatment), treatment can be delayed for up to 2 weeks to allow resolution of the toxicity, followed by re-treatment at a reduced dose.

Two dose reductions are permitted. A third dose reduction require evidence of clinical benefit and approval by the Medical Monitor.

[00425] Dose modifications for re-treatment following related Grade 3 and Grade 4 AEs (as permitted) is as follows. For DEP, patients are re-treated at the preceding dose level (per Table 1 and/or Table 2). For EXP, doses are reduced by 25% intervals (e.g., if the Phase II dose is 5 mg/kg, the dose is reduced sequentially to 3.75 mg/kg and 2.8 mg/kg). Two dose reductions are permitted. A third dose reduction requires evidence of clinical benefit and approval by the Medical Monitor.

[00426] If a clinically significant AE is observed in a patient during a treatment cycle, further dosing is delayed until the toxicity has resolved to an acceptable level. Treatment can be delayed by up to 2 weeks to allow for the resolution of AEs, and a dose reduction to the preceding level can be made at the discretion of the Investigator in consultation with Sponsor's Medical Monitor and Safety Physician representative. If a patient experiences multiple AEs, decisions on dosing delay or dose reduction can be based on the most severe AE. Any patient who experiences recurrent, clinically significant AE after one dose reduction can undergo one additional dose reduction. Patients who continue to experience clinically significant toxicity after a 2-week delay or the maximum allowed number of dose reductions are discontinued from the study.

[00427] Adverse events considered for dose reduction do not include the events assessed by the investigator as exclusively related to underlying disease or other medical condition or concomitant treatment. A patient who experiences an AE considered related to peptide 1 can continue on study if the patient is receiving clinical benefit and/or the Investigator feels continued participation is in the best interest of the patient. In such cases, at the Investigator's discretion and in agreement with Sponsor's Medical Monitor and Safety Physician representative, the dose for a patient can be reduced to the preceding lower level.

[00428] Up to two dose reductions for a patient are permitted. A third dose reduction requires evidence of clinical benefit and approval by the Medical Monitor, after which the patient is discontinued from the study.

[00429] A patient who experiences a DLT can continue treatment at the preceding lower level at the discretion of the Investigator and in agreement with Sponsor's Medical Monitor and Safety Physician representative until disease progression or unacceptable toxicity. Once the dose has been reduced for a patient, it can not be re-escalated.

[00430] Toxicity grading is based on NCI CTCAE v4.0.

Statistical Methods

[00431] Statistical analyses of safety and efficacy for DEP and EXP are primarily descriptive in nature because the objectives of the study are to determine the DLTs and MTD or OBD.. These objectives are achieved by the results of a deterministic algorithm: Continuous variables are summarized using descriptive statistics [n, mean, standard deviation, median, minimum, and maximum]. Categorical variables are summarized showing the number and percentage (n, %) of patients within each classification. Results are evaluated for all patients and liquid lymphoma patients. Results from DR-A and DR-B are compared for all Dose Levels and patient groups.

Example 3: Study Procedures

Schedule of study events

[00432] The schedule of study activities, including assessments, tests, exams, disease assessments, submission of tissue specimens, and study drug administration) that is conducted, beginning with screening and continuing through Cycle 1 [day 1, day 8, and day 15 of a 28 day cycle] is outlined in Table 7. The study that is conducted beginning with Cycle 2 [day 29 of cycle 1 = day 1 of cycle 2] is outlined in Table 8.

Table 7: Schedule of study activities through Cycle 1

	Molecular Screen	**Clinical Screen -21 days** for DR-A and DR-B, All Dose Levels	**Day -7** for DR-A and DR-B, All Dose Levels	**Day 1** for DR-A and DR-B, All Dose Levels	**Day 2 ±4 h**for DR-A and DR-B, All Dose Levels	**Day 3 ±4 h**for DR-A and DR-B, All Dose Levels	**Day 4 (DR-B only)**	**Day 8** for DR-A and DR-B, All Dose Levels	**Day 11 (DR-A only)** **Day 15 (DR-B only)**	**Day 12 (DR-B only)** **Day 16 (DR-A only) ±2 d**	**Day 18 (DR-B only)** **Day 22 (DR-A only) ±1 d**	**Day 22 (DR-B only)** **Day 1, Cycle 2** **Day 29 / Day 1, Cycle 2 ±3 d (DR-A only)**

				pre-dose	post-dose			pre-dose	post-dose	pre-dose	post-dose	pre-dose	post-dose			Refer to Table 7
Written informed consent	X	X														
Medical history		X														
Demographics		X														
Tumor biopsy or archive tissue sample for p53 WT confirmation and biomarker assessment	X	X														
Confirm eligibility		X	X													
Blood test for HIV, hepatitis B and C		X														
Serum or urine pregnancy		X														
Vital signs: Blood pressure, pulse, respiration rate, body temperature		X	X	X	X	X	X	X	X	X	X		X	X	X	
Physical exam		X		X				X		X						
12-lead ECG		X		X	X			X	X							
Laboratory assessments: Clinical chemistry (glucose, calcium, albumin, total protein, sodium, potassium, CO_2, chloride, BUN [blood urea nitrogen], serum creatinine, uric acid, ALP, ALT, AST,phosphate, total and direct bilirubin), hematology (complete blood count, platelets and differential), urinalysis		X	X			X	X	X	X	X				X	X	

(dipstick measurement [pH, specific gravity, protein, glucose, ketones, nitrite, leukocyte esterase] with microscopic analysis, if results of the dipstick indicate additional testing required), coagulation (PT, INR, aPTT).																
Collection of blood for immunogenicity				X				X								
Collection of blood for biomarker assessments				X	X	X	X	X	X	X	X		X	X	X	
Collection of blood for PK assessments				X	X	X	X	X	X	X	X		X	X		
Collection of blood for PK assessments														X		
FLT-PET for patients who received FLT-PET at screen and have SUV $\geq$ 5														X		
ECOG Performance Status		X	X							X						
Needle biopsy for biomarker assessments		X												X		
Tumor Assessment		X														
peptide 1 dosing				X						X						
Concomitant medications		X	X	X	X	X	X	X	X	X	X		X	X	X	
AE assessment					X	X	X	X	X	X	X		X	X	X	
TLS monitoring (via						X										

routine laboratory assessment sample)																

Table 8: Dose Regimen A - Study Activities Through Cycle 1

(DR-A)	**Molecular Screen**	**Clinical Screen -21 days**	**Within 7 days prior to Day 1**	**Day 1**		**Day 2** ±4 h	**Day 3** ±4 h	**Day 8** ±1 d		**Day 15** ±1 d		**Day 16** ±2 d	**Day 22** ±1 d	**Day 29 / Day 1, Cycle 2**[1] ±3 d
				Pre-Dose	Post-Dose			Pre-Dose	Post-Dose	Pre-Dose	Post-Dose			
Written informed consent	X	X												
Medical history[2]		X												
Demographics Pre-dose CT & FDG-PET / FLT possibly		X										X		
Tumor biopsy or archive tissue sample for p53 WT confirmation DL 4 and beyond and biomarker assessment	X													
Confirm eligibility		X	X											
Blood test for HIV, hepatitis B and C		X												
Serum or urine pregnancy			X											
Vital signs		X	X	X	X	X	X	X	X	X	X	X	X	
Physical exam		X		X				X		X				
12-lead ECG		X		X	X									
Laboratory assessments		X	X			X	X	X		X		X	X	
Blood Collection - immunogenicity				X										
Blood Collection - biomarker assessments				X	X	X	X	X	X	X	X	X	X	
Blood				X	X	X	X	X	X	X	X	X		

Collection - PK assessments														
ECOG Performance Status		X	X					X		X				
Needle biopsy for biomarker assessments												X		
Tumor Assessment		X												
peptide 1 dosing				X				X		X				
Concomitant medications		X	X	X	X	X	X	X	X	X	X	X	X	
AE assessment					X	X	X	X	X	X	X	X	X	

Table 9: Dose Regimen B - Study Activities Through Cycle 1

(DR-B)	**Molecular Screen**	**Clinical Screen -21 days**	**Within 7 days prior to Day 1**	**Day 1**		**Day 2** ±4 h	**Day 3** ±4 h	**Days 4 and 8**		**Day 11**		**Day 12**	**Day 18** ± 1 d	**Day 21 / Day 1, Cycle 2[1]** ±2 d
				Pre-Dose	Post-Dose			Pre-Dose	Post-Dose	Pre-Dose	Post-Dose			
Written informed consent	**X***	X**												
Medical history		X												
Demographics Pre-dose CT & FDG-PET / FLT possibly		X										X		
Tumor biopsy or archive tissue sample for p53 WT confirmation DL 4 and beyond, and biomarker assessment	X													
Confirm eligibility		X	X											
Blood test for HIV, hepatitis B and C		X												
Serum or urine			X											

pregnancy														
Vital signs		X	X	X	X	X	X	X	X	X	X	X	X	
Physical exam		X		X				X		X				
12-lead ECG		X		X	X									
Laboratory assessments		X	X			X	X	X		X		X	X	
Blood Collection - immunogenicity				X				X						
Blood Collection - biomarker assessments				X	X	X	X	X	X	X	X	X	X	
Blood Collection - PK assessments				X	X	X	X	X	X	X	X	X		
ECOG Performance Status		X	X					X		X				
Needle biopsy for biomarker assessments												X		
Tumor Assessment		X												
peptide 1 dosing				X				X		X				
Concomitant medications		X	X	X	X	X	X	X	X	X	X	X	X	
AE assessment					X	X	X	X	X	X	X	X	X	

Table 10: Schedule of study activities through Cycle 2

	Day 29 for DR-A and Day 22 for DR-B **of prior cycle / Day 1 of next cycle for patients continuing treatment** ±3 d		**Day 8** of DR-A and Days 4 and 8 of DR-B ±1 d		**Day 15** of DR-A and Day 11 of DR-B ±1 d		**Day 16** DR-A and Day 12 of DR-B ±2 d	**After even numbered cycles**	**CT Imaging ***	**End-of-Study** 30 ±3 d after last dose or study withdrawal
	Pre-dose	post-dose	pre-dose	Post-dose	pre-dose	post-dose			Prior to first dose	
Serum pregnancy										X
Vital signs: Blood pressure, pulse, respiration rate, body temperature.	X	X	X	X	X	X	X			X
Physical exam	X		X		X					X
12-lead ECG	X pre-dose and EOI (+10	X At pre-dose and EOI (+10								X

	min)	min)								
Laboratory assessments: Clinical chemistry, hematology, urinalysis, coagulation (PT, INR, aPTT).	X		X (Hematology only)		X		X			X
Collection of blood for immunogenicity	X							X		X
Collection of blood for biomarker assessments (each cycle)	X (MIC-1 only)	X (MIC-1 only)			X (MIC-1 only)	X (MIC-1 only)	X			X
Collection of blood for PK assessments (Cycle 2 and End-of-Study only)	X	X			X	X	X			X
ECOG Performance status	X		X		X					X
Needle Biopsy for biomarker assessments							X			
Tumor assessment								X At end of even-numbered cycles. Prior to start of the next treatment cycle		X
peptide 1 dosing	X		X		X					
Concomitant medications	X	X	X	X	X	X	X			X
FLT-PET provided that an evaluable FDG-PET-scan was performed prior to starting treatment										
AE assessment (begins at the point of the first peptide 1 infusion and continues until 30 days after	X	X	X	X	X	X	X			X

last infusion)										

*All patients receive a CT image prior to the first dose. After dosing commences, in DR-A: CT images obtained at the end of Cycle 2 and every other cycle thereafter in DR-A, e.g., Cycles 4, 6, and 8 DR-B: CT images obtained after the last infusion in Cycle 3 and every third cycle thereafter in DR-B, e.g., Cycles 6, 9, and 12. Images are obtained after the last dose is administered in those cycles and prior to the Day 18 visit.

Table 11: Dose Regimen A - Study Activities Cycle 2 and Beyond

(DR-A)	**Day 29 of prior cycle / Day 1** ±3 d		**Day 8** ±1 d		**Day 15** ±1 d		**Day 16** ±2 d	**After even numbered cycles**	**End-of-Study** 30 ± 2 d after last dose or study withdrawal
	Pre-dose	Post-dose	Pre-dose	Post-dose	Pre-dose	Post-dose			
Serum or urine pregnancy									X
Vital signs	X	X	X	X	X	X	X		X
Physical exam	X		X		X				X
12-lead ECG	X	X							X
Laboratory assessments	X		X		X		X		X
Collection of blood for immunogenicity	X							X	X
Blood Collection - biomarker assessments (each cycle)	X	X			X	X	X		X
Blood Collection - PK assessments (Cycle 2 and End-of-Study only)	X	X			X	X	X		X
ECOG Performance status	X		X		X				X
Needle biopsy for biomarker assessments							X		
CT Imaging								X	X
peptide 1 dosing	X		X		X				
Concomitant medications	X	X	X	X	X	X	X		X
AE assessment	X	X	X	X	X	X	X		X

Table 12: Dose Regimen B - Study Activities Cycle 2 and Beyond

(DR-B)	**Day 23 of prior cycle / Day 1** ±3 d		**Day 4 and 8**		**Day 11**		**Day 12**	**After even numbered cycles**	**End-of-Study** 30 ± 2 d after last dose or study withdrawal
	Pre-dose	Post-dose	Pre-dose	Post-dose	Pre-dose	Post-dose			
Serum or urine pregnancy									X
Vital signs	X	X	X	X	X	X	X		X

Physical exam	X		X		X			X
12-lead ECG[3]	X	X						X
Laboratory assessments	X		X		X		X		X
Collection of blood for immunogenicity	X							X	X
Blood Collection - biomarker assessments (each cycle)	X	X			X	X	X		X
Blood Collection - PK assessments *(Cycle 2 and End-of-Study only)*	X	X			X	X	X		X
ECOG Performance status	X		X		X				X
Needle biopsy for biomarker assessments							X		
CT Imaging								X	X
peptide 1 dosing	X		X		X				
Concomitant medications	X	X	X	X	X	X	X		X
AE assessment	X	X	X	X	X	X	X		X

Example 4: Pharmacokinetic Analysis

[00433] Levels of peptide 1 and its metabolites are measured in blood samples collected at specific time points described below. Pharmacokinetic data are tabulated and summarized by individual patient and collectively by dose level for each dose regimen. Graphical displays are provided where useful in the interpretation of results.

[00434] Blood samples for PK assessment are collected at the following time points:

Table 13: Time points for collection of blood samples for PK assessment

Cycle 1	
Day 1 DR-A and DR-B	within one hour before SOI
	EOI (+5 min)
	30 min after EOI (± 5 min)
	1 hr after EOI (±5 min)
	2 hr after EOI (±10 min)
	4 hr after EOI (±10 min)
	8 hr after EOI (±10 min)
Day 2 DR-A and DR-B	24 hours (±4 hr) after SOI day prior

Day 3 DR-A and DR-B	48 hours (±4 hr) after SOI Day 1
Day 8, DR-A Days 4 & 8, DR-B	within one hour before SOI
	EOI (+5 min)
	30 min after EOI (± 5 min)
	1 hr after EOI (±5 min)
	2 hr after EOI (±10 min)
	4 hr after EOI (±10 min)
Day 15, DR-A Day 11, DR-B	within one hour before SOI
	EOI (+5 min)
	30 min after EOI (± 5 min)
	1 hr after EOI (±5 min)
	2 hr after EOI (±10 min)
	4 hr after EOI (±10 min)
	8 hr after EOI (±10 min)
Day 16, DR-A Day 12, DR-B	24 hours (±4 hrs) after SOI day prior
Cycle 2	
Cycle 1 Day 29/ Cycle 2 Day 1, DR-A Cycle 1 Day 23/Cycle 2 Day 1, DR-B	within one hour before SOI
	EOI (+5 min)
	30 min after EOI (±5 min)
	1 hr after EOI (±5 min)
	2 hr after EOI (±10 min)
	4 hr after EOI (±10 min)

[00435] SOI stands for start of infusion of peptide 1; EOI stands for the end of infusion of peptide 1.

Example 5: Pharmacokinetic Study

[00436] Pharmacokinetic studies characterize exposure kinetics following single IV administrations of peptide 1 in mice, rats and monkeys, including evaluations of two different dosing formulations in rats and monkeys. Using qualified liquid chromatography with tandem mass spectrometry (LC-MS-MS) methods for efficacy models and dose range-finding (DRF) studies, and validated methods for GLP safety studies, absorption was characterized in mice at the MED in efficacy models and in rats and monkeys at tolerated and non-tolerated doses in toxicology studies. Exposures generally increased proportionally with dose, although an apparent plateau was observed at the highest dose of the 4-week monkey toxicology study. No sex-based differences were observed in either species, and no accumulation was observed following multiple doses.

[00437] The *in vitro* protein binding of peptide 1 was evaluated over a range of concentrations in mouse, rat and monkey plasma, as well as human plasma samples from normal subjects and hypoalbuminemic patients. Protein binding ranged from 92% to 98% in plasma of mice, rats, dogs, monkeys, and humans following incubation of peptide 1at a single concentration of 2 μM, and exceeded 98% in mouse and rat plasma up 250 μM. In human

and monkey plasma, free peptide 1 fractions of 3-4% were measured at peptide 1concentrations up to 150 μM, corresponding to expected Cmax values from clinical doses up to 15 mg/kg, rising to 12-14% at concentrations >200 μM. In plasma from hypoalbuminemic patients, a similar rise was seen at >100 μM concentrations of peptide 1, corresponding to expected Cmax values from clinical doses up to 10 mg/kg. The concentration-dependent plasma protein binding is consistent with the plateau in exposure observed at the high-dose group (20 mg/kg) in the 4-week monkey GLP toxicity study, and suggests less-than-dose-proportional exposure at very high clinical doses, in particular for patients with hypoalbuminemia.

[00438] In vitro studies demonstrated a similar metabolite profile across species, including humans, providing support for the rat and the monkey as suitable species for toxicology studies. Proteolysis is the major biotransformation pathway of peptide 1. The predominant metabolite is a 3-amino acid truncation with the cyclic peptide portion intact, and the same metabolite profile was noted in in vitro stability studies with mouse, rat, monkey, and human cryopreserved hepatocytes. In a single-dose rat study, hepatobiliary metabolism and elimination represented the predominant clearance pathway for peptide 1, with the predominant metabolite being the major excretion product observed in the bile. The predominant metabolite was also observed in the plasma in both the rat and monkey 4-week GLP toxicology studies, with adequate exposures in these studies to provide characterization of its impact on the overall safety profile of peptide 1. In the monkey, the predominant metabolite plasma exposure was 10% of the predominant metabolite AUC, and in the rat, the predominant metabolite exposure was 6% of the peptide 1 AUC. Accumulation of the predominant metabolite was not observed with repeated twice-weekly dosing in rats or monkeys.

[00439] Inhibition or induction of cytochrome P450 (CYP) enzymes by peptide 1 appears to be negligible at clinically-relevant concentrations, although interactions are possible at high exposures of peptide 1with drugs that are predominantly cleared by hepatobiliary transporters.

Example 6: Pharmacodynamic Analysis

[00440] Levels of p53, MDM2, MDMX, p21 and caspase are measured in liquid cancer cell specimens collected before beginning treatment and at the end of Cycle 1 or Cycle 2. MIC-1 is measured in blood samples. The specific time points for blood and tissue collection for PD assessments are described below. Pharmacodynamic data are tabulated and

summarized by individual patient and collectively by dose level. Graphical displays are provided where useful in the interpretation of results.

[00441] Results available from previous genetic and biomarker tests, and additional tests of the blood and liquid cancer cell samples for biomarkers relevant to the safety and efficacy of peptide-1 can be investigated for possible correlation with patient outcome.

[00442] Blood samples for PD assessments are collected at the following time points:

Table 14: Time points for collection of blood samples for PD assessments

Cycle 1 DR-A, DR-B, or Both:		
Dose Regimens	**Assessment**	**Blood Sample Collection Schedule**
Day 1- Both (pre)	MIC-1 and CTC Samples	within 1 hour before the start of infusion (SOI)
Day 1- Both (post)		EOI (+ 5 min) & EOI + 1hr (± 5 min), 2, 4, and 8 hr (± 10 min)
Day 2- Both		24 hours (±4 hr) after SOI on Day 1
Day 3- Both		48 hours (±4 hr) after SOI on Day 1
Day 8 DR-A Day 4 & 8 DR-B		within 1 hour before SOI and within 1 hour after the end of infusion (EOI)
Day 15 DR-A Day 11 DR-B		within 1 hour before SOI and within 1 hour after EOI
Day 15 DR-A Day 11 DR-B		within 1 hour before SOI and EOI (+ 5 min) & EOI + 1hr (± 5 min), 2, 4, and 8 hr (± 10 min)
Day 16 DR-A Day 12 DR-B		24 hours (±4 hrs) after SOI day prior
Day 22 DR-A Day 18 DR-B		During Day visit
Each Subsequent Cycle Starting in Cycle (Cy) 2		
Dose Regimens	**Assessments**	**Blood Sample Collection Schedule**
Cy 1 Day 29 DR-A Cy 1 Day 23 DR-B = Cycle 2 Day 1	*MIC-1 Only*	within 1 hour before SOI and within 1 hour after EOI
Day 15 DR-A Day 11 DR-B		within 1 hour before SOI and within 1 hour after EOI
Day 16 DR-A Day 12 DR-B		24 hours (±4 hrs) after SOI day prior
End of study visit		During end of study visit
NOTE: no PD assessments for liquid lymphoma on Day 8 DR-A or Days 4 and 8 DR-B		

Example 7: Assessment of clinical activity of the peptidomimetic macrocycle

[00443] To evaluate clinical activity, response rates and duration of response based on IWG (2014) criteria or other appropriate criteria are provided with a case-by-case description of all patients who exhibit CR, PR or SD. A descriptive analysis of other evidence of anti-liquid cancer cell activity or other clinical benefit is provided based on clinical, radiographic or other appropriate assessment of efficacy or clinical anti-liquid cancer cell activity. Analysis of clinical activity is conducted on two patient populations: (1) the subset of patients who receive at least one cycle of therapy and have at least one post-baseline disease assessment (the efficacy-evaluable population) and (2) a larger group of patients that includes

the efficacy-evaluable population as well as patients who exhibit objective disease progression or experience a DLT and/or unacceptable toxicity prior to the end of Cycle 1.

[00444] Imaging scans, physical examination, and/or laboratory-based assays (e.g., prostate specific antigen) for patients with relevant disease indications are obtained at baseline (e.g., within 28 or 21 days of Cycle 1 Day 1), including, for example, a baseline PET- FDG and possibly FLT-PET scan(s) and for objective anti-liquid cancer cell activity as oulined below. The same type of imaging, physical examination, or laboratory-based assay procedure is used for each assessment for a patient. IWG (2014) criteria are used to assess liquid cancer response and duration of response. Scheduled scans (and/or other laboratory-based assay) are interpreted prior to the start of the next treatment cycle. If the criteria for a CR or PR are met, then the scan is repeated no earlier than within 4 weeks to confirm the response. A responding patient (CR, PR or SD) continues on study, with disease assessment after Cycle 2 and every other cycle thereafter in DR-A (e.g., Cycles 4 and 6) and after the last infusion in Cycle 3 and every third cycle thereafter in DR-B (e.g., Cycles 6 and 9), until disease progression, withdrawal of informed consent, or unacceptable toxicity.

[00445] Films or other records from imaging procedures, including those procedures performed at a regional or other facility outside of the primary institutions, are read and reviewed by the radiology staff at the corresponding primary study institution for the patient.

[00446] [^{18}F]-fluorodeoxyglucose positron emission tomographic (FDG-PET) imaging is performed at baseline using using IWG (2014) criteria for patients with liquid lymphoma. FDG-PET imaging post-baseline is only performed in patients at the first occurrence of stable disease as an adjunct to determine anti-liquid cancer cell activity. PET/CT scans can substitute for contrast-enhanced CT scans provided the CT performed as part of a PET–CT is of similar diagnostic quality as a diagnostic CT with IV and oral contrast.

[00447] FLT-PET imaging is performed at baseline for patients with liquid cancer cells commonly showing sufficient uptake of FLT tracer, e.g., patients with liquid lymphoma and other liquid cancers.

- DR-A assigned patients who demonstrate a standard uptake value (SUV) of $\geq$ 5 at baseline will have a repeat FLT image one day after their last infusion of study medication in Cycle 1, i.e., Day 16.
- DR-B patients who demonstrate a standard uptake value (SUV) of $\geq$ 5 at baseline will have a repeat FLT image one day after their last infusion of study medication in Cycle 1, i.e., Day 12.

Example 8: Molecular Screening Prior to Day 1 of Cycle 1

[00448] Molecular screening encompasses the following prior to the first administration of peptide 1 (Day 1 of Cycle 1).

- Collection of signed informed consent for molecular screening
- Collection of an archived liquid cancer cell sample or a fresh liquid cancer cell biopsy (unless a biopsy poses significant clinical risk) for p53 testing
  - If confirmed to be p53 WT, the remainder of the tissue sample from enrolled patients are used to test for PD biomarkers
- Confirmation of p53 WT status before administration of the first dose of peptide 1 is mandatory for enrollment in:
  - Stage 1 of DEP for patients starting at Dose Level 4 and higher
  - Stage 2 (if necessary) of DEP and EXP for all patients

[00449] At Dose Level 4 and higher in Stage 1 of the DEP (as well as for all patients enrolled in Stage 2 of the DEP), molecular screening in patients with unknown p53 status is done prior to initiating the clinical screening. If the p53 status is known to be WT, these patients can proceed to clinical screening and can be enrolled and receive peptide 1 before confirmation of p53 WT by the central laboratory.

[00450] In the EXP, patients must have completed molecular screening at the central laboratory prior to proceeding to enrolment. These patients can only be enrolled and receive peptide 1 after confirmation of p53 WT by the central laboratory.

Example 9: Management of Tumor Lysis Syndrome (TLS)

[00451] There is a potential for tumor lysis syndrome (TLS) in patients with liquid lymphoma, especially those with large liquid cancer cell burden, pre-dose elevated lactate dehydrogenase and leukocyte counts, renal dysfunction, or dehydration. TLS can be caused by treatment-induced abrupt cancer cell disintegration. It is usually observed shortly after initiating treatment. Patients at risk for TLS can receive liquid cancer cell lysis prophylaxis as part of standard of care according to local clinical protocols.

[00452] Laboratory TLS is defined as a 25% increase in the levels of serum uric acid, potassium, or phosphorus or a 25% decrease in calcium levels. Therefore, patients are monitored for these laboratory parameters 24 hours (Day 2) after infusion of peptide 1 on

Day 1 in DR-A and DR-B during Cycle 1. Signs and symptoms of TLS are monitored until resolved.

Example 10: Multiplexed Cytotoxicity Assay

[00453] The objective of this study was to concurrently evaluate peptide 1-induced cytotoxicity, p21 up-regulation and caspase-3 activation in multiple liquid cancer cell cell lines characterized as having either wild-type or mutated p53 in order to determine whether the cytotoxicity is PD-mediated.

[00454] Cell lines from hematologic liquid cancer cells, characterized for p53 mutant/wild-type status, were seeded into 384-well plates and incubated in a humidified atmosphere of 5% CO_2 at 37 ^{o}C. Peptide 1 was serially diluted and assayed over 10 concentrations, up to 30 μM, in a final assay concentration of 0.1% DMSO. Treatment was added 24 hours post cell seeding, when a time zero untreated cell plate was also generated to determine the number of doublings in the 72 hour assay period. About one hundred cells per well were evaluated, with each test condition run in duplicate wells. After a 72 hour incubation period, cells were fixed and stained with fluorescently labeled antibody and nuclear dye. In the same wells, nuclei were assessed for toxicity (dye uptake) by automated fluorescence microscopy; apoptosis was assayed by elevations in anti-active caspase-3 antibody; and cell cycle arrest was assayed by elevations in anti-p21 monoclonal antibody EA10. Characteristics of the 32 hematologic cell lines evaluated in this study are listed in Table 15.

Table 15: Hematologic Tumor Cell Lines Evaluated for Cytotoxicity and for Induction of Caspase and p21 following 72-Hour Incubations with peptide 1

Mutant p53		Wild-Type p53	
Cell Line	**Tumor Origin**	**Cell Line**	**Tumor Origin**
J-RT3-T3-5	Leukemia	MOLT-3	Leukemia
MEG01	Leukemia	CML-T1	Leukemia
CCRFCEM	Leukemia	MV-4-11	Leukemia
MHH-PREB-1	Leukemia	BV-173	Leukemia
K562	Leukemia	NALM-6	Leukemia
EM-2	Leukemia	SR	Lymphoma
CEM-C1	Leukemia	Daudi	Lymphoma
Thp1	Leukemia	DOHH-2	Lymphoma
Jurkat	Leukemia	CRO-AP2	Lymphoma
HEL-92-1-7	Leukemia	RPMI 6666	Lymphoma
MOLT-16	Leukemia	BC-1	Lymphoma
DB	Lymphoma		
L-428	Lymphoma		
Ramos (RA 1)	Lymphoma		
HT	Lymphoma		
ST486	Lymphoma		
Raji	Lymphoma		
EB-3	Lymphoma		

RPMI 8226	Myeloma		
ARH-77	Myeloma		
U266B1	Myeloma		

[00455] Cell proliferation was measured by relative cell count, which was expressed as percent of control. The activated caspase-3 marker labels cells from early to late stage apoptosis, and output is shown as a fold increase of apoptotic cells over vehicle background normalized to the relative cell count in each well (Emax); a ≥5-fold induction indicates significant induction of apoptosis. For example, peptide 1 was able to induce robust apoptotic responses in p53 wild-type hematopoietic cell lines (see **Figure 2**).

[00456] Total p21 level indicates relative activity of p53, and output is shown as a fold induction of p21 concentrations over vehicle background normalized to the relative cell count in each well (Emax); a ≥2-fold increase or decrease in total p21 protein per cell is considered significant. For example, peptide 1 was able to show significant induction of p21 and yielded on-mechanism p21 pharmacodynamic responses in p53 wild-type hematopoietic cell lines (see **Figure 3**).

[00457] For each cell line, an EC_{50} estimated the concentration at which 50% of the cells were killed. Additional parameters that characterized the responses include IC_{50} (peptide 1 concentration at 50% maximal possible response), GI_{50} (concentration need to reduce growth by 50%), and activity area (the integrated area over the survival curve). For example, proliferation and survival of cell lines with wild-type p53 protein was sensitive to peptide 1, with IC_{50} values ranging from 0.2 to 3.3 μM. Not all cell lines exhibited cytotoxicity at the peptide 1 concentrations tested. Those that did were most often characterized by significant inductions of both caspase-3 and p21. Results with BV-173 leukemia cells (Table 16) are representative of the typical responses with these cell lines.

Table 16: Apoptotic Cytotoxicity in Wild Type P53-Containing BV-173 Tumor Cells

Conc.	Relative Cell Count (%)		Caspase Fold Induction		p21 Fold Change	
(μM)	Mean	SD	Mean	SD	Mean	SD
9.55E-04	100.8	2.7	1.1	0.2	1.1	0.1
3.02E-03	99.9	4.5	1.1	0.3	1.0	0.1
9.53E-03	94.9	0.9	1.2	0.2	1.0	0.1
3.01E-02	84.8	2.8	1.4	0.2	1.0	0.1
9.52E-02	64.4	2.9	2.4	0.7	1.1	0.2
3.01E-01	31.8	2.3	4.1	1.0	1.3	0.1
9.51E-01	14.3	0.3	6.3	1.1	2.3	0.3
3.00E+00	15.0	8.3	3.7	2.0	3.3	0.9
9.49E+00	4.3	0.5	N/A	N/A	N/A	N/A
3.00E+01	2.2	1.1	N/A	N/A	N/A	N/A

[00458] Cytotoxicity in liquid cancer cell lines with mutant p53, when observed, was most often characterized by significant induction of p21 without significant caspase-3 induction. Results with HEL-92-1-7 leukemia cells (Table 17) are representative of the typical responses with these cell lines.

Table 17: Non-Apoptotic Cytotoxicity in Mutant P53-Containing HEL-92-1-7 Tumor Cells

Conc. (μM)	Relative Cell Count (%)		Caspase Fold Induction		p21 Fold Change	
	Mean	SD	Mean	SD	Mean	SD
9.55E-04	98.5	4.9	1.2	0.2	1.3	0.2
3.02E-03	96.8	6.3	1.2	0.1	1.5	0.1
9.53E-03	98.2	2.6	1.1	0.1	1.7	0.2
3.01E-02	89.8	1.7	1.0	0.1	2.2	0.2
9.52E-02	89.7	2.6	1.0	0.2	2.9	0.0
3.01E-01	77.8	2.3	1.1	0.1	3.2	0.1
9.51E-01	81.9	7.7	1.1	0.2	3.7	0.3
3.00E+00	79.2	4.3	1.1	0.1	3.9	0.4
9.49E+00	76.9	1.8	0.7	0.1	4.4	0.7
3.00E+01	67.9	5.1	0.6	0.1	4.2	0.6

[00459] Using an EC_{50} cut-off of 1 μM for all hematologic liquid cancer cell lines, induction of apoptosis was found to have very good agreement with the p53 status of the cells (Table 18). Therefore, p53 status can be a sensitive biomarker for testing cytotoxicity of compounds, such as peptide 1.

Table 18: Sensitivity of Tumor Cells Containing Wild-Type and Mutant p53 to peptide 1-Induced Cytotoxicity

EC_{50} for Cytotoxicity	Wild Type p53	Mutant p53
>1 μM	11	160
≤1 μM	60	2

Peptide 1 selectively induced p53-mediated apoptotic cell death in liquid cancer cell lines (e.g. hematopoietic cancer cells) containing wild-type p53 protein. As shown in Figure 4, all eleven p53 WT (6 lymphoma and 5 leukemia) hematologic cancer cell lines were highly sensitive to peptide 1 intervention as all lines exhibited EC_{50} less than 0.6 μM. Taken together, these lines of evidence suggested effectiveness of peptide 1 against liquid tumor cell lines across multiple histological origins that retain the p53 WT status. In liquid cancer cell lines containing mutated p53, cytotoxicity was associated with cell cycle arrest without elevated apoptosis. These findings demonstrate the pharmacodynamic selectivity of peptide 1 towards liquid cancer cells with active wild-type p53.

Example 11: The effect of peptide 1 on tumor growth inhibition

[00460] In another study, MV 4;11 human leukemia xenograft model was used in mice to assess the ability of peptide 1 to inhibit tumor growth and improve overall survival in AML, a highly aggressive liquid tumor. In this study, 25 mg/kg dose of peptide 1 was administered in six bi-weekly doses and compared to the results of mice treated with only cyclophosphamide, the control group. Mice were monitored individually for an endpoint of morbidity due to progression of the leukemia. All ten mice that received the control exited the study between days 21 and 28, offering a sensitive assay for activity. As shown in Figure 5, treatment with peptide 1 resulted in median overall survival of 40 days as compared to 22 days for untreated mice, an 81% increase for those receiving peptide 1. Peptide 1 can have an effect in liquid tumors with WT p53 and in AML.

Example 12: The safty and toxicology of peptide 1

[00461] The 4-week multiple-dose GLP studies in rats and monkeys utilized twice-weekly IV dosing of peptide 1. The studies provided dose- and exposure-related assessments during both dosing and recovery periods, and results were utilized to define the maximum tolerated doses (MTD) and estimate the severely toxic dose for 10% (STD_{10}) of rats and the highest non-severely toxic dose (HNSTD) in monkeys. All gross and microscopic signs of intolerance (e.g., reduced organ weights, sporadic findings of multi-tissue hemorrhage and hepatic necrosis) and changes in serum chemistry parameters were considered as secondary to red blood cell (RBC), platelet and/or white blood cell (WBC) depletions or anorexia and dehydration in both species. Recovery assessments revealed regenerative and compensatory changes consistent with marrow cell survival and reversibility of all related hematologic and secondary toxicities.

[00462] The dose limiting toxicities (DLT) in both animal species appears to be related to the suppression of hematopoietic cells in the bone marrow, in particular cells of the megakaryocyte lineage, resulting in significant decreases in peripheral blood platelets that demonstrated recovery upon the cessation of dosing. For example, dose-dependent decreases in platelets with recovery were shown in a representative 4-week monkey GLP toxicity study using different dosings of peptide 1 (*see* Figure 6).

[00463] The STD_{10} in rats was determined at 10 mg/kg based on the mortality of one animal in a satellite group for hematology sampling during recovery. The HNSTD in monkeys was determined at 5 mg/kg, based on a complete lack of significant thrombocytopenia at this lowest dose level. However, almost all of the monkeys at the mid- and high-dose levels tolerated peptide 1 administration well; only one animal at each of these dose levels developed significant thrombocytopenia ($<100{,}000 \times 10^6$/ml).

[00464] Rats were more sensitive to the bone marrow and hematologic effects of peptide 1 than monkeys on the basis of exposures at maximally tolerated doses. Exposure at rat STD_{10} ($AUC_{0-\infty}$=562 μg•hr/mL at 10 mg/kg) was below that of HNSTD in monkeys ($AUC_{0-\infty}$=813 μg•hr/mL at 5 mg/kg). These *in vivo* results correlated with those obtained from *in vitro* hemotoxicity assays via luminescence output (HALO). In these investigations, peptide 1 in general inhibited the induced proliferation of bone marrow precursor cells from rats to a greater extent than those from monkeys or humans. IC_{50} values were ~2- to 8-fold higher for rat cells than for monkey or human cells, with the largest difference noted for megakaryocyte colony forming cells, the platelet precursors. These results correlated with *in vivo* findings indicating that rats are more sensitive to the bone marrow and hematologic effects of peptide 1 than monkeys on the basis of dose and exposures at maximally tolerated doses. These results also suggested that, in terms of projecting potential bone marrow and hematological toxicity levels in humans, the monkey PK-PD data can be more clinically relevant than the rat data.

[00465] Peptide 1 was negative in genetic toxicology studies, including bacterial mutagenicity (Ames), chromosomal aberrations (human peripheral blood lymphocyte) and *in vivo* micronucleus (rat bone marrow) assays. Safety pharmacology studies were performed to assess the effects of peptide 1 on hERG potassium channels *in vitro* and on cardiac function in cynomolgus monkeys.

[00466] The above studies demonstrated that peptide 1 showed a favorable profile in preclinical GLP safety studies in rodents and monkeys. Genotoxicity, gastrointestinal toxicity, cardiotoxicity, and immunogenicity were not observed. Histopathology showed bone marrow hypocellularity consistent with mild to moderate myelosuppression.

Example 13: Pharmacokinetics of peptide 1

[00467] In rats, peptide 1 generally showed linear, dose-proportional increases in C_{max} and AUC. In the 4-week rat GLP toxicity study, C_{max} of peptide 1 ranged from 49.9 to 186 μg/mL, $AUC_{0-\infty}$ ranged from 90.5 to 562 μg•hr/mL, and clearance ranged from 19.2 to 28.3 mL/hr/kg.

[00468] In non-human primates, peptide 1 generally showed exposures that increased proportionally with dose, although an apparent plateau in exposure was observed at the high-dose group (20 mg/kg) in the 4-week monkey GLP toxicity study. In the study, C_{max} of Aileron peptide 1 ranged from 133 to 562 μg/mL, $t_{1/2}$ ranged from 3.7 to 6.0 hrs, $AUC_{0-\infty}$ ranged from 813 to 1,600 μg•hr/mL, and clearance ranged from 6.5 to 13.8 mL/hr/kg.

[00469] No significant sex-based differences in PK parameters were observed in either rats or monkeys, and no accumulation was observed following repeated doses on a twice-weekly schedule in the GLP toxicity studies.

[00470] *In vitro* studies revealed that peptide 1 is not an inhibitor of any cytochrome P450 (CYP) isoforms tested. *In vitro* assays for CYP induction also did not indicate any significant treatment-related effects with peptide 1. Based on these findings, the potential of clinically relevant drug-drug interactions for concomitant medications that are cleared through CYP-mediated mechanisms can be low.

CLAIMS

WHAT IS CLAIMED IS:

1. A method of treating a liquid tumor determined to lack a p53 deactivating mutation, in a human subject in need thereof wherein the method comprises administering to the human subject a pharmaceutical composition comprising a therapeutically effective amount of a peptidomimetic macrocycle or a pharmaceutically acceptable salt thereof, wherein the peptidomimetic macrocycle binds to MDM2 and/or MDMX proteins.

2. A method of treating a liquid tumor that lacks a p53 deactivating mutation, in a human subject in need thereof wherein the method comprises administering to the human subject a pharmaceutical composition comprising a therapeutically effective amount of a peptidomimetic macrocycle or a pharmaceutically acceptable salt thereof, wherein the peptidomimetic macrocycle binds to MDM2 and/or MDMX proteins.

3. A method of treating a liquid tumor that has a p53 deactivating mutation in a p53 gene, in a human subject in need thereof wherein the method comprises administering to the human subject a pharmaceutical composition comprising a therapeutically effective amount of a peptidomimetic macrocycle or a pharmaceutically acceptable salt thereof, wherein the peptidomimetic macrocycle binds to MDM2 and/or MDMX proteins.

4. A method of treating a liquid tumor in a human subject in need thereof, wherein the method comprises administering to the human subject a pharmaceutical composition comprising a therapeutically effective amount of a peptidomimetic macrocycle or a pharmaceutically acceptable salt thereof, wherein the peptidomimetic macrocycle binds to MDM2 and/or MDMX proteins and wherein the liquid tumor is not negative for p53 protein expression (such as liquid tumors that express wild-type p53 protein or mutated p53 protein with partial functionality).

5. A method of treating a liquid tumor in a human subject in need thereof, wherein the method comprises administering to the human subject a pharmaceutical composition comprising a therapeutically effective amount of a peptidomimetic macrocycle or a pharmaceutically acceptable salt thereof, wherein the peptidomimetic macrocycle binds to MDM2 and/or MDMX proteins and wherein the liquid tumor expresses a p53 protein with a gain of function mutation (such as a super apoptotic p53).

6. A method of treating a liquid tumor in a human subject in need thereof, wherein the method comprises administering to the human subject a pharmaceutical composition comprising a therapeutically effective amount of a peptidomimetic macrocycle or a pharmaceutically acceptable salt thereof, wherein the peptidomimetic macrocycle binds to MDM2 and/or MDMX proteins and wherein the liquid tumor express a p53 protein with a mutation that causes a partial loss of function.

7. A method of treating a liquid tumor a human subject in need thereof wherein the method comprises administering to the human subject a pharmaceutical composition comprising a therapeutically effective amount of a peptidomimetic macrocycle or a pharmaceutically acceptable salt thereof, wherein the peptidomimetic macrocycle binds to MDM2 and/or MDMX proteins and wherein cells in the liquid tumor express p53 from only a single genomic copy of the p53 gene.

8. A method of treating a liquid tumor a human subject in need thereof wherein the method comprises administering to the human subject a pharmaceutical composition comprising a therapeutically effective amount of a peptidomimetic macrocycle or a pharmaceutically acceptable salt thereof, wherein the peptidomimetic macrocycle binds to MDM2 and/or MDMX proteins and wherein the liquid tumor express a p53 protein with one or more silent mutations.

9. A method of treating a liquid tumor a human subject in need thereof wherein the method comprises administering to the human subject a pharmaceutical composition comprising a therapeutically effective amount of a peptidomimetic macrocycle or a pharmaceutically acceptable salt thereof, wherein the peptidomimetic macrocycle binds to MDM2 and/or MDMX proteins and wherein cells in the liquid tumor are negative for p53 expression.

10. The method of claim 3, wherein cells in the liquid tumor have the p53 deactivating mutation in one copy of the p53 gene.

11. The method of claim 10, wherein cells in the liquid tumor have a second p53 deactivating mutation in a second copy of a p53 gene.

12. The method of claim 11, wherein the p53 deactivating mutation in one copy of the p53 gene is the same as the second p53 deactivating mutation in the second copy of a p53 gene.

13. The method of claim 11, wherein the p53 deactivating mutation in one copy of the p53 gene is different from the second p53 deactivating mutation in the second copy of a p53 gene.

14. The method of any one of claims 3 and 10-13, wherein the p53 deactivating mutation in the p53 gene results in the lack of p53 protein expression from the p53 gene or in expression of partial a p53 protein with partial loss of function.

15. The method of any one of claims 3 and 10-13, wherein the second p53 deactivating mutation in the second copy of a p53 gene results in the lack of p53 protein expression from the p53 gene or in expression of partial a p53 protein with partial loss of function.

16. The method of any one of claims 3-15, wherein the cells of the liquid tumor have at least one mutation in a copy of a p53 gene, wherein the mutation eliminates or reduces the activity of a p53 protein expressed from the copy of the p53 gene, as compared to wild type p53 expressed from a copy of a non-mutated p53 gene.

17. A method of treating a liquid tumor in a human subject in need thereof wherein the method comprises administering to the human subject a pharmaceutical composition comprising a therapeutically effective amount of a peptidomimetic macrocycle or a pharmaceutically acceptable salt thereof, wherein the peptidomimetic macrocycle binds to MDM2 and/or MDMX proteins.

18. The method of any one of claims 1-17, wherein the peptidomimetic macrocycle disrupts the interaction between p53 and MDM2 and MDMX.

19. The method of any one of claims 1 to 18, comprising determining the lack of the p53 deactivating mutation in the liquid tumor prior to the administration of the pharmaceutical composition.

20. The method of claim 19, wherein the determining the lack of the p53 deactivating mutation comprises confirming the presence of wild type p53 in the liquid tumor.

21. The method of any one of claims 1 to 18, comprising determining a presence of a p53 gain of function mutation in the liquid tumor.

22. The method of any one of claims 2 to 18, comprising determining a presence of a deactivating mutation of p53 in the liquid tumor.

23. The method of any one of claims 2 to 18, comprising determining a presence of a copy loss mutation of p53 in the liquid tumor.

24. The method of any one of claims 2 to 18, comprising determining a presence of a partial loss of function mutation of P53 in the liquid tumor.

25. The method of any one of claims 1 to 24, further comprising confirming the lack of the p53 deactivating mutation in the liquid tumor prior to the administration of the pharmaceutical composition.

26. The method of claim 25, wherein the confirming the lack of the p53 deactivating mutation comprises confirming the presence of wild type p53 in the liquid tumor.

27. The method of any one of claims 1 to 18, comprising confirming a presence of a p53 gain of function mutation in the liquid tumor.

28. The method of any one of claims 2 to 18, comprising confirming a presence of a deactivating mutation of p53 in the liquid tumor.

29. The method of any one of claims 2 to 18, comprising confirming a presence of a copy loss mutation of p53 in the liquid tumor.

30. The method of any one of claims 2 to 18, comprising confirming a presence of a partial loss of function mutation of P53 in the liquid tumor.

31. The method of any one of claims 19-30, wherein the determining or the confirming is performed within 1-15 months prior to the administration of the pharmaceutical composition.

32. The method of any one of claim 19-30, wherein the determining or the confirming is performed within 1-12 months prior to the administration of the pharmaceutical composition.

33. The method of any one of claim 19-30, wherein the determining or the confirming is performed within 1-3 months prior to the administration of the pharmaceutical composition.

34. The method of any one of claim 19-30, wherein the determining or the confirming is performed within 1 month prior to the administration of the pharmaceutical composition.

35. The method of any one of claim 19-30, wherein the determining or the confirming is performed within 21 days prior to the administration of the pharmaceutical composition.

36. The method of any one of claim 19-30, wherein the determining or the confirming is performed up to about 1 year prior to the administration of the pharmaceutical composition.

37. The method of any one of claim 19-30, wherein the determining or the confirming is performed up to about 2 years prior to the administration of the pharmaceutical composition.

38. The method of any one of claim 19-30, wherein the determining or the confirming is performed up to about 3 years prior to the administration of the pharmaceutical composition.

39. The method of any one of the preceding claims, wherein the treatment results in re-activation of the p53 pathway, decreased liquid cancer cell proliferation, increased p53 protein, increased p21, and/or increased apoptosis in the human subject.

40. The method of any one of claims 1-39, wherein the pharmaceutical composition is administered two or three times a week.

41. The method of any one of claim 1-39, wherein the pharmaceutical composition is administered two times a week.

42. The method of any one of claims 1-39, wherein the pharmaceutical composition is administered once every 2 or 3 weeks.

43. The method of any one of claims 1-39, wherein the pharmaceutical composition is administered once every 1 or 2 weeks.

44. The method of any one of claims 1-39, wherein the pharmaceutical composition is administered on days 1, 4, 8, and 11 of a 21-day cycle.

45. The method of any one of claims 1-39, wherein the pharmaceutical composition is administered on days 1, 8, and 15 of a 28-day cycle.

46. The method of any one of claims 1-45, wherein the therapeutically effective amount is about 0.5 - about 30 mg per kilogram body weight of the human subject.

47. The method of any one of claims 1-45, wherein the therapeutically effective amount is about 0.5 - about 20 mg per kilogram body weight of the human subject.

48. The method of any one of claims 1-45, wherein the therapeutically effective amount is about 0.5 - about 10 mg per kilogram body weight of the human subject.

49. The method of any one of claims 1-45, wherein the therapeutically effective amount is about 0.04 mg, about 0.08 mg, about 0.16 mg, about 0.32 mg, about 0.64 mg, about 1.25 mg, about 1.28 mg, about 1.92 mg, about 2.5 mg, about 3.56 mg, about 3.75 mg, about 5.0 mg, about 7.12 mg, about 7.5 mg, about 10 mg, about 14.24 mg, about 15 mg, about 20 mg, or about 30 mg per kilogram body weight of the human subject.

50. The method of any one of claims 1-45, wherein the therapeutically effective amount is about 1.92 mg, about 3.75 mg, about 7.5 mg, about 15.0 mg, or about 30.0 mg per kilogram body weight of the human subject and the pharmaceutical composition is administered two times a week.

51. The method of any one of claims 1-45, wherein the therapeutically effective amount is about 1.28 mg, about 2.56 mg, about 5.0 mg, about 10 mg, or about 20 mg per kilogram body weight of the human subject and the pharmaceutical composition is administered two times a week.

52. The method of any one of claims 1-45, wherein the therapeutically effective amount is about 1.92 mg, about 3.75 mg, about 7.5 mg, about 15.0 mg, or about 30.0 mg per kilogram body weight of the human subject and the pharmaceutical composition is administered once a week.

53. The method of any one of claims 1-45, wherein the therapeutically effective amount is about 1.28 mg, about 2.56 mg, about 5.0 mg, about 10 mg, or about 20 mg per kilogram body weight of the human subject and the pharmaceutical composition is administered once a week.

54. The method of any one of claims 1-45, wherein the therapeutically effective amount is about 1.92 mg, about 3.75 mg, about 7.5 mg, about 15.0 mg, or about 30.0 mg mg per kilogram body weight of the human subject and the pharmaceutical composition is administered once a day three, five or seven times in a seven day period.

55. The method of claim 54, wherein the pharmaceutical composition is administered intravenously once a day, seven times in a seven day period.

56. The method of any one of claims 1-45, wherein the therapeutically effective amount is about 1.28 mg, about 2.56 mg, about 5.0 mg, about 10 mg, or about 20 mg per kilogram body

weight of the human subject and the pharmaceutical composition is administered once a day three, five or seven times in a seven day period.

57. The method of claim 56, wherein the pharmaceutical composition is administered intravenously once a day, seven times in a seven day period.

58. The method of any one of claims 1-57, wherein the pharmaceutical composition is administered over a period of 0.25 h, 0.5 h, 1 h, 2h, 3 h, 4 h, 5 h, 6 h, 7 h, 8 h, 9 h, 10 h, 11 h, or 12 h.

59. The method of any one of claims 1-57, wherein the pharmaceutical composition is administered over a period of 0.25-2.0 h.

60. The method of any one of claims 1-57, wherein the pharmaceutical composition is gradually administered over a period of 1 h.

61. The method of any one of the preceding claims any one of claims 1-57, wherein the pharmaceutical composition is gradually administered over a period of 2 h.

62. The method of any one of claims 1-61, wherein the treatment results in about 95%, 90%, 85%, 80%, 75%, 70%, 65%, 60%, 55%, 50%, 45%, 40%, 35%, 30%, 25%, 20%, 15% , 10%, or 5% reduction in the number of liquid cancer cells within a period of 1 month after treatment initiation.

63. The method of any one of claims 1-61, wherein the treatment results in at least 60%, 65%, 70%, 75%, 80%, 85%, 90%, or 95% reduction in the number of liquid cancer cells within a period of 1 month after treatment initiation.

64. The method of any one of claims 1-61, wherein the treatment results in about 95%, 90%, 85%, 80%, 75%, 70%, 65%, 60%, 55%, 50%, 45%, 40%, 35%, 30%, 25%, 20%, 15% , 10%, or 5% reduction in the number of liquid cancer cells within a period of 1 year after treatment initiation.

65. The method of any one of claims 1-61, wherein the treatment results in at least 60%, 65%, 70%, 75%, 80%, 85%, 90%, or 95% reduction in the number of liquid cancer cells within a period of 1 year after treatment initiation.

66. The method of any one of claims 1-61, wherein the treatment results in about 95%, 90%, 85%, 80%, 75%, 70%, 65%, 60%, 55%, 50%, 45%, 40%, 35%, 30%, 25%, 20%, 15% ,

10%, or 5% reduction the number of liquid cancer cells within a period of 6 months after treatment initiation.

67. The method of any one of claims 1-61, wherein the treatment results in at least 60%, 65%, 70%, 75%, 80%, 85%, 90%, or 95% reduction in the number of liquid cancer cells within a period of 6 months after treatment initiation.

68. The method of any one of claims 1-61, wherein the treatment results in about 95%, 90%, 85%, 80%, 75%, 70%, 65%, 60%, 55%, 50%, 45%, 40%, 35%, 30%, 25%, 20%, 15% , 10%, or 5% reduction in the number of liquid cancer cells within a period of 3 months after treatment initiation.

69. The method of any one of claims 1-61, wherein the treatment results in at least 60%, at least 65%, at least 70%, at least 75%, at least 80%, at least 85%, at least 90%, or at least 95% reduction in the number of liquid cancer cells within a period of 3 months after treatment initiation.

70. The method of any one of claims 62-69, wherein the liquid cancer is a stable disease.

71. The method of any one of claims 1-70, wherein the treatment results in an increased survival time of the human subject as compared to the expected survival time of the human subject if the human subject was not treated with the pharmaceutical composition.

72. The method of claim 71, wherein the increase in the survival time of the human subject is at least 30 days.

73. The method of claim 71, wherein the increase in the survival time of the human subject is at least 3 months.

74. The method of claim 71, wherein the increase in the survival time of the human subject is at least 6 months.

75. The method of claim 71, wherein the increase in the survival time of the human subject is at least 1 year.

76. The method of any one of claims 1-75, wherein the in vivo circulating half-life of the pharmaceutical composition is about 1 h, about 2h, about 3 h, about 4 h, about 5 h, about 6 h, about 7 h, about 8 h, about 9 h, about 10 h or about 12 h.

77. The method of any one of claims 1-75, wherein the in vivo circulating half-life of the pharmaceutical composition is about 4 h.

78. The method of any one of claims 1-75, wherein in vivo circulating the half-life of the pharmaceutical composition is about 6 h.

79. The method of any one of claims 1-78, wherein the biological tissue half-life of the pharmaceutical composition is about 1 h, about 2h, about 3 h, about 4 h, about 5 h, about 6 h, about 7 h, about 8 h, about 9 h, about 10 h or about 12 h.

80. The method of any one of claims 1-78, wherein the biological tissue half-life of the pharmaceutical composition is about 10 h.

81. The method of any one of the preceding claims, wherein the human subject is refractory and/or intolerant to one or more other treatment of the liquid cancer.

82. The method of any one of the preceding claims, wherein the human subject has had at least one unsuccessful prior treatment and/or therapy of the liquid cancer.

83. The method of any one of the preceding claims, wherein the liquid cancer expresses wild-type p53 protein.

84. The method of any one of the preceding claims, wherein the liquid cancer is selected from a group consisting of liquid lymphoma, leukemia, and myeloma.

85. The method of any one of the preceding claims, wherein the liquid cancer is a liquid lymphoma.

86. The method of any one of the preceding claims, wherein the liquid cancer is a leukemia.

87. The method of any one of the preceding claims, wherein the liquid cancer is a myeloma.

88. The method of any one of claims 84-87, wherein the liquid cancer is not a HPV positive cancer.

89. The method of claim 84, wherein the liquid cancer is not HPV positive cervical cancer, HPV positive anal cancer or HPV positive head and neck cancer, such as oropharyngeal cancers.

90. The method of any one of the preceding claims, wherein the pharmaceutical composition is administered intravenously.

91. The method of any one of the preceding claims, further comprising administering in addition to the pharmaceutical composition, a therapeutically effective amount of at least one additional therapeutic agent and/or therapeutic procedure to the human subject.

92. The method of any one of the preceding claims, wherein the human subject exhibits a complete response to the treatment.

93. The method of any one of the preceding claims, wherein the human subject exhibits a partial response to the treatment.

94. The method of any one of the preceding claims, wherein the liquid cancer is a progressive disease.

95. The method of any one of the preceding claims, wherein the liquid cancer is a stable disease.

96. The method of any one of the preceding claims, further comprising determining clinical activity of the administered pharmaceutical composition.

97. The method of claim 96, wherein the clinical activity is determined by an imaging method selected from a group consisting of computed tomography (CT), magnetic resonance imaging (MRI), and bone scanning.

98. The method of any one of the preceding claims, further comprising obtaining a biological sample from the human subject at one or more specific time-points and analyzing the biological sample with an analytical procedure.

99. The method of claim 98, wherein the analytical procedure is blood chemistry analysis, chromosomal translocation analysis, needle biopsy, tissue biopsy, fluorescence in situ hybridization, laboratory biomarker analysis, immunohistochemistry staining method, flow cytometry, or a combination thereof.

100. The method of claim 98, further comprising tabulating and/or plotting results of the analytical procedure.

101. The method of claim 98, wherein the one or more specific time-points comprise a time-point before the administration of the pharmaceutical composition to the human subject.

102. The method of claim 98, wherein the one or more specific time-points comprise a time-point after the administration of the pharmaceutical composition to the human subject.

103. The method of claim 98, wherein the one or more specific time-points comprise a time-point before and a time-point after the administration of the pharmaceutical composition to the human subject.

104. The method of claim 103, further comprising comparing the biological samples collected before and after the administration of the pharmaceutical composition to the human subject.

105. The method of claim 98, wherein the one or more specific time-points comprise multiple time-points before and after the administration of the pharmaceutical composition to the human subject.

106. The method of claim 105, further comprising comparing the biological samples collected at the multiple time-points.

107. The method of claim 98, wherein the biological sample is used for biomarker assessment.

108. The method of claim 98, wherein the biological sample is used for pharmacokinetic assessment.

109. The method of claim 108, wherein the pharmacokinetic assessment comprises studying the level of the peptidomimetic macrocycle and/or its metabolites in the biological sample at the specific time-points.

110. The method of claim 109, wherein the biological sample is a blood sample or a bone marrow sample.

111. The method of claim 98, wherein the biological sample is used for pharmacodynamic assessment.

112. The method of claim 111, wherein the pharmacodynamic assessment comprises studying the level of p53, MDM2, MDMX, p21 and/or caspase in the biological sample at the specific time-points.

113. The method of claim 112, wherein the biological sample is a liquid cancer cell specimen.

114. The method of claim 98, wherein the biological sample is used for immunogenicity assays.

115. The method of any one of the preceding claims, further comprising selecting and/or identifying at least one circulating tumor cells (CTC) or a mononuclear blood cells (MNBC) in the human subject prior to the administration of the pharmaceutical composition to the human subject.

116. The method of claim 115, further comprising measuring the number of circulating tumor cells (CTCs) or mononuclear blood cells (MNBCs) at one or more specific time-points, wherein the number of circulating tumor cells (CTCs) or mononuclear blood cells (MNBCs) is the total number of the at least one circulating tumor cells (CTC) or a mononuclear blood cells (MNBC) at the specific time-point.

117. The method of claim 116, further comprising measuring a baseline sum diameter, wherein the baseline sum diameter is a sum of the diameters of the at least one circulating tumor cells (CTC) or a mononuclear blood cells (MNBC) prior to the administration of the pharmaceutical composition to the human subject.

118. The method of claim 115, wherein the treatment results in disappearance of the least one circulating tumor cells (CTC) or a mononuclear blood cells (MNBC).

119. The method of any one of the preceding claims, wherein after the treatment the number of CTCs and/or MNBCs is reduced.

120. The method of claim 117, wherein the one or more specific time-points, comprise a time-point after the treatment.

121. The method of claim 120, wherein the number of CTCs and/or MNBCs at the time-point after the treatment is at least 30% less than the baseline number of CTCs and/or MNBCs.

122. The method of claim 117, wherein the treatment results in neither sufficient increase nor a sufficient decrease in the number of CTCs and/or MNBCs at the one or more specific time-points, taking as reference the baseline number of CTCs and/or MNBCs.

123. The method of any one of the preceding claims, wherein the peptidomimetic macrocycle is not an inhibitor of cytochrome P450 isoforms.

124. The method of any one of the preceding claims, wherein the treatment results in essentially no dose-limiting thrombocytopenia.

125. The method of any one of the preceding claims, wherein the treatment causes essentially no adverse effects in a normal-hematopoietic organ and/or tissue.

126. The method of any one of the preceding claims, wherein the treatment results in essentially no adverse event in the human subject that can be possibly, probably, or definitely related to the administration of the pharmaceutical composition.

127. The method of any one of the preceding claims, wherein the treatment results in essentially no serious adverse event in the human subject that can be probably, probably, or definitely related to the administration of the pharmaceutical composition.

128. The method of any one of the preceding claims, wherein the lack of p53 deactivation mutation in the liquid cancer is determined by DNA sequencing of the nucleic acid encoding the p53 protein.

129. The method of any one of the preceding claims, wherein the lack of p53 deactivation mutation in the liquid cancer is determined by RNA array based testing.

130. The method of any one of the preceding claims, wherein the lack of p53 deactivation mutation in the liquid cancer is determined by RNA analysis.

131. The method of any one of the preceding claims, wherein the lack of p53 deactivation mutation in the liquid cancer is determined by polymerase chain reaction (PCR).

132. The method of any one of the preceding claims, wherein the p53 deactivating mutation comprises mutations in DNA-binding domain of the protein.

133. The method of any one of the preceding claims, wherein the p53 deactivating mutation comprises missense mutation.

134. The method of any one of the preceding claims, wherein the p53 deactivating mutation is a dominant deactivating mutation.

135. The method of any one of the preceding claims, wherein the p53 deactivating mutation comprises one or more mutations selected from a groups consisting of V173L, R175H, G245C, R248W, R249S and R273H.

136. The method of any one of the preceding claims, wherein the p53 deactivating mutation comprises one or more of mutations shown in Table 1.

137. A method of treating liquid cancer in a human subject determined to lack a p53 deactivating mutation, wherein the method comprises administering to the human subject 0.5-20 mg of a peptidomimetic macrocycle per kilogram body weight of the human subject or a pharmaceutically acceptable salt thereof on days 1, 8 and 15 of a 28-day cycle.

138. The method of claim 137, wherein 0.5-10 mg of the peptidomimetic macrocycle per kilogram body weight of the human subject or a pharmaceutically acceptable salt thereof is administered to the human subject.

139. The method of claim 137, wherein the amount of the peptidomimetic macrocycle entered on day 8 and/or day 15 is greater than the amount of the peptidomimetic macrocycle entered on day 1.

140. The method of claim 137, wherein the amount of the peptidomimetic macrocycle entered on day 8 and/or day 15 is equal than the amount of the peptidomimetic macrocycle entered on day 1.

141. The method of claim 137, wherein the amount of the peptidomimetic macrocycle entered on day 1 and/or day 8 is greater than the amount of the peptidomimetic macrocycle entered on day 15.

142. The method of claim 137, wherein equal amounts of the peptidomimetic macrocycle is administered on days 1, 8 and 15.

143. The method of any of one of claims 137-142, wherein the 28-day cycle is repeated 2 or 3 times.

144. A method of treating liquid cancer in a human subject determined to lack a p53 deactivating mutation, wherein the method comprises administering to the human subject

0.25-10 mg of a peptidomimetic macrocycle per kilogram body weight of the human subject or a pharmaceutically acceptable salt thereof on days 1, 4, 8 and 11 of a 21-day cycle.

145. The method of claim 144, wherein 0.25-5 mg of the peptidomimetic macrocycle per kilogram body weight of the human subject or a pharmaceutically acceptable salt thereof is administered to the human subject.

146. The method of claim 144, wherein the amount of the peptidomimetic macrocycle entered on day 4, 8, and/or day 11 is greater than the amount of the peptidomimetic macrocycle administered on day 1.

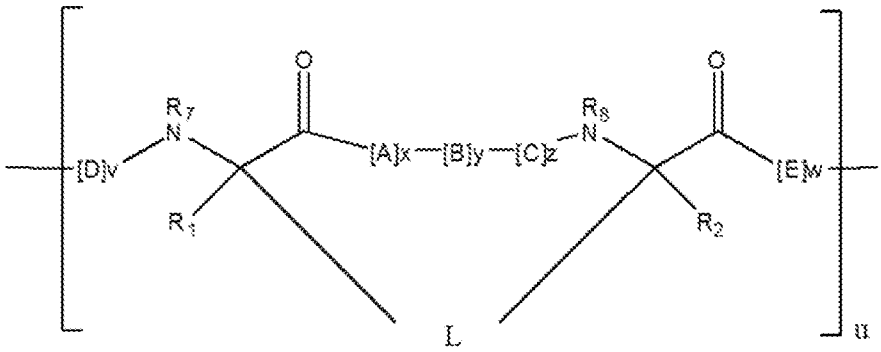
147. The method of claim 144, wherein the amount of the peptidomimetic macrocycle entered on day 4, 8, and/or day 11 is equal than the amount of the peptidomimetic macrocycle administered on day 1.

148. The method of claim 144, wherein the amount of the peptidomimetic macrocycle entered on day 1, 4, and/or day 8 is greater than the amount of the peptidomimetic macrocycle administered on day 11.

149. The method of claim 144, wherein equal amounts of the peptidomimetic macrocycle is administered on days 1, 4, 8, and 151.

150. The method of any of one of claims 144-149, wherein the 21-day cycle is repeated 2 or 3 times.

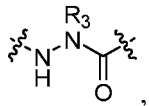
151. The method of any one of the preceding claims, wherein the peptidomimetic macrocycle comprises an amino acid sequence which is at least about 60%, about 70%, about 80%, about 90%, or about 95% identical to an amino acid sequence in any of Table 3, Table 3a, Table 3b, and Table 3c, wherein the peptidomimetic macrocycle has the formula:



Formula (I)

wherein:

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

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

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

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

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

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

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

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

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

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

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

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

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

each v is independently an integer;

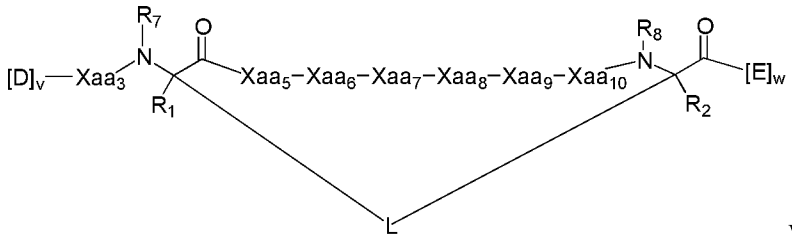
each w is independently an integer from 3–1000;

u is an integer from 1–10;

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

each n is independently an integer from 1–5.

152. The method of any one of the preceding claims, wherein the peptidomimetic macrocycle has formula:



wherein:

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

each D is independently an amino acid;

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

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

forms a macrocycle-forming linker L' connected to the alpha position of one of said D or E amino acids;
each L or L' is independently a macrocycle-forming linker
each R_5 is independently halogen, alkyl, $-OR_6$, $-N(R_6)_2$, $-SR_6$, $-SOR_6$, $-SO_2R_6$, $-CO_2R_6$, a fluorescent moiety, a radioisotope or a therapeutic agent;
each R_6 is independently –H, alkyl, alkenyl, alkynyl, arylalkyl, cycloalkylalkyl, heterocycloalkyl, a fluorescent moiety, a radioisotope or a therapeutic agent;
each R_7 is independently –H, alkyl, alkenyl, alkynyl, arylalkyl, cycloalkyl, heteroalkyl, cycloalkylalkyl, heterocycloalkyl, cycloaryl, or heterocycloaryl, optionally substituted with R_5, or part of a cyclic structure with a D residue;
each R_8 is independently –H, alkyl, alkenyl, alkynyl, arylalkyl, cycloalkyl, heteroalkyl, cycloalkylalkyl, heterocycloalkyl, cycloaryl, or heterocycloaryl, optionally substituted with R_5, or part of a cyclic structure with an E residue;
v is an integer from 1-1000; and
w is an integer from 0-1000.

153. The method of claim 151 or 152, wherein at least one of the macrocycle-forming linker has a formula $–L_1–L_2–$, wherein
L_1 and L_2 are independently alkylene, alkenylene, alkynylene, heteroalkylene, cycloalkylene, heterocycloalkylene, cycloarylene, heterocycloarylene, or $[-R_4-K-R_4-]_n$, each being optionally substituted with R_5;
each R_4 is independently alkylene, alkenylene, alkynylene, heteroalkylene, cycloalkylene, heterocycloalkylene, arylene, or heteroarylene;
each K is independently O, S, SO, SO_2, CO, CO_2, or $CONR_3$;
each R_3 is independently hydrogen, alkyl, alkenyl, alkynyl, arylalkyl, heteroalkyl, cycloalkyl, heterocycloalkyl, cycloalkylalkyl, cycloaryl, or heterocycloaryl, optionally substituted with R_5; and
n is an integer from 1-5.

154. The method of claim 151, wherein w is an integer from 3-1000, for example 3-500, 3-200, 3-100, 3-50, 3-30, 3-20, or 3-10.

155. The method of claim 151, wherein Xaa_5 is Glu or an amino acid analog thereof.

156. The method of any one of claims 151-155, wherein each E is independently Ala (alanine), Ser (serine) or an analog thereof.

157. The method of any one of claims 151-156, wherein $[D]_v$ is $–Leu_1\text{-}Thr_2$.

158. The method of any one of claims 151-157, wherein w is 3-10.

159. The method of any one of claims 151-157, wherein w is 3-6.

160. The method of any one of claims 151-157, wherein w is 6-10.

161. The method of any one of claims 151-157, wherein w is 6.

162. The method of any one of claims 151-161, wherein v is 1-10.

163. The method of any one of claims 151-161, wherein v is 2-10.

164. The method of any one of claims 151-161, wherein v is 2-5.

165. The method of any one of claims 151-161, wherein v is 2.

166. The method of claim 151 or 153, wherein L_1 and L_2 are independently alkylene, alkenylene, alkynylene, heteroalkylene, cycloalkylene, heterocycloalkylene, cycloarylene, or heterocycloarylene, each being optionally substituted with R_5.

167. The method of claim 151 or 153, wherein L_1 and L_2 are independently alkylene or alkenylene.

168. The method of claim 151 or 152, wherein L is alkylene, alkenylene, or alkynylene.

169. The method of claim 151 or 152, wherein L is alkylene.

170. The method of claim 151 or 152, wherein L is C_3-C_{16} alkylene.

171. The method of claim 151 or 152, wherein L is C_{10}-C_{14} alkylene.

172. The method of any one of claims 151, wherein R_1 and R_2 are independently –H, alkyl, alkenyl, alkynyl, arylalkyl, cycloalkyl, cycloalkylalkyl, heteroalkyl, or heterocycloalkyl, unsubstituted or substituted with halo–.

173. The method of any one of claims 151, wherein R_1 and R_2 are H.

174. The method of any one of claims 151, wherein R_1 and R_2 are independently alkyl.

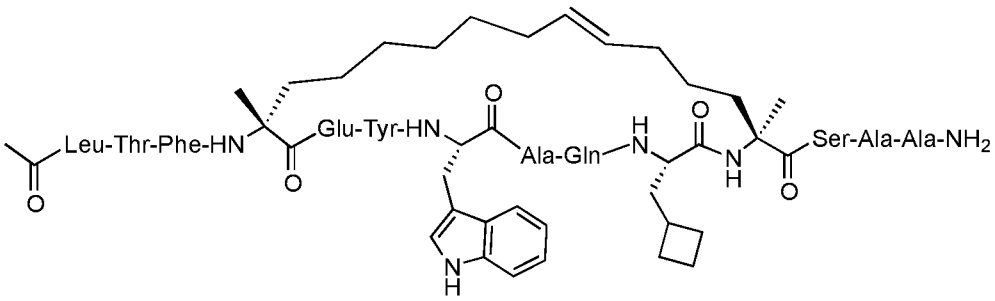
175. The method of any one of claim 151, wherein R_1 and R_2 are methyl.

176. The method of claim 151, wherein x+y+z = 6.

177. The method of claim 151, wherein u is 1.

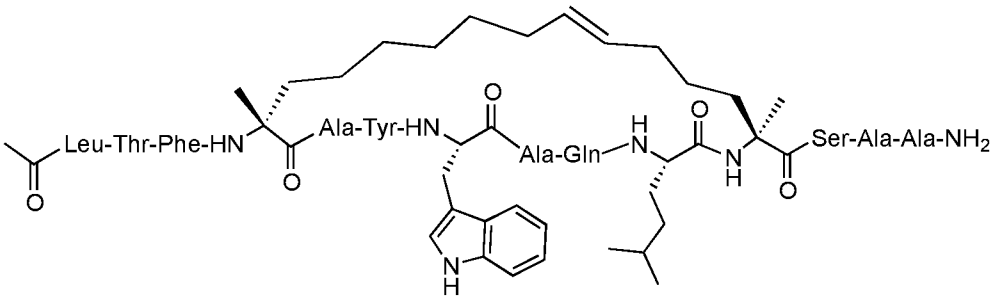
178. The method of any one of claims 151-177, the peptidomimetic macrocycle comprises at least one amino acid which is an amino acid analog.

179. The method of claim 151, wherein the peptidomimetic macrocycle has formula:



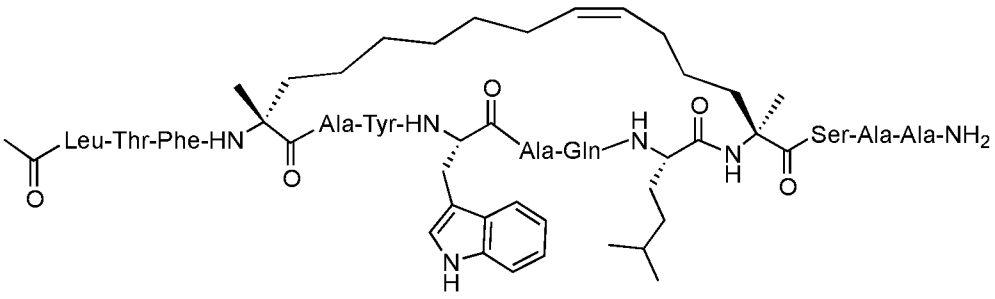
or a pharmaceutically acceptable salt thereof.

180. The method of claim 151, wherein the peptidomimetic macrocycle has formula:



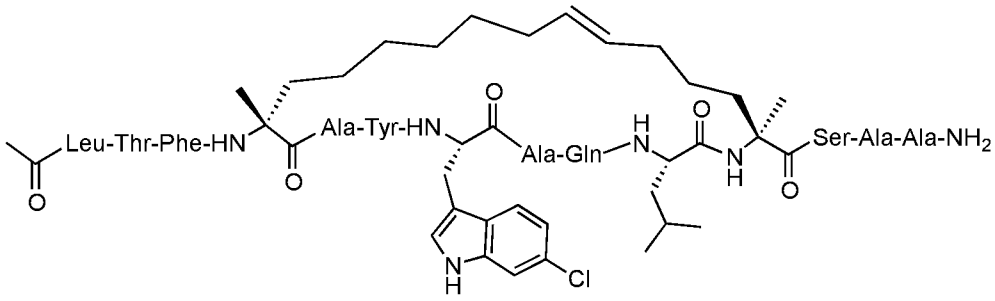
or a pharmaceutically acceptable salt thereof.

181. The method of claim 151, wherein the peptidomimetic macrocycle has formula:



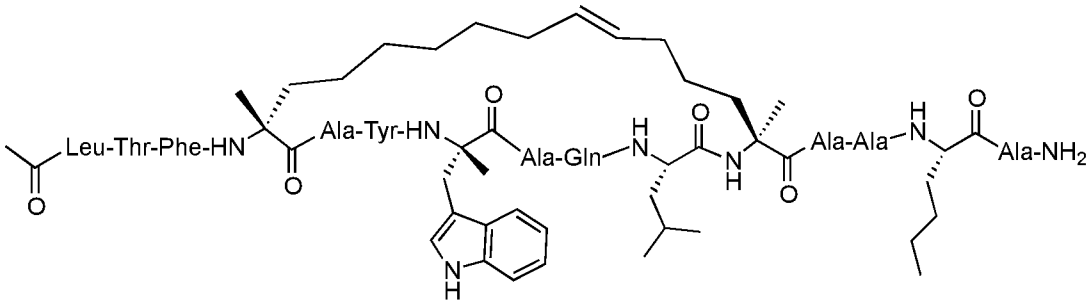
or a pharmaceutically acceptable salt thereof.

182. The method of claim 151, wherein the peptidomimetic macrocycle has formula:



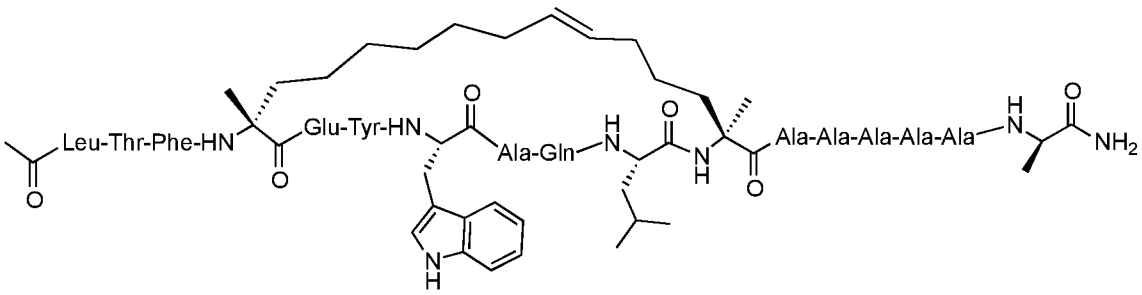
or a pharmaceutically acceptable salt thereof.

183. The method of claim 151, wherein the peptidomimetic macrocycle has formula:



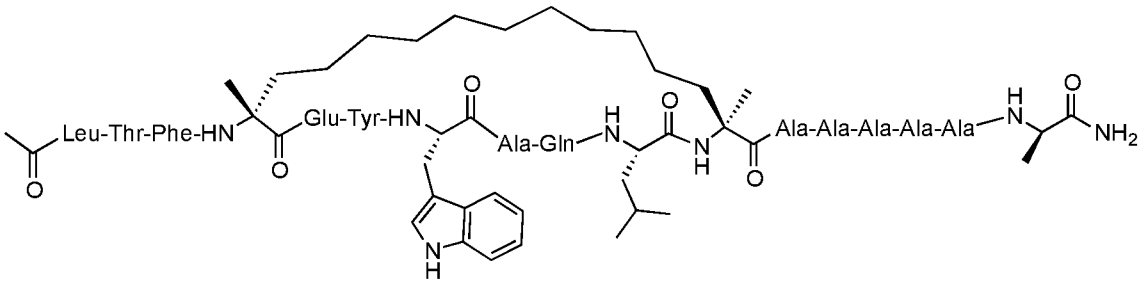
or a pharmaceutically acceptable salt thereof.

184. The method of claim 151, wherein the peptidomimetic macrocycle has formula:



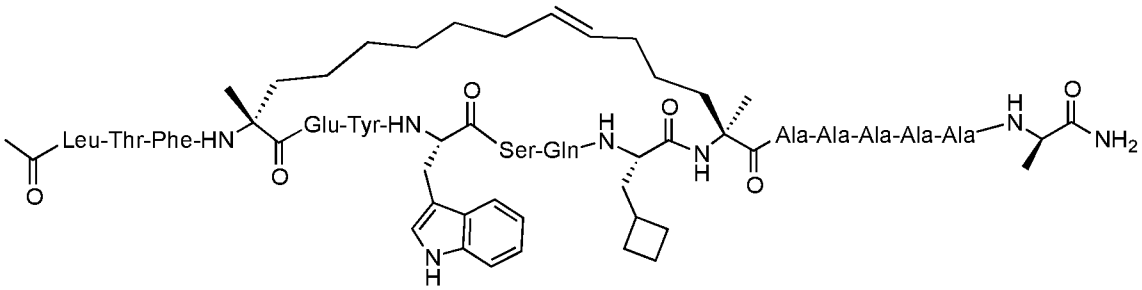
or a pharmaceutically acceptable salt thereof.

185. The method of claim 151, wherein the peptidomimetic macrocycle has formula:



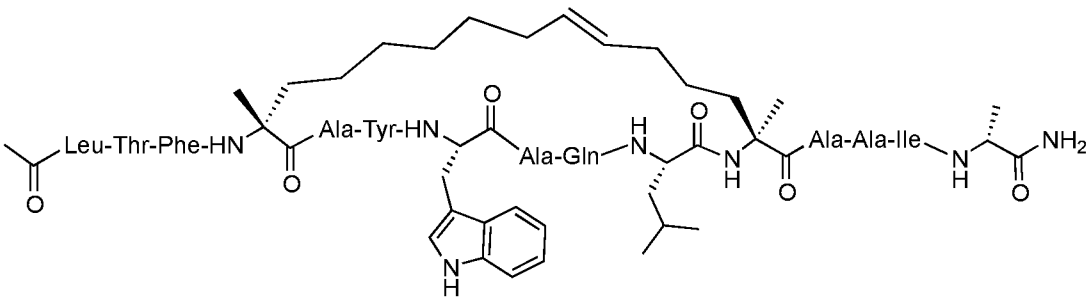
or a pharmaceutically acceptable salt thereof.

186. The method of claim 151, wherein the peptidomimetic macrocycle has formula:



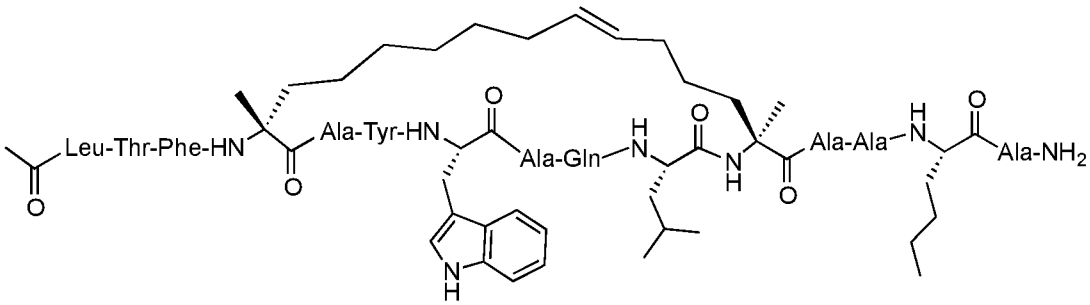
or a pharmaceutically acceptable salt thereof.

187. The method of claim 151, wherein the peptidomimetic macrocycle has formula:



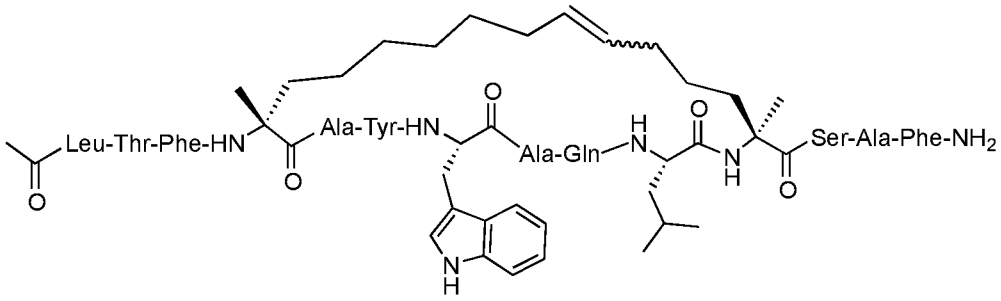
or a pharmaceutically acceptable salt thereof.

188. The method of claim 151, wherein the peptidomimetic macrocycle has formula:



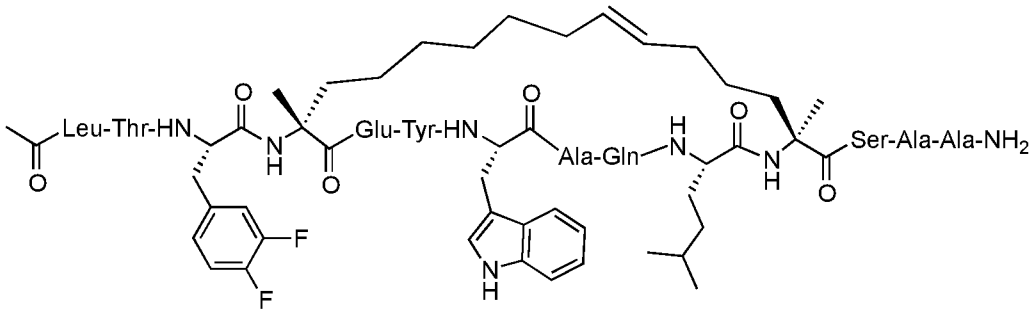
or a pharmaceutically acceptable salt thereof.

189. The method of claim 151, wherein the peptidomimetic macrocycle has formula:



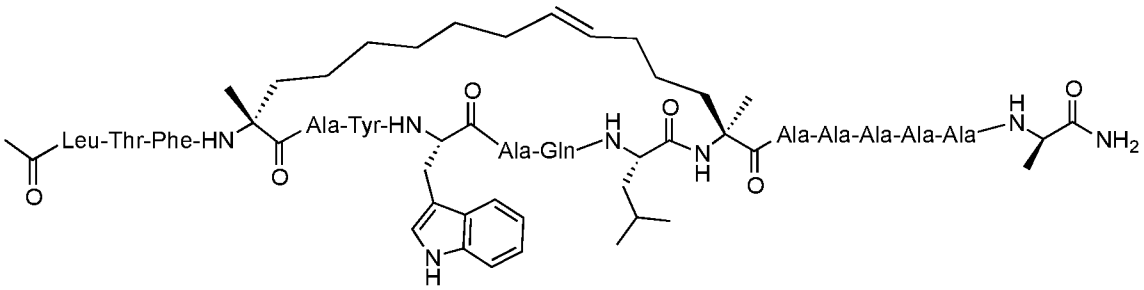
or a pharmaceutically acceptable salt thereof.

190. The method of claim 151, wherein the peptidomimetic macrocycle has formula:



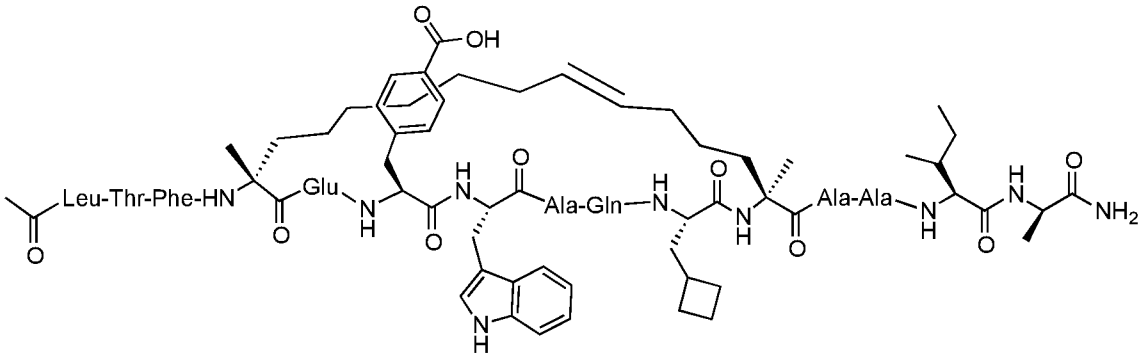
or a pharmaceutically acceptable salt thereof.

191. The method of claim 151, wherein the peptidomimetic macrocycle has formula:



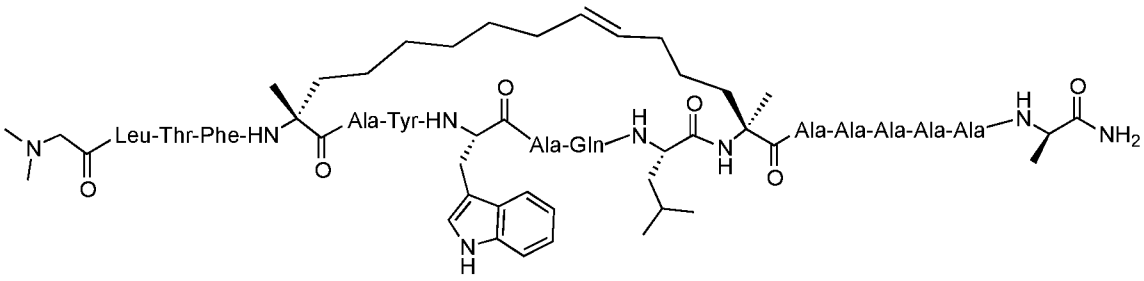
or a pharmaceutically acceptable salt thereof.

192. The method of claim 151, wherein the peptidomimetic macrocycle has formula:



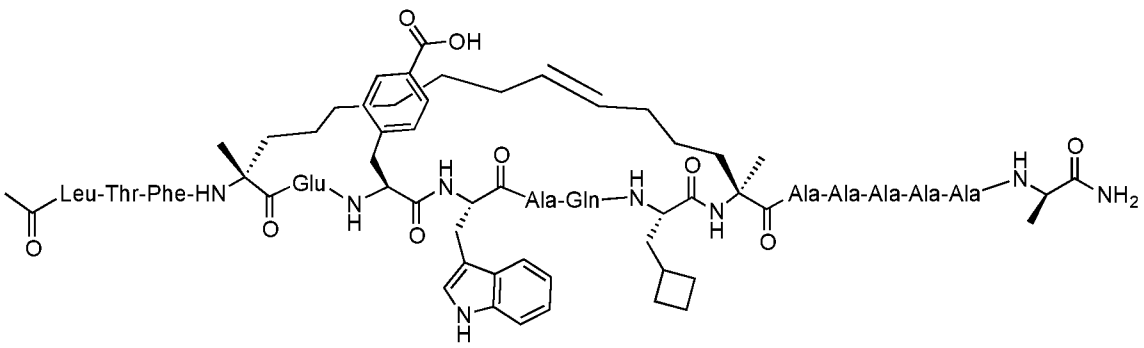
or a pharmaceutically acceptable salt thereof.

193. The method of claim 151, wherein the peptidomimetic macrocycle has formula:



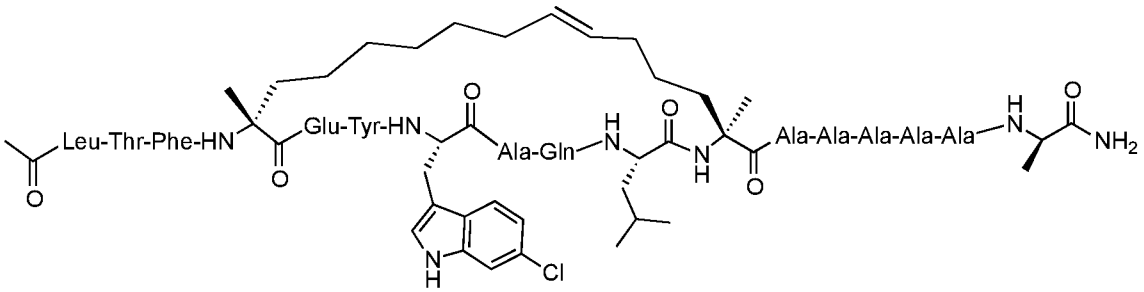
or a pharmaceutically acceptable salt thereof.

194. The method of claim 151, wherein the peptidomimetic macrocycle has formula:



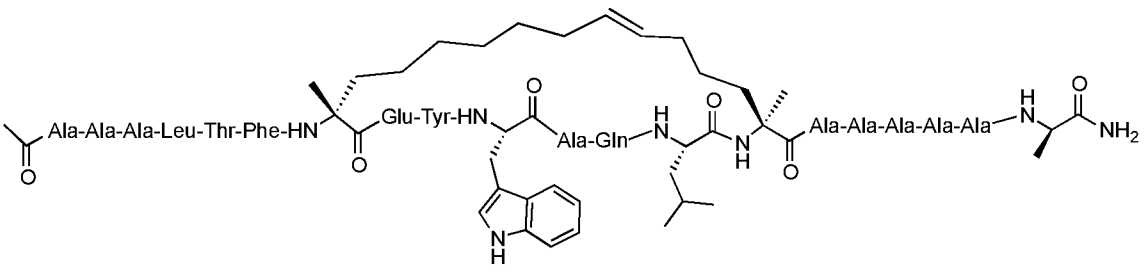
or a pharmaceutically acceptable salt thereof.

195. The method of claim 151, wherein the peptidomimetic macrocycle has formula:



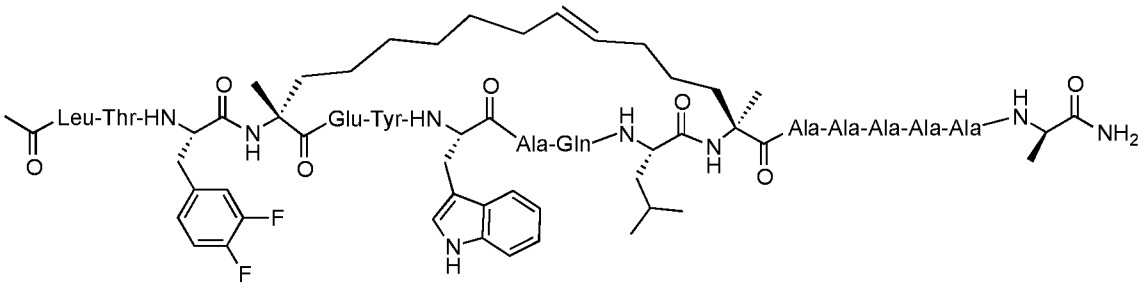
or a pharmaceutically acceptable salt thereof.

196. The method of claim 151, wherein the peptidomimetic macrocycle has formula:



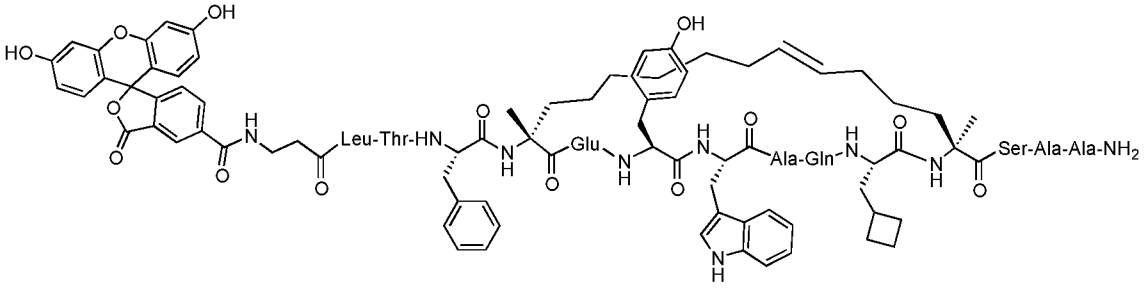
or a pharmaceutically acceptable salt thereof.

197. The method of claim 151, wherein the peptidomimetic macrocycle has formula:



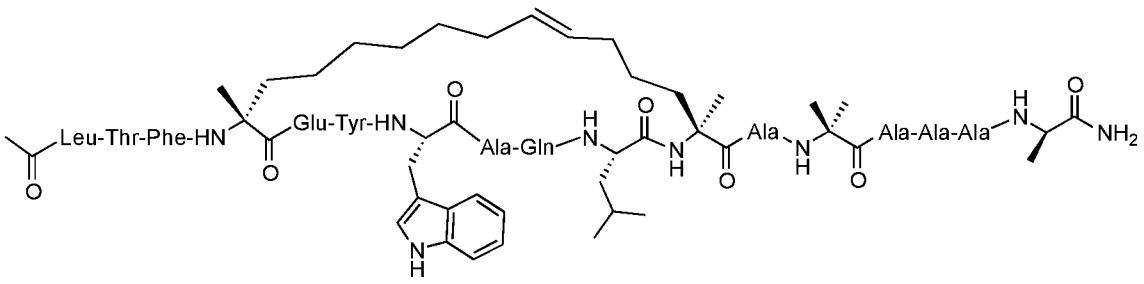
or a pharmaceutically acceptable salt thereof.

198. The method of claim 151, wherein the peptidomimetic macrocycle has formula:



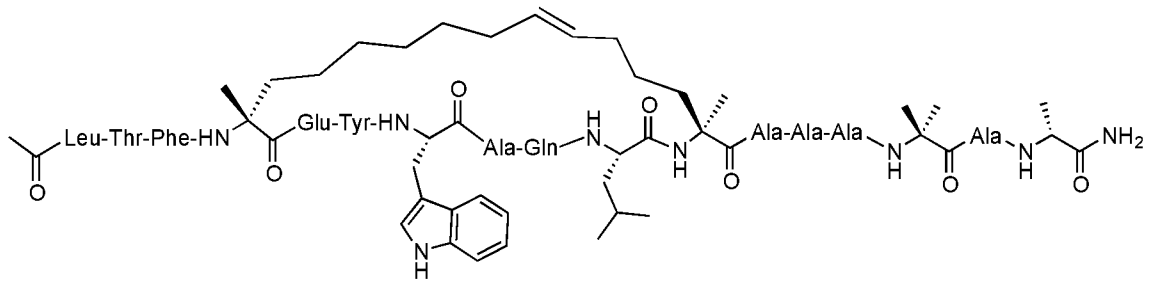
or a pharmaceutically acceptable salt thereof.

199. The method of claim 151, wherein the peptidomimetic macrocycle has formula:



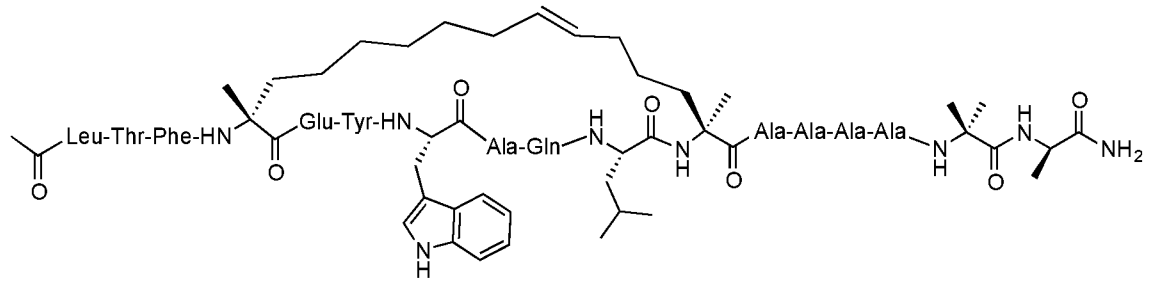
or a pharmaceutically acceptable salt thereof.

200. The method of claim 151, wherein the peptidomimetic macrocycle has formula:



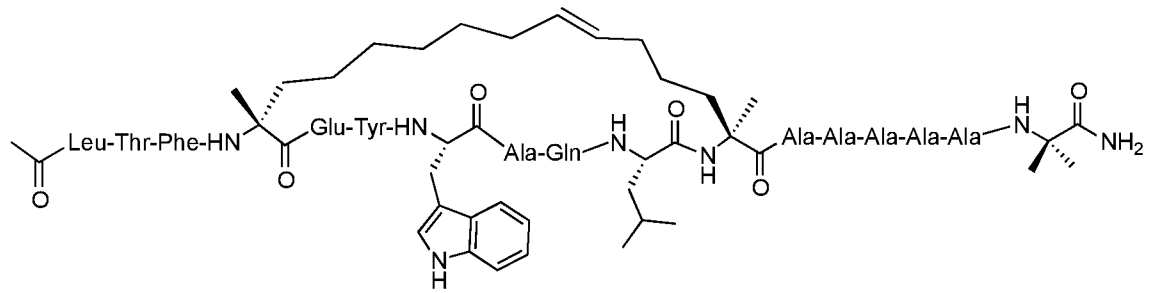
or a pharmaceutically acceptable salt thereof.

201. The method of claim 151, wherein the peptidomimetic macrocycle has formula:



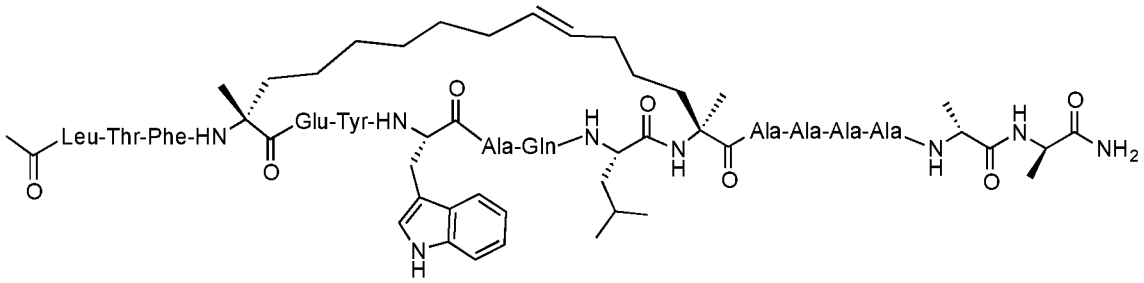
or a pharmaceutically acceptable salt thereof.

202. The method of claim 151, wherein the peptidomimetic macrocycle has formula:



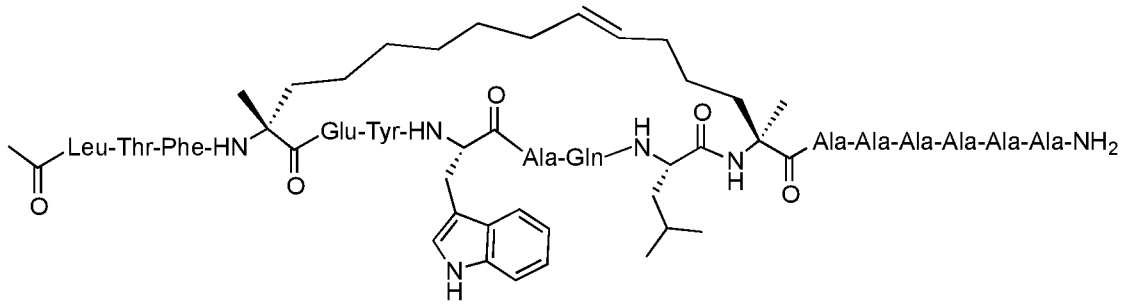
or a pharmaceutically acceptable salt thereof.

203. The method of claim 151, wherein the peptidomimetic macrocycle has formula:



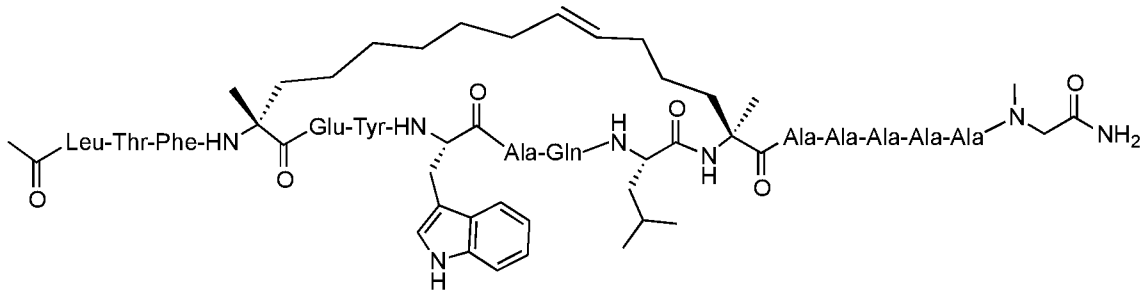
or a pharmaceutically acceptable salt thereof.

204. The method of claim 151, wherein the peptidomimetic macrocycle has formula:



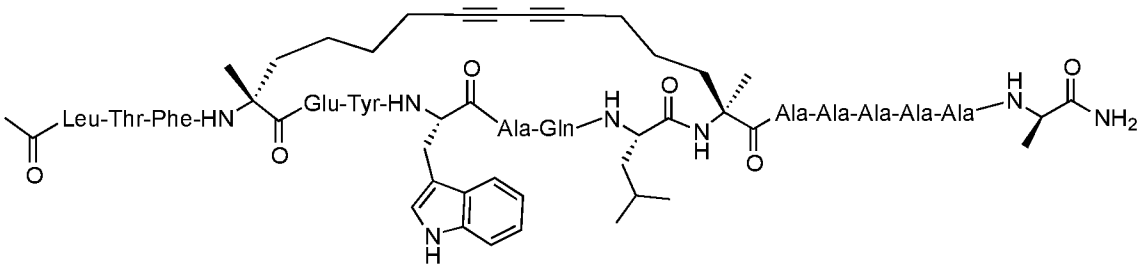
or a pharmaceutically acceptable salt thereof.

205. The method of claim 151, wherein the peptidomimetic macrocycle has formula:



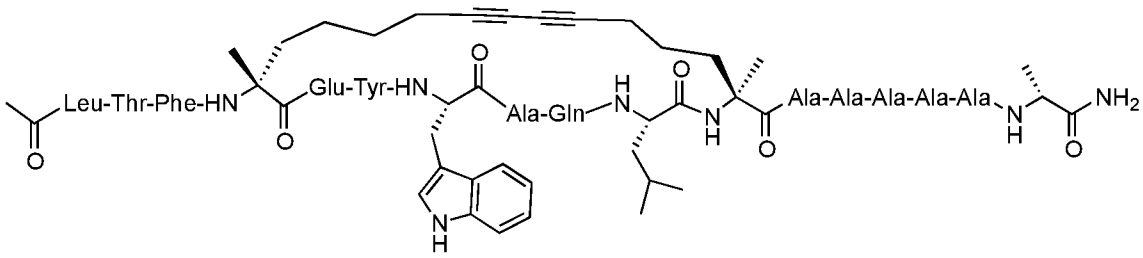
or a pharmaceutically acceptable salt thereof.

206. The method of claim 151, wherein the peptidomimetic macrocycle has formula:



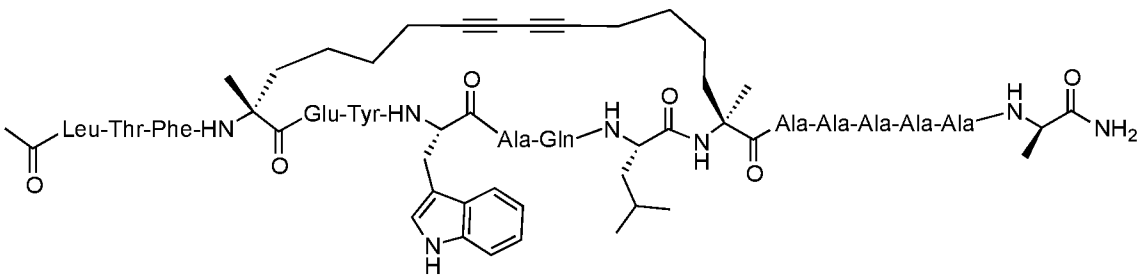
or a pharmaceutically acceptable salt thereof.

207. The method of claim 151, wherein the peptidomimetic macrocycle has formula:



or a pharmaceutically acceptable salt thereof.

208. The method of claim 151, wherein the peptidomimetic macrocycle has formula:



or a pharmaceutically acceptable salt thereof.

209. A method of identifying one or more liquid cancer biomarkers in a human subject lacking a p53 deactivating mutation, comprising administering to the human subject a therapeutically effective amount of a peptidomimetic macrocycle.

210. The method of claim 209, wherein the biomarkers are p53 status, MDM2 expression level or MDMX expression level.

Human wild type P53 protein sequence

MEEPQSDPSVEPPLSQETFSDLWKLLPENNVLSPLPSQAMDDLMLSPDDIEQWFTEDPGP
DEAPRMPEAAPPVAPAPAAPTPAAPAPAPSWPLSSSVPSQKTYQGSYGFRLGFLHSGTAK
SVTCTYSPALNKMFCQLAKTCPVQLWVDSTPPPGTRVRAMAIYKQSQHMTEVVRRCPHHE
RCSDSDGLAPPQHLIRVEGNLRVEYLDDRNTFRHSVVVPYEPPEVGSDCTTIHYNYMCNS
SCMGGMNRRPILTIITLEDSSGNLLGRNSFEVRVCACPGRDRRTEEENLRKKGEPHHELP
PGSTKRALPNNTSSSPQPKKKPLDGEYFTLQIRGRERFEMFRELNEALELKDAQAGKEPG
GSRAHSSHLKSKKGQSTSRHKKLMFKTEGPDSD

FIGURE 1

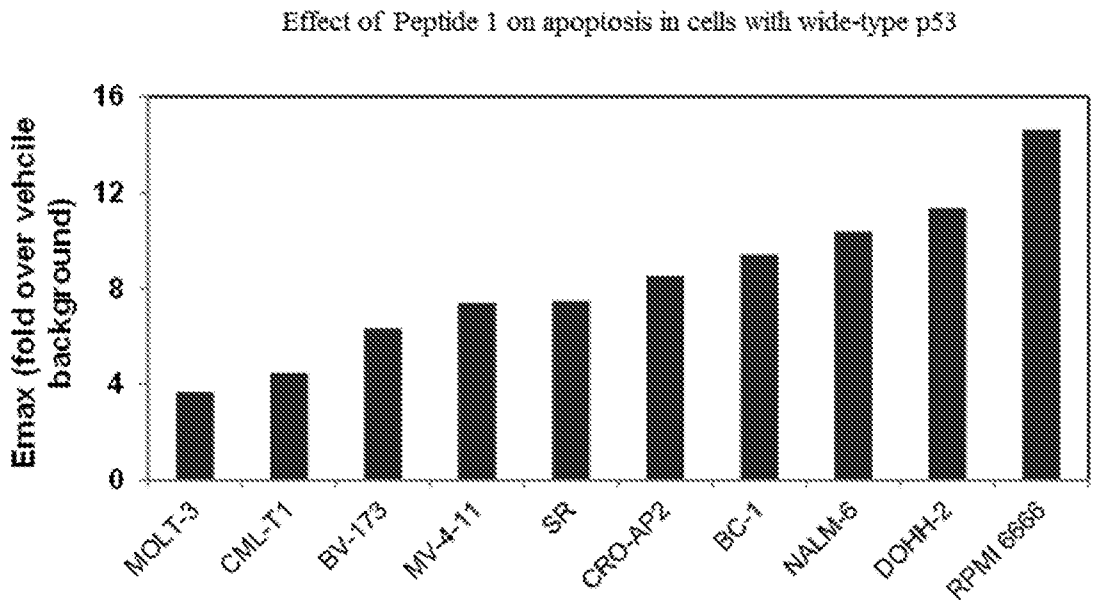

Effect of Peptide 1 on apoptosis in cells with wide-type p53
Emax (fold over vehicle background)
16
12
8
4
0
MOLT-3
CML-T1
BV-173
MV-4-11
SR
CRO-AP2
BC-1
NALM-6
DOHH-2
RPMI 6666

FIGURE 2

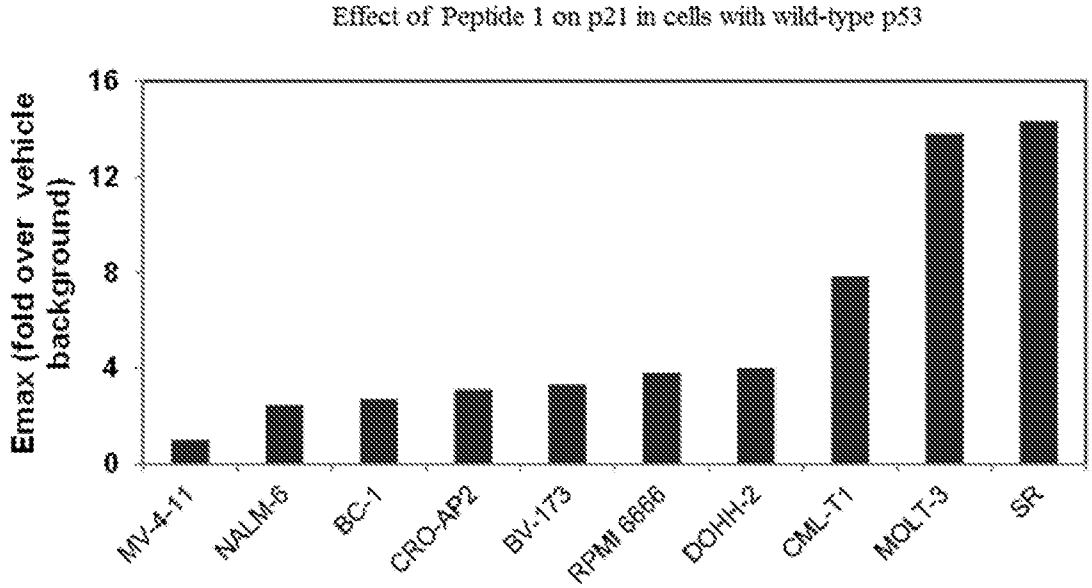

Effect of Peptide 1 on p21 in cells with wild-type p53
Emax (fold over vehicle background)
16
12
8
4
0
MV-4-11
NALM-6
BC-1
CRO-AP2
BV-173
RPMI 8866
DOHH-2
CML-T1
MOLT-3
SR

FIGURE 3

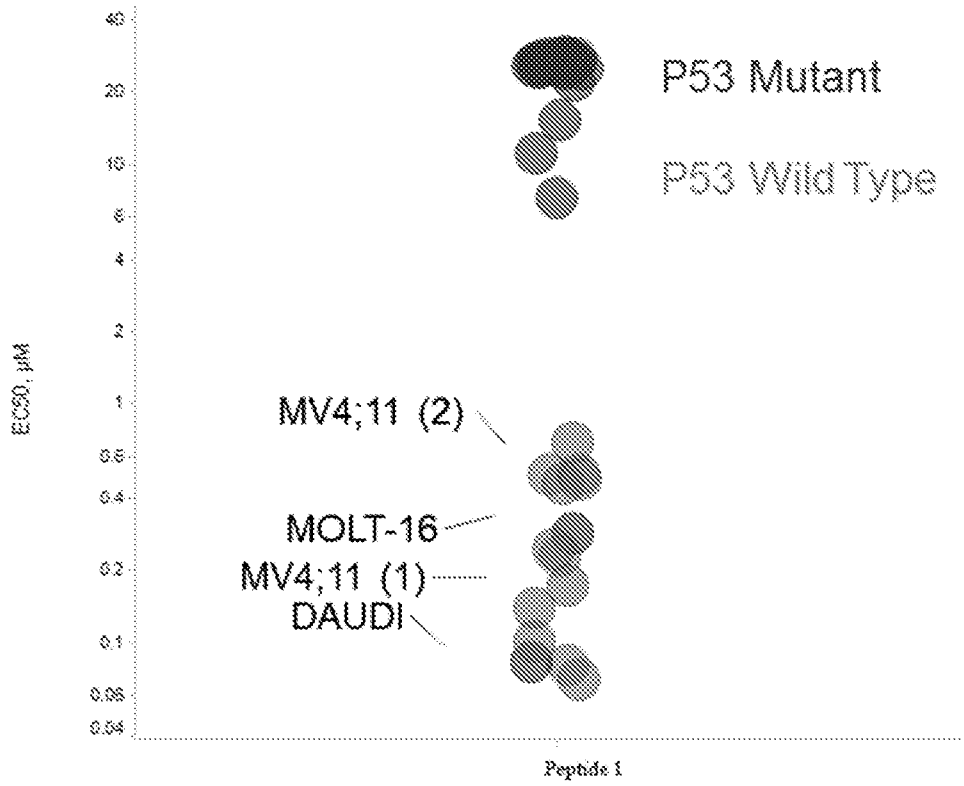

P53 Mutant
P53 Wild Type
MV4;11 (2)
MOLT-16
MV4;11 (1)
DAUDI
EC50, µM
Peptide 1

FIGURE 4

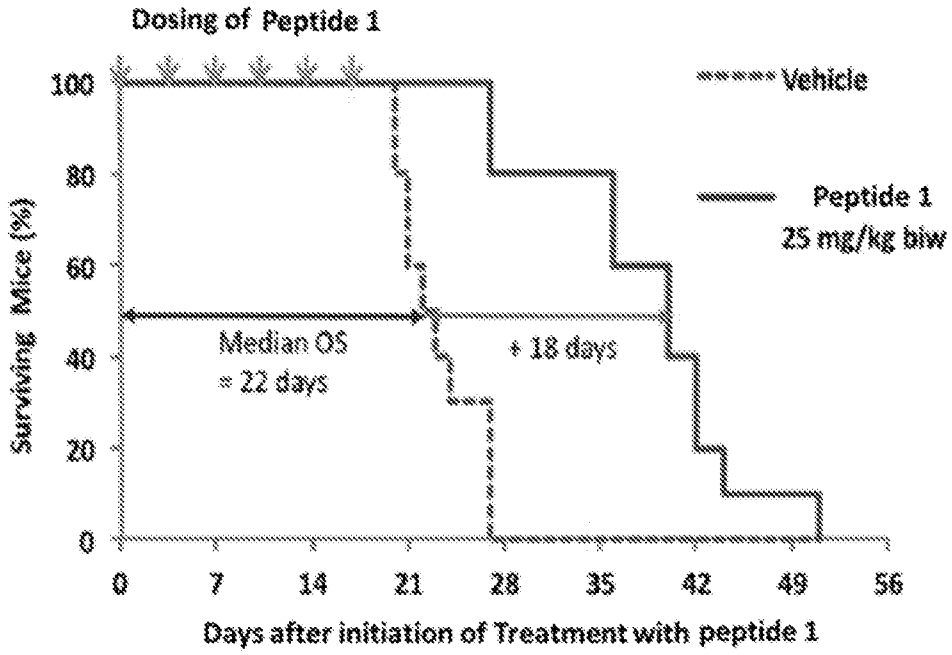

Dosing of Peptide 1
Vehicle
Peptide 1
25 mg/kg biw
Surviving Mice (%)
100
80
60
40
20
0
Median OS
= 22 days
+ 18 days
0
7
14
21
28
35
42
49
56
Days after initiation of Treatment with peptide 1

FIGURE 5

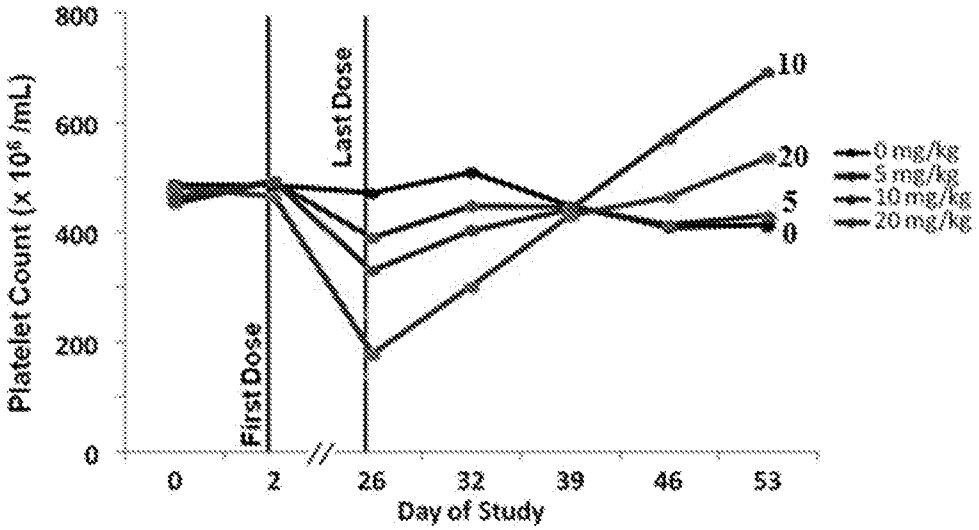

Platelet Count (x 10^6 /mL)
800
600
400
200
0
First Dose
Last Dose
0
2
26
32
39
46
53
Day of Study
10
20
5
0
0 mg/kg
5 mg/kg
10 mg/kg
20 mg/kg

FIGURE 6

INTERNATIONAL SEARCH REPORT

International application No.
PCT/US2016/023275

A. CLASSIFICATION OF SUBJECT MATTER

A61K 38/12 (2006.01) A61P 35/02 (2006.01)

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)

Databases: Patentscope, EPODOC, MEDLINE, WPIAP, BIOSIS, EMBASE & keywords: Liquid cancer, blood cancer, leukaemia, myeloma, liquid lymphoma, peptidomimetic, analog, p53, MDM2, MDMX and like terms

Patentscope, PubMed: CHEN U, ANNIS D, CHANG Y, AIVADO M, OLSON K, VIAU C, AILERON

Applicant(s)/Inventor(s) name searched in internal databases provided by IP Australia

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
	Documents are listed in the continuation of Box C	

[X] Further documents are listed in the continuation of Box C [X] See patent family annex

* Special categories of cited documents:

"A" document defining the general state of the art which is not considered to be of particular relevance

"E" earlier application or patent but published on or after the international filing date

"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)

"O" document referring to an oral disclosure, use, exhibition or other means

"P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art

"&" document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
9 May 2016	09 May 2016
Name and mailing address of the ISA/AU	**Authorised officer**
AUSTRALIAN PATENT OFFICE PO BOX 200, WODEN ACT 2606, AUSTRALIA Email address: pct@ipaustralia.gov.au	Nathalie Tochon-Danguy AUSTRALIAN PATENT OFFICE (ISO 9001 Quality Certified Service) Telephone No. 0262833101

INTERNATIONAL SEARCH REPORT		International application No.
C (Continuation).	DOCUMENTS CONSIDERED TO BE RELEVANT	**PCT/US2016/023275**

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	WO 2013/123266 A1 (AILERON THERAPEUTICS, INC.) 22 August 2013 pages 1, 2, 50-55, examples 9-15, Figures 3-6, claims	1-210
A	FISCHER P. M., "Peptide, peptidomimetic, and small-molecule antagonists of the p53-HDM2 protein-protein interaction", International Journal of Peptide Research and Therapeutics, 2006, vol. 12, no. 1, pages 3-19 Abstract, pages 4-5	1-210
A	ZHANG Q. et al., "Targeting p53-MDM2-MDMX loop for cancer therapy, Subcell. Biochem., 2014, vol. 85, pages 281-319 (Author Manuscript available in PMC page 1-31) Abstract, Introduction, Targeting the p53-MDM2-MDMX loop for cancer therapy, alpha-helix mimetic based chemistry or combinational chemistry	1-210
P,A	WO 2016/049355 A1 (AILERON THERAPEUTICS, INC.) 31 March 2016 Abstract, pages 34, 38, 178-188, Tables 1d, 1e, 1f, claims, Figure 3	1-210
P,A	WO 2016/049359 A1 (AILERON THERAPEUTICS, INC.) 31 March 2016 Abstract, pages 1-8, 71-72, 78-88, Tables 3-5, Examples 2-4, Claims, Figures 2, 7, 9, 14	1-210

INTERNATIONAL SEARCH REPORT Information on patent family members	International application No. **PCT/US2016/023275**

This Annex lists known patent family members relating to the patent documents cited in the above-mentioned international search report. The Australian Patent Office is in no way liable for these particulars which are merely given for the purpose of information.

Patent Document/s Cited in Search Report		**Patent Family Member/s**	
Publication Number	**Publication Date**	**Publication Number**	**Publication Date**
WO 2013/123266 A1	22 August 2013	WO 2013123266 A1	22 Aug 2013
		AR 089993 A1	01 Oct 2014
		AU 2013221432 A1	14 Aug 2014
		CA 2862038 A1	22 Aug 2013
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		KR 20140122759 A	20 Oct 2014
		MX 2014009880 A	10 Nov 2014
		PH 12014501844 A1	17 Nov 2014
		RU 2014137107 A	10 Apr 2016
		SG 11201404648P A	26 Sep 2014
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		US 2015051155 A1	19 Feb 2015
WO 2016/049355 A1	31 March 2016	WO 2016049355 A1	31 Mar 2016
		US 2016101145 A1	14 Apr 2016
WO 2016/049359 A1	31 March 2016	WO 2016049359 A1	31 Mar 2016

End of Annex

Due to data integration issues this family listing may not include 10 digit Australian applications filed since May 2001.