PEPTIDOMIMETIC MACROCYCLES AND USES THEREOF

CROSS REFERENCE

[0001] This application calims priority to U.S. Provisional Application No. 62/054,861, filed September 24, 2014, U.S. Provisional Application No. 62/213,831, filed September 03, 2015 and U.S. Provisional Application No. 62/216,670, filed September 10, 2015 each of which is incorporated herein by reference in its entirety.

BACKGROUND OF THE INVENTION

[0001] 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.

[0002] There remains a considerable need for methods for treating solid tumor. 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 solid tumors and other hyperproliferative diseases.

SUMMARY OF THE INVENTION

[0003] In one aspect, the disclosure provides a method of treating solid tumor determined to lack a p53 deactivating mutation, in a human subject, wherein the method comprises administering to the human

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.

[0004] In another aspect, the disclosure provides a method of treating a solid 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 therapeutically equivalent amount of a pharmaceutically acceptable salt thereof, wherein the peptidomimetic macrocycle binds to MDM2 and/or MDMX proteins.

[0005] In another aspect, the disclosure provides a method of treating a solid 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 therapeutically equivalent amount of a pharmaceutically acceptable salt thereof, wherein the peptidomimetic macrocycle binds to MDM2 and/or MDMX proteins.

[0006] In another aspect, the disclosure provides a method of treating a solid 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, wherein the peptidomimetic macrocycle binds to MDM2 and/or MDMX proteins and wherein the solid tumor is not negative for p53 protein expression (such as solid tumors that express wild-type p53 protein or mutated p53 protein with partial functionality).

[0007] In another aspect, the disclosure provides a method of treating a solid 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, wherein the peptidomimetic macrocycle binds to MDM2 and/or MDMX proteins and wherein the solid tumor expresses a p53 protein with a gain of function mutation (such as a super apoptotic p53).

[0008] In another aspect, the disclosure provides a method of treating a solid 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, wherein the peptidomimetic macrocycle binds to MDM2 and/or MDMX proteins and wherein the solid tumor express a p53 protein with a mutation that causes a partial loss of function.

[0009] In another aspect, the disclosure provides a method of treating a solid 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 wherein cells in the solid 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).

[0010] In another aspect, the disclosure provides a method of treating a solid 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 wherein the solid tumor express a p53 protein with one or more silent mutations.

[0011] In another aspect, the disclosure provides a method of treating a solid 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 wherein cells in the solid tumor are negative for p53 expression.

[0012] In another aspect, the disclosure provides a method of treating a solid 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 therapeutically equivalent amount of a pharmaceutically acceptable salt thereof, wherein the peptidomimetic macrocycle binds to MDM2 and/or MDMX proteins and wherein cells in the solid tumor have the p53 deactivating mutation in one copy of the p53 gene. In some embodiments, the cells in the solid tumor have a second p53 deactivating mutation in a second copy of a p53 gene. In some embodiments, 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 some embodiments, 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.

[0013] In some embodiments, 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 some embodiments, 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 of the methods described herein, the cells of the solid tumor have at least one mutation in a copy of a p53 gene, wherein the mutation eliminates or reduces the or 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.

[0015] In another aspect, the disclosure provides a method of treating a solid 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, wherein the peptidomimetic macrocycle binds to MDM2 and/or MDMX proteins.

[0016] In some embodiments, the peptidomimetic macrocycle used in the various methods described herein is a peptidomimetic macrocycle that disrupts the interaction between p53 and MDM2 and MDMX.

[0017] In some embodiments, the various methods described herein further comprise determining the lack of the p53 deactivating mutation in the solid tumor prior to the administration of the pharmaceutical composition. In some embodiments, the determining the lack of the p53 deactivating mutation comprises confirming the presence of wild type p53 in the solid tumor.

[0018] In some embodiments, the various methods described herein further comprise determining a presence of a p53 gain of function mutation in the solid tumor.

[0019] In some embodiments, the various methods described herein further comprise determining a presence of a deactivating mutation of p53 in the solid tumor.

[0020] In some embodiments, the various methods described herein further comprise determining a presence of a copy loss mutation of p53 in the solid tumor.

[0021] In some embodiments, the various methods described herein further comprise determining a presence of a partial loss of function mutation of P53 in the solid tumor.

[0022] In some embodiments, the methods described herein can further comprise confirming the lack of the p53 deactivating mutation in the solid tumor, prior to the administration of the peptidomimetic macrocycle. For example, confirming the presence of wild type p53 in the solid tumor.

[0023] In some embodiments, the methods described herein can further comprise confirming a presence of a p53 gain of function mutation in the solid tumor.

[0024] In some embodiments, the methods described herein can further comprise confirming a presence of a deactivating mutation of p53 in the solid tumor.

[0025] In some embodiments, the methods described herein can further comprise confirming a presence of a copy loss mutation of p53 in the solid tumor.

[0026] In some embodiments, the methods described herein can further comprise confirming a presence of a partial loss of function mutation of P53 in the solid tumor.

[0027] In various embodiments, the determining or confirming is performed within 3 years, 2 years, within 1 year, within 1-12 months, within 1-3 months, within 1 month, or within 21 days prior to the administration of the peptidomimetic macrocycle.

[0028] In various embodiments, the treatment methods provided herein can result in re-activation of the p53 pathway, decreased tumor cell proliferation, increased p53 protein, increased p21, and/or increased apoptosis in the human subject.

[0029] The peptidomimetic macrocycle can be administered two or three times a week, for example two times a week. In some examples, the peptidomimetic macrocycle is administered once every 2 or 3 weeks. In other examples the peptidomimetic macrocycle is administered once every 1 or 2 weeks. In some embodiments, the peptidomimetic macrocycle is administered on days 1, 8 and 15 of a 28-day cycle. In other examples the peptidomimetic macrocycle is administered once every week. In some examples, a dose of the pharmaceutical composition is administered on days 1, 4, 8 and 11 of a 21-day cycle.

[0030] The amount of the peptidomimetic macrocycle administered is about 0.5-20 mg per kilogram body weight of the human subject, for example 0.5-10 mg per kilogram body weight of the human subject. In some embodiments, the amount of the peptidomimetic macrocycle administered is about 0.04 mg, 0.08 mg, 0.16 mg, 0.32 mg, 0.64 mg, 1.28 mg, 3.56 mg, 7.12 mg, or 14.24 mg per kilogram body weight of the human subject. In some examples, the amount of the peptidomimetic macrocycle administered is about 1.25 mg, 2.5 mg, 5.0 mg 10.0 mg, or 20.0 mg per kilogram body weight of the human subject and the peptidomimetic macrocycle is administered two times a week. In other examples, the amount of the peptidomimetic macrocycle administered is about 1.25 mg, 2.5 mg, 5.0 mg or 10.0 mg per kilogram body weight of the human subject and the peptidomimetic macrocycle is administered two times a week. In other examples, 0.32 mg, 0.64 mg, 1.25 mg 2.5 or 5.0 mg per kilogram body weight of the human subject and the pharmaceutical composition is administered two times a week. In some examples, about 0.32 mg, 0.64 mg, 1.25 mg 2.5 or 5.0 mg per kilogram body weight of the human subject and the pharmaceutical composition is administered on day 1, 4, 8, 11 of a 21-day cycle. In some examples, about 0.16 mg, 0.32 mg, 0.64 mg, 1.25 mg, 2.5, 5.0 mg or 10 mg per kilogram body weight of the human subject and the pharmaceutical composition is administered on day 1, 8, and 15 of a 28 day cycle.

[0031] In other examples, the amount of the peptidomimetic macrocycle administered is about 1.25 mg, 2.5 mg, 5.0 mg, 10.0 mg, or 20.0 mg per kilogram body weight of the human subject and the peptidomimetic macrocycle is administered once a week. In some examples, the amount of the peptidomimetic macrocycle administered is about 1.25 mg, 2.5 mg, 5.0 mg or 10.0 mg per kilogram body weight of the human subject and the peptidomimetic macrocycle is administered once a week.

[0032] In some examples, the amount of the peptidomimetic macrocycle administered is about 1.25 mg, 2.5 mg, 5.0 mg 10.0 mg, or 20.0 mg per kilogram body weight of the human subject and the peptidomimetic macrocycle is administered once daily, three, five or seven times in a seven day period. For example, the peptidomimetic macrocycle is administered once daily intravenously, seven times in a seven day period.

[0033] In some examples, the amount of the peptidomimetic macrocycle administered is about 1.25 mg, 2.5 mg, 5.0 mg, or 10.0 mg per kilogram body weight of the human subject and the peptidomimetic macrocycle is administered once daily three, five or seven times in a seven day period. For example,

the peptidomimetic macrocycle is administered once daily intravenously, seven times in a seven day period.

[0034] The peptidomimetic macrocycle can be administered gradually over a period of 0.25-12 h, for example 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. In some examples, the peptidomimetic macrocycle is administered over a period of 0.25-2.0 h. In some embodiments, the peptidomimetic macrocycle is gradually administered over a period of 1 h. In other embodiments, the peptidomimetic macrocycle is gradually administered over a period of 2 h.

[0035] The method provided herein can result in reduction of tumor volume. For example, treatment according to methods provided herein can result in about 95%, 90%, 85%, 80%, 75%, 70%, 65%, 60%, 55%, 50%, 45%, 40%, 35%, 30%, 25%, 20%, 15%, 10%, or 5% reduction in tumor volume within a period of 1 month after treatment initiation. In some example, the treatment results in at least 60%, 65%, 70%, 75%, 80%, 85%, 90%, or 95% reduction in tumor volume within a period of 1 month after treatment initiation. In some examples, 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 tumor volume within a period of 1 year after treatment initiation. In some embodiments, the treatment results in at least 60%, 65%, 70%, 75%, 80%, 85%, 90%, or 95% reduction in tumor volume within a period of 1 year after treatment initiation. In some examples, 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 tumor volume within a period of 6 months after treatment initiation. In some examples, the treatment results in at least 60%, 65%, 70%, 75%, 80%, 85%, 90%, or 95% reduction in tumor volume within a period of 6 months after treatment initiation. In some examples, 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 tumor volume within a period of 3 months after treatment initiation. In some examples, the treatment results in at least 60%, 65%, 70%, 75%, 80%, 85%, 90%, or 95% reduction in tumor volume within a period of 3 months after treatment initiation. In some embodiments, the solid tumor is a stable disease. In some embodiments, the solid tumor is a progressive disease.

[0036] In some embodiments, the methods provided herein can result 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 peptidomimetic macrocycle. In some examples, the increase in the survival time of the human subject is at least 30 days, at least 3 months, at least 6 months or at least 1 year.

[0037] The in vivo circulating half-life of the peptidomimetic macrocycle is about 1 h-12 h, for example about 1 h, 2h, 3 h, 4 h, 5 h, 6 h, 7 h, 8 h, 9 h, 10 h or 12 h. In some examples, the in vivo circulating half-life of the peptidomimetic macrocycle is about 4 h, about 6 h.

[0038] The biological tissue half-life of the peptidomimetic macrocycle is about 1 h-12 h, for example about 1 h, 2h, 3 h, 4 h, 5 h, 6 h, 7 h, 8 h, 9 h, 10 h or 12 h. In some examples, the biological tissue half-life of the peptidomimetic macrocycle is about 10 h.

[0039] In some embodiments, the human subject treated in accordance to the methods of the disclosure is refractory and/or intolerant to one or more other treatment of the solid tumor. In some embodiments, the human subject has had at least one unsuccessful prior treatment and/or therapy of the solid tumor.

[0040] In some embodiments, the solid tumor expresses wild-type p53 protein.

[0041] The solid tumor treated by the methods of the disclosure is selected from a group consisting of pancreatic cancer, bladder cancer, colon cancer, liver cancer, colorectal cancer, breast cancer, prostate cancer, renal cancer, hepatocellular cancer, lung cancer, ovarian cancer, cervical cancer, gastric cancer, esophageal cancer, head and neck cancer, melanoma, neuroendocrine cancers, CNS cancers, brain tumors, bone cancer, skin cancer, ocular tumor, rectal cancer, choriocarcinoma (tumor of the placenta), sarcoma and soft tissue cancer, testicular cancer, gall bladder cancer, and biliary cancer. In some embodiments, the solid tumor is selected from a group consisting of bladder cancer, bone cancer, breast cancer, cervical cancer, CNS cancer, colon cancer, ocular tumor, renal cancer, liver cancer, lung cancer, pancreatic cancer, choriocarcinoma (tumor of the placenta), prostate cancer, sarcoma, skin cancer, soft tissue cancer, gastric cancer, gall bladder cancer, biliary cancer, renal cancer, or neuroendocrine cancer. The ocular tumor can be choroidal nevus, choroidal melanoma, choroidal metastasis, choroidal hemangioma, choroidal osteoma, iris melanoma, uveal melanoma, melanocytoma, metastasis retinal capillary hemangiomas, congenital hypertrophy of the RPE, RPE adenoma or retinoblastoma. In some embodiments, the solid tumor is selected from non-small cell lung cancer, small-cell lung cancer, colon cancer, CNS cancer, melanoma, ovarian cancer, renal cancer, prostate cancer and breast cancer. In some embodiments, the solid tumor is breast cancer. In some embodiments, the solid tumor is gall bladder cancer. In some embodiments, the solid tumor is the solid tumor is biliary cancer. In some embodiments, the solid tumor is neuroendocrine cancer. In some embodiments, the solid tumor is bone cancer. In some embodiments, the solid tumor is osteosarcoma. In some embodiments, the solid tumor is skin cancer. In some embodiments, the solid tumor is melanoma.

[0042] In some examples, the solid tumor treated by the methods of the disclosure is not a HPV positive cancer.

[0043] In some examples, the solid tumor treated by the methods of the disclosure is not HPV positive cervical cancer, HPV positive anal cancer or HPV positive head and neck cancer, such as oropharyngeal cancers.

[0044] In some embodiments, the peptidomimetic macrocycle is administered intravenously.

[0045] In some embodiments, the methods of the disclosure further comprise administering in addition to the peptidomimetic macrocycle or pharmaceutically acceptable salt thereof, a therapeutically effective amount of at least one additional therapeutic agent and/or therapeutic procedure to the human subject.

[0046] In some embodiments, the human subject exhibits a complete response to the treatment. In some embodiments, the human subject exhibits a partial response to the treatment.

[0047] In some embodiments, the methods of the disclosure further comprise determining clinical activity of the administered peptidomimetic macrocycle. The clinical activity can be determined by an imaging method selected from a group consisting of computed tomography (CT), magnetic resonance imaging (MRI), and bone scanning.

[0048] The methods of the disclosure can further comprise obtaining a biological sample from the human subject at one or more specific time-points and analyzing the biological sample with an analytical procedure. The biological samples can be used for biomarker assessment, pharmacokinetic assessment, immunogenicity assays and/or pharmacodynamic assessment. The pharmacokinetic assessment can comprise studying the level of the peptidomimetic macrocycle and/or its metabolites in the biological sample at the specific time-points. The pharmacodynamic assessment can comprise studying the level of p53, MDM2, MDMX, p21 and/or caspase in the biological sample at the specific time-points.

[0049] The analytical procedure can be 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. The methods can further comprise tabulating and/or plotting results of the analytical procedure. The one or more specific time-points can comprise a time-point before the administration of the peptidomimetic macrocycle to the human subject. The one or more specific time-points can comprise a time-point after the administration of the peptidomimetic macrocycle to the human subject. The one or more specific time-points can comprise a time-point before and a time-point after the administration of the peptidomimetic macrocycle to the human subject. The one or more specific time-points comprise multiple time-points before and after the administration of the peptidomimetic macrocycle to the human subject. The method can further comprise comparing the biological samples collected before and after the administration of the peptidomimetic macrocycle to the human subject or comparing the biological samples collected at the multiple time-points. The biological sample can be a blood sample or a tumor specimen.

[0050] The method of the disclosure can further comprise selecting and/or identifying at least one target lesion in the human subject prior to the administration of the peptidomimetic macrocycle to the human subject. The methods can also comprise measuring cumulative diameters at one or more specific time-points, wherein the cumulative diameter is a sum of the diameters of the at least one target lesions at the specific time-point. The one or more specific time-points, can comprise a time-point after the treatment. The methods can also comprise measuring a baseline sum diameter, wherein the baseline sum diameter is a sum of the diameters of the at least one target lesions prior to the administration of the pharmaceutical composition to the human subject. In some examples, the treatment in accordance to the methods of the disclosure results in disappearance of the least one target lesion. In some embodiments, after the treatment all pathological lymph nodes in the human subject exhibit a reduction in short axis to less than 10 mm. In some examples, the cumulative

diameter at the time-point after the treatment is at least 30% less than the baseline sum diameter. In some examples, the treatment results in neither a sufficient increase nor a sufficient decrease in the cumulative diameters at the one or more specific time-points, taking as reference the baseline sum diameter.

[0051] In some examples, the peptidomimetic macrocycle is not an inhibitor of cytochrome P450 isoforms. In some examples, the treatment results in essentially no dose-limiting thrombocytopenia. In some examples, the treatment causes essentially no adverse effects in a normal-hematopoietic organ and/or tissue. In some examples, 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 peptidomimetic macrocycle. In some examples, 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 peptidomimetic macrocycle.

[0052] The lack of p53 deactivation mutation can be determined by any known method known in the art. In some examples, the lack of p53 deactivation mutation can be determined by DNA sequencing of the nucleic acid encoding the p53 protein. In some examples, the lack of p53 deactivation mutation can be determined by RNA array based testing. In some examples, the lack of p53 deactivation mutation can be determined by RNA analysis. In some examples, the lack of p53 deactivation mutation can be determined by polymerase chain reaction (PCR).

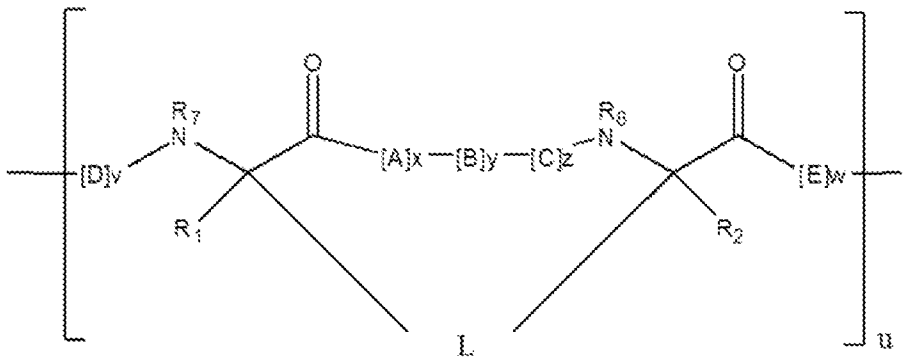
[0053] In some embodiments, the p53 deactivating mutation can comprise mutations in DNA-binding domain of the protein. In some embodiments, the p53 deactivating mutation can comprise missense mutation. In some embodiments, the p53 deactivating mutation is a dominant deactivating mutation. In some embodiments, the p53 deactivating mutation comprises one or more mutations selected from a groups consisting of V173L, R175H, G245C, R248W, R249S and R273H. In some embodiments, the p53 deactivating mutation comprises one or more of mutations shown in **Table 1a**. In some embodiments, the p53 gain of function mutation comprises one or more of mutations shown in **Table 1b**.

[0054] In another aspect, the disclosure provides a method of treating solid tumor in a human subject determined to lack a p53 deactivating mutation, wherein the method comprises administering to the human subject 0.5-20 mg, for example 0.5-10 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. 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 some embodiments, 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 some embodiments, t 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 some embodiments, an equal amount of the

peptidomimetic macrocycle is administered on days 1, 8 and 15. In some embodiments, the 28-day cycle is repeated 2 or 3 times.

[0055] In another aspect, the disclosure provides a method of treating solid tumor in a human subject, wherein the method comprises administering to the human subject 0.32-10 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. In some embodiments, the solid tumor is determined to lack a p53 deactivating mutation. In some embodiments, 0.32 mg of the peptidomimetic macrocycle per kilogram body weight of the human subject or the pharmaceutically acceptable salt thereof is administered on days 1, 4, 8 and 11 respectively of a 21-day cycle. In some embodiments, 0.64 mg of the peptidomimetic macrocycle per kilogram body weight of the human subject or the pharmaceutically acceptable salt thereof is administered on days 1, 4, 8 and 11 respectively of a 21-day cycle. In some embodiments, 1.25 mg of the peptidomimetic macrocycle per kilogram body weight of the human subject or the pharmaceutically acceptable salt thereof is administered on days 1, 4, 8 and 11 respectively of a 21-day cycle. In some embodiments, 2.5 mg of the peptidomimetic macrocycle per kilogram body weight of the human subject or the pharmaceutically acceptable salt thereof is administered on days 1, 4, 8 and 11 respectively of a 21-day cycle. In some embodiments, 5.0 mg of the peptidomimetic macrocycle per kilogram body weight of the human subject or the pharmaceutically acceptable salt thereof is administered on days 1, 4, 8 and 11 respectively of a 21-day cycle.

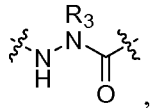
[0056] In various embodiments, the peptidomimetic macrocycle used in the methods described herein comprises an amino acid sequence which is at least about 60%, 70%, 80%, 90%, or 95% identical to an amino acid sequence in any of **Table 3**, **Table 3a**, **Table 3b**, and **Table 3c**, wherein the peptidomimetic macrocycle has the formula:



Formula (I)

wherein:

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

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

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

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

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

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

each R_4 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;

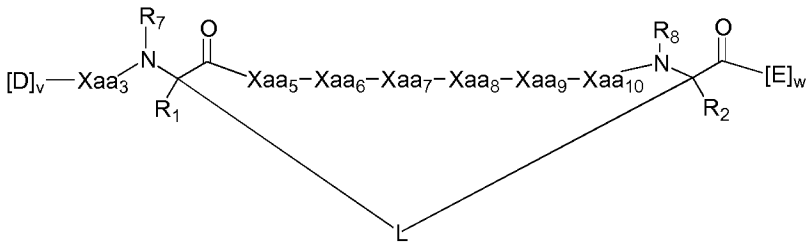
each w is independently an integer from 3–1000;

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.

[0057] In various embodiments, the peptidomimetic macrocycle used in the methods described herein 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} (SEQ ID NO: 8) or Phe_3-X_4-Glu_5-Tyr_6-Trp_7-Ala_8-Gln_9-Leu_{10}/Cba_{10}-X_{11}-Ala_{12} (SEQ ID NO: 9), where each X_4 and X_{11} is independently an amino acid;

each D and E is independently an amino acid;

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

w is an integer from 0-1000.

[0058] In some embodiments, at least one of the macrocycle-forming linker in the Formulas described herein has a formula $–L_1–L_2–$, wherein

each 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 each n is independently an integer from 1-5.

[0059] In some embodiments, at least one of the macrocycle-forming linker in the Formulas described herein each w is independently an integer from 3-1000, for example 3-500, 3-200, 3-100, 3-50, 3-30, 3-20, or 3-10.

[0060] In some embodiments, Xaa5 is Glu or an amino acid analog thereof.

[0061] In some embodiments, each E is independently Ala (alanine), Ser (serine) or an analog thereof.

[0062] In some embodiments, [D]v is $-Leu_1-Thr_2$.

[0063] In some embodiments, w is 3-10. In some embodiments, w is 3-6. In some embodiments, w is 6-10. In some embodiments, w is 6.

[0064] In some embodiments, v is 1-10. In some embodiments, v is 2-10. In some embodiments, v is 2-5. In some embodiments, v is 2.

[0065] In some embodiments, each L_1, L_2 and L_3 in the Formulas described herein are independently alkylene, alkenylene, alkynylene, heteroalkylene, cycloalkylene, heterocycloalkylene, cycloarylene, or heterocycloarylene, each being optionally substituted with R_5.

[0066] In some embodiments, each L_1, L_2 and L_3 are independently alkylene or alkenylene.

[0067] In some embodiments, L is alkylene, alkenylene, or alkynylene. In some embodiments, L is alkylene. In some embodiments, L is C3-C16 alkylene. In some embodiments, L is C10-C14 alkylene.

[0068] In some embodiments, each R_1 and R_2 in the Formulas described herein are independently –H, alkyl, alkenyl, alkynyl, arylalkyl, cycloalkyl, cycloalkylalkyl, heteroalkyl, or heterocycloalkyl, unsubstituted or substituted with halo–. In some embodiments, R_1 and R_2 are H. In some embodiments, each R_1 and R_2 are independently alkyl. In some embodiments, R_1 and R_2 are methyl.

[0069] In some embodiments, x+y+z in the Formulas described herein is 6.

[0070] In some embodiments, u in the Formulas described herein is 1.

[0071] The some embodiments, peptidomimetic macrocycles comprise at least one amino acid which is an amino acid analog. In some embodiments, the peptidomimetic macrocycle is chosen from the peptidomimetic macrocycles shown in **Table 3c**.

[0072] In one aspect, the disclosure provides a method of identifying one or more solid tumor biomarkers in a human subject lacking a p53 deactivating mutation, comprising administering to the human subject a therapeutically effective amount of a peptidomimetic macrocycle described herein. In some examples, the biomarkers are selected from a group comprising p53 status, MDM2 expression level and MDMX expression level.

[0073] In the various embodiments,the pharmaceutical composition comprises the pharmaceutically acceptable salt of the peptidomimetic macrocycle. In some embodiments, the pharmaceutically acceptable salt is a sodium salt, potassium salt or calcium salt. In some embodiments, the pharmaceutically acceptable salt is a sodium salt.

INCORPORATION BY REFERENCE

[0074] 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

[0075] 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:

[0076] ***FIG. 1***. Shows human wild type P53 protein sequence.

[0077] ***FIG. 2.*** Shows an exemplary dose level and Dose Regimen.

[0078] ***FIG. 3.*** Shows an exemplary dosing overview.

[0079] ***FIG. 4.*** Shows the amount of Aileron peptide-1 administered for each dose level (DL) and dose regimen.

[0080] ***FIG. 5***. Shows an exemplary dose escalation strategy of the disclosure.

[0081] ***FIG. 6***. Shows one way Aileron peptide-1 was designed to inhibit both MDMX and MDM2, to reactivate WT p53.

[0082] ***FIG. 7***. Shows potential indications of Aileron peptide-1 (from orphan indications or large market opportunities).

[0083] ***FIG. 8***. Shows the effect of Aileron peptide-1 across a variety of different cancers.

[0084] ***FIG. 9***. Shows the effect of Aileron peptide-1 administered by an intravenous, or IV, injection in an MDMX-driven MCF-7 breast cancer xenograft model

[0085] ***FIG. 10***. Shows dose escalation based on a "3+3" dose escalation design.

[0086] ***FIG. 11a*** and ***11b*** Show drug concentration (measured or projected) in dose levels for Cohorts.

[0087] ***FIG. 12***. Shows the pharmacokinetic model of Aileron peptide-1 which shows a 2-compartment, parallel nonlinear Michaelis-Menten clearance and linear elimination.

[0088] ***FIG. 13***. Shows dose dependent increase of MIC-1.

[0089] ***FIG. 14***. Shows that patients who have completed at least two cycles of treatment have stable disease. Aileron peptide-1 shows a stable disease rate.

[0090] ***FIG. 15.*** Shows that Aileron peptide 1 shows on target activation of p21 and p53 in patient blood cells.

DETAILED DESCRIPTION OF THE INVENTION

[0091] 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

[0092] 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.

[0093] 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.

[0094] 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.

[0095] 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.

[0096] 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.

[0097] The term "β-amino acid" refers to a molecule containing both an amino group and a carboxyl group in a β configuration.

[0098] 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.

[0099] The following table shows a summary of the properties of natural amino acids:

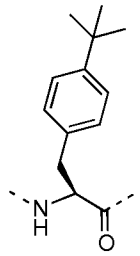
Amino Acid	3-Letter Code	1-Letter Code	Side-chain Polarity	Side-chain charge (pH 7.4)	Hydropathy Index
Alanine	Ala	A	nonpolar	neutral	1.8
Arginine	Arg	R	polar	positive	−4.5
Asparagine	Asn	N	polar	neutral	−3.5
Aspartic acid	Asp	D	polar	negative	−3.5
Cysteine	Cys	C	polar	neutral	2.5
Glutamic acid	Glu	E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

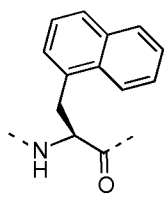
[00100] "Hydrophobic amino acids" include small hydrophobic amino acids and large hydrophobic amino acids. "Small hydrophobic amino acid" are glycine, alanine, proline, and analogs thereof. "Large hydrophobic amino acids" are valine, leucine, isoleucine, phenylalanine, methionine, tryptophan, and analogs 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.

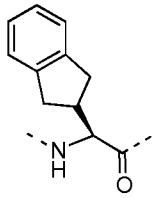
[00101] The term "amino acid analog" refers to a molecule which is structurally similar to an amino acid and which can be substituted for an amino acid in the formation of a peptidomimetic macrocycle. Amino acid analogs include, without limitation, β-amino acids and amino acids where the amino or carboxy 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).

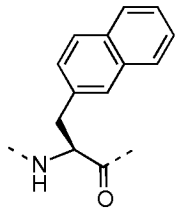
[00102] The term "non-natural amino acid" refers to an amino acid which is not one of the twenty amino acids commonly found in peptides synthesized in nature, and known by the one letter abbreviations A, R,

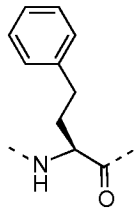
N, C, D, Q, E, G, H, I, L, K, M, F, P, S, T, W, Y and V. Non-natural amino acids or amino acid analogs include, without limitation, structures according to the following:

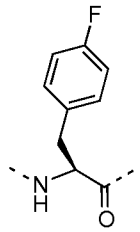

4-t-butylphenylalanine (F4tBu)

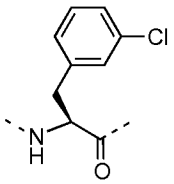

1-Naphthylalanine (1Nal)

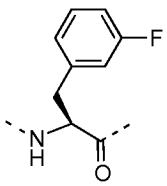

Indanyl glycine (Igl)

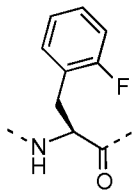

2-Naphthylalanine (2Nal)

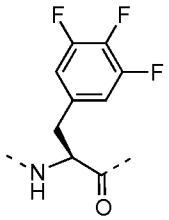

homophenylalanine (hF)

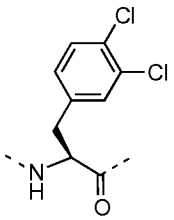

4-fluorophenylalanine (F4F)

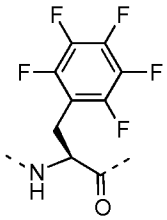

3-chlorohenylalanine (F3Cl=3cf)

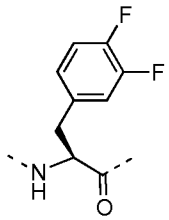

3-fluorophenylalanine (F3F=3ff)

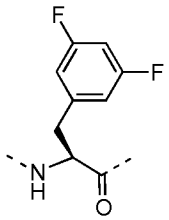

2-fluorophenylalanine (F2F=2ff)

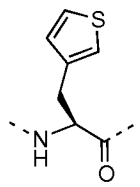

3,4,5-trifluoro phenylalanine (F345F3)

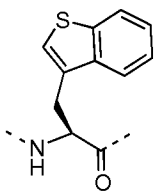

3,4-difluoro phenylalanine (F34Cl2)

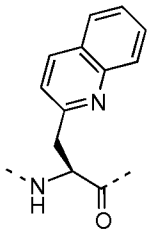

pentafluoro phenylalanine (F5F)

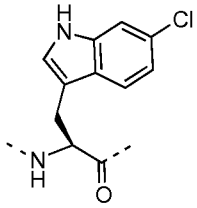

3,4-difluoro phenylalanine (F34F2)

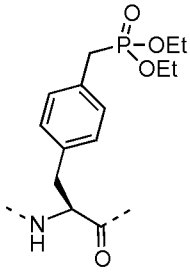

3,5-difluoro phenylalanine (F35F2)

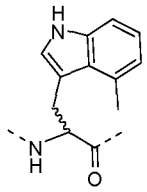

3-thienylalanine (2Thi)

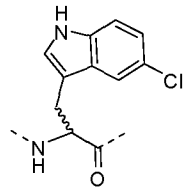

3-(1-Benzothiophen-3-yl) alanine (3BthA)

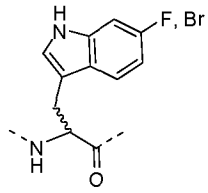

3-(2-quinolyl) alanine (2qA)

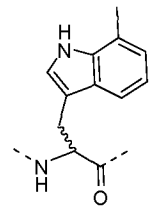

6-chlorotryptophan (6clW)

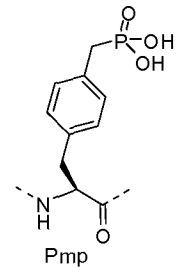

4-[di-(ethyl)phosphono methyl]phenylalanine (pmpEt)

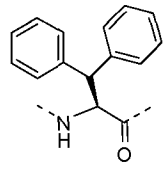

dl4mW

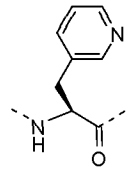

dl5clW

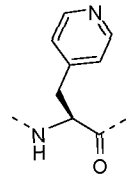

dl6fW & dl6brW

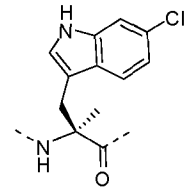

dl7mW

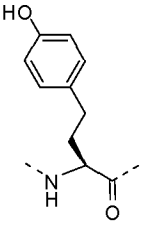

Pmp

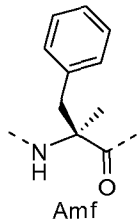

3,3-diphenyl-alanine (Dip)

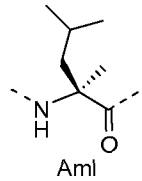

3-pyridyl-alanine (3Pal)

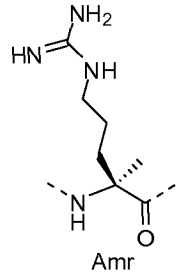

4-pyridyl-alanine (4Pal)

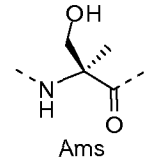

Me6clW

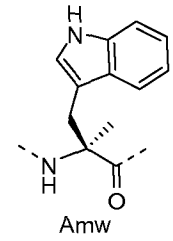

homotyrosine (hY)

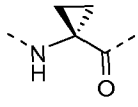

Amf

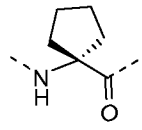

Aml

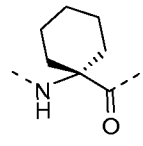

Amr

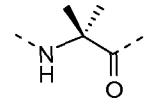

Ams


Amw

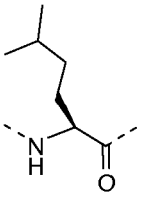

Ac3c

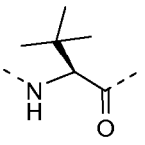

Ac5c

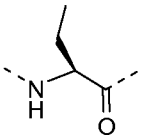

Ac6c

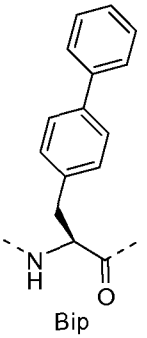

Aib

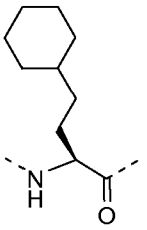

Norleucine
(Nle)

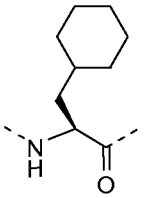

Homoleucine
(hL)

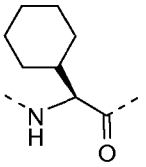

tert-Butyl glycine
(Tle)

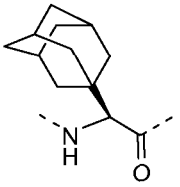

Abu

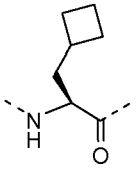

Bip

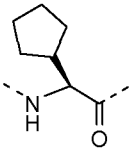

homocyclohexyl alanine
(hCha)

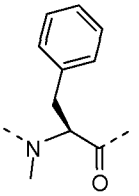

cyclohexyl alanine
(Cha)

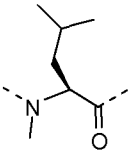

cyclohexyl glycine
(Chg)

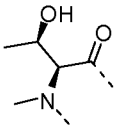

Adamantyl glycine
(Adm)

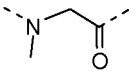

cyclobutyl alanine
(Cba)

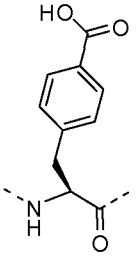

cyclopentyl glycine
(Cpg)

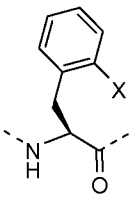

NmF

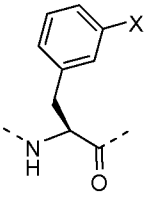

NmL

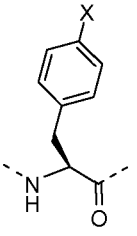

NmT

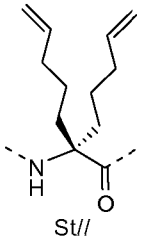

Sar

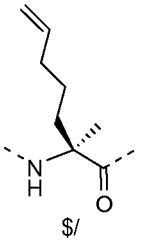

F4cooh

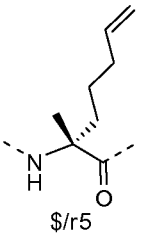

F2X
X=Cl, Br, CF3, CN, Me, NO2


F3X
X=Cl, Br, CF3, CN, Me, NO2

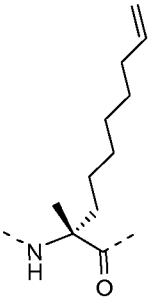

F4X
X=Cl, Br, CF3, CN, Me, NO2, I

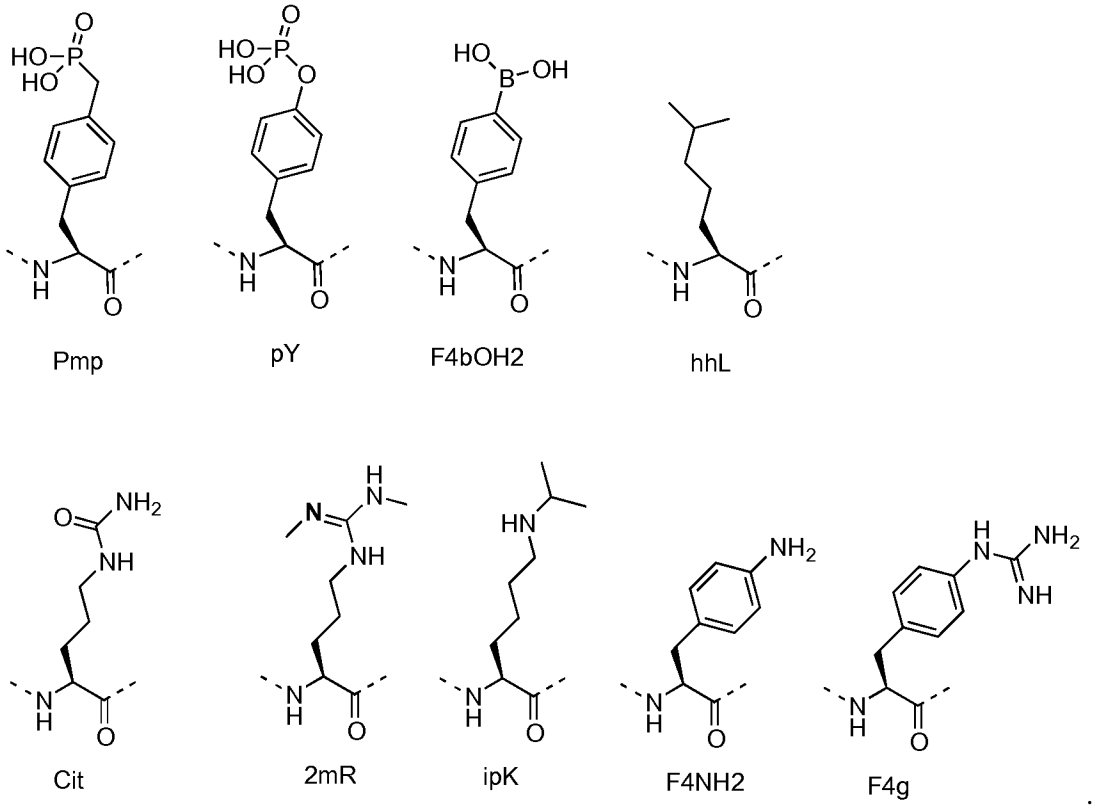

St//


$/


$/r5


$/s8


$/r8



[00103] 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.

[00104] 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.

[00105] 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.

[00106] 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.

[00107] 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.

[00108] 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.

[00109] 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.

[00110] 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.

[00111] 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 -

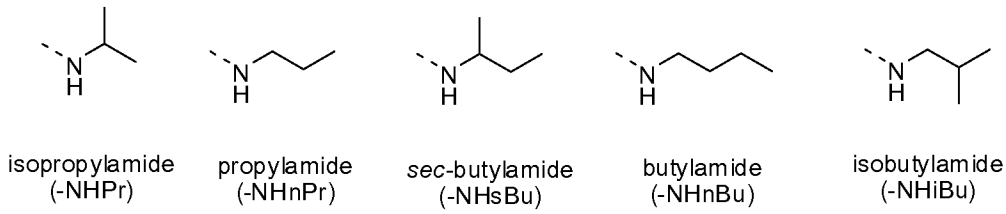
methoxy - 1,2,3,4 - tetrahydronorharman - 1 - carboxylic acid; 7 - azatryptophan; L - 1,2,3,4 - tetrahydro - norharman - 3 - carboxylic acid; 5 - methoxy - 2 - methyl - tryptophan; and 6 - chloro - L - tryptophan.

[00112] 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.

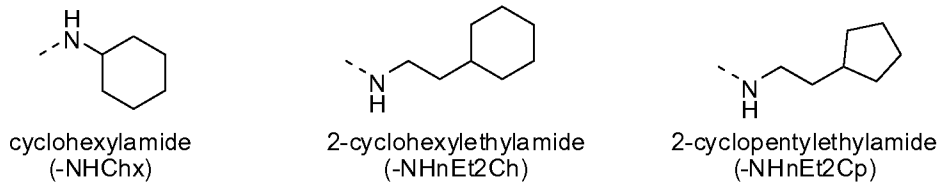
[00113] A "non-essential" amino acid residue is a residue that can be altered from the wild-type sequence of a polypeptide without abolishing or substantially altering its essential biological or biochemical activity (*e.g.*, receptor binding or activation). An "essential" amino acid residue is a residue 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.

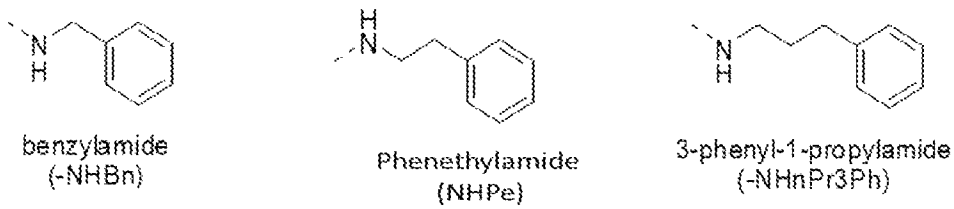
[00114] A "conservative amino acid substitution" is one in which the amino acid residue is replaced with an amino acid residue having a similar side chain. Families of amino acid residues having similar side chains have been defined in the art. These families include amino acids with basic side chains (*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).

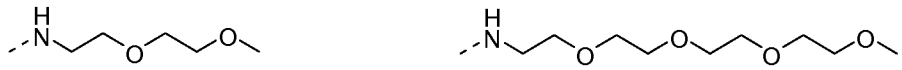
[00115] The term "capping group" refers to the chemical moiety occurring at either the carboxy or amino terminus of the polypeptide chain of the subject peptidomimetic macrocycle. The capping group of a carboxy terminus includes an unmodified carboxylic acid (i.e. –COOH) or a carboxylic acid with a substituent. 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:



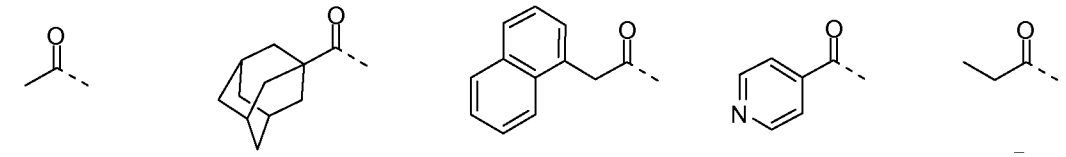
isopropylamide
(-NHPr)
propylamide
(-NHnPr)
sec-butylamide
(-NHsBu)
butylamide
(-NHnBu)
isobutylamide
(-NHiBu)



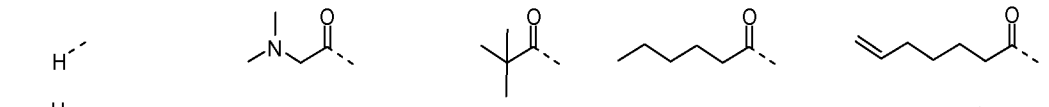




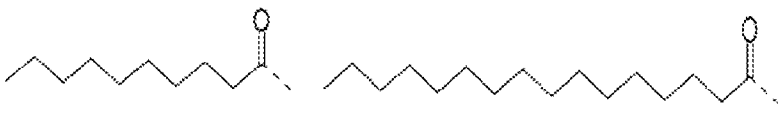
[00116] The capping group of an amino terminus includes an unmodified amine (ie $-NH_2$) or an amine with a substituent. For example, the amino terminus can be substituted with an acyl group to yield a carboxamide at the N-terminus. Various substituents include but are not limited to substituted acyl groups, including C_1-C_6 carbonyls, C_7-C_{30} carbonyls, and pegylated carbamates. Representative capping groups for the N-terminus include, but are not limited to, 4-FBzl (4-fluoro-benzyl) and the following:



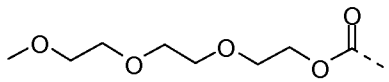
Ac- Adamantylcarbonyl (Admac-) 1-Napthylacetyl (Napac-) Isonicotinyl (Isonac-) Pr-



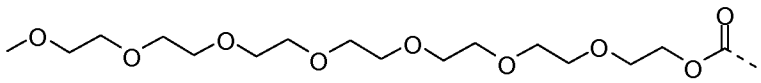
H- (uncapped) N,N-Dimethylaminoacetyl (Dmaac) Trimethylacetyl (Tmac) Hexanoyl (Hexac) Hep/



Decanoyl (Decac) Palmitoyl (Pam)



mdPEG3



mdPEG7

[00117] 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.

[00118] The symbol "" when used as part of a molecular structure refers to a single bond or a *trans* or *cis* double bond.

[00119] 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).

[00120] 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.

[00121] 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).

[00122] 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.

[00123] 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 $Pd(dppf)Cl_2$.

[00124] The term "halo" or "halogen" refers to fluorine, chlorine, bromine or iodine or a radical thereof.

[00125] 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.

[00126] The term "alkylene" refers to a divalent alkyl (*i.e.*, -R-).

[00127] 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.

[00128] 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.

[00129] 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.

[00130] "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.

[00131] "Arylamido" refers to an aryl group, as defined above, wherein one of the aryl group's hydrogen atoms has been replaced with one or more -$C(O)NH_2$ groups. Representative examples of an arylamido group include 2-$C(O)NH_2$-phenyl, 3-$C(O)NH_2$-phenyl, 4-$C(O)NH_2$-phenyl, 2-$C(O)NH_2$-pyridyl, 3-$C(O)NH_2$-pyridyl, and 4-$C(O)NH_2$-pyridyl,

[00132] "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.

[00133] "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=$CH_2$.

[00134] "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 -$C(CH_3)_2CH_2OH$.

[00135] "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 -$C(CH_3)_2CH_2COOH$.

[00136] 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.

[00137] 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.

[00138] 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.

[00139] 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.

[00140] 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.

[00141] 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.

[00142] 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.

[00143] 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%.

[00144] 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 $\geq$ 0 and $\leq$ 2 if the variable is inherently continuous.

[00145] 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."

[00146] The term "on average" represents the mean value derived from performing at least three independent replicates for each data point.

[00147] 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.

[00148] 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.

[00149] 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.

[00150] 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.

[00151] The term "solid tumor" or "solid cancer" as used herein refers to tumors that usually do not contain cysts or liquid areas. Solid tumors as used herein include sarcomas, carcinomas and lymphomas. In various embodiments leukemia (cancer of blood) is not solid tumor.

[00152] 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.

[00153] 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 may 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 may 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.

[00154] 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.

[00155] A "Dose-Limiting Toxicity" (DLT) as used herein is defined as any Grade ≥3 AE that is considered to be possibly, probably, or definitely related to the study drug, with the following exceptions: (1) for nausea, emesis, diarrhea, rash, or mucositis, only Grade ≥3 AE that do not respond within 48 hours to standard supportive/pharmacological treatment 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. 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

[00156] 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.

[00157] 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 may 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.

[00158] "Measurable disease" (MD) as used herein is defined by the presence of at least one measurable lesion.

[00159] Measurable lesions are defined as those that can be accurately measured in at least one dimension [longest diameter (LD) in the plane of measurement to be recorded] with a minimum size of:10 mm by CT scan (CT scan slice thickness no greater than 5 mm), 10 mm caliper measurement by clinical exam (lesions which cannot be accurately measured with calipers can be recorded as non-measurable), or 20 mm by chest x-ray.

[00160] "Malignant lymph nodes" is to be considered pathologically enlarged and measurable if the lymph node is ≥ 15 mm in short axis when assessed by CT scan (CT scan slice thickness no greater than 5 mm).

[00161] "Non-measurable Disease" as used herein include all other lesions (or sites of disease) that are not measurable, including small lesions (longest diameter < 10 mm or pathological lymph nodes with ≥ 10 to < 15 mm short axis) are considered non-measurable disease. Lesions considered truly non-measurable include: leptomeningeal disease, ascites, pleural/pericardial effusions, lymphangitis cutis/pulmonis, inflammatory breast disease, abdominal masses/abdominal organomegaly identified by physical exam and not followed by CT or MRI.

[00162] "Target lesions" as used herein include all measurable lesions up to a maximum of two lesions per organ and five lesions in total, representative of all involved organs identified as target lesions and recorded and measured at baseline. Target lesions can be selected on the basis of their size (lesions with the longest diameter) and their suitability for accurate repeated measurements (either by imaging techniques or clinically). A sum of the diameters (longest for non-nodal lesions, short axis for nodal lesions) for all target lesions can be calculated and reported as the baseline sum diameters. The baseline sum diameters can be used as reference by which to characterize the objective tumor response.

[00163] "Non-target lesions" as used herein include all other lesions (or sites of disease) including pathological lymph nodes that are not target lesions. Non-target lesions can be identified as non-target lesions and can also be recorded at baseline. Measurements of these lesions may not be required and these lesions can be followed as "present," "absent," or in rare cases "unequivocal progression." In addition, it can be possible to record multiple non-target lesions involving the same organ as a single item on the case report form (e.g., 'multiple enlarged pelvic lymph nodes' or 'multiple liver metastases').

[00164] "Complete response" (CR) as used herein is defined as the disappearance of all target lesions. Any pathological lymph nodes (whether target or non-target) must have reduction in short axis to < 10 mm.

[00165] "Partial response (PR)" as used herein is defined as at least a 30% decrease in the sum of diameters of target lesions, taking as reference the baseline sum diameters.

[00166] "Progressive disease (PD)" as used herein is defined as at least a 20% increase in the sum of diameters of target lesions, taking as reference the smallest sum on study (this includes the baseline sum if that is the smallest). In addition to the relative increase of 20%, the sum must also demonstrate an absolute increase of at least 5 mm. The appearance of one or more new lesions can also be considered progression.

[00167] "Stable disease" (SD) as used herein is defined as neither sufficient shrinkage to qualify for PR nor sufficient increase to qualify for PD, taking as reference the smallest sum diameters while on study.

[00168] 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.

[00169] The term "haploinsufficient" means a condition that occurs when a diploid organism has only a single functional copy of a gene (with the other copy inactivated by mutation) and the single functional copy does not produce enough of a gene product (typically a protein) to bring about a wild-type condition, leading to an abnormal or diseased state.

[00170] The term "silent mutation" as used herein silent mutation is a type of mutation in the coding region of a gene that doesn't actually change the amino acid sequence of the protein that is made.

[00171] 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

[00172] In one aspect, the disclosure provides a method of treating solid tumor in a subject. For example, the methods disclosed herein can be used for treating solid tumors that are not p53 negative. In some cases the methods disclosed herein can be used for treating solid tumor which has been determined to lack a p53 deactivating mutation. The methods of the disclosure can also be used to treat solid tumors that express gain of function mutant p53 i.e. a super apoptotic p53. In other examples, the methods of the disclosure are useful in treating solid tumors, wherein the solid tumor expresses p53 with a partial loss of function mutation, p53 with a copy loss mutation, or p53 with one or more silent mutations. In some example, the solid tumor expresses p53 with a copy loss mutation and a deactivating mutation.

[00173] The method comprises administering to the 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. In some embodiments, the peptidomimetic macrocycle disrupts the interaction between p53 and MDM2 and MDMX.

[00174] In another aspect, the disclosure provides a method of treating solid tumor in a subject expressing wild type p53. The method comprises administering to the 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. In some embodiments, the peptidomimetic macrocycle disrupts the interaction between p53 and MDM2 and MDMX.

[00175] In some embodiments the subject treated by the methods disclosed herein is a human. In some embodiments, a subject treated in accordance with the methods provided herein is a human who has or is diagnosed with solid tumor lacking p53 deactivating mutation and/or expressing wild type p53. In some embodiments, a subject treated for solid tumor in accordance with the methods provided herein is a human predisposed or susceptible to solid tumor lacking p53 deactivating mutation and/or expressing wild type p53. In some embodiments, a subject treated for solid tumor in accordance with the methods provided herein is a human at risk of developing solid tumor lacking p53 deactivating mutation and/or expressing wild type p53. A p53 deactivating mutation in some examples 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 solid tumor 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 solid tumor can be determined by any suitable method known in art, for example by sequencing, array based testing, RNA analysis and amplifications methods like PCR.

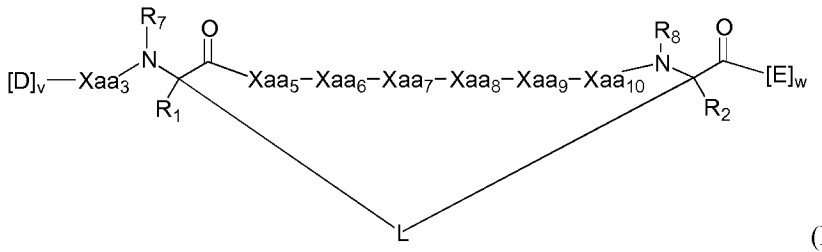
[00176] In certain embodiments, the human subject is refractory and/or intolerant to one or more other standard treatment of the solid tumor known in art. In some embodiments, the human subject has had at least one unsuccessful prior treatment and/or therapy of the solid tumor.

[00177] In some embodiments, the subject treated in accordance with the methods of the disclosure is a human who has or is diagnosed with solid tumor that is not p53 negative. In some embodiments, the subject treated in accordance with the methods of the disclosure is a human who has or is diagnosed with solid tumor that express gain of function mutant p53 i.e. a super apoptotic p53. In some embodiments, the subject treated in accordance with the methods of the disclosure is a human who has or is diagnosed with solid tumor that expresses p53 with a partial loss of function mutation. In some embodiments, the subject treated in accordance with the methods provided herein is a human who has or is diagnosed with solid tumor that expresses p53 with a copy loss mutation. In some embodiments, the subject treated in accordance with the methods provided herein is a human who has or is diagnosed with solid tumor that expresses p53 with one or more silent mutations. In some embodiments, the subject treated in accordance with the methods provided herein is a human who has or is diagnosed with solid tumor that expresses p53 with a copy loss mutation and a deactivating mutation.

[00178] In some embodiments, the methods for treating solid tumor provided herein inhibit, reduce, diminish, arrest, or stabilize a tumor associated with the solid tumor. In some embodiments, the methods for treating solid tumor provided herein inhibit, reduce, diminish, arrest, or stabilize the blood flow, metabolism, or edema in a tumor associated with the solid tumor or one or more symptoms thereof. In some embodiments, the methods for treating solid tumor provided herein cause the regression of a tumor, tumor blood flow, tumor metabolism, or peritumor edema, and/or one or more symptoms associated with the solid tumor. In some embodiments, the methods for treating solid tumor provided herein maintain the size of the tumor so that it does not increase, or so that it increases by less than the increase of a tumor 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 solid tumor provided herein decrease tumor size. In some embodiments, the methods for treating solid tumor provided herein reduce the formation of a tumor. In certain embodiments, the methods for treating solid tumor provided herein eradicate, remove, or control primary, regional and/or metastatic tumors associated with the solid tumor. In some embodiments, the methods for treating solid tumor provided herein decrease the number or size of metastases associated with the solid tumor. In some embodiments, the methods for treating solid tumor provided herein result in complete response to the treatment. In some embodiments, the methods for treating solid tumor provided herein result in partial response to the treatment. In some embodiments, the solid tumor treated by the methods disclosed herein is a stable disease. In some embodiments, the solid tumor treated by the methods disclosed herein is a progressive disease.

[00179] Solid tumor cancers that can be treated by the methods provided herein include, but are not limited to, sarcomas, carcinomas, and lymphomas. In specific embodiments, solid tumors that can be treated in accordance with the methods described include, but are not limited to, cancer of the breast, liver, neuroblastoma, head, neck, eye, mouth, throat, esophagus, esophagus, chest, bone, lung, kidney, colon, rectum or other gastrointestinal tract organs, stomach, spleen, skeletal muscle, subcutaneous tissue, prostate, breast, ovaries, testicles or other reproductive organs, skin, thyroid, blood, lymph nodes, kidney, liver, pancreas, and brain or central nervous system.

[00180] 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} (SEQ ID NO: 8) or Phe_3-X_4-Glu_5-Tyr_6-Trp_7-Ala_8-Gln_9-Leu_{10}/Cba_{10}-X_{11}-Ala_{12} (SEQ ID NO: 9), where each X is an amino acid;

each D and E is independently an amino acid;

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

each L or L' is independently a macrocycle-forming

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

each w is an integer from 0-1000, for example 1-500, 1-200, 1-100, 1-50, 1-30, 1-20, or 1-10.

[00181] Administration of the a pharmaceutical composition comprising a therapeutically effective amount of a peptidomimetic macrocycle or a therapeutically equivalent amount of a pharmaceutically acceptable salt thereof can be achieved by any suitable means. For example the pharmaceutical compositioncan 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.

[00182] In some embodiments, the methods disclosed herein additionally or optionally comprise evaluating the safety and/or tolerability of a pharmaceutical composition comprising a therapeutically effective amount of a peptidomimetic macrocycle or a therapeutically equivalent amount of a pharmaceutically acceptable salt thereof, of the disclosure in subjects with solid tumors determined to lack a p53 deactivating mutation or with solid tumors expressing wild-type (WT) p53 protein.

[00183] Also provided here in are methods to determine the dose limiting toxicities (DLT) and the maximum tolerated dose (MTD) of the peptidomimetic macrocycles disclosed herein in subjects with solid tumors determined to lack a p53 deactivating mutation or with solid tumors expressing wild-type (WT) p53 protein.

[00184] 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.

[00185] In some embodiments, the methods disclosed herein additionally or optionally comprise studying the effect of the peptidomimetic macrocycles on pharmacodynamic biomarkers in tumor biopsy samples (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.

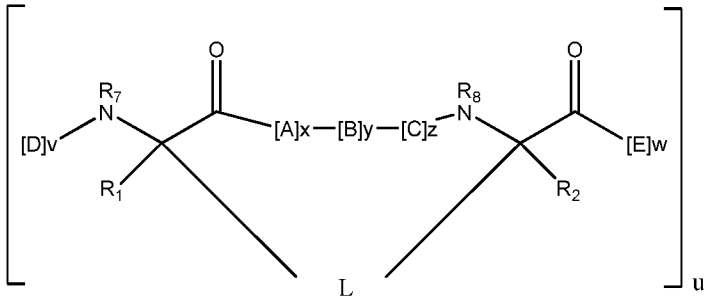
[00186] In some embodiments, the methods disclosed herein additionally or optionally include steps to assess potential patient biomarkers (e.g., p53 status, MDM2 and MDMX expression levels), the effect of the peptidomimetic macrocycles treatment on these biomarkers, and possible correlation between these biomarkers and clinical response of the peptidomimetic macrocycles.

[00187] Also provided herein are methods to evaluate clinical activity of the peptidomimetic macrocycles in subjects with specific tumor types lacking a p53 deactivating mutation and/or expressing WT p53 in the dose expansion phase.

COMPOUND AND COMPOSITIONS

Peptidomimetic macrocycles

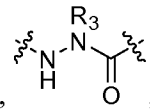
[00188] In some embodiments, a peptidomimetic macrocycle has the Formula (I):



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;

each w is independently an integer from 3–1000;

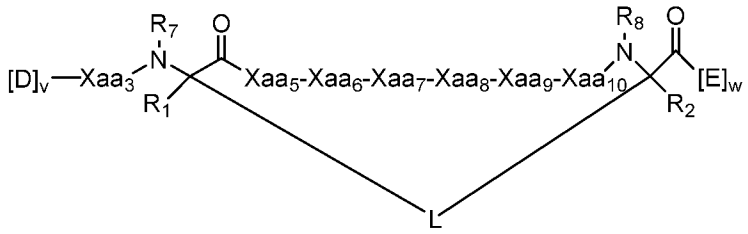
u is an integer from 1–10;

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

each n is independently an integer from 1–5.

[00189] In some embodiments, each v and w is independently integers between 1-30. In some embodiments, w is an integer from 3-1000, for example 3-500, 3-200, 3-100, 3-50, 3-30, 3-20, or 3-10. In some embodiments, the sum of x+y+z is 3 or 6. In some embodiments, the sum of x+y+z is 3. In other embodiments, the sum of x+y+z is 6.

[00190] 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} (SEQ ID NO: 8), where each X is an amino acid;

each D and E is independently an amino acid;

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

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

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

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

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

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

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

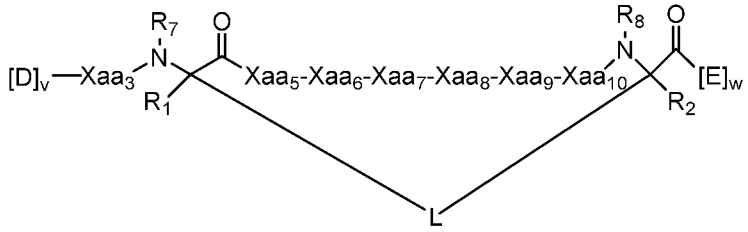
w is an integer from 3-1000, for example 3-500, 3-200, 3-100, 3-50, 3-30, 3-20, or 3-10.

[00191] In some embodiments, each v and w is independently an integer between 1-30. In some embodiments, w is an integer from 3-1000, for example 3-500, 3-200, 3-100, 3-50, 3-30, 3-20, or 3-10. In some embodiments, the sum of x+y+z is 3 or 6. In some embodiments, the sum of x+y+z is 3. In other embodiments, the sum of x+y+z is 6.

[00192] 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} (SEQ ID NO: 8). 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} (SEQ ID NO: 8). 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} (SEQ ID NO: 8). 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} (SEQ ID NO: 8). 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} (SEQ ID NO: 8).

[00193] 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} (SEQ ID NO: 9), where each X is an amino acid;

each D is independently an amino acid;

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

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

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

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

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

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

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

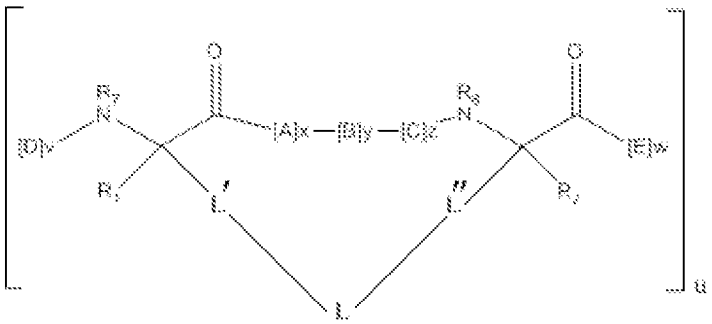
v is an integer from 1-1000, for example 1-500, 1-200, 1-100, 1-50, 1-30, 1-20, or 1-10;

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

[00194] 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} (SEQ ID NO: 9). 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} (SEQ ID NO: 9). 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} (SEQ ID NO: 9). 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} (SEQ ID NO: 9). 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} (SEQ ID NO: 9).

[00195] 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.

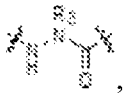
[00196] In some embodiments, a peptidomimetic macrocycle of Formula (I) has Formula (Ic):



Formula (Ic)

wherein:

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

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

each L is independently a macrocycle-forming linker;

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

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

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

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

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

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

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

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

each n is an integer from 1-5;

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

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

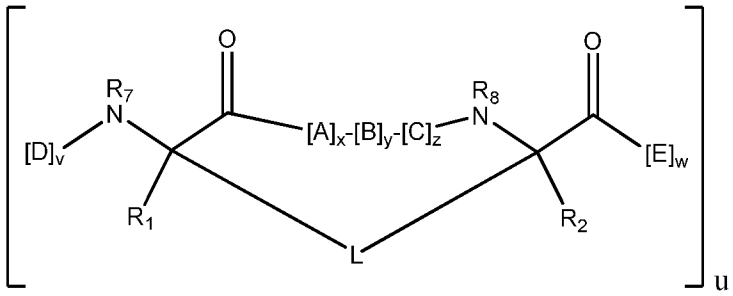
each R_7 is independently –H, alkyl, alkenyl, alkynyl, arylalkyl, cycloalkyl, heteroalkyl, cycloalkylalkyl, heterocycloalkyl, aryl, or heteroaryl, optionally substituted with R_5, or part of a cyclic structure with a D residue;

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

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

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

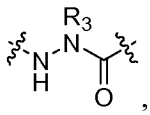
[00197] In some embodiments, the peptidomimetic macrocycles have the Formula (I):



Formula (I)

wherein:

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

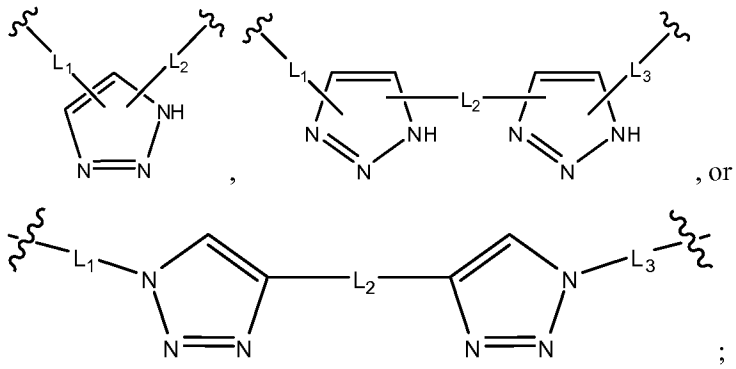
each B is independently a natural or non-natural amino acid, amino acid analog, ,

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

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

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

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



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

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

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

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

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

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

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

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

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

n is an integer from 1-5.

[00198]

[00199] In an embodiment of any of the Formulas described herein, of the macrocycle-forming linker (L) has a formula $–L_1–L_2–$, wherein

each 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;

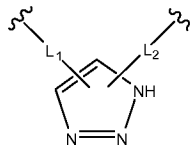
each R_4 is independently alkylene, alkenylene, alkynylene, heteroalkylene, cycloalkylene, heterocycloalkylene, arylene, or heteroarylene;

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

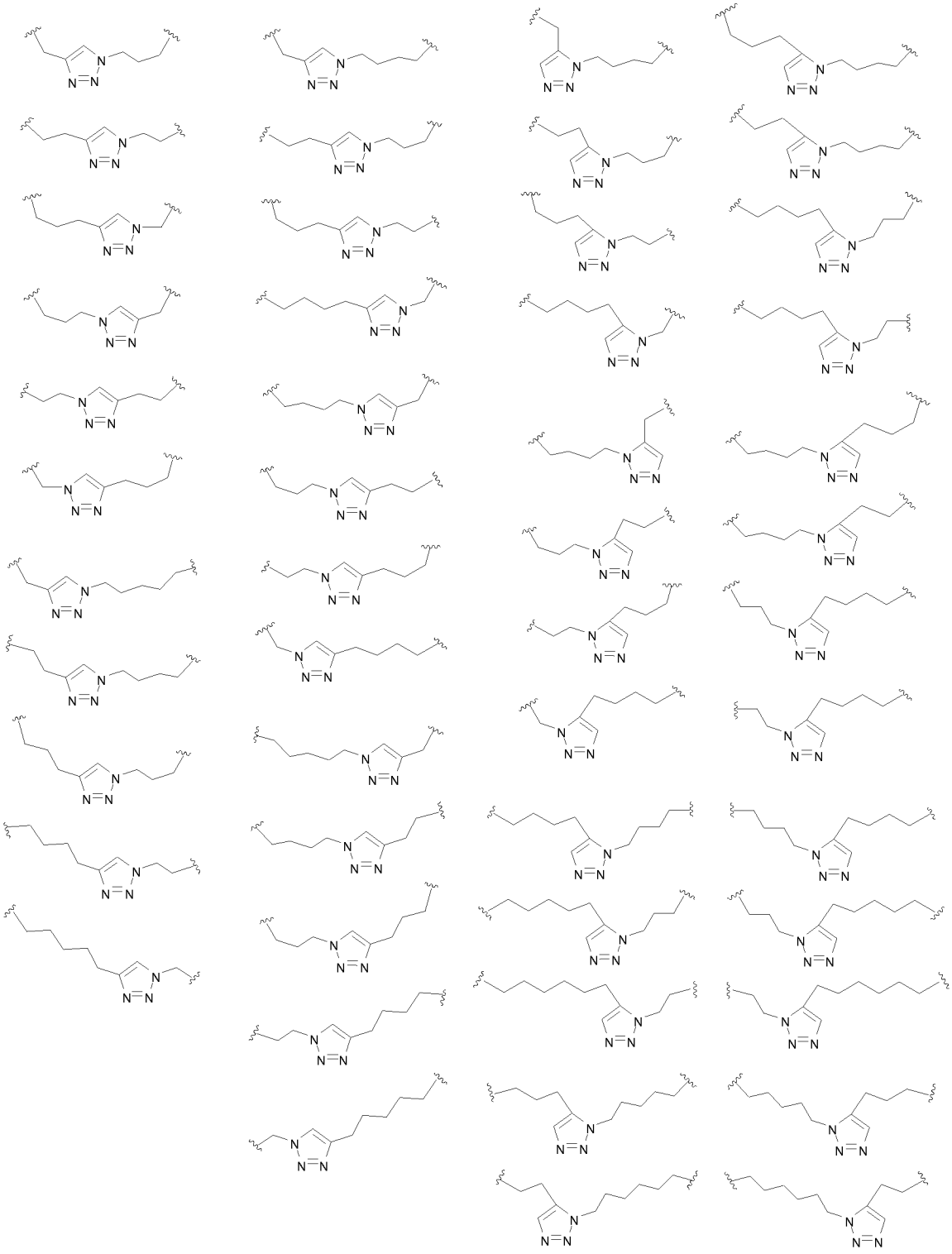
n is an integer from 1-5.

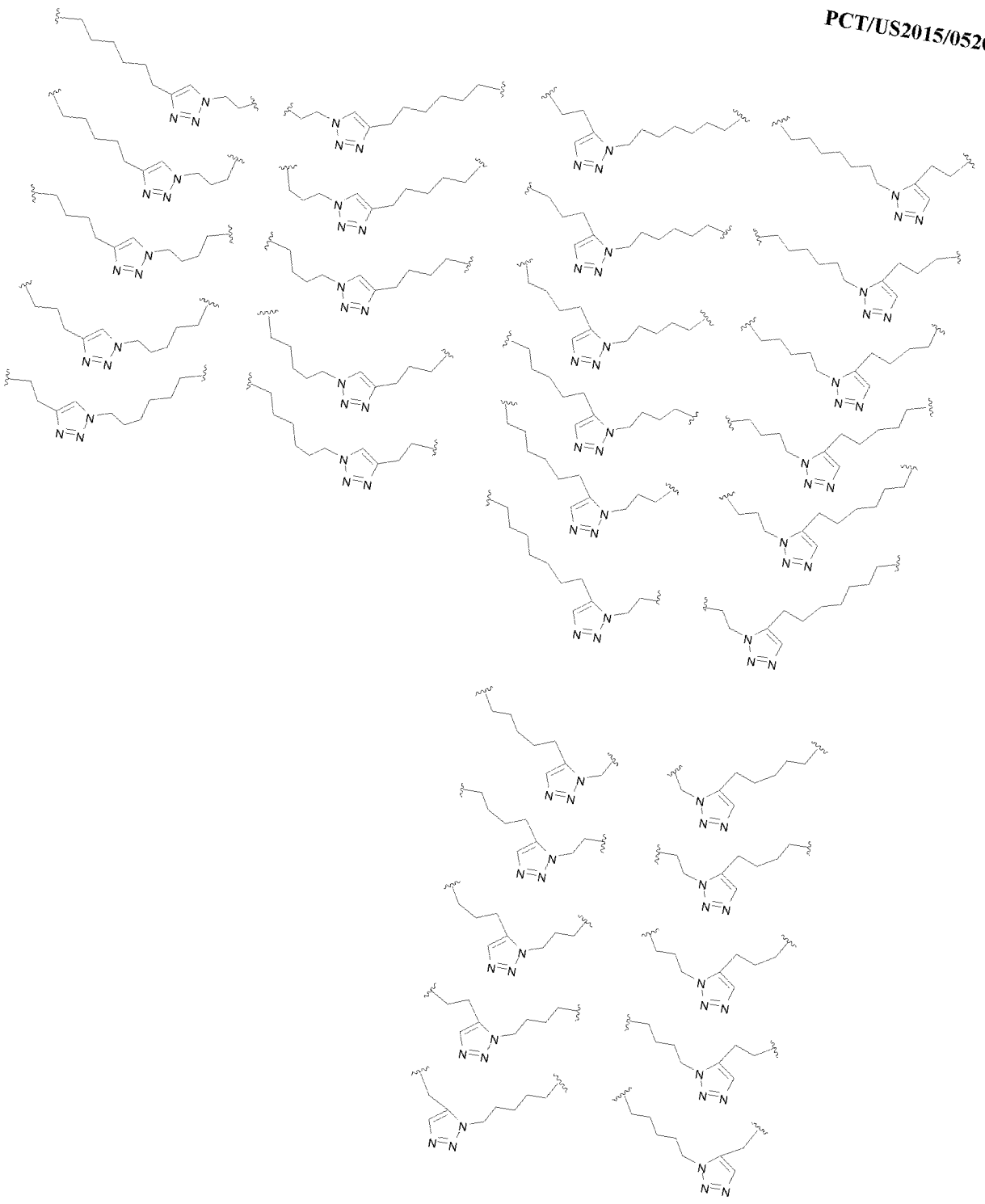
[00200] In some embodiments in the Formulas described herein, L (or L') is a macrocycle-forming linker of the formula



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[00201] Exemplary embodiments of such macrocycle-forming linkers L are shown below.



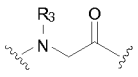


[00202] In an embodiment of any of the Formulas described herein, L_1 and L_2, either alone or in combination, form a triazole or a thioether.

[00203] 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.

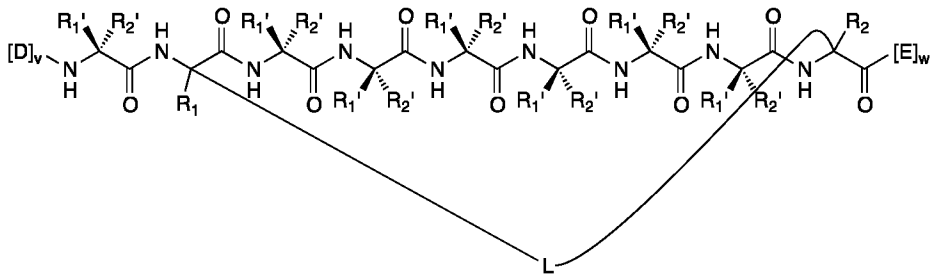
[00204] In one example, at least one of R_1 and R_2 is alkyl, unsubstituted or substituted with halo–. In another example, each R_1 and R_2 are independently alkyl, unsubstituted or substituted with halo–. In some embodiments, at least one of R_1 and R_2 is methyl. In other embodiments, R_1 and R_2 are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

[00205] In some embodiments, x+y+z is at least 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.

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

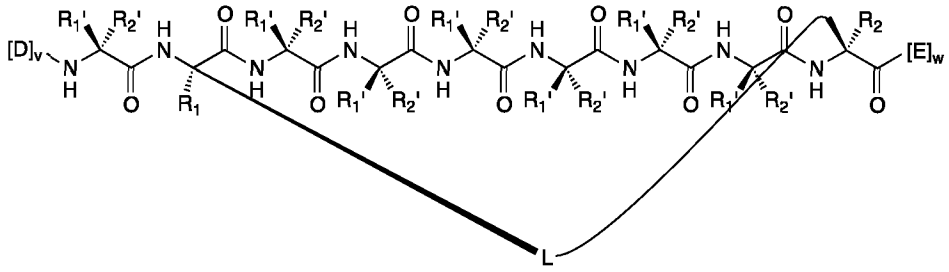
[00207] In other embodiments, the length of the macrocycle-forming linker L as measured from a first Cα to a second Cα is selected to stabilize a desired secondary peptide structure, such as an α-helix formed by residues of the peptidomimetic macrocycle including, but not necessarily limited to, those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

[00208] In one embodiment, the peptidomimetic macrocycle of Formula (I) is:



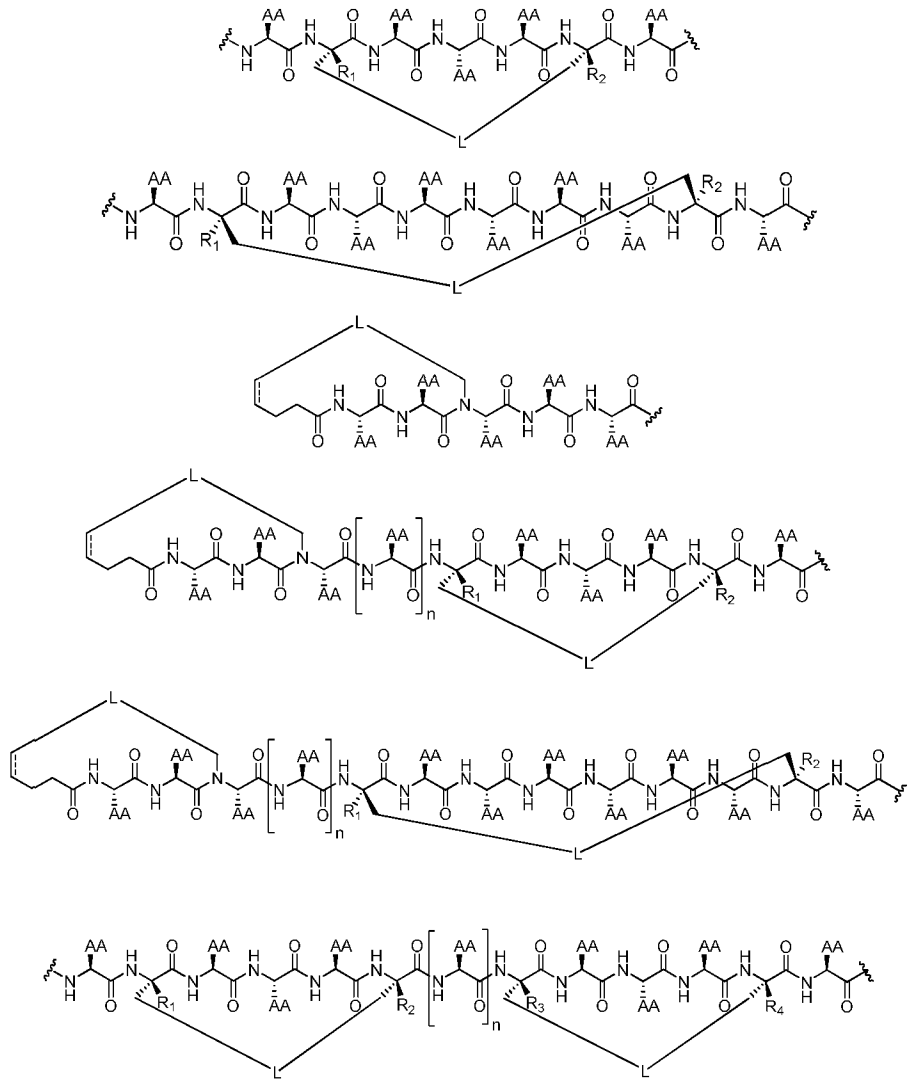
wherein each R_1 and R_2 is independently –H, alkyl, alkenyl, alkynyl, arylalkyl, cycloalkyl, cycloalkylalkyl, heteroalkyl, or heterocycloalkyl, unsubstituted or substituted with halo–.

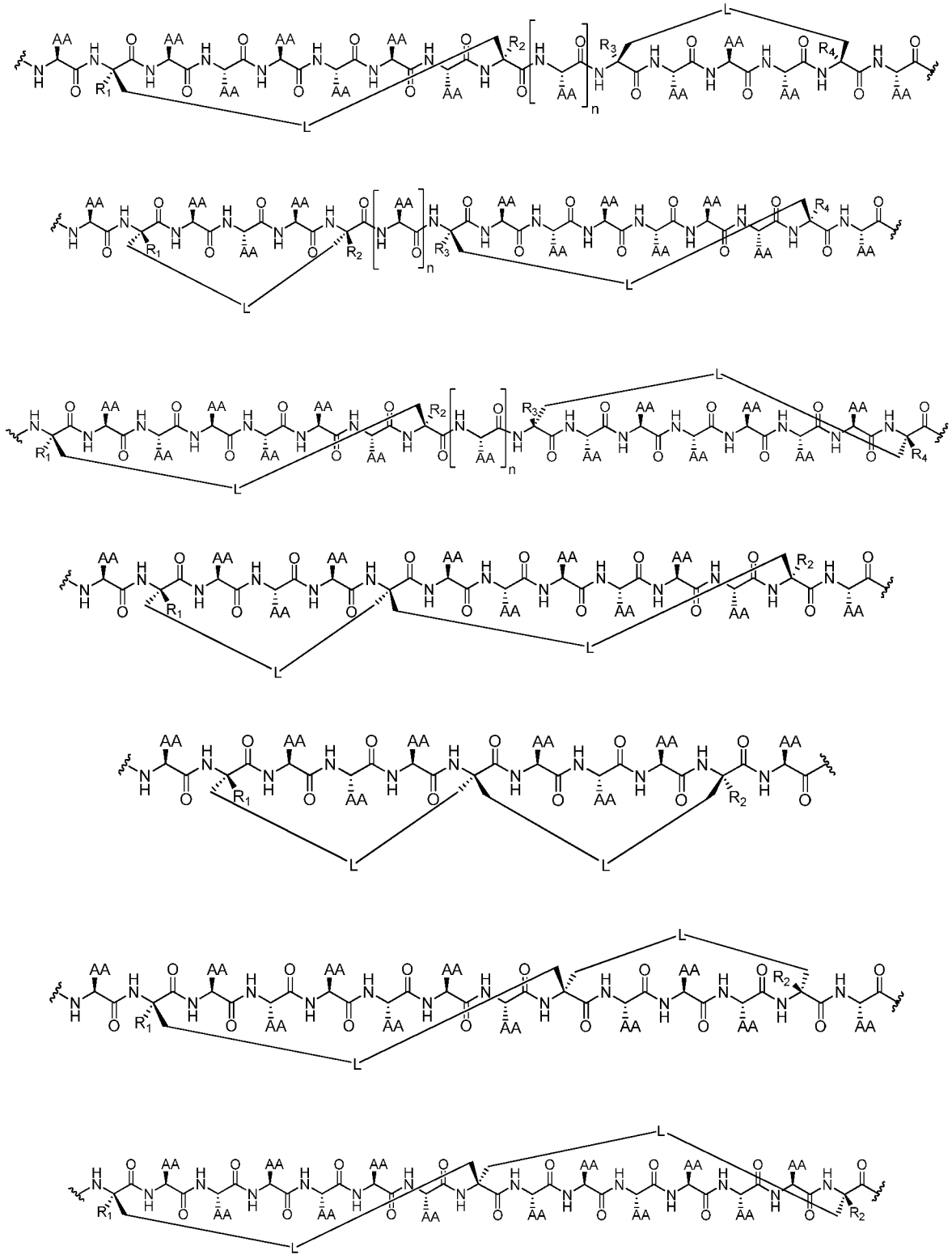
[00209] In related embodiments, the peptidomimetic macrocycle of Formula (I) is:



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

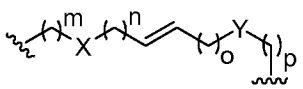
[00210] In other embodiments, the peptidomimetic macrocycle of Formula (I) is a compound of any of the formulas shown below:



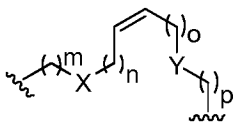


wherein "AA" represents any natural or non-natural amino acid side chain and "~" is $[D]_v$, $[E]_w$ as defined above, and n is an integer between 0 and 20, 50, 100, 200, 300, 400 or 500. In some embodiments, n is 0. In other embodiments, n is less than 50.

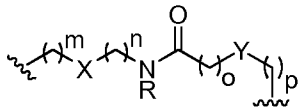
[00211] Exemplary embodiments of the macrocycle-forming linker L are shown below.



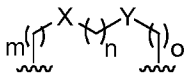
where X, Y = -CH_2-, O, S, or NH
m, n, o, p = 0-10



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

[00212] 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.

[00213] 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.

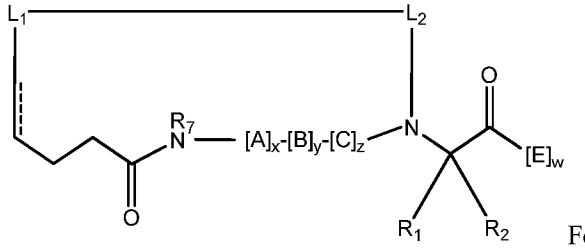
[00214] In some embodiments, any of the macrocycle-forming linkers described herein can be used in any combination with any of the sequences shown in **Table 3**, **Table 3a**, **Table 3b**, or **Table 3c** and also with any of the R– substituents indicated herein.

[00215] 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

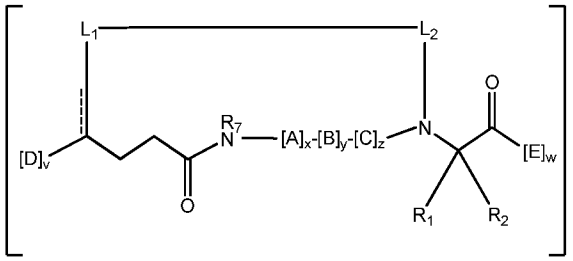
approximately 5 Å to 9 Å per turn of the α-helix, or approximately 6 Å to 8 Å per turn of the α-helix. Where the macrocycle-forming linker spans approximately 1 turn of an α-helix, the length is equal to approximately 5 carbon-carbon bonds to 13 carbon-carbon bonds, approximately 7 carbon-carbon bonds 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.

[00216] In other embodiments, provided are peptidomimetic macrocycles of Formula (IV) or (IVa):



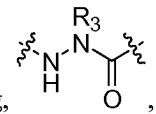
Formula (IV)



Formula (IVa)

wherein:

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

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

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

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

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

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

each R_4 is 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;

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

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

u is an integer from 1-10;

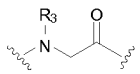
each x, y and z are independently integers from 0-10; and

each n is an integer from 1-5.

[00217] In one example, L_1 and L_2, either alone or in combination, do not form a triazole or a thioether.

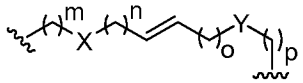
[00218] In one example, at least one of R_1 and R_2 is alkyl, unsubstituted or substituted with halo–. In another example, both R_1 and R_2 are independently alkyl, unsubstituted or substituted with halo–. In some embodiments, at least one of R_1 and R_2 is methyl. In other embodiments, R_1 and R_2 are methyl.

[00219] 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.

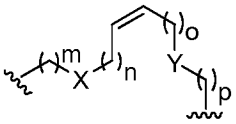
[00220] In some embodiments, the peptidomimetic macrocycle comprises a secondary structure which is an α-helix and R_8 is –H, allowing intrahelical hydrogen bonding. In some embodiments, at least one of A, B, C, D or E is an α,α-disubstituted amino acid. In one example, B is an α,α-disubstituted amino 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 .

[00221] 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.

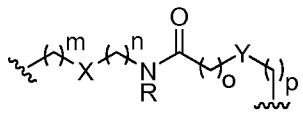
[00222] Exemplary embodiments of the macrocycle-forming linker -L_1-L_2- are shown below.



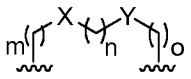
where X, Y = -CH_2-, O, S, or NH
m, n, o, p = 0-10



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

[00223] 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.

[00224] 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.

[00225] 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 be 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.

[00226] 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 be 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.

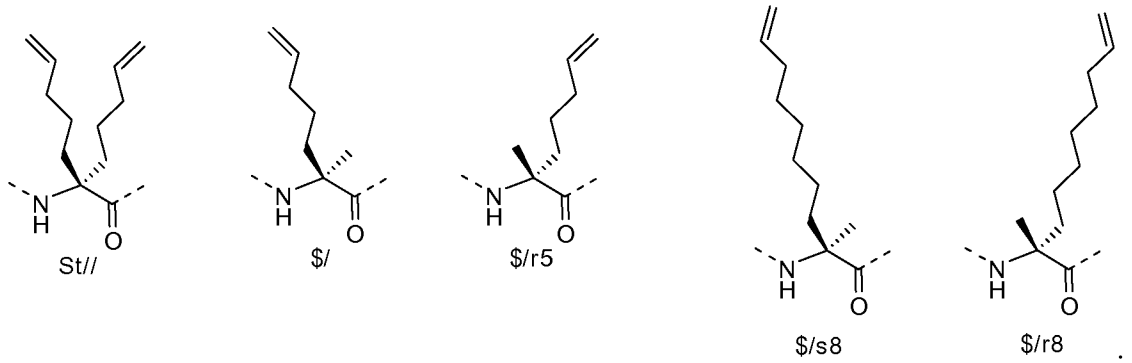
[00227] The circulating half-life of the peptidomimetic macrocycles in human blood can be greater than, equal to, or less than the half -life of the peptidomimetic macrocycles in biological tissue. In some examples, the circulating half-life of the peptidomimetic macrocycles in human blood can be greater than the half -life of the peptidomimetic macrocycles in biological tissue. In some examples, the circulating half-life of the peptidomimetic macrocycles in human blood can be equal to the half -life of the peptidomimetic macrocycles in biological tissue. In some examples, the half -life of the peptidomimetic macrocycles in biological tissue is greater than the circulating half-life of the peptidomimetic macrocycles in human blood. This can facilitate administration of the peptidomimetic macrocycles at a lower dose and/or at lower frequency. In some embodiments, the half -life of the peptidomimetic macrocycles in biological tissue is at least 1 h, 2 h, 3 h, 4 h, 5 h , 6 h, 7 h, 8 h, 9 h, 10 h, 11 h, or 12 h greater than the than the circulating half-life of the peptidomimetic macrocycles in human blood. In some examples, the circulating half-life of the peptidomimetic macrocycles in human blood is about 4 h and the half -life of the in biological tissue is about 10 h. In some examples, the circulating half-life of the peptidomimetic macrocycles in human blood is about 6 h and the half -life of the in biological tissue is about 10 h.

Preparation of Peptidomimetic Macrocycles

[00228] 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.

[00229] 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:



[00230] 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.

[00231] 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.

[00232] The peptidomimetic macrocycles described herein can be at least 1% pure, at least 2% pure, at least 3% pure, at least 4% pure, at least 5% pure, at least 6% pure, at least 7% pure, at least 8% pure, at least 9% pure, at least 10% pure, at least 11% pure, at least 12% pure, at least 13% pure, at least 14% pure, at least 15% pure, at least 16% pure, at least 17% pure, at least 18% pure, at least 19% pure, at least 20% pure, at least 21% pure, at least 22% pure, at least 23% pure, at least 24% pure, at least 25% pure, at least 26% pure, at least 27% pure, at least 28% pure, at least 29% pure, at least 30% pure, at least 31% pure, at least 32% pure, at least 33% pure, at least 34% pure, at least 35% pure, at least 36% pure, at least 37% pure, at least 38% pure, at least 39% pure, at least 40% pure, at least 41% pure, at least 42% pure, at least 43% pure, at least 44% pure, at least 45% pure, at least 46% pure, at least 47% pure, at least 48% pure, at least 49% pure, at least 50% pure, at least 51% pure, at least 52% pure, at least 53% pure, at least 54% pure, at least 55% pure, at least 56% pure, at least 57% pure, at least 58%

pure, at least 59% pure, at least 60% pure, at least 61% pure, at least 62% pure, at least 63% pure, at least 64% pure, at least 65% pure, at least 66% pure, at least 67% pure, at least 68% pure, at least 69% pure, at least 70% pure, at least 71% pure, at least 72% pure, at least 73% pure, at least 74% pure, at least 75% pure, at least 76% pure, at least 77% pure, at least 78% pure, at least 79% pure, at least 80% pure, at least 81% pure, at least 82% pure, at least 83% pure, at least 84% pure, at least 85% pure, at least 86% pure, at least 87% pure, at least 88% pure, at least 89% pure, at least 90% pure, at least 91% pure, at least 92% pure, at least 93% pure, at least 94% pure, at least 95% pure, at least 96% pure, at least 97% pure, at least 98% pure, at least 99% pure, at least 99.1% pure, at least 99.2% pure, at least 99.3% pure, at least 99.4% pure, at least 99.5% pure, at least 99.6% pure, at least 99.7% pure, at least 99.8% pure, or at least 99.9% pure on a chemical, optical, isomeric, enantiomeric, or diastereomeric basis. Purity can be assessed, for example, by HPLC, MS, LC/MS, melting point, or NMR.

[00233] Two or more peptides/ peptidomimetic macrocycles can share a degree of homology. A pair of peptides/ peptidomimetic macrocycles can have, for example, up to about 20% pairwise homology, up to about 25% pairwise homology, up to about 30% pairwise homology, up to about 35% pairwise homology, up to about 40% pairwise homology, up to about 45% pairwise homology, up to about 50% pairwise homology, up to about 55% pairwise homology, up to about 60% pairwise homology, up to about 65% pairwise homology, up to about 70% pairwise homology, up to about 75% pairwise homology, up to about 80% pairwise homology, up to about 85% pairwise homology, up to about 90% pairwise homology, up to about 95% pairwise homology, up to about 96% pairwise homology, up to about 97% pairwise homology, up to about 98% pairwise homology, up to about 99% pairwise homology, up to about 99.5% pairwise homology, or up to about 99.9% pairwise homology. A pair of peptides can have, for example, at least about 20% pairwise homology, at least about 25% pairwise homology, at least about 30% pairwise homology, at least about 35% pairwise homology, at least about 40% pairwise homology, at least about 45% pairwise homology, at least about 50% pairwise homology, at least about 55% pairwise homology, at least about 60% pairwise homology, at least about 65% pairwise homology, at least about 70% pairwise homology, at least about 75% pairwise homology, at least about 80% pairwise homology, at least about 85% pairwise homology, at least about 90% pairwise homology, at least about 95% pairwise homology, at least about 96% pairwise homology, at least about 97% pairwise homology, at least about 98% pairwise homology, at least about 99% pairwise homology, at least about 99.5% pairwise homology, at least about 99.9% pairwise homology.

[00234] Various methods and software programs can be used to determine the homology between two or more peptides, such as NCBI BLAST, Clustal W, MAFFT, Clustal Omega, AlignMe, Praline, or another suitable method or algorithm.

Assays

[00235] 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

[00236] 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)

[00237] 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

[00238] 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

[00239] 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

[00240] 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).

[00241] 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

[00242] 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.

[00243] 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).

[00244] 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

[00245] 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

[00246] 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

[00247] 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

[00248] 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

[00249] 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

[00250] 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

[00251] 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

[00252] 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

[00253] To determine the suitability of the peptidomimetic macrocycles for treatment of humans, clinical trials are performed. For example, patients diagnosed with solid tumor and in need of treatment can be selected and separated in treatment and one or more control groups, wherein the treatment group is administered a peptidomimetic macrocycle, while the control groups receive a placebo or a known anti-cancer drug. The treatment safety and efficacy of the peptidomimetic macrocycles can thus be evaluated by performing comparisons of the patient groups with respect to factors such as survival and quality-of-life. In this example, the patient group treated with a peptidomimetic macrocycle can show improved long-term survival compared to a patient control group treated with a placebo.

FORMULATION AND ADMINISTRATION

Mode of Administration

[00254] An effective amount of a peptidomimetic macrocycles or a pharmaceutically acceptable salt thereof of the disclosure can be administered in a pharmaceutical composition, as either single or multiple doses by an accepted mode of administration. In some embodiments, a pharmaceutical composition comprising a therapeutically effective amount of a peptidomimetic macrocycle or a therapeutically equivalent amount of a pharmaceutically acceptable salt thereof, of the disclosure are administered parenterally, for example, by subcutaneous, intramuscular, intrathecal, intravenous or epidural injection. For example, a pharmaceutical composition comprising a therapeutically effective amount of a peptidomimetic macrocycle or a therapeutically equivalent amount of a pharmaceutically acceptable salt thereof is administered intravenously, intraarterially, subcutaneously or by infusion. In some examples, a pharmaceutical composition comprising a therapeutically effective amount of a peptidomimetic macrocycle or a therapeutically equivalent amount of a pharmaceutically acceptable salt thereof is administered intravenously. In some examples, a pharmaceutical composition comprising a therapeutically effective amount of a peptidomimetic macrocycle or a therapeutically equivalent amount of a pharmaceutically acceptable salt thereof is administered intraarterially.

[00255] 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 by conventional methods known to those of skill in the art. 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.

[00256] In one aspect, the disclosure provides pharmaceutical composition 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 a pharmaceutical composition 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. A pharmaceutical composition 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 a pharmaceutical composition. In addition, prolonged absorption of an injectable pharmaceutical composition can be brought about by the inclusion of agents which delay absorption such as aluminum monostearate and gelatin. If desired a pharmaceutical composition 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

[00257] Dosing can be determined using techniques known to one skilled in the art. 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.

[00258] A physician or veterinarian having ordinary skill in the art can readily determine and prescribe the effective amount of the pharmaceutical composition required. For example, the physician or veterinarian could start doses of the compounds of the disclosure employed in the pharmaceutical composition at levels lower than that required in order to achieve the desired therapeutic effect and gradually increase the dosage until the desired effect is achieved.

[00259] 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.

[00260] Dosage can be based on the amount of the peptidomimetic macrocycle per kg body weight of the patient. Other amounts are known to those of skill in the art and readily determined. 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.

[00261] In some embodiment, the subject is a human subject and the amount of the peptidomimetic macrocycle administered is 0.01-100 mg per kilogram body weight of the human subject. For example, in various examples, the amount of the peptidomimetic macrocycle administered is about .01-50 mg/kg, about 0.01-20 mg/kg, about 0.01-10 mg/kg, about 0.1-100 mg/kg, about 0.1-50 mg/kg, about 0.1-20 mg/kg, about 0.1-10 mg/kg, about 0.5-100 mg/kg, about 0.5-50 mg/kg, about 0.5-20 mg/kg, about 0.5-10 mg/kg, about 1-100 mg/kg, about 1-50 mg/kg, about 1-20 mg/kg, about 1-10 mg/kg body weight of the human subject. In one embodiment, about 0.5 mg-10 mg of the peptidomimetic macrocycle per kilogram body weight of the human subject is administered. In some examples the amount of the peptidomimetic macrocycle administered is about 0.16 mg, 0.32 mg, 0.64 mg, 1.28 mg, 3.56 mg, 7.12 mg, 14.24, or 20 mg per kilogram body weight of the human subject. In some examples the amount of the peptidomimetic macrocycle administered is about 0.16 mg, 0.32 mg, 0.64 mg, 1.28 mg, 3.56 mg, 7.12 mg, or 14.24 mg per kilogram body weight of the human subject. In some examples the amount of the peptidomimetic macrocycle administered is 0.16 mg per kilogram body weight of the human subject. In some examples the amount of the peptidomimetic macrocycle administered is 0.32 mg per kilogram body weight of the human subject. In some examples the amount of the peptidomimetic macrocycle administered is 0.64 mg per kilogram body weight of the human subject. In some examples the amount of the peptidomimetic macrocycle administered is 1.28 mg per kilogram body weight of the human subject. In some examples the amount of the peptidomimetic macrocycle administered is 3.56 mg per kilogram body weight of the human subject. In some examples the amount of the peptidomimetic macrocycle administered is 7.12 mg per kilogram body weight of the human subject. In some examples the amount of the peptidomimetic macrocycle administered is 14.24 mg per kilogram body weight of the human subject.

[00262] In some embodiments about 0.5-20 mg or 0.5-10 mg of the peptidomimetic macrocycle per kilogram body weight of the human subject is administered two times a week. For example about 0.5-1.0 mg, 0.5-5.0 mg, 0.5-10.0 mg, 0.5-15 mg, or 1-5 mg, 1-10 mg, 1-15 mg, 1-20 mg, 5-10 mg, 1-15 mg, 5-20 mg, 10-15 mg, 10-20 mg, 15-20 mg of the peptidomimetic macrocycle per kilogram body weight of the human subject is administrated about twice a week. In some examples about 1.0 mg, 1.25 mg, 1.5 mg, 1.75 mg, 2.0 mg, 2.25 mg, 2.5 mg, 2.75 mg, 3.0 mg, 3.25 mg, 3.5 mg, 3.75 mg, 4.0 mg, 4.25 mg, 4.5 mg, 4.75 mg, 5.0 mg, 5.25 mg, 5.5 mg, 5.75 mg, 6.0 mg, 6.25 mg, 6.5 mg, 6.75 mg, 7.0 mg, 7.25 mg, 7.5 mg, 7.75 mg, 8.0 mg, 8.25 mg, 8.5 mg, 8.75 mg, 9.0 mg, 9.25 mg, 9.5 mg, 9.75 mg, 10.0 mg, 10.25 mg, 10.5 mg, 10.75 mg, 11.0 mg, 11.25 mg, 11.5 mg, 11.75 mg, 12.0 mg, 12.25 mg, 12.5 mg, 12.75 mg, 13.0 mg, 13.25 mg, 13.5 mg, 13.75 mg, 14.0 mg, 14.25 mg, 14.5 mg, 14.75 mg, 15.0 mg, 15.25 mg, 15.5 mg, 15.75 mg, 16.0 mg, 16.5 mg, 17.0 mg, 17.5 mg, 18.0 mg, 18.5 mg, 19.0 mg, 19.5 mg, or 20.0 mg of the peptidomimetic macrocycle per kilogram body weight of the human subject is administered two times a week. In some examples, the amount of the peptidomimetic macrocycle administered is about 1.25 mg, 2.5 mg, 5.0 mg, 10.0, or 20 mg per kilogram body weight of the human subject and the peptidomimetic macrocycle is administered two times a week. In some

examples, the amount of the peptidomimetic macrocycle administered is about 1.25 mg, 2.5 mg, 5.0 mg or 10.0 mg per kilogram body weight of the human subject and the peptidomimetic macrocycle is administered two times a week.

[00263] In some embodiments about 0.5-20 mg or 0.5-10 mg of the peptidomimetic macrocycle per kilogram body weight of the human subject is administered once a week. For example about 0.5-1.0 mg, 0.5-5.0 mg, 0.5-10.0 mg, 0.5-15 mg, or 1-5 mg, 1-10 mg, 1-15 mg, 1-20 mg, 5-10 mg, 1-15 mg, 5-20 mg, 10-15 mg, 10-20 mg, 15-20 mg of the peptidomimetic macrocycle per kilogram body weight of the human subject is administrated once a week. In some examples about 1.0 mg, 1.25 mg, 1.5 mg, 1.75 mg, 2.0 mg, 2.25 mg, 2.5 mg, 2.75 mg, 3.0 mg, 3.25 mg, 3.5 mg, 3.75 mg, 4.0 mg, 4.25 mg, 4.5 mg, 4.75 mg, 5.0 mg, 5.25 mg, 5.5 mg, 5.75 mg, 6.0 mg, 6.25 mg, 6.5 mg, 6.75 mg, 7.0 mg, 7.25 mg, 7.5 mg, 7.75 mg, 8.0 mg, 8.25 mg, 8.5 mg, 8.75 mg, 9.0 mg, 9.25 mg, 9.5 mg, 9.75 mg, 10.0 mg, 10.25 mg, 10.5 mg, 10.75 mg, 11.0 mg, 11.25 mg, 11.5 mg, 11.75 mg, 12.0 mg, 12.25 mg, 12.5 mg, 12.75 mg, 13.0 mg, 13.25 mg, 13.5 mg, 13.75 mg, 14.0 mg, 14.25 mg, 14.5 mg, 14.75 mg, 15.0 mg, 15.25 mg, 15.5 mg, 15.75 mg, 16.0 mg, 16.5 mg, 17.0 mg, 17.5 mg, 18.0 mg, 18.5 mg, 19.0 mg, 19.5 mg, or 20.0 mg of the peptidomimetic macrocycle per kilogram body weight of the human subject is administered once a week. In some examples, the amount of the peptidomimetic macrocycle administered is about 1.25 mg, 2.5 mg, 5.0 mg 10.0 mg, or 20.0 mg per kilogram body weight of the human subject and the peptidomimetic macrocycle is administered once a week. In some examples, the amount of the peptidomimetic macrocycle administered is about 1.25 mg, 2.5 mg, 5.0 mg or 10.0 mg per kilogram body weight of the human subject and the peptidomimetic macrocycle is administered once a week

[00264] In some embodiments about 0.5-20 mg or 0.5-10 mg of the peptidomimetic macrocycle per kilogram body weight of the human subject is administered 3, 4, 5, 6 or 7 times a week. For example about 0.5-1.0 mg, 0.5-5.0 mg, 0.5-10.0 mg, 0.5-15 mg, or 1-5 mg, 1-10 mg, 1-15 mg, 1-20 mg, 5-10 mg, 1-15 mg, 5-20 mg, 10-15 mg, 10-20 mg, 15-20 mg of the peptidomimetic macrocycle per kilogram body weight of the human subject is administrated 3, 4, 5, 6, or 7 times a week. In some examples about 1.0 mg, 1.25 mg, 1.5 mg, 1.75 mg, 2.0 mg, 2.25 mg, 2.5 mg, 2.75 mg, 3.0 mg, 3.25 mg, 3.5 mg, 3.75 mg, 4.0 mg, 4.25 mg, 4.5 mg, 4.75 mg, 5.0 mg, 5.25 mg, 5.5 mg, 5.75 mg, 6.0 mg, 6.25 mg, 6.5 mg, 6.75 mg, 7.0 mg, 7.25 mg, 7.5 mg, 7.75 mg, 8.0 mg, 8.25 mg, 8.5 mg, 8.75 mg, 9.0 mg, 9.25 mg, 9.5 mg, 9.75 mg, 10.0 mg, 10.25 mg, 10.5 mg, 10.75 mg, 11.0 mg, 11.25 mg, 11.5 mg, 11.75 mg, 12.0 mg, 12.25 mg, 12.5 mg, 12.75 mg, 13.0 mg, 13.25 mg, 13.5 mg, 13.75 mg, 14.0 mg, 14.25 mg, 14.5 mg, 14.75 mg, 15.0 mg, 15.25 mg, 15.5 mg, 15.75 mg, 16.0 mg, 16.5 mg, 17.0 mg, 17.5 mg, 18.0 mg, 18.5 mg, 19.0 mg, 19.5 mg, or 20.0 mg of the peptidomimetic macrocycle per kilogram body weight of the human subject is administered 3, 4, 5, 6, or 7 times a week. In some examples, the amount of the peptidomimetic macrocycle administered is about 1.25 mg, 2.5 mg, 5.0 mg 10.0 mg, or 20.0 mg per kilogram body weight of the human subject and the peptidomimetic macrocycle is administered 3, 4, 5, 6, or 7 times a week. In some examples, the amount of the peptidomimetic macrocycle

administered is about 1.25 mg, 2.5 mg, 5.0 mg or 10.0 mg per kilogram body weight of the human subject and the peptidomimetic macrocycle is administered 3, 4, 5, 6, or 7 times a week.

[00265] In some embodiments about 0.5-20 mg or 0.5-10 mg of the peptidomimetic macrocycle per kilogram body weight of the human subject is administered once every 2, 3, or 4 weeks. For example about 0.5-1.0 mg, 0.5-5.0 mg, 0.5-10.0 mg, 0.5-15 mg, or 1-5 mg, 1-10 mg, 1-15 mg, 1-20 mg, 5-10 mg, 1-15 mg, 5-20 mg, 10-15 mg, 10-20 mg, 15-20 mg of the peptidomimetic macrocycle per kilogram body weight of the human subject is administrated 3, 4, 5, 6, or 7 once every 2 or 3 week. In some examples about 1.0 mg, 1.25 mg, 1.5 mg, 1.75 mg, 2.0 mg, 2.25 mg, 2.5 mg, 2.75 mg, 3.0 mg, 3.25 mg, 3.5 mg, 3.75 mg, 4.0 mg, 4.25 mg, 4.5 mg, 4.75 mg, 5.0 mg, 5.25 mg, 5.5 mg, 5.75 mg, 6.0 mg, 6.25 mg, 6.5 mg, 6.75 mg, 7.0 mg, 7.25 mg, 7.5 mg, 7.75 mg, 8.0 mg, 8.25 mg, 8.5 mg, 8.75 mg, 9.0 mg, 9.25 mg, 9.5 mg, 9.75 mg, 10.0 mg, 10.25 mg, 10.5 mg, 10.75 mg, 11.0 mg, 11.25 mg, 11.5 mg, 11.75 mg, 12.0 mg, 12.25 mg, 12.5 mg, 12.75 mg, 13.0 mg, 13.25 mg, 13.5 mg, 13.75 mg, 14.0 mg, 14.25 mg, 14.5 mg, 14.75 mg, 15.0 mg, 15.25 mg, 15.5 mg, 15.75 mg, 16.0 mg, 16.5 mg, 17.0 mg, 17.5 mg, 18.0 mg, 18.5 mg, 19.0 mg, 19.5 mg, or 20.0 mg of the peptidomimetic macrocycle per kilogram body weight of the human subject is administered once every 2 or 3 weeks. In some examples, the amount of the peptidomimetic macrocycle administered is about 1.25 mg, 2.5 mg, 5.0 mg 10.0 mg, or 20.0 mg per kilogram body weight of the human subject and the peptidomimetic macrocycle is administered once every 2 weeks. In some examples, the amount of the peptidomimetic macrocycle administered is about 1.25 mg, 2.5 mg, 5.0 mg or 10.0 mg per kilogram body weight of the human subject and the peptidomimetic macrocycle is administered once every 2 weeks. In some examples, the amount of the peptidomimetic macrocycle administered is about 1.25 mg, 2.5 mg, 5.0 mg 10.0 mg, or 20.0 mg per kilogram body weight of the human subject and the peptidomimetic macrocycle is administered once every 3 weeks. In some examples, the amount of the peptidomimetic macrocycle administered is about 1.25 mg, 2.5 mg, 5.0 mg or 10.0 mg per kilogram body weight of the human subject and the peptidomimetic macrocycle is administered once every 3 weeks.

[00266] In some embodiments, the peptidomimetic macrocycle is administered gradually over a period of time. A desired amount of peptidomimetic macrocycle can be administered gradually over a period of from about 0.1 h -24 h. In some cases a desired amount of peptidomimetic macrocycle is administered gradually over a period of 0.1 h, 0.5 h, 1 h, 1.5 h, 2 h, 2.5 h, 3 h, 3.5 h, 4 h, 4.5 h, 5 h, 6 h, 7 h, 8 h, 9 h, 10 h, 11 h, 12 h, 13 h, 14 h, 15 h, 16 h, 17 h, 18 h, 19 h, 20 h, 21 h, 22 h, 23 h, or 24 h. In some examples, a desired amount of peptidomimetic macrocycle is administered gradually over a period of 0.25 -12 h, for example over a period of 0.25-1 h, 0.25-2 h, 0.25-3 h, 0.25-4 h, 0.25-6 h, 0.25-8 h, 0.25-10 h. In some examples, a desired amount of peptidomimetic macrocycle is administered gradually over a period of 0.25-2 h. In some examples, a desired amount of peptidomimetic macrocycle is administered gradually over a period of 0.25-1 h. In some examples, a desired amount of peptidomimetic macrocycle is administered gradually over a period of 0.25 h, 0.3 h, 0.4 h, 0.5 h, 0.6 h, 0.7 h, 0.8 h, 0.9 h, 1.0 h, 1.1 h, 1.2 h, 1.3 h, 1.4 h, 1.5 h, 1.6 h, 1.7 h, 1.8 h, 1.9 h, or 2.0 h. In

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

[00267] Administration of the peptidomimetic macrocycles can continue as long as necessary to treat a solid tumor in a subject in need thereof. In some embodiments, one or more peptidomimetic macrocycle of the disclosure is administered for more than 1 day, 1 week, 1 month, 2 months, 3 months, 4 months, 5 months, 6 months, 7 months, 8 months, 9 months, 10 months, 11 months , 12 months , 13 months , 14 months , 15 months , 16 months , 17 months , 18 months , 19 months , 20 months , 21 months , 22 months , 23 months , or 24 months. In some embodiments, one or more peptidomimetic macrocycle of the disclosure is administered for less than 1 week, 1 month, 2 months, 3 months, 4 months, 5 months, 6 months, 7 months, 8 months, 9 months, 10 months, 11 months , 12 months , 13 months , 14 months , 15 months , 16 months , 17 months , 18 months , 19 months , 20 months , 21 months , 22 months , 23 months , or 24 months.

[00268] In some embodiments, the peptidomimetic macrocycle is administered on day 1, 8, 15 and 28 of a 28 day cycle. In some embodiments, the peptidomimetic macrocycle is administered on day 1, 8, 15 and 28 of a 28 day cycle and administration is continued for two cycles. In some embodiments, the peptidomimetic macrocycle is administered on day 1, 8, 15 and 28 of a 28 day cycle and administration is continued for three cycles. In some embodiments, the peptidomimetic macrocycle is administered on day 1, 8, 15 and 28 of a 28 day cycle and administration is continued for 4, 5, 6, 7, 8, 9, 10, or more cycles.

[00269] In some embodiments, one or more peptidomimetic macrocycle of the disclosure is administered chronically on an ongoing basis. In some embodiments administration of one or more peptidomimetic macrocycle of the disclosure is continued until documentation of disease progression, unacceptable toxicity, or patient or physician decision to discontinue administration.

METHOD AND USES

[00270] In one aspect, the disclosure provides a method of treating solid tumor in a subject, the method comprising administering to the 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. 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 tumor cell proliferation, increased p53 protein, increased p21, and/or increased apoptosis in the human subject.

[00271] In one aspect, the disclosure provides a method of treating solid tumor, that lacks a p53 deactivating mutation, in a subject the method comprising administering to the 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. In some embodiments, the solid tumor is determined to lack a p53 mutation prior to treatment 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 tumor cell proliferation, increased p53 protein, increased p21, and/or increased apoptosis in the human subject.

[00272] In one aspect, the disclosure provides a method of treating solid tumor in a subject expressing wild type p53, the method comprising administering to the 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. 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 tumor cell proliferation, increased p53 protein, increased p21, and/or increased apoptosis in the human subject.

[00273] In some embodiments, the methods for treating solid tumor provided herein inhibit, reduce, diminish, arrest, or stabilize a tumor associated with the solid tumor. In other embodiments, the methods for treating solid tumor provided herein inhibit, reduce, diminish, arrest, or stabilize the blood flow, metabolism, or edema in a tumor associated with the solid tumor or one or more symptoms thereof. In some examples, the methods for treating solid tumor provided herein cause the regression of a tumor, tumor blood flow, tumor metabolism, or peritumor edema, and/or one or more symptoms associated with the solid tumor. In other examples, the methods for treating solid tumor provided herein maintain the size of the tumor so that it does not increase, or so that it increases by less than the increase of a tumor 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 some examples, the methods for treating solid tumor provided herein decrease tumor size. In some examples, the methods for treating solid tumor provided herein reduce the formation of a tumor. In some examples, the methods for treating solid tumor provided herein eradicate, remove, or control primary, regional and/or metastatic tumors associated with the solid tumor. In some examples, the methods for treating solid tumor provided herein decrease the number or size of metastases associated with the solid tumor. In some examples, the methods for treating solid tumor provided herein reduce the tumor volume or tumor size (e.g., diameter) in a subject by an amount in the range of about 5-10%, 5-20%, 10-20%, 15-20%, 10-30%, 20-30%, 20-40%, 30-40%, 10-50%, 20-50%, 30-50%, 40-

50%, 10-60%, 20-60%, 30-60%, 40-60%, 50-60%, 10-70%, 20-70%, 30-70%, 40-70%, 50-70%, 60-70%, 10-80%, 20-80%, 30-80%, 40-80%, 50-80%, 60-80%, 70-80%, 10-90%, 20-90%, 30-90%, 40-90%, 50-90%, 60-90%, 70-90%, 80-90%, 10-100%, 20% -100%, 30-100%, 40-100%, 50-100%, 60-100%, 70-100%, 80-100%, 90-100%, 95-100% , or any range in between, relative to tumor size (e.g., volume or diameter) in a subject prior to administration of the peptidomimetic macrocycles as assessed by methods well known in the art, e.g., CT Scan, MRI, DCE-MRI, or PET Scan. In certain embodiments, the methods herein reduce the tumor size (e.g., volume or diameter) in a subject by at least about 5%, 10%, 15%, 20%, 25%, 30%, 35%, 40%, 45%, 50%, 55%, 60%, 65%, 80%, 85%, 90%, 95%, 99%, or 100%, relative to tumor volume or tumor size (e.g., diameter) prior to administration of the peptidomimetic macrocycle as assessed by methods well known in the art, e.g., CT Scan, MRI, DCE-MRI, or PET Scan.

[00274] In some embodiments, the methods provided herein reduce the tumor perfusion in a subject by an amount in the range of about 5-10%, 5-20%, 10-20%, 15-20%, 10-30%, 20-30%, 20-40%, 30-40%, 10-50%, 20-50%, 30-50%, 40-50%, 10-60%, 20-60%, 30-60%, 40-60%, 50-60%, 10-70%, 20-70%, 30-70%, 40-70%, 50-70%, 60-70%, 10-80%, 20-80%, 30-80%, 40-80%, 50-80%, 60-80%, 70-80%, 10-90%, 20-90%, 30-90%, 40-90%, 50-90%, 60-90%, 70-90%, 80-90%, 10-100%, 20% -100%, 30-100%, 40-100%, 50-100%, 60-100%, 70-100%, 80-100%, 90-100%, 95-100% , or any range in between, relative to tumor perfusion prior to administration of the peptidomimetic macrocycle, as assessed by methods well known in the art, e.g., MRI, DCE-MRI, or PET Scan. In certain embodiments, the methods provided herein reduce the tumor perfusion in a subject by at least about 5%, 10%, 15%, 20%, 25%, 30%, 35%, 40%, 45%, 50%, 55%, 60%, 65%, 80%, 85%, 90%, 95%, 99%, or 100%, relative to tumor perfusion prior to administration of the peptidomimetic macrocycle as assessed by methods well known in the art, e.g., MRI, DCE-MRI, or PET Scan.

[00275] In some embodiments, the methods provided herein inhibit or decrease tumor metabolism in a subject in the range of about 5-10%, 5-20%, 10-20%, 15-20%, 10-30%, 20-30%, 20-40%, 30-40%, 10-50%, 20-50%, 30-50%, 40-50%, 10-60%, 20-60%, 30-60%, 40-60%, 50-60%, 10-70%, 20-70%, 30-70%, 40-70%, 50-70%, 60-70%, 10-80%, 20-80%, 30-80%, 40-80%, 50-80%, 60-80%, 70-80%, 10-90%, 20-90%, 30-90%, 40-90%, 50-90%, 60-90%, 70-90%, 80-90%, 10-100%, 20% -100%, 30-100%, 40-100%, 50-100%, 60-100%, 70-100%, 80-100%, 90-100%, 95-100%, or any range in between, relative to tumor metabolism prior to administration of the peptidomimetic macrocycle, as assessed by methods well known in the art. In certain embodiments, the methods provided herein inhibit or decrease tumor metabolism in a subject as assessed by methods well known in the art, e.g., PET scanning. In specific embodiments, the methods provided herein inhibit or decrease tumor metabolism in a subject by at least about 5%, 10%, 15%, 20%, 25%, 30%, 35%, 40%, 45%, 50%, 55%, 60%, 65%, 80%, 85%, 90%, 95%, or 100%, relative to tumor metabolism prior to administration of the peptidomimetic macrocycle, as assessed by methods well known in the art.

[00276] In other aspect, the disclosure provides a method for increasing the survival time of a subject with solid tumor determined to lack a p53 deactivating mutation and/or with solid tumor expressing wild type p53, the method comprising administering to the 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. 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.

[00277] In one aspect, the disclosure provides a method to access presence, absence or amount of the biomarker biomarkers in a subject suffering with solid tumor, the method comprising. 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.

[00278] 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.

[00279] Also provided herein is a method to re-activate the p53 pathway in a subject with a solid tumor lacking a p53 deactivating mutation and/or expressing wild type p53, the method comprising administering to the 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.

[00280] Also provided herein is a method to decrease tumor cell proliferation in a human subject with a solid tumor lacking a p53 deactivating mutation and/or expressing wild type p53, the method comprising administering to the 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.

[00281] Also provided herein is a method to increased p53 protein in a subject with a solid tumor lacking a p53 deactivating mutation and/or expressing wild type p53, the method comprising administering to the 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.

[00282] Also provided herein is a method to increased p21 in a subject with a solid tumor lacking a p53 deactivating mutation and/or expressing wild type p53, the method comprising administering to the 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.

[00283] Also provided herein is a method to increased apoptosis in a subject with a solid tumor lacking a p53 deactivating mutation and/or expressing wild type p53, the method comprising administering to the 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.

[00284] In some embodiments, the disclosure also provides a method to determine the dose limiting toxicities (DLTs) and /or maximum tolerated dose (MTD) of the peptidomimetic macrocycles disclosed herein in subject with a solid tumor lacking a p53 deactivating mutation and/or expressing wild type p53.

[00285] 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 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, 23 h, 22 h, 21 h, 20 h, 19 h, 18 h, 17 h, 16 h, 15 h, 14 h, 13 h, 12 h, 11 h, 10 h, 9 h, 8 h, 7 h, 6 h, 5 h, 4 h, 3 h, 2 h, 1 h, 30 min, 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 from 0-about 72 h, 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, or 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).

[00286] 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 any conventional method for detecting the type of biomarker, e.g., 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 tumor specimen from the subject, for example biological sample for pharmacodynamic analysis can be a blood sample or a tumor 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, 23 h, 22 h, 21 h, 20 h, 19 h, 18 h, 17 h, 16 h, 15 h, 14 h, 13 h, 12 h, 11 h, 10 h, 9 h, 8 h, 7 h, 6 h, 5 h, 4 h, 3 h, 2 h, 1 h, 30 min, 15 min, 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, 24 h, 36 h or 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. Tumor specimens 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 tumor samples for pharmacodynamic analysis are collected before administration on day 1 and between day 14-day 18, for example of day 16.

[00287] 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.

Biological Samples

[00288] 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 tumor samples or specimens. Tumor sample can be a tumor tissue sample. Methods of obtaining tumor tissue samples are well known in the art and can vary according to the type and location of a tumor and preferences of the physician. In some embodiments, the tumor 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).

[00289] 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.

[00290] 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, as is known in the art. 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.

[00291] In some cases, the assay includes a step of cell or tissue culture. Culture methods are well known in the art. 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

[00292] In some embodiments, a subject treated for solid tumor in accordance with the methods provided herein is a human, who has or is diagnosed with a solid tumor. In other embodiments, a subject treated for solid tumor in accordance with the methods provided herein is a human, predisposed or susceptible to a solid tumor. In some embodiments, a subject treated for solid tumor in accordance with the methods provided herein is a human, at risk of developing a solid tumor.

[00293] In some embodiments, a subject treated for solid tumor in accordance with the methods provided herein is a human, who has or is diagnosed with a solid tumor, determined to lack a p53 deactivating mutation and/or expressing wild type p53. In other embodiments, a subject treated for solid tumor in accordance with the methods provided herein is a human, predisposed or susceptible to a solid tumor, determined to lack a p53 deactivating mutation and/or expressing wild type p53. In some embodiments, a subject treated for solid tumor in accordance with the methods provided herein is a human, at risk of developing a solid tumor, determined to lack a p53 deactivating mutation and/or expressing wild type p53. A p53 deactivating mutation, as used herein is any mutation that leads to loss of (or a decrease in) the *in vitro* apoptotic activity of p53. Non limiting examples of p53 deactivating mutations are included in **Table 1a**. Accordingly, in some embodiments, a subject with a solid tumor in accordance with the composition as provided herein is a human who has or is diagnosed with a solid tumor that is determined to lack a p53 deactivation mutation, such as those shown in **Table 1a**.

[00294] In some embodiments, the subject treated for solid tumor in accordance with the methods provided herein is a human, who has or is diagnosed with a solid tumor, determined to have a p53 gain of function mutation. In other embodiments, a subject treated for solid tumor in accordance with the methods provided herein is a human, predisposed or susceptible to a solid tumor, determined to have a p53 gain of function mutation. In some embodiments, a subject treated for solid tumor in accordance with the methods provided herein is a human, at risk of developing a solid tumor, determined to have a p53 gain of function mutation. A p53 gain of function mutation, as used herein is any mutation such that the mutant p53 exerts oncogenic functions beyond their negative domination over the wild-type

p53 tumor suppressor functions. The p53 gain of function mutant protein mat exhibit new activities that can contribute actively to various stages of tumor progression and to increased resistance to anticancer treatments. Non limiting examples of p53 gain of function mutation mutations are included in **Table 1b**. Accordingly, in some embodiments, a subject with a solid tumor in accordance with the composition as provided herein is a human who has or is diagnosed with a solid tumor that is determined to have a p53 gain of function mutation, such as those shown in **Table 1b**.

[00295] In some embodiments, the subject treated for solid tumor in accordance with the methods provided herein is a human, who has or is diagnosed with a solid tumor that is not p53 negative. In other embodiments, a subject treated for solid tumor in accordance with the methods provided herein is a human, predisposed or susceptible to a solid tumor that is not p53 negative. In some embodiments, a subject treated for solid tumor in accordance with the methods provided herein is a human, at risk of developing a solid tumor that is not p53 negative.

[00296] In some embodiments, the subject treated for solid tumor in accordance with the methods provided herein is a human, who has or is diagnosed with a solid tumor that expresses p53 with partial loss of function mutation. In other embodiments, a subject treated for solid tumor in accordance with the methods provided herein is a human, predisposed or susceptible to a solid tumor that expresses p53 with partial loss of function mutation. In some embodiments, a subject treated for solid tumor in accordance with the methods provided herein is a human, at risk of developing a solid tumor that expresses p53 with partial loss of function mutation. As used herein "a partial loss of p53 function" mutation means that the mutant p53 exhibits some level of function of normal p53, but to a lesser or slower extent. For example, a partial loss of p53 function can mean that the cells become arrested in cell division to a lesser or slower extent.

[00297] In some embodiments, the subject treated for solid tumor in accordance with the methods provided herein is a human, who has or is diagnosed with a solid tumor that expresses p53 with a copy loss mutation and a deactivating mutation. In other embodiments, a subject treated for solid tumor in accordance with the methods provided herein is a human, predisposed or susceptible to a solid tumor that expresses p53 with a copy loss mutation and a deactivating mutation. In some embodiments, a subject treated for solid tumor in accordance with the methods provided herein is a human, at risk of developing a solid tumor that expresses p53 with a copy loss mutation and a deactivating mutation.

[00298] In some embodiments, the subject treated for solid tumor in accordance with the methods provided herein is a human, who has or is diagnosed with a solid tumor that expresses p53 with a copy loss mutation. In other embodiments, a subject treated for solid tumor in accordance with the methods provided herein is a human, predisposed or susceptible to a solid tumor that expresses p53 with a copy loss mutation. In some embodiments, a subject treated for solid tumor in accordance with the methods provided herein is a human, at risk of developing a solid tumor that expresses p53 with a copy loss mutation.

[00299] In some embodiments, the subject treated for solid tumor in accordance with the methods provided herein is a human, who has or is diagnosed with a solid tumor that expresses p53 with one or more silent mutations. In other embodiments, a subject treated for solid tumor in accordance with the methods provided herein is a human, predisposed or susceptible to a solid tumor that expresses p53 with one or more silent mutations. In some embodiments, a subject treated for solid tumor in accordance with the methods provided herein is a human, at risk of developing a solid tumor that expresses p53 with one or more silent mutations. Silent mutations as used herein are mutations which cause no change in the encoded p53 amino acid sequence.

[00300] In some embodiments, a subject treated for solid tumor in accordance with the methods provided herein is a human, who has or is diagnosed with a solid tumor, determined to lack a dominant p53 deactivating mutation. Dominant p53 deactivating mutation or dominant negative mutation, as used herein, is a mutation wherein the mutated p53 inhibits or disrupt the activity of the wild-type p53 gene.

Table 1a: Exemplary 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 1b. Exemplary p53 activating mutations

AA position	AAchange
46	S46F
121	S121F
123	T123A
288	N288K

Table 1a and 1b refer 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 lysine (K) at the 344 position in the wild type sequence is replaced by a proline (P).

[00301] In some embodiments, a subject treated for solid tumor 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 solid tumor is refractory to a therapy when the solid tumor 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 solid tumor. In various embodiments, a patient with solid tumor is refractory when one or more tumors associated with the solid tumor, have not decreased or have increased. In various embodiments, a patient with solid tumor is refractory when one or more tumors metastasize and/or spread to another organ.

[00302] In some embodiments, a subject treated for solid tumor 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 solid tumor 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 tumors despite treatment with existing therapies.

[00303] In some embodiments, the subject is a human who has had at least one unsuccessful prior treatment and/or therapy of the solid tumor.

Methods of detecting wild type p53 and/or p53 mutations

[00304] The tumor 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.

[00305] 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. Means for enriching a tissue preparation for tumor cells are known in the art. For example, the tissue can be isolated from paraffin or cryostat sections. Cancer cells can also be separated from normal cells by flow cytometry. These as well as other techniques for separating tumor from normal cells are well known in the art. If the tumor tissue is highly contaminated with normal cells, detection of mutations can be more difficult.

[00306] Detection of point mutations can be accomplished by molecular cloning of the p53 allele (or alleles) present in the tumor tissue and sequencing that allele(s) using techniques well known in the art. Alternatively, the polymerase chain reaction can be used to amplify p53 gene sequences directly from a genomic DNA preparation from the tumor tissue. The DNA sequence of the amplified sequences can then be determined. The polymerase chain reaction itself is well known in the art. 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.

[00307] 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. Other techniques for detecting deletions, as are known in the art can be used.

[00308] 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 which are well known in the art. The cDNA can also be sequenced via the polymerase chain reaction (PCR).

[00309] 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 tumor 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.

[00310] 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.

[00311] DNA sequences of the p53 gene from the tumor 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 tumor tissue as in the allele-specific probe.

[00312] The identification of p53 gene structural changes in tumor cells has been facilitated through the development and 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. Each has advantages and disadvantages but it is now possible to survey genome wide DNA copy number abnormalities and expression levels to allow correlations between losses, gains and amplifications in tumor cells with genes that are over- and under- expressed in the same samples. The gene expression arrays that provide estimates of mRNA levels in tumors 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. Ultimately DNA sequencing arrays will allow resequencing of chromosome regions and whole genomes.

[00313] 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. An SNP array is a useful tool to study the whole genome.

[00314] 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. Recent studies based on the SNP array technology have shown that not only solid tumors (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).

[00315] 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.

[00316] 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 which are well known in the art. 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 would 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. 2. Assessment of p53 Protein Level

[00317] 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.

[00318] 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.

[00319] Determination of the lack of p53 deactivating mutation and/or expression of wild type p53 in the subject with solid tumor can be performed 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 – 1 month, 4 years – 1month, 3 years – 1 month, 2 years-1 month, 1 years – 1 month, 5 years – 1 week, 4 years – 1 week, 3 years – 1 month, 2 years-1 week, 1 year – 1 week, 5 years – 1 day, 4 years – 1 day, 3 years – 1 days,2 years-1day, 1 year – 1 day, 15 months-1 month, 15 months-1 week, 15 months -1 day, 12 months-1 month, 12 months-1 week, 12 months-1 day, 6 months-1 month, 6 months-1 week, 6 months-1 day, 3 months-1 month, 3 months-1week, or 3 months-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.

Solid tumors

[00320] Solid tumors that can be treated by the instant methods include tumors and/or metastasis (wherever located) other than lymphatic cancer, for example brain and other central nervous system tumors (including but not limited to tumors of the meninges, brain, spinal cord, cranial nerves and other parts of central nervous system, e.g. glioblastomas or medulla blastomas); head and/or neck cancer; breast tumors; circulatory system tumors (including but not limited to heart, mediastinum and pleura, and other intrathoracic organs, vascular tumors and tumor-associated vascular tissue); excretory system tumors (including but not limited to tumors of kidney, renal pelvis, ureter, bladder, other and unspecified urinary organs); gastrointestinal tract tumors (including but not limited to tumors of oesophagus, stomach, small intestine, colon, colorectal, rectosigmoid junction, rectum, anus and anal canal, tumors involving the liver and intrahepatic bile ducts, gall bladder, other and unspecified parts of biliary tract, pancreas, other and digestive organs); oral cavity tumors (including but not limited to tumors of lip, tongue, gum, floor of mouth, palate, and other parts of mouth, parotid gland, and other parts of the salivary glands, tonsil, oropharynx, nasopharynx, pyriform sinus, hypopharynx, and other sites in the lip, oral cavity and pharynx); reproductive system tumors (including but not limited to tumors of vulva, vagina, Cervix uteri, Corpus uteri, uterus, ovary, and other sites associated with female genital organs, placenta, penis, prostate, testis, and other sites associated with male genital organs); respiratory tract tumors (including but not limited to tumors of nasal cavity and middle ear, accessory sinuses, larynx, trachea, bronchus and lung, e.g. small cell lung cancer or non-small cell lung cancer); skeletal system tumors (including but not limited to tumors of bone and articular cartilage of limbs, bone articular cartilage and other sites); skin tumors (including but not limited to malignant melanoma of the skin, non-melanoma skin cancer, basal cell carcinoma of skin, squamous cell carcinoma of skin, mesothelioma, Kaposi's sarcoma); and tumors involving other tissues including peripheral nerves and autonomic nervous system, connective and soft tissue, retroperitoneum and peritoneum, eye and adnexa, thyroid, adrenal gland and other endocrine glands

and related structures, secondary and unspecified malignant neoplasm of lymph nodes, secondary malignant neoplasm of respiratory and digestive systems and secondary malignant neoplasm of other sites.

[00321] In some examples, the solid tumor treated by the methods of the instant disclosure is pancreatic cancer, bladder cancer, colon cancer, liver cancer, colorectal cancer (colon cancer or rectal cancer), breast cancer, prostate cancer, renal cancer, hepatocellular cancer, lung cancer, ovarian cancer, cervical cancer, gastric cancer, esophageal cancer, head and neck cancer, melanoma, neuroendocrine cancers, CNS cancers, brain tumors, bone cancer, skin cancer, ocular tumor, choriocarcinoma (tumor of the placenta), sarcoma or soft tissue cancer.

[00322] In some examples, the solid tumor to be treated by the methods of the instant disclosure is selected bladder cancer, bone cancer, breast cancer, cervical cancer, CNS cancer, colon cancer, ocular tumor, renal cancer, liver cancer, lung cancer, pancreatic cancer, choriocarcinoma (tumor of the placenta), prostate cancer, sarcoma, skin cancer, soft tissue cancer or gastric cancer.

[00323] In some examples, the solid tumor treated by the methods of the instant disclosure is breast cancer. Non limiting examples of breast cancer that can be treated by the instant methods include ductal carcinoma in situ (DCIS or intraductal carcinoma), lobular carcinoma in situ (LCIS), invasive (or infiltrating) ductal carcinoma, invasive (or infiltrating) lobular carcinoma, inflammatory breast cancer, triple-negative breast cancer, paget disease of the nipple, phyllodes tumor (phylloides tumor or cystosarcoma phyllodes), angiosarcoma, adenoid cystic (or adenocystic) carcinoma, low-grade adenosquamous carcinoma, medullary carcinoma, papillary carcinoma, tubular carcinoma, metaplastic carcinoma, micropapillary carcinoma, and mixed carcinoma.

[00324] In some examples, the solid tumor treated by the methods of the instant disclosure is bone cancer. Non limiting examples of bone cancer that can be treated by the instant methods include osteosarcoma, chondrosarcoma, the Ewing Sarcoma Family of Tumors (ESFTs).

[00325] In some examples, the solid tumor treated by the methods of the instant disclosure is skin cancer. Non limiting examples of skin cancer that can be treated by the instant methods include melanoma, basal cell skin cancer, and squamous cell skin cancer.

[00326] In some examples, the solid tumor treated by the methods of the instant disclosure is ocular tumor. Non limiting examples of ocular tumor that can be treated by the methods of the instant disclosure include ocular tumor is choroidal nevus, choroidal melanoma, choroidal metastasis, choroidal hemangioma, choroidal osteoma, iris melanoma, uveal melanoma, intraocular lymphoma, melanocytoma, metastasis retinal capillary hemangiomas, congenital hypertrophy of the RPE, RPE adenoma or retinoblastoma.

[00327] In some embodiments solid tumors treated by the methods disclosed herein exclude cancers that are known to be associated with HPV (Human papillomavirus). The excluded group includes HPV positive cervical cancer, HPV positive anal cancer, and HPV head and neck cancers, such as oropharyngeal cancers.

[00328] The effectiveness and/or response of cancer treatment by the methods disclosed herein can be determined by any method known in art. 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 solid tumors as described in Therese et al., New Guidelines to Evaluate the Response to Treatment in Solid Tumors, J. of the National Cancer Institute 92(3):205-207 (2000), 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 tumor size, tumor volume, or tumor metabolism, or based upon overall tumor burden, or based upon levels of serum markers especially where elevated in the disease state.

[00329] The response in individual patients can be characterized as a complete response, a partial response, stable disease, and progressive disease, as these terms are understood in the art. In some embodiments, the response is complete response (CR). Complete response, in some examples can be defined as disappearance of all target lesions i.e. any pathological lymph nodes (whether target or non-target) must have reduction in short axis to < 10 mm. 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 target lesions, taking as reference the baseline sum diameters. In some embodiments, the response is progressive disease (PD). Progressive disease can be defined as at least a 20% increase in the sum of diameters of target lesions, taking as reference the smallest sum on study (this includes the baseline sum if that is the smallest) and an absolute increase of at least 5 mm in the sum of diameters of target lesions. 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 shrinkage to qualify for PR nor sufficient increase to qualify for PD, taking as reference the smallest sum diameters 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 invasive tumor cells in the surgical specimen.

COMBINATION TREATMENT

[00330] Also provided herein are combination therapies for the treatment of a solid tumor which involve the administration of the peptidomimetic macrocycles disclosed herein in combination with one or more additional therapies to a subject with solid tumor 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 solid tumor 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 solid tumor determined to lack a p53 deactivating mutation and/or with a solid tumor expressing wild type p53.

[00331] 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 solid tumor. 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 1-5 minutes, 1-30 minutes, 30 minutes to 60 minutes, 1 hour, 1-2 hours, 2-6 hours, 2-12 hours, 12-24 hours, 1-2 days, 2 days, 3 days, 4 days, 5 days, 6 days, 7 days, 1 week, 2 weeks, 3 weeks, 4 weeks, 5 weeks, 6 weeks, 7 weeks, 8 weeks, 9 weeks, 10 weeks, 15 weeks, 20 weeks, 26 weeks, 52 weeks, 11-15 weeks, 15-20 weeks, 20-30 weeks, 30-40 weeks, 40-50 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, 1 year, 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, 1 week, 2 weeks, 3 weeks, 4 weeks, one month, 2 months, 3 months, 6 months, 1 year, 2 years, or 5 years apart.

[00332] 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.

[00333] In some embodiments, the methods for treating solid tumor 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.

[00334] 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.

[00335] 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 solid tumor. 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.

[00336] 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.

[00337] 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.

[00338] 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.

[00339] 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.

[00340] 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®)).

[00341] 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).

[00342] 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).

[00343] 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).

[00344] 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 lovastatin (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 α5β1-antagonist (e.g., JSM6427); (25) nuclear factor kappa beta (NF-κβ) 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.

[00345] In some embodiments a peptidomimetic macrocycles disclosed herein can inhibit one or more transporter enzymes (e.g., OATP1B1, OATP1B3, BSEP) at concentrations that can be clinically relevant. Therefore such a 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) may not be dosed within 48 h, 36 h, 24 h, or 12 h ((for example within 24 h) of the administration of such a peptidomimetic macrocycle. Exemplary medications that can be affected by co-administration of such a peptidomimetic macrocycles are listed below. In various embodiments one or more of the medications selected from **Table 2** may not be dosed within 48 h, 36 h, 24 h, or 12 h (for example within 24 h) of the administration of such a peptidomimetic macrocycle.

[00346] **Table 2:** Exemplary medications that can be affected by co-administration with a 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

EXAMPLES

Example 1: Peptidomimetic macrocycles

[00347] 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.

[00348] 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).

[00349] 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.

[00350] The following protocol was used in the synthesis of single alkyne-crosslinked peptidomimetic macrocycles, including SP665. Fully protected resin-bound peptides were synthesized on a Rink amide MBHA resin (loading 0.62 mmol/g) on a 0.1 mmol scale. Deprotection of the temporary Fmoc group was achieved by 2 × 20 min treatments of the resin bound peptide with 25% (v/v) piperidine in NMP. After extensive flow washing with NMP and dichloromethane, coupling of each successive amino acid was achieved with 1 × 60 min incubation with the appropriate preactivated Fmoc-amino acid derivative. All protected amino acids (1 mmol) were dissolved in NMP and activated with HCTU (1 mmol) and DIEA (1 mmol) prior to transfer of the coupling solution to the deprotected resin-bound peptide. After coupling was completed, the resin was extensively flow washed in preparation for the next deprotection/coupling cycle. Acetylation of the amino terminus was carried out in the presence of acetic anhydride/DIEA in NMP /NMM. The LC-MS analysis of a cleaved and deprotected sample obtained from an aliquot of the fully assembled resin-bound peptide was accomplished in order to verifying the completion of each coupling. In a typical example, the peptide resin (0.1 mmol) was washed with DCM. Resin was loaded into a microwave vial. The vessel was evacuated and purged with nitrogen. Molybdenumhexacarbonyl (0.01 eq, Sigma Aldrich 199959) was added. Anhydrous chlorobenzene was added to the reaction vessel. Then 2-fluorophenol (1eq, Sigma Aldrich F12804) was added. The reaction was then loaded into the microwave and held at 130°C for 10 minutes. Reaction may need to be pushed a subsequent time for completion. The alkyne metathesized resin-bound peptides were deprotected and cleaved from the solid support by treatment with TFA/H_2O/TIS (94/3/3 v/v) for 3 h at room temperature. After filtration of the resin the TFA solution was precipitated in cold diethyl ether and centrifuged to yield the desired product as a solid. The crude product was purified by preparative HPLC.

[00351] Table 3 shows a list of peptidomimetic macrocycles prepared.

Table 3

	Sequence	SEQ ID NO:	Isomer	Exact Mass	Found Mass	Calc (M+1)/1	Calc (M+2)/2	Calc (M+3)/3
1	Ac-F$r8AYWEAc3cL$AAA-NH_2	10		1456.78	729.44	1457.79	729.4	486.6
2	Ac-F$r8AYWEAc3cL$AAibA-NH_2	11		1470.79	736.4	1471.8	736.4	491.27
3	Ac-LTF$r8AYWAQL$SANle-NH_2	12		1715.97	859.02	1716.98	858.99	573
4	Ac-LTF$r8AYWAQL$SAL-NH_2	13		1715.97	859.02	1716.98	858.99	573
5	Ac-LTF$r8AYWAQL$SAM-NH_2	14		1733.92	868.48	1734.93	867.97	578.98
6	Ac-LTF$r8AYWAQL$SAhL-NH_2	15		1729.98	865.98	1730.99	866	577.67
7	Ac-LTF$r8AYWAQL$SAF-NH_2	16		1749.95	876.36	1750.96	875.98	584.32
8	Ac-LTF$r8AYWAQL$SAI-NH_2	17		1715.97	859.02	1716.98	858.99	573
9	Ac-LTF$r8AYWAQL$SAChg-NH_2	18		1741.98	871.98	1742.99	872	581.67
10	Ac-LTF$r8AYWAQL$SAAib-NH_2	19		1687.93	845.36	1688.94	844.97	563.65
11	Ac-LTF$r8AYWAQL$SAA-NH_2	20		1673.92	838.01	1674.93	837.97	558.98
12	Ac-LTF$r8AYWA$LSNle-NH_2	21		1767.04	884.77	1768.05	884.53	590.02
13	Ac-LTF$r8AYWA$LSA-NH_2	22		1724.99	864.23	1726	863.5	576
14	Ac-F$r8AYWEAc3cL$AANle-NH_2	23		1498.82	750.46	1499.83	750.42	500.61
15	Ac-F$r8AYWEAc3cL$AAL-NH_2	24		1498.82	750.46	1499.83	750.42	500.61
16	Ac-F$r8AYWEAc3cL$AAM-NH_2	25		1516.78	759.41	1517.79	759.4	506.6
17	Ac-F$r8AYWEAc3cL$AAhL-NH_2	26		1512.84	757.49	1513.85	757.43	505.29
18	Ac-F$r8AYWEAc3cL$AAF-NH_2	27		1532.81	767.48	1533.82	767.41	511.94
19	Ac-F$r8AYWEAc3cL$AAI-NH_2	28		1498.82	750.39	1499.83	750.42	500.61

	Sequence	SEQ ID NO:	Isomer	Exact Mass	Found Mass	Calc (M+1)/1	Calc (M+2)/2	Calc (M+3)/3
20	Ac-F$r8AYWEAc3cL$AAChg-NH_2	29		1524.84	763.48	1525.85	763.43	509.29
21	Ac-F$r8AYWEAc3cL$AACha-NH_2	30		1538.85	770.44	1539.86	770.43	513.96
22	Ac-F$r8AYWEAc3cL$AAAib-NH_2	31		1470.79	736.84	1471.8	736.4	491.27
23	Ac-LTF$r8AYWAQL$AAAibV-NH_2	32		1771.01	885.81	1772.02	886.51	591.34
24	Ac-LTF$r8AYWAQL$AAAibV-NH_2	33	iso2	1771.01	886.26	1772.02	886.51	591.34
25	Ac-LTF$r8AYWAQL$SAibAA-NH_2	34		1758.97	879.89	1759.98	880.49	587.33
26	Ac-LTF$r8AYWAQL$SAibAA-NH_2	35	iso2	1758.97	880.34	1759.98	880.49	587.33
27	Ac-HLTF$r8HHWHQL$AANleNle-NH_2	36		2056.15	1028.86	2057.16	1029.08	686.39
28	Ac-DLTF$r8HHWHQL$RRLV-NH_2	37		2190.23	731.15	2191.24	1096.12	731.08
29	Ac-HHTF$r8HHWHQL$AAML-NH_2	38		2098.08	700.43	2099.09	1050.05	700.37
30	Ac-F$r8HHWHQL$RRDCha-NH_2	39		1917.06	959.96	1918.07	959.54	640.03
31	Ac-F$r8HHWHQL$HRFV-NH_2	40		1876.02	938.65	1877.03	939.02	626.35
32	Ac-HLTF$r8HHWHQL$AAhLA-NH_2	41		2028.12	677.2	2029.13	1015.07	677.05
33	Ac-DLTF$r8HHWHQL$RRChgl-NH_2	42		2230.26	1115.89	2231.27	1116.14	744.43
34	Ac-DLTF$r8HHWHQL$RRChgl-NH_2	43	iso2	2230.26	1115.96	2231.27	1116.14	744.43
35	Ac-HHTF$r8HHWHQL$AAChav-NH_2	44		2106.14	1053.95	2107.15	1054.08	703.05
36	Ac-F$r8HHWHQL$RRDa-NH_2	45		1834.99	918.3	1836	918.5	612.67
37	Ac-F$r8HHWHQL$HRAibG-NH_2	46		1771.95	886.77	1772.96	886.98	591.66
38	Ac-F$r8AYWAQL$HHNleL-NH_2	47		1730.97	866.57	1731.98	866.49	578
39	Ac-F$r8AYWSAL$HQANle-NH_2	48		1638.89	820.54	1639.9	820.45	547.3
40	Ac-F$r8AYWVQL$QHChgl-NH_2	49		1776.01	889.44	1777.02	889.01	593.01
41	Ac-F$r8AYWTAL$QQNlev-NH_2	50		1671.94	836.97	1672.95	836.98	558.32
42	Ac-F$r8AYWYQL$HAibAa-NH_2	51		1686.89	844.52	1687.9	844.45	563.3
43	Ac-LTF$r8AYWAQL$HHLa-NH_2	52		1903.05	952.27	1904.06	952.53	635.36
44	Ac-LTF$r8AYWAQL$HHLa-NH_2	53	iso2	1903.05	952.27	1904.06	952.53	635.36
45	Ac-LTF$r8AYWAQL$HQNlev-NH_2	54		1922.08	962.48	1923.09	962.05	641.7
46	Ac-LTF$r8AYWAQL$HQNlev-NH_2	55	iso2	1922.08	962.4	1923.09	962.05	641.7
47	Ac-LTF$r8AYWAQL$QQMl-NH_2	56		1945.05	973.95	1946.06	973.53	649.36
48	Ac-LTF$r8AYWAQL$QQMl-NH_2	57	iso2	1945.05	973.88	1946.06	973.53	649.36
49	Ac-LTF$r8AYWAQL$HAibhLV-NH_2	58		1893.09	948.31	1894.1	947.55	632.04
50	Ac-LTF$r8AYWAQL$AHFA-NH_2	59		1871.01	937.4	1872.02	936.51	624.68
51	Ac-HLTF$r8HHWHQL$AANlel-NH_2	60		2056.15	1028.79	2057.16	1029.08	686.39
52	Ac-DLTF$r8HHWHQL$RRLa-NH_2	61		2162.2	721.82	2163.21	1082.11	721.74
53	Ac-HHTF$r8HHWHQL$AAMv-NH_2	62		2084.07	1042.92	2085.08	1043.04	695.7
54	Ac-F$r8HHWHQL$RRDA-NH_2	63		1834.99	612.74	1836	918.5	612.67
55	Ac-F$r8HHWHQL$HRFCha-NH_2	64		1930.06	966.47	1931.07	966.04	644.36
56	Ac-F$r8AYWEAL$AA-NHAm	65		1443.82	1445.71	1444.83	722.92	482.28
57	Ac-F$r8AYWEAL$AA-NHiAm	66		1443.82	723.13	1444.83	722.92	482.28
58	Ac-F$r8AYWEAL$AA-NHnPr3Ph	67		1491.82	747.3	1492.83	746.92	498.28
59	Ac-F$r8AYWEAL$AA-NHnBu33Me	68		1457.83	1458.94	1458.84	729.92	486.95
60	Ac-F$r8AYWEAL$AA-NHnPr	69		1415.79	709.28	1416.8	708.9	472.94
61	Ac-F$r8AYWEAL$AA-NHnEt2Ch	70		1483.85	1485.77	1484.86	742.93	495.62
62	Ac-F$r8AYWEAL$AA-NHnEt2Cp	71		1469.83	1470.78	1470.84	735.92	490.95
63	Ac-F$r8AYWEAL$AA-NHHex	72		1457.83	730.19	1458.84	729.92	486.95
64	Ac-LTF$r8AYWAQL$AAIA-NH_2	73		1771.01	885.81	1772.02	886.51	591.34
65	Ac-LTF$r8AYWAQL$AAIA-NH_2	74	iso2	1771.01	866.8	1772.02	886.51	591.34
66	Ac-LTF$r8AYWAAL$AAMA-NH_2	75		1731.94	867.08	1732.95	866.98	578.32
67	Ac-LTF$r8AYWAAL$AAMA-NH_2	76	iso2	1731.94	867.28	1732.95	866.98	578.32
68	Ac-LTF$r8AYWAQL$AANleA-NH_2	77		1771.01	867.1	1772.02	886.51	591.34
69	Ac-LTF$r8AYWAQL$AANleA-NH_2	78	iso2	1771.01	886.89	1772.02	886.51	591.34
70	Ac-LTF$r8AYWAQL$AAIa-NH_2	79		1771.01	886.8	1772.02	886.51	591.34
71	Ac-LTF$r8AYWAQL$AAIa-NH_2	80	iso2	1771.01	887.09	1772.02	886.51	591.34
72	Ac-LTF$r8AYWAAL$AAMa-NH_2	81		1731.94	867.17	1732.95	866.98	578.32
73	Ac-LTF$r8AYWAAL$AAMa-NH_2	82	iso2	1731.94	867.37	1732.95	866.98	578.32
74	Ac-LTF$r8AYWAQL$AANlea-NH_2	83		1771.01	887.08	1772.02	886.51	591.34
75	Ac-LTF$r8AYWAQL$AANlea-NH_2	84	iso2	1771.01	887.08	1772.02	886.51	591.34
76	Ac-LTF$r8AYWAAL$AAIv-NH_2	85		1742.02	872.37	1743.03	872.02	581.68
77	Ac-LTF$r8AYWAAL$AAIv-NH_2	86	iso2	1742.02	872.74	1743.03	872.02	581.68
78	Ac-LTF$r8AYWAQL$AAMv-NH_2	87		1817	910.02	1818.01	909.51	606.67
79	Ac-LTF$r8AYWAAL$AANlev-NH_2	88		1742.02	872.37	1743.03	872.02	581.68
80	Ac-LTF$r8AYWAAL$AANlev-NH_2	89	iso2	1742.02	872.28	1743.03	872.02	581.68

	Sequence	SEQ ID NO:	Isomer	Exact Mass	Found Mass	Calc (M+1)/1	Calc (M+2)/2	Calc (M+3)/3
81	Ac-LTF$r8AYWAQL$AAIl-NH_2	90		1813.05	907.81	1814.06	907.53	605.36
82	Ac-LTF$r8AYWAQL$AAIl-NH_2	91	iso2	1813.05	907.81	1814.06	907.53	605.36
83	Ac-LTF$r8AYWAAL$AAMl-NH_2	92		1773.99	887.37	1775	888	592.34
84	Ac-LTF$r8AYWAQL$AANlel-NH_2	93		1813.05	907.61	1814.06	907.53	605.36
85	Ac-LTF$r8AYWAQL$AANlel-NH_2	94	iso2	1813.05	907.71	1814.06	907.53	605.36
86	Ac-F$r8AYWEAL$AAMA-NH_2	95		1575.82	789.02	1576.83	788.92	526.28
87	Ac-F$r8AYWEAL$AANleA-NH_2	96		1557.86	780.14	1558.87	779.94	520.29
88	Ac-F$r8AYWEAL$AAIa-NH_2	97		1557.86	780.33	1558.87	779.94	520.29
89	Ac-F$r8AYWEAL$AAMa-NH_2	98		1575.82	789.3	1576.83	788.92	526.28
90	Ac-F$r8AYWEAL$AANlea-NH_2	99		1557.86	779.4	1558.87	779.94	520.29
91	Ac-F$r8AYWEAL$AAIv-NH_2	100		1585.89	794.29	1586.9	793.95	529.64
92	Ac-F$r8AYWEAL$AAMv-NH_2	101		1603.85	803.08	1604.86	802.93	535.62
93	Ac-F$r8AYWEAL$AANlev-NH_2	102		1585.89	793.46	1586.9	793.95	529.64
94	Ac-F$r8AYWEAL$AAIl-NH_2	103		1599.91	800.49	1600.92	800.96	534.31
95	Ac-F$r8AYWEAL$AAMl-NH_2	104		1617.86	809.44	1618.87	809.94	540.29
96	Ac-F$r8AYWEAL$AANlel-NH_2	105		1599.91	801.7	1600.92	800.96	534.31
97	Ac-F$r8AYWEAL$AANlel-NH_2	106	iso2	1599.91	801.42	1600.92	800.96	534.31
98	Ac-LTF$r8AY6clWAQL$SAA-NH_2	107		1707.88	855.72	1708.89	854.95	570.3
99	Ac-LTF$r8AY6clWAQL$SAA-NH_2	108	iso2	1707.88	855.35	1708.89	854.95	570.3
100	Ac-WTF$r8FYWSQL$AVAa-NH_2	109		1922.01	962.21	1923.02	962.01	641.68
101	Ac-WTF$r8FYWSQL$AVAa-NH_2	110	iso2	1922.01	962.49	1923.02	962.01	641.68
102	Ac-WTF$r8VYWSQL$AVA-NH_2	111		1802.98	902.72	1803.99	902.5	602
103	Ac-WTF$r8VYWSQL$AVA-NH_2	112	iso2	1802.98	903	1803.99	902.5	602
104	Ac-WTF$r8FYWSQL$SAAa-NH_2	113		1909.98	956.47	1910.99	956	637.67
105	Ac-WTF$r8FYWSQL$SAAa-NH_2	114	iso2	1909.98	956.47	1910.99	956	637.67
106	Ac-WTF$r8VYWSQL$AVAaa-NH_2	115		1945.05	974.15	1946.06	973.53	649.36
107	Ac-WTF$r8VYWSQL$AVAaa-NH_2	116	iso2	1945.05	973.78	1946.06	973.53	649.36
108	Ac-LTF$r8AYWAQL$AVG-NH_2	117		1671.94	837.52	1672.95	836.98	558.32
109	Ac-LTF$r8AYWAQL$AVG-NH_2	118	iso2	1671.94	837.21	1672.95	836.98	558.32
110	Ac-LTF$r8AYWAQL$AVQ-NH_2	119		1742.98	872.74	1743.99	872.5	582
111	Ac-LTF$r8AYWAQL$AVQ-NH_2	120	iso2	1742.98	872.74	1743.99	872.5	582
112	Ac-LTF$r8AYWAQL$SAa-NH_2	121		1673.92	838.23	1674.93	837.97	558.98
113	Ac-LTF$r8AYWAQL$SAa-NH_2	122	iso2	1673.92	838.32	1674.93	837.97	558.98
114	Ac-LTF$r8AYWAQhL$SAA-NH_2	123		1687.93	844.37	1688.94	844.97	563.65
115	Ac-LTF$r8AYWAQhL$SAA-NH_2	124	iso2	1687.93	844.81	1688.94	844.97	563.65
116	Ac-LTF$r8AYWEQLStSA$-NH_2	125		1826	905.27	1827.01	914.01	609.67
117	Ac-LTF$r8AYWAQL$SLA-NH_2	126		1715.97	858.48	1716.98	858.99	573
118	Ac-LTF$r8AYWAQL$SLA-NH_2	127	iso2	1715.97	858.87	1716.98	858.99	573
119	Ac-LTF$r8AYWAQL$SWA-NH_2	128		1788.96	895.21	1789.97	895.49	597.33
120	Ac-LTF$r8AYWAQL$SWA-NH_2	129	iso2	1788.96	895.28	1789.97	895.49	597.33
121	Ac-LTF$r8AYWAQL$SVS-NH_2	130		1717.94	859.84	1718.95	859.98	573.65
122	Ac-LTF$r8AYWAQL$SAS-NH_2	131		1689.91	845.85	1690.92	845.96	564.31
123	Ac-LTF$r8AYWAQL$SVG-NH_2	132		1687.93	844.81	1688.94	844.97	563.65
124	Ac-ETF$r8VYWAQL$SAa-NH_2	133		1717.91	859.76	1718.92	859.96	573.64
125	Ac-ETF$r8VYWAQL$SAA-NH_2	134		1717.91	859.84	1718.92	859.96	573.64
126	Ac-ETF$r8VYWAQL$SVA-NH_2	135		1745.94	873.82	1746.95	873.98	582.99
127	Ac-ETF$r8VYWAQL$SLA-NH_2	136		1759.96	880.85	1760.97	880.99	587.66
128	Ac-ETF$r8VYWAQL$SWA-NH_2	137		1832.95	917.34	1833.96	917.48	611.99
129	Ac-ETF$r8KYWAQL$SWA-NH_2	138		1861.98	931.92	1862.99	932	621.67
130	Ac-ETF$r8VYWAQL$SVS-NH_2	139		1761.93	881.89	1762.94	881.97	588.32
131	Ac-ETF$r8VYWAQL$SAS-NH_2	140		1733.9	867.83	1734.91	867.96	578.97
132	Ac-ETF$r8VYWAQL$SVG-NH_2	141		1731.92	866.87	1732.93	866.97	578.31
133	Ac-LTF$r8VYWAQL$SSa-NH_2	142		1717.94	859.47	1718.95	859.98	573.65
134	Ac-ETF$r8VYWAQL$SSa-NH_2	143		1733.9	867.83	1734.91	867.96	578.97
135	Ac-LTF$r8VYWAQL$SNa-NH_2	144		1744.96	873.38	1745.97	873.49	582.66
136	Ac-ETF$r8VYWAQL$SNa-NH_2	145		1760.91	881.3	1761.92	881.46	587.98
137	Ac-LTF$r8VYWAQL$SAa-NH_2	146		1701.95	851.84	1702.96	851.98	568.32
138	Ac-LTF$r8VYWAQL$SVA-NH_2	147		1729.98	865.53	1730.99	866	577.67
139	Ac-LTF$r8VYWAQL$SVA-NH_2	148	iso2	1729.98	865.9	1730.99	866	577.67
140	Ac-LTF$r8VYWAQL$SWA-NH_2	149		1816.99	909.42	1818	909.5	606.67
141	Ac-LTF$r8VYWAQL$SVS-NH_2	150		1745.98	873.9	1746.99	874	583

	Sequence	SEQ ID NO:	Isomer	Exact Mass	Found Mass	Calc (M+1)/1	Calc (M+2)/2	Calc (M+3)/3
142	Ac-LTF$r8VYWAQL$SVS-NH_2	151	iso2	1745.98	873.9	1746.99	874	583
143	Ac-LTF$r8VYWAQL$SAS-NH_2	152		1717.94	859.84	1718.95	859.98	573.65
144	Ac-LTF$r8VYWAQL$SAS-NH_2	153	iso2	1717.94	859.91	1718.95	859.98	573.65
145	Ac-LTF$r8VYWAQL$SVG-NH_2	154		1715.97	858.87	1716.98	858.99	573
146	Ac-LTF$r8VYWAQL$SVG-NH_2	155	iso2	1715.97	858.87	1716.98	858.99	573
147	Ac-LTF$r8EYWAQCha$SAA-NH_2	156		1771.96	886.85	1772.97	886.99	591.66
148	Ac-LTF$r8EYWAQCha$SAA-NH_2	157	iso2	1771.96	886.85	1772.97	886.99	591.66
149	Ac-LTF$r8EYWAQCpg$SAA-NH_2	158		1743.92	872.86	1744.93	872.97	582.31
150	Ac-LTF$r8EYWAQCpg$SAA-NH_2	159	iso2	1743.92	872.86	1744.93	872.97	582.31
151	Ac-LTF$r8EYWAQF$SAA-NH_2	160		1765.91	883.44	1766.92	883.96	589.64
152	Ac-LTF$r8EYWAQF$SAA-NH_2	161	iso2	1765.91	883.89	1766.92	883.96	589.64
153	Ac-LTF$r8EYWAQCba$SAA-NH_2	162		1743.92	872.42	1744.93	872.97	582.31
154	Ac-LTF$r8EYWAQCba$SAA-NH_2	163	iso2	1743.92	873.39	1744.93	872.97	582.31
155	Ac-LTF3Cl$r8EYWAQL$SAA-NH_2	164		1765.89	883.89	1766.9	883.95	589.64
156	Ac-LTF3Cl$r8EYWAQL$SAA-NH_2	165	iso2	1765.89	883.96	1766.9	883.95	589.64
157	Ac-LTF34F2$r8EYWAQL$SAA-NH_2	166		1767.91	884.48	1768.92	884.96	590.31
158	Ac-LTF34F2$r8EYWAQL$SAA-NH_2	167	iso2	1767.91	884.48	1768.92	884.96	590.31
159	Ac-LTF34F2$r8EYWAQhL$SAA-NH_2	168		1781.92	891.44	1782.93	891.97	594.98
160	Ac-LTF34F2$r8EYWAQhL$SAA-NH_2	169	iso2	1781.92	891.88	1782.93	891.97	594.98
161	Ac-ETF$r8EYWAQL$SAA-NH_2	170		1747.88	874.34	1748.89	874.95	583.63
162	Ac-LTF$r8AYWVQL$SAA-NH_2	171		1701.95	851.4	1702.96	851.98	568.32
163	Ac-LTF$r8AHWAQL$SAA-NH_2	172		1647.91	824.83	1648.92	824.96	550.31
164	Ac-LTF$r8AEWAQL$SAA-NH_2	173		1639.9	820.39	1640.91	820.96	547.64
165	Ac-LTF$r8ASWAQL$SAA-NH_2	174		1597.89	799.38	1598.9	799.95	533.64
166	Ac-LTF$r8AEWAQL$SAA-NH_2	175	iso2	1639.9	820.39	1640.91	820.96	547.64
167	Ac-LTF$r8ASWAQL$SAA-NH_2	176	iso2	1597.89	800.31	1598.9	799.95	533.64
168	Ac-LTF$r8AF4coohWAQL$SAA-NH_2	177		1701.91	851.4	1702.92	851.96	568.31
169	Ac-LTF$r8AF4coohWAQL$SAA-NH_2	178	iso2	1701.91	851.4	1702.92	851.96	568.31
170	Ac-LTF$r8AHWAQL$AAIa-NH_2	179		1745	874.13	1746.01	873.51	582.67
171	Ac-ITF$r8FYWAQL$AAIa-NH_2	180		1847.04	923.92	1848.05	924.53	616.69
172	Ac-ITF$r8EHWAQL$AAIa-NH_2	181		1803.01	903.17	1804.02	902.51	602.01
173	Ac-ITF$r8EHWAQL$AAIa-NH_2	182	iso2	1803.01	903.17	1804.02	902.51	602.01
174	Ac-ETF$r8EHWAQL$AAIa-NH_2	183		1818.97	910.76	1819.98	910.49	607.33
175	Ac-ETF$r8EHWAQL$AAIa-NH_2	184	iso2	1818.97	910.85	1819.98	910.49	607.33
176	Ac-LTF$r8AHWVQL$AAIa-NH_2	185		1773.03	888.09	1774.04	887.52	592.02
177	Ac-ITF$r8FYWVQL$AAIa-NH_2	186		1875.07	939.16	1876.08	938.54	626.03
178	Ac-ITF$r8EYWVQL$AAIa-NH_2	187		1857.04	929.83	1858.05	929.53	620.02
179	Ac-ITF$r8EHWVQL$AAIa-NH_2	188		1831.04	916.86	1832.05	916.53	611.35
180	Ac-LTF$r8AEWAQL$AAIa-NH_2	189		1736.99	869.87	1738	869.5	580
181	Ac-LTF$r8AF4coohWAQL$AAIa-NH_2	190		1799	900.17	1800.01	900.51	600.67
182	Ac-LTF$r8AF4coohWAQL$AAIa-NH_2	191	iso2	1799	900.24	1800.01	900.51	600.67
183	Ac-LTF$r8AHWAQL$AHFA-NH_2	192		1845.01	923.89	1846.02	923.51	616.01
184	Ac-ITF$r8FYWAQL$AHFA-NH_2	193		1947.05	975.05	1948.06	974.53	650.02
185	Ac-ITF$r8FYWAQL$AHFA-NH_2	194	iso2	1947.05	976.07	1948.06	974.53	650.02
186	Ac-ITF$r8FHWAQL$AEFA-NH_2	195		1913.02	958.12	1914.03	957.52	638.68
187	Ac-ITF$r8FHWAQL$AEFA-NH_2	196	iso2	1913.02	957.86	1914.03	957.52	638.68
188	Ac-ITF$r8EHWAQL$AHFA-NH_2	197		1903.01	952.94	1904.02	952.51	635.34
189	Ac-ITF$r8EHWAQL$AHFA-NH_2	198	iso2	1903.01	953.87	1904.02	952.51	635.34
190	Ac-LTF$r8AHWVQL$AHFA-NH_2	199		1873.04	937.86	1874.05	937.53	625.35
191	Ac-ITF$r8FYWVQL$AHFA-NH_2	200		1975.08	988.83	1976.09	988.55	659.37
192	Ac-ITF$r8EYWVQL$AHFA-NH_2	201		1957.05	979.35	1958.06	979.53	653.36
193	Ac-ITF$r8EHWVQL$AHFA-NH_2	202		1931.05	967	1932.06	966.53	644.69
194	Ac-ITF$r8EHWVQL$AHFA-NH_2	203	iso2	1931.05	967.93	1932.06	966.53	644.69
195	Ac-ETF$r8EYWAAL$SAA-NH_2	204		1690.86	845.85	1691.87	846.44	564.63
196	Ac-LTF$r8AYWVAL$SAA-NH_2	205		1644.93	824.08	1645.94	823.47	549.32
197	Ac-LTF$r8AHWAAL$SAA-NH_2	206		1590.89	796.88	1591.9	796.45	531.3
198	Ac-LTF$r8AEWAAL$SAA-NH_2	207		1582.88	791.9	1583.89	792.45	528.63
199	Ac-LTF$r8AEWAAL$SAA-NH_2	208	iso2	1582.88	791.9	1583.89	792.45	528.63
200	Ac-LTF$r8ASWAAL$SAA-NH_2	209		1540.87	770.74	1541.88	771.44	514.63
201	Ac-LTF$r8ASWAAL$SAA-NH_2	210	iso2	1540.87	770.88	1541.88	771.44	514.63
202	Ac-LTF$r8AYWAAL$AAIa-NH_2	211		1713.99	857.39	1715	858	572.34

	Sequence	SEQ ID NO:	Isomer	Exact Mass	Found Mass	Calc (M+1)/1	Calc (M+2)/2	Calc (M+3)/3
203	Ac-LTF$r8AYWAAL$AAIa-NH_2	212	iso2	1713.99	857.84	1715	858	572.34
204	Ac-LTF$r8AYWAAL$AHFA-NH_2	213		1813.99	907.86	1815	908	605.67
205	Ac-LTF$r8EHWAQL$AHIa-NH_2	214		1869.03	936.1	1870.04	935.52	624.02
206	Ac-LTF$r8EHWAQL$AHIa-NH_2	215	iso2	1869.03	937.03	1870.04	935.52	624.02
207	Ac-LTF$r8AHWAQL$AHIa-NH_2	216		1811.03	906.87	1812.04	906.52	604.68
208	Ac-LTF$r8EYWAQL$AHIa-NH_2	217		1895.04	949.15	1896.05	948.53	632.69
209	Ac-LTF$r8AYWAQL$AAFa-NH_2	218		1804.99	903.2	1806	903.5	602.67
210	Ac-LTF$r8AYWAQL$AAFa-NH_2	219	iso2	1804.99	903.28	1806	903.5	602.67
211	Ac-LTF$r8AYWAQL$AAWa-NH_2	220		1844	922.81	1845.01	923.01	615.67
212	Ac-LTF$r8AYWAQL$AAVa-NH_2	221		1756.99	878.86	1758	879.5	586.67
213	Ac-LTF$r8AYWAQL$AAVa-NH_2	222	iso2	1756.99	879.3	1758	879.5	586.67
214	Ac-LTF$r8AYWAQL$AALa-NH_2	223		1771.01	886.26	1772.02	886.51	591.34
215	Ac-LTF$r8AYWAQL$AALa-NH_2	224	iso2	1771.01	886.33	1772.02	886.51	591.34
216	Ac-LTF$r8EYWAQL$AAIa-NH_2	225		1829.01	914.89	1830.02	915.51	610.68
217	Ac-LTF$r8EYWAQL$AAIa-NH_2	226	iso2	1829.01	915.34	1830.02	915.51	610.68
218	Ac-LTF$r8EYWAQL$AAFa-NH_2	227		1863	932.87	1864.01	932.51	622.01
219	Ac-LTF$r8EYWAQL$AAFa-NH_2	228	iso2	1863	932.87	1864.01	932.51	622.01
220	Ac-LTF$r8EYWAQL$AAVa-NH_2	229		1815	908.23	1816.01	908.51	606.01
221	Ac-LTF$r8EYWAQL$AAVa-NH_2	230	iso2	1815	908.31	1816.01	908.51	606.01
222	Ac-LTF$r8EHWAQL$AAIa-NH_2	231		1803.01	903.17	1804.02	902.51	602.01
223	Ac-LTF$r8EHWAQL$AAIa-NH_2	232	iso2	1803.01	902.8	1804.02	902.51	602.01
224	Ac-LTF$r8EHWAQL$AAWa-NH_2	233		1876	939.34	1877.01	939.01	626.34
225	Ac-LTF$r8EHWAQL$AAWa-NH_2	234	iso2	1876	939.62	1877.01	939.01	626.34
226	Ac-LTF$r8EHWAQL$AALa-NH_2	235		1803.01	902.8	1804.02	902.51	602.01
227	Ac-LTF$r8EHWAQL$AALa-NH_2	236	iso2	1803.01	902.9	1804.02	902.51	602.01
228	Ac-ETF$r8EHWVQL$AALa-NH_2	237		1847	924.82	1848.01	924.51	616.67
229	Ac-LTF$r8AYWAQL$AAAa-NH_2	238		1728.96	865.89	1729.97	865.49	577.33
230	Ac-LTF$r8AYWAQL$AAAa-NH_2	239	iso2	1728.96	865.89	1729.97	865.49	577.33
231	Ac-LTF$r8AYWAQL$AAAibA-NH_2	240		1742.98	872.83	1743.99	872.5	582
232	Ac-LTF$r8AYWAQL$AAAibA-NH_2	241	iso2	1742.98	872.92	1743.99	872.5	582
233	Ac-LTF$r8AYWAQL$AAAAa-NH_2	242		1800	901.42	1801.01	901.01	601.01
234	Ac-LTF$r5AYWAQL$s8AAIa-NH_2	243		1771.01	887.17	1772.02	886.51	591.34
235	Ac-LTF$r5AYWAQL$s8SAA-NH_2	244		1673.92	838.33	1674.93	837.97	558.98
236	Ac-LTF$r8AYWAQCba$AANleA-NH_2	245		1783.01	892.64	1784.02	892.51	595.34
237	Ac-ETF$r8AYWAQCba$AANleA-NH_2	246		1798.97	900.59	1799.98	900.49	600.66
238	Ac-LTF$r8EYWAQCba$AANleA-NH_2	247		1841.01	922.05	1842.02	921.51	614.68
239	Ac-LTF$r8AYWAQCba$AWNleA-NH_2	248		1898.05	950.46	1899.06	950.03	633.69
240	Ac-ETF$r8AYWAQCba$AWNleA-NH_2	249		1914.01	958.11	1915.02	958.01	639.01
241	Ac-LTF$r8EYWAQCba$AWNleA-NH_2	250		1956.06	950.62	1957.07	979.04	653.03
242	Ac-LTF$r8EYWAQCba$SAFA-NH_2	251		1890.99	946.55	1892	946.5	631.34
243	Ac-LTF34F2$r8EYWAQCba$SANleA-NH_2	252		1892.99	947.57	1894	947.5	632
244	Ac-LTF$r8EF4coohWAQCba$SANleA-NH_2	253		1885	943.59	1886.01	943.51	629.34
245	Ac-LTF$r8EYWSQCba$SANleA-NH_2	254		1873	937.58	1874.01	937.51	625.34
246	Ac-LTF$r8EYWWQCba$SANleA-NH_2	255		1972.05	987.61	1973.06	987.03	658.36
247	Ac-LTF$r8EYWAQCba$AAIa-NH_2	256		1841.01	922.05	1842.02	921.51	614.68
248	Ac-LTF34F2$r8EYWAQCba$AAIa-NH_2	257		1876.99	939.99	1878	939.5	626.67
249	Ac-LTF$r8EF4coohWAQCba$AAIa-NH_2	258		1869.01	935.64	1870.02	935.51	624.01
250	Pam-ETF$r8EYWAQCba$SAA-NH_2	259		1956.1	979.57	1957.11	979.06	653.04
251	Ac-LThF$r8EFWAQCba$SAA-NH_2	260		1741.94	872.11	1742.95	871.98	581.65
252	Ac-LTA$r8EYWAQCba$SAA-NH_2	261		1667.89	835.4	1668.9	834.95	556.97
253	Ac-LTF$r8EYAAQCba$SAA-NH_2	262		1628.88	815.61	1629.89	815.45	543.97
254	Ac-LTF$r8EY2NalAQCba$SAA-NH_2	263		1754.93	879.04	1755.94	878.47	585.98
255	Ac-LTF$r8AYWAQCba$SAA-NH_2	264		1685.92	844.71	1686.93	843.97	562.98
256	Ac-LTF$r8EYWAQCba$SAF-NH_2	265		1819.96	911.41	1820.97	910.99	607.66
257	Ac-LTF$r8EYWAQCba$SAFa-NH_2	266		1890.99	947.41	1892	946.5	631.34
258	Ac-LTF$r8AYWAQCba$SAF-NH_2	267		1761.95	882.73	1762.96	881.98	588.32
259	Ac-LTF34F2$r8AYWAQCba$SAF-NH_2	268		1797.93	900.87	1798.94	899.97	600.32
260	Ac-LTF$r8AF4coohWAQCba$SAF-NH_2	269		1789.94	896.43	1790.95	895.98	597.65
261	Ac-LTF$r8EY6clWAQCba$SAF-NH_2	270		1853.92	929.27	1854.93	927.97	618.98
262	Ac-LTF$r8AYWSQCba$SAF-NH_2	271		1777.94	890.87	1778.95	889.98	593.65
263	Ac-LTF$r8AYWWQCba$SAF-NH_2	272		1876.99	939.91	1878	939.5	626.67

	Sequence	SEQ ID NO:	Isomer	Exact Mass	Found Mass	Calc (M+1)/1	Calc (M+2)/2	Calc (M+3)/3
264	Ac-LTF$r8AYWAQCba$AAIa-NH_2	273		1783.01	893.19	1784.02	892.51	595.34
265	Ac-LTF34F2$r8AYWAQCba$AAIa-NH_2	274		1818.99	911.23	1820	910.5	607.34
266	Ac-LTF$r8AY6clWAQCba$AAIa-NH_2	275		1816.97	909.84	1817.98	909.49	606.66
267	Ac-LTF$r8AF4coohWAQCba$AAIa-NH_2	276		1811	906.88	1812.01	906.51	604.67
268	Ac-LTF$r8EYWAQCba$AAFa-NH_2	277		1875	938.6	1876.01	938.51	626.01
269	Ac-LTF$r8EYWAQCba$AAFa-NH_2	278	iso2	1875	938.6	1876.01	938.51	626.01
270	Ac-ETF$r8AYWAQCba$AWNlea-NH_2	279		1914.01	958.42	1915.02	958.01	639.01
271	Ac-LTF$r8EYWAQCba$AWNlea-NH_2	280		1956.06	979.42	1957.07	979.04	653.03
272	Ac-ETF$r8EYWAQCba$AWNlea-NH_2	281		1972.01	987.06	1973.02	987.01	658.34
273	Ac-ETF$r8EYWAQCba$AWNlea-NH_2	282	iso2	1972.01	987.06	1973.02	987.01	658.34
274	Ac-LTF$r8AYWAQCba$SAFa-NH_2	283		1832.99	917.89	1834	917.5	612
275	Ac-LTF$r8AYWAQCba$SAFa-NH_2	284	iso2	1832.99	918.07	1834	917.5	612
276	Ac-ETF$r8AYWAQL$AWNlea-NH_2	285		1902.01	952.22	1903.02	952.01	635.01
277	Ac-LTF$r8EYWAQL$AWNlea-NH_2	286		1944.06	973.5	1945.07	973.04	649.03
278	Ac-ETF$r8EYWAQL$AWNlea-NH_2	287		1960.01	981.46	1961.02	981.01	654.34
279	Dmaac-LTF$r8EYWAQhL$SAA-NH_2	288		1788.98	896.06	1789.99	895.5	597.33
280	Hexac-LTF$r8EYWAQhL$SAA-NH_2	289		1802	902.9	1803.01	902.01	601.67
281	Napac-LTF$r8EYWAQhL$SAA-NH_2	290		1871.99	937.58	1873	937	625
282	Decac-LTF$r8EYWAQhL$SAA-NH_2	291		1858.06	930.55	1859.07	930.04	620.36
283	Admac-LTF$r8EYWAQhL$SAA-NH_2	292		1866.03	934.07	1867.04	934.02	623.02
284	Tmac-LTF$r8EYWAQhL$SAA-NH_2	293		1787.99	895.41	1789	895	597
285	Pam-LTF$r8EYWAQhL$SAA-NH_2	294		1942.16	972.08	1943.17	972.09	648.39
286	Ac-LTF$r8AYWAQCba$AANleA-NH_2	295	iso2	1783.01	892.64	1784.02	892.51	595.34
287	Ac-LTF34F2$r8EYWAQCba$AAIa-NH_2	296	iso2	1876.99	939.62	1878	939.5	626.67
288	Ac-LTF34F2$r8EYWAQCba$SAA-NH_2	297		1779.91	892.07	1780.92	890.96	594.31
289	Ac-LTF34F2$r8EYWAQCba$SAA-NH_2	298	iso2	1779.91	891.61	1780.92	890.96	594.31
290	Ac-LTF$r8EF4coohWAQCba$SAA-NH_2	299		1771.92	887.54	1772.93	886.97	591.65
291	Ac-LTF$r8EF4coohWAQCba$SAA-NH_2	300	iso2	1771.92	887.63	1772.93	886.97	591.65
292	Ac-LTF$r8EYWSQCba$SAA-NH_2	301		1759.92	881.9	1760.93	880.97	587.65
293	Ac-LTF$r8EYWSQCba$SAA-NH_2	302	iso2	1759.92	881.9	1760.93	880.97	587.65
294	Ac-LTF$r8EYWAQhL$SAA-NH_2	303		1745.94	875.05	1746.95	873.98	582.99
295	Ac-LTF$r8AYWAQhL$SAF-NH_2	304		1763.97	884.02	1764.98	882.99	589
296	Ac-LTF$r8AYWAQhL$SAF-NH_2	305	iso2	1763.97	883.56	1764.98	882.99	589
297	Ac-LTF34F2$r8AYWAQhL$SAA-NH_2	306		1723.92	863.67	1724.93	862.97	575.65
298	Ac-LTF34F2$r8AYWAQhL$SAA-NH_2	307	iso2	1723.92	864.04	1724.93	862.97	575.65
299	Ac-LTF$r8AF4coohWAQhL$SAA-NH_2	308		1715.93	859.44	1716.94	858.97	572.98
300	Ac-LTF$r8AF4coohWAQhL$SAA-NH_2	309	iso2	1715.93	859.6	1716.94	858.97	572.98
301	Ac-LTF$r8AYWSQhL$SAA-NH_2	310		1703.93	853.96	1704.94	852.97	568.98
302	Ac-LTF$r8AYWSQhL$SAA-NH_2	311	iso2	1703.93	853.59	1704.94	852.97	568.98
303	Ac-LTF$r8EYWAQL$AANleA-NH_2	312		1829.01	915.45	1830.02	915.51	610.68
304	Ac-LTF34F2$r8AYWAQL$AANleA-NH_2	313		1806.99	904.58	1808	904.5	603.34
305	Ac-LTF$r8AF4coohWAQL$AANleA-NH_2	314		1799	901.6	1800.01	900.51	600.67
306	Ac-LTF$r8AYWSQL$AANleA-NH_2	315		1787	894.75	1788.01	894.51	596.67
307	Ac-LTF34F2$r8AYWAQhL$AANleA-NH_2	316		1821	911.79	1822.01	911.51	608.01
308	Ac-LTF34F2$r8AYWAQhL$AANleA-NH_2	317	iso2	1821	912.61	1822.01	911.51	608.01
309	Ac-LTF$r8AF4coohWAQhL$AANleA-NH_2	318		1813.02	907.95	1814.03	907.52	605.35
310	Ac-LTF$r8AF4coohWAQhL$AANleA-NH_2	319	iso2	1813.02	908.54	1814.03	907.52	605.35
311	Ac-LTF$r8AYWSQhL$AANleA-NH_2	320		1801.02	901.84	1802.03	901.52	601.35
312	Ac-LTF$r8AYWSQhL$AANleA-NH_2	321	iso2	1801.02	902.62	1802.03	901.52	601.35
313	Ac-LTF$r8AYWAQhL$AAAAa-NH_2	322		1814.01	908.63	1815.02	908.01	605.68
314	Ac-LTF$r8AYWAQhL$AAAAa-NH_2	323	iso2	1814.01	908.34	1815.02	908.01	605.68
315	Ac-LTF$r8AYWAQL$AAAAAa-NH_2	324		1871.04	936.94	1872.05	936.53	624.69
316	Ac-LTF$r8AYWAQL$AAAAAAa-NH_2	325	iso2	1942.07	972.5	1943.08	972.04	648.37
317	Ac-LTF$r8AYWAQL$AAAAAAa-NH_2	326	iso1	1942.07	972.5	1943.08	972.04	648.37
318	Ac-LTF$r8EYWAQhL$AANleA-NH_2	327		1843.03	922.54	1844.04	922.52	615.35
319	Ac-AATF$r8AYWAQL$AANleA-NH_2	328		1800	901.39	1801.01	901.01	601.01
320	Ac-LTF$r8AYWAQL$AANleAA-NH_2	329		1842.04	922.45	1843.05	922.03	615.02
321	Ac-ALTF$r8AYWAQL$AANleAA-NH_2	330		1913.08	957.94	1914.09	957.55	638.7
322	Ac-LTF$r8AYWAQCba$AANleAA-NH_2	331		1854.04	928.43	1855.05	928.03	619.02
323	Ac-LTF$r8AYWAQhL$AANleAA-NH_2	332		1856.06	929.4	1857.07	929.04	619.69
324	Ac-LTF$r8EYWAQCba$SAAA-NH_2	333		1814.96	909.37	1815.97	908.49	605.99

	Sequence	SEQ ID NO:	Isomer	Exact Mass	Found Mass	Calc (M+1)/1	Calc (M+2)/2	Calc (M+3)/3
325	Ac-LTF$r8EYWAQCba$SAAA-NH_2	334	iso2	1814.96	909.37	1815.97	908.49	605.99
326	Ac-LTF$r8EYWAQCba$SAAAA-NH_2	335		1886	944.61	1887.01	944.01	629.67
327	Ac-LTF$r8EYWAQCba$SAAAA-NH_2	336	iso2	1886	944.61	1887.01	944.01	629.67
328	Ac-ALTF$r8EYWAQCba$SAA-NH_2	337		1814.96	909.09	1815.97	908.49	605.99
329	Ac-ALTF$r8EYWAQCba$SAAA-NH_2	338		1886	944.61	1887.01	944.01	629.67
330	Ac-ALTF$r8EYWAQCba$SAA-NH_2	339	iso2	1814.96	909.09	1815.97	908.49	605.99
331	Ac-LTF$r8EYWAQL$AAAAAa-NH_2	340	iso2	1929.04	966.08	1930.05	965.53	644.02
332	Ac-LTF$r8EY6clWAQCba$SAA-NH_2	341		1777.89	890.78	1778.9	889.95	593.64
333	Ac-LTF$r8EF4cooh6clWAQCba$SANleA-NH_2	342		1918.96	961.27	1919.97	960.49	640.66
334	Ac-LTF$r8EF4cooh6clWAQCba$SANleA-NH_2	343	iso2	1918.96	961.27	1919.97	960.49	640.66
335	Ac-LTF$r8EF4cooh6clWAQCba$AAIa-NH_2	344		1902.97	953.03	1903.98	952.49	635.33
336	Ac-LTF$r8EF4cooh6clWAQCba$AAIa-NH_2	345	iso2	1902.97	953.13	1903.98	952.49	635.33
337	Ac-LTF$r8AY6clWAQL$AAAAAa-NH_2	346		1905	954.61	1906.01	953.51	636.01
338	Ac-LTF$r8AY6clWAQL$AAAAAa-NH_2	347	iso2	1905	954.9	1906.01	953.51	636.01
339	Ac-F$r8AY6clWEAL$AAAAAAa-NH_2	348		1762.89	883.01	1763.9	882.45	588.64
340	Ac-ETF$r8EYWAQL$AAAAAa-NH_2	349		1945	974.31	1946.01	973.51	649.34
341	Ac-ETF$r8EYWAQL$AAAAAa-NH_2	350	iso2	1945	974.49	1946.01	973.51	649.34
342	Ac-LTF$r8EYWAQL$AAAAAAa-NH_2	351		2000.08	1001.6	2001.09	1001.05	667.7
343	Ac-LTF$r8EYWAQL$AAAAAAa-NH_2	352	iso2	2000.08	1001.6	2001.09	1001.05	667.7
344	Ac-LTF$r8AYWAQL$AANleAAa-NH_2	353		1913.08	958.58	1914.09	957.55	638.7
345	Ac-LTF$r8AYWAQL$AANleAAa-NH_2	354	iso2	1913.08	958.58	1914.09	957.55	638.7
346	Ac-LTF$r8EYWAQCba$AAAAAa-NH_2	355		1941.04	972.55	1942.05	971.53	648.02
347	Ac-LTF$r8EYWAQCba$AAAAAa-NH_2	356	iso2	1941.04	972.55	1942.05	971.53	648.02
348	Ac-LTF$r8EF4coohWAQCba$AAAAAa-NH_2	357		1969.04	986.33	1970.05	985.53	657.35
349	Ac-LTF$r8EF4coohWAQCba$AAAAAa-NH_2	358	iso2	1969.04	986.06	1970.05	985.53	657.35
350	Ac-LTF$r8EYWSQCba$AAAAAa-NH_2	359		1957.04	980.04	1958.05	979.53	653.35
351	Ac-LTF$r8EYWSQCba$AAAAAa-NH_2	360	iso2	1957.04	980.04	1958.05	979.53	653.35
352	Ac-LTF$r8EYWAQCba$SAAa-NH_2	361		1814.96	909	1815.97	908.49	605.99
353	Ac-LTF$r8EYWAQCba$SAAa-NH_2	362	iso2	1814.96	909	1815.97	908.49	605.99
354	Ac-ALTF$r8EYWAQCba$SAAa-NH_2	363		1886	944.52	1887.01	944.01	629.67
355	Ac-ALTF$r8EYWAQCba$SAAa-NH_2	364	iso2	1886	944.98	1887.01	944.01	629.67
356	Ac-ALTF$r8EYWAQCba$SAAAa-NH_2	365		1957.04	980.04	1958.05	979.53	653.35
357	Ac-ALTF$r8EYWAQCba$SAAAa-NH_2	366	iso2	1957.04	980.04	1958.05	979.53	653.35
358	Ac-AALTF$r8EYWAQCba$SAAAa-NH_2	367		2028.07	1016.1	2029.08	1015.04	677.03
359	Ac-AALTF$r8EYWAQCba$SAAAa-NH_2	368	iso2	2028.07	1015.57	2029.08	1015.04	677.03
360	Ac-RTF$r8EYWAQCba$SAA-NH_2	369		1786.94	895.03	1787.95	894.48	596.65
361	Ac-LRF$r8EYWAQCba$SAA-NH_2	370		1798.98	901.51	1799.99	900.5	600.67
362	Ac-LTF$r8EYWRQCba$SAA-NH_2	371		1828.99	916.4	1830	915.5	610.67
363	Ac-LTF$r8EYWARCba$SAA-NH_2	372		1771.97	887.63	1772.98	886.99	591.66
364	Ac-LTF$r8EYWAQCba$RAA-NH_2	373		1812.99	908.08	1814	907.5	605.34
365	Ac-LTF$r8EYWAQCba$SRA-NH_2	374		1828.99	916.12	1830	915.5	610.67
366	Ac-LTF$r8EYWAQCba$SAR-NH_2	375		1828.99	916.12	1830	915.5	610.67
367	5-FAM-BaLTF$r8EYWAQCba$SAA-NH_2	376		2131	1067.09	2132.01	1066.51	711.34
368	5-FAM-BaLTF$r8AYWAQL$AANleA-NH_2	377		2158.08	1080.6	2159.09	1080.05	720.37
369	Ac-LAF$r8EYWAQL$AANleA-NH_2	378		1799	901.05	1800.01	900.51	600.67
370	Ac-ATF$r8EYWAQL$AANleA-NH_2	379		1786.97	895.03	1787.98	894.49	596.66
371	Ac-AAF$r8EYWAQL$AANleA-NH_2	380		1756.96	880.05	1757.97	879.49	586.66
372	Ac-AAAF$r8EYWAQL$AANleA-NH_2	381		1827.99	915.57	1829	915	610.34
373	Ac-AAAAF$r8EYWAQL$AANleA-NH_2	382		1899.03	951.09	1900.04	950.52	634.02
374	Ac-AATF$r8EYWAQL$AANleA-NH_2	383		1858	930.92	1859.01	930.01	620.34
375	Ac-AALTF$r8EYWAQL$AANleA-NH_2	384		1971.09	987.17	1972.1	986.55	658.04
376	Ac-AAALTF$r8EYWAQL$AANleA-NH_2	385		2042.12	1023.15	2043.13	1022.07	681.71
377	Ac-LTF$r8EYWAQL$AANleAA-NH_2	386		1900.05	952.02	1901.06	951.03	634.36
378	Ac-ALTF$r8EYWAQL$AANleAA-NH_2	387		1971.09	987.63	1972.1	986.55	658.04
379	Ac-AALTF$r8EYWAQL$AANleAA-NH_2	388		2042.12	1022.69	2043.13	1022.07	681.71
380	Ac-LTF$r8EYWAQCba$AANleAA-NH_2	389		1912.05	958.03	1913.06	957.03	638.36
381	Ac-LTF$r8EYWAQhL$AANleAA-NH_2	390		1914.07	958.68	1915.08	958.04	639.03
382	Ac-ALTF$r8EYWAQhL$AANleAA-NH_2	391		1985.1	994.1	1986.11	993.56	662.71
383	Ac-LTF$r8ANmYWAQL$AANleA-NH_2	392		1785.02	894.11	1786.03	893.52	596.01
384	Ac-LTF$r8ANmYWAQL$AANleA-NH_2	393	iso2	1785.02	894.11	1786.03	893.52	596.01
385	Ac-LTF$r8AYNmWAQL$AANleA-NH_2	394		1785.02	894.11	1786.03	893.52	596.01

	Sequence	SEQ ID NO:	Isomer	Exact Mass	Found Mass	Calc (M+1)/1	Calc (M+2)/2	Calc (M+3)/3
386	Ac-LTF$r8AYNmWAQL$AANleA-NH_2	395	iso2	1785.02	894.11	1786.03	893.52	596.01
387	Ac-LTF$r8AYAmwAQL$AANleA-NH_2	396		1785.02	894.01	1786.03	893.52	596.01
388	Ac-LTF$r8AYAmwAQL$AANleA-NH_2	397	iso2	1785.02	894.01	1786.03	893.52	596.01
389	Ac-LTF$r8AYWAibQL$AANleA-NH_2	398		1785.02	894.01	1786.03	893.52	596.01
390	Ac-LTF$r8AYWAibQL$AANleA-NH_2	399	iso2	1785.02	894.01	1786.03	893.52	596.01
391	Ac-LTF$r8AYWAQL$AAibNleA-NH_2	400		1785.02	894.38	1786.03	893.52	596.01
392	Ac-LTF$r8AYWAQL$AAibNleA-NH_2	401	iso2	1785.02	894.38	1786.03	893.52	596.01
393	Ac-LTF$r8AYWAQL$AaNleA-NH_2	402		1771.01	887.54	1772.02	886.51	591.34
394	Ac-LTF$r8AYWAQL$AaNleA-NH_2	403	iso2	1771.01	887.54	1772.02	886.51	591.34
395	Ac-LTF$r8AYWAQL$ASarNleA-NH_2	404		1771.01	887.35	1772.02	886.51	591.34
396	Ac-LTF$r8AYWAQL$ASarNleA-NH_2	405	iso2	1771.01	887.35	1772.02	886.51	591.34
397	Ac-LTF$r8AYWAQL$AANleAib-NH_2	406		1785.02	894.75	1786.03	893.52	596.01
398	Ac-LTF$r8AYWAQL$AANleAib-NH_2	407	iso2	1785.02	894.75	1786.03	893.52	596.01
399	Ac-LTF$r8AYWAQL$AANleNmA-NH_2	408		1785.02	894.6	1786.03	893.52	596.01
400	Ac-LTF$r8AYWAQL$AANleNmA-NH_2	409	iso2	1785.02	894.6	1786.03	893.52	596.01
401	Ac-LTF$r8AYWAQL$AANleSar-NH_2	410		1771.01	886.98	1772.02	886.51	591.34
402	Ac-LTF$r8AYWAQL$AANleSar-NH_2	411	iso2	1771.01	886.98	1772.02	886.51	591.34
403	Ac-LTF$r8AYWAQL$AANleAAib-NH_2	412		1856.06		1857.07	929.04	619.69
404	Ac-LTF$r8AYWAQL$AANleAAib-NH_2	413	iso2	1856.06		1857.07	929.04	619.69
405	Ac-LTF$r8AYWAQL$AANleANmA-NH_2	414		1856.06	930.37	1857.07	929.04	619.69
406	Ac-LTF$r8AYWAQL$AANleANmA-NH_2	415	iso2	1856.06	930.37	1857.07	929.04	619.69
407	Ac-LTF$r8AYWAQL$AANleAa-NH_2	416		1842.04	922.69	1843.05	922.03	615.02
408	Ac-LTF$r8AYWAQL$AANleAa-NH_2	417	iso2	1842.04	922.69	1843.05	922.03	615.02
409	Ac-LTF$r8AYWAQL$AANleASar-NH_2	418		1842.04	922.6	1843.05	922.03	615.02
410	Ac-LTF$r8AYWAQL$AANleASar-NH_2	419	iso2	1842.04	922.6	1843.05	922.03	615.02
411	Ac-LTF$/r8AYWAQL$/AANleA-NH_2	420		1799.04	901.14	1800.05	900.53	600.69
412	Ac-LTFAibAYWAQLAibAANleA-NH_2	421		1648.9	826.02	1649.91	825.46	550.64
413	Ac-LTF$r8Cou4YWAQL$AANleA-NH_2	422		1975.05	989.11	1976.06	988.53	659.36
414	Ac-LTF$r8Cou4YWAQL$AANleA-NH_2	423	iso2	1975.05	989.11	1976.06	988.53	659.36
415	Ac-LTF$r8AYWCou4QL$AANleA-NH_2	424		1975.05	989.11	1976.06	988.53	659.36
416	Ac-LTF$r8AYWAQL$Cou4ANleA-NH_2	425		1975.05	989.57	1976.06	988.53	659.36
417	Ac-LTF$r8AYWAQL$Cou4ANleA-NH_2	426	iso2	1975.05	989.57	1976.06	988.53	659.36
418	Ac-LTF$r8AYWAQL$ACou4NleA-NH_2	427		1975.05	989.57	1976.06	988.53	659.36
419	Ac-LTF$r8AYWAQL$ACou4NleA-NH_2	428	iso2	1975.05	989.57	1976.06	988.53	659.36
420	Ac-LTF$r8AYWAQL$AANleA-OH	429		1771.99	887.63	1773	887	591.67
421	Ac-LTF$r8AYWAQL$AANleA-OH	430	iso2	1771.99	887.63	1773	887	591.67
422	Ac-LTF$r8AYWAQL$AANleA-NHnPr	431		1813.05	908.08	1814.06	907.53	605.36
423	Ac-LTF$r8AYWAQL$AANleA-NHnPr	432	iso2	1813.05	908.08	1814.06	907.53	605.36
424	Ac-LTF$r8AYWAQL$AANleA-NHnBu33Me	433		1855.1	929.17	1856.11	928.56	619.37
425	Ac-LTF$r8AYWAQL$AANleA-NHnBu33Me	434	iso2	1855.1	929.17	1856.11	928.56	619.37
426	Ac-LTF$r8AYWAQL$AANleA-NHHex	435		1855.1	929.17	1856.11	928.56	619.37
427	Ac-LTF$r8AYWAQL$AANleA-NHHex	436	iso2	1855.1	929.17	1856.11	928.56	619.37
428	Ac-LTA$r8AYWAQL$AANleA-NH_2	437		1694.98	849.33	1695.99	848.5	566
429	Ac-LThL$r8AYWAQL$AANleA-NH_2	438		1751.04	877.09	1752.05	876.53	584.69
430	Ac-LTF$r8AYAAQL$AANleA-NH_2	439		1655.97	829.54	1656.98	828.99	553
431	Ac-LTF$r8AY2NalAQL$AANleA-NH_2	440		1782.01	892.63	1783.02	892.01	595.01
432	Ac-LTF$r8EYWCou4QCba$SAA-NH_2	441		1947.97	975.8	1948.98	974.99	650.33
433	Ac-LTF$r8EYWCou7QCba$SAA-NH_2	442		16.03	974.9	17.04	9.02	6.35
434	Ac-LTF%r8EYWAQCba%SAA-NH_2	443		1745.94	874.8	1746.95	873.98	582.99
435	Dmaac-LTF$r8EYWAQCba$SAA-NH_2	444		1786.97	894.8	1787.98	894.49	596.66
436	Dmaac-LTF$r8AYWAQL$AAAAAa-NH_2	445		1914.08	958.2	1915.09	958.05	639.03
437	Dmaac-LTF$r8AYWAQL$AAAAAa-NH_2	446	iso2	1914.08	958.2	1915.09	958.05	639.03
438	Dmaac-LTF$r8EYWAQL$AAAAAa-NH_2	447		1972.08	987.3	1973.09	987.05	658.37
439	Dmaac-LTF$r8EYWAQL$AAAAAa-NH_2	448	iso2	1972.08	987.3	1973.09	987.05	658.37
440	Dmaac-LTF$r8EF4coohWAQCba$AAIa-NH_2	449		1912.05	957.4	1913.06	957.03	638.36
441	Dmaac-LTF$r8EF4coohWAQCba$AAIa-NH_2	450	iso2	1912.05	957.4	1913.06	957.03	638.36
442	Dmaac-LTF$r8AYWAQL$AANleA-NH_2	451		1814.05	908.3	1815.06	908.03	605.69
443	Dmaac-LTF$r8AYWAQL$AANleA-NH_2	452	iso2	1814.05	908.3	1815.06	908.03	605.69
444	Ac-LTF%r8AYWAQL%AANleA-NH_2	453		1773.02	888.37	1774.03	887.52	592.01
445	Ac-LTF%r8EYWAQL%AAAAAa-NH_2	454		1931.06	966.4	1932.07	966.54	644.69
446	Cou6BaLTF$r8EYWAQhL$SAA-NH_2	455		2018.05	1009.9	2019.06	1010.03	673.69

	Sequence	SEQ ID NO:	Isomer	Exact Mass	Found Mass	Calc (M+1)/1	Calc (M+2)/2	Calc (M+3)/3
447	Cou8BaLTF$r8EYWAQhL$SAA-NH_2	456		1962.96	982.34	1963.97	982.49	655.32
448	Ac-LTF4I$r8EYWAQL$AAAAAa-NH_2	457		2054.93	1028.68	2055.94	1028.47	685.98
449	Ac-LTF$r8EYWAQL$AAAAAa-NH_2	458		1929.04	966.17	1930.05	965.53	644.02
550	Ac-LTF$r8EYWAQL$AAAAAa-OH	459		1930.02	966.54	1931.03	966.02	644.35
551	Ac-LTF$r8EYWAQL$AAAAAa-OH	460	iso2	1930.02	965.89	1931.03	966.02	644.35
552	Ac-LTF$r8EYWAEL$AAAAAa-NH_2	461		1930.02	966.82	1931.03	966.02	644.35
553	Ac-LTF$r8EYWAEL$AAAAAa-NH_2	462	iso2	1930.02	966.91	1931.03	966.02	644.35
554	Ac-LTF$r8EYWAEL$AAAAAa-OH	463		1931.01	967.28	1932.02	966.51	644.68
555	Ac-LTF$r8EY6clWAQL$AAAAAa-NH_2	464		1963	983.28	1964.01	982.51	655.34
556	Ac-LTF$r8EF4bOH2WAQL$AAAAAa-NH_2	465		1957.05	980.04	1958.06	979.53	653.36
557	Ac-AAALTF$r8EYWAQL$AAAAAa-NH_2	466		2142.15	1072.83	2143.16	1072.08	715.06
558	Ac-LTF34F2$r8EYWAQL$AAAAAa-NH_2	467		1965.02	984.3	1966.03	983.52	656.01
559	Ac-RTF$r8EYWAQL$AAAAAa-NH_2	468		1972.06	987.81	1973.07	987.04	658.36
560	Ac-LTA$r8EYWAQL$AAAAAa-NH_2	469		1853.01	928.33	1854.02	927.51	618.68
561	Ac-LTF$r8EYWAibQL$AAAAAa-NH_2	470		1943.06	973.48	1944.07	972.54	648.69
562	Ac-LTF$r8EYWAQL$AAibAAAa-NH_2	471		1943.06	973.11	1944.07	972.54	648.69
563	Ac-LTF$r8EYWAQL$AAAibAAa-NH_2	472		1943.06	973.48	1944.07	972.54	648.69
564	Ac-LTF$r8EYWAQL$AAAAibAa-NH_2	473		1943.06	973.48	1944.07	972.54	648.69
565	Ac-LTF$r8EYWAQL$AAAAAiba-NH_2	474		1943.06	973.38	1944.07	972.54	648.69
566	Ac-LTF$r8EYWAQL$AAAAAiba-NH_2	475	iso2	1943.06	973.38	1944.07	972.54	648.69
567	Ac-LTF$r8EYWAQL$AAAAAAib-NH_2	476		1943.06	973.01	1944.07	972.54	648.69
568	Ac-LTF$r8EYWAQL$AaAAAa-NH_2	477		1929.04	966.54	1930.05	965.53	644.02
569	Ac-LTF$r8EYWAQL$AAaAAa-NH_2	478		1929.04	966.35	1930.05	965.53	644.02
570	Ac-LTF$r8EYWAQL$AAAaAa-NH_2	479		1929.04	966.54	1930.05	965.53	644.02
571	Ac-LTF$r8EYWAQL$AAAaAa-NH_2	480	iso2	1929.04	966.35	1930.05	965.53	644.02
572	Ac-LTF$r8EYWAQL$AAAAaa-NH_2	481		1929.04	966.35	1930.05	965.53	644.02
573	Ac-LTF$r8EYWAQL$AAAAAA-NH_2	482		1929.04	966.35	1930.05	965.53	644.02
574	Ac-LTF$r8EYWAQL$ASarAAAa-NH_2	483		1929.04	966.54	1930.05	965.53	644.02
575	Ac-LTF$r8EYWAQL$AASarAAa-NH_2	484		1929.04	966.35	1930.05	965.53	644.02
576	Ac-LTF$r8EYWAQL$AAASarAa-NH_2	485		1929.04	966.35	1930.05	965.53	644.02
577	Ac-LTF$r8EYWAQL$AAAASara-NH_2	486		1929.04	966.35	1930.05	965.53	644.02
578	Ac-LTF$r8EYWAQL$AAAAASar-NH_2	487		1929.04	966.08	1930.05	965.53	644.02
579	Ac-7LTF$r8EYWAQL$AAAAAa-NH_2	488		1918.07	951.99	1919.08	960.04	640.37
581	Ac-TF$r8EYWAQL$AAAAAa-NH_2	489		1815.96	929.85	1816.97	908.99	606.33
582	Ac-F$r8EYWAQL$AAAAAa-NH_2	490		1714.91	930.92	1715.92	858.46	572.64
583	Ac-LVF$r8EYWAQL$AAAAAa-NH_2	491		1927.06	895.12	1928.07	964.54	643.36
584	Ac-AAF$r8EYWAQL$AAAAAa-NH_2	492		1856.98	859.51	1857.99	929.5	620
585	Ac-LTF$r8EYWAQL$AAAAa-NH_2	493		1858	824.08	1859.01	930.01	620.34
586	Ac-LTF$r8EYWAQL$AAAa-NH_2	494		1786.97	788.56	1787.98	894.49	596.66
587	Ac-LTF$r8EYWAQL$AAa-NH_2	495		1715.93	1138.57	1716.94	858.97	572.98
588	Ac-LTF$r8EYWAQL$Aa-NH_2	496		1644.89	1144.98	1645.9	823.45	549.3
589	Ac-LTF$r8EYWAQL$a-NH_2	497		1573.85	1113.71	1574.86	787.93	525.62
590	Ac-LTF$r8EYWAQL$AAA-OH	498		1716.91	859.55	1717.92	859.46	573.31
591	Ac-LTF$r8EYWAQL$A-OH	499		1574.84	975.14	1575.85	788.43	525.95
592	Ac-LTF$r8EYWAQL$AAA-NH_2	500		1715.93	904.75	1716.94	858.97	572.98
593	Ac-LTF$r8EYWAQCba$SAA-OH	501		1744.91	802.49	1745.92	873.46	582.64
594	Ac-LTF$r8EYWAQCba$S-OH	502		1602.83	913.53	1603.84	802.42	535.28
595	Ac-LTF$r8EYWAQCba$S-NH_2	503		1601.85	979.58	1602.86	801.93	534.96
596	4-FBzl-LTF$r8EYWAQL$AAAAAa-NH_2	504		2009.05	970.52	2010.06	1005.53	670.69
597	4-FBzl-LTF$r8EYWAQCba$SAA-NH_2	505		1823.93	965.8	1824.94	912.97	608.98
598	Ac-LTF$r8RYWAQL$AAAAAa-NH_2	506		1956.1	988.28	1957.11	979.06	653.04
599	Ac-LTF$r8HYWAQL$AAAAAa-NH_2	507		1937.06	1003.54	1938.07	969.54	646.69
600	Ac-LTF$r8QYWAQL$AAAAAa-NH_2	508		1928.06	993.92	1929.07	965.04	643.69
601	Ac-LTF$r8CitYWAQL$AAAAAa-NH_2	509		1957.08	987	1958.09	979.55	653.37
602	Ac-LTF$r8GlaYWAQL$AAAAAa-NH_2	510		1973.03	983	1974.04	987.52	658.68
603	Ac-LTF$r8F4gYWAQL$AAAAAa-NH_2	511		2004.1	937.86	2005.11	1003.06	669.04
604	Ac-LTF$r82mRYWAQL$AAAAAa-NH_2	512		1984.13	958.58	1985.14	993.07	662.38
605	Ac-LTF$r8ipKYWAQL$AAAAAa-NH_2	513		1970.14	944.52	1971.15	986.08	657.72
606	Ac-LTF$r8F4$NH_2$YWAQL$AAAAAa-NH_2	514		1962.08	946	1963.09	982.05	655.03
607	Ac-LTF$r8EYWAAL$AAAAAa-NH_2	515		1872.02	959.32	1873.03	937.02	625.01
608	Ac-LTF$r8EYWALL$AAAAAa-NH_2	516		1914.07	980.88	1915.08	958.04	639.03

	Sequence	SEQ ID NO:	Isomer	Exact Mass	Found Mass	Calc (M+1)/1	Calc (M+2)/2	Calc (M+3)/3
609	Ac-LTF$r8EYWAAibL$AAAAAa-NH_2	517		1886.03	970.61	1887.04	944.02	629.68
610	Ac-LTF$r8EYWASL$AAAAAa-NH_2	518		1888.01	980.51	1889.02	945.01	630.34
611	Ac-LTF$r8EYWANL$AAAAAa-NH_2	519		1915.02	1006.41	1916.03	958.52	639.35
612	Ac-LTF$r8EYWACitL$AAAAAa-NH_2	520		1958.07		1959.08	980.04	653.7
613	Ac-LTF$r8EYWAHL$AAAAAa-NH_2	521		1938.04	966.24	1939.05	970.03	647.02
614	Ac-LTF$r8EYWARL$AAAAAa-NH_2	522		1957.08		1958.09	979.55	653.37
615	Ac-LTF$r8EpYWAQL$AAAAAa-NH_2	523		2009.01		2010.02	1005.51	670.68
616	Cbm-LTF$r8EYWAQCba$SAA-NH_2	524		1590.85		1591.86	796.43	531.29
617	Cbm-LTF$r8EYWAQL$AAAAAa-NH_2	525		1930.04		1931.05	966.03	644.35
618	Ac-LTF$r8EYWAQL$SAAAAa-NH_2	526		1945.04	1005.11	1946.05	973.53	649.35
619	Ac-LTF$r8EYWAQL$AAAASa-NH_2	527		1945.04	986.52	1946.05	973.53	649.35
620	Ac-LTF$r8EYWAQL$SAAASa-NH_2	528		1961.03	993.27	1962.04	981.52	654.68
621	Ac-LTF$r8EYWAQTba$AAAAAa-NH_2	529		1943.06	983.1	1944.07	972.54	648.69
622	Ac-LTF$r8EYWAQAdm$AAAAAa-NH_2	530		2007.09	990.31	2008.1	1004.55	670.04
623	Ac-LTF$r8EYWAQCha$AAAAAa-NH_2	531		1969.07	987.17	1970.08	985.54	657.36
624	Ac-LTF$r8EYWAQhCha$AAAAAa-NH_2	532		1983.09	1026.11	1984.1	992.55	662.04
625	Ac-LTF$r8EYWAQF$AAAAAa-NH_2	533		1963.02	957.01	1964.03	982.52	655.35
626	Ac-LTF$r8EYWAQhF$AAAAAa-NH_2	534		1977.04	1087.81	1978.05	989.53	660.02
627	Ac-LTF$r8EYWAQL$AANleAAa-NH_2	535		1971.09	933.45	1972.1	986.55	658.04
628	Ac-LTF$r8EYWAQAdm$AANleAAa-NH_2	536		2049.13	1017.97	2050.14	1025.57	684.05
629	4-FBz-BaLTF$r8EYWAQL$AAAAAa-NH_2	537		2080.08		2081.09	1041.05	694.37
630	4-FBz-BaLTF$r8EYWAQCba$SAA-NH_2	538		1894.97		1895.98	948.49	632.66
631	Ac-LTF$r5EYWAQL$s8AAAAAa-NH_2	539		1929.04	1072.68	1930.05	965.53	644.02
632	Ac-LTF$r5EYWAQCba$s8SAA-NH_2	540		1743.92	1107.79	1744.93	872.97	582.31
633	Ac-LTF$r8EYWAQL$AAhhLAAa-NH_2	541		1999.12		2000.13	1000.57	667.38
634	Ac-LTF$r8EYWAQL$AAAAAAAa-NH_2	542		2071.11		2072.12	1036.56	691.38
635	Ac-LTF$r8EYWAQL$AAAAAAAAa-NH_2	543		2142.15	778.1	2143.16	1072.08	715.06
636	Ac-LTF$r8EYWAQL$AAAAAAAAAa-NH_2	544		2213.19	870.53	2214.2	1107.6	738.74
637	Ac-LTA$r8EYAAQCba$SAA-NH_2	545		1552.85		1553.86	777.43	518.62
638	Ac-LTA$r8EYAAQL$AAAAAa-NH_2	546		1737.97	779.45	1738.98	869.99	580.33
639	Ac-LTF$r8EPmpWAQL$AAAAAa-NH_2	547		2007.03	779.54	2008.04	1004.52	670.02
640	Ac-LTF$r8EPmpWAQCba$SAA-NH_2	548		1821.91	838.04	1822.92	911.96	608.31
641	Ac-ATF$r8HYWAQL$S-NH_2	549		1555.82	867.83	1556.83	778.92	519.61
642	Ac-LTF$r8HAWAQL$S-NH_2	550		1505.84	877.91	1506.85	753.93	502.95
643	Ac-LTF$r8HYWAQA$S-NH_2	551		1555.82	852.52	1556.83	778.92	519.61
644	Ac-LTF$r8EYWAQCba$SA-NH_2	552		1672.89	887.18	1673.9	837.45	558.64
645	Ac-LTF$r8EYWAQL$SAA-NH_2	553		1731.92	873.32	1732.93	866.97	578.31
646	Ac-LTF$r8HYWAQCba$SAA-NH_2	554		1751.94	873.05	1752.95	876.98	584.99
647	Ac-LTF$r8SYWAQCba$SAA-NH_2	555		1701.91	844.88	1702.92	851.96	568.31
648	Ac-LTF$r8RYWAQCba$SAA-NH_2	556		1770.98	865.58	1771.99	886.5	591.33
649	Ac-LTF$r8KYWAQCba$SAA-NH_2	557		1742.98	936.57	1743.99	872.5	582
650	Ac-LTF$r8QYWAQCba$SAA-NH_2	558		1742.94	930.93	1743.95	872.48	581.99
651	Ac-LTF$r8EYWAACba$SAA-NH_2	559		1686.9	1032.45	1687.91	844.46	563.31
652	Ac-LTF$r8EYWAQCba$AAA-NH_2	560		1727.93	895.46	1728.94	864.97	576.98
653	Ac-LTF$r8EYWAQL$AAAAA-OH	561		1858.99	824.54	1860	930.5	620.67
654	Ac-LTF$r8EYWAQL$AAAA-OH	562		1787.95	894.48	1788.96	894.98	596.99
655	Ac-LTF$r8EYWAQL$AA-OH	563		1645.88	856	1646.89	823.95	549.63
656	Ac-LTF$r8AF4bOH2WAQL$AAAAAa-NH_2	564						
657	Ac-LTF$r8AF4bOH2WAAL$AAAAAa-NH_2	565						
658	Ac-LTF$r8EF4bOH2WAQCba$SAA-NH_2	566						
659	Ac-LTF$r8ApYWAQL$AAAAAa-NH_2	567						
660	Ac-LTF$r8ApYWAAL$AAAAAa-NH_2	568						
661	Ac-LTF$r8EpYWAQCba$SAA-NH_2	569						
662	Ac-LTF$rda6AYWAQL$da5AAAAAa-NH_2	570		1974.06	934.44			
663	Ac-LTF$rda6EYWAQCba$da5SAA-NH_2	571		1846.95	870.52		869.94	
664	Ac-LTF$rda6EYWAQL$da5AAAAAa-NH_2	572						
665	Ac-LTF$ra9EYWAQL$a6AAAAAa-NH_2	573			936.57		935.51	
666	Ac-LTF$ra9EYWAQL$a6AAAAAa-NH_2	574						
667	Ac-LTF$ra9EYWAQCba$a6SAA-NH_2	575						
668	Ac-LTA$ra9EYWAQCba$a6SAA-NH_2	576						
669	5-FAM-BaLTF$ra9EYWAQCba$a6SAA-NH_2	577						

	Sequence	SEQ ID NO:	Isomer	Exact Mass	Found Mass	Calc (M+1)/1	Calc (M+2)/2	Calc (M+3)/3
670	5-FAM-BaLTF$r8EYWAQL$AAAAAa-NH_2	578		2316.11				
671	5-FAM-BaLTF$/r8EYWAQL$/AAAAAa-NH_2	579		2344.15				
672	5-FAM-BaLTA$r8EYWAQL$AAAAAa-NH_2	580		2240.08				
673	5-FAM-BaLTF$r8AYWAQL$AAAAAa-NH_2	581		2258.11				
674	5-FAM-BaATF$r8EYWAQL$AAAAAa-NH_2	582		2274.07				
675	5-FAM-BaLAF$r8EYWAQL$AAAAAa-NH_2	583		2286.1				
676	5-FAM-BaLTF$r8EAWAQL$AAAAAa-NH_2	584		2224.09				
677	5-FAM-BaLTF$r8EYAAQL$AAAAAa-NH_2	585		2201.07				
678	5-FAM-BaLTA$r8EYAAQL$AAAAAa-NH_2	586		2125.04				
679	5-FAM-BaLTF$r8EYWAAL$AAAAAa-NH_2	587		2259.09				
680	5-FAM-BaLTF$r8EYWAQA$AAAAAa-NH_2	588		2274.07				
681	5-FAM-BaLTF$/r8EYWAQCba$/SAA-NH_2	589		2159.03				
682	5-FAM-BaLTA$r8EYWAQCba$SAA-NH_2	590		2054.97				
683	5-FAM-BaLTF$r8EYAAQCba$SAA-NH_2	591		2015.96				
684	5-FAM-BaLTA$r8EYAAQCba$SAA-NH_2	592		1939.92				
685	5-FAM-BaQSQQTF$r8NLWRLL$QN-NH_2	593		2495.23				
686	5-TAMRA-BaLTF$r8EYWAQCba$SAA-NH_2	594		2186.1				
687	5-TAMRA-BaLTA$r8EYWAQCba$SAA-NH_2	595		2110.07				
688	5-TAMRA-BaLTF$r8EYAAQCba$SAA-NH_2	596		2071.06				
689	5-TAMRA-BaLTA$r8EYAAQCba$SAA-NH_2	597		1995.03				
690	5-TAMRA-BaLTF$/r8EYWAQCba$/SAA-NH_2	598		2214.13				
691	5-TAMRA-BaLTF$r8EYWAQL$AAAAAa-NH_2	599		2371.22				
692	5-TAMRA-BaLTA$r8EYWAQL$AAAAAa-NH_2	600		2295.19				
693	5-TAMRA-BaLTF$/r8EYWAQL$/AAAAAa-NH_2	601		2399.25				
694	Ac-LTF$r8EYWCou7QCba$SAA-OH	602		1947.93				
695	Ac-LTF$r8EYWCou7QCba$S-OH	603		1805.86				
696	Ac-LTA$r8EYWCou7QCba$SAA-NH_2	604		1870.91				
697	Ac-LTF$r8EYACou7QCba$SAA-NH_2	605		1831.9				
698	Ac-LTA$r8EYACou7QCba$SAA-NH_2	606		1755.87				
699	Ac-LTF$/r8EYWCou7QCba$/SAA-NH_2	607		1974.98				
700	Ac-LTF$r8EYWCou7QL$AAAAAa-NH_2	608		2132.06				
701	Ac-LTF$/r8EYWCou7QL$/AAAAAa-NH_2	609		2160.09				
702	Ac-LTF$r8EYWCou7QL$AAAAA-OH	610		2062.01				
703	Ac-LTF$r8EYWCou7QL$AAAA-OH	611		1990.97				
704	Ac-LTF$r8EYWCou7QL$AAA-OH	612		1919.94				
705	Ac-LTF$r8EYWCou7QL$AA-OH	613		1848.9				
706	Ac-LTF$r8EYWCou7QL$A-OH	614		1777.86				
707	Ac-LTF$r8EYWAQL$AAAASa-NH_2	615	iso2		974.4		973.53	
708	Ac-LTF$r8AYWAAL$AAAAAa-NH_2	616	iso2	1814.01	908.82	1815.02	908.01	605.68
709	Biotin-BaLTF$r8EYWAQL$AAAAAa-NH_2	617		2184.14	1093.64	2185.15	1093.08	729.05
710	Ac-LTF$r8HAWAQL$S-NH_2	618	iso2	1505.84	754.43	1506.85	753.93	502.95
711	Ac-LTF$r8EYWAQCba$SA-NH_2	619	iso2	1672.89	838.05	1673.9	837.45	558.64
712	Ac-LTF$r8HYWAQCba$SAA-NH_2	620	iso2	1751.94	877.55	1752.95	876.98	584.99
713	Ac-LTF$r8SYWAQCba$SAA-NH_2	621	iso2	1701.91	852.48	1702.92	851.96	568.31
714	Ac-LTF$r8RYWAQCba$SAA-NH_2	622	iso2	1770.98	887.45	1771.99	886.5	591.33
715	Ac-LTF$r8KYWAQCba$SAA-NH_2	623	iso2	1742.98	872.92	1743.99	872.5	582
716	Ac-LTF$r8EYWAQCba$AAA-NH_2	624	iso2	1727.93	865.71	1728.94	864.97	576.98
717	Ac-LTF$r8EYWAQL$AAAAAaBaC-NH_2	625		2103.09	1053.12	2104.1	1052.55	702.04
718	Ac-LTF$r8EYWAQL$AAAAAadPeg4C-NH_2	626		2279.19	1141.46	2280.2	1140.6	760.74
719	Ac-LTA$r8AYWAAL$AAAAAa-NH_2	627		1737.98	870.43	1738.99	870	580.33
720	Ac-LTF$r8AYAAAL$AAAAAa-NH_2	628		1698.97	851	1699.98	850.49	567.33
721	5-FAM-BaLTF$r8AYWAAL$AAAAAa-NH_2	629		2201.09	1101.87	2202.1	1101.55	734.7
722	Ac-LTA$r8AYWAQL$AAAAAa-NH_2	630		1795	898.92	1796.01	898.51	599.34
723	Ac-LTF$r8AYAAQL$AAAAAa-NH_2	631		1755.99	879.49	1757	879	586.34
724	Ac-LTF$rda6AYWAAL$da5AAAAAa-NH_2	632		1807.97		1808.98	904.99	603.66
725	FITC-BaLTF$r8EYWAQL$AAAAAa-NH_2	633		2347.1	1174.49	2348.11	1174.56	783.37
726	FITC-BaLTF$r8EYWAQCba$SAA-NH_2	634		2161.99	1082.35	2163	1082	721.67
733	Ac-LTF$r8EYWAQL$EAAAAa-NH_2	635		1987.05	995.03	1988.06	994.53	663.36
734	Ac-LTF$r8AYWAQL$EAAAAa-NH_2	636		1929.04	966.35	1930.05	965.53	644.02
735	Ac-LTF$r8EYWAQL$AAAAAaBaKbio-NH_2	637		2354.25	1178.47	2355.26	1178.13	785.76
736	Ac-LTF$r8AYWAAL$AAAAAa-NH_2	638		1814.01	908.45	1815.02	908.01	605.68

	Sequence	SEQ ID NO:	Isomer	Exact Mass	Found Mass	Calc (M+1)/1	Calc (M+2)/2	Calc (M+3)/3
737	Ac-LTF$r8AYAAAL$AAAAAa-NH_2	639	iso2	1698.97	850.91	1699.98	850.49	567.33
738	Ac-LTF$r8AYAAQL$AAAAAa-NH_2	640	iso2	1755.99	879.4	1757	879	586.34
739	Ac-LTF$r8EYWAQL$EAAAAa-NH_2	641	iso2	1987.05	995.21	1988.06	994.53	663.36
740	Ac-LTF$r8AYWAQL$EAAAAa-NH_2	642	iso2	1929.04	966.08	1930.05	965.53	644.02
741	Ac-LTF$r8EYWAQCba$SAAAAa-NH_2	643		1957.04	980.04	1958.05	979.53	653.35
742	Ac-LTF$r8EYWAQLStAAA$r5AA-NH_2	644		2023.12	1012.83	2024.13	1012.57	675.38
743	Ac-LTF$r8EYWAQL$AAAAA-NH_2	645		2108.17	1055.44	2109.18	1055.09	703.73
744	Ac-LTF$r8EYWAQL$AAAAAA-NH_2	646		2179.21	1090.77	2180.22	1090.61	727.41
745	Ac-LTF$r8EYWAQL$AAAAAAA-NH_2	647		2250.25	1126.69	2251.26	1126.13	751.09
746	Ac-AAALTF$r8EYWAQL$AAA-OH	648		1930.02		1931.03	966.02	644.35
747	Ac-AAALTF$r8EYWAQL$AAA-NH_2	649		1929.04	965.85	1930.05	965.53	644.02
748	Ac-AAAALTF$r8EYWAQL$AAA-NH_2	650		2000.08	1001.4	2001.09	1001.05	667.7
749	Ac-AAAAALTF$r8EYWAQL$AAA-NH_2	651		2071.11	1037.13	2072.12	1036.56	691.38
750	Ac-AAAAAALTF$r8EYWAQL$AAA-NH_2	652		2142.15		2143.16	1072.08	715.06
751	Ac-LTF$rda6EYWAQCba$da6SAA-NH_2	653	iso2	1751.89	877.36	1752.9	876.95	584.97
752	Ac-t$r5wya$r5f4CF3ekllr-NH_2	654			844.25			
753	Ac-tawy$r5nf4CF3e$r5llr-NH_2	655			837.03			
754	Ac-tawya$r5f4CF3ek$r5lr-NH_2	656			822.97			
755	Ac-tawyanf4CF3e$r5llr$r5a-NH_2	657			908.35			
756	Ac-t$s8wyanf4CF3e$r5llr-NH_2	658			858.03			
757	Ac-tawy$s8nf4CF3ekll$r5a-NH_2	659			879.86			
758	Ac-tawya$s8f4CF3ekllr$r5a-NH_2	660			936.38			
759	Ac-tawy$s8naekll$r5a-NH_2	661			844.25			
760	5-FAM-Batawy$s8nf4CF3ekll$r5a-NH_2	662						
761	5-FAM-Batawy$s8naekll$r5a-NH_2	663						
762	Ac-tawy$s8nf4CF3eall$r5a-NH_2	664						
763	Ac-tawy$s8nf4CF3ekll$r5aaaaa-NH_2	665						
764	Ac-tawy$s8nf4CF3eall$r5aaaaa-NH_2	666						

[00352] Table 3a shows a selection of peptidomimetic macrocycles.

Table 3a

	Sequence	SEQ ID NO:	Iso	Exact Mass	Found Mass	Calc (M+1)/1	Calc (M+2)/2	Calc (M+3)/3
244	Ac-LTF$r8EF4coohWAQCba$SANleA-NH_2	667		1885	943.59	1886.01	943.51	629.34
331	Ac-LTF$r8EYWAQL$AAAAAa-NH_2	668	iso2	1929.04	966.08	1930.05	965.53	644.02
555	Ac-LTF$r8EY6clWAQL$AAAAAa-NH_2	669		1963	983.28	1964.01	982.51	655.34
557	Ac-AAALTF$r8EYWAQL$AAAAAa-NH_2	670		2142.15	1072.83	2143.16	1072.08	715.06
558	Ac-LTF34F2$r8EYWAQL$AAAAAa-NH_2	671		1965.02	984.3	1966.03	983.52	656.01
562	Ac-LTF$r8EYWAQL$AAibAAAa-NH_2	672		1943.06	973.11	1944.07	972.54	648.69
564	Ac-LTF$r8EYWAQL$AAAAibAa-NH_2	673		1943.06	973.48	1944.07	972.54	648.69
566	Ac-LTF$r8EYWAQL$AAAAAiba-NH_2	674	iso2	1943.06	973.38	1944.07	972.54	648.69
567	Ac-LTF$r8EYWAQL$AAAAAAib-NH_2	675		1943.06	973.01	1944.07	972.54	648.69
572	Ac-LTF$r8EYWAQL$AAAAaa-NH_2	676		1929.04	966.35	1930.05	965.53	644.02
573	Ac-LTF$r8EYWAQL$AAAAAA-NH_2	677		1929.04	966.35	1930.05	965.53	644.02
578	Ac-LTF$r8EYWAQL$AAAAASar-NH_2	678		1929.04	966.08	1930.05	965.53	644.02
551	Ac-LTF$r8EYWAQL$AAAAAa-OH	679	iso2	1930.02	965.89	1931.03	966.02	644.35
662	Ac-LTF$rda6AYWAQL$da5AAAAAa-NH_2	680		1974.06	934.44		933.49	

367	5-FAM-BaLTF$r8EYWAQCba$SAA-NH_2	681		2131	1067.09	2132.01	1066.51	711.34
349	Ac-LTF$r8EF4coohWAQCba$AAAAAa-NH_2	682	iso2	1969.04	986.06	1970.05	985.53	657.35
347	Ac-LTF$r8EYWAQCba$AAAAAa-NH_2	683	iso2	1941.04	972.55	1942.05	971.53	648.02

[00353] Table 3b shows a further selection of peptidomimetic macrocycles.

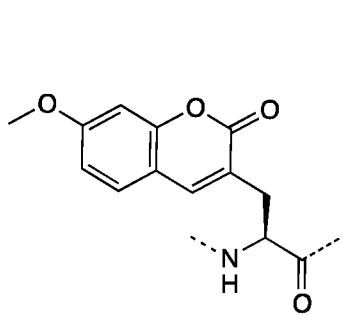
Table 3b

SP	Sequence	SEQ ID NO:	Iso	Exact Mass	Found Mass	Calc (M+1)/1	Calc (M+2)/2	Calc (M+3)/3
581	Ac-TF$r8EYWAQL$AAAAAa-NH_2	684		1815.96	929.85	1816.97	908.99	606.33
582	Ac-F$r8EYWAQL$AAAAAa-NH_2	685		1714.91	930.92	1715.92	858.46	572.64
583	Ac-LVF$r8EYWAQL$AAAAAa-NH_2	686		1927.06	895.12	1928.07	964.54	643.36
584	Ac-AAF$r8EYWAQL$AAAAAa-NH_2	687		1856.98	859.51	1857.99	929.5	620
585	Ac-LTF$r8EYWAQL$AAAAa-NH_2	688		1858	824.08	1859.01	930.01	620.34
586	Ac-LTF$r8EYWAQL$AAAa-NH_2	689		1786.97	788.56	1787.98	894.49	596.66
587	Ac-LTF$r8EYWAQL$AAa-NH_2	690		1715.93	1138.57	1716.94	858.97	572.98
588	Ac-LTF$r8EYWAQL$Aa-NH_2	691		1644.89	1144.98	1645.9	823.45	549.3
589	Ac-LTF$r8EYWAQL$a-NH_2	692		1573.85	1113.71	1574.86	787.93	525.62

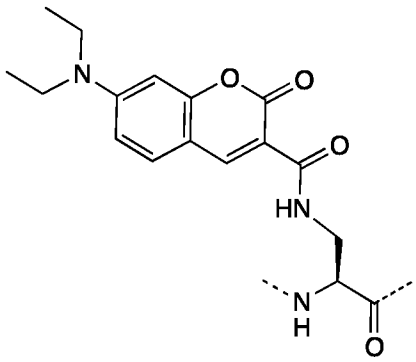
[00354] In the sequences shown above and elsewhere, the following abbreviations are used: "Nle" represents norleucine, "Aib" represents 2-aminoisobutyric acid, "Ac" represents acetyl, and "Pr" represents propionyl. Amino acids represented as "$" are alpha-Me S5-pentenyl-alanine olefin amino acids connected by an all-carbon crosslinker comprising one double bond. Amino acids represented as "$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.

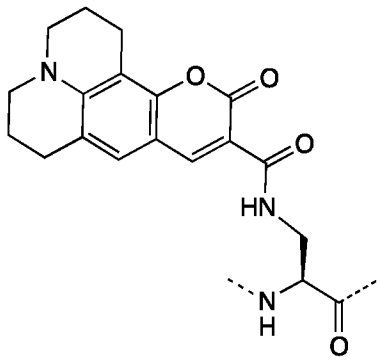
[00355] Amino acids designated as "Cit" represent citrulline. Amino acids designated as "Cou4", "Cou6", "Cou7" and "Cou8", respectively, represent the following structures:



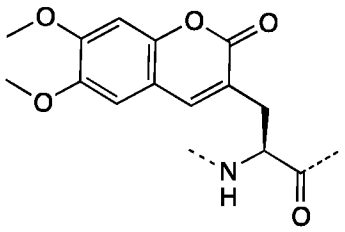
Cou



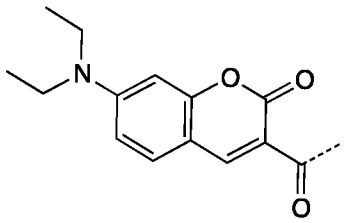
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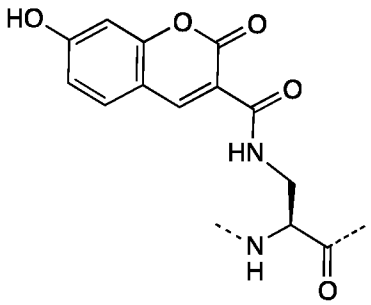
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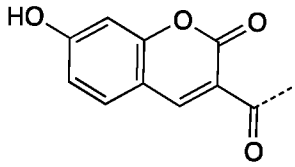
Cou4



Cou6



Cou7

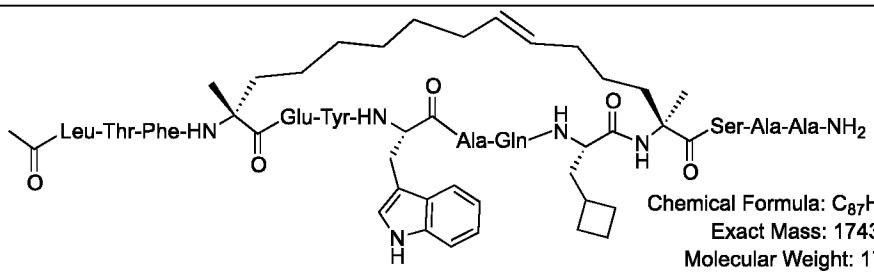
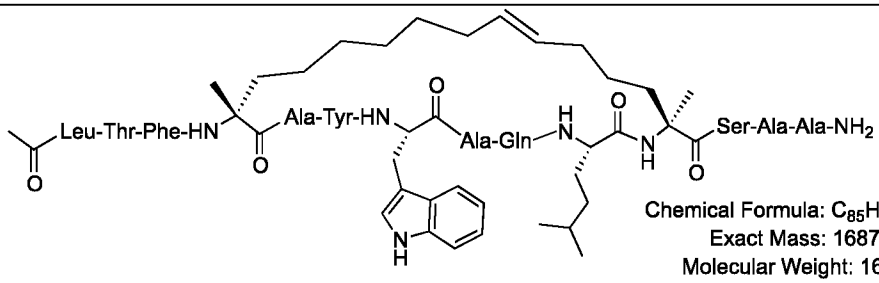
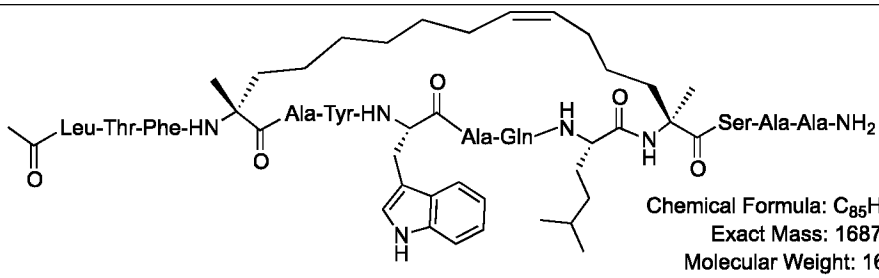
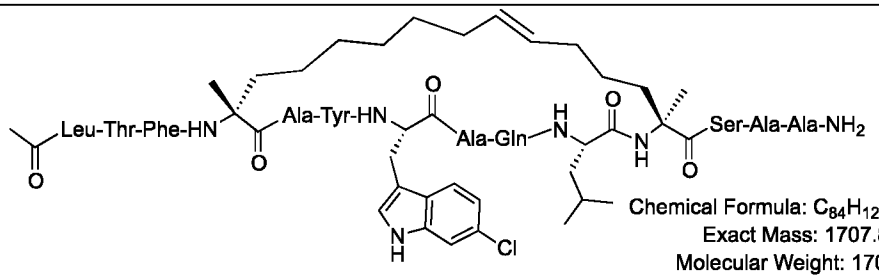
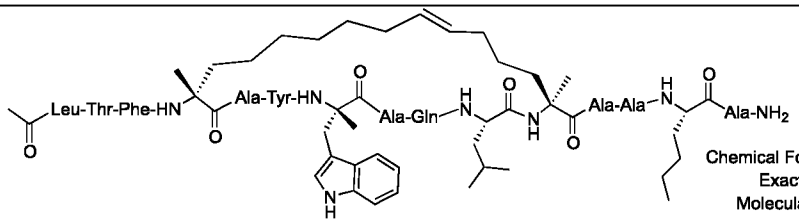


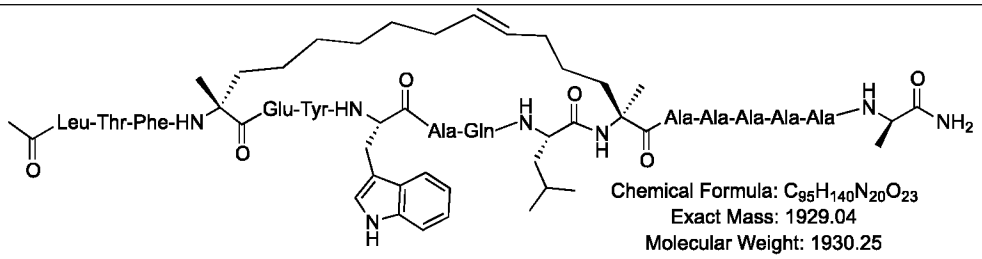
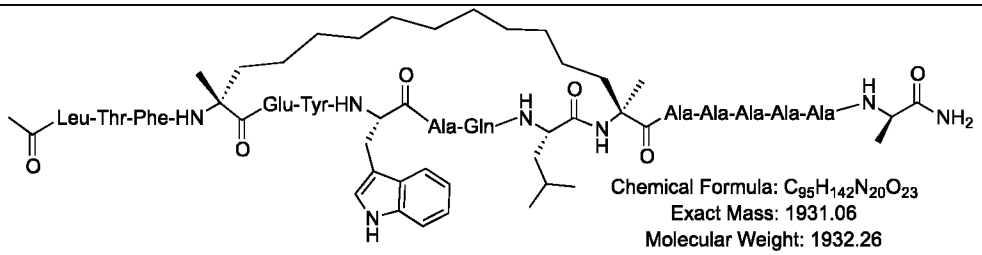
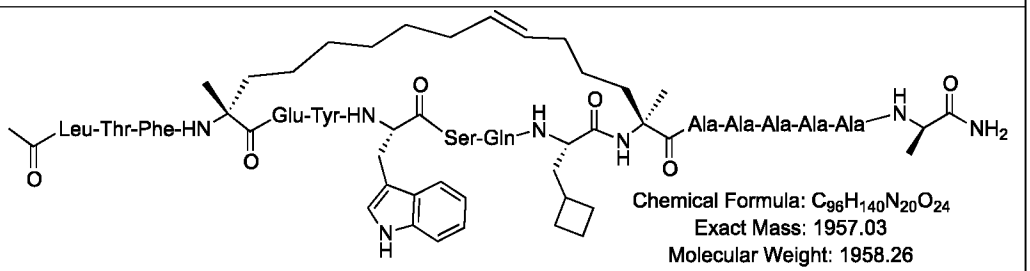
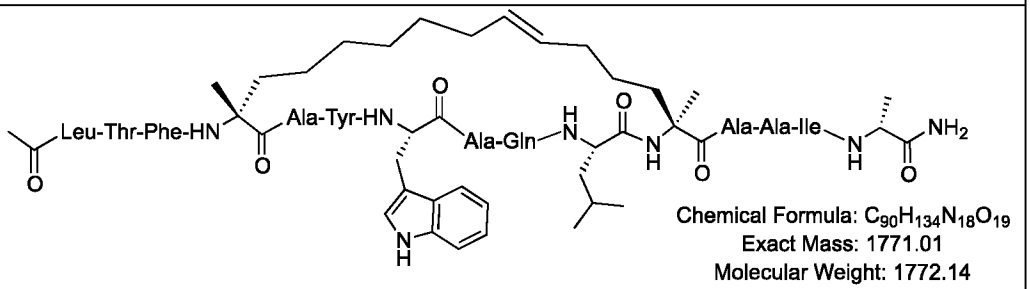
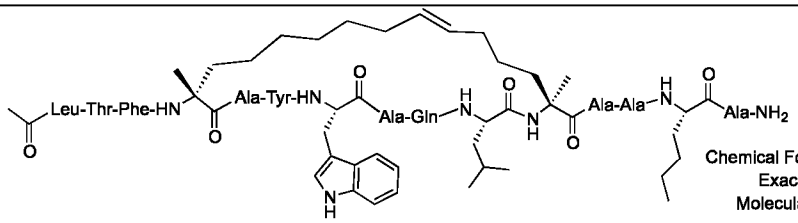
Cou8

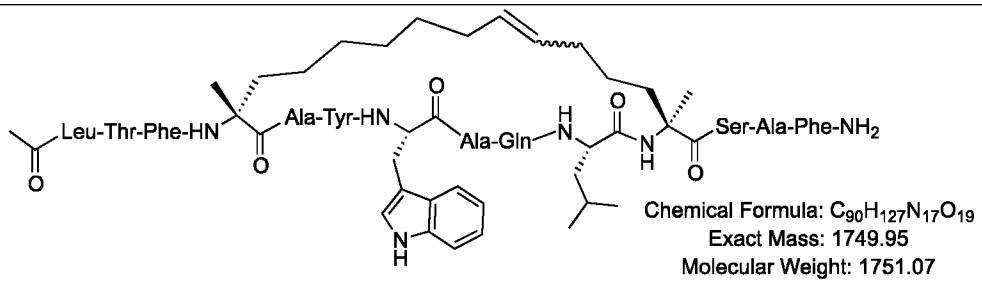
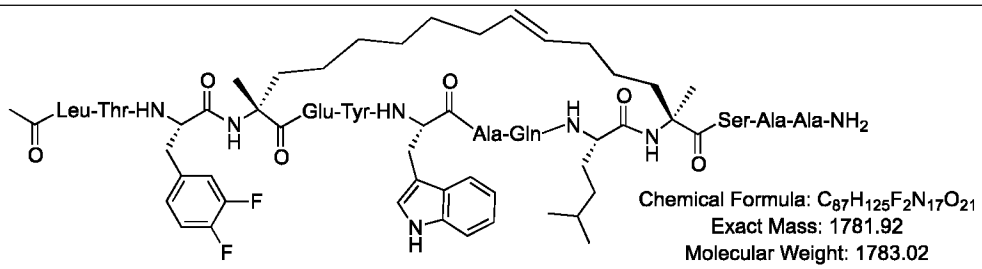
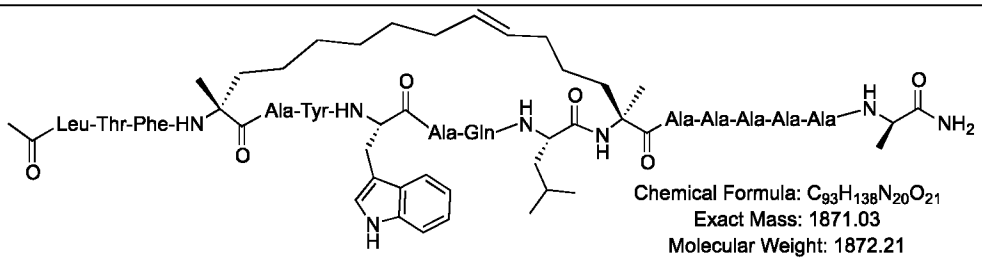
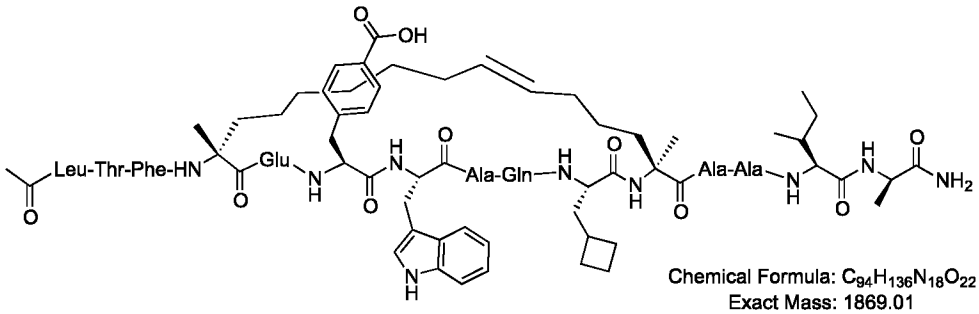
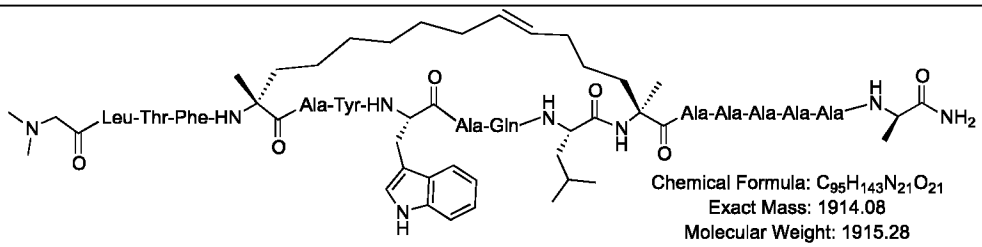
[00356] In some embodiments, a peptidomimetic macrocycle is obtained in more than one isomer, for example due to the configuration of a double bond within the structure of the crosslinker (*E* vs *Z*). Such isomers can or cannot be separable by conventional chromatographic methods. In some embodiments, one isomer has improved biological properties relative to the other isomer. In one embodiment, an *E* crosslinker olefin isomer of a peptidomimetic macrocycle has better solubility, better target affinity, better in vivo or in vitro efficacy, higher helicity, or improved cell permeability relative to its *Z* counterpart. In another embodiment, a *Z* crosslinker olefin isomer of a peptidomimetic macrocycle has better solubility, better target affinity, better in vivo or in vitro efficacy, higher helicity, or improved cell permeability relative to its *E* counterpart.

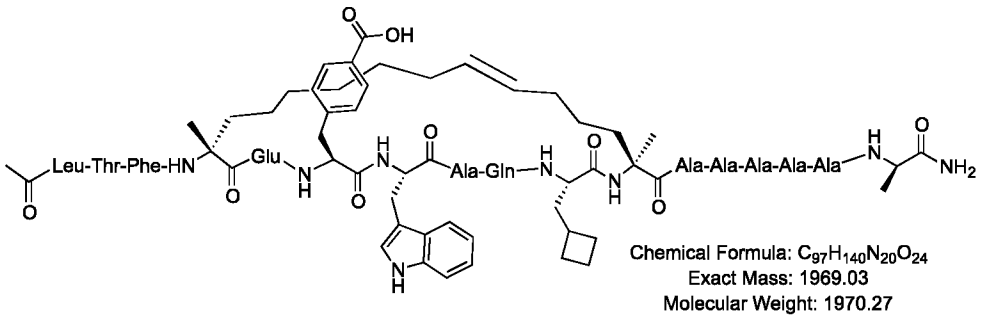
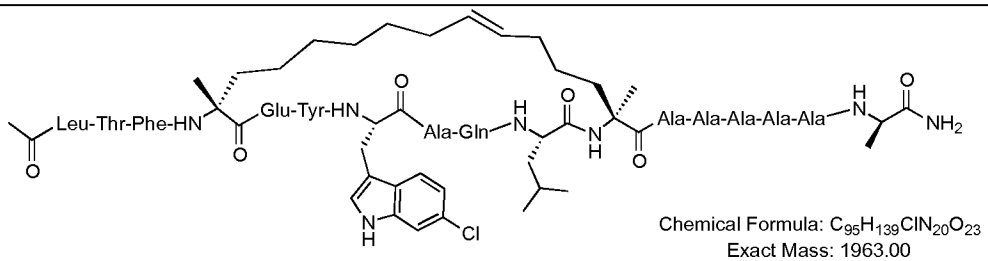
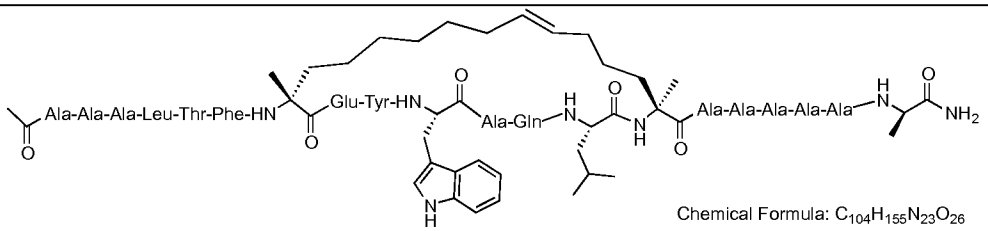
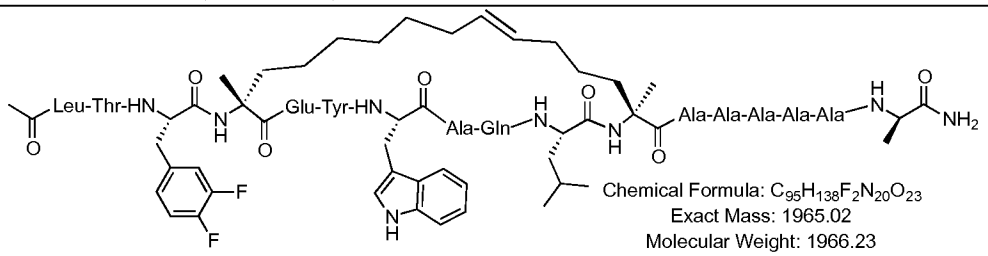
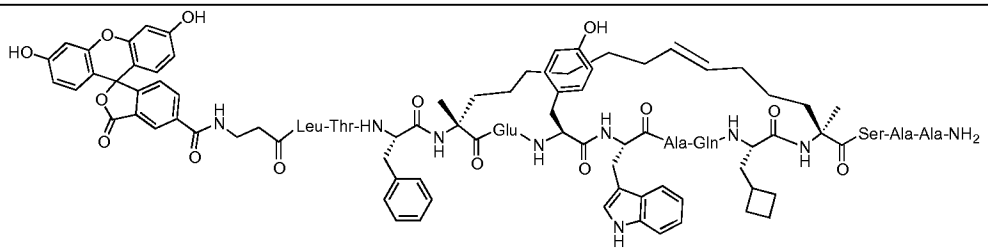
[00357] Table 3c shows exemplary peptidomimetic macrocycle:

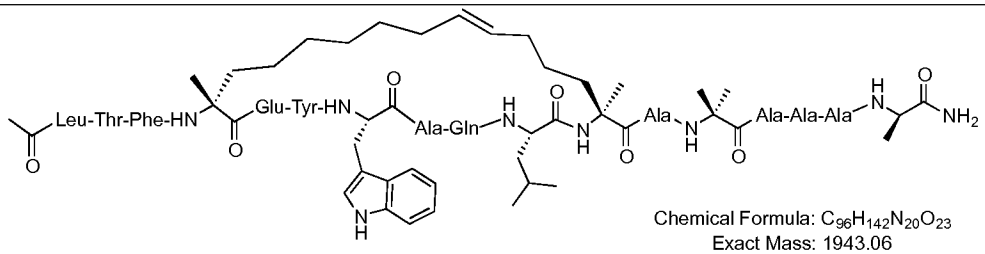
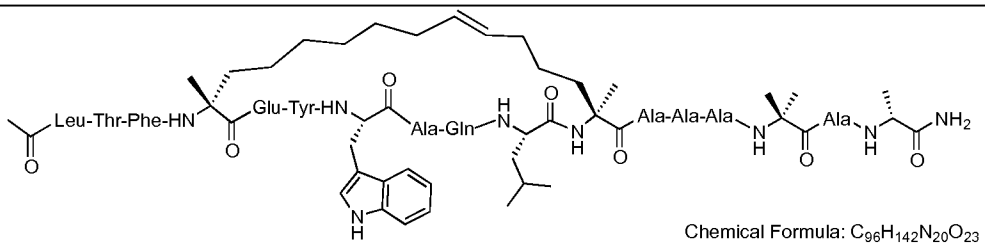
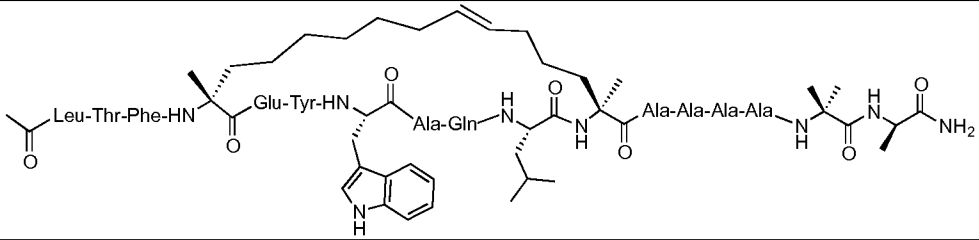
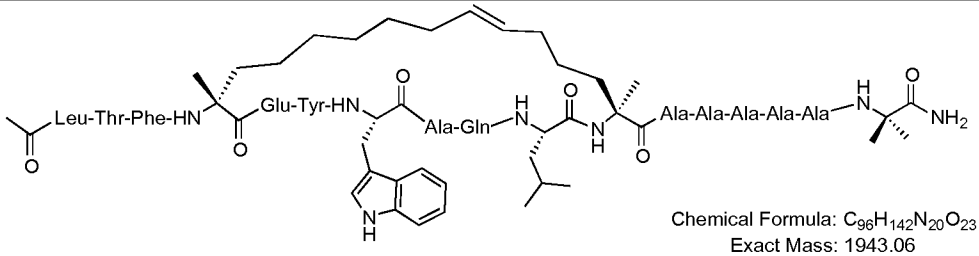
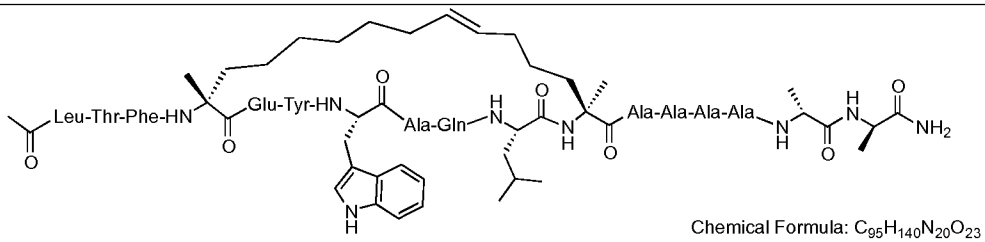
Table 3c

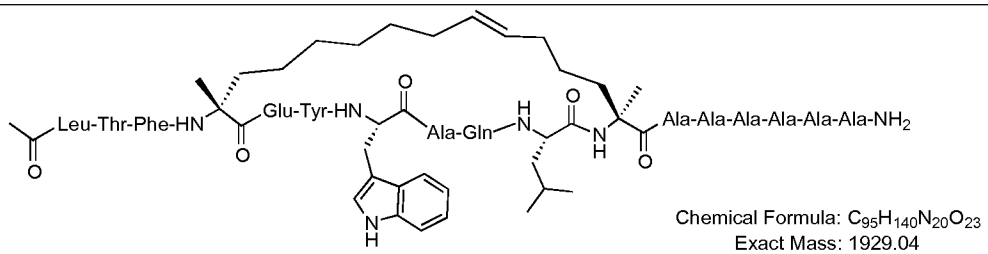
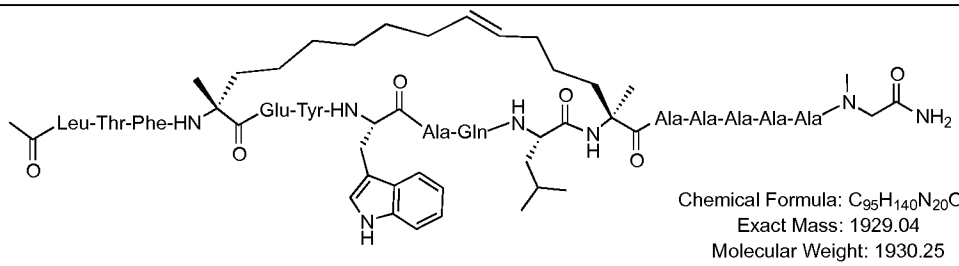
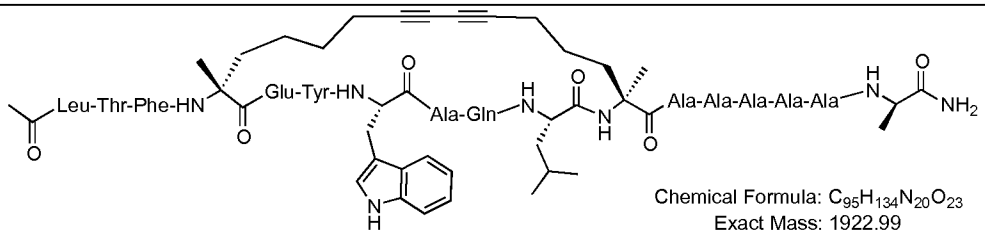
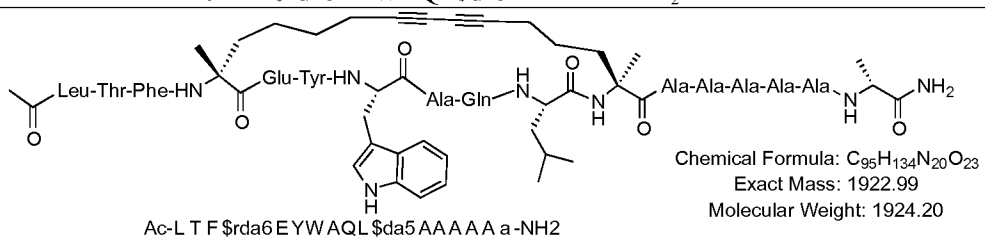
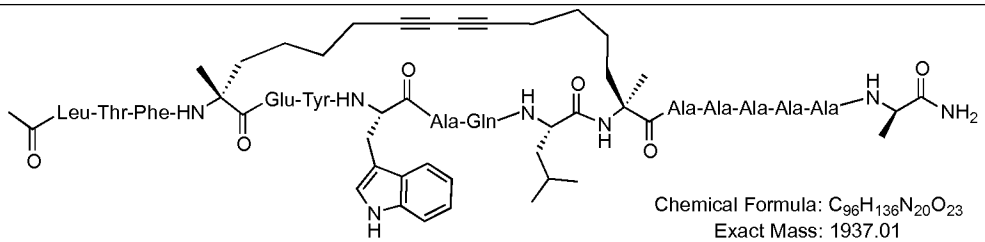
	Structure
SP154 (SEQ ID NO: 163)	 Chemical Formula: $C_{87}H_{125}N_{17}O_{21}$ Exact Mass: 1743.92 Molecular Weight: 1745.02 Ac-L T F $er8 E Y W A Q Cba $e S A A -NH2
SP115 (SEQ ID NO: 124)	 Chemical Formula: $C_{85}H_{125}N_{17}O_{19}$ Exact Mass: 1687.93 Molecular Weight: 1689.00 Ac-L T F $er8 A Y W A Q hL $e S A A -NH2
SP114 (SEQ ID NO: 123)	 Chemical Formula: $C_{85}H_{125}N_{17}O_{19}$ Exact Mass: 1687.93 Molecular Weight: 1689.00 Ac-L T F $zr8 A Y W A Q hL $z S A A -NH2
SP99 (SEQ ID NO: 108)	 Chemical Formula: $C_{84}H_{122}ClN_{17}O_{19}$ Exact Mass: 1707.88 Molecular Weight: 1709.42 Ac-L T F $er8 A Y 6cl W A Q L $e S A A -NH2
SP388 (SEQ ID NO: 397)	 Chemical Formula: $C_{91}H_{136}N_{18}O_{19}$ Exact Mass: 1785.02 Molecular Weight: 1786.16 Ac-L T F $er8 A Y **Amw** A Q L $e A A Nle A -NH2

SP331 (SEQ ID NO: 340)	 Chemical Formula: $C_{95}H_{140}N_{20}O_{23}$ Exact Mass: 1929.04 Molecular Weight: 1930.25 Ac-L T F $er8 E Y W A Q L $e A A A A A a-NH2
SP445 (SEQ ID NO: 454)	 Chemical Formula: $C_{95}H_{142}N_{20}O_{23}$ Exact Mass: 1931.06 Molecular Weight: 1932.26 Ac-L T F %r8 E Y W A Q L % A A A A A a-NH2
SP351 (SEQ ID NO: 360)	 Chemical Formula: $C_{96}H_{140}N_{20}O_{24}$ Exact Mass: 1957.03 Molecular Weight: 1958.26 Ac-L T F $er8 E Y W S Q Cba $e A A A A A a-NH2
SP71 (SEQ ID NO: 80)	 Chemical Formula: $C_{90}H_{134}N_{18}O_{19}$ Exact Mass: 1771.01 Molecular Weight: 1772.14 Ac-L T F $er8 A Y W A Q L $e A A I a-NH2
SP69 (SEQ ID NO: 78)	 Chemical Formula: $C_{90}H_{134}N_{18}O_{19}$ Exact Mass: 1771.01 Molecular Weight: 1772.14 Ac-L T F $er8 A Y W A Q L $e A A Nle A-NH2

SP7 (SEQ ID NO: 16)	 Chemical Formula: $C_{90}H_{127}N_{17}O_{19}$ Exact Mass: 1749.95 Molecular Weight: 1751.07 Ac-L T F $r8 A Y W A Q L $ S A F -NH2
SP160 (SEQ ID NO: 169)	 Chemical Formula: $C_{87}H_{125}F_2N_{17}O_{21}$ Exact Mass: 1781.92 Molecular Weight: 1783.02 Ac-L T F34F2 $er8 E Y W A Q hL $e S A A -NH2
SP315 (SEQ ID NO: 324)	 Chemical Formula: $C_{93}H_{138}N_{20}O_{21}$ Exact Mass: 1871.03 Molecular Weight: 1872.21 Ac-L T F $er8 A Y W A Q L $e A A A A A a -NH2
SP249 (SEQ ID NO: 258)	 Chemical Formula: $C_{94}H_{136}N_{18}O_{22}$ Exact Mass: 1869.01 Molecular Weight: 1870.19 Ac-L T F $er8 E F4cooh W A Q Cba $e A A-l-a -NH2
SP437 (SEQ ID NO: 446)	 Chemical Formula: $C_{95}H_{143}N_{21}O_{21}$ Exact Mass: 1914.08 Molecular Weight: 1915.28 Dmaac- L T F $er8 A Y W A Q L $e A A A A A a -NH2

SP349 (SEQ ID NO: 358)	 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
SP555 (SEQ ID NO: 464)	 Chemical Formula: $C_{95}H_{139}ClN_{20}O_{23}$ Exact Mass: 1963.00 Molecular Weight: 1964.69 Ac-L T F $er8 E Y6clW AQ L $e A A A A A a -NH2
SP557 (SEQ ID NO: 466)	 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
SP558 (SEQ ID NO: 467)	 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 Y W AQ L $e A A A A A a -NH2
SP367 (SEQ ID NO: 376)	 5-FAM- Ba L T F $er8 E Y W AQ Cba $e SAA -NH2

SP562 (SEQ ID NO: 471)	 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 Aib A A A a -NH2
SP564 (SEQ ID NO: 473)	 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 Aib A a -NH2
SP566 (SEQ ID NO: 475)	 Ac-L T F $er8 E Y W A Q L $e A A A A Aib -NH2
SP567 (SEQ ID NO: 476)	 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
SP572 (SEQ ID NO: 481)	 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

SP573 (SEQ ID NO: 482)	 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
SP578 (SEQ ID NO: 487)	 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
SP664 (SEQ ID NO: 572)	 Chemical Formula: $C_{95}H_{134}N_{20}O_{23}$ Exact Mass: 1922.99 Molecular Weight: 1924.20 Ac-LTF$rda6EYWAQL$da5AAAAAa-NH_2
SP664 (SEQ ID NO: 572)	 Chemical Formula: $C_{95}H_{134}N_{20}O_{23}$ Exact Mass: 1922.99 Molecular Weight: 1924.20 Ac-L T F $rda6 E Y W A Q L $da5 A A A A A a -NH2
(SEQ ID NO: 1500)	 Chemical Formula: $C_{96}H_{136}N_{20}O_{23}$ Exact Mass: 1937.01 Molecular Weight: 1938.23

[00358] In some embodiments, peptidomimetic macrocycles exclude peptidomimetic macrocycles shown in **Table 4a**:

Table 4a

Number	Sequence	SEQ ID NO:
765	L$r5QETFSD$s8WKLLPEN	693

766	LSQ$r5TFSDLW$s8LLPEN	694
767	LSQE$r5FSDLWK$s8LPEN	695
768	LSQET$r5SDLWKL$s8PEN	696
769	LSQETF$r5DLWKLL$s8EN	697
770	LXQETFS$r5LWKLLP$s8N	698
771	LSQETFSD$r5WKLLPE$s8	699
772	LSQQTF$r5DLWKLL$s8EN	700
773	LSQETF$r5DLWKLL$s8QN	701
774	LSQQTF$r5DLWKLL$s8QN	702
775	LSQETF$r5NLWKLL$s8QN	703
776	LSQQTF$r5NLWKLL$s8QN	704
777	LSQQTF$r5NLWRLL$s8QN	705
778	QSQQTF$r5NLWKLL$s8QN	706
779	QSQQTF$r5NLWRLL$s8QN	707
780	QSQQTA$r5NLWRLL$s8QN	708
781	L$r8QETFSD$WKLLPEN	709
782	LSQ$r8TFSDLW$LLPEN	710
783	LSQE$r8FSDLWK$LPEN	711
784	LSQET$r8SDLWKL$PEN	712
785	LSQETF$r8DLWKLL$EN	713
786	LXQETFS$r8LWKLLP$N	714
787	LSQETFSD$r8WKLLPE$	715
788	LSQQTF$r8DLWKLL$EN	716
789	LSQETF$r8DLWKLL$QN	717
790	LSQQTF$r8DLWKLL$QN	718
791	LSQETF$r8NLWKLL$QN	719
792	LSQQTF$r8NLWKLL$QN	720
793	LSQQTF$r8NLWRLL$QN	721
794	QSQQTF$r8NLWKLL$QN	722
795	QSQQTF$r8NLWRLL$QN	723
796	QSQQTA$r8NLWRLL$QN	724
797	QSQQTF$r8NLWRKK$QN	725
798	QQTF$r8DLWRLL$EN	726
799	QQTF$r8DLWRLL$	727
800	LSQQTFDLWLL	728
801	QQTFDLWLL	729
802	QQTA$r8DLWRLL$EN	730
803	QSQQTF$r5NLWRLL$s8QN (dihydroxylated olefin)	731
804	QSQQTA$r5NLWRLL$s8QN (dihydroxylated olefin)	732
805	QSQQTF$r8DLWRLL$QN	733
806	QTF$r8NLWRLL$	734
807	QSQQTFNLWLLPQN	735
808	QSQTFNLWRLLPQN	736
809	TFSLWKLL	737
810	ETFDLWLL	738
811	QTFNLWLL	739
812	SQEFSNLWKLL	740

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.

[00359] In some embodiments, peptidomimetic macrocycles do not comprise a peptidomimetic macrocycle structure as shown in **Table 4a**.

[00360] In other embodiments, peptidomimetic macrocycles exclude peptidomimetic macrocycles shown in **Table 4b**.

Table 4b

SP#	Sequence	SEQ ID NO:	Exact Mass	M+2	Observed mass (m/e)
813	Ac-LSQETF$r8DLWKLL$EN-NH_2	741	2068.13	1035.07	1035.36
814	Ac-LSQETF$r8NLWKLL$QN-NH_2	742	2066.16	1034.08	1034.31
815	Ac-LSQQTF$r8NLWRLL$QN-NH_2	743	2093.18	1047.59	1047.73
816	Ac-QSQQTF$r8NLWKLL$QN-NH_2	744	2080.15	1041.08	1041.31
817	Ac-QSQQTF$r8NLWRLL$QN-NH_2	745	2108.15	1055.08	1055.32
818	Ac-QSQQTA$r8NLWRLL$QN-NH_2	746	2032.12	1017.06	1017.24
819	Ac-QAibQQTF$r8NLWRLL$QN-NH_2	747	2106.17	1054.09	1054.34
820	Ac-QSQQTFSNLWRLLPQN-NH_2	748	2000.02	1001.01	1001.26
821	Ac-QSQQTF$/r8NLWRLL$/QN-NH_2	749	2136.18	1069.09	1069.37
822	Ac-QSQAibTF$r8NLWRLL$QN-NH_2	750	2065.15	1033.58	1033.71
823	Ac-QSQQTF$r8NLWRLL$AN-NH_2	751	2051.13	1026.57	1026.70
824	Ac-ASQQTF$r8NLWRLL$QN-NH_2	752	2051.13	1026.57	1026.90
825	Ac-QSQQTF$r8ALWRLL$QN-NH_2	753	2065.15	1033.58	1033.41
826	Ac-QSQETF$r8NLWRLL$QN-NH_2	754	2109.14	1055.57	1055.70
827	Ac-RSQQTF$r8NLWRLL$QN-NH_2	755	2136.20	1069.10	1069.17
828	Ac-RSQQTF$r8NLWRLL$EN-NH_2	756	2137.18	1069.59	1069.75
829	Ac-LSQETFSDLWKLLPEN-NH_2	757	1959.99	981.00	981.24
830	Ac-QSQTFSLWRLLPQN-NH_2	758	2008.09	1005.05	1004.97
831	Ac-QSQQFSNWRLLPQN-NH_2	759	2036.06	1019.03	1018.86
832	Ac-QSQQTSNLRLLPQN-NH_2	760	1917.04	959.52	959.32
833	Ac-QSQQTFNLWLLPQN-NH_2	761	2007.06	1004.53	1004.97
834	Ac-RTQATF$r8NQWAibANle$TNAibTR-NH_2	762	2310.26	1156.13	1156.52
835	Ac-QSQQTF$r8NLWRLL$RN-NH_2	763	2136.20	1069.10	1068.94
836	Ac-QSQRTF$r8NLWRLL$QN-NH_2	764	2136.20	1069.10	1068.94
837	Ac-QSQQTF$r8NNleWRLL$QN-NH_2	765	2108.15	1055.08	1055.44
838	Ac-QSQQTF$r8NLWRNleL$QN-NH_2	766	2108.15	1055.08	1055.84
839	Ac-QSQQTF$r8NLWRLNle$QN-NH_2	767	2108.15	1055.08	1055.12

840	Ac-QSQQTY$r8NLWRLL$QN-NH_2	768	2124.15	1063.08	1062.92
841	Ac-RAibQQTF$r8NLWRLL$QN-NH_2	769	2134.22	1068.11	1068.65
842	Ac-MPRFMDYWEGLN-NH_2	770	1598.70	800.35	800.45
843	Ac-RSQQRF$r8NLWRLL$QN-NH_2	771	2191.25	1096.63	1096.83
844	Ac-QSQQRF$r8NLWRLL$QN-NH_2	772	2163.21	1082.61	1082.87
845	Ac-RAibQQRF$r8NLWRLL$QN-NH_2	773	2189.27	1095.64	1096.37
846	Ac-RSQQRF$r8NFWRLL$QN-NH_2	774	2225.23	1113.62	1114.37
847	Ac-RSQQRF$r8NYWRLL$QN-NH_2	775	2241.23	1121.62	1122.37
848	Ac-RSQQTF$r8NLWQLL$QN-NH_2	776	2108.15	1055.08	1055.29
849	Ac-QSQQTF$r8NLWQAmlL$QN-NH_2	777	2094.13	1048.07	1048.32
850	Ac-QSQQTF$r8NAmlWRLL$QN-NH_2	778	2122.17	1062.09	1062.35
851	Ac-NlePRF$r8DYWEGL$QN-NH_2	779	1869.98	935.99	936.20
852	Ac-NlePRF$r8NYWRLL$QN-NH_2	780	1952.12	977.06	977.35
853	Ac-RF$r8NLWRLL$Q-NH_2	781	1577.96	789.98	790.18
854	Ac-QSQQTF$r8N2ffWRLL$QN-NH_2	782	2160.13	1081.07	1081.40
855	Ac-QSQQTF$r8N3ffWRLL$QN-NH_2	783	2160.13	1081.07	1081.34
856	Ac-QSQQTF#r8NLWRLL#QN-NH_2	784	2080.12	1041.06	1041.34
857	Ac-RSQQTA$r8NLWRLL$QN-NH_2	785	2060.16	1031.08	1031.38
858	Ac-QSQQTF%r8NLWRLL%QN-NH_2	786	2110.17	1056.09	1056.55
859	HepQSQ$TFSNLWRLLPQN-$NH_2$	787	2051.10	1026.55	1026.82
860	HepQSQTFr8NLWRLL$QN-$NH_2$	788	2159.23	1080.62	1080.89
861	Ac-QSQQTF$r8NL6clWRLL$QN-NH_2	789	2142.11	1072.06	1072.35
862	Ac-QSQQTF$r8NLMe6clwRLL$QN-NH_2	790	2156.13	1079.07	1079.27
863	Ac-LTFEHYWAQLTS-NH_2	791	1535.74	768.87	768.91
864	Ac-LTFHYWQLTS-NH_2	792	1585.83	793.92	794.17
865	Ac-LTFEYWALTS-NH_2	793	1520.79	761.40	761.67
866	Ac-LTF$zr8HYWAQL$zS-NH_2	794	1597.87	799.94	800.06
867	Ac-LTF$r8HYWRQL$S-NH_2	795	1682.93	842.47	842.72
868	Ac-QS$QTFStNLWRLL$s8QN-NH_2	796	2145.21	1073.61	1073.90
869	Ac-QSQQTASNLWRLLPQN-NH_2	797	1923.99	963.00	963.26
870	Ac-QSQQTA$/r8NLWRLL$/QN-NH_2	798	2060.15	1031.08	1031.24
871	Ac-ASQQTF$/r8NLWRLL$/QN-NH_2	799	2079.16	1040.58	1040.89
872	Ac-SQQFSNLWRLLAibQN-NH_2	800	2009.09	1005.55	1005.86
873	Ac-QSQTFNLWRLLAibQN-NH_2	801	2023.10	1012.55	1012.79
874	Ac-QSQQFSNWRLLAibQN-NH_2	802	2024.06	1013.03	1013.31

875	Ac-QSQQTFNLWLLAibQN-NH_2	803	1995.06	998.53	998.87
876	Ac-QSQQTFSLWRLAibQN-NH_2	804	2011.06	1006.53	1006.83
877	Ac-QSQQTFSNLWLLAN-NH_2	805	1940.02	971.01	971.29
878	Ac-$/SQQ$/FSNLWRLLAibQN-NH_2	806	2037.12	1019.56	1019.78
879	Ac-QS$/QTF$/NLWRLLAibQN-NH_2	807	2051.13	1026.57	1026.90
880	Ac-QSQQ$/FSN$/WRLLAibQN-NH_2	808	2052.09	1027.05	1027.36
881	Ac-QSQQTF$/NLW$/LLAibQN-NH_2	809	2023.09	1012.55	1013.82
882	Ac-QSQTFSLWRLLAibQN-NH_2	810	1996.09	999.05	999.39
883	Ac-QSQ$/TFS$/LWRLLAibQN-NH_2	811	2024.12	1013.06	1013.37
884	Ac-QS$/QTFSt//NLWRLL$/s8QN-NH_2	812	2201.27	1101.64	1102.00
885	Ac-$r8SQQTFS$LWRLLAibQN-NH_2	813	2038.14	1020.07	1020.23
886	Ac-QSQ$r8TFSNLW$LLAibQN-NH_2	814	1996.08	999.04	999.32
887	Ac-QSQQTFS$r8LWRLLA$N-NH_2	815	2024.12	1013.06	1013.37
888	Ac-QS$r5QTFStNLW$LLAibQN-NH_2	816	2032.12	1017.06	1017.39
889	Ac-$/r8SQQTFS$/LWRLLAibQN-NH_2	817	2066.17	1034.09	1034.80
890	Ac-QSQ$/r8TFSNLW$/LLAibQN-NH_2	818	2024.11	1013.06	1014.34
891	Ac-QSQQTFS$/r8LWRLLA$/N-NH_2	819	2052.15	1027.08	1027.16
892	Ac-QS$/r5QTFSt//NLW$/LLAibQN-NH_2	820	2088.18	1045.09	1047.10
893	Ac-QSQQTFSNLWRLLAibQN-NH_2	821	1988.02	995.01	995.31
894	Hep/QSQ$/TF$/r8NLWRLL$/QN-$NH_2$	822	2215.29	1108.65	1108.93
895	Ac-ASQQTF$r8NLRWLL$QN-NH_2	823	2051.13	1026.57	1026.90
896	Ac-QSQQTF$/r8NLWRLL$/Q-NH_2	824	2022.14	1012.07	1012.66
897	Ac-QSQQTF$r8NLWRLL$Q-NH_2	825	1994.11	998.06	998.42
898	Ac-AAARAA$r8AAARAA$AA-NH_2	826	1515.90	758.95	759.21
899	Ac-LTFEHYWAQLTSA-NH_2	827	1606.78	804.39	804.59
900	Ac-LTF$r8HYWAQL$SA-NH_2	828	1668.90	835.45	835.67
901	Ac-ASQQTFSNLWRLLPQN-NH_2	829	1943.00	972.50	973.27
902	Ac-QS$QTFStNLW$r5LLAibQN-NH_2	830	2032.12	1017.06	1017.30
903	Ac-QSQQTFAibNLWRLLAibQN-NH_2	831	1986.04	994.02	994.19
904	Ac-QSQQTFNleNLWRLLNleQN-NH_2	832	2042.11	1022.06	1022.23
905	Ac-QSQQTF$/r8NLWRLLAibQN-$NH_2$	833	2082.14	1042.07	1042.23
906	Ac-QSQQTF$/r8NLWRLLNleQN-$NH_2$	834	2110.17	1056.09	1056.29
907	Ac-QSQQTFAibNLWRLL$/QN-$NH_2$	835	2040.09	1021.05	1021.25
908	Ac-QSQQTFNleNLWRLL$/QN-$NH_2$	836	2068.12	1035.06	1035.31
909	Ac-QSQQTF%r8NL6clWRNleL%QN-NH_2	837	2144.13	1073.07	1073.32

910	Ac-QSQQTF%r8NLMe6clWRLL%QN-NH_2	838	2158.15	1080.08	1080.31
911	Ac-FNleYWEL-NH_2	839	1160.63	-	1161.70
912	Ac-F$r8AYWELL$A-NH_2	840	1344.75	-	1345.90
913	Ac-F$r8AYWQLL$A-NH_2	841	1343.76	-	1344.83
914	Ac-NlePRF$r8NYWELL$QN-NH_2	842	1925.06	963.53	963.69
915	Ac-NlePRF$r8DYWRLL$QN-NH_2	843	1953.10	977.55	977.68
916	Ac-NlePRF$r8NYWRLL$Q-NH_2	844	1838.07	920.04	920.18
917	Ac-NlePRF$r8NYWRLL$-NH_2	845	1710.01	856.01	856.13
918	Ac-QSQQTF$r8DLWRLL$QN-NH_2	846	2109.14	1055.57	1055.64
919	Ac-QSQQTF$r8NLWRLL$EN-NH_2	847	2109.14	1055.57	1055.70
920	Ac-QSQQTF$r8NLWRLL$QD-NH_2	848	2109.14	1055.57	1055.64
921	Ac-QSQQTF$r8NLWRLL$S-NH_2	849	1953.08	977.54	977.60
922	Ac-ESQQTF$r8NLWRLL$QN-NH_2	850	2109.14	1055.57	1055.70
923	Ac-LTF$r8NLWRNleL$Q-NH_2	851	1635.99	819.00	819.10
924	Ac-LRF$r8NLWRNleL$Q-NH_2	852	1691.04	846.52	846.68
925	Ac-QSQQTF$r8NWWRNleL$QN-NH_2	853	2181.15	1091.58	1091.64
926	Ac-QSQQTF$r8NLWRNleL$Q-NH_2	854	1994.11	998.06	998.07
927	Ac-QTF$r8NLWRNleL$QN-NH_2	855	1765.00	883.50	883.59
928	Ac-NlePRF$r8NWWRLL$QN-NH_2	856	1975.13	988.57	988.75
929	Ac-NlePRF$r8NWWRLL$A-NH_2	857	1804.07	903.04	903.08
930	Ac-TSFAEYWNLLNH_2	858	1467.70	734.85	734.90
931	Ac-QTF$r8HWWSQL$S-NH_2	859	1651.85	826.93	827.12
932	Ac-FMYWEL-NH_2	860	1178.58	-	1179.64
933	Ac-QTFEHWWSQLLS-NH_2	861	1601.76	801.88	801.94
934	Ac-QSQQTF$r8NLAmwRLNle$QN-NH_2	862	2122.17	1062.09	1062.24
935	Ac-FMAibY6clWEAc3cL-NH_2	863	1130.47	-	1131.53
936	Ac-FNle$Y6clWE$L-NH_2	864	1194.59	-	1195.64
937	Ac-F$zr8AY6clWEAc3cL$z-NH_2	865	1277.63	639.82	1278.71
938	Ac-F$r8AY6clWEAc3cL$A-NH_2	866	1348.66	-	1350.72
939	Ac-NlePRF$r8NY6clWRLL$QN-NH_2	867	1986.08	994.04	994.64
940	Ac-AF$r8AAWALA$A-NH_2	868	1223.71	-	1224.71
941	Ac-TF$r8AAWRLA$Q-NH_2	869	1395.80	698.90	399.04
942	Pr-TF$r8AAWRLA$Q-NH_2	870	1409.82	705.91	706.04
943	Ac-QSQQTF%r8NLWRNleL%QN-NH_2	871	2110.17	1056.09	1056.22
944	Ac-LTF%r8HYWAQL%SA-NH_2	872	1670.92	836.46	836.58

945	Ac-NlePRF%r8NYWRLL%QN-NH_2	873	1954.13	978.07	978.19
946	Ac-NlePRF%r8NY6clWRLL%QN-NH_2	874	1988.09	995.05	995.68
947	Ac-LTF%r8HY6clWAQL%S-NH_2	875	1633.84	817.92	817.93
948	Ac-QS%QTF%StNLWRLL%s8QN-NH_2	876	2149.24	1075.62	1075.65
949	Ac-LTF%r8HY6clWRQL%S-NH_2	877	1718.91	860.46	860.54
950	Ac-QSQQTF%r8NL6clWRLL%QN-NH_2	878	2144.13	1073.07	1073.64
951	Ac-%r8SQQTFS%LWRLLAibQN-NH_2	879	2040.15	1021.08	1021.13
952	Ac-LTF%r8HYWAQL%S-NH_2	880	1599.88	800.94	801.09
953	Ac-TSF%r8QYWNLL%P-NH_2	881	1602.88	802.44	802.58
954	Ac-LTFEHYWAQLTS-NH_2	882	1535.74	768.87	769.5
955	Ac-F$er8AY6clWEAc3cL$e-NH_2	883	1277.63	639.82	1278.71
956	Ac-AF$r8AAWALA$A-NH_2	884	1277.63	639.82	1277.84
957	Ac-TF$r8AAWRLA$Q-NH_2	885	1395.80	698.90	699.04
958	Pr-TF$r8AAWRLA$Q-NH_2	886	1409.82	705.91	706.04
959	Ac-LTF$er8HYWAQL$eS-NH_2	887	1597.87	799.94	800.44
960	Ac-CCPGCCBaQSQQTF$r8NLWRLL$QN-NH_2	888	2745.30	1373.65	1372.99
961	Ac-CCPGCCBaQSQQTA$r8NLWRLL$QN-NH_2	889	2669.27	1335.64	1336.09
962	Ac-CCPGCCBaNlePRF$r8NYWRLL$QN-NH_2	890	2589.26	1295.63	1296.2
963	Ac-LTF$/r8HYWAQL$/S-NH_2	891	1625.90	813.95	814.18
964	Ac-F%r8HY6clWRAc3cL%-NH_2	892	1372.72	687.36	687.59
965	Ac-QTF%r8HWWSQL%S-NH_2	893	1653.87	827.94	827.94
966	Ac-LTA$r8HYWRQL$S-NH_2	894	1606.90	804.45	804.66
967	Ac-Q$r8QQTFSN$WRLLAibQN-NH_2	895	2080.12	1041.06	1041.61
968	Ac-QSQQ$r8FSNLWR$LAibQN-NH_2	896	2066.11	1034.06	1034.58
969	Ac-F$r8AYWEAc3cL$A-NH_2	897	1314.70	658.35	1315.88
970	Ac-F$r8AYWEAc3cL$S-NH_2	898	1330.70	666.35	1331.87
971	Ac-F$r8AYWEAc3cL$Q-NH_2	899	1371.72	686.86	1372.72
972	Ac-F$r8AYWEAibL$S-NH_2	900	1332.71	667.36	1334.83
973	Ac-F$r8AYWEAL$S-NH_2	901	1318.70	660.35	1319.73
974	Ac-F$r8AYWEQL$S-NH_2	902	1375.72	688.86	1377.53
975	Ac-F$r8HYWEQL$S-NH_2	903	1441.74	721.87	1443.48
976	Ac-F$r8HYWAQL$S-NH_2	904	1383.73	692.87	1385.38
977	Ac-F$r8HYWAAc3cL$S-NH_2	905	1338.71	670.36	1340.82
978	Ac-F$r8HYWRAc3cL$S-NH_2	906	1423.78	712.89	713.04
979	Ac-F$r8AYWEAc3cL#A-$NH_2$	907	1300.69	651.35	1302.78

980	Ac-NlePTF%r8NYWRLL%QN-NH_2	908	1899.08	950.54	950.56
981	Ac-TF$r8AAWRAL$Q-NH_2	909	1395.80	698.90	699.13
982	Ac-TSF%r8HYWAQL%S-NH_2	910	1573.83	787.92	787.98
983	Ac-F%r8AY6clWEAc3cL%A-NH_2	911	1350.68	676.34	676.91
984	Ac-LTF$r8HYWAQI$S-NH_2	912	1597.87	799.94	800.07
985	Ac-LTF$r8HYWAQNle$S-NH_2	913	1597.87	799.94	800.07
986	Ac-LTF$r8HYWAQL$A-NH_2	914	1581.87	791.94	792.45
987	Ac-LTF$r8HYWAQL$Abu-NH_2	915	1595.89	798.95	799.03
988	Ac-LTF$r8HYWAbuQL$S-NH_2	916	1611.88	806.94	807.47
989	Ac-LTF$er8AYWAQL$eS-NH_2	917	1531.84	766.92	766.96
990	Ac-LAF$r8HYWAQL$S-NH_2	918	1567.86	784.93	785.49
991	Ac-LAF$r8AYWAQL$S-NH_2	919	1501.83	751.92	752.01
992	Ac-LTF$er8AYWAQL$eA-NH_2	920	1515.85	758.93	758.97
993	Ac-LAF$r8AYWAQL$A-NH_2	921	1485.84	743.92	744.05
994	Ac-LTF$r8NLWANleL$Q-NH_2	922	1550.92	776.46	776.61
995	Ac-LTF$r8NLWANleL$A-NH_2	923	1493.90	747.95	1495.6
996	Ac-LTF$r8ALWANleL$Q-NH_2	924	1507.92	754.96	755
997	Ac-LAF$r8NLWANleL$Q-NH_2	925	1520.91	761.46	761.96
998	Ac-LAF$r8ALWANleL$A-NH_2	926	1420.89	711.45	1421.74
999	Ac-A$r8AYWEAc3cL$A-NH_2	927	1238.67	620.34	1239.65
1000	Ac-F$r8AYWEAc3cL$AA-NH_2	928	1385.74	693.87	1386.64
1001	Ac-F$r8AYWEAc3cL$Abu-NH_2	929	1328.72	665.36	1330.17
1013	Ac-F$r8AYWEAc3cL$Nle-NH_2	930	1356.75	679.38	1358.22
1014	Ac-F$r5AYWEAc3cL$s8A-NH_2	931	1314.70	658.35	1315.51
1015	Ac-F$AYWEAc3cL$r8A-NH_2	932	1314.70	658.35	1315.66
1016	Ac-F$r8AYWEAc3cI$A-NH_2	933	1314.70	658.35	1316.18
1017	Ac-F$r8AYWEAc3cNle$A-NH_2	934	1314.70	658.35	1315.66
1018	Ac-F$r8AYWEAmlL$A-NH_2	935	1358.76	680.38	1360.21
1019	Ac-F$r8AYWENleL$A-NH_2	936	1344.75	673.38	1345.71
1020	Ac-F$r8AYWQAc3cL$A-NH_2	937	1313.72	657.86	1314.7
1021	Ac-F$r8AYWAAc3cL$A-NH_2	938	1256.70	629.35	1257.56
1022	Ac-F$r8AYWAbuAc3cL$A-NH_2	939	1270.71	636.36	1272.14
1023	Ac-F$r8AYWNleAc3cL$A-NH_2	940	1298.74	650.37	1299.67
1024	Ac-F$r8AbuYWEAc3cL$A-NH_2	941	1328.72	665.36	1329.65
1025	Ac-F$r8NleYWEAc3cL$A-NH_2	942	1356.75	679.38	1358.66

1026	5-FAM-BaLTFEHYWAQLTS-NH_2	943	1922.82	962.41	962.87
1027	5-FAM-BaLTF%r8HYWAQL%S-NH_2	944	1986.96	994.48	994.97
1028	Ac-LTF$r8HYWAQhL$S-NH_2	945	1611.88	806.94	807
1029	Ac-LTF$r8HYWAQTle$S-NH_2	946	1597.87	799.94	799.97
1030	Ac-LTF$r8HYWAQAdm$S-NH_2	947	1675.91	838.96	839.09
1031	Ac-LTF$r8HYWAQhCha$S-NH_2	948	1651.91	826.96	826.98
1032	Ac-LTF$r8HYWAQCha$S-NH_2	949	1637.90	819.95	820.02
1033	Ac-LTF$r8HYWAc6cQL$S-NH_2	950	1651.91	826.96	826.98
1034	Ac-LTF$r8HYWAc5cQL$S-NH_2	951	1637.90	819.95	820.02
1035	Ac-LThF$r8HYWAQL$S-NH_2	952	1611.88	806.94	807
1036	Ac-LTIgl$r8HYWAQL$S-NH_2	953	1625.90	813.95	812.99
1037	Ac-LTF$r8HYWAQChg$S-NH_2	954	1623.88	812.94	812.99
1038	Ac-LTF$r8HYWAQF$S-NH_2	955	1631.85	816.93	816.99
1039	Ac-LTF$r8HYWAQIgl$S-NH_2	956	1659.88	830.94	829.94
1040	Ac-LTF$r8HYWAQCba$S-NH_2	957	1609.87	805.94	805.96
1041	Ac-LTF$r8HYWAQCpg$S-NH_2	958	1609.87	805.94	805.96
1042	Ac-LTF$r8HhYWAQL$S-NH_2	959	1611.88	806.94	807
1043	Ac-F$r8AYWEAc3chL$A-NH_2	960	1328.72	665.36	665.43
1044	Ac-F$r8AYWEAc3cTle$A-NH_2	961	1314.70	658.35	1315.62
1045	Ac-F$r8AYWEAc3cAdm$A-NH_2	962	1392.75	697.38	697.47
1046	Ac-F$r8AYWEAc3chCha$A-NH_2	963	1368.75	685.38	685.34
1047	Ac-F$r8AYWEAc3cCha$A-NH_2	964	1354.73	678.37	678.38
1048	Ac-F$r8AYWEAc6cL$A-NH_2	965	1356.75	679.38	679.42
1049	Ac-F$r8AYWEAc5cL$A-NH_2	966	1342.73	672.37	672.46
1050	Ac-hF$r8AYWEAc3cL$A-NH_2	967	1328.72	665.36	665.43
1051	Ac-Igl$r8AYWEAc3cL$A-NH_2	968	1342.73	672.37	671.5
1052	Ac-F$r8AYWEAc3cF$A-NH_2	969	1348.69	675.35	675.35
1053	Ac-F$r8AYWEAc3cIgl$A-NH_2	970	1376.72	689.36	688.37
1054	Ac-F$r8AYWEAc3cCba$A-NH_2	971	1326.70	664.35	664.47
1055	Ac-F$r8AYWEAc3cCpg$A-NH_2	972	1326.70	664.35	664.39
1056	Ac-F$r8AhYWEAc3cL$A-NH_2	973	1328.72	665.36	665.43
1057	Ac-F$r8AYWEAc3cL$Q-NH_2	974	1371.72	686.86	1372.87
1058	Ac-F$r8AYWEAibL$A-NH_2	975	1316.72	659.36	1318.18
1059	Ac-F$r8AYWEAL$A-NH_2	976	1302.70	652.35	1303.75
1060	Ac-LAF$r8AYWAAL$A-NH_2	977	1428.82	715.41	715.49

1061	Ac-LTF$r8HYWAAc3cL$S-NH_2	978	1552.84	777.42	777.5
1062	Ac-NleTF$r8HYWAQL$S-NH_2	979	1597.87	799.94	800.04
1063	Ac-VTF$r8HYWAQL$S-NH_2	980	1583.85	792.93	793.04
1064	Ac-FTF$r8HYWAQL$S-NH_2	981	1631.85	816.93	817.02
1065	Ac-WTF$r8HYWAQL$S-NH_2	982	1670.86	836.43	836.85
1066	Ac-RTF$r8HYWAQL$S-NH_2	983	1640.88	821.44	821.9
1067	Ac-KTF$r8HYWAQL$S-NH_2	984	1612.88	807.44	807.91
1068	Ac-LNleF$r8HYWAQL$S-NH_2	985	1609.90	805.95	806.43
1069	Ac-LVF$r8HYWAQL$S-NH_2	986	1595.89	798.95	798.93
1070	Ac-LFF$r8HYWAQL$S-NH_2	987	1643.89	822.95	823.38
1071	Ac-LWF$r8HYWAQL$S-NH_2	988	1682.90	842.45	842.55
1072	Ac-LRF$r8HYWAQL$S-NH_2	989	1652.92	827.46	827.52
1073	Ac-LKF$r8HYWAQL$S-NH_2	990	1624.91	813.46	813.51
1074	Ac-LTF$r8NleYWAQL$S-NH_2	991	1573.89	787.95	788.05
1075	Ac-LTF$r8VYWAQL$S-NH_2	992	1559.88	780.94	780.98
1076	Ac-LTF$r8FYWAQL$S-NH_2	993	1607.88	804.94	805.32
1077	Ac-LTF$r8WYWAQL$S-NH_2	994	1646.89	824.45	824.86
1078	Ac-LTF$r8RYWAQL$S-NH_2	995	1616.91	809.46	809.51
1079	Ac-LTF$r8KYWAQL$S-NH_2	996	1588.90	795.45	795.48
1080	Ac-LTF$r8HNleWAQL$S-NH_2	997	1547.89	774.95	774.98
1081	Ac-LTF$r8HVWAQL$S-NH_2	998	1533.87	767.94	767.95
1082	Ac-LTF$r8HFWAQL$S-NH_2	999	1581.87	791.94	792.3
1083	Ac-LTF$r8HWWAQL$S-NH_2	1000	1620.88	811.44	811.54
1084	Ac-LTF$r8HRWAQL$S-NH_2	1001	1590.90	796.45	796.52
1085	Ac-LTF$r8HKWAQL$S-NH_2	1002	1562.90	782.45	782.53
1086	Ac-LTF$r8HYWNleQL$S-NH_2	1003	1639.91	820.96	820.98
1087	Ac-LTF$r8HYWVQL$S-NH_2	1004	1625.90	813.95	814.03
1088	Ac-LTF$r8HYWFQL$S-NH_2	1005	1673.90	837.95	838.03
1089	Ac-LTF$r8HYWWQL$S-NH_2	1006	1712.91	857.46	857.5
1090	Ac-LTF$r8HYWKQL$S-NH_2	1007	1654.92	828.46	828.49
1091	Ac-LTF$r8HYWANleL$S-NH_2	1008	1582.89	792.45	792.52
1092	Ac-LTF$r8HYWAVL$S-NH_2	1009	1568.88	785.44	785.49
1093	Ac-LTF$r8HYWAFL$S-NH_2	1010	1616.88	809.44	809.47
1094	Ac-LTF$r8HYWAWL$S-NH_2	1011	1655.89	828.95	829
1095	Ac-LTF$r8HYWARL$S-NH_2	1012	1625.91	813.96	813.98

1096	Ac-LTF$r8HYWAQL$Nle-NH_2	1013	1623.92	812.96	813.39
1097	Ac-LTF$r8HYWAQL$V-NH_2	1014	1609.90	805.95	805.99
1098	Ac-LTF$r8HYWAQL$F-NH_2	1015	1657.90	829.95	830.26
1099	Ac-LTF$r8HYWAQL$W-NH_2	1016	1696.91	849.46	849.5
1100	Ac-LTF$r8HYWAQL$R-NH_2	1017	1666.94	834.47	834.56
1101	Ac-LTF$r8HYWAQL$K-NH_2	1018	1638.93	820.47	820.49
1102	Ac-Q$r8QQTFSN$WRLLAibQN-NH_2	1019	2080.12	1041.06	1041.54
1103	Ac-QSQQ$r8FSNLWR$LAibQN-NH_2	1020	2066.11	1034.06	1034.58
1104	Ac-LT2Pal$r8HYWAQL$S-NH_2	1021	1598.86	800.43	800.49
1105	Ac-LT3Pal$r8HYWAQL$S-NH_2	1022	1598.86	800.43	800.49
1106	Ac-LT4Pal$r8HYWAQL$S-NH_2	1023	1598.86	800.43	800.49
1107	Ac-LTF2CF3$r8HYWAQL$S-NH_2	1024	1665.85	833.93	834.01
1108	Ac-LTF2CN$r8HYWAQL$S-NH_2	1025	1622.86	812.43	812.47
1109	Ac-LTF2Me$r8HYWAQL$S-NH_2	1026	1611.88	806.94	807
1110	Ac-LTF3Cl$r8HYWAQL$S-NH_2	1027	1631.83	816.92	816.99
1111	Ac-LTF4CF3$r8HYWAQL$S-NH_2	1028	1665.85	833.93	833.94
1113	Ac-LTF4tBu$r8HYWAQL$S-NH_2	1029	1653.93	827.97	828.02
1114	Ac-LTF5F$r8HYWAQL$S-NH_2	1030	1687.82	844.91	844.96
1115	Ac-LTF$r8HY3BthAAQL$S-NH_2	1031	1614.83	808.42	808.48
1116	Ac-LTF2Br$r8HYWAQL$S-NH_2	1032	1675.78	838.89	838.97
1117	Ac-LTF4Br$r8HYWAQL$S-NH_2	1033	1675.78	838.89	839.86
1118	Ac-LTF2Cl$r8HYWAQL$S-NH_2	1034	1631.83	816.92	816.99
1119	Ac-LTF4Cl$r8HYWAQL$S-NH_2	1035	1631.83	816.92	817.36
1120	Ac-LTF3CN$r8HYWAQL$S-NH_2	1036	1622.86	812.43	812.47
1121	Ac-LTF4CN$r8HYWAQL$S-NH_2	1037	1622.86	812.43	812.47
1122	Ac-LTF34Cl2$r8HYWAQL$S-NH_2	1038	1665.79	833.90	833.94
1123	Ac-LTF34F2$r8HYWAQL$S-NH_2	1039	1633.85	817.93	817.95
1124	Ac-LTF35F2$r8HYWAQL$S-NH_2	1040	1633.85	817.93	817.95
1125	Ac-LTDip$r8HYWAQL$S-NH_2	1041	1673.90	837.95	838.01
1126	Ac-LTF2F$r8HYWAQL$S-NH_2	1042	1615.86	808.93	809
1127	Ac-LTF3F$r8HYWAQL$S-NH_2	1043	1615.86	808.93	809
1128	Ac-LTF4F$r8HYWAQL$S-NH_2	1044	1615.86	808.93	809
1129	Ac-LTF4I$r8HYWAQL$S-NH_2	1045	1723.76	862.88	862.94
1130	Ac-LTF3Me$r8HYWAQL$S-NH_2	1046	1611.88	806.94	807.07
1131	Ac-LTF4Me$r8HYWAQL$S-NH_2	1047	1611.88	806.94	807

1132	Ac-LT1Nal$r8HYWAQL$S-NH_2	1048	1647.88	824.94	824.98
1133	Ac-LT2Nal$r8HYWAQL$S-NH_2	1049	1647.88	824.94	825.06
1134	Ac-LTF3CF3$r8HYWAQL$S-NH_2	1050	1665.85	833.93	834.01
1135	Ac-LTF4NO2$r8HYWAQL$S-NH_2	1051	1642.85	822.43	822.46
1136	Ac-LTF3NO2$r8HYWAQL$S-NH_2	1052	1642.85	822.43	822.46
1137	Ac-LTF$r82ThiYWAQL$S-NH_2	1053	1613.83	807.92	807.96
1138	Ac-LTF$r8HBipWAQL$S-NH_2	1054	1657.90	829.95	830.01
1139	Ac-LTF$r8HF4tBuWAQL$S-NH_2	1055	1637.93	819.97	820.02
1140	Ac-LTF$r8HF4CF3WAQL$S-NH_2	1056	1649.86	825.93	826.02
1141	Ac-LTF$r8HF4ClWAQL$S-NH_2	1057	1615.83	808.92	809.37
1142	Ac-LTF$r8HF4MeWAQL$S-NH_2	1058	1595.89	798.95	799.01
1143	Ac-LTF$r8HF4BrWAQL$S-NH_2	1059	1659.78	830.89	830.98
1144	Ac-LTF$r8HF4CNWAQL$S-NH_2	1060	1606.87	804.44	804.56
1145	Ac-LTF$r8HF4NO2WAQL$S-NH_2	1061	1626.86	814.43	814.55
1146	Ac-LTF$r8H1NalWAQL$S-NH_2	1062	1631.89	816.95	817.06
1147	Ac-LTF$r8H2NalWAQL$S-NH_2	1063	1631.89	816.95	816.99
1148	Ac-LTF$r8HWAQL$S-NH_2	1064	1434.80	718.40	718.49
1149	Ac-LTF$r8HY1NalAQL$S-NH_2	1065	1608.87	805.44	805.52
1150	Ac-LTF$r8HY2NalAQL$S-NH_2	1066	1608.87	805.44	805.52
1151	Ac-LTF$r8HYWAQI$S-NH_2	1067	1597.87	799.94	800.07
1152	Ac-LTF$r8HYWAQNle$S-NH_2	1068	1597.87	799.94	800.44
1153	Ac-LTF$er8HYWAQL$eA-NH_2	1069	1581.87	791.94	791.98
1154	Ac-LTF$r8HYWAQL$Abu-NH_2	1070	1595.89	798.95	799.03
1155	Ac-LTF$r8HYWAbuQL$S-NH_2	1071	1611.88	806.94	804.47
1156	Ac-LAF$r8HYWAQL$S-NH_2	1072	1567.86	784.93	785.49
1157	Ac-LTF$r8NLWANleL$Q-NH_2	1073	1550.92	776.46	777.5
1158	Ac-LTF$r8ALWANleL$Q-NH_2	1074	1507.92	754.96	755.52
1159	Ac-LAF$r8NLWANleL$Q-NH_2	1075	1520.91	761.46	762.48
1160	Ac-F$r8AYWAAc3cL$A-NH_2	1076	1256.70	629.35	1257.56
1161	Ac-LTF$r8AYWAAL$S-NH_2	1077	1474.82	738.41	738.55
1162	Ac-LVF$r8AYWAQL$S-NH_2	1078	1529.87	765.94	766
1163	Ac-LTF$r8AYWAbuQL$S-NH_2	1079	1545.86	773.93	773.92
1164	Ac-LTF$r8AYWNleQL$S-NH_2	1080	1573.89	787.95	788.17
1165	Ac-LTF$r8AbuYWAQL$S-NH_2	1081	1545.86	773.93	773.99
1166	Ac-LTF$r8AYWHQL$S-NH_2	1082	1597.87	799.94	799.97

1167	Ac-LTF$r8AYWKQL$S-NH_2	1083	1588.90	795.45	795.53
1168	Ac-LTF$r8AYWOQL$S-NH_2	1084	1574.89	788.45	788.5
1169	Ac-LTF$r8AYWRQL$S-NH_2	1085	1616.91	809.46	809.51
1170	Ac-LTF$r8AYWSQL$S-NH_2	1086	1547.84	774.92	774.96
1171	Ac-LTF$r8AYWRAL$S-NH_2	1087	1559.89	780.95	780.95
1172	Ac-LTF$r8AYWRQL$A-NH_2	1088	1600.91	801.46	801.52
1173	Ac-LTF$r8AYWRAL$A-NH_2	1089	1543.89	772.95	773.03
1174	Ac-LTF$r5HYWAQL$s8S-NH_2	1090	1597.87	799.94	799.97
1175	Ac-LTF$HYWAQL$r8S-NH_2	1091	1597.87	799.94	799.97
1176	Ac-LTF$r8HYWAAL$S-NH_2	1092	1540.84	771.42	771.48
1177	Ac-LTF$r8HYWAAbuL$S-NH_2	1093	1554.86	778.43	778.51
1178	Ac-LTF$r8HYWALL$S-NH_2	1094	1582.89	792.45	792.49
1179	Ac-F$r8AYWHAL$A-NH_2	1095	1310.72	656.36	656.4
1180	Ac-F$r8AYWAAL$A-NH_2	1096	1244.70	623.35	1245.61
1181	Ac-F$r8AYWSAL$A-NH_2	1097	1260.69	631.35	1261.6
1182	Ac-F$r8AYWRAL$A-NH_2	1098	1329.76	665.88	1330.72
1183	Ac-F$r8AYWKAL$A-NH_2	1099	1301.75	651.88	1302.67
1184	Ac-F$r8AYWOAL$A-NH_2	1100	1287.74	644.87	1289.13
1185	Ac-F$r8VYWEAc3cL$A-NH_2	1101	1342.73	672.37	1343.67
1186	Ac-F$r8FYWEAc3cL$A-NH_2	1102	1390.73	696.37	1392.14
1187	Ac-F$r8WYWEAc3cL$A-NH_2	1103	1429.74	715.87	1431.44
1188	Ac-F$r8RYWEAc3cL$A-NH_2	1104	1399.77	700.89	700.95
1189	Ac-F$r8KYWEAc3cL$A-NH_2	1105	1371.76	686.88	686.97
1190	Ac-F$r8ANleWEAc3cL$A-NH_2	1106	1264.72	633.36	1265.59
1191	Ac-F$r8AVWEAc3cL$A-NH_2	1107	1250.71	626.36	1252.2
1192	Ac-F$r8AFWEAc3cL$A-NH_2	1108	1298.71	650.36	1299.64
1193	Ac-F$r8AWWEAc3cL$A-NH_2	1109	1337.72	669.86	1338.64
1194	Ac-F$r8ARWEAc3cL$A-NH_2	1110	1307.74	654.87	655
1195	Ac-F$r8AKWEAc3cL$A-NH_2	1111	1279.73	640.87	641.01
1196	Ac-F$r8AYWVAc3cL$A-NH_2	1112	1284.73	643.37	643.38
1197	Ac-F$r8AYWFAc3cL$A-NH_2	1113	1332.73	667.37	667.43
1198	Ac-F$r8AYWWAc3cL$A-NH_2	1114	1371.74	686.87	686.97
1199	Ac-F$r8AYWRAc3cL$A-NH_2	1115	1341.76	671.88	671.94
1200	Ac-F$r8AYWKAc3cL$A-NH_2	1116	1313.75	657.88	657.88
1201	Ac-F$r8AYWEVL$A-NH_2	1117	1330.73	666.37	666.47

1202	Ac-F$r8AYWEFL$A-NH_2	1118	1378.73	690.37	690.44
1203	Ac-F$r8AYWEWL$A-NH_2	1119	1417.74	709.87	709.91
1204	Ac-F$r8AYWERL$A-NH_2	1120	1387.77	694.89	1388.66
1205	Ac-F$r8AYWEKL$A-NH_2	1121	1359.76	680.88	1361.21
1206	Ac-F$r8AYWEAc3cL$V-NH_2	1122	1342.73	672.37	1343.59
1207	Ac-F$r8AYWEAc3cL$F-NH_2	1123	1390.73	696.37	1392.58
1208	Ac-F$r8AYWEAc3cL$W-NH_2	1124	1429.74	715.87	1431.29
1209	Ac-F$r8AYWEAc3cL$R-NH_2	1125	1399.77	700.89	700.95
1210	Ac-F$r8AYWEAc3cL$K-NH_2	1126	1371.76	686.88	686.97
1211	Ac-F$r8AYWEAc3cL$AV-NH_2	1127	1413.77	707.89	707.91
1212	Ac-F$r8AYWEAc3cL$AF-NH_2	1128	1461.77	731.89	731.96
1213	Ac-F$r8AYWEAc3cL$AW-NH_2	1129	1500.78	751.39	751.5
1214	Ac-F$r8AYWEAc3cL$AR-NH_2	1130	1470.80	736.40	736.47
1215	Ac-F$r8AYWEAc3cL$AK-NH_2	1131	1442.80	722.40	722.41
1216	Ac-F$r8AYWEAc3cL$AH-NH_2	1132	1451.76	726.88	726.93
1217	Ac-LTF2NO2$r8HYWAQL$S-NH_2	1133	1642.85	822.43	822.54
1218	Ac-LTA$r8HYAAQL$S-NH_2	1134	1406.79	704.40	704.5
1219	Ac-LTF$r8HYAAQL$S-NH_2	1135	1482.82	742.41	742.47
1220	Ac-QSQQTF$r8NLWALL$AN-NH_2	1136	1966.07	984.04	984.38
1221	Ac-QAibQQTF$r8NLWALL$AN-NH_2	1137	1964.09	983.05	983.42
1222	Ac-QAibQQTF$r8ALWALL$AN-NH_2	1138	1921.08	961.54	961.59
1223	Ac-AAAATF$r8AAWAAL$AA-NH_2	1139	1608.90	805.45	805.52
1224	Ac-F$r8AAWRAL$Q-NH_2	1140	1294.76	648.38	648.48
1225	Ac-TF$r8AAWAAL$Q-NH_2	1141	1310.74	656.37	1311.62
1226	Ac-TF$r8AAWRAL$A-NH_2	1142	1338.78	670.39	670.46
1227	Ac-VF$r8AAWRAL$Q-NH_2	1143	1393.82	697.91	697.99
1228	Ac-AF$r8AAWAAL$A-NH_2	1144	1223.71	612.86	1224.67
1229	Ac-TF$r8AAWKAL$Q-NH_2	1145	1367.80	684.90	684.97
1230	Ac-TF$r8AAWOAL$Q-NH_2	1146	1353.78	677.89	678.01
1231	Ac-TF$r8AAWSAL$Q-NH_2	1147	1326.73	664.37	664.47
1232	Ac-LTF$r8AAWRAL$Q-NH_2	1148	1508.89	755.45	755.49
1233	Ac-F$r8AYWAQL$A-NH_2	1149	1301.72	651.86	651.96
1234	Ac-F$r8AWWAAL$A-NH_2	1150	1267.71	634.86	634.87
1235	Ac-F$r8AWWAQL$A-NH_2	1151	1324.73	663.37	663.43
1236	Ac-F$r8AYWEAL$-NH_2	1152	1231.66	616.83	1232.93

1237	Ac-F$r8AYWAAL$-NH_2	1153	1173.66	587.83	1175.09
1238	Ac-F$r8AYWKAL$-NH_2	1154	1230.72	616.36	616.44
1239	Ac-F$r8AYWOAL$-NH_2	1155	1216.70	609.35	609.48
1240	Ac-F$r8AYWQAL$-NH_2	1156	1230.68	616.34	616.44
1241	Ac-F$r8AYWAQL$-NH_2	1157	1230.68	616.34	616.37
1242	Ac-F$r8HYWDQL$S-NH_2	1158	1427.72	714.86	714.86
1243	Ac-F$r8HFWEQL$S-NH_2	1159	1425.74	713.87	713.98
1244	Ac-F$r8AYWHQL$S-NH_2	1160	1383.73	692.87	692.96
1245	Ac-F$r8AYWKQL$S-NH_2	1161	1374.77	688.39	688.45
1246	Ac-F$r8AYWOQL$S-NH_2	1162	1360.75	681.38	681.49
1247	Ac-F$r8HYWSQL$S-NH_2	1163	1399.73	700.87	700.95
1248	Ac-F$r8HWWEQL$S-NH_2	1164	1464.76	733.38	733.44
1249	Ac-F$r8HWWAQL$S-NH_2	1165	1406.75	704.38	704.43
1250	Ac-F$r8AWWHQL$S-NH_2	1166	1406.75	704.38	704.43
1251	Ac-F$r8AWWKQL$S-NH_2	1167	1397.79	699.90	699.92
1252	Ac-F$r8AWWOQL$S-NH_2	1168	1383.77	692.89	692.96
1253	Ac-F$r8HWWSQL$S-NH_2	1169	1422.75	712.38	712.42
1254	Ac-LTF$r8NYWANleL$Q-NH_2	1170	1600.90	801.45	801.52
1255	Ac-LTF$r8NLWAQL$Q-NH_2	1171	1565.90	783.95	784.06
1256	Ac-LTF$r8NYWANleL$A-NH_2	1172	1543.88	772.94	773.03
1257	Ac-LTF$r8NLWAQL$A-NH_2	1173	1508.88	755.44	755.49
1258	Ac-LTF$r8AYWANleL$Q-NH_2	1174	1557.90	779.95	780.06
1259	Ac-LTF$r8ALWAQL$Q-NH_2	1175	1522.89	762.45	762.45
1260	Ac-LAF$r8NYWANleL$Q-NH_2	1176	1570.89	786.45	786.5
1261	Ac-LAF$r8NLWAQL$Q-NH_2	1177	1535.89	768.95	769.03
1262	Ac-LAF$r8AYWANleL$A-NH_2	1178	1470.86	736.43	736.47
1263	Ac-LAF$r8ALWAQL$A-NH_2	1179	1435.86	718.93	719.01
1264	Ac-LAF$r8AYWAAL$A-NH_2	1180	1428.82	715.41	715.41
1265	Ac-F$r8AYWEAc3cL$AAib-NH_2	1181	1399.75	700.88	700.95
1266	Ac-F$r8AYWAQL$AA-NH_2	1182	1372.75	687.38	687.78
1267	Ac-F$r8AYWAAc3cL$AA-NH_2	1183	1327.73	664.87	664.84
1268	Ac-F$r8AYWSAc3cL$AA-NH_2	1184	1343.73	672.87	672.9
1269	Ac-F$r8AYWEAc3cL$AS-NH_2	1185	1401.73	701.87	701.84
1270	Ac-F$r8AYWEAc3cL$AT-NH_2	1186	1415.75	708.88	708.87
1271	Ac-F$r8AYWEAc3cL$AL-NH_2	1187	1427.79	714.90	714.94

1272	Ac-F$r8AYWEAc3cL$AQ-NH_2	1188	1442.76	722.38	722.41
1273	Ac-F$r8AFWEAc3cL$AA-NH_2	1189	1369.74	685.87	685.93
1274	Ac-F$r8AWWEAc3cL$AA-NH_2	1190	1408.75	705.38	705.39
1275	Ac-F$r8AYWEAc3cL$SA-NH_2	1191	1401.73	701.87	701.99
1276	Ac-F$r8AYWEAL$AA-NH_2	1192	1373.74	687.87	687.93
1277	Ac-F$r8AYWENleL$AA-NH_2	1193	1415.79	708.90	708.94
1278	Ac-F$r8AYWEAc3cL$AbuA-NH_2	1194	1399.75	700.88	700.95
1279	Ac-F$r8AYWEAc3cL$NleA-NH_2	1195	1427.79	714.90	714.86
1280	Ac-F$r8AYWEAibL$NleA-NH_2	1196	1429.80	715.90	715.97
1281	Ac-F$r8AYWEAL$NleA-NH_2	1197	1415.79	708.90	708.94
1282	Ac-F$r8AYWENleL$NleA-NH_2	1198	1457.83	729.92	729.96
1283	Ac-F$r8AYWEAibL$Abu-NH_2	1199	1330.73	666.37	666.39
1284	Ac-F$r8AYWENleL$Abu-NH_2	1200	1358.76	680.38	680.39
1285	Ac-F$r8AYWEAL$Abu-NH_2	1201	1316.72	659.36	659.36
1286	Ac-LTF$r8AFWAQL$S-NH_2	1202	1515.85	758.93	759.12
1287	Ac-LTF$r8AWWAQL$S-NH_2	1203	1554.86	778.43	778.51
1288	Ac-LTF$r8AYWAQI$S-NH_2	1204	1531.84	766.92	766.96
1289	Ac-LTF$r8AYWAQNle$S-NH_2	1205	1531.84	766.92	766.96
1290	Ac-LTF$r8AYWAQL$SA-NH_2	1206	1602.88	802.44	802.48
1291	Ac-LTF$r8AWWAQL$A-NH_2	1207	1538.87	770.44	770.89
1292	Ac-LTF$r8AYWAQI$A-NH_2	1208	1515.85	758.93	759.42
1293	Ac-LTF$r8AYWAQNle$A-NH_2	1209	1515.85	758.93	759.42
1294	Ac-LTF$r8AYWAQL$AA-NH_2	1210	1586.89	794.45	794.94
1295	Ac-LTF$r8HWWAQL$S-NH_2	1211	1620.88	811.44	811.47
1296	Ac-LTF$r8HRWAQL$S-NH_2	1212	1590.90	796.45	796.52
1297	Ac-LTF$r8HKWAQL$S-NH_2	1213	1562.90	782.45	782.53
1298	Ac-LTF$r8HYWAQL$W-NH_2	1214	1696.91	849.46	849.5
1299	Ac-F$r8AYWAbuAL$A-NH_2	1215	1258.71	630.36	630.5
1300	Ac-F$r8AbuYWEAL$A-NH_2	1216	1316.72	659.36	659.51
1301	Ac-NlePRF%r8NYWRLL%QN-NH_2	1217	1954.13	978.07	978.54
1302	Ac-TSF%r8HYWAQL%S-NH_2	1218	1573.83	787.92	787.98
1303	Ac-LTF%r8AYWAQL%S-NH_2	1219	1533.86	767.93	768
1304	Ac-HTF$r8HYWAQL$S-NH_2	1220	1621.84	811.92	811.96
1305	Ac-LHF$r8HYWAQL$S-NH_2	1221	1633.88	817.94	818.02
1306	Ac-LTF$r8HHWAQL$S-NH_2	1222	1571.86	786.93	786.94

1307	Ac-LTF$r8HYWHQL$S-NH_2	1223	1663.89	832.95	832.38
1308	Ac-LTF$r8HYWAHL$S-NH_2	1224	1606.87	804.44	804.48
1309	Ac-LTF$r8HYWAQL$H-NH_2	1225	1647.89	824.95	824.98
1310	Ac-LTF$r8HYWAQL$S-NHPr	1226	1639.91	820.96	820.98
1311	Ac-LTF$r8HYWAQL$S-NHsBu	1227	1653.93	827.97	828.02
1312	Ac-LTF$r8HYWAQL$S-NHiBu	1228	1653.93	827.97	828.02
1313	Ac-LTF$r8HYWAQL$S-NHBn	1229	1687.91	844.96	844.44
1314	Ac-LTF$r8HYWAQL$S-NHPe	1230	1700.92	851.46	851.99
1315	Ac-LTF$r8HYWAQL$S-NHChx	1231	1679.94	840.97	841.04
1316	Ac-ETF$r8AYWAQL$S-NH_2	1232	1547.80	774.90	774.96
1317	Ac-STF$r8AYWAQL$S-NH_2	1233	1505.79	753.90	753.94
1318	Ac-LEF$r8AYWAQL$S-NH_2	1234	1559.84	780.92	781.25
1319	Ac-LSF$r8AYWAQL$S-NH_2	1235	1517.83	759.92	759.93
1320	Ac-LTF$r8EYWAQL$S-NH_2	1236	1589.85	795.93	795.97
1321	Ac-LTF$r8SYWAQL$S-NH_2	1237	1547.84	774.92	774.96
1322	Ac-LTF$r8AYWEQL$S-NH_2	1238	1589.85	795.93	795.9
1323	Ac-LTF$r8AYWAEL$S-NH_2	1239	1532.83	767.42	766.96
1324	Ac-LTF$r8AYWASL$S-NH_2	1240	1490.82	746.41	746.46
1325	Ac-LTF$r8AYWAQL$E-NH_2	1241	1573.85	787.93	787.98
1326	Ac-LTF2CN$r8HYWAQL$S-NH_2	1242	1622.86	812.43	812.47
1327	Ac-LTF3Cl$r8HYWAQL$S-NH_2	1243	1631.83	816.92	816.99
1328	Ac-LTDip$r8HYWAQL$S-NH_2	1244	1673.90	837.95	838.01
1329	Ac-LTF$r8HYWAQTle$S-NH_2	1245	1597.87	799.94	800.04
1330	Ac-F$r8AY6clWEAL$A-NH_2	1246	1336.66	669.33	1338.56
1331	Ac-F$r8AYdl6brWEAL$A-NH_2	1247	1380.61	691.31	692.2
1332	Ac-F$r8AYdl6fWEAL$A-NH_2	1248	1320.69	661.35	1321.61
1333	Ac-F$r8AYdl4mWEAL$A-NH_2	1249	1316.72	659.36	659.36
1334	Ac-F$r8AYdl5clWEAL$A-NH_2	1250	1336.66	669.33	669.35
1335	Ac-F$r8AYdl7mWEAL$A-NH_2	1251	1316.72	659.36	659.36
1336	Ac-LTF%r8HYWAQL%A-NH_2	1252	1583.89	792.95	793.01
1337	Ac-LTF$r8HCouWAQL$S-NH_2	1253	1679.87	840.94	841.38
1338	Ac-LTFEHCouWAQLTS-NH_2	1254	1617.75	809.88	809.96
1339	Ac-LTA$r8HCouWAQL$S-NH_2	1255	1603.84	802.92	803.36
1340	Ac-F$r8AYWEAL$AbuA-NH_2	1256	1387.75	694.88	694.88
1341	Ac-F$r8AYWEAI$AA-NH_2	1257	1373.74	687.87	687.93

1342	Ac-F$r8AYWEANle$AA-NH_2	1258	1373.74	687.87	687.93
1343	Ac-F$r8AYWEAmlL$AA-NH_2	1259	1429.80	715.90	715.97
1344	Ac-F$r8AYWQAL$AA-NH_2	1260	1372.75	687.38	687.48
1345	Ac-F$r8AYWAAL$AA-NH_2	1261	1315.73	658.87	658.92
1346	Ac-F$r8AYWAbuAL$AA-NH_2	1262	1329.75	665.88	665.95
1347	Ac-F$r8AYWNleAL$AA-NH_2	1263	1357.78	679.89	679.94
1348	Ac-F$r8AbuYWEAL$AA-NH_2	1264	1387.75	694.88	694.96
1349	Ac-F$r8NleYWEAL$AA-NH_2	1265	1415.79	708.90	708.94
1350	Ac-F$r8FYWEAL$AA-NH_2	1266	1449.77	725.89	725.97
1351	Ac-LTF$r8HYWAQhL$S-NH_2	1267	1611.88	806.94	807
1352	Ac-LTF$r8HYWAQAdm$S-NH_2	1268	1675.91	838.96	839.04
1353	Ac-LTF$r8HYWAQIgl$S-NH_2	1269	1659.88	830.94	829.94
1354	Ac-F$r8AYWAQL$AA-NH_2	1270	1372.75	687.38	687.48
1355	Ac-LTF$r8ALWAQL$Q-NH_2	1271	1522.89	762.45	762.52
1356	Ac-F$r8AYWEAL$AA-NH_2	1272	1373.74	687.87	687.93
1357	Ac-F$r8AYWENleL$AA-NH_2	1273	1415.79	708.90	708.94
1358	Ac-F$r8AYWEAibL$Abu-NH_2	1274	1330.73	666.37	666.39
1359	Ac-F$r8AYWENleL$Abu-NH_2	1275	1358.76	680.38	680.38
1360	Ac-F$r8AYWEAL$Abu-NH_2	1276	1316.72	659.36	659.36
1361	Ac-F$r8AYWEAc3cL$AbuA-NH_2	1277	1399.75	700.88	700.95
1362	Ac-F$r8AYWEAc3cL$NleA-NH_2	1278	1427.79	714.90	715.01
1363	H-LTF$r8AYWAQL$S-NH_2	1279	1489.83	745.92	745.95
1364	mdPEG3-LTF$r8AYWAQL$S-NH_2	1280	1679.92	840.96	840.97
1365	mdPEG7-LTF$r8AYWAQL$S-NH_2	1281	1856.02	929.01	929.03
1366	Ac-F$r8ApmpEt6clWEAL$A-NH_2	1282	1470.71	736.36	788.17
1367	Ac-LTF3Cl$r8AYWAQL$S-NH_2	1283	1565.81	783.91	809.18
1368	Ac-LTF3Cl$r8HYWAQL$A-NH_2	1284	1615.83	808.92	875.24
1369	Ac-LTF3Cl$r8HYWWQL$S-NH_2	1285	1746.87	874.44	841.65
1370	Ac-LTF3Cl$r8AYWWQL$S-NH_2	1286	1680.85	841.43	824.63
1371	Ac-LTF$r8AYWWQL$S-NH_2	1287	1646.89	824.45	849.98
1372	Ac-LTF$r8HYWWQL$A-NH_2	1288	1696.91	849.46	816.67
1373	Ac-LTF$r8AYWWQL$A-NH_2	1289	1630.89	816.45	776.15
1374	Ac-LTF4F$r8AYWAQL$S-NH_2	1290	1549.83	775.92	776.15
1375	Ac-LTF2F$r8AYWAQL$S-NH_2	1291	1549.83	775.92	776.15
1376	Ac-LTF3F$r8AYWAQL$S-NH_2	1292	1549.83	775.92	785.12

1377	Ac-LTF34F2$r8AYWAQL$S-NH_2	1293	1567.83	784.92	785.12
1378	Ac-LTF35F2$r8AYWAQL$S-NH_2	1294	1567.83	784.92	1338.74
1379	Ac-F3Cl$r8AYWEAL$A-NH_2	1295	1336.66	669.33	705.28
1380	Ac-F3Cl$r8AYWEAL$AA-NH_2	1296	1407.70	704.85	680.11
1381	Ac-F$r8AY6clWEAL$AA-NH_2	1297	1407.70	704.85	736.83
1382	Ac-F$r8AY6clWEAL$-NH_2	1298	1265.63	633.82	784.1
1383	Ac-LTF$r8HYWAQLSt/S-$NH_2$	1299	16.03	9.02	826.98
1384	Ac-LTF$r8HYWAQL$S-NHsBu	1300	1653.93	827.97	828.02
1385	Ac-STF$r8AYWAQL$S-NH_2	1301	1505.79	753.90	753.94
1386	Ac-LTF$r8AYWAEL$S-NH_2	1302	1532.83	767.42	767.41
1387	Ac-LTF$r8AYWAQL$E-NH_2	1303	1573.85	787.93	787.98
1388	mdPEG3-LTF$r8AYWAQL$S-NH_2	1304	1679.92	840.96	840.97
1389	Ac-LTF$r8AYWAQhL$S-NH_2	1305	1545.86	773.93	774.31
1390	Ac-LTF$r8AYWAQCha$S-NH_2	1306	1571.88	786.94	787.3
1391	Ac-LTF$r8AYWAQChg$S-NH_2	1307	1557.86	779.93	780.4
1392	Ac-LTF$r8AYWAQCba$S-NH_2	1308	1543.84	772.92	780.13
1393	Ac-LTF$r8AYWAQF$S-NH_2	1309	1565.83	783.92	784.2
1394	Ac-LTF4F$r8HYWAQhL$S-NH_2	1310	1629.87	815.94	815.36
1395	Ac-LTF4F$r8HYWAQCha$S-NH_2	1311	1655.89	828.95	828.39
1396	Ac-LTF4F$r8HYWAQChg$S-NH_2	1312	1641.87	821.94	821.35
1397	Ac-LTF4F$r8HYWAQCba$S-NH_2	1313	1627.86	814.93	814.32
1398	Ac-LTF4F$r8AYWAQhL$S-NH_2	1314	1563.85	782.93	782.36
1399	Ac-LTF4F$r8AYWAQCha$S-NH_2	1315	1589.87	795.94	795.38
1400	Ac-LTF4F$r8AYWAQChg$S-NH_2	1316	1575.85	788.93	788.35
1401	Ac-LTF4F$r8AYWAQCba$S-NH_2	1317	1561.83	781.92	781.39
1402	Ac-LTF3Cl$r8AYWAQhL$S-NH_2	1318	1579.82	790.91	790.35
1403	Ac-LTF3Cl$r8AYWAQCha$S-NH_2	1319	1605.84	803.92	803.67
1404	Ac-LTF3Cl$r8AYWAQChg$S-NH_2	1320	1591.82	796.91	796.34
1405	Ac-LTF3Cl$r8AYWAQCba$S-NH_2	1321	1577.81	789.91	789.39
1406	Ac-LTF$r8AYWAQhF$S-NH_2	1322	1579.84	790.92	791.14
1407	Ac-LTF$r8AYWAQF3CF3$S-NH_2	1323	1633.82	817.91	818.15
1408	Ac-LTF$r8AYWAQF3Me$S-NH_2	1324	1581.86	791.93	791.32
1409	Ac-LTF$r8AYWAQ1Nal$S-NH_2	1325	1615.84	808.92	809.18
1413	Ac-LTF$r8AYWAQBip$S-NH_2	1326	1641.86	821.93	822.13
1414	Ac-LTF$r8FYWAQL$A-NH_2	1327	1591.88	796.94	797.33

1415	Ac-LTF$r8HYWAQL$S-NHAm	1328	1667.94	834.97	835.92
1416	Ac-LTF$r8HYWAQL$S-NHiAm	1329	1667.94	834.97	835.55
1417	Ac-LTF$r8HYWAQL$S-NHnPr3Ph	1330	1715.94	858.97	859.79
1418	Ac-LTF$r8HYWAQL$S-NHnBu3,3Me	1331	1681.96	841.98	842.49
1419	Ac-LTF$r8HYWAQL$S-NHnPr	1332	1639.91	820.96	821.58
1420	Ac-LTF$r8HYWAQL$S-NHnEt2Ch	1333	1707.98	854.99	855.35
1421	Ac-LTF$r8HYWAQL$S-NHHex	1334	1681.96	841.98	842.4
1422	Ac-LTF$r8AYWAQL$S-NHmdPeg2	1335	1633.91	817.96	818.35
1423	Ac-LTF$r8AYWAQL$A-NHmdPeg2	1336	1617.92	809.96	810.3
1424	Ac-LTF$r8AYWAQL$A-NHmdPeg4	1337	1705.97	853.99	854.33
1425	Ac-F$r8AYdl4mWEAL$A-NH_2	1338	1316.72	659.36	659.44
1426	Ac-F$r8AYdl5clWEAL$A-NH_2	1339	1336.66	669.33	669.43
1427	Ac-LThF$r8AYWAQL$S-NH_2	1340	1545.86	773.93	774.11
1428	Ac-LT2Nal$r8AYWAQL$S-NH_2	1341	1581.86	791.93	792.43
1429	Ac-LTA$r8AYWAQL$S-NH_2	1342	1455.81	728.91	729.15
1430	Ac-LTF$r8AYWVQL$S-NH_2	1343	1559.88	780.94	781.24
1431	Ac-LTF$r8HYWAAL$A-NH_2	1344	1524.85	763.43	763.86
1432	Ac-LTF$r8VYWAQL$A-NH_2	1345	1543.88	772.94	773.37
1433	Ac-LTF$r8IYWAQL$S-NH_2	1346	1573.89	787.95	788.17
1434	Ac-FTF$r8VYWSQL$S-NH_2	1347	1609.85	805.93	806.22
1435	Ac-ITF$r8FYWAQL$S-NH_2	1348	1607.88	804.94	805.2
1436	Ac-2NalTF$r8VYWSQL$S-NH_2	1349	1659.87	830.94	831.2
1437	Ac-ITF$r8LYWSQL$S-NH_2	1350	1589.89	795.95	796.13
1438	Ac-FTF$r8FYWAQL$S-NH_2	1351	1641.86	821.93	822.13
1439	Ac-WTF$r8VYWAQL$S-NH_2	1352	1632.87	817.44	817.69
1440	Ac-WTF$r8WYWAQL$S-NH_2	1353	1719.88	860.94	861.36
1441	Ac-VTF$r8AYWSQL$S-NH_2	1354	1533.82	767.91	768.19
1442	Ac-WTF$r8FYWSQL$S-NH_2	1355	1696.87	849.44	849.7
1443	Ac-FTF$r8IYWAQL$S-NH_2	1356	1607.88	804.94	805.2
1444	Ac-WTF$r8VYWSQL$S-NH_2	1357	1648.87	825.44	824.8
1445	Ac-FTF$r8LYWSQL$S-NH_2	1358	1623.87	812.94	812.8
1446	Ac-YTF$r8FYWSQL$S-NH_2	1359	1673.85	837.93	837.8
1447	Ac-LTF$r8AY6clWEAL$A-NH_2	1360	1550.79	776.40	776.14
1448	Ac-LTF$r8AY6clWSQL$S-NH_2	1361	1581.80	791.90	791.68
1449	Ac-F$r8AY6clWSAL$A-NH_2	1362	1294.65	648.33	647.67

1450	Ac-F$r8AY6clWQAL$AA-NH_2	1363	1406.72	704.36	703.84
1451	Ac-LHF$r8AYWAQL$S-NH_2	1364	1567.86	784.93	785.21
1452	Ac-LTF$r8AYWAQL$S-NH_2	1365	1531.84	766.92	767.17
1453	Ac-LTF$r8AHWAQL$S-NH_2	1366	1505.84	753.92	754.13
1454	Ac-LTF$r8AYWAHL$S-NH_2	1367	1540.84	771.42	771.61
1455	Ac-LTF$r8AYWAQL$H-NH_2	1368	1581.87	791.94	792.15
1456	H-LTF$r8AYWAQL$A-NH_2	1369	1473.84	737.92	737.29
1457	Ac-HHF$r8AYWAQL$S-NH_2	1370	1591.83	796.92	797.35
1458	Ac-aAibWTF$r8VYWSQL$S-NH_2	1371	1804.96	903.48	903.64
1459	Ac-AibWTF$r8HYWAQL$S-NH_2	1372	1755.91	878.96	879.4
1460	Ac-AibAWTF$r8HYWAQL$S-NH_2	1373	1826.95	914.48	914.7
1461	Ac-fWTF$r8HYWAQL$S-NH_2	1374	1817.93	909.97	910.1
1462	Ac-AibWWTF$r8HYWAQL$S-NH_2	1375	1941.99	972.00	972.2
1463	Ac-WTF$r8LYWSQL$S-NH_2	1376	1662.88	832.44	832.8
1464	Ac-WTF$r8NleYWSQL$S-NH_2	1377	1662.88	832.44	832.6
1465	Ac-LTF$r8AYWSQL$a-NH_2	1378	1531.84	766.92	767.2
1466	Ac-LTF$r8EYWARL$A-NH_2	1379	1601.90	801.95	802.1
1467	Ac-LTF$r8EYWAHL$A-NH_2	1380	1582.86	792.43	792.6
1468	Ac-aTF$r8AYWAQL$S-NH_2	1381	1489.80	745.90	746.08
1469	Ac-AibTF$r8AYWAQL$S-NH_2	1382	1503.81	752.91	753.11
1470	Ac-AmfTF$r8AYWAQL$S-NH_2	1383	1579.84	790.92	791.14
1471	Ac-AmwTF$r8AYWAQL$S-NH_2	1384	1618.86	810.43	810.66
1472	Ac-NmLTF$r8AYWAQL$S-NH_2	1385	1545.86	773.93	774.11
1473	Ac-LNmTF$r8AYWAQL$S-NH_2	1386	1545.86	773.93	774.11
1474	Ac-LSarF$r8AYWAQL$S-NH_2	1387	1501.83	751.92	752.18
1475	Ac-LGF$r8AYWAQL$S-NH_2	1388	1487.82	744.91	745.15
1476	Ac-LTNmF$r8AYWAQL$S-NH_2	1389	1545.86	773.93	774.2
1477	Ac-TF$r8AYWAQL$S-NH_2	1390	1418.76	710.38	710.64
1478	Ac-ETF$r8AYWAQL$A-NH_2	1391	1531.81	766.91	767.2
1479	Ac-LTF$r8EYWAQL$A-NH_2	1392	1573.85	787.93	788.1
1480	Ac-LT2Nal$r8AYWSQL$S-NH_2	1393	1597.85	799.93	800.4
1481	Ac-LTF$r8AYWAAL$S-NH_2	1394	1474.82	738.41	738.68
1482	Ac-LTF$r8AYWAQhCha$S-NH_2	1395	1585.89	793.95	794.19
1483	Ac-LTF$r8AYWAQChg$S-NH_2	1396	1557.86	779.93	780.97
1484	Ac-LTF$r8AYWAQCba$S-NH_2	1397	1543.84	772.92	773.19

1485	Ac-LTF$r8AYWAQF3CF3$S-NH_2	1398	1633.82	817.91	818.15
1486	Ac-LTF$r8AYWAQ1Nal$S-NH_2	1399	1615.84	808.92	809.18
1487	Ac-LTF$r8AYWAQBip$S-NH_2	1400	1641.86	821.93	822.32
1488	Ac-LT2Nal$r8AYWAQL$S-NH_2	1401	1581.86	791.93	792.15
1489	Ac-LTF$r8AYWVQL$S-NH_2	1402	1559.88	780.94	781.62
1490	Ac-LTF$r8AWWAQL$S-NH_2	1403	1554.86	778.43	778.65
1491	Ac-FTF$r8VYWSQL$S-NH_2	1404	1609.85	805.93	806.12
1492	Ac-ITF$r8FYWAQL$S-NH_2	1405	1607.88	804.94	805.2
1493	Ac-ITF$r8LYWSQL$S-NH_2	1406	1589.89	795.95	796.22
1494	Ac-FTF$r8FYWAQL$S-NH_2	1407	1641.86	821.93	822.41
1495	Ac-VTF$r8AYWSQL$S-NH_2	1408	1533.82	767.91	768.19
1496	Ac-LTF$r8AHWAQL$S-NH_2	1409	1505.84	753.92	754.31
1497	Ac-LTF$r8AYWAQL$H-NH_2	1410	1581.87	791.94	791.94
1498	Ac-LTF$r8AYWAHL$S-NH_2	1411	1540.84	771.42	771.61
1499	Ac-aAibWTF$r8VYWSQL$S-NH_2	1412	1804.96	903.48	903.9
1500	Ac-AibWTF$r8HYWAQL$S-NH_2	1413	1755.91	878.96	879.5
1501	Ac-AibAWTF$r8HYWAQL$S-NH_2	1414	1826.95	914.48	914.7
1502	Ac-fWTF$r8HYWAQL$S-NH_2	1415	1817.93	909.97	910.2
1503	Ac-AibWWTF$r8HYWAQL$S-NH_2	1416	1941.99	972.00	972.7
1504	Ac-WTF$r8LYWSQL$S-NH_2	1417	1662.88	832.44	832.7
1505	Ac-WTF$r8NleYWSQL$S-NH_2	1418	1662.88	832.44	832.7
1506	Ac-LTF$r8AYWSQL$a-NH_2	1419	1531.84	766.92	767.2
1507	Ac-LTF$r8EYWARL$A-NH_2	1420	1601.90	801.95	802.2
1508	Ac-LTF$r8EYWAHL$A-NH_2	1421	1582.86	792.43	792.6
1509	Ac-aTF$r8AYWAQL$S-NH_2	1422	1489.80	745.90	746.1
1510	Ac-AibTF$r8AYWAQL$S-NH_2	1423	1503.81	752.91	753.2
1513	Ac-AmfTF$r8AYWAQL$S-NH_2	1424	1579.84	790.92	791.2
1514	Ac-AmwTF$r8AYWAQL$S-NH_2	1425	1618.86	810.43	810.7
1515	Ac-NmLTF$r8AYWAQL$S-NH_2	1426	1545.86	773.93	774.1
1516	Ac-LNmTF$r8AYWAQL$S-NH_2	1427	1545.86	773.93	774.4
1517	Ac-LSarF$r8AYWAQL$S-NH_2	1428	1501.83	751.92	752.1
1518	Ac-TF$r8AYWAQL$S-NH_2	1429	1418.76	710.38	710.8
1519	Ac-ETF$r8AYWAQL$A-NH_2	1430	1531.81	766.91	767.4
1520	Ac-LTF$r8EYWAQL$A-NH_2	1431	1573.85	787.93	788.2
1521	Ac-WTF$r8VYWSQL$S-NH_2	1432	1648.87	825.44	825.2

1522	Ac-YTF$r8FYWSQL$S-NH_2	1433	1673.85	837.93	837.3
1523	Ac-F$r8AY6clWSAL$A-NH_2	1434	1294.65	648.33	647.74
1524	Ac-ETF$r8EYWVQL$S-NH_2	1435	1633.84	817.92	817.36
1525	Ac-ETF$r8EHWAQL$A-NH_2	1436	1563.81	782.91	782.36
1526	Ac-ITF$r8EYWAQL$S-NH_2	1437	1589.85	795.93	795.38
1527	Ac-ITF$r8EHWVQL$A-NH_2	1438	1575.88	788.94	788.42
1528	Ac-ITF$r8EHWAQL$S-NH_2	1439	1563.85	782.93	782.43
1529	Ac-LTF4F$r8AYWAQCba$S-NH_2	1440	1561.83	781.92	781.32
1530	Ac-LTF3Cl$r8AYWAQhL$S-NH_2	1441	1579.82	790.91	790.64
1531	Ac-LTF3Cl$r8AYWAQCha$S-NH_2	1442	1605.84	803.92	803.37
1532	Ac-LTF3Cl$r8AYWAQChg$S-NH_2	1443	1591.82	796.91	796.27
1533	Ac-LTF3Cl$r8AYWAQCba$S-NH_2	1444	1577.81	789.91	789.83
1534	Ac-LTF$r8AY6clWSQL$S-NH_2	1445	1581.80	791.90	791.75
1535	Ac-LTF4F$r8HYWAQhL$S-NH_2	1446	1629.87	815.94	815.36
1536	Ac-LTF4F$r8HYWAQCba$S-NH_2	1447	1627.86	814.93	814.32
1537	Ac-LTF4F$r8AYWAQhL$S-NH_2	1448	1563.85	782.93	782.36
1538	Ac-LTF4F$r8AYWAQChg$S-NH_2	1449	1575.85	788.93	788.35
1539	Ac-ETF$r8EYWVAL$S-NH_2	1450	1576.82	789.41	788.79
1540	Ac-ETF$r8EHWAAL$A-NH_2	1451	1506.79	754.40	754.8
1541	Ac-ITF$r8EYWAAL$S-NH_2	1452	1532.83	767.42	767.75
1542	Ac-ITF$r8EHWVAL$A-NH_2	1453	1518.86	760.43	760.81
1543	Ac-ITF$r8EHWAAL$S-NH_2	1454	1506.82	754.41	754.8
1544	Pam-LTF$r8EYWAQL$S-NH_2	1455	1786.07	894.04	894.48
1545	Pam-ETF$r8EYWAQL$S-NH_2	1456	1802.03	902.02	902.34
1546	Ac-LTF$r8AYWLQL$S-NH_2	1457	1573.89	787.95	787.39
1547	Ac-LTF$r8EYWLQL$S-NH_2	1458	1631.90	816.95	817.33
1548	Ac-LTF$r8EHWLQL$S-NH_2	1459	1605.89	803.95	804.29
1549	Ac-LTF$r8VYWAQL$S-NH_2	1460	1559.88	780.94	781.34
1550	Ac-LTF$r8AYWSQL$S-NH_2	1461	1547.84	774.92	775.33
1551	Ac-ETF$r8AYWAQL$S-NH_2	1462	1547.80	774.90	775.7
1552	Ac-LTF$r8EYWAQL$S-NH_2	1463	1589.85	795.93	796.33
1553	Ac-LTF$r8HYWAQL$S-NHAm	1464	1667.94	834.97	835.37
1554	Ac-LTF$r8HYWAQL$S-NHiAm	1465	1667.94	834.97	835.27
1555	Ac-LTF$r8HYWAQL$S-NHnPr3Ph	1466	1715.94	858.97	859.42
1556	Ac-LTF$r8HYWAQL$S-NHnBu3,3Me	1467	1681.96	841.98	842.67

1557	Ac-LTF$r8HYWAQL$S-NHnBu	1468	1653.93	827.97	828.24
1558	Ac-LTF$r8HYWAQL$S-NHnPr	1469	1639.91	820.96	821.31
1559	Ac-LTF$r8HYWAQL$S-NHnEt2Ch	1470	1707.98	854.99	855.35
1560	Ac-LTF$r8HYWAQL$S-NHHex	1471	1681.96	841.98	842.4
1561	Ac-LTF$r8AYWAQL$S-NHmdPeg2	1472	1633.91	817.96	855.35
1562	Ac-LTF$r8AYWAQL$A-NHmdPeg2	1473	1617.92	809.96	810.58
1563	Ac-LTF$r5AYWAAL$s8S-NH_2	1474	1474.82	738.41	738.79
1564	Ac-LTF$r8AYWCouQL$S-NH_2	1475	1705.88	853.94	854.61
1565	Ac-LTF$r8CouYWAQL$S-NH_2	1476	1705.88	853.94	854.7
1566	Ac-CouTF$r8AYWAQL$S-NH_2	1477	1663.83	832.92	833.33
1567	H-LTF$r8AYWAQL$A-NH_2	1478	1473.84	737.92	737.29
1568	Ac-HHF$r8AYWAQL$S-NH_2	1479	1591.83	796.92	797.72
1569	Ac-LT2Nal$r8AYWSQL$S-NH_2	1480	1597.85	799.93	800.68
1570	Ac-LTF$r8HCouWAQL$S-NH_2	1481	1679.87	840.94	841.38
1571	Ac-LTF$r8AYWCou2QL$S-NH_2	1482	1789.94	895.97	896.51
1572	Ac-LTF$r8Cou2YWAQL$S-NH_2	1483	1789.94	895.97	896.5
1573	Ac-Cou2TF$r8AYWAQL$S-NH_2	1484	1747.90	874.95	875.42
1574	Ac-LTF$r8ACou2WAQL$S-NH_2	1485	1697.92	849.96	850.82
1575	Dmaac-LTF$r8AYWAQL$S-NH_2	1486	1574.89	788.45	788.82
1576	Hexac-LTF$r8AYWAQL$S-NH_2	1487	1587.91	794.96	795.11
1577	Napac-LTF$r8AYWAQL$S-NH_2	1488	1657.89	829.95	830.36
1578	Pam-LTF$r8AYWAQL$S-NH_2	1489	1728.06	865.03	865.45
1579	Ac-LT2Nal$r8HYAAQL$S-NH_2	1490	1532.84	767.42	767.61
1580	Ac-LT2Nal$/r8HYWAQL$/S-NH_2	1491	1675.91	838.96	839.1
1581	Ac-LT2Nal$r8HYFAQL$S-NH_2	1492	1608.87	805.44	805.9
1582	Ac-LT2Nal$r8HWAAQL$S-NH_2	1493	1555.86	778.93	779.08
1583	Ac-LT2Nal$r8HYAWQL$S-NH_2	1494	1647.88	824.94	825.04
1584	Ac-LT2Nal$r8HYAAQW$S-NH_2	1495	1605.83	803.92	804.05
1585	Ac-LTW$r8HYWAQL$S-NH_2	1496	1636.88	819.44	819.95
1586	Ac-LT1Nal$r8HYWAQL$S-NH_2	1497	1647.88	824.94	825.41

[00361] Observed mass was measured by electrospray ionization-mass spectrometry.

[00362] In some embodiments, a peptidomimetic macrocycles disclosed herein do not comprise a peptidomimetic macrocycle structure as shown in **Table 4b**.

[00363] **Table 4c** shows examples of non-crosslinked polypeptides comprising D-amino acids.

Table 4c

SP	Sequence	SEQ ID NO:	Isomer	Exact Mass	Found Mass	Calc (M+1)/1	Calc (M+2)/2	Calc (M+3)/3
1587	Ac-tawyanfekllr-NH_2	1498			777.46			
1588	Ac-tawyanf4CF3ekllr-NH_2	1499			811.41			

Example 2: Cell Viability assay

[00364] Cells were thawed from a liquid nitrogen preserved state. Once cells were expanded and divide at their expected doubling times, screening began. Cells were seeded in growth media in black 384-well tissue culture treated plates at 500 cells/well. Cells were equilibrated in assay plates via centrifugation and placed in incubators attached to the Dosing Modules at 37 °C for 24 hr before treatment, resulting in cell densities of approximately 500 cells/plate. At the time of treatment, a set of assay plates (which did not receive treatment) were collected and ATP levels were measured by adding ATPLite (Perkin Elmer). These T-zero (T_0) plates were read using ultra-sensitive luminescence on Envision Plate Readers. Using an automated acoustic dispensing system, assay plates were treated with compound or peptide from a 1000x DMSO stock, achieving a 1:1000 working dilution. Final treatment concentrations in the plates were 0 (vehicle), 0.001, 0.003, 0.01, 0.03, 0.1, 0.3, 1, 3, 10 and 30 μM. The assay plates (4 replicates per treatment) were incubated with compound or peptide for 72 hr. After 72 hr, plates were developed for endpoint analysis using ATPLite. All data points were collected via automated processes; quality controlled; and analyzed using Zalicus proprietary software. Assay plates were accepted if they passed the following quality control standards: relative luciferase values were consistent throughout the entire experiment, Z-factor scores were greater than 0.6, and untreated/vehicle controls behaved consistently on the plate.

[00365] Growth Inhibition (GI), used as a measure of cell viability, was measured at the time of dosing (T_0) and after 72 hr (T_{72}). A GI reading of 0% represents no growth inhibition; a GI 100% represents complete growth inhibition, a cytostatic effect. A GI 200% represents complete death of all cells in the culture well. Compounds reaching an activity plateau of GI 200% were considered cytotoxic. GI was calculated by the following test and equation:

If $T < V_0$:$100 * (1 - \frac{T - V_0}{V_0})$

If $T \geq V_0$:$100 * (1 - \frac{T - V_0}{V - V_0})$

[00366] Where T is the signal measure for a test article, V is the vehicle-treated control measure, and V_0 is the vehicle control measure at time zero. This formula was derived from the Growth Inhibition calculation used in the National Cancer Institute's NCI-60 high throughput screen

[00367] Cell lines were assigned as p53 wild-type, mutant, or null from information available from the Cancer Cell Line Encyclopedia. Results for exemplary p53 peptidomimetic macrocycles are shown in **Table 5** below

Table 5: Cell Viability in **$p53^{WT}$ / $p53^{MUT}$** cancer cell lines

Cell lines	Cancer Type	$p53^{WT}$ / $p53^{MUT}$	SP-154	SP-763
			EC_{50} (μM)	EC_{50} (μM)
A2058	skin	$p53^{MUT}$	18.6	30
AsPC-1	Pancreas	$p53^{MUT}$	30	30
Caov-3	ovary	$p53^{MUT}$	12.9	30
Caov-4	ovary	$p53^{MUT}$	30	30
COLO-679	skin	$p53^{MUT}$	13.5	30
COLO-684	endometrium	$p53^{MUT}$	10.1	30
COLO-741	skin	$p53^{MUT}$	18.5	30
EBC-1	Lung-NSCLC	$p53^{MUT}$	30	30
ECC10	gastric	$p53^{MUT}$	15.2	30
KM12	colorectal	$p53^{MUT}$	30	30
LS-123	colorectal	$p53^{MUT}$	30	30
MIA PaCa-2	pancreas	$p53^{MUT}$	30	30
NCI-H508	colorectal	$p53^{MUT}$	30	30
OVCAR-3	ovary	$p53^{MUT}$	30	30
RPMI-7951	skin	$p53^{MUT}$	10.8	30
SF126	brain	$p53^{MUT}$	11	30
SK-OV-3	ovary	$p53^{MUT}$	14.3	30
SW480	colorectal	$p53^{MUT}$	30	30
HCT-116	colorectal	$p53^{WT}$	0.464	1.02
HEC-151	endometrium	$p53^{WT}$	1.19	30
HEC-265	endometrium	$p53^{WT}$	1.78	30
HUH-6-clone5	liver	$p53^{WT}$	0.865	0.791
IST-MES1	lung	$p53^{WT}$	1.43	30
KP-N-RT-BM-1	nerve	$p53^{WT}$	0.285	0.255
KP-N-S19s	nerve	$p53^{WT}$	0.176	0.0168
LoVo	colorectal	$p53^{WT}$	0.431	0.134
LS-174T	colorectal	$p53^{WT}$	0.402	0.205
MSTO-211H	lung	$p53^{WT}$	0.288	0.209
MV-4-11	AML	$p53^{WT}$	0.159	0.307
NCI-H929	multiple myeloma	$p53^{WT}$	0.858	0.24
PA-1	ovary	$p53^{WT}$	0.339	0.592
WM-115	skin	$p53^{WT}$	0.425	0.429
COLO-205	colorectal	$p53^{WT}$	0.646	0.429
COLO-849	skin	$p53^{WT}$	1.66	0.501
NCI-H28	lung	$p53^{WT}$	3.42	30

Example 3: Safety and/or tolerability study- I

Study Objectives

[00368] This study was designed to (i) evaluate the safety and/or tolerability of Aileron peptide 1, and to (ii) determine the DLTs and the MTD of the Aileron peptide 1 in patients with advanced solid tumors,

including patients with tumors expressing WT p53 protein. Aileron peptide 1is an alpha helical hydrocarbon cross-linked polypeptide macrocycle, with an amino acid sequence less than 20 amino acids long that is derived from the transactivation domain of wild type human P53 protein and that contains a phenylalanine , a tryptophan and a leucine amino acid in the same positions relative to each other as in the transactivation domain of wild type human P53 protein. Aileron peptide 1 has a single cross link spanning amino acids in the i to the i+7 position of the amino acid sequence and has more than three amino acids between the i+7 position and the carboxyl terminus. Aileron peptide 1 binds to human MDM2 and MDM4 and has an observed mass of 950-975 m/e as measured by electrospray ionization-mass spectrometry.

Investigational Plan

Study Design

[00369] The study consisted of a Dose Escalation Phase (DEP) and an Expansion Phase (EXP). The DEP was a "3+3" dose escalation design to establish the MTD of Aileron peptide-1. The EXP enrolled patients with specific solid tumors at the MTD 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 solid cancer cell lines (e.g., breast, bladder, head/neck, gastrointestinal, liver, lung, pancreas, prostate, sarcoma) that facilitates the comparison of cell line sensitivity to Aileron peptide-1 across and within tumor types.

[00370] After completing the screening, eligible patients received a single IV dose of Aileron peptide-1 on Days 1, 8, and 15, and remained in the clinic for approximately 8 hours after dosing completion for clinical evaluation, laboratory testing and pharmacokinetic assessments. In addition, a tumor biopsy was performed within 48 hours of Dose 3 (last dose) in Cycle 1 or 2 for pharmacodynamic assessment, unless the biopsy posed a significant risk to the patient. The selection of Cycle 1 or 2 was made at the discretion of the Investigator. Patients returned to the clinic for additional observation and laboratory assessments on Day 22 and for end-of-cycle assessments on Day 29.

[00371] Treatment of patients in the dose escalation and the dose expansion phases of the study continued until documentation of disease progression, unacceptable toxicity, or patient or physician decision to discontinue therapy.

p53 Status Determination and Tumor Sampling Requirement prior to Enrollment:

[00372] A central laboratory tested both archived tissue samples or fresh biopsy samples from all patients enrolled in the study for p53 status using Next-Generation Sequencing (NGS).

[00373] For the First 3 Dose Levels of Stage 1:

[00374] Patients were enrolled irrespective of p53 status. Nevertheless, patients were still tested for p53 status at the central laboratory. To this end, archived tissue was used (sample were not older than 3 years), or alternatively, a fresh biopsy was considered, unless the biopsy posed a significant risk to the patient.

[00375] Starting at Dose Level 4 of Stage 1 (and for patients enrolled in Stage 2 of the DEP):

[00376] Only patients with tumors expressing WT p53 protein were enrolled. This key inclusion criterion was based on the proposed mechanism of action of Aileron peptide-1, which requires WT p53 protein to be pharmacologically active. The inclusion criterion is also supported by results of *in vitro* tumor growth assays, in which Aileron peptide-1 demonstrated activity in tumor cells expressing WT p53 protein, but not in cells with null-mutations of p53. Patients met the p53 requirement through one of the following scenarios:

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

[00377] For patients enrolling into the EXP:

- Only patients with tumors expressing p53 WT were enrolled, and all patients were tested for p53 status using NGS at the central laboratory PRIOR to enrollment. Archived tissue were used (if sample were not older than 1 year), or alternatively, a fresh biopsy was considered, unless the biopsy posed a significant risk to the patient. Patients who didn't have archived tissue and for whom a biopsy posed a significant risk, were not enrolled.

[00378] Only patients with tumors expressing WT p53 protein were enrolled. The determination of p53 status was performed on tumor samples obtained during the screening period. The assay was performed by study sites with required capabilities; otherwise it was performed at a central laboratory. Results from archival tissue samples, if available, could also be used to determine patient eligibility in the DEP. The total number of patients enrolled in the study depended on the number of dose levels and the number of patients in each cohort before MTD is established. Approximately 27 adult patients, exclusive of replacements for patients who discontinue for non-safety reasons, were enrolled in the DEP, and approximately 30 additional patients were enrolled in the EXP. Enrollment of a total of up to 60 patients was planned for the study. Up to 6 clinical sites in the US were planned. The expected accrual phase is approximately 24 months. The expected follow-up phase is approximately 9 months after the last patient is enrolled, for a total study duration of approximately 33 months.

[00379] Patients who satisfy all inclusion and exclusion criteria, including documentation of WT p53 status, were enrolled in cohorts of 3 to 6 patients to receive Aileron peptide 1. Aileron peptide 1 was administered by IV infusion over 1 hour (±15 min) on Days 1, 8 and 15 of each 28-day cycle. Treatment continued until disease progression, unacceptable toxicity or patient or physician withdrawal of consent. After the MTD was established, approximately 30 additional patients were

enrolled in an expansion cohort to gain further experience at this dose level and in particular patient or tumor types.

[00380] Safety was 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 used the NCI CTCAE version 4.0 to assess the severity of AEs.

[00381] Because the primary objectives of this study were based on safety and pharmacokinetic, statistical analyses were descriptive in nature and accounted 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 RECIST 1.1. Patients who received at least one dose of Aileron peptide 1 constituted the safety population and were be included in all safety analyses. Patients who completed at least one cycle of Aileron peptide 1 and underwent a post-treatment objective disease assessment constituted the efficacy-evaluable patient population.

[00382] PATIENT POPULATION

[00383] Inclusion criterias

[00384] All patients were 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 malignancy that is metastatic or unresectable and for which standard curative measures do not exist or are no longer effective; (iii) WT p53 status for the relapsing or treatment-refractory solid 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 RECIST 1.1; (v) ECOG performance status 0-1; (vi) predicted life expectancy of $\geq$3 months; (vii) adequate hematologic function, measured within 7 days prior to the first dose of Aileron peptide 1 (defined as: ANC $\geq 1.5 \times 10^9$/L, Hemoglobin $\geq$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 Aileron peptide 1 (defined as: in the absence of disease involvement in the liver:bilirubin $\leq$1.5 times institutional ULN: AST and ALT $\leq$2.5 times ULN; in the presence of disease involvement in the liver:bilirubin $\leq$2 times ULN: AST and ALT $\leq$5 times ULN, (ix) adequate renal function, measured within 7 days prior to the first dose of Aileron peptide 1, (defined as: urinalysis with no evidence of +2 or higher proteinuria, serum creatinine $\leq$1.5 times institutional ULN or calculated creatinine clearance $\geq$50 mL/min (Cockcroft-Gault formula)); (x) acceptable coagulation profile, measured within 7 days prior to the first dose of Aileron peptide 1 (defined as: PT or INR $\leq$1.5 times ULN; aPTT $\leq$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 $\leq$2 weeks prior to the first dose of Aileron peptide 1 is acceptable if acute toxicity has resolved; (xii) negative serum pregnancy test within 14 days prior to the first dose of Aileron 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 Aileron peptide 1 and for 30 days after the last dose of Aileron 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 Aileron peptide 1.

[00385] Exclusion criterias

[00386] Patients who meet any of the following criteria at screening or Day -1 were 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 Aileron 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 Aileron 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 Aileron 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 Aileron peptide 1 infusion; (xvii) the use of any investigational agents within 4 weeks or 5 circulating half-lives prior to the first dose of Aileron peptide 1.

Patient removal/replacement from study therapy

[00387] A patient was 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

[00388] Any patient who completed enrollment and did not receive a dose of Aileron peptide 1 was replaced. A patient in the dose escalation portion of the study who discontinued the study prior to completion of the first cycle for reasons other than safety was replaced. A patient in the dose expansion portion of the study who discontinued the study participation prior to the completion of the first cycle of treatment for any reason was replaced.

TREATMENT PLAN

Drug administration Study -1

[00389] The study drug was the investigational agent Aileron peptide 1. This investigational agent was be distributed to clinical sites. Patients began treatment with Aileron peptide 1 within 21 days following the start of screening. Aileron peptide 1 drug was be a frozen liquid product supplied in single-use glass vials. The peptidomimetic macrocycle for injection was stored frozen at ≤ -15°C. Aileron peptide 1 was introduced into an IV infusion bag containing D5W; known as Aileron peptide 1 dosing solution, and was provided by the site pharmacy for administration to the patient. Aileron peptide 1 dosing solution was labeled with a patient identification number. An investigative staff confirmed this information and its relevancy to the intended patient.

[00390] Aileron peptide 1 was administered by IV infusion in D5W over 1 hour (±15 min) on Days 1, 8 and 15 of each 28-day treatment cycle. The pre-defined dose were calculated for each patient based on body weight at the start of each cycle. Aileron peptide 1 was not administered outside of the planned schedule (i.e., infusions on Days 1, 8 and 15 of a 28-day cycle). Deviations if any were noted on the

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

[00391] In case of infusion-related reactions, Aileron peptide 1 infusion were temporarily discontinued. Pharmacologic agents and other therapeutic interventions were administered per institutional guidelines. The decision to re-start Aileron peptide 1 infusion was made after a careful assessment of the patient.

Starting dose, dose escalation and dose reduction

Dose Levels for the Dose Escalation Portion of Study

[00392] In the Dose Escalation portion of the study, increasing dose levels of Aileron peptide 1 was evaluated in cohorts of 3-6 patients. Aileron peptide 1 was administered by IV infusion over 1 hour (±15 min) on Days 1, 8 and 15 of each 28-day cycle. Patients enrolled in Cohort 1 received Aileron peptide 1 at Dose Level 1 (0.16 mg/kg). 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.

[00393] In the absence of DLT, subsequent cohorts of 3 to 6 patients received escalated doses until the MTD was established.

[00394] A 2-stage dose escalation design was employed. During the initial Stage 1 Escalation Phase (**Table 6**), 100% dose increments was 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 continued using 3-patient cohorts and the modified Fibonacci sequence (i.e., Stage 2 Escalation Phase; **Table 7**), until the MTD was established.

Table 6: Stage 1 Dose escalation schedule

Dose Level	Aileron peptide 1 Dose (mg/kg)
Level -2	0.04
Level -1	0.08
Level 1	0.16
Level 2	0.32
Level 3	0.64
Level 4	1.25
Level 5	2.5
Level 6	5
Continue 100% dose increase in subsequent cohorts until the MTD is established or Stage 2 escalation schedule is initiated	

Table 7: Stage 2 Dose escalation Schedule

Dose Level	Aileron peptide 1 Dose (mg/kg)
Level 1	Last Stage 1 Dose x 1.67
Level 2	Previous Dose x 1.5
Level 3	Previous Dose x 1.4

Level 4	Previous Dose x 1.33
In the absence of DLT, continue dose escalation at 33% increments after Stage 2 Level 4 until the MTD is established	

[00395] The escalation scheme were switched to the Stage 2 Escalation Schedule at any point that the Investigators, Sponsor's Medical Monitor and Safety Physician representative agreed on a more conservative progression.

[00396] The observation of DLT(s) was used to make individual patient determinations regarding dose reductions, interruptions or discontinuation throughout the course of the trial, but DLTs occurring during Cycle 1 were used to inform safety and tolerability assessments for dose escalation decisions.

[00397] If DLTs was observed in the first cohort, the dose was de-escalated to Dose Level -1. If DLTs were observed at Dose Level -1, the dose was de-escalated to Dose Level -2. If DLTs was observed at Dose Level -2, other dose levels were considered and implemented after discussions among the Investigators, Sponsor's Medical Monitor and Safety Physician representative.

[00398] At least three patients were treated at each dose level. If no patients experience a DLT, then the subsequent 3 patients were treated at the next planned dose level.

[00399] If DLT was observed in ≥2 of 3 patients in a cohort, then no further dose escalation occurred, and the current dose was defined as the MAD.

[00400] If DLT was observed in 1 of 3 patients, then up to 3 additional patients were enrolled at that same dose level. If DLT was observed in ≥2 patients in the expanded cohort, then no further dose escalation will occur, and the current dose was defined as the MAD.

[00401] After the MAD was defined, either the previously administered lower dose was expanded to a total of 6 patients, or an intermediate (between the MAD and the next lower dose level) was investigated in up to six patients. The highest dose tolerated without DLT in at least 5 of 6 patients in a cohort was defined as the MTD.

Dose Level for the Expansion Portion of Study

[00402] After the MTD was defined, approximately 30 additional patients were enrolled in an expansion study to gain further experience at this dose level and investigate the effect of Aileron peptide 1 in specific patient or tumor types. Two disease types were selected for evaluation, and 15 patients of each disease type were enrolled in each of two cohorts in the expansion study. The dose of Aileron peptide 1 administered to patients in the expansion cohort was derived from evaluation of available safety and other information from patients in the dose escalation portion of the study.

Intra-Patient Dose Escalation

[00403] Intra-patient dose escalation was not permitted.

Dose and Schedule Adjustments for Toxicity

[00404] Toxicity that occurred during a cycle was required to recover as outlined below for treatment to continue.

[00405] 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.

[00406] If a clinically significant AE was observed in a patient during a treatment cycle, further dosing was be 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 was based on the most severe AE. Any patient who experienced recurrent, clinically significant AE after one dose reduction underwent one additional dose reduction. Patients who continued to experience clinically significant toxicity after a 2-week delay or two dose reductions were discontinued from the study.

[00407] Adverse events considered for dose reduction did not include the events assessed by the investigator as exclusively related to underlying disease or other medical condition or concomitant treatment. A patient who experienced an AE considered related to Aileron peptide 1 continued on study if the patient was receiving clinical benefit and/or the Investigator felt continued participation was 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 was reduced to the preceding lower level.

[00408] Up to two dose reductions for a patient were permitted, after which the patient were discontinued from the study.

[00409] A patient who experienced a DLT continued 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 had been reduced for a patient, it was not re-escalated.

[00410] Toxicity grading was based on NCI CTCAE v4.0.

Statistical Methods

[00411] Statistical analyses of safety and efficacy for DEP and EXP were primarily descriptive in nature because the objectives of the study were to determine the DLTs and MTD. These objectives were achieved by the results of a deterministic algorithm; thus, statistical hypothesis testing was neither intended nor appropriate within this context. Continuous variables were summarized using descriptive statistics [n, mean, standard deviation, median, minimum, and maximum]. Categorical variables were=e summarized showing the number and percentage (n, %) of patients within each classification.

Study Procedures

Schedule of study events

[00412] The schedule of study activities, including assessments, tests, exams, disease assessments, submission of tissue specimens, and study drug administration) that will be conducted, beginning with screening and continuing through Cycle 1 [day 1, day 8, and day 15 of a 28 day cycle] are outlined in **Table 8**. Study that will be conducted beginning with Cycle 2 [day 29 of cycle 1 = day 1 of cycle 2] are listed on **Table 9**.

Table 8: Schedule of study activities through Cycle 1

	Molecular Screen	**Clinical Screen -21 days**	**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 ±3 d**
				pre-dose	post-dose			pre-dose	post-dose	pre-dose	post-dose			Refer to **Table 9**
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	
Physical exam		X		X				X		X				
12-lead ECG		X		X	X									
Laboratory assessments: Clinical chemistry (glucose, calcium, albumin, total protein, sodium, potassium, CO_2, chloride, BUN [blood urea nitrogen], serum creatinine, ALP, ALT, AST, total		X	X			X	X	X		X		X	X	

and direct bilirubin), hematology (complete blood count, platelets and differential), urinalysis (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										
Collection of blood for biomarker assessments				X		X	X	X	X	X	X	X	X	
Collection of blood for pharmacokinetic assessments				X	X	X	X	X	X	X	X	X		
ECOG Performance Status		X	X					X		X				
Needle biopsy for biomarker assessments		X										X		
Tumor Assessment		X												
Aileron 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: Schedule of study activities through Cycle 2

	Day 29 of prior cycle / Day 1 of next cycle for patients continuing treatment ±3 d		**Day 8** ±1 d		**Day 15** ±1 d		**Day 16** ±2 d	**After even numbered cycles**	**End-of-Study** 30 ±3 d after last dose or study withdrawal
	Pre-dose	post-dose	pre-dose	Post-dose	pre-dose	post-dose			
Serum pregnancy									X
Vital signs: Blood pressure,	X	X	X	X	X	X	X		X

pulse, respiration rate, body temperature.									
Physical exam	X		X		X				X
12-lead ECG	X pre-dose and EOI (+10 min)	X At pre-dose and EOI (+10 min)							X
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	X			X		X		X
Collection of blood for pharmacokinetic 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
Aileron peptide 1 dosing	X		X		X				
Concomitant medications	X	X	X	X	X	X	X		X
AE assessment (begins at the point of the first Aileron peptide 1 infusion and continues until	X	X	X	X	X	X	X		X

30 days after last infusion)									

Pharmacokinetic Analysis

[00413] Levels of Aileron peptide 1 and its metabolites will be measured in blood samples collected at specific time points described below. Pharmacokinetic data will be tabulated and summarized by individual patient and collectively by dose level. Graphical displays will be provided where useful in the interpretation of results.

[00414] Blood samples for pharmacokinetic assessment will be collected at the following time points:

Table 10: Time points for collection of blood samples for pharmacokinetic assessment

Cycle 1	
Day 1	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	24 hours (±4 hr) after the start of Day 1 infusion
Day 3	48 hours (±4 hr) after the start of Day 1 infusion
Day 8	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	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	24 hours (±4 hrs) after the start of Day 15 infusion
Cycle 2	
Cycle 1 Day 29/ Cycle 2 Day 1	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	within one hour SOI
	EOI (±5 min)
	30 min after EOI (±5 min)
Day 15 (cont.)	1 hr after EOI (±5 min)
	2 hr after EOI (±10 min)

	4 hr after EOI (±10 min)
Day 16	24 hours (±4 hrs) after the start of Day 15 infusion
End of study visit	During end of study visit

[00415] SOI stands for start of infusion of the Aileron peptide 1; EOI stands for the end of infusion of the Aileron peptide 1.

Pharmacodynamic Analysis

[00416] Levels of p53, MDM2, MDMX, p21 and caspase will be measured in tumor specimens collected before beginning treatment and at the end of Cycle 1 or Cycle 2. MIC-1 will be measured in blood samples. The specific time points for blood and tissue collection for pharmacodynamic assessments are described below. Pharmacodynamic data will be tabulated and summarized by individual patient and collectively by dose level. Graphical displays will be provided where useful in the interpretation of results.

[00417] Results available from previous genetic and biomarker tests, and additional tests of the blood and tumor samples for biomarkers relevant to the safety and efficacy of Aileron peptide-1 can be investigated for possible correlation with patient outcome.

[00418] Blood samples for pharmacodynamic assessments will be collected at the following time points:

Table 11: Time points for collection of blood samples for pharmacodynamic assessments

Cycle 1	
Day 1	within 1 hour before the start of infusion (SOI)
Day 2	24 hours (±4 hr) after the start of Day 1 infusion
Day 3	48 hours (±4 hr) after the start of Day 1 infusion
Day 8	within 1 hour before SOI within 1 hour after the end of infusion (EOI)
Day 15	within 1 hour before SOI within 1 hour after EOI
Day 16	24 hours (±4 hrs) after the start of Day 15 infusion
Day 22	During Day 22 visit
Each Subsequent Cycle Starting in Cycle 2	
Cycle 1 Day 29/ Cycle 2 Day 1	within 1 hour before SOI within 1 hour after EOI
Day 15	within 1 hour before SOI
Day 16	24 hours (±4 hrs) after the start of Day 15 infusion
End of study visit	During end of study visit

Assessment of clinical activity of the peptidomimetic macrocycle

[00419] To evaluate clinical activity, response rates and duration of response based on RECIST 1.1 or other appropriate criteria will be provided with a case-by-case description of all patients who exhibit CR, PR or SD. A descriptive analysis of other evidence of anti-tumor activity or other clinical benefit will be provided based on clinical, radiographic or other appropriate assessment of efficacy or clinical anti-tumor activity. Analysis of clinical activity will be 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.

[00420] Imaging scans, physical examination, and/or laboratory-based assays (e.g., prostate specific antigen) for patients with relevant disease indications will be obtained at baseline (within 21 days of Cycle 1 Day 1) and for objective tumor assessment after the second cycle of treatment and after every second treatment cycle thereafter (Cycle 4, Cycle 6, etc.). The same type of imaging, physical examination, or laboratory-based assay procedure will be used for each assessment for a patient. RECIST 1.1 will be used to assess tumor response and duration of response. Scheduled scans (and/or other laboratory-based assay) will be interpreted prior to the start of the next treatment cycle. If the criteria for a CR or PR are met, then the scan will be repeated no earlier than within 4 weeks to confirm the response. A responding patient (CR, PR or SD) will continue on study, with disease assessment after every second cycle, until disease progression, withdrawal of informed consent, or unacceptable toxicity.

[00421] Films or other records from imaging procedures, including those procedures performed at a regional or other facility outside of the primary institutions, will be read and reviewed by the radiology staff at the corresponding primary study institution for the patient.

Drug administration Study -II

[00422] Study Objectives

[00423] This Phase I open-label, multi-center, dose-escalation, 2-arm study was designed to evaluate the safety, tolerability, pharmacokinetic, pharmacodynamic, and anti-tumor effects of Aileron peptide-1 administered by IV infusion using 2 different dosing regimens of a 28- or 21-day cycle, in patients with advanced solid tumors or lymphomas expressing WT p53 protein (see p53 Status Determination below). Patients received Aileron 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 solid tumor or lymphoma present circulating tumor cells (CTC) in peripheral blood, which can be detected and analyzed using flow cytometry. This enabled the detection of study drug-specific target engagement in these cells.

[00424] This study consisted of a DEP and a EXP. The DEP was a "3+3" dose escalation designed to establish the MTD or the OBD of Aileron peptide-1. The EXP enrolled up to 2 distinct groups of patients with specific solid tumors to further investigate the clinical safety profile and potential efficacy of Aileron peptide-1 at the MTD or OBD.

Starting Dose, Dose Escalation, and Dose Reduction

[00425] All subjects were dosed at a pre-defined level based on body weight. Starting at Dose Level (DL) 3, patients was sequentially assigned to one of two treatment arms: Dose Regimen (DR) A testing administration of Aileron peptide-1 once per week, or Dose Regimen (DR) B testing administration of Aileron peptide-1 twice per week. For Dose Level 3, DR- A were enrolled first, DR-B were enrolled

second. The starting dose (DL-1) in DEP, based on results from nonclinical toxicology assessments, was 0.16 mg/kg.

[00426] During the first 2 dose levels, patients received Aileron peptide-1 on Days 1, 8, and 15 of a 28-day cycle. Starting with DL 3, patients in DR- A continued being treated once a week on Days 1, 8, and 15 of a 28-day cycle, whereas patients in DR- B were treated twice a week, on Days 1 and 4, 8 and 11 of a 21-day cycle. This dosing schedule is summarized in Figure 2.

[00427] Doses were doubled in subsequent dose levels until ≥ 1 of 3 patients in a cohort experienced any drug-related Grade ≥ 2 adverse event (AE). A drug-related AE is an event that is possibly, probably or definitely attributed to Aileron peptide-1. Grading of AEs was defined by the NCI Common Terminology Criteria for Adverse Events (CTCAE) version 4.03. Subsequent dose escalation continued using modified Fibonacci sequence (i.e., 67%, 50%, 40%, and 33%; Figure 3 and 4).

[00428] Escalation to the next dose level within each DR proceeded in the absence of DLT at the completion of Cycle 1 (treatment cycle = 28 days for DR-A and 21 days for DR-B). Escalation to the next dose level within each DR was decided by a Safety Review Committee (SRC), consisting of the Principal Investigators, Sponsor's Medical Monitor, and Safety Physician representative, which reviewed all available safety information from all patients.

[00429] Within each Dose Regimen cohort, if no DLT was observed in a cohort, the subsequent patient group was enrolled at the next planned dose level of that dose regimen. If a DLT was observed in ≥2 of 3 patients at any dose level no further dose escalation occurred in that DR, and the current dose was defined as the maximum administered dose (MAD). If a DLT was observed in 1 of 3 patients in a cohort at any dose level, then up to 3 additional patients were enrolled in the same DR at that dose level. If a DLT was observed in 2 or more patients in the expanded cohort, then no further dose escalation occurred, and the current dose was defined as the MAD. After the MAD was defined, either the previously administered lower dose was expanded to a total of 6 patients, or an intermediate dose (between the MAD and the previous dose level) was investigated in a total of 6 patients. The highest dose tolerated in at least 5 of 6 patients was defined as the MTD or OBD.

[00430] The selection of dose regimen and dose level for up to 2 EXP cohorts was based on the MTD determination in Cycle 1, as well as the cumulative safety, efficacy and pharmacokinetic / pharmacodynamic profile of Aileron peptide-1 in subsequent treatment cycles in DEP.

[00431] Dose levels were not increased between cycles within each cohort, and patients were assigned only one dose level (i.e., no intra-patient dose escalation).

Statistical Methods

[00432] Results from DR-A and DR-B will be compared for all dose levels and patient groups.

Screening Assessments and Other Requirements Prior to Day 1 of Cycle 1

[00433] Molecular Screening Prior to Day 1 of Cycle 1: Molecular screening encompassed the following prior to the first administration of Aileron peptide-1 (Day 1 of Cycle 1): (i) collection of signed informed consent for molecular screening; (ii) collection of an archived tumor sample or a fresh tumor biopsy

(unless a biopsy poses significant clinical risk) for p53 testing; (i) if confirmed to be p53 WT, the remainder of the tissue sample from enrolled patients was used to test for pharmacodynamic biomarkers. Confirmation of p53 WT status before administration of the first dose of Aileron peptide-1 was mandatory for enrollment in stage 1 of DEP for patients starting at Dose Level 4 and higher and stage 2 (if necessary) of DEP and EXP for all patients.

[00434] Molecular Screening Prior 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 was done prior to initiating the clinical screening. If the p53 status was known to be WT, these patients proceeded to clinical screening and were enrolled and receive Aileron peptide-1 before confirmation of p53 WT by the central laboratory.

[00435] In the EXP, patients had completed molecular screening at the central laboratory prior to proceeding to enrolment. These patients were only enrolled and received Aileron peptide-1 after confirmation of p53 WT by the central laboratory.

Clinical Screening Within 21 Calendar Days Prior to Day 1 of Cycle 1 for DR-A and DR-B, All Dose Levels

[00436] The screening assessments and procedures performed within 21 calendar days (or as noted) prior to the first administration of Aileron peptide-1 (Day 1 of Cycle 1) included collection of signed informed consent, medical history (evaluation of baseline signs and symptoms), demographics, eligibility assessment, blood test for HIV, hepatitis B and C, vital signs (includes blood pressure, pulse, respiration rate, body temperature), physical examination, ECG, laboratory assessments including clinical chemistry (glucose, calcium, albumin, total protein, sodium, potassium, CO_2, chloride, phosphate, BUN [blood urea nitrogen], serum creatinine, uric acid, ALP, ALT, AST, total and direct bilirubin), hematology (complete blood count, platelets and differential), urinalysis (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), ECOG performance status, RECIST- (for solid tumor patients) or IWG- (for lymphoma patients) compliant imaging for disease assessment and tumor measurements as well as laboratory-based assays (e.g., prostate specific antigen) for patients with relevant disease indications, including a baseline PET- FDG and possibly FLT-PET scan(s), concomitant medications (current medications and those taken within 28 days of Cycle 1, Day 1).

[00437] *Within 7 Calendar Days Prior to Day 1 of Cycle 1 for DR-A and DR-B, All Dose Levels*

[00438] The screening assessments that was completed within 7 calendar days prior to the first administration of Aileron peptide-1 (Day 1 of Cycle 1) included serum or urine pregnancy test (β-hCG) for women of child-bearing potential: performed within 2 days prior to first dose of Aileron peptide-1, confirm eligibility, vital signs, laboratory assessments - can be omitted if screening tests were performed within 7 days prior, ECOG performance status, and concomitant medications.

[00439] Requirements During Cycle 1

[00440] *Day 1 of Cycle 1, for DR-A and DR-B, All Dose Levels*

[00441] The study procedures that were performed prior to administration of Aileron peptide-1 included vital signs: within 30 minutes prior to SOI, physical exam, ECG: within 30 minutes prior to SOI (performed in triplicate (5-10 min between readings)), collection of blood for immunogenicity within 1 hr prior to SOI, collection of blood for all biomarker assessments within 1 hr prior to SOI, collection of blood for pharmacokinetic assessments: within 1 hr prior to SOI, and concomitant medications.

[00442] The study procedures that were performed after administration of Aileron peptide-1 included vital signs: (During infusion) 30 min (± 3 min); (Post-infusion) At EOI (+5 min), and 1 (±5 min) and 2 hrs (±10 min) following EOI; ECG: At EOI (+5 min) and 1 hr (±5 min) and 2 hrs (±10 min) following EOI. Perform in triplicate (5-10 min between readings) only if patient has a QTc that is a) >500 msec; b) increased by 60 msec over pre-dose; or c) decreased by 50 msec below pre-dose recording.; collection of blood for pharmacokinetic assessments: At EOI (+5 min), 30 min (±5 min) and 1 hr (±5min), 2 (±10 min), 4 (±10 min) and 8 hrs (±10 min) following EOI; collection of blood for all biomarker assessments, EOI (+ 5 min) and 1 hr (± 5 min) and 2, 4, and 8 hrs (± 10 min) following EOI.; concomitant medications; and adverse event (AE) assessment

[00443] *Day 2 of Cycle 1, for DR-A and DR-B, All Dose Levels*

[00444] The study procedures that were performed included vital signs, laboratory assessments , collection of blood for all biomarker assessments at 24 hr (±4 hr) after Day 1 SOI, collection of blood for pharmacokinetic assessments at 24 hr (±4 hr) after Day 1 SOI, concomitant medications, AE assessment, and TLS monitoring (via routine laboratory assessment sample)

[00445] *Day 3 of Cycle 1, for DR-A and DR-B, All Dose Levels*

[00446] The study procedures performed included vital signs, laboratory assessments (collection of blood for all biomarker assessments at 48 hr (±4 hr) after Day 1 SOI), collection of blood for pharmacokinetic assessments at 48 hr (±4 hr) after Day 1 SOI, concomitant medications and AE assessment.

[00447] *Day 4 of Cycle 1, for DR-B ONLY, All Dose Levels*

[00448] The study procedures performed prior to administration of Aileron peptide-1 included vital signs: within 30 minutes prior to SOI, physical exam, ECG: within 30 minutes prior to SOI. Perform in triplicate (5-10 min between readings), laboratory assessments, collection of blood for immunogenicity within 1 hr prior to SOI, collection of blood for all biomarker assessments within 1 hr prior to SOI, collection of blood for pharmacokinetic assessments: within 1hr prior to SOI, concomitant medications, and dverse Event (AE) Assessments

[00449] The study procedures performed after administration of Aileron peptide-1 included vital signs: (During infusion) 30 min (± 3 min); (Post-infusion) At EOI (+5 min), and 1 and 2 hrs (±10 min) following EOI; ECG: At EOI (+5 min) and 1 hr (± 5 min) and 2 hr (±10 min) following EOI. Perform in triplicate (5-10 min between readings) only if patient has a QTc that is a) >500 msec; b) increased by 60 msec over pre-dose; or c) decreased by 50 msec below pre-dose recording; laboratory assessments; collection of blood for all biomarker assessments within 1 hr after EOI; ollection of

blood for pharmacokinetic assessments at EOI (+5 min), 30 min (±5 min) and 1 hr (±5 min), 2 (±10 min), 4 (±10 min) after EOI; concomitant medications and adverse event (AE) assessment

[00450] *Day 8 of Cycle 1 for DR-A and DR-B, All Dose Levels*

[00451] The study procedures performed prior to administration of Aileron peptide-1 included vital signs: within 30 minutes prior to SOI; physical exam; laboratory assessments, collection of blood for all biomarker assessments within 1 hr prior to SOI, collection of blood for pharmacokinetic assessments within 1 hr prior to SOI, ECOG performance status, concomitant medications and AE assessment.

[00452] The study procedures performed after administration of Aileron peptide-1 include vital signs: (During infusion) 30 min (± 3 min); (Post-infusion) At EOI (+5 min), and 1 hr (±5 min) and 2 hrs (±10 min) following EOI; collection of blood for all biomarker assessments within 1 hr after EOI; collection of blood for pharmacokinetic assessments at EOI (+5min) and 30 min (± 5 min), 1hr (±5 min), 2 and 4 hrs (±10 min) after EOI; concomitant medications and AE assessment.

[00453] *Day 15 for DR-A and Day 11 for DR-B of Cycle 1*

[00454] The study procedures performed prior to administration of Aileron peptide-1 included vital signs: within 30 minutes prior to SOI; physical exam; laboratory assessments; collection of blood for all biomarker assessments within 1 hr prior to SOI; collection of blood for pharmacokinetic assessments within 1 hr prior to SOI; ECOG performance status; concomitant medication and AE assessment.

[00455] The study procedures performed after administration of Aileron peptide-1 included vital signs: (During infusion) 30 min (± 3 min); (Post-infusion) At EOI (+5 min), and 1 hr (±5 min) and 2 hrs (±10 min) following EOI; collection of blood for pharmacokinetic assessments At EOI (+5min) and 30 min (±5 min), 1 hr (±5 min); 2, 4, and 8 hrs (±10 min) after EOI; collection of blood for all biomarker assessments within 1 hr at EOI (+ 5 min); EOI plus 1 hr (±5 min); 4, and 8 hr (±10 min) after EOI; concomitant medications; and AE assessment.

[00456] *Day 16 DR-A and Day 12 DR-B for Cycle 1*

[00457] The study procedures performed included vital signs; laboratory assessments; collection of blood for biomarker assessments: at 24 hr (±4 hr) after SOI on the day prior; only for patients with a successful study biopsy performed prior to start of study medication: Needle biopsy for biomarker assessments- to be performed within 48 hours of Cycle 1, Day 15 (DR-A) or Day 11 (DR-B) infusion OR Cycle 2, Day 15 (DR-A) or Day 11 (DR-B) infusion, at the discretion of the Investigator (unless the biopsy poses significant risk to the patient); collection of blood for pharmacokinetic assessments at 24 hr (±4 hr) after Day 15 (DR-A) or Day 11 (DR-B) SOI; collection of blood for all pharmacodynamic assessments at 24 hr (±4 hr) after SOI on the day prior; concomitant medications; cAE assessment; and FLT-PET for patients who received FLT-PET at screen and have SUV $\geq$ 5.

[00458] *Day 22 for DR-A and Day 18 for DR-B or of Cycle 1*

[00459] The study procedures performed included vital signs; laboratory assessments – hematology only; collection of blood for all biomarker assessments ; concomitant medications; and AE assessment.

[00460] *Day 29 for DR-A and Day 22 for DR-B of Cycle 1 (-1 day up to +3 days) / Cycle 2 Day 1*

[00461] Procedures listed below under Requirements During Subsequent Cycles Beginning with Cycle 2 were performed. Note: "Day 22 or 29" = Day 1 of next cycle for patients continuing treatment. Cycle 1 Day 22 or 29/Cycle 2 Day 1 pre-dose evaluations were to be done within 3 days prior to next cycle drug administration.

[00462] If the patient was not continuing treatment beyond Cycle 1 the procedures listed below under End-of-Study Visit section were performed.

[00463] Requirements During Subsequent Cycles Beginning with Cycle 2

[00464] *Day 29 for DR-A and Day 22 for DR-B of prior cycle / Day 1 of Cycle 2 and subsequent cycles*

[00465] Note: "Day 22 or 29" = Day 1 of next cycle for patients continuing treatment. Day 22 or 29 of prior cycle/ Day 1 of current cycle pre-dose evaluations were done within 3 days prior to drug administration.

[00466] Note: Blood samples to evaluate CTC were not collected in Cycle 2 or subsequent cycles.

[00467] The study procedures performed prior to administration of Aileron peptide-1 included vital signs: within 30 minutes prior to SOI; physical exam; ECG: within 30 minutes prior to SOI. Perform in triplicate (5-10 min between readings); laboratory assessments; collection of blood for immunogenicity: within 1 hr prior to SOI; collection of blood for biomarker assessments (*MIC-1 only)*: within 1 hr prior to SOI; collection of blood for pharmacokinetic assessments (Cycle 2 Only): within 1 hr prior to SOI; ECOG performance status; concomitant medications; and AE assessment.

[00468] The study procedures performed **after** administration of Aileron peptide-1 included vital signs: (During infusion) 30 min (± 3 min); (Post-infusion) at EOI (+5 min) and as clinically indicated following EOI; ECG: at EOI (+ 5 min). Perform in triplicate (5-10 min between readings) only if patient has a QTc that is a) >500 msec; b) increased by 60 msec over pre-dose; or c) decreased by 50 msec below pre-dose recording; collection of blood for biomarker assessments (*MIC-1 only)*: within 1 hr after EOI; collection of blood for pharmacokinetic assessments (Cycle 2 Only) : At EOI (+5 min) and 30 min ((±5 min), 1 hr (±5 min), 2 and 4 hrs (±10 min) after EOI; concomitant medications; and AE assessment.

[00469] *Day 8 of DR-A and Days 4 and 8 of DR-B of Cycle 2 and beyond*

[00470] The study procedures performed prior to administration of Aileron peptide-1 included vital signs: within 30 minutes prior to SOI; physical exam; laboratory assessments- hematology only; ECOG performance status; concomitant medications; and AE assessment.

[00471] The study procedures performed **after** administration of Aileron peptide-1 included vital signs: (During infusion) 30 min (± 3 min); (Post-infusion) at EOI (+5 min) and as clinically indicated following EOI; concomitant medications; and AE assessment.

[00472] *Day 15 of DR-A and Day 11 of DR-B of Cycle 2 and beyond*

[00473] The study procedures performed prior to administration of Aileron peptide-1 included vital signs: within 30 min prior to SOI; physical exam; laboratory assessments; collection of blood for biomarker assessments (*MIC-1 only)*: within 1 hr prior to SOI; collection of blood for pharmacokinetic

assessments (Cycle 2 Only): within 1 hr prior to SOI; ECOG performance status; concomitant medications; and AE assessment.

[00474] The study procedures performed **after** administration of Aileron peptide-1 included: vital signs: (During infusion) 30 min (± 3 min); (Post-infusion) at EOI (+5 min) and as clinically indicated following EOI; collection of blood for biomarker assessments (*MIC-1 only)*: within 1 hr after EOI; collection of blood for pharmacokinetic assessments (Cycle 2 Only) at EOI (+5 min) and 30 min (±5 min), 1hr (±5 min), 2 and 4 hrs (±10 min) after EOI; concomitant medications and AE assessment.

[00475] *Day 16 DR-A and Day 12 of DR-B of Cycle 2 and beyond*

[00476] The study procedures performed included vital signs, laboratory assessments, collection of blood for biomarker assessments: at 24 hr (±4 hr) after Day 15 or 11 SOI, collection of blood for pharmacokinetic assessments (Cycle 2 Only): at 24 hr (±4 hr) after Day 15 or 11 SOI, concomitant medications, and AE assessment.

[00477] *After Even Numbered Cycles*

[00478] Blood was collected for immunogenicity. Tumor assessment was performed following same procedure used for baseline measurement, for example imaging, physical exam as well as laboratory-based assays (e.g., prostate specific antigen) for patients with relevant disease indications.

[00479] For patients who achieved "Stable Disease" as defined by RECIST or IWG criteria, a FDG-PET scan was indicated, provided that an evaluable FDG-PET-scan was performed prior to starting treatment with study drug.

[00480] *CT Imaging*

[00481] All patients receive a CT image prior to the first dose. After dosing commences in Dosing Regimen – A (DR-A), CT images will be obtained at the end of Cycle 2 and every other cycle thereafter in DR-A, e.g., Cycles 4, 6, and 8. In Dosing Regimen-B (DR-B) CT images will be obtained after the last infusion in Cycle 3 and every third cycle thereafter in DR-B, e.g., Cycles 6, 9, and 12. Images will be obtained after the last dose is administered in those cycles but prior to the Day 18 visit.

[00482] End-of-Study Visit

[00483] The end-of-study visit was to be conducted 30 (± 2) calendar days after the last administration of Aileron peptide-1 or withdrawal from the study. The study procedures performed included serum or urine pregnancy, vital signs, physical exam, ECG, laboratory assessments, collection of blood for immunogenicity, collection of blood for biomarker assessment, collection of blood for pharmacokinetic assessment, ECOG performance status, tumor assessment following same procedure used for baseline measurement, for example imaging, physical exam as well as laboratory-based assays (e.g., prostate specific antigen) for patients with relevant disease indications, concomitant medication and AE assessment.

[00484] Pharmacodynamic Assessment

[00485] Blood samples for pharmacodynamic assessments were collected at the following timepoints:

Table 12: Cycle 1 and Cycle 2 Dose Regimen Pharmacodynamic 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 pharmacodynamic assessments for solid tumors or lymphoma on Day 8 DR-A or Days 4 and 8 DR-B		

[00486] Pharmacokinetic (PK) Assessments

[00487] Blood samples for pharmacokinetic assessment were collected at the following timepoints:

Table 13: Cycle 1 and Cycle 2 Dose Regimen Pharmacokinetic Assessments

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	24 hours (±4 hr) after SOI day prior

DR-A and DR-B	
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)

Cycle 2	
Day 15, DR-A Day 11, DR-B	within one hour 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 16, DR-A Day 12, DR-B } Cycle 2 Only	24 hours (±4 hrs) after SOI day prior
NOTE: no PK assessments on Day 8 in DR-A or Days 4 and 8 in DR-B	
End of study visit	During end of study visit

Example 4: Further studies

[00488] Aileron peptide-1 was evaluated for safety, tolerability, pharmacokinetics and pharmacodynamics in adult patients with advanced solid tumors or lymphomas expressing WT p53 that are refractory to or

intolerant of standard therapy, or for which no standard therapy exists. FIG. 6 shows one way Aileron peptide-1 was designed to inhibit MDMX and/or MDM2, which leads to reactivation of WT p53.

[00489] Aileron peptide-1 was able to penetrate the cell membrane and localize within the nucleus. Further Aileron peptide-1 can disrupt protein-protein interactions within the cell such as the interactions between p53 and MDM2 and MDMX.

[00490] Several in-vivo and in-vitro studies of Aileron peptide-1 were conducted. In these studies, Aileron peptide-1 binded to both MDM2 and MDMX with nanomolar affinities and demonstrated evidence of specific on-target mechanism *in vitro* by gene expression profiling. In addition, Aileron peptide-1 demonstrated tumor growth suppression, p53-dependent cell cycle arrest, apoptosis and anti-tumor activity in an MDM2/MDMX-overexpressing xenograft cancer model with clear correlation to on-target pharmacokinetic and pharmacodynamic, or pharmacokinetic/pharmacodynamic, activity.

[00491] Dose escalation phase were designed to evaluate Aileron peptide-1 in patients with solid tumors or lymphoma. The dose escalation phase was not limited by type of tumor or lymphoma. Aileron peptide-1 was administered to patients with sarcoma, gastric cancer, non-small cell lung cancer, ovarian cancer and thymoma. In some cases Aileron peptide-1 was used to treat tumors and lymphomas in which WT p53 is prevalent in greater than 50% of patients. p53 wild-type status is prevalent in greater than 50% of patients suffering from at least 19 different tumor types. Thus, indication potential can vary from orphan indications or large market opportunities. *See e.g.*, Fig. 7.

[00492] p53 signal activation study was conducted to determine if Aileron peptide-1 had a differential effect on cancer cell lines with mutant p53 compared to WT p53. In the study, we measured the effect of Aileron peptide-1 in 312 cell lines across a variety of different cancers to compare the effect of Aileron peptide-1 in cell lines with mutant p53 and cell lines with WT p53. *See* Fig. 8. In the 207 mutant p53 cell lines, Aileron peptide-1 had no discernable effect, but in the 105 WT p53 cell lines, nearly all showed tumor cell death. *See* Fig. 8. The WT p53 cell lines that did not show tumor cell death included WT p53 cell lines associated with Human Papilloma Virus, or HPV, related cancers, such as cervical and head and neck. By concentrating on WT p53 and responsive tumors, we are able to predict patient populations that can have a better chance of response from our product candidate.

[00493] In another study, the binding affinity of Aileron peptide-1 for MDM2 or MDMX relative to the binding affinity for MDM2 and MDMX of WT p53 and of an MDM2 small molecule inhibitor was measured. The affinity of a drug to a receptor is the measure of how effectively that drug binds to its target and can provide insight on the potential for on-target effect and off-target toxicity. Aileron peptide-1 was designed to bind to MDM2 and/or MDMX with a higher affinity than WT p53 so that Aileron peptide-1 disrupts the binding of MDM2 and/or MDMX to WT p53 by binding to MDM2 and/or MDMX in lieu of p53. Such binding can enable p53 to be released and activated. In this study, we also measured a small molecule MDM2 inhibitor's binding affinity to MDMX, which showed no binding to this target. **Table 14** below shows Aileron peptide-1's ability to bind to MDM2 and MDMX relative to WT p53 and the small molecule MDM2 inhibitor.

[00494] Table 14: Aileron peptide-1's ability to bind to MDM2 and MDMX relative to WT p53 and the small molecule MDM2 inhibitor.

Kd, nM	WT p53	Aileron peptide-1	MDM2 Inhibitor
MDM2	770	13.7	9.8
MDMX	480	8.9	>3000

In Vivo

[00495] We studied the effects of Aileron peptide-1 in both solid tumors. In the study depicted Fig. 9a and 9b, we evaluated the effect of Aileron peptide-1 administered by an intravenous, or IV, injection in an MDMX-driven MCF-7 breast cancer xenograft model. In this study, we evaluated different doses, schedules and durations of treatment with Aileron peptide-1 and vehicle to determine effect on tumor volume growth. Aileron peptide-1 showed statistically significant tumor growth inhibition at doses ranging from 2.5 mg/kg to 5mg/kg to 10mg/kg and 20mg/kg when these doses were administered twice a week for a 28 day period. *See* Fig 11a and 11b.

[00496] Toxicology and Nonclinical Safety Experiments

[00497] The pivotal 4-week multiple-dose GLP studies in rats and monkeys utilized twice-weekly IV dosing rather than the once-weekly IV dosing planned as the initial clinical regimen. 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.

[00498] The 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. *See* Fig. 7.

[00499] The STD_{10} in rats was defined 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 defined 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 Aileron peptide-1 administration well; only one animal at each of these dose levels developed significant thrombocytopenia (<100,000 x 10^6/ml).

[00500] Rats are more sensitive to the bone marrow and hematologic effects of Aileron 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 correlate with those obtained from *in vitro* hemotoxicity assays via luminescence

output (HALO). In these investigations, Aileron 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 correlate with *in vivo* findings indicating that rats are more sensitive to the bone marrow and hematologic effects of Aileron peptide-1 than monkeys on the basis of dose and exposures at maximally tolerated doses. These results also suggest that, in terms of projecting potential bone marrow and hematological toxicity levels in humans, the monkey pharmacokinetic-pharmacodynamic data can be more clinically relevant than the rat data.

[00501] Aileron 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 Aileron peptide-1 on hERG potassium channels *in vitro* and on cardiac function in cynomolgus monkeys. There were no significant adverse findings in these studies.

[00502] Compared to the twice-weekly IV dosing schedule utilized in the 4-week GLP toxicity studies, the first-in-human clinical trial of Aileron peptide-1 will initially assess once-weekly IV dosing for three weeks. In addition, the demonstrated reversibility of Aileron test peptide-1-induced hematologic effects, the ability to detect such findings with routine laboratory measurements, and the availability of effective supportive therapies, all provide additional safety margin in the clinic.

[00503] *Pharmacokinetics and Absorption, Distribution, Metabolism and Excretion*

[00504] In rats, Aileron peptide-1 generally showed linear, dose-proportional increases in C_{max} and AUC. In the 4-week rat GLP toxicity study, C_{max} of Aileron 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. Half-life ($t_{1/2}$) values could not be calculated due to variable coefficients of determination ($r^2 < 0.9$).

[00505] In non-human primates, Aileron 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.

[00506] No significant sex-based differences in pharmacokinetic 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.

[00507] Proteolysis is the expected major biotransformation pathway of Aileron peptide-1. The predominant metabolite, Aileron peptide metabolite-1 , 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 monkey, rat, mouse and human cryopreserved hepatocytes. In a single-dose rat study, hepatobiliary metabolism and

elimination represented the predominant clearance pathway for Aileron peptide-1, with Aileron peptide metabolite-1 as the major excretion product observed in the bile.

[00508] *In vitro* studies revealed that Aileron peptide-1 is not an inhibitor of any cytochrome P450 (CYP) isoforms tested. I*n vitro* assays for CYP induction also did not indicate any significant treatment-related effects with Aileron peptide-1. Based on these findings, the potential of clinically relevant drug-drug interactions for concomitant medications that are cleared through CYP-mediated mechanisms is deemed to be low.

[00509] Aileron peptide-1 was tested *in vitro* against common transporters, and >90% inhibition of organic anion transporter polypeptide (OATP) members OATP1B1 and OATP1B3 and bile salt export pump (BSEP) at concentrations that can be clinically relevant (e.g., at C_{max} of high-dose levels) was observed. Based on these findings, the potential of clinically relevant drug-drug interactions by Aileron peptide-1 with medications (e.g., methotrexate, statins) that are significantly cleared by hepatobiliary transporters should be considered.

In Vivo

[00510] An open-label, multi-center, dose-escalation, two-arm study was used to design to evaluate the safety, tolerability, pharmacokinetic, pharmacodynamic and anti-tumor effects of Aileron peptide-1 administered by intravenous (IV) infusion in patients with advanced solid tumors or lymphomas expressing WT p53 that are refractory to or intolerant of standard therapy, or for which no standard therapy exists. The study included a dose escalation phase to establish the maximum tolerated dose, or MTD, or the optimum biologic dose, or OBD, of Aileron peptide-1, and a dose expansion phase to investigate the clinical safety profile and potential efficacy of Aileron peptide-1 at the MTD or OBD. In the expansion phase of the study, Aileron peptide-1 was studied in distinct groups of patients with specific solid tumors or lymphomas. The selection of the solid tumors or lymphomas was finalized based on results of the dose escalation phase, as well as data from additional nonclinical pharmacology studies. The latter included the investigation of multiple solid cancer cell lines such as breast, bladder, head/neck, gastrointestinal, or GI, liver, lung, pancreas, prostate and sarcoma to facilitate the comparison of cell line sensitivity to Aileron peptide-1 across and within tumor types. Treatment of patients in the dose escalation and the dose expansion phases of the trial continued until documentation of disease progression, unacceptable toxicity, or patient or physician decision to discontinue therapy.

[00511] The dose escalation phase is based on a "3+3" dose escalation design. In the dose escalation phase, patients in the first two dose levels received Aileron peptide-1 once a week for three weeks every 28 days. Patients in the higher dose levels received Aileron 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. *See* Fig. 10.

[00512] Patients with solid tumors or lymphoma were enrolled in the dose escalation phase who had exhausted standard therapies or for whom standard therapies are not available, completed enrollment up to dose group 4b and are enrolled patients in dose group 5a. Patients suffering from cancers with known HPV-association were excluded from enrollment, because HPV is known to deactivate WT p53. The tumor types included as of such date are non-small cell lung cancer, various types of sarcoma, cholangiocarcinoma, cystic adenoid carcinoma, follicular non-hodgkin lymphoma, thymoma, prostate cancer, endometrial cancer, and ovarian cancer. Since our trial was primarily safety and tolerability focused, we started dosing at relatively low dose levels and the protocol did not require patients in the first three dose levels to be p53-wildtype or HPV-negative.

[00513] To identify specific p53 patients for our trial, we employed a central laboratory to test both archived tumor tissue samples and fresh biopsy samples from patients enrolled in the trial for p53 status using Next-Generation Sequencing. 12 of 13 patients enrolled in those dose levels were confirmed to have WT status. Starting in dose level 4, WT p53 status was a mandatory eligibility criterion.

[00514] In this trial, clinical activity or response to Aileron peptide-1 was assessed through the use of both pharmacodynamic biomarkers and imaging assessment. Pharmacodynamic biomarkers provided us with information as to on-target activity, specific patient type response and early insight as to effect on tumor. As part of the trial, we were also assessing the effect of Aileron peptide-1 on potential Pharmacodynamic biomarkers in various different sources of biological samples such as tumor biopsies, circulating tumor cells where detectable, mononuclear blood cells and blood samples. Dependent on the sample type, those pharmacodynamic biomarkers include measurements of MDMX, MDM2, p21, p53, apoptosis and macrophage inhibitory cytokine-1, or MIC-1. In addition, we received standard imaging assessments, such as computed tomography, or CT, magnetic resonance imaging, bone scans and PET scans from patients, depending on number cycles administered. CT-imaging was performed at the end of cycle 2, and every two cycles thereafter in the 28-day cycle group and at the end of cycle 3 and every three cycles thereafter in the 21-day cycle group. We were measuring anti-tumor activity using RECIST for patients with solid tumors and 2014 International Working Group, or IWG, criteria for patients with lymphomas, enabling us to objectively evaluate whether a tumor has progressed, stabilized or shrunk. In addition, anti-tumor effects can be determined by physical examination or clinically validated serum tumor markers.

Pharmacokinetic Profile

[00515] Aileron peptide-1 was delivered systemically in an IV administration given potential advantages of avoiding metabolic impact from hepatic and gastrointestinal enzymes as well as ability for reproducible systemic bioavailability with dose escalation. As shown in the Fig. 11a, drug concentration was measured in dose levels for Cohorts 1 (.16 mg/kg), 2 (.32 mg/kg), 3a (.64 mg/kg), 3b (.32 mg/kg), 4a (1.25 mg/kg). In patients, Aileron peptide-1 has consistently produced a dose dependent increase in maximum drug serum concentration observed, or Cmax, as well as longer

corresponding half-life of between eight and 10 hours. This half-life is adequate to re-activate WT p53 and begin the process of initiating the regulation of the transcription of genes.

[00516] Aileron peptide-1 shows reproducible profiles from patient to patient and dose-to dose enabling exposure projections for higher dose levels to predict efficacy and safety. Fig. 11b shows the measured drug concentration in dose levels 1 (.16 mg/kg), 2 (.32 mg/kg) and 3 (.64 mg/kg); and projected for dose levels 4 (1.25 mg/kg), 5 (2.5 mg/kg), and 6 (5.0 mg/kg).

[00517] Figure 12 shows the pharmacokinetic model of Aileron peptide-1. The peptide shows nonlinear Michaelis-Menten clearance and linear elimination.

Safety Results

[00518] Aileron peptide-1 was considered to be well tolerated at all dose levels by the investigators. There were no reported dose-limiting toxicities nor study-related serious adverse events. Looking at non-hematologic safety, the most common related adverse events are nausea and fatigue. Looking at hematologic safety, the first two dose levels 1 and 2 showed no cytopenias during cycles 1 and 2, whereas at dose levels 3A, 3B and 4A, patients showed drug-related events of mild to moderate anemia, mild thrombocytopenia and mild neutropenia. One patient at dose level 3B experienced a grade 4 neutropenia which Investigators reported as probably related to study medication. The patient's complete blood count presented trough values of grade 2 leukocytopenia, grade 1 anemia and grade 1 thrombocytopenia. Two concomitant medications were initiated around the same time that treatment with Aileron peptide-1 was started, both of which have been suspected to be associated with the occurrence of neutropenia. There was no association between the patient's neutropenia and drug exposure, the patient's last complete blood count showed an improvement to grade 3 neutropenia, no treatment was administered for neutropenia and no infectious complications were reported.]

[00519] 4 formal Safety Review Meetings with Investigators confirm no DLTs. For DL1, 2 and 3A there was an unanimous decision to escalate at double the dose. For DL3B, there was an unanimous decision to escalate via Fibonacci in DL4B. New Dose may be 0.53 mg/Kg instead of 0.64 mg/Kg.

[00520] Hematologic and non-hematologic adverse events were generally consistent with our preclinical toxicology profile:

- No genotoxicity
- No immunogenicity
- No relevant findings in cardiovascular safety
- No relevant findings suggestive of GI toxicity
- No Myelosuppression as the dose-limiting toxicity

Biomarker Assessments

[00521] In the dose escalation phase, we used several exploratory biomarkers to confirm Aileron peptide-1's pharmacological or on-target biological activity, aid patient recruitment and help inform dose selection.

[00522] Pharmacodynamic biomarkers were received on MDMX, MDM2, p21, p53, apoptosis and MIC-1. The first biomarker for which we received data is MIC-1. MIC-1 is a secreted p53-regulated cytokine that is readily measured in blood if p53 is activated , and can serve as a biomarker for p53 activation. Under normal conditions, p53 expression remains low, resulting in corresponding negligible levels of MIC-1. However, when WT p53 activation occurs in response to a tumor, this also leads to increased levels of MIC-1. We measured MIC-1 one hour before initial infusion and again 24 hours after initial infusion. In patients at dose levels ranging from dose level 1 to dose level 4A, we observed a statistically significant dose dependent response in the increase of MIC-1. *See* Fig. 13.

[00523] Further, mononuclear blood cells from 4 patients confirmed that Aileron peptide-1 penetrates cell membrane and activates p53-signalling. We measured the amount of intracellular p53 and p21 in mononuclear blood cells from 4 patients at: (a) end of infusion of Aileron peptide-1, (b) 1 hour after the end of infusion of Aileron peptide-1 and (c) 4 hour after the end of infusion of Aileron peptide-1. As seen in Figure 14, a 1.8 times increase in the levels of intracellular p53 and about 3 times increase in the levels of intracellular p21 was observed.

[00524] Thus, we conclude that Aileron peptide-1 is penetrating the cell membrane, localizing within the nucleus and releasing WT p53. An increase of at least eight fold in MIC-1 levels from baseline serves as guidance for the minimum dose needed for p53 re-activation.

[00525] Overall, at least two independent biomarker studies support Aileron peptide-1-mediated activation of intracellular p53 signaling: (i) MIC-1 serum-protein (as measured by ELISA): dose-response relationship, and (ii) p53 and p21 increase (as measured by flow-cytometry) in blood cells.

[00526] Efficacy

[00527] Objective tumor response is an endpoint for efficacy in trials. Patients in the 28-day cycle group are measured at baseline and again after two cycles of therapy, or approximately within 56 days following initial dosing. Patients in the 21-day cycle group are measured at baseline and again after three cycles of therapy, or approximately within 63 days following initial dosing. RECIST criteria definitions are as follows:

- Stable Disease, or SD: Neither sufficient shrinkage to qualify for partial response nor sufficient increase to qualify for progression, taking as reference the smallest sum diameters while on study.
- Partial Response, or PR: At least a 30% decrease in the sum of the diameters of target lesions, taking as reference the baseline sum diameters.
- Complete Response, or CR: Disappearance of all target lesions. Any pathological lymph nodes, whether target or non-target, must have reduction in short axis to less than 10 millimeters.

[00528] Tests show that patients who have completed at least two cycles of treatment, some patients have stable disease. Aileron peptide-1 has shown a stable disease rate. *See* Fig. 15.

[00529] **Table15** below shows exemplary patients who were treated with Aileron peptide-1. These patients encompassed a range of solid tumors with either wild type or mutant p53. As seen in **Table 16**, after

2/3 cycle treatment each of the patient 4, 5, 7, 8, 10, 11 and 15 have stable disease, while only patients 2, 6 and 12 showed a progressive disease. After completing 3/4 treatment cycles, patient 11 continued to show stable disease. As used here, stable disease refers to the situation where there is neither a sufficient shrinkage of the tumor to qualify for partial response nor sufficient increase to qualify for progression, taking as reference the smallest sum diameters while on study.

[00530] Table 15. Patient information

Patient No.	1° Cancer	Histopath	2° Cancer	P53 WT	NGS Tissue(s) Tested	Organ	Tumor Size mm	Tumor Burden mm
1	Salivary gland	squamous cell		UNK	liver	Lymph node	30	55
						Right Hepatic Lobe Posterior	25	
2	liposarcoma	liposarcoma		Yes	retroperitoneal:	soft tissue mass	48	48
3	Gall bladder	adenocarcinoma		Yes	Gall bladder	liner	16	36
						endoperitoneal	20	
4	Submandibular adenocarcinoma	Adenoid cystic Carcinoma		Yes	adenoid	oropharynx	43	65
						lung	22	
5	liposarcoma	Liposarcoma		Yes	liposarcoma	retroperitoneal	175	301
						retroperitoneal	126	
6	GIST (sarcoma)	GASTROINTESTINAL STROMAL TUMOR		UNK	N/A	MESENTRIC MASS	25	135
						lung	20	
						lung	16	
						liver	84	
7	NSCLC	invasive andenocarcinoma	Brain/head	UNK	N/A	lung	10	71
						Lymph node	20	
						lung	20	
						Lymph node	21	
8	liposarcoma	Basal Cell		Yes	tumor resection-retroperitoneal lymph node	Stomach	147	443
						Stomach	127	
						Bone	155	
						Liver	14	
9	prostate	Adenocarcinoma		UNK	N/A	Lymph node	48	86
						liver	15	
						Lymph node	23	
10	NSCLS	Stage IV adenocarcinoma the left lung		Yes	right lung nodule	Lymph node	15	99
						Lymph node	21	
						Lymph node	21	
						Lung	25	
						Lung	17	
11	ovarian	met. ov cancer stage iv ca with liver mets		No	Tumor resection-uterus	Liver	17	64
						Liver	30	
						Other	17	
12	endometrial	ENDOMETRIAL		No		Liver	13	78

		SEROUS CARCINOMA				Liver	17	
						Lymph node	18	
						Lymph node	20	
13	breast	Carcinoma	osteosarcoma	Yes	Tumor resection-osteosarcoma	lung	64	181
						lung	117	
14	leiomyosarcoma	Unknown		UNK		Lung	54	195
						Liver	12	
						Liver	99	
						Liver	30	
15	leiomyosarcoma	Uterine		Yes		Lymph node	44	76
						Lymph node	32	
16	lymphona	b-cell lymphoma-follicular				Lymph node	300 (CT & PET)	
17	thymoma							

Table 16: Patient response after treatment with Aileron Peptide -1 for 2/3 cycle

Patient No.	Organ	Tumor Size mm	Tumor Burder mm	% change from bsln	New Lesions?	Target	Non-Target	Overall
1	Lymph node	[redacted]						Off Study: Non-compliance
	Right Hepatic Lobe Posterior							
2	soft tissue mass	62	62	29%	No	Progression	Not Done	Progressive Disease
3	liner	[redacted]						Off Study: CDP
	endoperitoneal							
4	oropharynx	45	69	6%	Yes	Stable Disease	Progressive Disease	Stable Disease
	lung	24						
5	retroperitoneal	186	336	11.2%	NO	Stable Disease	Not done	Stable Disease
	retroperitoneal	150						
6	MESENTRIC MASS	29	159	17.8%	Yes (SUPERIOR HEPATIC LOBE UP TO 1.5 CM)	Stable Disease	Non-complete Response/Non-progression	Progressive Disease
	lung	11						
	lung	19						
	liver	100						
7	lung	13	77	8%	No	Stable Disease	Non-complete Response/Non-progression	Stable Disease
	Lymph node	20						
	lung	20						
	Lymph node	24						
8	Stomach	157	518	16.9%	No	Stable Disease	Progressive Disease	Stable Disease
	Stomach	145						
	Bone	180						
	Liver	36						
9	Lymph node	53	122	41.86%	No	Progressive Disease	Non-Complete Response/Non-	Off Study: Objective
	liver	35						

	Lymph node	34					Progression	Disease Progression
10	Lymph node	21	116	17.20%	No	Stable Disease	Not done	Stable Disease
	Lymph node	24						
	Lymph node	24						
	Lung	28						
	Lung	19						
11	Liver	17	71	10.90%	No	Stable Disease	Not done	Stable Disease
	Liver	24						
	Other	30						
12	Liver	15	100	28.21%	Yes (LIVER LESION)	Progression	Not all Evaluated or Not Assessable	Progressive Disease
	Liver	19						
	Lymph node	32						
	Lymph node	32						
13	lung	--	--	--				
	lung	--						
14	Lung	69	233	19.48%	Yes (left subhepatic mass)	Not entered yet	Not entered yet	Not entered yet
	Liver	19						
	Liver	105						
	Liver	40						
15	Lymph node	44	77	1.30%	No	Stable Disease	Non-complete Response/Non-progression	Stable Disease
	Lymph node	33						

CLAIMS

WHAT IS CLAIMED IS:

1. A method of treating a solid 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 therapeutically equivalent amount of a pharmaceutically acceptable salt thereof, wherein the peptidomimetic macrocycle binds to MDM2 and/or MDMX proteins.
2. A method of treating a solid 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 therapeutically equivalent amount of a pharmaceutically acceptable salt thereof, wherein the peptidomimetic macrocycle binds to MDM2 and/or MDMX proteins.
3. A method of treating a solid 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 therapeutically equivalent amount of a pharmaceutically acceptable salt thereof, wherein the peptidomimetic macrocycle binds to MDM2 and/or MDMX proteins.
4. A method of treating a solid 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, wherein the peptidomimetic macrocycle binds to MDM2 and/or MDMX proteins and wherein the solid tumor is not negative for p53 protein expression (such as solid tumors that express wild-type p53 protein or mutated p53 protein with partial functionality).
5. A method of treating a solid 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, wherein the peptidomimetic macrocycle binds to MDM2 and/or MDMX proteins and wherein the solid tumor expresses a p53 protein with a gain of function mutation (such as a super apoptotic p53).
6. A method of treating a solid 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, wherein the peptidomimetic macrocycle binds to MDM2 and/or MDMX proteins and wherein the solid tumor express a p53 protein with a mutation that causes a partial loss of function.
7. A method of treating a solid 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 wherein cells in the solid 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).

8. A method of treating a solid 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 wherein the solid tumor express a p53 protein with one or more silent mutations.

9. A method of treating a solid 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 wherein cells in the solid tumor are negative for p53 expression.

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

11. The method of claim 10, wherein cells in the solid 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 claims 3 or 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 claims 3 or 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 2-15, wherein the cells of the solid tumor have at least one mutation in a copy of a p53 gene, wherein the mutation eliminates or reduces the or 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 solid 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, 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 solid 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 solid 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 solid tumor.
22. The method of any one of claims 2 to 18, comprising determining a presence of a deactivating mutation of p53 in the solid 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 solid 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 solid tumor.
25. The method of any one of claims 1 to 24, further comprising confirming the lack of the p53 deactivating mutation in the solid 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 solid 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 solid tumor.
28. The method of any one of claims 2 to 18, comprising confirming a presence of a deactivating mutation of p53 in the solid 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 solid 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 solid 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 tumor cell proliferation, increased p53 protein, increased p21, and/or increased apoptosis in the human subject.
40. The method of any one of the preceding claims, wherein a dose of the pharmaceutical composition is administered two or three times a week.
41. The method of any one of claim 1-39, wherein a dose of the pharmaceutical composition is administered two or more times a week.
42. The method of any one of claims 1-39, wherein a dose of the pharmaceutical composition is administered once every 2 or 3 weeks.
43. The method of any one of claims 1-39, wherein a dose of the pharmaceutical composition is administered once every 1 or 2 weeks.
44. The method of any one of claims 1-39, wherein a dose of the pharmaceutical composition is administered on days 1, 8 and 15 of a 28-day cycle.
45. The method of any one of claims 1-39, wherein a dose of the pharmaceutical composition is administered on days 1, 4, 8 and 11 of a 21-day cycle.
46. The method of any one of the preceding claims, wherein the amount of the peptidomimetic macrocycle or a pharmaceutically acceptable salt thereof administered is about 0.5-20 mg per kilogram body weight of the human subject.
47. The method of any one of the preceding claims, wherein the amount of the peptidomimetic macrocycle or a pharmaceutically acceptable salt thereof administered is about 0.5-10 mg per kilogram body weight of the human subject.
48. The method of any one of claims 1-45, wherein the amount of the peptidomimetic macrocycle or a pharmaceutically acceptable salt thereof administered is about 0.04 mg, 0.08 mg, 0.16 mg, 0.32 mg, 0.64 mg, 1.28 mg, 3.56 mg, 7.12 mg, or 14.24 mg per kilogram body weight of the human subject.
49. The method of any one of claims 1-45, wherein the amount of the peptidomimetic macrocycle or a pharmaceutically acceptable salt thereof administered is about 1.25 mg, 2.5 mg, 5.0 mg 10.0 mg, or 20.0 mg per kilogram body weight of the human subject and the pharmaceutical composition is administered two times a week.

50. The method of any one of claims 1-45, wherein the amount of the peptidomimetic macrocycle or a pharmaceutically acceptable salt thereof administered is about 1.25 mg, 2.5 mg, 5.0 mg or 10.0 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 of the peptidomimetic macrocycle or a pharmaceutically acceptable salt thereof administered is about 0.32 mg, 0.64 mg, 1.25 mg 2.5 or 5.0 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 claims 1-39, wherein the peptidomimetic macrocycle or a pharmaceutically acceptable salt thereof administered is about 0.32 mg, 0.64 mg, 1.25 mg 2.5 or 5.0 mg per kilogram body weight of the human subject and the pharmaceutical composition is administered on day 1, 4, 8, 11 of a 21-day cycle.
53. The method of any one of claims 1-39, wherein the peptidomimetic macrocycle or a pharmaceutically acceptable salt thereof administered is about 0.16 mg, 0.32 mg, 0.64 mg, 1.25 mg, 2.5, 5.0 mg or 10 mg per kilogram body weight of the human subject and the pharmaceutical composition is administered on day 1, 8, and 15 of a 28 day cycle.
54. The method of any one of claims 1-39, wherein the amount of the peptidomimetic macrocycle or a pharmaceutically acceptable salt thereof administered is about 1.25 mg, 2.5 mg, 5.0 mg 10.0 mg, or 20.0 mg per kilogram body weight of the human subject and the pharmaceutical composition is administered once a week.
55. The method of any one of claims 1-39, wherein the amount of the peptidomimetic macrocycle or a pharmaceutically acceptable salt thereof administered is about 1.25 mg, 2.5 mg, 5.0 mg or 10.0 mg per kilogram body weight of the human subject and the pharmaceutical composition is administered once a week.
56. The method of any one of claims 1-39, wherein the amount of the peptidomimetic macrocycle or a pharmaceutically acceptable salt thereof administered is about 1.25 mg, 2.5 mg, 5.0 mg 10.0 mg, or 20.0 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 39, 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 1-45, wherein the amount of the peptidomimetic macrocycle or a pharmaceutically acceptable salt thereof administered is about 1.25 mg, 2.5 mg, 5.0 mg, or 10.0 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.
59. The method of any one of claims 1-812, wherein the pharmaceutical composition is administered intravenously once a day, seven times in a seven day period.

60. The method of any one of the preceding claims, 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.
61. The method of any one of the preceding claims, wherein the pharmaceutical composition is administered over a period of 0.25-2.0 h
62. The method of any one of the preceding claims, wherein the pharmaceutical composition is gradually administered over a period of 1 h.
63. The method of any one of the preceding claims, wherein the pharmaceutical composition is gradually administered over a period of 2 h.
64. The method of any one of the preceding claims, 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 tumor volume within a period of 1 month after treatment initiation.
65. The method of any one of claims 1-63, wherein the treatment results in at least 60%, 65%, 70%, 75%, 80%, 85%, 90%, or 95% reduction in tumor volume within a period of 1 month after treatment initiation.
66. The method of any one of the preceding claims, 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 tumor volume within a period of 1 year after treatment initiation.
67. The method of any one of the preceding claims, wherein the treatment results in at least 60%, 65%, 70%, 75%, 80%, 85%, 90%, or 95% reduction in tumor volume within a period of 1 year after treatment initiation.
68. The method of any one of the preceding claims, 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 tumor volume within a period of 6 months after treatment initiation.
69. The method of any one of the preceding claims, wherein the treatment results in at least 60%, 65%, 70%, 75%, 80%, 85%, 90%, or 95% reduction in tumor volume within a period of 6 months after treatment initiation.
70. The method of any one of the preceding claims, 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 tumor volume within a period of 3 months after treatment initiation.
71. The method of any one of the preceding claims, wherein the treatment results in at least 60%, 65%, 70%, 75%, 80%, 85%, 90%, or 95% reduction in tumor volume within a period of 3 months after treatment initiation.
72. The method of any one of the preceding claims, wherein the solid tumor is a stable disease.
73. The method of any one of the preceding claims, 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 peptidomimetic macrocycle.

74. The method of claim 73, wherein the increase in the survival time of the human subject is at least 30 days.
75. The method of claim 73, wherein the increase in the survival time of the human subject is at least 3 months.
76. The method of claim 73, wherein the increase in the survival time of the human subject is at least 6 months.
77. The method of claim 73, wherein the increase in the survival time of the human subject is at least 1 year.
78. The method of any one of the preceding claims, wherein the in vivo circulating half-life of the peptidomimetic macrocycle is about 1 h, 2h, 3 h, 4 h, 5 h, 6 h, 7 h, 8 h, 9 h, 10 h or 12 h.
79. The method of any one of the preceding claims, wherein the in vivo circulating half-life of the peptidomimetic macrocycle is about 4 h.
80. The method of any one of claims 1-78, wherein in vivo circulating the half-life of the peptidomimetic macrocycle is about 6 h.
81. The method of any one of the preceding claims, wherein the biological tissue half-life of the peptidomimetic macrocycle is about 1 h, 2h, 3 h, 4 h, 5 h, 6 h, 7 h, 8 h, 9 h, 10 h or 12 h.
82. The method of any one of the preceding claims, wherein the biological tissue half-life of the peptidomimetic macrocycle is about 10 h.
83. 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 solid tumor.
84. 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 solid tumor.
85. The method of any one of claims 1, 4 and 18-84, wherein the solid tumor expresses wild-type p53 protein.
86. The method of any one of the preceding claims, wherein the solid tumor is selected from a group consisting of pancreatic cancer, bladder cancer, colon cancer, liver cancer, colorectal cancer, breast cancer, prostate cancer, renal cancer, hepatocellular cancer, lung cancer, ovarian cancer, cervical cancer, gastric cancer, esophageal cancer, head and neck cancer, melanoma, neuroendocrine cancers, CNS cancers, brain tumors, bone cancer, skin cancer, ocular tumor, rectal cancer, choriocarcinoma (tumor of the placenta), sarcoma and soft tissue cancer, testicular cancer, gall bladder cancer, cancer of salivary gland, liposarcoma, submandibular adenocarcinoma, GIST (sarcoma), endometrial cancer, leiomyosarcoma, lymphoma, thymoma and biliary cancer.
87. The method of any one of the preceding claims, wherein the solid tumor is selected from a group consisting of bladder cancer, bone cancer, breast cancer, cervical cancer, CNS cancer, colon cancer, ocular tumor, renal cancer, liver cancer, lung cancer, pancreatic cancer, choriocarcinoma (tumor of the placenta), prostate cancer, sarcoma, skin cancer, soft tissue cancer, gastric cancer, gall bladder cancer, biliary cancer, renal cancer, neoblastoma, or neuroendocrine cancer.

88. The method of claims 86 or 87, wherein the ocular tumor is choroidal nevus, choroidal melanoma, choroidal metastasis, choroidal hemangioma, choroidal osteoma, iris melanoma, uveal melanoma, melanocytoma, metastasis retinal capillary hemangiomas, congenital hypertrophy of the RPE, RPE adenoma or retinoblastoma.
89. The method of any one claims 1-88, wherein the solid tumor is selected from non-small cell lung cancer, small-cell lung cancer, colon cancer, CNS cancer, melanoma, ovarian cancer, renal cancer, prostate cancer and breast cancer.
90. The method of any one of claims 1-85, wherein the solid tumor is breast cancer.
91. The method of any one of claims 1-88, wherein the solid tumor is gall bladder cancer.
92. The method of any one of claims 1-88, wherein the solid tumor is biliary cancer.
93. The method of any one of claims 1-85, wherein the solid tumor is neuroendocrine cancer.
94. The method of any one of claims 1-85, wherein the solid tumor is bone cancer.
95. The method of claim 94, wherein the bone cancer is osteosarcoma.
96. The method of any one of the preceding claims, wherein the solid tumor is skin cancer.
97. The method of claim 96, wherein the skin cancer is melanoma.
98. The method of any one of the preceding claims, wherein the solid tumor is not a HPV positive cancer.
99. The method of claim 98, wherein the solid tumor is not HPV positive cervical cancer, HPV positive anal cancer or HPV positive head and neck cancer, such as oropharyngeal cancers.
100. The method of any one of the preceding claims, wherein the pharmaceutical composition is administered intravenously.
101. The method of any one of the preceding claims, further comprising administering in addition to the pharmaceutical composition, administering a therapeutically effective amount of at least one additional therapeutic agent and/or providing a therapeutic procedure to the human subject.
102. The method of any one of the preceding claims, wherein the human subject exhibits a complete response to the treatment.
103. The method of any one of the preceding claims, wherein the human subject exhibits a partial response to the treatment.
104. The method of any one of the preceding claims, wherein the solid tumor is a progressive disease.
105. The method of any one of the preceding claims, wherein the solid tumor is a stable disease.
106. The method of any one of the preceding claims, further comprising determining clinical activity of the administered pharmaceutical composition.
107. The method of claim 106, 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.
108. 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.

109. The method of claim 108, wherein 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.
110. The method of claim 108, further comprising tabulating and/or plotting results of the analytical procedure.
111. The method of claim 108, wherein the one or more specific time-points comprise a time-point before the administration of the pharmaceutical composition to the human subject.
112. The method of claim 108, wherein the one or more specific time-points comprise a time-point after the administration of the pharmaceutical composition to the human subject.
113. The method of claim 108, 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.
114. The method of claim 113, further comprising comparing the biological samples collected before and after the administration of the pharmaceutical composition to the human subject.
115. The method of claim 108, 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.
116. The method of claim 115, further comprising comparing the biological samples collected at the multiple time-points.
117. The method of claim 108, wherein the biological sample is used for biomarker assessment.
118. The method of claim 108, wherein the biological sample is used for pharmacokinetic assessment.
119. The method of claim 118, wherein the pharmacokinetic assessment comprises studying the level of the peptidomimetic macrocycle, a pharmaceutically acceptable salt and/or a metabolite thereof in the biological sample at the specific time-points.
120. The method of claim 119, wherein the biological sample is a blood sample.
121. The method of claim 108, wherein the biological sample is used for pharmacodynamic assessment.
122. The method of claim 121, 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.
123. The method of claim 122, wherein the biological sample is a tumor specimen.
124. The method of claim 108, wherein the biological sample is used for immunogenicity assays.
125. The method of any one of the preceding claims, further comprising selecting and/or identifying at least one target lesion in the human subject prior to the administration of the pharmaceutical composition to the human subject.
126. The method of claim 125, further comprising measuring cumulative diameters at one or more specific time-points, wherein the cumulative diameter is a sum of the diameters of the at least one target lesions at the specific time-point.

127. The method of claim 126, further comprising measuring a baseline sum diameter, wherein the baseline sum diameter is a sum of the diameters of the at least one target lesions prior to the administration of the pharmaceutical composition to the human subject.
128. The method of claim 125, wherein the treatment results in disappearance of the least one target lesion.
129. The method of any one of the preceding claims, wherein after the treatment all pathological lymph nodes in the human subject exhibit a reduction in short axis to less than 10 mm.
130. The method of claim 127, wherein the one or more specific time-points, comprise a time-point after the treatment.
131. The method of claim 130, wherein the cumulative diameter at the time-point after the treatment is at least 30% less than the baseline sum diameter.
132. The method of claim 127, wherein the treatment results in neither sufficient increase nor a sufficient decrease in the cumulative diameters at the one or more specific time-points, taking as reference the baseline sum diameter.
133. The method of any one of the preceding claims, wherein the peptidomimetic macrocycle or a pharmaceutically acceptable salt thereof is not an inhibitor of cytochrome P450 isoforms.
134. The method of any one of the preceding claims, wherein the treatment results in essentially no dose-limiting thrombocytopenia.
135. 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.
136. The method of any one of the preceding claims, wherein the treatment results in essentially no adverse event in the human subject related to the administration of the pharmaceutical composition.
137. The method of any one of the preceding claims, wherein the treatment results in essentially no serious adverse event in the human subject related to the administration of the peptidomimetic macrocycle.
138. The method of any one of the preceding claims, wherein the lack of p53 deactivation mutation in the solid tumor is determined by DNA sequencing of the nucleic acid encoding the p53 protein.
139. The method of any one of the preceding claims, wherein the lack of p53 deactivation mutation in the solid tumor is determined by RNA array based testing.
140. The method of any one of the preceding claims, wherein the lack of p53 deactivation mutation in the solid tumor is determined by RNA analysis.
141. The method of any one of the preceding claims, wherein the lack of p53 deactivation mutation in the solid tumor is determined by polymerase chain reaction (PCR).
142. The method of any one of the preceding claims, wherein the p53 deactivating mutation comprises mutations in DNA-binding domain of the protein.
143. The method of any one of the preceding claims, wherein the p53 deactivating mutation comprises missense mutation.
144. The method of any one of the preceding claims, wherein the p53 deactivating mutation is a dominant deactivating mutation.

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

146. 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.

147. The method of claim 5, wherein the p53 gain of function mutation comprises one or more of mutations shown in **Table 1b**.

148. A method of treating solid tumor in a human subject, 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.

149. The method of claim 148, wherein the solid tumor is determined to lack a p53 deactivating mutation.

150. The method of claim 148 or 149, 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.

151. The method of any one of claims 148-150, 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.

152. The method of any one of claims 148-150, 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.

153. The method of any one of claims 148-150, 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.

154. The method of any one of claims 148-150, wherein equal amounts of the peptidomimetic macrocycle is administered on days 1, 8 and 15.

155. The method of any of one of claims 148-154, wherein the 28-day cycle is repeated 2 or 3 times.

156. A method of treating solid tumor in a human subject, wherein the method comprises administering to the human subject 0.32-10 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.

157. The method of claim 156, wherein the solid tumor is determined to lack a p53 deactivating mutation.

158. The method of any one of claim 156 or 157, wherein 0.32 mg of the peptidomimetic macrocycle per kilogram body weight of the human subject or the pharmaceutically acceptable salt thereof is administered on days 1, 4, 8 and 11 respectively of a 21-day cycle.

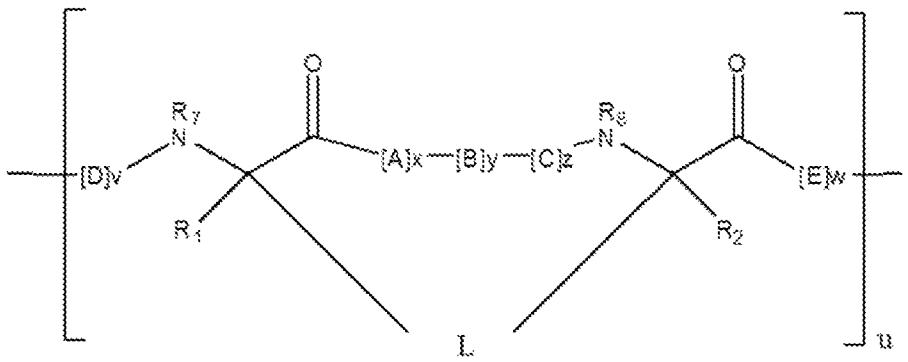
159. The method of claim 156 or 157, wherein 0.64 mg of the peptidomimetic macrocycle per kilogram body weight of the human subject or the pharmaceutically acceptable salt thereof is administered on days 1, 4, 8 and 11 respectively of a 21-day cycle.

160. The method of claim 156 or 157, wherein 1.25 mg of the peptidomimetic macrocycle per kilogram body weight of the human subject or the pharmaceutically acceptable salt thereof is administered on days 1, 4, 8 and 11 respectively of a 21-day cycle.

161. The method of any one of claims 156 or 157, wherein 2.5 mg of the peptidomimetic macrocycle per kilogram body weight of the human subject or the pharmaceutically acceptable salt thereof is administered on days 1, 4, 8 and 11 respectively of a 21-day cycle.

162. The method of claim 156 or 157, wherein 5.0 mg of the peptidomimetic macrocycle per kilogram body weight of the human subject or the pharmaceutically acceptable salt thereof is administered on days 1, 4, 8 and 11 respectively of a 21-day cycle.

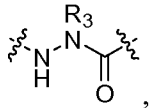
163. The method of any one of the preceding claims, wherein the peptidomimetic macrocycle comprises an amino acid sequence which is at least about 60%, 70%, 80%, 90%, or 95% identical to an amino acid sequence in any of **Table 3**, **Table 3a**, **Table 3b**, and **Table 3c**, wherein the peptidomimetic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



Formula (I)

wherein:

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

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

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

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

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

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

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

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

each 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;

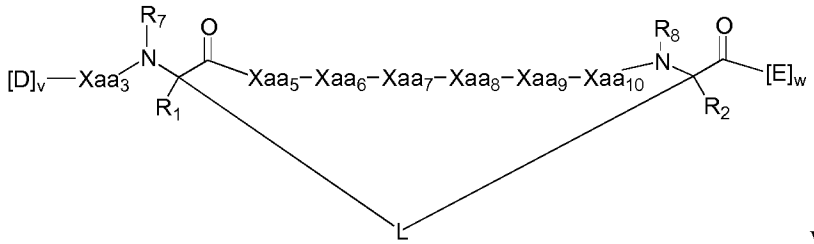
each w is independently an integer from 3–1000;

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.

164. 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} (SEQ ID NO: 8) or Phe_3-X_4-Glu_5-Tyr_6-Trp_7-Ala_8-Gln_9-Leu_{10}/Cba_{10}-X_{11}-Ala_{12} (SEQ ID NO: 9), where each X_4 and X_{11} is independently an amino acid;

each D and E is independently an amino acid;

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

w is an integer from 0-1000.

165. The method of claim 163 or 163, wherein at least one of the macrocycle-forming linker has a formula $–L_1–L_2–$, wherein

each 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

each n is independently an integer from 1-5.

166. The method of claim 163, 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.

167. The method of claim 163, wherein Xaa_5 is Glu or an amino acid analog thereof.

168. The method of any one of claims 163-167, wherein each E 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)

169. The method of any one of claims 163-167, wherein each E is independently Ala (alanine), Ser (serine) or an analog thereof.

170. The method of any one of claims 163-169, wherein $[D]_v$ is $–Leu_1-Thr_2$.

171. The method of any one of claims 163-170, wherein w is 1, 2, 3, 4, 5, 6, 7, 8, 9, or 10.

172. The method of any one of claims 163-170, wherein w is 3-10.

173. The method of any one of claims 163-170, wherein w is 3-6.

174. The method of any one of claims 163-170, wherein w is 6-10.

175. The method of any one of claims 163-170, wherein w is 6.

176. The method of any one of claims 163-175, wherein v is 1-10.

177. The method of any one of claims 163-175, wherein v is 2-10.

178. The method of any one of claims 163-175, wherein v is 2-5.

179. The method of any one of claims 163-175, wherein v is 2.

180. The method of claim 163 or 163, wherein each L_1 and L_2 are independently alkylene, alkenylene, alkynylene, heteroalkylene, cycloalkylene, heterocycloalkylene, cycloarylene, or heterocycloarylene, each being optionally substituted with R_5.

181. The method of claim 163 or 164 wherein L_1 and L_2 are independently alkylene or alkenylene.

182. The method of claim 163 or 164, wherein L is alkylene, alkenylene, or alkynylene.

183. The method of claim 163 or 164, wherein L is alkylene.

184. The method of claim 163 or 164, wherein L is C_3-C_{16} alkylene.

185. The method of claim 163 or 164, wherein L is C_{10}-C_{14} alkylene.

186. The method of any one of claims 163, wherein each R_1 and R_2 are independently –H, alkyl, alkenyl, alkynyl, arylalkyl, cycloalkyl, cycloalkylalkyl, heteroalkyl, or heterocycloalkyl, unsubstituted or substituted with halo–.

187. The method of any one of claims 163, wherein R_1 and R_2 are H.

188. The method of any one of claims 163, wherein each R_1 and R_2 are independently alkyl.

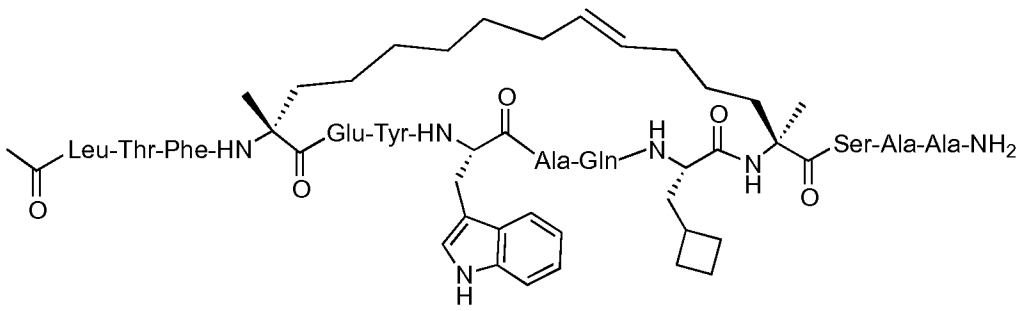
189. The method of any one of claim 163, wherein R_1 and R_2 are methyl.

190. The method of claim 163, wherein x+y+z = 6.

191. The method of claim 163, wherein u is 1.

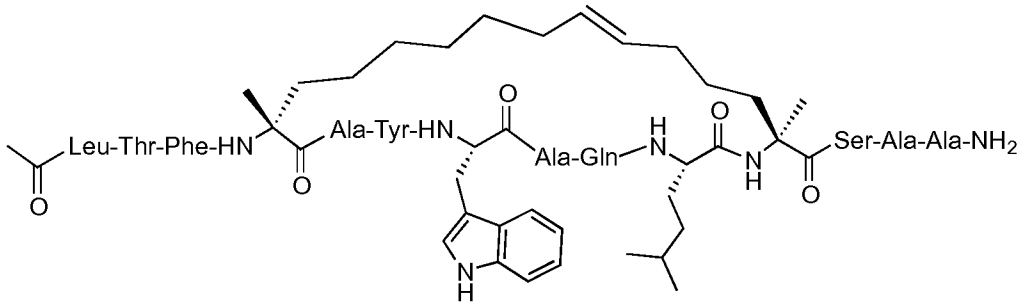
192. The method of any one of claims 163-191, the peptidomimetic macrocycle comprises at least one amino acid which is an amino acid analog.

193. The method of claim 163 or 164, wherein the peptidomimetic macrocycle has formula:



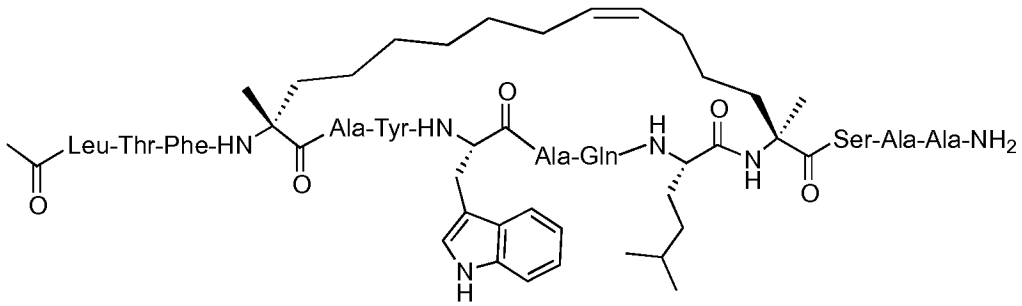
(SEQ ID NO: 163) or a pharmaceutically acceptable salt thereof.

194. The method of claim 163 or 164, wherein the peptidomimetic macrocycle has formula:



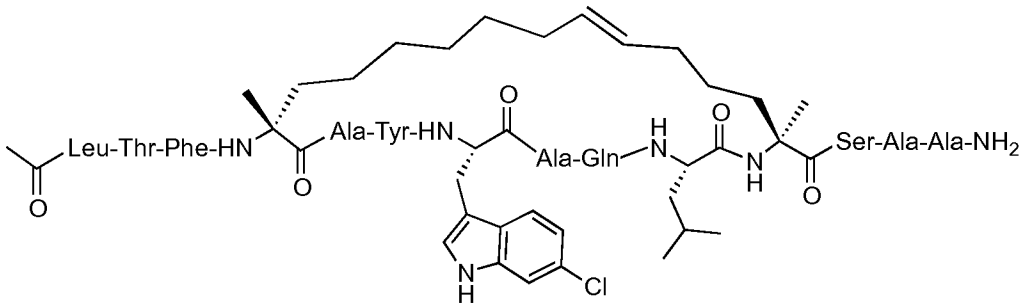
(SEQ ID NO: 124) or a pharmaceutically acceptable salt thereof.

195. The method of claim 163 or 164, wherein the peptidomimetic macrocycle has formula:



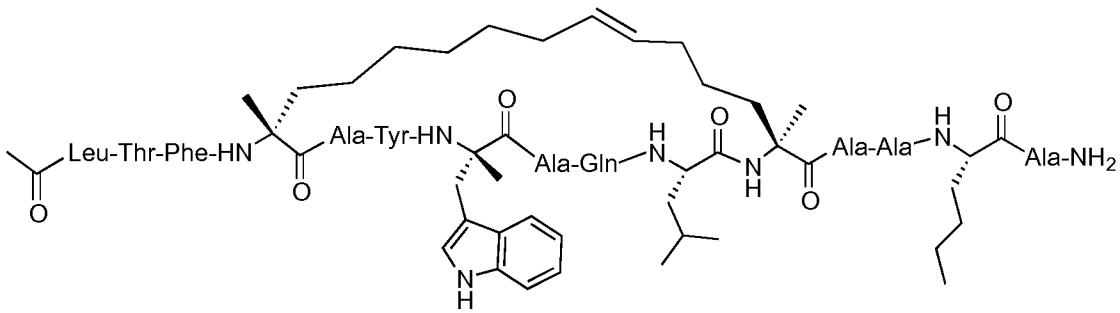
(SEQ ID NO: 123) or a pharmaceutically acceptable salt thereof.

196. The method of claim 163 or 164, wherein the peptidomimetic macrocycle has formula:



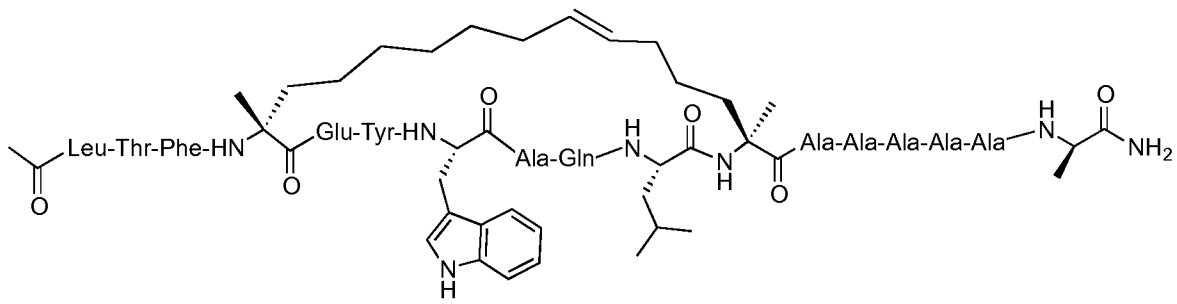
(SEQ ID NO: 108) or a pharmaceutically acceptable salt thereof.

197. The method of claim 163 or 164, wherein the peptidomimetic macrocycle has formula:



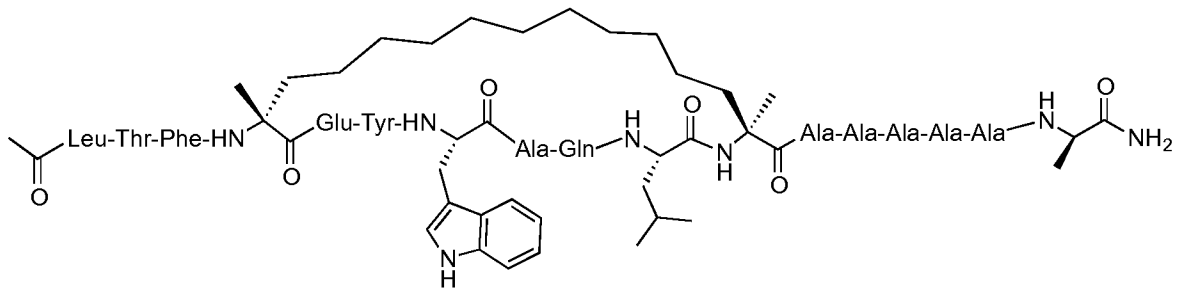
(SEQ ID NO: 397) or a pharmaceutically acceptable salt thereof.

198. The method of claim 163 or 164, wherein the peptidomimetic macrocycle has formula:



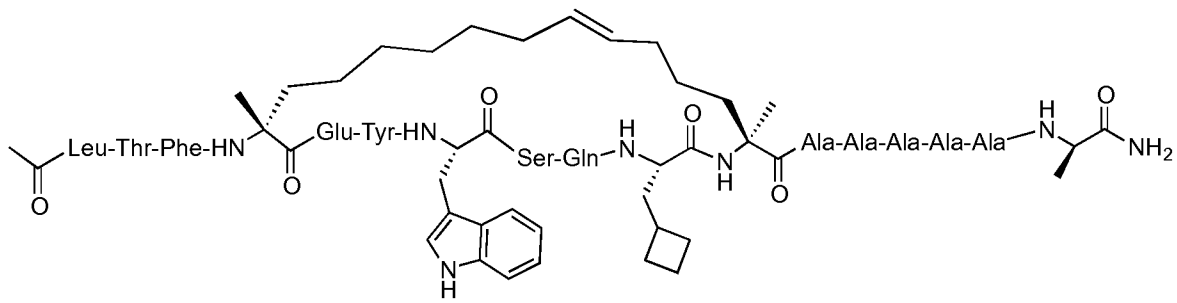
(SEQ ID NO: 340) or a pharmaceutically acceptable salt thereof.

199. The method of claim 163 or 164, wherein the peptidomimetic macrocycle has formula:



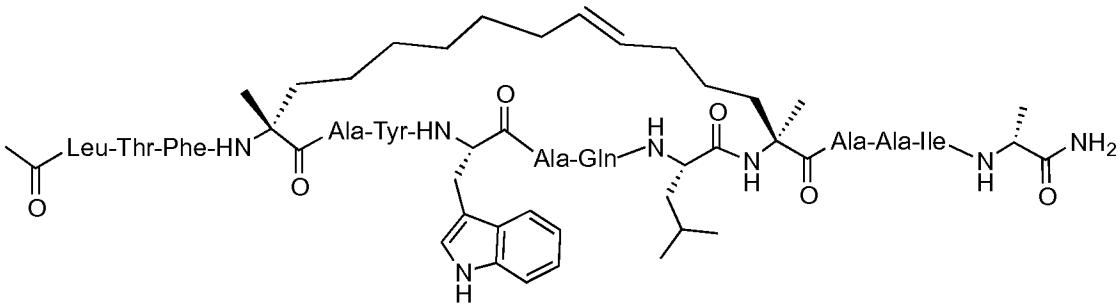
(SEQ ID NO: 454) or a pharmaceutically acceptable salt thereof.

200. The method of claim 163 or 164, wherein the peptidomimetic macrocycle has formula:



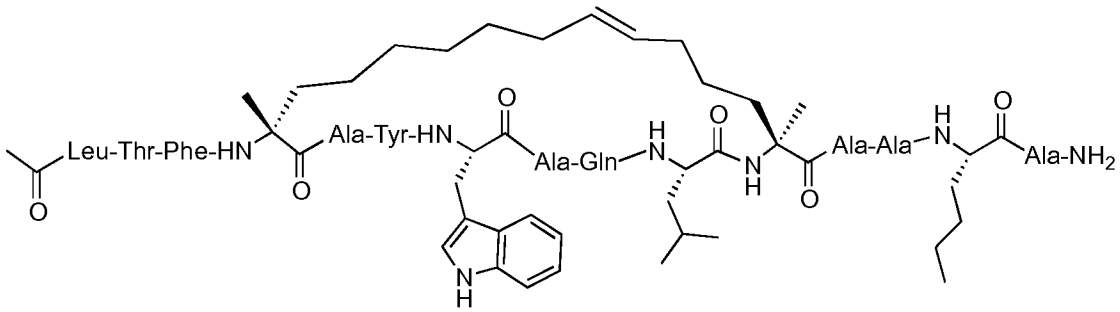
(SEQ ID NO: 360) or a pharmaceutically acceptable salt thereof.

201. The method of claim 163 or 164, wherein the peptidomimetic macrocycle has formula:



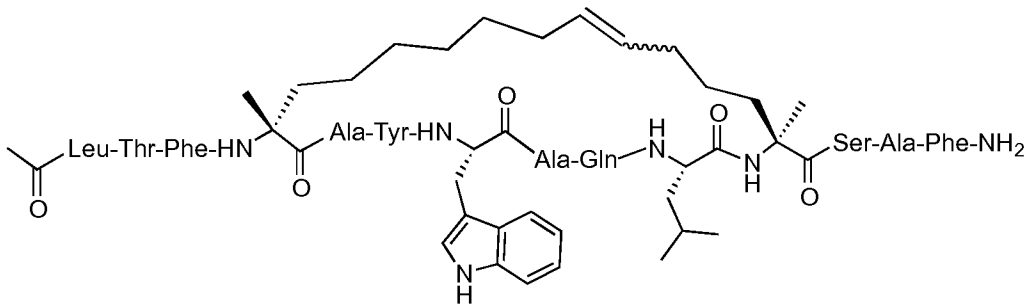
(SEQ ID NO: 80) or a pharmaceutically acceptable salt thereof.

202. The method of claim 163 or 164, wherein the peptidomimetic macrocycle has formula:



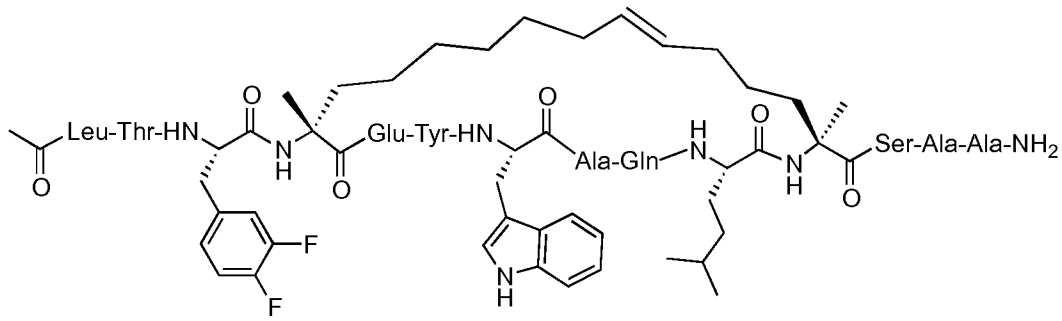
(SEQ ID NO: 78) or a pharmaceutically acceptable salt thereof.

203. The method of claim 163 or 164, wherein the peptidomimetic macrocycle has formula:



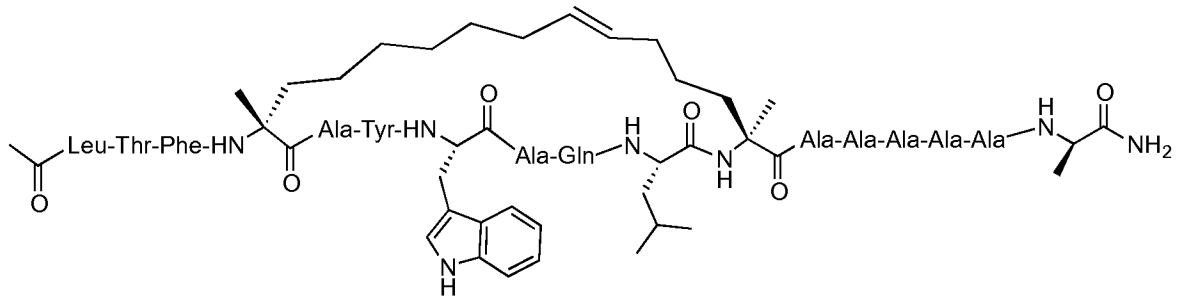
(SEQ ID NO: 16) or a pharmaceutically acceptable salt thereof.

204. The method of claim 163 or 164, wherein the peptidomimetic macrocycle has formula:



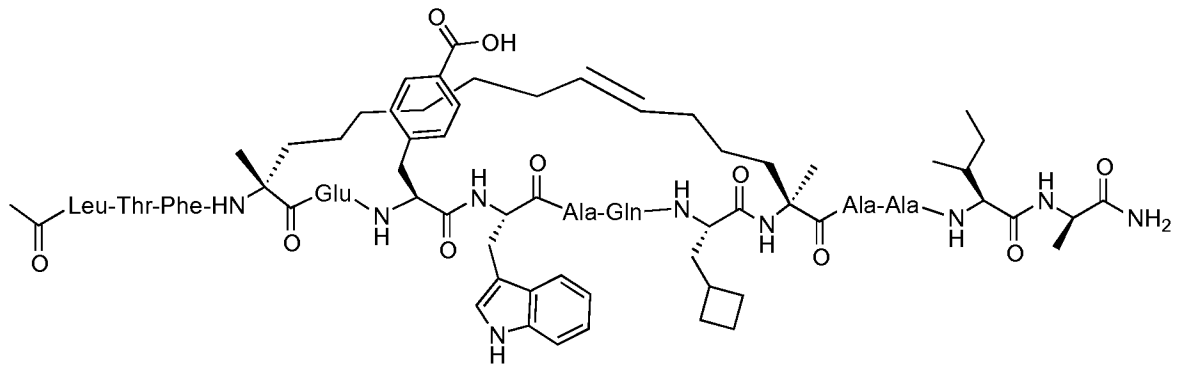
(SEQ ID NO: 169) or a pharmaceutically acceptable salt thereof.

205. The method of claim 163 or 164, wherein the peptidomimetic macrocycle has formula:



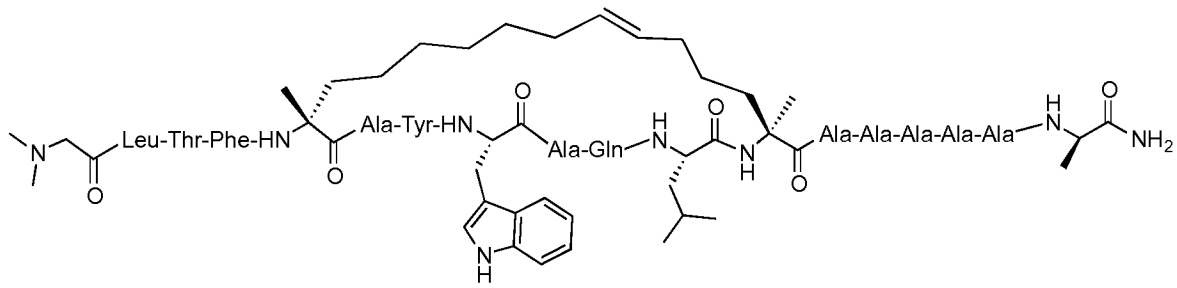
(SEQ ID NO: 324) or a pharmaceutically acceptable salt thereof.

206. The method of claim 163 or 164, wherein the peptidomimetic macrocycle has formula:



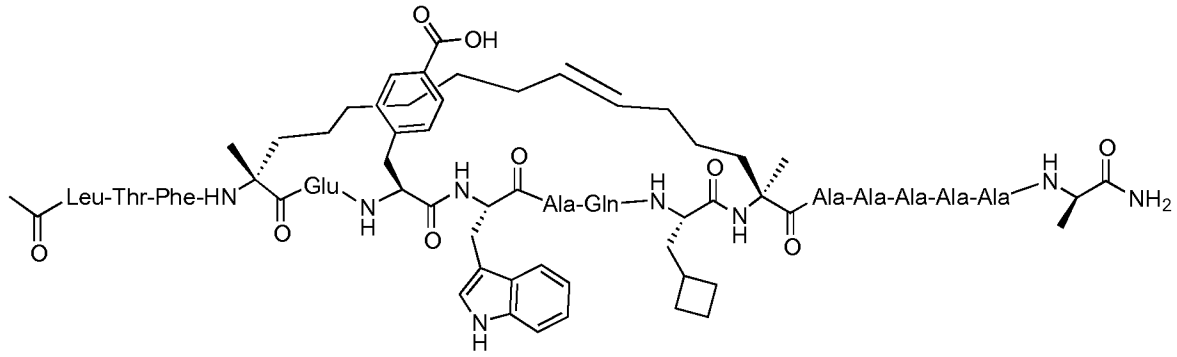
(SEQ ID NO: 258) or a pharmaceutically acceptable salt thereof.

207. The method of claim 163 or 164, wherein the peptidomimetic macrocycle has formula:



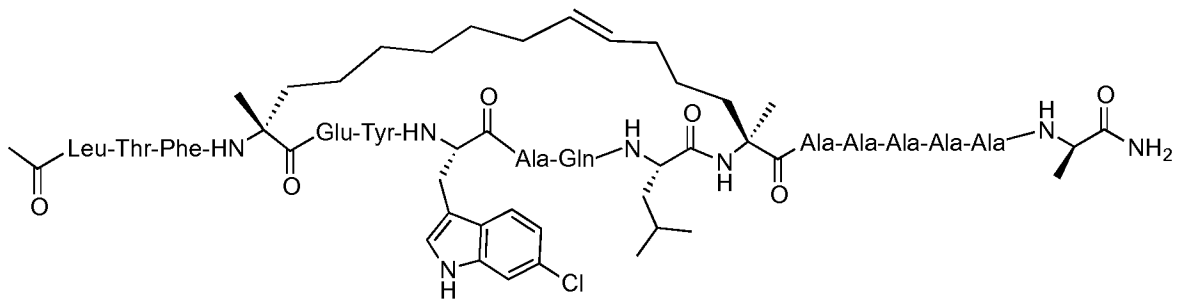
(SEQ ID NO: 446) or a pharmaceutically acceptable salt thereof.

208. The method of claim 163 or 164, wherein the peptidomimetic macrocycle has formula:



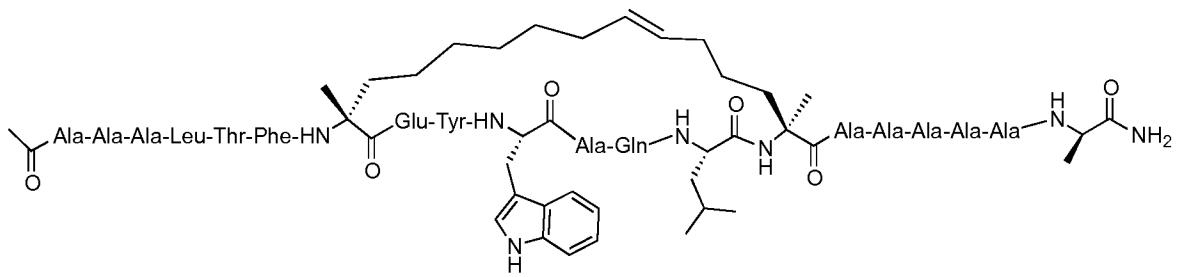
(SEQ ID NO: 358) or a pharmaceutically acceptable salt thereof.

209. The method of claim 163 or 164, wherein the peptidomimetic macrocycle has formula:



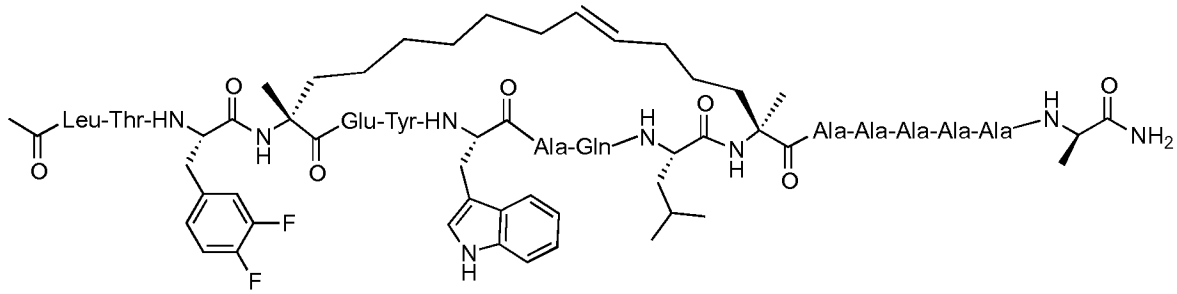
(SEQ ID NO: 464) or a pharmaceutically acceptable salt thereof.

210. The method of claim 163 or 164, wherein the peptidomimetic macrocycle has formula:



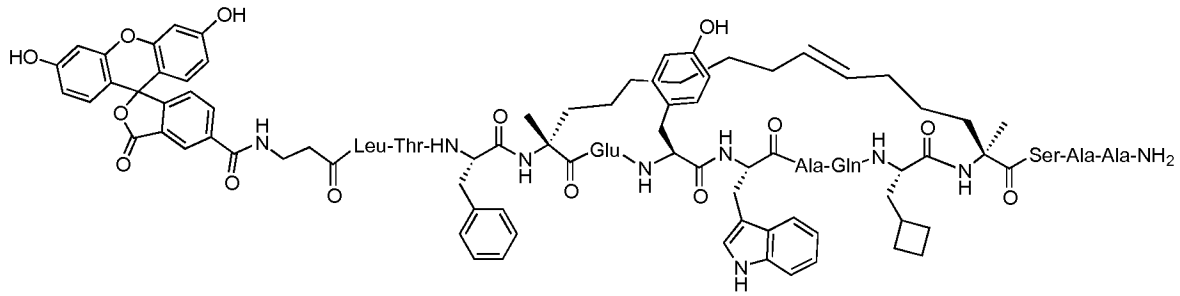
(SEQ ID NO: 466) or a pharmaceutically acceptable salt thereof.

211. The method of claim 163 or 164, wherein the peptidomimetic macrocycle has formula:



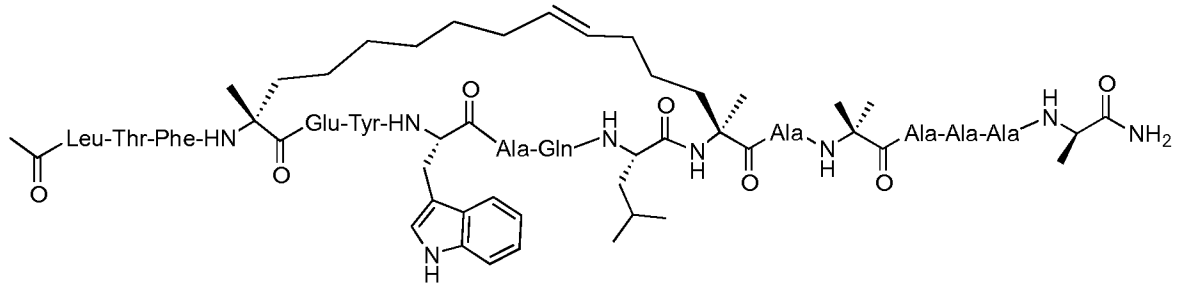
(SEQ ID NO: 467) or a pharmaceutically acceptable salt thereof.

212. The method of claim 163 or 164, wherein the peptidomimetic macrocycle has formula:



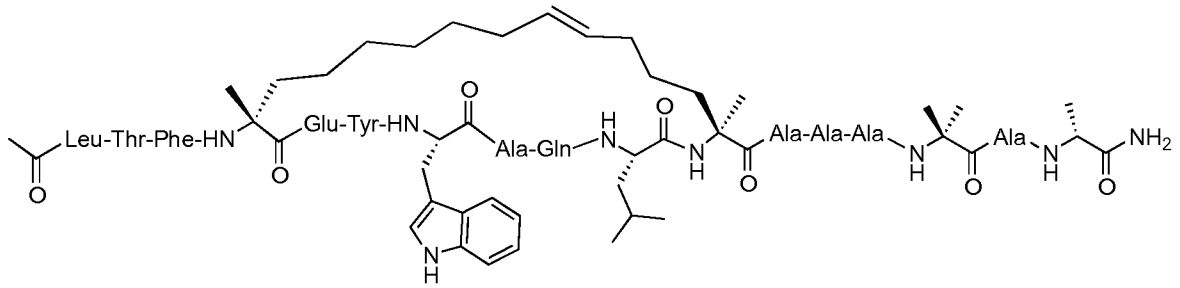
(SEQ ID NO: 376) or a pharmaceutically acceptable salt thereof.

213. The method of claim 163 or 164, wherein the peptidomimetic macrocycle has formula:



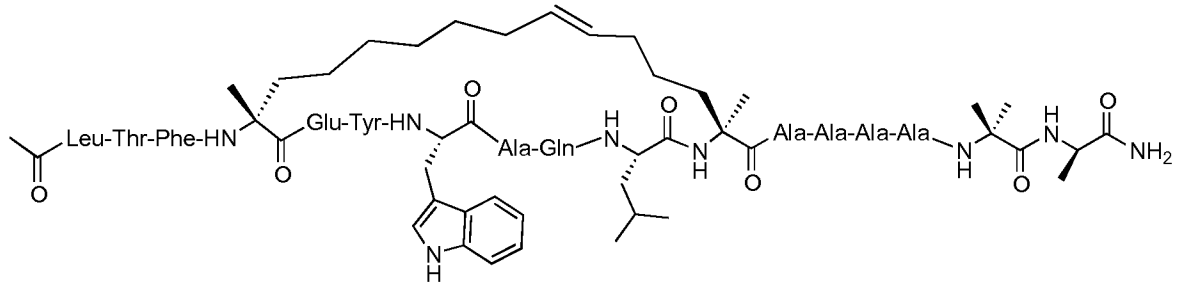
(SEQ ID NO: 471) or a pharmaceutically acceptable salt thereof.

214. The method of claim 163 or 164, wherein the peptidomimetic macrocycle has formula:



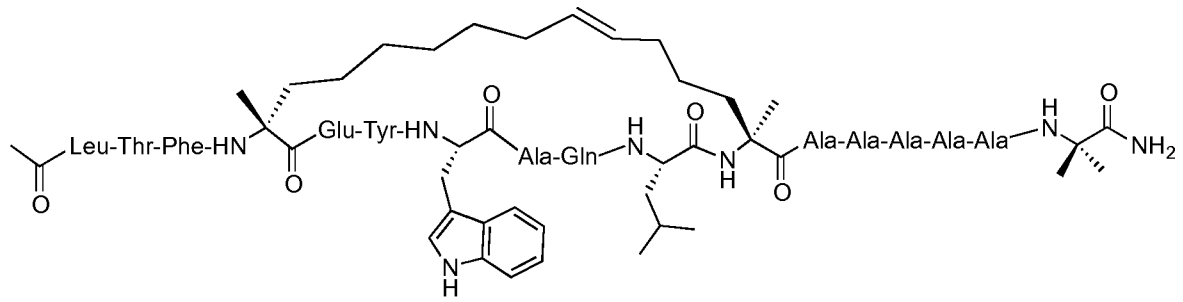
(SEQ ID NO: 473) or a pharmaceutically acceptable salt thereof.

215. The method of claim 163 or 164, wherein the peptidomimetic macrocycle has formula:



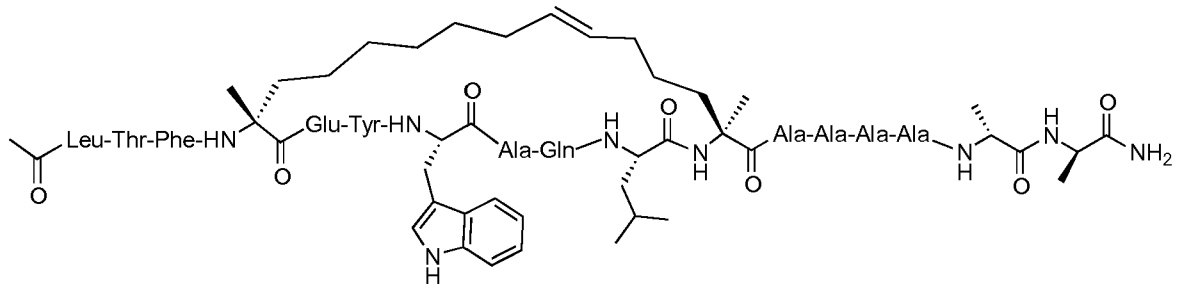
(SEQ ID NO: 475) or a pharmaceutically acceptable salt thereof.

216. The method of claim 163 or 164, wherein the peptidomimetic macrocycle has formula:



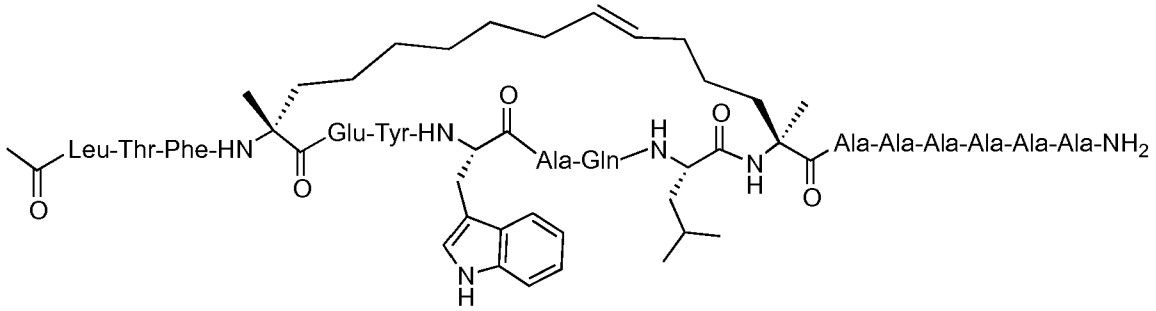
(SEQ ID NO: 476) or a pharmaceutically acceptable salt thereof.

217. The method of claim 163 or 164, wherein the peptidomimetic macrocycle has formula:



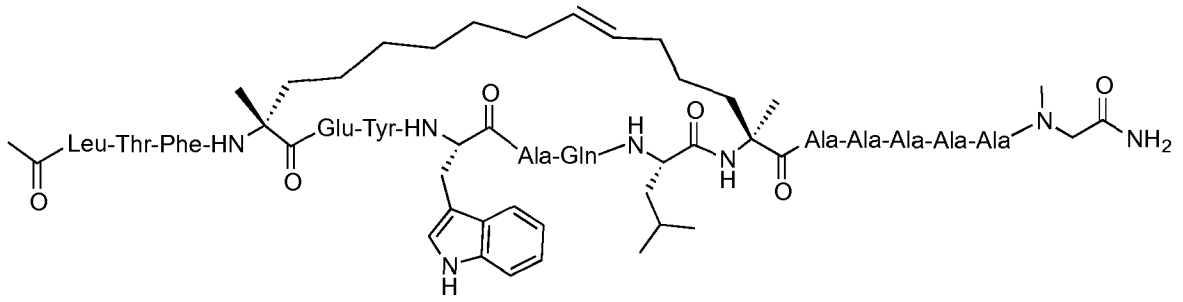
(SEQ ID NO: 481) or a pharmaceutically acceptable salt thereof.

218. The method of claim 163 or 164, wherein the peptidomimetic macrocycle has formula:



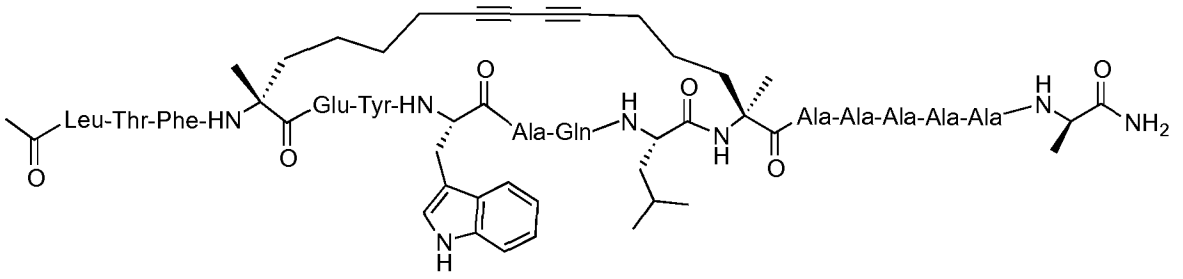
(SEQ ID NO: 482) or a pharmaceutically acceptable salt thereof.

219. The method of claim 163 or 164, wherein the peptidomimetic macrocycle has formula:



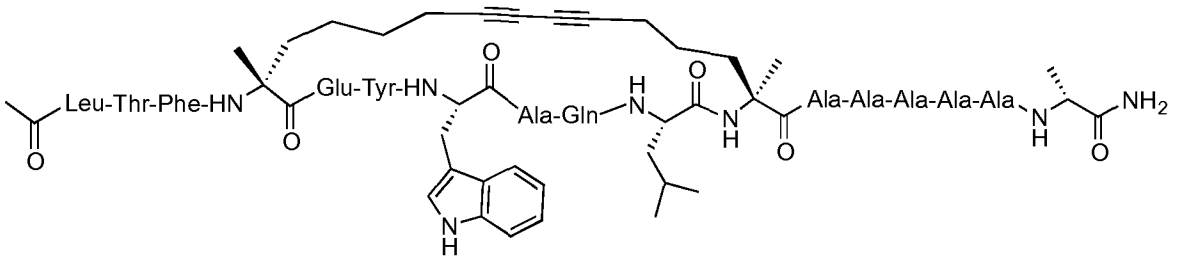
(SEQ ID NO: 487) or a pharmaceutically acceptable salt thereof.

220. The method of claim 163 or 164, wherein the peptidomimetic macrocycle has formula:



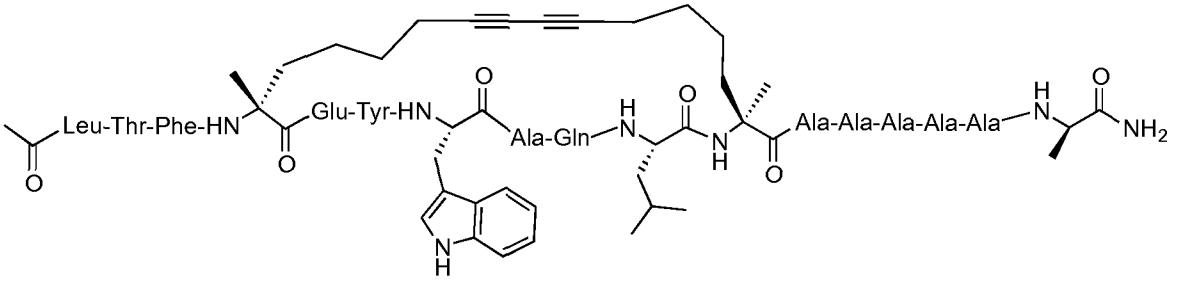
(SEQ ID NO: 572) or a pharmaceutically acceptable salt thereof.

221. The method of claim 163 or 164, wherein the peptidomimetic macrocycle has formula:



(SEQ ID NO: 572) or a pharmaceutically acceptable salt thereof.

222. The method of claim 163 or 164, wherein the peptidomimetic macrocycle has formula:



(SEQ ID NO: 1500) or a pharmaceutically acceptable salt thereof.

223. A method of identifying one or more solid tumor biomarkers in a human subject lacking a p53 deactivating mutation, comprising administering to the human subject a pharmaceutical composition comprising a therapeutically effective amount of a peptidomimetic macrocycle.

224. The method of claim 223, wherein the biomarkers are selected from a group comprising p53 status, MDM2 expression level and MDMX expression level.

225. The method of any one of the proceeding claims, wherein the pharmaceutical composition comprises the pharmaceutically acceptable salt of the peptidomimetic macrocycle.

226. The method of claim 223, wherein the pharmaceutically acceptable salt is a sodium salt, potassium salt or calcium salt.

227. The method of claim 224 wherein the pharmaceutically acceptable salt is a sodium salt.